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NEW SYNTHESIS OF SUBSTITUTED INDOLE DERIVATIVES VIA VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN[1]

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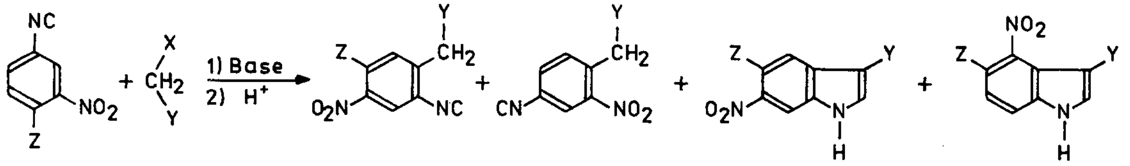
Summary: Carbanions bearing leaving groups react with m-nitrophenyl isocyanides to form products of vicarious nucleophilic substitution of hydrogen which subsequently cyclize to corresponding indoles.

The indole ring system is present in a great variety of natural and important synthetic products[2], thus there is a great and continuous interest in development of methods for synthesis of indole derivatives.[3] In the last years there have been numerous papers presenting new and modified approaches to this problem.[4] Here we would like to report a new, simple method for synthesis of nitroindole derivatives based on the vicarious nucleophilic substitution of hydrogen in nitroarenes.

We have shown previously that carbanions containing leaving groups at the carbanion centers replace hydrogen o- and p- to the nitro group in nitroarenes with the carbanion moiety.[5] This process known as the vicarious nucleophilic substitution has practically no limitations concerning substituents in the nitroaromatic ring.[6] We have therefore expected that m-nitrophenyl isocyanide and its derivatives should also enter this reaction, the products containing an acidic methylene group ortho to the isocyano group should cyclize to form substituted indole derivatives.[7] This indeed was the case. The reaction of m-isocyanonitrobenzene 1a with chloromethyl phenyl sulfone 2a carried out in presence of an excess of powdered NaOH in DMSO or liquid ammonia resulted in the formation of a mixture of four products 3a, 4a, 5a and 6a, two of them 3a and 4a were nitrobenzyl phenyl sulfone derivatives, the others were 3-phenylsulfonyl 6- and 4-nitroindoles 5a and 6a. Isolated 3a, when treated with a base, can be converted into 5a. 2-Isocyano-6-nitrobenzyl phenyl sulfone was not isolated due to high rate of its cyclisation to 6a. Further examples of this process are shown in the table.



1 2 3 4 5 6

When position 4 in 3-nitrophenyl isocyanide e.g. (1b, 1e) is occupied with a substituent the reaction proceeds mainly or exclusively at the position 6 thus one isomer of the intermediate sulfone 3b,e and subsequently indole 5b,e is formed. Depending on the conditions (solvent, temperature, time) one can obtain both such products or the indole only.

Detailed results of this studies will be published later.

Table

		2										
	Z	X	Y	Base	Reaction conditions temp., °C	time, min.	Total Yield %	% of 3	4	5	6	Products[a] mp. °C
a	H	Cl	SO_2Ph	A	20-40	5	88	10	41	36	13	3a, 156-157[b] 4a, 111[b]; 5a, 268-270; 6a, 235-236.
b	CH_3	Cl	SO_2Ph	A	20	15	82	55	-	45	d	3b, 176-177, 5b, 239-241
c	CH_3	Cl	$SO_3CH_2Bu^t$	B	- 33	30	65	c	-	100	d	5c, 141-142
d	CH_3	SPh	CN	B	- 33	30	50	c	-	100	d	5d, 254-255
e	Cl	Cl	SO_2Ph	A	20	5	59	34	-	66	d	3e, 135[b], 5e, 212-213
					20	5 then						
					60-70	60	70	-	-	100	d	

A - NaOH/DMSO; B - $NaOH/NH_3$ liq.

[a] All compounds gave satisfactory elemental analysis. Their structure was confirmed by ^1H NMR spectra. Melting points are uncorrected. [b] Decomposition. [c] Traces, not isolated, detected by TLC. [d] The substitution of hydrogen in position 2 and subsequent formation of 6 has not been observed in these conditions.

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