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PREPARATION OF OXAZINE DERIVATIVES AND 2,4-DIARYLPYRROLES FROM METHYL ARYL KETOXIMES

L. W. DEADY[1]

Chemistry Department, University of Otago, Dunedin, New Zealand

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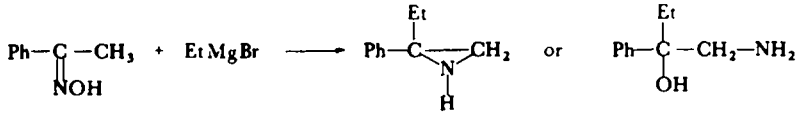
Abstract—Some methyl aryl ketoximes have been shown to condense in the presence of EtMgBr to give 3,5-diaryloxazine derivatives. These in turn rearrange in conc hydriodic acid, with the formation of 2,4-diarylpyrroles in reasonable yields. Possible mechanisms for these reactions are discussed.

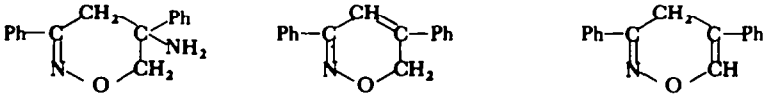
THE reaction of alkyl aryl ketoximes with Grignard reagents has been the subject of a number of publications.[2-4] Thus, acetophenone oxime and EtMgBr were found to give 2-ethyl-2-phenylaziridine (I), or 1-amino-2-phenyl-2-butanol (II), depending on the method of hydrolysis used.



I II

These reactions were carried out at ca. 100°, as, apart from replacement of "active" hydrogen, little reaction was noted at lower temperature, i.e. in diethyl ether as solvent.

In contrast to these reports, I have found that reaction does occur under normal conditions. Acetophenone oxime, when added to an ethylmagnesium bromide Grignard in ether, reacted vigorously and hydrolysis of the mixture with conc hydrochloric acid resulted in III being precipitated as the hydrochloride. The free base, III, was obtained from this by treatment with alkali.



III IV V

The structure of this condensation product, $C_{16}H_{16}N_2O$, was obtained from spectral measurements. The NMR spectrum in benzene (the compound reacted

[1] Present address, Chemistry Department, La Trobe University, Melbourne, Australia.

[2] J. Hoch, *C.R. Acad. Sci., Paris*, **198**, 1865 (1934).

[3] K. N. Campbell and F. J. 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).

[4] S. Eguchi and Y. Ishii, *Bull. Chem. Soc. Japan* **36**, 1434 (1963).

rapidly with CCl_4 and $CDCl_3$) contained two AB systems [(i): $H_A = 3{\cdot}46$, $H_B = 3{\cdot}00$ ppm., $J = 17$ c/s. (ii): $H_A = 2{\cdot}97$, $H_B = 2{\cdot}76$ ppm., $J = 13{\cdot}5$ c/s] and a sharp two proton singlet at 0·88 ppm. The latter disappeared in CF_3COOH and was replaced by a broad three proton singlet at 7·10 ppm, indicating the presence of an $—NH_2$ group. The low fields of the AB systems are consistent with isolated methylene groups next to —C=N and —O— groups.

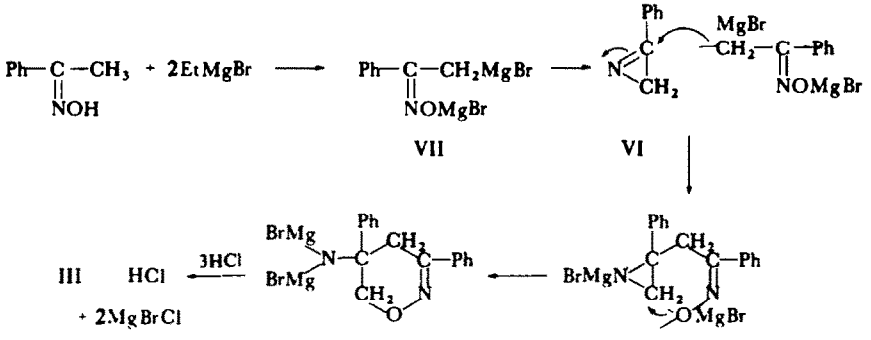
IR assignments in agreement with structure III were 3380 cm^{-1} (N—H stretch), 1595 cm^{-1} (cyclic C=N), 925 cm^{-1} (N—O stretch), 820 cm^{-1} (N—H wag), 760 and 700 cm^{-1} (monosubstituted aromatic).

The UV absorption spectrum in ethanol had λ_{max} 264 mμ, ε_{max} 18,300. Cope and Haven[5] report λ_{max} ca. 266 mμ, ε_{max} ca. 16,000 as characteristic of C=N—O—R. Formulation of III as a nitrone is inconsistent with the IR and UV data.

Treatment of III with nitrous acid caused deamination and elimination to take place, with the formation of 3,5-diphenyl-1,2,6-oxazine (IV). The protons on C_4 in III are more acidic than those on C_6 so that IV rather than V was the expected product. Spectral evidence confirmed this assignment. The NMR spectrum (in $CDCl_3$) contained a two proton singlet at 4·03 ppm and a one proton singlet at 6·14 ppm. The proton at C_6 in V would be expected at much lower field. The N—O peak in the IR spectrum was shifted to 950 cm^{-1}. This high frequency shift (25 cm^{-1}) is expected for IV as the N—O bond would be strengthened by increased resonance, whereas the reverse would be the case for V.

Mechanism of formation of III. The formation of III takes place before hydrolysis with conc hydrochloric acid. This was shown by hydrolysing the reaction mixture with ice-cold ammonium chloride solution, when a mixture of III and unchanged oxime was recovered.

Eguchi and Ishii[4] have shown that both the oxime hydrogen and a methyl hydrogen of acetophenone oxime are "active" to a Grignard reagent and that the rearrangement



of oximes to aziridines and aminoalcohols under these conditions proceeds *via* an intermediate azirine (VI). The condensation is therefore formulated as nucleophilic attack by a second "oxime base", (VII), instead of more Grignard reagent, on the azirine as shown. The α carbon of VII must be an appreciably strong nucleophile to form the azirine and therefore it reacts with the more electrophilic C_2 of VI.

[5] A. C. Cope and A. C. Haven, *J. Am. Chem. Soc.* **62**, 4896 (1950).

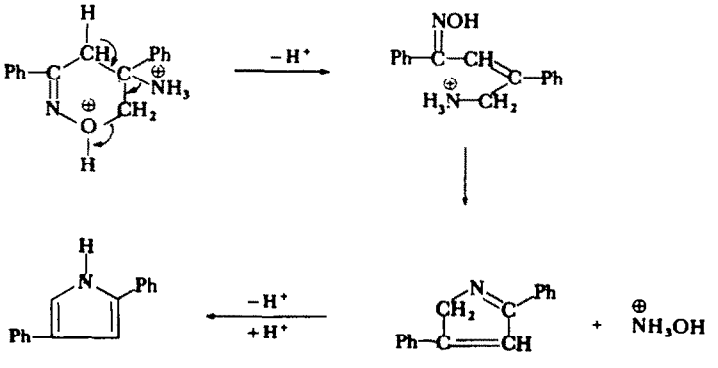
Reaction with acid. When III or its hydrochloride was refluxed with conc hydriodic acid, a rearrangement occurred to give 2,4-diphenylpyrrole. Another transformation of an oxazine (VIII) to a pyrrole (IX) has been reported.[6]

VIII IX

These conditions are known[5] to cause rupture of the N—O bond in >C=N—O—C. However, in the present work it appears that the exocyclic nitrogen, rather than the ring nitrogen, appears in the pyrrole ring. Iodine was produced during the reaction, consistent with the formation of hydroxylamine. The reaction could also be brought about, in lower yield, by refluxing in concentrated hydrochloric acid. After removal of the diphenylpyrrole, the filtrate reduced Fehlings solution after being made alkaline, again indicating the presence of hydroxylamine. The hydroxylamine is unlikely to have come from hydrolysis breakdown of the oxazine ring as IV was unaffected by boiling hydriodic acid. This stability of IV also eliminates the possible formation of this compound as an intermediate by elimination of ammonia from III.

Convincing evidence for the participation of the exocyclic nitrogen in the rearrangement was obtained by reacting the N,N-dimethyl derivative of III with hydriodic acid. No diphenylpyrrole was formed and an IR spectrum of the reaction product contained a strong CO band. Further condensation with the $-NMe_2$ group was not possible so the reaction stopped at this stage.

The scheme shown below is therefore suggested as a possible mechanism. The better reaction with hydriodic than hydrochloric acid may be indicative of the need for the stronger acid to initially protonate the ring oxygen. Subsequent reaction involves a 1,2-shift of the NH_2 group, the stimulus for this being provided by the formation of a strongly conjugated system by elimination from C_4.



[6] V. Sprio and I. Fabra, *Ann. Chim. Rome* **51**, 135 (1961).

Extensions. The oximes of methyl *p*-tolyl ketone and methyl *p*-chlorophenyl ketone were reacted similarly and gave the *p*-tolyl- and *p*-chlorophenyl- analogues, respectively of III. HCl. These, in turn, reacted with hydriodic acid to give 2,4-di-*p*-tolyl- and 2,4-di-*p*-chlorophenylpyrrole and the yields were better than those obtained with the parent compound.

This reaction provides a simple alternative to the accepted method of preparing 2,4-diphenylpyrrole from 2-benzoyl-1-phenylpropionitrile.[7] The absence of any observable substituent effect suggests that this method may afford a general method of preparing 2,4-diarylpyrroles for substituents inert to (i) Grignard reagents and (ii) hydriodic acid.

EXPERIMENTAL

Microanalyses were carried out in this department under Dr A. D. Campbell. IR spectra were determined as Nujol mulls on a Perkin-Elmer 421 spectrophotometer. NMR spectra were determined on a Varian HA 100 spectrometer using TMS as internal standard.

Methyl *p*-tolyl ketone and methyl *p*-chlorophenyl ketone were prepared according to Noller and Adams.[8] The oximes were prepared by a standard method using $NH_2OH \cdot HCl$ and pyridine in EtOH as solvent and had m.ps 59°, (lit.[9]: 60°), (phenyl); 88°, (lit.[9]: 88°), (*p*-tolyl); 98°, (lit.[9]: 95°), (*p*-chlorophenyl).

5-Amino-4,5-dihydro-3,5-diphenyl-1,2,6-oxazine hydrochloride—(III HCl). Acetophenone oxime (9·0 g) in ether (25 ml) was added dropwise, with stirring, to a Grignard reagent made from Mg (4·5 g) and EtBr (25 g) in ether (100 ml). A vigorous reaction occurred and the mixture was refluxed for 1 hr after the addition was complete. Conc HCl (150 ml) was then added slowly. The crude product was filtered off from the chilled mixture. This was recrystallized from EtOH and washed with acetone and ether to give 5·15 g (27%) of product, m.p. 208–209°. (Found: C, 66·2; H, 6·3; N, 9·5. $C_{16}H_{17}ClN_2O$ requires: C, 66·5; H, 5·9; N, 9·7%).

The free base (III) was obtained by treating the hydrochloride with alkali and extracting with ether. This was recrystallized from pet. ether and had m.p. 89·5°. (Found: C, 76·0; H, 6·3; N, 10·85. $C_{16}H_{16}N_2O$ requires: C, 76·2; H, 6·35; N, 11·1%).

N-Acetyl derivative, m.p. 90–92° (EtOH/H_2O). (Found: N, 9·4. $C_{18}H_{18}N_2O_2$ requires: N, 9·5%).

Similarly prepared were *5-amino-4,5-dihydro-3,5-di-p-tolyl-1,2,6-oxazine*. HCl, (43·5% after recrystallization from EtOH), m.p. 202°. (Found: C, 67·9; H, 7·0; $C_{18}H_{21}ClN_2O$ requires: C, 68·2; H, 6·6%), and *5-amino-4,5-dihydro-3,5-di-p-chlorophenyl-1,2,6-oxazine*. HCl, (45% after recrystallization from EtOH), m.p. 204–205°. (Found: C, 53·5; H, 4·7. $C_{16}H_{15}Cl_3N_2O$ requires: C, 53·7; H, 4·2%).

Reaction of oxazine hydrochlorides with hydriodic acid. Compound III HCl (0·95 g) was refluxed with HI (10 ml; sg. 1·7) for 3 hr. I_2 was formed and material precipitated out during the refluxing. This was filtered off, washed with water, aq. $Na_2S_2O_3$, water, and dried. Recrystallization from pet. ether gave 0·4 g (55%) 2,4-diphenylpyrrole, m.p. 180° (lit.[10]: 180°). (Found: N, 6·3. Calc. for $C_{16}H_{13}N$: N, 6·4%). Nitroso derivative, m.p. 138° (MeOH/H_2O) (lit.[10]: 139°).

Similarly prepared were *2,4-di-p-tolylpyrrole* (57% after recrystallization from EtOH), m.p. 224°. (Found: C, 87·4; H, 7·2; N, 5·4. $C_{18}H_{17}N$ requires: C, 87·5; H, 6·9; N, 5·6%), and *2,4-di-p-chlorophenylpyrrole* (56% after recrystallization from EtOH), m.p. 196°. (Found: C, 66·75; H, 4·1; Cl, 24·7. $C_{16}H_{11}Cl_2N$ requires: C, 66·6; H, 3·8; Cl, 24·6%).

5-Dimethylamino-4,5-dihydro-3,5-diphenyl-1,2,6-oxazine. Compound III (2·6 g) was refluxed with 40% formalin (10 ml) and formic acid (14 ml) for 1·5 hr. The cooled reaction mixture was made alkaline and extracted with ether. This extract was washed with water, dried (Na_2SO_4), and the ether removed. Recrystallization of the residue from EtOH/H_2O gave the product (1·0 g), m.p. 110°. (Found: C, 77·4; H, 7·15; N, 9·75. $C_{18}H_{20}N_2O$ requires: C, 77·1; H, 7·15; N, 10·0%). The IR spectrum showed no N—H stretching vibration.

This was refluxed with HI for 4 hr. Some tar formed but no crystals precipitated during the refluxing. The cooled reaction mixture was made alkaline and ether soluble material was extracted. This was washed with water, dried, and the ether removed. An IR spectrum of the residual oil contained no N—O stretch, but showed a strong C=O stretch at 1680 cm^{-1}.

[7] C. F. Allen and C. V. Wilson, *Organic Syntheses*, Vol. 27; p. 22. Wiley, New York (1947).
[8] C. R. Noller and R. Adams, *J. Am. Chem. Soc.* **46**, 1889 (1924).
[9] I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*. Eyre and Spottiswoode, London (1953).
[10] M. Rogers, *J. Chem. Soc.* 590 (1943).

3,5-*Diphenyl*-1,2,6-*oxazine* (IV). Compound III (0·5 g) was dissolved in 50% aqueous HOAc (10 ml) and the soln was cooled below 5°. A slight excess of $NaNO_2$ aq was added dropwise, with stirring. Gas was evolved and a white solid formed. This was filtered off, washed with water, and recrystallized from EtOH–H_2O to give the product (0·37 g), m.p. 81°. (Found: C, 82·1; H, 5·9; N, 6·1. $C_{16}H_{13}NO$ requires: C, 81·7; H, 5·6; N, 5·95%).

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