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Visible-Light Induced Copper(I)-Catalysed Denitrogenative Oxidative Coupling of hydrazinylpyridines with Terminal Alkynes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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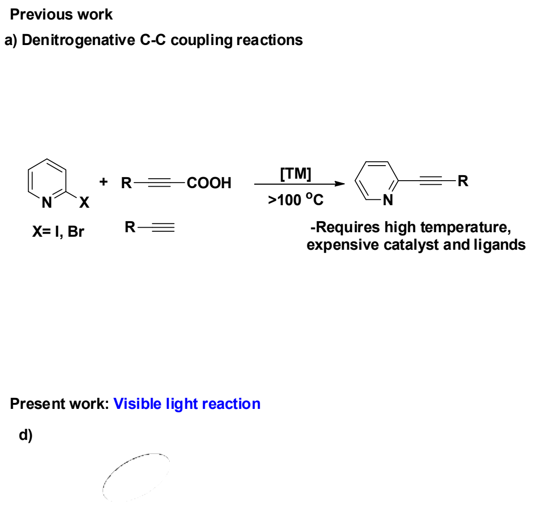
Visible light mediated copper catalysed denitrogenative oxidative coupling of 2-hydrazino pyridines with terminal alkynes to form 2-(alkyl/arylethynyl) pyridines in the presence of O_2 at room temperature was reported with 42 examples. This is the first report on visible light stimulated N_2 elimination by *in-situ* generated copper(II) superoxo/ peroxo complex. N_2 and water are the only by-products. The green chemistry metrics evaluation signifies that the current method is ecofriendly and economically feasible. This method allows green synthesis of mGluR5 receptor antagonists 2-methyl-6-(phenylethynyl)pyridine (MPEP) and 2-((3-methoxyphenyl)ethynyl) -6-methylpyridine (M-MPEP).

With respect to sustainable and atom-step chemical processes, the development of new C-C bond formation reactions by utilization of readily available starting materials with simple and inexpensive catalytic system (eg., copper and O_2) under low energy visible light irradiation has become a challenging goal in modern synthetic chemistry and has always been desired. To this end, visible-light-mediated photoredox catalysis (transition metal polypyridyl complexes or organic dyes) recently becomes a powerful and efficient protocol for the development of series of unique bond-forming reactions via involvement of single electron transfer or energy transfer process. Indeed, recent studies have demonstrated the photo induced copper-catalysed process for an array of powerful C-C, C-N, and C-S cross-coupling reactions at mild condition[1]. In this regards, our group recently demonstrated the visible light induced copper catalysed process for C-C/C-N cross coupling and C-H annulation reactions.[2] Particularly, in 2012, we have reported the first photo induced Sonogashira C_{sp2}-C_{sp} coupling reaction, where aryl halides were coupled with terminal alkynes to form C_{sp2}-C_{sp} coupled product (eq. c, Scheme 1).[2a] We hypothesised that the copper(I) acetylide acts as a photocatalyst under visible light irradiation and undergoes photo- induced single electron transfer (SET) with oxidants (benzoquinone or O_2) to achieve essential coupling reactions.

Scheme 1. Comparison of transition metal-catalysed oxidative thermal coupling reactions and the current photoredox process.



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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C8GC01180J

of an unactivated C-N bond remains as a great challenge due to its stability (inactive) and high bond dissociation energy.[3a] Previously, transition metal catalysed C-N bond activation reactions have been accomplished for formation of C-C coupling products through activation of pre-functionalized N-containing moieties; such as ammonium salts, diazonium salts, tosylhydrazones or azaheterocycles.[3] However, these processes are economically unfeasible due to pre-synthesis of starting materials, instability of starting materials and limited substrate scopes.

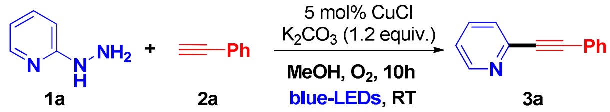
To address the above-mentioned challenge, Pd-catalysed denitrogenative C-C coupling reactions of arylhydrazines were recently demonstrated, such as; a) denitrogenative coupling of arylhydrazine with olefins,[4a] b) Hiyama and Suzuki cross-coupling reactions with arylhydrazine.[4b,c,d] Moreover, Q. Song et al depicted Sonogashira type coupling of arylhydrazine with terminal aryl/alkyl alkynes[4e] (eq. a, Scheme 1) in which excess of aryl hydrazine was required for increasing the reaction efficiency, also the scope of heteroacetylenes was not explored. Thus, these methods were confined to certain applications. Despite the many advantages, these processes have several limitations, such as a) use of expensive catalyst, additives, ligands, b) the use of excess amount of starting material, c) harsh reaction conditions, and d) produces high amount of wastes (with high E-factor) and thus are not feasible at industrial scale and have a deleterious effect on the environment. To overcome these limitations, there is a need to explore the eco-friendly and green process for the C-C coupling reactions.

Recently, Lei Zhou et al[5] reported that organic dye (eosin B/ eosin Y) generates aryl radical species from arylhydrazine or biarylazonium salts via N_2 elimination upon visible light irradiation. Despite this important advance, direct oxidative coupling of 2-hydrazinylpyridine with terminal alkyne to form a 2-(alkyl/arylethynyl) pyridine (N_2 and water as by-products) via N_2 elimination by *in-situ* generated copper(II)superoxo/peroxo complex remains unexplored.

Pyridine[6a] core structure is the key building block widely involved in various kinds of natural products, pharmaceutical drugs, polymers and ligands. 2-(Alkyl/arylethynyl) pyridine is a simple structure and commonly used in organic synthesis as it is an important precursor for the synthesis of pharmaceutical drugs.[6] For instance, the substituted 2-(arylethynyl) pyridine acts as an antagonist for human metabotropic glutamate receptors subtype mGluR5[6c] (antidepressant drug).

Conventionally, 2-(alkyl/arylethynyl) pyridine was synthesised by the Sonogashira[7] protocol. Recently, several methods have been developed (eq. b, Scheme 1), mainly via, a) transition metal catalysed decarboxylative coupling of alkynyl carboxylic acid and aryl halides[8a,b,c]; b) collaborative (N-heterocyclic carbene) copper and Pd-complexes catalysed Sonogashira coupling[8d]; or c) metal catalysed coupling of arene diazonium salts[3e] with terminal alkynes. In spite of the utility of these processes, these methods, however, share some common drawbacks, such as a) the use of an expensive catalyst; b) pre-synthesis of starting materials; c) harsh reaction conditions; d) formation organic wastes with higher E-factor. The significance of the current photoredox process includes; i) the first report of oxidative coupling via N_2 elimination through the cleavage of non-activated C-N bond at room temperature under low energy visible light; ii) use of simple CuCl as catalyst, O_2 as oxidant and forms N_2 and water are the only two by-products; iii) industrially and academically useful green process for the synthesis of 2-(alkyl/arylethynyl) pyridine; iv) demonstrates a green and cost efficient C-C coupling reaction with high reaction mass efficiency (increased by 2.5 times) and with lower E-factor (decreased by 2.3 fold). In terms of cost efficiency, the current method can produce 1 g of product 42.1% cheaper than the previously reported method.

Table 1. Optimization of reaction conditions[a]



Entry	[Cu] Catalyst	Base	Solvent	Yield [%][b]
1	**CuCl**	**K_2CO_3**	**CH_3OH**	**89**
2	CuCl	Cs_2CO_3	CH_3OH	78
3	CuCl	Na(OAc)	CH_3OH	74
4	CuCl	K_2CO_3	CH_3CN	71
5	CuCl	K_2CO_3	CH_3CN-MeOH	78
6	CuCl	K_2CO_3	THF	18
7	$CuCl_2$	K_2CO_3	CH_3OH	68
8	CuBr	K_2CO_3	CH_3OH	64
9	$FeCl_2$	K_2CO_3	CH_3OH	0
10	$CoCl_2$	K_2CO_3	CH_3OH	0
11	$NiCl_2$	K_2CO_3	CH_3OH	0
12	$ZnCl_2$	K_2CO_3	CH_3OH	0
13[c]	CuCl	K_2CO_3	CH_3OH	83
14[d]	CuCl	K_2CO_3	CH_3OH	79
15[e]	CuCl	K_2CO_3	CH_3OH	46
16[f]	CuCl	K_2CO_3	CH_3OH	0
17[g]	none	K_2CO_3	CH_3OH	0
18[h]	CuCl	none	CH_3OH	0
19[i]	CuCl	K_2CO_3	CH_3OH	0

[a] Unless otherwise noted, reaction conditions are as follows; **1a** (0.5 mmol), **2a** (0.55 mmol), [Cu] catalyst (5 mol%), base (1.2 equiv.), solvent (7 mL). The mixture was irradiated with blue LEDs (power density: 40 mW/cm^2 at 460 nm) for 10 h in an O_2 (1 atm.) atmosphere. [b] Yield of the isolated product. [c] 0.5 mL water was added. [d] In the presence of air (1 atm.). [e] Reaction irradiated with an ambient white light bulb for 24 h (power density: 8 mW/cm^2 at 460 nm). [f] Reaction conducted in the dark at 80 °C. [g] In the absence of [Cu] catalyst. [h] In the absence of base. [i]In the absence of O_2. THF= tetrahydrofuran.

We commenced the study by using 2-hydrazinylpyridine **(1a)** and phenylacetylene **(2a)** as standard substrates (Table 1). Initially, the reaction of **1a** with **2a** in the presence of CuCl (5 mol%), K_2CO_3 (1.2 eqv.), O_2 in MeOH affords **3a** in 89% yield upon irradiation for 10 h under blue LEDs (460 nm) irradiation. The reaction was then carried out with different bases, among which K_2CO_3 was found to be more effective for the formation of **3a**. In the solvent screening, the product **3a** was obtained in good yield in MeOH solvent.

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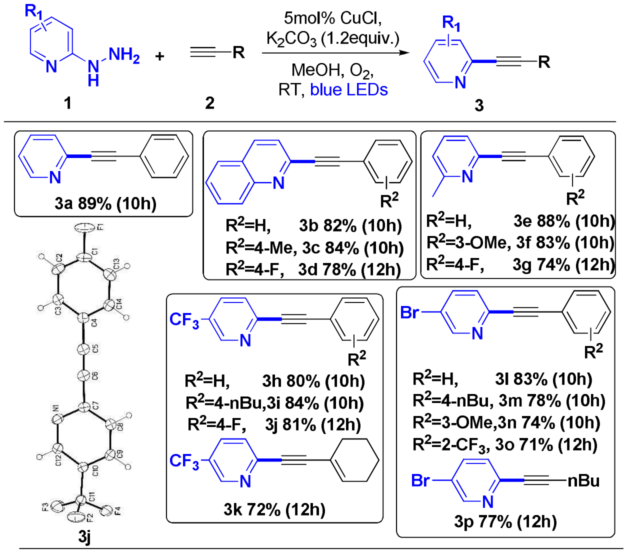
Various copper catalysts, such as CuX (X=Cl or Br), $CuCl_2$ and other first row transition metal salts such as $FeCl_2$, $CoCl_2$, $NiCl_2$, $ZnCl_2$ were examined. Among which only copper catalysts are able to form the product **3a**, especially, CuCl catalyses formation of the product in highest yields. Further, the addition of water to the reaction mixture and the use of air balloon, instead of O_2, in the reaction slightly decrease the yield from 89% to 83% and 79%, respectively. When the reaction mixture was irradiated for 24 h under low light density (white bulb), the product afforded in a lower yield (only 46%). Under dark thermal condition (80 °C), no product was obtained. Further optimization studies demonstrate that the CuCl, base (K_2CO_3), O_2 and visible light are required for the formation of product in good yields.

Table 2. Substrate scope of 2-hydrazinopyridines and terminal alkynes[a]

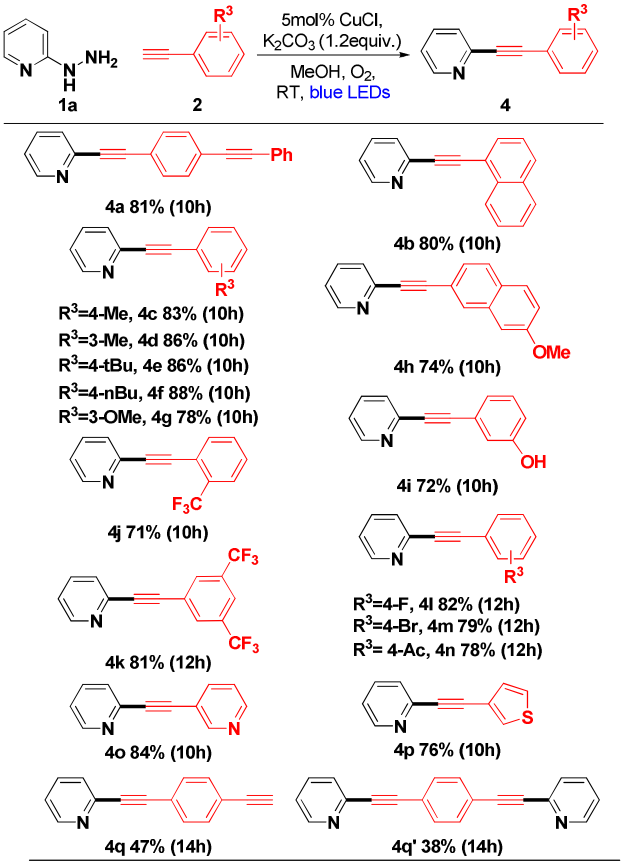


[a]Standard condition. Isolated yield after purification by column chromatography on silica gel.

With the optimized condition, we next examined the substrate scope of 2-hydrazinylpyridine derivatives with different alkyl/ arylacetylenes as coupling partners (Table 2).

First, the reaction of 2-hydrazinylquinoline with arylacetylenes (R=H, 4-Me, 4-F) formed the products **3b**, **3c** and **3d** in good yields. Also, the coupling of electron-rich 2-hydrazinyl-6-methylpyridine with aryl acetylenes (R=H, 3-OMe, 4-F) resulted in the formation of products **(3e-3g)** in good yields (74-88%). Noticeably, the products 2-methyl-6-(phenylethynyl)pyridine (MPEP) **(3e)** and 2-((3-methoxyphenyl)ethynyl)-6-methylpyridine (M-MPEP) **(3f)** are mGluR5 receptor antagonists. The IC_{50} values for MPEP and M-MPEP are well reported in the literature to be 36 and 8 μM, respectively.[6c] Thus, the current protocol can be used to synthesize the potent mGluR5 noncompetitive antagonists **MPEP** and **M-MPEP** (See SI) in a one step process with good yields (88% and 83%, respectively). Further, the electron deficient 2-hydrazinyl-5-(trifluoromethyl)pyridine worked well with aryl acetylenes (R=H, 4-nBu, 4-F) to form **(3h-3j)**. Similarly, the products **(3l-3o)** were obtained in 71-83% yields by coupling halogen-substituted 5-bromo-2-hydrazinylpyridine with aryl acetylenes (R=H, 4-nBu, 3-OMe, 2-CF_3). In addition, reaction of electron deficient and halogen-substituted 2-hydrazinylpyridine derivatives with aliphatic alkynes worked smoothly to form products **3k** and **3p** with 72% and 77% yields. It is worth to note that the bromine-substituted products **(3l-3p)** could not be selectively synthesised by conventional thermal Sonogashira method[7], whereas this method successfully synthesised bromine-substituted internal alkynes. Overall, the coupling reactions in Table 2 exhibit the versatility of 2-hydrazinylpyridine derivatives with different alky/aryl acetylenes. The structure of **3j** was confirmed by single-crystal X-ray diffraction.[9]

Table 3. Substrate scope of aryl terminal alkynes[a]



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

Next, we explored the substrate scope of aryl alkynes with 2-hydrazinylpyridine **(1a)** as a coupling partner under the optimized condition. Table 3 presents the coupling of 2-hydrazinylpyridine **(1a)** with aryl/hetero alkynes to form corresponding 2-(arylethynyl)pyridine products. The reaction of **1a** with 1-ethynyl-4-(phenylethynyl)benzene afforded a product **4a** in 81% yield. Derivatives of the product **4a** have been widely used as precursors in organic synthesis. The aryl alkynes bearing electron-neutral and electron-rich groups readily react to form corresponding products

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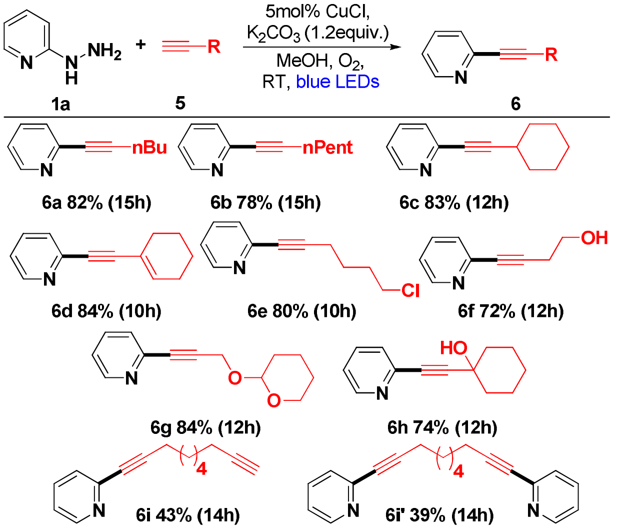
(4b-4f) in good yields. Arylalkynes bearing electron-donating groups (-OMe, -OH) also proceeded well to form products **4g, 4h** and **4i**. The presence of hydroxyl functionality in the product is useful for the later synthetic modifications.[7] The aryl alkynes with halogen substituted (-F, -Br) and electron withdrawing groups were well tolerated by the current oxidative coupling reaction **(4j-4n)**. Importantly, the hetero aryl alkynes (**4o, 4p**) and 1,4-diyne (**4q and 4q'**) also successfully coupled with **1a** to form corresponding products in good yields.

Table 4. Substrate scope of aliphatic terminal alkynes[a]



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

Furthermore, Table 4 shows the substrate scope of aliphatic alkynes. Gratifyingly, a variety of aliphatic alkynes successfully coupled with **1a** to form desired products. The coupling reactions of aliphatic alkynes, including cyclohexyl, cyclohex-1-ene and linear chain alkynes (hexyl, heptyl) with **1a**, furnished to form the desired products **(6a-6d)** in good yields (78-84%). The other aliphatic alkynes, such as 6-chlorohex-1-yne **(6e)**, but-3-yn-1-ol **(6f)**, 2-(prop-2-ynyloxy)tetrahydro-2H-pyran **(6g)**, 1-ethynyl cyclohexanol **(6h)** and 1,9-decadiyne **(6i and 6i')** could also react smoothly to form products in good yields (72-84%). It is important to note that, in the current reaction homocoupling product formed in trace amount. Whereas, in thermal C-C coupling reactions (with terminal alkynes), alkyne homocoupling product always formed as a major by-product.

Additionally, this coupling reaction can be readily scaled up to a gram scale. The **1a** (0.55 g, 5.0 mmol) was coupled with **2a** (0.61 g, 0.6 mmol) and produced 0.68 g of **3a** (76% yield) after 15 h of irradiation with blue LEDs at room temperature in the presence of O_2 (1 atm.). We have also evaluated the green chemistry metrics[2c] for this reaction in a preparative scale (Table 5). Our green process can be used to synthesize 2-(phenylethynyl)pyridine **(3a)** with an E-factor of 15.9, 73.7% atom economy, 56 % atom efficiency, 100% carbon efficiency and 58.6% reaction mass efficiency, which are far better than the reported thermal coupling reaction of arylhydrazine with terminal alkynes[4e] (E-factor is 36.4, and reaction mass efficiency is 23.8%). Thus, for the current process, the E-factor was reduced by 2.3 times and reaction mass efficiency was increased by 2.5 times. In terms of cost, it takes approximately $26 USD/g for the synthesis of the product 3a, which is ~ 57.9% of the cost using literature thermal method (see green matrix comparison in the S.I.). In addition, the N_2 gas and water are the only two by-products of this process along with trace amount of homocoupling of alkyne. Importantly, current photochemical process does not require any strong organic oxidants, high temperature, and expensive metal catalysts. Thus, all these parameters make this a good green process.

Table 5. Evaluation of green chemistry metrics for the synthesis of **3a**

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

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

Reactant 1	2-hydrazinylpyridine	0.55g	5.0 mmol	FW 109.12
Reactant 2	Phenylacetylene	0.61g	6.0 mmol	FW 102.13
Base	K_2CO_3 (1.2equiv.)	0.83g	6.0 mmol	FW 138.2
Solvent	MeOH	9.5g	----	----
Auxiliary	----	----	----	----
Product	**2-(phenylethynyl)pyridine**	**0.68g**	**3.8 mmol**	**FW 179.22**

Product yield = 76%

$$\textbf{E-factor} = \frac{0.55\text{g} + 0.61\text{g} + 0.83\text{g} + 9.5 - 0.68\text{g}}{0.68\text{g}} = \textbf{15.9 Kg waste/ 1 Kg product}$$

$$\textbf{Atom economy} = \frac{179}{243} \times 100 = \textbf{73.7\%}$$

$$\textbf{Atom efficiency} = 76\% \times 73.7\% / 100 = \textbf{56\%}$$

$$\textbf{Carbon efficiency} = \frac{13}{5+8} \times 100 = \textbf{100\%}$$

$$\textbf{Reaction mass efficiency} = \frac{0.68\text{g}}{0.55\text{g} + 0.61\text{g}} \times 100 = \textbf{58.6\%}$$

Many control experiments were performed in order to gain mechanistic insights. First, different heteroaryl/aryl hydrazine derivatives **(1aa, 1ab, 1ac and 1ad)**, instead of **1a**, were used to react with phenylacetylene **(2a)**, but no product was formed (eqns 1 & 2). The results indicate that the pyridine N-atom, along with the adjacent hydrazine substituent, is required (to form the complex **A** with Cu-superoxo anion radical (**Scheme 3)** for the reaction to occur. When the pre-synthesized copper (I) phenylacetylide **(2a')** was used to react with **1a** in the absence of CuCl, the coupling product was obtained in less yield (62%) after 24 h of irradiation **(eqn 3).** This decrease in reaction efficiency is due to the polymeric form of the isolated copper(I) phenylacetylide powder.[2c] This demonstrates that *in-situ* generated copper(I) phenylacetylide might be the key photocatalyst responsible for this oxidative coupling reaction.[2] Under a N_2, instead of O_2 atmosphere, no coupling product was formed (eq. 2).

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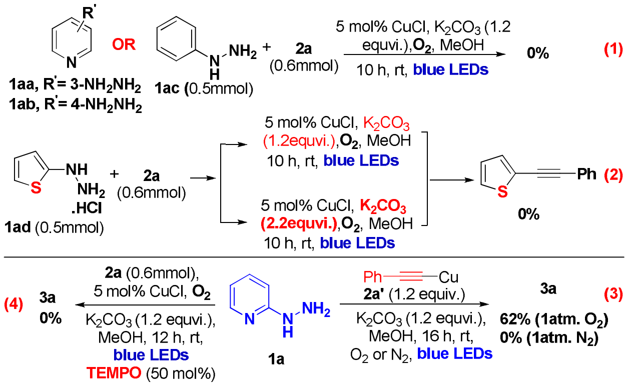
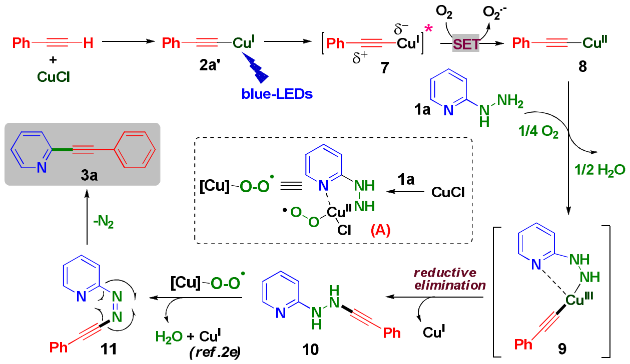
When the coupling reaction of **1a** and **2a** was conducted in the presence of radical trapping agent 2,2,6,6- tetramethylpiperidine 1-oxyl (TEMPO, 50 mol%) under the optimized condition **(eqn. 4)**, the formation of 2-(phenylethynyl)pyridine was totally inhibited, indicating that a radical intermediate might be involved in this coupling reaction.[2h]

Scheme 2. Control experiments for the formation of 2-(phenylethynyl)pyridine under the standard condition.



Based on these above control experiments and our previous studies[2c,d,e], a reaction mechanism was proposed and shown in **Scheme 3**. Photo excitation (λ_{abs}= 474 nm) of in situ generated copper(I) phenylacetylide (**2a'**) generates a long lived triplet photo excited copper(I) phenylacetylide **(7)**[10] (see Figure S1 for IR spectrum of **2a'**, and Figure S4 for UV-visible spectra of **2a**'), which then undergoes a SET process by donating an electron to O_2, generating the intermediates Cu(II)-phenylacetylide **(8)** and a superoxide radical anion[11], as evidenced by EPR measurements[12] (see the **SI**, Figure S2).

Scheme 3. Proposed reaction mechanism.



Next, the nucleophilic addition of 2-hydrazinopyridine**(1a)** to Cu(II) phenylacetylide **(8)** results in the formation of the complex Cu(III) **(9)** species.[2c,e,13] Reductive elimination of Cu(III) to Cu(I) generates the intermediate **10**.[2c,e] Residual 2-hydrazinopyridine (act as a bidentate ligand) coordinates to Cu^I and its reaction with molecular oxygen leads to the formation of bidentate chelated copper(II) superoxo/-peroxo complex **(A)**[2e,14,15], which can abstract the acidic protons from the intermediate **10** to form **11**. N_2 elimination of the intermediate **11**, followed by recombination of *sp$_2$* and *sp* C-centered radicals, leads to the formation of the product **3a**. The intermediate **11** was caught by ESI mass measurements. (see SI for details of ESI measurements).

Conclusions

In summary, we have significantly demonstrated the visible-light-initiated copper(I) catalysed denitrogenative coupling of 2-hydrazinopyridine with terminal alkynes to form 2-(alkyl/aryl or heteroarylethynyl)pyridine. This coupling reaction includes a SET process with O_2, followed by copper(II)-superoxo or -peroxo complex assisted N_2 elimination. This is the first report of N_2 elimination (cleavage of non-activated C-N bond) at room temperature. This photochemical process works well for a wide range of substrates (42 examples), forms N_2 and water as benign by-products, uses simple CuCl as catalyst, O_2 as an oxidant, readily available substrates as starting materials, mild reaction conditions and applicable for the synthesis of potent mGluR5 noncompetitive antagonists MPEP and M-MPEP. In addition, the green chemistry metrics and the overall reaction cost evaluation signify that the process is green and highly cost efficient. Thus, this method is a simple, green and effective approach for the synthesis of 2-(alkyl/arylethynyl) pyridine.

Acknowledgements

This work was supported by the Ministry of Science and Technology, Taiwan.

Conflicts of interest

There are no conflicts to declare.

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View Article Online
DOI: 10.1039/C8GC01180J

Graphical Abstract

Visible-Light Induced Copper(I)-Catalysed Denitrogenative Oxidative Coupling of hydrazinylpyridines with Terminal Alkynes

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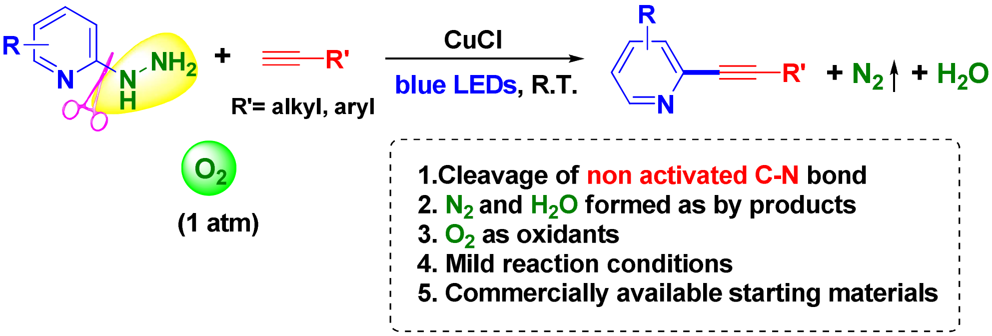
An effective and green approach to oxidative C_{sp2}-C_{sp} coupling of 2-hydrazinylpyridine with Terminal Alkynes to form 2-(alkyl/arylethynyl) pyridine *via* N_2 elimination through the cleavage of non-activated C-N bond under low energy visible light at room temperature (42 examples).



1.Cleavage of non activated C-N bond
2. N_2 and H_2O formed as by products
3. O_2 as oxidants
4. Mild reaction conditions
5. Commercially available starting materials