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Desilylative Carboxylation of Aryltrimethylsilanes Using CO_2 in the Presence of Catalytic Phosphazenium Salt

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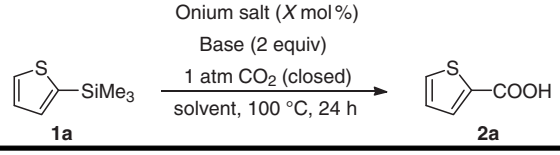
An efficient method for the desilylative carboxylation of aryltrimethylsilanes with CO_2 catalyzed by phosphazenium salt has been developed. This protocol can provide various arylcarboxylic acids that are important structural motifs in biologically active chemical compounds.

Synthetic application in the construction of the C–C bond involving fixations of carbon dioxide into useful molecules has been widely developed in recent years because CO_2 is an environmentally friendly, nontoxic, nonflammable, and abundant resource.[1]

Arylcarboxylic acids are important structural motifs in the research and development of fine chemicals, including biologically active molecules.[2] For instance, numerous chemical compounds that are widely used for medical treatment contain carboxylic acid motif, such as anti-inflammatory drugs. It has been well known that the most straightforward and well-studied approaches for the syntheses of arylcarboxylic acids are the fixation of carbon dioxide into certain carbon nucleophiles.[3–10] In this context, highly reactive organometallic reagents such as organolithium and Grignard reagents have been employed for the nucleophilic addition to CO_2 as low-cost syntheses of arylcarboxylic acids; however, these methods are not compatible with various electrophilic functional groups. As an alternative approach for functional-group compatibility, less nucleophilic organozinc[3] and organoboron[4] reagents were successfully employed for the carboxylation reaction catalyzed by transition-metal or by transition-metal-free processes. The carboxylation of aryl halides with CO_2 is also accomplished in the presence of suitable transition-metal catalysts.[5] Direct carboxylation of activated C–H bond using CO_2 coupling reactions was reported by the transition-metal-catalyzed process,[6] base-mediated deprotonative addition,[7] or the Friedel–Crafts-type carboxylation.[8] In addition to these methods, carboxylation of arylsilanes is considered to be attractive because of their low toxicity, chemical stability, and ease of handling. In 1985, Effenberger and co-workers demonstrated KF-mediated carboxylation of aryltrimethylsilanes using HMPA as a solvent.[9] However, the substrate of this reaction was limited to *o*-Cl and *o*-NO_2 phenyltrimethylsilane, and the reaction required relatively high pressure of CO_2 (5 MPa). As another type of carboxylation of arylsilanes, Hattori et al. disclosed that the utilization of trihaloaluminum was effective for the electrophilic carboxylation of aryltrimethylisilanes with CO_2.[10] To smoothly perform this Lewis acidic system, it is also necessary to carry out the reaction under high pressure (3 MPa).

We have recently focused our interest on the potential applicability of organic onium salt for the catalytic in situ generation of highly reactive nucleophiles.[11] In connection with our recent work on the investigation of CO_2-fixation reactions,[12] we report here the development of phosphazenium-salt-catalyzed carboxylation of aryltrimethylsilanes in the presence of CsF, providing arylcarboxylic acids with the atmospheric pressure of carbon dioxide.[13]

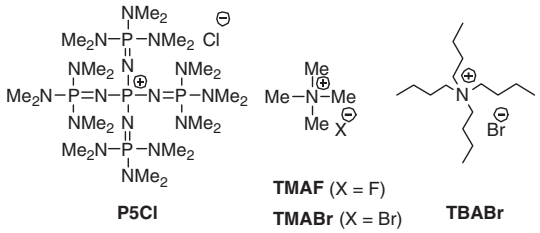
Table 1. Carboxylation of 2-trimethylsilylthiophene with CO_2[a]



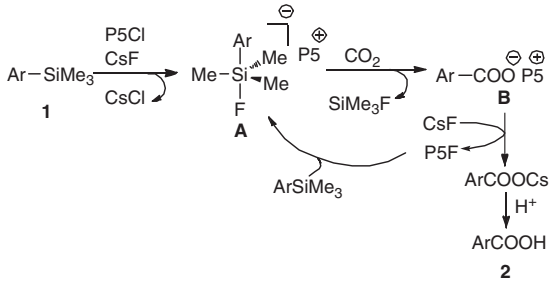
1a **2a**

Entry	Onium salt (*X* mol %)	Base (2 equiv)	Solvent	Yield/%[b]
1	none	CsF	*o*-xylene	trace
2	P5Cl (10)	CsF	*o*-xylene	(89)
3	TBABr (10)	CsF	*o*-xylene	58
4	TMABr (10)	CsF	*o*-xylene	5
5	PPh_4Cl (10)	CsF	*o*-xylene	0
6	PPh_4Br (10)	CsF	*o*-xylene	0
7	TMAF (110)	none	*o*-xylene	23
8	P5Cl (10)	KF	*o*-xylene	63
9	P5Cl (10)	*t*-BuOK	*o*-xylene	34
10	P5Cl (10)	CsF	dioxane	48
11	P5Cl (10)	CsF	cyclohexane	60
12	P5Cl (10)	CsF	toluene	60
13	P5Cl (10)	CsF	DMF	46
14	P5Cl (10)	CsF	DMSO	52

[a]Reaction was carried out on a 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR. Isolated yields is in parentheses.



Our investigation with an examination of carboxylation of 2-trimethylsilylthiophene (**1a**) with CO_2 (1 atm) at 100 °C in a closed system (sealed tube) (Table 1). Unlike the CO_2 fixation into alkynylsilanes,[12a] the use of CsF afforded only trace amounts of carboxylated product (Entry 1).[14] To our surprise, the combination of 10 mol % phosphazenium chloride (P5Cl) and 2 equivalents of CsF in *o*-xylene dramatically increased the reactivity to afford 2-thiophenecarboxylic acid (**2a**) in 89% yield (Entry 2).[15] The use of 10 mol % of other



Scheme 1. Plausible mechanism of the phosphazenium-salt-catalyzed carboxylation of aryltrimethylsilane with CO_2.

organic onium salts such as TBABr showed less reactivity compared to P5Cl; other salts such as TMABr did not activate the reaction (Entries 3 and 4) and phosphonium catalyst did not afford the desired product (Entries 5 and 6). On the other hand, when the reaction was carried out with 110 mol % of TMAF in the absence of CsF, the product was obtained in 23% yield showing some activity (Entry 7). Compared to KF or *t*-BuOK, the use of CsF showed better performance for the desilylative carboxylation reaction (Entries 2, 8, and 9). The screening of solvents revealed that *o*-xylene is the best solvent for this carboxylation reaction (Entries 2 and 10–14).

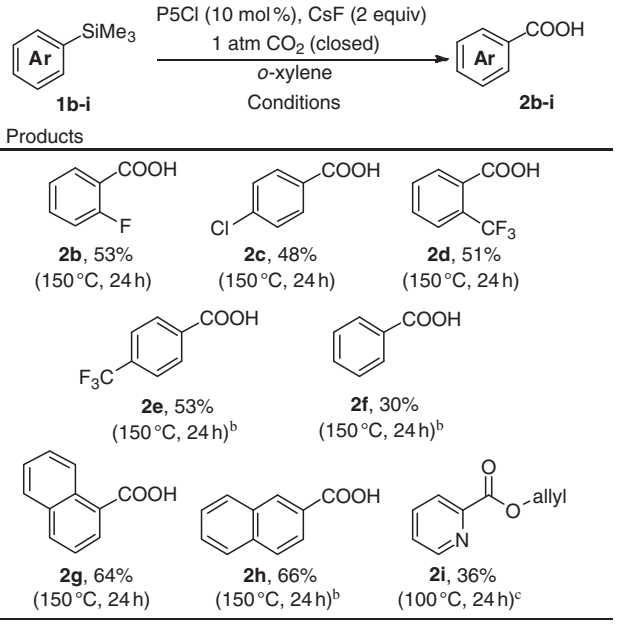
A plausible mechanism for the carboxylation promoted by phosphazenium catalyst is shown in Scheme 1. Initially, highly reactive silicate **A** forms by P5Cl and CsF, which attacks CO_2 to generate phosphazenium carboxylate intermediate **B**. The subsequent reaction of **B** with CsF affords cesium carboxylate and the P5F catalyst; the former then afford carboxylic acid **2** by the workup with acid. We considered that the phosphazenium cation may play an important role in acceleration of desilylation as well as addition to carbon dioxide.[16]

Under the optimized reaction conditions employed for Entry 2 in Table 1, we examined the desilylative carboxylation of various aryltrimethylsilanes (Table 2).[17] Although higher temperatures varying from 100 to 150 °C were required, it was found that the carboxylation reactions proceed using the combination of CsF and catalytic amount of P5Cl. Arylsilanes with halogen such as *o*-F and *p*-Cl were first examined to afford the corresponding carboxylic acids **2b** and **2c** in moderate yield. The reaction of phenyltrimethylsilane bearing CF_3 on the *o*- and *p*-positions afforded the desired products **2d** and **2e** in 51% and 53% yields. Unsubstituted phenyltrimethylsilane was also reacted with CO_2, affording benzoic acid (**2f**) in 30% yield. The use of 1- and 2-naphthyltrimethylsilanes (**1g** and **1h**) proceeded smoothly to generate **2g** or **2h** as a single regioisomer, respectively. The reaction of 2-(trimethylsilyl)pyridine (**1i**) afforded allyl ester **2i** using allyl bromide as a quenching agent.

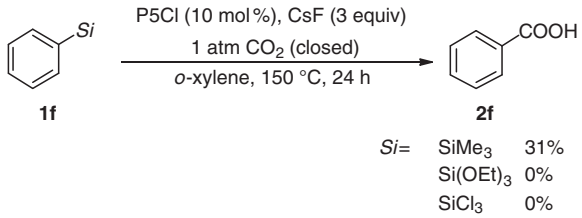
We further investigated the influence of the silyl substituent on phenylsilane **1f** (Scheme 2). Arylsilanes that have $Si(OEt)_3$ or $SiCl_3$ on the aromatic ring decomposed under the carboxylation condition and did not afford the desired benzoic acid **2f**. This is in sharp contrast to the fact that trialkoxysilanes have been widely used for the Hiyama cross-coupling reaction.[18]

Interestingly, in the reaction of *o*-chlorophenyltrimethylsilane (**1j**) with CO_2 under the reaction conditions, unexpected xanthone (**3**) was isolated as a major product (Scheme 3). Larock and co-workers have developed a novel xanthone

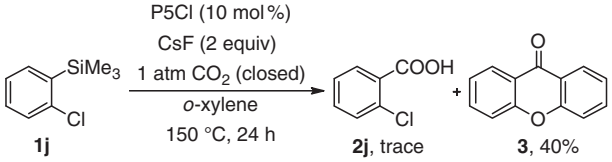
Table 2. Carboxylation of aryltrimethylsilanes with CO_2[a]



[a]Reaction was carried out on a 0.1 mmol scale. [b]CsF (3.0 equiv) was used. [c]Allyl bromide (12 equiv) was used as a quenching agent.

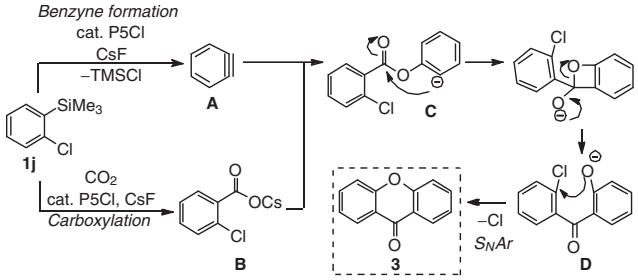


Scheme 2. Substituent effect on the silyl group of phenylsilane.



Scheme 3. Reaction of *o*-chlorophenyltrimethylsilane with CO_2.

synthesis through the reaction of *o*-halobenzoic acids with benzyne precursor.[19] Based on the mechanism proposed on the literature,[19a] the reaction pathway was assumed (Scheme 4). The carboxylate intermediate **B** formed by the carboxylation of **1j** with CO_2 can react with benzyne **A**, which is also generated from **1j** through fluoride activation. The aryl anion **C** undergoes intramolecular addition to carbonyl and the rearrangement produces phenoxide **D**. Finally, xanthone (**3**) could arise from an intramolecular nucleophilic aromatic substitution of phenoxide **D**. This protocol could provide a facile one-pot synthesis of xanthone, which shows a wide variety of pharmacological activities.[20]



Scheme 4. Plausible mechanism for the formation of xanthone.

In summary, we have developed the desilylative carboxylation of aryltrimethylsilanes promoted by the phosphazenium salt catalyst using CO_2 as a C_1-feedstock. The present method provides a convenient entry for synthesizing functionalized benzoic acids under transition-metal-free conditions. Further works on the disclosing reaction mechanism, as well as the investigation for expanding the reaction scope, are underway.[21]

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