

Regioselective Carboxylation of Phenols with Carbon Dioxide

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A few novel methods were developed for the regioselective preparation of *p*-hydroxybenzoic acid (*p*HBA) and its amino derivative by means of the Kolbe–Schmitt reaction. Thus, the carboxylation of tetraalkylammonium phenoxide at 125 °C under the CO₂ pressure of 5.0 MPa in the presence of K₂CO₃ gave *p*HBA in a maximum yield of 56% with the regioselectivity of 97–100%. The carboxylation of potassium phenoxide (PhOK) at 230 °C under the CO₂ pressure of 0.5 MPa also gave *p*HBA regioselectively in a 39% yield, together with unaltered phenol (61%). Under such conditions, the potassium salt of salicylic acid (SA) once formed was transformed into *p*HBA. Heat treatment of the dipotassium salt of ¹³C labeled SA indicated that the transformation occurs via two pathways, i.e., the intramolecular rearrangement of the salicylate (66%) and the decarboxylation of the salicylate followed by the recarboxylation of the resulting PhOK (34%). Furthermore, the carboxylation of cesium *m*-aminophenoxide and 5-amino-1-naphthoxide with CO₂ gave regioselectively 4-hydroxyanthranilic and 8-amino-4-hydroxy-1-naphthoic acids, respectively, in good yields. This is a simple one-pot reaction giving these industrially useful acids with good yields.

The most convenient and popular method for the preparation of aromatic hydroxycarboxylic acids is the carboxylation of alkali metal phenoxides (PhOM) with carbon dioxide (CO₂). The reaction is known as the Kolbe–Schmitt reaction and has been used for over a century.¹ It has been thought for a long time¹ that the reaction proceeds via a complex (PhOM·CO₂) composed of PhOM and CO₂. However, recent mechanistic studies² have revealed that the reaction proceeds by a direct attack of CO₂ on the benzene ring. The attack occurs on electron-rich *ortho* and *para* positions to give salicylic acid (SA) and *p*-hydroxybenzoic acid (*p*HBA). It is favorable for the industrial production that the attack occurs regioselectively on the *para* position, since *p*HBA and 6-hydroxy-2-naphthoic acid (2H6NA) prepared from phenol and 2-naphthol, respectively, are key compounds for totally aromatic liquid-crystal polymers. We recently found³ that cesium phenoxide and 2-naphthoxide give *p*HBA and 2H6NA, respectively, in much higher yields than the widely used methods with sodium or potassium phenoxide and 2-naphthoxide. The prominently selective carboxylation is ascribed to the large ionic radius (0.169 nm^{4a}) of cesium, which interferes with the direct attack of CO₂ at the *ortho* positions of the phenoxide and naphthoxide. Sodium and potassium are too small in ionic radii (0.095 and 0.133 nm, respectively^{4a}) to interfere effectively with the CO₂ attack at the *ortho* positions.

The present paper describes some experiments directed toward other methods for the regioselective preparation of *p*HBA by the Kolbe–Schmitt reaction. First, we describe the carboxylation of tetraalkylammonium phenoxides (PhONR₄), in place

of PhOM, by CO₂. Tetraalkylammonium ions (R₄N⁺) have larger ionic radii (0.347, 0.400, 0.452, and 0.494 nm for Me₄N⁺, Et₄N⁺, Pr₄N⁺, and Bu₄N⁺, respectively^{4b}) than alkali metal ions and will effectively interfere with the attack of CO₂ at the *ortho* positions of PhONR₄ to give selectively *p*HBA. Second, we describe the carboxylation of PhOK at high temperature and low CO₂ pressure, at which mono- (SAK₁) and dipotassium salicylates (SAK₂) are transformed into potassium salts of *p*HBA.^{5,6} The mechanism of the transformation is also discussed on the basis of experiments with ¹³C-labeled SAK₂. Finally, we describe the regioselective carboxylation of cesium *m*-aminophenoxide and 5-amino-1-naphthoxide with CO₂ to give industrially useful 4-hydroxyanthranilic acid and 8-amino-4-hydroxy-1-naphthoic acid, respectively.

Experimental

Reagents. Phenol, *m*-aminophenol, and alkali metal hydroxides (NaOH, KOH, and CsOH·H₂O) were purchased from Kanto Chemical Co. 5-Amino-1-naphthol, carbonates (Na₂CO₃ and K₂CO₃), and sulfate (K₂SO₄) were supplied by Wako Pure Chemical Industries. Tetramethyl- (Me₄NOH), tetraethyl- (Et₄NOH), tetrapropyl- (Pr₄NOH), and tetrabutylammonium hydroxides (Bu₄NOH) were purchased from Aldrich Chemical Co. These chemicals were of guaranteed grade and were used without further purification. CO₂ of purity more than 99.9% and nitrogen were supplied by Sanin Sanso Co. ¹³C-enriched CO₂ (more than 99%) was supplied by ISOTEC INC (Miami, Ohio, USA).

Preparation of PhONR₄. Me₄NOH (0.8 mL of 25 wt % aqueous solution, 2.3 mmol) and phenol (0.2 g, 2.1 mmol) were added to 50 mL of water and stirred for 2–3 min. When necessary, an additive (K₂CO₃, Na₂CO₃, or K₂SO₄) was mixed together. The solution was concentrated on a rotary evaporator at 45 °C. The concentrated solution was lyophilized in a flask at <10 Pa for 30–40 h

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to give tetramethylammonium phenoxide (PhONMe₄). PhONe₄, PhONPr₄, and PhONBu₄ were prepared similarly by mixing phenol (0.2 g, 2.1 mmol) with Et₄NOH (1.0 mL of 35 wt % aqueous solution, 2.3 mmol), Pr₄NOH (2.1 mL of 20 wt % aqueous solution, 2.3 mmol), and Bu₄NOH (1.5 mL of 40 wt % aqueous solution, 2.3 mmol), respectively.

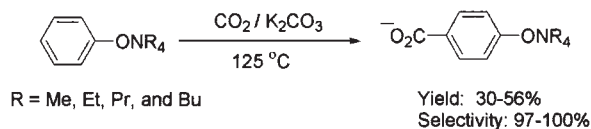
Preparation of PhOM. Phenol (5.00 g, 53.2 mmol) was dissolved in a 100 mL of aqueous solution containing 10% excess alkali metal hydroxides. Water was removed on a rotary evaporator at 80 °C, followed by vacuum drying at 180 °C for 3 h. The prepared phenoxides were ground to fine powders in a dry box under dry nitrogen stream.

General Reactions and Analyses. The prepared PhONR₄ or PhOM was placed in an autoclave (200 mL) and CO₂ of a requisite pressure was introduced after flushing with nitrogen. The autoclave was heated quickly to the reaction temperature and maintained there for a requisite reaction time. The reaction mixture in the autoclave was then cooled in a water bath and next dissolved in a small amount of aqueous methanol. The solution was acidified (pH 3–4) with the addition of dilute HCl and analyzed by high-performance liquid chromatography (HPLC) with a column (ODS column 150 × 4.6φ mm) on a Shimadzu LC-10 AD chromatograph. ¹H NMR spectra were taken in CDCl₃ using tetramethylsilane as an internal standard on a JEOL JNM-A400 (400 MHz) spectrometer. Mass spectra were obtained at 70 eV on a Hitachi M-80B spectrometer. All the products were known and were identified by comparing the retention times in HPLC, ¹H NMR spectra, and mass spectra with those of the authentic samples.

Results and Discussion

Carboxylation of PhONR₄. PhONR₄ was subjected to carboxylation under conditions employed in the usual Kolbe–Schmitt reaction. The results are summarized in Table 1. Reaction temperature (125 °C) was somewhat lower than usual (150 °C), since it seemed that PhONR₄ was labile and decomposed to give brownish products at 150 °C. Interestingly, the regioselectivity of the carboxylation for *p*HBA was very high, i.e., 96% for PhONMe₄ and PhONe₄, and virtually 100% for PhONPr₄ and PhONBu₄. It is evident that these cations are large enough in size to interfere with the attack of CO₂ on the *ortho* positions of the phenoxide. However, the yields of

*p*HBA were low (7–27%), and significant amounts of unaltered phenol were recovered (72–93%). We could not increase the yield of *p*HBA by changing reaction time, temperature, or the mole ratio of the hydroxide to phenol. The only effective method we found was the addition of K₂CO₃ to the reactant. Thus, the carboxylation of PhONMe₄ (2.12 mmol) in the presence of K₂CO₃ (1 g, 7.22 mmol) gave *p*HBA in a 56% yield, together with a small amount of alkyl esters of *p*HBA, and the recovery of unaltered phenol decreased to 37%. The regioselectivity for *p*HBA was virtually unchanged (97%). The improving effect of K₂CO₃ was also found in the other PhONR₄, though the yields (30–35%) of *p*HBA were significantly less than that in the case of PhONMe₄ (Scheme 1). The addition of K₂SO₄, in place of K₂CO₃, to the reactant showed no improving effect, whereas Na₂CO₃ showed an improving effect similar to that of K₂CO₃. It is not clear why K₂CO₃ shows such an improving effect. We can rule out the possibility that K₂CO₃ contributed to increasing the surface area of the reactant in contact with CO₂, since K₂SO₄ showed no such effect. A possible explanation is as follows: The reactant phenol is monobasic acid, whereas the product *p*HBA is dibasic acid. Since the carboxyl group is stronger in acidity than phenol, the carboxyl group of *p*HBA formed will react with neighboring PhONR₄ to give the carboxylate ion and inactive phenol. If K₂CO₃ is present in the neighborhood of *p*HBA, the carboxyl group is neutralized by K₂CO₃, and the phenoxide is not consumed for the neutralization of the carboxyl group. There was a fear that a cation-exchange reaction occurs between PhONR₄ and K₂CO₃ to form PhOK, of which the regioselectivity for *p*HBA is considerably lower than PhONR₄. However, the regioselectivity was unchanged by the addition of K₂CO₃, indicating that the effect of the cation-exchange reaction is mi-



Scheme 1. Regioselective preparation of *p*HBA by the Kolbe–Schmitt reaction of PhONR₄.

Table 1. Products in the Carboxylation of PhONR₄ (2.1 mol)^{a)} with CO₂ (5.0 MPa) in a 200 mL Autoclave

Entry	R	Additive mmol	Reaction condition		Recov. phenol /%	Yield ^{b)} /%				Selectivity for <i>p</i> HBA ^{d)}
			Temp. /°C	Time /h		SA	<i>p</i> HBA	4HIPA	Ester ^{c)}	
1	Me	None	125	2	71.9	1.0	26.5	0.5	0	96
2	Me	K ₂ CO ₃ (7.22)	125	2	37 ± 5	2 ± 0	56 ± 4	3 ± 1	1.4 ± 0.2	97 ± 1
3	Me	K ₂ SO ₄ (7.22)	125	2	90.6	0.6	8.6	0	0	93
4	Et	None	125	5	85 ± 2	0.5 ± 0.1	14 ± 2	trace	0	96 ± 1
5	Et	None	150	2	84.6	3.9	11.3	trace	0	74
6	Et	K ₂ CO ₃ (7.22)	125	2	64 ± 1	0.5 ± 0	30 ± 1	trace	1.0 ± 0.1	99 ± 1
7	Pr	None	125	2	92.8	0	7.1	0	0	100
8	Pr	K ₂ CO ₃ (7.22)	125	2	67 ± 1	trace	30 ± 1	0	3.1 ± 0.9	>99
9	Bu	None	125	5	89 ± 3	trace	11 ± 3	0	trace	>99
10	Bu	K ₂ CO ₃ (7.22)	125	5	56 ± 1	0	35 ± 1	0	10 ± 1	100

a) PhONR₄ was prepared under conditions of [R₄NOH]/[PhOH] = 1.1–1.5. b) The mean and standard error are shown for duplicated or triplicated runs. c) The corresponding alkyl *para*-hydroxybenzoates. d) The selectivity was calculated based on the yields of *p*HBA and the corresponding ester, but 4HIPA was not included.

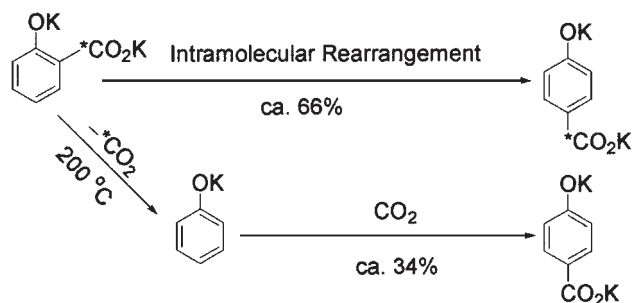
Table 2. Products in the Reactions of PhOK (3.78 mmol), SAK₁ (2.84 mmol), SAK₂ (2.33 mmol), pHBAK₁ (2.84 mmol), and pHBAK₂ (2.33 mmol) under High (5.0 MPa) or Low (0.5 MPa) CO₂ Pressure for 1 h in a 200 mL Autoclave

Entry	Reactant	Reaction condition		Yield			
		CO ₂ /MPa	Temp. /°C	phenol	SA	pHBA	4HIPA
1	PhOK	0.5	230	61.1	0.0	38.8	trace
2	PhOK	5.0	230	17.0	54.5	2.1	26.0
3	SAK ₁	0.5	200	34.2	24.6	40.6	0.8
4	SAK ₂	0.5	200	55.0	6.9	34.7	1.0
5	SAK ₁	5.0	200	17.4	74.2	trace	8.6
6	SAK ₂	5.0	200	1.3	62.1	22.8	13.9
7	pHBAK ₁	0.5	200	35.2	2.0	60.9	1.0
8	pHBAK ₂	0.5	200	4.0	0.0	96.0	trace
9	pHBAK ₁	5.0	200	45.3	4.7	48.5	1.7
10	pHBAK ₂	5.0	200	1.1	1.9	95.6	1.3

nor, if any. The R₄N⁺ and PhO[−] ions have large polarizability, and belong to soft acid and base classes, respectively.⁷ On the other hand, K⁺ and CO₃^{2−} belong to hard acid and base classes, respectively. Thus, the soft PhO[−] ion prefers to associate with the soft R₄N⁺ ion, rather than with the hard K⁺ ion.⁷

Carboxylation of PhOK at High Temperature and Low Pressure. It is known^{5,6} that mono- (SAK₁) and dipotassium salicylates (SAK₂) are rapidly converted to the salts of pHBA at high temperature above 200 °C and low pressure. Thus, it is anticipated that the carboxylation of PhOK at high temperature and low CO₂ pressure will give regioselectively pHBA, since the salicylate once formed is converted to pHBA during reaction. In fact, the carboxylation of PhOK at 230 °C and CO₂ pressure of 0.5 MPa gave exclusively pHBA in a yield of 34–39% (Table 2), though the recovery of unaltered phenol was significantly high (61–65%). Only minor amounts of SA (less than 0.7%) and 4-hydroxyisophthalic acid (4HIPA, less than 0.1%) were found in the reaction mixture. This result was in sharp contrast to the carboxylation at higher CO₂ pressure of 5.0 MPa: The recovery of phenol was only 17%, and SA and 4HIPA were the main products (55 and 26%, respectively). The yield of pHBA was only 2%. It is evident that the salicylate once formed by the direct attack of CO₂ on the *ortho* positions of the phenoxide is transformed into the potassium salt of pHBA at low CO₂ pressure of 0.5 MPa. The activation volume of the salicylate for transformation into pHBA may be so large that the reaction is unlikely to occur at high CO₂ pressure. In order to confirm this assumption, SAK₁ and SAK₂ were treated at 200 °C for 1 h under the CO₂ pressures of 0.5 and 5.0 MPa (Table 2). The recovery of unaltered SA was 25% for SAK₁ and only 7% for SAK₂ under the CO₂ pressure of 0.5 MPa, whereas the values were 74% for SAK₁ and 62% for SAK₂ under the CO₂ pressure of 5.0 MPa, indicating that the salicylates are reactive at low CO₂ pressure and relatively stable at high CO₂ pressure. SAK₁ and SAK₂ gave pHBA in 41% and 35% yields, respectively, together with significant amounts of phenol (28–34%) formed by decarboxylation, after the treatment under the CO₂ pressure of 0.5 MPa. On the other hand, the treatment at the high CO₂ pressure of 5.0 MPa gave only a trace amount of pHBA for SAK₁ and a significant amount (23%) of pHBA for SAK₂, together with 4HIPA (9–14%).

These data show that low CO₂ pressure is advantageous for the regioselective preparation of pHBA. Table 2 also contains experimental data in the case of pHBA. The mono- and dipotassium salts of pHBA were treated under the same conditions as the salicylates. The dipotassium salt of pHBA was stable, and the recovery of pHBA after treatment was 96%, irrespective of applied CO₂ pressure. The monopotassium salt was less stable, and the recovery decreased to 49–61%. The main product was phenol (35–45%), and small amounts of SA and 4HIPA were involved. The results indicate that the potassium salts of pHBA are thermodynamically more stable than those of SA. In order to clarify the pathways in the transformation of the salicylate into the salt of pHBA, we prepared SA (SA*) labeled at the carboxyl group with ¹³C,^{2g} and the dipotassium salt of SA* was subjected to heat treatment under the same conditions as described above. The reaction products were esterified to give methyl *p*-hydroxybenzoate (MepHBA) and analyzed by GC/MS as previously reported.^{2g} The relative peak intensities of *m/z* 152 and *m/z* 153 were 100 and ca. 203, respectively, for MepHBA produced by heat treatment under the CO₂ pressure of 0.5 MPa. Virtually the same result was obtained for MepHBA given by treatment under the CO₂ pressure of 5.0 MPa. Considering the natural abundance of ¹³C (1.1% for each C), we evaluated that ca. 66% of pHBA is transformed by the intramolecular rearrangement from the salicylate.⁸ The rest (34%) of pHBA will be produced via the decarboxylation of the salicylate, followed by recarboxylation at the *para* position of the phenoxide (Scheme 2).

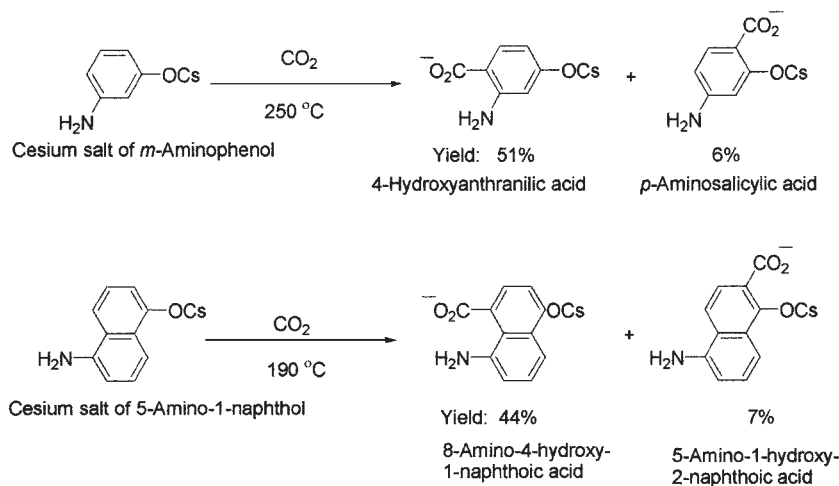


Scheme 2. Two pathways from dipotassium salt of SA to that of pHBA.

Table 3. Products in the Carboxylation of Alkali Metal Salts of Aminophenols with CO₂ (5.0 MPa) in a 100 mL Autoclave

Entry	Phenols	Alkali metal	Reaction condition			Yield /%	
			CO ₂ /MPa	Temp. /°C	Time /h	<i>o</i> -COOH ^{a)}	<i>p</i> -COOH ^{b)}
1	<i>m</i> -Aminophenol	Na	5	200	1	80.0	0
		K	5	200	1	80.0	0
		Cs	5	250	1	5.9	50.6
2	5-Amino-1-naphthol	Na	5	160	3	53.5	0
		K	5	230	5	72.1	0
		Cs	5	190	10	7.2	43.9

a) *ortho*-Carboxylated products, i.e., *p*-aminosalicylic acid for *m*-aminophenol and 5-amino-1-hydroxy-2-naphthoic acid for 5-amino-1-naphthol. b) *para*-Carboxylated products, i.e., 4-hydroxyanthranilic acid for *m*-aminophenol and 8-amino-4-hydroxy-1-naphthoic acid for 5-amino-1-naphthol.



Scheme 3. Regioselective carboxylations of cesium salts of aminophenols.

Carboxylations of Cesium Salts of Aminophenols. We recently found³ that cesium phenoxide and 2-naphthoxide give *p*HBA and 2H6NA, respectively, in much higher yields than the widely used methods with sodium or potassium phenoxide and 2-naphthoxide. The selective carboxylation is ascribed to the large ionic radius of cesium, which interferes with the direct attack of CO₂ at the *ortho* positions of the phenoxide and naphthoxide. In the present work, we extended the method to the regioselective preparation of industrially useful 4-hydroxyanthranilic and 8-amino-4-hydroxy-1-naphthoic acids from *m*-aminophenol and 5-amino-1-naphthol, respectively. According to reports,⁹ *m*-aminophenol gives only *p*-aminosalicylic acid by the ordinary Kolbe–Schmitt reaction with sodium or potassium salts, but not 4-hydroxyanthranilic acid at all. Thus, we investigated an effect of alkali metal ion on product composition after the carboxylation of *m*-aminophenoxide (Table 3). The carboxylation of sodium or potassium salt of *m*-aminophenol under the CO₂ pressure of 5.0 MPa gave only *p*-aminosalicylic acid in a 80% yield. In sharp contrast, the cesium salt gave selectively 4-hydroxyanthranilic acid in a 51% yield, together with a small amount (6%) of *p*-aminosalicylic acid (Scheme 3). This is the simplest one-pot reaction giving the best yield among a number of synthetic methods¹⁰ for 4-hydroxyanthranilic acid. We also examined an effect of alkali metal ion on the product composition after the carboxylation

of 5-amino-1-naphthoxide (Table 3). Upon carboxylating the cesium salt, we obtained 8-amino-4-hydroxy-1-naphthoic acid in a good yield (44%), together with 5-amino-1-hydroxy-2-naphthoic acid as a minor product (7%). On the other hand, the sodium and potassium salts gave only 5-amino-1-hydroxy-2-naphthoic acid (54 and 72% yields, respectively). The markedly regioselective *para*-carboxylation of the cesium aminophenoxides will be attributed to the large ionic radius of the cesium ion, which interferes with the direct attack of CO₂ at the *ortho* positions of the aminophenoxides.

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8 In this calculation, we assumed that the incorporation of $^{13}\text{CO}_2$ into pHBA via the decarboxylation–recarboxylation pathway was negligible, since the amount of $^{13}\text{CO}_2$ released from the dipotassium salt of SA* was far less than that of added CO_2 . Based on the natural abundance of ^{13}C , we estimated the relative amounts of labeled and unlabeled MepHBA from the GC/MS data as fol-

lows: The unlabeled MepHBA gives the peak of m/z 153 with the relative height of ca. 9 ($= 100 \times 0.088$). Then, the relative height of m/z 153 due to the labeled MepHBA is 194 ($= 203 - 9$). The labeled MepHBA also contains ^{13}C due to natural abundance and gives the peak of m/z 154 with the relative height of 15 ($= 194 \times 0.077$). Thus, the total relative peak heights of labeled and unlabeled MepHBA are 209 ($= 194 + 15$) and 109 ($= 100 + 9$), respectively, and the relative amounts of labeled and unlabeled MepHBA are 66% [$= 100 \times 209 / (209 + 109)$] and 34%, respectively.

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