



Silver-catalyzed decarboxylative halogenation of carboxylic acids

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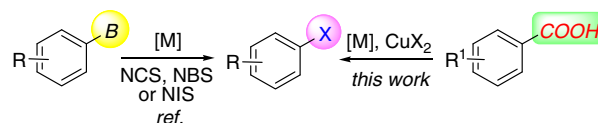
ABSTRACT

Decarboxylative halogenation of carboxylic acids catalyzed by silver carbonate is reported. *ortho*-Nitrobenzoic acids react with copper(II) chloride or bromide in DMF/DMSO at 130–140 °C leading to the corresponding aryl halides in moderate to good yields.

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Recently, intense interest has been directed toward the development of new methods for the transition metal-catalyzed decarboxylative coupling reactions.^{1–5} As highlighted by Baudoin,^{1e} one of the advantages of the reactions over C–H activation is the excellent regioselectivity. In addition, compared to the conventional metal-catalyzed cross-coupling reactions using organometallic reagents as substrates, the decarboxylative coupling reaction is regarded as an environmentally benign process since only CO₂ is released as the byproduct during the conversion of carboxylic acid into carbon nucleophile in the reaction. In the last several years, remarkable progress in the field of decarboxylative coupling reactions has been witnessed.

On the other hand, it is well established that aryl halides are useful synthetic intermediates⁶ and can be found as essential components in many pharmaceutical compounds.⁷ Usually, access to halogenated arenes is through classic methods via direct electrophilic aromatic substitution. Recently, much attention has been paid to boron–halogen exchange reaction^{8–11} for generation of halogenated arenes (Scheme 1). For instance, Hynes and co-workers described a Cu(I)-mediated method for the conversion of arylboronic acids into aryl chlorides in the presence of NCS.^{11d} Although in some cases, the boron–halogen exchange was efficient for the aryl halides formation, stoichiometric amounts of costly organometallic reagent could not be avoided. Recently, we described palladium-catalyzed decarboxylative 1,2-addition of carboxylic acids to aldehydes or imines under mild conditions.^{4a} In this reaction



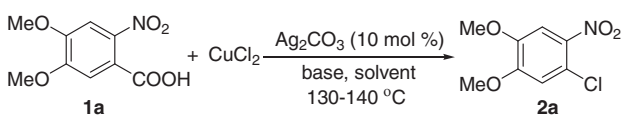
Scheme 1. Proposed route for decarboxylative halogenation of carboxylic acids.

process, carboxylic acid was utilized as a replacement of organometallic reagent for addition reaction. Additionally, copper(II) halide has been demonstrated as a convenient halide source. Prompted by these results and the advancement of decarboxylative coupling reactions, we envisioned that carboxylic acid might be a good alternative for the halogenated reaction under suitable conditions (Scheme 1). Thus, investigation aimed toward the development of decarboxylative halogenation of carboxylic acids was explored.

An initial experiment using 4,5-dimethoxy-2-nitrobenzoic acid **1a** as substrate in the reaction of copper(II) chloride (2.0 equiv) catalyzed by 10 mol % of Ag₂CO₃ in the presence of KOH (2.0 equiv) in DMF at 130 °C under nitrogen atmosphere afforded no reaction (Table 1, entry 1). Interestingly, the desired 1-chloro-4,5-dimethoxy-2-nitrobenzene **2a** could be obtained in 74% yield when the reaction occurred under oxygen atmosphere (Table 1, entry 2). Subsequently, a variety of bases and solvents were examined. No better yields were observed when K₂CO₃, KOAc, or NaO^tBu was utilized as the base (Table 1, entries 3–5). Only a trace amount of product **2a** was detected when DMSO was used as a solvent (Table 1, entry 6). Similar result was generated when the solvent was replaced to NMP (Table 1, entry 7). Gratifyingly, aryl chloride **2a** could be isolated in 85% yield when the reaction was performed

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Table 1
Initial studies for the decarboxylative halogenation of carboxylic acids



Entry	Base	Solvent	Atmosphere	Yield ^a (%)
1	KOH	DMF	N ₂	—
2	KOH	DMF	O ₂	74
3	K ₂ CO ₃	DMF	O ₂	31
4	KOAc	DMF	O ₂	51
5	NaO ^t Bu	DMF	O ₂	62
6	KOH	DMSO	O ₂	Trace
7	KOH	NMP	O ₂	Trace
8	KOH	DMF/DMSO	O ₂	85
9	KOH	DMF/NMP	O ₂	—
10	KOH	NMP/DMSO	O ₂	—
11 ^b	KOH	DMF	O ₂	Trace
12 ^c	KOH	DMF	O ₂	Trace
13 ^d	KOH	DMF	O ₂	Trace

^a Isolated yield based on carboxylic acid **1**.

^b In the presence of 20 mol % of CuCl₂, 2.0 equiv of LiCl.

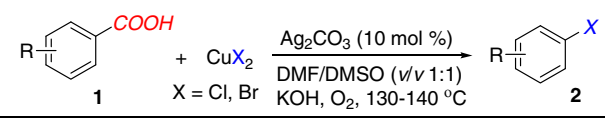
^c In the presence of 20 mol % of CuCl₂, 2.0 equiv of NaCl.

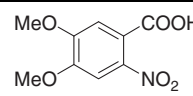
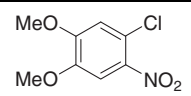
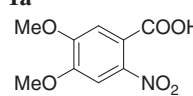
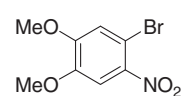
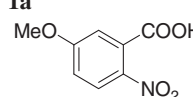
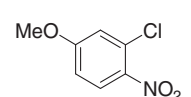
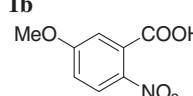
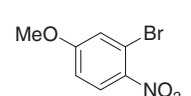
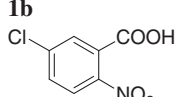
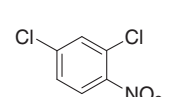
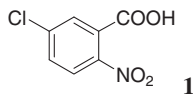
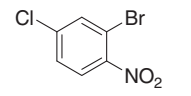
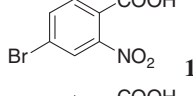
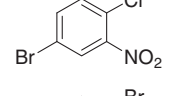
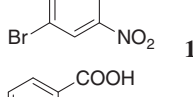
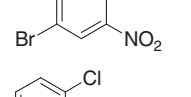
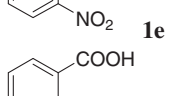
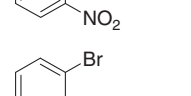
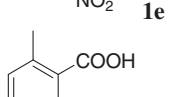
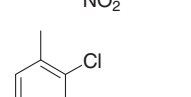
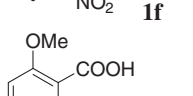
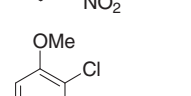
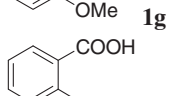
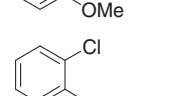
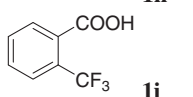
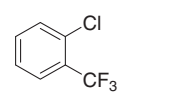
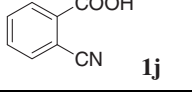
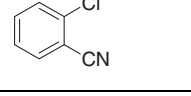


^d In the presence of 20 mol % of CuCl₂, 2.0 equiv of ^tBu₄NCl.

in a mixed solvent DMF/DMSO (v/v, 1:1) (Table 1, entry 8). No reaction occurred when the mixed solvent was changed to DMF/NMP or DMSO/NMP (Table 1, entries 9 and 10). This result was accordant with the previous report,^{1c} wherein the rate of decarboxylation was much faster in a mixture of DMF and DMSO. We also tested the reaction in the presence of 20 mol % of copper(II) chloride and 2.0 equiv of LiCl, NaCl, or ^tBu₄NCl (Table 1, entries 11–13). However, a trace amount of product was furnished. Diminished reactivity was displayed when the amount of copper(II) chloride was reduced to 1.0 equiv. The reaction was retarded when the reaction temperature was lower or the catalytic amount of Ag₂CO₃ was reduced. Blank experiment indicated that no reaction took place in the absence of silver catalyst. Inferior results were obtained when other silver catalysts were screened (data not shown in Table 1). From the results shown in Table 1, it seemed that the reaction proceeded through a radical process, as mentioned by Kochi and others.¹²

We next sought to understand the scope of the reaction and examined a number of carboxylic acids under the optimized conditions [Ag₂CO₃ (10 mol %), CuX₂ (2.0 equiv), KOH (2.0 equiv), DMF/DMSO (v/v, 1:1), 130–140 °C] (Table 2). This silver-catalyzed decarboxylative halogenation of carboxylic acids was shown to be effective for *ortho*-nitrobenzoic acids. In addition, not only copper(II) chloride but also copper(II) bromide worked well under the standard conditions. For instance, 4,5-dimethoxy-2-nitrobenzoic acid **1a** reacted with CuBr₂ leading to the corresponding aryl bromide **2b** in 63% yield (Table 2, entry 2). 5-Methoxy-2-nitrobenzoic acid **1b** was a suitable substrate as well in the reaction of CuCl₂, which afforded the desired product **2c** in 83% yield (Table 2, entry 3). However, the yield was dramatically decreased when CuBr₂ was used in the reaction (Table 2, entry 4). Other 2-nitrobenzoic acids with various substituents in the aromatic ring were examined meanwhile, and the corresponding products were generated as expected in moderate to good yields (Table 2, entries 5–11). However, no reaction took place when benzoic acids **1g–1j** were employed in the reaction with copper(II) chloride (Table 2, entries 12–15). Since directed processes, that is, the use of neighboring groups to control either the reactivity or regioselectivity of organic transformations has been well established,^{13,14} it seems that the nitro group in the *ortho*-position is crucial for the decarboxylative halogenation reaction.

Table 2
Silver-catalyzed decarboxylative halogenation of carboxylic acids¹⁵



Entry	R ¹ , R ²	X	product	Yield ^a (%)
1		Cl		85 (2a)
2		Br		63 (2b)
3		Cl		83 (2c)
4		Br		25 (2d)
5		Cl		80 (2e)
6		Br		65 (2f)
7		Cl		61 (2g)
8		Br		60 (2h)
9		Cl		83 (2i)
10		Br		35 (2j)
11		Cl		56 (2k)
12		Cl		—
13		Cl		—
14		Cl		Trace
15		Cl		Trace

^a Isolated yield based on carboxylic acid **1**.

In conclusion, we have demonstrated the concept of decarboxylative halogenation of carboxylic acids, which provides a new route for aryl halides formation. Clearly, this reaction has scope limitation currently. However, this new discovery with environmentally benign process will prompt us for its further development.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.054.

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- General procedure for silver-catalyzed decarboxylative halogenation of carboxylic acids: Carboxylic acid (0.2 mmol), copper(II) salts (0.4 mmol), KOH (0.4 mmol), and Ag₂CO₃ (10 mol %) were placed in the test tube. The tube was sealed and filled with O₂. Then DMF (1.0 mL) and DMSO (1.0 mL) were added via the syringe. The mixture was heated at 130–140 °C. After completion of reaction as indicated by TLC, the solvent was diluted by EtOAc (10 mL), washed with saturated brine (2 × 10 mL), and dried by Na₂SO₄. Evaporation of the solvent followed by purification on silica gel provided the product **2**. For details, please see the ESI.