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# THE REACTION OF DIMETHYLSULPHONIUM METHYLIDE WITH AROMATIC ORTHO-AMINOCARBONYL COMPOUNDS: A NEW SYNTHESIS OF INDOLES

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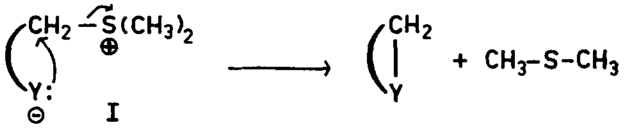
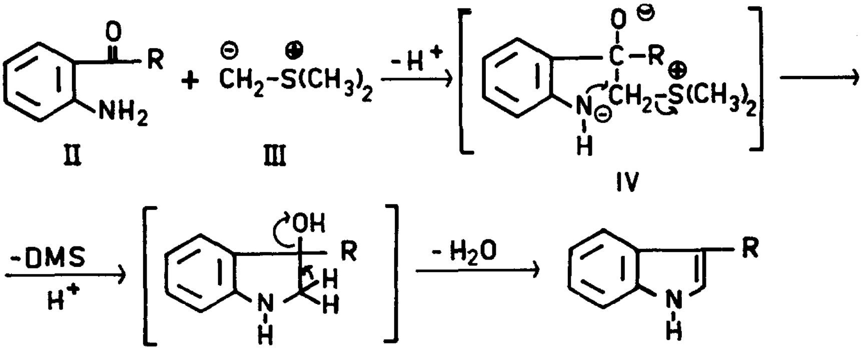
In the last years dimethylsulphonium and dimethyloxosulphonium methylides have received much attention for their reactivity towards several classes of electrophilic reagents (1). In particular they have been employed in the synthesis of different classes of heterocycles, most commonly epoxides (1) and five-membered heterocycles such as pyrrolidones (2), furanes (3,4), dihydrofuranes (3,5), isoxazolines (6,7), pyrazolines (6), triazolines (6a,8) etc.

Syntheses of this type are possible whenever the intermediate (I) arising from the attack of the ylide on the substrate bears a nucleophilic center (Y) which can bring about cyclization by an intramolecular displacement of dimethylsulphide (or dimethylsulphoxide) :



According to this trend we have now found a new method of synthesis of indoles consisting in the reaction of dimethylsulphonium methylide (III) with aromatic o-aminocarbonyl compounds (II) (9). The reaction can be outlined as follows :



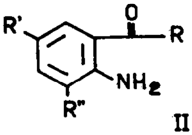
SCHEME 1

The o-aminocarbonyl compounds employed in the reaction with (III) to yield indoles are reported in the Table. With the only exception of the o-aminobenzaldehyde which gives low yields, perhaps because of its unstability, yields are in general quite satisfactory, so that the reaction appears to be of synthetic value, at least when R is alkyl, aryl or carboxylate.

In some cases, beside the expected indoles, the corresponding N-methylindoles were also obtained. This N-methylation is particularly important in the reaction of o-aminobenzaldehyde (II A) where the main product was N-methylindole. Perhaps the N-methylation occurs after the indole is formed. Actually indole, on treatment with (III), is converted in N-methylindole[▲].

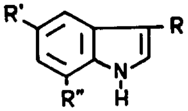
TABLE

Indoles from o-aminocarbonyl compounds by dimethylsulphonium methylide [a,b]



II

o-aminocarbonyl compounds



indoles

| | R | R' | R" | Yields % [c] |
|---|---|---|---|---|
| A | H | H | H | 5 (15) |
| B | $CH_3$ | H | H | 80 (14) |
| C | $C_6H_5$ | H | H | 69 (traces) |
| D | $C_6H_5$ | Cl | H | 72 [d] |
| E | COOH [e] | H | H | 40 |
| F | COOH [e] | Br | H | 60 |
| G | COOH [e] | H | $CH_3$ | 61 |
| H | COOH [e] | Br | $CH_3$ | 95 [f] |

a All the indoles reported, except D and H, were known. Their structures were usually determined by nmr and mass spectrometry and by comparison with the data from the literature, when available.

b The reaction between (III) (2 moles) (10) and the aminocarbonyl compounds (1 mole) were performed at -5°C, in a DMSO-THF solution.

c The yields reported in brackets are referred to N-methylindoles.

d m.p. 91°C.

e The compounds (II E) to (II H) were used as K-salts, obtained from the corresponding isatines.

f m.p. 238°C (dec.).

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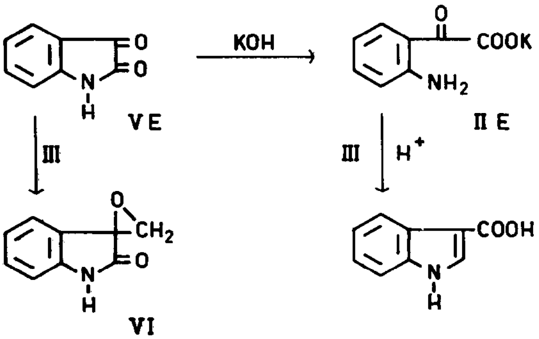
[▲] No C-methylation was observed.

The lack of formation of any significant amount of epoxides (1) from all the aminocarbonyl compounds tested clearly shows that in the zwitterionic intermediate (IV) of the reaction outlined in Scheme 1, the formation of the five-membered ring is much more favored than the formation of the three-memberd ring of the epoxide. This is probably due to both the more powerful nucleophilic character of nitrogen respect to oxygen, and the different strain of the two rings. Moreover the gain of energy in the aromatic indole system may also play an important role.

It is important to note that while the K-salt of isatic acid (II E) gives the indole-3-carboxylic acid, the corresponding isatine (V E), as expected, on treatment with (III), affords the spiroepoxide (VI) in high yields :



Dimethyloxosulphonium methylide, $CH_2=SO(CH_3)_2$, when reacted with o-aminoacetophenone (II B) at room temperature for 12 hours, gave only a 5% yield of scatole together with about 90% of unreacted ketone. o-Aminobenzaldehyde (II A), when reacted with the same ylide at 60°C, gave only a small amount of indole, as revealed by t.l.c., no traces of the aldehyde being recovered. Even if dimethyloxosulphonium methylide seems to be less suited than (III) to this indole synthesis, because of its lower reactivity, as yet no systematic investigation has been done on this point.

## References

1. Several reviews on sulphur ylides have appeared in the last years. See for example: a) J.C.Bloch, Ann.Chim., 60, 419 (1965); b) A.W.Johnson, Ylid Chemistry, p. 304, Academic Press, New York (1966); A.Hochreiner, Österr.Chem.Zeitg., 67, 297 (1966); d) H.König, Fortsch.Chem.Forsch., 9, 488 (1968).
2. H.König, H.Metzger and K.Seelert, Ber., 98, 3712 (1965).
3. B.Holt and P.A.Lowe, Tetrahedron Letters, 1966, 683.
4. T.M.Harris, C.M.Harris and J.C.Cleary, Tetrahedron Letters, 1967, 1427.
5. H.G.Lehmann, Tetrahedron Letters, 1968, 607.
6. a) G.Gaudiano, A.Umani-Ronchi, P.Bravo and M.Acampora, Tetrahedron Letters, 1967, 107; b) G.Gaudiano, P.P.Ponti and A.Umani-Ronchi, Gazz., 98, 48 (1968).
7. P.Bravo, G.Gaudiano, C.Ticozzi and A.Umani-Ronchi, Chem.Comm., 1968, 1311.
8. G.Gaudiano, C.Ticozzi, A.Umani-Ronchi and P.Bravo, Gazz., 97,1411 (1967).
9. A two-steps synthesis of an indoxyl derivative, starting from an isatoic anhydride by dimethyloxosulphonium methylide, through an oxosulphonium salt, has been recently reported by A.M. van Leusen and E.C.Taylor [J.Org.Chem., 33, 66 (1968)].
10. E.J.Corey and M.Chaykovsky, J.Am.Chem.Soc., 87, 1353 (1965).