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Authors: Bhahwal Ali Shah

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Acyl radicals from terminal alkynes: Photoredox-catalyzed acylation of heteroarenes

Shaista Sultan,[a] Masood Ahmad Rizvi,[b] Jaswant Kumar[a] and Bhahwal Ali Shah*[a]

Abstract: A photoredox-mediated acylation reaction of electron deficient heteroarenes with terminal alkynes is reported. The method relies on oxidative cleavage of phenylacetylenes for generation of acyl radicals as a key enabling advance. The reaction is regioselective with broad substrate scope. Quantum yield investigations support a radical chain mechanism.

Acyl radicals are one of the most investigated synthetic organic building blocks owing to their application in the synthesis of multitude of natural/medicinally important molecules.[1] These radicals are conventionally generated via C-X bond cleavage involving the use of toxic organotin reagents, carbonylation of C-X bond and fragmentation of C-C bond in ketones and α-ketoacids/esters.[1] Recently, some milder photocatalytic approaches have also emerged to produce these radicals, involving the use of aldehydes,[2] acid chlorides,[3] anhydrides[4] and acyl silanes (Figure 1).[5] Among these use of α-ketoacid presents most attractive and widely used synthon to make acyl radical, because of the fact that its anionic form easily oxidises in presence of catalysts such as Eosin, Ir(III) complexes, acridinium salts, Ru(II) complexes via elimination of carbon dioxide.[6] Also, recently Zang et al.,[6k] developed an electrochemical method of generating acyl radical from α-ketoacid. The α-ketoacids in turn are commonly sourced from acetophenones using strong oxidizing agents like selenium dioxide.[7]

In this regard, the oxidative reactions of alkynes offers an interesting proposition,[8] however, their use in the generation of acyl radicals and its subsequent applications in acylation reactions are hitherto unreported. This intrigued us to develop a direct and facile protocol for the generation of acyl radicals from terminal alkynes via glyoxylic acid and their subsequent use in acylation reactions. Thus, in continuation of our interests,[9] herein we present a novel photoredox catalysed oxidative cleavage of terminal arylacetylenes, enabling their use as acyl precursors for acylation of heteroarenes (Scheme 1). Notably, acylated heterocycles are present in myriad drugs/naturally occurring molecules of pharmacological significance, generally accessed through Minisci reaction.[10,11] The appeal of the present method also lies in obviating the traditional requirements of Minisci acylation reaction such as high temperatures or harsh reaction conditions with excess amounts of radical precursors, low site selectivity, longer reaction times (around 20 h) and incomplete conversion of starting materials. Additionally, the reaction is regioselective with broad substrate scope, excellent functional group tolerance and short reaction times.

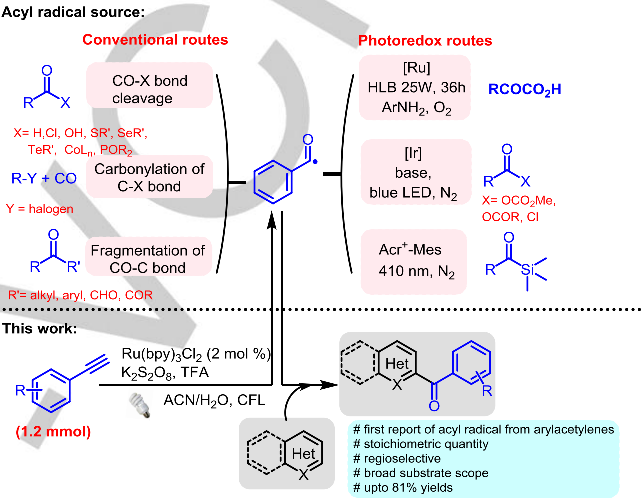

Figure 1. Acyl radical sources

Our studies initiated with the reaction of isoquinoline **1** and phenylacetylene **2** as model substrates (Table 1). The reaction was irradiated under a 27 W CFL bulb in presence of potassium persulfate ($K_2S_2O_8$) and trifluoroacetic acid (TFA) with Eosin-Y as photocatalyst using MeCN/H_2O as solvent (Table 1, entry 1). The reaction led to the formation of product **3a** in 40% yields in 18 h. We next screened different photocatalysts to improve reaction yields. The use of 9-mesityl-10-methylacridinium tetrafluoroborate (Mes-Acr$^+$BF$_4^-$) resulted in no product formation, whereas, 9-fluorenone and Rose Bengal produced **3a** in 55 and 46% yields, respectively (Table 1, entries 2-4). Remarkably, the use of Ru(bpy)$_3$Cl$_2$.6H$_2$O as a photocatalyst resulted in an improved yield of 81% with quantitative consumption of starting materials and considerably reduced reaction time (Table 1, entry 5). Notably, the reaction returned lower yields and took longer time when irradiated under blue LEDs (Table 1, entry 6) possibly because of faster oxidative cleavage of phenylacetylene to acyl radicals in blue light resulting in the formation of benzaldehyde as a by-product. We also screened various solvents to study their impact on reaction yields. The use of CH_2Cl_2/H_2O led to a decrease in the product yields, while no product formation was observed in MeOH/H_2O (Table 1, entries 7 and 8). Solvents such as DCE, DMF and DMSO were also screened; however, they did not result in the product formation (Table 1, entries 9-11). Also, control experiments revealed light source to be critical for the reaction as trace amounts of **3a** were obtained in its absence (Table 1, entry 12). The reaction at 55 °C in absence of photocatalyst and light led to the formation of desired product in 20% yields (Table 1, entry 13).

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[a] S. Sultan, J. Kumar, Dr. B.A. Shah
Natural Product Microbes and ACSIR
CSIR-Indian Institute of Integrative Medicine, Jammu-180001
E-mail: bashah@iiim.ac.in
Home page: http://www.iiim.res.in/People/CV/cv_bhahwal.php
Orcid ID: 0000-0001-6629-0002
[b] Dr. M.A. Rizvi
Department of Chemistry, University of Kashmir, Srinagar, 190006

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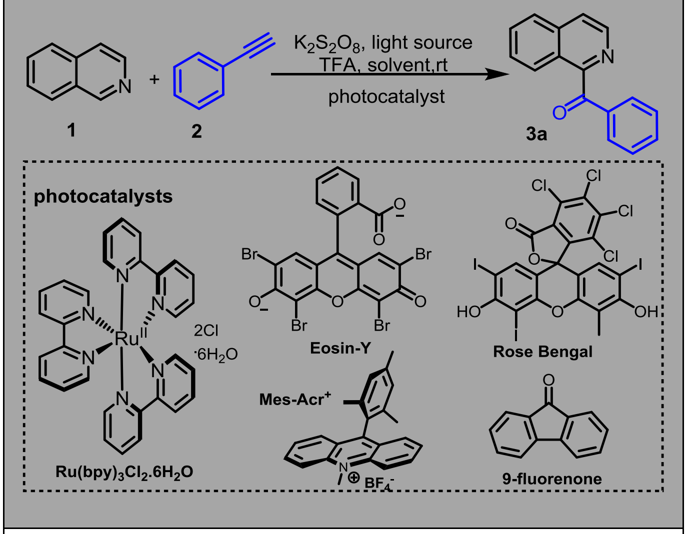
Table 1. Optimization of the reaction conditions.[a]

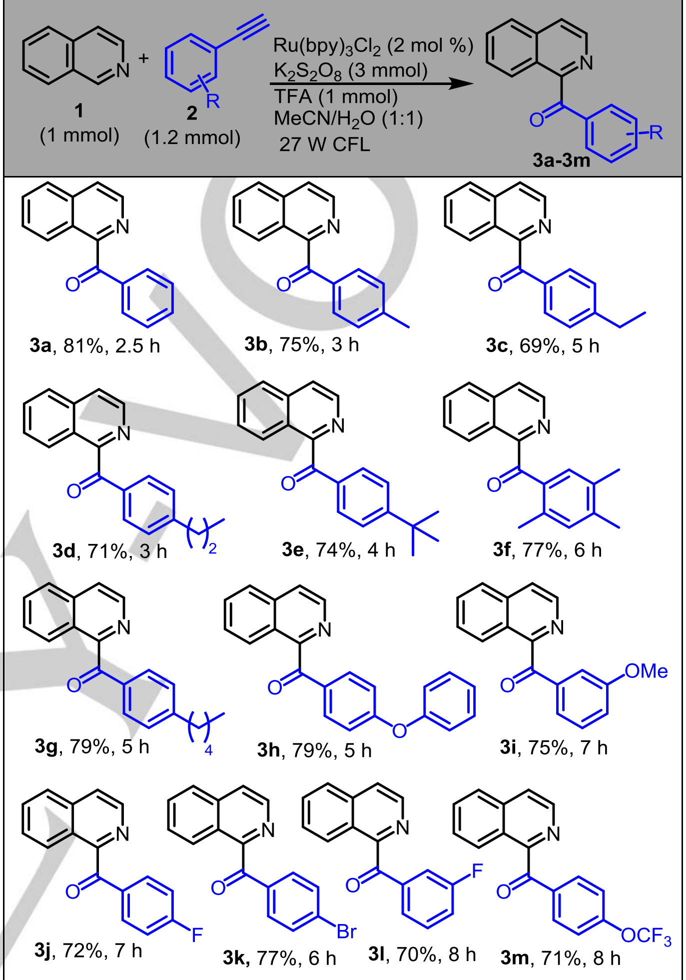


entry	photocatalyst	light source	solvent	time (h)	yield (%)
1	Eosin-Y$^{\#}$	CFL	MeCN/H$_2$O	18	40
2	Mes-Acr^{+}BF$_4^{-\#}$	CFL	MeCN /H$_2$O	18	traces
3	9-fluorenone$^{\#}$	CFL	MeCN /H$_2$O	18	55
4	Rose Bengal$^{\#}$	CFL	MeCN /H$_2$O	18	46
5	Ru(bpy)$_3$Cl$_2$	CFL	MeCN /H$_2$O	4	81
6	Ru(bpy)$_3$Cl$_2^{\#}$	Blue LEDs	MeCN /H$_2$O	18	53
7	Ru(bpy)$_3$Cl$_2^{\#}$	CFL	CH$_2$Cl$_2$/H$_2$O	18	43
8	Ru(bpy)$_3$Cl$_2^{\#}$	CFL	MeOH/H$_2$O	18	traces
9	Ru(bpy)$_3$Cl$_2^{\#}$	CFL	DCE	18	Nd
10	Ru(bpy)$_3$Cl$_2^{\#}$	CFL	DMF	18	Nd
11	Ru(bpy)$_3$Cl$_2^{\#}$	CFL	DMSO	18	Nd
12	Ru(bpy)$_3$Cl$_2^{\#}$	-	MeCN /H$_2$O	18	Traces
13$^{\|}$	-	-	MeCN /H$_2$O	18	20

[a] **Reaction conditions:** 1 (1.0 mmol), 2 (1.2 mmol), photocatalyst (2 mol %), persulfate salt (3 mmol), trifluoroacetic acid (TFA, 1 mmol), solvent (2-3 mL), rt = 25-30 °C. #Note: These reactions were not monitored beyond 18 h. ‖The reaction was carried out at 55°C in the absence of photocatalyst and light.

Having conditions optimized, we turned our attention towards expanding the scope of the reaction to various substituted phenylacetylenes (Scheme 1). A range of alkyl-substituted phenylacetylenes viz., methyl, ethyl, propyl, *tert*-butyl, 2,4,5-trimethyl and pentyl phenylacetylene reacted efficiently with the model substrate isoquinoline to generate the corresponding products (**3b-3g**) in good yields. The electron-rich alkoxy-substituted phenylacetylenes 4-phenoxy and 3-methoxy phenylacetylene were also found to participate in the reaction smoothly to give products **3h** and **3i** in 79 and 75% yields, respectively. Furthermore, the scope of acylation of heteroarenes was extended to halo-substituted phenylacetylenes, which can offer the possibility of further functionalization. The reaction with 4-fluoro, 4-bromo and 3-fluoro phenylacetylene was amenable to reaction with isoquinoline, producing the corresponding products (**3j-3l**) in good yields. The reaction with electron deficient 4-trifluoromethoxy phenylacetylene also proceeded efficiently to give corresponding acylated heteroarenes **3m** in 71% yield. Notably, the reaction with aliphatic alkynes did not yield the desired product.

Scheme 1. Substrate Scope with different phenylacetylenes



3a, 81%, 2.5 h **3b**, 75%, 3 h **3c**, 69%, 5 h

3d, 71%, 3 h **3e**, 74%, 4 h **3f**, 77%, 6 h

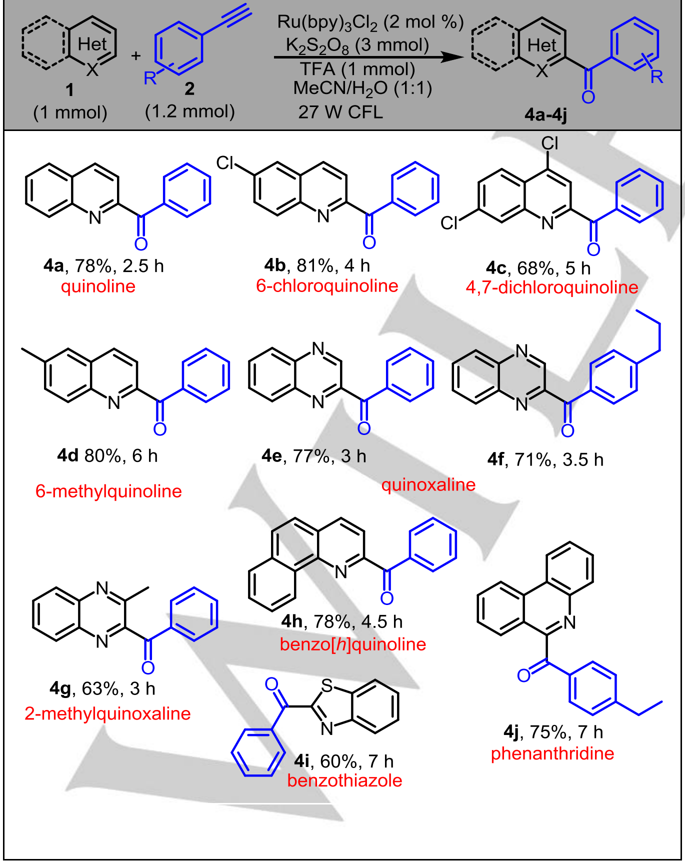
3g, 79%, 5 h **3h**, 79%, 5 h **3i**, 75%, 7 h

3j, 72%, 7 h **3k**, 77%, 6 h **3l**, 70%, 8 h **3m**, 71%, 8 h

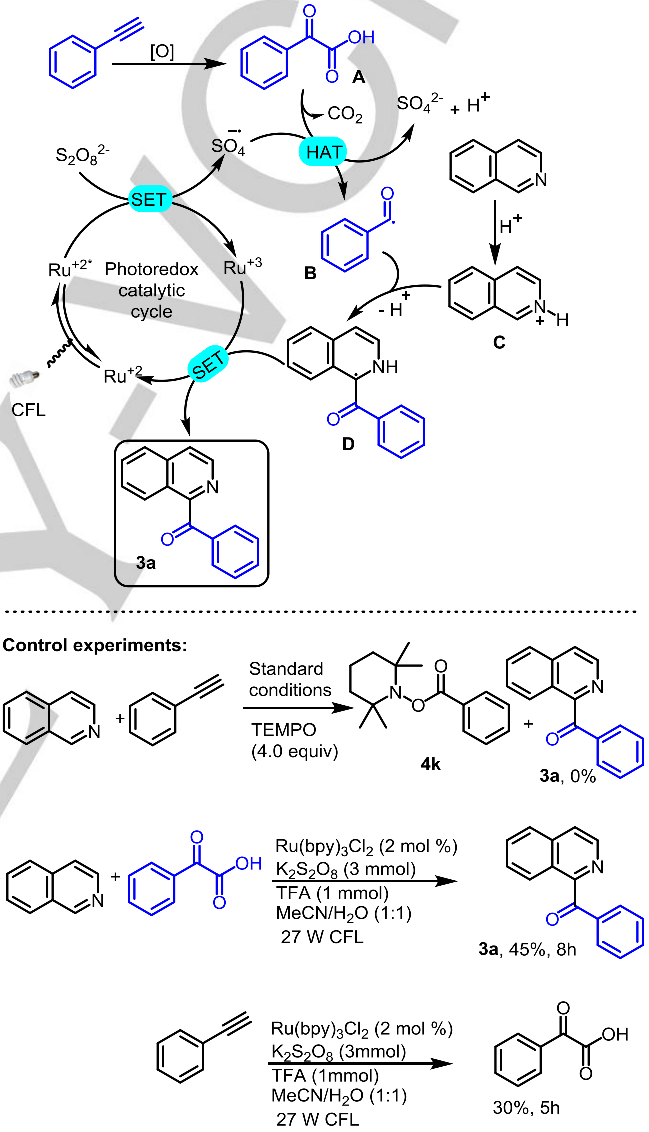
To demonstrate the functional group tolerance and applicability of this method further, we examined the scope of this reaction with different electron-deficient heteroarenes (Scheme 2). As demonstrated by the reaction with simple phenylacetylene, a range of substituted quinolines served as suitable substrates, generating the corresponding acylated products as single regioisomers in good yields (**4a-4d**). Similarly, quinoxaline and its methyl derivative underwent coupling with phenylacetylenes to produce acylated products in good yields (**4e-4g**). The reaction also works well with polycyclic heteroarene benzo[*h*]quinoline to give the corresponding product (**4h**) in 78% yield. Benzothiazole was also found to be a suitable substrate for acylation utilizing phenylacetylene, thereby generating the corresponding product (**4i**) in 60% yield. Phenanthridine was also observed to participate in the acylation producing **4j** in 75% yields.

The reaction possibly proceeds *via* photo-excitation of Ru(bpy)$_3$Cl$_2$, which is known to undergo single electron transfer (SET) in the presence of persulfate salt, thereby, generating sulphate radical anion (SO$_4^{-\bullet}$) and Ru(III).[12] On the other hand, phenylglyoxylic acid **A** generated *in-situ* from phenylacetylene[8a-c] undergoes decarboxylation followed by hydrogen atom transfer (HAT) with sulphate radical anion $(SO_4^{\bullet -})$ to produce acyl radical **B**,[13] and subsequently couples with protonated heteroarene **C** to give intermediate **D**. The final product **3a** is produced as a result of an SET reaction between intermediate **D** and Ru(III), which also completes the photoredox catalytic cycle of Ru catalyst and hence its regeneration (Scheme 3). The reaction under standard conditions in presence of radical quencher viz., TEMPO failed to give desired product and instead lead to the trapping of acyl radical to give its radical adduct. The role of phenylglyoxylic acid as an intermediate was unambiguously proved by the reaction of isoquinoline with phenylglyoxylic acid under the stipulated conditions to give the final product **3a** in 45% yields (Scheme 3). Furthermore, in the absence of heteroarene as a reactant under standard conditions, the reaction led to the formation of phenylglyoxylic acid from phenylacetylene. Notably, in both the cases benzaldehyde accompanied as a side product, which explains lower than expected yields. We also studied the emission profile of $[Ru(bpy)_3]^{2+}$ fluorophore with the increasing concentration of potassium persulfate as quencher (see supporting information). The Stern−Volmer analysis revealed that the photoluminescence of $Ru(bpy)_3Cl_2$ was quenched by $K_2S_2O_8$ in $MeCN/H_2O$ at 25 °C and the results are well in accordance with the literature reports.[14] Furthermore, reaction quantum yield of 7.2 show that reaction propagates via a radical chain mechanism.

Scheme 2. Substrate Scope with different heteroarenes



In summary, we have demonstrated for the first time, the use of arylacetylenes as precursors of acyl radicals in the acylation reaction of *N*-heteroarenes. The reaction is applicable to a wide range of heteroarenes and arylacetylenes to afford structurally diverse acylated nitrogen heteroarenes as single regioisomers in good yields. Stoichiometric use of acyl precursor and shorter reaction times are some of the advantages of the protocol. This study opens a new way of utilizing terminal alkynes as a source of acyl groups which can find application in multitude of synthetic reactions. The further reactivity and applicability of this reaction system is currently under investigation in our laboratory.



Scheme 3. Plausible mechanism

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Keywords: phenylacetylene • acyl radical • photoredox • heteroarene • acylation

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Entry for the Table of Contents

COMMUNICATION

Ms. Shaista Sultan[a], Dr. Masood Ahmad Rizvi,[b] Mr. Jaswant Kumar[b] and Dr. Bhahwal Ali Shah[a]*

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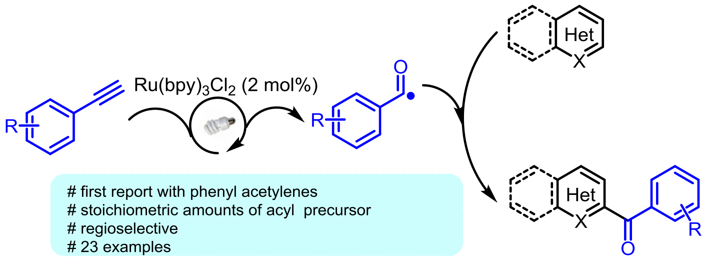
Acyl radicals from terminal alkynes: Photoredox-catalyzed acylation of heteroarenes



A photoredox-mediated acylation reaction of electron deficient heteroarenes with terminal alkynes is reported. The method relies on oxidative cleavage of phenylacetylenes for generation of acyl radicals as a key enabling advance. The reaction is regioselective with broad substrate scope.