The Direct Alkylamination of 1-Aminoanthraquinone Promoted by Cobalt(II) Chloride

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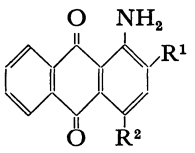
Synopsis. The reaction of 1-aminoanthraquinone with primary aliphatic amines in the presence of cobalt(II) chloride under atmospheric oxygen preferentially gave the corresponding 1-amino-4-(alkylamino)anthraquinones. The reaction did not proceed with aqueous ammonia, bidentate amines, secondary aliphatic amines, and primary arylamines. While, with alicyclic amines the reaction mainly afforded 1-amino-2,4-bis(alkylamino)anthraquinones.

In our previous paper,[1] we have reported a novel direct 4-butylamination of 1-aminoanthraquinone (**1**) promoted by metal ions and proposed the possible mechanism of the reaction: the formation of a metal complex, in which the 1-amino and 9-carbonyl groups of **1** coordinate to the metal ion, increases the electrophilicity of the substituted anthraquinone nucleus and facilitates the nucleophilic attack of butylamine to the 4-position. This direct amination appeared to be a convenient method to introduce amino groups to the anthraquinone nucleus of **1**.

In this paper, similar reactions of **1** with various amines in the presence of cobalt(II) chloride under atmospheric oxygen are examined. The results are summarized in Table 1.



Compd No.	Substituent R^1	Substituent R^2
1	H	H
2	H	NH_2
3	H	NHMe
4	H	*n*-BuNH
5	H	*s*-BuNH
6	H	$CH_3(CH_2)_7NH$
7	$CH_3(CH_2)_7NH$	H
8	H	$C_6H_{11}NH$
9	H	$PhCH_2NH$
10	piperidino	piperidino
11	morpholino	morpholino

The reaction of **1** with aqueous ammonia was unsuccessful, while almost primary aliphatic amines reacted with **1** to give the corresponding 1-amino-4-(alkylamino)anthraquinones, which are valuable as dyes and dye intermediates. The reaction of **1** with 40% aqueous methylamine gave 1-amino-4-(methylamino)anthraquinone (**3**) in 39% yield along with a 47% recovery of **1** after 26 h at 30 °C. 1,4-Diaminoanthraquinone (**2**) formed by the demethylation of **3** was also obtained in 8.2% yield. The dealkylation of alkylamino group in 1-amino-4-(alkylamino)anthraquinone was generally observed in the other cases. Especially, with benzylamine the reaction gave **2** (29% yield), the dealkylation product of **9**, much more than the expected 1-amino-4-(benzylamino)anthraquinone (**9**) (5.5%). The reaction of **1** with 1-octylamine was also successful. From the column chromatography of the products, unchanged **1** (45%), 1-amino-4-(octylamino)anthraquinone (**6**) (34%), 1-amino-2-(octylamino)anthraquinone (**7**) (2.4%), and a trace amount of **2** were isolated. The formation of **7**, though only a small amount, suggests that not only the 4-position but also the 2-position of **1** is activated by the formation of a chelate complex between **1** and the cobalt(II) ion. However, with the other primary aliphatic amines the reaction gave only the 4-aminated products but not the 2-aminated products.

The preferential 4-amination may be assisted by the formation of hydrogen-bonding between the *N*-hydrogen atom of alkylamino group and the oxygen atom of the 10-carbonyl group, as suggested in our previous paper.[1]

The amination proceeded smoothly with primary aliphatic amines, while, with bidentate amines such as

Table 1. Alkylamination of 1-aminoanthraquinone (**1**) in the presence of $CoCl_2$[a]

Run	Amine	Temp °C	Time h	Recovery/% (**1**)	Aminated products/% Yield 4-Isomer	2-Isomer	2,4-Isomer	(**2**)
1	CH_3NH_2[b]	30	26	47	(**3**) 39	0	0	8.2
2	*n*-$BuNH_2$	30	8	0	(**4**) 79	0	0	trace
3	*s*-$BuNH_2$	30	50	47	(**5**) 38	0	0	trace
4	$CH_3(CH_2)_7NH_2$	30	30	45	(**6**) 34	(**7**) 2.4	0	trace
5	$C_6H_{11}NH_2$	40	20	44	(**8**) 52	0	0	trace
6	$PhCH_2NH_2$	40	12	53	(**9**) 5.5	0	0	29
7	Piperidine[c]	30	70	13	—	—	(**10**) 58	0
8	Morpholine[c]	40	48	83	—	—	(**11**) 9.1	0
9	Morpholine[c]	40	170	49	—	—	(**11**) 23	0

a) Reactant **1** (9 mmol) was stirred in pyridine (20 ml) with amine (30 ml) and $CoCl_2$ (9 mmol). b) 40% Aqueous methylamine solution (60 ml) was used as reactant and pyridine (60 ml) was added as solvent. c) Piperidine (50 ml) or morpholine (50 ml) was used as reactant without solvent. An addition of pyridine as solvent rather depressed the yields of products.

ethylenediamine and 2-aminoethanol the amination did not proceed. It is reasonable to consider that the cobalt ion is preferentially combined with bidentate amines than with **1**, because the bidentate amines can act as an effective chelating agent. Therefore, the formation of the cobalt complex of **1** was disturbed and the amination was inhibited.

Aromatic amines also did not react with **1**. This lack of reactivity is probably due to the lower nucleophilicity of arylamines compared to the alkylamines. These facts support the nucleophilic attack of alkylamines to the substituted anthraquinone nucleus activated by the formation of a cobalt complex. With diethylamine the amination was also unsuccessful and no amination products were obtained. The lack of reactivity of diethylamine may be attributed to a steric hindrance.

The attack of alkylamine at the 4-position of **1** would cause a considerable steric crowding. Therefore, the increase in the size of the alkyl residue may decrease the reactivity of the amine. For example, *s*-butylamine was much less reactive than *n*-butylamine in spite of their similar basicities. Thus, both the basicity and the size significantly affected the reactivity of amines.

Reaction of **1** with alicyclic amines was very specific and afforded the corresponding 1-amino-2,4-bis(alkylamino)anthraquinones. Trace amounts of some by-products were also noted on chromatography but could not be identified.[2] The cause of the differences in the amination products between primary aliphatic amines and alicyclic amines are not yet clear.

The structure of compounds (**10** and **11**) were confirmed by the elementary analysis, ^{1}H-NMR spectra, and the alternative synthesis of the compounds from 1-amino-2,4-dibromoanthraquinone with the corresponding amines.

Experimental

All the melting points are uncorrected. The visible spectra in methanol solution were measured using a Hitachi EPS-3T spectrometer.

The ^{1}H-NMR spectra were taken on a JEOL Model MH-100 spectrometer with TMS as an internal standard. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Column chromatography was carried out on activated alumina (Sumitomo KCG-30) using xylene as an eluent.

Reaction Procedure. The general procedure is as follows. A mixture of **1** (9 mmol), $CoCl_2$ (9 mmol), amine (30 ml), and pyridine (20 ml) was stirred in an open flask. After the reaction, the solvent and the excess amine were distilled off under reduced pressure. The mixture was poured into an aqueous NaOH solution (pH=10), and then H_2S gas was introduced into the solution to decompose a chelate complex of the products. The separated precipitate was filtered, washed with water and dried. The crude products were extracted with xylene, separated by column chromatography and recrystallized from benzene.

Characterization and Identification of Products. Compound **2** was identified by comparison with the authentic sample obtained from commercial source. Some properties of the compounds (**3**,[3] **4**,[1] and **8**[4]) were already known, and these were identified by the data described in the literature together with additional following data.

3: ^{1}H-NMR ($CDCl_3$) δ=3.07 (3H, d, $-CH_3$), 6.8—7.2 (4H, m, $H^{2,3}$, and NH_2), 7.68 (2H, m, $H^{6,7}$), 8.30 (2H, m, $H^{5,8}$), 10.45 (1H, b, N<u>H</u>–Me).

8: ^{1}H-NMR ($CDCl_3$) δ=1.0—2.3 (10H, m, $-(CH_2)_5-$), 3.64 (1H, m, –NH–C<u>H</u>–), 6.9—7.4 (4H, m, $H^{2,3}$ and NH_2), 7.85 (2H, m, $H^{6,7}$), 8.50 (2H, m, $H^{5,8}$), 11.12 (1H, b, –N<u>H</u>–).

1-Amino-4-(s-butylamino)anthraquinone (5): Mp 135—136 °C. UV_{max} (CH_3OH), nm, 573 (ε 15400), 616 (ε 18100). Found: C, 73.61; H, 6.33; N, 9.27%. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%. ^{1}H-NMR ($CDCl_3$) δ=1.03 (3H, t, $-CH_3$), 1.34 (3H, d, $-CH_3$), 1.71 (2H, m, $-CH_2-$), 3.76 (1H, m, –CH–), 7.0—7.4 (4H, m, $H^{2,3}$ and NH_2), 7.80 (2H, m, $H^{6,7}$), 8.46 (2H, m, $H^{5,8}$), 11.06 (1H, b, N<u>H</u>– *s*-Bu).

1-Amino-4-(octylamino)anthraquinone (6): Mp 112.5—113.5 °C. UV_{max} 573 (ε 14400), 617 (ε 17000). Found: C, 75.49; H, 7.54; N, 7.63%. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%. ^{1}H-NMR ($CDCl_3$) δ=0.84 (3H, t, $-CH_3$), 1.1—1.9 (12H, m, $-(CH_2)_6-$), 3.32 (2H, q, –NH–C<u>H</u>$_2$–), 6.8—7.2 (4H, m, $H^{2,3}$ and NH_2), 7.64 (2H, m, $H^{6,7}$), 8.30 (2H, m, $H^{5,8}$), 10.73 (1H, b, N<u>H</u>–Octyl).

1-Amino-2-(octylamino)anthraquinone (7): Mp 197—198 °C. UV_{max} 539 (ε 10700). Found: C, 74.88; H, 7.67; N, 7.78%. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%. ^{1}H-NMR (DMSO-d_6) δ=0.89 (3H, t, $-CH_3$), 1.0—1.9 (12H, m, $-(CH_2)_6-$), 3.20 (2H, q, NH–C<u>H</u>$_2$–), 6.13 (1H, b, N<u>H</u>–Oc), 6.56 (1H, d, H^3), 7.59 (1H, d, H^4), 7.70 (2H, m, $H^{6,7}$), 8.0—8.4 (4H, m, $H^{5,8}$ and NH_2).

1-Amino-4-(benzylamino)anthraquinone (9): Mp 167.0—167.5 °C. UV_{max} 571 (ε 13800), 613 (ε 15200). Found: C, 76.62; H, 4.90; N, 8.17%. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53%. ^{1}H-NMR ($CDCl_3$) δ=4.62 (2H, d, $-CH_2-$), 6.7—7.2 (4H, m, $H^{2,3}$ and NH_2), 7.32 (5H, s, C_6H_5), 7.71 (2H, m, $H^{6,7}$), 8.36 (2H, m, $H^{5,8}$), 11.00 (1H, b, –NH–).

1-Amino-2,4-dipiperidinoanthraquinone (10): Mp 145—145.5 °C. UV_{max} 580 (ε 8200). Found: C, 73.85; H, 7.04; N, 10.34%. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79%. ^{1}H-NMR ($CDCl_3$) δ=1.5—2.0 (12H, m, $-(CH_2)_3\times 2$), 2.8—3.3 (8H, m, N–C<u>H</u>$_2\times 4$), 7.14 (1H, s, H^3), 7.60 (2H, b, NH_2), 7.78 (2H, m, $H^{6,7}$), 8.42 (2H, m, $H^{5,8}$).

1-Amino-2,4-dimorpholinoanthraquinone (11): Mp 220—221 °C. UV_{max} 565 (ε 8400). Found: C, 67.34; H, 5.83; N, 10.50%. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68%. ^{1}H-NMR ($CDCl_3$) δ=2.9—3.4 (8H, m, N–C<u>H</u>$_2\times 4$), 3.8—4.3 (8H, m, O–C<u>H</u>$_2\times 4$), 7.16 (1H, s, H^3), 7.56 (2H, b, NH_2), 7.84 (2H, m, $H^{6,7}$), 8.41 (2H, m, $H^{5,8}$).

References

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2) From their UV spectra, it was considered that some of them should be 1-amino-2(or 4)-(alkylamino)anthraquinones.

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