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Demethylation of eugenol with LiCl in DMF

Conception, Characterization and Correlation of New Marine Odorants

Philip Kraft, Walter Eichenberger

[Eur. J. Org. Chem., 2003, 19, 3745-3743](#)

see also: [Patent EP1136481](#)

LiCl (292 g, 6.89 mol) was added to a solution of eugenol (354 mL, 2.30 mmol) in DMF (3.7 L), and the mixture was refluxed for 44 h, with additional portions of LiCl (292 g, 6.89 mol) being added after 4 h, 22 h and 29 h. The reaction mixture was allowed to cool down to room temp., and diluted with toluene (2 L). The formed precipitate was filtered off and washed with toluene, the washings were combined with the organic solution and concentrated in a rotary evaporator. Silicagel FC (Et₂O/pentane, 1:1, R_f = 0.37) provided 4-allylpyrocatechol (173 g, 50%).

Cleavage of aromatic methyl ethers with ethanethiol (EtSH) and aluminium chloride (AlCl₃)

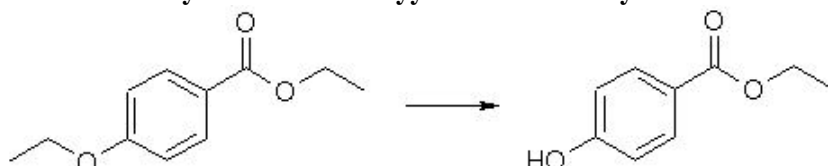
Hard Acid and Soft Nucleophile System.

2. Demethylation of Methyl Ethers (of Alcohol and Phenol with an Aluminum Halide-Thiol System

Manabu Node, Kiyoharu Nishide, Kaoru Fuji, and Eiichi Fujita

[J. Org. Chem., 1980, 45\(22\), 4275-4277](#)

Selective Deethylation of 4-ethoxybenzoic acid ethylester



To a mixture of dry ethanethiol (1 mL) and dichloromethane (1 mL) was added aluminum chloride (0.40 g, 3.0 mmol) at 0 °C. The resulting solution was warmed to room temperature, and 4-methoxybenzoic acid methylester (0.194 g, 1.0 mmol) was added with stirring. After being stirred for 9.5 h, the reaction mixture was poured into water, acidified with dilute HCl, and extracted with dichloromethane. The organic layer was treated as usual to give a crude product. Chromatography over a silica gel column gave 4-hydroxybenzoic acid ethyl ester (0.157 g, 95.5%) identical with an authentic sample.

Demethylenation of 1,3-benzodioxole



To a solution of aluminum bromide (0.683 g, 2.4 mmol) in dry ethanethiol (2 mL) was added 1,3-benzodioxole (0.122 g, 1.0 mmol) at 0 °C. After being stirred for 0.5 h, the reaction mixture was poured into water, acidified with 3% HCl, and then extracted with ether. The ethereal layer was shaken with 1% aqueous KOH. The aqueous layer was acidified with 3% HCl and again extracted with ether. The ethereal layer upon the usual workup gave a crude product, which was chromatographed over a silica gel column to afford pyrocatechol (86.5 mg, 78.4%).

Selective Demethylenation of 3,4-methylenedioxy benzoic acid methyl ester



To a solution of aluminum bromide (0.537 g, 2.0 mmol) in dry ethanethiol (2.3 mL) was added 3,4-methylenedioxy benzoic

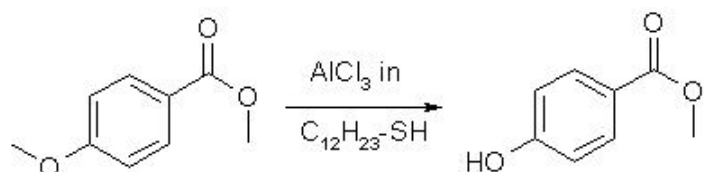
acid methyl ester (0.091 g, 0.5 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into water, acidified with 5% HCl, and then extracted with ether. The ethereal layer was treated as usual to give a crude product, and chromatography over a silica gel column gave protocatechuic acid methyl ester (61.3 mg, 72.4%), identical with an authentic sample prepared from protocatechuic acid.

Cleavage of aromatic methyl ethers with 1-dodecanethiol ($C_{12}H_{25}SH$) and aluminium chloride ($AlCl_3$)

Odorless substitutes for foul-smelling thiols: syntheses and applications

Manabu Node, Kamal Kumar, Kiyoharu Nishide, Shin-ichi Ohsugi and Tetsuo Miyamoto

[Tet. Lett., 2001, 42\(52\), 9207-9210](#)



4-methoxybenzoic acid methyl ester is cleaved to 4-hydroxybenzoic acid methyl ester at r.t. in 4,5 h (yield: 77%).

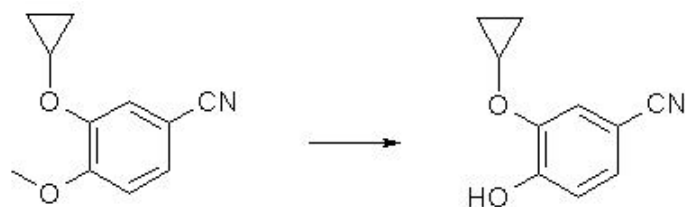
Cleavage of aromatic methyl ethers with 1-dodecanethiol ($C_{12}H_{25}SH$) and sodium methoxide ($NaOMe$)

Practical synthesis of a highly functionalized thiazole ketone

Lisa F. Frey, Karen M. Marcantonio, Cheng-yi Chen, Debra J. Wallace, Jerry A. Murry, Lushi Tan, Weirong Chen, Ulf H. Dolling and Edward J. J. Grabowski

[Tetrahedron, 2003, 59\(33\), 6363-6373](#)

Many standard demethylation conditions were screened for the transformation of **6** to **8** (Scheme 4). In several cases (i.e. boron tribromide), competing cleavage of the cyclopropyl ether was a problem. Fortunately, the use of a slight excess of sodium ethanethiolate in N,N-dimethylformamide (1-Methyl-2-pyrrolidinone and dimethylacetamide were also acceptable solvents for this reaction) at 100°C effected clean demethylation of **6** with no detected cleavage of the cyclopropyl ether.

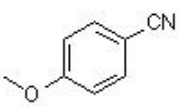
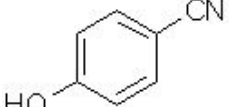
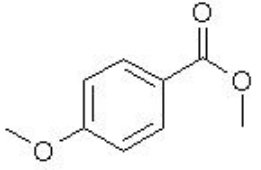
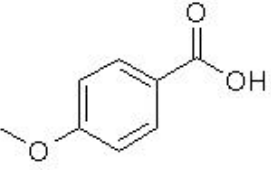
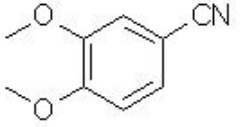
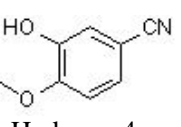
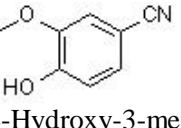
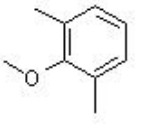
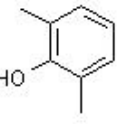


Scheme 4: EtSNa or $CH_3(CH_2)_{11}SH$ and NaOMe, DMF, 100°C, 1 h

Because the stench of sodium ethanethiolate and the reaction byproduct, ethyl methyl sulfide, made this reaction unpleasant to run on a large scale, we were interested in carrying out the same transformation under non-odorous conditions. Recent papers discuss the use of long chain thiols to minimize odor so we used this work as a basis for choosing a long chain thiol for our demethylation reaction. Following a literature result, the use of mixtures of a thiol and various lewis acids was explored.¹⁹ Unfortunately, these reactions were not successful on our substrate; however, employing the sodium salt of a thiol afforded clean demethylation. Hence, the use of 1.7 equiv. of dodecanethiol and 1.7 equiv. of sodium methoxide in N,N-dimethylformamide at 100°C gave an almost quantitative yield of phenol **8**. Work up involved extraction of the product into aqueous base with thiol byproducts left behind in the organic phase. The product was extracted from the aqueous layer simply by adjusting to acidic pH. This work up provided an odor free solution of compound **8** that was used in the next reaction without further purification. Due to our success with demethylation using a non-odorous long chain thiol, we explored the generality of the method with a few model compounds. Using the procedure described above for the conversion of **6** to **8**, the compounds shown in Table 1 were readily demethylated by heating each substrate with sodium methoxide and dodecanethiol in N,N-dimethylformamide at 100°C. Demethylation of 4-methoxybenzonitrile and methyl 2-methoxybenzoate (Table 1, entries 1 and 2) proceeded in high yield. Demethylation of hindered 2,6-dimethylanisole (Table 1, entry 3) was sluggish and did not go to completion. Interestingly, selective

(4.9:1) demethylation of 3,4-dimethoxybenzonitrile (Table 1, entry 4) was observed, with preference for demethylation para to the electron withdrawing nitrile substituent. Clearly, these results demonstrated that demethylation using a non-odorous long chain thiol and sodium methoxide was a viable alternative to sodium ethanethiolate for a range of anisole related substrates.

Table 1: Demethylation using sodium methoxide and 1-dodecanethiol in N,N-dimethylformamide at 100°C

Entry	Starting material	Product(s)	Yield
1	 4-Methoxybenzonitrile	 4-Hydroxybenzonitrile	97%
2	 4-Methoxy benzoic acid methyl ester	 4-Methoxy benzoic acid	89%
3	 3,4-Dimethoxy benzonitrile	 3-Hydroxy-4-methoxy benzonitrile	17%
		 4-Hydroxy-3-methoxy benzonitrile	83%
4	 2,6-Dimethylanisole	 >2,6-Dimethylphenol	75% ^a

^a 21% starting material recovered

3-(Cyclopropyloxy)-4-hydroxybenzonitrile **8**

To a solution of **6** (47.7 g, 0.252 mol) in DMF (450 mL) was added 1-dodecanethiol (104 mL, 0.432 mol) followed by NaOMe (23.4 g, 0.432 mol). The mixture was heated to 100°C and aged for 1 h (monitoring by HPLC). After cooling to RT, iPAc (404 mL), water (518 mL), and 5N NaOH (45 mL) were added and the layers mixed well. The aqueous layer was washed with iPAc (350 mL) to remove more thiol byproducts. The aqueous layer was neutralized to pH 6 by addition of conc HCl (45 mL), and the product was extracted into iPAc (518 mL). The aqueous layer was extracted with iPAc (278 mL then 150 mL). The organic layers were concentrated and flushed with 160 mL DMF (43.7 g, 99% yield of **8** as compared to a chromatographed standard) before being used directly in the difluoromethylation.