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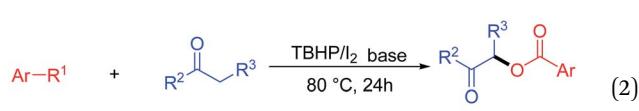
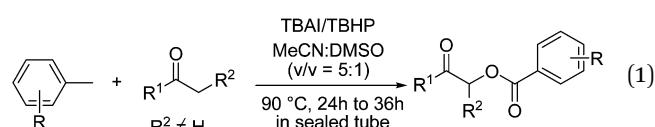
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Introduction

α -Acyloxy carbonyl compounds have received considerable interest from the organic chemistry community during the last few years because of their unique structural properties. Furthermore, compounds belonging to this structural class can be found in a wide variety of biologically interesting natural products, pharmaceuticals and synthetic intermediates.¹ Traditionally, these compounds are prepared by the substitution reaction of a functionalized carbonyl compound with an alkaline carboxylate or carboxylic acid,² as well as the direct oxidative coupling of a ketone with a carboxylic acid (or surrogates),³ all of which require the use of a highly toxic heavy metal oxidant.⁴ Several interesting alternatives have been developed to avoid the many drawbacks associated with the use of toxic heavy metals. Most notably, organohypervalent iodine reagents and peroxides have been widely used as surrogates for heavy metal oxidants to promote the α -benzoyloxylation of ketones.⁵ More recently, there have been several reports pertaining to the use of oxyacylating reagents, such as aldehydes, benzylic alcohols and acetophenones, as surrogates of carboxylic acids.⁶ However, to the best of our knowledge, there have been very few reports describing the α -benzoyloxylation of ketones using toluene derivatives as oxyacylating reagents. Li and co-workers recently reported an efficient method for the α -benzoyloxylation of ketones using toluene derivatives as oxyacylating reagents under metal-free conditions (eqn (1)).⁷ However, the substrate scope of this procedure was limited to α -substituted ketones, whereas acetophenones and 2-iodo-1-phenylpropan-1-

one were found to be unsuitable for this transformation. In addition, this method afforded low yields of the desired product. Hence, the development of novel, environmentally benign and high yielding procedures for the preparation of α -acetoxy ketones from simple and readily available starting materials with a broad substrate scope is still highly desirable.

Rather than only serving as effective solvents,⁸ toluene and its derivatives can also be used as reagents in organic synthesis for the construction of structurally complex compounds.⁹ Herein, we report the development of a novel route for the facile α -benzoylation of a wide range of ketone substrates (e.g., acetophenones, propiophenones, butyrylbenzenes, heterocyclic arones and aliphatic ketones) using toluene and its derivatives as oxyacetylating precursors in the presence of *tert*-butyl hydroperoxide (TBHP) and iodine to the synthesis of α -benzoylxy ketones (eqn (2)). The key features of this new oxidation system include (i) metal-free oxidation conditions; (ii) the use of toluene and its derivatives as readily available and inexpensive oxyacetylating precursors; (iii) a broad substrate scope, including aryl ketones, heterocyclic ketones, aliphatic ketones, toluenes, phenylmethanols, benzaldehydes, benzoic acids and ethylbenzenes; and (iv) milder reaction conditions than existing methods for this transformation.



R^1 = Me, Et, CH_2OH R^2 = Ar, HetAr, Alkyl
 CHO , $COOH$ R^3 = H, Alkyl

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Results and discussion

The reaction of toluene (**1a**) with acetophenone (**2a**) was initially selected as a model reaction to determine the optimum conditions for this transformation (Table 1). The results revealed that the reaction was completed after 24 h, with no further increases observed in the product yield following extended reaction time (Table 1, entries 1–3). It is noteworthy that no reaction occurred in the absence of TBHP or iodine (I_2), which indicated that these two reagents were critical to the success of the reaction (Table 1, entries 4–5). Notably, we observed a remarkable increase in the product yield when the amount of TBHP was increased to 5.0 equivalents. Further increasing the amount of TBHP to 7.0 or 9.0 equivalents did not result in any further increases in the yield, indicating that the optimum value of this reagent was 5.0 equivalents (Table 1, entries 6–8). We subsequently evaluated a variety of different peroxides in this reaction, including di-*tert*-butyl peroxide (DTBP), benzoyl peroxide, dicumyl peroxide (DCP), cumene hydroperoxide (CHP) and potassium hydrogen persulfate. However, all of these peroxides afforded much lower yields of the desired product than TBHP except benzoyl peroxide (Table 1, entries 9–13). We then proceeded to investigate the effects of adding different amounts of I_2 and Na_2CO_3 to

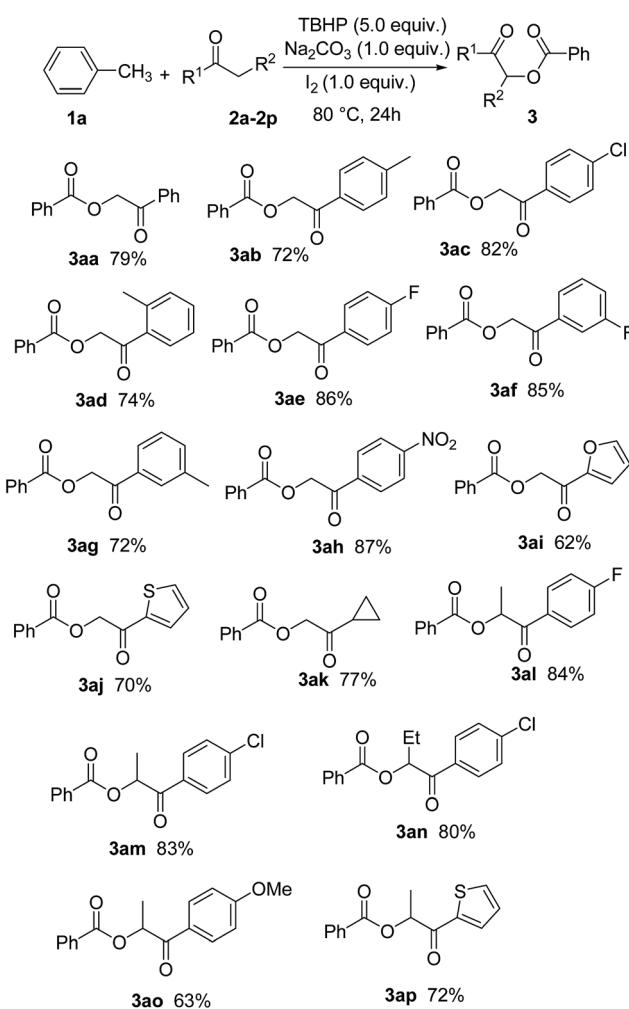
Table 1 Optimization of reaction conditions^a

Entry	Cat. (1.0 equiv.)	Peroxide (equiv.)	Time (h)	Yield ^b %
1	I_2	Tert-butyl hydroperoxide (TBHP) (3)	12	17
2	I_2	TBHP (3)	24	24
3	I_2	TBHP (3)	36	24
4	I_2	—	24	0
5	—	TBHP (3)	24	0
6	I_2	TBHP (5)	24	79
7	I_2	TBHP (7)	24	86
8	I_2	TBHP (9)	24	86
9	I_2	Di- <i>tert</i> -butyl peroxide (DTBP) (5)	24	39
10	I_2	Benzoyl peroxide (5)	24	83
11	I_2	Dicumyl peroxide (DCP) (5)	24	58
12	I_2	Cumene hydroperoxide (CHP) (5)	24	36
13	I_2	Potassium hydrogen persulfate (5)	24	71
14 ^c	I_2	TBHP (5)	24	59
15 ^d	I_2	TBHP (5)	24	86
16 ^e	I_2	TBHP (5)	24	66
17 ^f	I_2	TBHP (5)	24	0
18 ^g	I_2	TBHP (5)	24	86

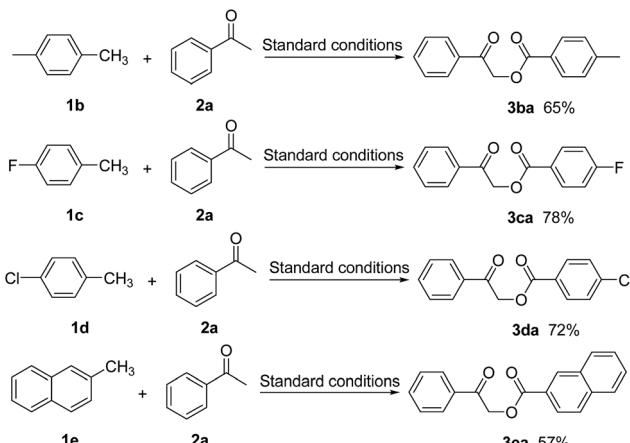
^a Unless otherwise specified, all of these reactions were carried out as follows: **2a** (0.25 mmol scale), catalyst (1.0 equiv.) and Na_2CO_3 (1.0 equiv.) in toluene (2.0 mL). ^b GC yield. ^c Iodine (0.2 equiv.). ^d Iodine (1.5 equiv.). ^e Na_2CO_3 (0.5 equiv.). ^f Without Na_2CO_3 . ^g N_2 (balloon).

the reaction. The results of these screening experiments indicated that 1.0 equivalent was the optimal charge for both I_2 and Na_2CO_3 (Table 1, entries 14–17). Notably, this reaction failed to afford the desired product when it was conducted in the absence of Na_2CO_3 (Table 1, entry 17). Finally, we did not observe any changes in the product yield when the reaction was performed under a N_2 atmosphere (Table 1, entry 18).

With the optimized conditions in hand, we proceeded to explore the scope of this newly developed α -benzoyloxylation reaction using a wide range of different ketones with toluene (**1a**) (Scheme 2). Acetophenones **2a–p** and propiophenones **2l–o** bearing a variety of electron-rich and electron-poor substituents were all tolerated under the optimized reaction conditions. Substrates bearing electron-withdrawing substituents (*i.e.*, F^- , Cl^- and O_2N^-) performed more effectively in this reaction than those bearing electron-donating substituents (*i.e.*, Me^- and Methoxy $^-$), to give the corresponding α -oxyacetylated products **3** in relatively high yield. It is noteworthy that the yield of this α -benzoyloxylation reaction appeared to be largely unaffected by the position of the substituents on the phenyl ring. For example, 1-*p*-tolylethanone, 1-*o*-tolylethanone and 1-*m*-tolylethanone



Scheme 1 α -Benzoyloxylation of different ketones (all of these reactions were carried out on **2** (1.0 mmol) in toluene (2.0 mL)).

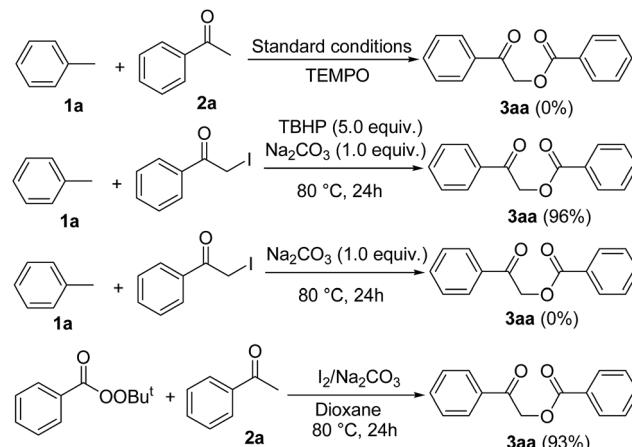


Scheme 2 α -Benzoyloxylation of acetophenone with different arylmethanes (all of these reactions were carried out on **2a** (1.0 mmol) with 2.0 mL of **1**).

gave almost identical yields of the corresponding products. In addition, the inclusion of different R^2 groups ($R^2 = \text{H, Me, Et}$) had no discernible impact on the outcome of this transformation. Pleasingly, we found that this newly developed procedure was also amenable to heteroaryl (such as thienyl and furyl, see **3ai**, **3aj** and **3ap**) and alkyl (**3ak**) ketones.

We also investigated the scope of substituted arylmethane used in this reaction and the results are summarized in Scheme 2. The results revealed that a variety of different substituents, such as Me^- , Cl^- and F^- , were tolerated on the phenyl group of the toluene additive, with no discernible difference in the yield of the α -oxyacylated products compared with toluene. Most notably, 2-methylnaphthalene (**1e**) reacted with acetophenone (**2a**) to give the corresponding product **3ea** in an isolated yield of 57%.

To further extend the scope of this reaction, we also tested the possibility of using phenylmethanol, benzaldehyde, benzoic acid and ethylbenzene as substrates (Scheme 3). Pleasingly, all of these substrates reacted efficiently with acetophenone to

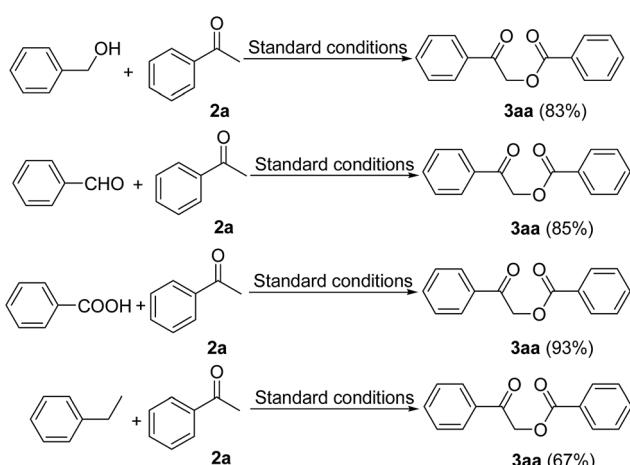


Scheme 4 Control experiments to determine the reaction mechanism.

afford 1-oxo-1-phenylethyl benzoate (**3aa**) in 67–93% yields. Benzoic acid, in particular, afforded the desired product with almost quantitative yield. These results therefore clearly indicate that phenylmethanol, benzaldehyde, benzoic acid and ethylbenzene are suitable alternatives of toluene for this transformation, thereby greatly expanding the substrate scope of this reaction.

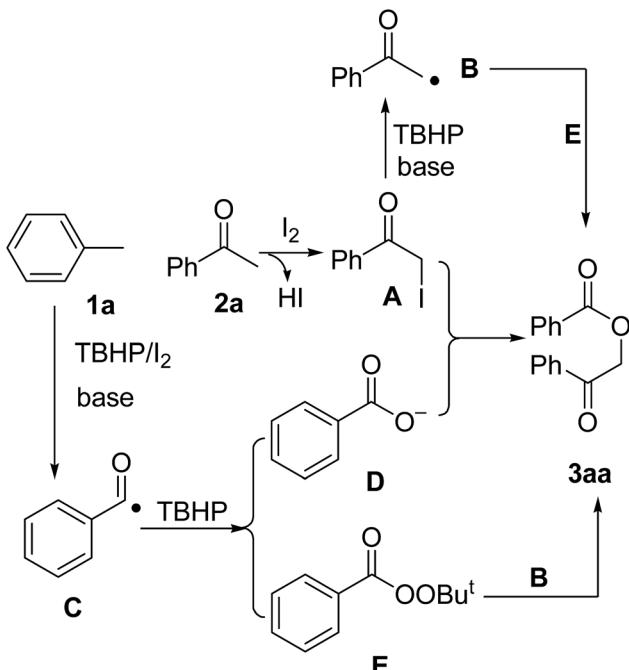
The following control experiments were carried out to gain an insight into the mechanism of our newly developed reaction (Scheme 4). The addition of an excess of the radical scavenger TEMPO under the standard conditions completely inhibited the α -benzoyloxylation reaction, suggesting that this transformation proceeds *via* a radical pathway. Fortunately, 2-iodo-1-phenylethanone worked well as a surrogate for acetophenone under our standard reaction conditions, affording an almost quantitative yield of the desired α -oxyacylated products, which suggested that 2-iodo-1-phenylethanone was being formed as an intermediate in this reaction. However, this reaction failed to afford the desired α -oxyacylated products when it was conducted in the absence of TBHP. Remarkably, the addition of *tert*-butylperoxybenzoate to **2a** resulted in the formation of the desired α -benzoylation product **3aa** in 93% yield. In addition, we noticed that these reactions afforded **3aa** in excellent yields when phenylmethanol, benzaldehyde and benzoic acid were used as surrogates for acetophenone (Scheme 2). These findings therefore suggested that benzoic acid or *tert*-butylperoxybenzoate was being formed *in situ* as an intermediate from toluene.

Based on the results above and previous reports from the literature, we proposed a plausible mechanism for the current α -benzoyloxylation reaction, which is shown in Scheme 5. The initial reaction of acetophenone (**2a**) with molecular iodine would afford 2-iodo-1-phenylethanone **A**,¹⁰ which would be oxidized by TBHP to produce α -carbonyl radical **B**.¹¹ Toluene (**1a**) would also be oxidized by TBHP to produce the radical intermediate **C**, which would be further oxidized to form the *tert*-butylperoxybenzoate intermediate **E**.¹² The subsequent coupling of **B** and **E** would lead to the formation of the desired product **3aa**, in a manner similar to that reported by Li.⁷



Scheme 3 α -Benzoyloxylation reactions of acetophenone with phenylmethanol, benzaldehyde, benzoic acid and ethylbenzene.





Scheme 5 A reaction pathway for the formation of **3aa**.

Alternatively, in the presence of TBHP, **C** could be further converted to carboxylate anion **D**.^{7,13} Finally, the reaction of **A** with **D** affords the final product **3aa**.

Experimental

General information

All the reactions were carried out at 80 °C for 24 h in a round-bottom flask equipped with magnetic stir bar. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. Melting points were measured on a melting point apparatus equipped with a thermometer. ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz spectrometer in solutions of CDCl₃ using tetramethylsilane as the internal standard, δ values are given in ppm and coupling constants (\mathcal{J}) in Hz. HR-MS were obtained on a Q-TOF micro spectrometer.

Typical procedure: 1-oxo-1-phenylethyl benzoate (Scheme 1, **3aa**)

A mixture of acetophenone (**2a**) (120 mg, 1.0 mmol), Na₂CO₃ (106 mg, 1.0 mmol), TBHP (70% aqueous solution, 0.65 g, 5.0 mmol), iodine (254 mg, 1.0 mmol) and toluene (2.0 mL) was added successively in a round-bottom flask, and the resulting soln stirred for 24 h at 80 °C. The mixture was purified by column chromatography on silica gel to afford product **3aa** with PE/ethyl acetate as the eluent.

Conclusions

In summary, we have developed an efficient approach for the facile preparation of α -benzoyloxy ketones by the direct oxidative α -benzoyloxylation of a structurally diverse range of ketones

using simple arylmethane compounds in good to excellent yields. It is noteworthy that the TBHP oxidant used in this reaction also acted as a source of oxygen for the introduction of the benzoyloxy group.

Acknowledgements

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