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ARTICLE TYPE

NBS/DBU mediated one-pot synthesis of α-acyloxyketones from benzylic secondary alcohols and carboxylic acids†

Minghui Zhu, Wei Wei*, Daoshan Yang, Hong Cui, Huanhuan Cui, Xuejun Sun, Hua Wang*

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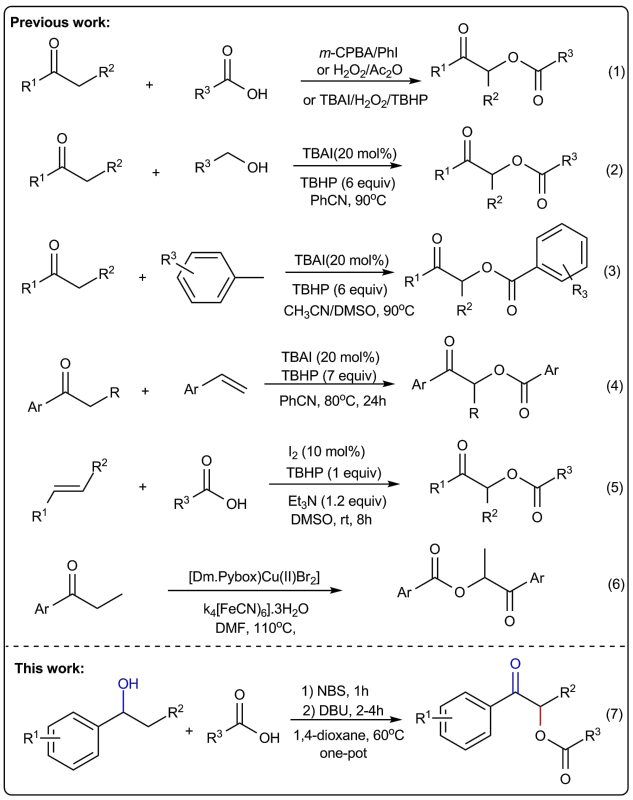
A simple and efficient one-pot NBS/DBU-mediated method has been developed for the synthesis of α-acyloxyketones from various benzylic secondary alcohols and carboxylic acids. Through this methodology, a series of α-acyloxyketones could be obtained in good to excellent yields under mild conditions. Importantly, this new reaction avoids the direct usage of toxic metal catalysts or potentially dangerous peroxide oxidants.

α-Acyloxy carbonyl compounds represent the basic building blocks in synthetic organic chemistry, which are the important structural motifs existing widely in a large number of pharmaceuticals and biologically active compounds.[1] The installation of acyloxy substituents at the carbonyl α-position is a longstanding goal in organic synthesis and a number of methods have been thereby developed. Traditionally, α-acyloxy carbonyl compounds can be prepared by the substitution of α-halo carbonyl compounds[2]/ insertion of α-diazoketones[3] with alkaline carboxylates and the coupling reaction of ketones with toxic heavy metal oxidants such as $Pb(OAc)_4$, $Mn(OAc)_3$, and $Tl(OAc)_3$.[4] Recently, hypervalent iodine compounds as effective oxidants to promote acyloxylation reaction have been reported.[5-8] For example, the direct oxidative coupling of ketones with carboxylic acids using a hypervalent iodine catalyst in the presence of an excess amount of *m*-CPBA[5] or peracetic acid[6] as a co-oxidant, and TBAI-catalyzed the intra- and intermolecular oxidative couplings of carbonyl compounds with carboxylic acids[7]/benzylic alcohols[8]/ toluene derivatives[9] using H_2O_2 or TBHP as a co-oxidant were presented (eqns (1-3)). Alternative methods including the using N-methyl-O-benzoylhydroxylamine,[10] benzoyl peroxide[11] aldehydes,[12] and alkenes[13] (eqn (4)) as a carboxylic acid source, iodine-catalyzed oxo-acyloxylation of alkenes (eqn (5)),[14] and pybox–Cu(II) complex catalyzed synthesis of α-acyloxy carbonyl compounds from ketones (eqn (6))[15] have also been developed. However, most of these well-established protocols may suffer from some certain disadvantages such as use of a large excess of ketone motifs, harsh reaction conditions, an excess amount of potentially



dangerous peroxide oxidants, toxic metal catalysts, or low yields. Therefore, the development of mild, efficient, metal- and peroxide-free methods to access α-acyloxy carbonyl compounds is still highly desirable in synthetic and pharmaceutical chemistry.

As part of our continuous interest in the metal-free synthetic transformations,[16] herein, we report a simple NBS/DBU-mediated one-pot protocol for the synthesis of α-acyloxyketones via α-acyloxylation reaction of benzylic secondary alcohols with various carboxylic acids (eqn (7)). The present method provides a simple and highly efficient approach to a variety of α-acyloxyketones in good to excellent yields under the metal and peroxide-free conditions.

Initially, the 1-phenylpropan-1-ol **1a** and benzoic acid **2a** were used as model substrates to determine the optimized reaction conditions (Table 1). Various organic and inorganic bases were firstly investigated when the model reactions were

[a] *The Key Laboratory of Life-Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong, China. E-mail: weiweiqfnu@163.com; huawang_qfnu@126.com*

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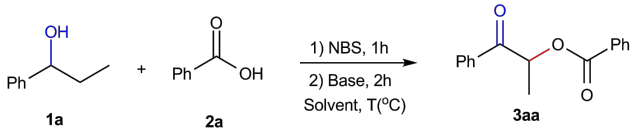
Table 1 Optimization of the reaction conditions[a]



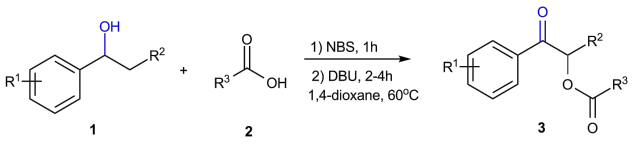
Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	THF	0
2	Na_2CO_3	THF	0
3	NaOH	THF	0
4	Et_3N	THF	32
5	DABCO	THF	74
6	DBU	THF	93
7	DBU	DME	50
8	**DBU**	**1,4-dioxane**	**99**
9	DBU	DCE	76
10	DBU	DMF	71
11	DBU	CH_3CN	18
12	DBU	H_2O	19
13	DBU	Toluene	0
14	DBU	EtOH	0
15	DBU	DMSO	0
16	DBU	1,4-dioxane	0[c]
17	DBU	1,4-dioxane	93[d]
18	--	1,4-dioxane	0
19	DBU	1,4-dioxane	0[e]

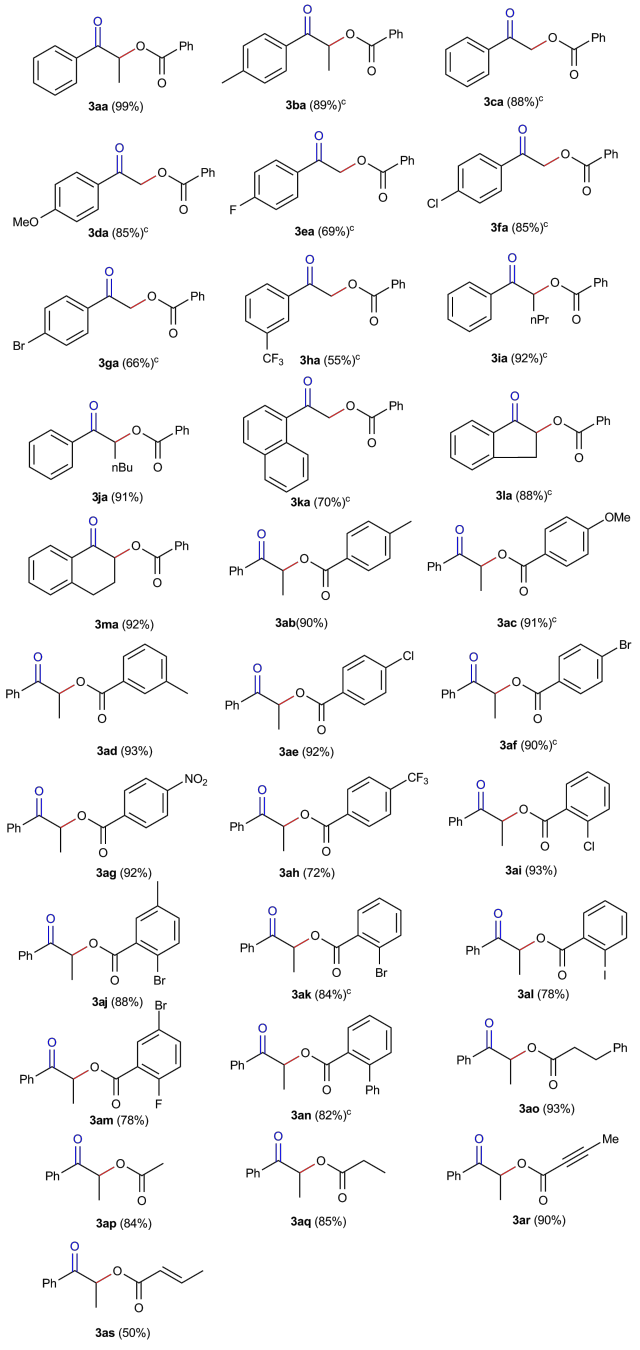
[a] Reaction conditions: 1) **1a** (0.25 mmol), **2a** (0.375 mmol), NBS (0.5 mol), 1h; 2) Base (0.5 mmol), solvent (2 mL), 60°C, air, 2 h. DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DME: 1,2-Dimethoxyethane, DCE: 1,2-Dichloroethane; [b] Isolated yields based on **1a**. [c] 25°C. [d] 80°C. [f] without of NBS.

performed in the presence of NBS at 60°C for 1h. Among a range of bases examined, organic base DBU (1,8-diazabicycloundec-7-ene) was found to be the best one to promote this transformation, while inorganic bases such as K_2CO_3, Na_2CO_3 and NaOH did not lead to the formation of the desired product **3aa** (Table 1, entries 1-6). Further optimization of solvents suggested that 1,4-dioxane was the best reaction medium (Table 1, entry 8). In contrast, when the reaction was performed in CH_3CN or H_2O, the desired product **3aa** was isolated in low yield (Table 1, entries 11 and 12). The reaction did not occur in toluene, EtOH, or DMSO (Table 1, entries 13-15). Moreover, no conversion was observed when the reaction was performed at room temperature (Table 1, entry 16). The optimized reaction temperature is 60°C, and a higher temperature (80°C) led to the slightly lower yield (93%) (Table 1, entries 8 and 17). Additionally, no product was detected when the reaction was conducted in the absence of DBU or NBS (Table 1, entries 18 and 19).

With the optimized conditions in hand, we next explored the scope and generality of this reaction using various alcohols and carboxylic acids. As shown in Table 2, in general, benzylic secondary alcohol derivatives with both electron-donating and electron-withdrawing substituents on the aromatic ring could be successfully transformed into the desired products in moderate to excellent yields (**3aa-3ha**). Furthermore, long chain alkyl substituted benzylic secondary alcohols did not hinder the reaction, affording the corresponding products in good yields (**3ia** and **3ja**). Moreover, 1-(naphthalen-1-yl)ethanol and cyclic secondary alcohol such as 1,2,3,4-tetrahydronaphthalen-1-ol and 2,3-dihydro-1H-inden-1-ol were also discovered to be suitable

Table 2 Results for NBS/DBU mediated synthesis of α-acyloxyketones from various benzylic secondary alcohols and carboxylic acids[ab,]





[a] Reaction conditions: 1) **1** (0.25 mmol), **2** (0.375 mmol), NBS (0.5 mmol), 1,4-dioxane (2 mL), 60°C, air, 1h; 2) DBU (0.5 mmol), 2 h. [b] Isolated yields based on **1**. [c] 2) DBU (0.5 mmol), 4h.

substrates, which delivered the desired products in 70%-92% yields (**3ka-3ma**). The scope of the present transformation was further expanded to a variety of carboxylic acids. In addition to

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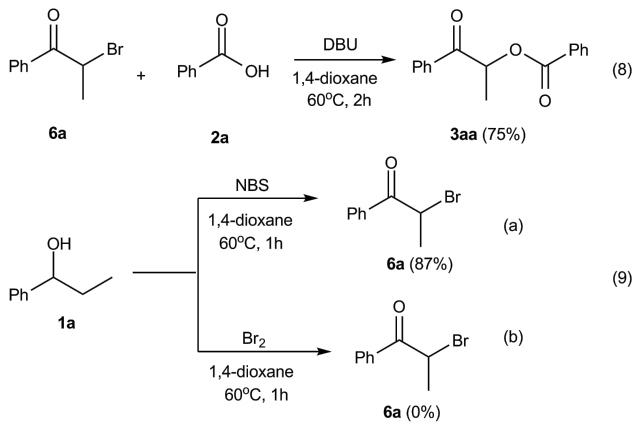
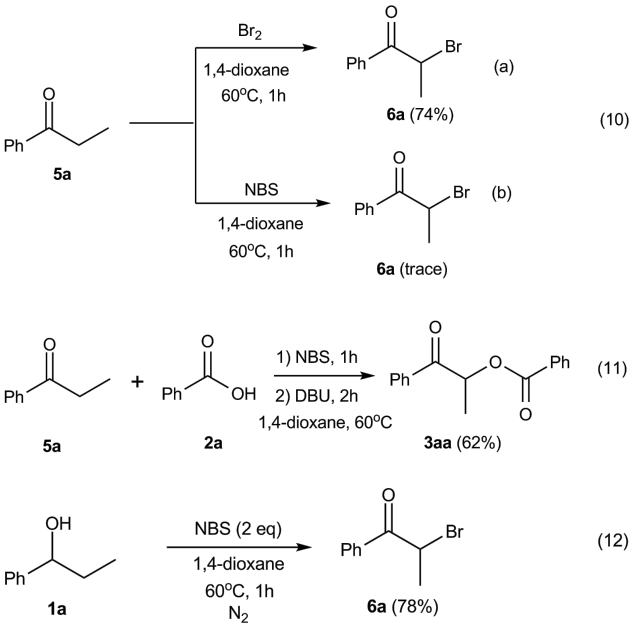
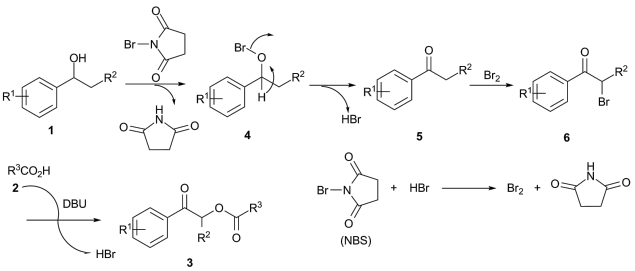
benzoic acid **2a**, a series of substituted benzoic acids containing either electron-rich or electron-deficient groups were all compatible with this process to give the corresponding products in excellent yields (**3ab**-**3an**). Notably, various functional substituents including halogen, methoxyl, and nitro group could be tolerated in this procedure, thus providing the chances for further modification of these products. As expected, alkyl acids such as 3-phenylpropanoic acid **2o**, propionic acid **2p**, acetic acid **2q**, but-2-ynoic acid **2r**, and but-2-enoic acid **2s** were also suitable for this reaction, and the desired products (**3ao**-**3as**) were obtained in moderate to good yields.

To obtain some insights into this reaction, several control experiments were carried out (eqns. (8-10)). Initially, when the α-bromo ketone **6a** with benzoic acid **2a** was performed in the presence of DBU, the desired product **3aa** was isolated in 75% yield (eqn 8). Furthermore, when the reaction of 1-phenylpropan-1-ol **1a** with N-bromosuccinimide (NBS) was performed in the absence of acid and DBU, α-bromo ketone **6a** was obtained in 87% yield (eqn 9 (a)). Nevertheless, when the reaction of alcohol **1a** with Br_2 was performed in 1,4-dioxane at 60°C, none of α-bromo ketone **6a** was detected (eqn 9 (b)). Moreover, the reactions of propiophenone **5a** with Br_2 and NBS were also investigated. As shown in eqn (10), when the reaction of propiophenone with Br_2 was performed in 1,4-dioxane at 60°C, α-bromo ketone **6a** was isolated in 74% yield (eqn 10 (a)), however, the direct treatment of propiophenone **5a** with NBS only gave a trace amount of α-bromo ketone **6a** (eqn 10 (b)). The above results indicated that α-bromo ketone should be a key intermediate, which was formed through sequential alcohol oxidation and α-bromination of ketone in the present reaction system. It should be noted that the desired product **3aa** would be obtained in 62% yield when the reaction of propiophenone **5a** with benzoic acid **2a** was performed under the standard conditions (eqn 11). The formation of product **3aa** should be caused by acid promoted the α-bromination of ketone with NBS leading to α-bromo ketone **6a**,[17] which further reacted with benzoic acid **2a** to give the product **3aa** in the presence of DBU. In addition, when the reaction of 1-phenylpropan-1-ol **1a** with N-bromosuccinimide (NBS) was conducted in the absence of acid and DBU under N_2, α-bromo ketone **6a** was still isolated in 78% yield, suggesting that dioxygen is not key oxidant to promote the formation of intermediate α-bromo ketone **6** (eqn 12).





On the basis of the above results and referring to previous reports,[18,19] a tentative reaction pathway was proposed in Scheme 1. Initially NBS may react with alcohol **1** to form hypobromite intermediate **4**, which will be further transformed to give ketone along with the generation of HBr. Subsequently, the interaction of NBS with HBr would lead to the formation of Br_2.[19] Next, α-bromination of ketone **5** with Br_2 gave the key intermediate α-bromo ketone **6**. Finally, the nucleophilic substitution of α-bromo ketone **6** by acid **2** in the presence of base would produce the desired product **3**.



Scheme 1. Tentative reaction pathway

In conclusion, a simple and efficient one-pot synthesis method has been developed for the construction of α-acyloxyketones via the NBS/DBU mediated α-acyloxylation reaction of benzylic secondary alcohols and carboxylic acids under mild conditions. Through this methodology, various α-acyloxyketones could be conveniently and efficiently obtained in good to excellent yields from readily-available starting materials. The present protocol avoids the direct usage of toxic metal catalysts or potentially dangerous peroxide oxidants, which is expected to expand the potential applications of α-acyloxyketones in the pharmaceutical and synthetic chemistry.

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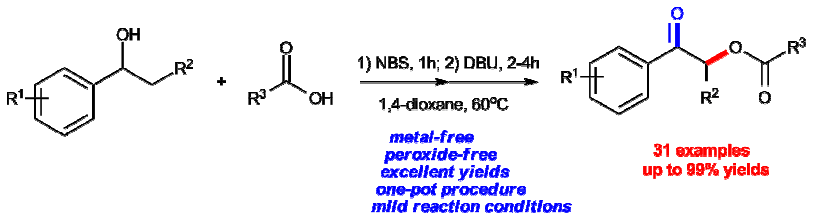

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