PAPER

Mechanically induced solvent-free esterification method at room temperature†

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Herein, we describe two novel strategies for the synthesis of esters, as achieved under high-speed ball-milling (HSBM) conditions at room temperature. In the presence of I_2 and KH_2PO_2, the reactions afford the desired esterification derivatives in 45% to 91% yields within 20 min of grinding. Meanwhile, using KI and $P(OEt)_3$, esterification products can be obtained in 24% to 85% yields after 60 min of grinding. In addition, the I_2/KH_2PO_2 protocol was successfully extended to the late-stage diversification of natural products showing the robustness of this useful approach. Further application of this method in the synthesis of inositol nicotinate was also discussed.

Introduction

Mechanochemistry has been a popular topic in recent decades because it is a solution-free and energy-efficient approach, which complies with green chemistry. High-speed ball-milling (HSBM) is a green mechanical technique used in organic synthesis and has opened unique opportunities in synthetic organic chemistry.[1] HSBM facilitates reactions with insoluble reactants, and enables solvent-free synthetic procedures to successfully avoid the use of environmentally harmful and toxic solvents, among other advantages.[2] What's more, HSBM can directly break or stretch chemical bonds because the role of mechanical action is usually to provide better contact between the reagents.[3] More experimental results indicate that solvent-free milling can lead to different product compositions or catalyst combinations compared to those obtained by analogous solution-based protocols. The Faraday Discussion Mechanochemistry which took place 2014 in Montreal have indicated that the importance of mechanical processing in the context of pharmaceuticals materials science.[3b] For these reasons, much catalysts can be used in high-speed ball-milling to optimize organic reactions.[4]

The ester bond is found in a plethora of naturally occurring and pharmaceutically relevant molecules.[5] This bond occupies an important role in pharmaceutical chemistry with esterification reactions being among the most commonly used reactions in medicinal chemistry.[6] Natural products modified by esterification reactions show better biological activity than before modification, but these reactions often require large amounts of environmentally harmful solvents and catalysts.[7]

In recent years, many researchers have devoted themselves to exploring green and efficient esterification reactions. Common strategies of transition metal catalysis and pre-functionalization are reported for the synthesis of ester groups. Previously, Buchwald *et al.* described a method for the preparation of phenyl esters from aryl chlorides *via* palladium-catalysed carbonylation (Scheme 1a).[8] In 2011, Robles *et al.* demonstrated a mild and regioselective method of esterification and amidation using Gregg-Samuelson-type conditions (Scheme 1b).[9] In 2018, Szostak and coworkers reported an alternative transition-metal-free method for esterification of amides (Scheme 1c).[10] Recently, Lee and coworkers developed a new disconnection approach for the formation of aryl esters by a nickel-catalysed radical cross-coupling reaction of a redox-active ester with an aryl zinc reagent (Scheme 1d).[11] When transition metals are used in drug synthesis, the purification of the reaction becomes tedious. Prefunctionalization will reduce atom economy and increase the experimental procedures. We have currently been focusing on the development of novel, atom-economical, environmentally friendly methods for esterification under HSBM conditions.

Herein, we report two novel strategies for the synthesis of ester groups under solvent-free milling (Scheme 1e). Through modification of the reaction conditions, modes of reactivity have been observed that are different from those in solution. Compared with the preceding procedures of esterification, I_2/KH_2PO_2 system and $KI/P(OEt)_3$ system are solvent-free, transition-metal-free and prefunctionalization no need.
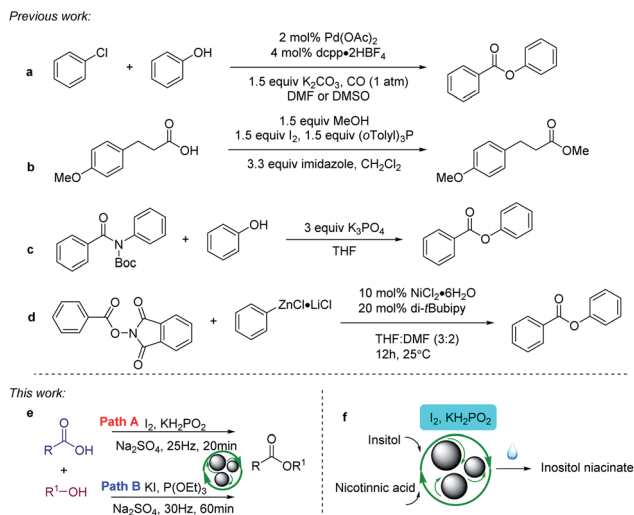
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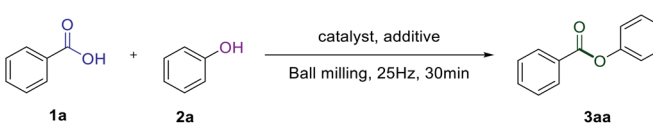[c] Institute of Solid State Chemistry and Mechanochemistry, Novosibirsk, Russia

Scheme 1 Mechanically induced synthetic of derivatives containing an ester group. (a) Buchwald's work; (b) Robles's work; (c) Szostak's work; (d) Lee's work; (e) this work; (f) mechanosynthesis of inositol nicotinate.

Moreover, KH_2PO_2 and $P(OEt)_3$ can be easily removed as effective substitutes of PPh_3. In addition, we discuss the advantages of this method in the synthesis of inositol nicotinate (Scheme 1f).

Results and discussion

At the outset, reactions between benzoic acid **1a** and phenol **2a** were evaluated with different combinations of additives and phosphine, where anhydrous sodium sulfate was chosen as a helpful grinding auxiliary for better substrate mixing on the basis of our previous research; the selected results were summarized in Table 1. To our delight, both I_2 and KI additives could afford desired product **3aa** in good yields after 30 min of grinding, where I_2 worked better than KI (Table 1, entries 1–7). We optimized both the I_2 and KI strategies in order to discuss the different reaction efficiencies and reaction mechanisms of similar additives under the mechanochemistry process. Next, several kinds of phosphines were tested (Table 1, entries 8–16). The I_2 with KH_2PO_2 gave the best result of 91%, while other phosphines gave lower yields under the same conditions (Table 1, entries 2–10). For KI, the reaction with $P(OEt)_3$ as phosphine gave the most satisfactory result, while others were inferior (Table 1, entries 13–15). To further optimize the reaction conditions, we tested the amount of additives and phosphines. The best yield of 75% was given by adding 0.75 mmol KI and 0.5 mmol $P(OEt)_3$ (Table 1, entry 17). Decreasing additive and phosphate loadings led to erosion in yield (Table 1, entries 11–13, 19 and 20). From the experimental results, the corresponding products were difficultly obtained without iodine or potassium iodide as additives (Table 1, entries 2 and 18). Furthermore, a simple comparison of the $KI/P(OEt)_3$ induced reaction under solvent-based conditions was conducted (Table 1, entries 19 and 22), and the reaction could hardly be promoted

Table 1 Optimization of the reaction conditions[a]

Entry	Additive	Phosphines	Yield[b] (%)
1	I_2	—	n.d.
2	—	PPh_3	n.d.
3	I_2	PPh_3	84
4	KI	PPh_3	66
5	NaI	PPh_3	52
6	CuI	PPh_3	n.d.
7	FeI_2	PPh_3	12
8	I_2	K_3PO_4	n.d.
9	I_2	NaH_2PO_2	34
10	I_2	KH_2PO_2	91
11[c]	I_2	KH_2PO_2	67
12[d]	I_2	KH_2PO_2	83
13	KI	$P(OEt)_3$	63
14	KI	$P(OMe)_3$	32
15	KI	$P(OBut)_3$	41
16	I_2	$P(OEt)_3$	83
17	KI	—	n.d.
18	—	$P(OEt)_3$	Trace
19[e]	KI	$P(OEt)_3$	75
20[f]	KI	$P(OEt)_3$	44
21[g]	KI	$P(OEt)_3$	33
22[h]	KI	$P(OEt)_3$	n.d.

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.5 mmol), **2a** (0.6 mmol), additive (0.5 mmol), phosphine (0.5 mmol), and anhydrous sodium sulfate (0.4 g) at 25 Hz for 30 min, using two stainless steel balls ($\phi = 1.2$ cm, $\Phi_{MB} = 0.036$) in 50 mL stainless steel vial. [b] Yield based on **1a**. [c] 0.5 equiv. I_2 was used. [d] 0.5 equiv. KH_2PO_2 was used. [e] 1.5 equiv. KI was used. [f] 0.5 equiv. KI was used. [g] 0.5 equiv. $P(OEt)_3$ was used. [h] Yield of the comparative experiment: **1a** (0.5 mmol), **2a** (0.6 mmol), KI (0.5 mmol), $P(OEt)_3$ (0.5 equiv.), and CH_2Cl_2 (20 mL) at room temperature.

at room temperature, which verified our hypothesis that HSBM may induce high activity when using $KI/P(OEt)_3$. To the best of our knowledge, there was no report of inorganic iodine salts or inorganic phosphorus salts promoted esterification reactions, which inspired our interest in probing these two systems.

The mechanochemistry process parameters usually have a strong influence on the outcomes, as previously shown by us and others.[12] Thus, a combined assessment of the grinding time and vibration frequency was carefully carried out; the results of
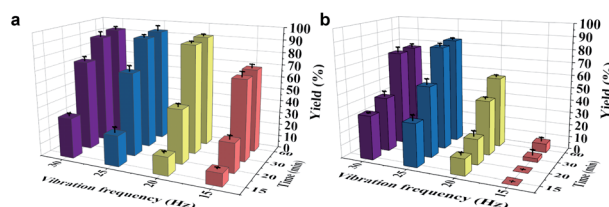
Fig. 1 Influence of milling time and frequency on the reaction. (a) Path a; (b) path b.

Table 2 Esterification between carboxylic acid and alcohol[ab]

I$_2$/KH$_2$PO$_2$ system strategy are summarized in Fig. 1a. The yields increased gradually as the frequency was increased from 15 to 20 Hz. However, in contrast to the apparent influence of frequency, variation in the grinding time did not show any obvious difference from 20 to 30 Hz, where the best result could

be obtained by milling at 30 Hz within 30 min (93% yield). However, the yield under optimal conditions did not change much from that conducted at 25 Hz with 20 min. For comprehensive energy consumption and environmental friendliness, we chose 25 Hz and 20 min as the subsequent experimental conditions. When we recorded the results of the KI/P(OEt)$_3$ strategy (Fig. 1b), the best result was obtained by milling at 25 Hz within 60 min (82% yield). Of note, further increase the vibration frequency (30 Hz) led to a decrease of yield (76%). Since the reaction substrates are the same in these two systems, we speculate that distinct intermediates with inconsistent sensitivity to reaction energy would be presence.

With the optimal conditions in hand, there was a large difference in yield between the two different reaction systems, so substrate expansion was divided into two parts for elucidation. The scopes and limitations of this I$_2$/KH$_2$PO$_2$ promoted methodology were investigated first by using various benzoic acids. The results are presented in Table 2. The electronic properties of the phenyl ring substituents of the carboxylic acids had some effect on the reaction. Generally, carboxylic acids possessing electron-withdrawing groups produced esters with lower yields (**3ad**, **3ae**, and **3af**). Carboxylic acids possessing electron-donating groups produced esters with higher yields (**3ag**, **3ah**, and **3ai**). The procedure tolerated a range of functional groups, such as chloro, bromo, naphthalene, and pyridine groups. The compatibility of halogen groups was synthetically useful since the products could easily be further modifiable (**3ab** and **3ac**). Notably, 2-naphthoic acid and nicotinic acid ran smoothly under the standard conditions, producing esters in 85 and 83% yields, respectively (**3aj** and **3ak**). Furthermore, butyric acid was explored. This reaction generated **3al** in moderate yields; the reason for the lower yield might be the volatility of fatty acids. Then, the esterification of benzoic acid with several phenols and alcohols was investigated. Gratifyingly, *p*-cresol and 4-(*tert*-butyl) phenol produced *p*-tolyl benzoate **3ba** and 4-(*tert*-butyl) phenyl benzoate **3bb** in 87 and 76% yields, respectively. As expected, the trifluoromethyl and halogen groups on the phenyl ring of phenol derivatives were well compatible under the standard procedure (**3bc**–**3bf**). The *ortho* steric hindrance will reduce the yield of the product, even with a prolonged reaction time (**3bj** and **3bk**). Phenolic compounds with electron withdrawing groups can produce corresponding esters in medium to good yields (**3bg**, **3bh**, and **3bi**). Methanol, ethanol, and butyl alcohol afforded the ester in 63%, 72% and 75% yield, respectively (**3ca**–**3cc**). Notably, the solketal could obtain the product **3cd** in a medium yield.

Next, the KI/P(OEt)$_3$ promoted esterification reaction was examined. Unfortunately, it was observed that the KI/P(OEt)$_3$
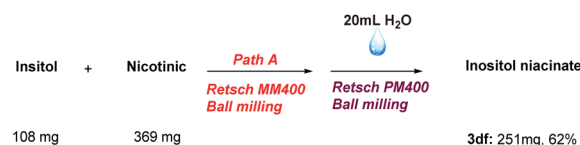
Scheme 2 Mechanosynthesis of inositol nicotinate.

Table 3 Chiral substrate[a]

3da: A 86%   **3da: B 65%**

3db: A 23%[b]   **3dc: A 27%[b]**
B trace[c]   **B 6%[c]**

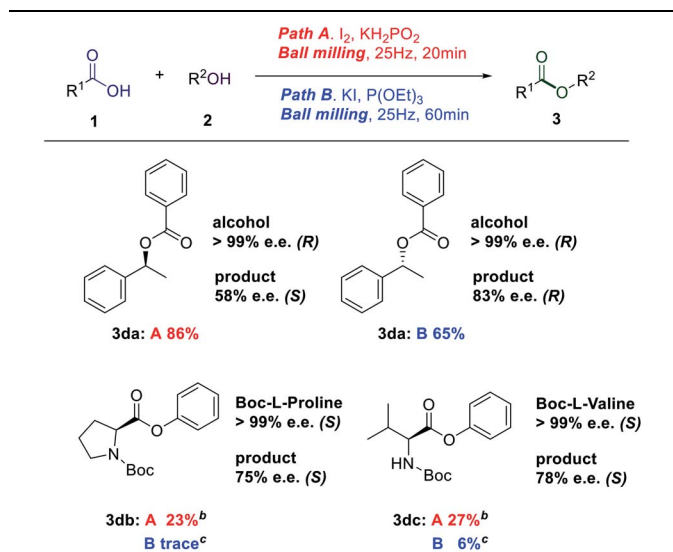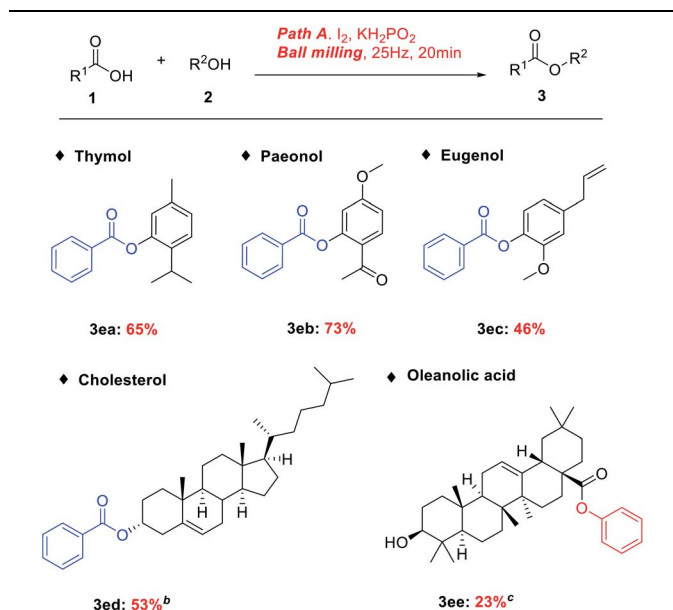[a] See Table 1. [b] **1** (1.0 mmol), **2** (0.5 mmol), I$_2$ (1.0 mmol), KH$_2$PO$_2$ (1.0 mmol) and anhydrous sodium sulfate (0.4 g) at 15 Hz within 60 min in mixer mill. [c] **1** (1.0 mmol), **2** (0.5 mmol), KI (1.50 mmol), P(OEt)$_3$ (1.0 mmol) and anhydrous sodium sulfate (0.4 g) at 15 Hz within 120 min in mixer mill.

did not show better reaction efficiency than the I$_2$/KH$_2$PO$_2$ system. As shown in Scheme 2, the varied substrate scope was evaluated. Compared with I$_2$/KH$_2$PO$_2$, the yield of esterification reaction through KI/P(OEt)$_3$ is reduced. Compared with that under I$_2$/KH$_2$PO$_2$ conditions, the activity of methanol, ethanol and n-butanol in the conversion to corresponding esters was greatly weakened under KI/P(OEt)$_3$ conditions (**3ca–3cc**). The

Table 4 Late-stage diversification[a]

♦ **Thymol**   ♦ **Paeonol**   ♦ **Eugenol**

3ea: 65%   **3eb: 73%**   **3ec: 46%**

♦ **Cholesterol**   ♦ **Oleanolic acid**

3ed: 53%[b]   **3ee: 23%[c]**

[a] See Table 1. [b] **1** (2.0 mmol). [c] **2** (3.0 mmol).

solketal could not afford product **3cd** under these conditions, and butyric acid failed to deliver the desired ester. The KI/P(OEt)$_3$ esterification reaction had serious substrate restrictions, which may be related to its possible reaction mechanism.

After that, the chiral molecule phenylethanol was tried. Phenylethyl benzoate could be obtained under two
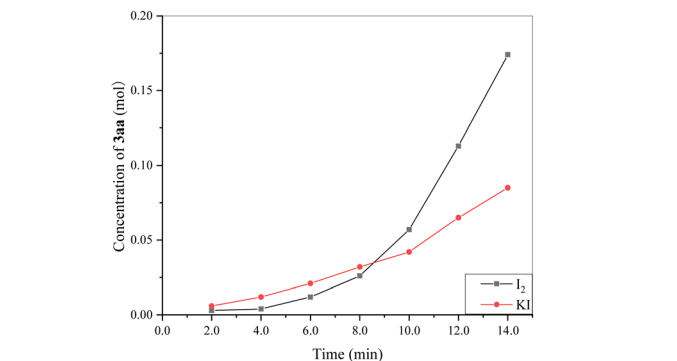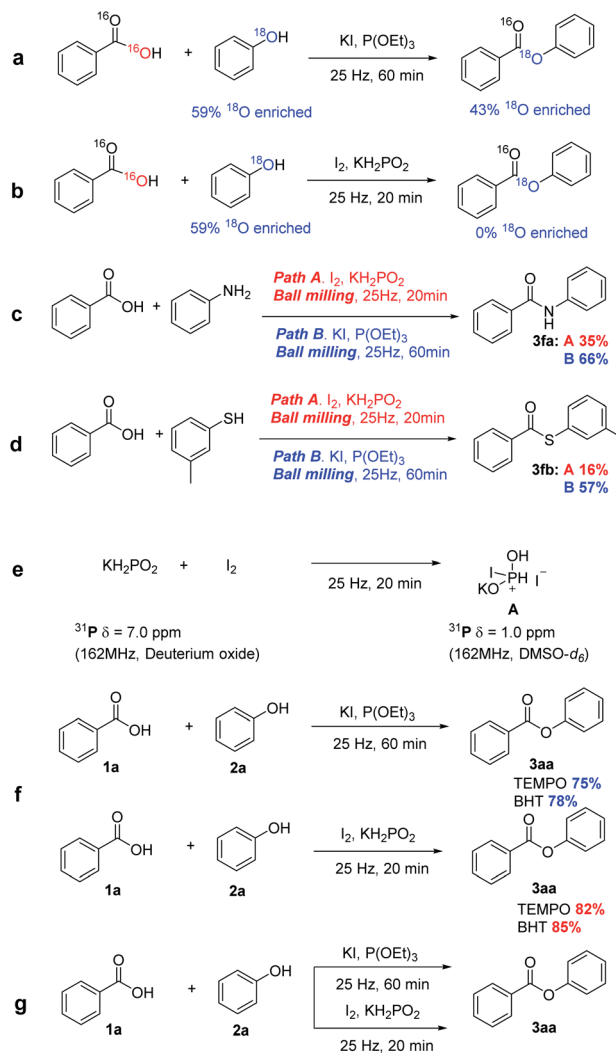
Scheme 3 Control experiments. (a) Mechanistic study of KI/P(OEt)$_3$-strategy; (b) mechanistic study of I$_2$/KH$_2$PO$_2$ strategy; (c) the synthesis of N-benzamide; (d) the sythesis of S-(m-tolyl) benzothioate; (e) the capture of possible intermediates in the I$_2$/KH$_2$PO$_2$ strategy; (f) verification of radical mechanism; (g) reaction kinetics.

esterification conditions, but it was interesting that the configurations of the product were different (Table 3, **3da**). Whatever, the expansion of amino acid substrates was not smooth, even if we reduced the milling frequency and prolonged the reaction time, poor yield was achieved (Table 3, **3db** and **3dc**).

The broad synthetic utility of this process is further highlighted by the late-stage diversification of natural products. To our delight, thymol, paeonol and eugenol were tolerated, producing the resulting esters in medium yields (**3da**, **3db**, and **3dc**).[13–15] We were pleased to find that the direct esterification of cholesterol (**3dd**),[16] a cyclopentane polyhydrophenanthrene derivative necessary for the human body; and oleanolic acid (**3de**),[17] a medicine for treating infectious acute jaundice hepatitis, furnished the esterification products in low to medium yields, demonstrating the synthetic advantage of the I_2/KH_2PO_2 protocol (Table 4). However, the $KI/P(OEt)_3$ protocol, delivered the esterification products only in trace amounts.

Afterwards, we explored the practicability of this method, which was exemplified through the synthesis of the anti-hyperlipidaemic agent inositol nicotinate (Scheme 2).[18] This method can afford inositol nicotinate in moderate yield without purification by column chromatography.

To shed light on the pathways of the two system dehydration platforms, several control experiments were performed. Firstly, we carried out mechanistic studies beginning with an isotope labelling experiment, whereby benzoic acid and ^{18}O enriched phenol were subjected to the reaction conditions (Scheme 3a).[19] In the presence of KI and $P(OEt)_3$, the ester product was obtained with high ^{18}O incorporation, which indicated oxygen transfer from the alcohol to the ester. In contrast, using I_2 and KH_2PO_2, the ester product was obtained with high ^{16}O

incorporation, demonstrating oxygen transfer from the acid to the ester (Scheme 3b). After that, we verified the reaction mechanism by aniline and m-methylthiophenol. In the presence of KI and $P(OEt)_3$, the yields of N-benzamide and S-(m-tolyl) benzothioate were higher than that of I_2/KH_2PO_2 strategy (Scheme 3c and d). Next, we examined changes to the additive under HSBM conditions. After HSBM of I_2 and KH_2PO_2, the ^{31}P chemical shift of KH_2PO_2 at 7.00 ppm was vanished, while a new peak at 1.00 ppm was formed, which was regarded as complex A, but not available in solution (Scheme 3e). We hypothesize that complex A (^{31}P 1.00 ppm) can be produced in the HSBM environment, which is not available in solution. Both esterification methods were completely still underwent in the presence of radical scavengers, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-$tert$-butyl-4-methyl-phenol (BHT), to give **3aa** in good yield (Scheme 3f). The difference of reaction kinetics was further studied by sampling in the first 15 minutes (the amount of **3aa** was detected by HPLC). $KI/P(OEt)_3$ reaction was almost carried out at a uniform rate. In the first 4 min, there was no obvious product formation in I_2/KH_2PO_2 reaction, and the formation of **3aa** product was accelerated after 6 min (Scheme 3g).

Based on the above results and Denton's work,[20a] a possible mechanistic pathway is proposed for the I_2/KH_2PO_2 strategy (Path A). First, activated additive **A** is formed by the mechano-chemical reaction of potassium hypophosphite and iodine. Then, as in the classical Mitsunobu reaction,[20b,c] the counter anion associated with phosphonium salt **B** may engage in nonproductive, reversible bonding and exchange at the phosphorus atom, but ultimately, intercepting phenol **1b** to afford the conventional intermediate, the phenoxyphosphonium-nucleophile ion pair **C**. Subsequent nucleophilic substitution between phenoxyphosphonium salt **C** and intermediate **B** afforded the substitution product **3aa** (Scheme 4a). Next, the mechanism of the $KI/P(OEt)_3$ strategy is proposed through the results of GC-MS (Fig. S3†). The benzoic acid in the $KI/P(OEt)_3$ system undergoes Michel–Arbuzov reaction to obtain diethyl benzoylphosphonate.[21a,b] According to previous reports, diethyl benzoylphosphonate can easily react with phenol to obtain the target product **3aa** (Scheme 4b).[21c]

Conclusions

In conclusion, we have disclosed two protocols under HSBM conditions that facilitated facile esterification of carboxyl and hydroxyl groups. The I_2/KH_2PO_2 strategy successfully replaced organic phosphorus (PPh$_3$) with inorganic phosphorus salts (KH_2PO_2), while $KI/P(OEt)_3$ strategy enabled the esterification with an easily removable $P(OEt)_3$. Both methods are solvent-free and transition metal-free. Additionally, the feasibility of I_2/KH_2PO_2 strategy was demonstrated by application to the esterification of natural products and the synthesis of inositol nicotinate. In addition, we discussed the different reaction mechanisms of the two systems through control experiment. Further investigation of environmentally friendly green chemistry reaction under HSBM conditions is underway in our lab.
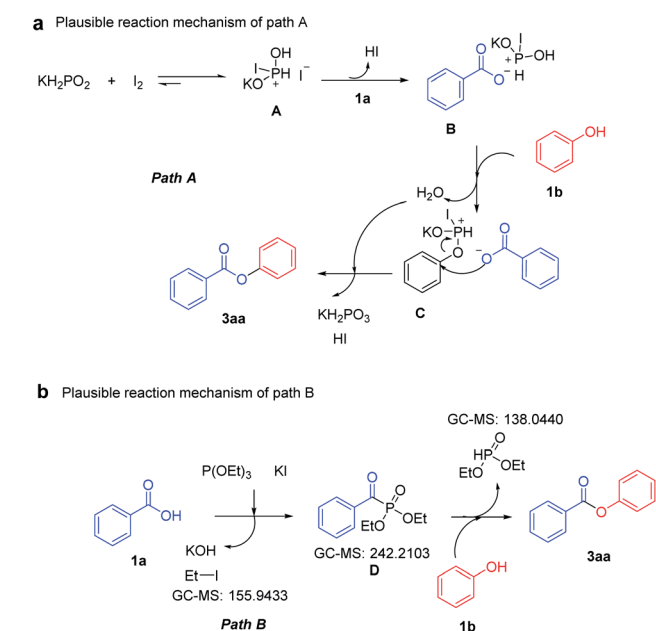
Scheme 4 Plausible reaction mechanism: (a) path A; (b) path B.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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