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A NOVEL SYNTHESIS OF 3-CYANOINDOLES AND A NEW ROUTE TO INDOLE-3-CARBOXYLIC ACID DERIVATIVES[1].

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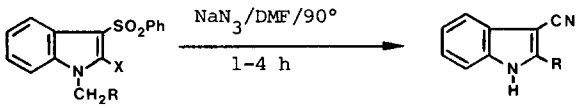
SUMMARY: 2-Alkyl-3-cyanoindoles are obtained when 1-alkylmethyl-2-chloro-(or 2-phenylsulfonyl)-3-phenylsulfonylindoles are reacted with excess azide ion (90°/DMF). The reaction is considered to occur by a fragmentation recombination process in which the Schiff's base 12 is of central importance. This proposal is supported by the formation of 2-substituted indole-3-carboxylates 17 from aldehydes and the α-phenylsulfonyl-o-aminophenylacetic acid ester derivative 16.

Although 2-chloro-3-acylindoles are relatively readily available[2], the nucleophilic substitution reactions of these compounds have hardly[3] been investigated. A facile synthesis of the electronically related 2-chloro-3-phenylsulfonylindoles (6) was recently devised in these laboratories and the susceptibility thereof to nucleophiles was examined. This report summarizes the results of the study with particular emphasis on the unique reaction which takes place between 6 and azide ion.

The 2-chloro-3-phenylsulfonylindoles were prepared most efficaciously by the routes shown in Scheme I. Thus, 3-phenylsulfenylindole (1)[4] was oxidized with 1 equiv. of m-chloroperoxybenzoic acid (MCPBA) to the sulfoxide 2[5], which was alkylated on nitrogen with various alkyl halides (e.g., $PhCH_2Br$, $BrCH_2CO_2Et$) in DMF solution containing sodium hydride. The conversion of the 1-alkyl-3-phenylsulfinylindoles (3) into the corresponding 2-chloro-3-phenylsulfenyl compounds 5 was effected with thionyl chloride (0°/$NaHCO_3$). This notably efficient process (80-95% yields), for which close analogies are known in non-aromatic systems[6,7], is considered to proceed via the sulfonium salt 4[8]. Oxidation of the chlorosulfides 5 with a slight excess of MCPBA (0°/CH_2Cl_2) gave the required chlorosulfones 6. These compounds could also be prepared by a reaction sequence wherein 3-phenylsulfinylindole was first converted into 2-chloro-3-phenylsulfenylindole (7), which was subsequently oxidized to the sulfone 8 and then N-alkylated ($ClCH_2CN$, $PhCOCH_2Br$).

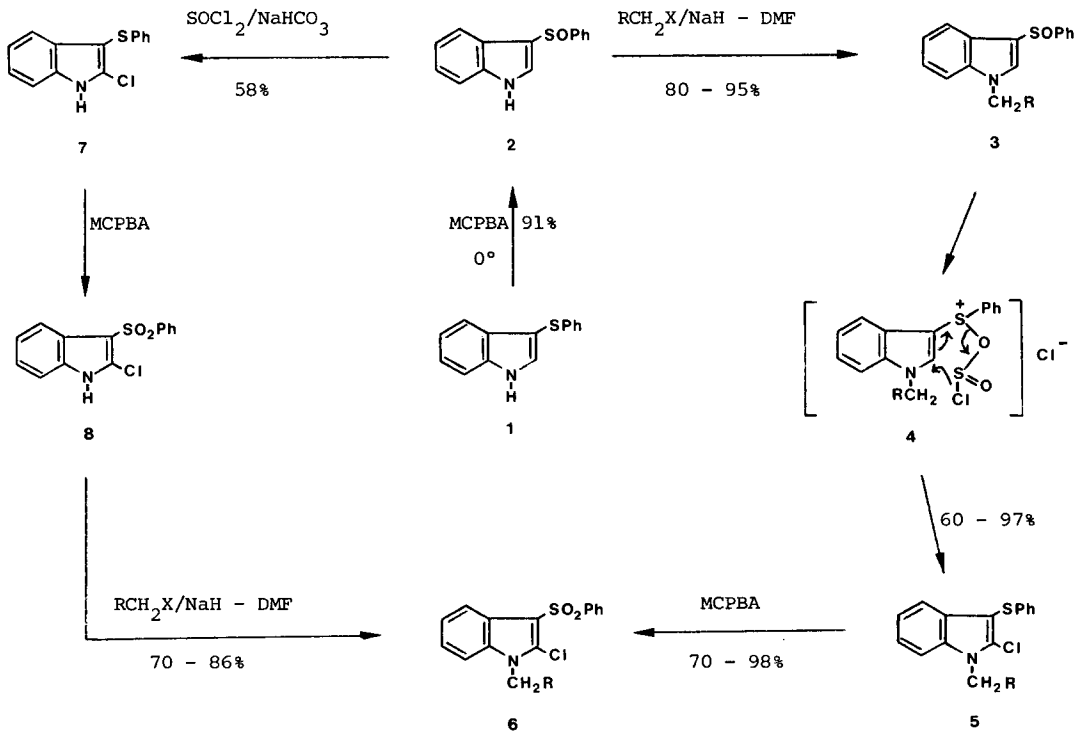
Whereas the reaction of 1-benzyl-2-chloro-3-phenylsulfonylindole (6,R = Ph) with nucleophiles such as diethyl sodiomalonate, sodium phenolates, sodium thiolates and primary amines gave the expected 2-substituted-3-phenylsulfonylindoles, the structure of the product obtained from 6(R = Ph), and excess sodium azide (3 equiv./DMF) at 90°, was completely unanticipated. This substance, mp 240°, analysed for $C_{15}H_{10}N_2$, had a mass spectral molecular weight of 218

Table. Synthesis of 2-Substituted-3-cyanoindoles

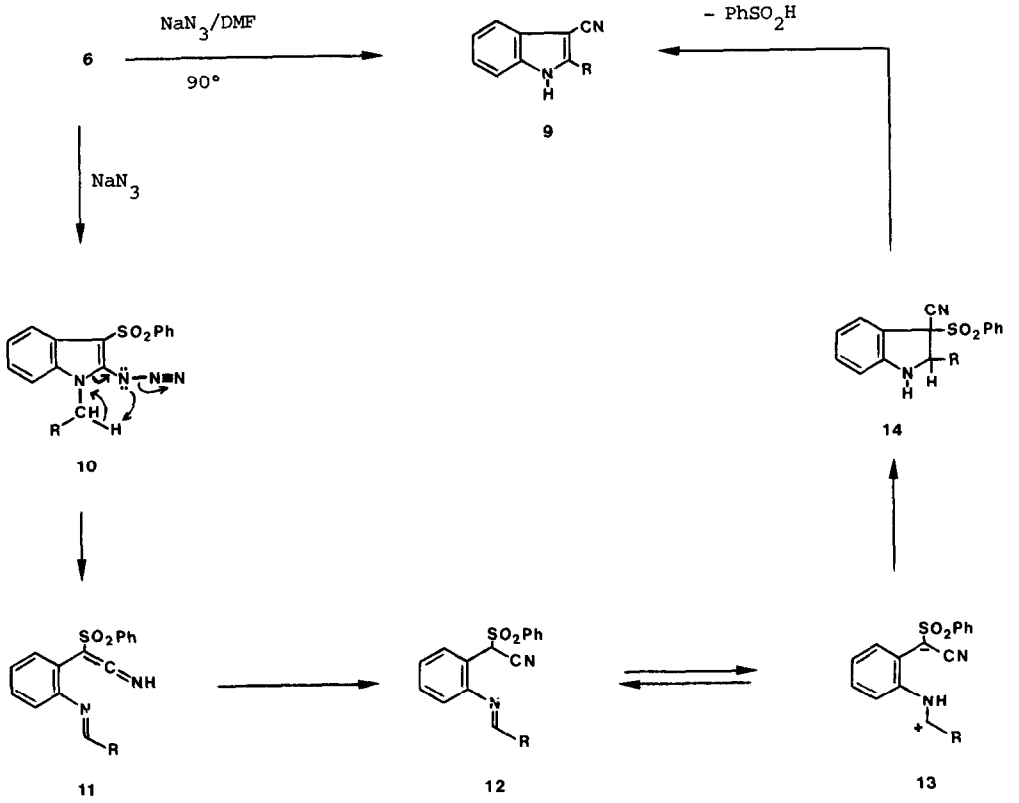


Entry	R	X	%[a]
1	Ph	Cl	99
2	Ph	SO_2Ph[b]	78
3	CH_3	SO_2Ph[b]	24
4	CO_2CH_3	Cl	84
5	CN	Cl	26
6	CN	SO_2Ph[b]	32
7	PhCO	Cl	59

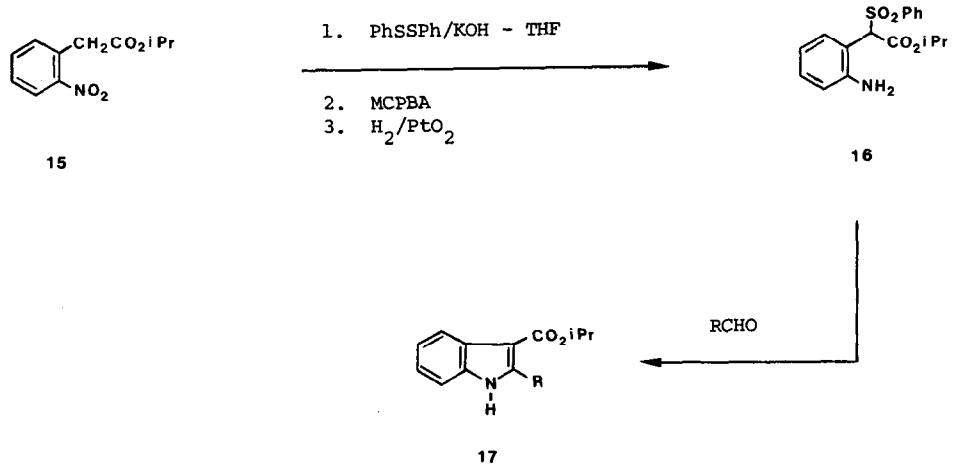
a) None of the reactions, except that of entry 1, was optimized.
b) These compounds were prepared by N-Alkylation of 2,3-bis-phenylsulfenylindole[4] followed by prolonged oxidation with MCPBA.



Scheme I



Scheme II



Scheme III

and strong IR bands at 3240 and 2195 cm^{-1}. The NMR spectrum showed absorptions only for aromatic hydrogens and one exchangeable proton. This data suggested that the product was either 2-phenyl-3-cyanoindole (9,R = H, Scheme II) or 2-cyano-3-phenylindole. The former was shown to be correct by direct comparison with an authentic sample synthesised from 2-phenylindole and chlorosulfonyl isocyanate[9].

The formation of 2-alkyl-3-cyanoindoles (9) from 1-alkylmethyl-2-chloro-3-phenylsulfonylindoles (6) does appear to have some generality as judged from the examples listed in the Table. Furthermore, the leaving group at C-2 need not be chloride ion since 1-alkylmethyl-2,3-bis-benzenesulfonylindoles (entries 2,3,7) yield the same products with azide ion. With regard to the mechanism of this remarkable reaction, it is noteworthy that 9(R = Ph) is slowly formed from 6(R = Ph), even at room temperature, and at no time is the azido compound 10 observed. It is therefore suggested that the transformation proceeds by simultaneous loss of nitrogen and fragmentation of the, presumably unstable, azide 10 to the imino ketenimine 11. The tautomeric α-phenylsulfonylnitrile 12, or the 1,5-dipole 13 corresponding thereto, would be expected to cyclize to 14, as in the syntheses of indolines (and indoles) recently described by Speckamp[10] and Grigg[11], and the loss of benzenesulfinic acid from 14 would complete the process. The feasibility of the latter stages of this process was examined as follows. The i-propyl ester of o-nitrophenylacetic acid 15 (Scheme III) was reacted sequentially with diphenyldisulfide (KOH powder/THF), excess MCPBA and hydrogen (PtO_2/50 psig). Brief heating of the resulting sensitive amino compound 16 with benzaldehyde (1 equiv.) in acetonitrile, at reflux temperature, gave i-propyl 2-phenylindole-3-carboxylate (17,R = Ph), mp 124° in 83% yield, identical to a sample synthesised from 2-phenyl-3-chlorocarbonylindole[12] and 2-propanol. Analogous products were obtained from n-decanal (57%) and cinnamaldehyde (76%). These results strongly support the suggested mechanistic sequence and demonstrate that 2-substituted-indole-3-carboxylic acid derivatives are readily available from o-nitrophenylacetic acid.

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