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A FACILE ROUTE TO CINNOLINES[1]

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A general procedure for the synthesis of cinnolines from 1-aminoindoles has been established.

In this paper, we wish to report a general synthesis of cinnolines from 1-aminoindoles.[2] Although we have noted that 1-aminoindole and some of its derivatives are readily converted to cinnoline derivatives in acidic media,[3] the yields of cinnolines were not satisfactory due to the concomitant formation of 1,4-dihydrocinnolines. Since 1,4-dihydrocinnolines are expected to be oxidized to cinnolines by an appropriate reagent, we have examined the above ring enlargement reaction in the presence of oxidizing agents such as MnO_2, H_2SO_4, chloranil, bubbling oxygen, etc., but poor results were obtained because of the sensitivity of 1-aminoindoles to these oxidizing agents. Finally, nitrobenzene was found to be a reagent of choice to meet our purpose.

In a typical experiment, a solution of 1-amino-2-methylindole (103.3 mg, 0.71 mmol) and nitrobenzene (537 mg, 4.36 mmol) in 3% HCl-MeOH (20 ml) was refluxed for 42 h under stirring. After evaporation of the solvent under a reduced pressure, the residue was made alkaline by adding 10% aqueous NaOH solution and extracted with MeOH-CH_2Cl_2 (3:97, v/v). The extract was washed with water, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to column chromatography on silica gel. Elution with MeOH-CH_2Cl_2 (5:95, v/v) gave 3-methylcinnoline in 92% yield. In this procedure, 1,4-dihydro-3-methylcinnoline was not detected in the reaction mixture.

In a similar manner, various 1-aminoindoles were converted into the corresponding cinnolines and the results are summarized in Table I where the result obtained without using nitrobenzene is also shown for comparison.

As evident from Table I, 1-aminoindoles having no substituent at the 3-position (run 1-3) were readily converted to cinnolines by the present modified procedure. In the case of 3-substituted 1-aminoindoles (run 4-6 and 8-10), the reaction time was found to play an important role as shown in Table II. The longer the reaction time, the better yield of cinnoline was achieved.

The modified procedure using nitrobenzene was especially effective in the case of 1-amino-3-cyanoethylindole, affording cinnoline-4-propionitrile and methyl cinnoline-4-propionate in 43% and 29% yields, respectively (run 6). Without using nitrobenzene, no substantial formation of both cinnoline and 1,4-dihydrocinnoline was observed and the recovered starting material and 1-aminoindole-3-propionic acid were obtained in the respective yields of 62% and 9% (run 7).

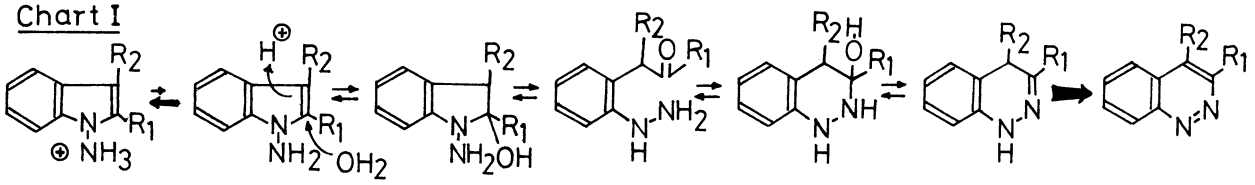
Table I

Run		R1	R2	Reaction conditions	reflux (hr)	NO2 (mol equiv)	R2, R1 (%)	Other products
1	a.	H	H	3%HCl-MeOH	49	5.2	89	
2	b.	Me	H	1.5% 〃	42	6.1	92	
3	c.	Ph	H	〃 〃	42	5.7	87	
4	d.	-(CH2)4-		〃 〃	46	5.8	86	
5	e.	H	Me	3 % 〃	91	5.8	80	
6	f.	H	-CH2CH2CN	〃 〃	115	5.6	43	COOMe 29%
7	g.	H	-CH2CH2CN	〃 〃	42	0	0	Recovery, 62%

Table II

Run		Reaction conditions reflux (hr)	NO2 (mol equiv)	Me (%)	Recovery (%)	+ COOH 9%
8	3%HCl-MeOH	46	6.0	54	37	
9	〃	64	3.0	62	7	
10	〃	91	5.8	80	0	

Chart I



Taking into account of the fact that a strong acid changes 1-aminoindoles to the corresponding ammonium salts and converts 1,4-dihydrocinnolines to the corresponding 1-aminoindoles,[4] the results obtained here suggest that the following mechanism would be operating for this ring enlargement reaction, in which an essential role of nitrobenzene is to oxidize 1,4-dihydrocinnolines into cinnolines irreversibly (Chart I).

Since 1-aminoindoles are readily available from the corresponding indoles,[2] the present reaction seems to constitute two step synthesis of cinnolines from indoles.

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References and Notes

1) This report is part IX of a series entitled "The Chemistry of Indoles." Part VIII: M.Somei, F.Yamada, and C.Kaneko, Chemistry Lett., preceding communication.
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