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Cu-Catalysed oxidative amidation of cinnamic acids/arylacetic acids with 2° amines: an efficient synthesis of α-ketoamides†

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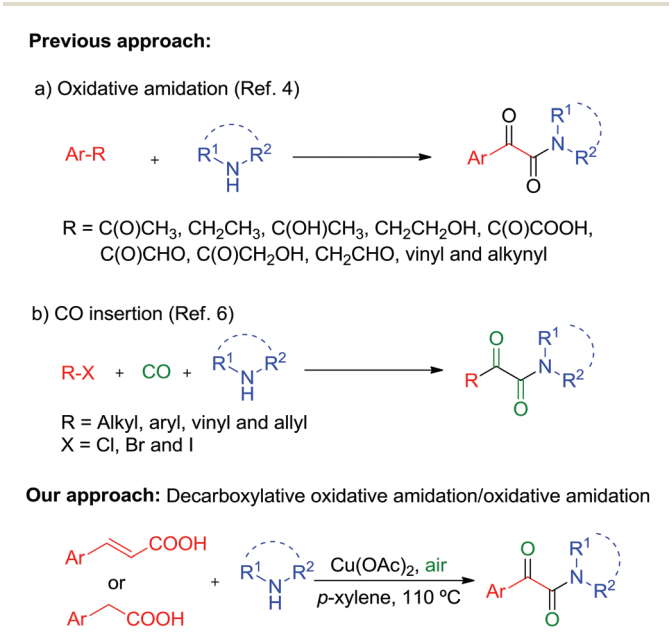
A new and convenient copper-catalysed synthesis of α-ketoamides has been accomplished using readily available cinnamic acids/arylacetic acids and 2° amines in an open atmosphere. The reaction between cinnamic acid and amine involves the formation of enamine followed by its aerobic oxidation, whereas the reaction of arylacetic acid with amine involves amide formation followed by benzylic methylene oxidation.

Introduction

α-Ketoamides are key structural motifs of a variety of natural products, bio-active molecules and pharmaceuticals such as anti-HIV, anti-tumor, anti-IBD, anti-bacterial, immunosuppressant and enzyme inhibitors.[1] They also act as valuable intermediates and synthons in a number of functional group transformations and total synthesis. Due to their potential significance, several methods have been explored for the synthesis of α-ketoamides using transition-metal catalysts based on Pd, Cu, Ag, Au, and Fe, as well as metal-free catalysts, especially iodine based.[2,3]

The synthesis of α-ketoamide scaffolds has been accomplished using diverse substrates such as ethylarenes, terminal alkenes, terminal alkynes, aryl methyl ketones, aryl acetaldehydes, 2-oxo aldehydes, 1-arylethanols, 2-arylethanols, 2-oxo alcohols, and phenylglyoxylic acids.[4] MW/UV-assisted oxidative synthesis of α-ketoamides is also reported using acetophenones and secondary amines.[5] Among various catalytic methods of α-ketoamide formation, the strategies involving oxidative amidation[4] and double aminocarbonylation[6] have received much more attention using carbon monoxide (CO) as a direct source of carbonyl functionality, and molecular oxygen (O_2)/air as a terminal oxidant and/or reactant (Scheme 1).

Decarboxylative reactions have recently cropped up as a powerful method to form carbon–carbon or carbon–heteroatom bonds in organic synthesis.[7] Carboxylic acids are stable, nontoxic, easy to store/handle, readily available at low costs in great structural diversity, and far less air and moisture sensitive in comparison with typical cross-coupling organometallic reagents. Zhao *et al.* have described a metal-free oxidative aryl migration and C–C bond cleavage for the synthesis of α-ketoamides from acrylic derivatives, whereas Liu *et al.* have reported a carbon degradation-based amidation to form pyridyl benzamides using phenylacetic acids and 2-aminopyridine.[8] Therefore, the development of fresh strategies for the synthesis of α-ketoamides employing easily available materials is in high demand. In view of the above, and as part of our ongoing research on decarboxylative coupling reactions,[9] we describe herein a new and efficient one-pot approach to α-ketoamides by the reaction of cinnamic/arylacetic acids with secondary amines under aerobic conditions (Scheme 1).



Scheme 1 Previous reports and the present strategy.

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Results and discussion

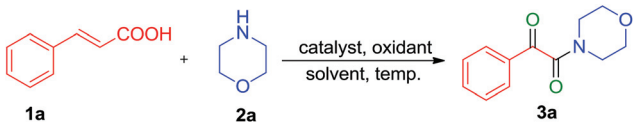
In order to optimize the reaction conditions, a model reaction employing cinnamic acid (**1a**) and morpholine (**2a**) was investigated in detail by varying different parameters such as catalyst, solvent, oxidant, base and temperature (Table 1).

The reaction commenced with 40 mol% $Cu(OAc)_2$ in DMSO in an open air atmosphere at 110 °C for 24 h, which gave rise to the product 1-morpholino-2-phenylethane-1,2-dione (**3a**) in 61% yield (entry 1). Upon changing the solvent from DMSO to DMF, 1,4-dioxane, *p*-xylene, toluene, ethanol, CH_3CN and PEG-600 (entries 2–8), only *p*-xylene could make some enhancement in the product yield (64%, entry 4). Notably the reaction remained completely futile in the absence of the catalyst (entry 9). Thereafter, the use of some other Cu salts such as CuI, CuBr, $CuCl_2$ and $Cu(OTf)_2$ was tried (entries 10–13), but none of them could surpass the efficacy of $Cu(OAc)_2$. The combination of $Cu(OAc)_2$ with other oxidants such as $K_2S_2O_8$ and TBHP also stayed worthless (entries 14 & 15). The role of base was also found to be insignificant with no increase in the product yield (entry 16), while replacing $Cu(OAc)_2$ by Ag_2CO_3 in the reaction rather decreased the product yield considerably (entry 17). The $Cu(OAc)_2/Ag_2CO_3$ combination also could not improve the product yield further (entry 18). The use of I_2 and DIB in combination with TBHP in acetonitrile at 80 °C also remained unproductive (entries 19 & 20). Then we screened the molar ratio of the reactants and catalyst at different temperatures and times (entry 21), which revealed a 1 : 2 molar ratio of **1a** and **2a** in the presence of 40 mol% of $Cu(OAc)_2$ in *p*-xylene at 110 °C in an open atmosphere as the best fit (entry 4).

Under the optimized set of conditions, the scope and versatility of the reaction were then thoroughly examined using different sets of cinnamic acids/arylacetic acids and amines having various substitution patterns, which readily delivered the desired products **3a–t** in moderate to good yields (Table 2).

Unsubstituted as well as substituted cinnamic acids bearing both electron-donating (OMe and Me) and electron-withdrawing substituents (Cl, F, Br, and NO_2) on the aromatic ring smoothly underwent the reaction to afford the α-ketoamides (**3**). The position of the substituent on the aromatic ring was noticed to have some effect on the product yield. *ortho*-Substitution provided somewhat inferior product yield as compared to *meta*- and *para*-substitution, which may be attributed to the steric effect (**3a–f**). To expand the adaptability of the reaction, investigations were also carried out using a number of arylacetic acids *viz*. phenylacetic acid, 3-methoxy-

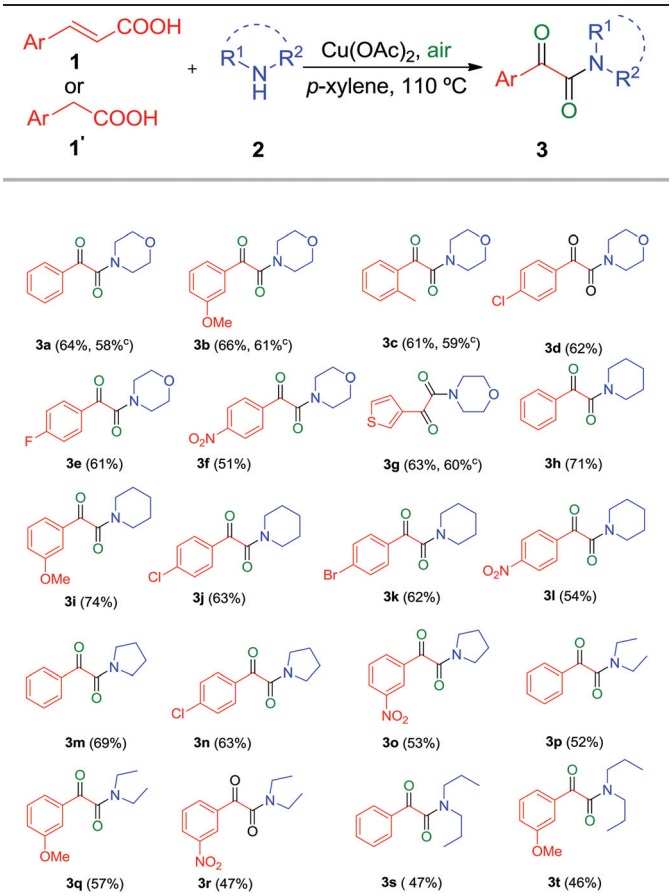
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$	Air	DMSO	61
2	$Cu(OAc)_2$	Air	DMF	54
3	$Cu(OAc)_2$	Air	1,4-Dioxane	Trace
4	$Cu(OAc)_2$	Air	*p*-Xylene	64
5	$Cu(OAc)_2$	Air	Toluene	62
6	$Cu(OAc)_2$	Air	EtOH	20[c]
7	$Cu(OAc)_2$	Air	CH_3CN	32[c]
8	$Cu(OAc)_2$	Air	PEG-600	28
9	—	Air	*p*-Xylene	Trace
10	CuI	Air	*p*-Xylene	35
11	CuBr	Air	*p*-Xylene	43
12	$CuCl_2$	Air	*p*-Xylene	48
13	$Cu(OTf)_2$	Air	*p*-Xylene	28
14	$Cu(OAc)_2$	$K_2S_2O_8$	*p*-Xylene	Trace
15	$Cu(OAc)_2$	TBHP	*p*-Xylene	15
16	$Cu(OAc)_2$	Air	*p*-Xylene	54[d], 15[e]
17	Ag_2CO_3	Air	*p*-Xylene	21
18	$Cu(OAc)_2/Ag_2CO_3$	Air	*p*-Xylene	64
19	I_2	TBHP	CH_3CN	21[c]
20	DIB	TBHP	CH_3CN	23[c]
21	$Cu(OAc)_2$	Air	*p*-Xylene	37[c], 63[f], 61[g], 58[h], 64[i,j]

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), catalyst (40 mol%), oxidant (2.0 equiv.), solvent (1.0 mL), 110 °C, 24 h. [b] Isolated yield after column chromatography. [c] At 80 °C. [d] Using K_2CO_3. [e] Using KO*t*Bu. [f] At 130 °C. [g] Catalyst (20 mol%). [h] **2a** (1.0 mmol). [i] **2a** (4.0 mmol). [j] Under O_2.

Table 2 Scope of the reaction[a,b]



[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $Cu(OAc)_2$ (40 mol%), *p*-xylene (1.0 mL), 110 °C, 24 h. [b] Isolated yield after column chromatography. [c] Using arylacetic acids.

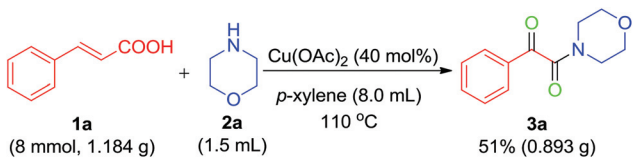
phenylacetic acid, 2-methylphenylacetic acid, and 3-thiopheneacetic acid, which underwent transformation adequately to give the products in good yields (**3a–3c**, **3g**). To increase the usefulness of the reaction, some other secondary amines such as piperidine, pyrrolidine, diethylamine and dipropylamine were also made to react with different cinnamic acids, which led to the formation of products **3h–3t** in fairly good yields. Piperidine and pyrrolidine gave better yields as compared to diethylamine and dipropylamine, which is perhaps controlled by the basicity and steric nature of the amines. In place of secondary amines, the reaction was also carried using primary amines such as benzylamine and 2-aminopyridine with cinnamic acid, which however furnished only a trace amount of the desired product, with a good yield of α,β-unsaturated amides. Furthermore, the reaction of primary amines with arylacetic acids led to one carbon degraded amides as the only isolable product, which is in close conformity with the observation of Liu's group.[8b]

To demonstrate the synthetic utility of the method, a gram scale reaction using 1.184 g of **1a** (8 mmol) with 1.5 mL of morpholine was carried out under the standard conditions (Scheme 2), which led to the formation of the desired product 1-morpholino-2-phenylethane-1,2-dione (**3a**) in 51% (0.893 g) yield.

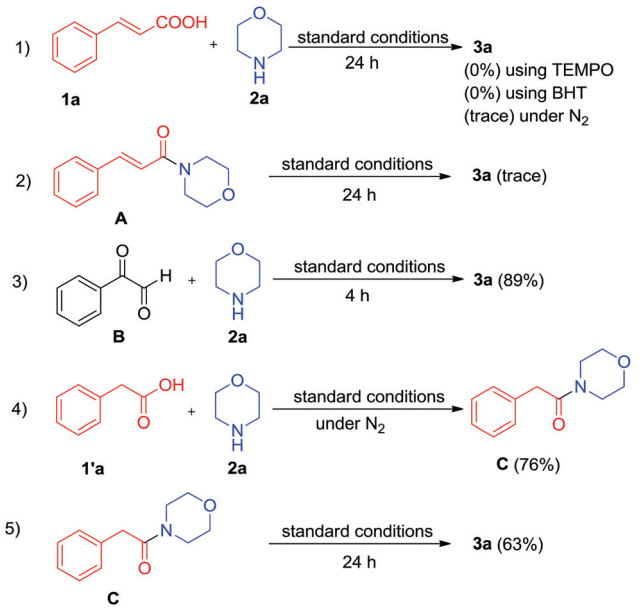
To gain insight into the reaction mechanism, various control experiments were carried out (Scheme 3). The standard reaction in the presence of radical scavengers such as TEMPO and BHT was fully suppressed implying a radical pathway (Scheme 3, eqn (1)). The reaction also remained futile when carried out under an N_2 atmosphere (Scheme 3, eqn (1)), which implicates the role of atmospheric oxygen in the reaction. In order to ascertain the intermediacy of (*E*)-1-morpholino-3-phenylprop-2-en-1-one (**A**), the reaction of the proposed intermediate **A** was separately carried out under the standard conditions, which did not afford the product at all (eqn (2)) thereby excluding the possibility of intermediate **A**. Assuming the involvement of phenylglyoxal (**B**) as an intermediate, a control experiment involving **B** with **2a** under established conditions was also carried out which gave rise to the product in 89% yield (eqn (3)). An additional experiment involving **1′a** and **2a** in the presence of $Cu(OAc)_2$ was also performed under an N_2 atmosphere to afford the corresponding amide **C** (eqn (4)). The isolated amide **C**, when made to react under the standard conditions, also gave rise to the desired product **3a**.

Based on control experiments, isolation of products, and the existing literature,[3,4,8,9] a plausible mechanism is outlined in Scheme 4. The reaction of cinnamic acid (**1a**) in the presence of **2a** and Cu(II) is assumed to pass through copper cinnamate to give the enamine, which on subsequent reaction with Cu/O_2 forms aminodioxetane. The O–O bond cleavage of the aminodioxetane then leads to the formation of aryl glyoxal.

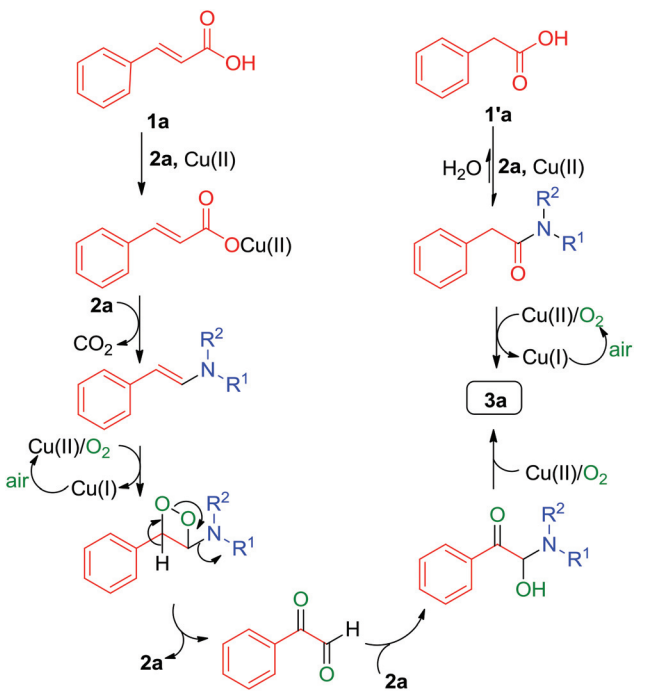
The reaction of the amine **2a** with aryl glyoxal affords a hemiaminal intermediate which is then oxidized by Cu/O_2 to produce product **3a**. Conversely, phenylacetic acid (**1′a**) reacts with **2a** in the presence of a copper catalyst to form the amide first followed by copper catalysed aerobic oxidation of the benzylic methylene to afford product **3a**.



Scheme 2 Gram scale synthesis of α-ketoamide **3a**.



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism.

Conclusions

In summary, a new and simple method for the synthesis of α-ketoamides has been developed *via* oxidative amidation of bench stable and readily available cinnamic acids/arylacetic acids with 2° amines in an open atmosphere in the presence of $Cu(OAc)_2$. The strategy involves *in situ* decarboxylation as well as oxidative amidation of cinnamic acids. The methodology is versatile and provides a useful alternative to access α-ketoamides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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