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A NOVEL ISOXAZOLE RING TRANSFORMATION. 5-OXIDOPYRIDAZINIUM BETAINES FROM ARYLHYDRAZONES OF 5-PHENACYLISOXAZOLES.

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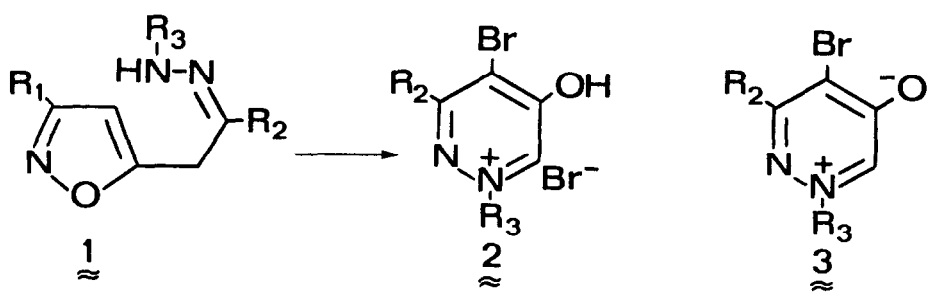
Summary. Under brominating conditions properly substituted isoxazoles lead to the title compounds through a new ring transformation. X-Ray structure analysis of an 5-oxidopyridazinium betaine is reported.

Isoxazoles are potential sources of several heterocycles through a variety of ring transformations[1]; many involve functional groups attached to the nucleus[2] and are promoted by reductive cleavage of the ring or rearrangements where three-atom side chains of properly substituted isoxazoles are implicated.

Regarding pyridazine ring formation from isoxazole precursors, the only examples reported are the hydrogenation of semicarbazones and phenylhydrazones of 3-acylisoxazoles which afford 4-aminopyridazines[3] and pyridazin-4-ones[4] respectively.

We wish to report here a novel type of rearrangement of arylhydrazones of 5-phenacyl--3-arylisoxazoles[5] 1 which leads to the 5-oxidopyridazinium betaines 3.



a, R_1 = Ph; R_2 = Ph; R_3 = pNO_2-C_6H_4
b, R_1 = Ph; R_2 = Ph; R_3 = Ph
c, R_1 = mCl-C_6H_4; R_2 = Ph; R_3 = pNO_2-C_6H_4
d, R_1 = mCl-C_6H_4; R_2 = Ph; R_3 = Ph

a, R_2 = Ph; R_3 = pNO_2-C_6H_4
b, R_2 = Ph; R_3 = Ph

When the arylhydrazones 1a,c reacted with bromine (two moles) in boiling chloroform, the same hydrobromide 2a precipitates in good yield (60%) from both solutions. From the mother

liquors of bromination of 1a and 1c benzonitrile and mCl-benzonitrile were recovered respectively. The bromination of 1b, d was carried out in CCl_4 with N-bromosuccinimide[8] to give 2b (24%), benzonitrile (from 1b) and mCl-benzonitrile[9] (from 1d). Treatment of 2[10] with $NaHCO_3$ solutions affords the corresponding zwitterionic compounds[11] 3 in quantitative yield.

The mass spectra of betaines 3[11] show $[M^+-28]$ peaks (loss of CO or N_2) and the pattern of molecular peaks indicates the presence of one bromine atom. In the ir spectra no carbonyl or hydroxyl bands are observed. ^1H nmr spectra[11] show the presence of a down field signal (3a:9.66δ ; 3b:9.25δ) which well accords with the resonance of a vinylic hydrogen adjacent to a positive/sp^2 nitrogen atom.[12]

Although the above spectroscopic measurements are in agreement with an oxidopyridazinium betaine structure, a full confirmation arises from the single-crystal X-ray analysis performed on 3a.[13]

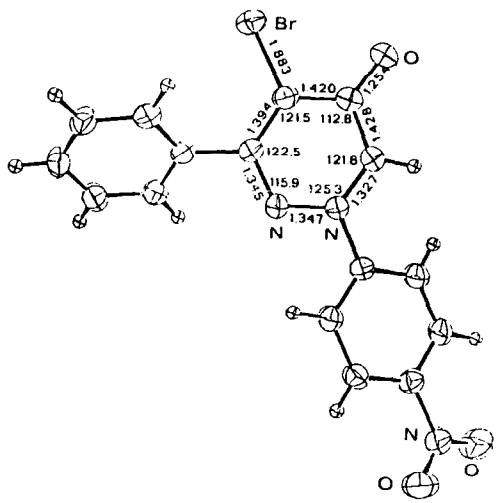


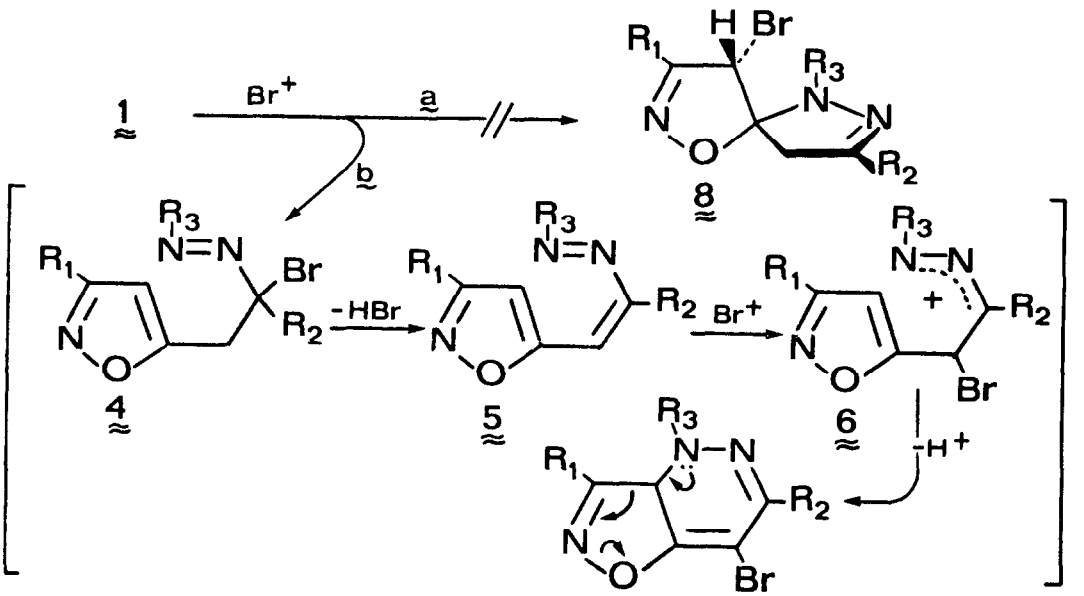
Figure 1. Molecular structure of betaine 3a, showing bond lengths (Å) and angles (deg.) involving atoms of betaine ring and 50% thermal ellipsoids.

The crystal is monoclinic, space group $P2_1/n$, with four molecules per unit cell of dimensions a=3.950(1), b=28.137(7), c=12.841(3) Å, β=94.40(2)°. The structure was solved using the "heavy atom Patterson" technique and refined with anisotropic Br, O, N, C and isotropic H (difference Fourier synthesis) to $R_1 \simeq 0.030$, $R_2 = 0.035$ for 2196 indipendent reflections having $2\vartheta_{CuK\alpha} < 130°$ and $I > 3\sigma(I)$ measured on a four circle Nicolet autodiffractometer.

A conceivable mechanism (see Scheme) for the formation of 2 arises from the following considerations.

Two reaction sites are in principle available for bromine attack: the isoxazole ring (path a) or the arylhydrazone moiety (path b).

According to the previously described neighbouring group participation in isoxazole ring bromination[14], the absence of spiroisoxazolines 8 in the reaction products indicates a reaction path b rather than a. Indeed hydrazones easily react with halogens to give unstable α-halo azo-compounds[15] similar to 4. Likely, in our case, elimination of hydrogen bromide from 4 may lead to the highly conjugated azo intermediate 5. An electrophilic attack on 5 by bromine generates the azallyl cation 6 which, owing to the calculated low aromaticity[16] of the isoxazole nucleus, cyclizes to 7. Fragmentation of 7 with loss of aryl cyanide gives the betaine hydrobromide 2.



Scheme.

The formation of the same compounds 2a from 1a, c and 2b from 1b, d clearly indicates that the aryl residue of the nitrile formed necessarily originates from the R_1 substituent.

To our knowledge, eliminations of nitriles from isoxazoles are not found under similar reaction conditions, while fragmentation of some 4, 5-fused-2-isoxazolines have been observed.[17] Thus isoxazoline 7 appears to be a plausible intermediate to explain the loss of R_1CN and the formation of 2. The driving force for the nitrile elimination may be the formation of 2 which has a substantial aromatic character.

5-Oxidopyridazinium betaines have been prepared by methylation of 4-hydroxypyridazines,[18] by heating 5-methoxy-1-methylpyridazinium iodides[19] and from 2,5-diketo-D-gluconate.[12] The above described isoxazole ring transformation represents a new entry to this class of compounds of intrinsic interest because of the potential 1,3-dipolar character.[20]

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5) Arylhydrazones are obtained by reaction of arylhydrazines on 5-phenacyl-3-phenylisoxazole[6] and 5-phenacyl-3-(mCl-phenyl)-isoxazole.[7] M.p.: 1a 211-213, 1b 165-168, 1c 198-201, 1d 117-123 °C. Satisfactory elemental analyses were obtained for all the compounds described.

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7) 5-Phenacyl-3-(mCl-phenyl)-isoxazole was obtained by cycloaddition of mCl-benzonitriloxide on phenacylacetylene. M.p. 132-134 °C; ^{1}H nmr in $CDCl_3$: δ 8.3-6.8 (m, 9H), 6.63 (bs, 1H), 4.50 (bs, 2H).

8) The bromination of 1b,d with free bromine was complicated by secondary reactions.

9) The amounts of nitriles obtained in the bromination of 1 result almost equimolecular to 2.

10) M.p.: 2a 230-235, 2b 222 dec. °C.

11) 3a: m.p. 213 °C dec.; δ(CF_3COOD) 9.66 (s, 1H), 8.7-8.2 (A_2B_2, 4H), 8.0-7.5 (m, 5H); m/z parent 373, 371 (1:1), parent-28 345,343 (1:1), parent-Br 293, base 119;
3b: m.p. 227 °C; δ(CF_3COOD) 9.25 (s, 1H), 7.7-7.0 (m, 10H); m/z parent 328, 326 (1:1), parent-28 300, 298 (1:1), parent-Br 247, base 82.

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13) The X-ray analysis was performed by the Crystalytics Company, Licoln, Nebraska 68501. Details of the results will be published elsewhere.

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