INTRAMOLECULAR CYCLISATION USING METHYL(BISMETHYLTHIO)SULPHONIUM SALTS. PART 4.[1] SYNTHESIS OF FUNCTIONALIZED INDOLES AND DIHYDROINDOLES

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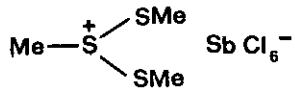
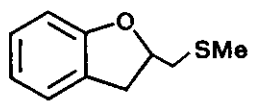
Abstract - The 3-methyl-2-methylthio-1-p-tolylsulphonylindole (7) and the 2-(methylthiomethyl)-1-p-tolylsulphonyldihydroindole (8) were synthesized in one pot reactions of methyl(bismethylthio)sulphonium hexachloroantimonate (1) with 2-(2-propenyl)-N-tosylaniline (5) and 2-allyl-N-tosylaniline (6) respectively.

The use of methyl(bismethylthio)sulphonium hexachloantimonate (1)[2,3] for the synthesis of methylthio-functionalized heterocycles like dihydrofurans (2)[4], methyleneoxazoles (3)[5], and dihydrooxazines (4)[1] from allylphenols, propargylamides and o-vinylbenzanilides respectively has been recently exploited.



(1)



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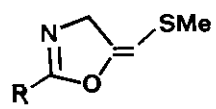

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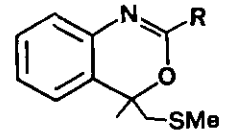
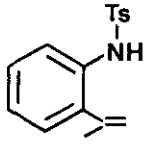


(4)

The general scheme for these reactions implies the transfer of a methylsulphenilium ion moiety from (1) to the multiple carbon-carbon bond with formation of thiiranium[6,7] or thiirenium[6,8,9] ions and releasing of dimethyldisulphide. The subsequent intramolecular nucleophylic attack at one carbon atom of the three-membered ring intermediate gives rise to the heterocyclic structure.

In this communication we report the reactions of (1) with 2-(2-propenyl)-N-tosylaniline (5) and with 2-allyl-N-tosylaniline (6) which give 3-methyl-2-methylthio-1-p-tolylsulphonylindole (7) and 2-(methylthiomethyl)-1-p-tolylsulphonyldihydroindole (8) respectively.



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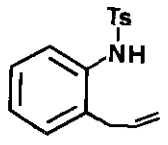

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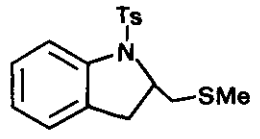
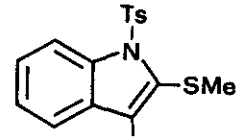


(8)



(7)

The reaction of (6)[10] has been carried out in dichloromethane at 0°C and gave (8) in 45% yield.[11]

The cyclic structure of (8) was deduced from the combination of analytical and spectroscopic data. The dihydroindole (8) shows correct elemental analysis and a mass spectrum with the parent ion at 333 m/z and the base peak at 272 m/z, corresponding to the loss of the $-CH_2SMe$ fragment from the parent ion. The ^1H nmr spectrum (see Table) is also consistent with the proposed structure.

Table

^1H nmr parameters for compounds (7), (8), and (9).[a]

Comp.	Aromatics	Me(Ts)	SMe	SO_2Me	Me	CH_2(exo)	CH_2(ring)	CH
(7)	8.35-7.13(m)	2.73(s)	2.30(s)[b]	--	2.32(s)[b]	--	--	--
(8)	7.68-7.00(m)	2.36(s)	2.21(s)	--	--	3.03 and 2.71[c]	2.84(d)[d]	4.36(m)
(9)	7.75-7.03(m)	2.37(s)	--	3.09(s)	--	3.72 and 3.34[e]	3.06[f]	4.70(m)

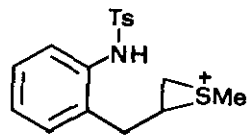
[a] Spectra recorded at 200 MHz in $CDCl_3$ solution; δ values from internal TMS; J in Hz. [b] The assignement may be reversed. [c] AB part of an ABX system; J_{AB} = 13.43; J_{AX} = 3.97; J_{BX} =9.46. [d] J = 6.10. [e] AB part of an ABX system; J_{AB} = 14.04; J_{AX} = 3.36; J_{BX} = 9.46. [f] Signal partially overlapped with the 3.09 singlet.

In order to properly assign the resonance frequencies of the two methylenic groups, (8) was oxidized to the corresponding sulphone (9)[12]. The comparison of the nmr spectra of (8) and (9) allowed to determine that the ring methylene protons were the isochronous ones and the splitted AB quartet was due to the exocyclic methylene group. In fact the change of the oxidation state of the sulphur atom causes a greater down-field shift of the latter; similarly the resonances of the two methyl groups of (8) and (9) could be assigned.

The reaction of the sulphonium salt (1) with (5)[13] in the same reaction conditions gave the indole (7)[14] which was recovered after usual work-up and column chromatography in 36% yield.

The structure of (7) was fully demostrated by comparison with a sample prepared from 3-methylindole by N-tosylation and reaction of the N-tosyl derivative with methanesulphenyl chloride.[15]

The formation of the dihydroindole derivative (8) can be easily interpreted assuming the attack of the nitrogen nucleophile at the substituted carbon atom of the intermediate thiiranium ion (10) formed by the transfer of a methylthio moiety from (1) to (6).



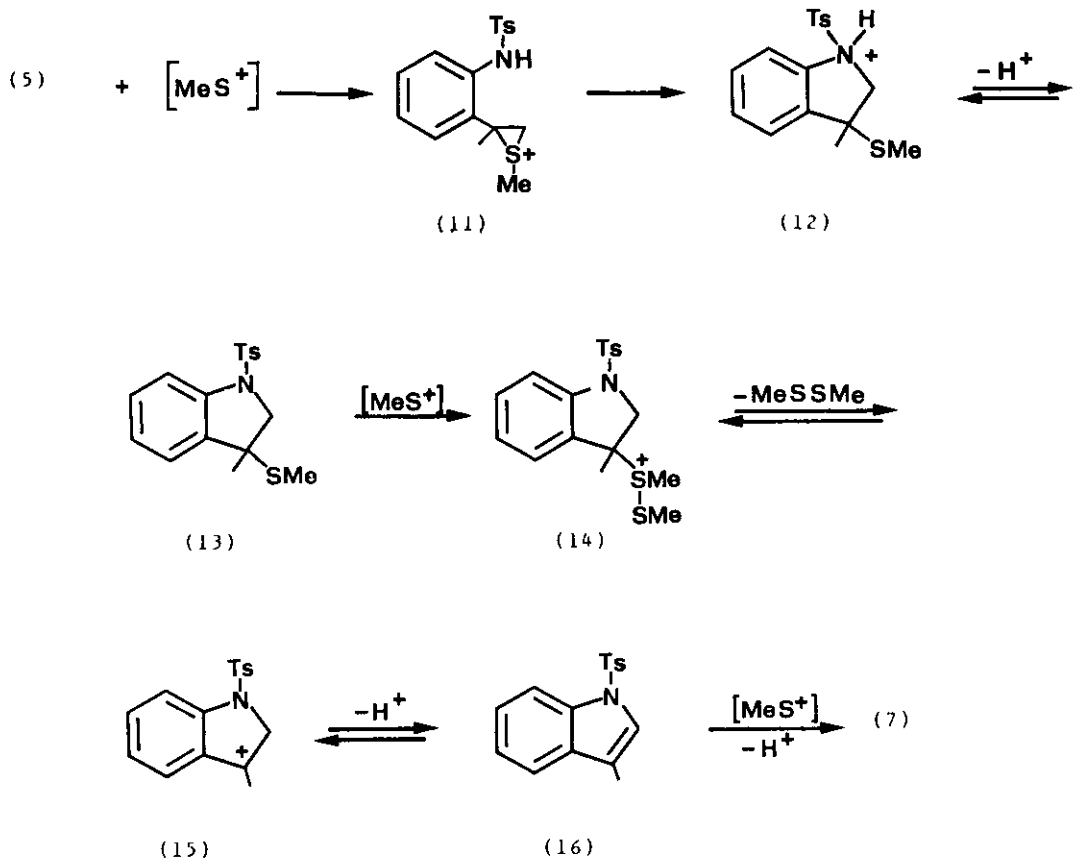
(10)

On the contrary a rationale for the formation of (7) in the reaction of (5) with (1) is not straightforward. The key intermediate is supposed to be the dihydroindole (13) which can be demethylthiolated via (14) and (15) to give (16). The reaction of (16) with the sulphenylating agent present in solution gives the isolated product (see Scheme).

This reaction scheme requires three equivalents of sulphenylating agents; however these species can be also generated in situ by reaction between the dimethyldisulphide and the strong hexachloroantimonic acid[2] formed during the reaction.

The reactions here reported represent an easy approach to methylthio-functionalized indole ring and show the wide applicability of the sulphonium salt (1) as useful reagent in heterocyclic chemistry.

Scheme



ACKNOWLEDGMENT

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11.Compound (8) was isolated after alkaline (Na_2CO_3 solution) work-up and column chromatography (SiO_2, eluant light petroleum-diethyl ether, 7:3 v/v); m.p. 80-83°C. Anal. Calcd. for $C_{17}H_{19}NO_2S_2$; C, 61.23; H, 5.74; N, 4.20. Found; C, 60.93; H, 5.75; N, 4.11%.

12.Obtained by oxidation of (8) with m-chloroperbenzoic acid in CH_2Cl_2 at room temperature. Usual work-up and column chromatography (SiO_2, eluant light petroleum-diethyl ether 7:3 v/v) gave pure (9); mp 159-160°C. Anal. Calcd. for $C_{17}H_{19}NO_4S_2$; C, 55.87; H, 5.24; N, 3.83. Found; C, 56.11; H, 5.62; N, 3.80%.

13.Obtained from commercial 2-(2-propenyl)aniline and tosyl chloride in pyridine solution; mp 78-80°C; ^1H nmr, δ 7.72-7.7 (m, aromatics, 8 H), 5.25 (broad s, 1 H), 4.67 (broad s, 1 H), 2.36 (s, 3 H), 1.69 (broad s, 3 H). Mass spectrum, molecular ion at m/z 287. Anal. Calcd. for $C_{16}H_{17}NO_2S$; C, 66.87; H, 5.96; N, 4.87. Found; C, 66.72; H, 5.88; N, 4.82%.

14.mp 70-71°C. Mass spectrum, molecular ion at m/z 331. Anal. Calcd.for $C_{17}H_{17}NO_2S_2$; C, 61.62; H, 5.17; N, 4.22. Found; C, 61.43; H, 5.13; N, 4.12%.

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