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A general metal free approach to α-ketoamides *via* oxidative amidation–diketonization of terminal alkynes†

Ramesh Deshidi, Manjeet Kumar, Shekaraiah Devari and Bhahwal Ali Shah*

A novel catalytic system TMSOTf/I_2/DMSO for the oxidative coupling of terminal alkynes with virtually any primary/secondary amine leading to α-ketoamides has been developed. The reaction possibly proceeds *via* iminium ion formation, wherein DMSO acts as a solvent as well as an oxidizing agent.

α-Ketoamide, a privileged motif, is a characteristic underlying element of many bio-active molecules such as FK506, rapamycin and FKBP12.[1] Furthermore, it is an attractive candidate to synthetic chemists due to its ability to access a wide range of functional group transformations.[2,3] Its varied and significant biological activities have been the impetus to the recent development of manifold synthetic methods, with each allowing for a greater scope in terms of coupling partners and milder approaches.[4,5] However, most of these methods involve metal catalysts in combination with co-oxidants and harsh reaction conditions. Remarkably, there is still no single route which can work without discriminating the basic reactivity of aromatic–aliphatic or primary–secondary coupling partners. Therefore, developing a general method for the synthesis of α-ketoamides is highly desirable.

In this context, we thought of exploiting terminal alkynes for the synthesis of α-ketoamides *via* C–H activation. To the best of our knowledge, the only example of terminal alkynes described by Zhang and Jiao,[6] for the synthesis of α-ketoamides, was applicable to only primary amines and employed a cocktail of reagents *i.e.*, metal catalyst, oxidizing agents, excessive base and alkyne (5–10 equiv.) (Fig. 1). Recently, Ahmed and co-workers[7] developed a new route involving highly reactive iminium ions as an intermediate to facilitate α-ketoamides synthesis using DMSO as the oxidant. However, the reaction suffered with limited substrate scope in terms of primary amines, as they failed to generate iminium ions due to the formation of a more stable Schiff base. We reasoned that developing a strategy for iminium ion formation through C–H activation of terminal alkynes might be a solution to this problem. Specifically, it was envisaged that employing a Lewis acid in combination with DMSO and I_2 could be a starting point.

To test our hypothesis, a test reaction between phenyl acetylene (**1**) and pyrrolidine (**2**) was run in the presence of TMSOTf (1 equiv.) and a catalytic amount of iodine in DMSO at room temperature. As anticipated, our proposition worked and the reaction gave the desired product (**3aa**), but in low yields (35%) (Table 1, entry 1). The reaction possibly involves *in situ* C–H activation of terminal alkynes which proceeds *via* iminium ion formation to give α-ketoamides. Intriguingly, the method circumvents the need for any metal catalysts or oxidizing agent and requires stoichiometric quantities of the reactants. However, the results warranted optimization of the reaction conditions. To monitor the effect of temperature, we carried out the reaction at 60 and 80 °C to afford **3aa** in 49 and 57% yields respectively (Table 1, entries 2 and 3). Further increasing the temperature to 120 °C had no significant effect on the overall yields (Table 1, entry 4). To establish the role of TMSOTf, we performed the reaction with other metal triflates such as $Yb(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$, but none afforded the product

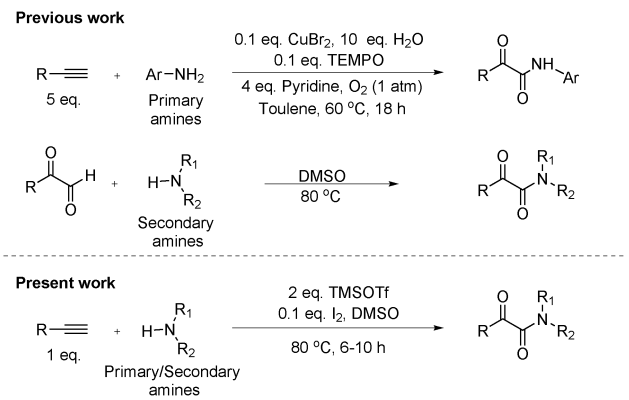

Fig. 1 Synthesis of α-ketoamides.

Academy of Scientific and Innovative Research (AcSIR), Natural Product Microbes, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-Tawi, 180001, India. E-mail: bashah@iiim.res.in

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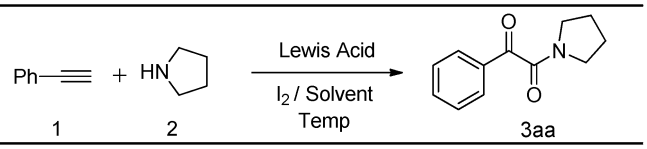
Table 1 Optimization studies for the oxidative amidation of phenylacetylene[a]



Entry	Solvent	Lewis acid	Equiv.	Temp. (°C)	Time (h)	Yield[b] (%)
1	DMSO	TMSOTf	1	rt	12	35
2	DMSO	TMSOTf	1	60	10	49
3	DMSO	TMSOTf	1	80	10	57
4	DMSO	TMSOTf	1	120	10	54
5	DMSO	$Yb(OTf)_3$	1	80	10	—
6	DMSO	$Sc(OTf)_3$	1	80	8	—
7	DMSO	$In(OTf)_3$	1	80	8	—
8	DMSO	TMSOTf	0.5	80	8	46
9	DMSO	TMSOTf	1.5	80	6	70
10	DMSO	TMSOTf	2	80	6	72
11	DMSO	TMSOTf	2.5	80	6	83
12	CH_3CN	TMSOTf	2	80	16	—
13	DMF	TMSOTf	2	80	22	—
14	THF	TMSOTf	2	80	12	—
15	Toluene	TMSOTf	2	80	12	—
16	DCM	TMSOTf	2	40	4	—

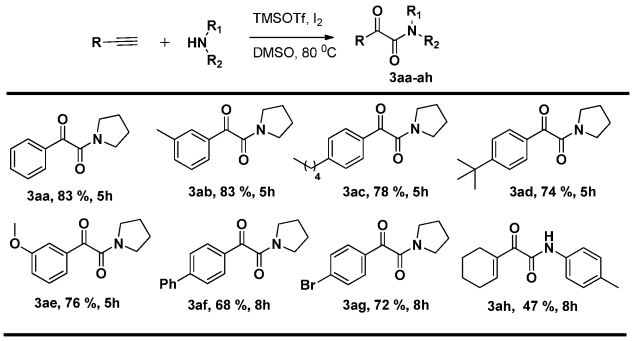
[a] Reactants: 1 (1 mmol), 2 (1.5 mmol). [b] Isolated yields.

(Table 1, entries 5–7). The identification of the optimum loading was another important aspect of the reaction strategy. Decreasing the amount of TMSOTf to 0.5 equiv. resulted in a considerable yield loss (Table 1, entry 8). However, an increase in loading to 1.5 equiv. resulted in the corresponding product in 70% yield, which increased to 72 and 83% when the amount was increased to 2 and 2.5 equiv. respectively (Table 1, entries 9–11). A further increase in TMSOTf loading didn't cause any significant change in the overall yield. Thus, TMSOTf loading of 2.5 equiv. at 80 °C were found to be the conditions of choice. We also examined the feasibility of the reaction in other solvents such as acetonitrile, DMF, THF and DCM, but found no product formation (Table 1, entries 12–16).

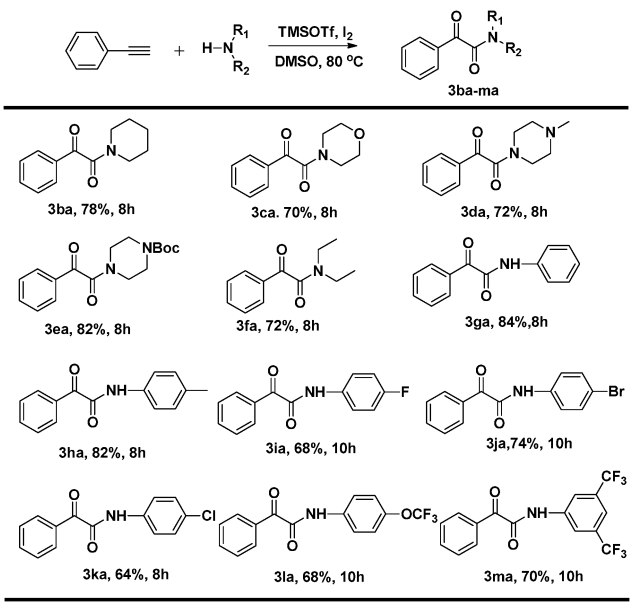
Having optimized the conditions, we explored the utility of this approach for the oxidative coupling of various substituted alkynes with pyrrolidine. The reaction with both electron-rich and electron-deficient aryl acetylenes afforded the desired products in quantitative yields. The reaction also tolerated 4-bromo phenyl acetylene and cyclohexenyl acetylene well to afford the desired products **3ag** and **3ah** in 72% and 47% yields respectively (Scheme 1).

Encouraged by these results, we decided to test the generality of our method with a range of substituted amines and phenyl acetylene (**1**) (Scheme 2). The reaction with secondary amines like pyrrolidine, piperidine, morpholine, *N*-methyl piperazine, *N*-Boc piperazine and *N*,*N*-diethyl amine gave the corresponding products in excellent yields. Moreover, aromatic primary amines which have both electron-releasing and electron-withdrawing groups were found to be good substrates for producing the corresponding α-ketoamides in good yields. In general, aromatic amines bearing electron-donating substituents gave comparatively higher yields than electron-withdrawing substituents. These results demonstrate the versatility of the present methodology.

The reaction possibly proceeds *via* trifluoromethylation of the terminal alkyne which was corroborated; (a) by the reaction without amine and iodine in DCM, which resulted in the



Scheme 1 Generality of the reaction in terms of alkynes for constructing various α-ketoamides.



Scheme 2 Generality of the reaction in terms of amines for constructing various α-ketoamides.

formation of acetophenone (**I**), and (b) by the use of TMSOTf in catalytic amounts (20 mol%) resulting in the dimerization of phenyl acetylene (**II**). The trifluoromethylated alkyne reacts with iodine to produce α-iodoacetophenone (**III**), which then undergoes Kornblum oxidation resulting in the formation of arylglyoxal (**IV**) with the release of HI.[8] HI in the presence of DMSO regenerates iodine, which activates the aldehyde group of arylglyoxal followed by the subsequent attack of amine to generate an iminium ion (**V**), which is the active intermediate required for further progress of the reaction. As we know, DMSO can act as an oxygen donor,[7] therefore, the more electrophilic carbon centre of the iminium ion creates a substrate available for nucleophilic attack from the DMSO, which on elimination of water and dimethyl sulfide (DMS) results in the formation of the product. The reaction between primary amines/anilines with phenylglyoxals, which is promoted by molecular iodine, generates a Schiff base that is eventually protonated resulting in an iminium ion (**V**), leading to the

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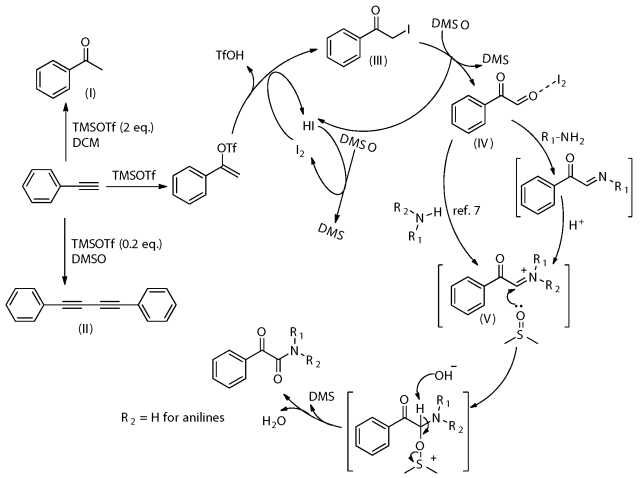

Fig. 2 Plausible mechanism of formation.

synthesis of α-ketoamides in a similar way as discussed already. Furthermore, to rule out the possibility of aerial oxidation, the reaction was carried out under inert conditions resulting in the product without any significant drop in yield (Fig. 2).

In conclusion, we demonstrated the first metal free catalytic system employing TMSOTf/I_2 in DMSO for the oxidative amidation–diketonization of terminal alkynes to produce a wide variety of α-ketoamides. The reaction circumvents the need for molecular oxygen and additional oxidizing agents. Furthermore, this may serve as an excellent method for studying the scope of C–H activation of terminal alkynes in other reactions.

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