Tetrahedron Letters No.4, pp. 307-310, 1971. Pergamon Press. Printed in Great Britain.

VILSMEIER-HAACK REACTION OF 2H-1,4-BENZOXAZIN-3-ONE: NOVEL ROUTE FOR CONDENSED BENZOXAZINES

M. Mazharuddin and G. Thyagarajan

Regional Research Laboratory, Hyderabad-9, India

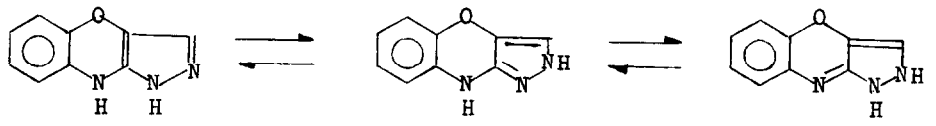
(Received in USA 7 December 1970; received in UK for publication 21 December 1970)

Recent reports on the application[1-4] of Vilsmeier-Haack reaction illustrating its several new potentialities, prompted this report of its action on 2H-1,4-Benzoxazin-3-one[5-7] and its usefulness in building condensed 1,4-benzoxazines.

Treatment of 1 mole of 2H-1,4-benzoxazin-3-one (I) with two moles of Vilsmeier complex ($POCl_3$+DMF) in chloroform at 0° followed by refluxing for four hours, gave on concentration, an orange-red salt, m.p. 182-4°(dec.). IR(nujol): 1655, 1630cm^{-1}. NMR(D_2O)δ: 3.33(s,6H,-NMe_2), 7.00(m,4H,aromatic), and 7.22(s,1H,methine). Basification of the salt gave orange-yellow needles in 90% yield. m.p. 91°. IR(nujol): 1650, 1620cm^{-1}. NMR($CDCl_3$)δ: 3.07(s,6H,-NMe_2), 6.35 (s,1H,methine), and 6.90(m,4H,aromatic). The spectral data and elemental analysis agreed for formulating the product as 2-dimethylaminoformylidene-3-chloro-1,4-benzoxazine(II), and the salt as the immonium salt (IIA) Scheme 1.

The enamine structure (II) was stable to boiling alkali (10%KOH). It could be dissolved and recovered from cold 5% HCL. Boiling with 1:1 HCL regenerated I. Nucleophilic reagents could displace either chlorine or both the chlorine and dimethylamino groups in II. Thus treatment with sodium ethoxide in ethanol gave the 3-ethoxy derivative (III), and with phosphorus pentasulphide the 3-thio compound (IV). However, treatment with excess of secondary amines such as morpholine, replaced both the chlorine and dimethylamino groups to give the corresponding dienamine(V). The structural assignments of the products were based on spectral data (IR and NMR).

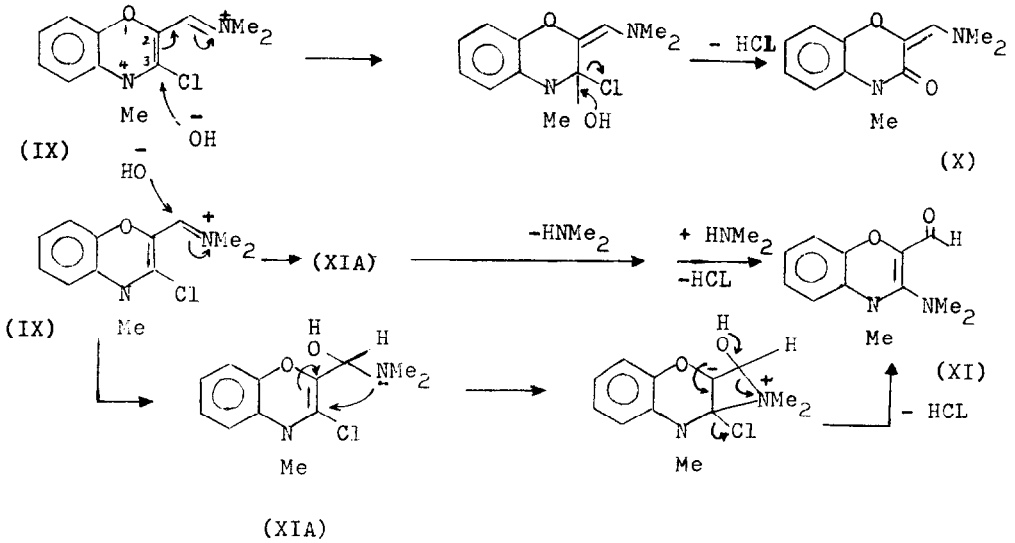
The two reactive centers for nucleophilic attack in II, situated as they are, offered interesting possibilities to build fused hetero systems. Thus treatment of II with hydrazine in ethanol gave pyrazolo (4,3-b)-1,4-benzoxazine (VI) in 95% yield: m.p. 209°; IR(nujol): 3300, 3100, 1640, 1590cm^{-1}. NMR(DMSO)δ: 6.75(m,4H,aromatic), 7.05(s,1H,CH=N), 8.20(s,1H,-NH) and 11.10 (broad s,1H,pyrazole-NH). II and methylhydrazine gave moderate yields (55%) of 2-methylpyrazolo (4,3-b)-1,4-benzoxazine (VII), m.p. 162-4°(dec.). IR(nujol): 3050, 1630, 1600cm^{-1}. NMR(DMSO)δ: 3.60 (s,3H,-NMe), 6.78(broad m,4H,aromatic), 6.92(s,1H,=CH-N), and 8.25(broad s, 1H,-NH). VI and VII have potential tautomeric forms as shown on the following page.



(VI)

(VII)

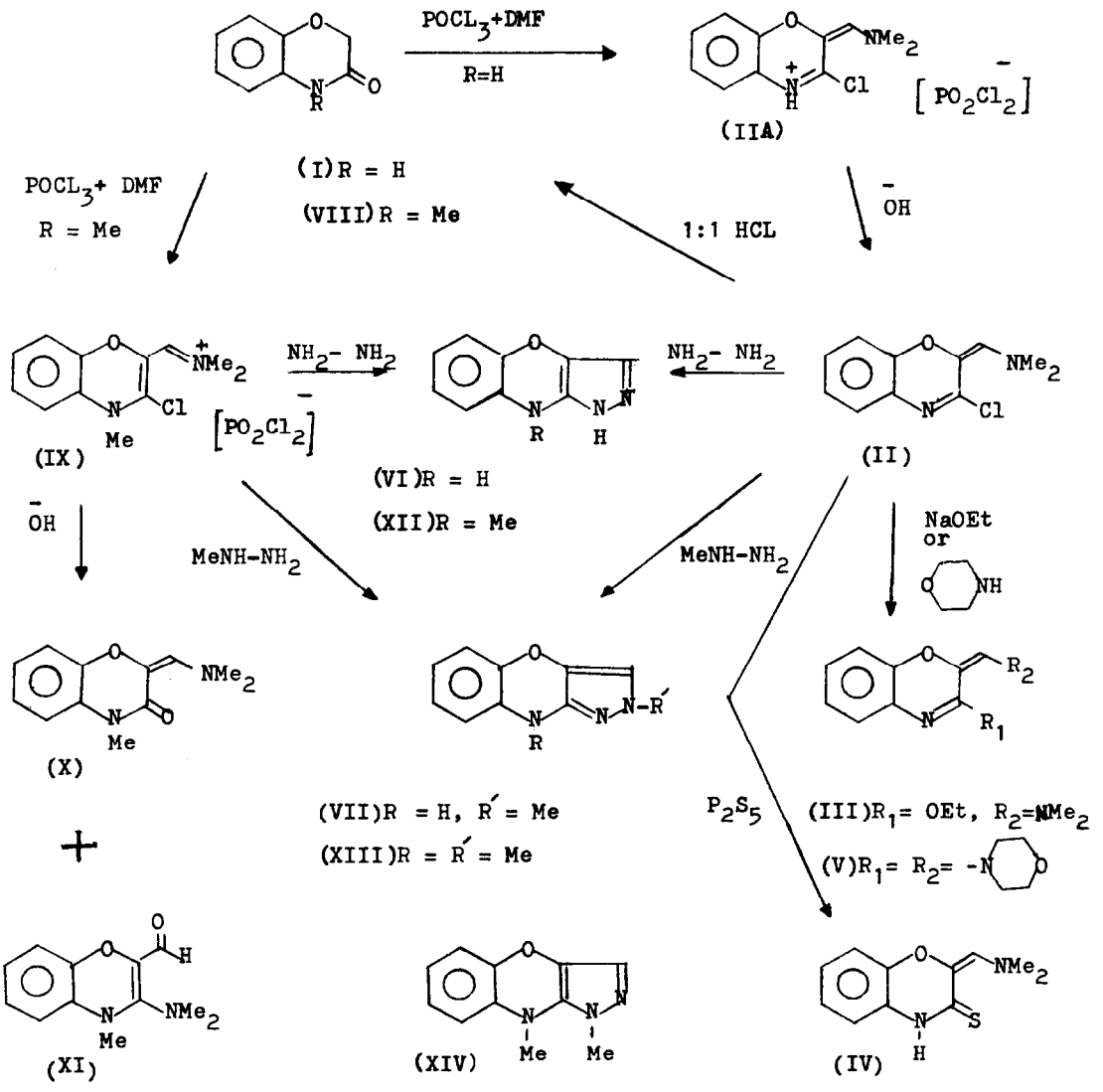
Extension of Vilsmeier reaction on 4-methyl-2H-1,4-benzoxazin-3-one (VIII) gave the stable orange-red immoniun salt of 2-dimethylaminoformylidene-3-chloro-4-methyl-1,4-benzoxazine (IX), m.p. 202° (85% yield). IR(nujol): 1640, 1620cm^{-1}. NMR(D_2O)δ: 3.40(s,3H,-NMe), 3.50(s,6H,-NMe_2), 7.00(m,4H, aromatic), and 7.60(s,1H,-CH=N). Basification of (IX) in cold with aqueous alkali gave two new products, separated by passing through a column of neutral alumina using benzene as eluent. The first fraction gave light yellow needles. m.p.79° (major) assigned the structure 2-dimethylamino-formylidene-4-methyl-1,4-benzoxazin-3-one(X). IR(nujol): 1685, 1620cm^{-1}. NMR($CDCl_3$)δ : 3.03 (s,6H,-NMe_2), 3.25(s,3H,N-Me), 6.60(s,1H,=CH-N), and 6.80(broad m,4H,aromatic). The last (minor) fraction gave orange-yellow needles, m.p.145°, formulated as 2-formyl-3-dimethylamino-4-methyl-1, 4-benzoxazine (XI) on the following spectral evidence: IR(nujol):1620, 1590cm^{-1}. NMR($CDCl_3$)δ : 3.00(s,6H,-NMe_2), 3.23(s,3H,-NMe), 6.90(broad m,4H,aromatic), and 9.00(s,1H,-CHO). The low IR absorbtion for carbonyl[8-9] may be due to the vinylogous amide nature of this carbonyl function. A suggested mechanism for the formation of X and XI from IX is illustrated below.



(XIA)

The formation of XI from XIA after the initial attack of base, can be a result of intramolecular or intermolecular attack of dimethylamino group on C-3 of XIA.

The isolation of X as major product on basification of immonium salt IX, suggests the preferential attack of base at C-3 position.



Scheme 1

Reaction of IX with hydrazine in ethanol gave pyrazolo(4,3-b)-4-methyl 1,4-benzoxazine(XII), m.p. 178° (85% yield). IR(nujol): 3100, 1640, 1605cm^{-1}. NMR(DMSO)δ: 3.15(s,3H,-NMe), 6.67(m,4H, aromatic), 6.93(s,1H,-CH=N), and 10.83(broad s,1H,-NH). Methylhydrazine and IX gave a mixture of two isomeric pyrazoles in a ratio of 4:1 based on the methyl signals[10] in the NMR. NMR($CDCl_3$)δ: 3.55, 3.72(pyrazolo-NMe), 3.10, 3.20(benzoxazine-NMe), 6.90, 7.00 (=CH-N and -CH=N), and 6.80, 6.95(aromatic).

Chromatography over alumina(neutral) using benzene-pet. ether 1:1 gave one of the isomers in pure form (65% yield). m.p. 102°. This was assigned the structure 2-methylpyrazolo(4,3-b)-4-methyl-1,4-benzoxazine (XIII); NMR($CDCl_3$)δ: 3.20(s,3H,benzoxazine-NMe), 3.72(s,3H,pyrazolo-NMe), 6.80(broad m,4H,aromatic), and 6.90(s,1H,=CH-N). The other isomer which could not be isolated in pure form may be 1-methylpyrazolo (4,3-b)-4-methyl-1,4-benzoxazine(XIV).

A detailed study of the different tautomeric forms of pyrazoles reported here and additional examples of the potentialities of II and IX for constructing fused hetero rings will be presented elsewhere.

Acknowledgement: We wish to thank Dr. G. S. Sidhu, Director, for his interest.

References:

* Present address: Chem. Dept., Western Michigan University, Kalamazoo, Michigan 49001.

** Present address: National Institute of Health, Bethesda, Maryland.

1. K. E. Schulte, J. Reisch, and U. Stoess, Angew. Chem. Int. Ed. 4, 1080 (1965).
2. C. H. Jutz and W. Muller, Angew. Chem. Int. Ed. 5, 1042 (1966).
3. S. Klutchko, H. V. Hansen, and R. I. Meltzer, J. Org. Chem., 30, 3454 (1965).
4. M. A. Khira, M. O. Abdelrahman, and K. Z. Gadalla, Tetrahedron Letters, 2, 109 (1969).
5. M. Mazharuddin and G. Thyagarajan, Tetrahedron, 25, 517 (1969).
6. M. Mazharuddin and G. Thyagarajan, Indian J. Chem. 7, 658 (1969).
7. G. Thyagarajan and U. T. Bhalerao, Indian J. Chem. 6, 176 (1968).
8. H. V. Hansen, J. A. Caputo, and R. I. Meltzer, J. Org. Chem., 31, 3845 (1966).
9. G. N. Walker, J. Org. Chem., 27, 4227 (1962).
10. J. D. Albright and L. Goldman, J. Org. Chem., 31, 273 (1966).