

A Three-Phase Four-Component Coupling Reaction: Selective Synthesis of *o*-Chloro Benzoates by KCl, Arynes, CO₂, and Chloroalkanes

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Supporting Information



chloroalkanes and CO_2 has been reported for the first time, enabling the incorporation of both chloro and CO_2 into an aryne simultaneously. The reactions for the synthesis of different types of *o*-chloro benzoates can be selectively modulated by the chloroalkane utilized. The corresponding products can be alternatively transformed for postsynthetic functionalizations conveniently.

M ulticomponent reactions (MCRs) are a class of reaction in which the starting materials (more than two) are incorporated in the final product by a one pot method.¹ In contrast with multistep synthesis, MCRs are commonly highlighted by their high step efficiency, atom economy, and synthetic convergence. According to different reactant states in the reaction, MCRs can be simply classified into three categories (Scheme 1): (a) 1P-MCRs, such as the Strecker 3CR,^{2a} Ugi 4CR^{2b} as well as recently elegant works,^{2c-h} are one of the most common reactions in which all reactants are dissolved in a homogeneous state, and (b) 2P-MCRs are defined as reactions in which the starting materials of MCRs consist of two states in the reaction. One is that organic



compounds react with various gases $(CO, {}^{3}CO_{2}, {}^{7,10-12}NH_{3}, {}^{4}$ etc.), and the other is the combination of organic components with different inorganics such as NaNO₂, {}^{13b}Na_2S, {}^{5a} and NaN₃. {}^{5b} Due to the poor transmission between two phases, 2P-MCRs become more complicated and challenging than the former one and (c) 3P-MCRs are a heterogeneous system containing three phases among various substrates. Although limited attention of 3P-MCRs 6,8j has been paid, the reactions show their enormous potential by utilizing both inexpensive and abundant gas and inorganics for organic synthesis. Therefore, the exploration of more novel and distinctive 3P-MCRs is highly desirable.

The utilization of carbon dioxide to construct various high value-added products is an appealing and challenging subject, as CO_2 is a low-cost, abundant, nontoxic but inert gas.⁷ Despite the intrinsic inactivity of CO_2 , a large amount of effort has been devoted to tackle the problem in recent years.⁸ Among various conceivable strategies, the combination of highly reactive aryne intermediates⁹ with CO_2 offers a unique opportunity to facilitate this transformation. Generally, the highly electrophilic aryne can be attacked by different uncharged nucleophiles such as imines,^{10a} amines,^{10b,c} and isocyanides^{10d} to form 1,3-zwitterionic intermediates respectively, which may be intercepted by CO_2 to afford diverse 1,2-difunctionolized arenes. In particular, our group has developed a multicomponent coupling reaction of CO_2 , amines, cyclic

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ethers, and 3-triflyloxybenzynes for the synthesis of various carbamates recently.¹¹ Apart from these elegant works, the other multicomponent reactions involving both $\rm CO_2$ and arynes are still in their infancy.¹²

o-Chloro benzoats are an important class of synthetic intermediate,¹³ and their unique structure units are also found in various pharmaceuticals and agrochemicals, such as Chloroprocaine,^{14a} Butafenacil and Fluazolate.^{14b} Several remarkable advances¹⁵ have been reported for the synthesis of o-chloro benzoates in recent decades. However, the use of expensive transition-metal catalysts and highly reactive reagents has limited their applications to some extent. Therefore, based on the above observations and our previous reports about CO_2 ,¹⁷ we envisioned that the reaction might proceed by employing KCl as anionic nucleophiles¹⁶ and using CO_2 as the source of ester to access o-chloro benzoate derivatives.

We commenced our study by employing Kobayashi aryne precursor $1a^{18}$ in the presence of KF/18-crown-6 in DCE (1,2-dichloroethane) at room temperature (rt) for 12 h under an atmosphere of CO₂ (Table 1, entry 1). Unfortunately, only a



OTf + CI TMS 2a		KF, 18-crown-6 additve CO ₂ (1 atm)		
entry	F ⁻ system	additive (equiv)	t (°C)	yield (%) ^b
1	KF+18-crown-6	_	rt	trace
2	KF+18-crown-6	KCl (2)	rt	37%
3	KF+18-crown-6	NaCl (2)	rt	trace
4	KF+18-crown-6	LiCl (2)	rt	n.d.
5	KF	KCl (2)	rt	n.d.
6 ^c	KF+18-crown-6	KCl (2)	rt	n.d.
7	KF+18-crown-6	KCl (2)	0	n.r.
8	KF+18-crown-6	KCl (2)	46	49%
9	KF+18-crown-6	KCl (2)	55	47%
10	KF+18-crown-6	KCl (0.2)	46	27%
11	KF+18-crown-6	KCl (3)	46	54%
12	KF+18-crown-6	KCl (4)	46	58%
13 ^d	KF+18-crown-6	KCl (4)	46	66%
14 ^e	CsF+18-crown-6	KCl (4)	46	34%
15 ^f	TBAF	KCl (4)	46	n.d.
16 ^g	KF+18-crown-6	KCl (4)	46	67%

^{*a*}Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mL), CO₂ (1 atm), KF (3 equiv), 18-crown-6 (3 equiv) at various temperatures for 12 h. ^{*b*}Yield based on **1a** and determined by ¹H NMR analysis using CH₃NO₂ as an internal standard. ^{*c*}Under a N₂ atmosphere. ^{*d*}KF (4 equiv), 18-crown-6 (4 equiv). ^{*c*}CsF (4 equiv), 18-crown-6 (4 equiv). ^{*f*}TBAF (4 equiv). ^{*g*}Reaction time: 24 h.

trace amount of the desired product **3aa** was detected by GC-MS. We wondered if the yield could be improved by introducing a more nucleophilic Cl source. To our delight, after a screen of different salts, KCl was found to be the best one (Table 1, entries 2–4). Subsequently, a series of control experiments confirmed that both crown ether and CO₂ played essential roles in this transformation (Table 1, entries 5–6). Further study revealed that 46 °C was the optimal temperature (Table 1, entries 7–9). Decreasing the loading of KCl was less effective,¹⁹ and the yield could be enhanced to 58% by increasing the amount of KCl to 4 equiv (Table 1, entries 10–12). Finally, the best results were obtained by adjusting the

concentration of the F source carefully (Table 1, entry 13). Further replacing KF with CsF or TBAF did not give better results (Table 1, entries 14-15), and prolonging the reaction time to 24 h did not alter the reaction outcome to a large extent either (Table 1, entry 16).

With the optimal conditions in hand, we next set out to investigate the scope of the four-component coupling reaction with various aryne precursors (Scheme 2). Interestingly,



"Reaction conditions: 1 (0.2 mmol), 2a (0.5 mL), CO₂ (1 atm), KCl (4 equiv), KF (4 equiv), 18-crown-6 (4 equiv), 46 °C for 12 h. ^bThe regioisomer ratio was determined by ¹H NMR analysis.

monosubstituted substrates, such as 3-methoxybenzyne (from 1b) and 3-fluoro benzyne (from 1c), could be transformed with complete regioselectivity, while the reactions of different 4-substituted aryne precursors 1d-1f only gave moderate to good yields with poor regioselectivity. Similarly, in the case of triflate 1g, an inseparable mixture of regioisomers (1:1.9) was isolated in 48% yield. The above results might be attributed to different degrees of aryne distortions, which influenced the regioselectivity signal.²⁰ Additionally, electronically dissimilar disubstituted symmetrical arynes (from 1h-1j) proceeded with good chemical efficiency and provided the expected products 3ha-3ja in 47%-55% yields. In the case of unsymmetrical disubstituted aryne 3,5-dimethoxybenzyne (from 1k), the carboxylated product 3ka could also be isolated in 54% yield with excellent regioselectivity. Furthermore, the fused ring systems 11-10 reacted smoothly under the standard reaction conditions, furnishing the desired products in

moderate yields. Specifically, the trisubstituted aryne precursor **1p** was also a suitable substrate in this reaction and converted to the corresponding benzoate **3pa** in 34% yield.

The scope of the reaction was further expanded to a range of dichlorides. As shown in Scheme 3, replacement of DCE with





^aReaction conditions: 1a (0.2 mmol), 2 (0.5 mL), CO_2 (1 atm), KCl (4 equiv), KF (4 equiv), 18-crown-6 (4 equiv), 46 °C for 12 h.

 CH_2Cl_2 failed to provide the product **3ab**. Compared with **3aa**, the reactions delivered **3ac** and **3ad** in lower yields gradually when we lengthened the carbo-chain of DCE slowly. In addition, the reactions were found to be applicable to dichloroalkanes (**2e–2f**) containing different forms of olefin skeletons, which provided ample opportunities for the products (**3ae–3af**) to construct more complicated organic architectures.

Encouraged by these preliminary results, we speculated that the reaction might be modulated alternatively by introducing another electrophile with a higher activity such as benzyl chlorides. After careful modification of preceding optimized reaction conditions,²¹ the best outcome was obtained by using 2 (0.2 mmol), 1a (3 equiv), KCl (4 equiv), KF (4 equiv), and 18-crown-6 (4 equiv), in DCE (0.2 mL) at 46 °C for 18 h. We then explored the substrate scope of different benzyl chlorides (Scheme 4). To our delight, a series of substituents, such as

Scheme 4. Scope of Benzyl Chlorides^a



^aReaction conditions: 1a (3 equiv), 2 (0.2 mmol), CO_2 (1 atm), KCl (4 equiv), KF (4 equiv), 18-crown-6 (4 equiv), DCE (0.2 mL), 46 °C for 18 h. ^bReaction conditions: 1a (3 equiv), 2g (1 mmol), CO_2 (balloon), KCl (4 equiv), KF (4 equiv), 18-crown-6 (4 equiv), DCE (1 mL), 46 °C for 12 h, isolated yield.

nitrile, methoxy, fluoro, bromo, and even nitro, were well tolerated at different positions on the aromatic ring of benzyl chlorides, leading to the desired products (**3ag**–**3al**) in good to excellent yields. In addition, a scale-up experiment was performed; carrying out the reaction on a 1 mmol scale of **2g** provided **3ag** in 74% isolated yield. Notably, several polysubstituted benzyl chlorides **2m** and **2n** were also suitable substrates for this transformation, providing the corresponding products in 85% and 78% yields, respectively. Moreover, the cinnamyl chloride **2o** performed well under our reaction conditions and afforded the *o*-chloro benzoate **3ao** in 75% yield, implying the versatility of this reaction.

A series of transformations were investigated to further demonstrate the synthetic utility of this method. As shown in Scheme 5, product 3aa could be converted to 4 in 79% yield





^aReaction Condition: (1) **3aa** (0.2 mmol), NaI (5 equiv), acetone (1 mL), reflux, 48 h. (2) **3aa** (0.2 mmol), NaN₃ (2 equiv), DMF (1 mL), 70 °C, 12 h. (3) **3aa** (0.5 mmol), NaI (6 mol %), 1-methyl piperazine (1 mmol), NaHCO₃ (2 equiv), CH₃CN (3.5 mL), 90 °C, 24 h. (4) **3aa** (0.2 mmol), 4-tolylboronic acid (2.6 equiv), Ni(PPh₃)₂Cl₂ (3 mol %), PPh₃ (6 mol %), K₃PO₄·3H₂O (2.6 equiv), toluene (0.6 mL), 120 °C for 12 h.

via a halogen-exchange reaction.²² The nucleophilic substitution of **3aa** with NaN₃ afforded alkyl azide **5** in 95% yield.²³ Notably, treatment of **3aa** with 1-methyl piperazine gave the piperazine derivative **6** in 42% yield, which is a potential drug analogue for the treatment of atherosclerosis.²⁴ Furthermore, the Suzuki–Miyaura cross-coupling reactions of **3aa** with 4-tolylboronic acid furnished the arylated compound 7 in 38% yield.²⁵

To gain insight into the mechanism, several control experiments were conducted. Deuterium labeling studies of 11 and KCl were carried out by adding 2 equiv of D_2O under a N_2 atmosphere in DCE and THF, respectively (Scheme 6, eq





1). The results indicated that DCE is a better solvent than THF to generate free chloride. In addition, we also tried to catch the possible intermediate by adding 1 N HCl to quench the reaction (Scheme 6, eq 2.1). To our delight, we could detect very small amounts of the carboxylic acid 9 by GC-MS. To further identify our assumption, treatment of potassium benzoate 10 instead of aryne in the model conditions could afford corresponding ester 11 in 88% isolated yield (Scheme 6, eq 2.2), indicating that the *o*-chloro benzoate anion might be

Based on previous studies^{10,17} and a series of control experiments, a plausible mechanism for the CO_2 incorporation reaction is presented (Scheme 7). Initially, the *in situ* formed

Scheme 7. Proposed Mechanism

the possible intermediate.



aryne intermediate **A** from **1a** undergoes nucleophilic attack with KCl²⁶ to generate the aryl anion intermediate **B**. Then, the aryl anion **B** is trapped by CO₂ to afford the *o*-chloro benzoate anion **C**. Finally, the intermediate **C** undergoes an intermolecular nucleophilic substitution on DCE, leading to the formation of the product **3aa** (Path I). Alternatively, when benzyl chlorides are introduced, the reactions can afford **3ag**–**3ao** predominantly (Path II). However, the nucleophilic substitution of the intermediate **B** with **2** has never been detected under our reaction conditions.²⁷

In summary, we have developed a novel 3P-4CR of KCl, arynes, chloroalkanes, and CO_2 , providing an operationally simple method for the synthesis of different types of *o*-chloro benzoates. Remarkably, the reaction involves the formation of three different new C–Cl, C–C, and C–O bonds in a one-pot fashion. In addition, both chloro and ester groups of the products can be alternatively utilized for diverse transformations. Further studies on exploring new arynes and CO_2 -incorporating reactions are in progress in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b03193.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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(19) We envisioned that the reaction might proceed by a catalytic mechanism. However, the reaction only afforded **3aa** in 27% yield (Table 1, entry 10). And we could detect several byproducts by GC-MS such as phenyl 2-chlorobenzoate. The results implied that the *in situ o*-chloro benzoate anion would compete with Cl^- to catch the highly active and electrophilic aryne intermediate. Therefore, an excessive amount of KCl is necessary to inhibit the side reactions and force the *o*-chloro benzoate anion to react with DCE.

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