Tetrahedron Letters No. 41, pp 3655 - 3658, 1977. Pergamon Press. Printed in Great Britain.

VILSMEIER-HAACK REACTION ON 5(4H)-ISOXAZOLONES

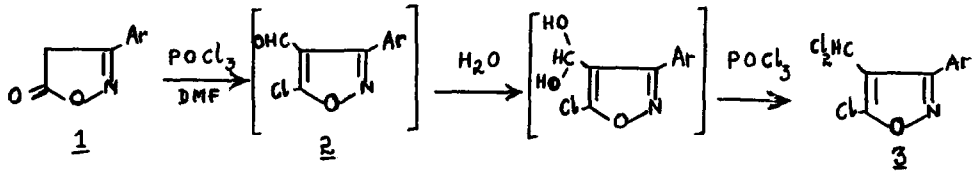
R.Krishna Mohan Rao Kallury and P.S.Uma Devi

(Dept. of Chemistry, Osmania University, Hyderabad-7, A.P., India)

(Received in UK 12 August 1977; accepted for publication 25 August 1977)

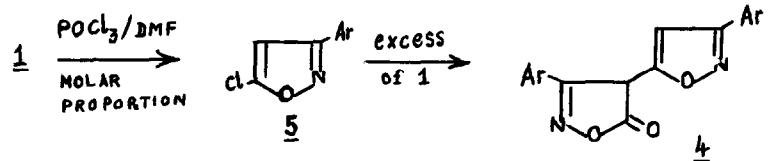
Very few isoxazole-4-carboxaldehydes have been reported in literature so far and even these are made from starting materials not easily accessible[1-4]. Since these can serve as intermediates for the pharmacologically important isoxazole-4-carboxylic acids and their derivatives[5], the title reaction on 3-aryl-5-isoxazolones (1) was tried as the simplest method for preparing them, in analogy with 5-pyrazolones[6a,b].

When 1 were treated with DMF and excess of $POCl_3$ under the said reaction conditions, two products were isolated - one insoluble in dilute alkali (product A) and the other soluble (product B). When molar proportions of the reagents were used, only B resulted. For A, although the I.R. (1640-1650 cm^{-1}) and NMR (δ 7.2 and 10.5) were consistent with the expected structures (2) from this reaction, the mass spectra did not reveal the requisite parent ion peaks. Instead, ions exhibiting a two-chlorine isotopic pattern were recorded in the highest mass region and metastable defocussing at low electron beam energies revealed that these were obtained from the corresponding parent ions (which were unrecorded at 70 eV) by loss of $Cl^{\cdot}$. The fragmentation pattern as well as U.V. (λ_{max} 236 nm, log E 4.0, compared to λ_{max} 240 nm, log E 4.0 of 3-phenyl isoxazole[5])enabled us to conclude that A were 3-aryl-5-chloro-4-dichloromethyl isoxazoles (3). These could result from the hydrated form of a pre-formed isoxazole-4-carboxaldehyde by nucleophilic displacement of the hydroxyls by chlorine. Since isoxazole-5-carboxaldehydes are known[7] to exist in hydrated form in solution, the present intermediates could behave analogously. Besides, treatment of 3-phenyl-5-isoxazolone with $POCl_3$ is known[8] to produce 5-chloro-3-phenyl isoxazole. Further, confirmation for 3 was obtained by oxidation of 3 (Ar=Ph) with alkaline permanganate to the earlier reported[8] 5-chloro-3-phenyl isoxazole-4-carboxylic acid in quantitative yield.



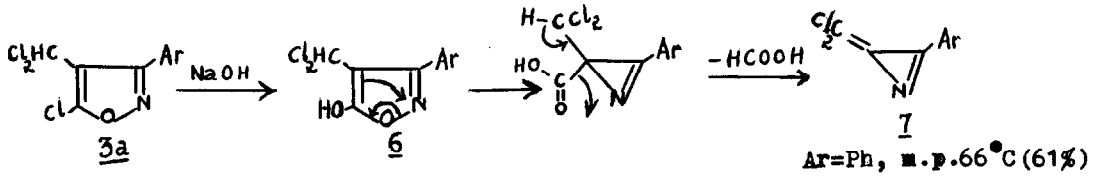
	Ar	M.P. (°C)	Yield
a)	Ph	118	58.5
b)	p-Toluyl	120	58.0
c)	p-Anisyl	152	59.5

Products B gave a red colour with neutral $FeCl_3$ and contained peaks at 234 nm (log E 4.05) and 290 nm (log E 3.9) in the U.V. and at 1790 cm^{-1} in the I.R. The NMR spectrum revealed signals at 3.9 δ (methine), 6.6 δ (ethylenic) and 7.3 δ (aromatic). The molecular ion (B, Ar=Ph) was registered in very low abundance and yielded the composition as $C_{18}H_{12}N_2O_3$. The UV, IR and NMR were similar to 4-methyl-3-phenyl-5(4H)-isoxazolone[9] and the low M^+ coupled with its fragmentation by the loss of CO, CO+NO and COOH· and appearance of a strong $PhC{\equiv}O^+$ peak enabled us to conclude that B is a 4-substituted 3-phenyl-5(4H)-isoxazolone. The nature of the 4-substituent can easily be deduced by mass peaks at m/e 144, 116 and 89 characteristic of 3-phenyl isoxazole[10]. Thus B could be assigned the structure 4-(3-aryl-5-isoxazolyl)-3-aryl-5(4H)-isoxazolone (4). These must be obtained by the condensation of 5-chloro-3-phenyl isoxazole (5) with excess of 1 present in the mixture.



Ar	M.P. (°C)	Yield With excess $POCl_3$	Yield With molar $POCl_3$
Ph	135	29.5	78.2
p-Toluyl	148	28.5	78.5
p-Anisyl	179	28.2	78.0

Hydrolysis of 3 (Ar=Ph): This product was resistant to acids (both cold and hot) and was completely cleaved by refluxing with NaOH. However, when reacted with 10% NaOH at room temparature for two hours, it yielded a low melting solid whose mass spectrum contained an abundant parent ion (m/e 197) that again revealed a two-chlorine isotopic pattern with a composition $C_9H_5NCl_2$. There was no OH or NH or C=O absorption in the I.R. and NMR indicated only aromatic protons (7.3δ). The primary mass fragments were due to successive loss of chlorine radicals. A 2-dichloromethylene-3-phenyl azirine structure (7) fits in well with these data and the mechanism of its formation must involve the hydrolysis of the 5-chloro group followed by the elimination of formic acid as indicated below:

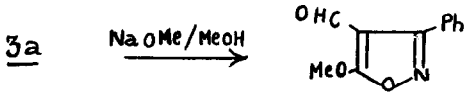


3a 6 7

Ar=Ph, m.p.66°C (61%)

The stability of the chlorines in 7 to hydrolysis must be ascribed to their situation on a vinylic carbon.

Treatment of 3 (Ar=Ph) with sodium methoxide in refluxing methanol resulted mostly in ring fissioned products, but a low yield (11.5%) of the aldehyde 8 could be recovered by acidification of the reaction mixture. Its structure was confirmed by NMR (3.9δ, 7.3δ and 10.6δ) and mass spectrum (M^+ at m/e 203 and fragments corresponding to CO and CH_2O loss coupled with ions at m/e 105, 116 and 89).



8, m.p. 110°C

REFERENCES

1) H.Kano and H.Ogata, Japanese Patent 17,572 (1962); Chem.Abstr. 59, 11498 (1963).
2) V.Dressler and K.Bodendorf, Arch.Pharm. (Weinheim), 303, 481 (1970).
3) P.Caramella and E.Cereda, Synthesis, 433 (1971).
4) T.D.Weaver, U.S.Patent 3,929,772 (1975); Chem.Abstr. 84, 91659 (1976).
5) A.Quilico, in Arnold Weisberger's "Chemistry of Heterocyclic Compounds", Vol. 17, R.H.Wiley (Ed.), Interscience Publishers (New York, 1962).
6) a) Mach-Phuoc Sinh and N.P.Buu-Hoi, Chem.Ther., 2, 106 (1967).
b) J.H.T.Ledrut and G.Combes, Chim.Ther., 3, 248 (1968).
7) Y.Kishida et al, Chem.Pharm.Bull. (Tokyo), 15, 1025 (1967).
8) R.G.Micetich and C.G.Chin, Can.J.Chem., 48, 1371 (1970).
9) R.Jacquier, C.Petrus, F.Petrus and J.Verducci, Bull.Soc.Chim.Fr., 2690 (1970).
10) J.H.Bowie, R.G.Cooks and R.K.M.R.Kallury, Austr.J.Chem., 22, 563 (1969).