Indian Journal of Chemistry
Vol. 41B, May 2002, pp. 1072-1074

Note

Reduction of oximes with sodium borohydride – copper (II) sulfate in methanol

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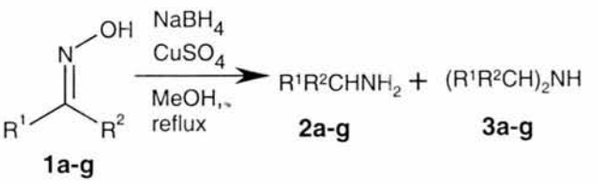
Received 20 December 2000; accepted (revised) 25 October 2001

Reduction of aldoximes and ketoximes with sodium borohydride in methanol reflux results in corresponding primary and secondary amines in good yields.

Reduction of oxime functionality to amine is an important synthetic transformation. As oximes are stable derivatives of carbonyl compounds, subsequent reduction to amines is an attractive two-step procedure for reductive amination. Reduction of oximes to amines can be performed by hydride reducing agents or by catalytic hydrogenation.[1] Among hydride reducing agents, lithium aluminium hydride is commonly employed for this purpose. However, this reagent is non-selective and difficult to handle. On the other hand, sodium borohydride is a mild reducing agent effective only for the reduction of aldehydes, ketones and acyl halides. Its reducing power can be enhanced as well as altered in the presence of transition metal salts such as nickel (II) chloride, cobalt (II) chloride, titanium (IV) chloride etc.[2] Complex metal borides in conjugation with sodium borohydride were proposed as the actual reducing reagents, mimicking catalytic hydrogenation.[2] Previously, we have found that sodium borohydride-copper sulfate is an efficient and convenient reagent for the reduction of azides to primary amines.[3] In continuation, we now report our studies on the reduction of oximes with this reagent. Previously, Ipakstschi[4] reported the reduction of some ketoximes to primary amines with sodium borohydride and nickel (II) chloride.[4] We now found that reduction of oximes with sodium borohydride and copper (II) sulfate yields primary as well as secondary amines in varying ratios depending on the nature of the oxime (**Scheme I**). Results obtained in this study are gathered in the **Table I**.

Reduction of benzaldehyde oxime **1a**, an aromatic aldoxime, was studied initially as a representative example. Addition of one equivalent of sodium borohydride to methanolic solution of copper (II) sulfate produced black colloidal suspension to which methanolic solution of oxime was added and the progress of the reaction was monitored by TLC. Reaction at room temperature (30 °C) was slow but at methanol reflux for 2hr reaction progressed to yield benzyl amine **2a** and dibenzyl amine **3a** in the ratio of 2:7 in 35% yield. However, when sodium borohydride (20 eq) was added, in portions, periodically during the reaction, total yield of the amines increased to 82% (see Experimental Section). Reduction of *p*-chloro-**1b** and *p*-methoxybenzaldehyde oximes **1c** were studied to find out if there is any effect of the aromatic ring substituents on product ratios. However, we did not find much substituent effects and ratio of primary **2b**, **2c** to secondary amines **3b**, **3c** remained approxi-mately same. Reduction of *p*-nitrobenzaldehyde oxime resulted in complex mixture of products from which *p*-aminobenzaldehyde oxime could be isolated in 15% yield. This result indicates that reduction of nitro-group precedes the reduction of oxime. Reduction of acetophenone oxime **1d**, an aromatic ketoxime, was next studied. This reaction yielded primary amine **2d** and secondary amine **3d** in the ratio of 2:1 in 89% yield. Increase in the steric demand at the reaction center is apparently responsible for the change in the product ratio.

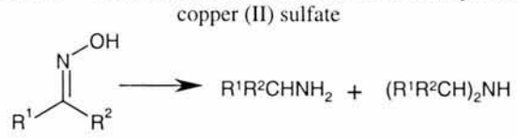


1a, 2a, 3a: $R^1 = C_6H_5$, $R^2 = H$; **1b, 2b, 3b**: $R^1 = p\text{-}ClC_6H_4$, $R^2 = H$; **1c, 2c, 3c**: $R^1 = p\text{-}MeC_6H_4$, $R^2 = H$; **1d, 2d, 3d**: $R^1 = C_6H_5$, $R^2 = CH_3$; **1e, 2e, 3e**: R^1, $R^2 = CH_2(CH_2)_3CH_2$; **1f, 2f, 3f**: R^1, $R^2 = CH_2(CH_2)_2CH_2$; **1g, 2g, 3g**: $R^1 = CH_3(CH_2)_5CH_2$, $R^2 = H$.

Scheme I

Reduction of cyclohexanone oxime **1e**, an aliphatic ketoxime, resulted in cyclohexylamine **2e** and dicyclohexylamine **3e** in the ratio of 5:3 in 91% combined yield. Recently, Yoon *et al.*[5] have shown, in an isolated case, that borohydride exchange resin-copper sulfate reduces cyclohexanone oxime to

Table I — Reduction of oximes with sodium borohydride-copper (II) sulfate



R^1	R^2	Ratio of $R^1R^2CHNH_2$ and $(R^1R^2CH)_2NH$	Combined yield (%)
C_6H_5	H	2:7	82
p-ClC_6H_4	H	2:7	84
p-$CH_3C_6H_4$	H	2:7	80
C_6H_5	CH_3	2:1	89
$CH_2(CH_2)_3CH_2$		5:3	91
$CH_2(CH_2)_2CH_2$		1:1	90
$CH_3(CH_2)_5CH_2$	H	1:4	87

cyclohexyl amine and dicyclohexylamine in the ratio of 1:3 ratio in 32% yield. However, with our reagent system and experimental procedure, we found greatly enhanced yields and different product ratio. Reduction of cyclopentanone oxime **1f** resulted in cyclopentylamine **2f** and dicyclopentylamine **3f** in the ratio of 1:1 in 90% yield. Subtle changes in steric environment may be responsible for change in the product ratio. Reduction of heptanal oxime **1g**, a aliphatic aldoxime, with above reagent resulted in heptylamine **2g** and diheptylamine **3g** in 1:4 ratio in 87% yield. Previously this transformation was achieved under drastic catalytic hydrogenation conditions.[6]

It is evident from our studies, that reduction with sodium borohydride-copper (II) sulfate is similar to catalytic hydrogenation. Finely divided colloidal copper generated *in situ* with large active metal surface area is expected to be responsible for the reduction. Previously, Henglein[7,8] and Jana *et al.*[9] have clearly shown that in the reduction of several organic dyes with metals, the reaction of sodium borohydride with salts resulted in finely divided metal particles of 10 nm size, which are responsible for the increased catalytic activity. In the reduction of oximes with copper (II) sulfate / sodium borohydride, imines are possible intermediates. Reduction of imine leads to primary amines. Further reaction of imine with primary amine result in intermediates, which on further transformation furnish secondary amines.

In conclusion, we have shown that sodium borohydride-copper (II) sulfate is a convenient and inexpensive reagent for reduction of oximes to corresponding primary and secondary amines. Its reactivity is similar to catalytic hydrogenation and is different from reducing profile of sodium borohydride-nickel (II) chloride.

Experimental Section

Aldehydes were procured commercially and were purified through distillation before use. Column chromatographic purification of amines were carried out on basic alumina (Acme) eluting with dichloromethane. TLC analysis was carried out with silica gel G-254 (Acme) and spots were visualized using iodine vapours. All the oximes used and the amines generated in this study are known compounds. The products were characterised based on the spectral data. ^1H NMR (60MHz) analysis was carried out on Hitachi NMR spectrometer in CCl_4 with TMS as internal standard (chemical shifts in δ ppm downfield from TMS). IR spectra were recorded as neat samples on Shimadzu FTIR spectrometer.

Representative procedure for the reduction of oximes with sodium borohydride -copper (II) sulfate; reduction of benzaldehyde oxime. To a stirred solution of copper (II) sulfate pentahydrate (100 mg, 0.4mmole) in methanol (10mL) sodium borohydride (15mg, 0.4mmole) was added at 0-5°C in one lot. To the resulting black colloidal suspension, benzaldehyde oxime (485mg, 1mmole) in methanol (5mL) was added and the reaction mixture was heated to reflux. After 15 min, the reaction mixture was cooled to 0-5°C, and excess sodium borohydride (190mg, 5mmoles) was added and the reaction was taken to reflux. This process was repeated four times for completion of the reaction (TLC). The reaction mixture was diluted with ice-cold water (100mL), *p*H was adjusted to 10 with 10% KOH solution and extracted with dichloromethane (30mL × 3). Combined organic solutions were washed with water (25mL) saturated brine solution (20mL) and the solvent was evaporated under reduced pressure to result in mixture of benzylamine and dibenzylamine which were separated on neutral alumina column and the ratio of the amines were computed on the basis of weights recovered from the column fractions.

Benzylamine **2a**: IR (neat): 3340, 3075, 1590 cm^{-1}; ^1H NMR: δ 1.28 (brs, 2H), 3.80 (s, 2H), 7.3 (s, 5H).

N,N-Dibenzylamine **3a**: IR (neat): 3030, 2950, 1635, 1590 cm^{-1}; ^1H NMR: δ 1.34 (brs, 1H), 3.75 (s, 4H), 7.3 (s, 10H); MS: m/z 197 (M^+), 196, 164, 134, 120, 106, 91, 77.

4-Chlorobenzylamine **2b**: IR (neat): 3345, 3070, 1600 cm^{-1}; ^1H NMR: δ 1.90 (brs, 2H), 3.85 (s, 2H), 7.15-7.3 (m, 4H).

N,N-Di(4-chlorobenzyl)amine **3b**: IR (neat): 3040, 2950, 1590, 750 cm^{-1}; ^1H NMR: δ 1.57 (brs, 1H), 3.64 (s, 4H), 7.157.3 (m, 8H).

4-Methylbenzylamine **2c**: IR (neat): 3345, 3075, 2945, 2859, 1590 cm^{-1}; ^1H NMR: δ 1.89 (brs, 1H), 2.29 (s, 3H), 3.85 (s, 2H), 6.95 (d, J = 8.0Hz, 2H), 7.22 (d, J = 8.0Hz, 2H).

N,N-Di(4-methylbenzyl)amine **3c**: IR (neat): 3032, 2945, 2854, 1623 cm^{-1}; ^1H NMR: δ 1.58 (brs, 1H), 2.31 (s, 6H), 3.64 (s, 4H), 6.94 (d, J = 8.0Hz, 4H), 7.20 (d, J = 8.0Hz, 4H).

1-Phenylethylamine **2d**: IR (neat): 3360, 3350, 3083, 2965, 1605 cm^{-1}; ^1H NMR: δ 1.40 (d, J = 7.2Hz, 3H), 2.15 (brs, 2H), 4.10 (q, J = 7.2Hz, 1H), 7.3 (br s, 5H).

N,N-Di(1-phenylethyl)amine **3d**: IR (neat): 3450, 3061, 3026, 2961, 1680, 1603 cm^{-1}; ^1H NMR: δ 1.38 (d, J = 7.3Hz, 6H), 2.72 (brs, 1H), 3.69 (q, J = 7.3Hz, 2H), 7.3 (brs, 10H) ppm; MS: m/z 225 (M^+), 210, 120, 106, 105, 91, 77, 65.

Cyclohexylamine **2e**: IR (neat): 3330, 3250, 2950, 1600, 1440 cm^{-1}; ^1H NMR: δ 0.85-2.05 (m, 10H), 1.55 (br s, 2H), 2.70 (m, 1H).

N,N-Dicyclohexylamine **3e**: IR (neat): 3281, 2928, 2853, 1645, 1468 cm^{-1}; ^1H NMR: δ 0.90-2.20 (m, 20H), 2.30 (s, 1H), 2.60 (m, 2H); ^{13}C NMR: δ 25.28, 26.09, 33.74, 53.08; MS: m/z 181 (M^+), 149, 138, 114, 98, 83, 79, 69, 57.

Cyclopentylamine **2f**: IR (neat): 3345, 3245, 2950, 1600, 1460 cm^{-1}; ^1H NMR: δ 1.10-2.02(m, 8H), 1.55 (br s, 2H), 3.45 (m, 1H).

N,N-Dicyclopentylamine **3f**: IR (neat): 3260, 2940, 2853, 1645, 1468, 1350 cm^{-1}; ^1H NMR: δ 1.52-2.15 (m, 16H), 2.40 (br s, 1H), 2.45 (m, 2H); ^{13}C NMR: δ 23.63, 29.75, 58.38; MS: m/z 153 (M^+), 124, 110, 84.

1-Heptylamine **2g**: IR (neat): 3345, 3330, 2953, 2854 cm^{-1}; ^1H NMR: δ 0.88 (t, J = 8.7Hz, 3H), 1.21-1.35 (m, 10H), 1.80 (br s, 2H), 2.6 (t, J = 7.1Hz, 2H).

N,N-Diheptylamine **3g**: IR (neat): 3045, 2950, 2845 cm^{-1}; ^1H NMR: δ 0.87 (t, J = 9.1Hz, 6H), 1.21-1.35 (m, 20H), 1.57 (br s, 1H), 2.46 (t, J = 7.2Hz, 4H).

Acknowledgement

Author (HSPR) thanks UGC, New Delhi, for financial support in the form of Major Research Grant, and author (BB) thanks Government of Pondicherry for study leave.

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