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THE REACTION OF $LiAlH_4$/HMPA WITH OXIMES: MECHANISM AND SYNTHETIC APPLICATIONS

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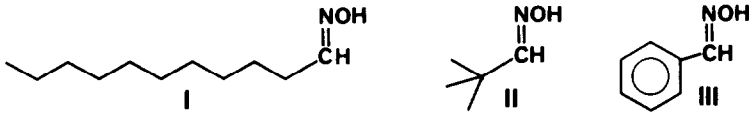
Summary: Three aspects of the reaction of $LiAlH_4$ in HMPA with oximes have been studied: the mechanism of the conversion of ketoximes into ketones, application of this reaction to the selective reduction of enones to ketones via the ene-oxime, and the conversion of aldoximes to either nitriles or aldehydes as a function of substrate structure.

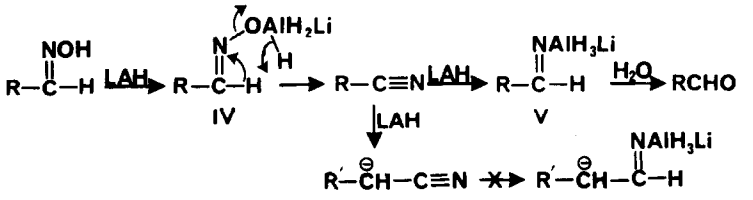
We have recently reported the use of $LiAlH_4$ in HMPA as an efficient reagent for the reductive reversion of ketoximes to ketones[1]. We report herein a series of experiments that clarify the scope and mechanism of this reaction for both aldoximes and ketoximes. We have also discovered a new method for reducing conjugated enones to ketones.

The reaction with aldoximes was studied using three known aldoximes (I, II, III). The reaction product in each case was the corresponding aldehyde or nitrile. No amines are observed in these reductions with $LiAlH_4$/HMPA at temperatures between 50° and 90°C.[2]



$LiAlH_4$/HMPA reduction of I (50°C, 18 hrs) yields undecanenitrile as the only product. The reductions of II and III (50°C, 18-36 hrs) yield only aldehyde.[3] When the syn and anti isomers[4] of I and III were treated with $LiAlH_4$/HMPA, the anti isomers (with the R group anti to the OH) reacted faster than the syn isomers.[5] These results, coupled with the observation that the nitriles of II and III are reduced to aldehydes in $LiAlH_4$/HMPA, lead us to suggest a single mechanistic scheme for the reactions of I-III in $LiAlH_4$/HMPA.

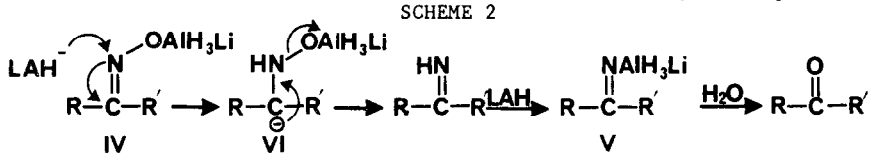
SCHEME 1



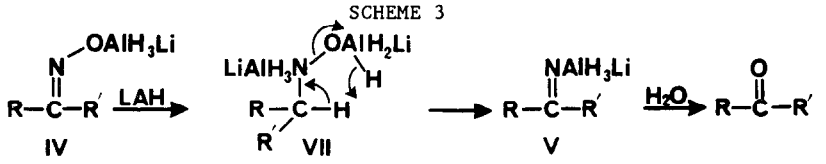
The important features of this scheme are as follows. The intramolecularity of the dehydration step and its cyclic six-electron transition state are suggested by the more rapid reaction of the anti aldoximes. The intermediacy of the nitrile in the reversions of II and III to aldehyde fits the independent observation that pivalonitrile and benzonitrile yield aldehyde under our reaction conditions. It is also consistent with the isolation of acyl-deuterated aldehyde from the reduction of III in $LiAlD_4$/HMPA.[1] The resistance of undecanenitrile to further reduction arises from the ease with which it deprotonates and the difficulty of developing a second negative charge in the HMPA medium.[6]

The scope of ketoxime reduction was demonstrated in our first report of this reaction[1]. Both aryl and alkyl ketoximes (with or without α protons) gave only ketone when treated with $LiAlH_4$/HMPA. We concluded that V (R'=alkyl or aryl instead of H) was the precursor to ketone production and that its resistance to further reduction in $LiAlH_4$/HMPA was due to HMPA complexation of Li cations making further hydride attack on V difficult. We argued for Scheme 2 as a likely pathway for the formation of V. Our aldoxime results suggest Scheme 3 as an alternative mechanism. Just as oxyaluminumhydride elimination from IV (Scheme 1) leads to nitrile formation, cyclic elimination from VII would be more favorable and would yield imine. This kind of imine formation resembles a selenoxide elimination reported by Barton[7].

SCHEME 2



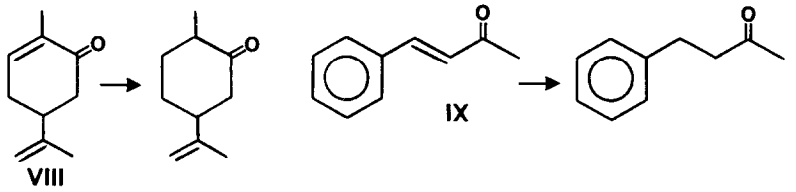
SCHEME 3



We considered whether it is the formation of VI/VII or their decomposition that would be the slow step in either Scheme 2 or 3. We addressed this question as follows. Diborane reduction of acetophenoneoxime[8] provided the corresponding hydroxylamine. GC analysis (15% OV-17, 130-170°C) of an incomplete $LiAlH_4$/HMPA reduction of acetophenoneoxime (130°C, 1 hr)

showed only unreacted oxime (43%) and ketone (57%) with no detectable amines or hydroxylamine. Since hydrolysis of any VI or VII that accumulated would have led to hydroxylamine, we conclude that it is the formation of VI or VII that is rate determining.

Finally, we have used the $LiAlH_4$/HMPA treatment of oximes for the selective 1,4 reduction of conjugated enones. Most solutions to this problem[9] are accompanied by 1,2 reduction or over-reduction. There is ample precedent for the use of HMPA to enhance conjugate reduction of enones as well as other conjugate addition processes[10]. We assessed the effect of HMPA on the $LiAlH_4$ reduction of two dissimilar enones (VIII & IX). These reductions gave 10% & 40% (respectively) 1,2 reduction in HMPA. Furthermore, for IX, we could not achieve >85% reduction of the enone without at least 45% over-reduction to saturated alcohol.[11]



VIII IX

To test the usefulness of the $LiAlH_4$/HMPA system for enone reduction via the oxime, we synthesized the oximes of VIII and IX[12] and subjected them to reaction with $LiAlH_4$/HMPA (130°/3 hrs). Oxime formation was quantitative for VIII and ≥90% for IX. Yields for the $LiAlH_4$/HMPA reaction were ≥85%. The overall isolated yield of saturated ketone starting from enone was thus 75%-85%. GC analysis (15% Carbowax, 180°C) showed <1% alcohol, ene-ol, or enone. We suggest that this approach to enone reduction is an attractive alternative to current synthetic methodology as well as an interesting new example of HMPA induced conjugate addition coupled with our oxime to ketone reversion. The high yield of oxime formation, along with the ease of the $LiAlH_4$/HMPA reaction[13], augur well for the general utility of this reaction.

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References and Notes

1) Wang, S.S.; Sukenik, C.N. J. Org. Chem. 1985, 50, 5448.
2) a) All aldoxime reactions were done with 1 mmole aldoxime and 2 mmole LAH in 7.1 mL (40 mmole) HMPA. b)Prolonged heating of I in $LiAlH_4$/HMPA at 155°C yields undecylamine.
3) As reported in ref 1, prolonged reaction of III in $LiAlH_4$/HMPA at higher temperatures, leads to formation of a coupling by-product (the imine of benzylamine and benzaldehyde).

4) Assignments of syn/anti aldoximes are based on: Karabatsos, A.J.; Taller, R.A. Tetrahedron 1968, 24, 3347. The simplest differentiation is by ^{1}H-NMR and is based on the chemical shift of the downfield triplet for the acyl H: I syn=6.69δ, anti=7.40δ; III syn=8.06δ, anti=8.19δ.
5) Reaction of pure oxime isomers and syn/anti mixtures were followed by ^{1}H-NMR and by TLC (3:7 Ether:Hexane). All reactions were run at 50°C with a 2:1 molar ratio of $LiAlH_4$ to oxime and were monitored until oxime was gone (≤18 hr). In reductions of syn/anti mixtures of I and III the anti isomer was always depleted faster even though it would be thermodynamically favored by any concurrent isomer equilibration. Reduction of pure anti III showed no trace of syn III at any point in the reaction, while reduction of pure syn III develops and maintains a low level of anti III as it reacts. These results require that the elimination of IV proceeds faster for the anti isomer, however, a slow competing elimination of the syn isomer cannot be rigorously excluded.
6) For support of this argument see: Wang, S.S.; Sukenik, C.N. J. Org. Chem. 1985, 50, 653.
7) Barton, D.H.R.; Billion, A.; Boivin, J. Tetrahedron Letters 1985, 26, 1229.
8)Feuer, H.; Vincent, B.F.; Bartlett, R.S. J. Org. Chem. 1965, 30, 2877.
9) A summary of approaches to selective enone reduction is found in: Hudlicky, M. Reductions in Organic Chemistry; Ellis Horwood Limited: West Sussex, England; 1984; pp 119-121.
10) HMPA enhanced conjugate reductions using K, Na, or Li in HMPA: House, H.O.; Giese, R.W.; Kronberger, K.; Kaplan, J.P.; Simeone, J.F. J. Amer. Chem. Soc. 1970, 92, 2800; Larchevque, M. Comptes Rend. (C) 1968, 268, 640; Angibeaud, P.; Larcheveque, M.; Normant, H.; Tchoubar, B. Bull. Soc. 1968, 595. HMPA enhanced conjugate additions: Hirama, M. Tetrahedron Letters 1981, 22, 1905; Binns, M.R.; Haynes, R.K.; Houston, T.L.; Jackson, W.R. Tetrahedron Letters 1980, 21, 573; Wartski, L.; El Bouz, M.; Seyden-Penne, J.; Dumont, W.; Krief, A. Tetrahedron Letters 1979, 20, 1543; Luchetti, J.; Dumont, W.; Krief, A. ibid, 2695; Brown, C.A.; Yamaichi, A. J. Chem. Soc. Chem. Comm. 1979, 100; Luchetti, J.; Krief, A. Tetrahedron Letters 1978, 19, 2697; Sauvetre, R.; Seyden-Penne, J. Tetrahedron Letters 1976, 17, 3949; Ogawa, M.; Takagi, M.; Matsuda, T. Tetrahedron 1973, 29, 3813.
11) Reductions of VIII and IX (1 mmole) in $LiAlH_4$(0.5 mmol)/HMPA(3.6 mL) were done at room temperature. Product ratios were determined by analytical GC (15% Carbowax, 180°C).
12) The oxime of IX was prepared analogously to that of VIII which is reported in: Bennet, A.H.; Donovan, F.K. Analyst 1922, 47, 148.
13) The procedure for the $LiAlH_4$/HMPA step (as described in ref 1) involves heating the oxime of the enone in a slurry of excess $LiAlH_4$ in HMPA followed by an aqueous workup.

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