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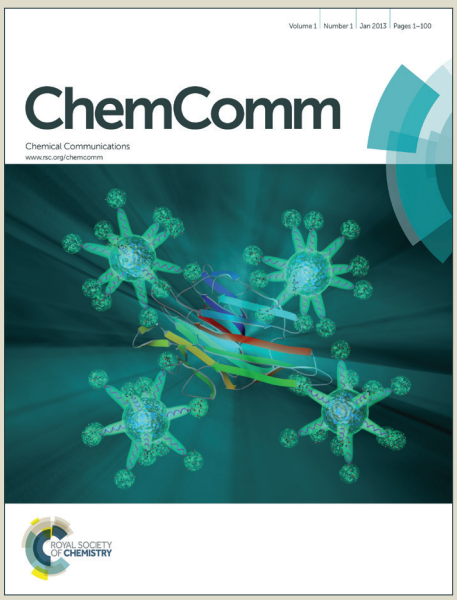

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A general metal free approach to α-ketoamides via oxidative amidation-diketonization of terminal alkynes

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A novel catalytic system TMSOTf/I_2/DMSO for 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 act as solvent as well as oxidizing agent.

α-Ketoamide, a privileged motif is characteristic underlying element of many bio-active molecules such as FK506, rapamycin and FKBP12.[1] Further it is an attractive candidate to synthetic chemists due to its ability to access wide range of functional group transformations.[2,3] Its varied and significant biological activities have been impetus to the development of manifold synthetic methods in recent past with each allowing greater scope in terms of coupling partners and milder approach.[4,5] However, most of these methods involve metal catalysts in combination with co-oxidants and harsh reaction conditions. Remarkably, still there is 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.

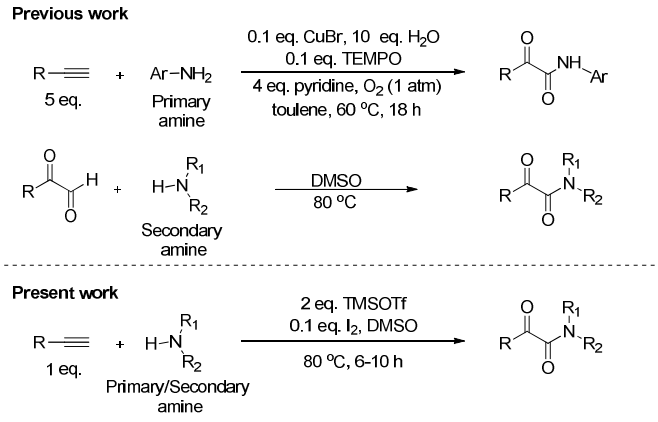


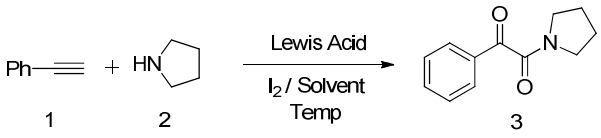
Figure 1. Synthesis of α-ketoamides

In this context, we thought of exploiting terminal alkynes towards 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 cocktail of reagents *i.e.*, metal catalyst, oxidizing agents, excessive base and alkyne (5-10 eq.) (Figure 1). Recently Qazi and co-workers,[7] developed a new route involving highly reactive iminium ion as intermediate to facilitate α-ketoamides synthesis using DMSO as oxidant. However reaction suffered with substrate scope in terms of primary amines, in which they failed to generate iminium ion, owing to the formation of more stable Schiff's 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 eq) and catalytic amount of iodine in DMSO at room temp. 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 of any metal catalysts or oxidizing agent and requires stoichiometric quantity of reactants. However, the results warranted optimization of the reaction conditions. To monitor the effect of temperature we carried out reaction at 60 and 80 °C to afford **3aa** in 49 and 57 % yields respectively (table 1, entry 2-3). Further increasing the temperature upto 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 $Cu(OTf)_2$, $Sc(OTf)_2$, $In(OTf)_3$, but none afforded the product (table 1, entry 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 loss of yields (table 1, entry 8).

However, an increase in loading to 1.5 equiv gave the corresponding product in 70 % yield, which increases to 72 and 83 % on increasing the amount to 2 and 2.5 equiv respectively (table 1, entry 9-11). Further increase of TMSOTf loading didn't cause any significant change in overall yields. Thus, the TMSOTf loading of 2.5 equiv at 80 °C was found to be the condition of choice. We also examined the feasibility of reaction in other solvents such as acetonitrile, DMF, THF and DCM, but found no product formation (table 1, entry 12-16).

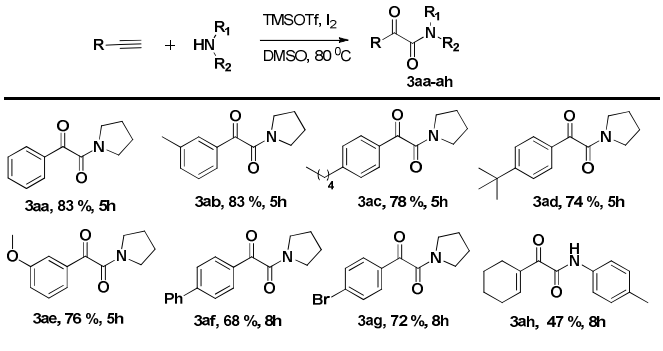
Table 1. Optimization studies for the oxidative amidation of phenylacetylene.[a]



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	$Cu(OTf)_2$	1	80	10	-
6	DMSO	$Sc(OTf)_2$	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	-

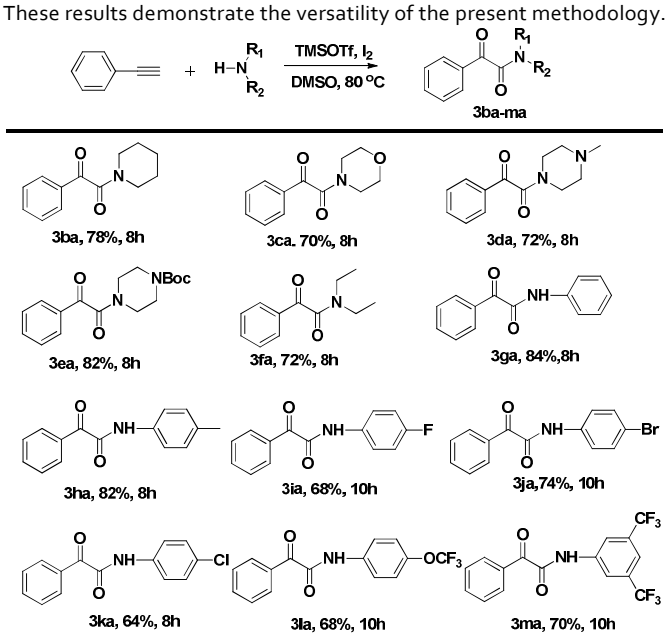
[a] Reactants: 1 (1 mmol), 2 (1.5 mmol). [b] Isolated Yields.

Having conditions optimized, 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 well tolerates 4-bromo phenyl acetylene and cyclohexenyl acetylene to afford the desired product **3ag** and **3ah** in 72% and 47% yields respectively.



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

Encouraged by the 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 having both electron-releasing and electron-withdrawing groups were found to be good substrates to access 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.



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

The reaction possibly proceeds via triflouro methylation of terminal alkyne which was corroborated; (a) by the reaction without amine and iodine in DCM, which resulted in the formation of acetophenone (**I**) and (b) the use of TMSOTf in catalytic amount (20 mol%) resulting in the dimerization of phenyl acetylene (**II**). The trifluoromethylated alkyne reacts with iodine to give α-iodo acetophenone (**III**), which then undergoes Kornblum oxidation resulting in the formation of arylglyoxal (**IV**) with the release of HI.[8] The HI in the presence of DMSO regenerates iodine which activates the aldehyde group of arylglyoxal followed by subsequent attack of amine to generate iminium ion (**V**) as the active intermediate required for further progress of the reaction. As we know DMSO can acts as an oxygen donor,[7] therefore, the more electrophilic carbon centre of iminium ion makes substrate available for nucleophilic attack from DMSO, which on elimination of water and dimethyl sulfide (DMS) results in the formation of product. The reaction between primary amines/anilines with phenylglyoxals promoted by molecular iodine generates Schiff's base, which eventually gets protonated to give iminium ion (**V**) leading to the synthesis of α-ketoamides in similar way as discussed already. Furthermore to rule out the possibility of aerial oxidation, the reaction was carried under inert conditions, which gave the product without any significant drop of yields.

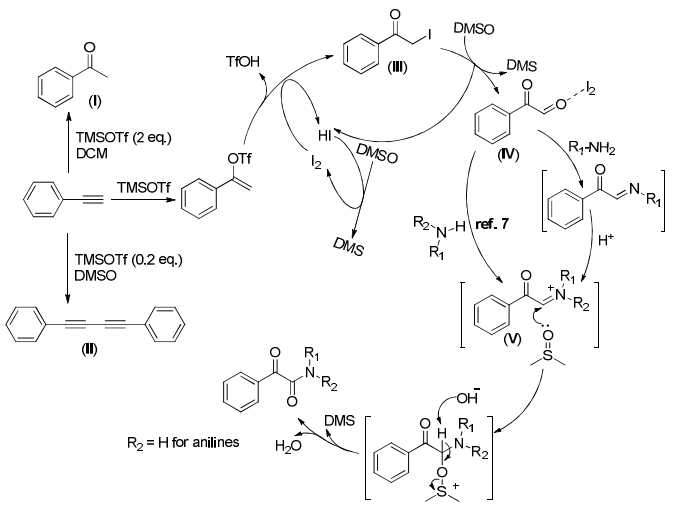


Figure 2. Plausible Mechanism.

Conclusions

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

Notes and references

[a] Academy of Scientific and Innovative Research (AcSIR); Natural Product Microbes, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu -Tawi, 180001.

† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectras. See DOI: 10.1039/c000000x/

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