Reusable ionic liquid-catalyzed oxidative esterification of carboxylic acids with benzylic hydrocarbons via benzylic Csp³–H bond activation under metal-free conditions†

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A metal-free protocol for the direct oxidative esterification of the Csp³–H bond in benzylic hydrocarbons with carboxylic acids using heterocyclic ionic liquid as catalyst has been reported. The catalyst 1-butylpyridinium iodide could be easily recycled and reused for at least four cycles without obvious loss of catalytic activity.

Introduction

It is well known that benzylic esters are prevalent functional groups in medicinal agents and natural products.¹ The traditional methods of preparing benzylic esters by utilizing benzylic alcohols/bromides/chlorides with carboxylic acids as coupling partners have been reported over the decades (Scheme 1a).² Furthermore, Khan’s group proposed benzylic esters can also be obtained by the reaction of aromatic carboxylic acids with substituted toluenes in the presence of NaBrO₃/NaHSO₃ in early 2003.³ However, some approaches have disadvantages of long reaction time or sensitivity to the environment. With increasing interest in transition metal-catalyzed C–H bonds activation to construct C–O bonds, several types of transition metals, including Cu, Pd, Pt and Rh have been recently revealed admirable catalytic activity in esterification.⁴ Among them, the approach of Pd-catalyzed benzylation of toluene with carboxylic acids under 1 atm of oxygen has been disclosed by Zhang’s group (Scheme 1b).⁴j It did not need to be pre-functionalized and provided a more facile, atom-economic method to prepare benzylic esters. Despite their obvious potential application, these transition metal-catalyzed C–H bond activation methods suffered from a few drawbacks such as expense and toxicity of transition metals, which limit their practicability. Hence, the development of a facile and practical approach for constructing benzylic esters under metal-free conditions is extremely desirable.

In 2012, Yu and co-workers established Bu₄NI-catalyzed esterification of benzylic Csp³–H bonds (Scheme 1c).⁵ Subsequently, Singh’s group applied carboxylic acids with alkyl benzenes to synthesis of benzyl esters catalyzed by NBS with TBHP as an oxidant under alkaline conditions.⁶ Moreover, Patel’s group presented a strategy for the efficient preparation of benzylic esters through Bu₄NI-catalyzed cross dehydrogenative coupling of alkylbenzenes as the only precursor.⁷ The main advantage of these methodologies is their environmentally friendliness.

In recent years, ionic liquids (ILs) are widely used as an environmentally eco-friendly and recyclable reaction medium or catalyst in green synthesis,⁸ which have attracted great attention of chemists all around the world. Compared with other organic agents, ILs have unique advantages such as low toxicity, easy recyclability, excellent chemical and thermal

Scheme 1 A variety of methods for the synthesis of benzyl esters.
stability, negligible vapor pressure, as well as good solubility with organic and inorganic compounds.\(^{7}\) Latterly, transition metal-catalyzed C–H activation reactions with ionic liquids as solvents have already been developed.\(^{8}\) Up to now, ionic liquids promoted C–C bond and catalyzed C–N bond formation reactions have been published by our group.\(^{13}\) However, as far as we know, classical heterocyclic ILs-catalyzed benzylic C\(^{sp3}\)–H activation for C–O bond formation to prepare benzyl esters have been rarely reported. With this background in mind, we herein report a heterocyclic IL-catalyzed the direct oxidative esterification between C\(^{sp3}\)–H bond of benzylic hydrocarbons and carboxylic acids for the synthesis of benzyl esters under metal-free conditions.

**Results and discussion**

We commenced our study using benzoic acid (1a) and toluene (2a) as a model system (Table 1). Firstly, the reaction of 1a and 2a was carried out at 80 \(^\circ\)C for 8 h to give the desired benzyl ester product 3a in 70% yield in the presence of 1.4 equiv. of TBHP and 20 mol% [BPy]II (Table 1, entry 1). Encouraged by this result, further optimization of conditions for the oxidative esterification was explored. Unfortunately, other ionic liquids such as 1-butylpyridinium bromide ([BPy]Br) and 1-butylpyridinium chloride ([BPy]Cl) were proved to be poor activity for this esterification (Table 1, entries 2–3). Meanwhile, it was found that essentially no reaction occurred in the catalyst-free system (Table 1, entry 4). The yield of product 3a was not improved obviously by increasing the amount of TBHP to 2 equiv. (Table 1, entry 5). Subsequently, when the dosage of [BPy]I was increased from 20 mol% to 25 mol%, there was no significant improvement in yield (Table 1, entry 6). In contrast, decreasing the amount of [BPy] resulted in dramatically reducing the yield of 3a (Table 1, entries 7–8). After a brief screening of oxidants such as 3-chloroperbenzoic acid, hydrogen peroxide, di-tert-butyl peroxide and iodobenzene diacetate, TBHP remained the optimal choice (Table 1, entries 1, 9–12). Finally, the effects of reaction temperature and reaction time were also screened (Table 1, entries 13–17), the results suggested that the optimized reaction temperature and time were 80 \(^\circ\)C and 8 h, respectively. Therefore, the reaction was carried out with [BPy]I (20 mol%) as the catalyst and TBHP (1.4 mmol, 70% aqueous solution) as the oxidant at 80 \(^\circ\)C for 8 h.

Under the optimized reaction conditions, the scope of carboxylic acids was explored. As shown in Table 2, a wide variety of benzoic acid derivatives with electron-donating substitutes and electron-withdrawing substitutes underwent this esterification smoothly and afforded the corresponding benzyl esters (3b–3t) in good to excellent yields. It is important to note that the methyl or nitro group substituted at ortho, meta- or para-position of benzene ring were all compatible (3b–3d, 3q–3s). In particular, the multisubstituted substrates such as 2,3,4,5,6-pentafluorobenzoic acid, 3,5-dinitrobenzoic acid could be transformed well with 73% and 93% yield, respectively (3k, 3l). All of the above results indicated that the electronic and steric effects had no significant influence on the yield of products. To our delight, cinnamic acid and terephthalic acid were also amenable substrates (3u, 3v). In order to better expand substrates scope, aromatic heterocyclic carboxylic acid such as 2-phenyl-2H-1,2,3-triazole-4-carboxylic acid and 2-furoic acid

| Entry | Catalyst (mol%) | Oxidant\(^a\) (1.4 mmol) | Temp. (°C) | Time (h) | Yield\(^c\) (%) |
|-------|------------|-----------------|---------|--------|----------|
| 1     | [BPy]I (20) | TBHP            | 80      | 8      | 70       |
| 2     | [BPy]Br (20) | TBHP            | 80      | 8      | Trace    |
| 3     | [BPy]Cl (20) | TBHP            | 80      | 8      | N.R.\(^d\) |
| 4     | —           | TBHP            | 80      | 8      | N.R.     |
| 5     | [BPy]I (25) | TBHP            | 80      | 8      | 72\(^e\) |
| 6     | [BPy]I (15) | TBHP            | 80      | 8      | 71       |
| 7     | [BPy]I (10) | TBHP            | 80      | 8      | 57       |
| 8     | [BPy]I (10) | TBHP            | 80      | 8      | Trace    |
| 9     | [BPy]I (20) | m-CPBA          | 80      | 8      | N.R.     |
| 10    | [BPy]I (20) | H\(_2\)O\(_2\)  | 80      | 8      | N.R.     |
| 11    | [BPy]I (20) | DTBP            | 80      | 8      | N.R.     |
| 12    | [BPy]I (20) | Phil(OAc\(_2\)) | 80    | 8     | N.R.     |
| 13    | [BPy]I (20) | TBHP            | 80      | 10     | 72       |
| 14    | [BPy]I (20) | TBHP            | 80      | 6      | 26       |
| 15    | [BPy]I (20) | TBHP            | 80      | 10     | 70       |
| 16    | [BPy]I (20) | TBHP            | 80      | 6      | 60       |

\(^a\) Reaction conditions: 1a (1 mmol), 2a (20 mmol), oxidant (1.4 mmol). \(^b\) TBHP: tert-butyl hydroperoxide 70% in water; m-CPBA: m-chloroperoxybenzoic acid; DTBP: di-tert-butyl peroxide; H\(_2\)O\(_2\): 30% in water. \(^c\) Isolated yield. \(^d\) Not reaction. \(^e\) TBHP: 2.0 mmol.
were explored and the corresponding products (3w, 3x) were obtained in 85% and 55% yields, respectively.

Subsequently, we investigated the scope of benzylic hydrocarbons. As shown in Table 3, a wide range of toluene derivatives with electron-donating groups and electron-withdrawing groups were well tolerated and obtained the desired products (4a–4g) in moderate to good yields. It is worth noting that p-xylene and mesitylene only gave monoesterification products (4a, 4b) in 78% and 82% yields, respectively. When the substrate with p-OCH3 was used, the target product (4c) was afforded in yield of 71%. In particular, the chloro group substituted at ortho-, meta- or para-position of benzene ring were all amenable substrates (4e–4g). Additionally, both ethylbenzene and cumene were suitable reactants, affording the corresponding products (4h, 4i) in moderate yields.

To further demonstrate the potential application of the esterification method in industry, an IL-catalyzed gram-scale esterification between 2-nitrobenzoic acid and toluene was investigated (Scheme 2). The result showed that the reaction was easily performed under the optimized reaction conditions to give the desired benzyl ester in 80% isolated yield.

In order to validate the reaction mechanism, control experiments were carried out (see the ESI†). In the presence of 2 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl) as a free radical scavenger, the esterification was almost inhibited under the optimal conditions. When the amount of TEMPO was increased to 3 equiv., benzyl benzoate as the target could not be obtained at all. The results showed that the esterification may involve a radical pathway.

Table 2 Esterification of toluene with various carboxylic acids

| R COOH | CH3 | [BPy]I | TBHP | Yield (%) |
|--------|-----|-------|------|-----------|
| 3a     | 70  |       |      |           |
| 3b     | 91  |       |      |           |
| 3c     | 75  |       |      |           |
| 3d     | 64  |       |      |           |
| 3e     | 84  |       |      |           |
| 3f     | 64  |       |      |           |
| 3g     | 88  |       |      |           |
| 3h     | 87  |       |      |           |
| 3i     | 88  |       |      |           |

Table 3 Esterification of benzoic acid with benzylic hydrocarbons

| R COOH | H R1 | [BPy]I | TBHP | Yield (%) |
|--------|------|-------|------|-----------|
| 4a     | 78   |       |      |           |
| 4b     | 82   |       |      |           |
| 4c     | 71   |       |      |           |
| 4d     | 82   |       |      |           |
| 4e     | 38   |       |      |           |
| 4f     | 45   |       |      |           |
| 4g     | 64   |       |      |           |

Scheme 2 Gram-scale oxidative esterification.

Fig. 1 Recycling reactions.
Based on the results of control experiments and previous studies, a possible radical mechanism is proposed (Scheme 3). Initially, [BPy][I] is oxidized by TBHP to generate \([\text{[BPy]}][\text{IO}_2^-]\) A or \([\text{[BPy]}][\text{IO}_2^+]\) B species. Subsequently, the benzyl radical C is obtained from the hemolytic cleavage of a benzylic C–H bond in the presence of A or B, followed by combination with benzoic acid to give the benzyl ester radical anion F. Finally, the desired product benzyl ester is produced by losing an electron from F with the assistance of hydroxyl radical (Scheme 3, path A). Furthermore, the benzyl radical is easily oxidized by active iodine species A or B to give the benzyl cation D and the hydroxide ion simultaneously. Subsequently, benzoic acid is deprotonated by the hydroxide ion to form the benzoate anion E. At last, the electrostatic attraction between the benzoate anion with specie E to yield corresponding product 3a (Scheme 3, path B).

It’s worth noting that ionic liquid could be easily recycled. 2-Chlorobenzoic acid and methylbenzene were chosen as model substrates to study the reusability of the catalyst [BPy][I] under standard reaction conditions. After completion of the reaction, ethyl acetate and water were added, and then the ionic liquid [BPy][I] was recovered from the aqueous phase and reused without the significant loss of its activity (Fig. 1).

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**Conclusions**

In summary, we have developed classic heterocyclic ionic liquid-catalyzed oxidative esterification of carboxylic acid derivatives with benzylic hydrocarbons. Most importantly, an inexpensive and recyclable ionic liquid [BPy][I] is reused for at least four cycles with similar catalytic activity. Ionic liquid catalyzed C–H bond activation reactions are ongoing in our laboratory.

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