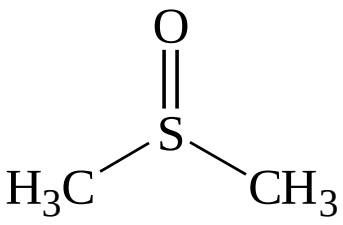
TECHNICAL BULLETIN
REACTION SOLVENT
DIMETHYL SULFOXIDE (DMSO)



CAS Name: Methane, sulfinylbis
CAS Registry Number: 67- 68- 5

Dimethyl sulfoxide as manufactured by Gaylord Chemical, is a water-white almost odorless liquid, boiling at 189°C. and melting at above 18.2° C. It is relatively stable and easy to recover, miscible in all proportions with water and most common organic solvents and has a low order of toxicity.

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Dimethyl sulfoxide or DMSO is a highly polar, high boiling, aprotic, water miscible, hygroscopic organic liquid. It is essentially odorless, water white and has a low order of toxicity.

Chemically, DMSO is stable above 100° C in alkaline, acidic or neutral conditions. Prolonged refluxing at atmospheric pressure will cause slow decomposition of DMSO. If this occurs, it can be readily detected by the odor of trace amounts of methyl mercaptan and bis(methylthio)methane. The rate of decomposition is a timetemperature function that can be accelerated by the addition of acids and retarded by some bases.

DMSO is a versatile and powerful solvent that will dissolve most aromatic and unsaturated hydrocarbons, organic nitrogen compounds, organo-sulfur compounds and many inorganic salts. It is miscible with most of the common organic solvents such as alcohols, esters, ketones, lower ethers, chlorinated solvents and aromatics. However, saturated aliphatic hydrocarbons are virtually insoluble in DMSO.

As a reaction solvent, DMSO is valuable for displacement, elimination, and condensation reactions involving anions. In DMSO, the rates of these reactions are often increased by several orders of magnitude. In free radical polymerizations, higher average molecular weights have been reported when DMSO was used as the reaction solvent.

The dominant characteristics of DMSO most important in its usefulness as a reaction solvent are its high polarity, its essentially aprotic nature, and its solvating ability toward cations. The high dipole moment of the sulfur-oxygen bond (4.3) and the high dielectric constant (approx. 48) for bulk DMSO suggest the solvating properties and ability to disperse charged solutes. DMSO is not a hydrogen donor in hydrogen bonding and poorly solvates anions except by dipolar association to polarizable anions. The hydrogen atoms of DMSO are quite inert, although they are replaceable under sufficiently severe conditions (bulk pKa = 35.1). The oxygen of DMSO is somewhat basic and participates strongly as a hydrogen bond acceptor. DMSO forms isolatable salts with several strong acids.

Owing to its chemical and physical properties, DMSO can be efficiently recovered from aqueous solutions. Commercial users of DMSO employ a variety of processing schemes in their recovery systems. All of these are based on evaporation or fractional distillation because of simplicity of design and operation. Unlike some other solvents, DMSO can be easily separated from water by distillation in substantially pure form. For example, DMSO containing less that 500 ppm water can be recovered from a solution containing 50 weight percent water with only 15 column plates at a reflux ratio of 1:1.

Dimethyl sulfoxide occurs widely in nature at levels of 3 ppm or less. It has been found in spearmint oil, corn, barley, malt, alfalfa, beets, cabbage, cucumber, oats, onions, swiss chard, tomatoes, raspberries, beer, coffee, milk and tea. DMSO is a common constituent of natural waters. It has been identified in seawater in the zone of light penetration where it may represent an end product of algal metabolism. Its occurrence in rainwater may result from oxidation of atmospheric dimethyl sulfide which in turn occurs as part of the natural transfer of sulfur of biological origin.

No attempt has been made in this bulletin to present a complete literature survey of all the uses of DMSO as a reaction solvent, solvent, or reactant. A few carefully chosen references have been selected to illustrate the most important areas of DMSO chemistry. For persons wishing to learn more about DMSO as a reaction solvent, ir any other information in this bulletin, please write or call:

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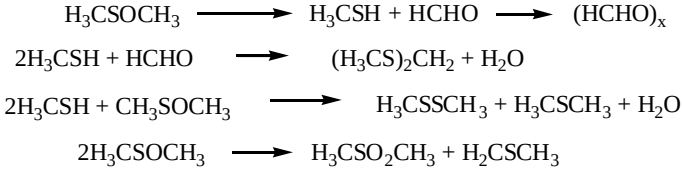
PART I. PROPERTIES OF DMSO

TABLE I. Physical Properties of DMSO

		Reference
Molecular Weight	78.13	
Boiling Point at 760 mm Hg	189 °C (372°F)	(342)
Freezing point	18.45°C (65.4°F)	(342)
Molal freezing point constant, °C/(mol)(kg)	4.07	(2151)
Refractive index nD25	1.4768	(581)
Surface tension at 20°C	43.53 dynes/cm	(2223)
Vapor pressure, at 25°C	0.600 mmHg	(372)
Density, g/cm3, at 25°C	1.099	(581)
Viscosity, cP, at 25°C	2.0 (see Figs. 3 & 4)	(581)
Specific heat at 29.5°C	0.47+/- 0.015 cal/g/°C	(3215)
Heat capacity (liq.), 25°C	0.47 cal/g/°C	(2900)
Heat capacity (ideal gas)	Cp(T°K)=6.94+5.6x10 –2T-0.227x10-4T2	(353)
Heat of fusion	41.3 cal/g	(232)
Heat of vaporization at 70°C	11.3 kcal/mol (260 BTU/lb)	
Heat of solution in water at 25°C	-54 cal/g, @ ∞ dilution	(3215)
Heat of combustion	6054 cal/g; (473 kcal/mole)	(342)
Flash point (open cup)	95°C (203°F)	
Auto ignition temperature in air	300-302°C (572-575°F)	
Flammability limits in air		
lower (100°C)	3-3.5% by volume	
upper	42-63% by volume	
Coefficient of expansion	0.00088/°C	(342)
Dielectric constant, 10MHz	48.9 (20°C)	(342)
	45.5 (40°C)	
Solubility parameter	Dispersion 9.0	(8070)
	Polar 8.0	
	H-bonding 5.0	
Dipole moment, D	4.3	(342)
Conductivity, 20°C	3x108(ohm –1cm-1)	(342)
80°C	7x108(ohm –1cm-1)	
PKa	35.1	(10411)

Thermal and Chemical Stability of DMSO

As shown in Figure 5, DMSO is highly stable at temperatures below 150° C. For example, holding DMSO at 150° C for 24 hours, one could expect a loss of between 0.1 and 1.0%. Retention times even in batch stills are usually considerably less than this, and therefore, losses would be correspondingly less.. It has been reported that only 3.7% of volatile materials are produced during 72 hours at the boiling point (189° C) of DMSO (1). Slightly more decomposition, however, can be expected with the industrial grade material. Thus, about 5% DMSO decomposes at reflux after 24 hours (3921). Almost half of the weight of the volatile materials is paraformaldehyde. Dimethyl sulfide, dimethyl disulfide, bis(methylthio)methane and water are other volatile products. A small amount of dimethyl sulfone can also be found. The following sequence of reactions explains the formation of these decomposition products (1):



DMSO is remarkably stable in the presence of most neutral or basic salts and bases (3922). When samples of DMSO (300g) are

refluxed for 24 hours with 100g each of sodium hydroxide, sodium carbonate, sodium chloride, sodium cyanide, sodium acetate and sodium sulfate, little or no decomposition takes place in most cases. The results are shown in Table II below (3922):

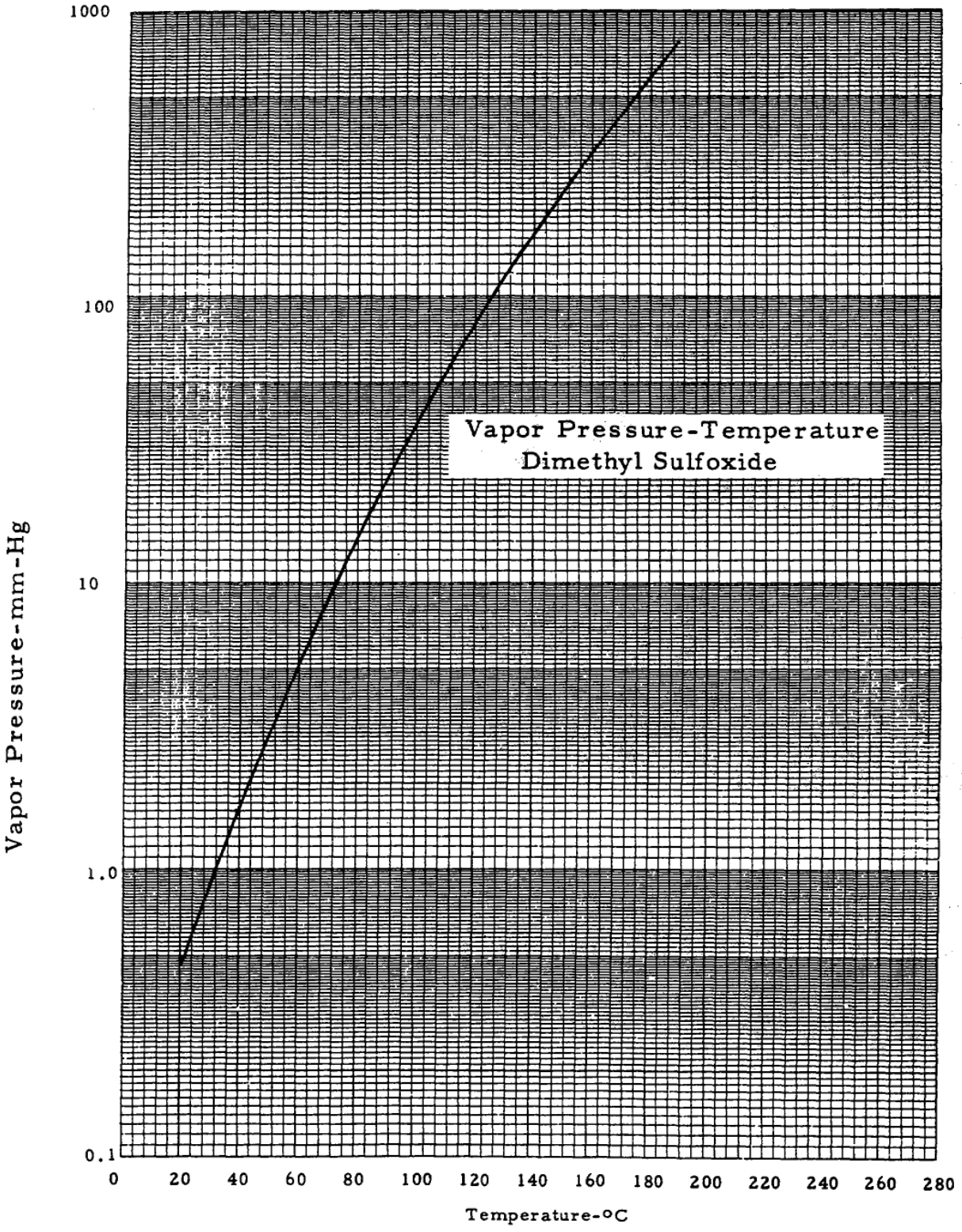


FIGURE 1

FREEZING POINT CURVES FOR DMSO-WATER SOLUTIONS

FIGURE 2a

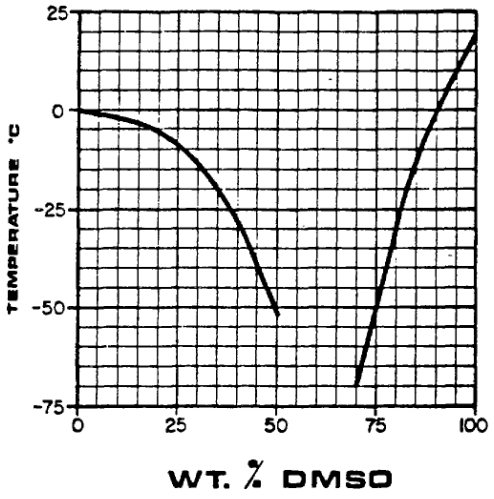
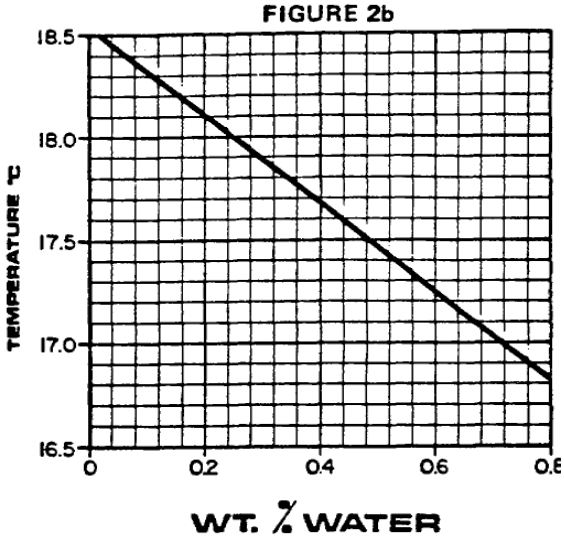


FIGURE 2b



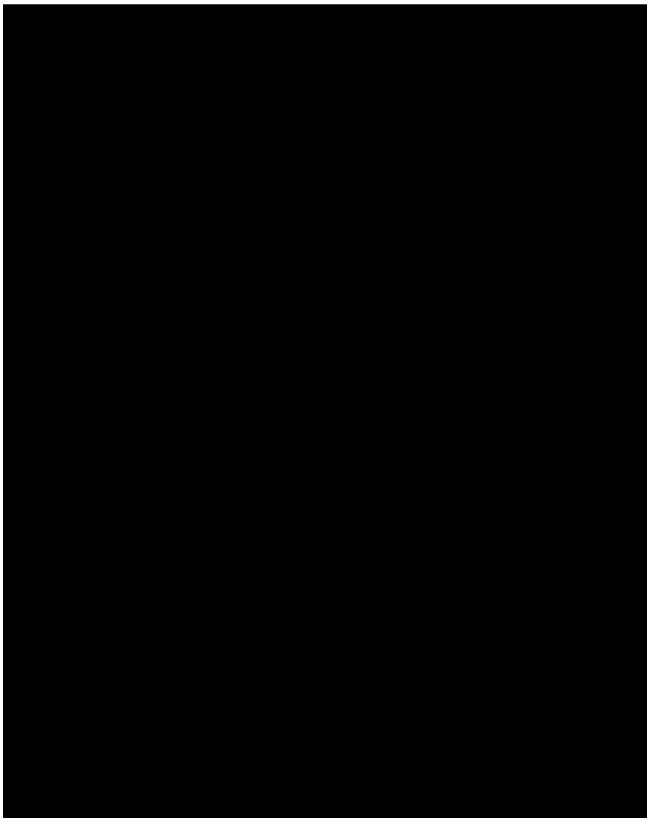


FIGURE 4

VISCOSITY OF DMSO—WATER SOLUTIONS

25°C

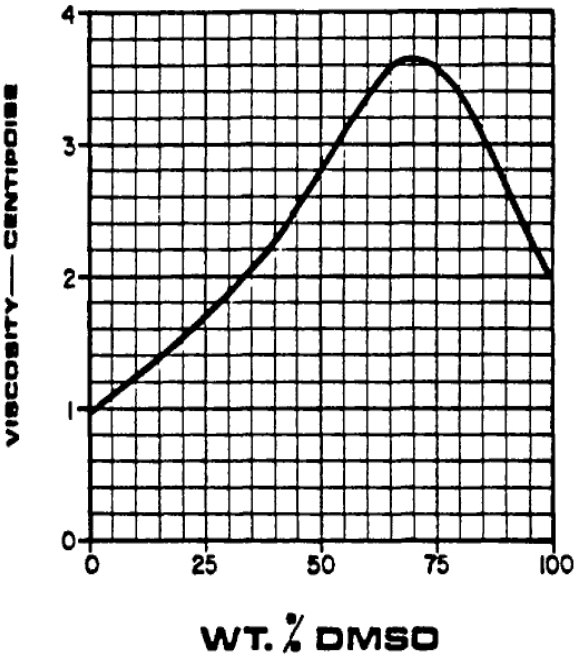


TABLE II

Results of Reflux of DMSO for 24 Hours with Various Compounds

Compound (1008) in 300 g DMSO	Reflux Temp.,° C.	DMSO Recovered % of Original	DMS[(a)]	% of Decomposition Products, DMDS[(b)]	BMTM[(c)]	HCHO	M Md
NaOH	185-140e	93.7	63	31			
Na_2CO_3	190	96.3		14			
NaCl	190	98.7		15			
NaCN	148-164f	100.0					
NaOAc	182-187	97.0	22	33	8	20	
Na_2SO_4	181-148g	85.4	66				11
DMSO only	189	98.0	15	30	30		

(a) Dimethyl sulfide
(b) Dimethyl disulfide
(c) Bis(methylthio)methane
(d) Methyl mercaptan
(e) Reflux temp. decreased from 185°C to 140°C over the first 16 hours.
(f) Reflux temp. was 148°C for 20 hours; increased to 164° C during the last 4 hours.
(g) Reflux temp. decreased gradually from 181°C to 148° C.

DMSO does not seem to be hydrolyzed by water and very little decomposition of DMSO takes place when it is heated under reflux for periods of 5 to 16 hours. The following tests, shown in Table III, have been performed: 1)10 parts DMSO + 1 part water, 2) 60 parts DMSO + 5 parts water + 1 part sodium hydroxide, 3) 60 parts DMSO + 12 parts water + 1 part sodium bicarbonate, 4) DMSO alone (3922):

TABLE III

Refluxing of DMSO and Mixtures For Shorter Periods

Composition of Sample, Parts	Reflux Time,°C.	Time Hr.	DMSO 100	Organic Product Composition, DMS 0	DMDS 0	BMTM 0
10 DMSO:1 H_2O	152	5				
		15	99.7	0.15	0	0.15
60 DMSO:5 H_2O:1 NaOH	155	5	99.8	0.1	0.1	0
		8	99.3	0.6	0.1	0
60 DMSO:12 H_2O:1 $NaHCO_3$	131	6	99.9	0.1	0	0
		12	99.8	0.2	0	0
DMSO only	191	5	99.8	0.1	0.1	0
		9	99.1	0.2	0.2	0.5
		16	99.0	0.2	0.2	0.6

DMSO is also stable in the presence of concentrated sulfuric or hydrochloric acid at 100° C for up to 120 minutes of heating at atmospheric

pressure. Phosphoric acid causes more rapid decomposition of DMSO than does sulfuric or hydrochloric acid. Detected decomposition products are dimethyl sulfide, dimethyl disulfide, and, in smaller quantity, formaldehyde. The results are shown in Table IV (3920):

TABLE IV

Effect of Heating DMSO with Concentrated Acids - (200g DMSO with 20g of concn. acid)

Acid	Conc.	Temp., ° C.	Time, Min.	DMSO Left, %	% of Decomposition Products		
					DMS[a]	**DMDS[b]**	**HCHO**
H2SO4	36N	100	15	99	100		
			30	99	100		
			120	98	100		
H2SO4	36N	125	- 15	86	7	93	
			150	86	7	93	
			210	80	10	90	
H3 P04	85%	100	15	92	25	75	
			30	89	45	55	
			45	89	45	55	
			60	87	46	54	
			120	87	46	54	
			150	86	50	50	some
H3 P04	85%	125	15	84	25	75	
			60	82	**33**	67	
			150	82	33	67	
HCl	12N	95	15	99	100		
			30	99	100		
			60	99	100		
			120	98	100		
HCl	12N	115	15	93	100		
			30	92	100		
			45	87	100		
			60	87	100		
			120	87	100		some

(a) Dimethyl Sulfide
(b) Dimethyl Disulfide

THERMAL STABILITY OF DMSO

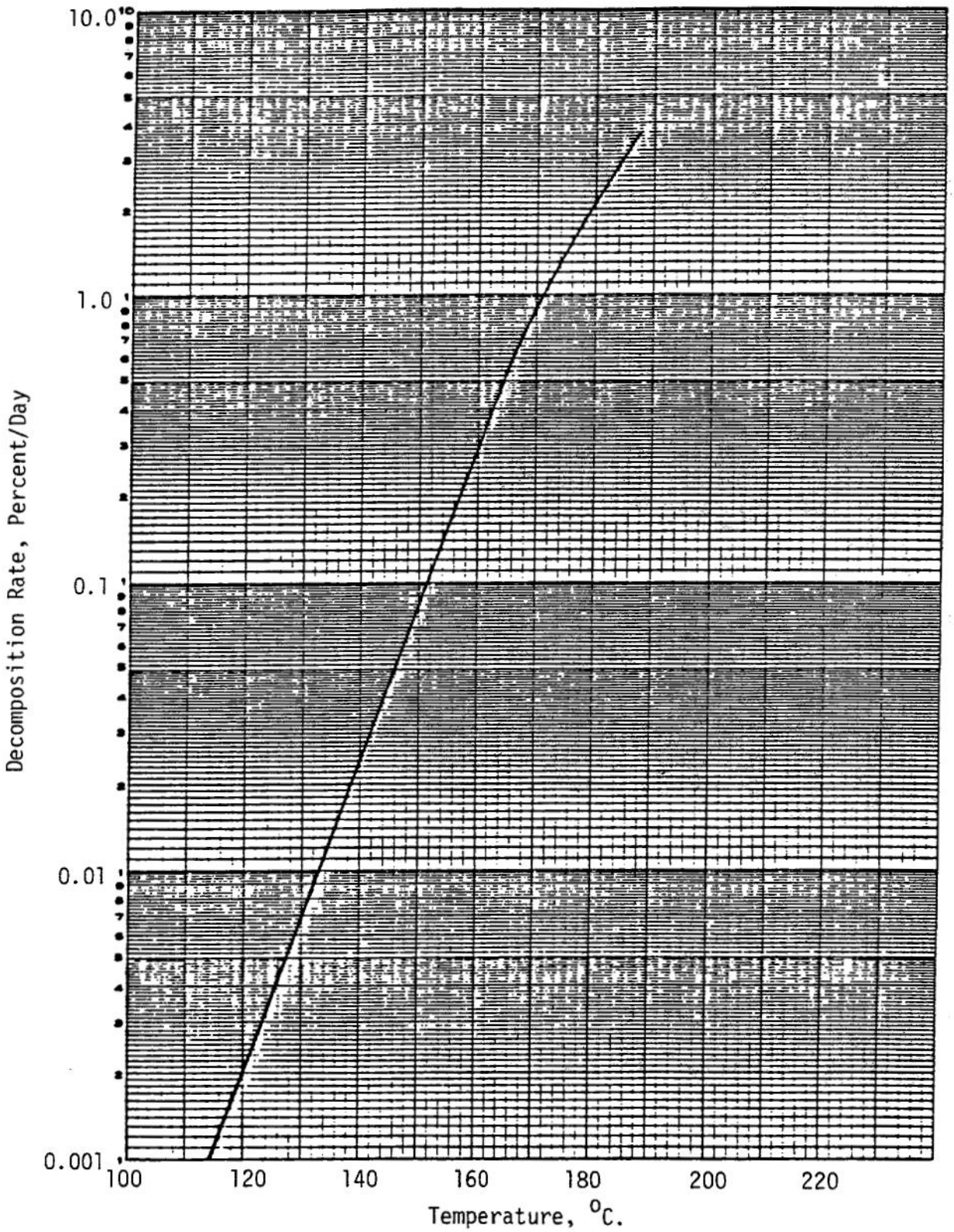


FIGURE 5

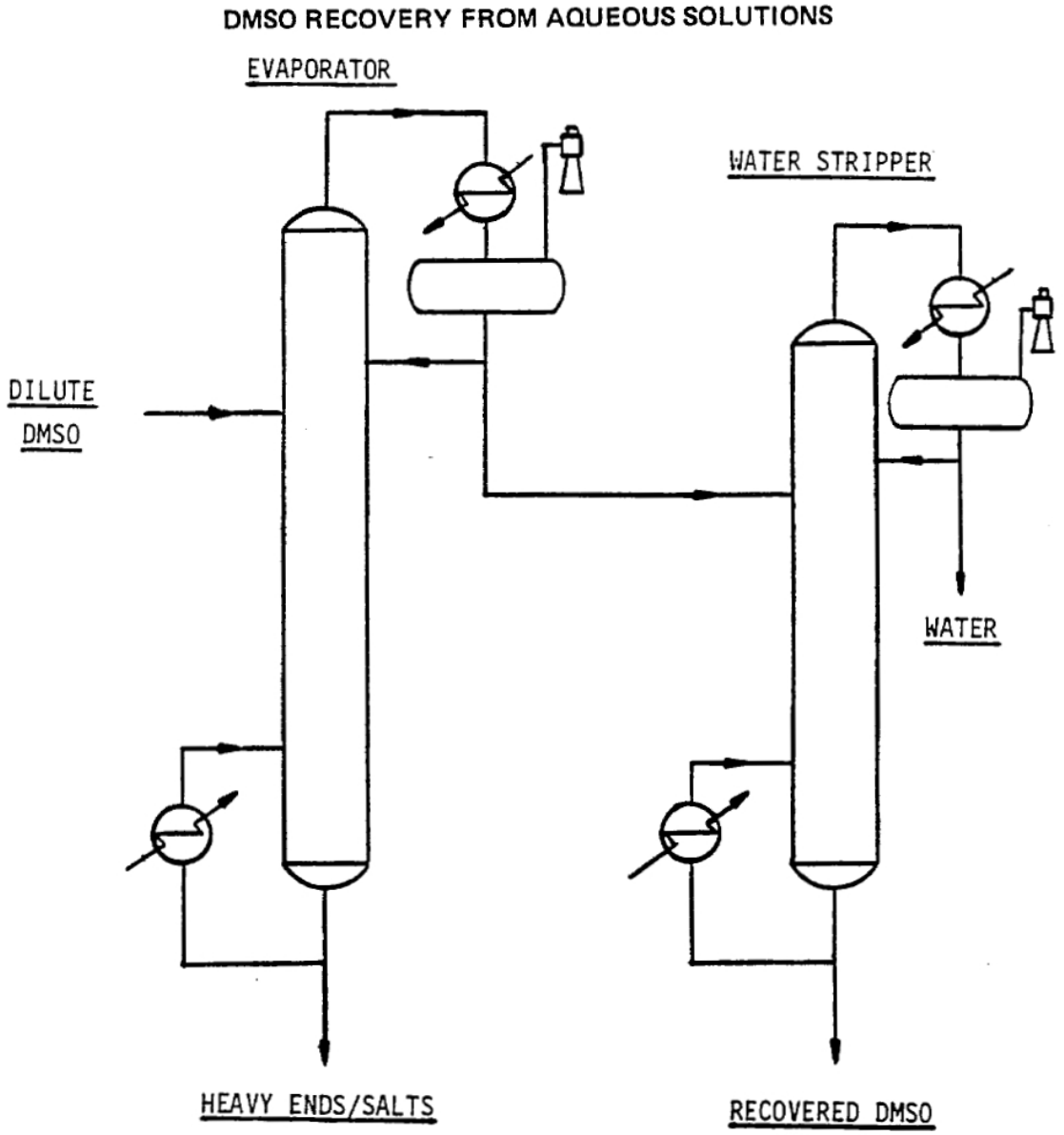


FIGURE 6

Recovery from Aqueous Solutions

Many chemical processes using DMSO require the addition of water to stop the reaction or to separate the product from the solvent (DMSO). DMSO can be separated efficiently and cleanly from this water and other impurities by distillation. DMSO distillations are not complicated by any known azeotropes.

A typical feed to a recovery operation is relatively weak in DMSO - 10 to 20%. There would usually be two vacuum distillation steps in the recovery:

1) Evaporation of the DMSO-water solution overhead to eliminate less volatile impurities, if any are present, and
2) Fractional distillation of the DMSO-water solution to recover pure DMSO.

Recovery may be done batchwise or continuously, employing moderate conditions. An operating pressure of about 100 mm Hg abs. would allow the use of 85 psig steam and normally available cooling water.

PART II
SOLVENCY CHARACTERISTICS OF DMSO

The solvent characteristics of DMSO derive mainly from its being highly polar and aprotic. Because of its high polarity it forms association bonds with other polar and polarizable molecules, including itself. Thus, it is miscible with water and almost all types of organic liquids except the saturated alkanes. It has a high solvency for the large organic molecules containing polar groups. DMSO has also exhibited an ability to dissolve many inorganic salts, particularly those of the transition metals or those which have nitrates, cyanides or dichromates as their anions.

The following tables of solubilities are offered as a guide and an easy reference.

Solubility of salts ---------- ----------Table V
Solubility of resins and polymers ----------Table V I
Solubility of miscellaneous materials ----------Table VII
Solubility of gases ----------Table VIII

The difficulty of predicting solubility characteristics suggests that each specific compound be checked for its solubility in DMSO rather then generalizing from reported solubilities. Because of the variability of resins and polymers from one manufacturer to another, tradenames and companies have been used to identify accurately the materials in Table VI.
The study of co-solvent possibilities utilizing DMSO has not been included as the complexity and diversity of this field are too broad to give adequate coverage. It will be noted however from Table VII that DMSO is compatible with most of the common solvents. This compatibility and the strong solvency properties of DMSO indicate numerous possibilities for co-solvent systems to perform given tasks efficiently and economically.

TABLE V
Solubility of Salts in DMSO (794)

	Solubility Grams/100 cc DMSO			Solubility Grams/100 cc DMSO	
	25°C.	**90-100°C.**		**25°C.**	**90-100°C**
Aluminum sulfate (18H_2O)	Insol.	5	Lithium dichromate (2 H_2O)	10	-
Ammonium borate (3H_2O)	10	-	Lithium nitrate	10	
Ammonium carbonate (H_2O)	1	-	Magnesium chloride (6 H_2O)	1	-
Ammonium chloride	Insol.	10	Magnesium nitrate (6 H_2O)	40	-
Ammonium chromate	1	-	Manganous chloride (4 H_2O)	20	-
Ammonium dichromate	50	-	Mercuric acetate	100	-
Ammonium nitrate	80	-	Mercuric bromide	90	-
Ammonium thiocyanate	30	-	Mercuric iodide	100	-
Barium nitrate	1	-	Molybdenum bromide	1	Reacts
Beryllium nitrate (4 H_2O)	10	-	Nickel chloride (6 H_2O)	60	-
Bismuth trichloride	1	-	Nickel nitrate (6 H_2O)	60	-
Cadmium chloride	20	-	Potassium iodide	20	20
Cadmium iodide	30	-	Potassium nitrate	10	-
Calcium chloride	Insol.	1	Potassium nitrite	2	-
Calcium dichromate (3 H_2O)	50	-	Potassium thiocyanate	20	50
Calcium nitrate (4 H_2O) 2	30	-	Silver nitrate	130	180
Ceric ammonium nitrate	1	-	Sodium dichromate (2 H_2O)	10	-
Cobaltous chloride (6 H_2O)	30	Misc. m.p. 86°C.	Sodium iodide	30	-
Cupric acetate (H_2O)	Insol.	6	Sodium nitrate	20	-
Cupric bromide	1	20 150°C.	Sodium nitrite	20	-
Cupric chloride (2 H_2O)	Insol.	27	Sodium thiocyanate	1	-
Cuprous iodide	1	-	Stannous chloride (2 H_2O)	40	-
Ferric ammonium sulfate (12 H_2O)	Insol.	Misc. m.p. 40° C.	Strontium bromide (6 H_2O)	5	-
Ferric chloride (6 H_2O)	30	90	Strontium chloride (2 H_2O)	10	-
Ferrous chloride (4 H_2O)	30	90	Tungsten hexachloride	5	-
Gold chloride	5	-	Uranyl nitrate (6 H_2O)	30	
Lead chloride	10	-	Vanadium chloride	-	1
Lead nitrate	20	60	Zinc chloride	30	60
			Zinc nitrate (6 H_2O)	55	-

TABLE VI
Solubility of Resins and Polymers in DMSO

	Grams Soluble in 100 cc DMSO		
Material	**20-30°C**	**90-100°C**	**Comments**
Polyacrylics			
Orlon (du Pont)	-	20	Viscous soln.
Acrilan (Monsanto)	>25	-	
Verel (Eastman)	>5		25 at 130°C with some decompostion
Creslan (Am. Cyanamid)	5		25 at 130°C
Zefran (DOW)	-	Insol.	
Polyamides			
Nylon 6	-	Insol.	40 at 150°C
Nylon 6/6	-	Insol.	25 at 150°C
Nylon 6/10	-	Insol.	40 at 150°C
Cellulose			
Cellulose triacetate	10	20	
Viscose rayon	-	<1	
Cellophane	-	Insol.	
Carboxymethyl cellulose	-	Insol.	
Epoxies			
Epon 1001 (Shell)	50	-	
Epon 1004 (Shell)	50	-	
Epon 1007 (Shell)	50	-	
Methacrylates			
Lucite 41, 45 (du Pont)	-	<1	
Plexiglass (Rohm & Haas)	-	<1	
Polycarbonates			
Lexan (General Electric)	-	>5	
Merlon (Mobay)	-	Insol.	
Polyesters			
Dacron (du Pont)	-	>1	Dissolves at 160°C ppts.
CX 1037 (Goodyear)	-	7	
Atlac (ICI-America)	-	50	
Silicones			
Dow Corning 803 soln.	Miscible	-	
Dow Corning 805 soln.	Miscible	-	
Dow Corning “Sylkyd 50”	Miscible	-	
Dow Corning Z6018 (flake)	70	-	
Urethanes			
Vithan (Goodyear)	-	100	
Vinyls – Polymers & Co-polymers			
Butvar B-76 (Monsanto)	-	20	Very viscous
Formvar 7/70 E (Montsanto)	-	42	Very viscous
Elvanol 51-05 (du Pont)	-	90	Viscous
Elvanol 52-22 (du Pont)	-	15	Viscous
Elvanol 71-24 (du Pont)	-	30	Viscous
Polyvinyl pyrrolidone (GAF)	30	>100	
Geon 101 (PVC Goodrich)	-	10	
Vinylite VYHH (Union Carbide)	2	30	
Teslar (du Pont)	-	-	Partially sol. at 160-170°C

Vinylidenes			
Darvan (Goodrich)	5	-	Soln. Cloudy and viscous
Saran film (Dow)	-	30	
Geon 200 x 20 (Goodrich)	-	20	
DNA (Goodrich)	>5	-	25 at 130°C
Other Resinous Materials			
Melmac 405 (Am. Cyanamid)	70	-	
Neoprene	Insol.	Insol.	
Polyethylene	Insol.	Insol.	
Polystyrene	-	-	Sol. At 150°C ppts at 130°C
Rosin (Hercules)	>100	-	
Penton (chlorinated polyether) (Hercules)	-	5	
Teflon (du Pont)	Insol.	Insol.	
Vinsol (Hercules)	50	>100	

TABLE VII
Solubility of Miscellaneous Materials in DMSO

	Solubility Grams/100 cc DMSO			Solubility Grams/100 cc DMSO	
Material	**20-30°C**	**90-100°C**	**Material**	**20-30°C**	**90-100°C**
Acetic acid	Miscible	-	Glycerine	Miscible	-
Acetone	Miscible	-	Glycine	<0.05	0.1
Acrawax	<1	>1	Hexane	2.9	-
Acrawax B	Insol.	4	Hy-wax 120	-	<1
Aniline	Miscible	-	Iodine	Soluble	-
Beeswax	-	<1	Isoprene	Miscible	-
Benzene	Miscible	-	Kerosene	0.05 (0.5% DMSO soluble in	11 (gets cold)
Benzidine	Soluble	-	Lanolin, hydrated (Lanette O)		
Benzidine methane sulfonate	Insol.	-	Lauryl amide (Amid 12)	10	>20
Bromine	Reacts	-	Lorol 5	Miscible	-
			Lubricating oil	0.4	-
Butenes	2.1	-	Methionine	0.1	0.3
Clacium methyl sulfonate	Soluble	-	Methyl borate	Miscible	-
Camphor	Soluble	Soluble	Methyl caprate	-	Miscible
Candelilla wax	-	<1	Methyl iodide	Miscible	Reacts
Carbon	Insol.	-	Methyl laurate	7	Miscible
Carbon disulfide	90	-	Methyl mercaptan	40	-
Carbon tetrachloride	Miscible	-	N-methyl morpholine	Miscible	-
Carbowax 600	Miscible	-	Methyl palmitate	Immiscible	Misc. 130-180°
Carbowax 6000	Insol.	8	Methyl salicylate	Miscible	-
Carnauba wax	-	<1	Methyl sulfonic acid	Miscible	-
Castor oil	Miscible	-	Methylene chloride	Miscible	-
Ceresin wax	-	<1	Microcrystalline wax	-	<1
Chlorine	Reacts	-	Morpholine	Miscible	Miscible-
Chloroform	Miscible	-	Naphthalene	40	Insol.
Chlorosulfonic acid	Reacts	-	Neoprene	Insol.	-
Citric acid	>70	-	Nitrobenzene	Miscible	-
Coconut oil	0.3	1.3	Oleic acid	Miscible	-
		Misc.-160°C	Ouricuri wax	-	1
Cork	Softens	Softens	Oxalic acid	38	-
Cresylic acid	Miscible	-	Paint (dried)	Softens & dissolves	
Cumene	Miscible	-	Palmitic acid	100	
Cyclohexane	4.67	-	Paraffin	Insoluble	-
Cyclohexylamine	Miscible	-	Paraformaldehyde	Insoluble	Slightly soluble
Decalin	4.5	-	Pentaerythritol	5-10	30
n-Decane	0.7	-	n-Pentane	0.35	-
Di-n-butylamine	11	-	Pentene 1 & 2	7.1	-
o-Dichlorobenzene	Miscible	-	Perchloric acid	Reacts violently	-
p-Dichlorobenzene	Very Soluble	-	Petroleum ether	3 (DMSO soluble 0.3-0.5% in	petroleum ether)
Dicholorodiphenyltrichloroethane	4	100			
Dicyandiamide	40	-	Phenol	Soluble	-
Dicyclohexylamine	4.5	-	Phosphoric acid	Miscible	-
Diethylamine	Miscible	-	Phosphorus trichloride	Reacts vigorously	-
Diethyl ether	Miscible	-	Phthalic acid	90	-
bis-(2-ethylhexyl)amine	Miscible	-	Isophthalic acid	68	76
Diethyl sulfide	0.7	-	Terephthalic acid	26	33
Di-isobutyl carbinol	Miscible		Picric acid	Soluble	-

Di-isobutylene	3.3 (0.6% DMSO soluble in di-isobutylene)	
		-
Dimethyl ether	4.4	-
Dimethyl formamide	Miscible	-
Dimethyl sulfide	Miscible	-
Dimethyl sulfone	33.9	Miscible
Dioxane	Miscible	-
Diphenyl	Very Soluble	-
Dipentene	10	-
n-Dodecane	0.38	-
Dodecylbenzene (Neolene 400)	3.5	-
Dyes		-
Burnt Sugar	Soluble	-
FD&C Blue	Soluble	-
Pistachio Green B	Soluble	-
Ethyl benzoate	Miscible	-
Ethyl alcohol	Miscible	-
Ethyl bromide	Miscible	Reacts
Ethyl ether	Miscible	-
Ethylene dichloride	Miscible	-
Formalin (37%)	Miscible	-
Formamide	Miscible	-
Formic Acid	Miscible	-

Pyridine	Miscible	-
Pyrogallol	50	-
Rosin	>100	-
Rosin soap (Hercules Dresinate X)	Slightly soluble	0.9
Sevin	50	-
Shellac, white, dried	-	80
Silicon tetrachloride	Reacts vigorously	
Sodium	-	Reacts
Sorbitan sesquioleate	2.5	-
Sorbitan trioleate	-	Miscible
Sorbitol	60	>180
Soybean oil	0.6	-
Starch, soluble	>2	-
Stearic acid	2	Miscible
Succinic acid	30	-
Sugar (sucrose)	30	100
Sulfamic acid	40	-
Sulfur	-	<1
Sulfuric acid	Miscible	-
Tallow	Insol.	1.9
Tallow amide, hydrogenated (Armour Armide HT)	Insol.	>40
Tetrahydrophthalic anhydride	50	-
Thiourea	40	85
Toluene	Miscible	-
Toluene di-isocyanate	Miscible	-
Tributylamine	0.9	-
Tricresyl phosphate	Miscible	-
Triethanolamine laurylsulfate	Soluble	-
Triethanolamine	Miscible	-
Triethylamine	10	-
Trinitrotoluene	Soluble	-
Turpentine	10	-
Urea	40	110
Water	Miscible	-
Xylene	Miscible	-

TABLE VIII
Solubility of Gases in DMSO at Atmospheric Pressure and 20°C
(from pure gases in each case)

	Grams Gas per 100 Grams Solution	**Gas Volume per Volume of DMSO**
Acetylene	2.99	28.1
Ammonia	2.6	40.0
Butadiene	4.35	-
Mixed butylenes	2.05	-
Carbon dioxide	0.5	3.0
Carbon monoxide	0.01	
Ethylene	0.32	2.8
Ethylene oxide	60.0	306.0
Freon 12	1.8	3.7
Helium	Insol.	
Hydrogen	0.00	
Hydrogen sulfide	0.5 (reacts)	
Isobutylene	2.5-3.0	-
Methane	0.00	
Nitric oxide (NO)	0.00	
Nitrogen	0.00	-
Nitrogen dioxide (NO_2, N_2O_4)	Miscible (possible reaction)	0.06
Oxygen	0.01	
Ozone	Reacts	
Sulfur dioxide	57.4 (reacts)	

PART III
REACTIONS OF DMSO

1. Oxidation of DMSO

DMSO reacts with strong oxidizing agents to give dimethyl sulfone, CH_3SO_2CH . Ozone gives a good yield of the sulfone (825)(8923). Both dichromate oxidation (321) and permanganate oxidation (9222) have been used for quantitative determination of DMSO (1612). Aqueous chlorine under acidic conditions gives dimethyl sulfone and methanesulfonyl chloride (1273)(8548), but under alkaline conditions the oxidation is accompanied by chlorination to give an 80% yield of hexachlorodimethyl sulfone (905):

$$CH_3SOCH_3 + NaOCl \longrightarrow CCl_3SO_2CCl_3$$

Sodium hypobromite similarly gives a 75% yield of hexabromodimethyl sulfone (229). DMSO reacts with hydrogen peroxide (10224), organic peroxides (1515), or hydroperoxides (8105), particularly in the presence of catalysts (4136), to give the sulfone. It has been reported that the persulfate ion can remove an electron from the sulfur of DMSO to give a radical cation, which is a suitable polymerization catalyst for acrylonitrile (1271). DMSO is also oxidized by peroxydiphosphate (9563) and chloramine-T (9678).

2. Reduction of DMSO

DMSO is reduced to dimethyl sulfide, CH SCH , by a number of strong reducing agents, including aluminum hydrides (1024)(1022) and boranes (1138)(3429)(3816)(8885). Mercaptans reduce acidified DMSO and are oxidized to the disulfides (428)(1373)(2532)(2779)(8054)(8095)(8405)(9949):

$$2RSH + CH_3SOCH_3 \xrightarrow{\text{acid}} RSSR + CH_3SCH_3 + H_2O$$

3. Reaction with Metals

The reaction of DMSO with sodium and potassium metals does not lead to simple removal of a hydrogen, but occurs by cleaving the carbon-sulfur bond (206):

$$CH_3SOCH_3 + 2M \longrightarrow CH_3SO^-M^+ + CH_3^-M^+$$

$$CH_3SOCH_3 + CH_3^-M^+ \longrightarrow CH_3SOCH_2^-M^+ + CH_4$$

The electrolytic reduction of sodium chloride or sodium iodide in DMSO similarly leads to a mixture of hydrogen and methane gases at the cathode (1508).

4. Reaction with Strong Bases - Dimsyl Ion

Methylsulfinyl carbanion, dimsyl ion, H_2CSOCH_3.

The activating influence of the sulfinyl group on α-hydrogens is considerably less than that of a carbonyl group but still sufficient to give a pKa of 35.1 for DMSO (10411). Consequently, strong bases such as sodium hydride or sodium amide react with DMSO to produce solutions of sodium methylsulfinyl carbanion (dimsyl ion) which have proved to be synthetically useful (634):

$$CH_3SOCH_3 + NaH \longrightarrow {}^{+}Na{}^{-}CH_2SOCH_3 + H_2$$

As the base, the dimsyl sodium solution can be employed to remove protons from carbohydrates, amines, amides, acetylenes, weakly acidic hydrocarbons and many other compounds. The dimsyl ion has also been used to prepare salts of carbonyl compounds, and for eliminations producing olefins, aromatics and cyclopropane derivatives. There are numerous applications of the dimsyl ion in the isomerization of alkynes and formation of phosphorus ylides in preparing Wittig reagents.

The dimsyl ion solutions provide a strongly basic reagent for generating other carbanions. The dimsyl ion shows the expected nucleophilicity of carbanions and serves as a source of methylsulfinylmethyl groups (634).

Thus, with alkyl halides or sulfonate esters, sulfoxides are obtained; carbonyl compounds yield β-hydroxysulfoxides and esters give β-ketosulfoxides (624):

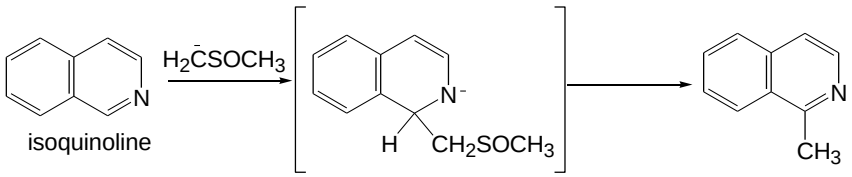
$$n\text{-}C_4H_9Br + :\bar{C}H_2SOCH_3 \longrightarrow n\text{-}C_4H_9CH_2SOCH_3$$

$$(C_6H_5)_2CO + :\bar{C}H_2SOCH_3 \longrightarrow (C_6H_5)_2C(OH)CH_2SOCH_3$$

$$C_6H_5COOEt + :\bar{C}H_2SOCH_3 \longrightarrow C_6H_5C(O)CH_2SOCH_3$$

Zinc and sulfuric acid have been used to reduce DMSO (86). Quantitative procedures for determining DMSO have been based on its reduction using stannous chloride and hydrochloric acid (982), or titanium trichloride in dilute hydrochloric acid (272). DMSO is reduced only very slowly with hypophosphorus acid unless catalyzed by dialkyl selenides (1005). Hydroiodic acid reduces DMSO (7073), and the kinetics of the reaction have been examined (84)(85)(1687)(1544). Hydrogen bromide, on the other hand, reduces DMSO only at temperatures about 80° C (1579). DMSO has also been reduced with iodine-sulfur dioxide or bromine-sulfur dioxide complexes (9464), cyclic phosphoranes derived from catechol (9944), silanes (10085)(10127), thiophosphoryl bromide (10139) and other reagents. Quantitative or almost quantitative yields of dimethyl sulfide are claimed in some of these reductions.

The dimsyl ion also adds to carbon-carbon double bonds, and if the mixture is heated for several hours, the initial adduct eliminates methanesulfenic acid. The overall result is methylation and with compounds such as quinoline or isoquinoline, yields are nearly quantitative (202):



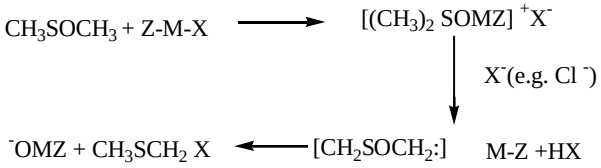
Care is required in running these reactions because the decomposition of the intermediate sulfoxide anion (and also dimsyl sodium) during the heating in the strongly alkaline system is exothermic and also produces a precipitate which can interfere with heat removal. Explosions have been observed which were not detonations but were due to a pressure build-up by an uncontrolled exotherm (8).

5. Reaction with Acid Halides

DMSO has long been known to react with chlorine or acid chlorides, such as sulfur monochloride, S_2Cl_2, to give chloromethyl methyl sulfide, whereas with sulfuryl chloride, SO_2Cl_2, only 13% of the chloromethyl methyl sulfide is obtained (720). Aromatic sulfonyl chlorides (463), thionyl chloride (595), and organic acid chlorides also give chloromethyl methyl sulfide (467)(8601). With thionyl chloride, it has been suggested that the reaction, in a simplified form, can be represented as follows:

$$CH_3SOCH_3 + SOCl_2 \longrightarrow CH_3SCH_2Cl + SO_2 + HCl$$

The reaction in many cases proceeds by way of initial attack of the chlorinating agent upon the oxygen of DMSO, followed by removal of a proton to give an ylide which is finally attacked by chlorine (459):



M= an atom (such as S) to which the halogen atom X is attached
Z=the remaining portion of the molecule

The kinetics of the reaction between DMSO and acetyl chloride has been studied using NMR spectroscopy. The decay of DMSO and acetyl chloride follows mainly 2nd order kinetics. The growth of the main products, acetic acid and chloromethyl methyl sulfide is mainly second order. The overall reaction is complicated by several side reactions, which generate acetoxymethyl methyl sulfide, acetic anhydride and chlorodimethylsulfonium chloride (9773):

$$CH_3SOCH_3 \xrightarrow{OCH_3CCl} CH_3SCH_2Cl + CH_3CO_2H + (CH_3CO)_2O + CIS(CH_3)_2 + Cl^-$$

This displacement of a reactive chloride by the DMSO oxygen has been used to introduce hydroxyl groups into compounds that are sensitive toward water (459)(294)(1016)(1383)(3152). Thus, DMSO reacts with cyanuric chloride to give cyanuric acid and with benzoyl chloride to give benzoic acid, (1383):

$$N_3C_3Cl + 3CH_3SOCH_3 \longrightarrow N_3C_3O_3H_3 + 3CH_3SCH_2Cl$$
$$PhCOCl + CH_3SOCH_3 \longrightarrow PhCO_2H + CH_3SCH_2Cl$$

The ability of sulfoxides to react with acid chlorides can be used for the quantitative determination of DMSO. When DMSO is reacted with acetyl chloride in the presence of iodide the following reaction, involving formation of the acyloxysulfonium salt, can be represented as follows:

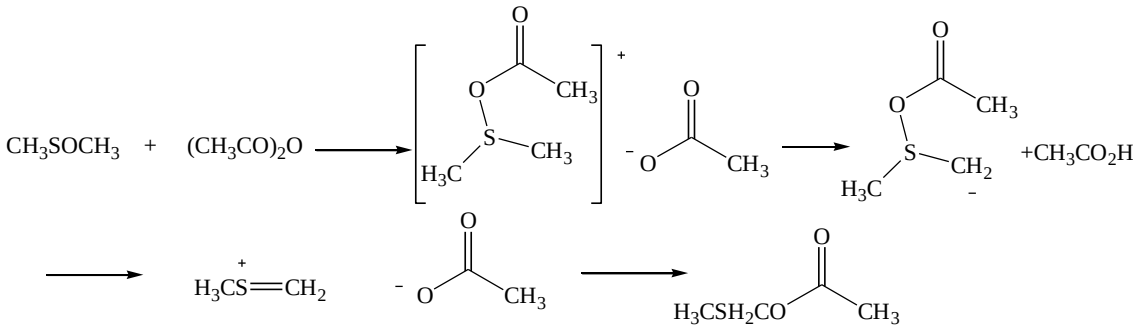
$$CH_3SOCH_3 + CH_3COCl \longrightarrow [(CH_3)_2SOCOCH_3]+ + Cl-$$
$$[(CH_3)_2SOCOCH_3]^+ + 2I^- \longrightarrow CH_3SCH_3 + I_2 + CH_3CO_2^-$$

The iodine is then titrated with sodium thiosulfate (1805).
The reaction of DMSO with reactive acid chlorides is vigorous and exothermic and should be conducted with care (669)(8601)(10470).

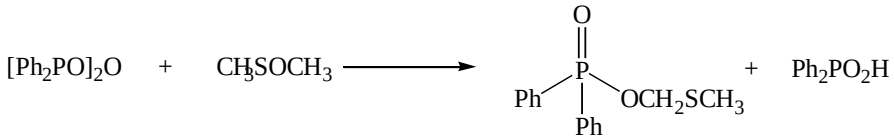
6. Reaction with Acid Anhydrides

Carboxylic acid anhydrides react with DMSO in a manner similar to that of acid halides. With acetic anhydride, the final product is acetoxymethyl methyl sulfide, $CH_3CO_2CH_2SCH_3$ (290)(291). Several mechanisms of the reaction, the Pummerer rearrangement, have been proposed. There seems to be little doubt that the first step in the reaction of DMSO with acetic anhydride is the formation of the acetoxysulfonium salt (2643)(2896). Various possible pathways of the rearrangement from the sulfonium salt have been proposed, but

the one going through the ylide seems likely (2643)(4820). The Pummerer rearrangement can then be represented by the following reactions



DMSO also reacts with trifluoroacetic anhydride to give the acetoxysulfonium salt. When this intermediate is reacted with aromatic amines, amides or sulfonamides the corresponding iminosulfuranes are obtained (7044). When aliphatic carboxylic acids are treated with DMSO activated by tert-butylbromide in the presence of NaHCO3 the corresponding methylthiomethyl esters are obtained in a Pummerer like reaction (10032). A Pummerer type rearrangement is also suggested in the reaction of diphenylphosphinic anhydride-DMSO reaction (4128):

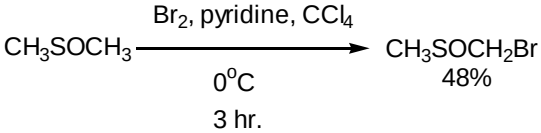


Inorganic anhydrides also attack the DMSO oxygen. The sulfur trioxide-DMSO complex reacts easily with cellulose to give cellulose sulfate esters with a high degree of substitution (1474).
Reactions of DMSO wlth some acid anhydrides, both organic and lnorganic, can be vigorous and should be conducted with care. Thus, acetic anhydride and benzoic anhydride react with DMSO even at room temperature (290), although higher temperatures, e.g. 85-90° C, are needed for faster reactions (7613).

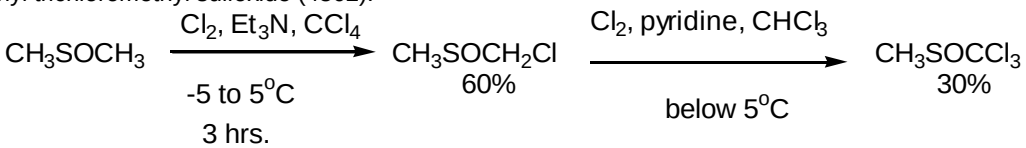
Complex formation between DMSO and sulfur trioxide is an exothermic reaction. To avoid overheating with consequent darkening and violent boiling of the mixture, sulfur trioxide should be added slowly to a cool well stirred and cooled DMSO (1474).
DMSO cannot be dried with phosphorus pentoxide because this may lead to an explosive mixture (354).

7. Halogenation of DMSO

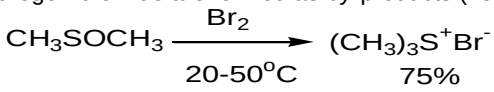
DMSO can be halogenated with chlorine or bromine in the presence of a base. Thus, stirring a solution of DMSO, pyridine, and bromine in chloroform results in the formation of bromomethyl methyl sulfoxide (3148):



Similarly, bubbling chlorine into a DMSO, pyridine and methylene chloride solution at 0° C for over 30 minutes produces chloromethyl methyl sulfoxide in a 77% yield (6268).
Chlorination of DMSO in the presence of triethylamine yields chloromethyl methyl sulfoxide. Further chlorination in the presence of pyridine yields methyl trichloromethyl sulfoxide (4802):



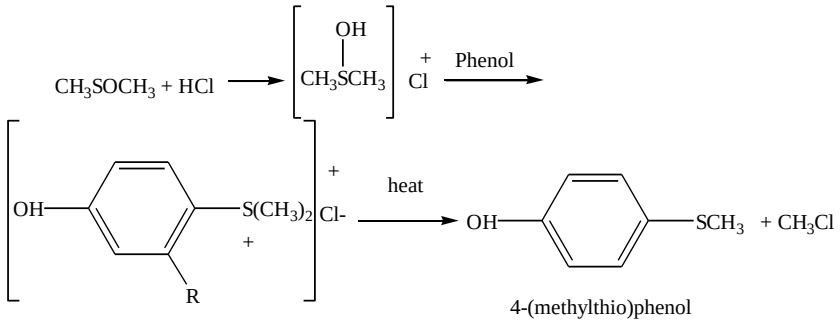
Bromination of DMSO with elemental bromine leads to the formation of trimethylsulfonium bromide. Methanesulfonic acid, paraformaldehyde, dimethyl disulfide, and hydrogen bromide are formed as by-products (4802):



A small amount of hydrogen halides or halogens, especially bromine or hydrogen bromide, catalyze the decomposition of DMSO in the absence of a base. This catalytic decomposition takes place sluggishly. The reaction of bromine proceeds via the initial α-bromination to afford α-bromethyl methyl sulfoxide which is oxidized (Kornblum reaction) to afford the products listed above [(4802)]. These consecutive reactions form an oxidation-reduction cycle between Br2-HBr and DMSO-dimethyl sulfide (8400).

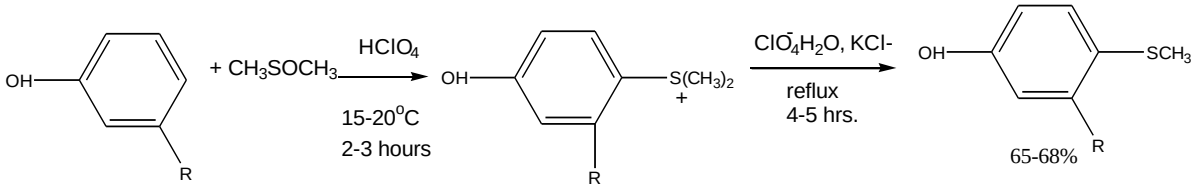
8. Reaction with Phenols and Aniline

a) **Acid chloride or hydrogen chloride catalysis.**
When a solution of phenol in DMSO is treated with an acid chloride, such as thionyl chloride, or saturated with hydrogen chloride, the initially formed adduct of DMSO reacts by electrophilic attack on the phenol to form the sulfonium salt. The sulfonium salt can be decomposed by heating to give hydroxyaryl methylthioethers (2075)(302)(296):



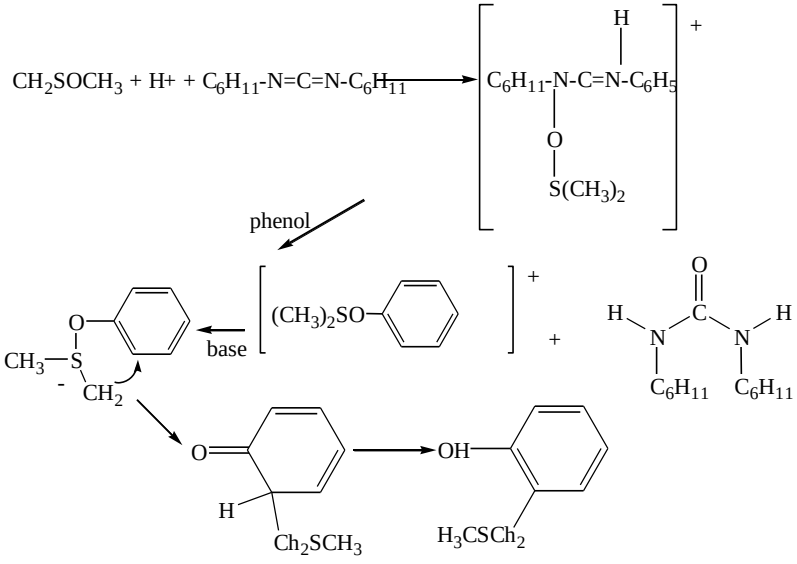
4-(methylthio)phenol

Up to 60% yields are obtained, depending on the structure of the phenol. p-Hydroxyaryl methylthioethers are also obtained when phenols are suspended in 70% perchloric acid and DMSO is added, followed by heating of sulfonium salts in hot, saturated potassium chloride solution (1268):



Similarly, hydroxyaryl thioethers can be prepared by reacting phenols with DMSO in sulfuric acid, and heating the crude reaction mixture with aqueous sodium chloride (6335) (6674)(6613).
N,N-dimethylaniline can be reacted with DMSO using phosphoryl chloride catalysis. However, the yield of the aryl thioether is lower in this case (348). Other aromatic amines and hydrazine derivatives also react with DMSO and dicyclohexylcarbodiimide (4651).

b) **Dicyclohexylcarbodiimide or acid anhydride catalysis**
The reaction of phenols with DMSO and dicyclohexylcarbodiimide in the presence of phosphoric acid or pyridinium trifluoroacetate affords a mixture of the products consisting mainly of 2-methylthiomethyl phenol and 2,6-bis(methylthiomethyl)phenol (540)(1234)(4898)(4891). It has been suggested that the mechanism proceeds according to the following steps (540)(1234)(4898):

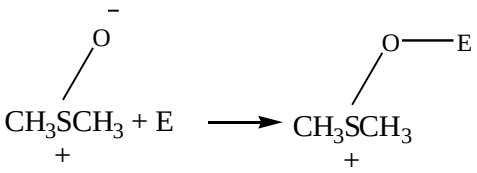


2-thiomethoxymethyl phenol

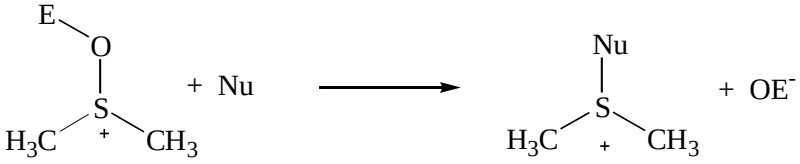
A similar reaction takes place when acetic anhydride (849)(1055) or the pyridine-sulfur trioxide complex (4636) is used to polarize the DMSO molecule instead of dicyclohexylcarbodiimide.
Finally, it has been found that phenols can be methylthiomethylated by boiling with excess DMSO. A mixture of isomeric methylthiomethylation products are obtained, but o-methylthiomethylation is preferred (4636)(4772).

9. Alcohol Oxidation with DMSO
A breakthrough in the preparation of carbonyl compounds from alcohols has been achieved with the development of reagents based on

DMSO (8551)(1503)(4820)(16359).
Several procedures have been developed which permit the selective oxidation of structurally diverse primary are secondary alcohols to the corresponding carbonyl compounds, i.e. aldehydes and ketones, respectively. Most of these reactions take place at room temperature or above. Nucleophilic attack occurs on the DMSO sulfur atom. Most reactions in which the nucleophilic attack takes place on sulfur are aided by prior electrophilic attack on the oxygen atom (10720):

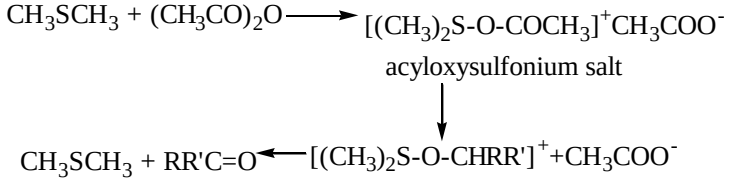


The electrophilic reagents which activate DMSO include acetic anhydride, trifluoroacetic anhydride, and other acid anhydrides, the sulfur trioxide-pyridine complex, thionyl chloride, oxalyl chloride, acetyl chloride, and other, acid chlorides, bromine, chlorine, t-butyl hypochlorite, dicyclohexylcarbodiimide, and others.
The labile intermediate, the DMSO-electrophile complex, can now be attacked by a nucleophile, such as an alcohol, to perform a displacement on sulfur with oxygen as the departing group:



Several of the above-mentioned activating agents and their use in the oxidation of alcohols are described below.

a) **Acetic anhydride**
In this procedure an alcohol is treated with a mixture of acetic anhydride and DMSO at room temperature (1127) (9926). DMSO first reacts with acetic anhydride to form the acyloxysulfonium salt which in turn reacts with the alcohol to give the alkoxydimethylsulfonium intermediate which decomposes to the carbonyl compound and dimethyl sulfide (DMS)(1127):



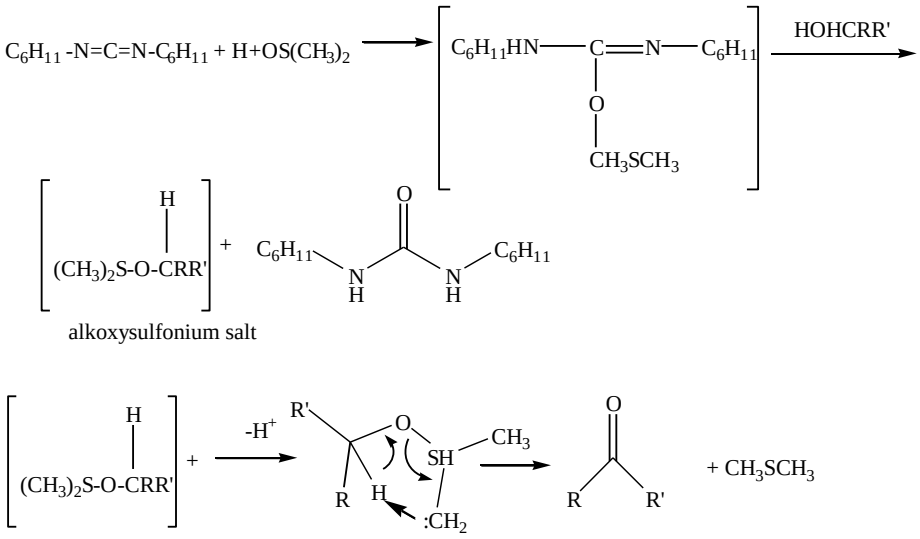
A number of side reactions take place when using the acetic anhydride-DMSO procedure. The usual side products are acetates and methylthiomethyl ethers, RR'CHOCH2SCH3. The advantage of the acetic anhydride-DMSO method is the fact that highly hindered alcohols, which would be inert to other DMSO-activator systems, are oxidized (4820).

b) **Trifluoroacetic anhydride**
Trifluoroacetic anhydride and DMSO react exothermally at -60° C. in methylene chloride to produce a white precipitate, presumably an ion pair, trifluoroacetoxydimethylsulfonium trifluoroacetate.



This reacts rapidly with alcohols, even sterically hindered ones (e.g. 2-adamantol and neopentyl-type alcohols) to give the corresponding carbonyls (7943)(8455). Trifluoroacetic anhydride is an excellent activator for DMSO because of short reaction times and high yields of carbonyl compounds with minimal by-product formation. The major drawback is the need to work at very low temperatures (-30 to -60° C) (10720).

c) **Dicyclohexylcarbodiimide**
This method of oxidation is generally referred to as the "Pfitzner-Moffatt" technique, after its originators (1503). The reaction involves addition of an alcohol substrate to a solution of dicyclohexylcarbodiimide (DCC) in DMSO with an acid, such as phosphoric acid or pyridinium trifluoroacetate (172), present as a proton source. This results in reaction conditions near neutrality at room temperature. The oxidation technique is applicable to primary or secondary alcohol groups in an almost unlimited variety of compounds, including alkaloids, steroids (173), and carbohydrates (4349). Steric effects are not important except in highly hindered systems (1503). In the reaction, the DMSO molecule is first converted to a labile intermediate which is susceptible to attack at the sulfur by an alcohol group to produce an alkoxysulfonium salt which undergoes base-catalyzed decomposition to the carbonyl compound (3049):



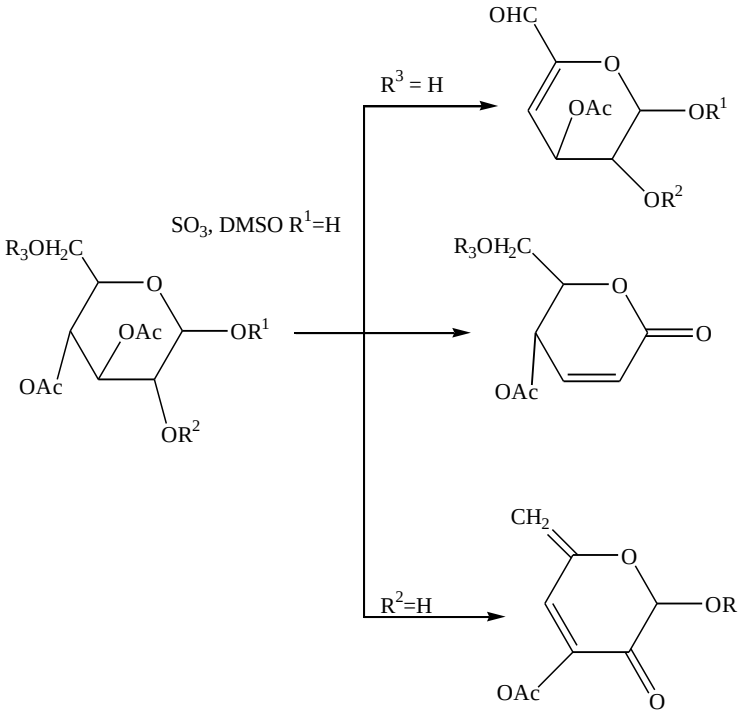
Protecting groups such as isopropylidene, benzylidene, acetate, benzoate, and sulfonate esters and ethers are stable in the conditions used for oxidation (3602)(175).

d) **Phosphorus pentoxide**

It has been found that DMSO containing phosphorus pentoxide rapidly oxidizes the alcoholic groups of carbohydrates and other compounds at room or elevated temperatures to the corresponding aldehydes or ketones (208). In general, oxidations proceed most efficiently in the presence of 3-4 molar equivalents of DMSO and 1.2-2.0 molar equivalents of phosphorus pentoxide (2327). The carbohydrate oxidation with DMSO-P4O10 should be run at about 60-65°C. This system catalyzes carbohydrate polymerization at temperatures below 35° C (5296) (6079). DMSO, DMF and pyridine seem to be the best solvents for this reaction (3602)(2327)(6691).

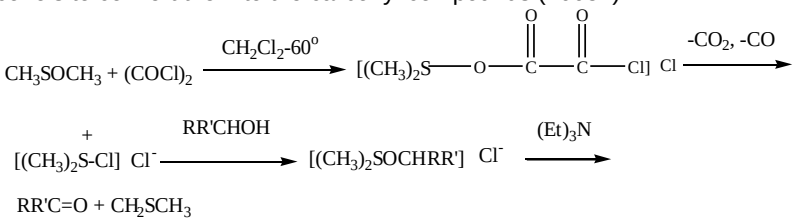
e) **Sulfur trioxide-pyridine**

The combination of DMSO with S03-pyridine complex in the presence of triethylamine yields a reagent that rapidly oxidizes primary and secondary alcohols in good yield at room temperature to aldehydes and ketones, respectively (9926)(10720). An attractive feature of this reagent is its property of effecting oxidation of allylic alcohols to the corresponding α , β-unsaturated carbonyl compounds (1752).
The S03-pyridine complex in DMSO can be used to oxidize acid-labile trans-diols (4037) or cis-diols (8033) to quinones. This reagent has also been used to oxidize alkaloid hydroxyl groups to ketone groups (2749)(8017). Application of the DMSO-S03-pyridine reagent to partially acetylated carbohydrates leads to oxidation as well as elimination of the elements of acetic acid, thus providing a high yield to novel unsaturated carbohydrates (2652):



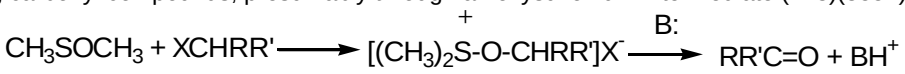
f) **Oxalyl chloride**

Oxalyl chloride is an efficient and useful activator, superior to trifluoroacetic anhydride, for the conversion of alcohols to their alkoxysulfonium salts which, upon basification, result in generally higher and frequently quantitative yields of the corresponding carbonyl compounds (9786)(9926). The unstable intermediate formed at low temperatures (usually-60° C) instantaneously loses carbon dioxide and carbon monoxide. The new intermediate is the same as that proposed for the dimethyl sulfide-chlorine reagent. This product has been reacted with a wide variety of alcohols to convert them to the carbonyl compounds (10084):



10. Kornblum Reaction

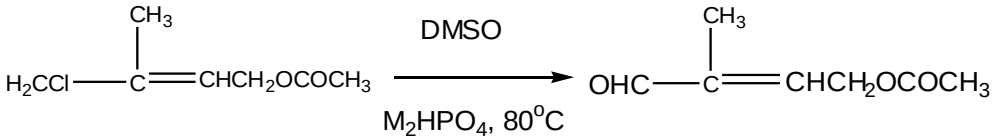
Kornblum and co-workers have demonstrated that in DMSO α -bromoketones at room temperature and primary alkyl tosylates on heating afford the corresponding carbonyl compounds, presumably through an oxysulfonium intermediate (273)(8551):



Some reactive alkyl halides, such as methyl iodide, also react with DMSO to form the oxosulfonium intermediate (the O-alkyl derivative). However, this intermediate rearranges readily to the more stable oxosulfonium salt, i.e. (CH3)3S+Ol-, and no oxidation takes place (324). Some reactive halides, such as benzyl, can also be oxidized to the corresponding carbonyl compounds but higher reaction temperatures are necessary. An acid acceptor, e.g. sodium hydrogen carbonate, is frequently used (105).

The relatively unreactive alkyl halides, such as 1 -chloroheptane, can be oxidized by DMSO if the chloride is first converted to the tosylate (106).

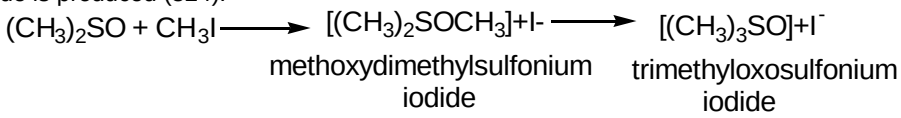
The DMSO oxidation of the primary allylic chloride, 4-chloro-3-methyl-2-buten-1-ol acetate, does not proceed well when sodium hydrogen carbonate is used as the acid acceptor. However, this reaction runs well when a dibasic metal phosphate, Na2HPO4 or K2HPO4, is used (9960):



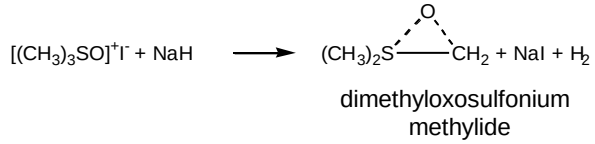
This particular reaction is catalyzed by sodium bromide (9960)(10066).

11. Methoxydimethylsulfonium Salts and Trimethyloxosulfonium Salts

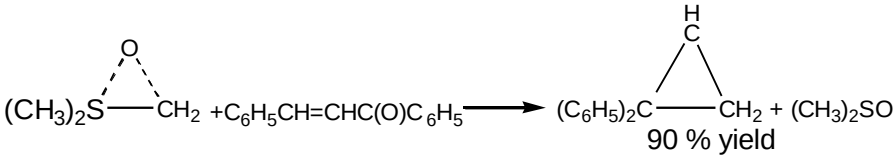
Alkylating agents, such as methyl iodide, react initially with DMSO at the oxygen to give methoxydimethylsulfonium iodide (see the previous section, Kornblum Reaction). These alkoxysulfonium salts are quite reactive and with continued heating either decompose to give the carbonyl compounds or rearrange to the more stable trimethyloxosulfonium salts. In the case of methyl iodide trimethylsoxosulfonium iodide is produced (324):



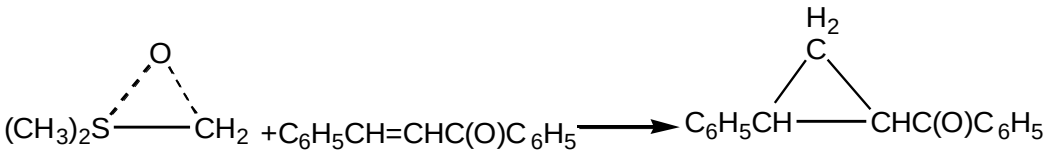
Trimethyloxosulfonium iodide is of interest because treatment with sodium hydride or dimsyl sodium produces dimethyloxosulfonium methylide which is an excellent reagent for introducing a methylene group into a variety of structures (632)(2463)(4820):



Many aldehydes and ketones react with the ylide to give better than 75% yields of epoxides (632):



In a similar case, the dimethyloxosulfonium methylide reacts with carbon-carbon double bonds that are conjugated with carbonyl groups to give cyclopropane derivatives (4820)(7361):



PART IV. DMSO AS A REACTION SOLVENT

A. DISPLACEMENT REACTIONS IN DMSO

These are reactions in which reactive groups are replaced by nucleophilic ions or molecules.

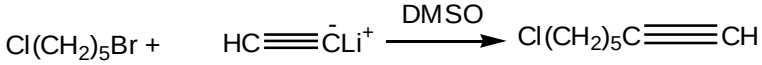
The largest category of reactions in which DMSO has been used as a solvent is that in which labile groups are replaced by nucleophilic ions or molecules. The reason for the particular utility of DMSO in these reactions has not always been established and derives from a number of factors. DMSO as one of the most polar of the common aprotic solvents. It is a favored solvent for displacement reactions because of its high dielectric constant and because anions are less solvated in it (9488). The high dielectric constant of a solvent insures that dissolving species or a solute bearing opposite charges do not come together to agglomerate. E.g. when sodium hydroxide is dissolved in DMSO, the interaction between Na' and OH- is minimized. Due to the polarity of the sulfoxide bond and the electron density at the oxygen, cations are much more solvated by DMSO than the anions. Conversely, the aprotic nature of DMSO precludes the solvation of anions by hydrogen bonding so that these are solvated only by dipolar attraction and thereby are more reactive. In other cases, the controlling influence is suggested to the ability of highly polar DMSO molecules to stabilize transition state structures and thereby lower the activation energy (22) (471)(399). This latter effect is evident in the cases where comparatively minor additions of DMSO cause significant enhancement of reaction rates (1262).

A great variety of displacement reactions can be run in DMSO and suitable nucleophiles include:

1. Acetylide ion
2. Alkoxide ion
3. Amides
4. Amines
5. Ammonia
6. Azide ion
7. Carbanions
8. Carboxylate ion
9. Cyanate ion
10. Cyanide ion
11. Halogen ion
12. Hydroxide ion
13. Mercaptide (or Thiophenoxide) ion
14. Nitrite ion
15. Phenoxide ion
16. Sulfide (or Hydrosulfide) and Thiosulfate ions
17. Thiocyanate ion

1. Acetylide Ion

The usual reactions of sodium acetylide may be accomplished in good yield by stirring a slurry of sodium acetylide in DMSO slightly below room temperature with reagents such as alkyl halides, epoxides or carbonyl compounds (544). Displacement of halides with the ethylene-diamine complex of lithium acetylide is also easily effected in DMSO (3178)(4175). Thus, the reaction of 1-bromo-5-chloropentane with lithium acetylide-ethylene diamine complex in DMSO gives 7-chloro-1 -heptyne (1826):



The use of lithium acetylide-ethylene diamine in DMSO has given higher yields of the desired products than sodium acetylide in liquid ammonia (4175).

The addition of lithium acetylide as the ethylene-diamine complex to 7-bromoheptanol tetrahydropyranyl ether in DMSO gives non-8-yn-1-ol tetrahydropyranyl ether in higher than 90% yield (4333).

2. Alkoxide Ion

The high activity of alkoxide ions in DMSO shows up in their enhanced basicity. The basicity of alkoxides reaches a maximum in DMSO when the mixture is substantially free of hydroxylic material. In this case, the acidity of the alcohols in dilute solutions is about 103 times that of DMSO so that only a minor equilibrium quantity of the DMSO anion is present (734). The reactivity of the alkoxide ion in DMSO is influenced by the cation and is greater with cesium and with lithium less (606)(1162). The vastly enhanced activity of alkoxide ions in DMSO over their activity in alcohols is attributed to the absence of alkoxide-solvent hydrogen bonds in DMSO which are present in the hydroxylic solvents (434).

The basicity of alkoxides in DMSO is conveniently expressed n terms of acidity functions, and a number of these are plotted in Figure 10 for bases n DMSO-water and DMSO-methanol systems.

Alkoxides differ in their solubilities n DMSO. Thus, potassium t-butoxide is more soluble than some lower alkoxides (17). The solubilities of these hydroxylic bases are also shown in Table IX for comparative purposes.

A review article on potassium t-butoxide and its use in nucleophilic displacements has been published (6815).

TABLE IX Solubilities of Various Bases in DMSO

Substance	moles/liter	Reference

NaOH	7.6 x 10'°	(725)
KOH	1 x 10'3	(17)
(CH) NOH	1 x 10'	(17)
NaOCH3	1.6 x 10'3	(725)
NaOEt	2 x 10'2	(17)
iso-PrONa	7 x 10'3	(17)
n-BuONa	5 x 10'3	(17)
t-BuOK	1 x 10'2	(17)

a) **Aliphatic halide displacement**

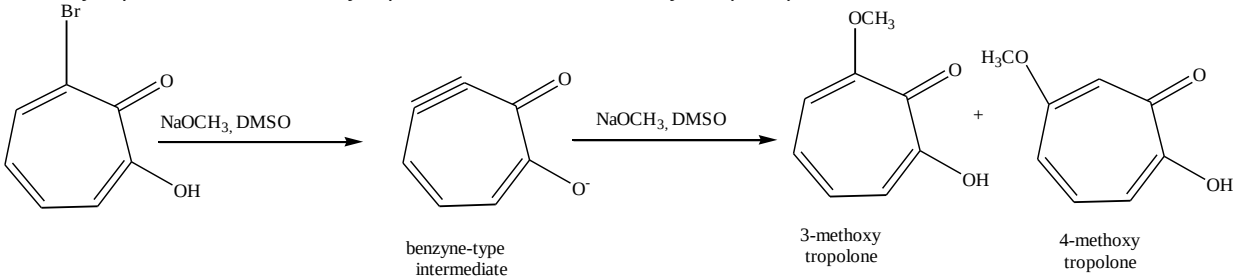
The rate of reaction of alkoxide ions with alkyl halides in alcohol-DMSO mixtures to form ethers increases with the increasing amount of DMSO. This is illustrated in the reaction of methyl iodide with methoxide ion or with ethoxide ion to make dimethyl- or methyl ethyl ethers, respectively (329), and in the reaction between benzyl chlorides and methoxide ion to make the corresponding benzyl methyl ethers (433). The rate increase at high DMSO concentrations is attributed to an increased activity of the methoxide ion caused by reduced solvation, but other factors are probably more important at low DMSO concentrations. The activation energy decreases continuously as the DMSO concentration increases (433). The Williamson ether synthesis from alcohols and alkyl halides (chlorides) with sodium hydroxide as the base can be considerably improved by using DMSO as the solvent in place of the excess alcohol (2924):

$$ROH + ClR' \xrightarrow[100^{o}C,\ 6\text{-}14\ hrs.]{NaOH,\ DMSO} ROR'$$

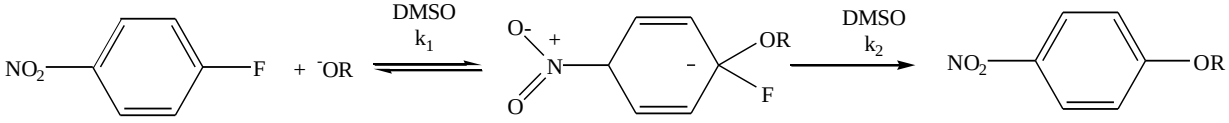
Secondary alkyl chlorides and primary alkyl bromides give little etherification, elimination being the major reaction.
The use of alkoxides in DMSO in some cases involves elimination n addition to displacement, followed by the addition of the alkoxide to the double bond in alicyclic compounds (1798).

b) **Aromatic halide displacement**

As with alkyl halides, the use of alkoxides in DMSO can involve both the displacement and elimination reactions with aromatic halogen compounds. Thus, when a solution of 3-bromo-tropolone in DMSO is heated with sodium methoxide, an almost 1:1 mixture of 3-methoxytropolone and 4-methoxytropolone is obtained in 96% yield (3572):

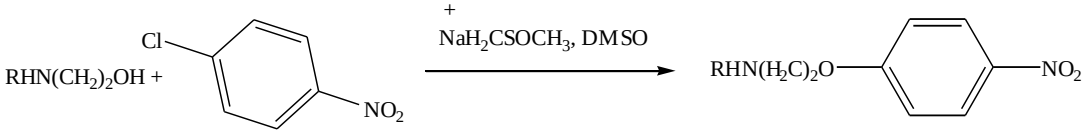


Aromatic halogens in nitroaryl halides can be displaced by the methoxide ion in DMSO-methanol. The reaction rate increases some 1000-fold when the DMSO concentration is increased to 80% (399):



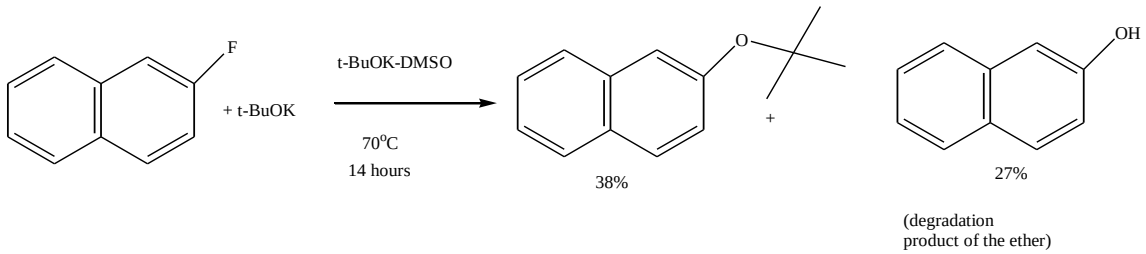
R = C2H5 or t-Bu

p-Nitrochlorobenzene also reacts with alkoxides. When 2-alkylamino-ethanol is first treated with dimsyl sodium to make the oxyanion base followed by the addition of p-nitrochlorobenzene, the preferential nucleophilic attack by oxygen (rather than the amino group) is insured (8399):

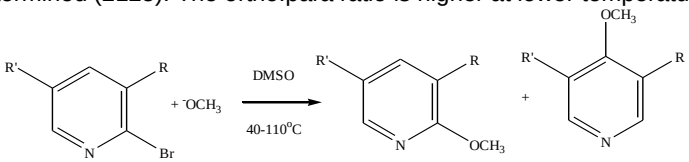


The reaction of monoiodo-, monobromo-, monochloro- and monofluoro-naphthalenes with potassium butoxide in butyl alcohol-DMSO has been examined (4058)(4059). The major products observed in the bromo-, iodo- and chloronaphthalene reactions are 1- and 2-butyl naphthyl ethers, 1- and 2-naphthols and 1-methylmercapto-2naphthol. This suggests that 1,2-dehydrohaphthalene is an intermediate in each of these reactions, and 1-methyl-mercapto-2-naphthol is probably the benzyne intermediate-DMSO reaction product (4059). The

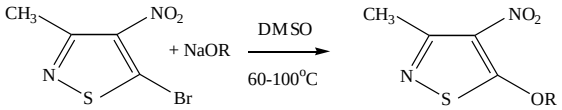
fluoronaphthalenes undergo only direct nucleophilic substitution with no formation of 1,2-dehydronaphthalene, i.e. no benzyne-type intermediate (4058)(5244):



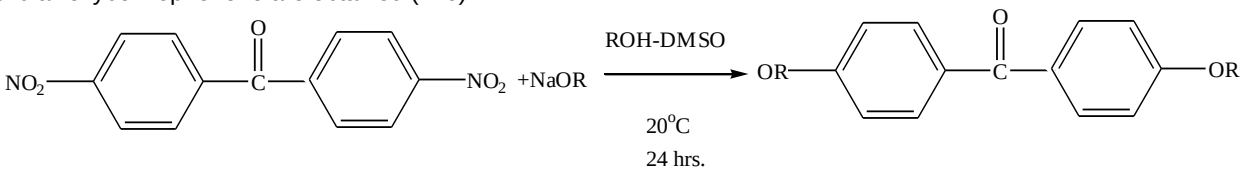
2,3-Dichloranisole can be prepared by reacting 1,2,3-trichlorobenzene with sodium methoxide in DMSOmethanol (9107).
The kinetics of the reaction of 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine and methoxide ion in DMSO containing small amounts of methanol have been determined (2125). The ortho:para ratio is higher at lower temperatures (2.5 at 40° C vs 1.44 at 110* C):



2-Bromopyridine reacts with potassium methoxide in DMSO containing 1 % of methanol 3000 times faster than it does with the same reagent in pure methanol at 110°C.
A number of 4-alkoxypyridines is prepared by reacting 4-chloropyridine with sodium alkoxides in DMSO in moderate to high yields (5038).
5-Bromo-3-methyl-4-nitroisothiazole reacts smoothly with sodium alkoxides in alcohols-DMSO to give the appropriate 5-alkoxy-3-methyl-4-nitroisothiazoles (4098):

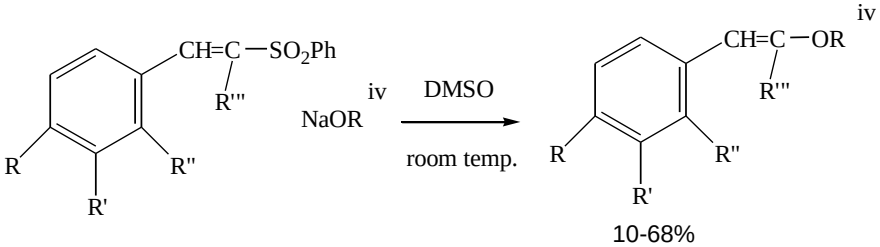


c) **Nitro group displacement**
When sodium methoxide or sodium ethoxide is added to p-nitro- or p,p'-dinitrobenzophenone in DMSO, almost quantitative yields of p-alkoxy- or p,p'-dialkoxybenzophenone are obtained (470):



Sulfonamides are also alkylated in DMSO.4,6-Dichloropyrimidine reacts with the sodium salt of p-nitrobenzenesulfonamide in DMSO to give 4-chloro-6-(p-nitrobenzenesulfonamido)pyrimidine (42):
With 2,2'-dibromo-4,4'-dinitrobenzophenone, there is no displacement of bromide ion, and 2,2'-dibromo-4,4'dimethoxybenzophenone (90%) is obtained. No reaction occurs in any instance when dioxane is used instead of DMSO (470).

d) **Sulfinate displacement**
When β-styrylsulfones are treated with one molar equivalent of sodium alkoxides in DMSO, β-alkoxystyrenes are formed by nucleophilic substitution (9761):

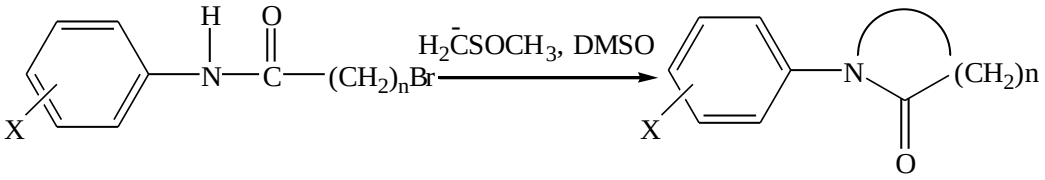


10-68%

e) **Sulfonate displacement**
Benzene sulfonates of common primary and secondary alcohols react rapidly with sodium methoxide in DMSO to give high yields of alkyl methyl ethers and/or alkenes. The ether-alkene ratio is significantly higher in reactions with sodium methoxide than with potassium t-butoxidesulfonyl ester groups from carbohydrate derivatives, the conversion to the ether with sodium methoxide or sodium e. More olefins are formed from secondary sulfonate esters than from primary esters (580)(592). In the displacement of methane thoxide in DMSO occurs by the attack on the sulfur, leading to the retention of configuration, rather than by the usual attack on carbon with inversion (1119)(653).

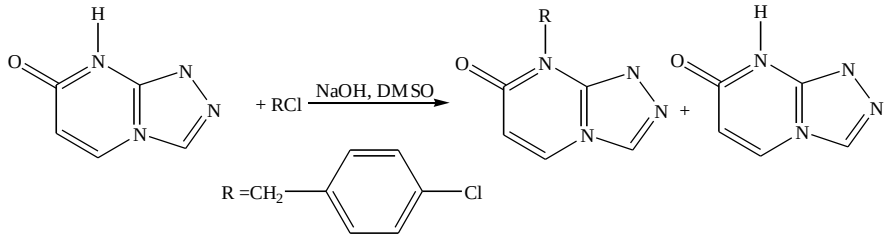
3. Amides

The N-alkylation of amides can take place in DMSO. The reaction of various ω-haloamides with the dimsyl ion in DMSO can be used to obtain good to high yields of 4-, 5- and 6-membered lactams. However, the reaction with dimsyl ion fails to produce the seven-membered heterocyclic ring (888):

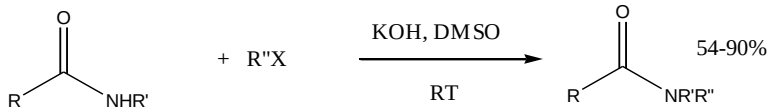


X = Br, Cl, F, I;
N = 2, 3, 4

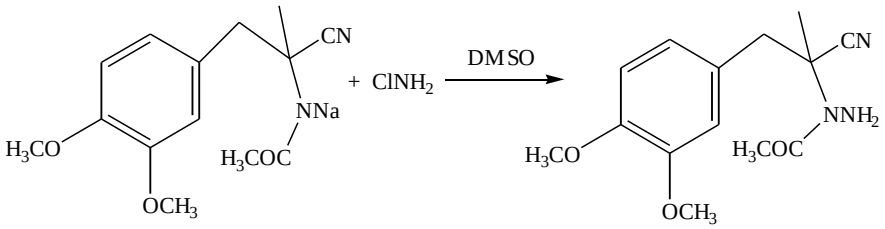
The readily available base, dimsyl ion, could be more convenient to work with than sodium in liquid ammonia (888). The alkylation of the sodium salt of saccharin with a benzyl chloride also proceeds well in DMSO to give a high yield of N-benzyl saccharin (947):
7-Oxo-7,8-dihydro-s-triazolo[4,3-a]pyrimidine can be alkylated as above using p-chlorobenzyl chloride in DMSO. In this case, however a mixture of the N-benzyl- and the O-benzyl deriviatives results (3885):



It has been found that the N-alkylation of carboxylic acid amides proceeds well in DMSO by using dry potassium hydroxide as the base. Good yields can be obtained even at room temperature (4355):

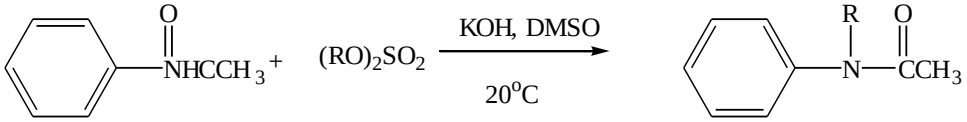


With DMSO as the solvent, the use of stronger bases, such as sodium hydride or potassium alkoxides, is not necessary.
When the sodium salt of an acetamidonitrile in DMSO is treated with chloramine, a smooth N-amination is achieved (4382):

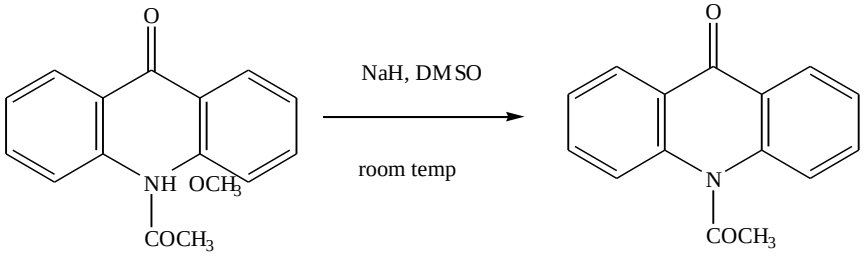


Peptides and proteins can also be N-alkylated with methyl iodide and benzyl bromide using DMSO as the solvent and the dimsyl ion as the base (4945).

A number of amides, such as acetanilide, have been N-alkylated with dialkyl sulfates using potassium hydroxide as the base and DMSO as the solvent (8276):



The sodium salt of an amide can displace a methoxy group from a benzene nucleus. Thus, the treatment of 2-acetamido-2'-methoxybenzophenone with sodium hydride in DMSO gives the 9-acridone (8564):



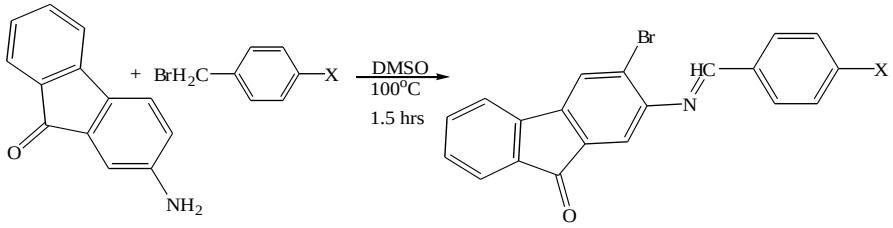
68%

4. **Amines**

In most displacement reactions, the nucleophiles are negatively charged. However, displacements can also take place involving uncharged nucleophiles, namely, amines (3433). Amines, like ammonia, do not hydrolyze DMSO. The presence of DMSO in the displacement reaction involving amines allows the reagents to surmount the energy barrier easier than in hydroxylic solvents, irrespective of the charge type of the reagents. The effect of DMSO, then, must be the decrease in- the energy of the transition state. It could also be said that DMSO polarizes a substrate (399). For a reaction involving neutral reactants, such as amines, and going through a charged transition state, it appears that DMSO can solvate the cationic part of the reacting system at the point of attack of the amine reagent (1240). Thus, displacement reactions by amines in DMSO generally proceed at a good rate. A catalytic effect is seen by adding DMSO to an alcohol system containing amines and aryl halides (399)(1262).

a) Aliphatic halide displacement-primary amines

Alkylation of weak aromatic amines with alkyl bromides (e.g. 2-aminofluorenone with ethyl bromide) in DMSO gives ring brominated N-alkyl derivatives (211). However, aralkylation of 2-aminofluorenone with aralkyl bromide, such as benzyl- and para-substituted benzyl bromides in DMSO leads to azomethines as the main products (264):

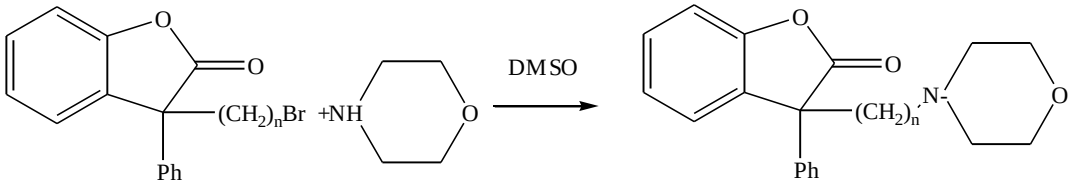


DMSO also catalyzes the reaction between 2-substituted carboxylic acids and amines. Thus, ethylenediamine reacts with chloroacetic acid to give ethylenediaminetetraacetic acid (EDTA) (4910):

$$H_2NCH_2CH_2NH_2 + 4ClCH_2CO_2H \xrightarrow[80^oC]{DMSO} (HO_2CCH_2)_2NCH_2CH_2N(CH_2CO_2H)_2$$

b) **Aliphatic halide displacement-secondary amines**

ω -Bromoalkylbenzofuranones react with morpholine in DMSO to give high yields of the N-alkylation products (613):



n=1,2,3,4

yield almost quantitive if n=1 or 2

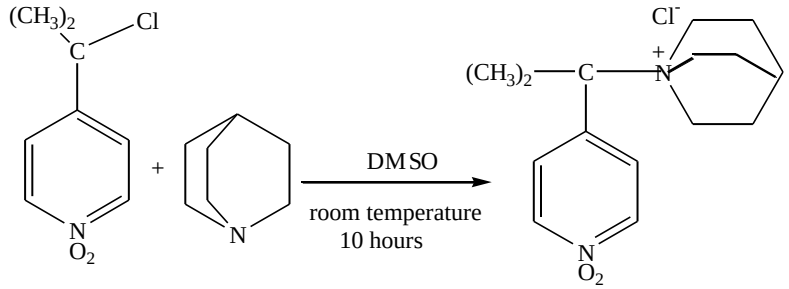
The morpholinoethylbenzofuranone is formed by direct halogen displacement and no rearrangement reactions take place.

c) **Aliphatic halide displacement-tertiary amines**

The reaction between triethylamine and ethyl iodine has been investigated in benzene, DMSO and various benzene-DMSO mixtures. The reaction rate increases with increasing DMSO concentration in the solvent. Although DMSO reacts slowly with alkylating agents, quaternizations, such as the reaction of triethylamine and ethyl iodide, proceed much more rapidly to give a high yield of tetraethylammonium iodide (585):

$$(C_2H_5)_3N + C_2H_5I \xrightarrow[20\text{-}50^oC]{DMSO} (C_2H_5)_4N^+I^-$$

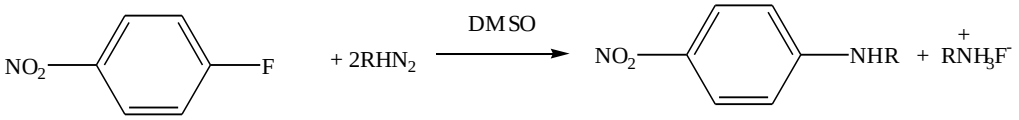
Similarly, when p-nitrocumyl chloride is treated with quinuclidine in DMSO, a 90% yield of pure quaternary ammonium chloride can be isolated (3433):



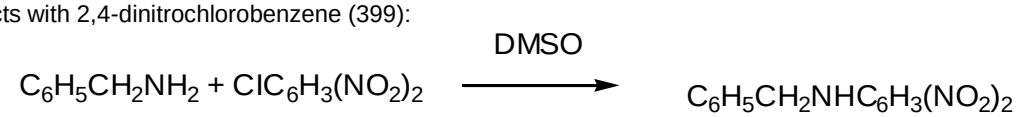
90%

d) **Aromatic halide displacement - primary amines**

A series of primary amines has been reacted with 4-nitrofluorobenzene in DMSO to determine the rate constants. DMSO was selected as the solvent because of its relatively high boiling point and the fact that most nucleophilic reactions in DMSO proceed at a fast rate (1638). These reactions are run in the presence of an excess of amines:

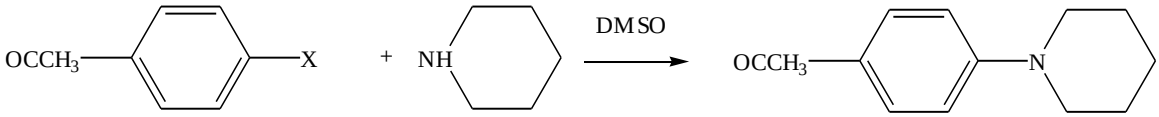


Similarly, benzylamine reacts with 2,4-dinitrochlorobenzene (399):



e) **Aromatic halide displacement - secondary amines**

The displacement of aromatic halides by secondary amines in DMSO has been studied rather extensively. The fluoro compounds undergo substitution by various nucleophiles, such as secondary aliphatic and alicyclic amines, at rates 100 to 1000 times faster than their chloro analogs. The rate of displacement of fluorine is further enhanced by the order of 103 to 105 in dipolar aprotic solvents, such as DMSO, as compared with reactions in aprotic solvents (471). Thus, 4-fluoroacetophenone undergoes a very rapid displacement of the halogen by amines, such as morpholine, in DMSO and affords in high yields the corresponding 4-amino derivatives, which are otherwise difficult to prepare (398):



X = F, Cl, Br

The yields of products obtained in DMSO are higher than those obtained with DMF under comparable conditions.

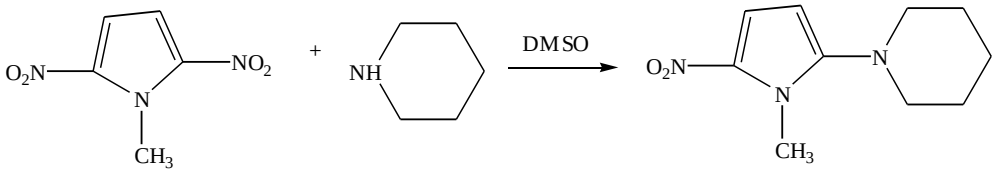
The reaction of 2,4-dinitrochlorobenzene with piperidine, which is known to be insensitive to base catalysis, is nevertheless accelerated by DMSO (538).

The rate constants for the reaction of 4-nitrofluorobenzene in DMSO with 19 secondary amines have also been determined. This reaction is the fastest with pyrrolidine, azacyclobutane and dimethylamine, and slowest with methylanisidine, diisobutylamine and diethanolamine (1639).

The dechlorination of 2- and 4-chloroquinolines, as well as 6- and 8-alkyl-substituted 4-chloroquinolines with piperidine in DMSO and other solvents has been studied (1240)(1239)(1238).

f) **Nitro group displacement**

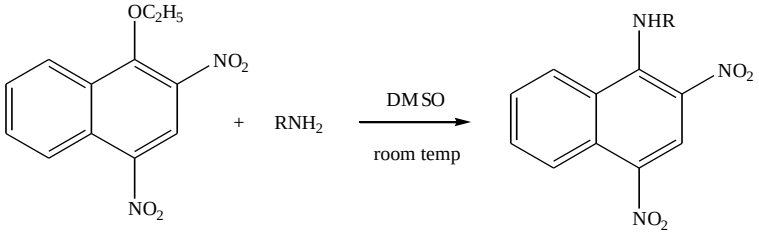
In some cases, activated nitro groups can be displaced by amines. Thus, 2,5-dinitro-1 -methylpyrrole undergoes nucleophilic aromatic substitution by piperidine (7756):



The reaction with the amine is favored by the accelerating effect of DMSO in aromatic substitutions by neutral nucleophiles.

g) **Alkoxide and phenoxide displacement**

The reaction of n-butylamine or t-butylamine with 2,4-dinitro-1 -naphthyl ethyl ether gives the corresponding 2,4-dinitro-1 -naphthylamines in high yields (3445):



1-Piperidino-2,4-dinitronaphthalene can be prepared by reacting 1-methoxy-2,4-dinitronaphthalene with piperidine in DMSO. 1 -Dimethylamino-2,4-dinitronaphthalene is prepared similarly (8408). The kinetics of the reaction of piperidine, n-butylamine, morpholine and benzylamine with 2,4-dinitrophenyl phenyl ether in DMSO has been studied as a function of amine concentration. The reactions of

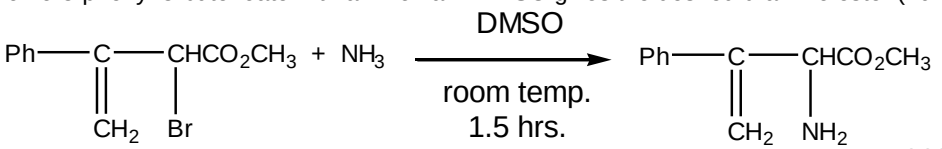
the secondary amines are base catalyzed; those of the primary amines are not (9138).

5. Ammonia

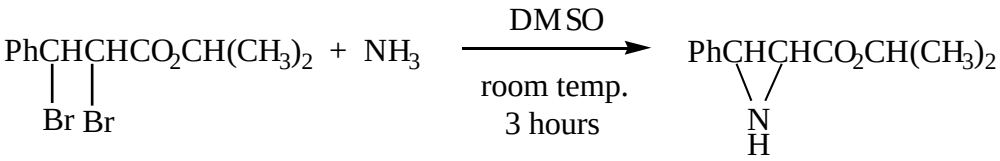
DMSO is stable to ammonia. Displacement reactions with ammonia and amines are examples where the nucleophile is uncharged (3433). The solubility of ammonia is 40 liters per liter of DMSO at 1 atmosphere or 2.6% by weight (5033).

a) **Aliphatic halide displacement**

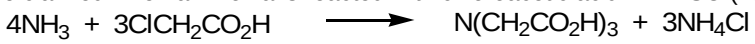
Reaction of methyl 2-bromo-3-phenyl-3-butenoate with ammonia in DMSO gives the desired α-amino ester (10134):



Secondary amine by-products are not found in any significant amounts in the above reaction. Somewhat similarly, isopropyl 2,3-dibromo-2,3-dihydrocinnamate reacts with ammonia to give isopropyl 2-phenyl 3-aziridine-carboxylate (10143):

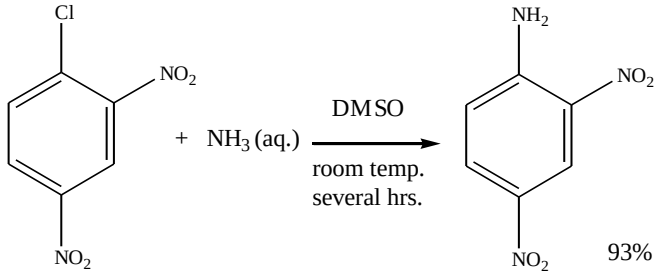


High yields of nitrilotriacetic acid are claimed when ammonia is reacted with chloroacetic acid in DMSO (4910):

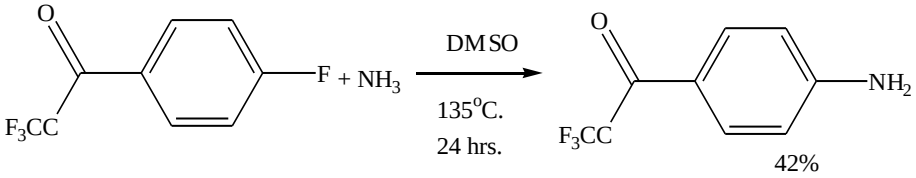


b) **Aromatic halide displacement**

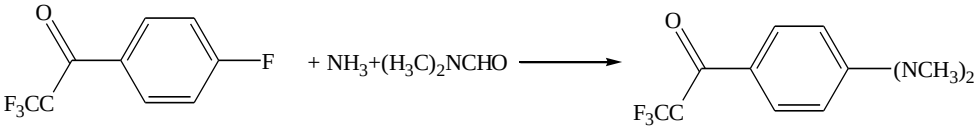
2,4-Dinitrochlorobenzene reacts with ammonia to give 2,4-dinitroaniline (402):



Similarly, p-aminotrifluoroacetophenone reacts with ammonia in DMSO (3399):

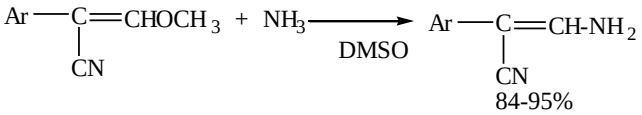


When DMF is used as the solvent in the above reaction, p-dimethylaminotrifluoroacetophenone results, apparently due to the hydrolysis of DMF to dimethylamine:



c) **Alkoxide displacement**

Displacement of an -OMe group by ammonia produces 3-amino-2-heteroarylpropenenitriles (10458):



6. Azide Ion

Rate constants for displacement reactions by the azide ion in DMSO are up to about 10,000 times greater than for the same reaction in protic solvents, such as methanol (471). Reactions are frequently run with an excess solid sodium azide, making it a pseudo first-order

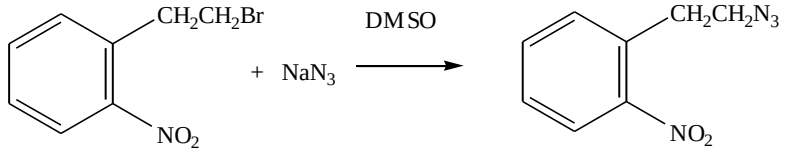
process. Under these conditions, the rate is also a function of the solubility of the reagent. Measurements of solubility show that sodium azide is much more soluble in DMSO than in some other solvents, and the solubility increases slightly with the addition of water (7527).

TABLE X
Solubility of Sodium Azide in Four Solvents

	Solubility, mol/l.			
	Dry	1% H_2O (110°)	5% H_2O (110°)	10% H_2O (110°)
2-Methoxyethanol	0.31 (124°)			
DMF	0.10-0.12	0.17	0.28	0.48 (25-150°)
DMSO	1.5-1.6	1.6	1.8	1.9 (95-150°)
HMPA	0.43	0.45	0.48	0.51 (110-150°)

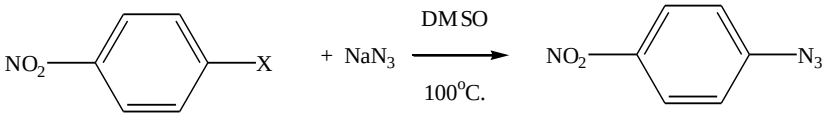
a**) Aliphatic halide displacement**

Some aliphatic halides are easily displaced by the azide ion in DMSO (4815). Thus, the reaction of 2-(2nitrophenyl)ethyl bromide with a 3-fold excess of sodium azide gives a 95% yield of 2-(2-nitrophenyl)ethyl azide (4360):



b) **Aromatic halide displacement**

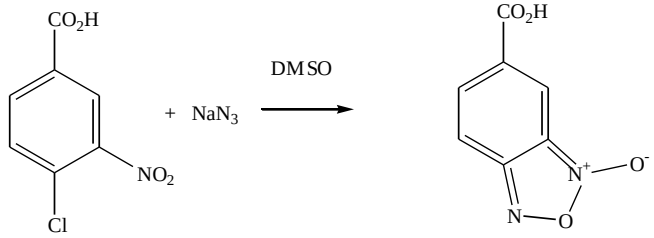
Treatment of 4-fluoro- or 4-iodonitrobenzene with sodium azide in DMSO produces a quantitative yield of 4-nitrophenyl azide (471):



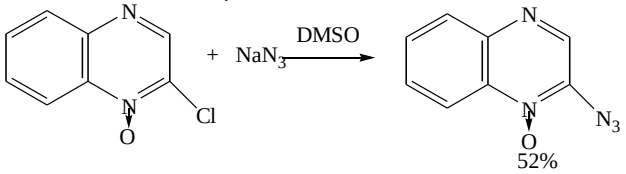
100 %

X = F or I

When 4-chloro-3-nitrobenzoic acid is treated with sodium azide in DMSO, the 5-carboxybenzofuroxan results (1007):



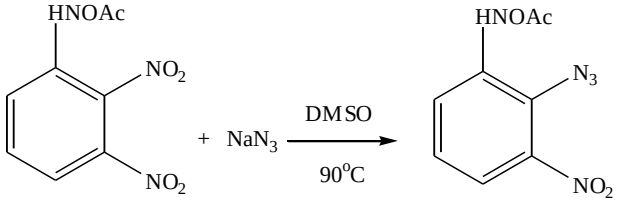
Reaction of 2-chloroquinoxzline 1-oxide with sodium azide in DMSO at room temperature gives 2-azidoquinoxaline (9767):



52%

c) **Nitro group displacement**

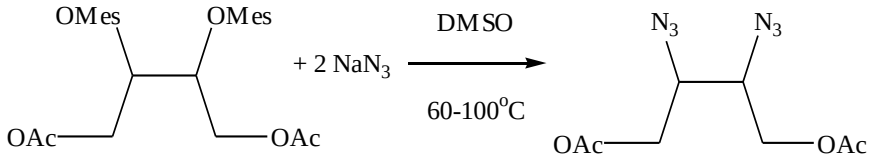
The aromatic nitro group can also be displaced by dry sodium azide in DMSO (6572). Thus, 2,3-dinitroacetanilide with sodium azide gives the monoazido-derivative (4600):



87%

d) **Sulfonate displacement**

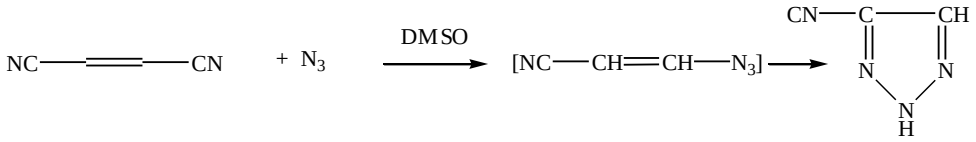
Sulfonates, such as toluenesulfonates and methanesulfonates are also readily displaced by the azide ion in DMSO (4920)(8339). A high yield of the 2,3-diazidobutane is obtained when meso-1,4-di-0-acetyl-2,3-di-0-(methylsulfonyl)erythrol is reacted with a slight excess of sodium azide (7692):



96%

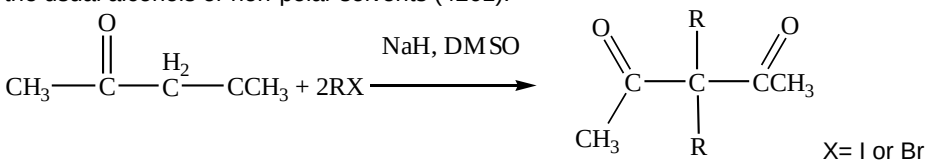
The above described displacements are frequently used to prepare amino sugar derivatives by reducing the azido to the corresponding amino group (5481)(7071).

e) **Other displacements**
Treatment of fumaronitrile with sodium azide in DMSO with subsequent acidification leads to 1,2,3-triazole-4-carbonitrile (4249):



7. Carbanions
The majority of carbanions which are usually prepared as reaction intermediates or as transistory species in chemical reactions are readily obtained in DMSO.

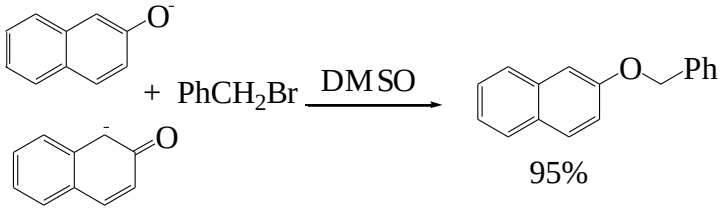
a) **Aliphatic halide displacement**
The alkylations of 2,4-pentanedione with alkyl iodides and sodium hydride as the base may be more conveniently and rapidly achieved when DMSO is used in place of the usual alcohols or non-polar solvents (4261):



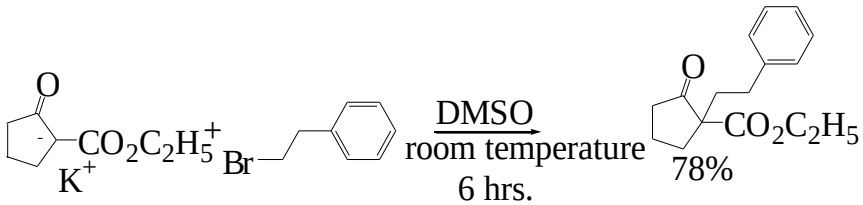
Similar results are obtained with malononitrile (599).

Alkylation of malonic esters in DMSO can be faster than in DMF, dimethoxyethane, THF and benzene. This alkylation is strongly accelerated by comparatively minor additions of DMSO to benzene. This could mean that DMSO disperses the ion aggregates (611)(612).

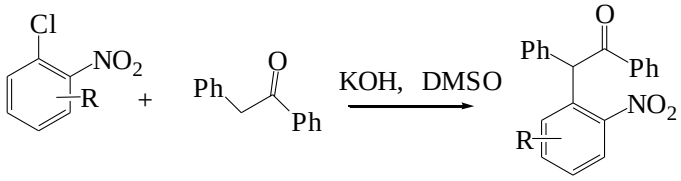
With ambient anions where either carbon or oxygen alkylation is possible, DMSO favors oxygen alkylation (690):



This is also demonstrated in the alkylation of β -ketoesters, where a proper choice of alkylating agent, temperature, and alkali metal can lead to significant amounts of O-alkylation (773)(1114)(1229).
Interaction of the potassium salt of 2-carbethoxy-cyclopentanone with an alkyl halide in DMSO at room temperature provides good yields of alkylated keto esters and probably constitutes the best method of alkylating this β-ketoester (1823):

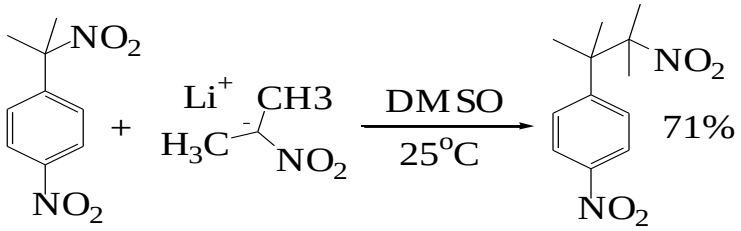


b) **Aromatic halide displacement**
Substituted o-nitrohalobenzenes reaction DMSO in the presence of powdered KOH with deoxybenzoin to form the corresponding nitroarylated deoxybenzoins (9439):

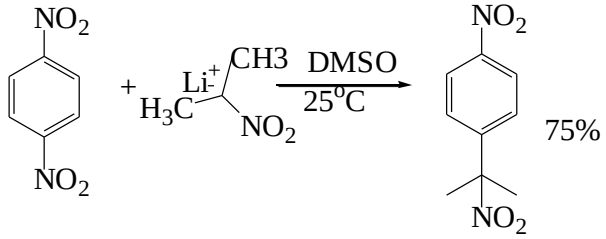


c) **Nitro and sulfinate group displacement**

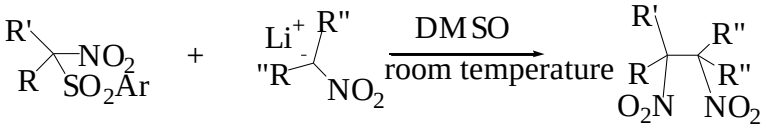
It has been discovered that aliphatic nitro and sulfone groups can be displaced at tertiary carbon. Thus, the treatment of α,-p-dinitrocumene with the lithium salt of 2-nitropropane in DMSO gives the alkylation product (1237):



Nitrobenzenes substituted by an electron withdrawing group, such as p-dinitrobenzene, readily undergo displacement by the lithium salt of 2-nitropropane in DMSO (8436):

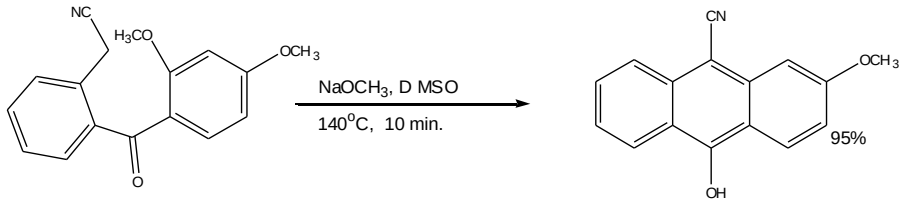


The sulfone group of α-nitrosulfones is also easily displaced by carbanions, e.g. the lithium salt of 2-nitropropane or the lithium salt of nitrocyclohexane (7108):

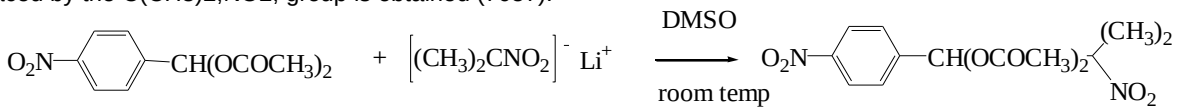


d) **Other displacement reactions**

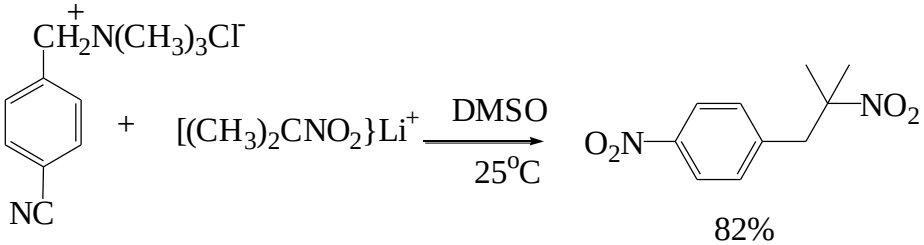
Treatment of 2-cyanomethyl-2',4'-dimethoxybenzophenone with sodium methoxide in DMSO gives 9-cyano-2-methoxyanthracen-10-ol (3112):



When p-nitrobenzylidene diacetate is reacted with the lithium salt of 2-nitropropane in DMSO, a compound in which one of the acetate groups is replaced by the C(CH3)2,NO2, group is obtained (7657):

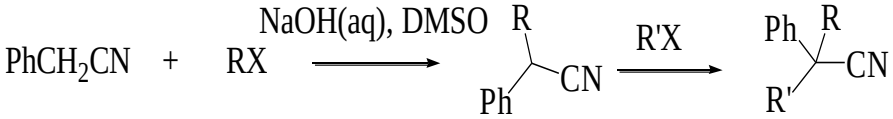


Treatment of (p-cyanobenzyl)trimethylammonium chloride with the lithium salt of 2-nitroprprane gives the carbon alkylate (10399):



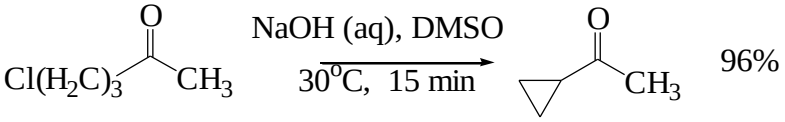
e) **Use of aqueous sodium hydroxide as the base**

It has been found that nitriles containing sufficiently activated methylene groups, such as phenylacetonitrile, can be conveniently alkylated in excellent yields and selectivities by using aqueous sodium hydroxide as the base and DMSO as the reaction solvent (3951):

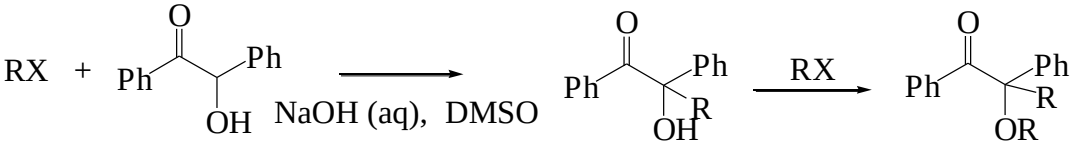


Previously, these reactions have usually been carried out by treating the nitrile with a strongly basic reagent, such as a metal amide, hydride, or alcoholate, followed by addition of the appropriate alkyl- or aryl hydride. These latter methods are generally cumbersome and

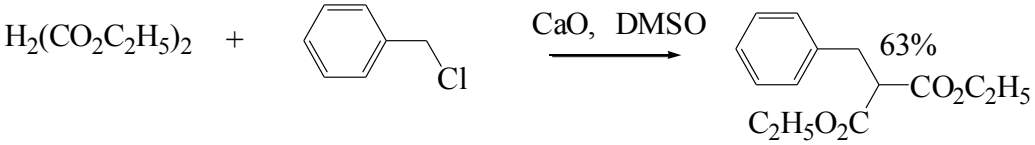
the selectivities are poor (3951).
Similarly, 50% aqueous sodium hydroxide in DMSO can be used as a base to induce an essentially quantitative cyclization of 5-chloro-2-pentanone to give cyclopropyl methyl ketone (3398):



O- and C-alkylation of benzoins is also easily achieved by the reaction of alkyl halides in aqueous sodium hydroxide in DMSO at ambient temperatures (4699):



f) **Use of calcium oxide as the base**
In some cases, calcium oxide has been used as a base to produce carbanions. Diethyl malonate can be alkylated with benzyl bromide to yield diethyl benzylmalonate (3931):



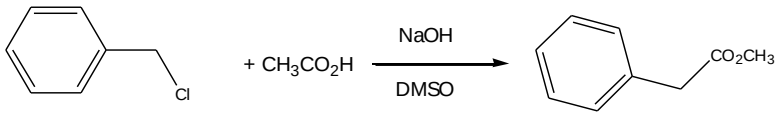
The use of lime in the dimethylation of 2,4-pentanedione gives a 73% yield of 3,3-dimethyl-2, 4-pentanedione (3931).

8. Carboxylate Ion

Alkylation of carboxylate ions with alkyl halides in DMSO or DMSO-water is an efficient method of esterification (7950)(365)(8809). Carboxylate ions have also been used to displace sulfonates (8254). In aqueous DMSO systems, the reaction rate increases as the concentration of DMSO increases both for intramolecular and intermolecular displacment (407).

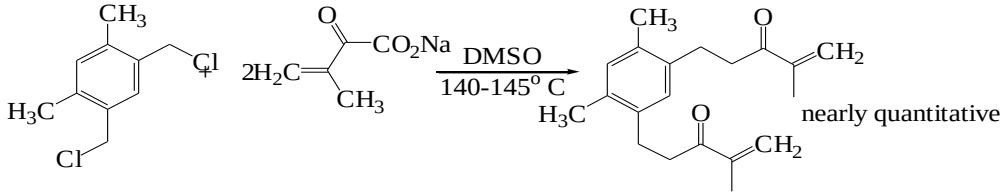
a) **Aliphatic halide displacement**

Simple alkyl halides, such as n-decylbromide, react with disodiurn phthalate in DMSO tog ive, e.g. didecylphthalate in 91 % yield (2597). Carboxylic acid esters are prepared by reacting an organic halide and potassium or sodium acetate in DMSO (574)(6847). Carboxylic acid esters are also prepared by reacting an acid with an organic halide in the presence of an alkali metal hydroxide in DMSO or DMSO-water, e.g. to obtain benzyl acetate (2969):

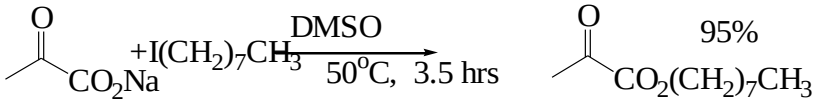


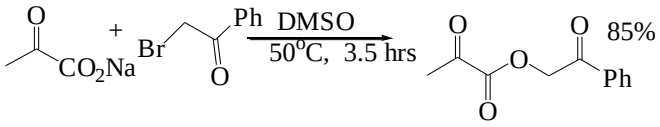
70-81%

Potassium and sodium methacrylates react in DMSO with xylylene dichlorides in DMSO to give unsaturated, polymerizable compounds (487):

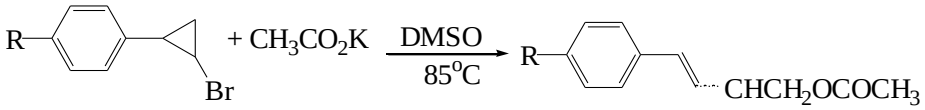


A convenient procedure for preparing pyruvic acid esters utilizes an organic halide as the starting material rather than the corresponding alcohol (9657). Thus, the reaction of sodium pyruvate with n-octyl iodide or phenacyl bromide in DMSO yields the esters:





A ring opening and displacement reaction takes place when E and Z 2-phenylcyclopropyl bromides react with potassium acetate in DMSO in the presence of a crown ether (1 8-crown-6) (10465):

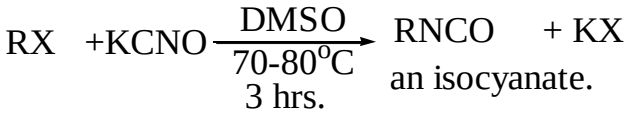


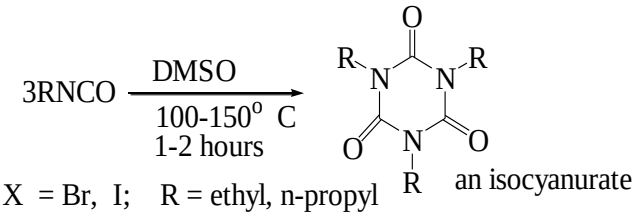
b) **Sulfonate displacement**

When the sodium or potassium 2-methanesulfonoxybicyclo[3.3.1]nonane-1 -carboxylate is heated in DMSO, the corresponding β-lactone is produced (6347):

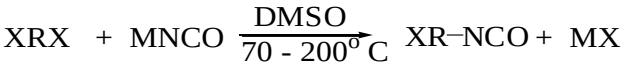
9. Cyanate Ion

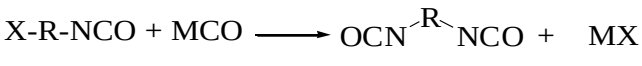
Sodium and potassium cyanates in DMSO can displace reactive halogens (26). When alkyl halides are reacted with cyanates, either isocyanates or isocyanurates result, depending on the reaction conditions and the solvent (440). DMSO plays a superior role in the displacement reaction and also in the subsequent trimerization of isocyanates. These reactions may be written as follows (386):





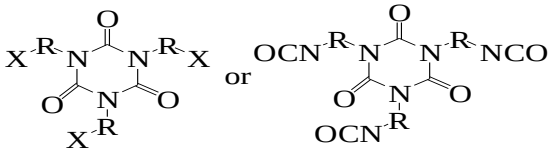
If an organic dihalogen compound is reacted with either potassium cyanate or sodium cyanate, the following reactions take place (9408):





M= sodium or potassium

Under conditions causing trimerization, the products can be converted to the corresponding cyanurates:



10. Cyanide Ion

Perhaps the most widely used of the displaycement reactions in DMSO are those involving the cyanide ion. Halogen atoms and sulfonate (tosyl) groups are displaced rapidly by cyanide ion. Often the yields of the desired products are higher and side reactions are minimized in DMSO. Many products are more easily isolated from reaction mixtures containing DMSO.

Certain inorganic cyanides are more soluble in DMSO than in other organic solvents. Thus, DMSO can be used advantageously in systems where water is undesirable. At 95°C, about 10 g of sodium cyanide and/or 2 g of potassium cyanide will dissolve in 100 cc of DMSO. At 25°C, 1 g of either is soluble (964)(1924).

The solubility of sodium cyanide in DMSO at various temperatures is shown in Figure 7 below. The solubility of sodium chloride, the usual inorganic by-product when reacting sodium cyanide with organic chlorine compounds, is illustrated in the phase diagram, Figure 8.

Also soluble in DMSO are mercury cyanide, cadmium cyanide, and mixtures of potassium cyanide with copper, nickel, zinc, cobalt, or silver cyanides. These mixtures appear to be complex salts (801).

In many cases it is not necessary to have a complete solubility of sodium cyanide in DMSO. Reactions can be run using an agitated, stirred slurry of sodium cyanide with DMSO. Yields are commonly good with primary aliphatic halides, but somewhat lower with secondary ones due to dehydrohalogenation (475)(577)(8843).

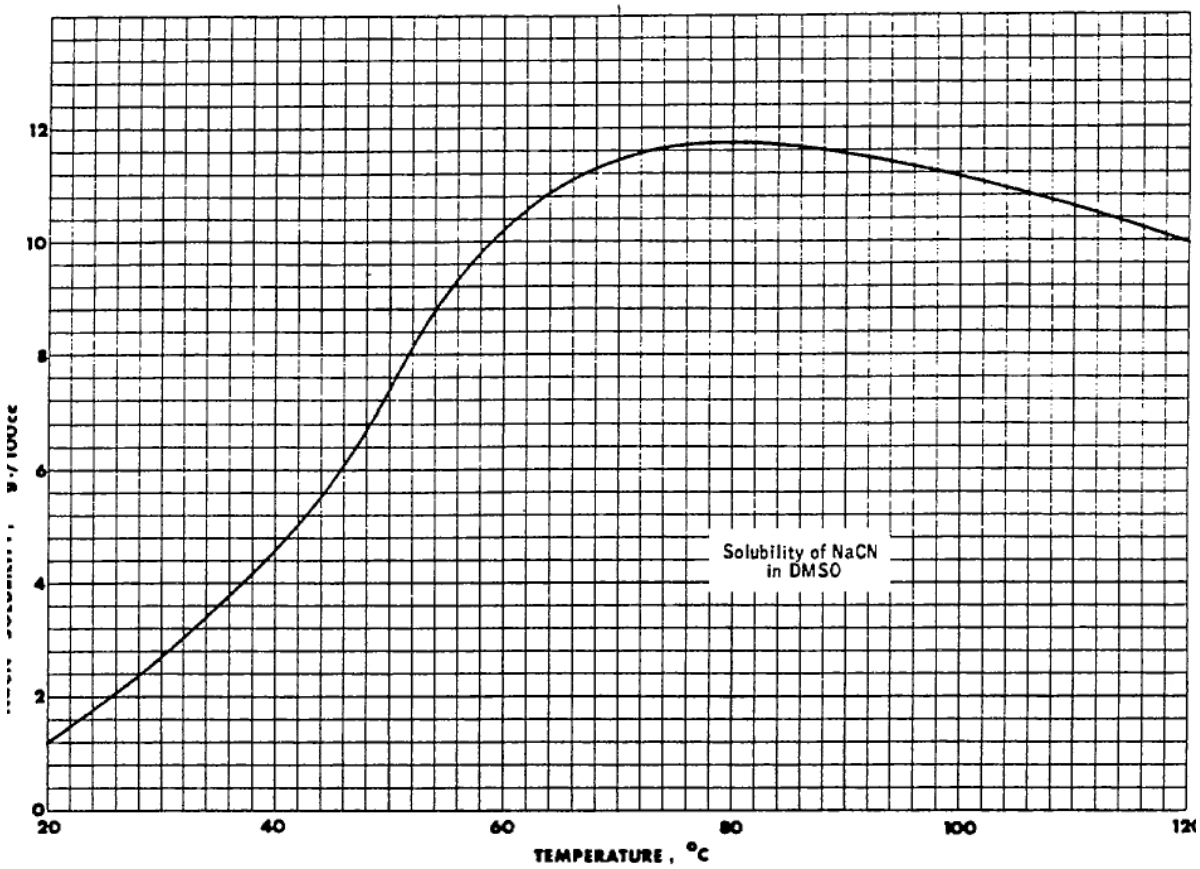


FIGURE 7

SOLUBILITY OF NaCl in DMSO-H_2O MIXTURES AT 25°C (WT %)

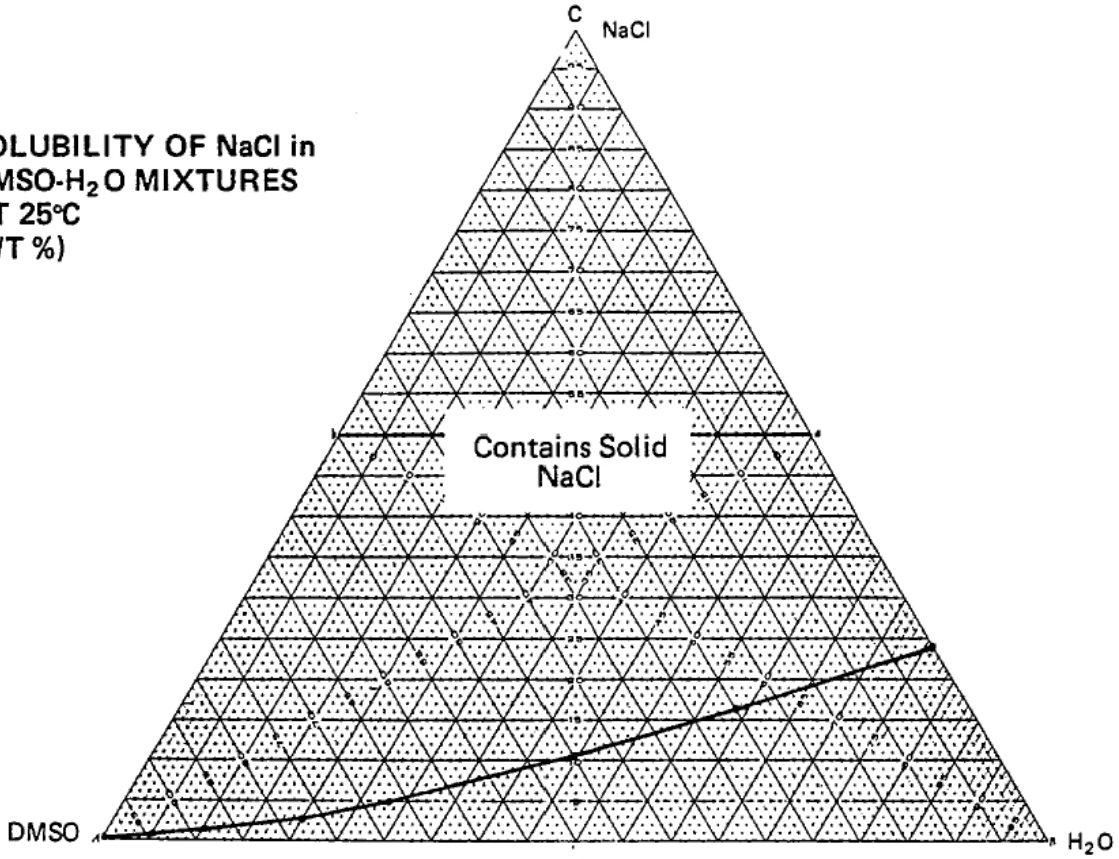


FIGURE 8

a) **Aliphatic halide displacement**

The reaction of sodium cyanide with ethyl 6-chlorohexanoate in DMSO gives a high yield of 6-cyanohexanoate (474):

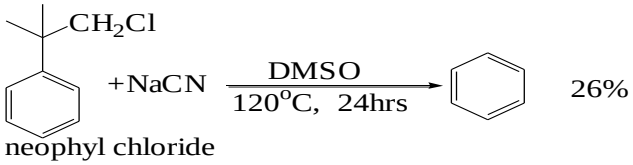
$$Cl(CH_2)_5CO_2C_2H_5 + NaCN \xrightarrow[95\text{-}100^oC,\ 1hr.]{DMSO} CN(CH_2)_5CO_2C_2H_5 + NaCl \quad 90\%$$

Similarly, ethylene dichloride reacts with sodium cyanide to give acrylonitrile (473):

$$ClCH_2CH_2Cl + 2\ NaCN \xrightarrow[100^oC]{DMSO} H_2C{=}CHCN + HCN + 2NaCl$$

In the above case, both the displacement and elimination reactions take place.

The use of DMSO allows the cyanide ion to displace halides from neophyl and neopentyl compounds without rearrangement (475)(7547):

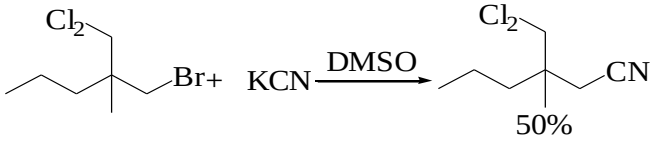


The displacement reactions of alkyl chlorides and bromides with potassium cyanide occur much more slowly when compared with sodium cyanide (475). This could be due to the lower solubility of potassium cyanide in DMSO. The yields are also lower and longer reaction times are required with DMF, sulfolane and dimethyl sulfolane as solvents (475). It has also been established that both primary and secondary alkyl chlorides react with sodium cyanide in DMSO to give high yields of the corresponding nitriles in shorter reaction times than have been obtained with bromides or iodides in aqueous alcohol solvent (577).

When 1-chloro-17-fluoro-8-heptadecyne is reacted with sodium cyanide in DMSO, 1-cyano-17-fluoro-8heptadecyne is produced in high yield (2189):

$$F(H_2C)_8C{\equiv}C(CH_2)_7Cl + NaCN \xrightarrow[135^o\text{-}140^oC,\ 50\ min.]{DMSO} F(H_2C)_8C{\equiv}C(CH_2)_7CN + NaCl \quad 93.5\%$$

The difference in the reactivity of halogens is also illustrated in the reaction of 1,1-dichloro-2-(bromomethyl)-2methylbutane with potassium cyanide (2769):

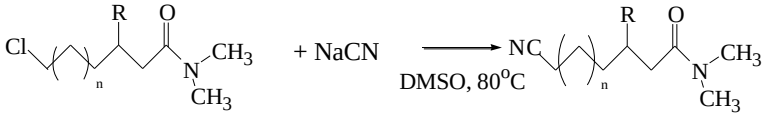


The use of sodium cyanide in the above reaction gives some undesirable by-products.

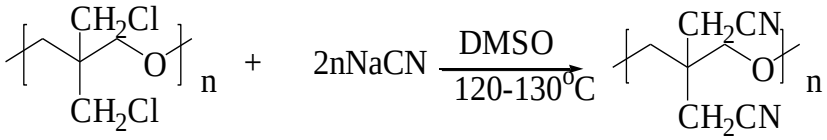
The enolate salt of ethyl 4-bromo-3-oxobutyrate reacts with the cyanide ion in DMSO (9135):



ω-Cyano N,N-disubstituted amides are conveniently prepared from halogenated amides by treatment with alkaline cyanides (9985):

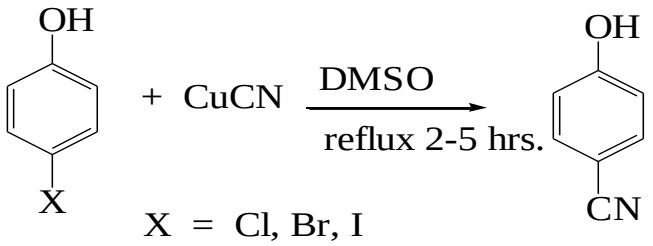


Poly[3,3-bis(chloromethyl)oxocyclobutane] reacts with sodium cyanide in DMSO to give the bis(cyanomethyl) derivative (6847):



b) **Aromatic halide displacement**

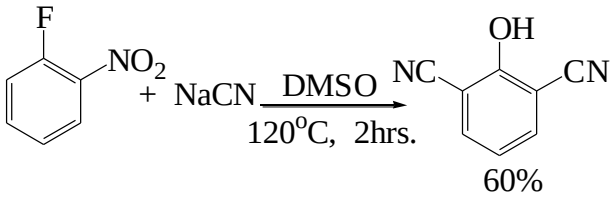
Aromatic halides, particularly those not activated by electron withdrawing groups, are best displaced by using cuprous cyanide (1593)(1774)(1946). Thus, p-halophenol reacts with cuprous cyanide in DMSO to give p-hydroxybenzonitrile (1946):



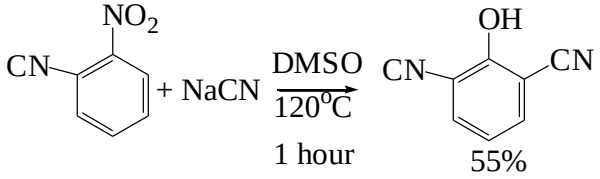
Cuprous cyanide and 9-bromoanthracene in DMSO give 9-cyanoanthracene in 91% yield (3247).
A procedure for the separation of isomers of dihalonitrobenzene consists of treating them with an alkali metal cyanide or cuprous cyanide in DMSO. When a mixture of 2,3- and 3,4-dichloronitrobenzene is thus treated, only the 2,3-isomer reacts, whereas the 3,4-isomer is recovered unchanged (1455):



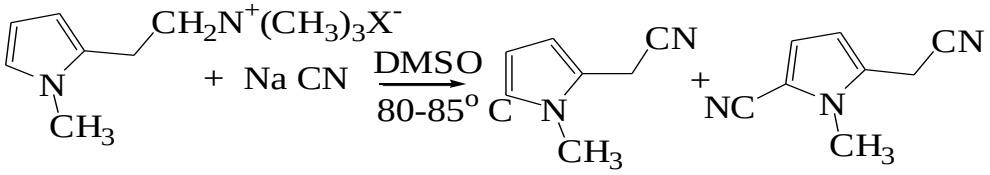
Sodium cyanide and o-fluoronitrobenzene in DMSO form 2-hydroxy-isophthalonitrile (8065):



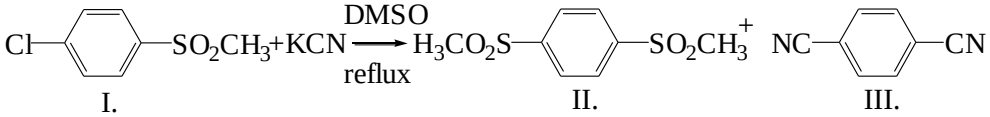
c) **Hydrogen displacement**
When o-nitrobenzonitrile is heated with sodium cyanide in DMSO hydroxy-isophthalonitrile is produced (8065).



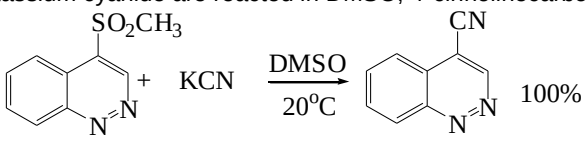
d) **Quarternary ammonium salt displacement**
When 2-pyrrolylmethylammonium salts are reacted with sodium cyanide both pyrrole-2-acetonitrile and "abnormal" nitrile are produced (8759):



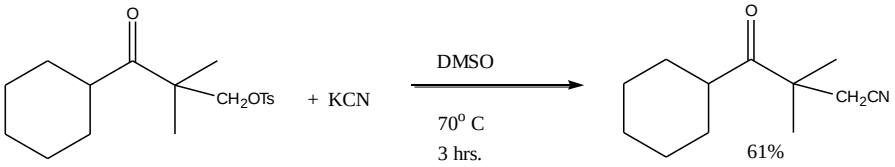
e) **Sulfinate displacement**
1-Chloro-4-(methylsulfonyl)benzene (I0 and cuprous cyanide fail to react to give the desired 1-cyano-4-(methylsulfonyl)benzene when refluxed for 24 hours in DMF. However, when equimolar amounts of I and potassium cyanide are allowed to react in DMSO for 30 minutes, a 1:1 mixture of 1,4-bis(methylsulfonyl)benzene (II) and terephthalonitrile (III) is obtained in about 80% yield (1711):



When 4- (methylsulfonyl)cinnoline and potassium cyanide are reacted in DMSO, 4-cinnolinecarbonitrile is produced quantitatively (1721):

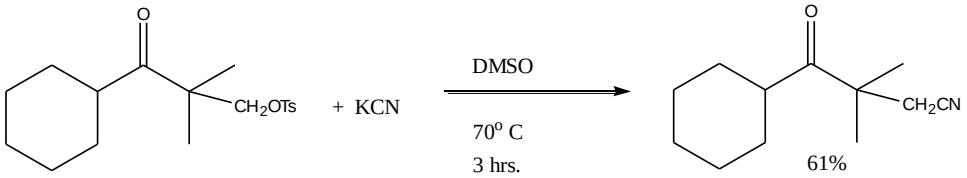


f) **Sulfonate displacement**
Sulfonates (e.g. tosylates) or disulfonates are converted in high yields to the corresponding nitriles or dinitriles with cyanides in DMSO (477)(2525)(10044). Thus, azulene-1,3-bis(hexanenitrile) and azulene-1, 3-bis-(pentanenitrile) are prepared by treating the corresponding tosylates (or chlorides) with sodium cyanide (2783).
A neopentyl substitution product can be obtained by treating the corresponding tosylate with potassium cyanide in DMSO (8255):



g) **Other displacement reactions**

Reacting a chloromethyl-1,2,3,4-tetrahydropyrimidine-2-one or4-(1-chlorethyl)- 4-dihydropyridine with sodium cyanide gives the ring-expansion products (4739)(9986). Thus, the above-mentioned pyrimidine produces a 7 membered ring compound (4739):



Displacement of primary or secondary hydroxyl groups by nitrile groups is accomplished by a short refluxing of the alcohol and triphenylphosphine in carbon tetrachloride, followed by the addition of DMSO and sodium cyanide to obtain 70-85% yields of the corresponding nitriles (872).

11. Halogen Ion

Displacement of halogen or other groups by halide ions is frequently easy in DMSO. Exchange reactions between halogens often require high temperatures and because of its boiling point of 189° C, DMSO is the solvent of choice.

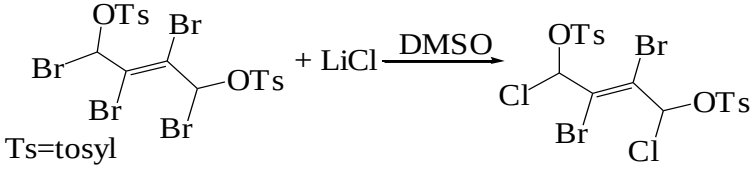
a) **Aliphatic halide displacement**

The kinetics of homogeneous isotope exchange between 36Cl in cyclic compounds (e.g. cyclopentyl chloride, cyclohexyl chloride, cycloheptyl chloride, cyclooctyl chloride) and lithium chloride has been studied in DMSO. This exchange is a bimolecular SN2 reaction (109)(651):

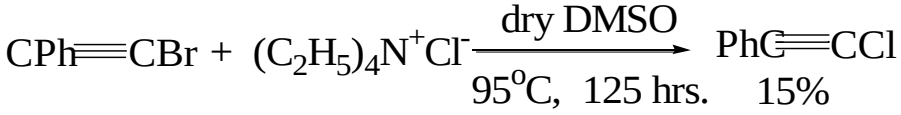


Similar exchange reactions between n-hexyl chlorides (containing36CI) and n-hexyl bromides (containing "Br) and lithium chloride and bromide have also been studied in DMSO (650).

By exchanging two bromine atoms in the 1,4-positions with lithium chloride in DMSO, 1,4-di-p-tolyl-1,4-dichloro2,3-dibromo-2-butene can be obtained (2760):

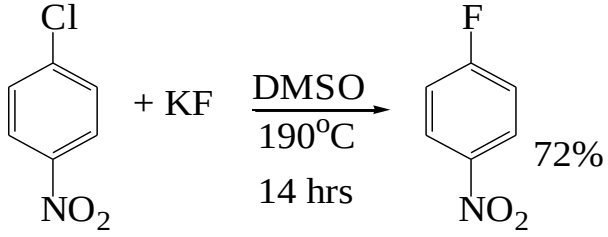


Nucleophilic reactions between halogeno(phenyl)acetylenes and halide ions have also been examined in DMSO (10394), eg.

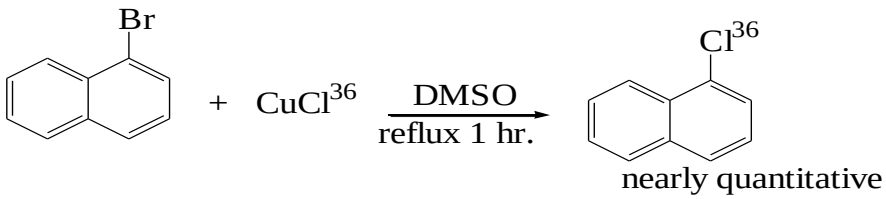


b) **Aromatic halide displacement**

The chloride ion in chloro nitrobenzenes can be replaced by fluoride with potassium fluoride in DMSO (438):



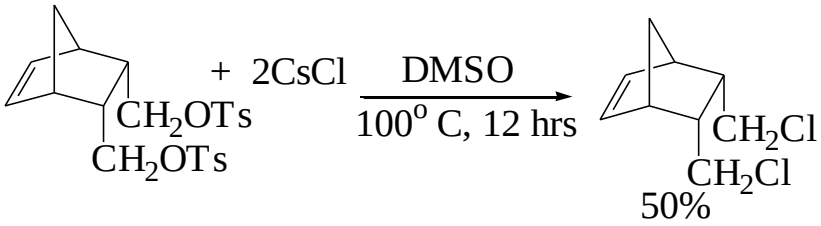
Quantitative studies are reported for substitution of the type ArHal + CuX → ArX + CuHal in DMSO and other polar solvents (541)(1593)(1214). Ease of replacement follows the order: H a I= I, Br, CI, F; X =CI,Br,I. The reaction rates are the highest in DMSO among the solvents examined. Thus [1-36Cl]chloronaphthalene can be prepared from 1 - bromonaphthalene and radioactive cuprous chloride (1593):



c) **Sulfonate displacement**

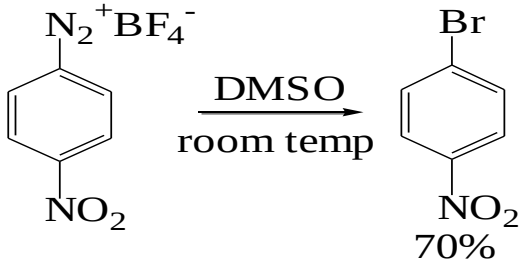
Sulfonates (e.g. tosylates, nosylates = p-O2N-Ph-S03) can be displaced by halogens by reacting them with lithium chloride, lithium iodide (4066)(5836), lithium bromide (4066) or sodium bromide (1027) in DMSO. Pure secondary alcohols can be converted to bromides without rearrangement by first preparing the tosylates and then reacting them with sodium bromide in DMSO at room temperature (1027).

Treatment of endo-5,6-bis(p-toluenesulfonyloxy-methyl)-2-norbornene with cesium chloride in DMSO gives the endo-5,6-bis(chloromethyl)-2-norbornene (10002):



d) **Displacement of diazonium ion**

p-Nitrobenzenediazonium tetrafluoroborate in DMSO reacts with iodides, bromides and chlorides to give the corresponding p-halonitrobenzene (99), e.g.:

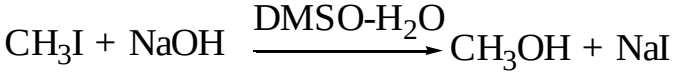


12. Hydroxide Ion

The basicity of hydroxides in DMSO closely parallels that obtainable with alkoxides, as shown in Figure 10 in which acidity functions up to 26 are obtained with 0.01 tetramethylammonium hydroxide in DMSO (1172). The solubility of the hydroxides is generally low, ranging from 7 x 103 mol/liter for sodium hydroxide (725) to 0.12 for tetramethylammonium hydroxide at room temperature (1172) (see Table IX). Additions of water increase the solubility of alkali metal hydroxides, but the increased solubility is accompanied by a decrease in the activity of the dissolved hydroxide ion. Figure 9 is a phase diagram of the water-DMSO-metal hydroxide systems for NaOH and KOH. Potassium hydroxide is consistently more soluble than sodium hydroxide at a given water content. In spite of the low solubility of alkali metal hydroxides in DMSO, satisfactory use of the strong basicity of the hydroxide ion is sometimes achieved by using a slurry of the powdered base in the reaction.

a) **Aliphatic halide displacement**

When the alkaline hydrolysis of methyl iodide is studied in the presence of hydroxyl ion in DMSO-water, the rate of hydrolysis increases with increasing DMSO content (329):



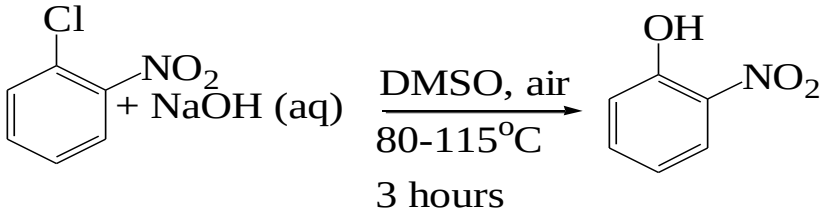
Similar results are obtained with other primary alkyl halides (iodides, bromides, chlorides)(913).

The rate constants for the reaction of hydroxide ion with ring substituted benzyl chlorides in acetone-water and DMSO-water mixtures are reported as a function of both solvent composition and temperature. The reaction rate increases with increasing DMSO concentration but decreases with increasing acetone concentration (432).

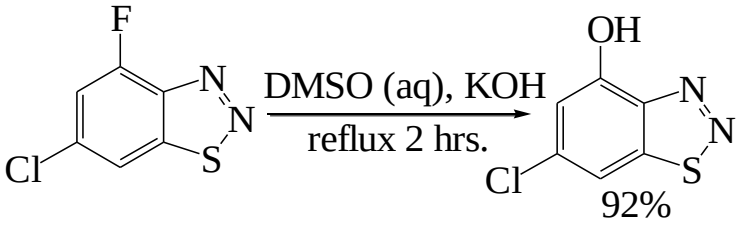
b) **Aromatic halide displacement**

The reaction of 2,4-dinitrofluorbenzene and 4-nitrofluorobenzene with hydroxide ion in DMSO-water are strongly accelerated by DMSO (328).

Hydrolysis of o- and p-nitrochlorobenzenes with caustic soda in DMSO produces o- and p-nitrophenols (3925):



Nucleophilic substitution reactions have also been carried out on a variety of mono- and dihalogen-1,2,3Denzothiadiazoles, e.g. 6-chloro-4-fluoro-1,2,3-benzothiadiazole, with potassium hydroxide in aqueous DMSO to give the corresponding phenol (4425):



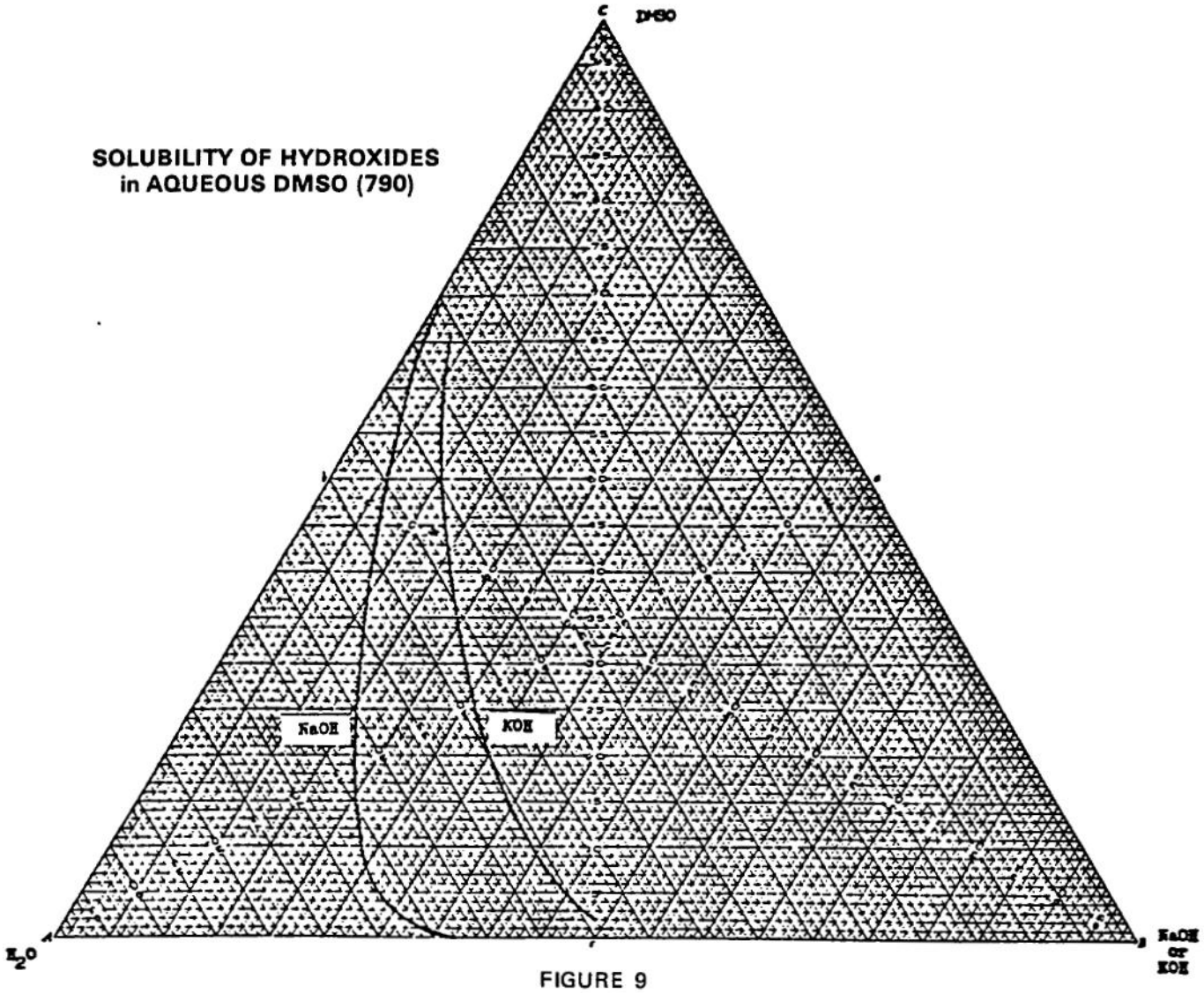


FIGURE 9

c) **Nitro group displacement**

The nitro group in 4-nitropyridine N-oxide, p-nitrobenzophenone and 1-nitroxanthone can be replaced with aqueous sodium hydroxide to give the corresponding phenols or 1-hydroxyxanthone, resp. (409)(470).

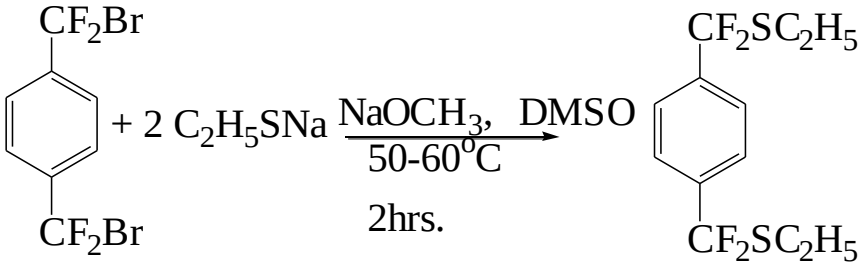
When p-dinitrobenzene is reacted with hydroxide ion in aqueous DMSO, one nitro group is displaced (6937).

13. Mercaptide (or Thiophenoxide) Ion

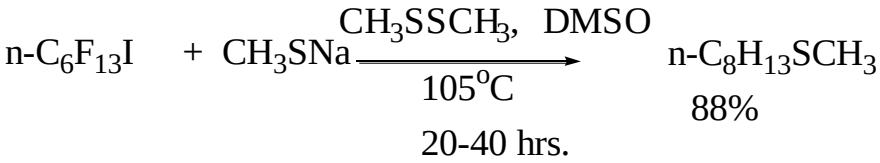
The mercaptide or thiophenoxide ions are known as good nucleophiles, and significant rate increases have been observed in DMSO when compared to the same reaction in alcohols (399).

a) **Aliphatic halide displacement**

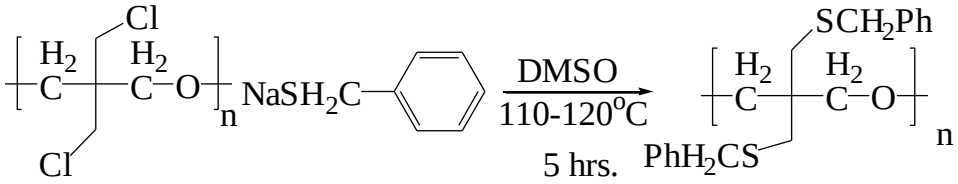
A number of alkyl halide displacements with mercaptides or thiophenoxides have been studied in DMSO (680) (712)(8779). Thus, the reaction of α, α' - dibromo- α, α, α', α'-tetrafluoro-p-xylene with sodium ethyl mercaptide gives the corresponding $^{\alpha}$, α'-bis(ethylthio)xylene (3386):



Methyl perfluoroalkyl sulfides may be prepared by reaction of the perfluoroalkyl iodides with sodium methyl mercaptide and dimethyl disulfide in DMSO (4792), e.g.:

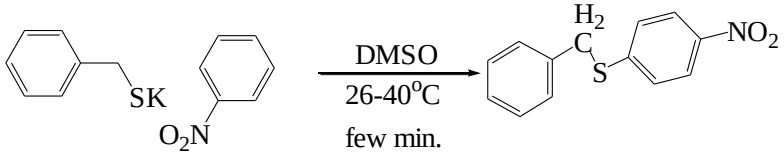


A derivative of poly-3,3-bis(chloromethyl)oxacyclobutane is prepared by reacting it with sodium benzyl mercaptide in DMSO (6847):



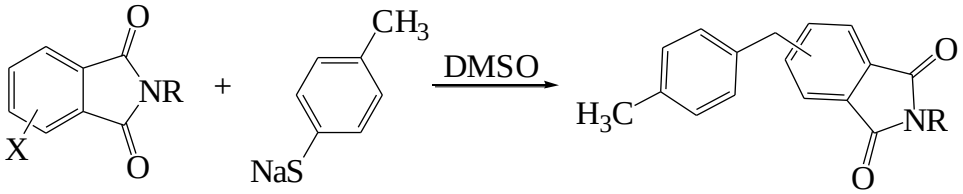
b) **Aromatic halide displacement**

Aromatic halogens are replaced by mercaptide or thiophenoxide ions in DMSO (541), particularly when the aromatic ring contains electron withdrawing groups in the ortho- or para-positions to the halogen (8344)(399). Thus, potassium benzyl mercaptide reacts with p-fluoronitrobenzene in DMSO-methanol under mild conditions (399):



The reaction rate of the above reaction increases significantly with increasing DMSO concentration.

The reactions of 4-methyithiophenoxide with 3- or4-halo-substituted phthalimide derivatives have been studied in DMSO (9771):

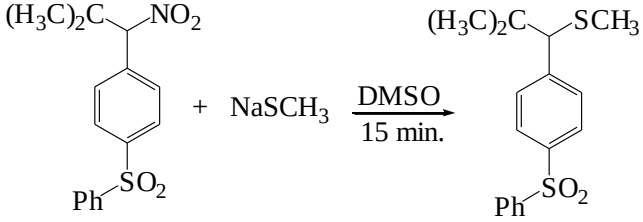


Nucleophilic substitution reactions have been carried out with mercaptide or thiophenoxide ions on a variety of mono- and dihalogen-1,2,3-benzothiadiazoles (4425).

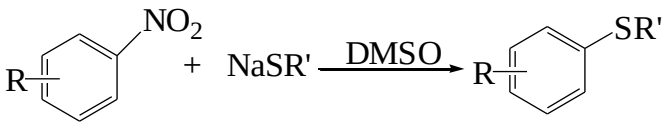
c) **Nitro group displacement**

The nitro group at certain tertiary carbon atoms can be displaced by thiophenoxide in DMSO-methanol (1237) or

methyl mercaptide ions in DMSO (10008). The yields of the tertiary sulfides are very high in both cases, e.g. (10008):



The nitro group in substituted nitrobenzenes is displaced by the thiophenoxide ion (9771) or mercaptide ion (4068) (9771) to give the diaryl or alkyl aryl sulfides, respectively, e.g. (4068):



d) Sulfonate group displacement

The reactions of the tosylate of 2,2,2-trifluoroethanol with the sodium salts of methyl, ethyl or 2-hydroxyethyl mercaptides in DMSO give the expected thio ethers (589):

$$CF_3CH_2OTs + RSNa \xrightarrow{DMSO} CF_3CH_2SR$$

14. Nitrite Ion

Sodium nitrite has good solubility in DMSO. Thus, in a few minutes, 100 cc of DMSO dissolves 19.2 g of sodium nitrite, whereas only 1.88 g dissolves in 100 cc of DMF at room temperature after 24 hours. In DMSO it is not necessary to add urea to increase the solubility of sodium nitrite, as is the case with DMF (685). Displacement reactions involving the nitrite ion have been studied rather extensively in DMSO.

a) **Aliphatic halide displacement**

The displacement of aliphatic iodide, bromide or chloride to give the corresponding nitro compound is readily accomplished in DMSO with yields ranging from 50-91 %, depending on the structures involved (684)(3686) (4562). Primary and secondary alkyl bromides and iodides react with sodium nitrite to produce the corresponding nitro compounds (486), e.g. 1 -bromooctane gives 1 -nitrooctane (685):

$$CH_3(CH_2)_7Br + NaNO_2 \longrightarrow CH_3(CH_2)_7NO_2$$

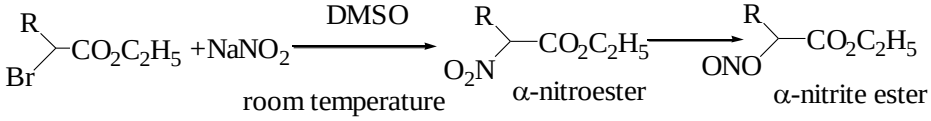
66%

Lower nitroparaffins are prepared by treating the corresponding C1-3 alkyl chlorides with alkali metal nitrites in DMSO (10286):

$$CH_3Cl + NaNO_2 \xrightarrow{DMSO} CH_3NO_2$$

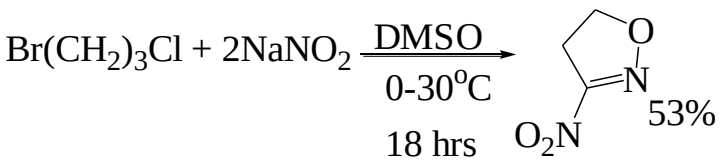
85%

When α -haloesters are reacted with sodium nitrite in DMSO, the nitro ester initially formed is quickly converted to the α-nitrite ester (684):

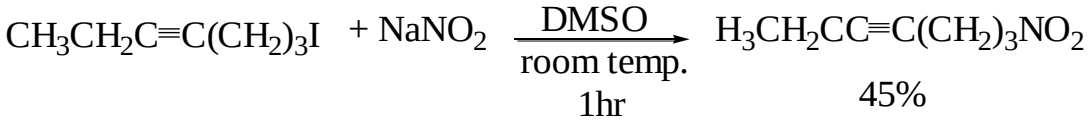


However, by adding phloroglucinol to the reaction mixture, the formation of nitrite ester is prevented and pure - nitroesters are produced in excellent yields (682)(684)(691).

When 1,3-dihalogen compounds, such as 3-bromo-l-chloropropane, are reacted with sodium nitrite, a heterocyclic compound is obtained, e.g. 3-nitro-2-isoxazole (366)(988):

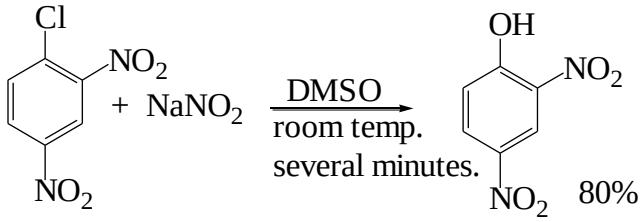


Other substitutions at tertiary carbon atoms involving the nitrite ion have been studied (2565)(2566)(3490). The reaction of 1 -iodo-4-heptyne with sodium nitrite in DMSO produces 1 -nitro-4-heptyne (4384)(6692):



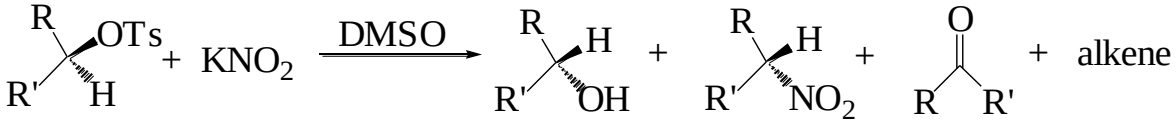
b) **Aromatic halide displacement**

Aromatic halides can also be displaced by the nitrite ion (8063). When 2,4-dinitrochlorobenzene is reacted with sodium nitrite in DMSO, 2,4-dinitrophenol is formed (402)(4562):



c) **Sulfonate displacement**

The reaction of the tosylate of the secondary alcohol (in the steroid or prostaglandin series) with potassium nitrite in DMSO affords the inverted alcohol as the main product together with the corresponding nitroalkane, ketone, and alkene (10454):

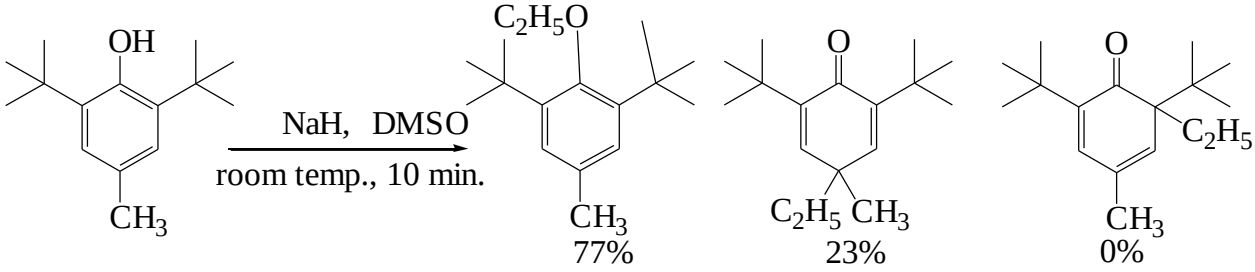


15. Phenoxide Ion

DMSO enhances the rate at which halides are displaced by phenoxides (phenol, catechol, hydroquinone) almost as much as it does for alkoxides or mercaptides (399). With ions such as naphthoxide, where a choice exists between carbon and oxygen alkylation, the reaction in DMSO gives almost exclusively oxygen alkylation (690). DMSO is a good solvent for phenoxide ions. Thus, the polymerizations of the dipotassium salt of bisphenol A with dihaloaromatic compounds proceeds best in DMSO when compared to other dipolar aprotic solvents (6026). The alkylation of phenoxide is enhanced more than the alkylation of amino groups in DMSO. The phenoxide group in tyrosine can be selectively etherified without blocking the amino group (442). DMSO is also a good solvent in the nucleophilic displacement of activated aromatic nitro groups by phenoxides for the synthesis of aromatic ethers (10434).

a) **Aliphatic halide displacement**

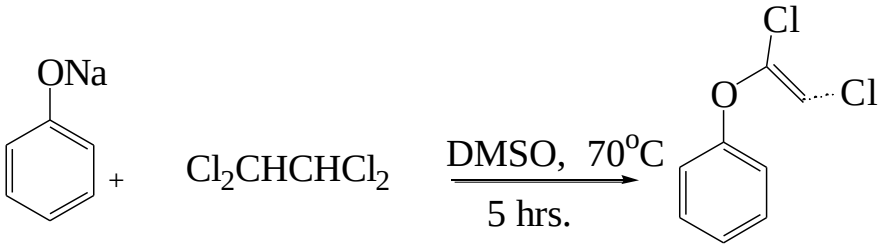
DMSO can be used as the solvent in alkylation of sterically hindered phenols (884)(3631)(3830)(4573). When 2,6-di-tert-butyl-4-methylphenoxide is reacted with ethyl iodide, the major product is the corresponding ether (517):



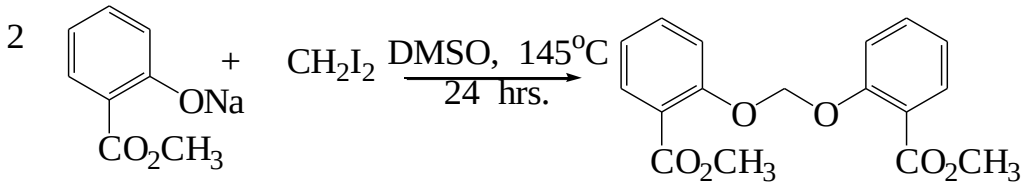
With tert-butyl alcohol as the solvent, the corresponding product distribution is 19%, 73%, 8%, and the reaction takes several days instead of 10 minutes, as in DMSO.

When 2-t- butyl-5-methyl phenol is alkylated with allyl bromide in DMSO with sodium methoxide as a base, a 97% yield of allyl-t-butyl-5-methylphenyl ether is obtained (885).

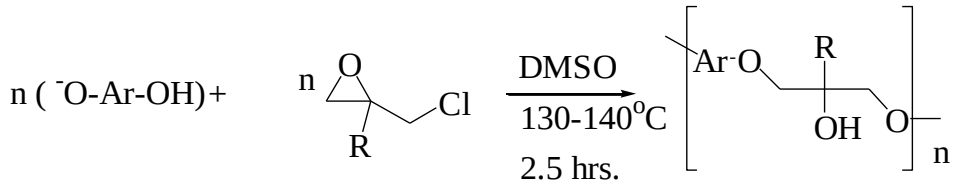
Reaction of polychloroethanes with sodium phenoxide in DMSO gives phenoxychloroethylenes (8410):



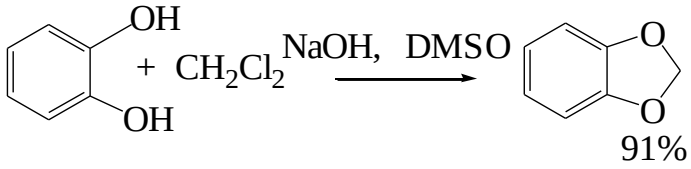
Sodium methyl salicylate and diiodomethane in DMSO give formaldehyde disalicyl acetal (6460):



Alkylation reactions of the bifunctional ω -bromo-1,2-epoxyalkanes have been found to be markedly dependent upon the solvent. In alcoholic media, phenoxides react by opening the epoxide ring to give β-hydroxy- ω- bromoalkyl derivatives. In DMSO, these same compounds react by displacement of bromide ion to give epoxylalkyl derivatives (3395). Polyhydroxyethers can be synthesized from mono-alkali metal salts of bisphenols, such as 4,4'sulfonyldiphenol, and 1-halo-2,3-epoxyalkanes in a one-step reaction in DMSO (10437):

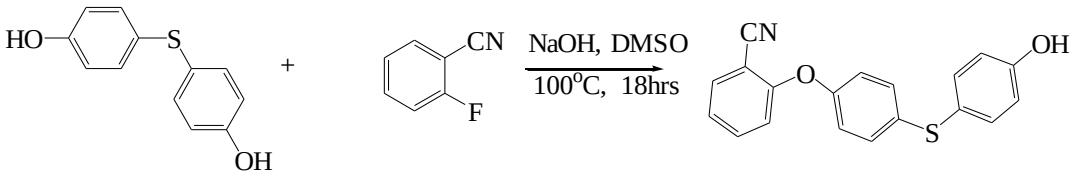


A number of catechol ethers have been prepared by using DMSO as the solvent (9145). Catechol reacts with methylene chloride in DMSO with sodium hydroxide as the base to give 1,2-methylenedioxybenzene (2887):

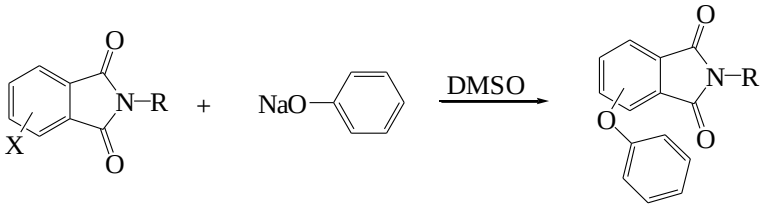


b) **Aromatic halide displacement**

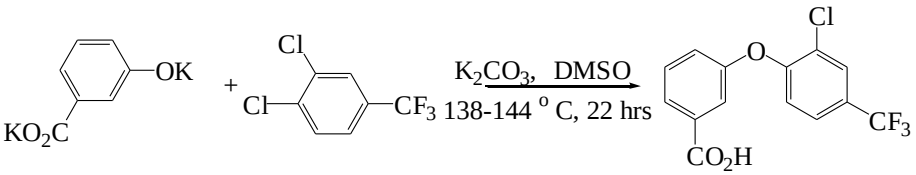
The phenoxide ions in DMSO have been used in many aromatic halide displacement reactions (399)(690). Activated fluorobenzenes react with alkali metal salts of divalent phenols to give aryloxy compositions (8683):



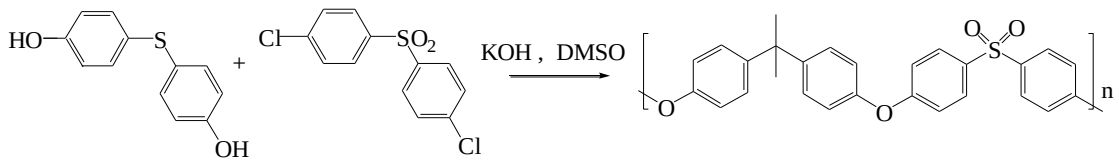
Phenoxides also react with halo-substituted phthalimide derivatives in DMSO to produce high yields of ether imides (9096):



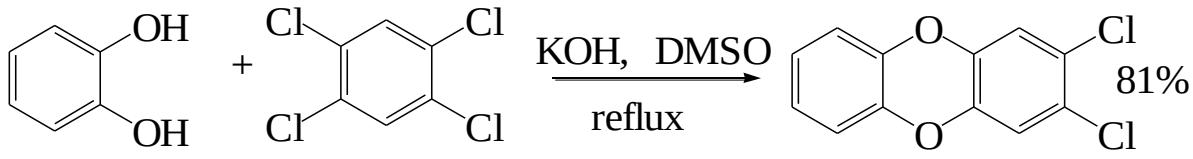
The dipotassium salt of 3-hydroxybenzoic acid reacts with 3,4-dichlorobenzotrifluoride in DMSO to yield 3-(2-chloro-4-trifluoromethylphenoxy)-benzoic acid (10320):



The ability of phenoxide ions in DMSO to displace aromatic halogens and the solubility of the phenoxide ions in DMSO are used in polycondensation reactions to obtain linear, high molecular weight aromatic polyethers (6026)(6830)(7699). Thus, bisphenol A can be polymerized with 4,4'-dichlorodiphenyl sulfone in DMSO to prepare a polyether sulfone (6831):

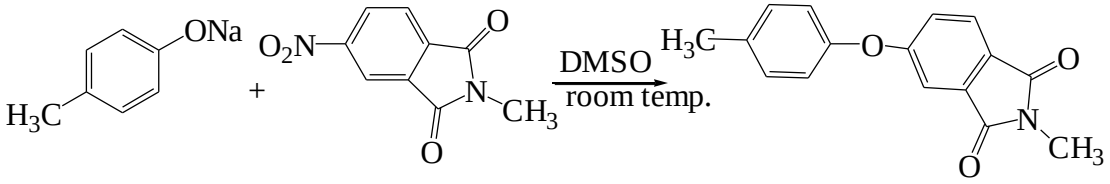


The dipotassium or disodium salt of catechol in DMSO reacts smoothly with some polyhalogenated benzenes (or heterocycles) to give good yields of the corresponding dibenzo-p-dioxins (7553)(8311), e.g. (7047):



c) **Nitro group displacement**

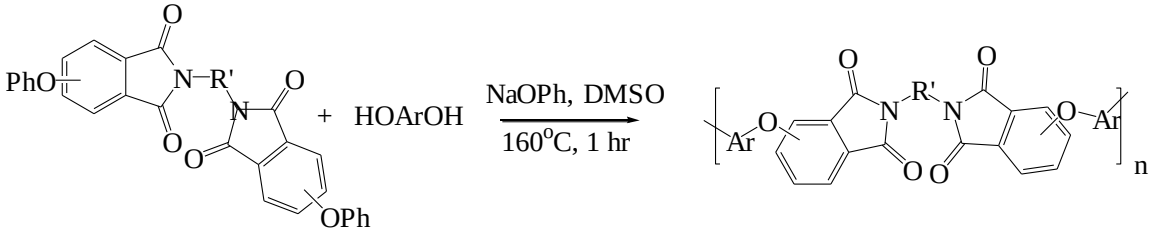
Some activated nitro groups are displaced with ease by phenoxide ions (8984)(8350)(8685):



Nucleophilic displacement of activated aromatic nitro groups with aryloxy anions in DMSO is a versatile and useful reaction for the synthesis of aromatic ethers (10434). This reaction has also found applications in polymers, particularly in the preparation of polyimides (7710)(8287).

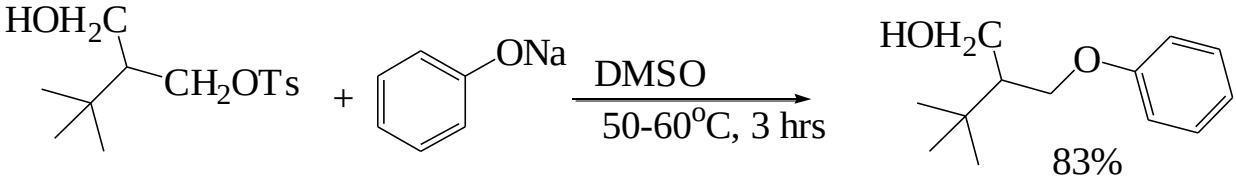
d) **Phenoxide displacement**

Polyetherimides can be made by effecting an interchange reaction, in the presence of an alkali phenoxide, between aryloxy-substituted bisphthalimide and disodium salt of, e.g., bisphenol A in DMSO (8714):



e) **Sulfonate displacement**

The monotosylate of 2-t-butyl-1,3-propane can be transformed to phenoxyalcohol with sodium phenoxide in DMSO 6315):

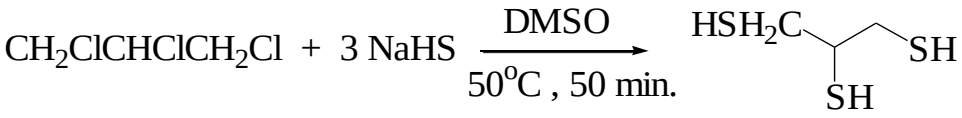


16. Sulfide (or Hydrosulfide) and Thiosulfate Ions

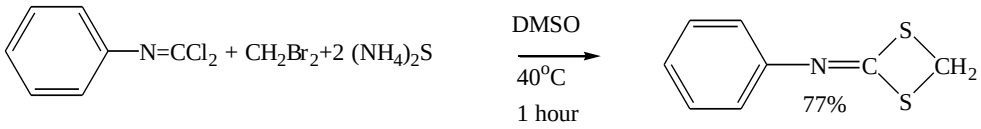
The sulfide and hydrosulfide ions act as nucleophiles and both these ions can be alkylated and/or arylated in DMSO. Water seems to be a necessary component for thiosulfate solubility. The rate constant for the reaction of thiosulfate in aqueous DMSO is at least an order of magnitude larger than in other solvents (656).

a) **Aliphatic halide displacement**

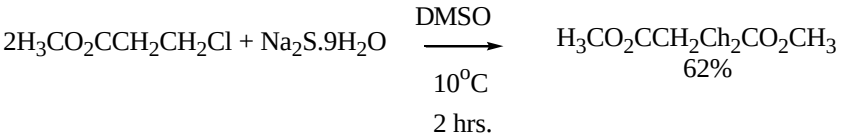
Polymercaptans can be produced by reacting polyhalo compounds with sodium sulfhydrate (sodium hydrogen sulfide) in DMSO, e.g., 1,2,3-trichlorpropane and sodium sulfhydrate give the corresponding trimercaptan (6192):



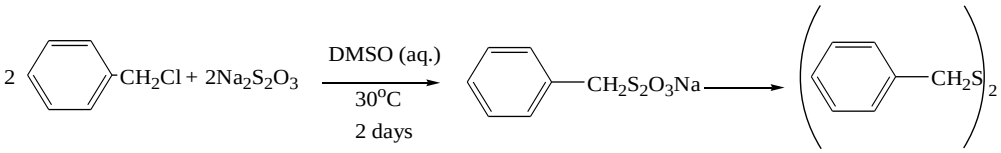
A mixture of either an aryl isothiocyanate or an aryl isocyanide dichloride, methylene bromide, and a sulfide source, such as ammonium sulfide or sodium sulfide, can be reacted in DMSO to provide a one-step synthesis of aromatic 2-imino-1,3-dithietanes (7528):



The β-activated diethyl sulfides can be prepared by reacting the appropriate chloride with sodium sulfide in DMSO (6398):

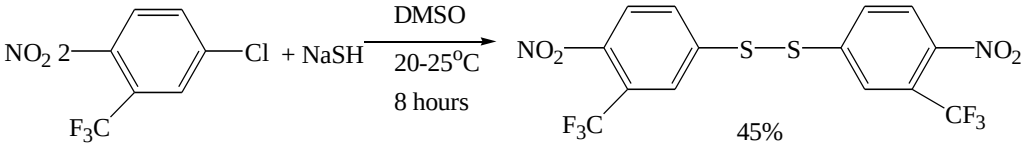


Sodium thiosulfate and benzyl chloride react to yield sodium benzylthiosulfate which forms dibenzyl disulfide (472):



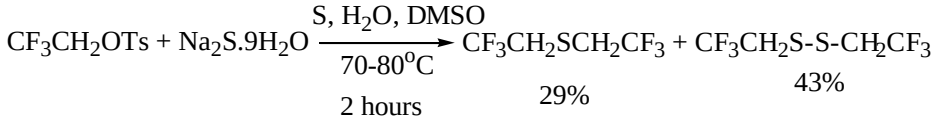
b) **Aromatic halide displacement**

Sodium sulfhydrate can also displace aromatic halogens from activated nuclei, as in the reaction with chloro-4-nitro-3-trifluorotoluene in DMSO. The major product is a disulfide (4123):



c) **Sulfonate displacement**

Sulfonates (tosylates) can be displaced by using either sodium sulfydrate or sodium sulfide in DMSO. Thus, 1,1-dihydrotrifluoroethyl p-toluene sulfonate reacts with sodium sulfide to give bis(1,1-dihydrotrifluoroethyl) sulfide (489):

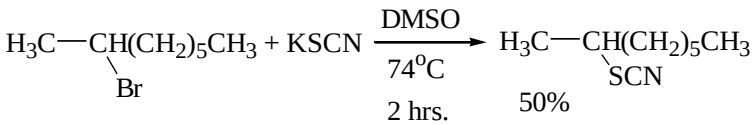


17. Thiocyanate Ion

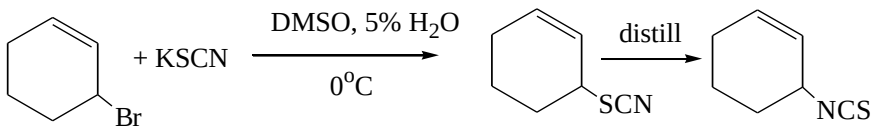
Sodium and potassium thiocyanates are very soluble in DMSO, and in most cases, the rate constants in displacement reactions are considerably greater than for reactions in protic solvents, e.g. methanol (471).

a**) Aliphatic halide displacement**

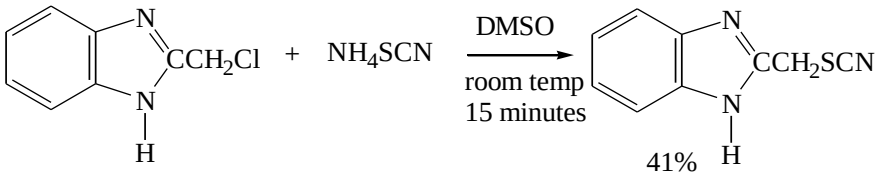
The reaction of 2-bromooctane with potassium thiocyanate yields 2-octyl thiocyanate (472):



3-Bromocyclohexene reacts with potassium thiocyanate in DMSO to form 3-thiocyanocyclohexene which is labile and rearranges to 3-isothiocyanocyclohexene (390):

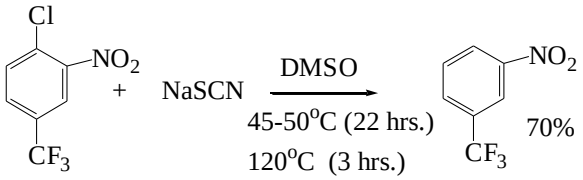


Ammonium thiocyanate and 2-chloromethylbenzimidazole in DMSO react to form thiocyanic acid (2benzimidozolyl)methyl ester (7173):



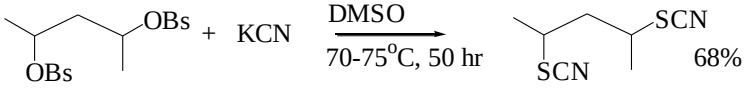
b) **Aromatic halide displacement**

Nitrotrifluoromethylchlorobenzenes react with sodium thiocyanate in DMSO to yield the corresponding phenylthiocyanates (4123)(7158):



c) **Sulfonate displacement**

Potassium thiocyanate in DMSO displaces the sulfonate groups from 2,4-pentane di-p-bromobenzenesulfonate to give 2,4-dithiocyanopentane (515):



Similarly, 2-methylbutyl p-toluenesulfonate and potassium thiocyanate in DMSO yield (62.5%) 2-methylbutyl thiocyanate (5435).

B. BASES AND BASE-CATALYZED REACTIONS IN DMSO

Basicities in DMSO

The reactivity of nucleophiles in DMSO mixtures with water or alcohols consistently increases as the content of DMSO in the mixture increases. When the nucleophile is the hydroxide ion in the aqueous system, or the alkoxide ion in the alcoholic system, the activities of the bases can be presented in terms of acidity function, shown in Figure 10. Since the acidity function is a logarithmic scale measuring the ability of the system to remove a proton from the reference indicator, the data show the basicity to be enhanced some 10^{14} fold upon going from water or alcohol to 99% DMSO. Such a protic-aprotic system offers a means of adjusting the basicity of a reaction medium over a wide range.

In the highly basic systems, obtained when the concentration of water or alcohol is low, an equilibrium amount of the DMSO anion will be present. The simple aliphatic alcohols are about 1,000 times as acidic as DMSO and they have about the same acidity as triphenylmethane (734)(1558). One chemical consequence of this effect shows up in the alkoxide-catalyzed autoxidation of fluorene where the oxidation rate is controlled by the rate of carbanion formation (1728). The reaction rate increases 220-fold upon changing the solvent from t-butanol to an 80:20 DMSO-t-butyl alcohol mixture. However, in the 80:20 mixture the concentration of DMSO anion is sufficient to react with the product so that instead of a 91 % yield of fluorenone a 78% yield of the DMSO adduct of fluorenone is obtained.

Although the equilibrium amount of DMSO anion produced by alkoxide ion in this system is small, the rate at which the protons transfer is fast (1758)(1759) so that a steady pool of DMSO anion is available for reaction.

Proton Removal

A number of different reactions require the removal of protons from carbon with the resultant formation of carbanions. The proton removal can be either an initial or the rate-determining step. Carbanions are formed in racemizations, in isomerizations and in a wide variety of elimination reactions. Just as the equilibrium basicity of alkoxides and hydroxides is enormously enhanced in DMSO versus in hydroxylic solvents, so also is the rate at which proton removal or hydrogen exchange reactions occur in DMSO. The rate of potassium t-butoxide-catalyzed hydrogen-deuterium exchange at a benzyllic carbon atom is 10^6 times greater in DMSO than in t-butanol (606).

A similar rate enhancement is observed in racemizations using ammonia as the base, with the reaction being 10^6-10^7 times faster in DMSO than in t-butanol (622)(524). The influence of the cation is greater in DMSO than in t-butanol. For example, in t-butanol, sodium and potassium t-butoxides are about equally effective in prompting hydrogen exchange, whereas in DMSO the potassium salt gives a reaction rate one hundred times that of the sodium salt (606).

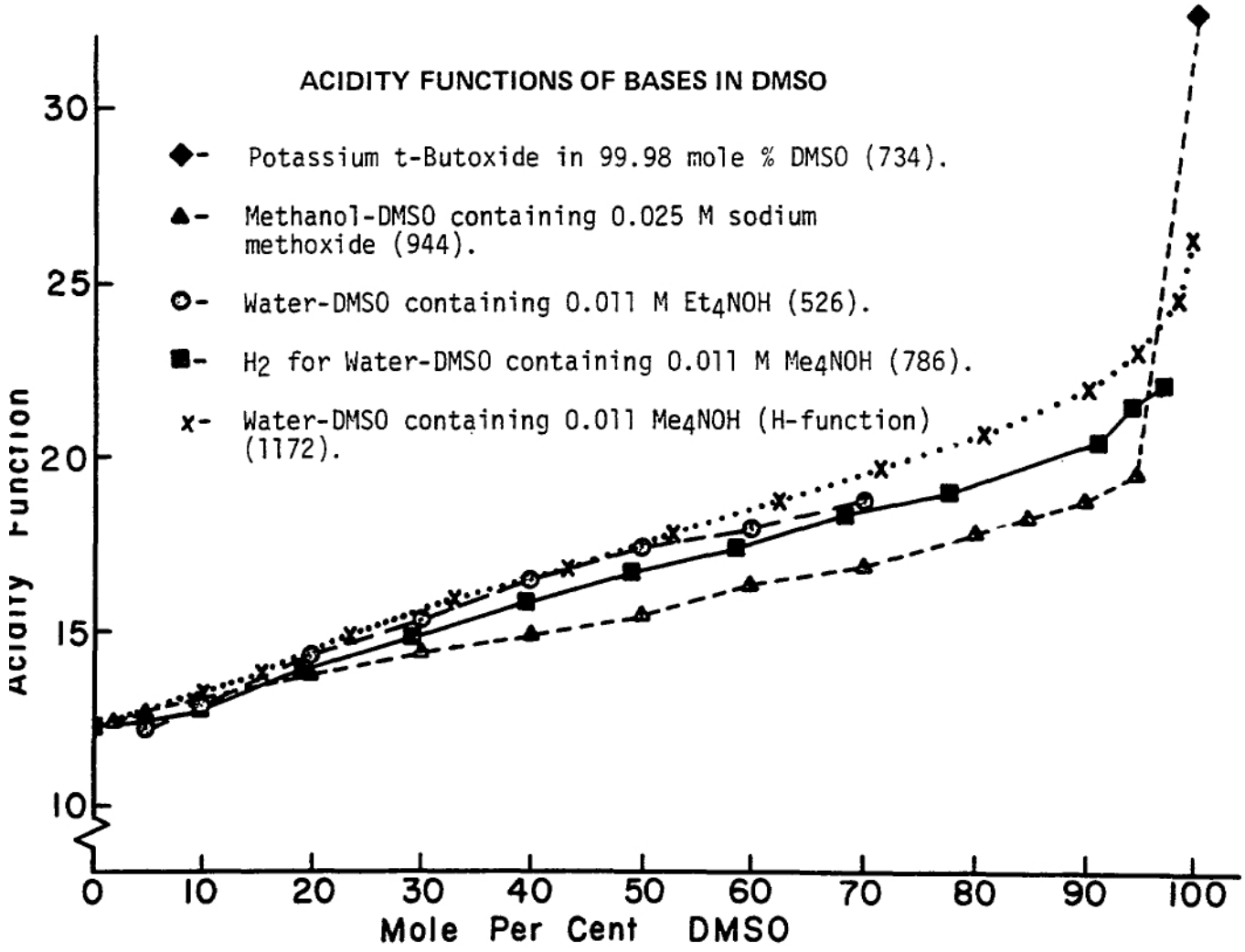

ACIDITY FUNCTIONS OF BASES IN DMSO
Potassium t-Butoxide in 99.98 mole % DMSO (734).
Methanol-DMSO containing 0.025 M sodium methoxide (944).
Water-DMSO containing 0.011 M Et4NOH (526).
H2 for Water-DMSO containing 0.011 M Me4NOH (786).
Water-DMSO containing 0.011 Me4NOH (H-function) (1172).
Acidity Function
30
25
20
15
10
0
10
20
30
40
50
60
70
80
90
100
Mole Per Cent DMSO

FIGURE 10

The table below (Table XI) lists the acidities (pKa) values of 132 organic compounds in DMSO, starting with the most acidic-protonated pyridine, and ending with the least acidic-propionitrile (10569). The pKa of DMSO is 35 (10411).

TABLE XI
Acidities in DMSO

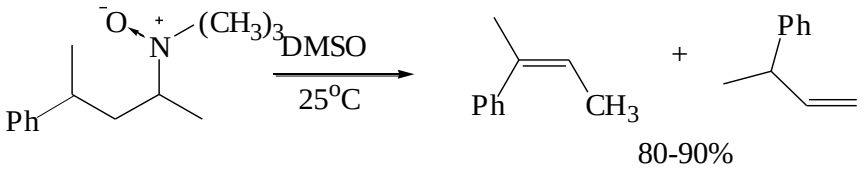
COMPOUND	pKa	COMPOUND	pKa
Protonated pyridine	3.5	Nitromethane	17.2,16.5
2,6-Dinitro-4-chlorophenol	3.6	Diphenylacetonitrile	17.5
Protonated analine	3.7	α, α, α', α'-Tetraphenylacetone	17.6
Protonated 2-methylpyridine	4.0	Phenyl benzyl ketone	17.7
Protonated 2,4-dimethylpyridine	4.5	Bis(2-nitrophenyl)amine	17.7
Protonated o-phenylenediamine	4.8	Nitrocyclobutane	17.8
Thiosalicylic acid	5.2	9-Phenylfluorene	17.9
Phthalic acid I	6.2	Nitrocyclohexane	17.9
Oxalic acid I	6.2	Nitroneopentane	18.1
Sulfamic acid	6.5	α, α-Diphenylacetophenone	18.7
Salicylic acid	6.8,6.6	α-Thiophenylaceton	18.7
Thioacetic acid	6.7	Methyl trifluoromethyl sulfone	18.8
Thiocyanuric acid	6.7	4-Chloro-2-nitroanaline	18.9
Bromocresol green	7.0	4-Nitroanaline	19.2
2,5-Dihydroxybenzoic acid	7.1	a, a-Diphenylacetone	19.4
Phenylsulfonylnitromethane	7.2	Methyl benzyl ketone	19.8
3,5-Dinitrobenzoic acid	7.3	2-Bromofluorene	20.0
2,4-Dihydroxybenzoic acid	7.5	Ethyl trifluoromethyl sulfone	20.4
Rhodanine	7.7	Thiourea	20.5
Nitromethyl phenyl ketone	7.7	Thiophenylacetonitrile	20.8
9-Cyanofluorene	8.3	Bis(n-chlorophenyl)amine	21.4
2,5-Dihydrophthalic acid	8.3	Phenylacetonitrile	21.9
Protonated tributylamine	8.3	9-Methylfluorene	22.3
Protonated diphenylguanidine	8.6	Phenylacetylene	22.6,28.8
Chloroacetic acid	8.9	2,6-Dichloroanaline	22.6
p-Nitrobenzoic acid	9.0	Fluorene	22.6
Ethyl nitroacetate	9.2	Trithiophenylmethane	22.8
Thiophenol	9.8	Phenyldithiophenylmethane	23.0
Protonated dibutylamine	10.0	1 -Phenyl-1 -cyanoethane	23.0
Bromo thymol blue	10.2	3-Methylfluorene	23.1
p-Chlorobenzoic acid	10.2	2,4 Dichloroanaline	23.4
9-Carboxymethylfluorene	10.2'	3-Methoxy-1 -propyne	23.5
9-Phenylsulfonylfluorene	10.3	Formamide (N-H)	23.5
Protonated piperidine	10.6	Diphenylamine	23.5,23.6
Protonated pyrrolidone	10.8	Dibenzyl sulfone	23.9
Benzoic acid	10.8,10.9	N,N-Dimethylprop-2-ynylamine	24.2
o-Toluic acid	11.0	9-tert-Butyl-fluorene	24.3
m-Toluic acid	11.0	Ethyl phenyl ketone	24.4
Malononitrile	11.1	Diphenylmethylphenyl sulfone	24.5
p-Toluic acid	11.2	2,5-Dichloroanaline	24.6
3-Nitro-l-propene	11.2	Acetophenone	24.7
Phenylacetic acid	11.6	Urea	25.1
Thiophenylnitromethane	11.8,11.9	2,4-Dichloroanaline	25.3
Phenylnitromethane	12.2	Acetamide (N-H)	25.5
Methylmalononitrile	12.4	Methyl benzyl sulfone	25.6
Acetic acid	12.6	1,3,3-Triphenylpropene	25.6
2-Thiohydantoin I	12.8	Isopropyl phenyl ketone	26.3
Acetylacetone	13.6	Acetone	26.5
Hydrogen cyanide	13.7	9-(3-Chlorophenyl)xanthene	26.6
Bis(ethylsulfonyl)methane	14.4	3-Chloroanaline	26.7
2,4-Dinitroanaline	14.8	Diphenylthiophenylmethane	26.7
Oxalic acid II	14.9	Nitrocyclopropane	26.9
Resorcinol	15.3	Diethyl ketone	27.1
9-Phenylthiofluorene	15.4	9-Phenylxanthene	27.9
2,5-Dihydrophthalic acid II	15.6	Water	28.0
Nitrocycloheptane	15.8	Benzyl methyl sulfoxide	29.0
Nitrocyclopentane	16.0	Methyl phenyl sulfone	29.0
p-Chlorophenol	16.1	Diphenylyldiphenylmethane	29.4
2,5-Dichloro-4-nitroanaline	16.2	Triphenylmethane	30.0,30.6
Nitromethylcyclopropane	16.5	Phenylthiophenylmethane	30.8
Nitroethane	16.7	Ethyl phenyl sulfone	31.0
1,1 Bis(ethylsulfonyl)ethane	16.7	Dimethyl sulfone	31.1
1 -Nitropropane	16.8	Acetonitrile	31.3
2-Nitropropane	16.9	Diphenylmethane	32.3
Phenol	16.9	Propionitrile	32.5
m-Cresol	17.0	DMSO	35

ELIMINATION REACTIONS

These are base-catalyzed reactions in which two atoms or groups are removed or eliminated, usually from one or two carbon atoms. A double bond is frequently formed as the result of this elimination.

1. Cope Elimination

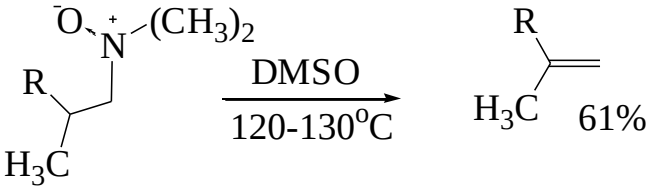
The pyrolysis oft-amine oxides (Cope elimination) in dry DMSO proceeds at a convenient rate at 25°C to give 80-90% yields of olefins. Temperatures of 132-138° are usually required in water. In addition, the rates in DMSO are 10,000 times faster than in water (495):



80-90%

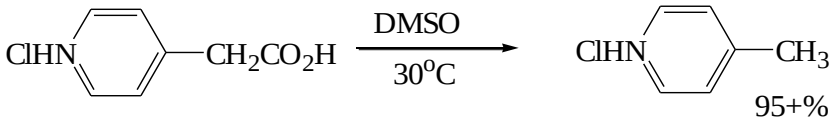
The rate is higher in wet DMSO than in dry THF because DM SO acts as an internal drying agent and competes with amine oxide for the water present (578).

5 α-Stigmasta-7,22,25-trien-3 β-ol, a steroid alcohol, is obtained by heating the appropriate t-amine oxide in DMSO (3481):



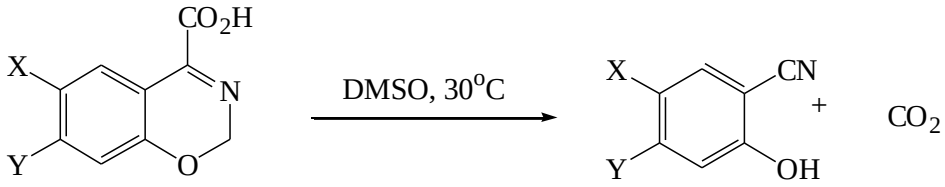
2. Decarboxylation and Decarbalkoxylation

DMSO promotes the decomposition of malonic (640), oxalic (604), and oxamic (643) acids at elevated temperatures, e.g. 140-160°C. Pyridylacetic acid hydrochloride decarboxylates in DMSO at moderate temperatures. The only product of this decarboxylation is 4-methyl-pyridine hydrochloride (2343)(3743):

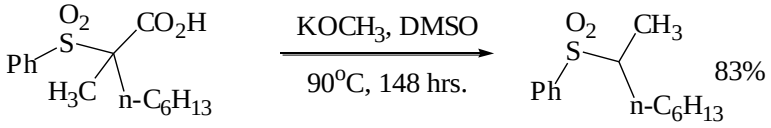


95+%

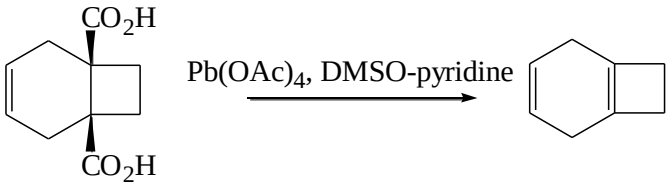
The decarboxylation of trichloroacetic acid also occurs as low as 25.0°C in the presence of DMSO and water. The reaction rate constant increases by a factor of 6-7 with a change in concentration of DMSO from 50 to 86%. Dramatic rate accelerations result in the decarboxylation of benzisoxazole-3-carboxylic acids if water is replaced by DMSO (3447):



Some acids, such as optically pure (+)-2-benzenesulfonyl-2-methyl-octanoic acid, decarboxylate more readily in the presence of base to give, in this case, (+)-2-octylphenylsulfone in 98% optical purity (631):

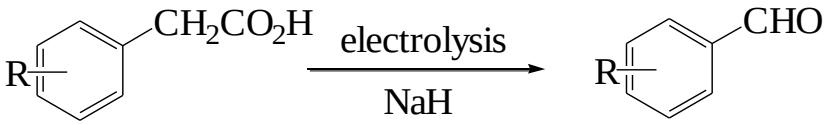


Tetrahalophthalic acids in DMSO in the presence of alkali and alkaline earth chlorides undergo double decarboxylation to form 1,2,3,4-tetrahalobenzenes, whereas, in the presence of other chlorides (e.g. $CoCl_2$, $NiCl_2$, $CuCl_2$) or no salts at all mostly single decarboxylation occurs to give 2,3,4,5-Cl_4(or Br_4)C_6HCO_2H (4602). Lead tetraacetate has been used in DMSO to decarboxylate dicarboxylic acids (5081). Thus, the treatment of 3,3-dimethylcyclohex-4-ene-1,2-dicarboxylic acid yields 3,3-dimethyl-1,4-cyclohexadiene (7533):

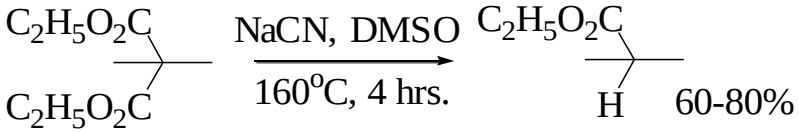


Rates of decarboxylation are reported for several phenylmalonic acids and esters in DMSO at 55.4°C. Only those compounds bearing at least one carboxylic proton are labile, which establishes that intramolecular proton transfer is an integral part of the reaction mechanism (7655).

Benzaldehydes can be prepared from the phenylacetic acids by electrolytic decarboxylation and oxidation in DMSO in the presence of sodium hydride. The yields are good in most cases (8766):



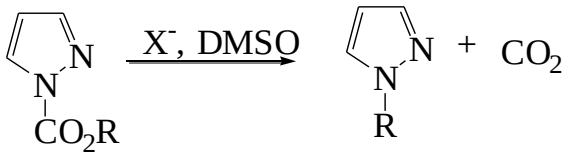
Decarbalkoxylation (mostly decarbethoxylation) is related to decarboxylation in that the -CO_2R group, instead of CO_2 (decarboxylation) is eliminated. Thus, geminal dicarboxy groups are eliminated when malonic ester derivatives are heated in DMSO (942):



The treatment of ethyl trichloroacetate with sodium methoxide in DMSO at 0°C produces dichlorocarbene which is oxidized by DMSO (1040).

Decarboxylation of geminal diesters, β-keto esters, and α-cyanoesters to the corresponding monoesters, ketones and nitriles can be accomplished in excellent yields (85-95%) in wet DMSO in the presence of sodium chloride at 140-186°C (6102)(7022)(9769). Other dipolar aprotic solvents, such as DMF, are less effective in the case of substrates with lower activity because of lower boiling points of these solvents (6102).

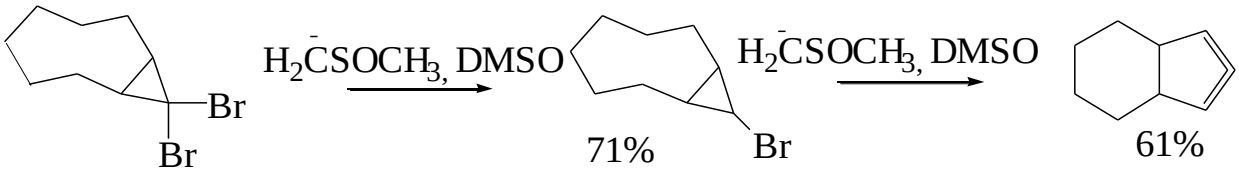
The alkylative decarboxylation of N-carbalkoxypyrozoles has been shown to require a polar aprotic solvent, such a DMSO, and to be subject to catalysis by nucleophiles, e.g. halide ions (7285):



The decarbalkoxylation of methyl or ethyl isohexylmalonates in DMSO in the presence of various alkali metal salts gives methyl or ethyl 6-methylheptanoates. The best results are obtained in the presence of 1 equivalent of salt and 2 equivalents of water (8861). Salts such as KCN, NaCl, or LiCl dramatically enhance the decarbalkoxylation rates of geminal diesters, β-keto esters, and α-cyanoesters by DMSO-water (9769).

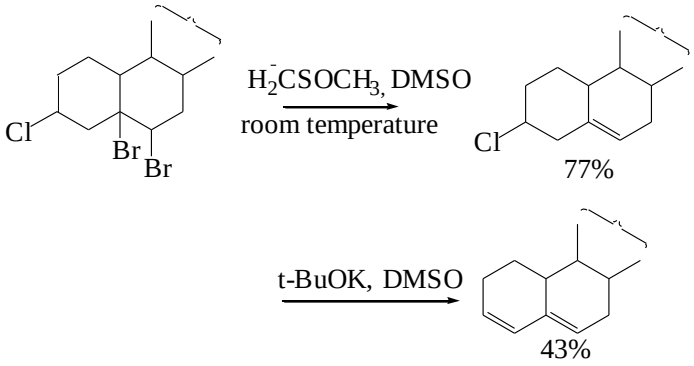
3. Dehalogenation

By a proper choice of reaction conditions or nucleophile in DMSO, one can obtain elimination of either bromine or hydrogen bromide in cases where both paths are available (454):

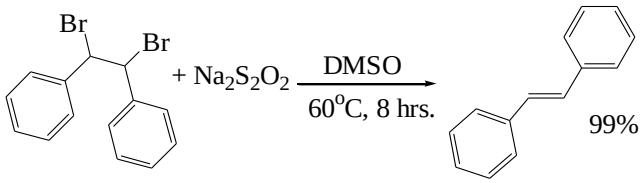


In the presence of excess dimsyl sodium in DMSO at room temperature, the debrominated intermediate results, while the use of a larger excess of dimsyl sodium and longer reaction times yield 1,2-cyclononadiene.

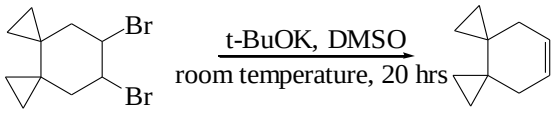
In the reaction of 3 β-chloro-5 α-bromo-6 β-bromocholestane with excess dimsyl sodium in DMSO, bromine elimination occurs. When this intermediate is treated with potassium t-butoxide in DMSO, HCl elimination occurs (455):



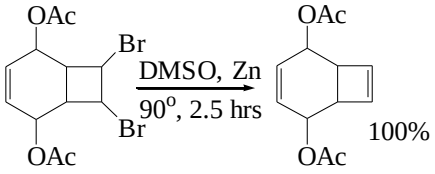
Pure olefins from their dibromides can be obtained by using sodium thiosulfate in DMSO as the debrominating agent. Thus, stilbene dibromide yields stilbene (6496):



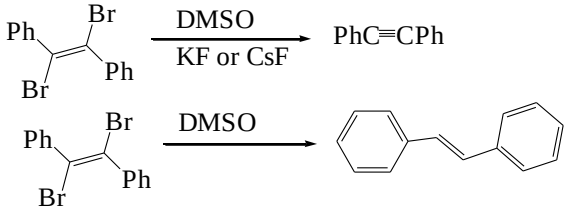
Treatment of 8,9-dibromodispiro[2.0.2.4]decane with potassium t-butoxide in DMSO gives spiro[2.0.2.4]dec-8 ene (7153):



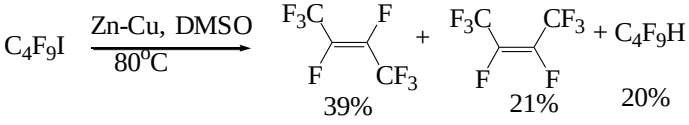
Another dibromide can be dehalogenated by heating with zinc dust in DMSO (7184):



Heating trans- α, β-dibromo derivatives of diphenylethylene and meso-stilbene with potassium fluoride and cesium fluoride in DMSO afford quantitative yields of diphenylacetylene and trans-stilbene, resp., via the intermediacy of dimsyl ion. These reactions do not occur in N-methylpyrrolidone, DMF, or sulfolane (9338):



The action of zinc-copper couples on perfluoroiodoalkanes, C_4F_9I, $C_6H_{33}I$ and $C_sF_{17}I$, has been studied in aprotic solvents, such as DMSO. A mixture of perfluoroolefins results (9928), e. g.



Some dehalogenation reactions using potassium t-butoxide as the base have been reviewed (6815).

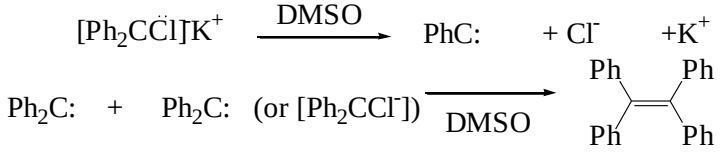
4. Dehydrohalogenation

A variety of bases have been used in the dehydrohaloge nation reaction. The most frequently used base has beer potassium t-butoxide, followed by other alkoxides. Other bases used include: sodium and potassium hydroxide the carbonate and bicarbonate ions, quaternary ammonium hydroxide, dimsyl ion, sodium cyanide and some relatively weak organic bases, such as ammonia and amines.
The effects of base strength and size upon the orientation in base-promoted β-elimination reactions have beer studied (6234)(6378)(6818)(8582)(10011).
Ionic association in base-promoted β-elimination reactions has been reviewed (8050).

a) **Potassium t-butoxide in dehydrohalogenations**

The enhanced basicity of potassium t-butoxide in DMSO has been suggested as the dominant factor which causes dehydrobrominations to occur much more readily in DMSO than in t-butanol (652).

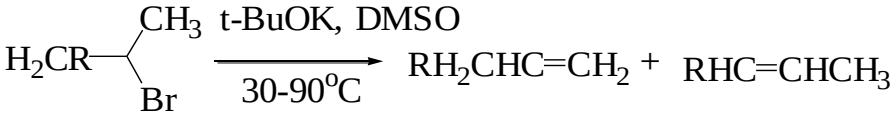
The reaction of benzhydryl chloride with potassium t-butoxide in t-butanol occurs slowly by displacement giving benzhydryl t-butyl ether, whereas the base in DMSO causes a very rapid elimination(α-elimination) giving nearly quantitative yields of tetraphenyl ethylene (696). The rapid reaction is suggested to occur by an initial formation of the carbanion which eleminates chloride ion to give a carbene intermediate, as shown below:



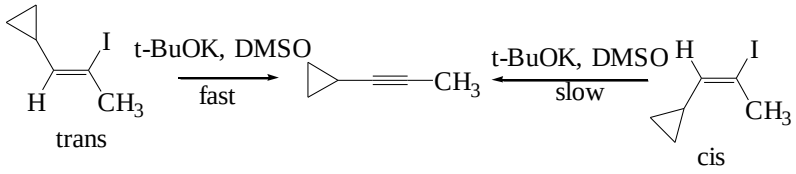
The rate of dehydrobromination of 2-arylethyl bromides with potassium t-butoxide in t-butanol-DMSO mixtures increases with increasing DMSO concentration at a much faster rate than the increase of acidity function (833).
The strongly basic reaction medium obtainable with potassium t-butoxide in DMSO in the case of aromatic bromine compounds produces aryne intermediates (434)(514) (see also Displacement reactions Alkoxide Ion, Aromatic halide displacement, p. 20).
2,7-Dichlorobicyclo[2.2.1]heptane on treatment with potassium t-butoxide in DMSO gives 7-chlorobicyclo[2.2.1] heptene (3360):



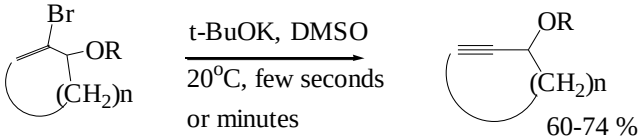
Olefinic products from reactions of a series of 2-bromoAlkanes with potassium t-butoxide are produced. The transcis 2-alkene ratio is dependent upon the alkyl group of the 2-bromoalkane (3368):



The trans-1 -iodocyclopropylpropene reacts at least ten times faster with potassium t-butoxide in DMSO than the cis isomer to yield 1 -cyclopropyl-2-methylacetylene (3503)(4176):

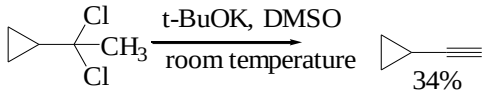


Six or seven-membered trans-cycloolefins may be transformed into the corresponding 3-alkoxycycloalkynes by reaction with potassium t-butoxide in DMSO (3707):

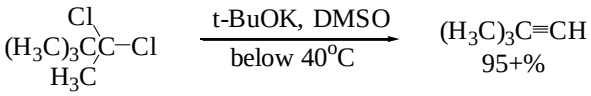


n = 5 or 6

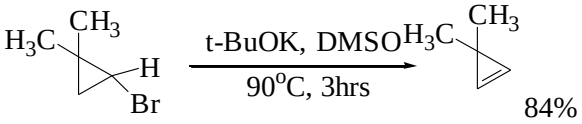
The reaction of 1,1 -dichloro-1 -cyclopropylethane with potassium t-butoxide in DMSO gives 1 -cyclopropylacetylene (5594):



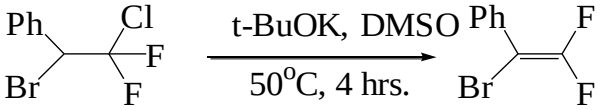
Similarly, treatment of pinacolone dichloride with potassium t-butoxide in DMSO produces tert-butylacetylene in high yield (7608):



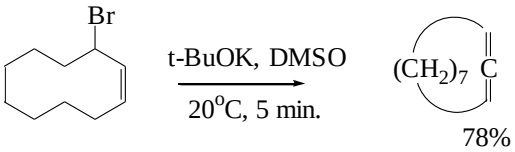
3,3-Dimethylcyclopropene is easily produced from 1 -bromo-2,2-dimethylcyclopropane (7028):



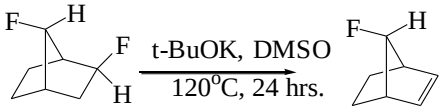
1-Bromo-2-chloro-2,2-difluoro-l-phenylethane reacts with potassium t-butoxide to give α-bromo- β, βdifluorostvrene (5980):



cis-3-Bromocyclodiene is easily dehydrobrominated to 1,2-cyclodecadiene (8960):



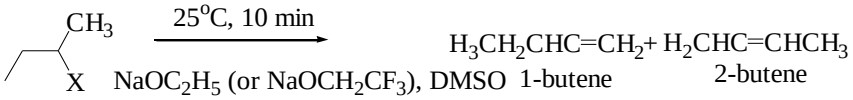
Dehydrofluorinations can also be accomplished with potassium t-butoxide in DMSO (5118):



b) **Other alkoxides in dehydrohalogenations**

Other alkoxides, such as sodium and potassium methoxides or ethoxides, have been used with good results in dehydrohalogenation reactions.

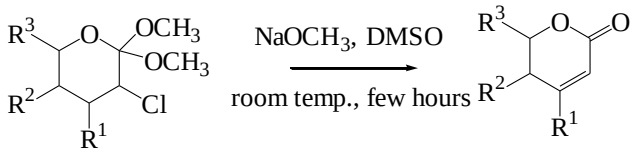
The olefinic products observed in reactions of sodium ethoxide or 2,2,2-trifluoroethoxide with 2-butyl iodide, bromide and chloride in DMSO are reported (3853):



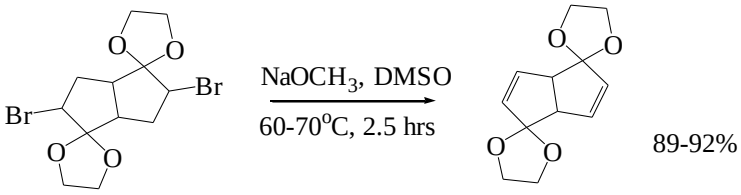
X = I, Br, Cl

In all cases in the above reaction, the change from ethoxide to 2,2,2-trifluoroethoxide results in a decrease in the percent 1 -butene (3853).

Treatment of 3-chloro-3,4-dihydro-2,2-dimethoxypyrans with an excess of sodium ethoxide in DMSO produces the corresponding α-pyrones (5834). (7737):

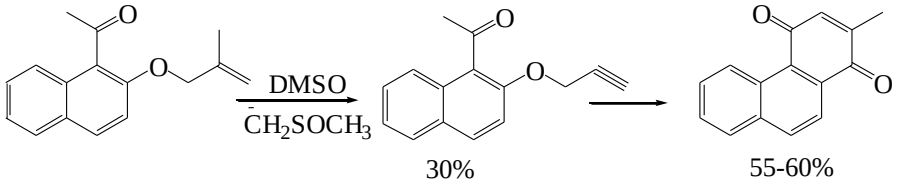


The addition of DMSO to the NaOCH -CH_3OH medium causes a significant increase in the rate of dehydrochlorination of Ph_2CHCH_2Cl (9142)(9143). Although double dehydrobromination of 2,6,6-bis-(ethylidenedioxy)-3,7-dibromobicyclo[3.3.0]octane with ethanolic potassium hydroxide requires refluxing for several days for complete reaction, the elimination may be effected in several hours with sodium methoxide in DMSO (9604):

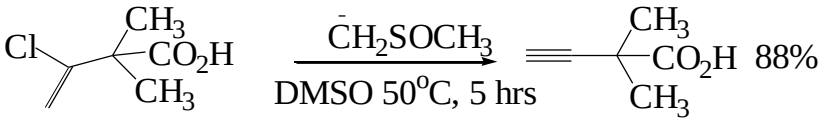


c) **Dimsyl ion in dehydrohalogenations**

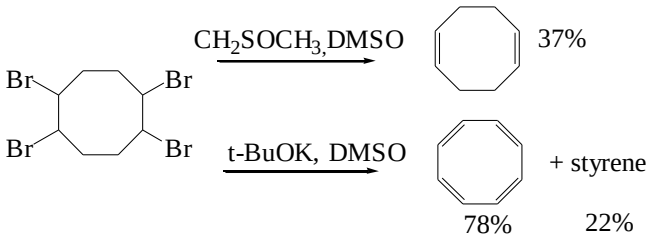
Treatment of 1-acetylnaphth-2-yl 2'-chloroallyl ether with dimsyl ion in DMSO yields 1-acetylnaphthyl-2-yl propargyl ether which cyclizes to 2-methyl- l,4-phenanthrenequinone (7552):



Reaction of 2,2-dimethyl-3-dimethyl-3-chloro-3-butenoic acid with dimsyl sodium in DMSO gives 2,2-dimethyl-3-butynoic acid (7865):

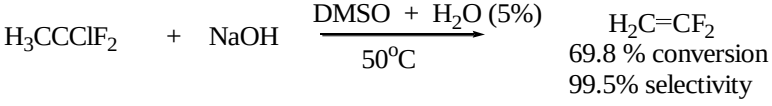


In some cases, potassium t-butoxide is a better dehydrohalogenating agent than the dimsyl ion. Thus, the dimsyl ion can act as a dehalogenating agent for vicinal dibromides (455):



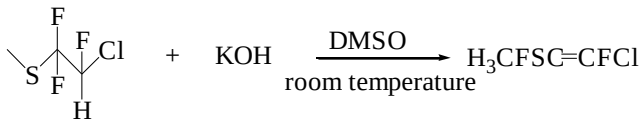
d) **Hydroxylic bases in dehydrohalogenations**

Hydroxylic bases, such as sodium hydroxide, potassium hydroxide and tetraalkylammonium hydroxide have been used for β -dehydrohalogenation reactions (8050). Tetra methylammonium hydroxide is more soluble in DMSO than either sodium hydroxide or potassium hydroxide (see Table IX). Thus, 1,1,1 -chlorodifluoroethane can be dehydrochlorinated to vinylidene fluoride in high yield in heterogeneous DMSO suspensions or aqueous DMSO suspensions or solutions in the presence of sodium hydroxide, potassium hydroxide or tetramethylammonium hydroxide (5279), e.g.:

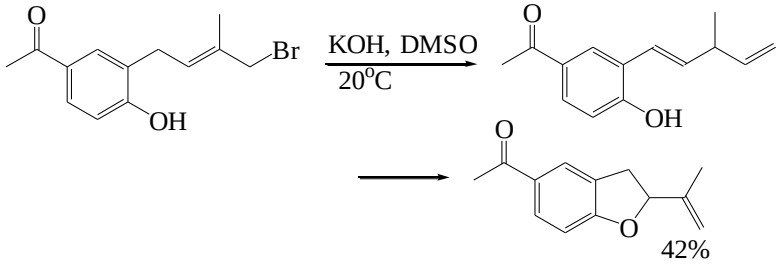


DMSO is a better reaction medium for the above reaction than some other solvents.

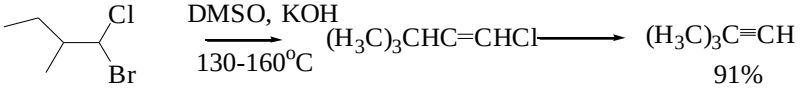
Methyl halogenated ethyl sulfides can be dehydrohalogenated with potassium hydroxide in DMSO (3142), e.g.



6-Hydroxy-2-isopropenyl-5-acetylcoumaran can be obtained from the corresponding vinyl bromide by dehydrohalogenation with potassium hydroxide and cyclization in DMSO (4892):



Relatively high yields of alkynes can be obtained from α, β-dihalides or α, α-dihalides in short reaction times at moderate temperatures in DMSO using moderately strong bases, such as potassium hydroxide, without isolation of the intermediate olefin (8238), e.g.:

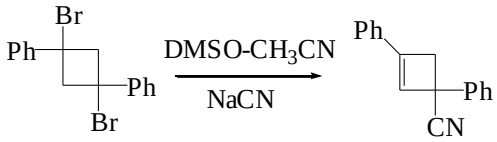


e) **Weak bases in dehydrohalogenations**

Although potassium t-butoxide in DMSO is an extremely strong and reactive base-solvent system, sometimes undesirable reactions take place after dehydrohalogenations. Thus, the freshly formed olefins tend to isomerize, and carbanions can be generated which can decompose in various ways (4180)(6163).

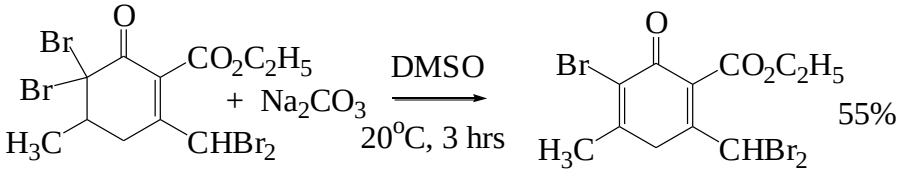
Dehydrohalogenations without olefin isomerization can sometimes be accomplished by using weaker bases, such as carbonates, cyanides, or amines.

Thus, the treatment of 1,3-dibromo-1,3-diphenylcyclobutane with sodium cyanide in DMSO produces 1,3diphenylcyclobut-2-enyl cyanide (4077):

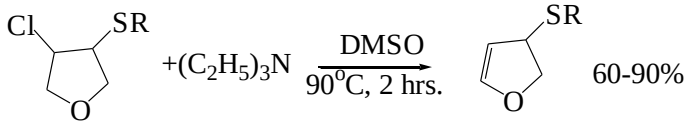


In the above reaction, both the β-elimination and displacement (substitution) reactions take place.

3,3-Dibromo-6-dibromomethyl-5-carbethoxy-2,3-dihydro-2-methyl-4H-pyran-4-one with sodium carbonate in DMSO yields 3-bromo-6-dibromomethyl-5-carbethoxy-2-methyl-4H-pyran-4-one (6215):



3-Alkylthio- or3-arylthio-4-chlorothiolane 1,1-dioxide can be dehydrohalogenated when warmed with triethyl. amine in DMSO (385):



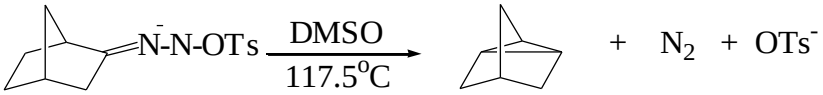
5. Nitrogen Elimination

Elemental nitrogen can be eliminated from a number of compounds by heating in DMSO in the presence or absence of bases. Usually these are compounds that contain the nitrogen-nitrogen bond, such as hydrazones, hydrazides, carbazides, azo compounds,

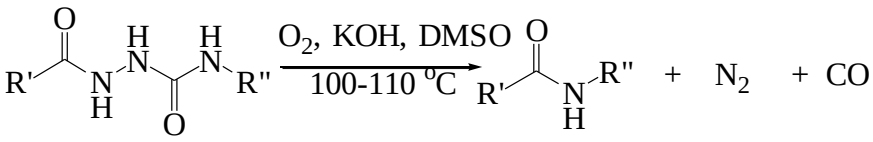
diazomethane derivatives, azides, diazonium salts and others.
Addition of hydrazones of aldehydes and ketones to a solution of potassium t-butoxide in DMSO produces an immediate evolution of nitrogen and formation of the corresponding hydracarbons in 60-90% yields. The reaction of the benzophenone hydrazone is typical (495).

$$Ph_2C{=}NNH_2 \xrightarrow[25^oC]{\text{t-BuOK, DMSO}} PH_2CH_2 + N_2$$

The above reaction, the so-called Wolff-Kishner reduction in DMSO, can be run even at room temperature.
The rate of the Wolff-Kishner reaction of benzophenone hydrazone in mixtures of butyl carbinol and DMSO in the range of 100-190°C increases as the concentration of DMSO is increased, but this effect passes through a maximum. The maxima tend to drift toward higher DMSO concentrations as the temperature is lowered (377).
The thermal decomposition of norbornan-2-one and norborn-5-en-2-one tosylhydrazone sodium salts has been studied over the temperature range 100-150°C in DMSO and two other solvents. First order kinetics have been observed in all cases (8955):



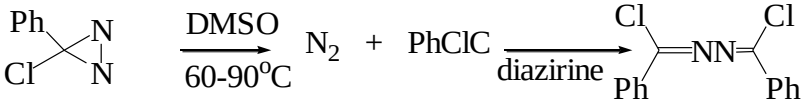
Treatment of 1-acylsemicarbazides in DMSO with air or oxygen gives rise to carboxamides in good yields (3721):



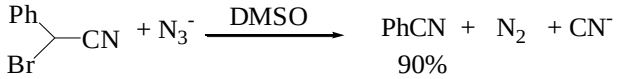
Thermal decomposition of two azobisamidines and their conjugate acids has been studied in DMSO (4748).
Rate coefficients are reported for the reaction of diazodiphenylmethane with benzoic acid and its orthosubstituted derivatives in DMSO and other solvents (2765):

$$Ph_2CN_2 + RCO_2H \xrightarrow[30^oC]{\text{DMSO}} RCO_2CHPh_2 + N_2$$

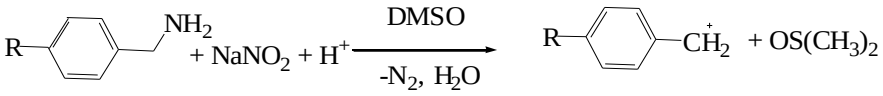
Thermal decomposition of several diazirines has also been investigated in DMSO (4906)(5635), e.g.

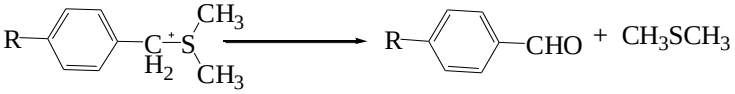


Sodium azide in DMSO reacts with α-bromophenylacetonitrile to yield benzonitrile (10077):

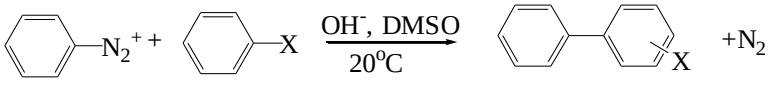


Diazonium salts can be prepared in DMSO by diazotizing primary amines with sodium nitrite. In the case of benzylamine, benzaldehydes can be prepared in good yields (167), e.g.:





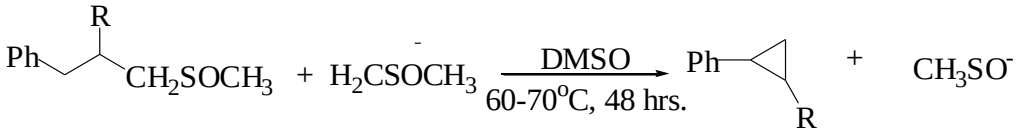
Benzenediazonium tetrafluoroborate in DMSO decomposes instantaneously with evolution of nitrogen upon addition of a DMSO solution of choline or tetramethylammonium hydroxide (5124):



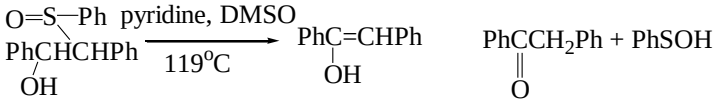
When p-nitrobenzenediazonium tetrafluoroborate is decomposed in the presence of DMSO-benzene or DMSOnitrobenzene systems, the respective biphenyl derivatives are obtained in good yields (5642).
The dediazotization of aromatic diazonium ions has been reviewed in various solvents, including DMSO (9423).

6. Sulfenate Elimination

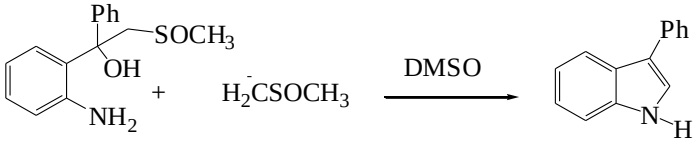
The t-butoxide ion or dimsyl ion in DMSO has been used to eliminate sulfenates from sulfoxides to produce olefins in moderate to high yields (501)(203)(672). When a number of 3-phenyl-2-alkylpropyl sulfoxides is allowed to react in DMSO with a large excess of dimsyl sodium, cyclopropanes and olefins are formed (396)(2842):



When isomeric 2-phenylsulfinyl-1,2-diphenyl-l-ethanols are pyrolyzed in DMSO in the presence of trace quantities of pyridine, deoxybenzoin is formed (4776):



3-Phenylindole is obtained from β-hydroxysulfoxide on treatment of the latter with dimsyl ion in DMSO (5300):



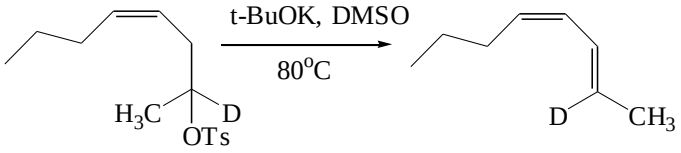
7. Sulfonate Elimination

Various bases have been used in the reaction of sulfonate esters of primary and secondary alcohols to give alkenes. Some of these bases are potassium t-butoxide, sodium methoxide, potassium ethoxide, phenoxides, and others. In a few cases, elimination reactions involving sulfonate esters have been achieved without the presence of a base by the action of heat alone.

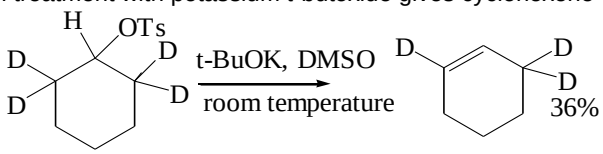
a) **Potassium t-butoxide in sulfonate elimination**

Most β-eliminations involving sulfonate esters seem to have been investigated with potassium t-butoxide as the base. Sulfonate esters of cyclic and secondary acyclic alcohols react rapidly with potassium t-butoxide in DMSO at 20-25°C to give about 80% yields of alkenes and no appreciable quantities of ethers. Esters of normal primary alcohols and of cyclohexylcarbinol give only 20-25% alkenes and 60-70% ethers, as the result of displacement reactions in the latter case (491).
Mesylate and tosylate derivatives of cholesterol, all easily prepared, undergo facile reactions in DMSO at room temperature to afford excellent yields of dienic materials (965).

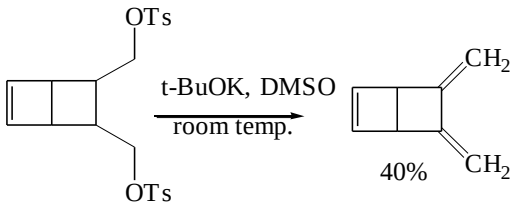
Treatment of the tosylate of (+)-(S)-3-methyl-7-deutero-octen-4-ol-7 with potassium t-butoxide in DMSO yields (+)-(S)-cis,trans-3-methyl-7-deuterooctadiene-4,6 (3482):



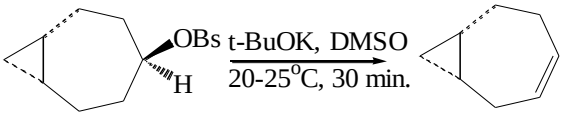
The tosylate of cyclohexanol-2,2,6,6-d_4 on treatment with potassium t-butoxide gives cyclohexene-1,3,3-d_3 (3584) :



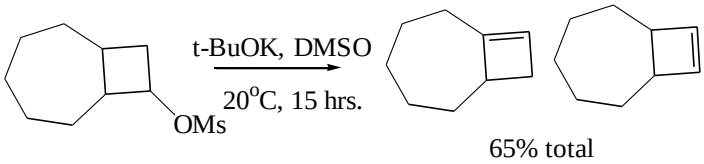
5,6 Dimethylenebicyclo[2.2.0]hexene-2, the Dewar o-xylylene, can be obtained by reacting the corresponding ditosylate with potassium t-butoxide in DMSO (3827):



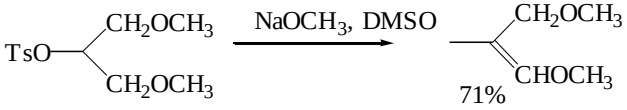
When 4- hydroxy-trans-bicyclo[5.1.0] octane p-bromobenzene-sulfonate is treated with potassium t-butoxide in DMSO, it is rapidly converted to trans-bicvclo[5.1.0]oct-3-ene (4039):



When 2-butyl and 2-pentyl halides or tosylates are treated with tetraethylammonium fluoride in acetonitrile, an olefin forming elimination takes place and an overwhelming Saytzeff orientation is observed. These results are compared with results of the elimination in other base-solvent systems, including potassium t-butoxide in DMSO (4524).
The reaction of trans-2-methylcyclooctyl tosylate with potassium t-butoxide in DMSO for 30 min at 25°C yields cis-3-methylcyclooctene, 93%, and cis-1 -methylcyclooctene, 4%. With t-butenol as the solvent, the ratio of the isomers is 2:1.
An approximately equimolar mixture of bicyclo[5.2.0]non-1 (9)-ene and bicyclo[5.2.0]non-8-ene is obtained by treatment of 8-methanesulfonyloxybicyclo[5.2.0]nonane with potassium 1-butoxide in DMSO (9727).



b) **Sodium methoxide in sulfonate elimination**
Benzenesulfonates of typical primary and secondary alcohols react rapidly at room temperature with sodium methoxide in DMSO to give high yields of alkenes and/or alkyl methyl ethers. Except for cyclohexyl benzenesulfonate, the ether-alkene ratio is higher in reactions with sodium methoxide than with potassium t-butoxide. This indicates that the displacement reactions are favored over elimination reactions with sodium methoxide in most cases (580).
1,3 -Dimethoxypropene can be obtained from p-toluenesulfonate of 1,3-dimethoxy-2-propanol by means of sodium methoxide in DMSO in good yield with cis/trans ratio of 2.1:1. Evidently little of the displacement reaction goes on (3875):

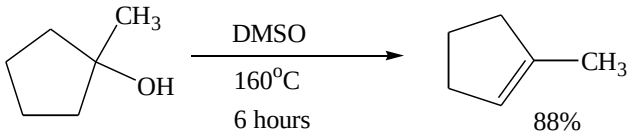


A double bond in a cyclic system, a precursor of dl-juvabione, is introduced by treatment of a tosylate with sodium methoxide in refluxing methanol containing 10% DMSO (6947).

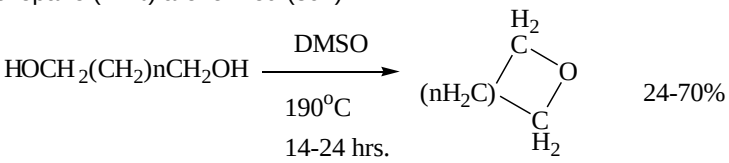
c) **Other bases in sulfonate elimination**
When cyclohexyl tosylate is reacted with potassium t-butylmercaptide in DMSO, cyclohexene is the major product. However potassium t-butoxide reacts much more ranidly than the mercaptide (496).
The effect of base strength upon orientation in base prompted elimination reactions has been studied. 2-Butyl p-toluenesulfonate is reacted with the following bases in DMSO: potassium t-butoxide, potassium ethoxide, potassium phenoxide, potassium 4-methoxyphenoxide, potassium 4-nitrophenoxide and potassium 2nitrophenoxide. The results are completely consistent with a correlation between orientation and base strength (882).
The trans:cis olefin ratios have been determined for the elimination reactions of 1-benzylethyl tosylate, $PhCH_2CH(OTs)CH_3$, in different base-solvent systems. The basicity of the nucleophile does not appear to significantly affect the trans:cis ratio (8372).

d) **Sulfonate elimination without a base**
DMSO has been found to be an excellent non-reacting solvent for the decomposition of (-)-menthyl, β-cholestanyl, cyclohexyl and 2-octyl aryl-sulfonates to the corresponding olefins. The sulfonates are heated at 89-91°C for 6 hours without a base (408).
The elimination reactions of some secondary acyclic and medium sized ring cyclic alcohol tosylates carried out in DMSO at 50°C and 90-95°C show that olefins are formed, especially with secondary alcohol tosylates.

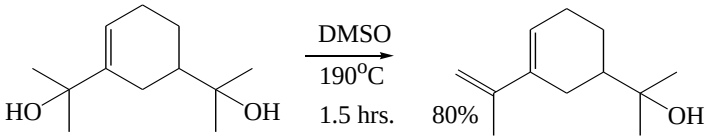
8. Water Elimination-dehydration
Many alcohols can be dehydrated in DMSO to olefins. Certain diols when heated in DMSO lead to cyclic ethers. A group of tertiary alcohols, such as 2-alkylcycloalkanes, at 160-190°C for several hours in DMSO give endocyclic olefins, 1 -alkylcycloalkenes, as the major products. Thus, 1 -methylcyclopentanol gives only 1 -methylcyclopentene (394):



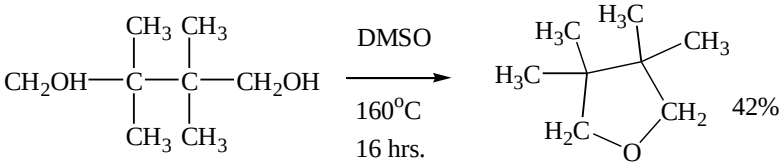
When certain diols are heated in DMSO, cyclic ethers result instead of the expected dienes (395). When 1,4-butanediol, 1,5-pentanediol and 1,6-hexanediol are heated, using 2 moles of alcohol per mole of DMSO, the corresponding heterocycles, tetrahydrofuran (70%), tetrahydropyran (47%), and oxepane (24%) are formed (394):



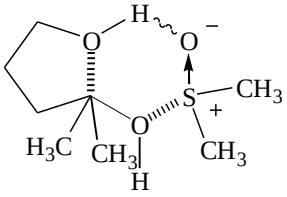
2,4-Di(2-hydroxy-2-propyl)cyclohexene can be selectively dehydrated to 2-(2-propenyl)-4-(2-hydroxy-2-propyl)1-cyclohexene in DMSO (4775):



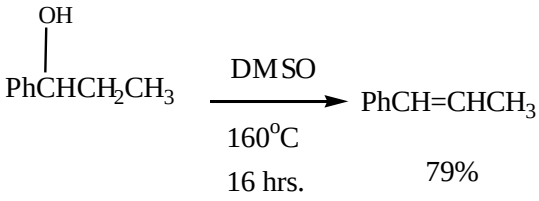
Heating of 2,2,3,3-tetramethylbutane-1,4-diol in a sublimation apparatus in DMSO gives the tetrahydrofuran (4934) :



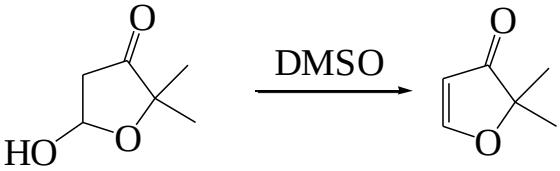
In the dehydration of 1,4-diols, a cyclic transition state with DMSO has been postulated (395)(6098):



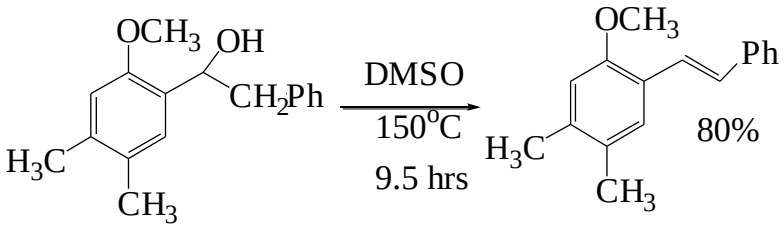
When sec- or tert-benzylic alcohols or tert-aliphatic alcohols are heated in DMSO at 160-185° C for 9-16 hours, dehydration produces olefins in 70-85% yields (405), e.g.



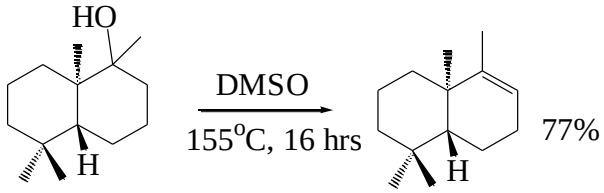
2,2-Dimethyl-3(2H)-furanone can be obtained by dehydrating the corresponding 5-hydroxy compound on heating in DMSO (4755):



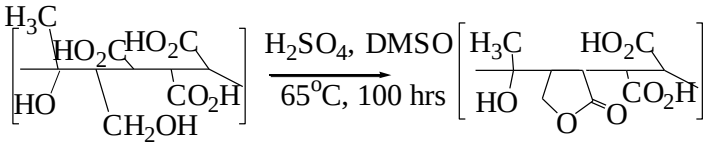
2-Methoxy-4,5-dimethylstilbene is obtained by heating 2-methoxy-4,5-dimethylphenylbenzylcarbinol in DMSO (9605):



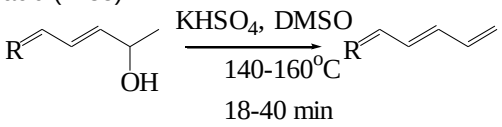
One of the key features of the stereoselective and regioselective total synthesis of two naturally occurring fungitoxic hydroquinones (±)-zonarol and (±)-isozonarol is the dehydration of a tertiary alcohol to an alkene without rearrangement (9780):



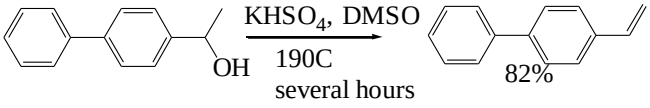
In some cases, the dehydration is achieved in DMSO in the presence of an inorganic acid. Thus, the lactonization of a hydrolyzed terpolymer can be carried out by reacting the polymer in the presence of a very small quantity of concentrated sulfuric acid in DMSO (2265):



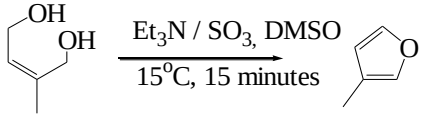
Potassium hydrogen sulfate in DMSO is an effective medium for elimination of water from some intermediate hydroxy derivatives in the preparation of various C_{19} analogs of retinoic acid (4235):



Dehydration of 4-(1 -hydroxyethyl) biphenyl in DMSO in e presence of a small amount of potassium hydrogen sulfate and hydroquinone gives p-phenyl-styrene (7867):



Dehydration of a diol can also be accomplished by using the triethylamine-sulfur trioxide complex in DMSO (7080):

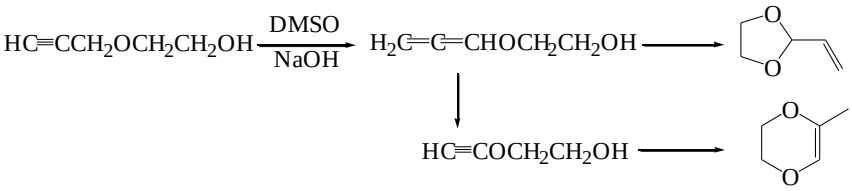


ISOMERIZATION REACTIONS

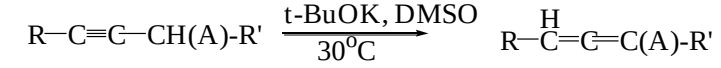
These are base-catalyzed reactions that convert olefins and other unsaturated compounds into molecules with different atomic arrangement. Included are also racemization reactions: the conversion of half a given quantity of an optically active compound into one enantiomer.

1. Acetylene Isomerization

The enhanced rate of base catalyzed isomerization in DMSO can be used to control the direction of a cyclization of acetylenes (600). When propargyloxyethanol is cyclized in DMSO in the presence of sodium hydroxide, 2-vinyl -1,3-dioxolane and 2-methyl-l,4-dioxene are the major products (101):

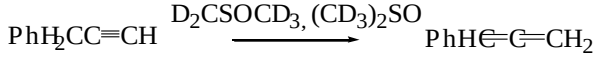


Treatment of an acetylenic compound with potassium tert-butoxide in DMSO gives the corresponding allenic compounds (2239):

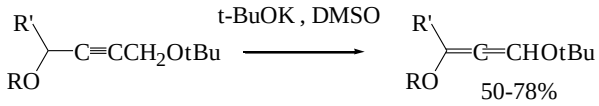


R = Alkyl or phenyl, R'= H, alkyl or phenyl, A=Alkoxy, phenoxy, alkylthio, phenylthio, dialkyulamino, etc.

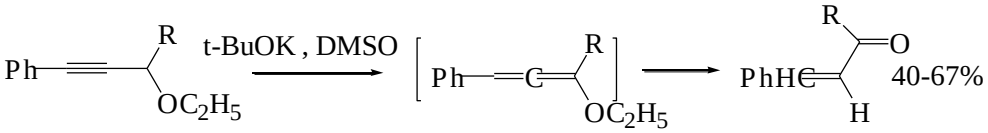
3-Phenylpropyne undergoes in DMSO a dimsyl ion-catalyzed isomerization with very little H-D exchange with the solvent (2987):



4-Alkoxy-4-alkyl-1 -t-butoxy-2- butyne, when heated with catalytic amounts of potassium t-butoxide in DMSO, is isomerized to allenic diethers (4257):

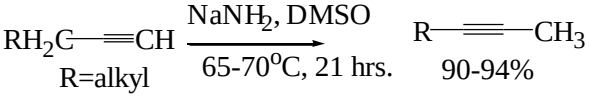


Similarly, 3-alkoxy-l -phenylpropynes are isomerized in DMSO under the catalytic influence of potassium tert-butoxide to give 3-alkoxy-1 -phenylallenes (4258):



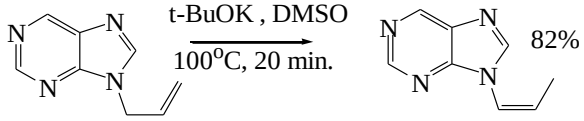
The rates of base-catalyzed isomerization of a series of 1,3,3-triphenyl- prop-1-yne and [3-^{2}H]-1,3,3-triphenylprop1-yne, have been measured in aqueous DMSO containing tetramethylammonium hydroxide and give linear correlations with the acidity function for the medium (5864).

Pure 2-alkynes are obtained upon heating 1-alkynes with sodamide in DMSO (6510):

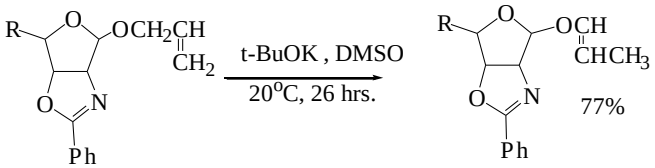


2. Allyl Group Isomerization

The isomerization of allyl ethers to propenyl ethers occurs 1000 times faster in DMSO than in dimethoxyethane and 10,000 times faster than in dimethoxyethane-t-butanol mixtures (481). This facile isomerization of allyl to easily hydrolyzed propenyl groups.enables the use of allyl groups as blocking agents (10043). For example, 9-allyladenine is isomerized with potassium t-butoxide in DMSO to the propenyl compound which is then easily hydrolyzed to regenerate the amino group (941):



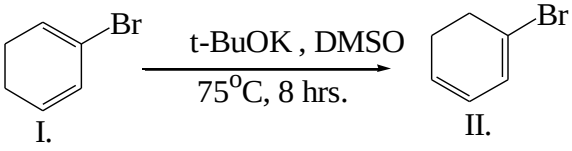
The allyl group of a glycoside can be isomerized to the prop-1 -enyl group by the action of potassium t-butoxide in DMSO, without affecting phenyloxazine group (8951):



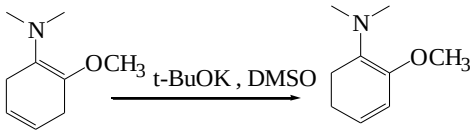
3. Diene, Triene Isomerization

Unconjugated dienes can be converted to the conjugated isomers by treating them with a strong base in DMSO. Thus, the treatment of 2-bromo-1,3-cyclohexadiene (I) with potassium t-butoxide in DMSO yields a mixture of 79% 1-bromo-l,3-cyclohexadiene (II) and 21 % of I.

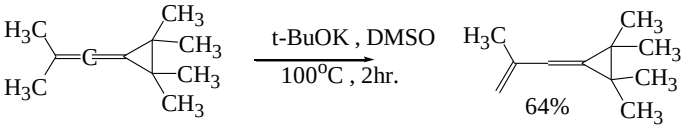
The difference in free energy between I and II appears to be the result of greater conjugation of bromine with cyclohexadiene system in 11 (596):



Several unconjugated dienamines on treatment with potassium t-butoxide in DMSO produce the conjugated dienamine by a pivoting of the double bond around the carbon carrying the nitrogen atom (4018):

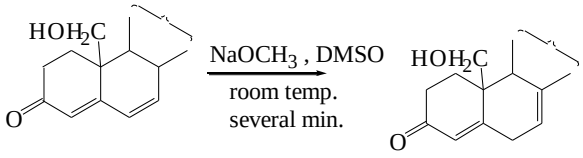


2-Methyl-1 -(tetramethylcyclopropylidene)propene is isomerized with potassium t-butoxide in DMSO to give 2methyl-3-(tetramethylcyclopropylidene)propane (4126):



Unsaturated fatty acid esters containing conjugated double bonds are manufactured by isomerization from the esters with unconjugated double bonds by heating them with alkali metal alkoxides in DMSO (8906).

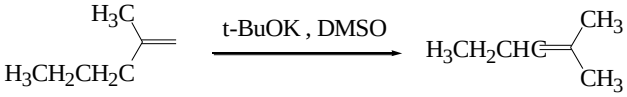
Steroids have been isomerized with a base in DMSO (3272)(2323). Thus, 19-hydroxy- $\Delta^{4,6}$-3-keto steroids are deconjugated to $\Delta^{4,7}$ -3 ketones by treatment with sodium methoxide in DMSO (4311):



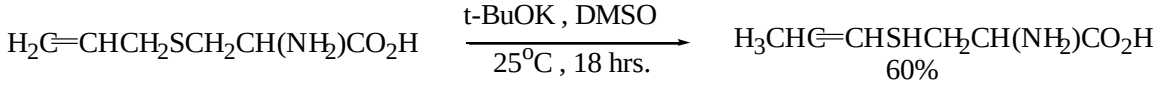
Sodium methoxide catalyzed deconjugation of cholesta-1,4-6-trien-3-one in DMSO to cholesta-1,5,7-trien-3-one is a key step in a reported route to 1- α -hydroxy-vitamin D_3 (10048).
1,3,6-Octatrienes and 1,3,7-octatrienes are isomerized to 2,4,6-octatriene in 70-85% yields with hydroxide bases in DMSO (3379).

4. Olefin Isomerization

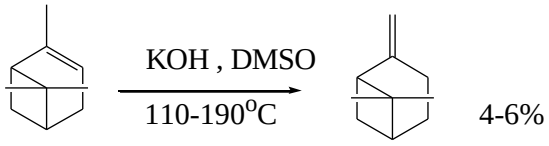
The isomerizations of simple alkenes (e.g. pentene-1,hexene-1) with potassium t-butoxide do not occur in tert-butanol, THF or 1,2-dimethoxyethane. However, in DMSO with potassium tert-butoxide as the base, 1-olefins can be converted to 2-olefins, e.g. 2-methylpentene to 2-methylpentene-2 (579):



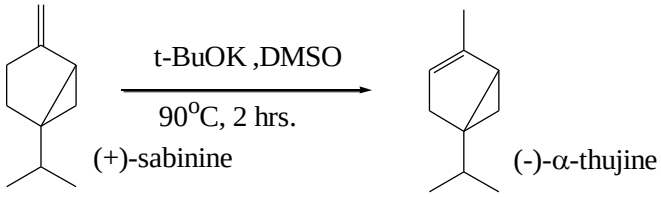
S-(2-propenyl)-L-cysteine is isomerized to cis-S-(1 -propenyl)-L-cysteine by reaction in potassium tert-butoxide and DMSO (1001):



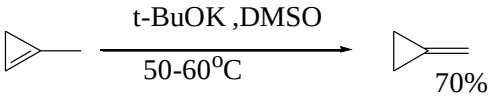
α-Pinene can be converted to β -pinene by using potassium hydroxide and DMSO (480)(7229):



Similarly, (+)-sabinine isomerizes to an equilibrium mixture of 91 % (-)- α-thujene and 9% (+)-sabinine under the influence of potassium t-butoxide in DMSO (2998):



Isomerization of a mixture consisting of 17.4% 1 -methylcyclopropene and 81.3% methylenecyclopropane with potassium t-butoxide and t-butanol in DMSO produces a 98% pure methylenecyclopropane (4262):



5. Racemization

In the racemization of saturated compounds by exchange of hydrogen at an asymmetric carbon, the rate of racemization correlates well with the acidity function of the reaction system containing DMSO (944). Similarly, the base-catalyzed rate of hydrogen-deuterium exchange correlates well with the racemization rate (1501). In solvents of high dissociating power which are not proton donors, e.g. DMSO, the carbanion (obtained with potassium t-butoxide) is long enough lived to become symmetrically solvated, and electrophilic substitution gives a racemic product (1161).

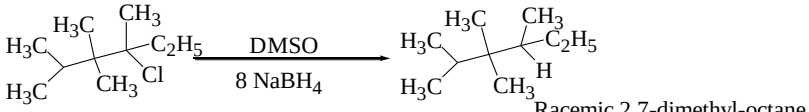
A variety of active functional groups can be attached to the saturated asymmetric carbon atom.

a) **Alcohols**

When optically pure tertiary alcohols with an asymmetric carbon atom are treated with a strong base in DMSO, the predominant steric course is racemization (1162)(2589).

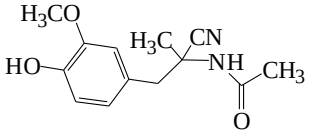
b) **Alkyl halides**

The reduction of optically active tertiary alkyl halides with sodium borohydride in DMSO proceeds with racemization presumably via an elimination mechanism (3519):



c) **Amides, amino acids**

D- α -Acetamide- α -vanillylpropionitrile is racemized using sodium cyanide as the base and DMSO as the solvent to give 96-97% pure DL- α -acetamido- α -vanillylpropionitrile (7772)(7984):



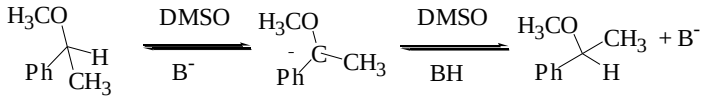
Optically active N-acylamino acids are racemized nearly quantitatively by heating with DMSO (8418).

d) **Esters**

The racemization and solvolysis of (+)-methyl 1 -cyano-2, 2-diphenyl-cyclopropane carboxylate has been studied in DMSO and six other solvents. In DMSO, racemization is the dominant reaction (6287).

e) **Ethers**

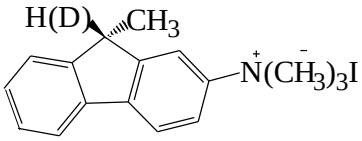
Potassium t-butylmercaptide in DMSO is a weaker kinetic base system than potassium t-butoxide in DMSO or than dimsyl sodium in DMSO in the racemization of optically pure (-)-1-methoxyphenylethane (496):



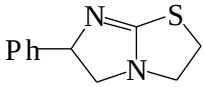
Rate constants for racemization of (-)-4-biphenyl-methoxyphenylmethane in methanol-0-d-DMSO-d_6 catalyzed by potassium methoxide have been measured (2007).

f) **Hydrocarbons**

The results of H-D exchange and racemization of (-)-9-deuterio-9-methyl-2-trimethylammonium fluorene iodide in t-butanol-DMSO catalyzed by tripropylamine are reported. Exchange (69%) and racemization (69%) take place (5339):



D-tetramisole or its 1 -tetramisole enantiomer is racemized in DMSO solution in the presence of a catalytically effective amount of potassium hydroxide (10315):

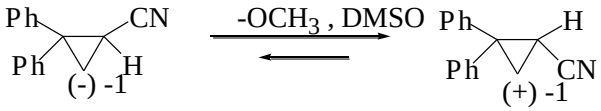


g) **Nitriles**

Racemization of 2-methyl-3-phenylpropionitrile in DMSO can proceed 1,000,000 times faster than in tert-butanol in the presence of the same base (434)(944).

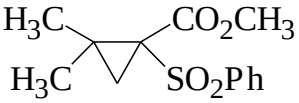
The mechanism of base-catalyzed racemization of α-acetamidonitriles bearing no enolizable α-hydrogen has been studied in DMSO and found to proceed via elimination and readdition of the elements of HCN (2013).

The base catalyzed racemization of 2,2-diphenylcyclopropylnitrile (1) has been studied in solvents containing various amounts of DMSO. With sodium methoxide as the base and nitrile 1 as a substrate, the rate for racernization in 1.5 mole % methanol-98.5 mol % DMSO is 3.6 x 10^8 times that observed in methanol (7282):



h) **Sulfones**

When the 2,2-dimethyl-1-phenylsulfonylcyclopropane is heated in DMSO for 6 hours at 175° C the material is 88% racemized (2035):



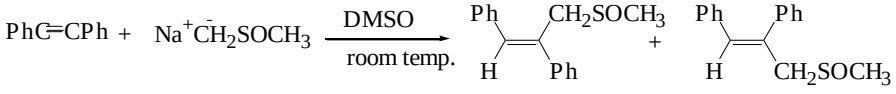
C. OTHER REACTIONS IN DMSO ADDITION REACTIONS

These are additions of nucleophilic compounds to carbon-carbon double bonds, carbon-carbon triple bonds, carbon-nitrogen triple bonds and others.

In a number of cases the use of DMSO improves the rate of addition of nucleophiles to olefins, such as acrylonitrile. The rate of addition of the glycine anion to acrylonitrile in an aqueous buffer is increased 200-fold by adding an equal amount of DMSO to the buffer (1233). Similarly, the cyanoethylation of methanol using potassium methoxide catalysis in methanol-DMSO occurs at a rate greater than in several other aprotic solvents. The order of effectiveness of the solvents for this reaction is also the order of their hydrogen bonding strength (1591).

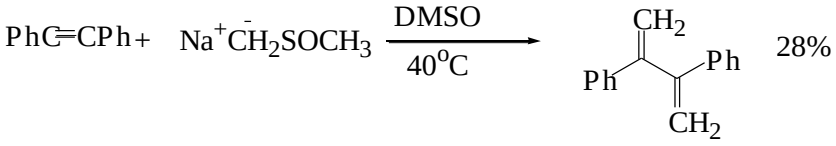
a) **Additions to acetylenes (carbon-carbon triple bonds)**

The DMSO anion (dimsyl sodium) adds to diphenyl acetylene to give a 95% yield of a cis-trans mixture of the expected unsaturated sulfoxide (203):

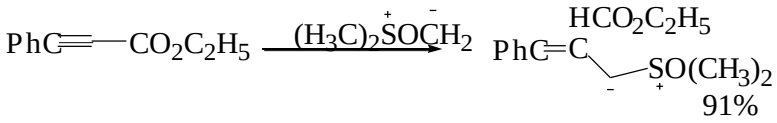


95%

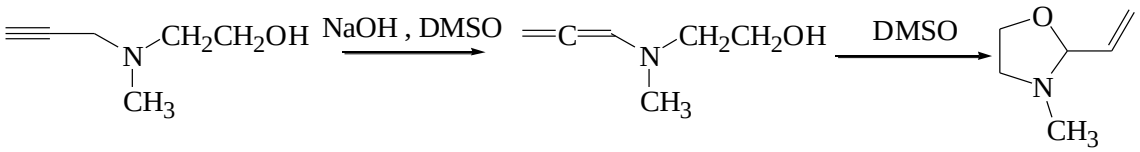
When the addition is conducted at 40°C, the reaction consumes 2 moles of the DMSO anion with elimination of two methane sulfenate groups to give 2,3-diphenyl-1,3-butadiene (203):



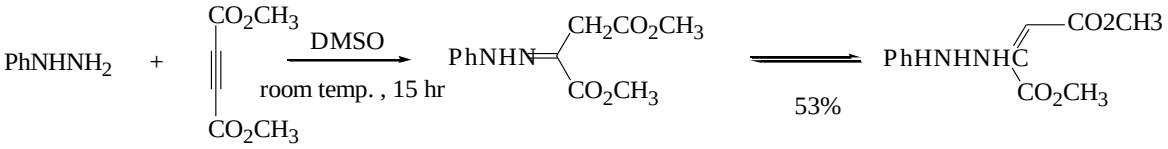
Ethyl phenylpropiolate reacts readily with dimethyloxosulfonium methylide to give 91 % of a stable ylide (217):



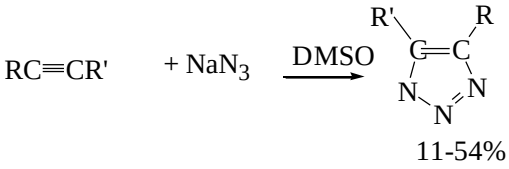
The addition of alkoxides to triple bonds in DMSO has been examined in structures where the intramolecular addition can occur(600)(101)(429). The rapid rearrangement of the triple bond to the allenic compound seems to precede the cyclization (600):



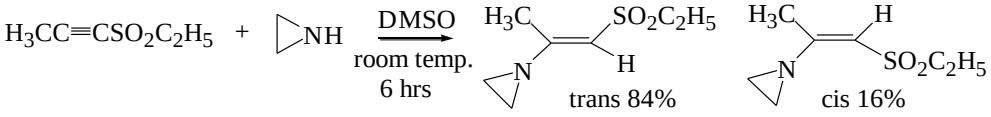
Dinitrophenylhydrazine reacts with dimethylacetylenedicarboxylate in DMSO-methanol to yield a 1:1 adduct which exists as an imine-emamine tautomer (3387):



The reaction of alkynes with sodium azide in DMSO, followed by hydrolysis, affords 1,2,3-triazoles (3456):

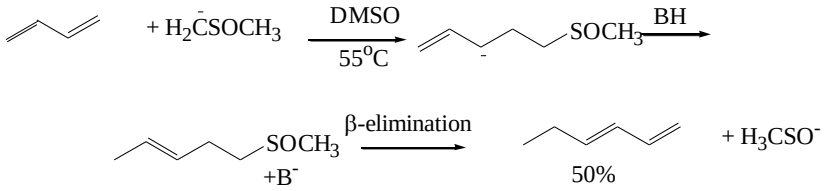


DMSO has been one of the solvents studied in the reaction of 1 -propyl-sulfones and sulfoxides with ethylenimine. The greatest amount of trans product (cis addition) is formed in DMSO. This may be explained on the basis that DMSO can stabilize the zwitterionic intermediate best (3660):

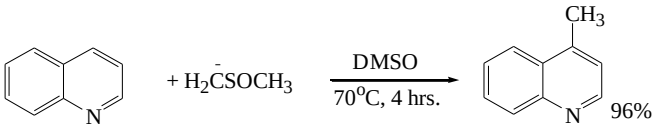


b) **Additions to olefins (carbon-carbon double bonds)**

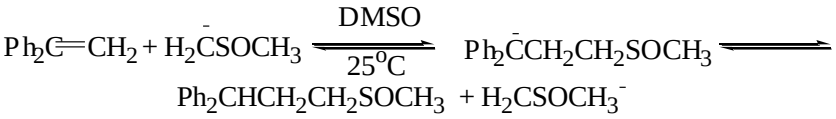
Aliphatic conjugated dienes add the dimsyl ion in DMSO to give sulfoxides. These unsaturated sulfoxides isomerize spontaneously and eliminate methanesulfenate upon continued warming in the strongly basic medium to produce the overall effect of methylation (411):



Although the yields of the aliphatic dienes are 50% or less, the yields using polynuclear aromatic compounds or some heterocyclic compounds, such as quinoline, are high (202):



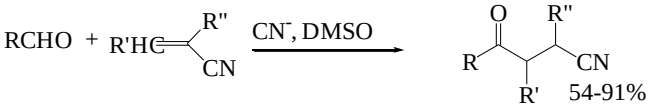
The dimsyl ion also adds to aryl conjugated olefins, such as styrene or 1,1-diphenylethylene, in DMSO to give the corresponding methyl 3-arylpropyl sulfoxides in almost quantitative yield (423):



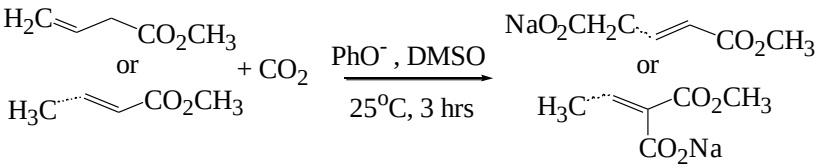
One stage sequential double methylation of the C=C bonds in stilbene, 2-methylstilbene and 4,4'-dimethoxystilbene with the dimsyl ion in DMSO leads to methyl diarylbutyl sulfoxides (7234):



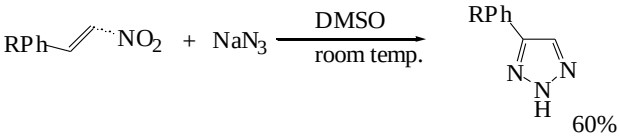
Kinetic rate measurements of the alkoxide catalyzed addition of methanol and ethanol to methyl esters of acrylic and methacrylic acid have been investigated in the mixed solvent alcohol-DMSO (3249).
1-Alkenecarbonitriles react with aromatic or heteroaromatic aldehydes in DMSO under the catalytic influence of cyanide ions to give Y-oxonitriles (6172)(7582):



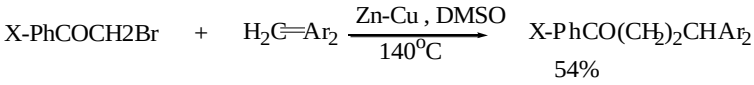
Alkyl esters of α , β - and β , Y -unsaturated carboxylic acids can be carboxylated at the α- or β - position using sodium phenoxide in DMSO (3506):



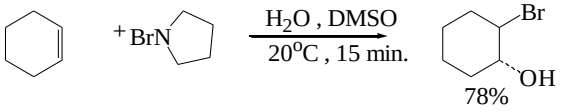
Sodium azide adds to α , β -unsaturated nitro compounds in DMSO to form 1,2,3-triazoles (4452):



Phenacyl bromide and its derivatives in the presence of zinc or a zinc-copper couple undergo anti-Markownikow additions to terminal olefins (6627):



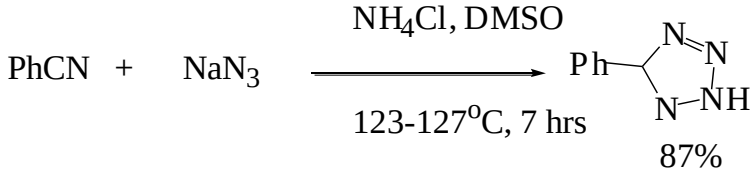
Phenacyl bromide in DMSO in the presence of the zinc-copper couple also adds to conjugated enynes and dienes (7536).
When olefins are treated with N-bromosuccinimide in DMSO containing a small quantity of water, the corresponding bromohydrins can be obtained after a short reaction time in high yields (705)(4026)(4817):



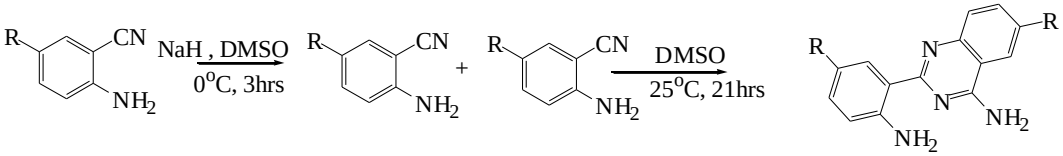
A variety of alkylaromatic compounds undergo nucleophilic addition to conjugated olefins (3384). Particularly when the reaction is performed in dipolar aprotic solvents, using potassium t-butoxide as a catalyst. The effectiveness of the solvents decreases in the following order. DMSO, HMPA, N-methyl-2-pyrrolidone, DMF, sulfolane, tetramethylurea (4339).

c) **Additions to nitriles (carbon-nitrogen triple bond)**

The reaction of sodium azide with nitriles, such as benzonitrile, occurs readily in DMSO to give 5-phenyl tetrazole (550):

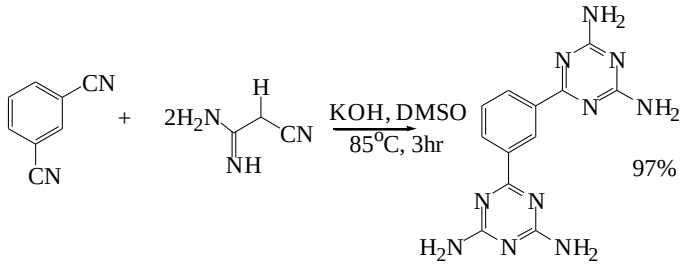


The reaction of anthranilonitrile with sodium hydride in DMSO yields 4-amino-2-(2-aminophenyl)quinazoline (8576):



R= H orBr

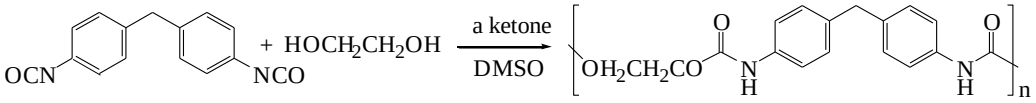
Phthalodinitriles react with dicyandiamide in DMSO in the presence of basic compounds, such as potassium hydroxide, to produce phthalo-bis-guanamines (8008):



d) **Additions to isocyanates**

The reactions of organic isocyanates and diisocyanates are catalyzed by DMSO, and they run at good rates in this solvent (392)(312)(1360). Thus, diisocyanates react in DMSO with active hydrogen compounds such as dihydrazides (450), polyols (449), or even with the hydroxyl groups of carbohydrates (cellulose) (443). In the last instance, DMSO is also used as an effective swelling agent for cellulosic rayon fibers.

Diisocyanates, such as bis(4-isocyanatophenyl)methane or 2,2-bis(4-isocyanatophenyl)propane, react with ethylene glycol in DMSO. Polyurethane filaments can then be spun from the reaction mixture (1880):



Dry DMSO is inert to alkyl or aryl isocyanates but it does react with isocyanates having electron withdrawing groups such as acyl (714) or sulfonyl (308)(391).

A number of synthetic polymers containing sugar residues, such as D-cellobiose (10116)(10439) and α , α -trehalose (10123), have been prepared by direct addition polymerization of the carbohydrate with diisocyanates, such as 4,4'-methylenedi(phenylisocyanate) in DMSO.

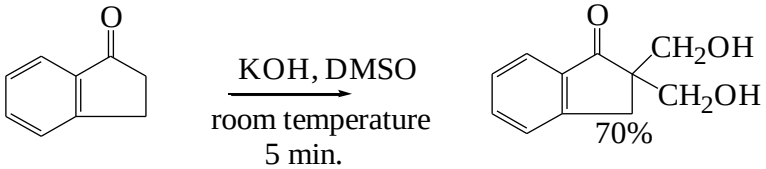
CONDENSATION REACTIONS

These are mostly specific reactions (e.g. aldol condensation, Mannich reaction) in which two or more molecules combine, usually with the separation of water or some other simple molecule.

Most of the ordinary reactions of carbonyl compounds can be accomplished in DMSO. Good results are often obtained either because of the greater solubility of generally insoluble reactants or because of enhanced reactivity of nucleophiles.

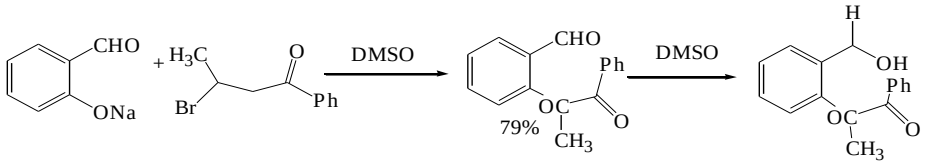
a) **Aldol-type condensations**

Alkyl aryl ketones react easily and at a high rate with paraformaldehyde in DMSO in the presence of base to yield hydroxymethyl compounds. The high reaction rates may be attributed to the high reactivity of the anionic catalyst in the DMSO medium (1099). Thus, 1-indanone and formaldehyde react rapidly in DMSO to yield 2,2-bis(hydroxymethyl)-1-indanone:

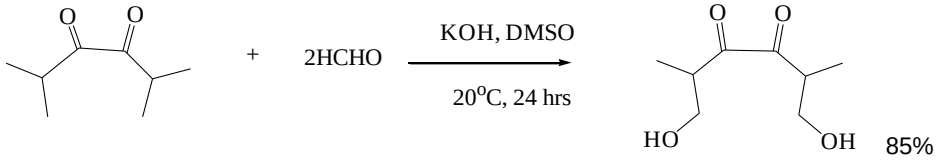


Fluorene and o- and p-nitrotoluene react similarly with paraformaldehyde in an aldol like addition in DMSO under the influence of a strong base to give hydroxymethyl compounds (1100).

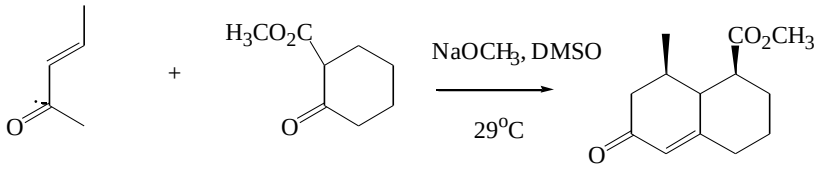
Racemic 2-(o-formylphenoxy)propiophenone can be prepared in 79% yield from equivalent amounts of a sodium salt of salicylaldehyde and 2-bromopropiophenone in DMSO. When the reaction product is kept in DMSO in the presence of quinine, two optically active diastereomeric ketols result (5613):



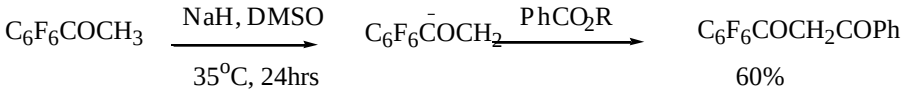
The reaction of 1-hydroxy-2,2,5-trimethyl-3,4-hexadione with paraformaldehyde in DMSO in the presence of potassium hydroxide gives 1,6-dihydroxy-2,2,5,5-tetramethyl-3,4-hexadione (6028):



2-Carbomethoxycyclohexanone condenses with 3-pent-2-one in DMSO in the presence of sodium methoxide to give methyl 4-methyl-1 (9)-octal-2-one-1O-carboxylate (4048):



The reaction of pentafluoracetophenone with methyl benzoate in the presence of sodium hydride in DMSO is the best way to the diketone (3376):

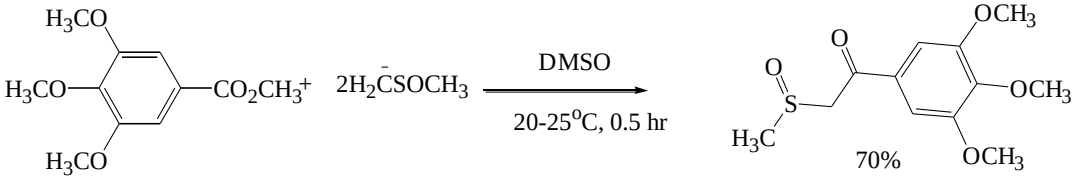


b) **Ester condensation**

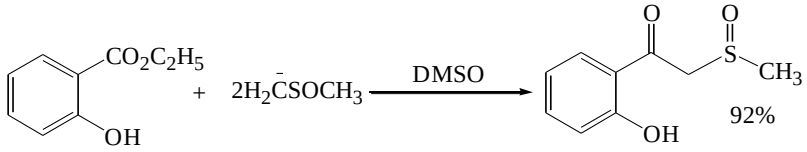
The esters of carboxylic acids react with the dimsyl ion in DMSO to yield β -keto sulfoxides (639)(1651):



This condensation reaction has found a fairly wide application in the synthesis of useful intermediates. Thus, a number of benzoic acid esters can be reacted with the dimsyl ion in DMSO to give the corresponding β -keto sulfoxides (9150):



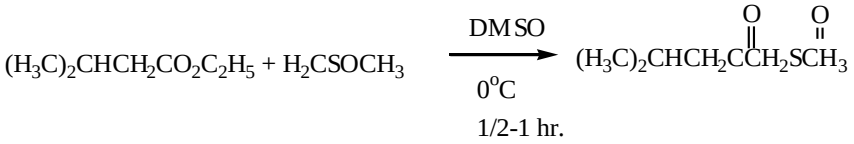
Ethyl salicylate reacts with 3.2 equivalents of dimsyl ion to give the β -keto sulfoxides (9196):



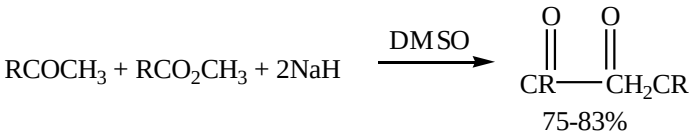
A number of β-keto sulfoxides have been prepared by condensing the dimsyl ion with substituted phenyl or naphthyl esters (9249)(9402). Thus, ethyl 1-hydroxy-2-naphthoate reacts with the dimsyl ion to give 3'-hydroxy-2-(methylsulfinyl)-2'-acetonaphthone (9244):



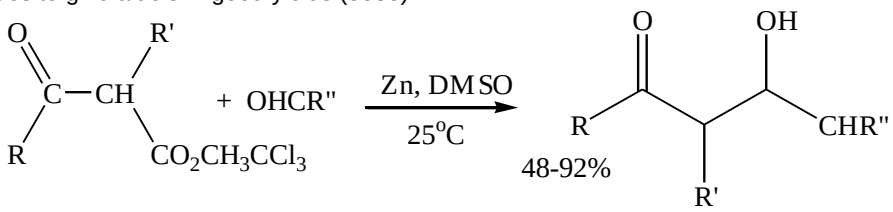
Ethyl isovalerate gives methyl sulfinyl methyl isobutyl ketone (9825):



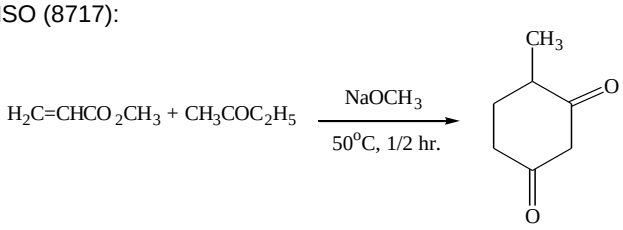
The preparation and synthetic applications of β-keto-sulfoxides have been reviewed (4820)(8529).
Symmetrical β -diketones are readily prepared by reacting methyl esters with methyl ketones in DMSO with sodium hydride as the base (193) :



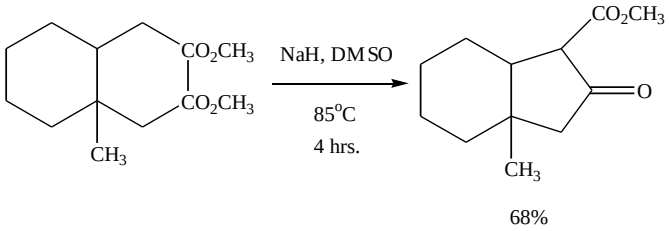
The yield is increased from 36% to 83% by using sodium hydride in DMSO instead of sodium methoxide in toluene.
In the presence of zinc-DMSO, 2,2,2-trichloroethyl esters of α -substituted β -keto acids react stereospecifically at the α -carbon to the ester carbonyl with aldehydes to give aldols in good yields (8833):



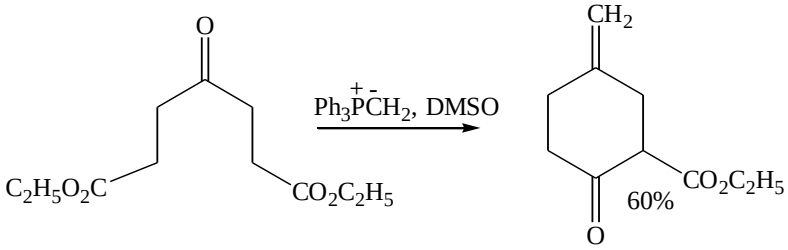
Cyclohexanediones-1,3 are prepared in good selectivity by reacting an α , β-unsaturated carboxylic acid ester with a ketone in the presence of a strong base in DMSO (8717):



c) **Dieckmann condensation-cyclization**
The Dieckmann condensation of dimethyl-l -methylcyclohexane 1,2-diacetate with sodium hydride in DMSO furnishes a crystalline keto ester (6593):

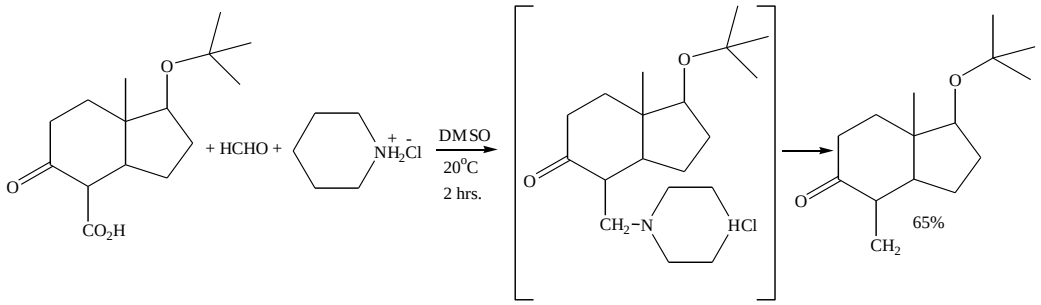


Reaction of diethyl Y-ketopimelate with an excess of methylenetriphenylphosphorane in DMSO provides for the introduction of an exocyclic methylene group and subsequent Dieckmann condensation to the carbethoxycyclohexanone (6648):



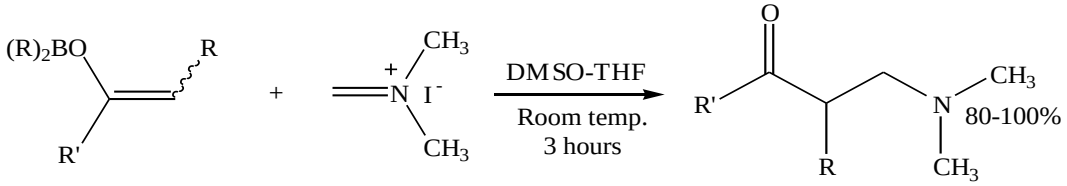
d) **Mannich reaction**

A β -keto carboxylic acid reacts with formaldehyde-piperidine hydrochloride in DMSO to give the corresponding α –methylene ketone in excellent yield (6463)(8888):



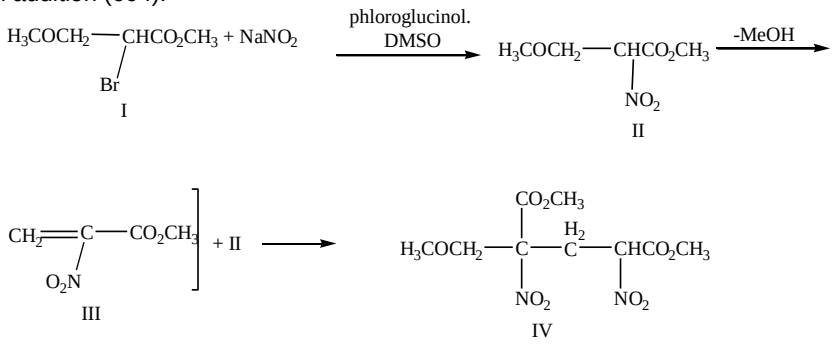
The first step in the reaction is probably decarboxylation. The Mannich reaction product is most likely formed, but it loses piperidine hydrochloride in the highly polar reaction medium.

The "Mannich reagent", dimethyl (methylene)ammonium iodide, reacts with enol borinates in DMSO-THF to provide excellent yields of β -dimethylamino ketones (6671):

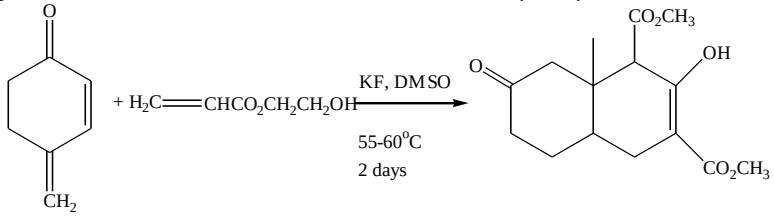


e) **Michael condensation**

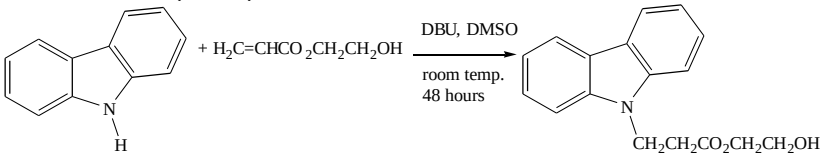
The reaction of methyl α-bromo- β-methoxypropionate (I) with sodium nitrite in DMSO in the presence of phloroglucinol gives dimethyl α -methoxymethyl- α , α'-dinitrogluturate (IV), which is formed from methyl α - nitro - β cnethoxypropionate (II) and methyl α - nitroacrylate (III) by Michael addition (664):



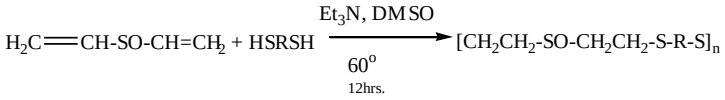
Double Michael reaction of 3-methyl-4-methylene-cyclohex-2-enone with dimethyl 3-oxoglutarate in DMSO in the presence of potassium fluoride as a catalyst gives a mixture of the stereomeric diketodiesters (9746):



Michael addition of carbazole to 2-hydroxyethyl acrylate in DMSO in the presence of 1,8-diazobicyclo[5.4.0]-7undecene (DBU) takes place under mild conditions (10091):

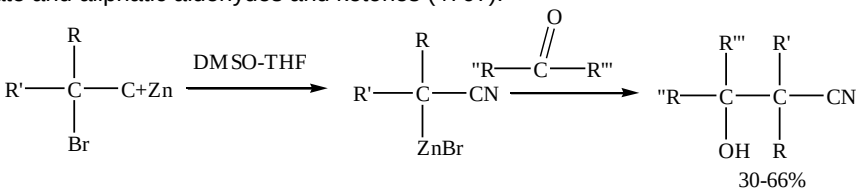


Michael-type polyaddition of dithiols to divinylsulfoxide in DMSO leads to the formation of poly(sulfinylethylene-thioalkene (or arylene)thioethylene)s (10443):



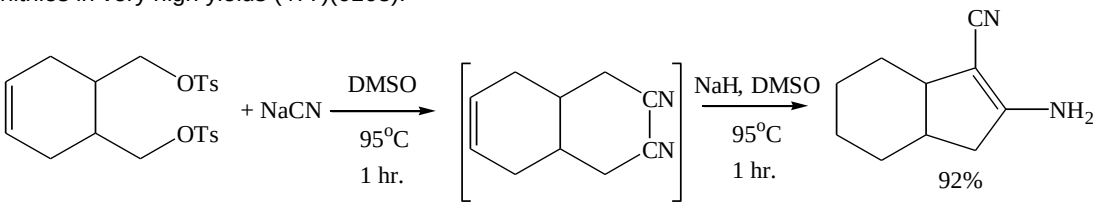
f) **Reformatsky reaction**

Bromonitriles, when treated with zinc in DMSO-THF, yield an intermediate organozinc compound. β - Hydroxynitriles are then prepared from this intermediate and aliphatic aldehydes and ketones (4767):

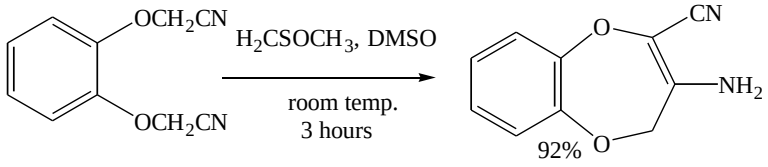


g) **Thorpe-Ziegler condensation**

1,4-Dinitriles, which can be prepared from dihalides or ditosylates and sodium cyanide in DMSO, can be cyclized directly to β-enamino nitriles in very high yields (477)(6163):

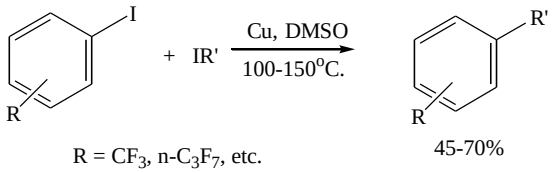


The cyclization of 1,2-di-(cyanomethoxy) benzene with dimsyl ion (sodamide + DMSO) in DMSO produces 3-amino-4-cyano-2H-1,5-benzodioxepin (8690)(9145):



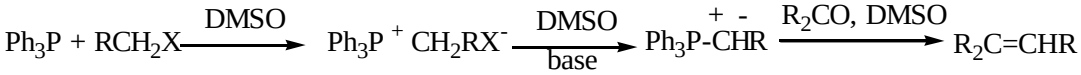
h) **Ullmann-type condensations**

Iodofluoroalkanes react with aryl iodides in DMSO in the presence of copper to give arylfluoroalkanes (5185) (7293):

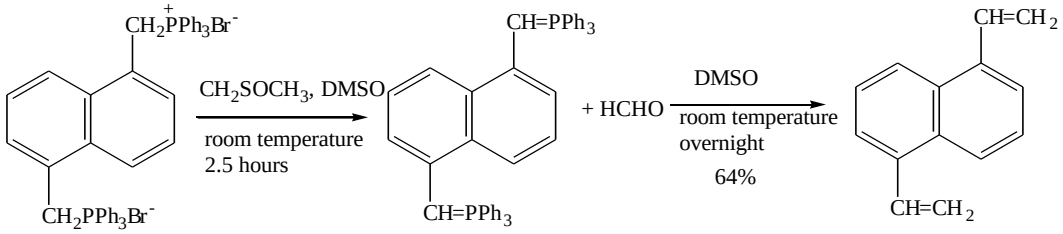


i) **Wittig reaction**

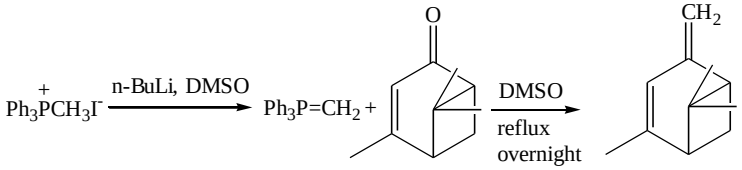
The reaction of a tertiary phosphine (usually triphenylphosphine) with an alkyl halide to yield a phosphonium salt can be done in DMSO (4669). DMSO also seems to be a good solvent for these salts. In these phosphonium salts, the α C-H bonds are sufficiently acidic (5551) for the hydrogen to be removed by a strong base in DMSO, e.g. an organolithium compound (4110), sodium hydride or the dimsyl ion (8360), to produce a phosphorus ylide (a phosphorane), the so-called Wittig reagent. Subsequent reactions of these ylides with aldehydes, ketones or hemiacetals in DMSO offer a useful synthesis for olefins. The overall reaction can be written as follows (49)(240)(5551):



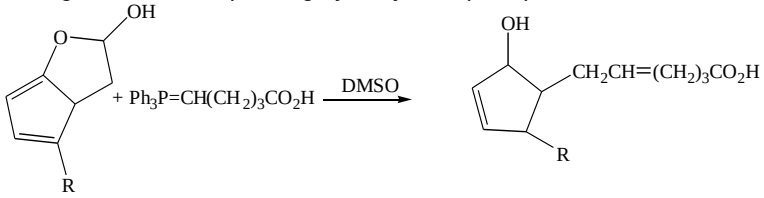
As mentioned above, the Wittig reaction converts carbonyl compounds to olefins. Thus, the reaction of formaldehyde and the phosphorane derived from 1 ,5-bis(triphenylphosphoniomethyl)naphthalene dibromide in DMSO gives 1,5-divinylnaphthalene (7641):



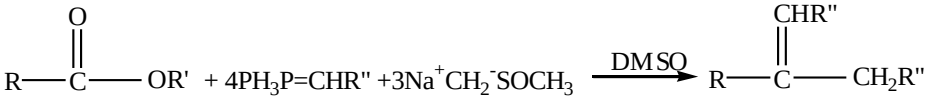
Ketones react with phosphoranes in a way similar to aldehydes. Verbinone with methylidenetriphosphorane in DMSO yields methylenedihydroterpine (7476):



Lactols (hemiacetals) can also be reacted with a Wittig reagent (7691). Treatment of a lactol with a Wittig reagent derived from 5-triphenylphosphovalerate ion in DMSO gives the corresponding hydroxy acid (7729):



It has also been found that aromatic and aliphatic esters can be directly converted to the corresponding isopropenyl compounds by reaction with methylenetriphenylphosphorane in DMSO (10078):



OXIDATION REACTIONS

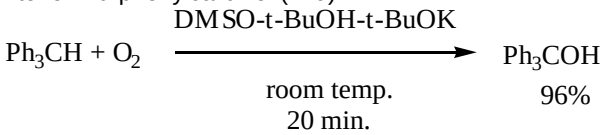
These are reactions in which oxygen combines chemically with another substance or reactions in which electrons are transferred from one substance to another. DMSO in these reactions, with a few exceptions, is a solvent and not a reactant, i.e. it gets neither reduced nor oxidized.

Many different reactions using oxygen have been conducted in DMSO, such as autoxidation (also chemiluminescence), dehydrogenation, hypohalite reactions, lead tetraacetate oxidation, silver compound oxidations, superoxide and peroxide oxidations and others not discussed here (e.g. electrooxidation, periodic acid oxidations, manganese dioxide oxidations, sulfur dioxide oxidations).

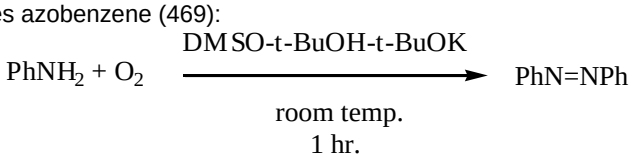
a) **Autoxidation**

The base-catalyzed oxidation of a number of compounds by oxygen in DMSO-t-butanol mixtures has been studied extensively. Formation of the carbanion of the substrate usually precedes the oxidation. The rate of carbanion formation and oxidation increases as the DMSO content is increased (728).

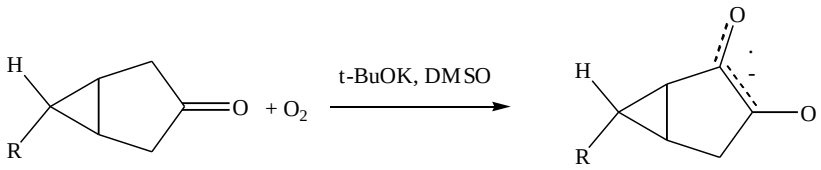
In the solution DMSO-t-butanol-potassium t-butoxide, a number of hydrocarbons can be oxidized easily. Thus, triphenylmethane reacts with oxygen in the above system to form triphenylcarbinol (479):



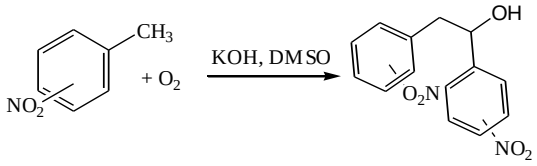
Aniline under the above conditions gives azobenzene (469):



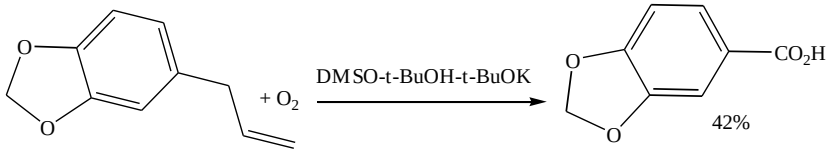
Ketones in DMSO-potassium t-butoxide are oxidized to semidiones (1787):



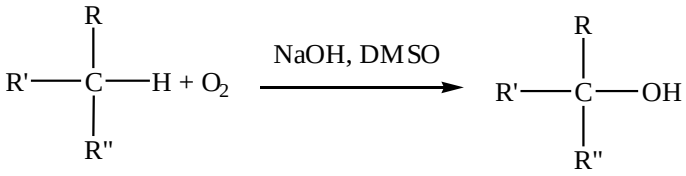
Some ketones can also be oxidized to the carboxy compounds (9707).
When nitrotoluenes are oxidized in DMSO-potassium t-butoxide, dimers or acidic products can be formed (568). Thus, the autoxidation of o- and p-nitrotoluene in DMSO under basic conditions result in the formation of 1,2-di(nitrophenyl)ethanol, presumably via the corresponding nitrobenzaldehydes (4812):



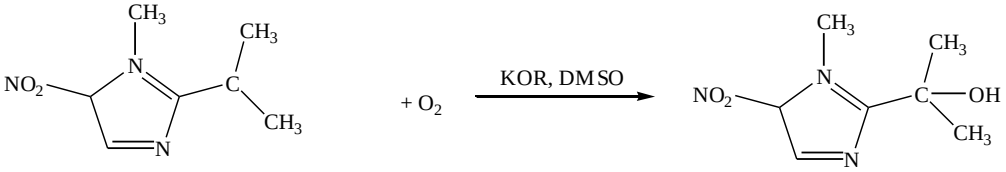
The above dimers can be further oxidized to ketones, or dehydrated to nitrostilbenes (4812).
The autoxidation of 1- and 3-arylpropenes has been induced with the DMSO-t-butanol system containing potassium t-butoxide. The autoxidation of safrole gives piperonylic acid. Without DMSO, no oxidation takes place (1140):



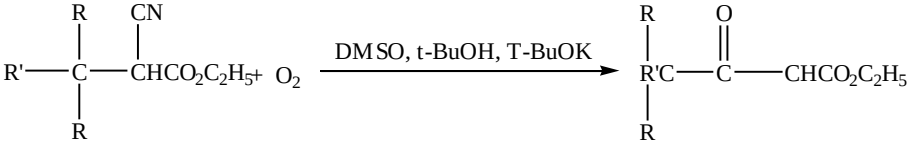
In the presence of alkali metal hydroxides, it is possible to oxidize various substituted methanes, such as α, α-diphenyl-2-pyridenemethane, to the corresponding alcohols using air or oxygen and DMSO as the sole solvent (6971):



1,2,5,6-Dibenzanthracene and several other aromatic hydrocarbons are oxidized to the corresponding quinone derivatives in basic DMSO (5587).
Autoxidation of 1 -methyl-2-isopropyl-5-nitroimidozole in DMSO with air or oxygen in the presence of a base gives 2-(2-hydroxy-2-propyl)-1-methyl-5-nitroimidazole (8867):



Base catalyzed autoxidation of ethyl 2-cyano 3,3-disubstituted carboxylates in DMSO gives good yields of the 2-oxo esters (3662):

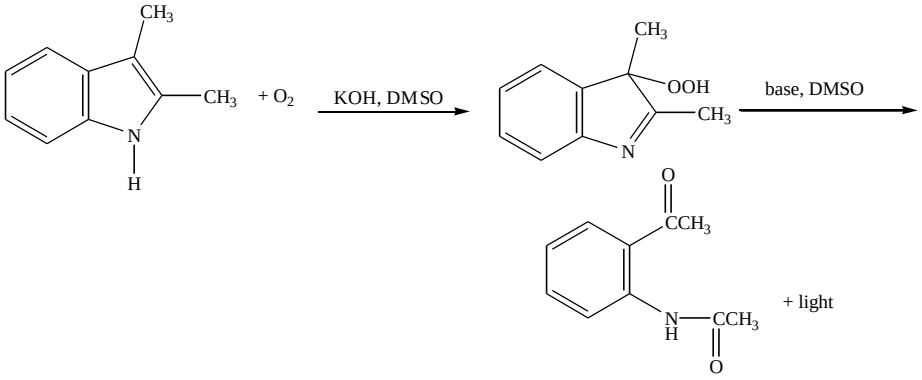


The system cobalt (II) and/or (III) acetylacetonate-t-butyl hydroperoxide has been used to initiate autoxidation of polyvinyl alcohol) in DMSO (8043).
9,10-Dihydroanthracene can be oxidized to anthraquinone with oxygen in DMSO containing an inorganic base, such as sodium hydroxide (2940).

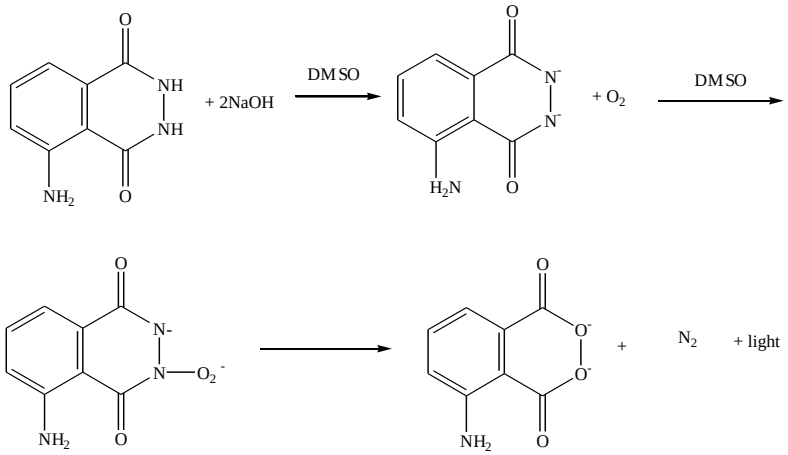
b) **Chemiluminescence**

Chemiluminescence reactions are very similar to autoxidation. Both these reactions require oxygen and the presence of a strong base. Chemiluminescence reactions can be classified as special autoxidation reactions that produce light emissions. As the basicity of alkoxides and hydroxides is enormously enhanced in DMSO over the value of hydroxylic solvents, it has also been observed with chemiluminescence reactions that the emission periods have been increased and the light intensities enhanced in DMSO containing a base (1025).

A bright green light is observed on the treatment of a solution of 2,3-dimethylindoie and its hydroperoxide in DMSO with a base, e.g. potassium t-butoxide or granular potassium hydroxide (2140)(2218):

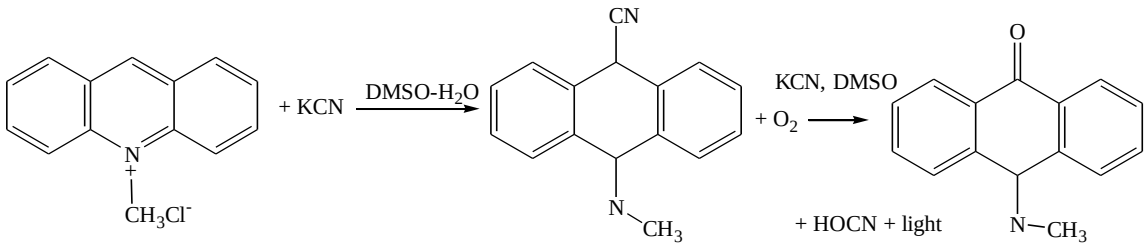


When DMSO, luminol, water and caustic solution are shaken in the presence of oxygen from air, an oxidation reaction produces considerable bright blue-green light. The reaction sequence can be represented as follows (3241):

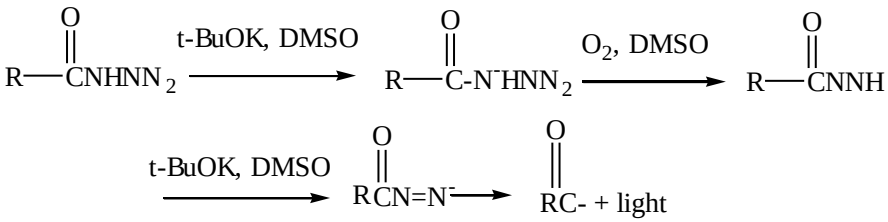


Some derivatives of luminol, containing methoxyl groups, are more efficient in chemiluminescence in DMSO solution than luminol itself (1668).

The reaction of potassium cyanide with N-methylacridinium chloride in 90% DMSO-10% water produces Nmethyl-90-cyanoacridan. With excess cyanide, the red N-methyl-9-cyanoacridanide ion is produced which, in the presence of oxygen, produces N-methylacridone and potassium cyanate with light emissions (3653):

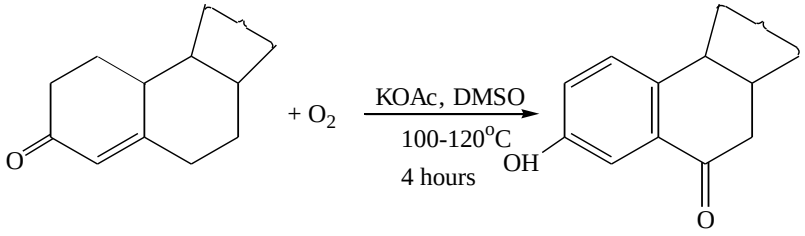


The chemiluminescence emission spectra of two efficient chemiluminescent linear hydrazides in DMSO with potassium t-butoxide and oxygen suggest that the corresponding acid anion is the light emitter (5116):

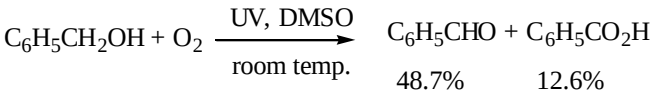


c) **Other oxidations with oxygen**

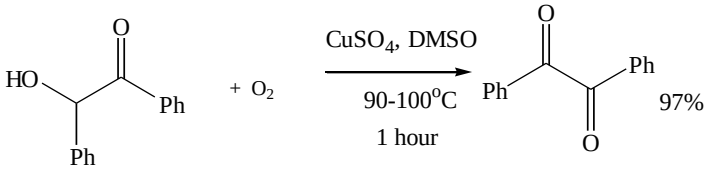
Carbonyl compounds can be manufactured by oxidation of olefins, such as ethylene, propylene, styrene, and cyclohexane, in water-DMSO mixture in the presence of a catalyst to give acetaldehyde, acetic acid, acetone, propanol, acetophenone and others (5800).
DMSO can be used as a catalyst component in the oxidation of olefins, e.g. DMSO can be a coordinate in complexes such as $Cu(ClO_4)_2(DMSO)_4$, or $Fe(ClO_4),(DMSO)_4$, (9412).
3-Oxo- Δ^4-(19)-norsteroids react with oxygen in DMSO to afford 1,3,5-(10)-oestratrien-6-ones (5912):



The liquid phase oxidation of s-butanol with oxygen under pressure has been examined in various solvents using vanadium pentoxide-molybdenum trioxide catalyst While no reaction occurs in water, benzene, or chlorobenzene, the oxidation in DMSO at 125°C for 13 hours converts 10.8% of s-butanol to methyl ethyl ketone with a selectivity of 89% (9434).
Terpenes can be oxidized with dry air in DMSO. Thus, α -longipinene is oxidized at 125-135°C to longiverbone as the major product (9871), and p-mentha-1,4(8)- and -2,4(8)- dienes at 100°C give p-methylacetophenone (9874).
In neutral solution, benzyl alcohols can be oxidized by oxygen in the presence of ultraviolet light to give the corresponding aldehydes (737)(1118):

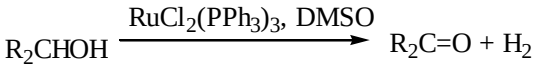


The oxidation of benzoin by cupric sulfate and oxygen in DMSO occurs to give a high yield of benzil (945):

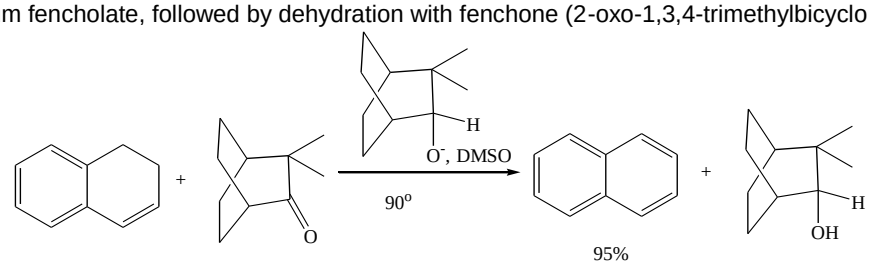


d) **Dehydrogenation**

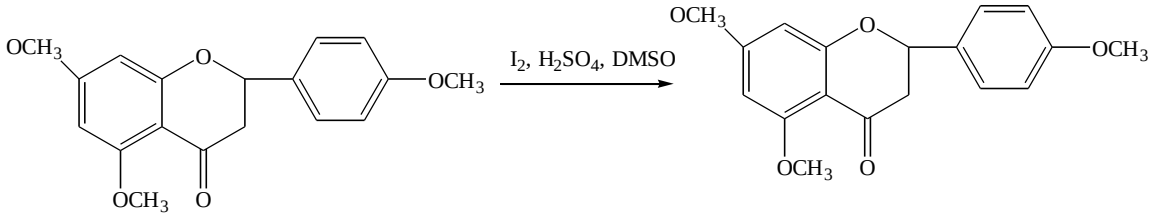
In the dehydrogenation reaction, oxidation (i.e., the removal of hydrogen) can take place without the presence of oxygen.
Several platenoid metal catalysts in DMSO promote dehydration, disproportionation and dehydrogenation of diarylcarbinols (10422). The dehydrogenation can be the main reaction when DMSO is used as the solvent instead of α -methylnaphthalene (8838):



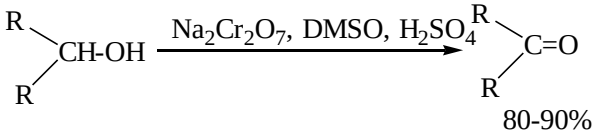
Dihydroarenes, e.g. 1,2-dihydronaphthalene, can be converted into the corresponding aromatic compounds, e.g. naphthalene, by deprotonation with potassium fencholate, followed by dehydration with fenchone (2-oxo-1,3,4-trimethylbicyclo [2.2.1]-heptane) (9707):



5,7,4'-Trimethoxyflavanone, when heated with DMSO in the presence of a catalytic amount of iodine and concentrated sulfuric acid, gives 5,7,4'-trimethoxyflavone in almost quantitative yield (10,000):

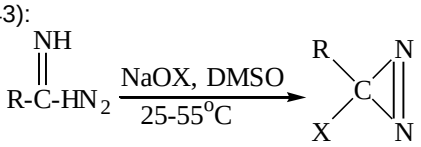


A solution of sodium dichromate and sulfuric acid in DMSO oxidizes primary alcohols to aldehydes and secondary alcohols to ketones. In these oxidations, DMSO acts as a solvent and not as a reactant (7609):



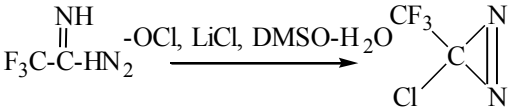
e) **Hypohalite oxidations**

Halogenations with sodium hypohalites of alkyl - or arylamidines and isoureas in DMSO solution afford the corresponding alkyl-, aryl- or alkoxy-3-halodiazirines in practical yields (843):



3-haloazirine, 60%

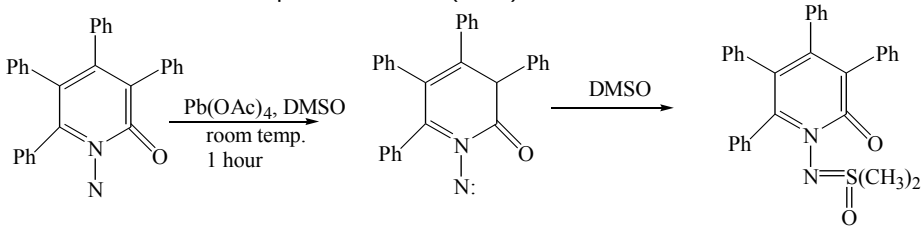
Oxidative cyclization of trifluoroacetamidine with hypochlorite and chloride ion in aqueous DMSO gives the corresponding diazirine (8108):



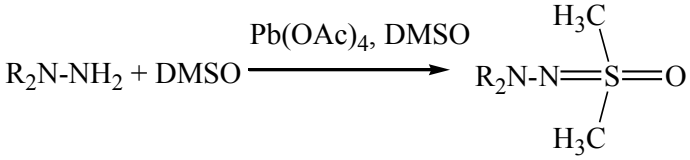
f) **Lead tetraacetate oxidations**

Polysaccharides, such as dextran and amylose, can be oxidized by lead tetraacetate in DMSO if 15-20% of glacial acetic acid is added to prevent oxidation of the solvent. This oxidation proceeds at a rate which is several times faster than the periodate oxidation in aqueous solution. Polysaccharides oxidized by lead tetraacetate contain free aldehyde groups. Oxidation follows the normal glycol-cleavage pattern (615).

Oxidation of 1 -amino-3,4,5,6-tetraphenyl-2-pyridone with lead tetraacetate in DMSO gives the corresponding 5,5-dimethyl-N-sulfoximide, indicating that DMSO is an efficient trap for N-nitrenes (4987):



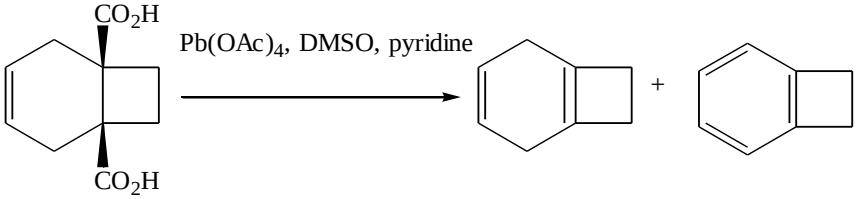
Similarly, lead tetraacetate oxidation of N-aminolactams in the presence of DMSO gives the sulfoximides in good yields (5846):



Oxidation of aminonaphth[2,3-b]azet-2(1 H) -one by lead tetraacetate in DMSO leads to 2-naphthoic acid (6243):

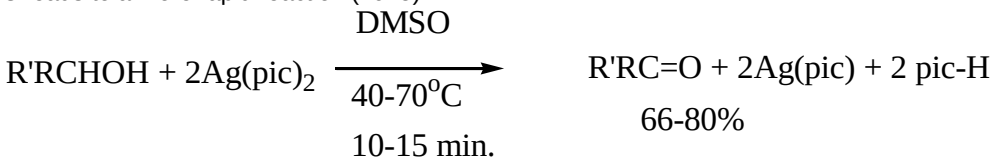


Treatment of a dicarboxylic acid (prepared from the Diels-Alder adduct of dimethyl - cyclobut-1-ene-1,2dicarboxylate with butadiene) with lead tetraacetate in DMSO containing pyridine gives a product which is mainly bicyclo [4,1,0]octa-1(6),3-diene, with a small amount of benzocyclobutene (7533):

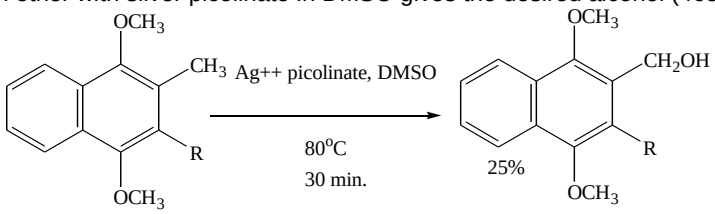


g) **Silver compound oxidations**

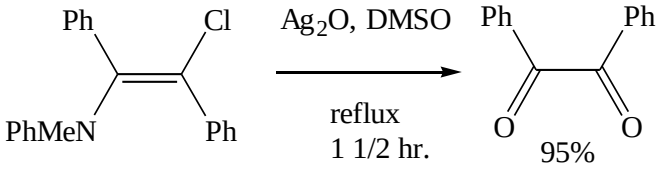
A number of alcohols, e.g. methanol, ethanol, n-propanol, isoborneol, can be oxidized by argentic picolinate to yield the corresponding aldehydes or ketones, i.e., formaldehyde, acetaldehyde, propionaldehyde, camphor. The rate of reaction is influenced by the solvent, and the use of DMSO leads to a more rapid reaction (2915):



Oxidation of menaquinol-1 dimethyl ether with silver picolinate in DMSO gives the desired alcohol (4653):

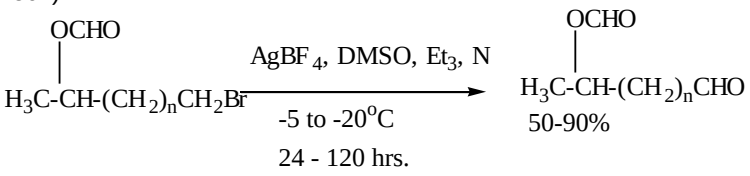


Reaction of 1,2-diphenyl-2-[(phenyl)methylamino]vinyl chloride with silver (II) oxide in DMSO gives benzil (5843):

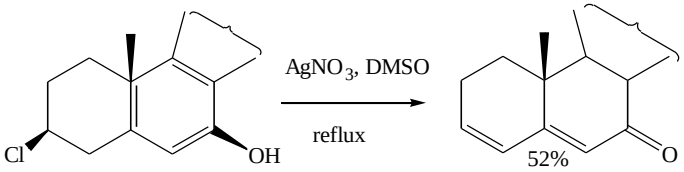


In boiling nitromethane with silver tetratluoroborate, the yield of benzil is only 60% (5843).

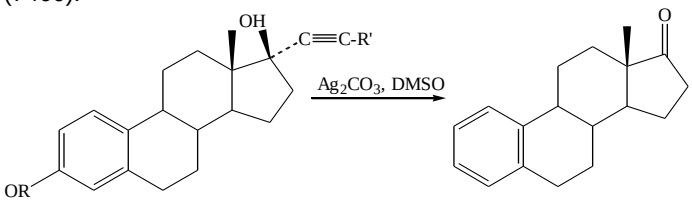
Bromoalkyl formates are easily converted to protected secondary hydroxyaldehydes by treatment with silver tetrafluoroborate in DMSO in the presence of triethylamine (7507):



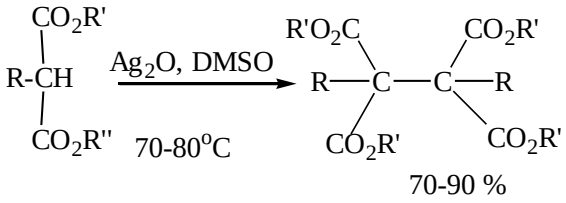
The use of silver nitrate in DMSO on a 3-chloro-7-hydroxy-1 7-oxo-androstane accomplishes two purposes. It oxidizes the 7-hydroxy group to the 7-oxo group, and it dehydrohalogenates the steroid (8340):



17 α-Ethynyl-17 β-hydroxysteroids are converted quantitatively to the corresponding 17-ketones by treatment with excess silver carbonate or silver oxide in DMSO (7460):

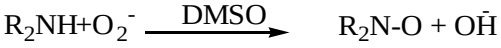


Dimethyl esters of monoalkylated malonic acids and β-keto esters are easily oxidatively dimerized by silver oxide in DMSO (8830), e.g.:

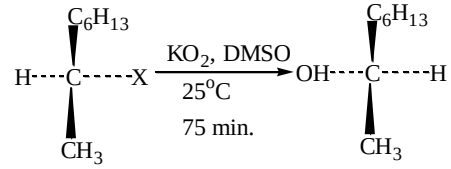


h) **Superoxide and peroxide oxidations**

Secondary amines are instantaneously oxidized to dialkylnitroxides by potassium superoxide in DMSO (6293):



Alcohols are the major end products resulting from the reaction of alkyl halides and tosylates with an excess of potassium superoxide in DMSO in a rapid process in which the C-O bond-forming step proceeds with inversion of configuration (8030):



X = Cl, Br, I, OTs

With 1 -bromooctane, the yield of 1 -octanol is 63%.

Phenolic compounds are prepared by oxidation of aromatic hydrocarbons with organic hydroperoxides in the presence of boron oxide, meta- or orthoboric acid ortheir lower alkyl esters, and DMSO. Thus, DMSO is added to a mixture of m-xylene, tetralin hydroperoxide and boron oxide to give 38:62 ratio of 2,6- and 2,4-xylenol, dihydronaphthalene and tetralone (8658).

REDUCTION REACTIONS

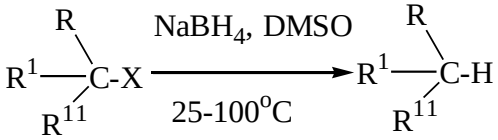
These are reactions in which hydrogen is added or oxygen or a halogen is removed. DMSO can be either a solvent or a catalyst component.

Although DMSO can be either oxidized or reduced, it is comparatively stable toward both changes and hence can be used as a solvent for many oxidation-reduction reactions. In polarography studies using tetraethylammonium perchlorate electrolyte, the usable potentials range from +0.3 volts anode potential to-2.8 volts cathode potential (both relative to the standard calomel electrode) (553)(772). In general, the halfwave potentials for inorganic ions in DMSO are quite similar to those in aqueous solutions (553). However, a more negative cathode potential is usable in DMSO as shown by the observation of the magnesium wave at -2.20 volts. Lithium metal is inert toward DMSO (206). The electrodeposition of cerium cannot be accomplished in aqueous solution because the metal is too positive but it can be deposited from a DMSO solution of cerium chloride (1744). The transfer of electrons between molecules of redox systems sometimes occurs very readily in DMSO as observed for isotope exchange between ferrous and ferric perchlorates (1036)(923) and in

the base-catalyzed transfer of electrons between unsaturated organic molecules and their dihydro derivatives (722).

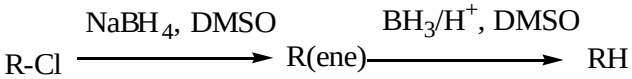
1. Reduction of Alkyl Halides and Sulfonates

a) **Reduction with sodium borohydride**
the selective substitution of hydrogen for primary, secondary or, in certain cases, tertiary halogen (or sulfonate) in alkyl halides without reduction of other functional groups present in the molecule may be effected by reduction with sodium borohydride in DMSO (2980)(3248):

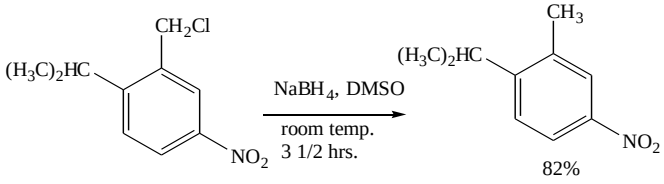


X=Cl, Br, I, tosylate

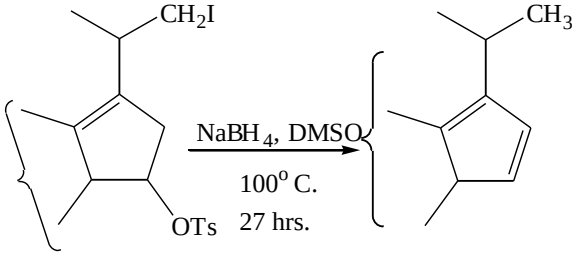
Sodium borohydride in DMSO is a convenient source of a nucleophilic hydride which may be used for the reductive displacement of primary and secondary alkyl halides, or sulfonate esters (e.g. tosylates). The mildness of borohydrides allows a number of chemoselective transformations without damage to groups (e.g. COOR, COOH, CN, NO_2) normally affected by harsher reagents such as lithium aluminum hydride (9783).
The reduction of optically active tertiary alkyl halides with sodium borohydride in DMSO proceeds with racemization, presumably via an elimination-addition mechanism (3519):



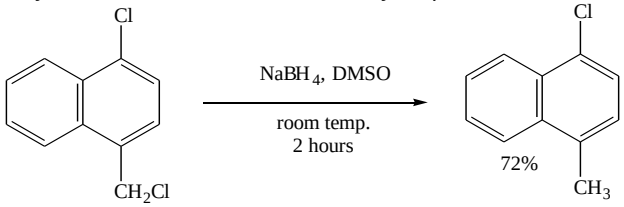
4-Nitro-2-chloromethyl-1-isopropylbenzene can be reduced with sodium borohydride in DMSO in good yield (4602):



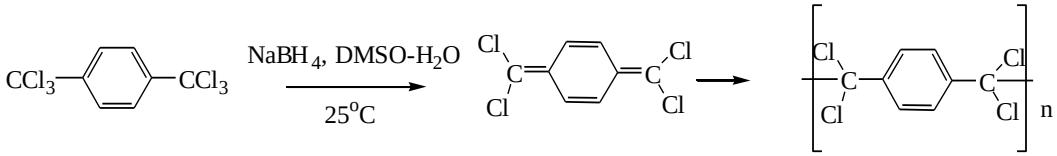
An iodo-tosylate can be reduced with sodium borohydride in DMSO to give one major product, a cyclopentadiene (6502):



In the above case, both reduction of the iodide and elimination of the tosylate take place.
Sodium borohydride in DMSO selectively reduces 2-chloro-4-chloromethyl naphthalene to 1-chloro-4methylnaphthalene (6785):

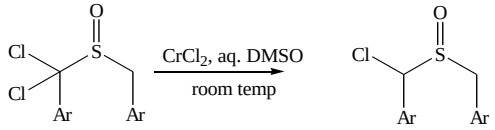


Sodium borohydride in DMSO-water reacts with α , α , α , α', α', α'-hexachloro-p-xylene to give an insoluble polymer (7205):

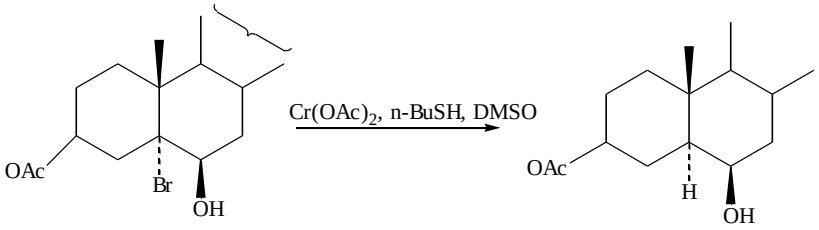


c) **Reductions with chromous ion**

Reduction of α, α-dichlorobenzyl benzyl sulfoxide to a mixture of diastereomeric α-chlorobenzylbenzyl sulfoxide can be carried out by chromous ion in aqueous DMSO (6972):

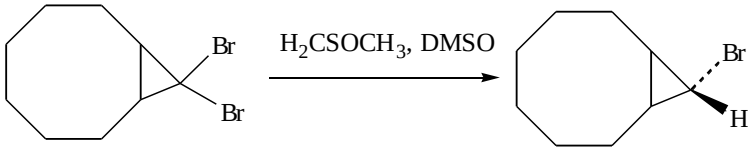


The use of n-butanethiol and chromium (II) acetate in DMSO in the reduction of a 5 α-bromo-6 β-hydroxysteroid permits the removal of the bromine and the isolation of the 6 β-hydroxy-steroid (6825)(6970):



c) **Reduction with dimsyl ion**

Treatment of 8,8-dibromobicyclo[5,1,0]octane with dimsyl sodium in DMSO produces exo-8-bromobicyclo [5,1,0]octane (454)(3009):



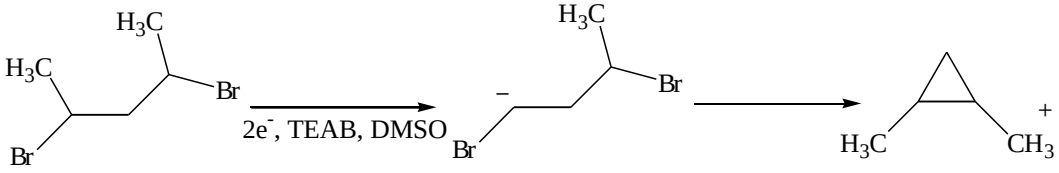
d) **Reductions with hydrazine**

Hydrazine can reduce meso-1,2-stilbene dibromide in DMSO to α -bromostilbene and some bibenzyl (6509):

$$PhCHBrCHBrPh + N_2H_4 \xrightarrow{DMSO} \underset{66\%}{PhCH{=}CBrPh} + \underset{18\%}{PhCH_2CH_2Ph}$$

e) **Reductions by electrolysis**

Controlled potential electrolysis of 2,4-dibromopentanes in DMSO containing tetraethylammonium bromide (TEAB) gives cis- and trans-dimethylcyclopropanes and small quantities of 1-pentene, 2-pentene and n-pentane (4492)(6659):



$$CH_3CH_2CH_2CH{=}CH_2 + CH_3CH_2CH{=}CHCH_3 + CH_3(CH_2)_3CH_3$$

2. Reduction of Carbonyl Compounds

Carbonyl compounds, aldehydes and ketones in DMSO can be reduced by electrochemical means or by Wolff-Kishner reduction of the corresponding hydrazones.

a) **Reductions with borohydrides**

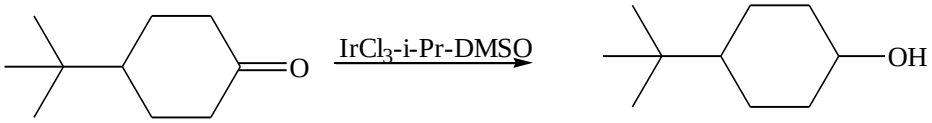
The kinetics of the reduction of acetone, pivalaldehyde, $(H_3C)_3CCHO$, and benzaldehyde by sodium borohydride and tetramethylammonium borohydride have been determined in DMSO-water systems. The reactions obey 2nd order kinetics (8953):

$$4R_2CO + BH_4^- + H_2O \xrightarrow{DMSO} R_2CHOH + B(OH)_4^-$$

The reduction product of benzaldehyde in DMSO is $NaB(OCH_2Ph)_4$, which is readily hydrolyzed to benzyl alcohol, $PhCH_2OH$ (8953). When benzaldehyde is reduced in DMSO and DMSO-water mixtures of tritiated sodium borohydride, the reduction is accompanied by the incorporation of tritium into the aldehyde group of unchanged benzaldehyde (8954).

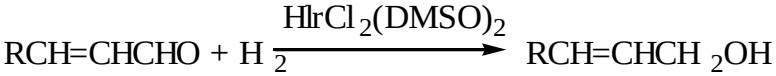
b) **Catalytic reduction**

The mechanism of reduction of cyclic ketones by the system iridium(III) salt-sulfoxide-isopropyl alcohol has been investigated. With 4-t-butyl cyclohexanone, a 97% conversion to 4-t-butylcyclohexanol, with a cis/trans ratio of 1.50, can be achieved with DMSO as the sulfoxide (4436):



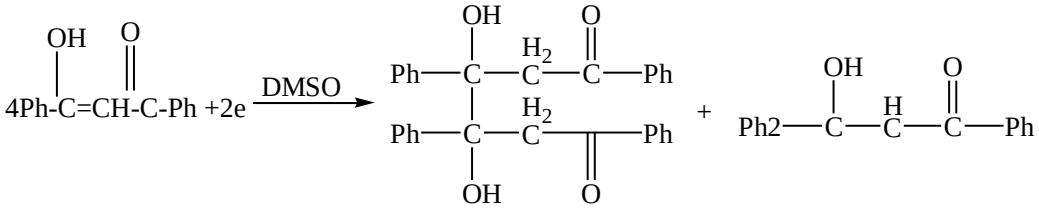
97% conversion

An unusually selective hydrogenation of α , β-unsaturated aldehydes to the unsaturated alcohols has been accomplished catalytically under mild conditions using the iridium complex $HIrCl_2(DMSO)_3$ in isopropanol, the solvent being the source of hydrogen (9752):



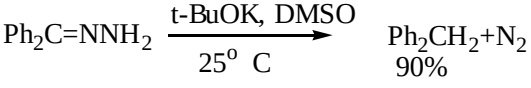
c) **Electrochemical reduction**

The electrochemical reduction of carbonyl compounds, particularly ketones and diketones, has been studied in DMSO (2567)(3217). The reduction of 1,3-diphenyl-1,3-propanedione in DMSO proceeds by an overall 0.5 electron process (5971):



d) **Wolff-Kishner reduction**

The Wolff-Kishner reduction, the reaction of hydrazones of aldehydes and ketones with a base to produce the corresponding hydrocarbons, has been run in DMSO (495)(377):



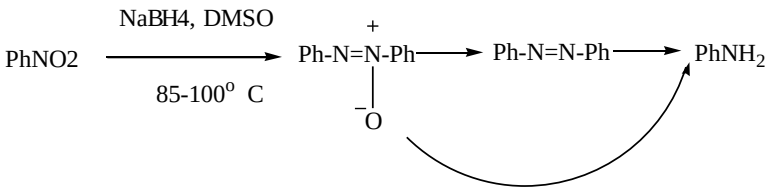
benzophenone hydrazone

diphenyl methane

The Wolff-Kishner reduction in DMSO has been carried out in the presence of potassium t-butoxide, dimsyl sodium, and other base catalysts, and the activation parameters have been determined (8735). The Wolff-Kishner reaction mechanism in DMSO has been reviewed (1942)(3048).

3. Reduction of nitroaromatics

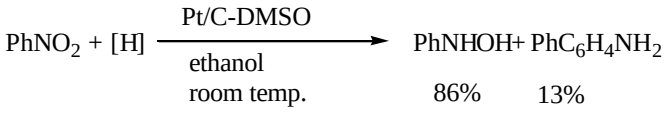
The reduction of aromatic nitro compounds with sodium borohydride in DMSO initially produces the azoxy compounds which, in most cases, are subsequently reduced to the corresponding azo derivatives and amines (4946), e.g.:



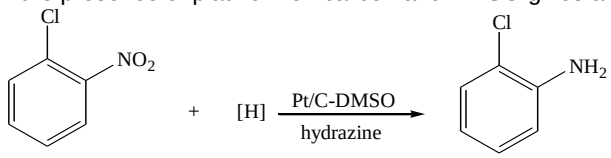
nitrobenzene azoxybenzene azobenzene aniline

In the case of o-nitroanisole, 63% of o-methoxyaniline and 23 % of the azobenzene are produced.

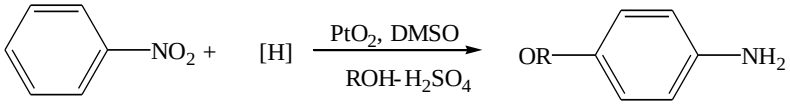
Nitroaromatics are selectively hydrogenated in neutral media in the presence of precious metal catalysts and DMSO to produce N-arylhydroxyamines in high yield. Thus, nitrobenzene in the presence of platinum on carbon and DMSO yields hydroxylamine and phenyl aniline (5663):



Catalysts of noble metals on activated carbon can be subjected to the action of DM SO together with hydrazine or its derivatives. The hydrogenation of 2-chloronitrobenzene in the presence of platinum on carbon and DMSO gives a high yield of 2-chloroaniline (8118):

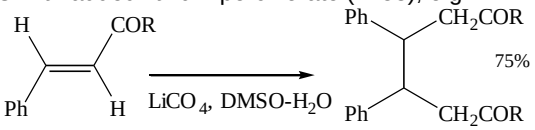


Similarly, the reduction of nitrobenzene with hydrogen over platinum oxide in alcohol (methanol or ethanol)sulfuric acid in the presence of DMSO produces p-alkoxyaniline (9294)(9581):



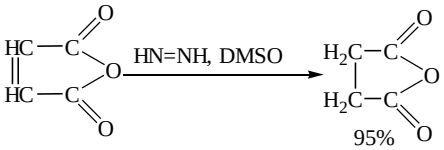
4. Reduction of C=C Systems

The electrochemical reduction of several aryl α , β -unsaturated ketones, $C_6H_5CH=CHCOR$, has been studied at mercury cathodes by the techniques of polarography, controlled potential coulometry and cyclic voltammetry. Conditions have been established under which a dimer of the α, β-unsaturated ketones is formed by coupling at the β-carbon atoms in good yields. A suitable medium for the reduction is tetra-n-butylammonium perchlorate in DMSO with added lithium perchlorate (4253), e.g.:

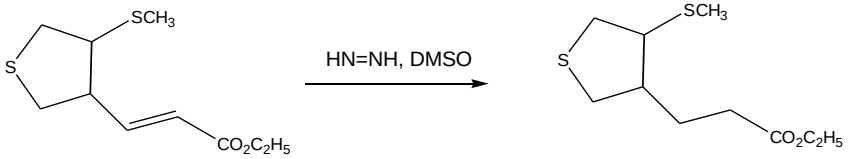


R = t-butyl

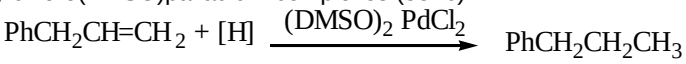
Diimide, generated by the sodium metaperiodate oxidation of hydrazine in DMSO, is a particularly useful reducing system for olefins or compounds which contain readily oxidized functional groups (4392), e.g. maleic anhydride can be reduced to succinic anhydride:



A thiophene derivative is reduced the same way (4392):

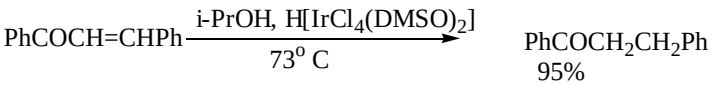


Allylbenzene can be hydrogenated by chloro(DMSO)palladium complexes (5526):

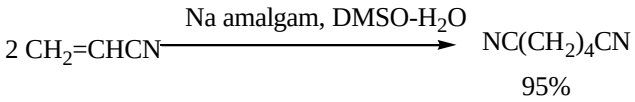


In the presence of the same catalyst, 1 -pentene is converted to isomers more rapidly than without the catalyst and the bond migration of the pentene is more rapid than its hydrogenation (5630).

Double bonds in some α, β-unsaturated ketones are reduced by propen-2-ol in the presence of soluble iridium-DMSO catalysts (7031):



Acrylic acid and its derivatives can be dimerized in high yields by means of alkali metal amalgam in DMSO-water. Acrylonitrile gives adiponitrile (4907):



Diethyl fumarate, $C_2H_5O_2CCH=CHCO_2C_2H_5$, can be dimerized by electrochemical reduction (7331).

SOLVOLYTIC REACTIONS

These are reactions in which the elements of water (also alcohols or amines) are added, usually with the formation of two new substances.

1. Hydrolysis

The DMSO-water system has been used in many hydrolysis reactions. The rates of base catalyzed reactions usually increase as the mole fraction of DMSO in the mixture increases, and the increase is particularly rapid above 0.7 mole fraction of DMSO (336)(367)(369)(464)(726)(730). The opposite is sometimes true in the case of hydrolysis in the presence of acids. The rate of acid hydrolysis decreases as the mole fraction of DMSO is increased, particularly above 25-30% DMSO (368). A similar decrease is seen for the acid catalyzed hydrolysis of acetals (742) and the reaction of tert-butyl chloride with aqueous DMSO (431)(1028)(1521).

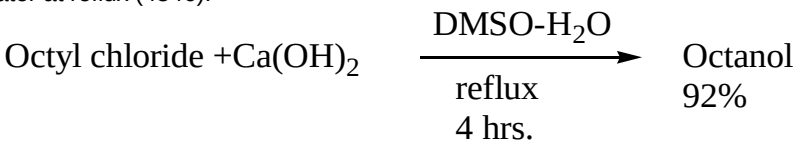
a) **Aliphatic halide hydrolysis**

The alkaline hydrolysis of alkyl halides has been studied in DMSO-water (329)(432)(2583)(4846). In the alkaline hydrolysis of methyl iodide, DMSO exerts a strong accelerating effect. The rate of the hydroxyl ion catalyzed reaction in DMSO is up to 10^6-10^7 times the rate in water (329).

The rate constants for the reaction of hydroxyl ion with benzyl chlorides in acetone-water decrease with increasing acetone concentration while the rates increase with increasing DMSO concentration in DMSO-water (432).

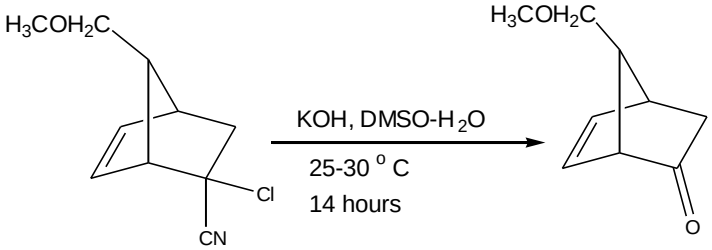
The rate of alkaline hydrolysis of chloroacetic acid increases with increasing concentration of the organic component in acetone-water, THF-water, dioxane-water and DMSO-water. However, the increase is greatest in DMSO-water (2583).

Alcohols can be prepared from alkyl halides in DMSO-water in the presence of a base. Thus, octanol is obtained from octyl chloride and calcium hydroxide in DMSO-water at reflux (4846):



Solvolysis of 2-adamantyl bromide and α-chloroethylbenzene decreases with increasing DMSO content (2194)(3766)(2196).

The Diels-Alder adduct, obtained by reacting 5-methoxymethyl-1,3-cyclopentadiene with chloroacrylonitrile, is converted with aqueous potassium hydroxide in DMSO to the anti-bicyclic ketone (3033):

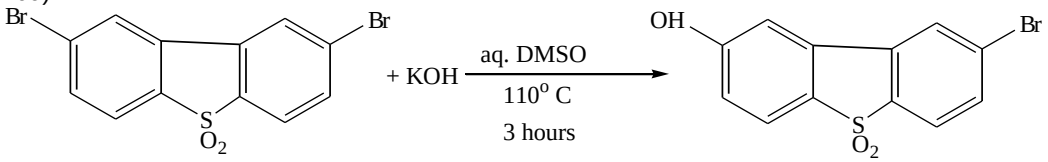


b) **Aromatic halide hydrolysis**

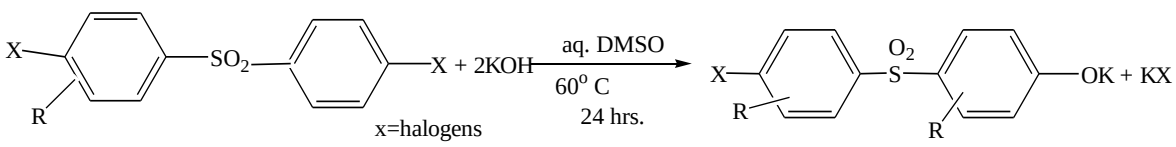
Aromatic halogens can be hydrolyzed from activated nuclei by aqueous bases in DMSO. The rate coefficients for the alkaline hydrolysis of a series 1-halogen substituted 2,4-dinitrobenzenes have been measured in aqueous DMSO. These rates have been correlated with the acidity function of medium (4467)(4520).

The aryl polyether that is prepared by the reaction of the disodium salt of bisphenol A with 4,4'-dichlorodiphenyl sulfone in DMSO depends on the moisture content of the polymerizing system. In the presence of water, hydrolysis of 4,4'-dichlorodiphenyl sulfone monomer occurs concomitant with the polymerization (4704).

The reaction of 2,8-dibromo-5,5-dioxodibenzothiophene with aqueous potassium hydroxide in DMSO gives 8-bromo-2-hydroxy-5,5-dibenzothiophene (7709):



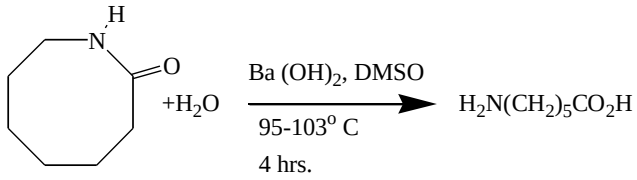
Several 4-halogenophenyl sulfonylphenols, useful for the synthesis of poly(arylene ether sulfones), have been prepared by partial hydrolysis of the corresponding dihalides in DMSO (8825):



c) **Amide hydrolysis**

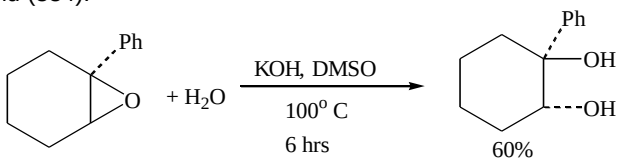
The rates of base catalyzed hydrolysis of anilides have been studied in DMSO-water (3820)(7573)(8696). Even a very small amount of DMSO (less than 1 %) facilitates the kinetic measurements in the hydrolysis of p-nitro- and pformylacetanilide (3820). Some increase with increasing DMSO has been found in the hydrolysis rate of trifluoroacetanilide (7573).

The reaction of ε-caprolatam with barium hydroxide in DMSO-water gives ε -aminocaproic acid on acidification (4972):



d) **Epoxide hydrolysis**

The most commonly encountered reactions of epoxides are those in which the ring is opened by a nucleophile. Such reactions are advantageously performed in DMSO because DMSO is inert to the epoxides and it also provides maximum reactivity for the nucleophile. When the relatively unreactive 1 -phenylcyclohexene oxide is heated with potassium hydroxide in aqueous DMSO, the corresponding trans-glycol is obtained in fairly good yield (334):



In the presence of acids a mixture of cis- and trans glycols results. The same reaction in aqueous dioxane after48 hours at 150°C gives only a 10% yield (334).

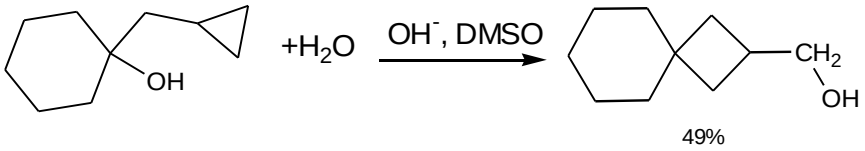
Treatment of 8,9-epoxyundec-5-en-ol with potassium hydroxide in refluxing aqueous DMSO produces undeca-4,6-diene-3,9-diol (8261):



The same treatment of the saturated epoxide, 8,9-epoxy-undecan-3-ol, leads to simple cleavage of the epoxy ring giving undecane-3,4,9-triol (8261):



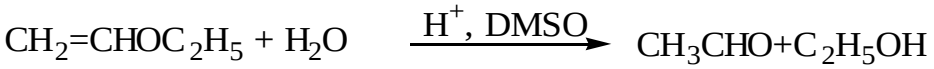
1 -(β, Y -Epoxypropyl)cyclohexan-1 -ol, when treated with base in 75% aqueous DMSO, gives the corresponding oxetan as the main product (8306):



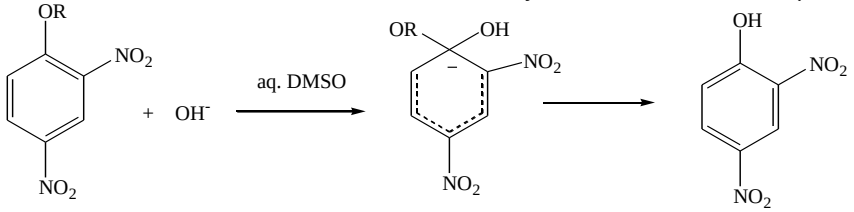
49%

e) **Ether hydrolysis**

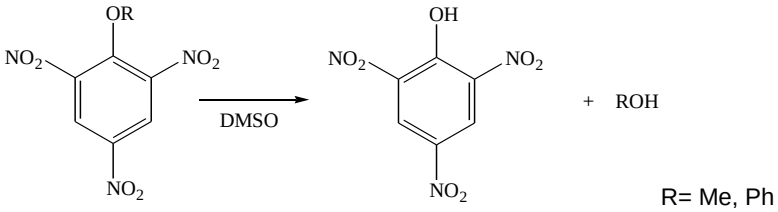
When water, strong acid, and ethyl vinyl ether are all solutes in DMSO, the rate of hydrolysis of the vinyl ether is still controlled by the rate of proton transfer to the carbon. The rate decreases with increasing DMSO concentration (2492)(7643):



The rate coefficients for the alkaline hydrolysis of 4-substituted 1-methoxy-2-nitrobenzenes and 1-alkoxy 2,4dinitrobenzenes have been measured in aqueous DMSO. These rates have been correlated with the acidity function of the medium (4467)(4520):



A similar study has been done with substituted 2-alkoxytropones in 40% aqueous DMSO (4521).
2,4,6-Trinitroanisole and 2,4,6-trinitrophenyl phenyl ether react with DMSO to give 2,4,6-trinitrophenol and methanol and phenol, resp. (6878):

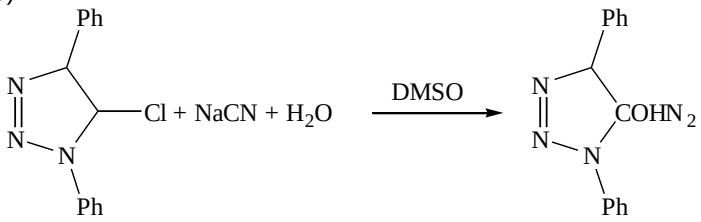


R= Me, Ph

f) **Nitrile hydrolysis**

Powdered anhydrous sodium hydroxide and potassium hydroxide in DMSO can be used to convert nitriles to amides, e.g. benzonitrile to benzamide, at a reaction rate that is approximately 10,000 times that in aqueous caustic. However, the solubility of the dry caustic in DMSO is very low which reduces the speed of converting the nitrile (725).

The reaction of 5-chloro-1,4-diphenyl-1,2,3-triazole with sodium cyanide in moist DMSO gives 1,4-diphenyl1,2,3-triazole-5-carboxamide due to hydrolysis of the nitrile (7115):



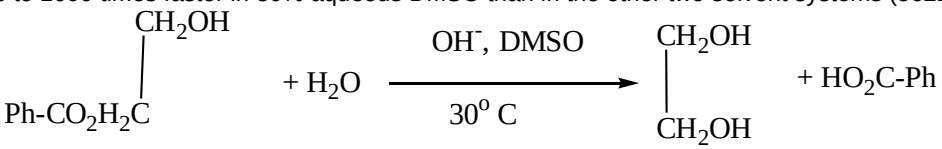
g) **Saponification**

In the base catalyzed hydrolysis of esters in aqueous DMSO, the rate of hydrolysis increases as the mole fraction of DMSO in the mixture increases. This increase is particularly rapid above 0.7 mol fraction of DMSO (336)(367)(369) (464)(726)(730).

The use of DMSO-water as a solvent for saponification increases the reaction rate difference between the first and second group of diesters. In 50% aqueous DMSO (v/v) the first ester group can be hydrolyzed more than nine times faster than the second one (1694).

There is a considerable rate enhancement for both steps in alkaline hydrolysis of a series of dicarboxylic acid esters in DMSO-water. The rates increase with increasing amount of DMSO and these rates are larger in aqueous DMSO than in aqueous ethanol (5969)(6543) or aqueous acetonitrile (5459).

When the saponification of glycol monobenzoates are carried out in 80% aqueous DMSO, 80% aqueous ethanol and 80% aqueous acetone, the rates are up to 1000 times faster in 80% aqueous DMSO than in the other two solvent systems (5622):

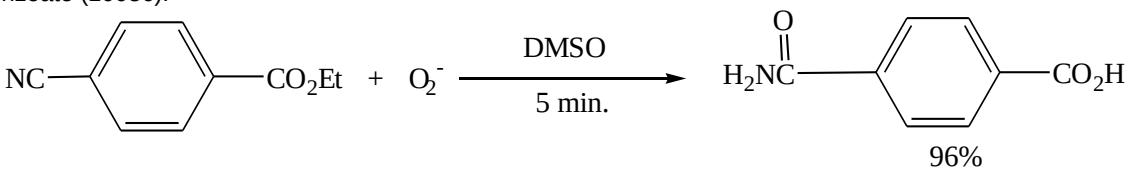


Similarly, the saponification rates of unsaturated esters in DMSO-water are faster than in ethanol-water (3356) (7540). Increased transition state solvation, not increased hydroxyl ion desolvation, is the major cause of rate enhancement in DMSO (6822).

The rate coefficients of neutral hydrolysis of methyl trifluoroacetate and chloromethyl dichloroacetate in DMSOwater are greater than in acetone-water and acetonitrile-water (6477).

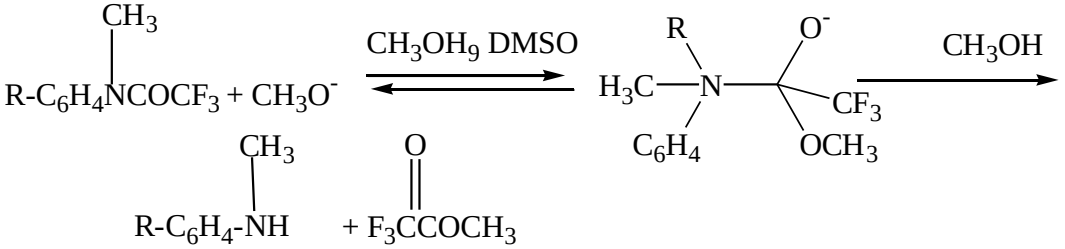
With hydrolysis on the acid side, however, the reaction rate decreases as the mole fraction of DMSO increases above 25-30% DMSO, as is the case with ethyl acetate (368).

The cleavage of highly hindered esters can be accomplished in DMSO using potassium t-butoxide as the base and heating until the cleavage is accomplished. In this case, the cleavage occurs by alkyl-oxygen fission (490). Esters are also cleaved by sodium superoxide in DMSO to give carboxylic acids in excellent yield, as is the case of ethyl p-cyanobenzoate (10086).



2. Alcoholysis, Aminolysis

In the basic methanolysis of some aryl substituted N-methyl-2,2,2-trifluoroacetanilides in DMSO-methanol rate increases with increasing amount of DMSO (6474):

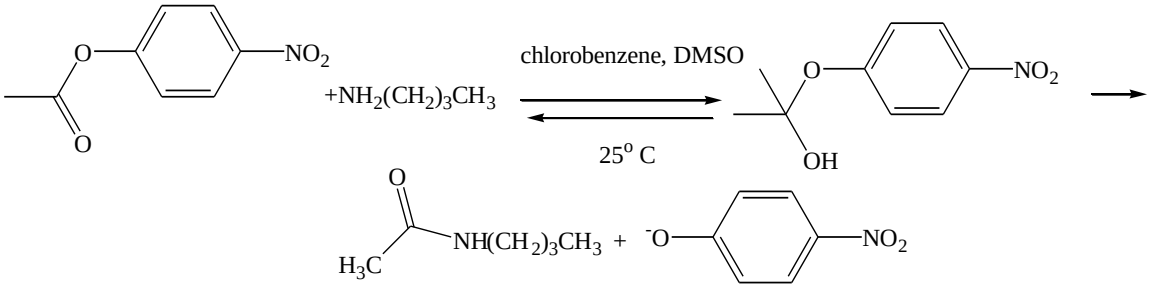


N-Methyl-4'-nitroanilides undergo basic methanolysis by way of rate determining methoxide addition to the amide, as shown above. The addition of DMSO produces a rate increase in each case (7844).

The mechanism of basic methanolysis of a series of N-aryl-N-phenylbenzamides in methanol and in 80% DMSOmethanol has been studied. In methanol the rate determining step seems to be the solvent assisted C-N bond breaking, while in 80% DMSO-methanol the rate determining step is methoxide attack (10409).

Markedly increased alcoholysis rates are obtained by the addition of DMSO to ethylene-vinyl ester interpolymer alcohol mixtures in the presence of either alkaline or acidic mixtures (7156).

DMSO is an effective catalyst for the n-butylaminolysis of p-nitrophenyl acetate in chlorobenzene (6988).

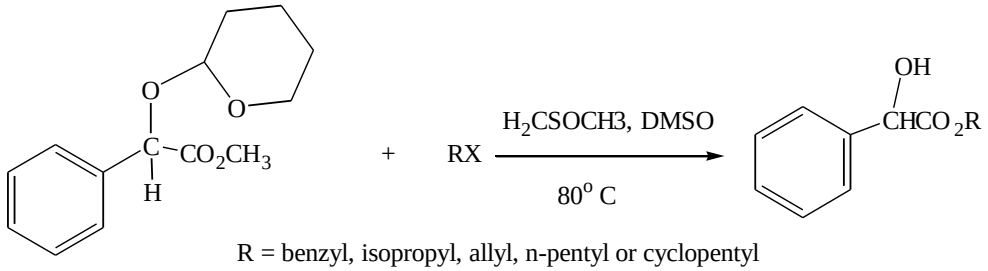


The aminolysis of polymeric macronet N-hydroxy-succinimide esters of Boc-amino acids by free amino acids and peptides in DMSO has been studied, both in the presence and in the absence of organic bases (8832).

3. Transesterification (Ester Interchange)

The reported work concerning the base catalyzed transesterification of fatty acid esters mainly describes esterification of carbohydrates and other polyhydroxylic materials. DMSO is a particularly suitable solvent in this area because of the enhanced activity of the base catalyst in DMSO and also because of the excellent solubility of most carbohydrate and polyhydroxylic substances in DMSO. A number of the reports are concerned with sucrose esters (160)(161)(181)(162)(164)(165). Others report esterifying hexitols and hexoses (1257) and inositols (166). The reaction of 1,2-0-isopropylidene-6-tosyl-glucose under the conditions of the Kornblum oxidation with potassium bicarbonate as the base gives none of the expected aldehyde but only the 5,6-carbonate ester(183) in a transesterification.

Alkylation of methyl 0-(tetrahydropyran-2-yl) mandelate using alkyl halides and sodium hydride in DMSO at 80°C produces transesterification products (4278):



R = benzyl, isopropyl, allyl, n-pentyl or cyclopentyl

Dimethyl terephthalate can be polymerized with ethylene glycol in the presence of a tin chloride-DMSO complex and trimethylphosphate to give a poly(ethylene terephthalate) (7255).

Thermoplastic polymers derived from natural products have been prepared by interesterifying starch with methyl palmitate in DMSO with potassium methoxide as the catalyst (8227).

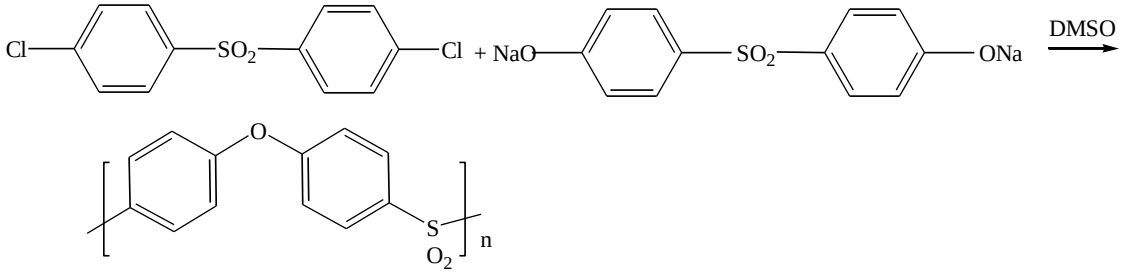
PART V USES

1. Polymerization and Spinning Solvent

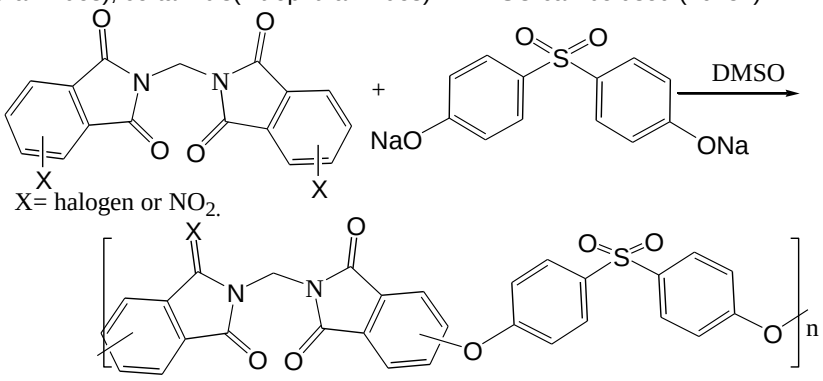
DMSO is used as a solvent for the polymerization of acrylonitrile and other vinyl monomers, e.g. methyl methacrylate (9638) and styrene (5192). Acrylonitrile is readily soluble in DMSO and the polymerization is carried out by the addition of initiators (8184)(8185). The low incidence of transfer from the growing chain to DMSO leads to high molecular weights. Copolymerization reactions of acrylonitrile with other vinyl monomers can also be run in DMSO. Monomer mixtures consisting of acrylonitrile, styrene, vinylidene chloride, methallyl sulfonic acid, styrene sulfonic acid, etc. are polymerized in DMSO-water (6713). In some cases, the fibers are spun from the reaction solution into DMSO-water baths (8501)(8603).

DMSO can also be used as a reaction solvent for other polymerizations. Thus, ethylene oxide is rapidly and completely polymerized in DMSO (9652). Diisocyanates and polyols and polyamines can be dissolved and reacted in DMSO to form solutions of polyurethanes (8677).

Polymerization Solvent for Heat Resistant Polymers. Poly(ether sulfones) are a family of polymers from which a series of tough thermoplastics can be selected for use under continuous stress in the temperature range of 150-250°C (7196)(7619). These poly(ether sulfones) are prepared by reacting dialkali metal salts of a bisphenol, such as bisphenol A or 4,4'-sulfonyldiphenol with 4,4'-dihyalodiphenyl sulfones by the displacementetherification reaction in DMSO (7104)(9961), e.g.:

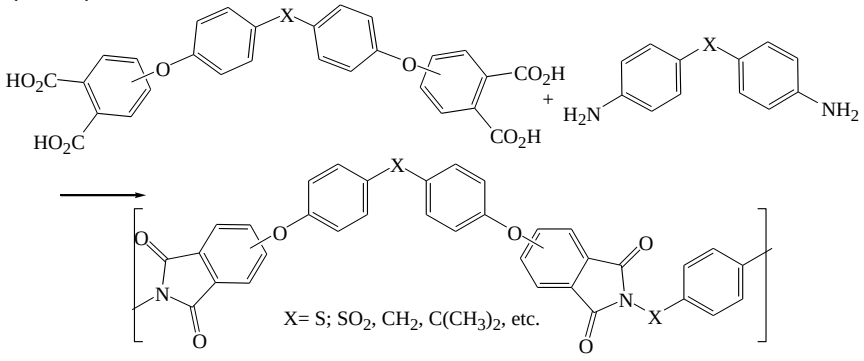


Interest in heat-resistant polymers has also lead to the development of polyetherimides. These polymers are prepared by the reaction of a dialkali metal salt of a bisphenol, such as bisphenol A or 4,4'-sulfonyl diphenol, with bis(halophthalimide) in DMSO as the solvent (9686). In place of bis(halophthalimides), certain bis(nitrophthalimides) in DMSO can be used (10434):



X= halogen or NO_2.

Somewhat similar polyetherimides can be prepared by reacting an aromatic bis(ether dicarboxylic acid) component with a diamine in DMSO-water (10762):



x-S; SO_2; CH_2; $C(CH_3)_2$, etc

2. Extraction Solvent

DMSO is immiscible with alkanes but a good solvent for most unsaturated and polar compounds. Thus it can be used to separate olefins from paraffins (10771). DMSO is used in the Institute Francais du Petrole (IFP) process for extracting aromatic hydrocarbons from refinery streams (8554). DMSO is also used in the analytical procedure for determining polynuclear hydrocarbons in food additives of petroleum origin (2371).

3. Solvent for Electrolytic Reactions

DMSO has been widely used as a solvent for polarographic studies and it permits the use of a more negative cathode potential than in water. In DMSO cations can be successfully reduced to form metals that would react with water. Thus, the following metals have been electrodeposited from their salts in DMSO: cerium (1749), actinides (2520), iron, nickel, cobalt, manganese – all amorphous deposits; zinc, cadmium, tin, bismuth – all crystalline deposits; (5488); chromium (6672), silver (7459), lead (9175), copper (9396), titanium (7260). Generally, no metal less noble than zinc, such as magnesium or aluminum, can be deposited from DMSO.

4. Cellulose Solvent

Although DMSO by itself does not dissolve cellulose, the following binary and ternary systems are listed as cellulose solvents: DMSO-methylamine, DMSO-sulfur trioxide, DMSO-carbon disulfide-amine, DMSO-ammoniasodamide, DMSO-dinitrogen tetroxide, DMSO-paraformaldehyde (8970)(10368), DMSO-sulfur dioxide-ammonia (9541). A least a ratio of 3 moles of active agent per mole of glucose unit is necessary for complete dissolution (8970). While only 80% of cellulose dissolves in DMSO-methylamine under cold anhydrous conditions (10368), DMSO-nitrogen tetroxide is a better solvent, particularly when a small quantity of water is added (9170). Most of these systems are capable of producting cellulose fibers. The recently discovered DMSO-paraformaldehyde system does not degrade cellulose and it can form solutions containing up to 10% cellulose (7763)(8506)(9850). It is believed that a methylol-cellulose compound forms which is stable for extended periods of storage at ambient conditions (9850). Regenerated cellulose articles such as films and fibers can be prepared by contacting the DMSO-paraformaldehyde solution with methanol and water (9850)(9895).

5. Pesticide Solvent

Many organic fungicides, insecticides and herbicides are soluble in DMSO, including such difficultly soluble materials as the substituted ureas and carbamates. DMSO forms cosolvent systems of enhanced solubility properties with many solvents.

6. Cleanup Solvent

DMSO is used to remove urethane polymers and other difficultly soluble materials from processing equipment. Hard crusts of poly(vinyl chloride) resin can be dissolved by using 85:15 ethyl acetate-DMSO mixture (8927).

7. Sulfiding Agent

DMSO (ENVIRO-S) can be used as a sulfiding agent in refineries because of its low odor, low toxicity and ease of handling.

8. Integrated Circuits

DMSO solutions are useful for etching resists in integrated circuit manufacture.

PART VI
TOXICITY, HANDLING, HAZARDS, ANALYSIS

1. Toxicity and Handling Precautions

Dimethyl sulfoxide is a relatively stable solvent of low toxicity. The LD_{50}, for single dose oral administration to rats is about 18,000 mg/kg. For comparison, the LD_{50} for ethyl alcohol is about 13,700 mg/kg. DMSO by itself presents less hazard than many chemicals and solvents commonly used in industry. However, DMSO has the ability to penetrate the skin and may carry with it certain chemicals with which it is combined under certain conditions.

The toxicity of DMSO solutions will depend, in part, on the nature and toxicity of the other chemicals used and the degree of penetration. The degree of penetration is determined by the concentration of DMSO and water in the solution and the length of time of skin contact. Not all chemicals will be carried through the skin even though the DMSO may penetrate. A 10% solution of DMSO in water causes only slight increase in skin penetration over the same solution without DMSO.

Conventional industrial safety procedures and practices should be observed when working with DMSO as with any organic solvent. Protective clothing is not necessary when handling DMSO in containers or in small amounts on limited occasions. However, when working with DMSO on a prolonged basis or in combinations with other materials, protective clothing is recommended, including suitable gloves or eye protectants. Butyl rubber gloves are suggested for DMSO service.

Contacts with DMSO Alone

Skin: Undiluted DMSO may have a mildly irritating effect on the skin and should be washed off promptly with cold water. As is the case with other organic solvents, dimethyl sulfoxide tends to dehydrate and de-fat the skin. Repeated skin contact overextended periods should be avoided since the effects of such contact, if any, are not yet known.

Eyes: DMSO in contact with the eye may cause temporary irritation but will not result in eye damage if washed out promptly with cold water.

Vapors: The normal ambient airborne DMSO concentration is low. (DMSO has a high boiling point, 189°C or 372°F, and a low vapor pressure.) Inhalation of vapors of hot DMSO or DMSO aerosol mists may be harmful and should be avoided.

Contact with DMSO solutions: When handling solutions of possibly toxic substances in DMSO, care must be taken to avoid contact with the skin and to wash such solutions off immediately and thoroughly with soap and water. If toxic substances penetrate into the system, serious harm may occur. Clothing contacted by such solutions should be removed and washed before reusing.

2. Comparative Toxicity of Commercial Solvents

All solvents are toxic to some extent, but DMSO is much less so than many in common usage. Toxicity, as measured by dermal and oral LD_{50} in rats, is shown for a number of common solvents. They are listed in order of increasing oral toxicity.

TABLE XII
Single-Dose Toxicity (Rats) of Some Common Solvents

	LD_{50}, mg/kg	
Solvent	**Oral**	**Dermal**
Glycerine	31600	10000
DMSO	17400	40000
Ethanol	13700	-
Acetone	9750	-
Dimethylacetamide	7500	5000
Ethylene glycol	7200	-
N-methyl-2-pyrrolidone	7000	-
Trichloroethylene	5860	-
Lsopropanol	5840	-
n-Propanol	4300	-
Benzene	4080	-
Diacetone alcohol	4000	-
Methyl ethyl ketone	3980	-
Xylene	3830	10000
Cyclohexanone	3460	-
Acetic acid	3310	-
n-Butenol	2610	5620
2-Heptanol	2580	-
Butyl cellosolve	2380	-
Dimethylformamide	2250	442
Sodium lauryl sulfate	1650	10000
Pyridine	891	1120
Aniline	442	1540
Phenol	14*	-

* Approximate lethal dose.

Most of the solvents in the above table were chosen because, like DMSO, they are polar.
Several studies have been made in comparing the toxicity of DMSO with other solvents. Table XIII shows the results of one of these studies.

TABLE XIII
Single-Dose Toxicities to Mice of 4M Solutions
LD_{50}, mg/kg (mice)

Compound	**Intravenous**	**Intraperitoneal**
DMSO	7176	14664
Glycerine	6164	6900
Dimethyl formamide	3650	6570
Dimethyl acetamide	3915	5916
N-methyl pyrrolidone	1980	3564

3. Chemicals and Reactions to be Avoided with DMSO

DMSO can react vigorously and even explosively with iodine pentafluoride, periodic acid, potassium permanganate, silver fluoride and other strong oxidizing agents such as magnesium perchlorate and perchloric acid.
DMSO cannot be used in Friedel-Crafts reactions or with Ziegler-Natta catalysts.
DMSO reacts vigorously with acid chlorides. These reactions proceed with about the same vigor as the reaction between acid chlorides and ethyl alcohol, and suitable precautions should be taken.
DMSO also reacts with carboxylic acid anhydrides, such as acetic anhydride, the major product being the acyloxymethyl methyl sulfide, $RCO_2CH_2SCH_3$.
Adequate heat removal should be provided when reacting DMSO with sodium hydride or potassium hydride when making the DMSO anion (dimsyl ion) (Please see PART III, Reactions of DMSO, 4. Reaction with Strong Bases).
An uncontrolled reaction took place when DMSO was heated with methyl bromide to prepare trimethyloxosulfonium bromide. This

reaction should be run in the presence of compounds that remove HBr or Br_2, such as methyl or ethyl orthoformate or tetramethyl orthocarbonate. These esters act as scavengers of HBr and Br_2, produced as byproducts in the reaction. Thus, the possible violent exothermic decomposition of the reaction mixture can be prevented with little, if any, loss in the yield of the product (9964).

4. Analytical Procedure

a) **Gas chromatographic analysis of DMSO**

Apparatus

Gas chromatograph with flame ionization detector and a 4 ft. x 1/8 inch o.d. stainless steel column packed with 15% FFAP (Varian Aerograph) on Chromosorb T (Johns-Manville), 40/60 mesh.

1.0 microliter syringe.

Chromatograph Conditions

Temperatures: Column - 150°C, Detector - 220°C, Inlet - 210°C Carrier gas flow - 30 ml/min

Adjust the instrument sensitivity so that a 0.5 microliter sample will give a DMSO peak between 75 and 100% of recorder full scale.

Procedure

Inject 0.5 microliters of the DMSO. Record the DMSO peak at the sensitivity determined above. Record the period before and after the DMSO peak at 100 times this sensitivity. Record the chromatogram for 20 minutes. Sum the areas of any extraneous peaks.

Calculations

[redacted]

b) **DMSO Freezing Point**

Pour 30-50 ml of DMSO into a clean, dry test tube, approximately 2.5x20 cm in size and fitted with a stopper containing thermometer and also containing a small magnetic stirring bar.

Cool the test tube in water at 15°C while agitating with a magnetic stirrer until crystallization starts. Once crystallization has begun read the thermometer while both liquid and solid DMSO are present. Purified DMSO - 18.3°C minimum (See Figure 2b, page 5)

c) **Water Determination by Karl Fischer Titration**

Discussion

Water is determined by Karl Fischer titration. Karl Fischer procedures other than the one described below may be used provided that their accuracy in this analysis has been determined.

Scope

This procedure may be used with all grades of DMSO.

Reagents

1. Pyridine-SO_2-methanol.

Mix 300 ml. C.P. pyridine and 300 ml anhydrous methanol. Bubble in 60 grams of SO_2. This can be done with the solution on a platform balance to weigh directly the SO_2 added.

2. Anhydrous methanol.

3. Karl Fischer Reagent - stablilized.

Fischer Scientific SO-K-3

4. Water-methanol standard.

1 ml = 1 mg of water. Can be obtained commercially.

Apparatus

Titration Assembly

The titration is contained in a screwcap glass jar of 100-200 ml capacity. The cap is drilled to admit2 platinum electrodes and one burette tip. During the titration the jar is mounted over a magnetic stirrer with the electrodes extending through the cap into the solution to be titrated. Reagents and sample are added through the third hole and a micro burette containing Karl Fischer Reagent is mounted above the third hole.

A preferred alternate to the above assembly can be constructed from both halves of a large diameter glass ball and socket joint.

End-Point Detecting Assembly

The end-point detecting assembly is of the "dead stop" type, which depends upon the depolarization of the electrodes on reaching the end-point of the titration.

[redacted]

Procedure

End-Point Detection

With the equipment set up as described and the material to be titrated in the bottle, start the magnetic stirrer. Adjust the variable resistance to produce a microammeter deflection of 1 or 2 microamps. Titrate with Karl Fischer Reagent. As the end-point is neared, the ammeter needle starts to swing with each addition of titrant, but returns to the original point of deflection after each swing. When the end-point is reached the needle will remain permanently displaced up scale.

Standardization of Reagents



The Karl Fischer solution must be standardized daily. Add 20 ml of anhydrous methanol and 5 ml of the pyridine-SO_2-methanol solution to the titration bottle (Note 1). Add Karl Fischer Reagent dropwise from a microburette to the end-point. Accurately pipette 20 ml of the water-methanol standard (a weighed amount of pure water may be used) into the titration bottle and titrate with Karl Fischer Reagent to the end-point. Record the volume of titrant used in the second titration and calculate its water equivalence.

Determination of Water



Add 20 ml of anhydrous methanol and 5 ml of the pyridine-SO_2-methanol solution to a clean titration bottle. Add Karl Fischer Reagent dropwise to the end-point. Add 2 to 3 grams (accurately weighed) of the DMSO to be tested (Notes 2, 3, and 4). Titrate with Karl Fischer Reagent to the end-point. Record the volume of titrant used in the second titration and calculate the water content of the dimethyl sulfoxide.

Notes

1. Response tends to be slow with the stabilized Karl Fischer Reagent. A sharper end-point is obtained with the addition of the pyridine-SO_2-methanol solution to the titration vessel.
2. DMSO is extremely hydroscopic. Exposure of the sample to atmospheric moisture must be kept to a minimum.
3. Samples larger than 2-3 grams of DMSO produce low results.
4. For convenience, with a sacrifice of accuracy, a 2 or 3 ml. volume of DMSO can be sampled with a volumetric pipette. The weight of DMSO samples is calculated by multiplying the volume in ml. by 1.10 (the specific gravity of pure DMSO @ 20°C.).
5. A titration assembly such as a Beckman Model KF-2 Aquameter may be used for the titration.

PART VII
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