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I_2- or NBS-Catalyzed Highly Efficient α-Hydroxylation of Ketones with Dimethyl Sulfoxide

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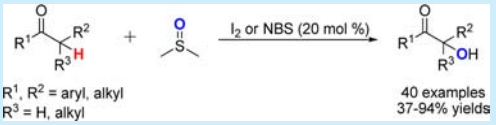
Supporting Information

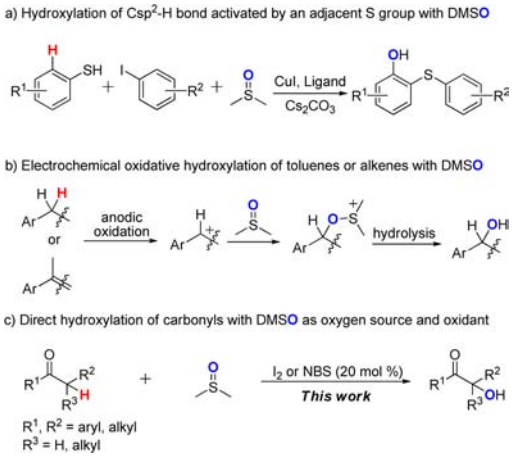
ABSTRACT: An efficient method for the direct preparation of high synthetic valuable α-hydroxycarbonyls is described. The simple and readily available I_2 or NBS was used as catalyst. DMSO acts as the oxidant, oxygen source, and solvent. A diverse range of tertiary Csp^3-H bonds as well as more challenging secondary Csp^3-H bonds could be hydroxylated in this transformation. The reaction is mild, less toxic and easy to perform.



Direct and selective hydroxylation of C−H bond is one of the most versatile approaches for the construction of diverse hydroxyl compounds.[1] Transition metal catalyzed Csp^2-H bond hydroxylation has been significantly developed in the past decades.[2] In contrast, the direct hydroxylation of Csp^3-H bond with stoichiometric oxidants such as PIDA, PIFA, TBHP, Oxone, H_2O_2, and O_2, suffers from incomparable difficulties due to the inert chemical bond and the reaction selectivity.[3,4] From a practical perspective, synthesis of important motifs via C−H functionalization with cheaper oxidants and under mild conditions with easy operation is highly desirable. Recently, the groups of Ritter[5] and Jiao[6] developed an elegant C−H hydroxylation approach to tertiary α-hydroxycarbonyls from ketones, respectively. However, these reactions were limited to tertiary Csp^3-H bond substrates and required Pd-catalyst or stoichiometric phosphorus reductant. The secondary Csp^3-H bond could not be hydroxylated by either of the methods. Furthermore, since the hydroxylation products are more reactive toward the oxidant than the substrates, overoxidation is always a competitive reaction in the direct oxidative process. Thus, a catalytic method for the selective conversion of carbonyls, especially α-methylene carbonyls, to corresponding α-hydroxycarbonyls,[7] which are ubiquitous structural motifs in bioactive compounds[8] and useful synthetic scaffolds,[9] using simple oxygen source and oxidant would be of significant importance.

Dimethyl sulfoxide (DMSO), an inexpensive, low-toxic solvent, has been widely used as the oxidant[10] in the well-known named reactions such as Swern oxidation,[11] Pwtizner-Moffatt oxidation,[12] as well as Corey-Chaykovsky epoxidation and cyclopropanation.[13] In addition, organic halides could be oxidized to the corresponding carbonyl compounds by Kornblum reaction using DMSO as the oxygen source.[14,15] However, the oxidative approach to alcohols with DMSO as the O-source was rarely achieved.[16] Significantly, Pan and co-workers developed an efficient hydroxylation reaction of arenes promoted by an adjacent S group with DMSO as the simple oxygen source (Scheme 1a).[17] By using an electrochemical process, Yoshida and co-workers achieved an elegant Csp^3 hydroxyl bond formation with DMSO through the oxidative process of alkenes or toluenes (Scheme 1b).[18] Despite the significant developments, the direct tertiary and secondary Csp^3-H bond hydroxylation under mild conditions is still desirable.

Scheme 1. Synthesis of Hydroxyl Compounds with DMSO



Herein, we report a simple and efficient method for the selective synthesis of α-hydroxycarbonyl compounds (Scheme 1c). In this reaction, 1) I_2 or NBS was used as the simple and inexpensive catalyst; 2) The simple DMSO played multiple roles as oxidant, oxygen source, and solvent; 3) Significantly, besides the tertiary Csp^3-H bond, the secondary Csp^3-H bonds of the α-methylene carbonyls which are the challenging substrates in the direct hydroxylation, worked well in this protocol for the preparation of secondary α-hydroxycarbonyls.

We initiated this project with the model reaction of propiophenone (**1a**). When 20 mol % of $CuBr_2$ was used, it

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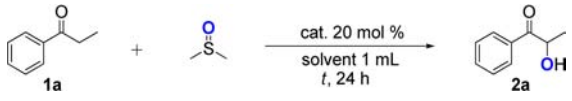
was very interesting to obtain hydroxylation product **2a** in 23% yield (Table 1, entry 1). Then we tried to optimize this

Table 1. Screening of the Reaction Conditions[a]



entry	cat.	solvent	temp (°C)	yield[b] (%)
1	$CuBr_2$	DMSO	60	23
2	NBS	DMSO	60	67
3	NCS	DMSO	60	0
4	NIS	DMSO	60	32
5	I_2	DMSO	60	72
6	I_2	DMSO	80	45
7	I_2	DMSO	100	trace

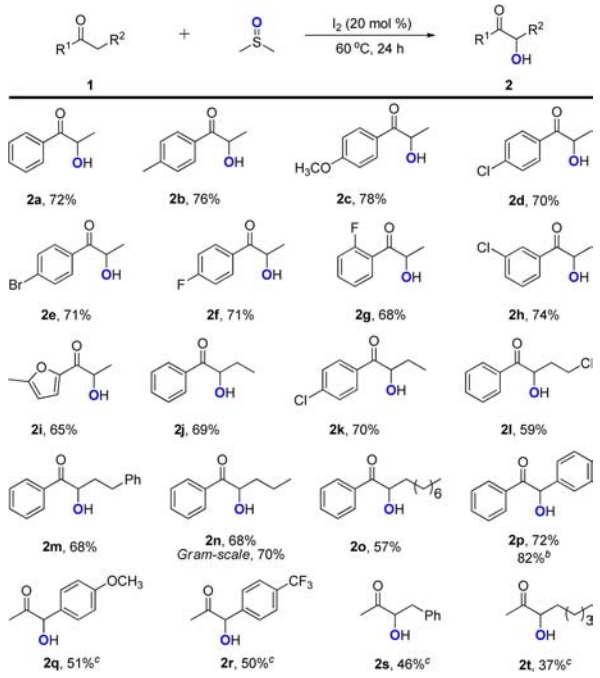
[a]Reaction conditions: **1a** (0.5 mmol), cat. (20 mol %), solvent (1 mL), under air for 24 h. NBS = *N*-bromosuccinimide. NIS = *N*-iodosuccinimide. NCS = *N*-chlorosuccinimide. [b]Isolated yields.

transformation by using other halide reagents in DMSO. Although DMSO has been used as a good oxidant,[10] various bromides such as NaBr, KBr, NH_4Br, and TBAB could not give any products (see the Supporting Information). Significantly, 67% yield of **2a** was obtained when NBS was used as catalyst (entry 2). NIS was less efficient than NBS in this transformation, whereas NCS failed to produce the desired product (entries 3–4). To our delight, the yield of hydroxylation product **2a** could be improved to 72% when I_2 was employed as the catalyst (entry 5). When the reaction was carried out at higher temperature (80, or 100 °C), the efficiency of this transformation decreased significantly (entries 6–7). The reactions with 10.0 equiv of DMSO in other solvents were also investigated; however, only a trace amount of hydroxylation product **2a** was obtained (see the Supporting Information).

With the optimized reaction conditions in hand, we first investigated the scope of α-methylene carbonyls (Scheme 2). The substrates with electron-donating and electron-withdrawing groups at the aromatic ring of the propiophenone moiety performed well in this reaction (**2b–h**). Halide substituents such as F, Cl, and Br were compatible in this transformation (**2d–h**). Furthermore, furanyl propanone was also a suitable substrate for this protocol (**2i**). For substrates with longer alkyl chains (**2j–o**), the reaction could also proceed well to generate the corresponding products in moderate to good yields. The chloro-substituted substrate **1l** afforded the corresponding C–H hydroxylated product **2l** in 59% yield, in which the potential nucleophilic substitution reaction was not detected. To our delight, 1,2-diphenylethanone performed well, and the corresponding hydroxylation product **2p**, which is more vulnerable to overoxidation to afford α-dicarbonyl, was obtained in good yield. It is noted that a higher yield could be obtained when NBS was used as catalyst instead of I_2 in this case. For the less hindered substrates, I_2 showed the superiority compared with NBS, and a higher yield of products could be obtained. Interestingly, the hydroxylation of aliphatic ketones could proceed under these simple conditions. A reduced reaction temperature was needed to prevent product decomposition, and the α-hydroxycarbonyls **2q–t** were obtained in moderate yields.

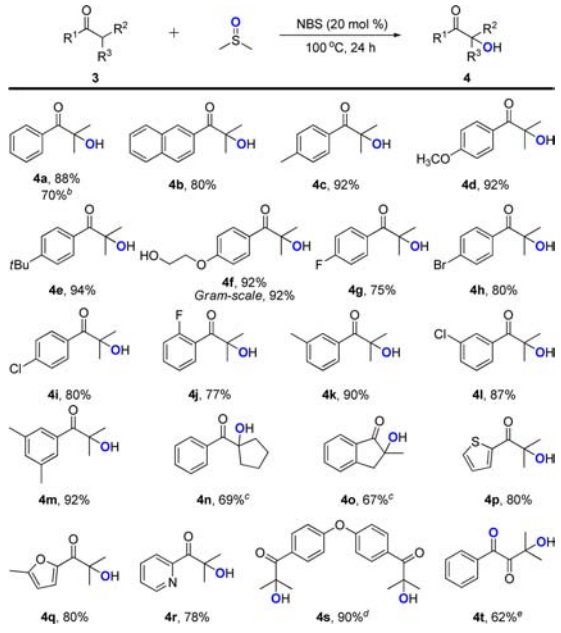
The scope of α-methine carbonyls was then tested (Scheme 3). Although the methine is more reactive than methylene, the steric effect has greater influence to this reaction. As a result, the reaction temperature needed to be increased to 100 °C for full

Scheme 2. Transformation of α-Methylene Carbonyls to Secondary α-Hydroxycarbonyls[a]



[a]Standard reaction conditions: **1** (0.5 mmol), I_2 (20 mol %), DMSO (1 mL), at 60 °C, under air for 24 h. [b]NBS (20 mol %) was used as catalyst. [c]At 50 °C.

Scheme 3. Transformation of α-Methine Carbonyls to Tertiary α-Hydroxycarbonyls[a]



[a]Standard reaction conditions: **3** (0.5 mmol), NBS (20 mol %), DMSO (1 mL), at 100 °C, under air for 24 h. [b]I_2 (20 mol %) was used as catalyst. [c]At 80 °C. [d]NBS (40 mol %) was used as catalyst. [e]3-Methyl-1-phenylbutan-2-one as the starting material.

consumption of starting material. 2-Methylpropiophenone **3a** reacted smoothly in the presence of I_2 to afford **4a** in 70% yield. Encouragingly, the yield could be improved to 88% with NBS as catalyst. Then the hydroxylation of α-methine carbonyls was

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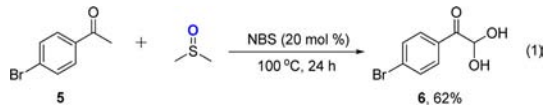
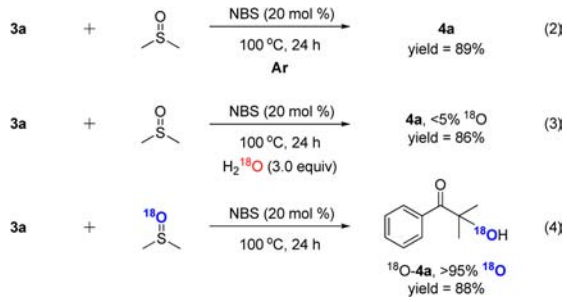
examined with NBS (20 mol %). The functional group compatibility of this transformation is broad. Several substituted 2-methylpropiophenones reacted smoothly to generate the corresponding tertiary α-hydroxycarbonyls in good to excellent yields (**4c**–**o**). Electron-rich substrates generally produced the desired products in relatively higher yields than electron-poor substrates. It is noteworthy that the Friedel–Crafts bromination on the aryl rings was not detected in this transformation. In addition, the hydroxylation of various heteroaryl substrates including thiophene, furan, and pyridine fragments proceeded smoothly to generate products **4p**–**r** in good yields. Furthermore, substrates containing two potential reactive tertiary C–H bonds could be completely hydroxylated to form dihydroxylation product **4s**. For substrate **3t** (3-methyl-1-phenylbutan-2-one), not only the tertiary Csp^3–H bond was hydroxylated but also the active benzyl was oxidized to carbonyl.

Finally, gram-scale reactions of **1n** (Scheme 2) and **3f** (Scheme 3) were performed. Delightedly, the yields were similar to those from the small-scale reactions. Therefore, the α-hydroxycarbonyls, which are versatile intermediates and building blocks in organic synthesis, could be easily obtained by the developed protocol. By using these α-hydroxycarbonyl substrates, cyclic sulfamidates,[9a] 1,2-diols,[9b] β-lactone,[9c] β-amino alcohol,[9d] and thiazole[9e] could be efficiently prepared. Notably, products **4a**, **4f**, and **4s** are widely used as efficient photoinitiators for UV-cured coatings.[19] Compared with reported methods,[5,6,20] this protocol is simple, efficient and practical.

When α-methyl carbonyls were tested, the corresponding arylglyoxal hydrates were obtained in moderate yield. For example, when *p*-bromoacetophenone **5** reacted under this NBS/DMSO system, *p*-bromophenylglyoxal hydrate **6** was isolated in 62% yield (eq 1).



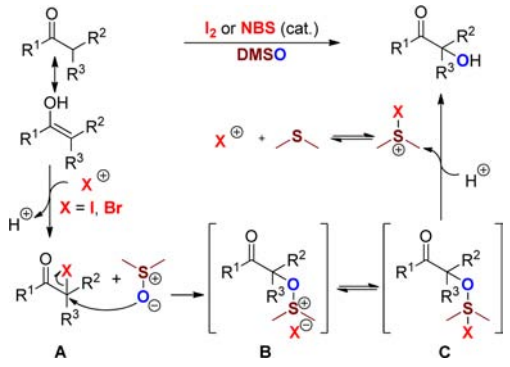
To understand the mechanism, some control experiments were investigated. There are three potential oxygen sources in the reaction system: molecular oxygen in air, a small amount of water in the solvent DMSO, and DMSO itself. The reaction proceeded well in Ar instead of air (eq 2). In addition, when the



reaction of **3a** was conducted in the presence of 3.0 equiv of $H_2{}^{18}O$, **4a** was obtained in 86% yield with <5% ^{18}O-labeled product (eq 3). Both of these results exclude the probability of hydroxylation from molecular oxygen[5,6] and H_2O.[16] In contrast, when the reaction performed with ^{18}O-labeled DMSO, the ^{18}O-labeled **4a** was obtained in 88% yield with >95% ^{18}O-labeled product (eq 4). These experimental results fully proved that the oxygen of the hydroxyl group in product was originated from the oxygen atom of DMSO but not from the molecular oxygen or water. In addition, dimethyl sulfide was detected by GC–MS analysis of reaction products.

Definitely, the mechanism is not completely clear yet. On the basis of the aforementioned results and reported literature,[14–16] a possible reaction pathway is proposed (Scheme 4). Initially,

Scheme 4. Proposed Mechanism



electrophilic halogenation of the substrate by halogen cation X^+ occurs to afford α-halogen carbonyl **A**. The subsequent S_N2 reaction with the nucleophilic oxygen atom of the DMSO generates the ion-pair intermediate **B**, which subsequently affords intermediate **C**.[21] Then intermediate **C** undergoes protonation[21] to produce the hydroxylation product along with the release of dimethyl sulfide and regeneration the halogen cation X^+ for the next catalytic cycle.

In summary, we have demonstrated an efficient method for the selective synthesis of α-hydroxycarbonyls. The simple I_2 or NBS was used as catalyst. DMSO serves as the oxygen source, oxidant, and solvent. A range of secondary α-hydroxycarbonyls and tertiary α-hydroxycarbonyls could be obtained with this hydroxylation protocol. Further studies on the substrate scope and synthetic applications of this efficient and practical hydroxylation are underway in this group.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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