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A New Synthesis of 1-Amino-4-butylaminoanthraquinone from 1-Aminoanthraquinone Promoted by Metal Ions

Katsuhira Yoshida,* Masaru Matsuoka,*,† Yoshio Yamashita, and Teijiro Kitao†

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780

†*Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai, Osaka 591*

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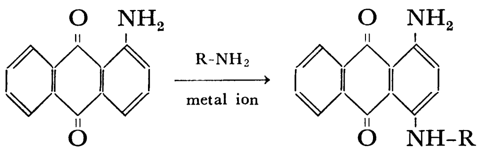
In the presence of some metal ions and atmospheric oxygen, 1-aminoanthraquinone(**1**) reacts readily with butylamine to give 1-amino-4-butylaminoanthraquinone(**2a**), along with a small amount of 1,4-diaminoanthraquinone, which is produced by the dealkylation of **2a**. The activity of the metal ions decreased in the following order: Co(II)$\gg$Ni(II)$>$Cu(II)$>$Al(III). The reaction is remarkably affected by the substitution of an alkyl group into the amino group of **1**, the addition of a chelating agent, the counter anion of metal ions, and the reaction temperature. By the use of cobalt(II) chloride, the reaction proceeds most smoothly at about 30 °C. Both anthraquinone and 2-aminoanthraquinone show no sign of the reaction under the same conditions. A possible mechanism involving the formation of a metal complex, followed by the nucleophilic attack of amine at the 4-position and the oxidative abstraction of the hydride anion by atmospheric oxygen is proposed.

Aminoanthraquinone derivatives are very important compounds as dyes or dye intermediates. A large number of papers and patents have been reported on reactions introducing amino groups into the anthraquinone nucleus. The displacement of sulfonyl, halogeno,[1] nitro, and hydroxy groups by amino groups is widely adopted.

The direct amination of anthraquinone or aminoanthraquinones with hydroxylamine in concentrated sulfuric acid catalyzed by iron(II) sulfate or vanadium pentaoxide has also been described, but it produces random substitution products.[2] Russkikh *et al.*[3] reported that the reaction of the boric esters of quinizarin with aromatic amines gave 2-arylaminoquinizarins in the presence of atmospheric oxygen. Recently, we ourselves reported a metal-promoted alkylamination of α-substituted anthraquinones, in which the amination products were obtained in good yields under mild conditions.[4] This is a useful method for preparing some 1-amino-4-alkylaminoanthraquinones from 1-aminoanthraquinone.

In this paper, we wish to report on the reaction of 1-aminoanthraquinone with butylamine in detail and to propose the possible mechanism of this direct amination.



1 **2**

a: R=$CH_2CH_2CH_2CH_3$
b: R=H

Results and Discussion

The reaction of 1-aminoanthraquinone(**1**) with butylamine in the presence of metal salts gave 1-amino-4-butylaminoanthraquinone(**2a**), along with a small amount of 1,4-diaminoanthraquinone(**2b**) produced by the dealkylation of **2a**.[5] A partial dealkylation of alkylaminoanthraquinones has already been noted in previous papers.[6] The activities of metal salts in this direct amination are shown in Table 1.

Table 1. Effect of metal chlorides on the butylamination of **1**[a]

Run	Metal chloride	Recovered(%)[b] **1**	Yield(%)[b] **2a**	**2b**
1	None	99.0	0	0
2	$CuCl_2$	70.9	5.4	3.2
3	$NiCl_2$	57.2	11.1	trace
4	$CoCl_2$	0	58.7	4.7
5	$AlCl_3$	65.9	3.1	trace
6	$FeCl_3\cdot 6H_2O$	99.1	0	0
7	$MgCl_2\cdot 6H_2O$	90.1	0	0
8	$ZnCl_2$	93.8	0	0

a) The reactant, **1** (9 mmol), was stirred in 1-butanol (15 ml) with butylamine (15 ml) and metal salt (9 mmol) at 80—82 °C for 24 h. b) Determined by means of a TLC-scanner.

No reaction occurred in the absence of metal salts, but in the presence of metal salts two direct amination products (**2a** and **2b**) were obtained. Metal chlorides were arranged in the order of the activity as follows: Co(II)$\gg$Ni(II)$>$Cu(II)$>$Al(III). The activity of the cobalt(II) ion was particularly superior to those of other metal ions, while the Fe(III), Mg(II), and Zn(II) ions did not promote the reaction. As is shown in Table 2, the activity of the cobalt ion is affected by its counter anion. Cobalt(II) chloride and cobalt(II) bromide have good activity, but cobalt(II) fluoride has poor activity.

The 1-amino group plays a great role on this reaction, since both anthraquinone and 2-aminoanthraquinone show no sign of the reaction.[4a] Furthermore, the butylamination of 1-alkylaminoanthraquinones, such as 1-methylamino- or 1-butylaminoanthraquinones, gave the corresponding 1,4-bis(alkylamino)anthraquinones, though in only low yields, in the presence of copper(II) acetate, but none of them in the presence of cobalt(II) chloride. These results suggest that the formation of a metal complex in which the amino and carbonyl groups of **1** coordinate to the metal ion may play an important role during the course of this direct amination. Neither anthraquinone nor 2-aminoanthraquinone can form such a chelate complex

Table 2. Effect of the counter anion of the cobalt ion on the butylamination of **1**[a)]

Run	Cobalt salt	Time (h)	Recovered(%)[b)] **1**	Yield(%)[b)] **2a**	Yield(%)[b)] **2b**
9	$CoF_2 \cdot 3H_2O$	24	74.1	0.2[c)]	0
10	$CoCl_2$	8	0	66.1	3.1
11	$CoCl_2 \cdot 6H_2O$	8	6.0	53.5	3.0
12	$CoBr_2 \cdot 6H_2O$	8	5.3	63.5	2.9
13	$Co(OCOCH_3)_2 \cdot 4H_2O$	24	19.2	32.1	1.8
14	$Co(CH_3COCHCOCH_3)_2 \cdot 2H_2O$	24	91.2	0	0

a) The reactant, **1** (4.5 mmol), was stirred in 1-butanol (5 ml) with butylamine (15 ml) and metal salt (4.5 mmol) at 30 °C. b) Determined by means of a TLC-scanner. c) Isolated yield.

with the metal ion. The substitution of an alkyl group into the amino group of **1** may prevent the formation of a chelate complex by its steric hindrance.

The addition of a small amount of ethylenediamine completely inhibited the reaction. This suggests that the metal ion is preferentially combined with ethylenediamine rather than with **1** and that, consequently, the reaction was prohibited.[4a)]

The effect of the molar ratio of cobalt(II) chloride to **1** on the yield of **2a** is shown in Table 3. The yield of **2a** increases with the increase in the molar ratio of cobalt(II) chloride up to 1.0. The addition of another mole of $CoCl_2$ depresses the yield to 54% because of such undesirable side reactions as dealkylation (Run 20). The yields of **2a**, based on $CoCl_2$, are approximately kept constant at about 64% up to the molar ratio of 1.0 (Runs 15, 17, and 18). In the presence of a 0.1 molar equivalent of $CoCl_2$, a prolonged reaction time results in an increase of the yield of **2a** (Run 16) but the yield based on $CoCl_2$ does not exceed 100%. From these results, the cobalt complex (**1**: Co(II) = 1 : 1) was proposed as an activated intermediate for this direct amination. Also, it was found that atmospheric oxygen is also necessary for this amination because, under a nitrogen atmosphere, the yield of **2a** is depressed drastically to 2.9% and 92% of **1** is recovered, even in the presence of an equimolar amount of cobalt(II) chloride (Run 19).

The reaction was also considerably affected by the reaction temperature. Figure 1 shows the effect of the reaction temperature on the butylamination of **1** in the presence of $CoCl_2$. The yield of **2a** increased up to 30 °C and then decreased gradually with the increase in the temperature. The optimum temperature for this reaction was 30 °C. The decrease in the yield of **2a** at higher temperatures seems to be caused by the fact that the chelate complex may be unstable at higher temperature.

On the basis of the experimental results described above, the following possible mechanism for this amination may be proposed (Scheme 1). The formation of the chelate complex (**3**) probably increases the electrophilicity of the substituted anthraquinone nucleus and, consequently, facilitates the nucleophilic attack of butylamine on the nucleus. Russkikh *et al.*[3,7)] reported that the formation of boron-chelate rings of 1,4-dihydroxy-, 1-amino-4-hydroxy-, and 1,4-diaminoanthraquinones increases the electrophilicity of the substituted anthraquinone nucleus and facilitates the direct amination at the 2-position of these compounds.

Table 3. Effect of the molar ratio of cobalt(II) chloride on the butylamination of **1**[a)]

Run	$CoCl_2$/**1**[b)]	Time (h)	Recovered (%)[c)] **1**	Yield(%)[c)] **2a**[d)]	Yield(%)[c)] **2a**[e)]
15	0.1	8	86.6	6.5	64.5
16	0.1	24	78.6	9.2	91.8
17	0.5	8	32.6	32.3	64.6
18	1.0	6	0	62.6	62.6
19	1.0[f)]	6	92.3	2.9	2.9
20	2.0	5	0	54.1	—

a) The reactant, **1** (4.5 mmol), was stirred with butylamine (15 ml) and $CoCl_2$ at 30 °C in the presence of air. b) Molar ratio. c) Determined by means of a TLC-scanner. d) Yield based on the **1** used. e) Yield based on the $CoCl_2$ used. f) Reaction carried out under a nitrogen atmosphere.

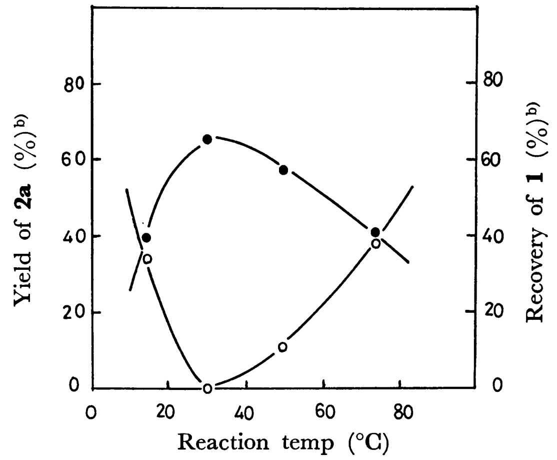
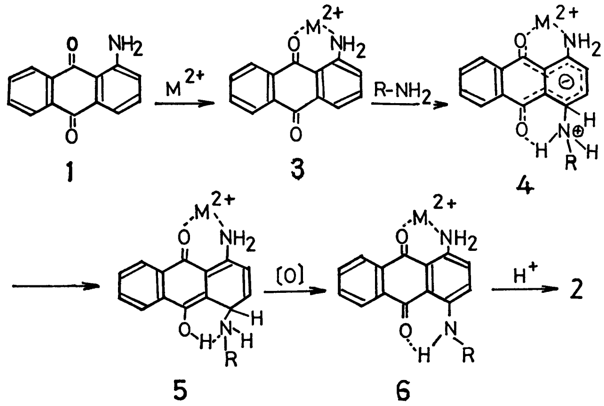


Fig. 1. Effect of reaction temperature on the butylamination of 1-aminoanthraquinone(**1**).[a)]
○: 1-Aminoanthraquinone(**1**), ●: 1-Amino-4-butylaminoanthraquinone(**2a**). a) Reactant **1** (4.5 mmol) was stirred with butylamine (15 ml) and $CoCl_2$ (4.5 mol) for 6 h. b) Determined by means of a TLC-scanner.

The preferential substitution of the amino group at the 4-position, but not at the 2-position, seems to be caused by the fact that the formation of hydrogen-bonding between the *N*-hydrogen atom and the oxygen atom of the carbonyl group stabilizes the adduct (**4**). A similar role of hydrogen-bonding has also been inferred in previous reports.[8] The oxidative abstraction of the hydride anion from the adduct (**5**) by atmospheric oxygen is proposed from the experimental results. The final step of acid hydrolysis of **6** gives rise to **2**. The details of the reaction mechanism for each step are still not clear, however, and are under investigation.



Scheme 1.

Experimental

All the melting points are uncorrected. The visible spectra 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 the internal standard. The 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 the eluent. Thin-layer chromatography was performed on silica gel (Merck Kieselgel 60) using the following solvent system (volume ratio); System A (benzene), and System B (cyclohexane: acetone: ethyl acetate=13:1:1). The resulting thin-layer chromatograms were measured on a chromatoscanner(Shimadzu CS-900). The yields were determined on the basis of measurements made using calibrations with standard solutions of the pure compounds.

Materials. The 1-aminoanthraquinone was supplied by the Mitsubishi Chemical Industry, Inc., and was purified by column chromatography, followed by recrystallization from xylene. 1,4-Diaminoanthraquinone (Mitsui Toatsu Chemicals), used as an authentic sample, was purified by column chromatography and subsequent recrystallization from ethanol. All the metal salts were reagent-grade and were used without further purification. The amines and solvents were purified by the ordinary methods.

*Reaction of **1** with Butylamine.* The general procedure was as follows. A mixture of **1**, metal salt, butylamine, and 1-butanol was stirred in a open flask (see Tables 1, 2, and 3, and Fig. 1). The mixture was then poured into a cold 3.0% hydrochloric acid solution, and the separated products were filtered, washed with water, and dried. The R_f values of the components were as follows:

1: R_f 0.43 (System A), R_f 0.26 (System B)
2a: R_f 0.26 (System A), R_f 0.20 (System B)
2b: R_f 0.10 (System A), R_f 0.05 (System B).

The yields were determined by means of a TLC-scanner or after isolation by column chromatography.

2a: λ max (Methanol) 617 (ε 17300), 573 (ε 15200); mp 140—141 °C (lit,[9] 142.6—143.1 °C(cor)); Found: C, 73.06; H, 6.14; N, 9.51%. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%. PMR ($CDCl_3$): δ=0.98 (3H, t, $-CH_3$), 1.2—2.0 (4H, m, $-(CH_2)_2-$), 3.36 (2H, q, NH-$\underline{CH_2}$-), 6.9—7.3 (4H, m, $H^{2,3}$, and NH_2), 7.72 (2H, m, $H^{6,7}$), 8.36 (2H, m, $H^{5,8}$), 10.68 (1H, broad, N$\underline{H}$-Bu).

Compound (**2b**) was identified with the authentic sample.

*Reaction of Anthraquinone (**7**) with Butylamine.* A mixture of **7** (4.5 mmol), $CoCl_2$ (4.5 mmol), butylamine (15 ml), and 1-butanol (5 ml) was stirred under reflux for 8 h. The subsequent procedures were the same as those in the case of **1**. Reactant **7** was recovered in a 99% yield.

*Reaction of 2-Aminoanthraquinone (**8**) with Butylamine.* A mixture of **8** (4.5 mmol), $CoCl_2$ (4.5 mmol), butylamine (15 ml), and 1-butanol (5 ml) was stirred under reflux for 8 h. The reactant, **8**, was recovered quantitatively.

*Reaction of 1-Methylamino-(**9**) or 1-Butylamino-anthraquinone (**10**) with Butylamine.* A mixture of the reactant (4.5 mmol), metal salt (4.5 mmol), butylamine (15 ml), and 1-butanol (5 ml) was stirred under reflux for 8 h. After the solvent and the excess amine had been distilled off under reduced pressure, the mixture was poured into a cold 3.0% hydrochloric acid solution. The separated precipitate was filtered, washed with water, and dried. The crude product was extracted with xylene and separated by column chromatography. The results are shown in Table 4.

TABLE 4.

Reactant	Metal salt	Recovered(%) Reactant	Yield(%) 1,4-(R-NH)₂-AQ
9	$Cu(OCOCH_3)_2$	80	2.0[a]
10	$Cu(OCOCH_3)_2$	65	1.7[b]
9	$CoCl_2$	96	0
10	$CoCl_2$	100	0

a) 1-Butylamino-4-methylaminoanthraquinone. b) 1,4-Bis(butylamino)anthraquinone.

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5) When a mixture of **2a** (0.5 g), $CoCl_2$ (0.22 g) and 1-butanol was heated under reflux for 16 h, the dealkylation of **2a** was observed and **2b** (32 mg) was obtained, together with the **2a** (0.35 g) recovered.

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