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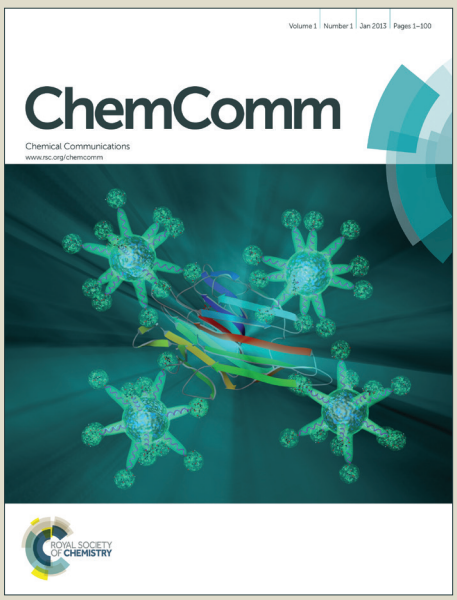

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ARTICLE TYPE

The Bu_4NI-catalyzed alfa-acyloxylation of ketones with benzylic alcohols

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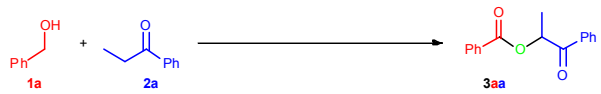
The Bu_4NI-catalyzed reaction of ketones with benzylic alcohols was achieved, leading to alfa-acyloxycarbonyl compounds in moderate to good yields. This metal-free procedure featured with the employing of facilely and commercially available starting materials and TBHP as a clean oxidant with high atom economy.

alfa-Acyloxylation of carbonyl compound is an important transformation because the formed alfa-acyloxyketones are useful building blocks[1] and can facilely transform into alfa-hydroxy ketones as structural subunit in a variety of biologically active natural products.[2] Traditionally, this molecular is prepared by the reaction between the derivatives of ketones and carboxylic acids to avoid the using of heavy metal oxidants.[3] For example, alfa-acyloxylation was achieved by the reaction of alfa-halocarbonyl compounds with carboxylates.[4] In 1998, Ohfune reported the copper-catalyzed insertion of alfa-diazoketones into carboxylic acids to give alfa-acyloxyketones.[5] The chiral amine-catalyzed alfa-oxybenzoylation with benzoyl peroxide has also been described.[6] In 2005, Tomkinson developed a general protocol for the alfa-acyloxylation of carbonyl compound by *N*-methyl-*O*-benzoylhydroxylamine.[7] However, among all the aforementioned transformations, further functionalization in either the ketones or carboxylic acids motifs is required to fulfill the alfa-acyloxylation, which is time consumed and decreases the atom economy. On the contrary, the ruthenium-catalyzed addition of carboxylic acids to propargyl alcohols was an atom economical pathway leading to alfa-acyloxyketones.[8] An elegant example on the (hypo)iodite-catalyzed direct alfa-oxyacylation of carbonyl compounds with carboxylic acids was demonstrated by Ishihara.[9] Miyamoto reported the iodobenzene-catalyzed alfa-acetoxylation of ketones via *in situ* generation of hypervalent (diacyloxyiodo)benzenes using *m*-chloroperbenzoic acid.[10] From the functional group transformation point of view, the development of such a reaction using surrogate of carboxylic acids is necessary.

Recently, the combination of Bu_4NI and *tert*-butyl hydroperoxide (TBHP) has been well documented in the C-O[11] and C-N[12] bond formation reaction. Herein, we report the employment of TBHP in TBAI-catalyzed alfa-oxyacylation of ketones by benzylic alcohols leading to alfa-acyloxyketones.

We started our study by using the model reaction shown in Table 1: benzylic alcohol (0.2 mmol), propiophenone (0.4 mmol), I_2 (0.2 equiv) and TBHP (70% aqueous, 6 equiv) in EtOAc (2 mL). However, no reaction took place after heating the mixture at 90 °C for 12 h. To our delight, replacing I_2 with Bu_4NI, the alfa-acyloxylation product was obtained in 66% yield (Table 1, entry 2); while KI delivered the alfa-acyloxyketone in 12% yield (Table 1, entry 3). CuI and $FeCl_2$ were totally ineffective for this transformation. Other oxidants, such as $K_2S_2O_8$, di-*tert*-butyl peroxide (DTBP) and H_2O_2 resulted in no product (Table 1, entries 6-8). The yield was further increased to 74 % (12 h) and 84 % (24 h) in PhCN, respectively (Table 1, entry 10). Using MeCN, a 67% yield was obtained (Table 1, entry 11). However, the reaction did not run in THF and DCE (Table 1, entries 9 and 12). No product was detected in the absence of either Bu_4NI or TBHP (Table 1, entries 13 and 14).

Table 1. Selected results of screening the optimal conditions.



Entry	Catalyst	Oxidant	Solvent	Yield(%)[a]
1	I_2	TBHP	EtOAc	<1
2	Bu_4NI	TBHP	EtOAc	66(71)[b]
3	KI	TBHP	EtOAc	12
4	CuI	TBHP	EtOAc	<1
5	$FeCl_2$	TBHP	EtOAc	<1
6	Bu_4NI	$K_2S_2O_8$	EtOAc	<1
7	Bu_4NI	DTBP	EtOAc	<5
8	Bu_4NI	H_2O_2	EtOAc	<1
9	Bu_4NI	TBHP	THF	<1
10	Bu_4NI	TBHP	PhCN	74(84)[b](73)[b,c]
11	Bu_4NI	TBHP	MeCN	67(75)[b]
12	Bu_4NI	TBHP	DCE	<1
13	--	TBHP	PhCN	<1
14	Bu_4NI	--	PhCN	<1

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.2 equiv), oxidant (6 equiv), air, 90 °C, 12 h, sealed tube, solvent (2 mL). [b] 24 h. [c] 70 °C.

After the establishment of the optimal reaction condition, the scope of benzylic alcohols was studied, as shown in Figure 1. As expected, all substrates ran smoothly under the standard procedure. The reaction were tolerant to the electronic nature of the benzylic alcohols as both electron-withdrawing and donating substituted substrates worked well to deliver the alfa-acyloxylation products in good to excellent yields. Chloro and bromo groups survived well under this procedure, which was suitable for potentially further functionalization (**3ca** and **3da**). Moreover, the steric hindrance had little effect on this transformation, as evidenced by the high yields of **3ha** and **3ia**. Importantly, the hetero-aryl methanols were also good reaction

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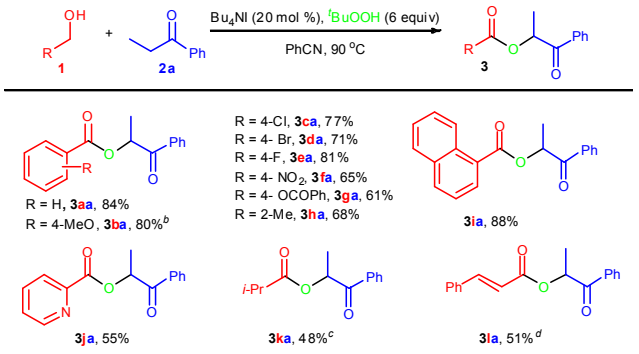
partners in this transformation. For example, pyridin-2-ylmethanol provided **3ja** in 55% yield. Notably, the scope of alcohol was not limited to benzylic alcohols since the aliphatic primary alcohols also worked to some extent under the standard procedure. For example, isobutyl alcohol provided the desired product **3ka** in 48% yield and 51% yield of **3la** was obtained for (*E*)-cinnamicalcohol.

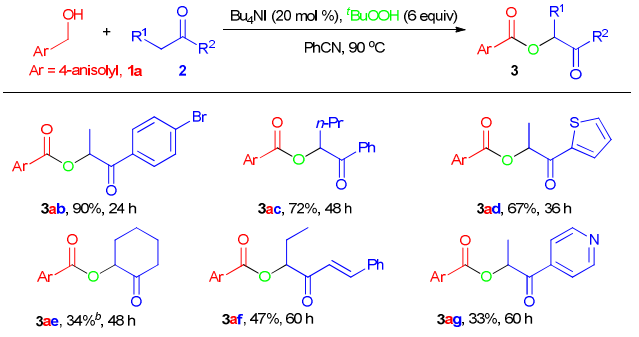
Figure 1. Scope of benzylic alcohol[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Bu_4NI (0.2 equiv), TBHP (70% aqueous, 6 equiv), PhCN (2 mL), air, 90 °C, 24 h. [b] **2a** (0.6 mmol), 36 h. [c] DMSO (1 mL), 48 h. [d] DMSO (1 mL).

Next, the substrates scope and limitation of ketones were studied, as shown in Figure 2. 1-Phenylbutan-1-one ran smoothly under the standard procedure, providing the alfa-acyloxylation product **3ac** in 72% yield. 1-(Thiophen-2-yl)propan-1-one provided the desired product **3ad** in 67% yield. Notably, aliphatic ketones was also suitable partnerfor this transformation. For example, cyclohexanone provided the product **3ae** in 34% yield.

Figure 2. Scope of ketone[a]

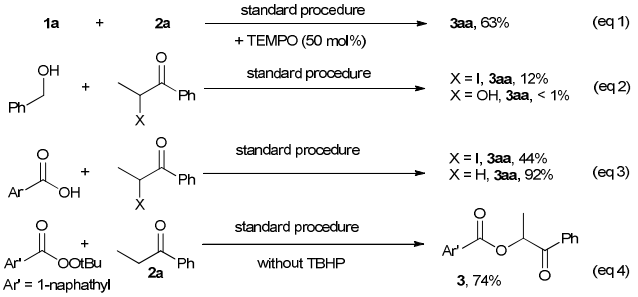


[a] Reaction conditions: **1a** (0.2 mmol), 2 (0.4 mmol), Bu_4NI (0.2 equiv), TBHP (70% aqueous, 6 equiv), PhCN (2 mL), air, 90 °C. [b] Ketone (5 equiv), 48 h.

To improve the practicability of this reaction, a 10 mmol scale reaction was conducted and **3aa** was isolated in a comparable 85% yield.

More experiments were conducted to gain some insights into this reaction. Firstly, adding 50 mol% of TEMPO decreased the yield of the model process (table 1) to 63%, indicating a radical pathway may be involved in this transformation (Scheme 1, eq 1). Secondly, heating the combination of 2-iodo-1-phenylpropan-1-one with benzylic alcohol produced the alfa-oxybenzoylation product in 12% yield under the standard reaction (Scheme 1, eq 2). In addition, ketones are prone to take place the oxidative alfa-hydroxylation in the presence of hypervalent iodine.[13] However, under the standard procedure, no reaction took place between benzylic alcohol and 2-hydroxy-1-phenylpropan-1-one (Scheme 1, eq 2). These results ruled out the possibility of 2-hydroxy-1-phenylpropan-1-one and 2-iodo-1-phenylpropan-1-one as the intermediates for this transformation. Thirdly, as shown in Table 1, the replacement of TBAI with I_2 inhibited the reaction. Moreover, the reaction of carboxylic acid with 2-iodo-1-phenylpropan-1-one resulted in 44% yield (Scheme 1, eq 3). Thus, a mechanism like MacMillan's procedure involving the sequential alfa-halogenation of ketone and S_N2 reactions of the formed alfa-iodo ketone attacked by carboxylic anion is ruled out.[14] Finally, both benzoic acid and *tert*-butyl perester was detected in the absence of ketone under the standard procedure. The reaction of benzoic acid with ketone under the standard procedure provided the product in 92% yield (Scheme 1, eq 3). Even in the absence of TBHP, *tert*-butyl perester reacted with ketone to produce the alfa-oxybenzoylation product in a comparable 74% yield (Scheme 1, eq 4).

Scheme 1. Preliminary mechanism study



Based on these experimental results, two proposed mechanisms are illustrated in Scheme 2. Firstly, the oxidation of TBAI by TBHP produces $[Bu_4N]^+[IO_n]^-$ (n = 1 or 2).[15] Then, the alfa-H of ketone was abstracted by $[Bu_4N]^+[IO]_n^-$ to produce the alfa-carbonyl radical **4**.[16] Meanwhile, in the presence of TBHP, benzylic alcohol is oxidized to benzoyl radical,[17a,17b] which subsequently converts to the *tert*-butyl perester.[17c] Then the reaction between the alfa-carbonyl radical **4** and the *tert*-butyl perester delivers the final alfa-acyloxylation product (Path **B**, Scheme 2). This step was confirmed by eq 4 in Scheme 1. Alternatively, similar with Yu's and Zhu's procedures, the formed radical is believed to be oxidized by $[Bu_4N]^+[IO_n]^-$ (n = 1 or 2) to form a cation intermediate **5**.[11c,12f] In this case, although the formed cation possessing a positive charge next to a carbonyl seems not stable, some examples involving such an alfa-carbonyl cation species were well documented.[18] Finally, the reaction between the cation intermediate **5** and carboxylic anion[19] produces the target molecular (Path **A**, Scheme 2). At the current stage, none of the two possible pathways can be thoroughly ruled out.

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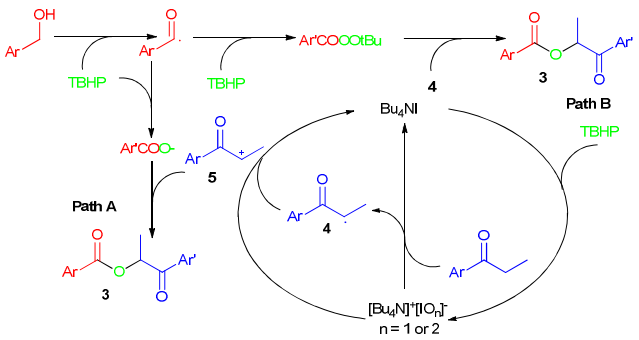
In conclusion, we have developed a TBAI-catalyzed alfa-acyloxylation of ketones with benzylic alcohols using TBHP as a clean oxidant. This procedure is featured with the application of facilely and commercially available starting materials as well as the mild metal-free reaction conditions. Thus, this work represents a practical pathway leading to alfa-acyloxyketones.

Scheme 2. Proposed mechanism



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