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Communication

1,2-Dibromoethane and KI mediated α-acyloxylation of ketones with carboxylic acids

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ABSTRACT

The 1,2-dibromoethane- and KI-mediated α-acyloxylation of ketones is reported in moderate to good yield without the use of transition metals and strong oxidants. Various acids are well tolerated with wide functional group compatibility. An 1,2-dibromoethane- and KI-catalysed reaction mechanism is proposed based on the results of control experiments.

α-Acyloxycarbonyl compounds are significant building blocks in synthetic organic chemistry [1] that can readily transform into various other functional groups, such as imidazoles, furans and oxazoles [2]. Traditionally, α-acyloxycarbonyl compounds can be prepared by the substitution reaction between α-halocarbonyl compounds [3] and α-diazoketones [4] with alkaline carboxylates or by the direct oxidative coupling of carbonyl compounds with toxic heavy metal oxidants such as $Pb(OAc)_4$, $Tl(OAc)_3$ and $Mn(OAc)_3$ [5]. Cu-catalysed oxidative coupling of ketones and carboxylic acids with oxygen as the sole oxidant have also been developed over the years [6]. Recently, to overcome the drawback from the use of toxic reagents or heavy metals, new metal-free oxidative coupling methods have been investigated. In 2005, Ochiai *et al.* first reported the iodobenzene-catalysed α-acyloxylation of ketones with acetic acid [7]. In 2011, Ishihara and co-workers reported the direct α-acyloxylation of carbonyl compounds with carboxylic acids under TBHP and TBAI conditions (Scheme 1a) [8]. Encouraged by this TBHP/TBAI system, chemists have achieved immense progress in the α-acyloxylation of ketones by using different substrates and mild oxidants, such as TBHP, $K_2S_2O_8$ and H_2O_2 [9]. While each of these approaches represents an important advance towards the objective of a general method for the synthesis of α-acyloxycarbonyl compounds, each of them still utilizes organic oxidants to complete the C-O coupling process. Although Tomkinson and co-workers have reported the α-acyloxylation of carbonyl compounds by treating ketones with *N*-methyl-*O*-benzoylhydroxylamine hydrochloride (Scheme 1b) [10], this method still needs a three-step reaction process to synthesize the substrates. Therefore, the development of a facile, environmentally benign and efficient protocol for the preparation of α-acyloxycarbonyl compounds from simple and readily available starting materials with a broad substrate scope is still highly desirable.

In this paper, we report the 1,2-dibromoethane (EDB)- and potassium iodide (KI)-mediated α-acyloxylation of ketones with carboxylic acids. The most important features of the present catalytic system include: (1) the direct use of commercially available materials, (2) transition-metal-free catalytic systems and (3) milder reaction conditions without the use of strong oxidants, wide functional group compatibility and a broad substrate scope.

In the investigation of the reaction conditions (Table 1), benzoic acid **1a** (1.0 equiv.) was initially treated with acetone **2a** (1 mL) in the presence of EDB (1.0 equiv.), potassium iodide (KI, 0.2 equiv.), and potassium carbonate (K_2CO_3, 1.5 equiv.) at 60 °C for 10 h to afford 2-oxopropyl benzoate **3a**, which was isolated by column chromatography in 72% yield (entry 1). The yield did not improve when examining different amounts of KI (entries 2-5). However, when we tried to replace the KI with NaI, the yield decreased to 64%, and **3a** was not detected when EDB was substituted with 1,2-dichloroethane (entries 6 and 7). Notably, we observed a satisfactory yield of 86% when the amount of additive EDB was increased to 1.5 equiv. (entry 10), and a further increase in EDB to 2.0 or 4.0 equiv. did not improve the yield of **3a** (entries 11 and 12). Subsequently, we found that 2 mL of acetone **2a** might be the most suitable equivalent, of which the isolated yield was improved to

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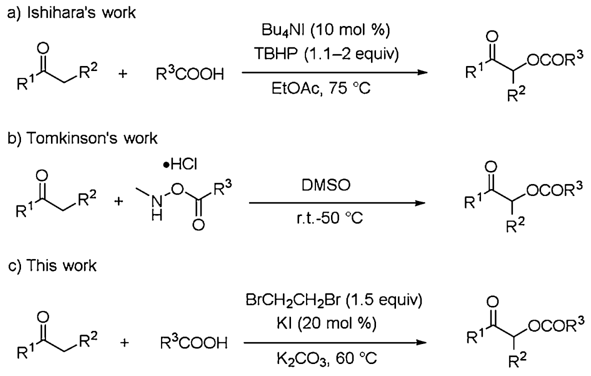
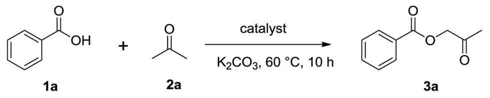


Scheme 1. Direct α-acyloxylation of ketones.

Table 1
Optimization of the reaction conditions.[a]



Entry	Additive (equiv.)	Catalyst (equiv.)	Acetone (equiv.)	Yield (%)[b]
1	EDB (1.0)	KI (0.2)	1.0 mL (26.0)	72[c]
2	EDB (1.0)	KI (0.1)	1.0 mL (26.0)	65
3	EDB (1.0)	KI (0.5)	1.0 mL (26.0)	70
4	EDB (1.0)	KI (1.0)	1.0 mL (26.0)	67
5	EDB (1.0)	KI (2.0)	1.0 mL (26.0)	50
6	EDB (1.0)	NaI (0.2)	1.0 mL (26.0)	64
7	DCE (1.0)	KI (0.2)	1.0 mL (26.0)	N.D.
8	EDB (0.2)	KI (0.2)	1.0 mL (26.0)	18
9	EDB (0.5)	KI (0.2)	1.0 mL (26.0)	28
10	EDB (1.5)	KI (0.2)	1.0 mL (26.0)	86
11	EDB (2.0)	KI (0.2)	1.0 mL (26.0)	85
12	EDB (4.0)	KI (0.2)	1.0 mL (26.0)	56
13	EDB (1.5)	KI (0.2)	0.5 mL (13.0)	42
14	EDB (1.5)	KI (0.2)	2.0 mL (52.0)	96 (94[c])
15	EDB (1.5)	KI (0.2)	4.0 mL (104.0)	92
16	EDB (1.5)	/	2.0 mL (52.0)	N.D.
17	/	KI (0.2)	2.0 mL (52.0)	N.D.

Abbreviations: EDB = 1,2-dibromoethane, DCE = 1,2-dichloroethane, N.D. = Not detected.

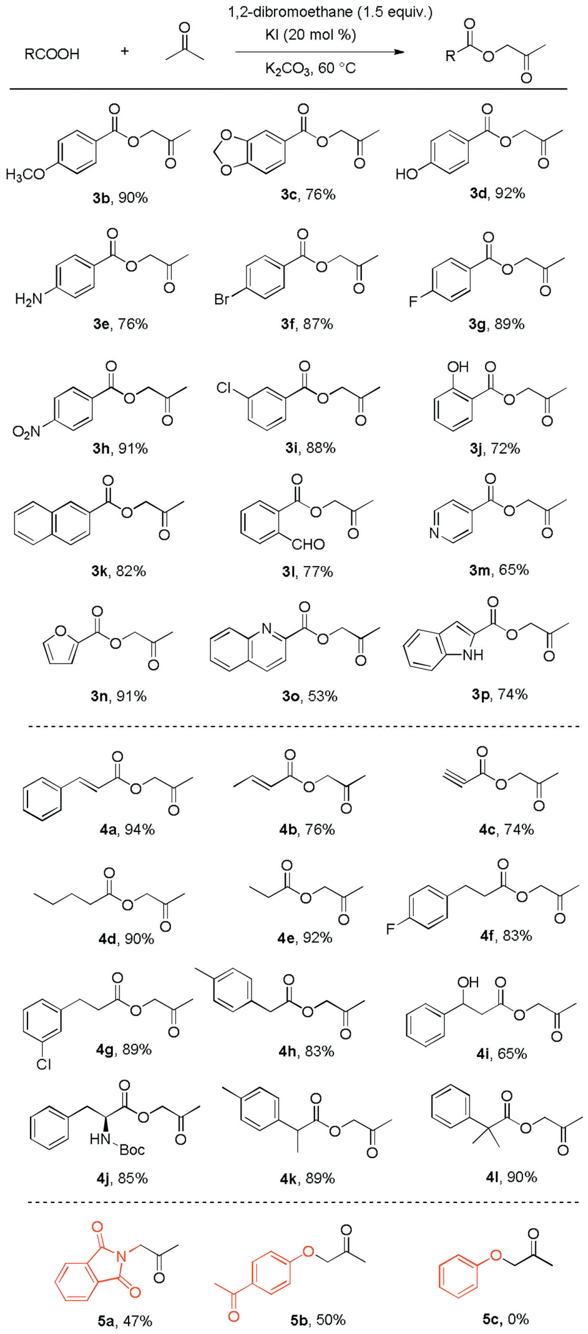
[a] Reaction conditions: **1a** (0.5 mmol), K_2CO_3, (0.75 mmol), additive, catalyst and acetone under air at 60 °C for 10 h.

[b] ^1H NMR yield, phloroglucinol as the internal standard.

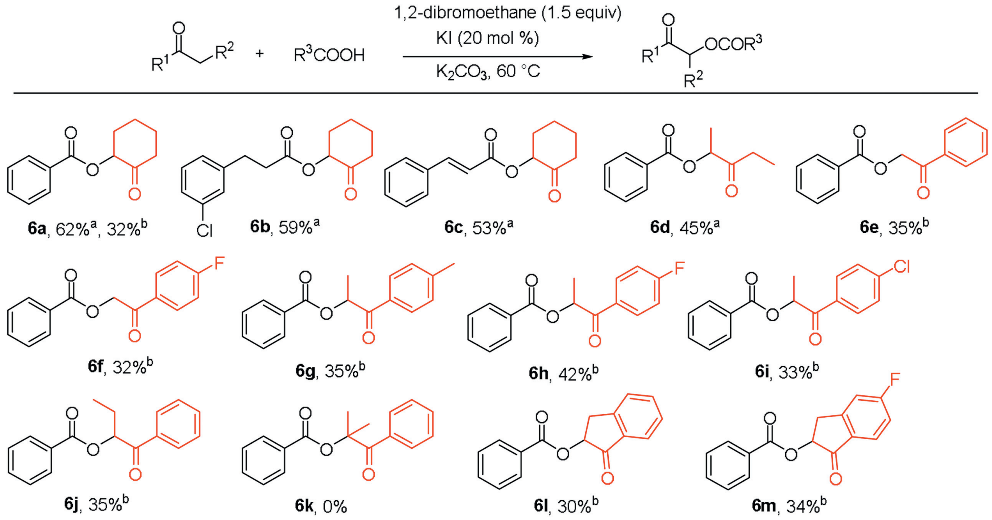
[c] Isolated yields.

94%, after evaluating a variety of different amounts of **2a** in the reaction (entries 13-15). Finally, it is important to mention that product **3a** was not detected in the absence of KI or EDB (entries 16 and 17). After a series of screening experiments, the optimal reaction conditions were obtained when **1a** was treated with an excess of acetone **2a** (2 mL, 52.0 equiv.), EDB (1.5 equiv.) and KI (0.2 equiv.) at 60 °C.

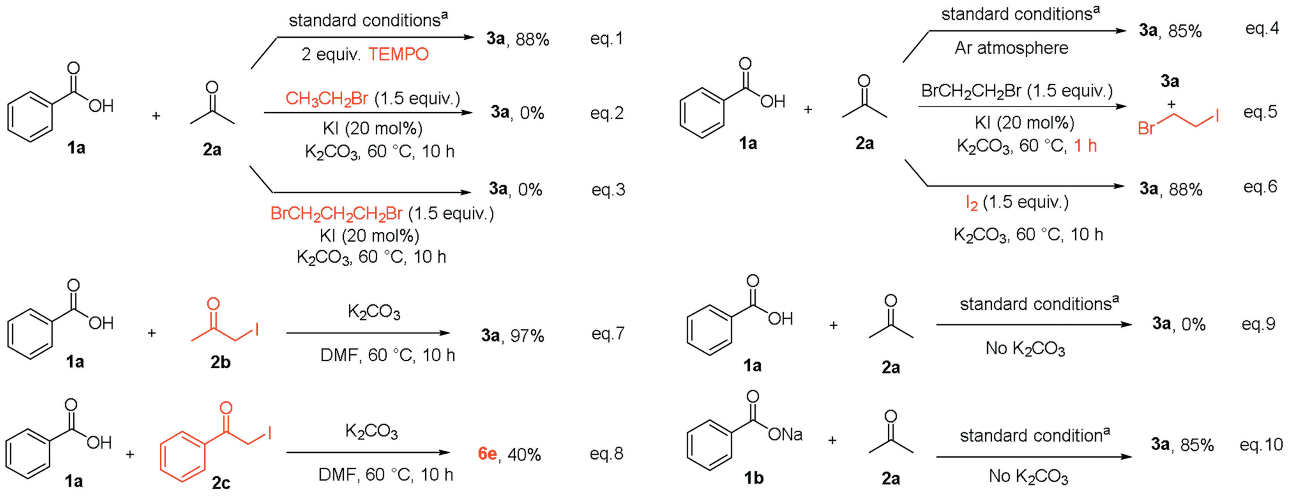
With the optimized reaction conditions in hand, we next evaluated the scope of the procedure by testing various carboxylic acids with acetone. First, a series of aromatic carboxylic acids were examined as shown in Scheme 2. Substrates with both electron-donating and electron-withdrawing substituents afforded the products in good to excellent yields under the standard conditions (**3b**-**3p**). Notably, hydroxy (**3d** and **3j**), amino (**3e**) and aldehyde (**3l**) groups on the aromatic ring were well tolerated, thus offering opportunities for further derivatization. Heterocyclic aromatic carboxylic acids were also investigated and afforded the desired products in 53%-91% yield (**3m**-**3p**). To test whether this method could be extended to other carboxylic acids, we examined the reaction of aliphatic carboxylic acids with acetone. To our excitement, the desired products were obtained in 65%-94% yield (**4a**-**4l**). Notably, cinnamic acid, crotonic acid and propiolic acid provided the desired products in high yield (**4a**-**4c**). Further exploration of acyloxylation to aliphatic carboxylic acids also worked smoothly and afforded the coupling products in very good yields (**4d**-**4h**). Notably, the hydroxy and *N*-protected amino groups on the aliphatic chain were well tolerated (**4i** and **4j**). It should be mentioned that steric hindrance proximal to the acid group also provided good yield, as exemplified by the successful synthesis of **4k** and **4l** (89% and 90% yield, respectively). We also attempted to use potassium phthalimide



Scheme 2. Scope of carboxylic acids. Reaction conditions: carboxylic acid (2.0 mmol), EDB (3.0 mmol), KI (0.4 mmol), K_2CO_3 (3.0 mmol), 8 mL acetone under air at 60 °C. Isolated yields.



Scheme 3. Scope of ketones. Isolated yields. Reaction conditions: [a] ketone (5 mL), carboxylic acid (2.0 mmol), EDB (3.0 mmol), KI (0.4 mmol), K_2CO_3 (3.0 mmol) under air at 60 °C; [b] ketone (2.0 mmol), carboxylic acid (3.0 mmol), EDB (3.0 mmol), KI (0.4 mmol), K_2CO_3 (3.0 mmol), 5 mL DMF under air at 60 °C.



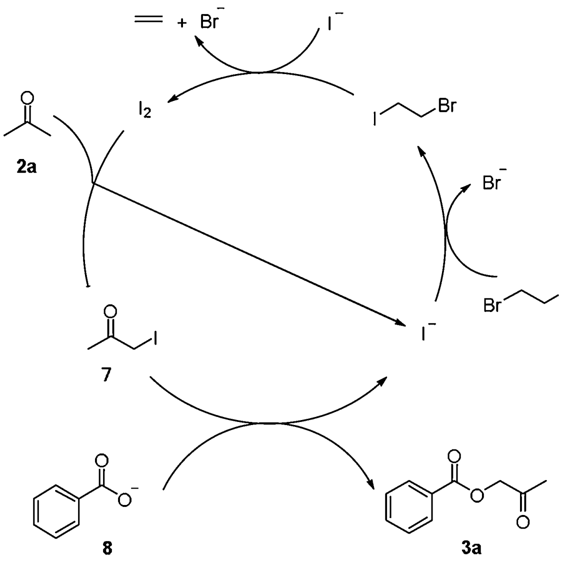
Scheme 4. Control experiments to determine the reaction mechanism.

and 4-hydroxyacetophenone with acetone under the standard reaction conditions to afford the corresponding products **5a** in 47% and **5b** in 50% yield, respectively.

To further investigate the utility of the EDB- and KI- mediated α-acyloxylation of a carboxylic acid with acetone in preparative organic synthesize, a gram-scale reaction was conducted. A total of 2.44 g of benzoic acid was treated with 40 mL of acetone **2a** (26.0 equiv.) to yield 2.98 g of product **3a** (84%), which was in accordance with the optimized reaction conditions (Table 1, entry 10).

After demonstrating a series of acids, we then investigated the scope of ketones with benzoic acid. Considering the excess use of acetone under our optimized conditions, we attempted to reduce the amount of ketone and use DMF as the solvent, as shown in Scheme 3. We first treated benzoic acid with both an excess and 1.0 equivalent of cyclohexanone, which provided the target products in 62% and 32% yield respectively (**6a**). When 3-(3-chlorophenyl)propanoic acid and cinnamic acid were treated with excess cyclohexanone, the desired products were isolated in 59% and 53% yield, respectively (**6b** and **6c**). An excess of 3-pentanone reacted with benzoic acid to provide the product in 45% yield (**6d**). We then turned our sights to the use of 1.0 equiv. of ketones. To our delight, acetophenone and 4-fluoroacetophenone reacted with benzoic acid to obtain desired products in 35% and 32% yield (**6e** and **6f**), respectively. Different substituted substrates of propiophenone were examined with benzoic acid to obtain the desired products in good yield (**6g**-**6i**). 1-Phenylbutan-1-one also gave the target product in 35% yield (**6j**). However, it should be noted that 2-methyl-1-phenylpropan-1-one was not suitable for the transformation, which indicated that steric effects had a strong influence on the transformation. 2,3-Dihydro-1*H*-inden-1-one and 5-fluoro-2,3-dihydro-1*H*-inden-1-one were also tested to generate the products in 30% and 34% yield (**6l** and **6m**), respectively.

The following control experiments were carried out to gain insight into the mechanism of the reaction. First, target product **3a** was isolated in 88% yield when 2 equiv. of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) as a radical scavenger was added to the standard reactions, indicating that this transformation may not proceed *via* a radical pathway (Scheme 4, Eq. (1)). The generation of I_2 was observed when treating EDB and KI in acetone at 60 °C while the I_2 was not found in the absence of EDB (details in Supporting information). Besides, bromoethane and 1,3-dibromopropane were used to replace EDB under the optimized conditions, which failed to provide the desired product (Scheme 4, Eqs. (2) and



Scheme 5. Proposed reaction mechanism.

(3)). The reaction was also carried out under an argon atmosphere, which afforded product **3a** in 85% yield (Scheme 4, Eq. (4)). The above experiments indicated that the EDB plays an important role in the generation of I_2. In addition, the generation of 1-bromo-2-iodoethane was detected by GC-MS when reduced the reaction process to one hour (Scheme 4, Eq. (5)). The product **3a** also formed when we replaced EDB and KI with I_2 (Scheme 4, Eq. (6)). Remarkably, the α-iodoacetone **2b** and α-iodoacetopheneone **2c** both could react with benzoic acid to afford the desired products **3a** and **6e**, respectively (Scheme 4, Eqs. (7) and (8)). Finally, the direct use of sodium benzoate **1b** obtained **3a** in 85% yield, while benzoic acid **1a** failed to afford product **3a** without the addition of K_2CO_3, which demonstrated that a carboxylic anion might be a key intermediate (Scheme 4, Eqs. (9) and (10)).

Based on the above control experiments and previous literature reports, a plausible mechanism was proposed in Scheme 5. First, the iodine anion reacted with 1,2-dibromoethane to form 1-bromo-2-iodoethane, which then reacted with the iodine anion to give molecular iodine [11]. The subsequent reaction between iodine and acetone generated the intermediate 1-iodoacetone **7** [12]. Meanwhile, benzoic acid **2a** was transformed into benzoate **8** in the presence of base. Finally, the reaction between intermediate **7** and benzoate **8** generated the desired product **3a**.

In conclusion, we have developed the 1,2-dibromoethane- and KI-mediated α-acyloxylation of ketones with carboxylic acids. Various acids, including aromatic and aliphatic acids, are well tolerated with wide functional group compatibility, and a series of ketones were also investigated. This protocol provides a convenient and environmentally benign method for the synthesis of α-acyloxycarbonyl compounds without the use of transition metal and strong oxidants, even on a gram scale. An 1,2-dibromoethane and KI-catalysed reaction mechanism is proposed based on the results of control experiments. Further investigation of the relevant reactions is underway in our laboratory.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.08.052.

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