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PIDA/Bu_4NBr/KOH-Oxidized Direct α-Acetoxylation of sp^3 C-H Bonds Adjacent to Carbonyl

Wei-Bing Liu,* Cui Chen, Qing Zhang, and Zhi-Bo Zhu†,*

*School of Chemistry and Life Science, Guangdong University of Petrochemical Technology, 2 Guangdu Road, Maoming 525000, China. *E-mail: lwb409@yahoo.com.cn*
*†College of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China. *E-mail: zzb24@yahoo.com*
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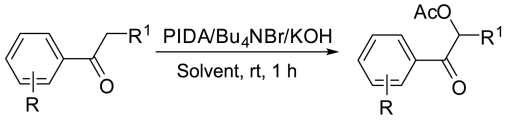
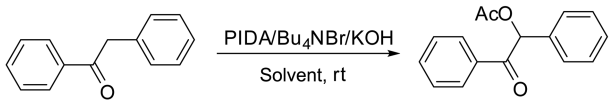
Hypervalent iodine(III) reagents,[1] serving as mild and chemoselective oxidants, have received much attention as reflected by the plethora of publications and reviews,[2] mainly owing to their low toxicity, ready availability, easy handling, clean transformation and reactivity. Furthermore, considering the high toxicity of metal oxidants, such as Pb(IV), Tl(III), and Hg(II),[3] hypervalent iodine reagents are considered as attractive alternatives to those toxic metal oxidants. In recent years, although transition metal-oxidized sp^3 C-H bond and subsequent C-hetero bond formations have attracted much interest,[4] and many excellent results have also been achieved, catalytic and oxidative functionlization of sp^3 C-H bonds to construct C-C and C-Hetro bonds is still a challenge. Various transition-metals such as Rh, Ru, Ir, Pd, Au, and Pt are always essential to activate sp^3 C-H bonds.[5] Recently, we reported an efficient non-metal catalytic oxidation method by using iodobenzene diacetate (PIDA) to functionalization of sp^3 and sp^2 C-H bonds.[6] In continuation of our studies, we became interested in functionalization of sp^3 C-H bonds under metal-free conditions, on which we report herein (Scheme 1).

Initially, we selected 1,2-diphenylethanone (**1a**) as the model substrate for reaction condition screening (Table 1). As shown in Table 1, when **1a** was treated with 1 equivalent of PIDA, or 1 equivalent of PIDA and 1 equivalent of Bu_4NBr without KOH in dioxane at room temperature for 1 h, no product was observed (Table 1, entries 1-2). In the presence of KOH (1.0 equiv.), 82% of **2a** was obtained (Table 1, entry 3). Then the amount of PIDA, Bu_4NBr and KOH were also examined, the best ratios of reagents, PIDA, Bu_4NBr, and KOH were 1:1.2:1.5:1 and 1:1.2:1.5:1.5, with which the yield increased to 88% (Table 1, entries 4-9). The screening of solvents revealed dioxane as the best choice, in which product **2a** was formed in 87% yield after 1 h (Table 1, entries 5, 10-13). Increasing the reaction time to 2 h can not enhance the reaction yield obviously (Table 1, entry 15), while shortening the reaction time to 0.5 h can decrease the yield to 63% (Table 1, entry 14). After screening, the optimal reaction conditions were obtained; that is, the mixture of 1,2-diphenylethanone (**1a**) with 1.2 equivalent of PIDA, 1 equivalent of Bu_4NBr and 1 equivalent of KOH reacted in dioxane at room temperature for 1 h (Table 1, entry 5).



Scheme 1. α-Acetoxylation of acetophenones.

Table 1. Optimization of reaction conditions

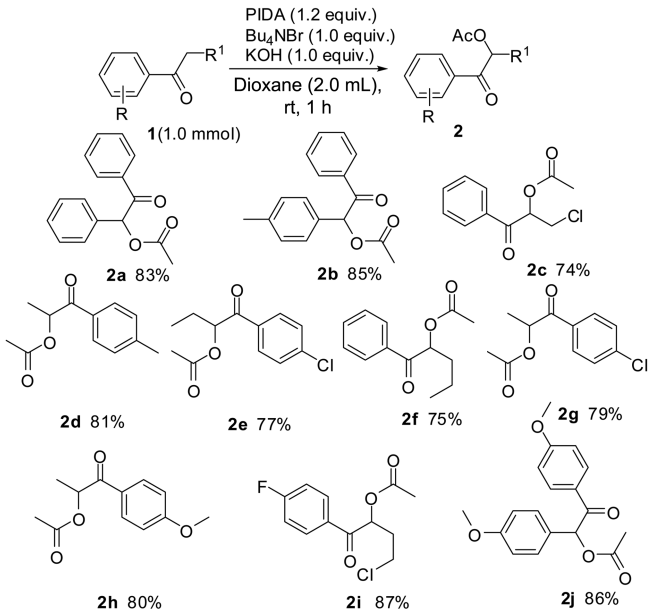


1a **2a**

Entry	Solvent	PIDA/Bu_4NBr/KOH (equiv.)	Yield (%)[b]
1	Dioxane	1/0/0	none
2	Dioxane	1/1/0	none
3	Dioxane	1/1/1	82
4	Dioxane	0.5/1/1	25
5	Dioxane	1.2/1/1	87
6	Dioxane	1.5/1/1	87
7	Dioxane	1.2/1.5/1	88
8	Dioxane	1.2/1.5/1.5	88
9	Dioxane	1.2/1.5/0.2	32
10	Cyclohexane	1.2/1/1	trace
11	DCE	1.2/1/1	trace
12	DMF	1.2/1/1	80
13	DMSO	1.2/1/1	35
14[c]	Dioxane	1.2/1/1	63
15[d]	Dioxane	1.2/1/1	88

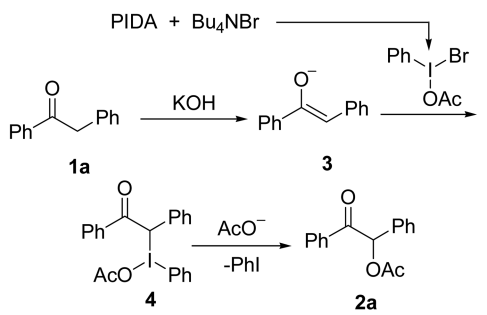
[a]Unless otherwise specified, all the reactions were carried out using 0.25 mmol of **1a** in 2.0 mL of solvent at room temperature for 1 hour. [b]GC yield. [c]Reactional time: 0.5 h. [d]Reactional time: 2 h.

Subsequently, we investigated the scope of the reaction substrates under the optimized conditions. All the tested substrates are smoothly oxidized at the α-positions adjacent to carbonyl and afford α-acetoxy hypnones in good to excellent yields.[7,8] As shown in Scheme 2, when the phenyl



Scheme 2. Catalytic α-acetoxylation of hypnones with PIDA/Bu_4NBr/KOH (Notes: All the listed yields were isolated yields).

ring adjacent to carbonyl bore the weak electron-withdrawing and electron-donating groups at the para position, such as halogen (Cl) (**1g**), methyl (**1d**) and methoxy group (**1h**), there was a negative effect on the reaction and the corresponding reaction yield was decreased slightly (Scheme 2, **2d**, **2g** and **2h**). It is noteworthy that the introduction of alkyl group or aryl group to the α-methylene adjacent to carbonyl of hypnones, regardless of the methyl group or aryl group, each of them could give the product with similar yield. For example, 1,2-diphenylethanone (**1a**), 1-phenyl-2-*p*-tolylethanone (**1b**) and 1,2-bis(4-methoxyphenyl)ethanone (**1j**) all could give the corresponding product with similar excellent yield and 3-chloro-1-phenylpropan-1-one (**1c**), 1-*p*-tolylpropan-1-one (**1d**), 1-(4-chlorophenyl)butan-1-one (**1e**), 1-phenylpentan-1-one (**1f**), 1-(4-chlorophenyl) propan-1-one (**1g**) and 1-(4-methoxyphenyl)propan-1-one (**1h**) also offered their corresponding product with similar yield, except for 4-chloro-1-(4-fluorophenyl)butan-1-one (**1i**). But, when the α-methylene adjacent to carbonyl of hypnones was occupied with one alkyl group, the reaction yield was decreased comparing to the phenyl group. For instance, **1c**, **1d**, **1e**, **1f**, **1g** and **1h** gave a decreased yield to the corresponding product than **1a**, **1b** and **1j**.



Scheme 3. Hypothesized reaction pathway.

On the basis of the literature evidence,[9] a mechanistic proposal for this transformation, exemplified by the formation of **2a**, is depicted in Scheme 3. Under the basic conditions, the enolate of the substrate reacts with the generated highly reactive iodine(III) species to form an α-hyperiodination intermediate **4**, which is ready to undergo an attack by the acetate to yield 2-oxo-1,2-diphenylethyl acetate **2a** accompanying by the reductive elimination of PhI.

In conclusion, we have developed an efficient method for catalytic α-oxidation of hypnone derivatives *via* an oxidizing reaction following sp^3 C-H functionalization using the combination of PIDA/Bu_4NI/KOH. This protocol provides a new convenient and useful route to activate sp^3 C-H bonds and construct C-O bonds. Besides, the acetoxyl of the resultant product is ready to be converted into other functional groups, such as, hydroxyl and carbonyl. The current direction for future research is aimed at extending the scope and potential synthesis applications.

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7. General method: All the reactions were carried out at room temperature in a Schlenk tube equipped with magnetic stir bar. Solvents and all reagents were used as received. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz and ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz. GC-MS was obtained using electron ionization (EI). TLC was performed using commercially prepared silica GF_{254}, and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.
8. **Typical procedure for the synthesis of 2-oxo-1,2-diphenylethyl acetate (2a):** To a 10 mL Schlenk tube was added DIB (386 mg, 1.2 mmol), Bu_4NBr (322 mg, 1.0 mmol), KOH (56 mg, 1.0 mmol), dioxane (2 mL) and 1,2-diphenylethanone (**1a**) (196 mg, 1.0 mmol). The mixture was stirred at room temperature for 1 h. The solution was directly subjected to isolation by PTLC (GF_{254}), developed with a 10:3 petroleum ether/ethyl acetate mixture, which furnished **2a** (210 mg, 83%) as white rosettes: ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.92-7.90 (d, J = 8.0 Hz, 2H), 7.36-7.29 (m, 8H), 6.85 (s, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 193.9, 170.7, 134.8, 133.8, 133.7, 129.5, 129.3, 129.0, 128.9, 128.8, 76.9, 20.9.
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