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SHORT COMMUNICATION

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Iodine-Promoted Oxidative Amidation of Terminal Alkenes – Synthesis of α-Ketoamides, Benzothiazoles, and Quinazolines[‡]

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Keywords: Alkenes / Iodine / α-Ketoamides / Benzothiazoles / Quinazolines / Green chemistry

A novel metal-free strategy for oxidative amidation of terminal alkenes by using I_2/DMSO for the synthesis of α-ketoamides has been developed. Intriguingly, the use of *tert*-butylhydroperoxide (TBHP) as co-oxidant can facilitate the synthesis of α-ketoamides at room temperature without any solvent, thereby making it a green protocol. The reaction with primary amines can be easily achieved by using SeO_2 as an oxidizing agent. Besides, the scope of the method was also extended to the synthesis of benzothiazolines and quinazolines.

Introduction

α-Ketoamides are attractive for organic chemists, because they are characteristically present in a wide range of biologically active molecules ranging from immunosuppressive drugs like FK506, FKBP12, and rapamycin to human cytosolic phospholipase A_2 ($GIVAPL_2$) cyclotheonamide, androgen, and estrogen receptors.[1,2] Their scope also expands into the synthesis of non-immunosuppressive compounds like V-10367 and GVI-1046, sodium channel blocker GW-356194, homoprotoberberines, α-diones, 11 *cis*- and *trans*-isomers of β-lactam, oxazolidin-4-ones, and 5-HT6 binding ligands. In addition, they are intermediates for a broad range of functional group transformations.[3,4] In the recent past, tremendous amount of work has gone into the development of newer synthetic approaches, each enabling greater scope in terms of coupling partners and milder reaction conditions (Figure 1).[5,6]

In this regard, terminal monosubstituted alkenes are ideal prospective starting materials for organic synthesis, because they are manufactured on very large scales and can be functionalized by a broad range of chemical transformations.[7] Thus, as a part of our continued studies,[8] we were interested in expanding the scope of these alkenes for the synthesis of α-ketoamides. Herein, we report a metal-free oxidative amidation protocol for the synthesis of α-ketoamides from a range of terminal alkenes and amines by using iodine and DMSO, which acts both as a solvent and an oxidant. Interestingly, the use of *tert*-butylhydroperoxide (TBHP) as a co-oxidant facilitates the reaction at room temperature without use of any solvent, thereby making it a green protocol. α-Ketoamides could easily be synthesized from primary amines by using SeO_2 as oxidant. The method was also successfully utilized for the synthesis of benzothiazoles and quinazolines.

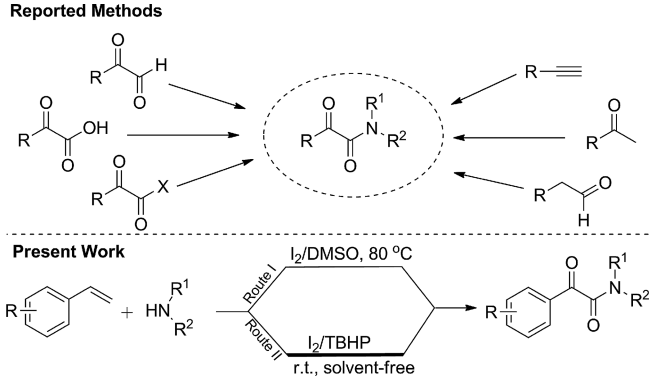

Figure 1. Synthesis of α-ketoamides.

Results and Discussion

Our study commenced with the reaction of styrene (**1a**) and pyrrolidine (**2a**) in the presence of iodine (0.5 equiv.) and DMSO as solvent at 80 °C. As expected the reaction afforded the desired product **3a** in 56% yield (Table 1 entry 1). The increase of iodine loading to 1 equiv. improved the yield of **3a** to 72% (Table 1 entry 2). Further increase of iodine loading to 1.5 equiv. had no significant impact on the outcome of the reaction (Table 1 entry 3). We also probed the effect of temperature on the reaction; decreasing the temperature to room temperature resulted in almost no product formation in 12 h (Table 1 entry 4). Furthermore, to establish the role of iodine we performed the reaction

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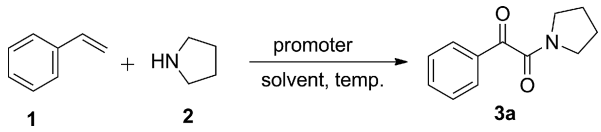
with *N*-iodosuccinimide (NIS) and tetrabutylamonium iodide (TBAI), while there was no product formation with NIS, TBAI gave the product in trace amounts. The feasibility of reaction in other solvents, namely DMF, THF, dichloromethane (DCM), and toluene was also explored, only to find that no product was formed in these solvents (Table 1 entry 7–10). Thus, the optimization studies showed that 1 equiv. of iodine at 80 °C in DMSO was found to be the reaction conditions of choice.

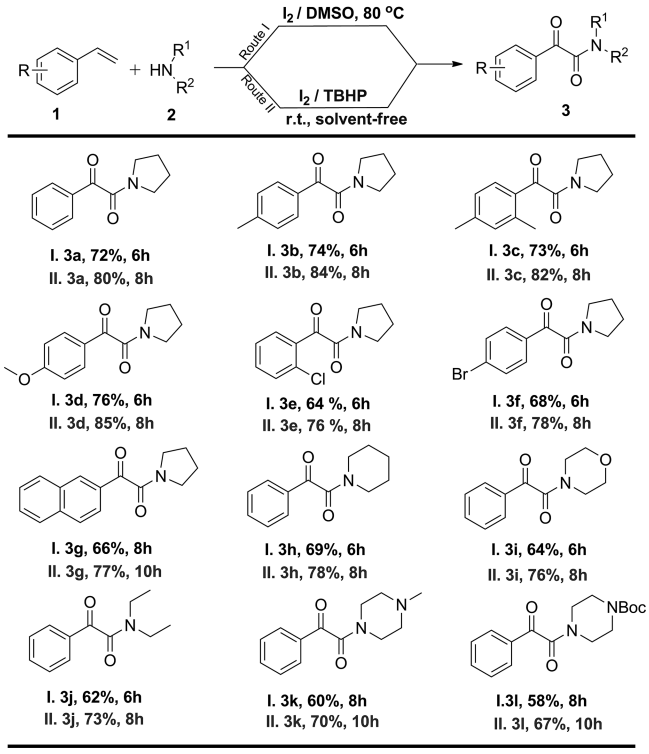
Table 1. Optimization studies for the oxidative coupling of styrene and pyrrolidine.[a]



Entry	Solvent	Promoter	Equivalents	Temperature [°C]	Yield [%][b]
1	DMSO	I_2	0.5	80	56
2	DMSO	I_2	1	80	72
3	DMSO	I_2	1.5	80	75
4	DMSO	I_2	1	r.t.	> 10
5	DMSO	NIS	1	80	–
6	DMSO	TBAI	1	80	trace
7	DMF	I_2	1	80	–
8	THF	I_2	1	40	–
9	DCM	I_2	1	80	–
10	Toluene	I_2	1	80	–

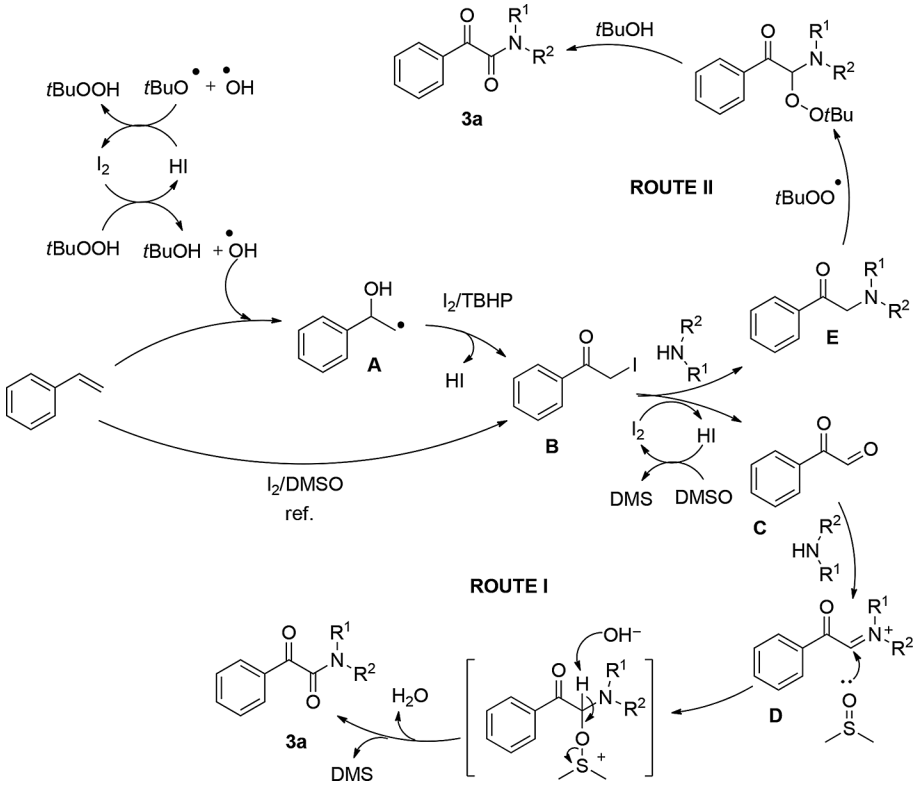
[a] Reactants: **1** (1 mmol), **2** (1.5 mmol), air, 6 h. [b] Isolated yields.

To determine whether terminal alkenes can be used in efficient synthesis of various α-ketoamides, the scope of the reaction with different styrenes and pyrrolidine under the optimized conditions was investigated. The reaction with a range of styrenes gave the corresponding products in good yields (Scheme 1). The results showed that the styrenes with electron-donating functions, that is, *p*-methyl-, 2,4-dimethyl-, and *p*-methoxystyrene, gave the corresponding products **3b**, **3c**, and **3d** in 74, 73, and 76% yield, respectively. The halogen-substituted styrenes, that is, *o*-chloro- and *p*-bromostyrene gave the corresponding products **3e** and **3f** in 64 and 68% yields, respectively. Also the reaction with naphthyl styrene proceeded efficiently to give product **3g** in 66% yield, which showed that steric hindrance had no impact on the outcome of the reaction. The reaction also efficiently led to the synthesis of a variety of α-ketoamides with secondary amines like piperidine, morpholine, *N*-methyl piperazine, *N*-Boc-piperazine, and *N*,*N*-diethylamine to give the corresponding products **3h**, **3i**, **3j**, **3k**, and **3l** in 69, 64, 62, 60, and 58% yield, respectively. The results show that the reaction is versatile as well as mild enough to encompass acid-sensitive and heterocyclic functionalities. To gain further insights into the special features of iodine-catalyzed synthesis of α-ketoamides, we performed a reaction in the presence of a co-oxidant like TBHP. To our delight, the reaction of styrene with pyrrolidine resulted in the formation of product **3a** in 80% yield. The special feature of this reaction is that it operates at room temperature and requires no solvent; this makes it a green protocol. Nevertheless, the reaction with TBHP led to product formation with all secondary amines at room temperature in comparatively better yields (Scheme 1). Importantly, the reaction with primary amines did not yield the desired product either by route I or by route II. With the reasonable assumption that TBHP is a better co-oxidant than DMSO, the outcome of the reaction suggests that product formation at room temperature is probably due to the greater oxidizing strength of TBHP as compared to DMSO.



Scheme 1. Generality of the reaction in terms of alkenes and secondary amines for constructing various α-ketoamides.

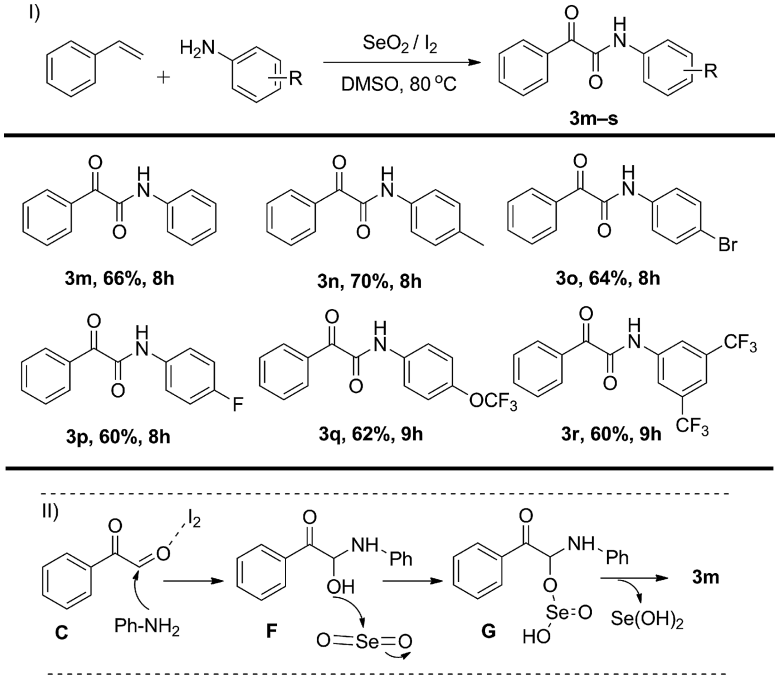
A possible explanation for the formation of α-ketoamides from styrenes and amines is shown in Scheme 2. For route I, the reaction possibly proceeds via α-iodoacetophenone (**B**),[9] which subsequently undergoes Kornblum oxidation to give 2-oxoaldehyde (2-OA, **C**) with the release of HI. The HI, in the presence of DMSO, regenerates iodine,[8] which activates the aldehyde group of **C** followed by subsequent attack of the amine to generate the iminium ion (**D**) as the active intermediate required for further progress of the reaction. As we know, DMSO can acts as an oxygen donor;[9] therefore, the more electrophilic carbon center of the iminium ion makes the substrate available for nucleophilic attack by DMSO, which, on elimination of water and dimethyl sulfide (DMS), results in the formation of products. For route II, the TBHP is decomposed to a *tert*-butoxyl and a hydroxy radical in the presence of I_2. The hydroxy radical in turn attacks on styrene to give a phenacyl radical (**A**), which undergoes further oxidation and iodination in presence of I_2/TBHP to give α-iodoacetophenone (**B**),[10] followed by nucleophilic substitution with



Scheme 2. Plausible mechanism.

amine to generate intermediate (**E**).[11] Finally, intermediate **E** is oxidized by TBHP to form the desired product **3a**.

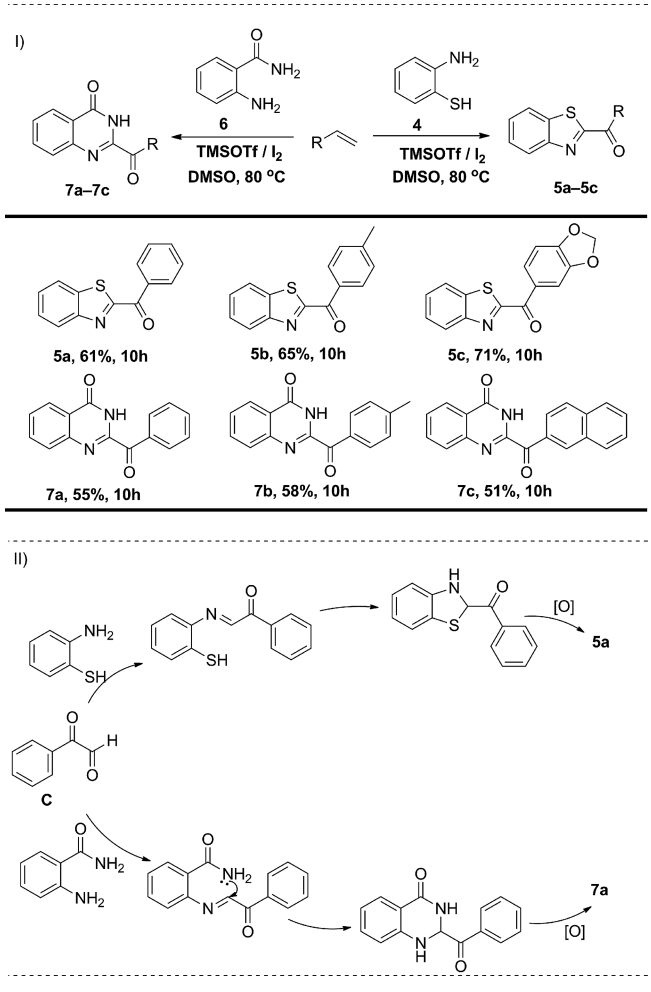
To further generalize the method and make it applicable to primary amines as well, we envisaged the use of SeO_2, as it is known to provide α-ketoamides with 2-OA, but only with secondary amines.[12] Thus, we placed a reaction of styrene with aniline, using I_2/SeO_2 in DMSO at 80 °C, to afford the corresponding product in 66% yield. We further extended this method to a variety of primary amines having both electron-withdrawing and electron-donating functions.



Scheme 3. (I) Generality of the reaction in terms of alkenes and primary amines for constructing various α-ketoamides; (II) plausible mechanism.

The reaction proceeded efficiently and gave the corresponding products in good yields (Scheme 3). Mechanistically the reaction probably proceeds by formation of 2-OA (**C**), as shown in Scheme 2. The iodine activates the aldehyde group; this is followed by the attack of aniline to generate α-hydroxyacetophenone (**F**). Intermediate **F** subsequently generates intermediate **G** upon reaction with SeO_2 to consequently afford the desired α-ketoamide, **3m**, with release of selanediol (Scheme 3).[12]

Prior studies of the mechanism suggest that the reaction possibly proceeds through the formation of imine with in situ generated 2-OA (Scheme 2). We reasoned that the reaction with 2-aminobenzothiol and 2-aminobenzamide may lead to the synthesis of benzothiazoles and quinazolines (Scheme 4).[13] Thus, we started with the synthesis of benzothiazoles, as they represent a class of heterocyclic compounds commonly encountered in a large number of natural products having biological and medicinal importance.[14] Under optimized reaction conditions (Table 1 entry 2), the reaction of styrene with 2-aminobenzothiol gave the product in poor yields and lot of side products. Approaching the reaction mechanistically, we thought of using an acid that is known to enhance the electrophilicity of the carbon center of the imine and make the nucleophilic attack more feasible. From our previous work,[8] we knew that using TMSOTf in conjunction with iodine can enhance the nucleophilicity of the iminium ion to such an extent that DMSO undergoes addition to iminium center. Thus, following this rationale, we used TMSOTf in combination with iodine, and to our delight the reaction gave product **5a** in 61% yield. The reaction also efficiently gave the corresponding products **5b**–**c** with *p*-methyl- and 3,4-methylenedioxystyrene in 65 and 71% yields. As mentioned earlier, we also extended the reaction for the construction of quinazolines, a motif commonly encountered in numerous bioactive natural and synthetic compounds.[15] Therefore, the reaction of styrene with commercially available 2-aminobenzamide in the presence of TMSOTf/I_2 resulted in the synthesis of 2-benzolylquinazoline **7a** in 55% yield. The reaction with *p*-methyl- and naphthylstyrene also gave products **7b** and **7c** in 58 and 51% yields, respectively. It would be pertinent to mention here that the present method gives access to benzothiazoles and quinazolines without use of a metal and oxidant.



Scheme 4. (I) Synthesis of benzothiazoles and quinazolines; (II) plausible mechanism.

Conclusion

In summary, we have developed an efficient metal-free strategy for the synthesis of α-ketoamides from terminal alkenes both at high temperatures and at room temperature. Furthermore, the method efficiently leads to the synthesis of benzothiazoles and quinazolines without use of a metal or oxidant. A simple experimental procedure, low catalyst loading, the stoichiometric quantity of the reactants, and the wide substrate scope are some of the advantages of the process.

Experimental Section

Synthesis of α-Ketoamides Form Secondary Amines

Route I: Iodine (1 mmol) was added to a solution of styrene **1** (1 mmol) in DMSO (2 mL) followed by the addition of **2** (1.5 mmol). The reaction mixture was then heated at 80 °C for 6 h, and the product formation was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3× 50 mL). The combined organic layers were washed with brine, concentrated in a rotary evaporator, and purified by column chromatography using ethyl acetate and hexane to afford **3a** in 72% yield.

Route II: To prepare α-ketoamides from primary amines and benzothiazoles/quinazolines, TBHP, SeO_2 and TMSOTf were used in addition (please see the Supporting Information for detailed procedures).

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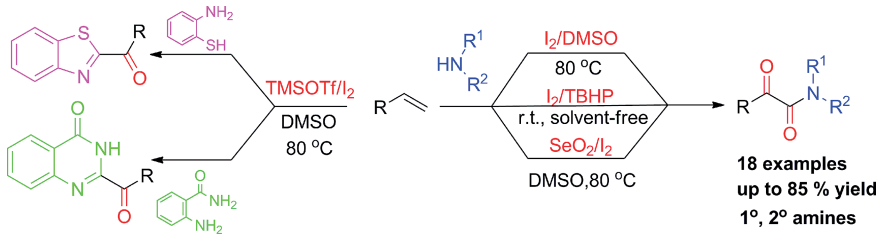
Oxidative Amidation



A novel metal-free strategy for oxidative amidation of terminal alkenes using I_2/DMSO for the synthesis of α-ketoamides has been developed. Intriguingly, the use of *tert*-butylhydroperoxide (TBHP) as co-oxidant can facilitate the synthesis of α-ketoamides at room temperature without any solvent, whereas for reaction with primary amines SeO_2 is required as oxidizing agent.

Keywords: Alkenes / Iodine / α-Ketoamides / Benzothiazoles / Quinazolines / Green chemistry

