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Regioselective 6-Arylation of 5,8-Quinolinedione with N-Alkyl- and N,N-Dialkyl-anilines Promoted by Metal Ions

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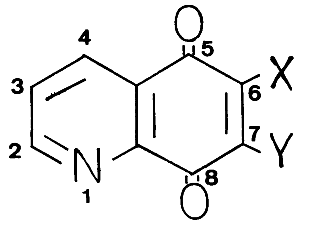
The reaction of 5,8-quinolinedione (1) with N,N-dialkylanilines in acetic acid was strongly promoted by some metal ions to give selectively the 6-arylated products, 6-(4-N,N-dialkylaminophenyl)-5,8-quinolinediones. With N-alkylanilines the reaction gave a mixture of the 6-aminated and 6-arylated products of 1.

In our previous paper,[1)] we have reported a catalytic action of metal salts in the regioselective 6-amination of 5,8-quinolinedione (1). The formation of a metal chelate complex, in which the 1-nitrogen atom and the oxygen atom of 8-carbonyl group of 1 are coordinated to the metal ion, increases the electrophilicity of the 6-carbon atom, and facilitates a nucleophilic attack of amines on that carbon to produce the 6-aminated products in preference to the 7-aminated products of 1. We now further report that 6-arylation of 1 can be achieved in the reaction with N-alkyl- and N,N-dialkyl-anilines (Table 1).

The reaction of 1 with N,N-dimethylaniline in acetic acid at 30 °C proceeded slowly to give a mixture of 6- and 7-(4-N,N-dimethylaminophenyl)-5,8-quinolinediones (2 and 3) in low yields (Run 1). Similar arylation of 1,4-naphthoquinone has been found by Griffiths et al.[2)] In the case of 5,8-quinolinedione, however, we newly found that the reaction was strongly promoted by some metal ions and gave the 6-arylated products, selectively (Runs 2–6). Metal acetates were arranged in the order of activity as follows: Cu(II) $>$ Ni(II) $>$ Co(II) $>$ Zn(II) $\gg$ Ce(III). The activity of Cu(II) ion was particularly superior to those of other metal ions in the arylation. The reaction was also remarkably affected by solvent.



	X		Y
1 :	H	,	H
2 :	p-$(CH_3)_2N$-C_6H_4-	,	H
3 :	H	,	p-$(CH_3)_2N$-C_6H_4-
4 :	p-$(C_2H_5)_2N$-C_6H_4-	,	H
5 :	p-$(H_3C)NH$-C_6H_4-	,	H
6 :	C_6H_5-$N(CH_3)$-	,	H
7 :	H	,	C_6H_5-$N(CH_3)$-
8 :	p-$(H_9C_4)NH$-C_6H_4-	,	H
9 :	C_6H_5-$N(C_4H_9)$-	,	H

The arylation hardly proceeded when ethanol, chloroform, or pyridine was used instead of acetic acid. Similar solvent effect has also been observed in the arylation of 1,4-naphthoquinone by Griffiths et al.2) They reported that many solvents, in which a charge-transfer complex between the quinone and N,N-diethylaniline is easily formed, gave no arylated product.

With N-alkylanilines, the reaction was also affected by the used solvents and metal salts. Pratt has reported that the reaction of 1 with N-methylaniline in alcohol solution gives a mixture of 6- and 7-(N-methylanilino)-5,8-quinolinediones (6 and 7) in low yields but in the presence of cerium(III) chloride the 6-amino isomer (6) is formed exclusively in satisfactory yield.3) In our reactions using copper(II) acetate in acetic acid, the corresponding reaction gave the 6-arylated product, 6-(4-N-methylaminophenyl)-5,8-quinolinedione (5), together with the 6-aminated product (6): the ratio of the yields was about 1:5 (Run 8). However, in the reaction with N-butylaniline the yield of the 6-arylated product (8) was higher than that of 6-aminated product (9): the ratio was about 4:3 (Run 9). These results reveal that in the reaction of 1 with N-alkylanilines in acetic acid the regioselective 6-arylation competes with the 6-amination and that the former proceeds predominantly with increase in the size of the alkyl residue of N-alkylaniline. The nucleophilic attack of the N-position of N-butylaniline would cause a considerable steric crowding in the transient state. The 6-arylation was presumably initiated by nucleophilic attack of para-position of the arylamine

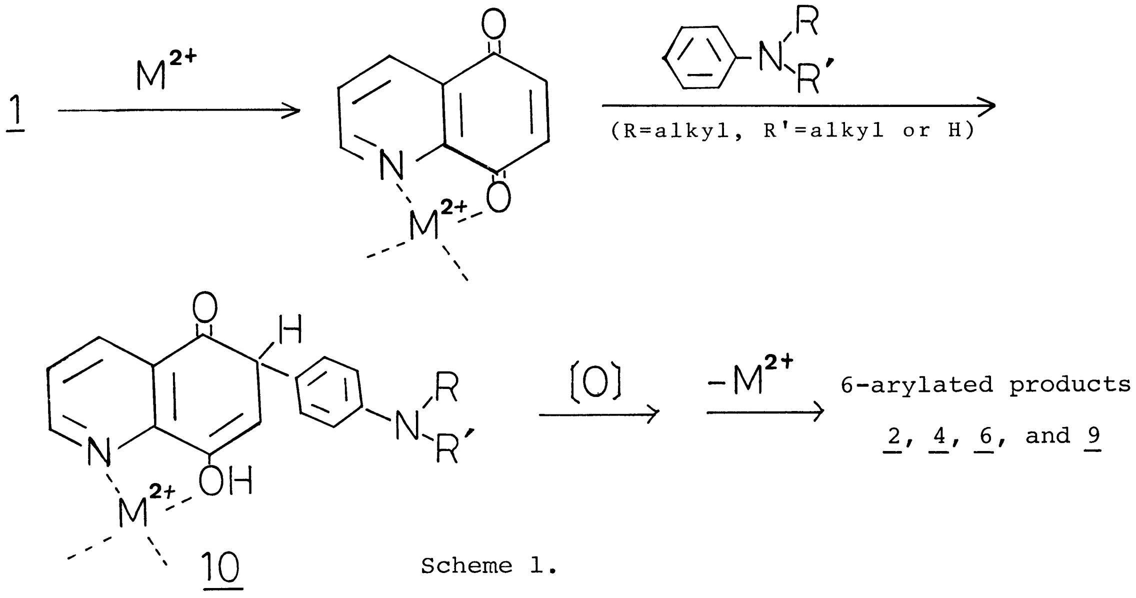
Table 1. Reaction of 5,8-quinolinedione (1) with N-alkyl- and N,N-dialkyl-anilines in the presence of metal salts a)

Run	Amine	Metal salt	Time	Temp	Yield b)			
			h	°C	%			
1	N,N-dimethylaniline	none	94.0	30	2	18	3	6
2	N,N-dimethylaniline	$Ni(CH_3CO_2)_2 \cdot 4H_2O$	1.0	30	2	62	3	0
3	N,N-dimethylaniline	$Cu(CH_3CO_2)_2 \cdot H_2O$	0.5	30	2	80	3	0
4	N,N-dimethylaniline	$Co(CH_3CO_2)_2 \cdot 4H_2O$	1.5	30	2	48	3	0
5	N,N-dimethylaniline	$Zn(CH_3CO_2)_2 \cdot 2H_2O$	5.5	30	2	32	3	0
6	N,N-dimethylaniline	$Ce(CH_3CO_2)_3 \cdot H_2O$	30.0	30	2	24	3	0
7	N,N-diethylaniline	$Cu(CH_3CO_2)_2 \cdot H_2O$	2.0	30	4	56		
8	N-methylaniline	$Cu(CH_3CO_2)_2 \cdot H_2O$	0.5	30	5	12	6	61
9	N-butylaniline	$Cu(CH_3CO_2)_2 \cdot H_2O$	1.0	30	8	40	9	29

a) A solution of 1 (0.5 g, 3.14 mmol) in 90 ml of acetic acid was added slowly to a solution of the N-substituted aniline (9.42 mmol) and metal salt (3.14 mmol) in 10 ml of acetic acid, with stirring in an open flask at 30 °C. The reaction was monitored by TLC analysis. After the starting material (1) was consumed, the products were extracted with chloroform from the reaction solution. The extraction was repeated several times. After the combined chloroform extracts were washed with saturated sodium carbonate aqueous solution, washed further with water, dried (Na_2SO_4) and then concentrated in vacuo. The crude products were separated by column chromatography (silica gel : Wakogel C-300) using chloroform or ethyl acetate as eluents.

b) Isolated yield after column chromatography.

to the electron deficient 6-position of 1 complexed with the metal ion, giving the 1,4-adduct (10) and was completed by subsequent oxidation of the adduct (Scheme 1).



Scheme 1.

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