AN UNEXPECTED REACTION OF A 3-AMINO-2H-AZIRINE WITH 1,3-BENZOXAZIN-2,4-DIONE

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Abstract - The reaction of 3-dimethylamino-2,2-dimethyl-2H-azirine (1) with 1,3-benzoxazin-2,4-dione (3) in refluxing 2-propanol led not to the formation of a medium sized heterocycle but to the formation of the imidazo[2,1-b]-1,3-benzoxazin-5-one 4 and the imidazolin-2-one 5 in 33% and 74% yield, respectively. The structure of 4 has been confirmed by X-ray crystallographic analysis while 5 has been identified by comparison with an independently synthesized material (cf. Scheme 2). In Scheme 3 a reaction mechanism for the formation of 4 and 5 is suggested.

During the last few years, we have studied some reactions of 3-amino-2H-azirines. These cyclic, three-membered amidines react with various proton-acidic compounds to give cyclic or noncyclic products[1-2]. Their formation has been explained via cleavage of the strained amidine ring, protonation of the azirine nitrogen being the first step in the reaction sequence. With some NH-acidic heterocycles, e.g., saccharine, phthalimide and 2,2-disubstituted malonimides, 3-dimethylamino-2,2-dimethyl-2H-azirine (1) reacts to yield ring-expanded heterocyclic compounds

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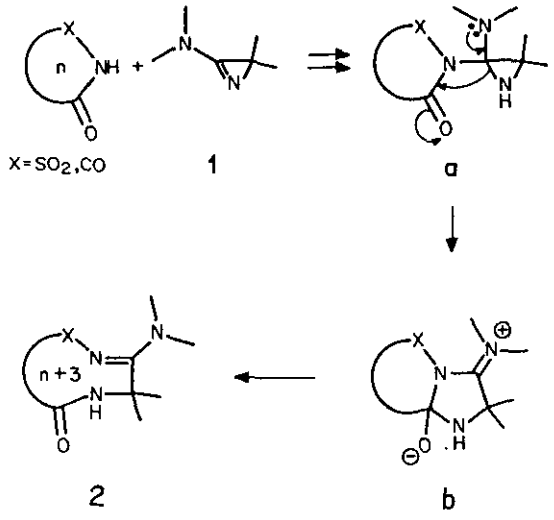
of type 2 with eight- and seven-membered rings, respectively[3-4] (Scheme 1). A reaction mechanism involving the primary adduct a and the zwitterionic intermediate b is reasonable.

We have also tried to apply this reaction to the formation of products of type 2 containing nine ring members, starting with six-membered NH-acidic heterocycles. All reactions studied until now have not led to the desired ring expansion, although

Scheme 1

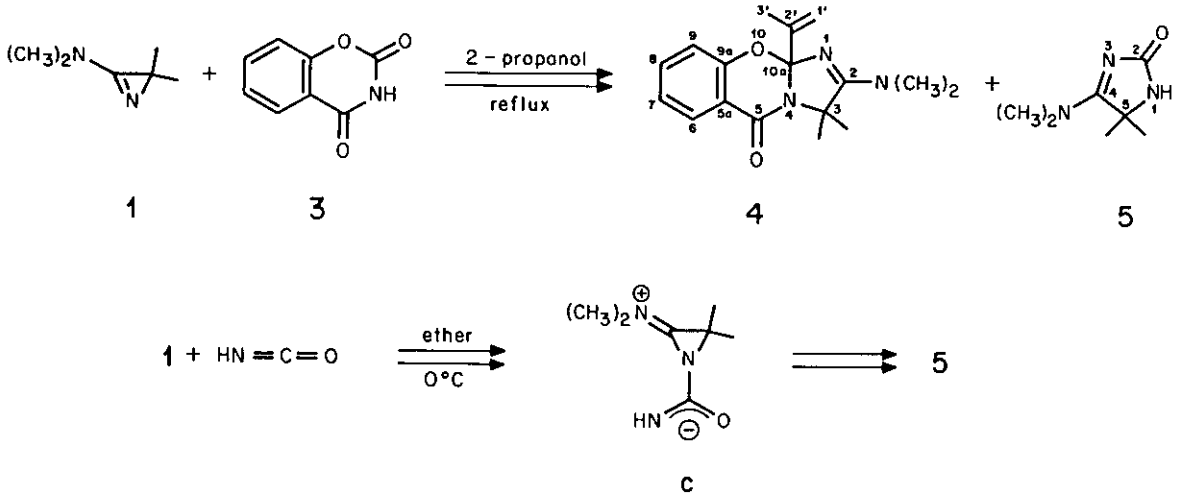


the zwitterionic intermediate b seems to be formed[2] (cf. also [5-8]). In the present paper, we wish to report the results of the reaction of 3-amino-2H-azirine 1 with 1,3-benzoxazin-2,4-dione (3) and the characterization of the products.

Refluxing a mixture of 448 mg (4 mmoles) of the azirine 1 and 326 mg (2 mmoles) of the NH-acidic heterocycle 3 in 20 ml of acetonitrile for 75 hours afforded two products 4 and 5 (Scheme 2). The reaction mixture was cooled and the solid material, identified as 4-dimethylamino-5,5-dimethyl-3-imidazolin-2-one (5) was separated by filtration. Thin layer chromatography (Al_2O_3, benzene/chloroform) of the mother liquor afforded another portion of 5, in addition to 2-dimethylamino-3,3-dimethyl-10a-(2-propenyl)-3,10a-dihydro-imidazo[2,1-b]-1,3-benzoxazin-5-one (4). After recrystallization, the two products were isolated in yields of 74% (5, mp 259-260°C from ethanol/ethyl acetate) and 33% (4, mp 177-178°C from dichloro-

methane/hexane), respectively.

Scheme 2



The structure of 5 has been deduced from elemental analysis[9] and spectroscopic data [10]. The material from the reaction of 1 and 3 was identical with an authentic reference, prepared from azirine 1 and isocyanic acid: Potassium isocyanate, suspended in ether at -10°C, was treated with cold sulfuric acid (cf.[11]), then the ethereal solution was added dropwise to a cold solution of azirine 1 in ether. Evaporation of the solvent and recrystallization of the residue from ethanol/ethyl acetate afforded 5 in 92% yield.[12]

Elemental analysis[13] and spectroscopic data[14] of the second reaction product 4 showed that it should be attributed to the reaction of 3 and two moles of azirine 1, as suggested by the presence of a geminal dimethyl group and an isopropenyl group. The spectroscopic data suggested structure 4 but were not unambiguous. Therefore, an X-ray crystallographic analysis was undertaken on colourless single crystals obtained from CH_2Cl_2/hexane.

The new heterocyclic compound 4 crystallizes in the triclinic space group $P\bar{1}$ with a = 14.552 (4), b = 14.083 (4), c = 8.982 (4) Å; α = 77.19 (3), β = 106.17 (3), γ = 112.42 (2)° and Z = 4. The intensities of 4794 independent reflexions were measured with monochromatized MoK_α radiation on a Syntex $P2_1$ automatic four-circle

diffractometer in the range $3°<2\theta<47°$ (ω-scan). The structure was solved by direct methods using the computer programs MULTAN-78[15] and SHELX-76.[16] In the least squares refinement all C-, N- and O-atoms were refined anisotropically while the attached H-atoms were allowed to ride upon them with the common isotropic temperature factors after calculation of their positions. The final R-value is 0.056 for 3755 observed reflexions with $I \geq 2.5\ \sigma(I)$.

Figure 1 shows the molecular structure of the reaction product 4.

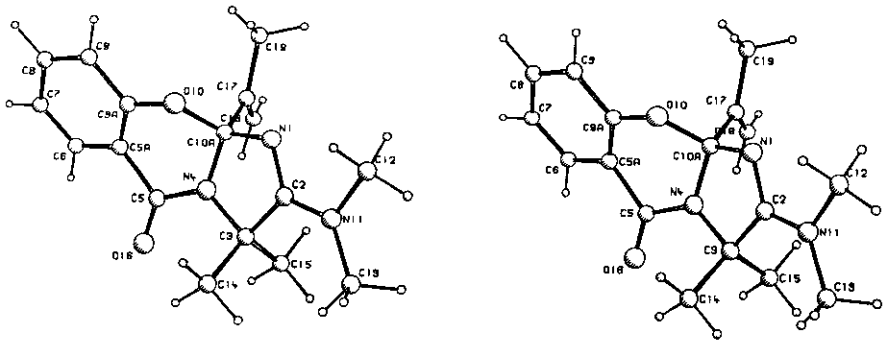
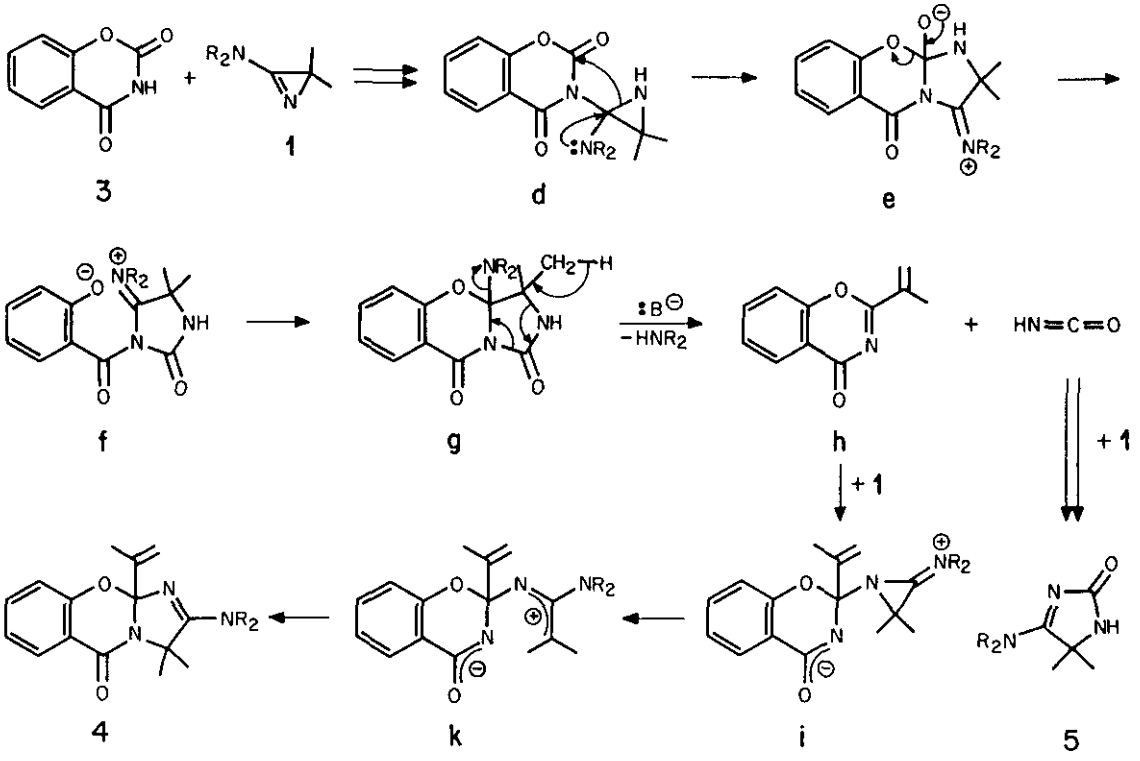


Fig. 1. Stereoscopic projection of the imidazo[2,1-b]-1,3-benzoxazin-5-one derivative 4

A plausible reaction mechanism for the formation of the products 4 and 5 is postulated in Scheme 3. Protonation of the azirine by the NH-acidic heterocycle 3 and nucleophilic attack of the anion to the amidinium C-atom leads to the aziridine d, which rearranges to yield the zwitterionic intermediate e. This zwitterion avoids breaking the central C-N bond to give a medium sized heterocycle (cf. Scheme 1), and is converted to the rearranged intermediate g. A fragmentation as indicated in Scheme 3 leads to the benzoxazinone h and isocyanic acid. The latter reacts quite readily (cf. Scheme 2) with aminoazirine 1 yielding the imidazolin-2-one 5. Formation of the second product 4 can be rationalized from h via nucleophilic attack of a third molecule of aminoazirine 1 to give i, followed by cleavage of the three-membered ring to the 1-aza-allyl-cation k and ring closure. All the different ring

Scheme 3



opening processes of the aminoazirine moiety suggested in Scheme 3 are formulated in analogy to known reactions (cf. [1]).

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9 5: $C_7H_{13}N_3O$ (155.20); calculated: C 54.17 H 8.44 N 27.07%; found: C 54.44 H 8.23 N 26.91%.

10 5: uv (ethanol): λmax 246.3 nm (log ε = 4.04); ir (KBr): 1695s (C=O), 1593s (C=N), 1409m, 1310s, and 903s cm^{-1}; ^{1}H-nmr (CD_2Cl_2): 6.2 (broad s, NH), 3.13 (s, $(CH_3)_2N$), 1.52 ppm (s, $(CH_3)_2C$); ^{13}C-nmr (CD_3OD): 183.6 (s, C(4)), 169.4 (s, C(2)), 62.6 (s, C(5)), 40.5 and 39.5 (2 broad signals, $(CH_3)_2N$; at 60°C: qa at 39.9), 24.9 ppm (qa, $(CH_3)_2C$); ms: 155 (M^+, 39), 154 (76), 140 (25), 111 (11), 99 ($C_4H_7N_2O$, 39), 98 (12), 97 (10), 83 (21), 71 ($C_3H_7N_2$, 100), 70 ($C_3H_6N_2$, 95), 69 (20), 56 (16), 44 (34), 43 (11), 42 (79), 41 (22).

11 Cf. H.P. Kaufmann and F. Kögler, Ber., 58, 1553 (1925); H. Lecher and F. Graf, ibid., 59, 2601 (1926).

12 A very similar reaction has been observed with aminoazirine 1 and thiocyanic acid, leading to 4-dimethylamino-5,5-dimethyl-3-imidazolin-2-thione: S. Chaloupka, H. Heimgartner, H. Schmid, H. Link, P. Schönholzer, and K. Bernauer, Helv. Chim. Acta, 59, 2566 (1976).

13 4: $C_{17}H_{21}N_3O_2$ (299.37); calculated: C 68.20 H 7.07 N 14.04%; found: C 68.26 H 7.15 N 14.00%; osmometric molecular weight determination ($CHCl_3$): found 281.

14 4: uv (ethanol): λmax 300 (log ε = 3.25), 232 nm (log ε = 4.39); ir (KBr): 1668s (C=O), 1600s (C=N), 1582m, 1468s, 1390s, 1280m, 1245m, 1230m, 1213m, 1165s, 1142m, and 1120m cm^{-1}; ^{1}H-nmr ($CDCl_3$): 8.0-7.7 (m, 1 arom. H), 7.6-6.8 (m, 3 arom. H), 5.00 and 4.90 (2 m, $=CH_2$), 3.08 (s, $(CH_3)_2N$), 1.88 and 1.85 ppm (2 s, $(CH_3)_2C$); ^{13}C-nmr ($CDCl_3$): 169.4 (s, C(5)), 160.3 (s, C(2)), 154.7 (s, C(9a)), 144.7 (s, C(2')), 133.7, 127.1, 121.7, and 116.9 (4 d, C(6)-C(9)), 120.7 (s, C(5a)), 113.5 (t, C(1')), 110.2 (s, C(10a)), 67.1 (s, C(3)), 39.0 (qa, $(CH_3)_2N$), 23.2 and 22.9 (2 qa, $(CH_3)_2C$), 18.4 ppm (qa, C(3')); ms: 299 ($C_{17}H_{21}N_3O_2$, 71), 284 ($C_{16}H_{18}N_3O_2$, 43), 270 ($C_{16}H_{20}N_3O$, 28), 258 ($C_{14}H_{16}N_3O_2$, 50), 256 ($C_{15}H_{18}N_3O$, 50), 254 ($C_{16}H_{20}N_3$, 52), 179 ($C_{10}H_{17}N_3$, 25), 164 ($C_9H_{14}N_3$, 26), 109 ($C_7H_{11}N$, 100), 68 (66), 44 (35), 42 (23), 41 (21), 40 (14).

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