INTRAMOLECULAR CYCLISATION USING METHYL(BISMETHYLTHIO)SULPHONIUM SALTS. PART 5.[1] SYNTHESIS OF FUNCTIONALIZED 4,5-DIHYDRO-3,1-BENZOXAZEPINES

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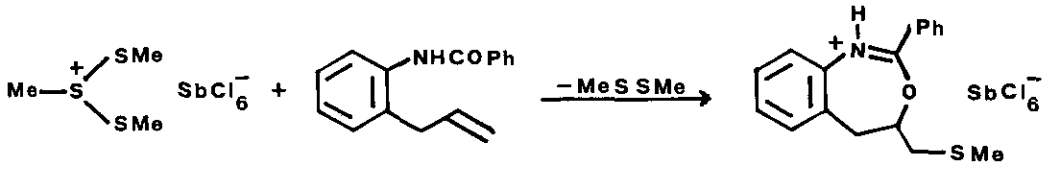
Abstract - The reaction of methyl(bismethylthio)sulphonium hexachloroantimonate 1 with N-(2-allylphenyl)benzamide 2 gives the 4-methylthiomethyl-4,5-dihydro-3,1-benzoxazepine 4. Other electrophilic reagents reacts with 2 to give exclusively or preferentially products of addition to the allylic double bond.

In recent years we have introduced the use of methyl(bismethylthio)sulphonium hexachloroantimonate 1 as a synthon of methylsulphenylium ion (MeS^+) for the cyclofunctionalization of properly substituted alkenes and alkynes.
In this way, methylthio-functionalized dihydrobenzofurans,[2] methylene-oxazoles,[3] dihydrooxazines,[4] indoles and dihydroindoles[1] have been obtained from o-allylphenols, propargylamides, o-vinylbenzanilides, o-vinylbenzenesulphonamides, and o-allylbenzensulphonamides respectively.
We report here some preliminary results on the application of this reaction to the synthesis of the 3,1-benzoxazepine system for which the available synthetic approaches are limited.[5]
The suitably substituted alkene 2, prepared from the corresponding aniline derivative,[6] was reacted with the sulphonium salt 1 in dichloromethane at 0°C. Addition of n-pentane to the reaction mixture gives the benzoxazepinium hexachloroantimonate 3 which was recrystallized from dichloromethane- n-pentane to give pure 3 in 60% yield[7] (equation).



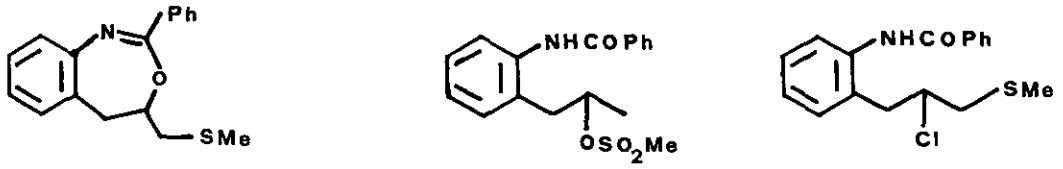
1 2 3

Treatment of 3 with aqueous sodium bicarbonate solution and column chromatography (eluant light petroleum - diethyl ether 7:3) gives 4-methylthiomethyl-4,5-dihydro-3,1-benzoxazepine 4 in quantitative yield.

Compound 4[8] gave correct elemental analysis and spectroscopic properties in agreement with the proposed structure. In particular the mass spectrum showed the molecular ion at 283 m/z and the ion at 222 m/z, corresponding to the loss of the CH_2SMe moiety as relatively intense peak. The ^1H nmr spectrum showed, besides the S-methyl and aromatic protons resonances, two ABX systems due to the two methylene groups coupled with the same methine proton.[9] The ^{13}C nmr spectrum gave more compelling informations on the structure of 4:[10] the 4-C was found as doublet at δ 81.71 and the 2-C as a singlet at δ 151.34.

Other electrophilic reagents were also tested for the ring closure of 2.

The attempt to cyclize 2 by acid catalysis using methanesulphonic acid gives 5 only,[11] the addition product of the acid to the carbon-carbon double bond. The reaction of 2 with methanesulphenyl chloride gives a 1:2 mixture of 4 and 6[12] which is the adduct of the sulphenyl chloride to 2.



4 5 6

The results above reported clearly show the stronger tendency of the sulphonium salt 1 with respect to other electrophilic reagents to promote the ring closure of 2 to the seven-membered ring product.

This behaviour is possibly due to the absence in this reagent of a strong nucleophilic counterpart which may compete with the poorly nucleophilic amidic oxygen of 2 for the attack at the positively charged intermediate which, in the case of the sulphenic electrophiles, should have the structure of a thiiranium ion.[13]

ACKNOWLEDGMENT

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5. J. T. Sharp in "Comprehensive Heterocyclic Chemistry", eds. A. R. Katritsky and C. W. Rees, Pergamon Press, New York, 1984, vol. 7, p. 626; J. K. Landquist in "Comprehensive Organic Chemistry", eds. D. Barton and D. Ollis, Pergamon Press, New York, 1979, vol. 4, p. 1153.
6. Compound 2 was synthesized by reaction of o-allylaniline and benzoyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature; yield 60%, mp 143-145°C from diethyl ether; ^1H nmr in $CDCl_3$: δ 8.10-7.10 (m, 10 H, aromatics and NH), 6.06 (m, 1 H), 5.18 (m, 2 H), 3.46 (d, J 5.80 Hz, 2 H). Mass spectrum, molecular ion at m/z 237. Satisfactory elemental analyses were obtained for this compound and for all the other new compounds described hereinafter.
7. mp 99-101°C; ^1H nmr in CD_3COCD_3: δ 8.35-7.47 (m, 9 H, aromatics), 5.65 (m, 1 H) 4.47 (broad s, NH), 3.82 (m, 2 H), 3.30 (m, 2 H), 2.27 (s, 3 H).
8. Compound 4 was purified by column chromatography (SiO_2, eluant light petroleum-diethyl ether, 7:3 v/v) and bulb to bulb distillation at 4 mm Hg, oil bath temperature, 200°C.
9. ^1H nmr in $CDCl_3$: δ 8.14 (m, 2 H, aromatics), 7.55-7.05 (m, 7 H, aromatics), 4.76 (m, 1 H), 3.21 (m, 2 H), 2.83 (m, 2 H), 2.17 (s, 3 H).
10. ^{13}C nmr in $CDCl_3$: δ 151.34 (s), 143.52 (s), 135.56 (s), 132.45 (s), 130.37 (d), 129.06 (d), 128.93 (d), 128.43 (d), 127.92 (d), 127.51 (d), 124.94 (d), 81.71 (d), 40.05 (t), 39.20 (t), 16.30 (q).
11. The reaction of 2 (1 mmol) with methanesulphonic acid (4 ml) was carried out at room temperature for 30 min. After usual work-up the reaction mixture was

chromatographed (SiO_2, eluant light petroleum-diethyl ether 7:3 v/v) to give the unreacted **2** (0.4 mmol) and **5** (0.44 mmol, 44% yield) mp 123-125°C. ^1H nmr in $CDCl_3$: δ 8.18 (broad s, NH), 7.95-7.15 (m, 9 H, aromatics), 4.90 (m, 1H), 3.10 and 2.92 (AB part of an ABX system, 2H, J_{AB} 14.65 Hz, J_{AX} 4.83 Hz, J_{BX} 8.54 Hz), 2.53 (s, 3H), 1.53 (A part of an A_3X system, 3 H, J_{AX} 6.10 Hz). Mass spectrum, molecular ion at m/z 333.

12. Equimolar amount of **1** and methane sulphenyl chloride in dichloromethane at 0°C were reacted for 2 h giving after work-up and column chromatography (SiO_2, eluant light petroleum-diethyl ether 7:3 v/v) **4** (25% yield) and **6** (52 % yield). Compound **6** gave correct elemental analysis and a mass spectrum with the molecular ion at 319 m/z. The regiochemistry of the addition of the methanesulphenyl chloride to **1** has been deduced from the chemical shift values of the ^1H nmr spectrum and in particular from the low value of the methine proton (δ 4.25). ^1H nmr in $CDCl_3$: δ 8.42 (broad s, NH), 7.95 (m, 2 H, aromatics), 7.42 (m, 7 H, aromatics), 4.25 (m, 1 H), 3.49 and 3.05 (AB part of an ABX system, 2 H, J_{AB} 14.95 Hz, J_{AX} 8.54 Hz, J_{BX} 3.34 Hz), 2.93 (m, 2 H), 2.07 (s, 3 H).

13. For recent reviews, see: G. Capozzi and G. Modena in "*Organic Sulfur Chemistry. Theoretical and Experimental Advances*", eds. F. Bernardi and A. Mangini, Elsevier, Amsterdam, 1985, p. 246. G. H. Schmid and D. G. Garratt in "The Chemistry of Functional Groups. Supplement A. The Chemistry of Double-Bonded Functional Groups", ed. S. Patai, Wiley, New York, 1977, part 2, p. 828.

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