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

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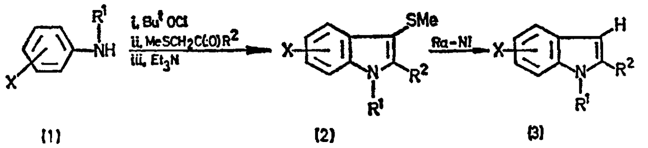
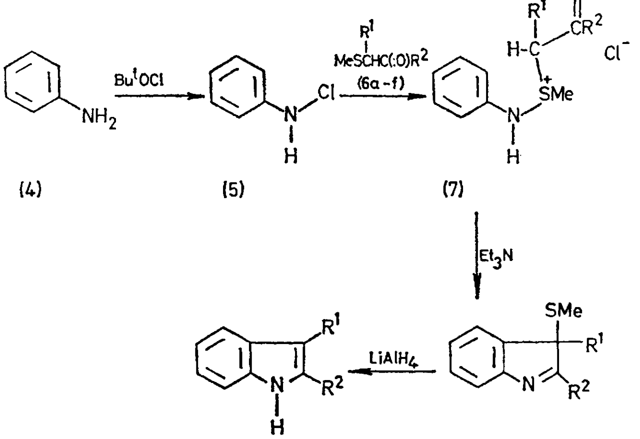
Summary A new, general method is described for the preparation of 2,3-disubstituted indole derivatives, including tetrahydrocarbazoles, from anilines.

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)OR^3, -NO$_2$; R^1 = -H, -alkyl; R^2 = -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.

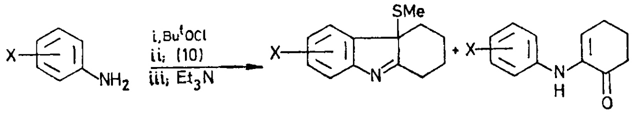


(1) (2) (3)



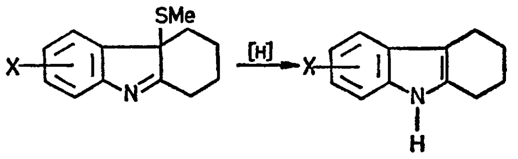
(9a-f) (8a-f)

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**).



	X		% yield		% yield
(11a)	H	(12a)	58	(13a)	23
(11b)	*o*-Me	(12b)	67	(13b)	15
(11c)	*o*-Cl	(12c)	46		
(11d)	*p*-Me	(12d)	32		
(11e)	*p*-Cl	(12e)	29	(13e)	25
(11f)	*p*-CO$_2$Et	(12f)	70		

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.



(12a-f) (14a-f)

The use of 2-thiomethoxycyclohexanone[7] (**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

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

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

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 particular 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.

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