The Mechanism of Ethylenimine Formation by the Action of Grignard Reagents on Ketoximes

By Shoji EGUCHI and Yoshio ISHII

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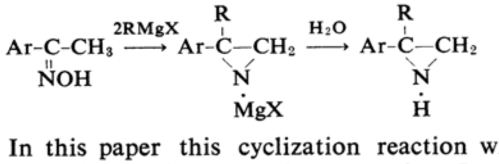
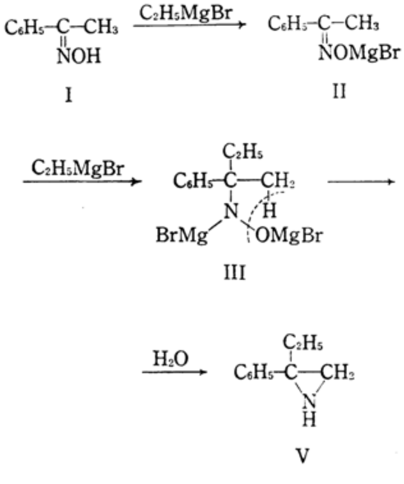
It has been known that certain substituted ethylenimines are obtained by the action of aliphatic or aromatic Grignard reagents on aryl alkyl ketoximes, followed by the non-acidic decomposition of Grignard complexes.[1]



In this paper this cyclization reaction will be examined using acetophenone oxime I as a ketoxime and ethylmagnesium bromide as a Grignard reagent; as will be seen, an azirine derivative VIII has been found to be an intermediate in these reactions.

Campbell et al.[1] proposed the following reaction process involving the Grignard complex III as an intermediate:



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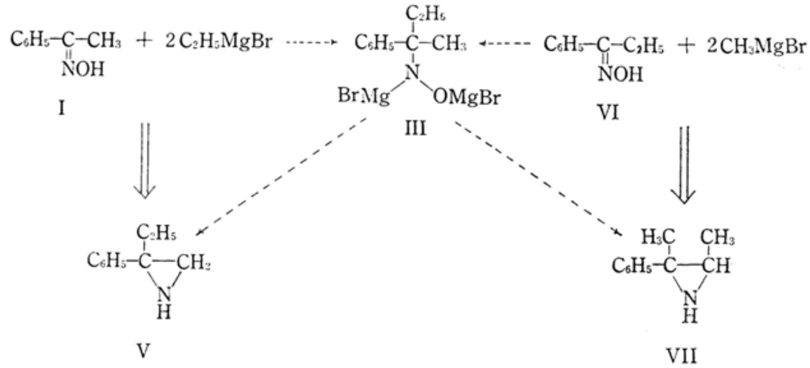
[1] K. N. Campbell and J. F. Mckenna, *J. Org. Chem.*, **4**, 198 (1939); K. N. Campbell, B. K. Campbell and E. P. Chaput, ibid., **8**, 99 (1943); K. N. Campbell, B. K. Campbell, J. F. Mckenna and E. P. Chaput, ibid., **8**, 103 (1943); K. N. Campbell, B. K. Campbell, L. G. Hess and I. J. Schaffner, ibid., **9**, 184 (1944).



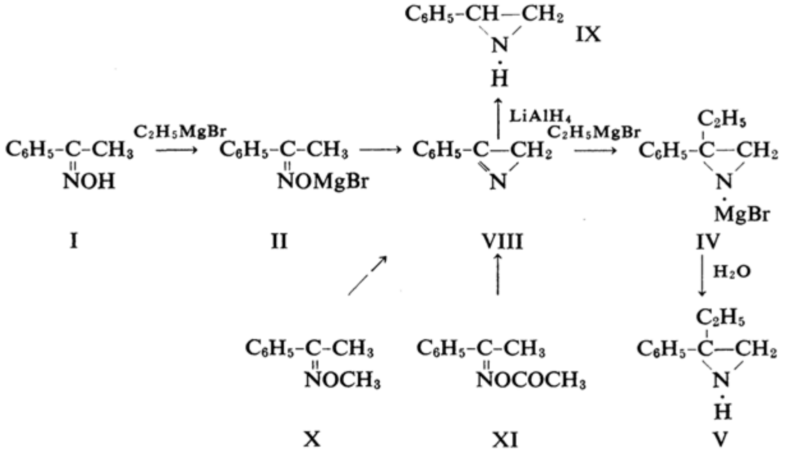
If this were actually the case, the same product would be expected from the reaction of acetophenone oxime (I) and ethylmagnesium bromide as from that of propiophenone oxime (VI) and methylmagnesium bromide, since the same intermediate complex III should be formed from these two reaction systems.

However, Henze and Compton[2] reported that the former reaction system afforded 2-phenyl-2-ethylethylenimine (V), while the latter yielded 2-phenyl-2, 3-dimethylethylenimine (VII). By gas chromatographic analysis we have confirmed their findings.

From these results, it may be concluded that an α-carbon atom of the alkyl group in the oxime becomes a member of the ethylenimine ring.

An explanation of this fact has been suggested based on the configuration of the starting oxime and the proximity of the **OMgBr** group to the hydrogen of the alkyl group.[2] In the intermediate complex III, however, the carbon-nitrogen single bond can not be fixed and no allylic hydrogen exists any longer; accordingly it is difficult to explain the selective cyclization in these reactions since the hydrogen atoms of the two alkyl groups become more or less equivalent.

An alternative and more plausible formulation is that the acidic hydrogen of the alkyl group is abstracted by an excess of the Grignard reagent, followed by cyclization to an azirine ring VIII, and that the reaction of the Grignard reagent on this azirine intermediate finally affords the substituted ethylenimine compounds as follows:



The Neber rearrangement[3] of an oxime tosylate by a base is an example similar to this cyclization process. The mechanism of the Neber rearrangement has been reported by Cram and his co-workers,[4] who proved the intermediate to be an azirine derivative.

When the phenylazirine (VIII) was treated with ethylmagnesium bromide and the resultant complex was decomposed by ice-ammonium chloride, 2-phenyl-2-ethylethylenimine (V) was obtained as expected. Lithium aluminum hydride reduction of the C=N double bond of the azirine gave styrenimine (IX).

The reaction of acetophenone oxime with

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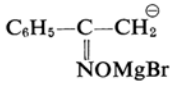
[2] H. R. Henze and W. D. Compton, ibid., **22**, 1036 (1957).

[3] P. W. Neber and A. Friedolsheim, *Ann.*, **449**, 109 (1926); P. W. Neber and G. Huh, ibid., **515**, 283 (1935); P. W. Neber, A. Burgard and W. Thier, ibid., **526**, 277 (1936).

[4] D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953).

ethylmagnesium bromide containing lithium aluminum hydride was examined, and the reaction products were analyzed by gas chromatography. It was found that 2-phenyl-2-ethylethylenimine (V) was produced in this reaction, together with a small amount of styrenimine (IX). On the other hand, from the reaction of lithium aluminum hydride with acetophenone oxime, no trace of styrenimine could be detected.

The intermediate complex II was obtained by the addition of one mole of ethylmagnesium bromide to the oxime I in ether. The complex II was stable upon being heated at 150°C without a solvent, but it yielded the ethylenimine V when treated with an excess of ethylmagnesium bromide (about 2 mol.) at about 95°C in a toluene-ether (1:1) mixture. The second mole of the Grignard reagent presumably reacts with the complex II as a base to produce a carbanion:



$$C_6H_5-\underset{\underset{\textstyle NOMgBr}{\|}}{C}-\overset{\ominus}{CH_2}$$

Acetophenone oxime methyl ether (X) and its acetate XI also reacted with an excess of the Grignard reagent under the same conditions to afford the ethylenimine V in a relatively high yield.

These findings clearly support the proposed mechanism for the ethylenimine formation from the action of the Grignard reagent on oximes.

Experimental

The infrared absorption spectra were measured with a Nippon Bunko IRS infrared spectrometer, using rock salt prisms. The gas chromatographic analyses were carried out on a Shimazu gas chromatograph, Model GC-1B.

2-Phenyl-2-ethylethylenimine (V). — Almost the same procedure as that of Campbell1) was employed in the reactions of oximes and Grignard reagents. One mole of ethylmagnesium bromide in 250 ml. of ether and 250 ml. of toluene was prepared. With the solution kept at ca. 100°C, 34 g. (0.25 mol.) of acetophenone oxime was added dropwise with stirring. After the addition of the oxime, the mixture was kept at 105°C for 1 hr. The reaction mixture was then poured onto a cracked ice-ammonium chloride mixture, and the organic layer was extracted with ether several times. The combined ether extracts were dried over anhydrous magnesium sulfate. After the mixture had stood overnight, the solvent was removed under reduced pressure (water aspirator) below 80°C. The vacuum distillation of the oily residue gave about 15～20 g. of 2-phenyl-2-ethylethylenimine (V); yield 40～54%; b. p. 85～87°C/7 mmHg, n_D^{20} 1.5319 [lit.,1) b. p. 85～86°C/7 mmHg, n_D^{20} 1.5318]. The infrared spectrum of V exhibited prominent bands at 3200, 3000, 2900, 1600, 1495, 1450, 1370, 1230, 1145, 870, 770, and 710 cm^{-1}. Phenyl thiourea, m. p. 98～99°C [lit.,1) m. p. 99～100°C], $\nu_{C=S}^{KBr}$ 1590 cm^{-1}. The gas chromatographic analyses of V through a 1.5 m. column packed with 30% Cerite-545 and PEG-6000 revealed a single peak.

Acetophenone oxime methyl ether (b. p. 80～81°C/10 mmHg) and acetophenone oxime acetate (m. p. 53～55°C, $\nu_{C=S}^{KBr}$ 1770 cm^{-1}) were also treated with the Grignard reagent under the same conditions, to give 2-phenyl-2-ethylethylenimine (V) in yields of 63% and 64%, respectively.

2-Phenyl-2, 3-dimethylethylenimine (VII).—Propiophenone oxime (VI) (0.25 mol.) was treated with 1 mol. of methylmagnesium bromide under conditions similar to those when I was treated with ethylmagnesium bromide. A 50% yield of VII resulted; b. p. 89～91°C/7 mmHg; n_D^{20} 1.5242 [lit.,2) b. p. 85～95°C/10 mmHg, n_D^{20} 1.5288]; phenyl thiourea, m. p. 120～122°C [lit.,2) m. p. 122～123°C], $\nu_{C=S}^{KBr}$ 1590 cm^{-1}. Gas chromatography showed two peaks which may correspond to a 98:2 mixture of the cis and trans isomers. No peak corresponding to 2-phenyl-2-ethylethylenimine (V) was observed.

The Reaction of Acetophenone Oxime with Lithium Aluminum Hydride-Grignard Reagent Mixture.*—Acetophenone oxime, 13.5 g. (0.1 mol.) in 50 ml. of toluene, was added drop by drop at 85°C to a Grignard reagent-lithium aluminum hydride mixture which had been prepared from 9.6 g. of magnesium (0.4 mol.), 50 g. of ethyl bromide and 1.0 g. (0.026 mol.) of lithium aluminum hydride in 300 ml. of an ether-toluene (1:1) mixture. After the addition, the mixture was refluxed for about 1 hr. The reaction mixture was poured onto a cracked ice-ammonium chloride mixture, and the organic layer was extracted with ether 5 times. The extracts were dried over anhydrous magnesium sulfate, and then the solvent was removed under reduced pressure (water aspirator). Distillation of the remaining oily material gave 6 g. of an amine-imine mixture, b. p. 94～95°C/10 mmHg, n_D^{20} 1.5352. Gas chromatographic analysis showed that this was a mixture of 64% 2-phenyl-2-ethylethylenimine, 1% styrenimine and 35% α-phenylethylamine.

The same reaction of acetophenone oxime with the Grignard reagent-lithium aluminum hydride mixture in ether at a lower temperature was also carried out, but gas chromatography showed the basic products were then 72% ethylaniline and 28% α-phenylethylamine. The lithium aluminum hydride reduction of acetophenone oxime in ether produced 60% α-phenylethylamine and 40% ethylaniline.5)

The Reaction of Phenylazirine (VIII) with Lithium Aluminum Hydride and the Grignard Reagent.—2-Phenylazirine (VIII), which had been obtained from the pyrolysis of α-azidostyrene,6) was treated with lithium aluminum hydride in the

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* It has been reported that the reducing properties of an ether solution of $Mg(AlH_4)_2$, formed from $LiAlH_4$ and the Grignard reagent, are similar to those of the ether solution of $LiAlH_4$; E. Wiberg and R. Bauer, *N. Naturforsch.*, **5b**, 397 (1950); *Chem. Abstr.*, **45**, 4593 (1951).

5) D. R. Smith, M. Maienthal and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

6) G. Smolinsky, ibid., **27**, 3557 (1962).

usual manner. Styrenimine (IX) was obtained in a 30% yield; b. p. 88∼90°C/9 mmHg, n_D^{20} 1.5610 [lit.,⁷⁾ b. p. 94∼95°C/10 mmHg, n_D^{20} 1.5588]. Gas chromatography showed a single peak. The reaction of phenylazirine with ethylmagnesium bromide in ether gave 2-phenyl-2-ethylethylenimine (V) in a 55% yield. The relatively low yield of styrenimine and V from these reactions may be due to the dimerization of phenylazirine, since an unidentified, yellow, high-boiling material (b. p. 140∼145°C/2 mmHg) was also obtained.

The Isolation of Complex II. — When one mole of ethylmagnesium bromide in ether was introduced into an ethereal solution of acetophenone oxime at room temperature, a white solid was obtained in a high yield (ca. 95%). This solid showed $\nu_{C=N}^{KBr}$ 1613 cm^{-1} (very strong⁸⁾), and by hydrolysis acetophenone oxime was reproduced. When the complex II was treated with an excess of ethylmagnesium bromide in a manner described before, 2-phenyl-2-ethylethylenimine (V) was obtained (65%). However, complex II neither reacts with one mole of the Grignard reagent nor changes upon being heated at 150°C for 1 hr. without a solvent.

Summary

The reactions of aryl alkyl ketoximes with aliphatic Grignard reagents have been carried out under various conditions.

Gas chromatographic analyses of the reaction products showed the formation of an ethylenimine ring in which an α-carbon of the alkyl group in oximes constitutes a member of the ethylenimine ring. The reaction of acetophenon oxime with ethylmagnesium bromide containging lithium aluminum hydride produced 2-phenyl-2-ethylethylenimine, together with styrenimine.

A reaction process similar to that of the Neber rearrangement has then been proposed on the basis of the above findings.

Department of Applied Chemistry
Faculty of Engineering
Nagoya University
Chikusa-ku, Nagoya

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7) S. J. Brois, ibid., **27**, 3532 (1962).

8) Y. Kuroda and M. Kimura, This Bulletin, **36**, 464 (1963).