

Synthesis of Cyanobenzaldehydes (*m*-, *o*-, *p*-) by Molecular Oxygen Oxidation Methods

ZHANG, Ling-Yue(张凌越) YANG, Fan(杨帆) ZHU, Hua-Ping(朱华萍)
TANG, Jie*(汤杰) HE, Ming-Yuan(何鸣元)

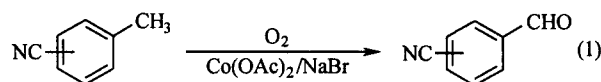
Center for the Chemistry of Ionic Liquids, Department of Chemistry, East China Normal University, Shanghai 200062, China

Cyanobenzaldehydes (*m*-, *o*-, *p*-) were synthesized by oxidation of corresponding tolunitriles with molecular oxygen, catalyzed by cobalt acetate and sodium bromide.

Keywords cyanobenzaldehyde, oxidation, molecular oxygen, tolunitrile

Cyanobenzaldehydes (*m*-, *o*-, *p*-) are valuable intermediates for the synthesis of antibacterial,¹ Factor Xa inhibitors,² anticarcinogen,³ and treatment of cardiovascular disease.⁴ Synthesis of these compounds usually involves two methods. One is chlorination or bromination of tolunitrile (*m*-, *o*-, *p*-) followed by hydrolysis of the resultant cyanobenzal chloride or cyanobenzal bromide,⁵ which is very difficult to control the reaction condition. The other is the reduction of cyanobenzoic acids,⁶ which is restricted to produce cyanobenzaldehydes in large scale for the high costs of the starting materials.

Molecular oxygen oxidation of various alkylbenzenes to aromatic aldehydes catalyzed by cobalt acetate and sodium bromide has been investigated in carboxylic acid solvent systems.⁷ We developed a new convenient method for the oxidation of tolunitriles (*m*-, *o*-, *p*-) to cyanobenzaldehydes by molecular oxygen, using cobalt(II) acetate and sodium bromide as catalysts [Eq. (1)]



The satisfactory result was achieved in the presence of 8 mol% of $\text{Co(OAc)}_2 \cdot 4\text{H}_2\text{O}$ and 5 mol% of NaBr. For comparison, the experiment was carried out in three solvent systems including acetic anhydride, the mixture of acetic acid and acetic anhydride or the mixture of chlorobenzene and acetic acid. The oxidation reactions were conducted at 90—120 °C. The results showed that the *o*-tolunitrile gave the higher substrate conversion (68.7%) and good aldehyde selectivity (85.4%) in the mixed solvent of chlorobenzene and acetic acid (10:1) at 110 °C (Entry 8). However, the *m*-tolunitrile and *p*-tolunitrile were mostly oxidized to corresponding carboxylic acid under the same condition (Entries 15 and 22). The *m*-tolunitrile and *p*-tolunitrile gave the higher aldehyde selectivity (82.4% and 85.3%, respectively) in the mixed solvent of acetic acid and acetic anhydride (1:1) at 90 °C (Entries 13 and 19). Therefore the mixed solvent of chlorobenzene and acetic acid was more effective for aldehyde selectivity of *o*-tolunitrile oxidation than those of *m*- and *p*-tolunitrile oxidation even though the higher substrate conversions of *m*- and *p*-tolunitrile were obtained under the same condition. There were three possible reasons for the above results. The first is the steric effect of *o*-cyano group, which may decrease the further oxidation reactivity of the *o*-cyanobenzaldehyde. The second is the weak intramolecular hydrogen bond between carbonyl and *o*-cyano groups, which may prevents the aldehyde from further oxidation to the corre-

* E-mail: tangecnu@sina.com

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Table 1 Reaction condition and selectivity^a

Entry	Substrate	Solv. ^b	Temp. (°C)	Time (h)	Conv. ^c	Aldehyde yield (%)	Acid yield (%)	Selectivity ^{c,d} of aldehyde (%)
1	<i>o</i> -CNC ₆ H ₄ Me	A	90	6	7.9	6.6	1.2	83.2
2	<i>o</i> -CNC ₆ H ₄ Me	A	100	6	13.2	10.7	2.4	80.9
3	<i>o</i> -CNC ₆ H ₄ Me	A	110	6	41.6	24.3	16.6	58.4
4	<i>o</i> -CNC ₆ H ₄ Me	A	120	4	70.2	27.2	41.0	38.7
5	<i>o</i> -CNC ₆ H ₄ Me	B	90	7	45.6	32.0	13.0	70.1
6	<i>o</i> -CNC ₆ H ₄ Me	B	100	7	64.3	42.2	21.0	65.6
7	<i>o</i> -CNC ₆ H ₄ Me	B	110	6	83.1	53.1	28.7	63.9
8	<i>o</i> -CNC ₆ H ₄ Me	C	110	6	68.7	58.7	9.6	85.4
9	<i>m</i> -CNC ₆ H ₄ Me	A	90	10	trace	trace	trace	—
10	<i>m</i> -CNC ₆ H ₄ Me	A	100	6	6.7	5.7	0.9	85.7
11	<i>m</i> -CNC ₆ H ₄ Me	A	110	6	71.2	33.3	36.1	46.8
12	<i>m</i> -CNC ₆ H ₄ Me	A	120	3.5	84.1	11.1	69.4	13.2
13	<i>m</i> -CNC ₆ H ₄ Me	B	90	7	43.4	35.8	7.2	82.4
14	<i>m</i> -CNC ₆ H ₄ Me	B	110	3	72.3	39.3	32.0	54.4
15	<i>m</i> -CNC ₆ H ₄ Me	C	110	3.5	94.2	9.6	81.2	10.2
16	<i>p</i> -CNC ₆ H ₄ Me	A	90	10	trace	trace	trace	—
17	<i>p</i> -CNC ₆ H ₄ Me	A	110	6	59.5	22.1	35.7	37.1
18	<i>p</i> -CNC ₆ H ₄ Me	A	120	4	87.2	6.5	76.8	7.5
19	<i>p</i> -CNC ₆ H ₄ Me	B	90	6	48.4	41.3	6.8	85.3
20	<i>p</i> -CNC ₆ H ₄ Me	B	110	6	67.5	19.8	45.8	29.4
21	<i>p</i> -CNC ₆ H ₄ Me	B	120	2.5	96.2	2.2	90.2	2.3
22	<i>p</i> -CNC ₆ H ₄ Me	C	110	2.5	97.2	1.4	93.6	1.5

^aCatalyst: Co(OAc)₂·H₂O (8 mol%), cocatalyst: NaBr (5 mol%). ^bA, (Ac)₂O; B, (Ac)₂O:HOAc (1:1 V:V); C, ClC₆H₅:HOAc (10:1 V:V). ^cSubstrate conversion and selectivity is determined with SRI 8610 GC [C₆H₅CH(OH)CN as internal standard]. Column: 25 m × 0.25 mm × 0.25 μm, crosslinked 5% Ph-Me silica; injector temperature: 250 °C; column temperature: from 55 °C, 5 °C/min, to 80 °C, 10 °C/min, to 200 °C and hold for 2 min. ^dSelectivity of aldehyde = aldehyde/(aldehyde + by-products).

sponding benzoic acid. The third is the solubility of the products. The *m*- and *p*-cyanobenzoic acids didn't dissolve in the mixed solvent of chlorobenzene and acetic acid (10:1), so the equilibrium moved to produce the corresponding carboxylic acids.

The results showed that the substrate conversion was just opposite to the aldehyde selectivity in some different solvent systems. When the conversion reached the highest value (97.2%), the aldehyde selectivity went to the lowest (1.5%), and almost all the substrate have been converted to the corresponding carboxylic acid. During the initial stage of the oxidation, the average oxidation rate of tolunitriles to cyanobenzaldehydes is higher than that of cyanobenzaldehyde to cyanobenzoic acid because the electron withdrawing effect of the cyano group increases the ionization potential of the cyanobenzalde-

hyde.⁸ Hence, an accumulation of cyanobenzaldehyde was observed in the course of reaction. Although the oxygen solubility in acetic acid was decreased at a high temperature,¹ the rate of liquid-phase air oxidation of alkylbenzenes was obviously increased and the ionization potentials of aldehyde was decreased. It was found that the substrate conversion was improved along with the increasing temperature in the same solvent systems, but the aldehyde selectivity was reversed.

The substrate conversion for the tolunitrile is low (<10%) in acetic anhydride at 90 °C (Entries 1, 9 and 16). On the contrary, it was improved (>40%) in mixture of acetic acid and acetic anhydride at the same temperature (Entries 5, 13 and 19). This kind of solvent effect on the reaction is complicated and is not clear at the moment. It might be related to the function of

acetic acid in the reaction. In acetic acid, the cobalt (II) to cobalt (III) conversion perhaps is easier than that in pure acetic anhydride. The high Co(III)/Co(II) ratio results in a great rate of oxidation.⁹

Experimental

Melting point measured with a Yanaco Mp 500 apparatus. ¹H NMR spectra were taken on a Bruker dsx-300 MHz spectrometer with tetramethylsilane as the internal standard.

General procedure

Tolunitrile (4 g, 18 mmol), Co(OAc)₂ · 4H₂O (0.32 g, 1.28 mmol), NaBr (0.096 g, 0.93 mmol) and solvents were added to a 100 mL three-necked flask fitted with a reflux condenser equipped with a drying tube, and the mixture was heated at 90–120 °C for 5 min, then oxygen was pumped for 4–6 h. After the reaction was finished, the mixture was cooled to room temperature. 20 mL of H₂O was added to the reaction mixture, and the product was extracted with ether. The organic phase was separated, dried, and concentrated. Chromatography on silica gel (10 : 1 petroleum ether-EtOAc) of the residue afforded cyanobenzaldehyde.

o-Cyanobenzaldehyde White solid; m. p. 102–104 °C (petroleum ether/EtOAc) [Lit.⁵ 104–106 °C (cyclohexane)]; ¹H NMR (CD₃COCD₃, 300 MHz) δ: 7.6–8.0 (m, 4H, ArH), 10.1 (s, 1H, CHO).

m-Cyanobenzaldehyde White solid; m. p. 73–75 °C (petroleum ether/EtOAc) (Lit.¹⁰ 76–77

°C); ¹H NMR (CD₃COCD₃, 300 MHz) δ: 7.5–8.2 (m, 4H, ArH), 10.0 (s, 1H, CHO).

p-Cyanobenzaldehyde White solid; m. p. 101–103 °C (petroleum ether/EtOAc) [Lit.¹¹ 101–102 °C (H₂O)]; ¹H NMR (CD₃COCD₃, 300 MHz) δ: 7.7–8.2 (m, 4H, ArH), 10.1 (s, 1H, CHO).

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