

# Oxidative Dealkylation of 4-Substituted *N,N*-Dialkylanilines with Molecular Oxygen in the Presence of Acetic Anhydride Promoted by Cobalt(II) or Copper(I) Chloride

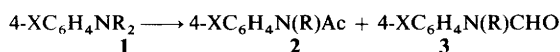
**Satoru Murata, Kaoru Suzuki, Akira Tamatani, Masahiro Miura\* and Masakatsu Nomura**

*Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan*

The reaction of 4-substituted *N,N*-dimethylanilines **1a–d** with acetic anhydride **5** proceeded efficiently in the presence of a catalytic amount of cobalt(II) or copper(I) chloride under oxygen to give the corresponding *N*-methylacetanilides **2a–d** along with *N*-methylformanilides **3a–d**. The reaction of *N*-alkyl-*N*-methyl-*p*-toluidines **1f–h** with cobalt chloride revealed that the order of reactivity of the *N*-substituents follows the sequence allyl > benzyl ≥ methyl > ethyl, while in the case of copper chloride the order was benzyl > allyl > methyl > ethyl. Aldehydes **18a–e** and phenylglyoxylic acid derivatives **18f** and **18g** were obtained in fair to good yield from the reaction of *N*-substituted *N*-ethyl-*p*-toluidines **17a–g**.

Dealkylation of tertiary amines is a fundamental reaction for synthesis of *N*-containing compounds.<sup>1</sup> The reaction is often carried out by acylation with acyl chlorides followed by hydrolysis. While acid anhydrides may be used, they react with only a limited range of amines such as *N,N*-dialkylbenzylamines at elevated temperatures.<sup>2</sup> Another important feature of amine dealkylation, especially using transition-metal catalysts, is of relevance to the oxidative degradation of *N*-containing drugs in biological systems, and tertiary amines have been subjected to reaction with a variety of model oxidising systems.<sup>3</sup>

During the course of our study of transition metal-catalysed oxidation of nitrogen-containing compounds with molecular oxygen,<sup>4</sup> we found that 4-substituted *N,N*-dialkylanilines react with acetic anhydride in the presence of a catalytic amount of cobalt(II) chloride under oxygen to give the corresponding *N*-alkylacetanilides in good yield along with *N*-alkylformanilides (Scheme 1).<sup>5,†</sup> In this paper, we report the details of the acylative dealkylation using either cobalt(II) or copper(I) chloride as the promoter.



**Scheme 1** *Reagents: Ac<sub>2</sub>O, O<sub>2</sub>, CoCl<sub>2</sub>, or CuCl, and acetonitrile*

## Results and Discussion

**Reaction of *N,N*-Dimethyl-*p*-toluidine 1a.**—When a solution of the aniline **1a** (2.5 mmol) containing cobalt(II) chloride (0.125 mmol) and acetic anhydride **5** (7.5 mmol) in acetonitrile (5 cm<sup>3</sup>) was stirred at 30 °C under oxygen (1 atm) for 4 h, 1.4 mmol of oxygen was consumed; formation of *N*,4-dimethylacetanilide **2a** (80%) together with *N*,4-dimethylformanilide **3a** (13%) was detected (Table 1). The reaction was also completed with cobalt chloride (0.005 mmol). In the absence of the anhydride **5**, a mixture of compound **3a** and *N*-methyl-*p*-toluidine **4** was produced, as for the reaction with iron catalysts reported previously,<sup>4b</sup> although the conversion of substrate **1a** was

† The following relevant work has been reported: (a) *N,N*-Dialkylanilines react with acetic anhydride in the presence of a stoichiometric amount of a metal oxidant such as lead(IV) acetate.<sup>6</sup> (b) Dealkylative acylation of tertiary amines with acid anhydrides occurs in the presence of a number of transition-metal salts under nitrogen at 160–180 °C.<sup>2e</sup>

**Table 1** Reaction of *N,N*-dimethyl-*p*-toluidine **1a**<sup>a</sup>

MCln (mmol)	(RCO) <sub>2</sub> O	Products [yield (%)] <sup>b</sup>	Recovery of substrate <b>1a</b> (%) <sup>b</sup>
CoCl <sub>2</sub> (0.125)	<b>5</b>	<b>2a</b> (80), <b>3a</b> (13)	5
CoCl <sub>2</sub> (0.125) <sup>c</sup>	<b>5</b>	<b>2a</b> (19), <b>3a</b> (2)	74
CoCl <sub>2</sub> (0.125) <sup>c,d</sup>	<b>5</b>	<b>2a</b> (46), <b>3a</b> (4), <b>4</b> (1)	44
CoCl <sub>2</sub> (0.005)	<b>5</b>	<b>2a</b> (60), <b>3a</b> (17)	
CoCl <sub>2</sub> (0.125)		<b>3a</b> (10), <b>4</b> (26)	42
	<b>5</b>	<b>2a</b> (12), <b>3a</b> (8), <b>4</b> (9)	61
CoCl <sub>2</sub> (0.125)	<b>6</b>	<b>9</b> (63), <b>3a</b> (8)	14
CoCl <sub>2</sub> (0.125)	<b>7</b>	<b>10</b> (61), <b>3a</b> (10), <b>4</b> (15)	4
CoCl <sub>2</sub> (0.125)	<b>8</b>	<b>11</b> (31), <b>3a</b> (11), <b>4</b> (5)	15
CuCl (0.125) <sup>e</sup>	<b>5</b>	<b>2a</b> (62), <b>3a</b> (24), <b>4</b> (3)	1
CuCl (0.125) <sup>c</sup>	<b>5</b>	<b>2a</b> (8)	91
CuCl (0.125) <sup>c,d</sup>	<b>5</b>	<b>2a</b> (15), <b>3a</b> (3)	79
CuCl (0.005)	<b>5</b>	<b>2a</b> (49), <b>3a</b> (31), <b>4</b> (3)	
CuCl (0.125)		<b>3a</b> (19), <b>4</b> (35)	20
CuCl (0.125)	<b>6</b>	<b>9</b> (57), <b>3a</b> (10)	17
CuCl (0.125)	<b>7</b>	<b>10</b> (53), <b>3a</b> (25), <b>4</b> (12)	2
CuCl (0.125)	<b>8</b>	<b>11</b> (9), <b>3a</b> (21), <b>4</b> (17)	20
FeCl <sub>3</sub> (0.125)	<b>5</b>	<b>2a</b> (1)	98
FeCl <sub>3</sub> (0.05)	<b>5</b>	<b>2a</b> (28), <b>3a</b> (2), <b>4</b> (3)	65

<sup>a</sup> The reaction of the aniline **1a** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) was carried out at 30 °C for 4 h under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>). <sup>b</sup> Determined by GLC analysis. <sup>c</sup> Reaction in the presence of BHT (0.25 mmol). <sup>d</sup> Reaction for 20 h. <sup>e</sup> Reaction for 2 h.

considerably lower in this case. While the reaction did not proceed without both anhydride **5** and cobalt chloride, about 40% of the substrate **1a** was consumed with anhydride **5** alone. Chloroacetic and propionic anhydrides **6** and **7** could be also used in place of anhydride **5**. Benzoic anhydride **8** was less effective. Copper(I) chloride also showed good catalytic activity, but the yield of product **2a** was somewhat decreased. Addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.25 mmol) affected both of the reactions, with CoCl<sub>2</sub> and CuCl: (a) The conversion of substrate **1a** was significantly decreased, and (b) the acetanilide **2a** was selectively formed. It appeared that iron(III) chloride behaved as an inhibitor at higher concentrations.

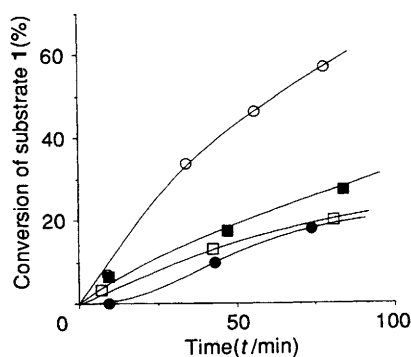
**Reaction of Aromatic (1b–h) and Aliphatic Tertiary Amines 13, 14.**—The results for the reaction of the amines **1b–h**, **13** and **14** with acetic anhydride **5** in the presence of either CoCl<sub>2</sub> or

4-XC <sub>6</sub> H <sub>4</sub> N(R <sup>1</sup> )R <sup>2</sup>	4-XC <sub>6</sub> H <sub>4</sub> N(R)Ac
<b>1a</b> X = R <sup>1</sup> = R <sup>2</sup> = Me	<b>2a</b> X = R = Me
<b>1b</b> X = OMe, R <sup>1</sup> = R <sup>2</sup> = Me	<b>2b</b> X = OMe, R = Me
<b>1c</b> X = OEt, R <sup>1</sup> = R <sup>2</sup> = Me	<b>2c</b> X = OEt, R = Me
<b>1d</b> X = Cl, R <sup>1</sup> = R <sup>2</sup> = Me	<b>2d</b> X = Cl, R = Me
<b>1e</b> X = H, R <sup>1</sup> = R <sup>2</sup> = Me	<b>2e</b> X = H, R = Me
<b>1f</b> X = R <sup>1</sup> = Me, R <sup>2</sup> = Et	<b>2f</b> X = Me, R = Et
<b>1g</b> X = R <sup>1</sup> = Me, R <sup>2</sup> = CH <sub>2</sub> CH=CH <sub>2</sub>	<b>2g</b> X = Me, R = CH <sub>2</sub> CH=CH <sub>2</sub>
<b>1h</b> X = R <sup>1</sup> = Me, R <sup>2</sup> = CH <sub>2</sub> Ph	<b>2h</b> X = Me, R = CH <sub>2</sub> Ph
4-XC <sub>6</sub> H <sub>4</sub> N(R)CHO	4-MeC <sub>6</sub> H <sub>4</sub> NHMe
<b>3a</b> X = R = Me	<b>4</b>
<b>3b</b> X = OMe, R = Me	
<b>3c</b> X = OEt, R = Me	
<b>3d</b> X = Cl, R = Me	
<b>3f</b> X = Me, R = Et	
<b>3g</b> X = Me, R = CH <sub>2</sub> CH=CH <sub>2</sub>	
<b>3h</b> X = Me, R = CH <sub>2</sub> Ph	
<b>5</b> Ac <sub>2</sub> O	4-MeC <sub>6</sub> H <sub>4</sub> N(Me)COR
<b>6</b> (ClCH <sub>2</sub> CO) <sub>2</sub> O	<b>9</b> R = CH <sub>2</sub> Cl
<b>7</b> (EtCO) <sub>2</sub> O	<b>10</b> R = Et
<b>8</b> (PhCO) <sub>2</sub> O	<b>11</b> R = Ph
(4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CH <sub>2</sub>	
<b>12</b>	
cyclo-C <sub>6</sub> H <sub>11</sub> NMe <sub>2</sub>	cyclo-C <sub>6</sub> H <sub>11</sub> N(Me)Ac
<b>13</b>	<b>15</b>
Bu <sub>3</sub> N	AcNBu <sub>2</sub>
<b>14</b>	<b>16</b>
4-MeC <sub>6</sub> H <sub>4</sub> N(Et)R	R <sup>1</sup> (C=O)R <sup>2</sup>
<b>17a</b> R = CH <sub>2</sub> Ph	<b>18a</b> R <sup>1</sup> = Ph, R <sup>2</sup> = H
<b>17b</b> R = CH <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -2,5-Me <sub>2</sub>	<b>18b</b> R <sup>1</sup> = C <sub>6</sub> H <sub>3</sub> -2,5-Me <sub>2</sub> , R <sup>2</sup> = H
<b>17c</b> R = CH <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -4-OMe-3-Me	<b>18c</b> R <sup>1</sup> = C <sub>6</sub> H <sub>3</sub> -4-OMe-3-Me, R <sup>2</sup> = H
<b>17d</b> R = CH <sub>2</sub> -(1-naphthyl)	<b>18d</b> R <sup>1</sup> = 1-naphthyl, R <sup>2</sup> = H
<b>17e</b> R = CH <sub>2</sub> CH=CHPh	<b>18e</b> R <sup>1</sup> = CH=CHPh, R <sup>2</sup> = H
<b>17f</b> R = CH(Ph)CO <sub>2</sub> Et	<b>18f</b> R <sup>1</sup> = Ph, R <sup>2</sup> = CO <sub>2</sub> Et
<b>17g</b> R = CH(Ph)CONHBu <sup>t</sup>	<b>18g</b> R <sup>1</sup> = Ph, R <sup>2</sup> = CONHBu <sup>t</sup>

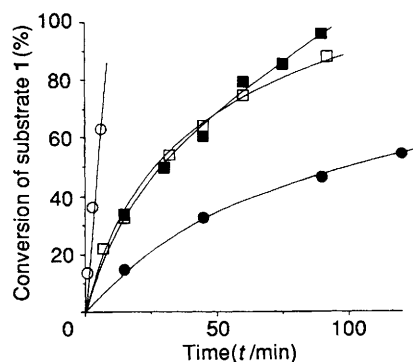
**Table 2** Reaction of aromatic (**1b–h**) and aliphatic tertiary amines **13** and **14**<sup>a</sup>

Amine	Cat.	Temp. (T/°C)	Time (t/h)	Products [yield (%)] <sup>b</sup>	Recovery of substrate <b>1a</b> (%) <sup>b</sup>
<b>1b</b>	CoCl <sub>2</sub>	30	5	<b>2b</b> (74), <b>3b</b> (9)	5
<b>1c</b>	CoCl <sub>2</sub>	30	5	<b>2c</b> (81), <b>3c</b> (8)	4
<b>1d</b>	CoCl <sub>2</sub>	60	20	<b>2d</b> (81), <b>3d</b> (13)	2
<b>1e</b>	CoCl <sub>2</sub>	60	20	<b>2e</b> (15), <b>12</b> (10)	22
<b>1f</b>	CoCl <sub>2</sub>	30	20	<b>2a</b> (9), <b>2f</b> (74), <b>3f</b> (9)	
<b>1g</b>	CoCl <sub>2</sub>	60	20	<b>2a</b> (52), <b>2g</b> (19), <b>3g</b> (2)	4
<b>1h</b>	CoCl <sub>2</sub>	60	20	<b>2a</b> (44), <b>2h</b> (43), <b>3h</b> (5)	5 <sup>c</sup>
<b>13</b>	CoCl <sub>2</sub>	60	20	<b>15</b> (60)	37
<b>14</b>	CoCl <sub>2</sub>	60	20	<b>16</b> (64)	
<b>1b</b>	CuCl	30	5	<b>2b</b> (65), <b>3b</b> (18)	3
<b>1c</b>	CuCl	30	5	<b>2c</b> (74), <b>3c</b> (15)	3
<b>1d</b>	CuCl	30	20	<b>2d</b> (54), <b>3d</b> (23)	11
<b>1e</b>	CuCl	30	20	<b>2e</b> (27)	16
<b>1f</b>	CuCl	30	20	<b>2a</b> (7), <b>2f</b> (64), <b>3f</b> (15)	
<b>1g</b>	CuCl	30	20	<b>2a</b> (55), <b>2g</b> (22), <b>3g</b> (6)	12
<b>1h</b>	CuCl	30	20	<b>2a</b> (63), <b>2h</b> (13), <b>3h</b> (3)	4 <sup>d</sup>
<b>13</b>	CuCl	60	20	<b>15</b> (20)	72

<sup>a</sup> The reaction of tertiary amines (2.5 mmol) with acetic anhydride **5** (7.5 mmol) was carried out under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>) in the presence of a catalyst (0.125 mmol). <sup>b</sup> Determined by GLC analysis. <sup>c</sup> The aldehyde **18a** was also obtained, in 40% yield. <sup>d</sup> The aldehyde **18a** was also obtained, in 55% yield.



**Fig. 1** Reaction of 4-substituted *N,N*-dimethylanilines **1a–d** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) in the presence of cobalt(II) chloride (0.125 mmol) under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>) at 30 °C: **1a** (○), **1b** (■), **1c** (□), **1d** (●)



**Fig. 2** Reaction of 4-substituted *N,N*-dimethylanilines **1a–d** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) in the presence of copper(I) chloride (0.125 mmol) under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>) at 30 °C: **1a** (○), **1b** (□), **1c** (■), **1d** (●)

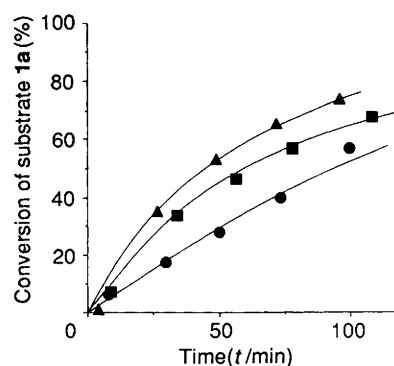
**Table 3** Reaction of *N*-substituted *N*-ethyl-*p*-toluidines **17a–g**<sup>a</sup>

Aniline	Cat.	Products [yield (%)] <sup>b</sup>	Recovery of substrate <b>17</b> (%) <sup>b</sup>
<b>17a</b>	CoCl <sub>2</sub>	<b>18a</b> (65), <b>2f</b> (84)	6
<b>17b</b>	CoCl <sub>2</sub>	<b>18b</b> (64), <b>2f</b> (72)	6
<b>17c</b>	CoCl <sub>2</sub>	<b>18c</b> (59 [53] <sup>c</sup> ), <b>2f</b> (75)	
<b>17d</b>	CoCl <sub>2</sub>	<i>d</i>	97
<b>17e</b>	CoCl <sub>2</sub>	<b>18e</b> (86), <b>2f</b> (78)	
<b>17f</b>	CoCl <sub>2</sub>	<i>d</i>	95
<b>17g</b>	CoCl <sub>2</sub>	<b>18g</b> [93 (75) <sup>c</sup> ], <b>2f</b> (84)	
<b>17a</b>	CuCl	<b>18a</b> (71), <b>2f</b> (80)	16
<b>17b</b>	CuCl	<b>18b</b> (77), <b>2f</b> (80)	5
<b>17c</b>	CuCl	<b>18c</b> (55), <b>2f</b> (78)	7
<b>17d</b>	CuCl	<b>18d</b> (72), <b>2f</b> (71)	
<b>17e</b>	CuCl	<b>18e</b> (62), <b>2f</b> (94)	
<b>17f</b>	CuCl	<b>18f</b> (78 [60] <sup>c</sup> ), <b>2f</b> (78)	
<b>17g</b>	CuCl	<b>18g</b> (80 [65] <sup>c</sup> ), <b>2f</b> (82)	

<sup>a</sup> The reaction of the anilines **17a–g** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) was carried out at 60 °C for 20 h in acetonitrile (5 cm<sup>3</sup>) under oxygen (1 atm) in the presence of a catalyst (0.125 mmol).

<sup>b</sup> Determined by GLC analysis. <sup>c</sup> Isolated yield. <sup>d</sup> No product **18** was detected.

CuCl are summarised in Table 2. The reaction of 4-substituted *N,N*-dimethylanilines **1b–d** also gave the corresponding acetanilides **2b–d** in good yield along with the formanilides **3b–d**. The product ratio of **2b–d** to **3b–d** in the reaction using CoCl<sub>2</sub> was larger than that using CuCl, as it was in the reaction of substrate **1a**. The time course of the conversion in the reaction of substrates **1a–d** at 30 °C, followed by GLC, is shown in Figs.



**Fig. 3** Effect of the concentration of cobalt(II) chloride on the reaction of *N,N*-dimethyl-*p*-toluidine **1a** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>) at 30 °C: CoCl<sub>2</sub> 0.060 mmol (●), 0.125 mmol (■), 0.190 mmol (▲)

**1** and **2**. The order of reactivity for the anilines **1a–d** in the reaction using CoCl<sub>2</sub> was **1a** > **1c** ≥ **1b** ≥ **1d**, and in the case of CuCl the order was **1a** > **1c** ≈ **1b** > **1d**. The reaction of the aniline **1e** afforded a dimerised product **12** in addition to the acetanilide **2e**.<sup>4b,c</sup> The reaction of *N*-alkyl-*N*-methyl-*p*-toluidines **1f–h** afforded the corresponding mixture of products **2a** and **2f–h** along with the formanilides **3f–h**. The reactivity order of the *N*-alkyl substituents judged from the product quotient (**2f–h** + **3f–h**)/**2a** from the reaction using CoCl<sub>2</sub> was found to follow the sequence allyl > benzyl ≥ methyl > ethyl, while in the reaction using CuCl the order was benzyl > allyl > methyl > ethyl. The aliphatic amines **13** and **14** also reacted, to give compounds **15** and **16**. The selective formation of compound **15** indicates that the *N*-cyclohexyl substituent is less reactive than the corresponding *N*-methyl group under the reaction conditions.

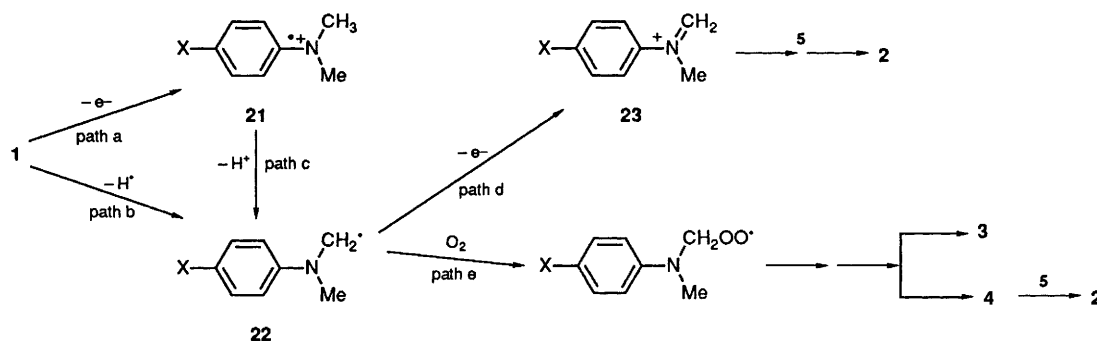
#### Reaction of *N*-Substituted *N*-Ethyl-*p*-toluidines **17a–g**

Lower reactivity of aliphatic moieties other than a methyl group attached to nitrogen, compared with *N*-benzyl and *N*-allyl substituents as above, is usually observed in chemical and electrochemical oxidations of tertiary amines.<sup>3i,7,8</sup> Consequently, we examined the reaction of the amines **17a–g**, which were prepared by reaction of *N*-ethyl-*p*-toluidine with the corresponding benzyl and allyl halides, with acetic anhydride **5** in the presence of either CoCl<sub>2</sub> or CuCl and the results obtained are presented in Table 3. The expected aldehydes **18a–e** and the phenylglyoxylic acid derivatives **18f** and **18g** were selectively produced in fair to good yield together with compound **2f**. It was somewhat surprising that substrates **17d** and **17f** did react when CuCl was used but with CoCl<sub>2</sub> the amines were almost quantitatively recovered.

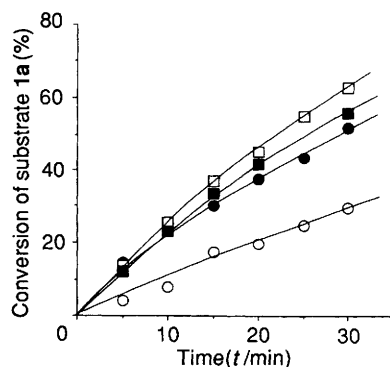
This method as a transformation reaction of benzyl and allyl halides to the corresponding carbonyl compounds seems to be useful, since the reaction can be carried out under mild conditions using reagents which are inexpensive and easily handled.\*

**Effect of Concentration of the Metal Chlorides and Acetic Anhydride 5.**—The reaction of *N,N*-dimethyl-*p*-toluidine **1a** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) in the presence of different amounts of CoCl<sub>2</sub> (0.06–0.19 mmol) at 30 °C under oxygen was followed by GLC. As is seen in Fig. 3, the rate of the reaction increased simply upon an increase in the concentration of CoCl<sub>2</sub>. The reaction using CuCl was considerably

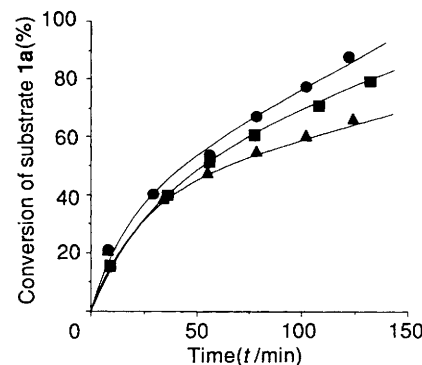
\* A method for aerial oxidation of allylamines in the presence of iodine under photoirradiation to give α,β-unsaturated aldehydes has been recently reported.<sup>9</sup> Other relevant work is cited therein.



Scheme 2



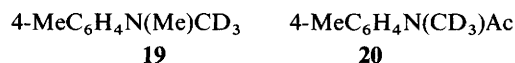
**Fig. 4** Effect of the concentration of copper(I) chloride on the reaction of *N,N*-dimethyl-*p*-toluidine **1a** (2.5 mmol) with acetic anhydride **5** (7.5 mmol) under air at 30 °C in acetonitrile (5 cm<sup>3</sup>); CuCl 0.013 mmol (○), 0.026 mmol (●), 0.050 mmol (□), 0.125 mmol (■)



**Fig. 5** Effect of the concentration of acetic anhydride **5** on the reaction of *N,N*-dimethyl-*p*-toluidine **1a** (2.5 mmol) in the presence of cobalt(II) chloride (0.125 mmol) under oxygen (1 atm) in acetonitrile (5 cm<sup>3</sup>) at 30 °C; **5** 3.7 mmol (▲), 7.5 mmol (■), 15 mmol (●)

faster than that using CoCl<sub>2</sub>. Therefore, the reaction was carried out in air (Fig. 4). The rate of the reaction was increased with an increase in the amount of CuCl (up to 0.05 mmol); a further increase retarded the reaction. Changing the amount of acetic anhydride **5** from 3.7 to 15 mmol in the reaction with CoCl<sub>2</sub> also increased the reaction rate (Fig. 5).

**Isotope Effect.**—The intramolecular kinetic isotope effect was measured using *N*-methyl-*N*-trideuteriomethyl-*p*-toluidine **19** as the substrate. The isotope effect ( $k_H/k_D$ ) in the reaction using acetic anhydride **5** and CoCl<sub>2</sub> under oxygen, as evaluated from the product quotient of 4-methyl-*N*-trideuteriomethylacetanilide **20** to product **2a** (by GLC–MS analysis) was found to be 4.3. Similarly, a value of 4.4 was also obtained in the reaction using CuCl in place of CoCl<sub>2</sub>.



**Reaction Scheme.**—A probable mechanism for the reaction of the aniline **1** with acetic anhydride **5** in the presence of either CoCl<sub>2</sub> or CuCl is illustrated in Scheme 2, which is similar to that proposed for the reaction using iron complexes in place of cobalt chloride without the anhydride **5**.<sup>4b</sup> The initial step in the reaction may involve one-electron oxidation to give aminium radical cation **21** (path a in Scheme 2), and successive loss of a proton would then afford  $\alpha$ -amino radical **22** (path c). Another possible path leading to radical **22** is the initial hydrogen abstraction (path b). A further one-electron oxidation of the radical **22** (path d) gives iminium cation **23** which is transformed into an acetanilide **2** via reaction with acetic anhydride **5**. The latter path has been proposed for oxidation of *N,N*-dialkylanilines with a stoichiometric amount of metal oxidants in the presence of anhydride **5**<sup>6d</sup> and also for the

Polonovsky reaction.<sup>10</sup> Alternatively, the radical **22** could react with oxygen to give a mixture of products **3** and **4** (path e). The aniline **4** would then react with anhydride **5** to afford product **2a**.

The fact that addition of BHT in the reaction of substrate **1a** with anhydride **5** retarded the reaction, compound **2a** being produced selectively (Table 1), suggests that both paths a and b participate in the reaction: In the presence of BHT, the reaction predominantly proceeds via paths a, c and d,\* while the free-radical chain process including paths b and e is suppressed by the radical inhibitor. The observed medium-sized isotope effect does not contradict the dual mechanism.<sup>3i,4b</sup> The initiation reaction of the radical route can also be path a, as is usual in aerial oxidation of compounds having relatively low oxidation potentials, including cobalt-catalysed oxidation of alkylbenzenes.<sup>12</sup> The unexpectedly low reactivity of compounds **1b** and **1c**<sup>4c</sup> may be attributable to the fact that proton loss from radical cation **21** is relatively slow.<sup>4c,13</sup> The effect of the concentration of the metal chlorides and the anhydride **5** on the reaction rate indicates that path a is synergistically promoted by both the metal species and the anhydride **5**, although the details are not clear. The relative reactivity of *N*-alkyl substituents is considered to be determined in paths b and c.<sup>3i,7,8</sup> The different observed reactivity orders between the reactions using CoCl<sub>2</sub> and CuCl may be due to the change of the relative rate of path a to path b depending on the catalysts employed. In the case of CuCl, the salt seems to act as both promoter and inhibitor (at a higher concentration). Such a phenomenon is often observed in transition metal-catalysed autoxidations, since the metal salts are capable of both enhancing the initiation step and hampering the propagation

\* The possibility that the iminium cation **23** is also formed from radical cation **21** by hydrogen abstraction cannot be excluded.<sup>3i,11</sup>



step, depending on their redox potentials.<sup>12,14</sup> It should be noticed that FeCl<sub>3</sub> almost completely inhibited the reaction of compound **1a** with anhydride **5** at a high concentration (Table 1). This might imply that the reaction predominantly proceeds *via* the radical process. However, the relative yield of compound **3a** compared with that of compound **2a** in the reaction using this salt is very low. Therefore, the effect of the salt is not definitive. The fact that the product quotient **2/3** in the reaction of anilines **1a–d** using CoCl<sub>2</sub> is higher than that with CuCl suggests that path d is more efficiently enhanced by the cobalt species compared with the copper catalyst.

## Experimental

<sup>1</sup>H NMR spectra were obtained with a JEOL JNM-PS-100 spectrometer for CDCl<sub>3</sub> solutions. *J*-Values are given in Hz. GLC-MS data were obtained with a JEOL JMS-DX-303 spectrometer. GLC analysis was carried out with a Shimadzu GC-8A gas chromatograph.

The anilines **1b**,<sup>15</sup> **1c**,<sup>16</sup> **1d**,<sup>15</sup> **1f**,<sup>17</sup> **1g**,<sup>18</sup> and **1h**<sup>19</sup> were prepared by the methods reported previously. *N,N*-Dialkyl-*p*-toluidines **17a–g** were prepared according to a published procedure;<sup>20</sup> alkylation of *N*-ethyl-*p*-toluidine with the corresponding halides in dimethylformamide (DMF) in the presence of potassium carbonate gave compounds **17a–g**. The aniline **17a** was an oil; *m/z* 225 (M<sup>+</sup>); δ<sub>H</sub> 1.17 (3 H, t, *J* 7.0), 2.22 (3 H, s), 3.46 (2 H, q, *J* 6.5), 4.48 (2 H, s), 6.60 (2 H, d, *J* 8.5), 6.99 (2 H, d, *J* 8.5) and 7.21–7.48 (5 H, m). The aniline **17b** was an oil; *m/z* 253 (M<sup>+</sup>); δ<sub>H</sub> 1.17 (3 H, t, *J* 6.5), 2.24 (9 H, s), 3.45 (2 H, q, *J* 6.7), 4.36 (2 H, s) and 6.45–7.20 (7 H, m). The aniline **17c** was an oil; *m/z* 269 (M<sup>+</sup>); δ<sub>H</sub> 1.12 (3 H, t, *J* 7.5), 2.18 (3 H, s), 2.22 (3 H, s), 3.42 (2 H, q, *J* 6.7), 3.77 (3 H, s), 4.36 (2 H, s) and 6.56–7.20 (7 H, m). The aniline **17d** had m.p. 89–90 °C (from benzene–hexane); *m/z* 275 (M<sup>+</sup>); δ<sub>H</sub> 1.20 (3 H, t, *J* 7.0), 2.24 (3 H, s), 3.53 (2 H, q, *J* 6.7), 4.94 (2 H, s), 6.64 (2 H, d, *J* 8.5), 7.00 (2 H, d, *J* 8.5) and 7.30–8.20 (7 H, m). The aniline **17e** was an oil; *m/z* 251 (M<sup>+</sup>); δ<sub>H</sub> 1.13 (3 H, t, *J* 7.0), 2.26 (3 H, s), 3.42 (2 H, q, *J* 6.7), 4.02 (2 H, d, *J* 4.7), 6.04–7.56 (11 H, m). The aniline **17f** had m.p. 47–48 °C (from benzene–hexane); *m/z* 297 (M<sup>+</sup>); δ<sub>H</sub> 0.88 (3 H, t, *J* 7.0), 1.20 (3 H, t, *J* 7.0), 2.26 (3 H, s), 3.24 (2 H, q, *J* 6.7), 4.23 (2 H, q, *J* 7.0), 5.45 (1 H, s), 6.78 (2 H, d, *J* 8.5), 7.05 (2 H, d, *J* 8.5) and 7.28–7.60 (5 H, m). The aniline **17g** had m.p. 98–99 °C (from benzene–hexane); *m/z* 324 (M<sup>+</sup>); δ<sub>H</sub> 0.90 (3 H, t, *J* 7.1), 1.25 (9 H, s), 2.94–3.01 (1 H, m), 3.03–3.17 (1 H, m), 4.96 (1 H, s), 6.63 (1 H, s), 6.85 (2 H, d, *J* 8.3), 7.07 (2 H, d, *J* 8.3) and 7.27–7.31 (5 H, m). *N*-Methyl-*N*-trideuteriomethyl-*p*-toluidine **19** was prepared by reduction of methyl *N*-methyl-*N*-(4-methylphenyl)carbamate with LiAlD<sub>4</sub> in diethyl ether.<sup>21</sup> Other starting materials were commercially available. The following experimental details may be regarded as typical in methodology and scale.

**Reaction of *N,N*-Dimethyl-*p*-toluidine **1a** with Acetic Anhydride **5** in the Presence of CoCl<sub>2</sub>.**—A mixture of substrate **1a** (338 mg, 2.5 mmol), cobalt(II) chloride (16 mg, 0.125 mmol), and acetic anhydride (766 mg, 7.5 mmol) in acetonitrile (5 cm<sup>3</sup>) was stirred under oxygen (1 atm) at 30 °C for 4 h. Analysis by GLC–MS and GLC confirmed formation of the acetanilide **2a** (326 mg, 80%) and formanilide **3a** (48 mg, 13%). The products were also isolated by column chromatography on silica gel with hexane–ethyl acetate (85:95 v/v) as eluent. The first fraction contained the formanilide **3a** (37 mg, 10%). From the second fraction the acetanilide **2a** was obtained (305 mg, 75%).

**Products.**—The acetamides **2a–c**,<sup>22</sup> **2d**,<sup>6d</sup> **2e** and **2f**,<sup>23</sup> **2h**,<sup>24</sup> **15**,<sup>25</sup> and **16**,<sup>2e</sup> the formanilides **3a** and **3b**,<sup>26</sup> **3c**,<sup>27</sup> **3d**,<sup>28</sup> **3f** and **3g**,<sup>17</sup> and **3h**,<sup>29</sup> the anilines **4**,<sup>3a</sup> the carboxamides **9**<sup>30</sup> and **11**,<sup>22</sup> the dimerised product **12**,<sup>31</sup> and phenylglyoxylic acid deriv-

atives **18f**<sup>32</sup> and **18g**<sup>33</sup> are known and were compared with authentic specimens. The acetamide **2g** was an oil; *m/z* 189 (M<sup>+</sup>); δ<sub>H</sub> 1.76 (3 H, s), 2.27 (3 H, s), 4.18 (2 H, d, *J* 6.4), 4.94–5.01 (2 H, m), 5.18–5.81 (1 H, m), 6.94 (2 H, d, *J* 8.3) and 7.10 (2 H, d, *J* 8.3). The propionamide **10** was an oil; *m/z* 177 (M<sup>+</sup>); δ<sub>H</sub> 1.04 (3 H, t, *J* 7.3), 2.08 (2 H, q, *J* 7.3), 2.38 (3 H, s), 3.24 (3 H, s), 7.06 (2 H, d, *J* 7.8) and 7.20 (2 H, d, *J* 7.8).

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Paper 2/00059H

Received 6th January 1992

Accepted 19th February 1992