

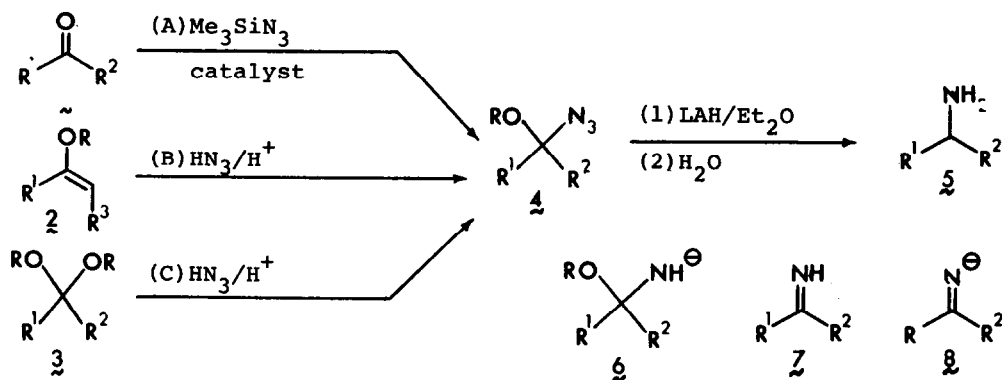
PRIMARY ALKYL AMINES. GENERATION BY REDUCTION OF α -ALKOXYAZIDES

Evan P. Kyba* and A. Meredith John

Department of Chemistry, University of Texas, Austin, Texas 78712

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A number of techniques have been developed for effecting reductive amination of aldehyde and ketones.¹ We now describe a novel, high yield alternative to these methods, which has reasonable generality. Treatment of α -alkoxyazides (4) with lithium aluminum hydride (LAH, four equivalents of H^-) at room temperature leads to primary amines 5 in isolated yields in excess of 83% (Table). The work-up involves destruction of excess hydride reagent,² and isolation of the amine



Scheme (See Table for identity of $R-R^2$)

by concentration of the dried ethereal solution. The amines were further characterized as the acetamide derivatives and also as the hydrochloride salts.³ Under the conditions described above, the reaction was poor for the reduction of 4f, where only a small amount (<10%) of α -phenethylamine 5f was isolated. The major product was methyl α -phenethyl ether in yields greater than 70%, even when a

Table. Reduction of Alkoxy Azides (4)

Structure Subletter	R	Azide 4 ^a R ¹	R ²	Method of Generation of 4 ^a	% Yield of Amine 5
a	Me ₃ Si	Bu ^t	H	A	86 ^b
b	Me ₃ Si	c-C ₆ H ₁₁	H	A	93
c	Me ₃ Si	PhCHMe	H	A	89
d	Me	(CH ₂) ₂ CH(Bu ^t)(CH ₂) ₂		B or C	83 ^c
e	t-BuCH ₂	C(Me) ₂ CH ₂ CH(Bu ^t)(CH ₂) ₂		B	94 ^d
f	Me	Ph	Me	B	85 ^e

^a See Scheme for structures. ^b Isolated only as the hydrochloride salt.

^c GLC analysis on the acetamide derivatives of 5d indicated that the cis/trans (?) isomer ratio was 3/7. ^d GLC analysis on the acetamide derivatives of 5e indicated a cis/trans (?) isomer ratio of 1/6. ^e Isolated as the benzamide derivative.

This reduction was carried out in the presence of one equivalent of TMEDA in ether. In the absence of the amine, the major product was methyl α-phenethyl ether (>70%) and α-phenethylamine was produced in less than 10%.

filtered, clear, colorless ethereal solution of LAH was utilized. We were able to eliminate completely this (major) side reaction by carrying out the reaction as described above, but with one equivalent of N, N, N', N'-tetramethylethylenediamine (TMEDA) added, whereby the amine was isolated as its benzamide derivative in 85% yield. Indeed, the use of TMEDA obviates the need for prefiltering the LAH solution, although the crude reaction mixture appears to be somewhat less clean under these conditions. We would like to point out also, that formation 5e represents the net reductive amination of a very hindered ketone which with other methods is quite difficult.^{ld}

We presume that the reduction proceeds via the alkoxy amide species 6, which then expels the alkoxide group to form imine 7. The N-H function on 7 is probably sufficiently acidic to react with LAH to give the lithio (or

aluminate) salt of 8, which then is further reduced to the amine 5. Consistent with this view is our observation that when Red-al⁴ (a less potent hydride source than LAH) is used with 4d and f, after a hydrolytic workup, only starting ketones (1d and f) were recovered in high yields, even though vigorous evolution of gas was observed upon treatment of the alkoxy azides with the hydride reagent. Quite possibly, the anion 8 is resistant to reduction by the less potent Red-al, and upon hydrolysis in the workup, generates the ketone.

Alkoxyazides 4 may be obtained in high yields from aldehydes (1, R²=H) by the addition of trimethylsilyl azide across the carbonyl double bond.^{5,6} Trimethylsilyl azide is unreactive towards ketones and α,β -unsaturated aldehydes.⁵ The alkoxyazides 4 derived from ketones can be synthesized by the trifluoroacetic acid-catalyzed addition of hydrazoic acid to the enol ether 2, or the acid-catalyzed substitution of azide for alkoxide in 3, both of which proceed in excellent yields in chloroform solution.

The following experimental description of the transformation 4b→5b is typical of those carried out in this work. The trimethylsilyloxyazide (4b) (2.25 g, 9.91 mmole) in dry ether (10 ml) was added slowly to a stirred suspension of lithium aluminum hydride (400 mg, 10.5 mmole) in 25 ml dry ether. Gas was evolved immediately. The reaction mixture was refluxed for 1.5 hours, cooled, and quenched, using water (0.4 ml), 20% sodium hydroxide (0.4 ml), and water (0.4 ml) sequentially.² The aluminum salts were then filtered from the ethereal solution of the amine and washed with ether (2 x 10 ml). The combined ether extractions were treated with brine, dried and concentrated to yield the amine (1.05 g, 93%).

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References and Notes

- (1) (a) F. Möller and R. Schröter in "Methoden der Organischen Chemie, Stickstoffverbindungen II, Amine," Vol. XI/1 (Houben-Weyl), E. Müller, Ed., George Thieme Verlag; Stuttgart, 1957, pp. 602-672; (b) M. L. Moore, Organic Reactions, 5, 301 (1949); (c) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley-Interscience, New York, NY, 1970, pp. 424-433; (d) R. F. Borch, M. D. Berstein, and H. D. Durst, J. Am. Chem. Soc., 93, 2897 (1971).
- (2) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, 1967, p. 584.
- (3) All new compounds gave satisfactory spectral data. Azides 4d and e gave satisfactory combustion data (C within .3% of theoretical) whereas the rest were somewhat more difficult to purify (Kugelrohr distillations were used), and these gave analyses within .8% of the theoretical carbon content.
- (4) A 70% benzene solution of bis(2-methoxyethoxy)aluminum hydride, obtained from Aldrich Chemical Co., Inc.
- (5) (a) L. Birkofer, F. Müller, and W. Kaiser, Tetrahedron Lett., 2781 (1967); (b) D. A. Evans and L. K. Truesdale, ibid., 4929 (1973).
- (6) Both Lewis acid ($ZnCl_2$ ^{5a,b}) and nucleophilic (18-crown-6/ NaN_3 ^{5b}) catalysts were used. In some cases one method was clearly better than the other, and in other cases comparable yields were obtained. In order to optimize yields, it is best to try both methods. We used the 18-crown-6 complex of sodium azide, instead of potassium azide, as done previously.^{5b}