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A Mild and Efficient Direct α-Amination of β-Dicarbonyl Compounds Using Iodosobenzene and *p*-Toluenesulfonamide Catalyzed by Perchlorate Zinc Hexahydrate

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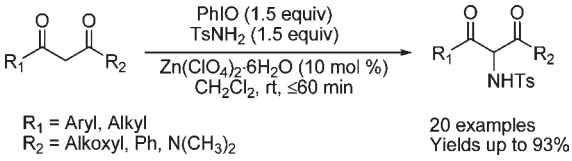
ABSTRACT



A direct α-amination of β-dicarbonyl compounds has been achieved by using iodosobenzene (PhIO) as an oxidant and *p*-toluenesulfonamide ($TsNH_2$) as an aminating reagent in the presence of a catalytic amount of perchlorate zinc hexahydrate. The present amination reaction proceeds quickly at rt (<30 min needed for most tested substrates) to provide the corresponding α-*N*-tosylamido β-dicarbonyl compounds in high to excellent yields.

α-Amido β-dicarbonyl compounds are versatile building blocks in organic synthesis. They not only constitute versatile intermediates for the synthesis of various heterocyclic compounds,[1] peptide mimetics,[2] α-amino acids and their derivatives,[3] and β-hydroxyl α-amino esters[4] but also serve as key precursors in the synthesis of a variety of natural products[5] and pharmaceuticals.[6] To date, a number of methods have been developed for the synthesis of α-amido β- dicarbonyl compounds. Examples include the strong base-mediated acylation of the ketimine derivatives of α-amino esters[2b] and N−C acyl migration of the *N*-*tert*-butoxycarbonyl-*N*-acylglycine ester;[3b,7] the reduction of α-hydroxyimino[8] and phenylazo[9] β-dicarbonyl compounds; the hydrolysis of oxazole-4-carboxylate

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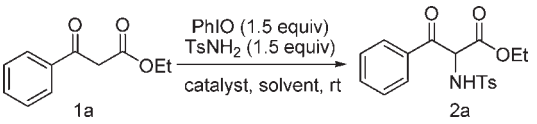
derivatives;[10] and N−H insertion of metal carbene.[1b,11] However, these methods suffer from some disadvantages such as the use of a strong base, inaccessibility of the substrates, and employment of a multistep synthesis. Obviously, the direct α-amination of the readily available β-dicarbonyl compounds is more convenient and efficient for the synthesis of α-amido β-dicarbonyl compounds. However, to our knowledge, this strategy has received little attention and there are only two examples of direct α-amination of β-dicarbonyl compounds. One is the insertion reaction of *in situ* generated (ethoxycarbonyl)nitrene at the α-position of β-dicarbonyl compounds, but in this case, the yield of the desired product is low to moderate.[12] Another is the conjugate additions of β-dicarbonyl compounds to azodicarboxylates.[13] Herein, as part of our continuous investigations on oxidation reactions induced by hypervalent iodine reagents,[14] we report a mild and efficient method for the direct and fast α-amination of β-dicarbonyl compounds using PhIO as the oxidant and $TsNH_2$ as the aminating reagent in the presence of a catalytic amount of perchlorate zinc hexahydrate.

In our initial study, the direct amination of ethyl benzoylacetate (**1a**) was examined using 1.5 equiv of PhIO and 1.5 equiv of $TsNH_2$ in dichloromethane at rt. It was found that the reaction produced a complex mixture after 2 h and the expected aminated product ethyl 3-oxo-3-phenyl-2-(tosylamino) propanoate (**2a**) was obtained in only 48% yield (Table 1, entry 1). To improve the efficiency of the reaction, several Lewis acids were tried which were believed to be capable of activating both the hypervalent iodine reagent and the substrate. $BF_3 \cdot Et_2O$, a normally used Lewis acid to activate PhIO, was first tried, and the reaction afforded **2a** in a slightly improved yield (entry 2). The use of $LiClO_4$ greatly facilitated the reaction, which gave **2a** in 81% yield within a very short reaction time of 10 min (entry 3). The employment of $Zn(ClO_4)_2 \cdot 6H_2O$ led to a more clean reaction, which produced **2a** in the highest yield of 86% also within 10 min (entry 4). Other Lewis acids including $Yb(OTf)_3 \cdot 4H_2O$, $Mg(NO_3)_2 \cdot 6H_2O$, and $CuSO_4$ were also checked, but none of them showed superior results compared with $Zn(ClO_4)_2 \cdot 6H_2O$ (entries 5−7 vs entry 4). Results of the screening study of the amount of $Zn(ClO_4)_2 \cdot 6H_2O$ (Table 1, entries 8−12) indicated that 0.1 equiv of $Zn(ClO_4)_2 \cdot 6H_2O$ was sufficient for the completion of the reaction. When chloroform and acetonitrile were used as the solvent, **2a** was obtained in a slightly lower yield compared with that using dichloromethane (entries 13−14 vs entry 11). Other solvents such as 1,1,1-trichloroethane, THF, and DMF were all less effective (entries 15−17 vs entry 11). Further investigation indicated that the use of $TsNH_2$ as the aminating reagent was essential to the reaction. When methanesulfonamide was employed, the reaction provided the corresponding amination product in a low yield (38% after 30 min). As for benzamide and acetamide, no desired amination product was obtained from the reactions.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (equiv)	solvent	time (min)	yield (%)[b]
1	none	CH_2Cl_2	2 h	48
2	$BF_3 \cdot Et_2O$(1.5)	CH_2Cl_2	20	56
3	$LiClO_4$ (1.5)	CH_2Cl_2	10	81
4	$Zn(ClO_4)_2 \cdot 6H_2O$(1.5)	CH_2Cl_2	10	86
5	$Yb(OTf)_3 \cdot 4H_2O$ (1.5)	CH_2Cl_2	10	69
6	$Mg(NO_3)_2 \cdot 6H_2O$(1.5)	CH_2Cl_2	7 h	45[c]
7	$CuSO_4$(1.5)	CH_2Cl_2	7 h	62[d]
8	$Zn(ClO_4)_2 \cdot 6H_2O$ (0.7)	CH_2Cl_2	10	86
9	$Zn(ClO_4)_2 \cdot 6H_2O$ (0.5)	CH_2Cl_2	10	85
10	$Zn(ClO_4)_2 \cdot 6H_2O$ (0.25)	CH_2Cl_2	10	87
11	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	CH_2Cl_2	10	85
12	$Zn(ClO_4)_2 \cdot 6H_2O$ (0.05)	CH_2Cl_2	10	67
13	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	$CHCl_3$	10	78
14	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	CH_3CN	10	83
15	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	CH_3CCl_3	10	50
16	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	THF	10	50
17	$Zn(ClO_4)_2 \cdot 6H_2O$(0.1)	DMF	20	50

[a] The reaction was conducted using 0.5 mmol of **1a**. [b] Isolated yield. [c] The conversion of **1a** is 67%. [d] The conversion of **1a** is 82%.

With the optimized conditions in hand (Table 1, entry 11), we then investigated the substrate scope of this method (Scheme 1). The methyl, benzyl, *tert*-butyl, and cinnamyl benzoylacetate were all efficiently transformed to their corresponding α-*N*-tosylamido products **2b**−**2e** in high to excellent yields. Substrates bearing either electron-donating or -withdrawing substituents at the para or meta positions of the phenyl ring of benzoyl moiety were also smoothly converted to the expected

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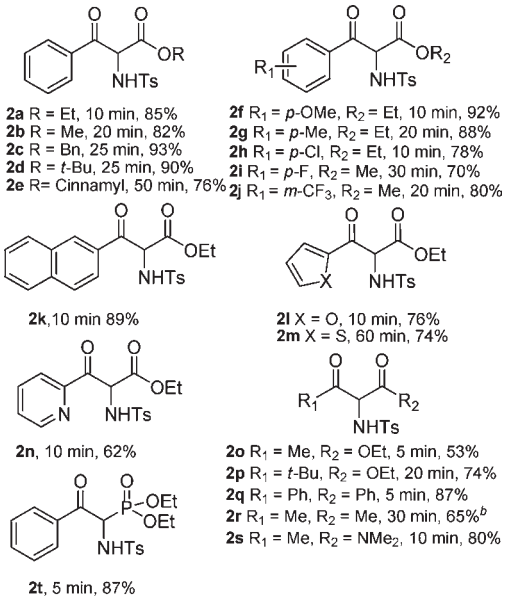
Scheme 1. Substrate Scope of α-Amination of β-Dicarbonyl Compounds[a]

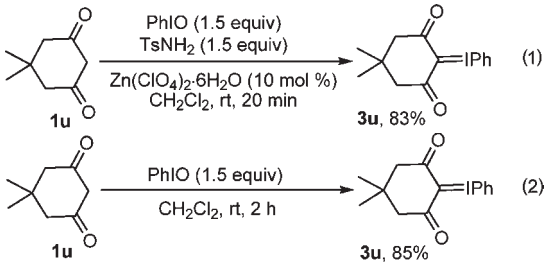


[a] The reaction was carried out using 0.5 mmol of β-dicarbonyl compounds. [b] The reaction was carried out at −10 °C using 1.5 equiv of $Zn(ClO_4)_2 \cdot 6H_2O$.

amination products **2f**−**2j** in good to excellent yields within 30 min. Other aromatic ring systems such as naphthalene, furan, thiophene, and pyridine were all well tolerated under the reaction conditions as indicated by the successful transformation of the substrates to the products **2k**−**2n**. As for aliphatic β-keto esters, their corresponding α-aminated products **2o** and **2p** were obtained in moderate to good yields. Two β-diketones were also smoothly α-aminated to give **2q** and **2r** in 87% and 65% yields respectively. A β-ketoamide, *N*,*N*-dimethyl-3-oxobutanamide, was also examined, which afforded the expected amination product **2s** in 80% yield within 10 min. α-Aminophosphonic acids and their phosphonate display a variety of intriguing biological properties and thus have found broad applications in the field of modern medicine and agriculture.[15] To demonstrate the further synthetic utility of this amination system, a β-ketophosphonate was then tested. It was found that the reaction successfully provided the desired α-*N*-tosylamido phosphonate **2t** in 87% yield within 5 min.

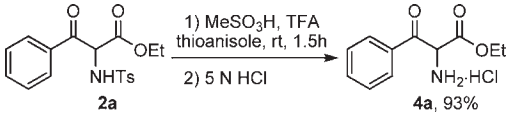
Notably, as for the cyclic β-diketone dimedone (**1u**) and a cyclic β-keto ester 6,6-dimethyldihydro-2*H*-pyran-2,4(3*H*)-dione, the present system produced their corresponding iodonium ylides in 83% yield for both.[16] Further investigation showed that the formation of iodonium ylide product **3u** came from the background reaction of **1u** with PhIO (Scheme 2, eq 2). And the addition of a catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ (10 mol %) could greatly enhance the reaction rate and therefore shorten the reaction time to 10 min still with an 80% yield of **3u** .

Scheme 2. Reactions of Dimedone with PhIO



Furthermore, the tosyl group could be readily removed from **2a** upon treatment with $MeSO_3H$ in TFA/thioanisole at rt to give the detosylation product **4a** in an excellent yield (Scheme 3).[15a]

Scheme 3. Detosylation of **2a**



To explore the mechanism, some control experiments were carried out (Scheme 4). In the amination reaction, perchloric acid may be generated from $Zn(ClO_4)_2 \cdot 6H_2O$. To check whether this Brønsted acid promotes the reaction, **1a** was treated with 1.5 equiv of PhIO and $TsNH_2$ in the presence of 0.2 equiv of $HClO_4$ (utmost amount generated in situ from 0.1 equiv of $Zn(ClO_4)_2$) in CH_2Cl_2 at rt. The reaction afforded **2a** in only 15% yield after 10 min. Hence, $HClO_4$ could not facilitate the amination reaction. Since cyclic dicarbonyl compounds like **1u** were transformed into their corresponding iodonium ylides, iodonium ylide was hypothesized as the intermediate in the present amination reaction. To check this possibility, iodonium ylide **3a**[17] was prepared and subjected to $TsNH_2$ with the catalytic amount of $Zn(ClO_4)_2$. It was found that no desired amination product was observed while a tricarbonyl compound **5a** was provided in 34% yield. Therefore, the intermediacy of **3a** in the amination reaction was excluded (Scheme 4, eq 3). On the other hand, when PhIO was treated with $TsNH_2$ in the presence

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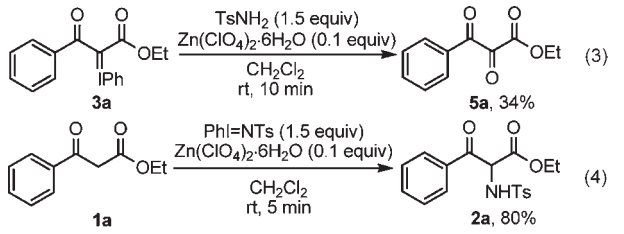
Scheme 4. Control Experiments

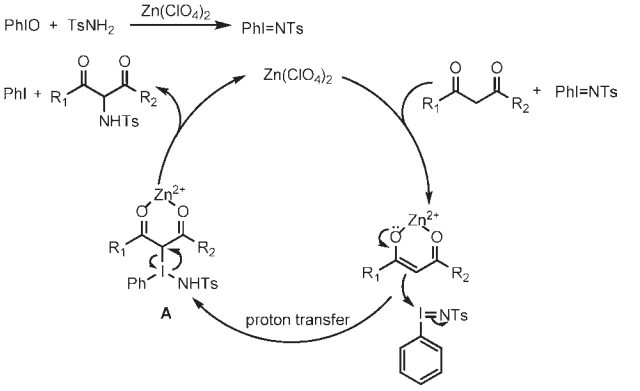


of $Zn(ClO_4)_2 \cdot 6H_2O$ in CH_2Cl_2 at rt for 10 min, *N*-tosyliminoiodane (PhI=NTs) could be obtained in 63% yield. To verify whether PhI=NTs was the real agent responsible for the formation of amination product, PhI=NTs was used directly as the oxidant replacing PhIO in the amination reaction. It was found that the reaction produced the aminated product **2a** in 80% yield within 5 min (Scheme 4, eq 4). This fact implied that the present amination reaction might be mediated by the *in situ* generated PhI=NTs.[18] To check whether a nitrene intermediate was involved as commonly reported in the reactions using PhI=NTs,[19] styrene was used to react with PhI=NTs in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$. NMR analysis of the reaction mixture revealed that no aziridine product was formed, which meant that a nitrene intermediate could not be generated when mixing PhI=NTs and $Zn(ClO_4)_2$.

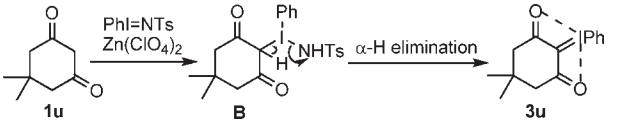
Based on the above results, a plausible mechanism for this direct and fast α-amination reaction of acyclic *β*-dicarbonyl compounds is proposed in Scheme 5. First, PhIO reacted with $TsNH_2$ to form PhI=NTs. Then, the electrophilic addition of PhI=NTs to the enol form of linear *β*-dicarbonyl compounds in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ gave the key intermediates **A**, which underwent reductive elimination[20] to provide α-*N*-tosylamido *β*-dicarbonyls. The presence of $Zn(ClO_4)_2 \cdot 6H_2O$ not only activated PhIO but also promoted the formation of enol of *β*-dicarbonyl compounds which made the reaction proceed quickly.

When cyclic dicarbonyl compound **1u** was treated with PhI=NTs, iodonium ylide **3u** was produced in 80% yield, the same product as that from the standard amination reaction using PhIO−$TsNH_2$ (Scheme 2, eq 1). It was believed that a similar intermediate **B** to **A** was formed when **1u** reacted with PhI=NTs. Due to the contribution of the intramolecular secondary bondings between two carbonyls and an iodine(III) center, the cyclic iodonium ylide **3u** was more stable than the linear one. The same idea was also given by

Scheme 5. Proposed Mechanism



Scheme 6. Explanation for the Formation of **3u**



Moriarty et al.[21] Therefore intermediate **B** was prone to α-H elimination to produce **3u** (Scheme 6).

In summary, we have developed a mild and efficient method for the direct amination of readily available *β*-dicarbonyl compounds employing commercially available PhIO as the oxidant and $TsNH_2$ as the aminating reagent catalyzed by $Zn(ClO_4)_2 \cdot 6H_2O$. It is the first time that the activation of PhIO using $Zn(ClO_4)_2 \cdot 6H_2O$ with high efficiency is reported, which makes the present amination reaction proceed quickly at rt to provide the aminated products in high to excellent yields. Also, the reactions are tolerant of a range of functional groups and thus effective for a broad scope of substrates. Considering the mildness and efficiency of the present method, the ready availability of *β*-dicarbonyl compounds, PhIO, and $TsNH_2$, this method should be an attractive approach to synthesize α-amido *β*-dicarbonyl compounds.

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Supporting Information Available. The experimental procedures, the characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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