Tetrahedron Letters, Vol. 33, No. 13, pp. 1687-1688, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Deoxygenation of *N,N*-Disubstituted Hydroxylamines by Carbon Disulfide

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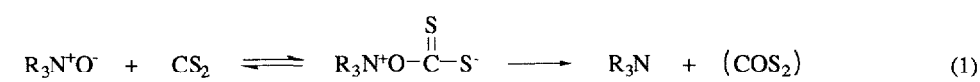
Key Words: carbon disulfide; deoxygenation; reduction of hydroxylamines; amine synthesis

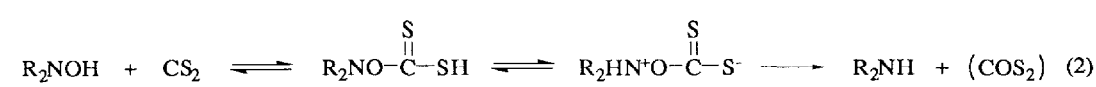
Abstract: Hindered N,N-dialkylhydroxylamines react rapidly with CS_2 to give the corresponding 2°-amines.

During the course of devising a new synthetic approach to hindered secondary amines,[1] we encountered the need to reduce *N,N*-disubstituted hydroxylamines to the corresponding amines. Standard methods for effecting this transformation include hydrogenation over Pd/C,[2] reduction with Zn/HCl [2] or with aqueous $TiCl_3$,[3,4] or reduction of the derived phosphate or carbonate esters with Li in liquid ammonia.[5,6] Since neither the direct hydrogenation nor the direct reduction methods gave satisfactory results in our hands with hydroxylamines that were both hindered and sensitive to C-N bond cleavage, we sought an alternate method.

Carbon disulfide is known to cause rapid deoxygenation of tertiary amine *N*-oxides by the proposed mechanism outlined in eq 1.[7,8] The structure of the byproduct "COS_2" is uncertain, but it is known to decompose primarily to carbon oxysulfide and sulfur,[7] or when generated in the presence of an alkene, to react to form the thiirane and carbon oxysulfide.[8] An analogous deoxygenation of hydroxylamines by carbon disulfide might also be expected to occur, as outlined in eq 2. The only precedent for this expectation that we could find[9] was a report that *N*-monosubstituted hydroxylamines reacted with carbon disulfide to give *N,N'*-disubstituted thioureas,[10] presumably via generation of the primary amine which underwent further reaction with carbon disulfide. We have now found that carbon disulfide reduces hindered *N,N*-disubstituted hydroxylamines to secondary amines smoothly and cleanly.



$$R_3N^+O^- + CS_2 \rightleftharpoons R_3N^+O-\overset{\overset{S}{\|}}{C}-S^- \longrightarrow R_3N + (COS_2) \quad (1)$$

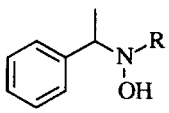
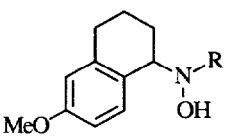
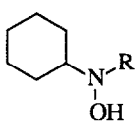


$$R_2NOH + CS_2 \rightleftharpoons R_2NO-\overset{\overset{S}{\|}}{C}-SH \rightleftharpoons R_2HN^+O-\overset{\overset{S}{\|}}{C}-S^- \longrightarrow R_2NH + (COS_2) \quad (2)$$

The results are summarized in Table 1. Dissolution of an *N,N*-disubstituted hydroxylamine bearing an *N-tert-butyl group in* CS_2 *at room temperature* resulted in a fairly rapid reaction with gas evolution (probably COS), to afford the corresponding 2°-amine in high yield; elemental sulfur could be isolated in 80-90% yields [based on ($COS_2 \rightarrow COS + S$) stoichiometry] by chromatography or by precipitation with methanol. The deoxygenation reaction was much slower with the *N*-methyl derivatives, but all of the reactions were accelerated by the use of acetonitrile as a cosolvent, as had previously been observed in the amine oxide deoxygenations.[7] Hydroxylamines bearing sterically undemanding substituents such as *N*-benzyl-*N*-methylhydroxylamine underwent reaction very slowly, and predominantly suffered *N*-dealkylation (also observed with amine oxides[8])

followed by condensation with CS_2 to give thioureas. On the other hand, the sterically very congested *N,N*-di-*tert*-butylhydroxylamine underwent very rapid deoxygenation to di-*tert*-butylamine (the reaction was over in 2 min using pure CS_2).[1] These observations are consistent with the reaction pathway suggested in eq 2, with the rate-determining last step being accelerated by the relief of steric compression in the highly hindered cases. This CS_2-mediated deoxygenation therefore nicely complements other methods for hydroxylamine reduction.[14]

Table 1. Deoxygenation of Hydroxylamines by CS_2.

Hydroxylamine[a]	R	Reaction Time (hr)		Amine	
		CS_2	CS_2/CH_3CN[b]	Yield[c] (%)	Ref.[d]
	*t*-Bu	1.5	0.5	90	11
	Me	30	20	87	*e*
	*t*-Bu	1.5	20 min	97	12
	Me	48	4	86	12
	*t*-Bu	1.5	5 min	93	13
	Me	5.5	1.5	71	*e*

[a] See ref. 1 for the preparation of the *N*-*tert*-butylhydroxylamines; the *N*-methylhydroxylamines used in this study were prepared by $NaBH_4$ reduction of the corresponding methylene nitrones. [b] Saturated solution, ca. 19% CS_2 (v/v). [c] Isolated yield of amine after flash chromatography. [d] Spectral data for product amines were in agreement with literature values. [e] Authentic sample prepared by reductive amination of the ketone with methylamine.

References and Notes

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14. See the following paper for representative experimental procedures.

(Received in USA 18 December 1991)