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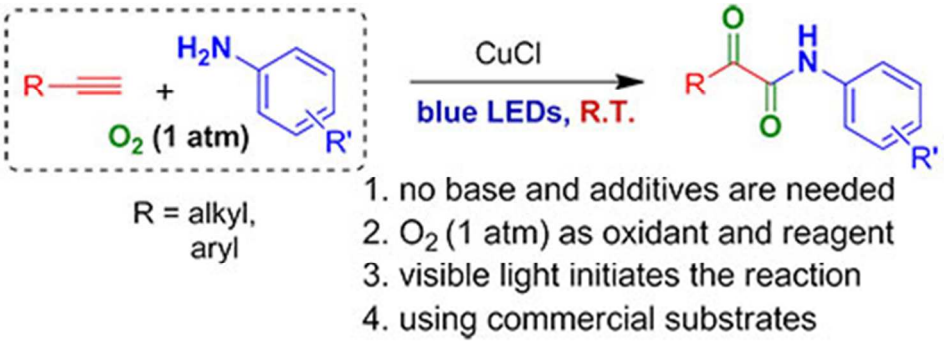

R = alkyl, aryl

1. no base and additives are needed
2. O_2 (1 atm) as oxidant and reagent
3. visible light initiates the reaction
4. using commercial substrates

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ARTICLE

Visible-Light Initiated Copper(I)-Catalysed Oxidative C-N Coupling of Anilines with Terminal Alkynes: One-Step Synthesis of α-Ketoamides

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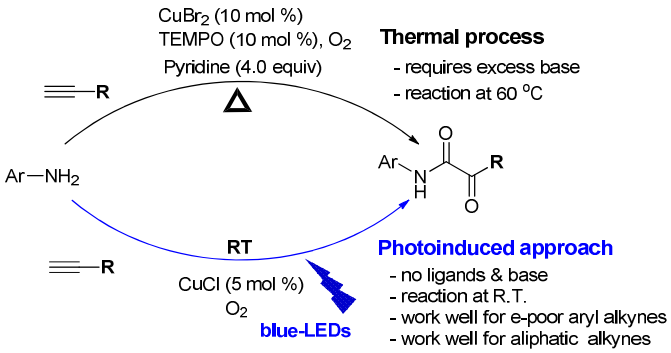
Development of C-N coupling processes is fundamentally important and challenging for the synthesis of biologically active molecules and drugs. Herein, we report highly atomic efficient green process for the synthesis of α-ketoamides via visible-light induced copper(I) chloride catalysed direct oxidative C_{sp}-N coupling reactions using commercially available alkynes and anilines at room temperature without the use of hazardous chemicals and harsh reaction conditions. Forty seven examples are presented using a broad range of substrates including electron deficient anilines and various terminal alkynes. The current photochemical process is able to achieve epoxide hydrolase inhibitors in one step with high yield (92~95%). This transformation is highly efficient and highly selective for the synthesis of α-ketoamides.

Introduction

The development of novel and highly efficient strategies for the formation of carbon-nitrogen bonds are fundamentally important reactions for the synthesis of nitrogen containing heterocyclic molecules and pharmaceuticals drugs.[1] Apart from the conventional Ullmann and Buchwald-Hartwig C-N coupling process,[2] the development of novel methods for different types of C-N bond forming reactions under mild conditions remains a very challenging subject. In recent years, visible-light-mediated metal/organic dye based photoredox catalysis has emerged as one of the most attractive and powerful alternative to thermal mediated metal-catalyzed reactions.[3] Recently, photoredox Cu-based complexes have been demonstrated as an inexpensive catalytic system for C-C coupling, allylic substitution and atom transfer radical addition (ATRA) reactions.[4] In addition, photoinduced copper(II) complex was also demonstrated as a powerful catalyst for spatial and temporal control of the alkyne-azide cycloaddition (CuAAC) click reactions,[5] where the catalyst Cu(I) can be generated by either direct photoreduction of Cu(II) or indirect reduction of Cu(II) using a photoinitiator. Recently, Fu et al., has reported photoinduced copper(I) catalysed C-N coupling reactions of hetrocyclic nucleophiles with aryl halides as well as aliphatic halides.[6] This strategy was also extended to the alkylation of amides[7] and reactions of arylthiols with arylhalides.[8] This method is considered to be versatile and utilized as a novel protocol for C-N and C-S cross-coupling reactions under mild conditions. Moreover, this reaction proceeds under UV light irradiation and also requires a strong base (LiOtBu or NaOtBu) for the formation of C-N coupling product. We recently reported a visible-light-induced strategy for copper(I)-catalysed Sonogashira C-C cross-coupling reaction[9] and oxidative coupling reactions of o-phenylenediamine with terminal acetylene for the synthesis of quinoxalines[10] at room temperature, where the key photocatalyst involved is copper(I) phenylacetylide. In this work, we further extend our methodology to catalyse C_{sp}-N coupling reaction of anilines with terminal alkynes, in the presence of molecular oxygen, to form biologically active α-ketoamides at room temperature, upon irradiation with blue LEDs and without the need of any base.

α-Ketoamides are important building blocks in organic synthesis and frequently found in a variety of natural products, pharmaceuticals and biologically important compounds, such as, FK506, cyclotheonamide, RARγ agonist, enzyme, protease and epoxide hydrolase inhibitors.[11] α-Ketoamides can also serve as an important starting material or intermediate for the synthesis of medicinally useful compounds, such as, tetrasubstituted 2-oxindoles and 2-oxazolidin-4-one.[12] To realize their bioactivities, a considerable number of synthetic approaches have been developed.[13-17] Despite the utility of such processes, the previous methods suffer the following factors; a) starting materials are needed to be prepared in advance or are not commercially available, b) usage of oxidants or ligands, and c) an elevated reaction temperature is required.

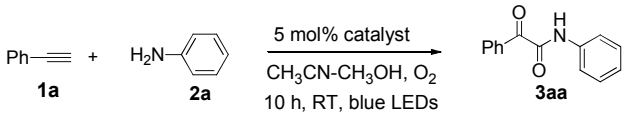


Scheme 1 Copper catalysed synthesis of α-ketoamides.

It was reported that copper(II) can also catalyse the oxidative amidation/diketonation of terminal alkynes with anilines in the presence of pyridine (4.0 equiv.) and TEMPO at elevated temperature (60 °C) (see Scheme **1**, thermal process).[18] However, the above reaction is limited to electron-rich and electron neutral-aryl terminal alkynes, and does not work for linear aliphatic alkynes, as well as electron-deficient substrates.[18] The aerobic oxidative cross dehydrogenative coupling (CDC)[19] reactions of terminal alkynes with nucleophiles (Nu= N, P & S) are also reported by using Cu(I)/Cu(II) complexes or Cu-acetylide as a substrate and air or O_2 as the sole oxidant to form C-N, C-P and C-S acetylenes at elevated temperatures (50~110 °C).[20] Although this thermal method can be used to synthesize acetylene C_{sp}-N, C_{sp}-P and C_{sp}-S coupling products, subsequent oxidation reaction cannot be achieved. Herein, we report a facile visible-light-mediated copper(I) chloride catalysed amidation/diketonation reaction of terminal alkynes by anilines for the synthesis of α-ketoamides at room temperature (see scheme **1,** photoinduced approach). The significance of the present work includes the following features: 1) an unprecedented visible-light-induced strategy for copper(I)-catalysed amidation/ diketonation of terminal alkynes by anilines to give α-ketoamides at room temperature; 2) as compared to copper(II) catalysed thermal process, the current photoinduced strategy does not require the use of any bases, or additional oxidants (Scheme **1**); 3) in-situ generated Cu(I)-phenylacetylide act as the key light absorbing species, which is different from the previously reported photoinduced Cu-catalyzed click reaction[5] and C-N coupling process[6].

Results and discussion

Table 1. Optimization studies on coupling reaction of (**1a**) and (**2a**)[a]

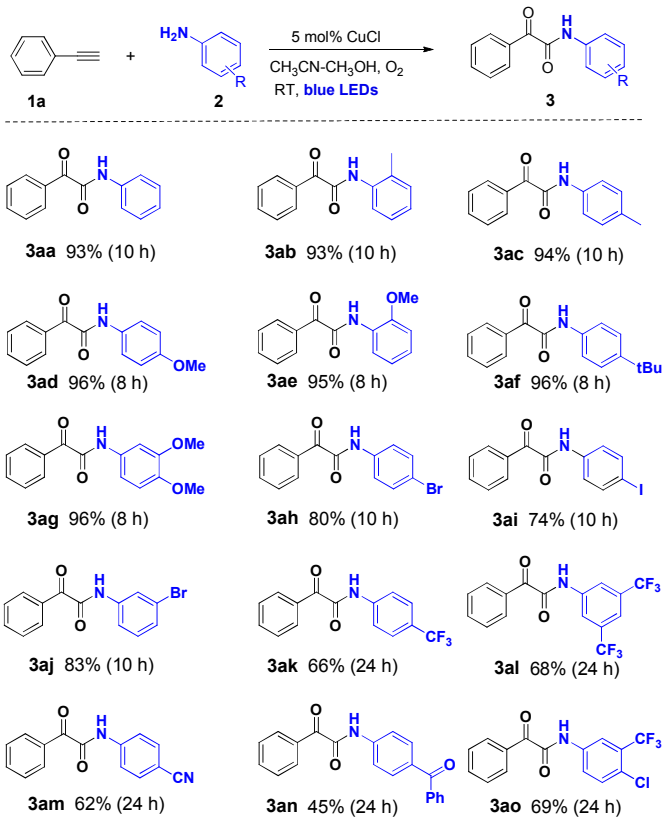


Entry	Catalyst	Base	Solvent	Yield [%][b]
1	CuCl	K_2CO_3 (1.05 eq)	CH_3CN-MeOH	10
2	CuCl	KOAc (1.2 eq)	CH_3CN-MeOH	78
3	CuCl	KOAc (0.25 eq)	CH_3CN-MeOH	84
4	CuCl	no base	CH_3CN-MeOH	93
5	$CuCl_2$	no base	CH_3CN-MeOH	trace
6	CuBr	no base	CH_3CN-MeOH	93
7	CuI	no base	CH_3CN-MeOH	93
8	CuCl	no base	CH_3CN	83
9	CuCl	no base	MeOH	67
10[c]	CuCl	no base	CH_3CN-MeOH	88

[a]0.6 mmol of **1a** (0.1 M), 0.5 mmol of **2a** (0.083 M), and 5 mol% of CuCl in 8 ml of solvent. The solution was irradiated with blue LEDs for 10 h in the presence of 1 atm O_2 (in balloon). [b]Yields were determined by the ^{1}H NMR integration method using mesitylene as an internal standard. [c]1 atm air (in balloon) was used in the reaction.

The reaction between aniline (**2a**) and phenylacetylene (**1a**) was chosen as the model reaction for optimization of the experimental parameters. In an initial study (Table 1), reaction of aniline (**2a**) (0.5 mmol) and phenylacetylene (**1a**) (0.6 mmol) in the presence of K_2CO_3 (1.05 equiv) and CuCl (5 mol%) in CH_3CN-CH_3OH (1:1 v/v) affords α-ketoamide (**3aa**) in 10% yield. The use of weak bases, such as, K(OAc) (0.25 equiv), dramatically improves the yield to 84 % (Table 1, entry 3). Complete removal of the base affords the product **3aa** in 93 % yield, indicating that base is not required for the observed reaction. However, unreacted/free aniline may acts as base to promote the formation of copper(I) phenylacetylide in the current reaction. In the solvent screening, a mixture of CH_3CN-CH_3OH (1:1 v/v) gave the best yield of the α-ketoamide product (Table 1, entry 4). The presence of water slightly decreases the yield of **3aa** from 93 to 80% (see Table S1, entry 13). Other solvents were also tested, but yields are poor (Table S1, entries 11-15). In the screening of metal salts, CuX (X: Cl, Br, I) affords the highest yield (93 %) of the product **3aa** (Table 1, entries 4, 6 & 7). In contrast, $CuCl_2$ turns out to be ineffective to catalyse the formation of product (Table 1, entry 5). Therefore, the catalyst responsible for this reaction might be the copper(I)-related species. Meanwhile, control experiments also reveal that the reaction did not proceed upon exclusion of light, CuCl or O_2 (Table S2).

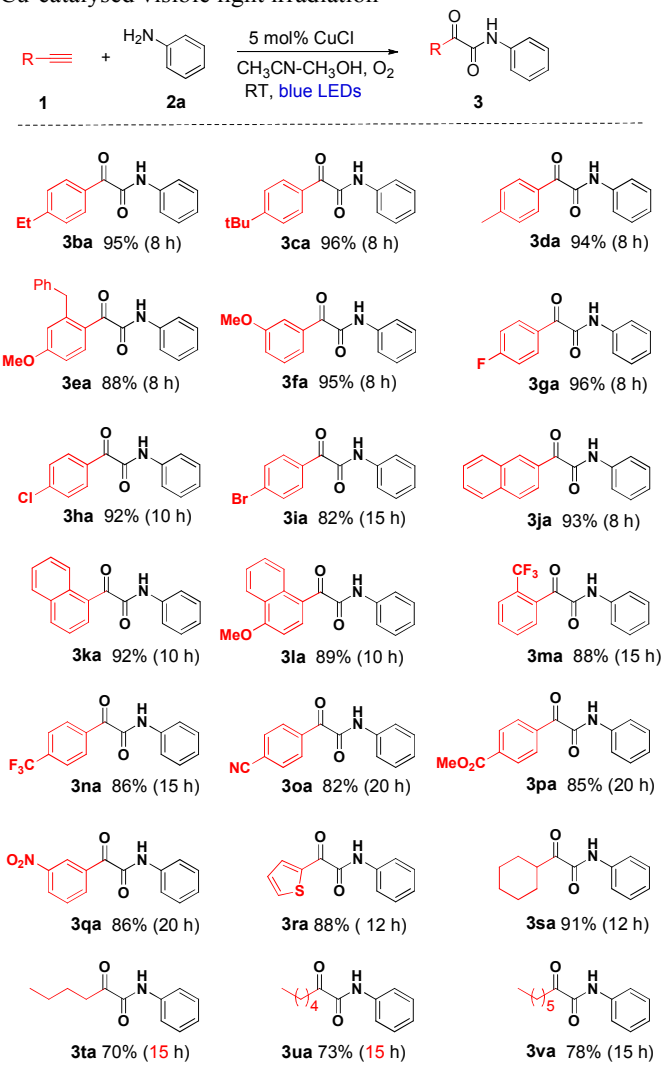
Table 2 Scope of aniline substrates (2) and phenylacetylene (**1a**) under Cu-catalyzed visible light irradiation[a]



[a]Standard condition. Isolated yield after purification by column chromatography on silica gel. [b]1.0 mmol of **1a** (0.125 M), 10 mol% CuCl and 5 mol% of NaOAc were used.

Under the optimized conditions (see Table 1, entry 4), the scope of the anilines (**2**) were further investigated (see Table 2). In general, both electron-rich and electron-neutral substituted anilines result in high yields of α-ketoamide products (Table 2, **3aa-3ag**). Notably, the current approach also works well for electron-withdrawing substituted groups with product yields in the range of 45-68 % over a period of 15-24 h reaction (Table 2, **3ak-3ao**). The slow reactivity (or the need of a longer reaction time) is due to the insufficient nucleophilic nature of anilines bearing electron-withdrawing groups. As a result, 5 mol% of a weak base NaOAc was added to promote the formation of Cu(I) phenylacetylide in all electron withdrawing substituted anilines (**2k-2o**) reactions. The reaction proceeds well also for halo-substituted anilines. Good product yields were obtained (see (Table 2, **3ah-3aj**). Note that the halo-substituted groups in α-ketoamides can provide good reactive sites for further synthetic modifications.

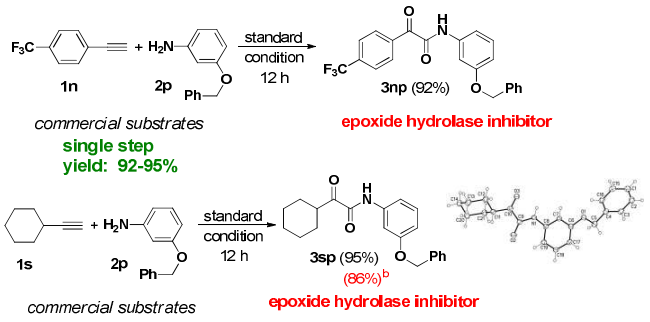
Table 3 Scope of terminal acetylenes (1) and aniline (**2a**) under Cu-catalysed visible light irradiation[a]



[a]Standard condition. Isolated yield after purification by column chromatography on silica gel

In a similar manner, the scope of various terminal alkynes was also investigated (see Table 3). Electron-rich phenylacetylenes (**1b-1f**) can easily react with aniline to afford the corresponding α-ketoamide products (**3ba-3fa)** in good yields (88-96 %) (Table 3). In general, electron-rich phenylacetylenes favor the formation of 1, 3-diynes in the presence of O_2, since these groups have more π-basicity on the C≡C triple bond and will certainly promote the reaction in the presence of soft Lewis acids, such as Cu(I) ion.[21] The homocoupling reaction can be effectively suppressed in the current process by diluting the concentration of phenylacetylene in the reaction mixture. In addition, aryl alkynes bearing halo-substituted groups **(1g-1i)** as well as naphthalene moieties (**1j-1l**) readily react with aniline to generate the corresponding α-ketoamides **3ga-3la** (Table 3). The electron-deficient phenylacetylenes (**1m-1q**) can also react with aniline (**2a**) over a period of 15-20 h to afford the corresponding α-ketoamide products **3ma-3qa** in good yields of 82-88 % (see Table 3). Moreover, heteroarylalkyne (**1r**) and aliphatic terminal alkynes (including linear chain alkynes **(1t-1v)** and cyclohexylacetylene (**1s**)) can also effectively couple with aniline to result in the formation of corresponding products (Table 3). Thus, the current amidation/diketonation reaction can occur for a broad range of electron-deficient phenylacetylenes/aliphatic linear chain terminal alkynes, and is a powerful method for the synthesis of α-ketoamides with no/negligible amount of formation of homocoupling products. Furthermore, many aryl acetylenes are also reactive with 4-methoxy-aniline **2d** to afford the α-ketoamide products in good to excellent yields (see Table S3). Unfortunately, the current strategy does not work for aliphatic amines and N-substituted anilines.

To extend our current visible-light-induced Cu(I)-catalyzed strategy for the synthesis of biologically active α-ketoamides,[11] we have synthesized *epoxide hydrolase inhibitors* (**3np & 3sp)** with a high yields (92~95 %) in a single step using commercially available substrates (see Scheme **2**). Previously, both epoxide hydrolase inhibitors (**3np & 3sp**) were prepared in five steps with an overall yield of less than 5 % using pre-synthesized starting materials.[11b] Recently, it was also reported that epoxide hydrolase inhibitor (**3np**) can also be synthesized in single step with a yield of 58 % using a modified process and pre-synthesized starting material, α-carbonyl aldehyde.[15b] In addition, the current synthesis of epoxide hydrolase inhibitor (**3sp**) could be readily scaled up gram scale, and 1.15 g of **3sp** (or 86% isolated yield) ca be obtained after 12 h irradiation in blue LEDs at room temperature (see, Scheme S1 & Figure S15). The structures of **3am** and **3sp** were confirmed by single-crystal X-ray diffraction.[22]



Scheme 2 One step synthesis of inhibitors (**3np** & **3sp**). [a] Standard condition: 1n or 1s (0.6 mmol), 2p (0.5 mmol), 5 mol% CuCl in 8 mL dry CH_3CN and CH_3OH (1:1), irradiated with blue LEDs at room temperature under 1 atm O_2 (in balloon). Isolated yield after purification by column chromatography on silica gel. [b]The reaction was performed on a 4 mmol scale (preparative scale).

We have evaluated the green chemistry metrics[23] for the synthesis of epoxide hydrolase inhibitor (**3sp**) in a preparative scale. Atom economy is defined as "how much of the reactants remain in the final desired product" (see equation (1)). Reaction mass efficiency (RME) is defined as "the percentage of the mass of the reactants that remain in the product" (see equation (2)).

$$\text{Atom economy (AE) (\%)} = \frac{\text{Molecular mass of desired product}}{\text{Molecular mass of all reactants}} \times 100 \quad (1)$$

$$\text{Reaction mass efficiency (RME) (\%)} = \frac{\text{mass of desired product}}{\text{mass of all reactants}} \times 100 \quad (2)$$

Table 4. Evaluation of Green chemistry metrics for the synthesis of inhibitors (**3sp**)

Reactant A	Ethynylcyclohexane (**1s**)	0.7g	0.0065 mol	FW 108.09
Reactant B	3-benzyloxyaniline (**2p**)	0.8g	0.004 mol	FW 199.09
Solvent	ACN-MeOH	54.6g	---	---
Auxiliary	---	---	---	---
Product	α-ketoamide (**3sp**)	1.15g	0.0034 mol	FW 337.16

Product yield= 86%

$$\text{E-factor} = \frac{0.7\text{g} + 0.8\text{g} + 54.6\text{ g} - 1.15\text{g}}{1.15\text{ g}} = 47.7 \text{ kg waste/kg product}$$

$$\text{Atom economy} = \frac{337}{355} \times 100 = 95\%$$

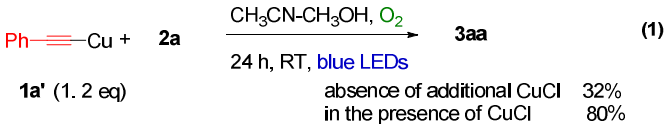
$$\text{Atom efficiency} = 86\ \% \times 95\% / 100 = 81.7\%$$

$$\text{Carbon efficiency} = \frac{21}{8 + 13} \times 100 = 100\%$$

$$\text{Reaction mass efficiency} = \frac{1.15\text{ g}}{0.70\text{g} + 0.80\text{g}} \times 100 = 76.6\%$$

Overall, our green process can enable to synthesis the Epoxide hydrolase inhibitors (**3sp**) in preparative scale with a E factor or 47.7, 95% atom economy, 81.7% atom efficiency, 100% carbon efficiency, and 76.6% reaction mass efficiency, which are far better than those for previously reported multi-step synthesis of epoxide hydrolase inhibitor with low yield (less than 5 % total yield) (Patent literature, see page **5**, ref **11b** in the main text).

In order to prove that the *in situ* generated copper(I) phenylacetylide is the key light absorbing photocatalyst, we used commercial copper(I) phenylacetylide (Alfa Aesar) to replace CuCl and phenylacetylene as a substrate and to check whether the same coupling product, **3aa**, can be formed or not. The yields of **3aa** were 80 and 32% in the presence and absence of CuCl, respectively (Eq. (1)). Such a result seems to be reasonable since isolated copper(I) phenylacetylide is known to exist in highly aggregated forms (higher order polynuclear Cu(I) phenylacetylide)[24] which may diminish the reaction rate.[24a] Addition of free CuCl could coordinate to the side of acetylene moiety via π-bonding, and activate the polynuclear Cu(I) phenylacetylide,[25] leading to the improved product yield.[25] As a supporting evidence, the binding constant ($K_a \sim 6550\ \mu M^{-1}$) of free CuCl to polynuclear Cu(I) phenylacetylide **1a'** was determined by isothermal titration calorimetry (ITC) experiment[26] (see more details in Figure **S16**). This control experiment (Eq. (1)) supports that the in situ generated copper(I) phenylacetylide may be the light absorbing photocatalyst in the reaction.



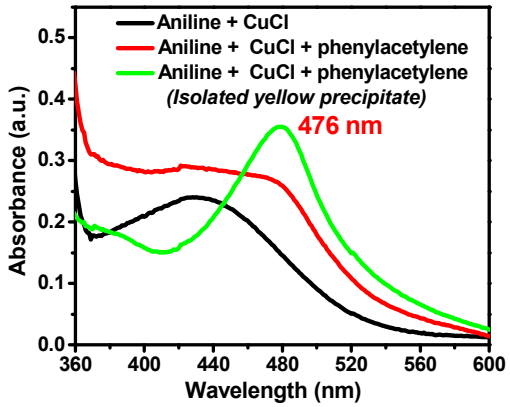


Figure 1 UV-visible spectra of reaction mixture in CH_3CN and CH_3OH (1:1 v/v). Black line indicates mixture of aniline and CuCl, red line indicates mixture of aniline, CuCl and phenylacetylene, green line indicates isolation of yellow suspension of copper(I) phenylacetylide.

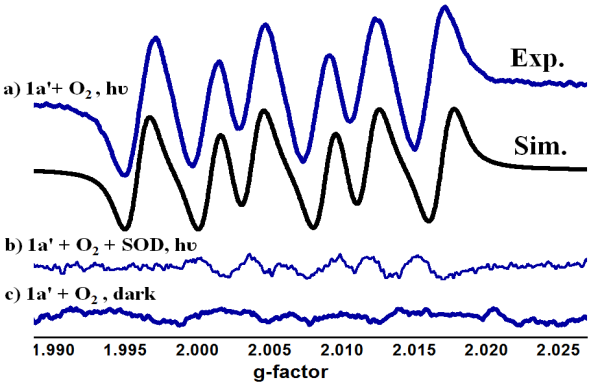
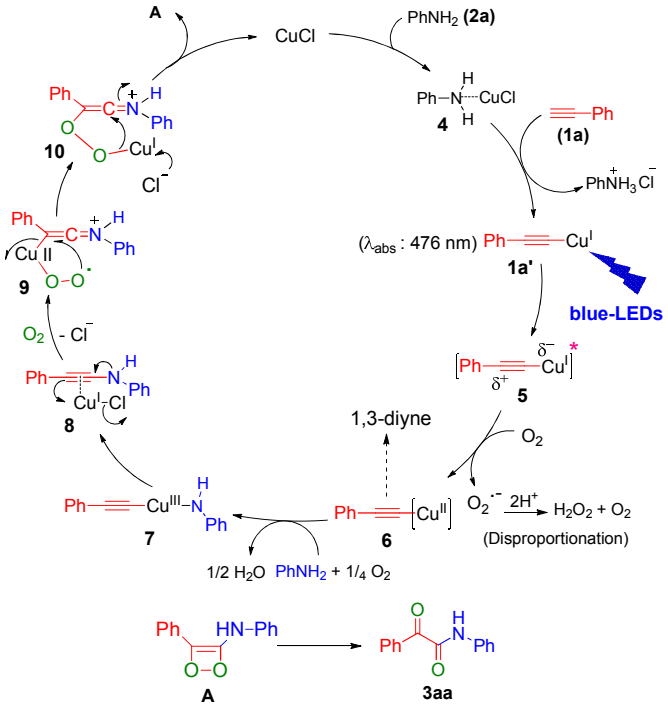


Figure 2 EPR spectra (X band, 9.8 GHz, room temperature) of (a) Cu(I) phenylacetylide **(1a')** in ACN-MeOH under blue-LED light irradiation in the presence of O_2 and a radical trapping reagent, DMPO (2.5×10^{-2} M). The parameters used in the simulation are the followings: g_{av}= 2.0059, a_N= 14.9 G (1N), and $a_{\beta H}$= 8.5 G (1H). b) The same reaction solution as in (a) with addition of superoxide dismutase (SOD), (1×10^{-2} M). c) The same reaction solution as in (a), but in the dark. All measurements were done at 25 °C

Overall, the reaction mechanism is proposed in Scheme **3**. First, weak Cu(I)-aniline complex **4** is initially formed[27] and upon addition of phenylacetylene, copper(I) phenylacetilyde (**1a'**) is preferentially formed. This was evidenced by (a) the formation of yellow suspension of copper(I) phenylacetylide (see optical picture in Figure S14); (b) the rise in the 476 nm absorption in the uv-visible absorption spectra (see Figure **1** and more details see Figure. S13); and (c) the observation of characteristic yellow fluorescence emission (λ_{em} at 524 & 583 nm) of copper(I) phenylacetilyde (see Figures S10 & S11). Direct photoexcitation of copper(I) phenylacetylide by blue LEDs (λ_{max} = 476 nm) leads to the formation of partial positive charge on the acetylene ligand and partial negative charge on the metal center via ligand to metal charge transfer (LMCT).[28] It is believed that the excited state of copper(I)

phenylacetylides undergo facile intersystem crossing (ISC),[9b,28] and hence undergoes single electron transfer (SET) to molecular oxygen to generate superoxide[29] and electron deficient Cu(II) phenylacetylide **6**. Supporting evidences include, a) the lifetime of excited state of copper(I) phenylacetylide **5** shortens from 15.95 μs in the absence of molecular oxygen to 10.47 μs in the presence of molecular oxygen (see Figure S12); b) the formation of superoxide free radical was detected by EPR measurements (see Figure **2** and Figure S1-S9) using 5,5-dimethyl-1-pyrroline N-oxide (DMPO) as a selective superoxide trapping reagent. The EPR signal of the DMPO-superoxide adduct (g_{av}= 2.006) matches with the simulated one (see Figure 2(a)), as well as in well agreement with the literature,[30] which can be significantly suppressed in the presence of superoxide dismutase (SOD) (see Figure 2(b)) or removal of light (see Figure 2(c)).



Scheme 3 Proposed mechanism for visible-light induced Cu(I)-catalyzed reaction of anilines and terminal alkynes**.**

In the next step, nucleophilic addition of aniline to complex **6** (Cu(II) phenylacetylide) results in the formation of the complex **7** (Cu(III) species).[31] Subsequent reductive elimination of Cu(III) leads to the formation of the Cu(I)-coordinated ynamine complex **8.**[32] At this stage, it is difficult to isolate the highly reactive ynamine (aniline type ynamine).[33] Based on the additional control experiments,[34] the electron rich ynamine could readily coordinate to Cu(I) ion[35] and subsequently, react with O_2 at the later stage. Indeed**,** Cu(I) containing complex **8** readily reacts with the molecular oxygen to form copper(II) peroxo complex **9**.[36] Isomerization of the resulting copper(II) peroxo complex **9** to copper(I) species **10** with concurrent formation of a carbon–oxygen bond.[37] Finally, this complex can undergo transformation to re-generate CuCl and formation of intermediate **(A)**.[15a] Subsequent cleavage[15a,38] of **(A)** will produce the desired α-ketoamide product **(3aa)**.

Conclusions

In summary, we have demonstrated a visible-light-initiated copper(I) catalysed strategy to achieve a facile one-step synthesis of biologically important α-ketoamides via oxidative C-N coupling of anilines with terminal alkynes without the need of base, ligands, and external oxidant. The current method is green, and highly atomic efficient without the use of hazardous chemicals, and harsh conditions. The current method works well for a wide range of substrates including electron deficient anilines and various terminal alkynes. The importance of the current photoinduced Cu(I) catalysed process has been applied to the rapid syntheses of two prominent epoxide hydrolase inhibitors **(3np & 3sp)** in a single step with high yields (92~95%) in preparative scale using commercially available substrates. The cost-effective nature and availability of the catalyst (CuCl), no requirement of base or ligands, practical feasibility and reaction under visible-light irradiation make this methodology a very efficient and green process for the synthesis of various biologically active α-ketoamides.

Acknowledgements

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Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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Graphical Abstract

Visible-Light Initiated Copper(I)-Catalysed Oxidative C-N Coupling of Anilines with Terminal Alkynes: One-Step Green Synthesis of α-Ketoamides

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A green photochemical method was reported for synthesis of biologically active α-ketoamides at room temperature using commercially available substrates.