RING EXPANSION OF 3-SUBSTITUTED 1,2-BENZOISOTHIAZOLE 1,1-DIOXIDES TO 1,2-BENZOTHIAZEPINE 1,1-DIOXIDES

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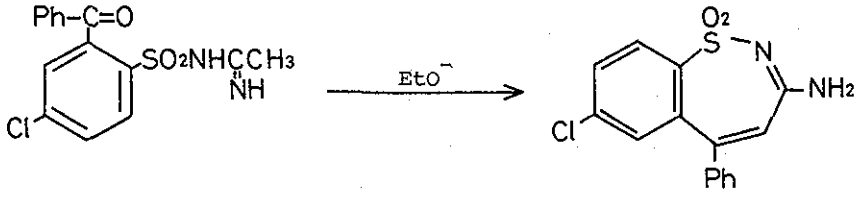
3-Substituted 1,2-benzoisothiazole 1,1-dioxides undergo a [2+2]cycloaddition with 1-diethylaminopropyne followed by ring expansion to give the very stable 5-substituted 3-diethylamino-4-methylbenzo-1,2-thiazepine 1,1-dioxides (4). These can, however, be cleaved with lithium aluminum hydride to o-styryl-sulfonamides. The stability of the ring system 4 is discussed briefly.

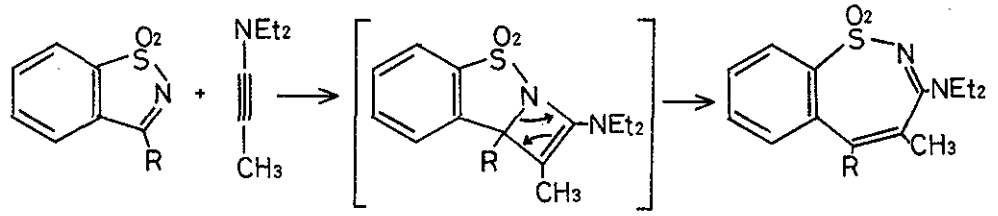
There has been only one report of the synthesis of a 1,2-benzothiazepine 1,1-dioxide, namely the cyclization of the o-benzoylbenzenesulfonylamidine derivative 1 to 2.[1] The compound was reported to have hypotensive and diuretic

activity. No other aromatic 1,2-benzothiazepines have been described. We now report a simple general two step synthesis of this ring system from saccharin by the ring expansion of the readily available 3-substituted 1,2-benzoisothiazole 1,1-dioxides (3).[2]



1 2

Addition of 1-diethylaminopropyne to 3 in acetonitrile at room temperature[3] gave the 5-substituted 3-diethylamino-4-methylbenzo-1,2-thiazepine 1,1-dioxides (4) in good yield. The [2+2] cycloadditions of ynamines with imines,[4] olefins,[5] and aldehydes and ketones[4] are well known and it is assumed that a similar addition takes place with 3 followed by ring-expansion:



3

4

a: R=CH_3; mp 154°

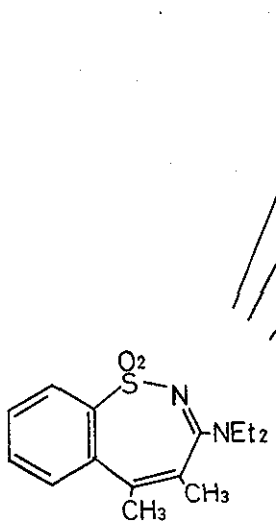
b: R=C_2H_5; mp 110°

c: R=Ph; mp 195°

d: R=OEt; mp 145°

e: R=SMe; mp 125°

The structural assignment of 4 was consistent with its spectral properties. For example, when R=CH_3 in 4, the compound showed the presence of a >C=N- bond (1620 cm^{-1}) and a sulfonyl group (1300, 1160 cm^{-1}) in the infrared, two methyl singlets (δ 3.22 and 3.12), a 4 H doublet of quartets at δ 3.43 due to the methylene protons in $(Et)_2$, and a 6 H doublet of triplets for the two methyl groups in $(Et)_2$. The mass spectrum also supported structure 4. Thus, loss of SO_2 resulted in the formation of a 2-diethylaminoquinolinium ion (m/e 228) and a number of important fragments, including the base peak (m/e 157), could be assigned quinolinium ion structures.



4a

30% NaOH, THF
65°, 12hr

conc. H_2SO_4, EtOH
78°, 12hr

H_2/Ra-Ni, 45 psi

Zn/AcOH
130°, 12hr

$Na_2Cr_2O_7$, AcOH
130°, 12 hr

$KMnO_4$
100°, 20hr

CH_3I, EtOH*
150°, 12 hr

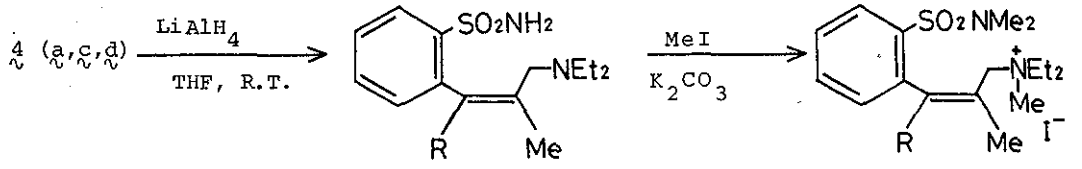
CH_3OSO_2F, C_6H_6*
60°, 12hr

NO REACTION

*:sealed tube

Scheme

On the other hand, this ring system is remarkably stable to a wide variety of chemical reagents (Scheme), which is reminiscent of compounds exhibiting 'aromatic' stability. It could be cleaved, however, with lithium aluminum hydride in tetrahydrofuran at room temperature to give the o-styryl-sulfonamide (5) which, on treatment with an excess of methyl iodide in the presence of potassium carbonate, gave the quaternary salt 6. The nmr spectra of 5 and 6 agree with the proposed structures and hence support the structure

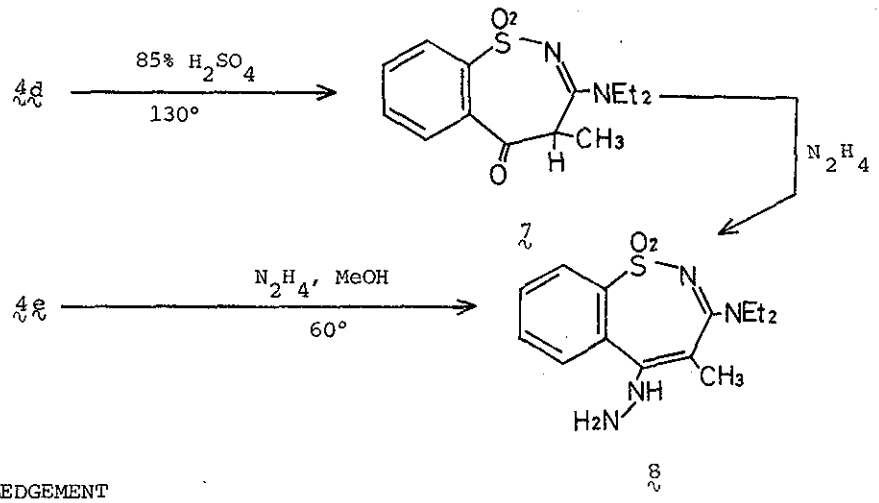


5 6

of 4. Thus, 5 (R=Ph) exhibits a methylene singlet at δ 3.0, a methyl singlet at δ 2.0, two N-ethyl groups and an NH_2 singlet (δ 4.80, exchangeable). The mass spectral fragmentations correspond to loss of $-SO_2NH_2$ (m/e 280), loss of $-CH_2NEt_2$ (m/e 272), and loss of the whole vinyl side chain (m/e 165). 6 (R=Ph) also exhibits a methylene singlet (δ 4.0), two N-Me singlets (δ 2.8), an $\overset{+}{N}Me$ singlet (δ 3.2), an allylic methyl (δ 2.2), and the NEt_2 group.

When 4 (R=OEt; colorless) was heated with 85% H_2SO_4 at 130° the ketone (7) mp 185° was formed [$\gamma_{C=O}$ 1685 cm^{-1}; Me doublet at δ 1.90 (J≈6.0 Hz)] which with hydrazine gave the hydrazine (8), mp 137° (rather than the hydrazone) (3 exchangeable H with D_2O, Me singlet at δ 1.85). The same hydrazine was obtained by heating 4 (R=SMe, red) with hydrazine in methanol

at 60°. That 8 exists exclusively in the ene-hydrazine rather than hydrazone form again speaks for the 'aromatic character' of this 1,2-thiazepine 1,1-dioxide system.



ACKNOWLEDGEMENT

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REFERENCES

1. J. J. Traverso, U.S. patent 3,377,357(1966); Chem. Abstr., 69, 52190f(1968).

2. R. A. Abramovitch, E. M. Smith, M. Humber, B. Purtschert, P. C. Srinivasan, and G. M. Singer, J.C.S. Perkin I, 2589(1974).

3. When R=OEt, much more vigorous (180°, sealed tube) conditions had to be used, but R=SMe reacted normally at room temperature.

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