

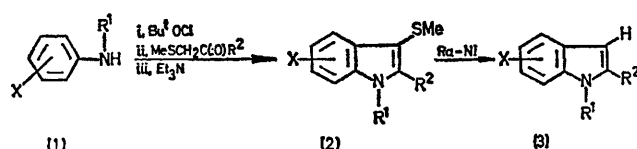
A General Method for the Synthesis of 2,3-Disubstituted Indole Derivatives

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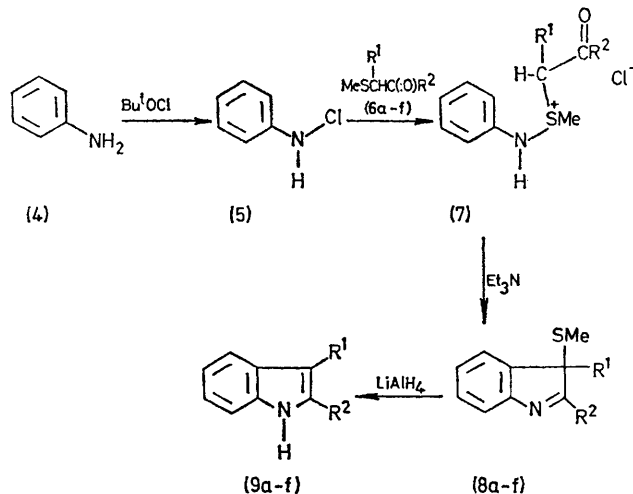
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Summary A new, general method is described for the preparation of 2,3-disubstituted indole derivatives, including tetrahydrocarbazoles, from anilines.

In a recent report, we described a new method for the synthesis of indole derivatives from anilines (1) *via* formation of the 3-methylthio derivative, (2), and subsequent Raney nickel reduction of (2) to (3).¹ Although this method was quite general [*i.e.*, X = -H, -Me, -Cl, -C(:O)OR³, -NO₂; R¹ = -H, -alkyl; R² = -H, -alkyl, -aryl], the nature of the process precluded its use in the synthesis of 3-substituted indoles, and thereby limited its applicability, as far

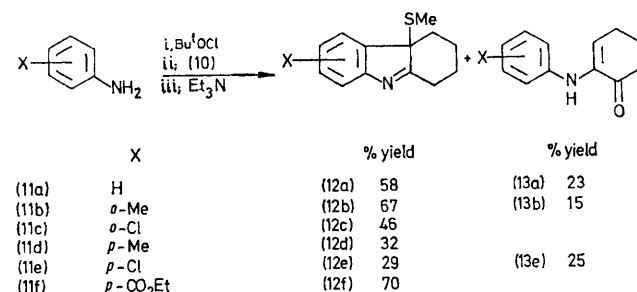


as the synthesis of many naturally occurring indoles was concerned. We now report a major modification of our original indole synthesis, which permits the synthesis of 3-alkylated and 3-arylated indoles.

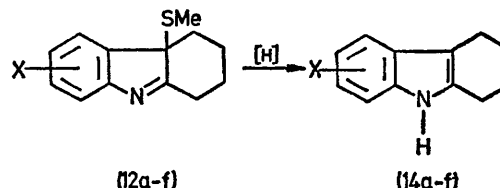


Treatment of 0.044 mol of aniline (4) in 150 ml of dichloromethane with 0.044 mol of t-butyl hypochlorite in 20 ml of dichloromethane at -70° gave *N*-chloroaniline (5), which was not isolated. Addition of 0.044 mol of sulphide (6)² with stirring at -70° for 6–48 h, produced the azasulphonium salts, (7).[†] Addition of 0.044 mol of triethylamine in

20 ml of dichloromethane at -70°, followed by warming to room temperature, gave good yields of (8). Due to their relatively unstable nature, the crude indolenines, (8a–f), were characterized by i.r. and n.m.r. spectroscopy and used without further purification. The conversion of (7) into (8) appears to involve initial ylid formation followed by a spontaneous Sommelet-Hauser type rearrangement^{1,3} to give a dienone imine. Hydrogen transfer and accompanying re-aromatization would then give a γ -aminoketone which on cyclization and dehydration would give the indolenine (8).



Reduction of (8) with lithium aluminum hydride gave the 2,3-disubstituted indoles, (9a–f), (Table). Although numerous intermediates are involved in the conversion of (4) into (9), yields were high and the laboratory procedure was relatively simple. Of particular interest was the high efficiency of the reductive desulphurization which occurred through the complex metal hydride reaction.



The use of 2-thiomethoxycyclohexanone⁷ (10) as the sulphide in our process provided a simple route to tetrahydrocarbazoles. Sequential treatment of a series of anilines, (11a–f), with (i) t-butyl hypochlorite, (ii) (10), and (iii) triethylamine gave the expected tetrahydrocarbazolenines (12a–f).[‡] In the case of (11a), (11b), and (11e), we obtained (13a), (13b), and (13e), as side products, presumably *via* a Stevens rearrangement of the ylid intermediate followed by elimination of methyl mercaptan. Desulphurization of (12a–f) to the corresponding tetrahydrocarbazoles, (14a–f),[§] could be accomplished with a variety of

[†] The azasulphonium salts were not isolated in this reaction sequence. The total reaction mixture was subjected to the next step in the sequence.

[‡] The yields of (12d), (12e), and (12f) were based on unrecovered starting materials. In these cases, the % conversions were 57, 65, and 50, respectively.

[§] The tetrahydrocarbazoles (14a–f) have all been reported previously in the literature. Spectral data and melting points of our products compared well with the available literature values.

reagents. The reduction of (12a) with W-2 Raney-nickel in ethanol, lithium aluminum hydride in ether, and sodium borohydride in 2-propanol gave (14a) in yields of 83, 80, and 64%, respectively. The ability to use sodium borohydride in the conversion of (12) into (14) was particularly useful

ticular advantage is its ability to place specific groups in the 2- and 3-positions, a feature not inherent in the classical Fischer indole synthesis. The reactions also established that the indole nucleus can be constructed on an already existing cyclic framework under mild conditions.

Yield of 2,3-disubstituted indoles based on starting aniline (4).

Sulphide	Indole	R ¹	R ²	Yield (%)	M.p. or b.p. (mm)	Lit. m.p. or b.p. (mm)	Ref.
(6a)	(9a)	Me	Me	85	104—106°	107°	4
(6b)	(9b)	Me	Et	60	64—66°	65—66°	4
(6c)	(9c)	Et	Me	81	107° (0.27)	156° (12)	4
(6d)	(9d)	Et	Ph	41	74—75°	65°	5
(6e)	(9e)	Me	Ph	69	91—93°	91—93°	4
(6f)	(9f)	Ph	Me	34	58—60°	60—60.5°	6

when easily reduced units, such as the carboethoxy group of (12f), were present.

The process provides a simple, high yield method for converting aniline into 2,3-disubstituted indoles, and should be applicable to the synthesis of certain indoles which are also substituted in the 4-, 5-, 6-, and 7-positions. A par-

We thank the National Cancer Institute of the Public Health Service for a grant which partially supported this investigation and the Netherlands Organization for the Advancement of Pure Research for a fellowship (to T.J.v.B.)

(Received, 18th September 1973; Com. 1304.)

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