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CYCLISATION OF N-o-NITROBENZYLIDENEANILINE DERIVATIVES BY CYANIDE ION IN METHANOL THE FORMATION OF 4-ARYLAMINO-3-METHOXYCINNOLINE-1-OXIDES

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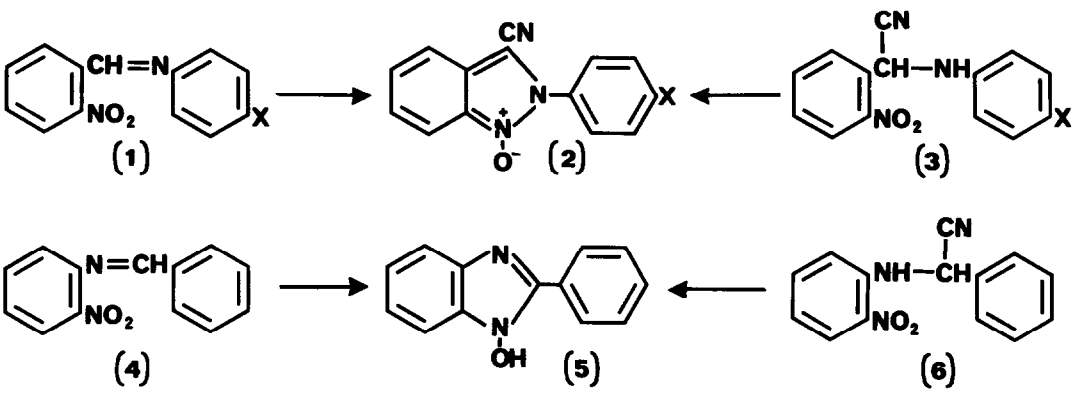
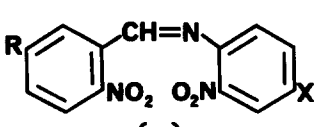
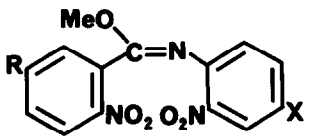
It has long been known[1-3] that N-o-nitrobenzylideneaniline and its derivatives (i e. 1) react with potassium cyanide in acetic acid giving 2-aryl-3-cyano-2H-indazole-1-oxides (2). These reactions probably involve addition of HCN to the double bond of (1) and cyclisation of the resulting adducts (3), since some such adducts have been made by alternative methods and yield the same indazole oxides on treatment with very mild base[2]. Similarly it is known that cyanide ion effects the cyclisation of N-benzylidene-o-nitroaniline (4) to 1-hydroxy-2-phenylbenzimidazole (5)[4], and here also the anilinonitrile, viz. (6), is a possible intermediate[4,5].



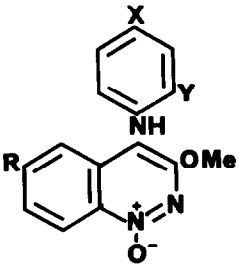
N-o-Nitrobenzylidene-o-nitroaniline and its analogues (7), however, give neither indazole nor benzimidazole derivatives by reaction with cyanide ion. Such reactions, in methanol solution, give two products the major component, which is sparingly soluble in the reaction medium, is a 3-methoxy-4-(o-nitroarylamino)cinnoline-1-oxide (8), and the



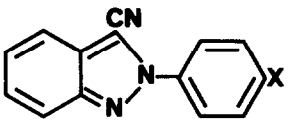
(7)



(9)



(8 : Y = NO_2)
(10 : R = Y = H)



(11)

TABLE 1

Products of the reaction (7) ⟶ (8) + (9)

Substituents R	Substituents X	Cinnoline oxide (8)	Yield(%)	m. p.	Imidate ester (9)	Yield(%)	m. p.
H	H	8a	25	249-250°	9a	14	114-116°
H	Me	8b	32	246-248°	9b	3	104-105°
H	OMe	8c	36	198-200°	9c	trace	
Cl	Me	8d	23	238-240°	9d	12	107-109°
Cl	OMe	8e	31	220°(d)	9e	10	122-124°

minor product is a methyl N-(o-nitroaryl)-o-nitrobenzimidate (9). Examples of this type of reaction are shown in Table 1.

Re-investigation of the reactions of the N-o-nitrobenzylideneaniline derivatives (1) with cyanide ion shows that these also yield 4-arylamino-3-methoxycinnoline-1-oxides (10) when methanol is used as solvent instead of acetic acid. In these cases, however, the cinnoline oxide is a minor product, the main product being the 2-aryl-3-cyanoindazole (11). No significant yield of the indazole oxide (2) is generally isolated under these conditions. Typical results of such reactions are collected in Table 2.

The 4-arylamino-3-methoxycinnoline-1-oxide structures follow from the analytical and spectroscopic properties of the compounds. In particular, the n. m. r. spectra show the arylamino groups and, additionally, methoxyl and aryl proton resonances which correspond closely to those of other 3-methoxycinnoline-1-oxides[6]. Confirmation of the assigned structures is provided by the synthesis of (10b) from sodium p-toluidide and 4-chloro-3-methoxycinnoline-1-oxide (which has previously been prepared in 9 stages from ethyl cyclohexanone-2-acetate[6])

The formation of the imidates (9) as by-products in some of these reactions has

analogy in the reactions of N-p-nitrobenzylideneaniline with methanolic hydrogen cyanide followed by base,[7] and the formation of indazoles, e. g (11), instead of the expected N-oxides, by cyclisation of ortho-substituted nitrobenzenes, is also not entirely without precedent[8]. However, the formation of cinnoline oxides from Schiff bases and cyanide ion is completely novel.

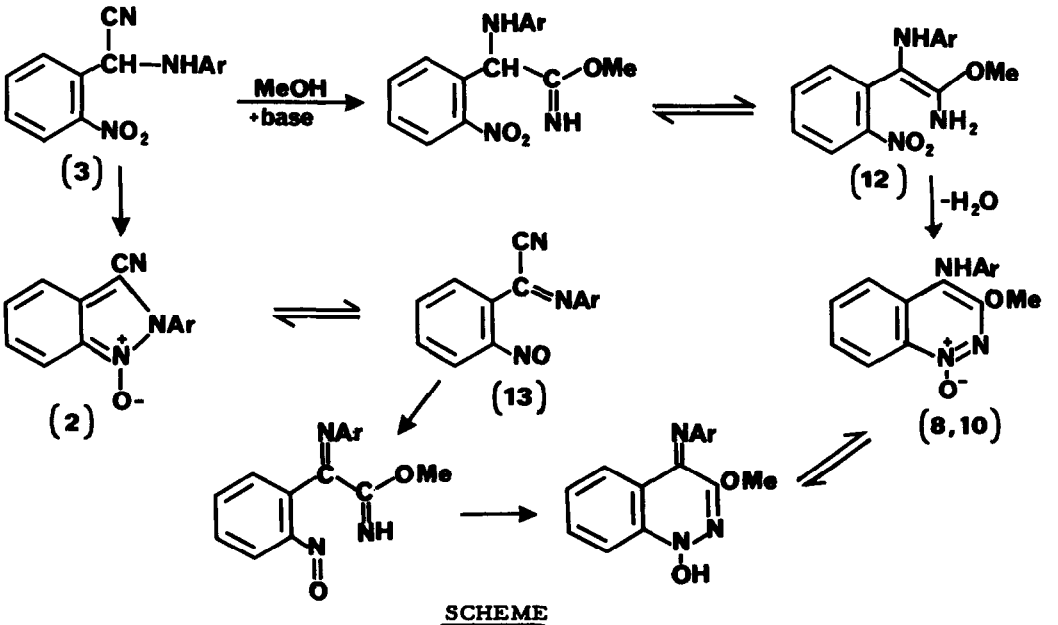
These cyclisation reactions are of twofold interest. Firstly, they give easy access to a group of new cinnoline derivatives which are otherwise obtainable only with extreme difficulty. Secondly, the mechanism presents an intriguing problem. The formation of

TABLE 2

Products of the reaction (1) ⟶ (10) + (11)

Substituent X	Cinnoline oxide (10)	Yield(%)	m. p.	Indazole (11)	Yield(%)	m. p.
H	10a	11	193-195°(d)	11a	18	105-106° (lit.[1] 105°)
Me	10b	9	186-188°(d)	11b	27	134-136° (lit.[1] 135°)
Cl	10c	16	212-215°(d)	11c	30	160-161° (lit.[1] 159°)
Br	10d	15	209-211°	11d	44	163-165°
OMe	10e	14	193-195°	11e	15‡	153-154°

‡ The indazole oxide (2e) was also isolated (25%).



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the cinnoline oxides is most simply rationalised by the sequence (3)—>(12)—>(8 or 10) (cf. Scheme), but those cases (Table 2) in which the amino-nitrogen of (3) is sufficiently nucleophilic to permit the formation of an indazole oxide (2) may also involve this latter compound as an intermediate, since we have shown that (2·X=CH_3 or Br) also gives the corresponding cinnoline oxide (10b or 10d) as well as the indazole (11b or 11d) by reaction with methanolic sodium hydroxide. In those cases the overall reaction may best be represented by the sequence (3)—>(2)—>(13)—>(10).

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