Carbonylation of Protected or Non-protected 2-Bromobenzaldehyde Catalyzed by Cobalt Carbonyl

Sang Chul Shim*, Dong Yub Lee, Heung Jin Choi, Chil Hoon Doh†, and Keun Tai Huh‡

**Department of Industrial Chemistry, Kyungpook National University, Taegu 701-702, Korea*
‡*Department of Materials Science and Engineering Kyungsung University, Pusan 608-736, Korea*
†*Korea Electrotechnology Research Institute, Changwon, Korea*
Received May 11, 1994

The cobalt catalyzed carbonylation of bromobenzene having protected aldehyde group gives the corresponding ester in good yields, but 2-bromobenzaldehyde gives 3-alkoxyphthalide in the noticeable yield instead of alkyl 2-formylbenzoates.

Introduction

The metal-catalyzed carbonylation of aryl halides has versatile utility in the preparative organic chemistry[1]. Of many catalysts[2] used in the carbonylation of aryl halides cobalt carbonyl species have been conducted under mild conditions, room temperature and one atmospheric pressure of carbon monoxide. More recently, using dicobalt octacarbonyl at room temperature under one atmospheric pressure of carbon monoxide many applications were reported on the carbonylation of benzal halides,[3-5] and halo (halomethyl)benzenes[6-8].

However, studies[2,9-11] on the carbonylation of aryl halides having other reactive functional groups are rare. We have reported that the cobalt-catalyzed carbonylation of 3-bromobenzenes having aldehyde and protected aldehyde groups with alcohol in the presence of catalytic amounts of $Co_2(CO)_8$ and CH_3I proceeds under one atomospheric pressure of carbon monoxide at room temperature to afford the corresponding esters[9] But, this reaction did not show any substituent effect because the substituents were at meta position to the bromide. In this article we have investigated the cobalt-catalyzed carbonylation of 2-bromobenzenes having aldehyde and protected aldehyde group, which are expected to show substituent effect and found very significant differences from the above reaction.

Results and Discussion

Treatment of 2-(2-bromophenyl)-1,3-dioxolane with CH_3I, K_2CO_3, and alcohol in the presence of a catalytic amount of $Co_2(CO)_8$ under one atomospheric pressure of carbon monoxide at room temperature gave the corresponding 2-(2-carboalkoxyphenyl)-1,3-dioxolane in good yields (eq. 1).

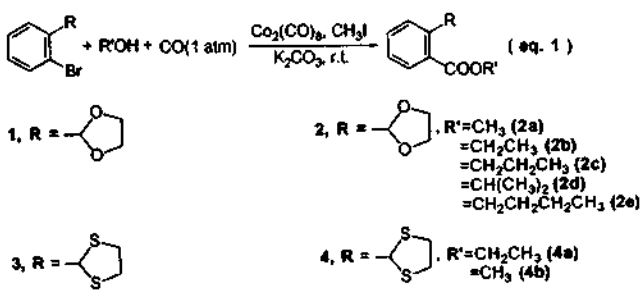


Table 1. Carbonylation of 2-Bromobenzenes Having Protected Aldehyde Groups to 2-Substituted Alkyl Benzoates Catalyzed by Cobalt Carbonyl[a]

Run	Reactant	Alcohol	Product	Yield (%)[b]
1	**1**	CH_3CH_2OH	**2b**	88
2	**1**	CH_3CH_2OH	**2b**	75[c]
3	**1**	CH_3CH_2OH	**2b**	38[d]
4	**1**	CH_3OH	**2a**	80
5	**1**	$CH_3CH_2CH_2OH$	**2c**	85
6	**1**	$(CH_3)_2CHOH$	**2d**	21
7	**1**	$CH_3CH_2CH_2CH_2OH$	**2e**	70
8	**3**	CH_3CH_2OH	**4a**	21
9	**3**	CH_3OH	**4b**	16

[a]Reactant (2.0 mmol), CH_3I (0.71 g, 5.0 mmol), $Co_2(CO)_8$ (0.034 g, 0.1 mmol), alcohol (20 ml), and K_2CO_3 (1.5 g, 10.0 mmol) were stirred under CO (1 atm) at room temperature for 5h. [b]Isolated yields. [c]50℃. [d]reflux temperature.

Several representative results were summarized in Table 1. Among the alcohols used in the reaction, *primary* alcohols such as methanol, ethanol, *n*-propanol, and *n*-butanol gave the good yield of the corresponding 2-(2-carboalkoxyphenyl)-1,3-dioxolane, but the yield was greatly decreased in *secondary* alcohol, 2-propanol. Such trends might be explained in terms of the solubility of K_2CO_3 and steric effect in the corresponding alcohols.

In the case of 2-(2-bromophenyl)-1,3-dithiane, the reactions proceeded only in ethanol and methanol and the chemical yields were not great due to sulfur group which was the catalyst poisoner and bulkier than acetal group. The reaction mechanism is well known according to published results[2,8].

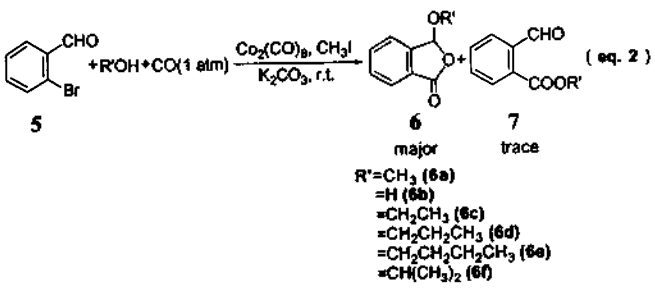
The carbonylation of 2-bromobenzaldehyde gave unexpected results. In the same reaction condition, 2-bromobenzaldehyde gave the 3-alkoxyphthalides as carbonylative cyclized products in noticeable yield, instead of the corresponding ester products (eq. 2). In the previous paper[9], the carbonylation of 3-bromobenzaldehyde gave the corresponding alkyl 3-formylbenzoate in good yields.

Several representative results were summaried in Table 2. Among the alcohols used in the reaction, ethanol gave

Table 2. Carbonylation of 2-Bromobenzaldehyde to 3-Alkoxyphthalides Catalyzed by Cobalt Carboyl[a]

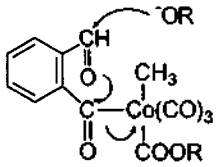
Run	Reactant	Alcohol	Product (6)	Yield (%)[b]
1	5	CH_3OH	**6a**	trace
2	5	CH_3OH	**6b**	53[c]
3	5	CH_3CH_2OH	**6c**	53
4	5	$CH_3CH_2CH_2OH$	**6d**	26
5	5	$CH_3CH_2CH_2CH_2OH$	**6e**	36
6	5	$(CH_3)_2CHOH$	**6f**	trace

[a]Reactant (2.0 mmol), CH_3I (0.71 g, 5.0 mmol), $Co_2(CO)_8$ (0.034 g, 0.1 mmol), alcohol (20 m*l*), and K_2CO_3 (1.5 g, 10.0 mmol) were stirred under CO (1 atm) at room temperature for 5h. [b]Isolated yields, [c]after the reaction solution was concentrated under reduced pressure and acidified with 10% HCl, a 3-hydroxyphthalide was obtained by extraction.



the highest yield and higher alcohols such as *n*-propanol and *n*-butanol gave the lower yields because of solubility of K_2CO_3 in the corresponding alcohols. In the case of methanol, only a trace amount of 3-methoxyphthalide was obtained, and after acidifying the reaction mixture with 10% HCl, a hydrolysed product, 3-hydroxyphthalide, obtained in a 53% isolated yield.

A possible intermediate leading to the 3-alkoxyphthalides **6** may be cobalt species(III) **8**[2,10]. It is likely that 3-alkoxyphthalides were formed *via* the nucleophilic attack of the *generated* alkoxide to the formyl carbon of **8** followed by the intramolecular cyclization[10-13]. The reason must be that *generated* alkoxide would prefer to attack to the formyl carbon than the aroyl carbon bonded to the cobalt carbonyl moiety because of steric hindrance.



8

Application and regioselective synthesis of 3-alkoxyphthalide is currently in progress.

Experimental

A mixture of 2-bromobenzaldehyde (0.37 g, 2.0 mmol), anhydrous potassium carbonate (1.4 g, 10.0 mmol), absolute ethanol (20 m*l*), iodomethane (0.71 g, 5.0 mmol), and dicobalt octacarbonyl (0.034 g, 0.10 mmol) was stirred under the atmospheric pressure of carbon monoxide at room temperature for 5 hours. After purging carbon monoxide, the reaction mixture was filtered through the short column (silica gel, 5 cm, ether), concentrated, and purified by the preparative thin layer chromatography (silica gel, ethyl acetate: *n*-hexane=3 : 10) to give 3-ethoxylphthalide (53%). In the same reaction condition, 2-(2-bromophenyl)-1,3-dioxolane and 2-(2-bromophenyl)-1,3-dithiane were carbonylated to give the corresponding esters.

Analytical data of 3-alkylphthalides were as follows

3-Ethoxyphthalide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J=7.1, 3H, CH_3), 3.84 (m, J=10.6, J=7.06, decoupled, 1H), 3.96 (m, J=10.6, J=7.06, decoupled, 1H), 6.33 (s, 1H, CH), 7.50-7.80 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 65.8, 102, 123, 125.3, 127.1, 130.7, 134.3, 144.9, 166.7; IR (ν_{max}) 1784 cm^{-1}; Anal. Cald for $C_{10}H_{10}O_3$; C, 67.42; H, 5.69. Found: C, 67.56; H, 5.79.

3-Methoxyphthalide. ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H, OCH_3), 6.20 (s, 1H, CH), 7.46-7.75 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 56.4, 102, 123.2, 124.9, 126.7, 130.5, 134.1, 144.4, 166.2; Mass (m/e) 164(M^+), 163 (1), 133 (31).

3-Hydroxyphthalide. ^{1}H NMR ($CDCl_3$) δ 5.33 (br, 1H, OH), 6.64 (s, 1H, CH), 7.53-7.82 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 97.9, 123.4, 125.3, 126.6, 130.8, 134.6, 146.3, 169; Mass (m/e) 134 (9), 133 (100), 105 (16).

3-Propylphthalide. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, CH_3), 1.68 (m, 2H, CH_2), 3.75 (m, 1H), 3.84 (m, 1H), 6.31 (s, 1H, CH), 7.35-7.92 (m, 4H, Ar-H); Mass (m/e) 191 (7), 149 (13), 148 (17), 133 (100), 134 (10), 132 (89).

3-Butylphthalide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=10.1, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 3.75 (dt, J=14.0, J=9.7, 1H), 3.86 (dt, J=14.0, J=9.7, 1H), 6.33 (s, 1H, CH), 7.5-7.8 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.0, 31.4, 69.9, 102.4, 123.3, 125.2, 127.1, 130.6, 134.2, 145.0, 168.6; Mass (m/e) 206(M^+, 1), 205 (1), 149 (6), 148 (5), 134 (10), 133 (100), 132 (94), 105 (34), 104 (32).

3-^{i}Propylphthalide. ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 6H, 2 CH_3), 4.18 (m, 1H, OCH), 6.38 (s, 1H, CH), 7.49-7.80 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.1, 73.6, 101.3, 123.2, 125.1, 127.0, 130.6, 134.2, 145.4, 168.8; Mass (m/e) 192 (M^+, 1), 151 (6), 150 (3), 149 (37), 148 (41), 147 (19), 134 (17), 133 (100), 132 (26).

Analytical data of the representative 2-(3-carboalkoxyphenyl)-1,3-dioxolane and 2(3-carboalkoxyphenyl)-1,3-dithiane were as follows

2-(3-Carbomethoxyphenyl)-1,3-dithiane. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 4H, $(CH_2)_2$), 3.91 (s, 3H, OCH_3), 6.53 (s, 1H, CH), 7.06-7.76 (m, 2H, aromatic H), 7.71-8.04 (m, 2H, aromatic H); Mass (m/e) 255 (13), 254 (M^+, 100), 223 (23), 222 (51), 181 (17), 179 (42), 149 (63), 121 (42), 119 (19), 105 (38); IR (ν_{max}) 1717 cm^{-1}.

2-(3-Carbomethoxyphenyl)-1,3-dioxolane. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H, OCH_3), 4.00 (s, 4H, $(CH_2)_2$), 6.50 (s, 1H, CH), 7.35-7.55 (m, 2H, aromatic H), 7.57-7.95 (m, 2H, aromatic H); Mass (m/e) 208 (M^+, 15), 207 (100), 193 (15), 177 (36), 163 (82), 149 (42), 136 (23), 135 (23), 133 (25), 119 (21), 105 (59), 77 (32), 73 (88); IR (ν_{max}) 1724 cm^{-1}.

2-(3-Carboethoxyphenyl)-1,3-dioxolane. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, CH_3), 3.91 (s, 4H, $(CH_2)_2$), 4.32 (q, 2H, OCH_2), 6.50 (s, 1H, CH), 7.26-7.55 (m, 2H, aroma-

tic H), 7.57-7.88 (m, 2H, aromatic H); Mass (m/e) 223 (M^+, 8), 221 (53), 193 (21), 177 (57), 149 (42), 105 (36), 77 (16), 73 (100); IR (ν_{co}) 1771 cm^{-1}.

Acknowledgement. This work was supported by the Organic Chemistry Research Center the Korea Science & Engineering Foundation and by the Basic Science Research Institute Program, Ministry of Education of Korea (BSRI-94-3408).

References

1. Weil, T. A.; Cassar, L.; Foa M. *Organic Syntheses via Metal Carbonyls*; Wender, I.; Pino, P. eds.; Wiley: New York, **1977**, *2*, 517.
2. Foa, M.; Francalanci, F.; Bincini, E.; Gardano, A. *J. Organomet. Chem.* **1985**, *285*, 293, *ibid.* **1986**, *301*, C27.
3. Shim, S. C.; Doh, C. H.; Park, W. H.; Kwon, Y. G.; Lee, H. S. *J. Organomet. Chem.* **1990**, *382*, 419.
4. Shim, S. C.; Doh, C. H.; Cho, C. S. *Bull. Korean. Chem. Soc.* **1990**, *11*, 474.
5. Shim, S. C.; Doh, C. H.; Lee, D. Y.; Youn, Y. Z.; Lee, H. S.; Chae, S. A.; Oh, H. *ibid.* **1992**, *13*, 20.
6. Shim, S. C.; Doh, C. H.; Youn, Y. Z.; Cho, C. S.; Woo, B. W. *J. Kor. Chem. Soc.* **1990**, *34*, 658.
7. Shim, S. C.; Doh, C. H.; Youn, Y. Z.; Cho, C. S.; Woo, B. W.; Oh, D. H. *ibid.* **1991**, *35*, 90.
8. Shim, S. C.; Doh, C. H.; Lee, D. Y.; Youn, Y. Z.; Lee, H. S.; Chae, S. A.; Oh, D. H.; Oh, H. *Bull. Korean Chem. Soc.* **1992**, *13*, 45.
9. Shim, S. C.; Doh, C. H.; Youn, Y. Z.; Lee, D. Y.; Lee, H. S.; Chae, S. A.; Oh, H. *Bull. Korean Chem. Soc.* **1992**, *13*, 444.
10. Miura, M.; Okuro, K.; Itoh, K.; Nomura, M. *J. Mol. Catal.* **1990**, *59*, 11.
11. Kashimura, T.; Kudo, K.; Mor, S.; Sugita, N. *Chem. Lett.* **1986**, 483.
12. Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Sbibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725.
13. Negishi, E. I.; Tour, J. M. *Tetrahedron Lett.* **1986**, *27*, 4869.

Comparable Structural Stabilities of Penta- and Hexa-coordinate Zn(II) in a Simple Model System of the Active Site of Carboxypeptidase A

Sik Lee, Seung Joo Cho, Jong Keun Park, Hag-Sung Kim, and Kwang S. Kim*

Center for Biofunctional Molecules and Department of Chemistry, Pohang University of Science and Technology, San 31, Hoyjadong, Pohang 790-784, Korea

Received May 8, 1994

Ab initio studies of simple model systems for the carboxypeptidase A active site indicate that penta- and hexa-coordinate Zn(II) complexes have comparable structural stabilities. These facile coordination structures can be responsible for the catalytic role. Although the hexa-coordinate Zn(II) complex is more stable in enthalpy than the penta-coordinate Zn(II) complex, the entropy effect makes the latter as stable as or slightly more stable in free energy than the former.

Introduction

Zinc chemistry is an area of great importance because its occurrence in biology is second only to that of iron among transition elements. More than 80 enzymes containing zinc have been reported[1]. For example, zinc is essential in biological functions of enzymes such as carboxypeptidase, alcohol dehydrogenase, carbonic anhydrase, β-lactamase and phospholipase. Bovine carboxypeptidase A (CPA) catalyzes the cleavage of the peptide bond of C-terminal amino acids. The hydrolytic mechanism of this enzyme has attracted much interest as a prototype of mechanistic study of metalloprotease, but is still of much controversy[2-5]. It is known that the zinc ion in the metalloprotease plays a central role in the catalytic mechanism from the fact that the complete loss of catalytic activity is observed in the case of apoenzyme[6]. X-ray study reported that the zinc ion in CPA is coordinated by two histidines (His-69 and His-198), a bidentate glutamate (Glu-72), and water molecules[7]. The distances from Zn^{2+} to the nearest water oxygen atoms are 2.05 and 3.23 Å (Table 1). Then, the number of ligating water molecules can be regarded as either one or two, because the second nearest water oxygen is in between first and second hydration shell water oxygens[8]. In complexation of CPA with inhibitors, the coordination number of Zn^{2+} varies between 5 and 6[9,10]. Previously, we studied the hydration structures[11] and ammoniation structures[12] of Zn, finding that the coordination number of the hydration slightly favors 6, while that of the ammoniation favors 4. Here, we study very simple model systems around Zn^{2+} mimicking the active site of CPA. Since the Zn^{2+}-ligand complexation in CPA is directly related to the enzymatic mechanism of CPA, we focus on the coordination structure of Zn^{2+}.