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THE LITHIUM ALUMINUM HYDRIDE - ALUMINUM CHLORIDE REDUCTION OF OXIMES

Mark N. Rerick, Claude H. Trottier, Ronald A. Daignault and
John D. DeFoe
Hickey Research Laboratories, Providence College
Providence, Rhode Island

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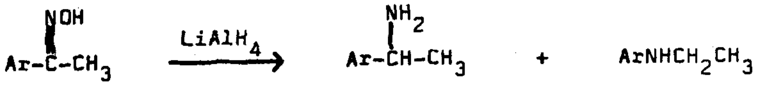
THE reduction of ketoximes and aldoximes with lithium aluminum hydride (LAH) has been reported in numerous instances to give the corresponding primary amine.[1] However, in the reduction of cyclodecanone oxime[2] and in the reduction of certain aryl ketoximes[3] the primary amine was accompanied by an isomeric secondary amine. Thus, acetophenone and substituted acetophenones (I) were reduced to mixtures of 1-arylethylamines (II) and N-ethylanilines (III).



$$\underset{\text{I}}{\text{Ar-}\overset{\text{NOH}}{\overset{\|}{\text{C}}}\text{-CH}_3} \xrightarrow{\text{LiAlH}_4} \underset{\text{II}}{\text{Ar-}\overset{\text{NH}_2}{\overset{|}{\text{C}}\text{H}}\text{-CH}_3} + \underset{\text{III}}{\text{ArNHCH}_2\text{CH}_3} \qquad (1)$$

I II III (1)

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[1] N. G. Gaylord, Reduction with Complex Metal Hydrides, Interscience Publishers, Inc., New York, N. Y., 1956, p. 751.

[2] A. T. Blomquist, B. F. Hallam and A. D. Josey, J. Am. Chem. Soc. 81, 678 (1959).

[3] E. Larsson, Svensk Kem. Tid. 61, 242 (1949), cf. Chem. Abstr. 44, 1898 (1950); D. R. Smith, M. Maienthal and J. Tipton, J. Org. Chem. 17, 294 (1950); R. E. Lyle and H. J. Troscianiec, ibid. 20, 1757 (1958).

In most of the systems investigated, the secondary amine has been a minor product of the reduction, but in special cases of highly substituted aryl ketoximes where the aryl group is part of the phenothiazine ring system, the exclusive product has been the amine of type III.[4]

Since the formation of the secondary amine had been postulated to arise by an electrophilic aluminum hydride-catalyzed Beckmann rearrangement of the oxime (followed by reduction),[2-4] it was our original purpose to inspect the course of reduction of oximes with a highly electrophilic "mixed hydride" prepared from LAH and aluminum chloride,[5] expecting that we might induce formation of predominantly, if not exclusively, the secondary amine of type III. These results and the results of a reinvestigation of the products of oxime reduction with LAH alone by vapor phase chromatography and infrared spectroscopy are cited in Table I. In all of the cases studied, the ratio of secondary to primary amine was increased by utilizing the mixed hydride rather than LAH alone, but the aliphatic and alicyclic ketoximes still gave predominantly the primary amine. Of the aryl ketoximes, all of which gave predominantly the secondary amine, only those with unsubstituted rings or those with rings substituted with electron donating groups gave nearly exclusively amines of type III.

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[4] M. Harfenist and E. Magnien, J. Am. Chem. Soc. **80**, 6080 (1958).

[5] The increased electrophilic character of the mixed hydrides of LAH and aluminum chloride has been reviewed recently, M. N. Rerick, Selective Reductions of Organic Compounds with Complex Metal Hydrides, Metal Hydrides, Inc., Beverly, Mass., 1959; E. L. Eliel, Rec. Chem. Progr. **23**, 129 (1961).

Table I

Reductions of Oximes

Reagent	LiAlH$_4$		LiAlH$_4$-AlCl$_3$[a]	
	Amine Composition			
Parent Ketone	1°, %	2°, %	1°, %	2°, %
Cyclopentanone	95-96	4-5	73-77	23-27
Cyclohexanone	98-100	0-2	99-100	0-1
Dibenzyl ketone	99-100	0-1	97-98	2-3
Benzophenone	41-42	58-59	0-1	99-100
p-Methoxyacetophenone	24-26	74-76	0-1	99-100
p-Methylacetophenone	51-52	48-49	2-3	97-98
Acetophenone	79-80	20-21	2-4	96-98
p-Bromoacetophenone	88-89	11-12	7-8	92-93
p-Chloroacetophenone	88-89	11-12	14-16	84-86
m-Chloroacetophenone	96-97	3-4	42-45	55-58
o-Chloroacetophenone	99-100	0-1	40-42	58-60
Isobutyrophenone[b]	29-30	70-71[c]	8-14	86-92[d]
Isobutyrophenone[e]	29-30	70-71[c]	8-12	88-92[f]

[a] Reductions with the mixed hydride were carried out at a mole ratio of hydride to chloride of 1:4. [b] Oxime contained 75% *syn*-phenyl, 25% *anti*-phenyl isomers. [c] The secondary amine fraction contained 99-100% N-isobutylaniline. [d] The secondary amine fraction contained 90% N-isobutylaniline and 10% N-isopropylbenzylamine. [e] Oxime contained 20% *syn*-phenyl, 80% *anti*-phenyl isomers. [f] The secondary amine fraction contained 96% N-isobutylaniline and 4% N-isopropylbenzylamine.

Should the primary amine arise *via* a Beckmann rearrangement, factors facilitating this rearrangement would be expected to enhance the ratio of secondary to primary amine. A number of the results shown in Table I have led us to question the validity of the interpretation of the formation of amines of type III by intervention of the Beckmann rearrangement of the oxime.[6] It is well documented that an ortho substituent increases the rate of Beckmann rearrangement of oximes in comparison to the meta and para substituent,[7] yet we have failed to note any substantial increase in the ratio of secondary to primary amine in the reduction (with either reagent) of o-chloroacetophenone oxime in comparison to the meta and para substituted isomers. In the rearrangement of alicyclic ketoximes and their derivatives, ring expansion of cyclohexanone is more facile than the cyclopentanone derivatives,[8,9] yet the contrary appears to be true in the reduction (with both reagents) of the oximes. Finally, the nearly complete non-stereospecificity of the reduction (with both reagents) of syn- and anti-isobutyrophenone oximes (under conditions which have been shown to be non-isomerizing) is completely unexpected for a mechanism involving the Beckmann rearrangement.

We have further studied the reduction of alkylhydroxyl-

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[6] After a part of this work was completed, the results of a study of the reduction of aryl ketoximes with LAH alone became available, A. E. Petrarca, Ph. D. Dissertation, Univ. of New Hampshire, 1959; cf. Dissertation Abstr. **20**, 1178 (1959). In part, similar arguments have been presented therein which render the intervention of the Beckmann rearrangement in these reductions untenable.

[7] L. G. Donaruma and W. Z. Heldt, R. Adams' Organic Reactions John Wiley and Sons, Inc., New York, N. Y., Vol. 11, 1960.

[8] W. Z. Heldt, J. Org. Chem. **26**, 1695 (1961).

[9] R. Huisgen, J. Witte and W. Jira, Chem. Ber. **90**, 1850 (1957).

amines corresponding to the parent oximes of benzophenone and benzaldehyde in order to ascertain the possibility of such a species as an intermediate in the reduction of oximes. The data indicated in Table II confirm such a possibility, at least in the cases investigated. We have, however, been unable to isolate the hydroxylamine from the reduction products,[10] but have detected its presence qualitatively in one instance.

Table II

Reductions of Oximes and Hydroxylamines

Starting Material	Solvent	Reagent[a]	Amine Composition	
			1°, %	2°, %
$(C_6H_5)_2C{=}NOH$	THF	LAH	41	59
$(C_6H_5)_2CHNHOH$	THF	LAH	54	46
$(C_6H_5)_2CHNHOH$	Ether	LAH	46	54
$(C_6H_5)_2C{=}NOH$	Ether	LAH-$AlCl_3$	0.5	99.5
$(C_6H_5)_2CHNHOH$	Ether	LAH-$AlCl_3$	0.5	99.5
$C_6H_5CH{=}NOH$[b]	Ether	LAH-$AlCl_3$	40	60
$C_6H_5CH_2NHOH$	Ether	LAH-$AlCl_3$	30	70
$C_6H_5CH{=}NOH$[b]	Ether	LAH	94	6
$C_6H_5CH_2NHOH$	Ether	LAH	95	5

[a] Reductions with mixed hydride were carried out at a mole ratio of hydride to chloride of 1:4. [b] *Syn*-benzaldoxime.

Hydroxylamines have also been shown to be intermediates in the reduction and rearrangement of alicyclic nitro com-

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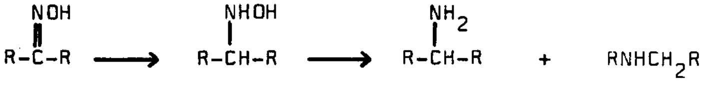
[10] With the milder reducing agent, diborane, oximes may be reduced to hydroxylamines, H. Feuer and B. F. Vincent, *J. Am. Chem. Soc.* **84**, 3771 (1962).

pounds to primary and secondary amines with LAH.[11] The slight discrepancies between the ratios of primary and secondary amine from the oxime and the corresponding hydroxylamine are being examined, yet these data lead us to modify (1) in terms of initial reduction to a hydroxylamine intermediate (IV) which is subsequently reduced to primary and secondary amines.



$$R{-}\overset{\overset{NOH}{\|}}{C}{-}R \longrightarrow R{-}\overset{\overset{NHOH}{|}}{CH}{-}R \longrightarrow R{-}\overset{\overset{NH_2}{|}}{CH}{-}R + RNHCH_2R \qquad (2)$$

IV

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[11] H. J. Barber and E. Lunt, J. Chem. Soc. 1187 (1960).