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Microwave-Assisted Cu-Catalyzed Protodecarboxylation of Aromatic Carboxylic Acids

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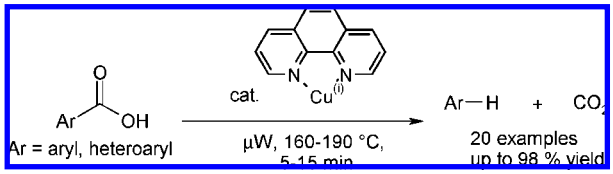
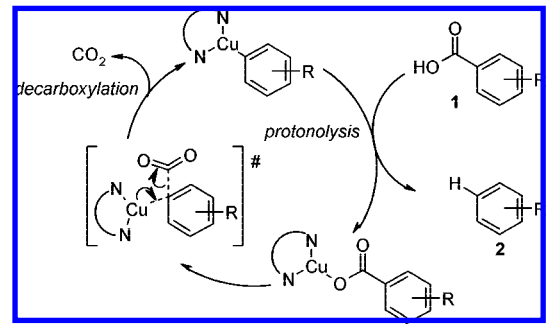


An effective protocol has been developed that allows the smooth protodecarboxylation of diversely functionalized aromatic carboxylic acids within 5−15 min. In the presence of at most 5 mol % of an inexpensive catalyst generated in situ from copper(I) oxide and 1,10-phenanthroline, even nonactivated benzoates were converted in high yields and with great preparative ease.

Decarboxylation reactions are useful for the removal of surplus carboxylate groups, which may arise from the use of highly functionalized natural product starting materials or may be left behind as a result of ring-closure reactions of oxocarboxylate intermediates.[1,2] While highly activated carboxylic acids, e.g., β-oxo acids, diphenylacetic acids, or polyfluorinated benzoic acids, decarboxylate reasonably easily even in the absence of a catalyst,[3] the release of CO_2 from simple aromatic carboxylic acids is much harder to accomplish. The use of copper as a stoichiometric mediator was disclosed already in 1930 by Shepard et al. for the decarboxylation of halogenated furancarboxylic acids at high temperatures.[4] Nilsson,[5] Shepard,[6] and Cohen[7] found that the copper source employed has little influence on the efficiency of protodecarboxylations but that the presence of bipyridine ligands at the copper and the use of aromatic amines as solvents is highly beneficial. Still, stoichiometric quantities of copper were required in virtually all published protocols, and the substrate scope was for a long time limited to aromatic carboxylates bearing electron-withdrawing groups such as nitro or halo in the ortho position as well as to certain heterocyclic carboxylates.

SCHEME 1. Proposed Mechanism for the Cu-Catalyzed Protodecarboxylation of Aromatic Carboxylates



We became interested in this transformation in the context of our research on decarboxylative cross-coupling reactions[8] when we optimized the copper cocatalyst that mediates the decarboxylation step by using protodecarboxylations as a model reaction.[9] This work led to the discovery that such protodecarboxylations can be made catalytic in copper and extended to the full range of benzoic acids, including even deactivated derivatives such as 4-methoxybenzoic acid, when 4,7-diphenyl-1,10-phenanthroline is employed as the ligand and a mixture of NMP and quinoline as the solvent. Based on mechanistic studies and DFT calculations, we proposed a reaction mechanism that involves a direct insertion of the copper catalyst into the aryl carboxylate bond without the previous formation of a π-coordinated intermediate (Scheme 1).[7a,9,10]

Whereas this protocol avoids stoichiometric amounts of heavy metals and thus represents major progress from an environmental standpoint, it has some practical disadvantages. The substrates are submitted to considerable thermal stress over the course of the reaction (170 °C for up to 24 h), volatile products are partially carried off by the CO_2 gas released, and the high cost of the ligand can become prohibitive for preparative applications.

We herein present an alternative protodecarboxylation protocol which involves performing the reactions in a laboratory microwave that combines efficient heating with the possibility to use small, contained vessels certified for pressure reactions.[11,12] This protocol allows for a dramatic reduction of the reaction times and leads to higher yields, even at lower loadings of a

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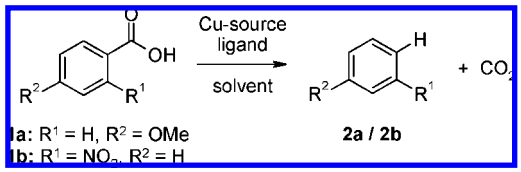
TABLE 1. Optimization of the Catalyst System[a]



no.	substrate	Cu source	ligand	solvent	T (°C)	**2** (%)
1[b]	**1a**	Cu_2O	**3a**	NMP/quin	170	9
2[b]	**1a**	Cu_2O	**3a**	NMP/quin	180	6
3[b]	**1a**	Cu_2O	**3a**	NMP/quin	190	43
4[b]	**1a**	Cu_2O	**3a**	NMP/quin	200	17
5[b,c]	**1a**	Cu_2O	**3a**	NMP/quin	190	88
6	**1a**	Cu_2O	**3a**	NMP	190	32
7	**1a**	Cu_2O	**3a**	quinoline	190	18
8[b]	**1a**	Cu_2O	**3a**	mesit/quin	190	9
9[b]	**1a**	Cu_2O	**3a**	DMF/quin	190	26
10[b]	**1a**	Cu_2O	**3a**	DMSO/quin	190	0
11[b]	**1a**	CuOAc	**3a**	NMP/quin	190	27
12[b]	**1a**	CuBr	**3a**	NMP/quin	190	0
13[b,d]	**1a**	CuBr	**3a**	NMP/quin	190	15
14[b]	**1a**	Cu_2O	**3b**	NMP/quin	190	97
15[b]	**1a**	Cu_2O	**3c**	NMP/quin	190	24
16[b]	**1a**	Cu_2O	**3d**	NMP/quin	190	10
17[b]	**1a**	Cu_2O	**4a**	NMP/quin	190	20
18[b]	**1a**	Cu_2O	**4b**	NMP/quin	190	21
19[b]	**1a**	Cu_2O	**5a**	NMP/quin	190	7
20[b]	**1a**	Cu_2O	**5b**	NMP/quin	190	13
21[b]	**1a**	Cu_2O	**6a**	NMP/quin	190	7
22[b]	**1a**	Cu_2O	**6b**	NMP/quin	190	5
23[b]	**1b**	Cu_2O	**3a**	NMP/quin	160	98
24[b,e]	**1b**	Cu_2O	**3a**	NMP/quin	160	95

[a] Reaction conditions: 1.0 mmol of carboxylic acid, 10 mol % of Cu source (5 mol % for Cu_2O), 10 mol % of ligand, 2 mL of degassed solvent, 5 min, 190 °C/150 W. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard; quin = quinoline, mesit = mesitylene. [b] 3:1 mixture of solvents. [c] 15 min. [d] 15 mol % of K_2CO_3. [e] 1 mol % of Cu_2O, 2 mol % of 1,10-phenanthroline.

less expensive catalyst. The loss of volatile products is avoided, as the release of CO_2 gas can be delayed until the end of the reaction, after the reaction mixture has reached room temperature.

We based the search for a microwave-assisted decarboxylation protocol on 4-methoxybenzoic acid (**1a**) as a test substrate because this electron-rich benzoic acid is of particularly low reactivity. In thermal decarboxylations, it gave only 82% yield after 24 h at 170 °C in the presence of 10 mol % of a customized copper(I)/4,7-diphenyl-1,10-phenanthroline complex and an unsatisfactory 35% yield with simple 1,10-phenanthroline.[9]

In contrast, when **1a** was heated in the presence of only 5 mol % of a copper(I) oxide/1,10-phenanthroline catalyst in a mixture of NMP and quinoline at 170 °C using a maximum of 150 W microwave irradiation, traces of product were detected after only 5 min (Table 1, entry 1). Increases in the reaction temperature resulted in a steady improvement of the yields until a turnaround point was reached at 190 °C, above which the yield dropped again (entries 3 and 4). Further test reactions performed at this temperature but at incomplete conversion (5 min) revealed that the protodecarboxylation is very sensitive

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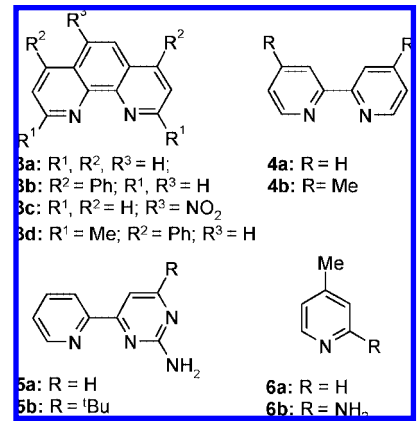


FIGURE 1. Cu ligands evaluated in the protodecarboxylation reaction.

to the solvent employed. Best results were obtained with a 3:1 mixture of NMP and quinoline, which was superior to either solvent alone or any other solvent combination tested (entries 3 and 6−10). The chosen solvent mixture strongly absorbs microwave radiation, causing a rapid increase in temperature and pressure during the first few seconds. Copper(I) oxide proved to be the copper source of choice, other copper(I) or copper(II) salts were less effective (entries 11−13).

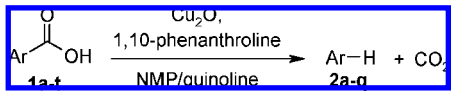
When extending the reaction time to 15 min at optimum reaction conditions, the yields could finally be improved up to an excellent 88% when using simple 1,10-phenanthroline (entry 5). Again, we found 4,7-diphenyl-1,10-phenanthroline to be even more effective, leading to almost quantitative formation of anisole (**2a**) after only 5 min (entry 14). Besides phenanthrolines, other ligands (Figure 1) can also be employed, but none of them was of similar effectiveness to the phenanthrolines (entries 14−22).

A second test reaction with 2-nitrobenzoic acid (**1b**) revealed that for such highly reactive substrates the decarboxylation proceeds in high yields even when the reaction temperature is reduced to 160 °C and the catalyst loading to 2 mol % (entries 23 and 24).

Encouraged by the results obtained with these two rather extreme model substrates, we set out to systematically explore the generality of the catalytic protocol using various aromatic and heteroaromatic carboxylic acids. Due to its easy availability and low price, we used Cu_2O/1,10-phenanthroline as the catalyst. We were pleased to find that even with this simple system, all substrates tested smoothly decarboxylated within 5−15 min. Usually, the yields were significantly in excess of those obtained after 16−24 h of conventional heating using the expensive 4,7-diphenyl-1,10-phenanthroline ligand. Selected results are summarized in Table 2.

The reactions are very easy to perform by irradiating a suspension of the carboxylic acid (**1a**−**t**), Cu_2O, and 1,10-phenanthroline in NMP/quinoline (3:1) at 190 °C for 5−15 min under inert conditions in a sealed crimp-top glass tube. After air-jet cooling, the pressure is carefully released, and the product is isolated by simple aqueous workup and removal of the solvents by fractional distillation. The conditions are sufficiently mild to be tolerated by a number of functionalities including ether, ester, formyl, nitro, cyano, and hydroxyl groups. The selectivity is high throughout, with at most traces of side products arising from homocoupling or substitution reactions. Lower yields were due only to incomplete conversion. All

TABLE 2. Scope of the Transformation[a]



	Ar-COOH	method	Ar-H	yield (GC) (%)
1a	4-MeO-C_6H_4-COOH	A	**2a**	77 (88)
1b	2-NO_2-C_6H_4-COOH	B	**2b**	85 (98)
1c	4-NO_2-C_6H_4-COOH	A	**2b**	86[b] (94)
1d	4-CN-C_6H_4-COOH	A	**2c**	81 (89)
1e	4-CHO-C_6H_4-COOH	A	**2d**	64 (77)
1f	4-MeC(O)-C_6H_4-COOH	A	**2e**	79 (87)
1g	4-Et-C_6H_4-COOH	A	**2f**	(80)
1h	4-CF_3-C_6H_4-COOH	A	**2g**	(22)
1i	4-Cl-C_6H_4-COOH	A	**2h**	(90)
1j	4-HO-C_6H_4-COOH	A	**2i**	(64)
1k	3-Me-C_6H_4-COOH	A	**2b**	(96)
1l	3-NO_2-C_6H_4-COOH	B	**2j**	(99)
1m	2-PhNH-C_6H_4-COOH	B	**2k**	63 (88)
1n	2-MeC(O)-C_6H_4-COOH	B	**2e**	84 (91)
1o	2-$MeS(O)_2$-C_6H_4-COOH	B	**2l**	70 (82)
1p	2-*i*PrOC(O)-C_6H_4-COOH	B	**2m**	85 (94)
1q	2-thienyl-COOH	B[c]	**2n**	(62)
1r	2-furyl-COOH	B[c]	**2o**	(99)
1s	1-naphthyl-COOH	B	**2p**	38 (56)
1t	2-NO_2-5-Me-C_6H_3-COOH	B	**2q**	80 (94)

[a] Reaction conditions. Method A: 1.0 mmol of carboxylic acid, 5 mol % of Cu_2O, 10 mol % of 1,10-phenanthroline, 1.5 mL of NMP, 0.5 mL of quinoline, 190 °C, 150 W, 15 min; isolated yields. Method B: 1.0 mmol of carboxylic acid, 1 mol % of Cu_2O, 2 mol % of 1,10-phenanthroline, 1.50 mL of NMP, 0.50 mL of quinoline, 190 °C, 150 W, 5 min; isolated yields. GC yields were determined using *n*-tetradecane as the internal standard and calibrated for each product. [b] a yield of 80% was isolated on 3 mmol scale [c] 160 °C.

reactions were performed on a 1 mmol scale in 10 mL vessels. When using these standard microwave vials, the reactions can be scaled up to a maximum of 3 mmol with comparable yields as shown for compound **2b**. Larger scales should also be possible but require additional equipment.

In conclusion, an efficient microwave-based protocol has been developed for Cu-catalyzed decarboxylations of arenecarboxylates. It is ideally suited for the demands of parallel synthesis as commonly used, for example, in drug discovery. Because test reactions can now be completed within a few minutes rather than an entire day, it will also serve to expedite the development of more effective catalyst systems.

Experimental Section

Protodecarboxylation of Aromatic Carboxylic Acids. Method A (Table 2). An oven-dried 10 mL microwave vial was charged with the carboxylic acid (**1a**,**c**−**k**) (1.0 mmol), Cu_2O (7.2 mg, 0.05 mmol), and 1,10-phenanthroline (18 mg, 0.10 mmol). After the reaction mixture was made inert, a mixture of NMP (1.5 mL) and quinoline (0.5 mL) was added via syringe. The resulting mixture was submitted to microwave irradiation at 190 °C for 15 min at a maximum power of 150 W and subsequently air-jet cooled to room temperature. The maximum pressure detected during the reaction was 5.5 bar. The mixture was then diluted with aqueous HCl (5N, 10 mL) and extracted repeatedly with diethyl ether (2 mL portions). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered. The corresponding arene **2** was obtained in pure form after removal of the solvents by distillation over a Vigreux column.

Method B (Table 2). Method B is analogous to method A but with a lower loading of the copper/phenanthroline catalyst and microwave irradiation at 190 °C for 5 min at a maximum power of 150 W. The following amounts were used: carboxylic acid (**1b**, **l**−**t**) (1.0 mmol), Cu_2O (1.5 mg, 0.01 mmol), and 1,10-phenanthroline (3.6 mg, 0.02 mmol).

Anisole (2a). Synthesized from 4-methoxybenzoic acid (**1a**) (152 mg, 1.00 mmol) following method A and obtained as a colorless liquid (84 mg, 77%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-66-3].

Nitrobenzene (2b). Synthesized from 2-nitrobenzoic acid (**1b**) (167 mg, 1.00 mmol) following method B (105 mg, 85%), from 3-nitrobenzoic acid (**1l**) (167 mg, 1.00 mmol) following method B (107 mg, 87%), and from 4-nitrobenzoic acid (**1c**) (167 mg, 1.00 mmol) following method A (105 mg, 86%), obtained each time as a yellow liquid. The spectroscopic data (NMR, GC−MS) all matched those reported in the literature [CAS no. 98-95-3]. A larger scale reaction starting from 4-nitrobenzoic acid (**1c**) (501 mg, 3 mmol) in 6 mL of NMP gave **2b** in 80% yield (293 mg).

Benzonitrile (2c). Synthesized from 4-cyanobenzoic acid (**1d**) (147 mg, 1.00 mmol) following method A and obtained as a colorless liquid (84 mg, 81%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-47-0].

Benzaldehyde (2d). Synthesized from 4-formylbenzoic acid (**1e**) (150 mg, 1.00 mmol) following method A and obtained as a yellow liquid (68 mg, 64%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-52-7].

Acetophenone (2e). Synthesized from 4-acetylbenzoic acid (**1f**) (164 mg, 1.00 mmol) following method A (95 mg, 79%) and from 2-acetylbenzoic acid (**1n**) (164 mg, 1.00 mmol) following method B (101 mg, 84%), both times obtained as a yellow liquid. The spectroscopic data (NMR, GC−MS) all matched those reported in the literature [CAS no. 98-86-2].

Ethylbenzene (2f). Synthesized from 4-ethylbenzoic acid (**1g**) (150 mg, 1.00 mmol) following method B. The identity of the product **2f** was confirmed by GC−MS and the yield determined by quantitative GC to be 80% based on a response factor obtained with commercial ethylbenzene [CAS no. 100-41-4] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Trifluoromethylbenzene (2g). Synthesized from 4-(trifluoromethyl)benzoic acid (**1h**) (190 mg, 1.00 mmol) following method B. The identity of the product **2g** was confirmed by GC−MS and the yield determined by quantitative GC to be 22%, based on a response factor obtained with commercial trifluoromethylbenzene [CAS no. 98-08-8] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Chlorobenzene (2h). Synthesized from 4-chlorobenzoic acid (**1i**) (156 mg, 1.00 mmol) following method A. The identity of the product **2h** was confirmed by GC−MS and the yield determined by quantitative GC to be 90% based on a response factor obtained with commercial chlorobenzene [CAS no. 108-90-7] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Phenol (2i). Synthesized from 4-hydroxybenzoic acid (**1j**) (138 mg, 1.00 mmol) following method A. The identity of the product **2i** was confirmed by GC−MS and the yield determined by quantitative GC to be 64%, based on a response factor obtained with commercial phenol [CAS no. 108-95-2] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Toluene (2j). Synthesized from 3-methylbenzoic acid (**1k**) (136 mg, 1.00 mmol) following method A. The identity of the product **2j** was confirmed by GC−MS and the yield determined by quantitative GC to be 99%, based on a response factor obtained with commercial toluene [CAS no. 108-88-3] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Diphenylamine (2k). Synthesized from 2-(phenylamino)benzoic acid (**1m**) (213 mg, 1.00 mmol) following method B and obtained as a white solid (107 mg, 63%): mp 49−51 °C. The spectroscopic data (NMR, GC−MS) matched those reported in the literature for diphenylamine [CAS no. 122-39-4].

Methyl Phenyl Sulfone (2l). Synthesized from 2-(methylsulfonyl)benzoic acid (**1o**) (200 mg, 1.00 mmol) following method B and obtained as a white solid (109 mg, 70%): mp. 85−87 °C. The

spectroscopic data (NMR, GC−MS) matched those reported in the literature for methyl phenyl sulfone [CAS no. 3112-85-4].

Isopropyl Benzoate (2m). Synthesized from 2-(isopropyloxycarbonyl)benzoic acid (**1p**) (208 mg, 1.00 mmol) following method B and obtained as a yellow liquid (139 mg, 85%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature for isopropyl benzoate [CAS no. 939-48-0].

Thiophene (2n). Synthesized from thiophene-2-carboxylic acid (**1q**) (128 mg, 1.00 mmol) following method B but at 160 °C reaction temperature. The identity of the product **2n** was confirmed by GC−MS and the yield determined by quantitative GC to be 62%, based on a response factor obtained with commercial thiophene [CAS no. 110-02-1] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Furan (2o). Synthesized from furan-2-carboxylic acid (**1r**) (112 mg, 1.00 mmol) following method B but at 160 °C reaction temperature. The identity of the product **2o** was confirmed by GC−MS and the yield determined by quantitative GC to be 99% based on a response factor obtained with commercial furan [CAS no. 110-00-9] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Naphthalene (2p). Synthesized from 1-naphthoic acid (**1s**) (172 mg, 1.00 mmol) following method B and obtained as a white solid (49 mg, 38%): mp.78−80 °C. The spectroscopic data (NMR, GC−MS) matched those reported in the literature for naphthalene [CAS no. 91-20-3].

4-Nitrotoluene (2q). Synthesized from 5-methyl-2-nitrobenzoic acid (**1t**) (197 mg, 1.00 mmol) following method B and obtained as a colorless liquid (109 mg, 80%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature for 4-nitrotoluene [CAS no. 99-99-0].

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Supporting Information Available: NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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