Tetrahedron Letters,Vol.30,No.12,pp 1477-1478,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

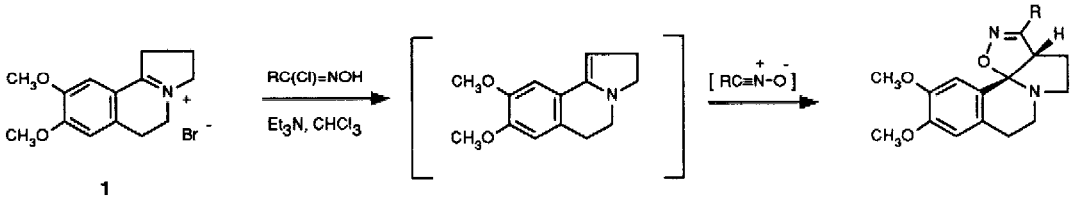
# THE SYNTHESIS OF NOVEL NITROGEN-CONTAINING MACROCYCLES FROM ISOXAZOLINE INTERMEDIATES

Mark P. Wentland
Medicinal Chemistry Department
Sterling Research Group
Rensselaer, NY 12144

Summary: Novel macrocyclic isoxazolo[4,5-g][3]benzazonine derivatives (**4**) have been prepared *via* 1,3-dipolar cycloaddition of an aryl nitrile oxide to a bridge polycyclic enamine followed by a quaternization-elimination sequence.

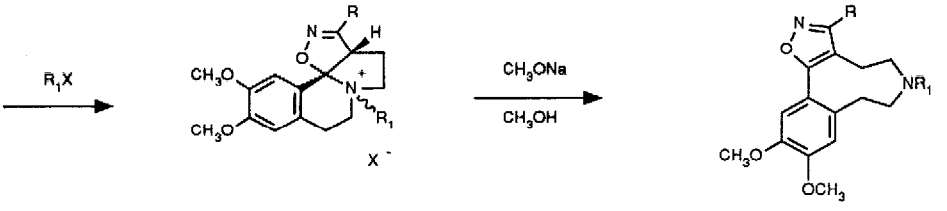
The chemistry of isoxazoles and isoxazolines has been the subject of numerous investigations.[1,2] The latent functionality preserved in these versatile heterocycles makes then ideally suited for elaboration into complex natural products.[2] Among the procedures used for the construction of isoxazoles, the 1,3-dipolar cycloaddition of a nitrile oxide to an acetylene, enamine, enolate, or equivalent enol derivative has proved to be efficient and regiospecific.[1,2]

It occurred to us that the 1,3-dipolar cycloaddition of a nitrile oxide to an enamine whose trigonal carbon-nitrogen bond is the bridge of a polycyclic ring system, would give an isoxazoline intermediate that upon aromatization to the isoxazole, would generate an isoxazolo-fused, nitrogen-containing macrocycle. We now wish to report the preparation of novel isoxazolo[4,5-g][3]benzazonine macrocycles (**4**) utilizing this methodology.




**1**

**2a**; R = 4-$ClC_6H_4$
**2b**; R = 4-$CH_3OC_6H_4$
**2c**; R = $C_6H_5$




**3a**; R = 4-$ClC_6H_4$, $R_1$ = $CH_3$, X = I
**3b**; R = 4-$CH_3OC_6H_4$, $R_1$ = $CH_3$, X = I
**3c**; R = $C_6H_5$, $R_1$ = $CH_3$, X = I
**3d**; R = 4-$ClC_6H_4$, $R_1$ = $CH_2CH{=}CH_2$, X = Br

**4a**; R = 4-$ClC_6H_4$, $R_1$ = $CH_3$
**4b**; R = 4-$CH_3OC_6H_4$, $R_1$ = $CH_3$
**4c**; R = $C_6H_5$, $R_1$ = $CH_3$
**4d**; R = 4-$ClC_6H_4$, $R_1$ = $CH_2CH{=}CH_2$

Slow addition of a chloroform solution of 4-$ClC_6H_4C(Cl)=NOH$[3] (1 equiv.) to an iced chloroform solution of triethylamine (2 equiv.) and iminium bromide **1**[4] (1 equiv.) gave, after an extractive workup, an 81% yield of isoxazoline **2a** (mp 153-154°C).[5,6] Acid-promoted aromatization of **2a** failed to give the isoxazolo-fused macrocycle **4** ($R_1$ = H); starting material was generally recovered. The stability of **2a** may well be a consequence of the amine leaving group being in the same molecule and in close proximity to the developing isoxazole. An alternative sequence was developed. Quaternization of **2a** in excess neat refluxing methyl iodide provided **3a**[7] [mp 203-210°C (d)] in 96% yield. A methanol solution of **3a** was treated with excess sodium methoxide at ambient temperature to give a 92% yield of 3-(4-chlorophenyl)-5,6,7,8-tetrahydro-10,11-dimethoxy-6-methyl-4*H*-isoxazolo[4,5-g][3]benzazonine, **4a** (mp 138.5-140°C).[8]

In similar fashion, isoxazolines **2b** (mp 167-169°C) and **2c** (mp 173-175°C) were made from the appropriate aryl hydroxamic acid chlorides[3] and **1**. Both were subjected to the methyl iodide-MeOH/MeONa sequence giving **4b** (mp 145-147°C, 93% from **2b**) and **4c** (mp 140-142°C, 71% from **2c**), respectively. In other experiments, **2a** was converted to **4d** (mp of the HCl salt 216-218°C) in 78% yield *via* allylation (neat allyl bromide at reflux) and base treatment.

Acknowledgment - Spectral data were obtained by the Analytical Chemistry Department of this Institute; their help is gratefully acknowledged.

## REFERENCES AND NOTES

1. a) Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed., Wiley-Interscience: New York, 1984; Vol. 2, pp. 291-392. b) Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Publishers: New York, 1988: pp. 55-74.
2. a) Baraldi, P.G.; Barco, A.; Benetti, S.; Pollini, G.P.; Simoni, D. *Synthesis*, **1987**, 857. b) Stevens, R.V. *Tetrahedron*, **1976**, *32*, 1599.
3. Battaglia, A.; Dondoni, A.; Exner, O. *J. Chem. Soc. Perkin II*, **1972**, 1911.
4. Wiesner, K.; Valenta, Z.; Manson, A.J.; Stonner, F.W. *J. Amer. Chem. Soc.*, **1955**, *77*, 675.
5. $^1$H-NMR, IR, and mass spectra were consistent with the assigned structures of all new compounds. Carbon, hydrogen, and nitrogen elemental analyses were also obtained and were within ±0.4% of the theoretical values.
6. Only one diastereomer was obtained. The regio- and stereochemistry were assigned on the basis of well-documented (ref. 1) electronic and steric considerations of 1,3-dipolar cycloadditions, as well as careful inspection of molecular models.
7. $^1$H-NMR indicates this to be a mixture of epimers at nitrogen.
8. This is an isoxazolo analogue of the alkaloid, protostephanine (see Bentley, K.W. *The Alkaloids*; Manske, R.H.F., Ed., Academic Press: New York, 1971; Vol. XIII p. 147).

(Received in USA 27 December 1988)