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One-Step O-Demethyl-Decarboxylation of ortho-Methoxy Aromatic **Carboxylic Acids**

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Abstract A highly selective decarboxydemethylation of o-methoxyarenecarboxylic acids is described. The reaction takes place in DMPU at 170 °C in the presence of TMEDA and iron powder. A similar reaction has not been reported until now.

Key words ether C–O cleavage, decarboxylation, aryl methyl ethers, phenols, iron catalysis

In recent years, metal-catalyzed decarboxylation of aromatic carboxylic acids has been studied extensively.^{1,2} Recently, we disclosed a new efficient and inexpensive catalytic system (Cu/TMEDA) to perform this reaction.³ We were surprised to observe that, under these conditions, the reaction of o-anisic acid leads not only to anisole, the expected decarboxylated product, but also to a significant amount (38%) of phenol resulting from decarboxydemethylation (Scheme 1).



As mentioned above, several procedures to perform the metal-catalyzed decarboxylation of aromatic carboxylic acids have been described previously.^{1,2} On the other hand, several methods have also been reported to cleave aryl methyl ethers.⁴ For example, two procedures are frequently used, the treatment with BCl₃ or BBr₃ at low temperature^{4,5}

or the reaction with an excess of EtSNa in refluxing DMF.^{4,6} However, no procedure has been reported to perform the one-pot O-demethyl-decarboxylation of o-methoxy aromatic carboxylic acids. Since it seemed to us that such a new selective procedure could be interesting, we decided to study the reaction described above, while trying to improve the yield of phenol (Table 1).

Table 1 Optimization of Reaction Conditions^a

СООН TMEDA Yield Solvent Catalyst (equiv) (%) 3 Cu₂O (5 mol%) NMP 38 3 NMP 62 1.2 NMP 60 NMP

5	1.2	NMP	$FeCl_2$ (20 mol%)	72
6	1.2	NMP	FeCl ₃ (20 mol%)	69
7	1.2	NMP	Fe (20 mol%) ^b	76
8	1.2	DMPU	Fe (10 mol%) ^b	74
9	1.2	DMPU	Fe (20 mol%) ^b	82
10	1.2	DMPU	Fe (50 mol%) ^b	53

^a Reaction conditions: carboxylic acid (5 mmol), TMEDA, cat., solvent,

170 °C. 24 h.

Entry

1

2

3

4

^b Iron powder 99%, 100 mesh, STREM Chemicals.

At first, we showed that the presence of copper oxide is not necessary to obtain phenol (Table 1, entry 2). In fact, the yield is even better without it. It should be noted that only a stoichiometric amount of TMEDA is enough to promote the

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reaction (1.2 equiv, entry 3). On the other hand, the formation of phenol was not observed in the absence of TMEDA (entry 4).

Then, we tried to improve the yield of the decarboxydemethylation product and found that a better yield is obtained in the presence of iron (entries 5–10). It is possible to use iron chlorides (entries 5 and 6), but the best result was obtained with iron powder (entry 7). It should be noted that other transition metals, for instance manganese or cobalt have no significant effect. The yield also increases when NMP is replaced by the more polar DMPU (entry 9 and Table 2, notes b–d).

We then investigated the scope of the reaction (Table 2). Interestingly, it is regio- and chemoselective. Thus, with 2,3- or 2,4-dimethoxybenzoic acids, only the methoxy in the *ortho* position is demethylated (entries 3 and 4). Moreover, with 2,6-dimethoxybenzoic acid, only one methoxy is demethylated (entry 5). Various functional groups such as chloro, fluoro, and amino are tolerated (entries 7–9). It should be noted that an ethoxy group in the *ortho* position is also dealkylated, whereas an isopropoxy hardly reacts (entries 11 and 12).

We were intrigued by the mechanism of this reaction. Thus, we identified and monitored all major compounds formed from 2-anisic acid. The results of our investigation are reported in Scheme 2. We observed that after 2 h the main product was methyl 2-hydroxybenzoate (**2**; 50%). Methyl 2-methoxybenzoate (**3**) and phenol (**1**) were also formed in 18 and 20% yield, respectively. During the course of the reaction, the two benzoic esters **2** and **3** progressively disappeared, to give phenol (**1**). After 24 h, **1** was obtained in 82% yield. At this time, only 3% of **2** and 1% of **3** remained in the reaction mixture.

On the basis of our observations, we propose the mechanism described in Scheme 3. At first, the reaction of 2-methoxybenzoic acid (**4**) with TMEDA gives a quaternary ammonium salt 5. In DMPU this salt is dissociated and the carboxylic anion attacks the methoxy group in the ortho position via an intramolecular nucleophilic substitution. The resulting phenolate 6 then leads to lactone 7 according to an intramolecular addition-elimination reaction. The four-membered lactone 7, which is very strained, undergoes a carbon monoxide extrusion (the reaction occurs at 170 °C) to give finally phenol (1) via the enolate of cyclohexadienone 8. The intramolecular nucleophilic substitution $\mathbf{5} \rightarrow \mathbf{6}$ is in agreement with the low reactivity of 2-isopropoxybenzoic acid (Table 2, entry 12) as well as with the beneficial effect when NMP is replaced by the more polar DMPU (Table 1, entries 7 and 8). The role of TMEDA would be to react with the carboxylic acid to form a salt 5, easily dissociated in DMPU to liberate the carboxylic anion. The formation of methyl 2-methoxybenzoate (3) could be interpreted as the result of an intermolecular substitution between two molecules of 2-methoxybenzoic acid. However, it is more reasonable to consider that it is formed by reaction of 2-methoxybenzoic acid with the methanol formed during the formation of the lactone 7.



Scheme 3 Mechanism of the O-demethyl-decarboxylation of o-anisic acid

The decarbonylation of lactone 7 is not very surprising, since the thermal decarbonylation of strained carbonyl derivatives has already been reported.⁷ The beneficial influence of iron powder is more difficult to understand. It is important to note that the reaction occurs without catalyst. The presence of iron only leads to an improvement in the yield of phenol 1. This leads to the consideration that the role of iron would be to facilitate the thermal reaction that probably occurs via a concerted pathway.7b However, it is well known that iron-based catalysts, including iron metal, are efficient for the decarbonylation of carboxylic acids⁸ and esters,⁹ likely via an oxidative addition to the C-O bond.⁸ Such a mechanism, which cannot be involved when the reaction takes place without a metal catalyst, cannot be completely discarded. It could contribute in part to the formation of **1**. Thus, at this point, the role of iron is not clear.

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 Table 2
 Scope of the O-Demethyl-Decarboxylation of o-Alkoxy
 Aromatic Acids^a



(1.2 equiv), Fe powder (20 mol%), DMPU 2.5 mL, 170 °C, 24 h.

^b Yield 76% in NMP.

^c Yield 57% in NMP.

^d Yield 53% in NMP.

^e Yield 43% in NMP.

In conclusion, we described herein a procedure to achieve the O-demethyl-decarboxylation of o-methoxy aromatic carboxylic acids. The reaction takes place very regioselectively with polymethoxy derivatives, since only one methoxy group in the ortho position is demethylated. Moreover, various functionalized o-methoxy aromatic carboxylic acids were used successfully. To the best of our knowledge, it is the first procedure to perform the direct conversion of o-methoxy aromatic carboxylic acids to the corresponding phenols.

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. NMP and DMPU were dried by distillation. Yields refer to isolated yields of compounds estimated to be ≥97% pure as determined by ¹H NMR, ¹³C NMR, and GC analysis. Column chromatography was carried out on silica gel silica gel 60 µm. All compounds give satisfactory MS analyses. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 spectrometer, with chemical shifts reported relative to the residual solvent peaks (CDCl₃: 7.26 ppm for ¹H and 77.16 ppm for ¹³C). GC analyses were recorded on a Hewlett-Packard HP 6890 chromatograph equipped with a capillary column HP-5MS (50 m × 0.25 mm × 0.25 µm). MS was carried out on a Hewlett-Packard HP 5973 (electronic impact). The analytical data of all products were found to match those of the commercial products.

Phenol by O-Demethyl-Decarboxylation of 2-Methoxybenzoic Acid; Typical Procedure

Under a nitrogen atmosphere, a mixture of 2-methoxybenzoic acid (761 mg, 5 mmol), metallic iron powder (56 mg, 1 mmol, 0.2 equiv), TMEDA (696 mg, 6 mmol, 1.2 equiv), and DMPU (2.5 mL) was stirred at 170 °C for 24 h. The reaction mixture was cooled to r.t., diluted with 1 N aq HCl (30 mL), and filtered through Celite. The aqueous phase was then extracted with EtOAc (3 × 50 mL) and the combined organic phases were washed with brine (50 mL) and dried over MgSO₄. EtOAc was removed in vacuo and the resulting crude material was purified by chromatography (silica gel, CH₂Cl₂/EtOAc/Et₃N, 20:1:1) to afford pure phenol as a white solid.

Atom-numbering for phenols is shown in Figure 1.



Figure 1

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Phenol¹⁰

Yield: 386 mg (82%); white solid, mp = 45 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.24 (dd, *J* = 8.6, 7.6 Hz, 2 H, H3+H5), 6.93 (tt, *J* = 7.6, 1.0 Hz, 1 H, H4), 6.83 (dd, *J* = 8.6, 1.0 Hz, 2 H, H2+H6), 5.13 (s, 1 H, H7).

MS (EI, 70 eV): m/z [M]⁺ = 94.

3-Methoxyphenol¹¹

Yield: 490 mg (79%); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.11 (t, J = 8.0 Hz, 1 H, H5), 6.53–6.38 (m, 3 H, H2+H4+H6), 3.74 (s, 3 H, H8).

¹³C NMR (100 MHz, CDCl₃): δ = 160.82 (C3), 156.74 (C1), 130.36 (C5), 108.14 (C6), 106.61 (C4), 101.71 (C2), 55.42 (C8). MS (EI, 70 eV): m/z [M]⁺ = 124.

4-Methoxyphenol¹²

Yield: 441 mg (71%); white solid, mp = 56 °C.

¹H NMR (400 MHz, CDCl₃): δ = 6.78 - 677 (m, 4 H, H2+H3+H5+H6), 4.84 (s, 1 H, H7), 3.76 (s, 3 H, H8).

¹³C NMR (100 MHz, CDCl₃): δ = 153.81 (C4), 149.59 (C1), 116.19 (C2+C6), 115.01 (C3+C5), 55.96 (C8). MS (EI, 70 eV): m/z [M]⁺ = 124.

2-Methoxyphenol¹³ Yield: 472 mg (76%); colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 6.95–6.84 (m, 4 H, H3+H4+H5+H6), 5.61 (s, 1 H, H7), 3.89 (s, 3 H, H8). ¹³C NMR (100 MHz, CDCl₃): δ = 146.68 (C2), 145.78 (C1), 121.58 (C5), 120.27 (C4), 114.64 (C6), 110.81 (C3), 56.00 (C8). MS (EI, 70 eV): m/z [M]⁺ = 124.

4-Methylphenol¹⁴

Yield: 379 mg (70%); white solid, mp = 34 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.03 (d, *J* = 8.3 Hz, 2 H, H3+H5), 6.73 (d, *J* = 8.3 Hz, 2 H, H2+H6), 4.84 (s, 1 H, H7), 2.27 (s, 3 H, H8). ¹³C NMR (100 MHz, CDCl₃): δ = 153.27 (C1), 130.21 (C3+C5), 130.14 (C4), 115.20 (C2+C6), 20.59 (C8). MS (EI, 70 eV): *m/z* [M]⁺ = 108.

4-Chlorophenol¹⁵

Yield: 411 mg (64%); white solid, mp = 43 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.19 (d, *J* = 8.8 Hz, 2 H, H3+H5), 6.77 (d, *J* = 8.8 Hz, 2 H, H2+H6), 4.86 (s, 1 H, H7). ¹³C NMR (100 MHz, CDCl₃): δ = 154.19 (C1), 129.67 (C3+C5), 125.82 (C4), 116.78 (C2+C6).

MS (EI, 70 eV): $m/z [M]^+ = 128$.

4-Fluorophenol¹⁶

Yield: 336 mg (60%); white solid, mp = 46 $^{\circ}$ C.

¹H NMR (400 MHz, CDCl₃): δ = 6.96–6.89 (m, 2 H, H3+H5), 6.80–6.74 (m, 2 H, H2+H6), 5.02 (s, 1 H, H7).

¹³C NMR (100 MHz, CDCl₃): δ = 157.44 (d, *J* = 238.4 Hz, C4), 151.47 (d, *J* = 2 Hz, C1), 116.37 (d, *J* = 8.1 Hz, C2+C6), 116.15 (d, *J* = 23.2 Hz, C3+C5).

MS (EI, 70 eV): *m*/*z* [M]⁺ = 112.

4-Aminophenol¹⁷

Yield: 431 mg (79%); white solid, mp = 190 °C.

¹H NMR (400 MHz, DMSO- d_6): δ = 6.48 (d, *J* = 8.9 Hz, 2 H, H2+H6), 6.42 (d, *J* = 8.9 Hz, 2 H, H3+H5), 4.40 (s, 1 H, H7).

 ^{13}C NMR (100 MHz, DMSO- d_6): δ = 148.28 (C1), 140.64 (C4), 115.58 (C2+C6), 115.31 (C3+C5).

MS (EI, 70 eV): *m*/*z* [M]⁺ = 109.

2-Naphthol¹⁸

Yield: 505 mg (70%); white solid, mp = 120 °C.

¹H NMR (400 MHz, DMSO- d_6): δ = 9.73 (s, 1 H, H11), 7.78–7.73 (m, 2 H, H4+H6), 7.70–7.65 (m, 1 H, H9), 7.38 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1 H, H7), 7.25 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1 H, H8), 7.15 (d, *J* = 2.4 Hz, 1 H, H1), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1 H, H3).

¹³C NMR (100 MHz, DMSO- d_6): δ = 155.35 (C2), 134.65 (C10), 129.34 (C4), 127.77 (C5), 127.58 (C6), 126.14 (C8), 126.03 (C9), 122.67 (C7), 118.66 (C3), 108.70 (C1).

MS (EI, 70 eV): *m*/*z* [M]⁺ = 144.

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Supporting Information

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