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Photocatalyst-Free Visible-Light Enabled Synthesis of Substituted Pyrroles from α -Keto Vinyl Azides

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Abstract. An efficient photocatalyst-free visible light enabled synthesis of substituted pyrroles from α -keto vinyl azides (readily prepared *via* Knoevenagel condensation of phenacyl azides with 2-oxo-2H-chromene-3-carbaldehydes) was developed. The reaction proceeds through a denitrogenative photodecomposition of α -keto vinyl azides, 1,3-amino group migration, and coupling of intermediates with secondary amines.

Keywords: photocatalyst-free; photochemical reaction; vinyl azides; pyrroles; 1,3-amine migration

Pyrrole is one of the most vital five membered *N*-heterocycles frequently found in a plethora of natural products, pharmaceuticals, drugs and other valuable materials.^[1] Molecular scaffolds with pyrrole as a key structural unit possess a broad range of biological properties such as antitumor, antipsychotic, anti-inflammatory, antioxidant, antifungal, and antibacterial activities.^[2] Therefore, chemists have always been fascinating for developing innovative synthetic routes to pyrrole scaffolds. It is not surprising that a variety of newer organic reactions for the construction of substituted pyrroles are incessantly being discovered.^[3] Apart from metal and non-metal catalyzed reactions, many photochemical methods to synthesize pyrrole derivatives were also reported recently.^[4]

Since the beginning, high energy ultra-violet (UV) light was mostly utilized in photochemical organic transformations. However, this trend has been dramatically changed over the past few years as a large numbers of visible light driven organic reactions are being explored.^[4,5] Visible light is often preferred over UV irradiations because of its product selectivity, little radiation safety requirements, simple

reaction set-up and sustainable perspective. This manuscript deals with a photocatalyst-free visible light enabled synthesis of a library of coumarin fused pyrroles from α -keto vinyl azides. These molecular scaffolds are found in pharmaceutically valuable natural products (Lamellarins **I**, Ningalins **II**) and other synthetic molecules (**III**, **IV**, **V**, **VI**) with unique photochemical as well as redox-switching properties (Figure 1). They possess promising anticancer, antitumor, and fluorescent neuroimaging properties.^[6]

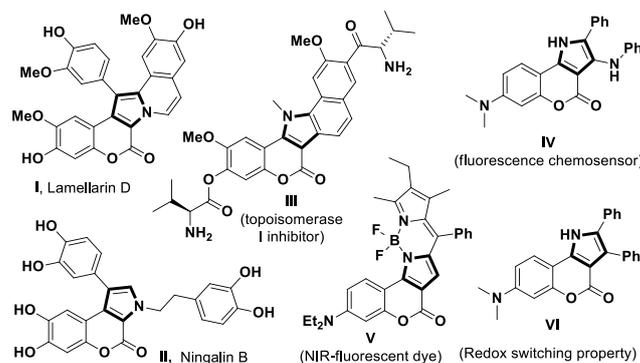
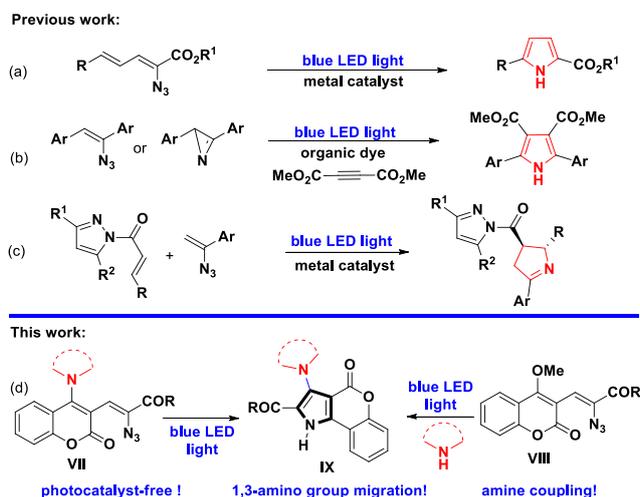


Figure 1. Examples of some important natural and synthetic fused pyrrole molecules.

Vinyl azides have long been known to decompose into nitrenes and/or 2*H*-azirines under thermal as well UV light exposure, and it has been widely utilized to synthesize various *N*-heterocycles.^[7] However, visible light enabled synthetically useful reactions of vinyl azides were unexplored until Yoon and co-workers reported a photosensitized decomposition of vinyl azides to access pyrroles (Scheme 1a).^[8a] In the same year, Xiao and co-workers also reported a visible light enabled coupling of vinyl azides and 2*H*-

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azirines with alkynes to yield pyrroles (Scheme 1b).^[8b] Recently, Meggers and co-workers reported a visible light triggered [2+3]cycloaddition of alkenes and vinyl azides to synthesize pyrrolines in high enantiomeric excess (Scheme 1c).^[8c] In continuation to our interest over the development of visible light enabled synthesis of *N*-heterocycles,^[9] we intended to study the photochemical reactions of α -keto vinyl azides (**VII** & **VIII**) to access pyrroles (**IX**) (Scheme 1d).

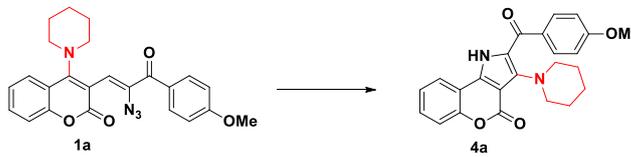


Scheme 1: Visible light enabled synthesis of pyrroles from vinyl azides.

To start with, vinyl azide **1a** was prepared by a Knoevenagel condensation reaction of 2-oxo-4-(piperidin-1-yl)-2*H*-chromene-3-carbaldehyde **2a** with 2-azido-1-(4-methoxyphenyl)ethanone **3a** using piperidinium acetate as an additive in dichloromethane (DCM). UV-Visible spectrum of compound **1a** showed strong absorption of light in 280-440 nm range with absorption maxima at 303 and 380 nm. Therefore, we envisioned that a photocatalyst might not be required and planned to study its photodecomposition using a blue LED light (Table 1). Irradiation of 0.1 M solution of the model substrate **1a** in DCE with a blue LED (7 W) light led to the formation of a clear yellow spot on TLC, which was isolated, and its chemical structure was assigned as **4a** by analysing its ¹H/¹³C NMR, IR, MS/HRMS spectral data (Table 1, entry 1). The yield of compound **4a** was same whether the reaction was carried out under inert (N₂) or open air atmosphere (Table 1, entries 1 & 4). It indicated that atmospheric oxygen did not interfere with reaction intermediates. Irradiation of **1a** with a 8 W compact fluorescent lamp (CFL) or heating at 60 °C in DCE also led to its complete decomposition, however **4a** was obtained in lower yields (Table 1, entries 2 & 3). Photodecomposition of **1a** in DCM gave good yield of **4a** whereas complex reaction mixtures were observed using MeOH and CH₃CN as the reaction solvents (Table 1, entries 5-7). It indicated that both

these solvents interfere with substrate or reaction intermediates leading to the formation of multiple products.

Table 1. Optimization studies of the decomposition of vinyl azide **1a**.^[a]



Entry	Energy source	Solvent	Time (h)	Yield (%) ^[b]
1	7 W blue LED	DCE	24	85
2	8 W CFL	DCE	24	65
3	heating (60 °C)	DCE	12	41
4 ^[c]	7 W blue LED	DCE	24	85
5	7 W blue LED	DCM	24	82
6	7 W blue LED	MeOH	24	NI
7	7 W blue LED	CH ₃ CN	24	NI

^[a] Reaction condition: Conc. of **1a** in solvent: 0.1 M, blue LED light (7 W kept in close contact with the reaction vessel), open air atmosphere.

^[b] Isolated yields.

^[c] Under nitrogen atmosphere.

NI = Not isolated (complex mixture).

With optimized reaction conditions in hand, we tried to study the scope of the reaction by synthesizing a series of substituted pyrroles (Figure 2). Several vinyl azides having electron donating (OMe, Me, Ph), electron withdrawing (CN), and halogen (Cl) in their aroyl residue got smoothly converted into corresponding pyrroles in high yields (80-85%).

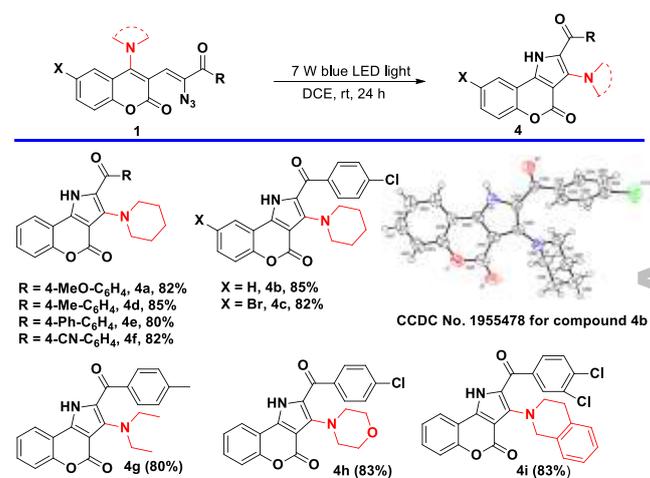
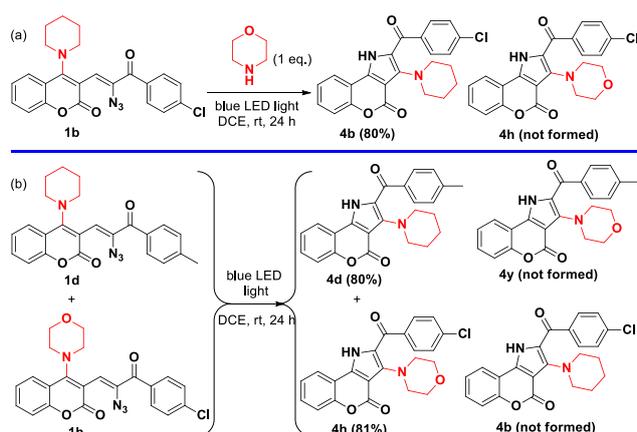


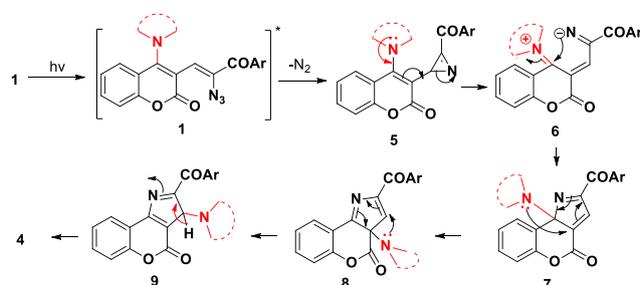
Figure 2. Scope of the photodecomposition of vinyl azides **1** to access substituted pyrroles **4**

Piperidine, diethylamine, morpholine and 1,2,3,4-tetrahydroisoquinoline units of the vinyl azides **1** migrated smoothly during the reaction to yield pyrroles **4**. The reaction was equally successful when a halogen (Br) substituent was taken in the coumarin residue of the vinyl azide (**1c**). Vinyl azides **1** having primary or secondary amino group could not be prepared using our standard protocol, therefore such photodecompositions could not be studied. All the synthesized compounds were fully characterized by their $^1\text{H}/^{13}\text{C}$ NMR, IR, MS/HRMS spectral data. X-ray crystallography studies for compound **4b** were also executed to give an unambiguous proof of its structural assignment.

We were curious to know whether the 1,3-amino group migration during the formation of pyrrole **4** from vinyl azide **1** was intramolecular or intermolecular process. Therefore, we planned a couple of control experiments. In the first experiment, photodecomposition of vinyl azide **1b** was performed in the presence of morpholine (Scheme 2a). In the second one, equimolar mixtures of vinyl azides **1d** and **1h** were irradiated with blue LED light in DCE (Scheme 2b). In none of the cases, a crossover product was obtained thereby suggesting the intramolecular nature of the 1,3-amino group migration.



Scheme 2. Control experiments.

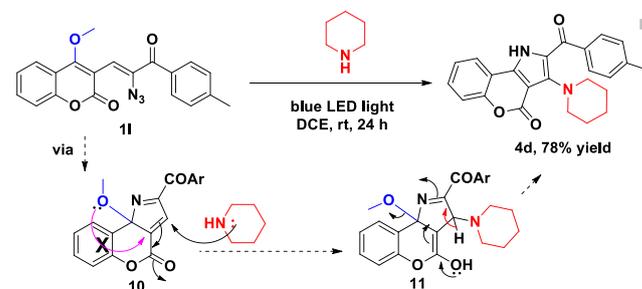


Scheme 3. Mechanistic hypotheses for the conversion of vinyl azides **1** into pyrroles **4**.

A mechanistic rationalisation of the photodecomposition of vinyl azide **1** to pyrrole **4** is

presented in Scheme 3. Upon absorption of light, the vinyl azide **1** expels a molecule of nitrogen from its excited state to form a *2H*-azirine **5**. Being in conjugation with the *2H*-azirine, the amino group drives its ring opening to give intermediate **6** which subsequently undergoes an intramolecular cyclization to yield **7**. Next, an intermediate **9** is formed *via* two successive [1,5] sigmatropic shift of the amine group. The net result of the process is an apparent 1,3-amino group migration. Finally the intermediate **9** isomerises to the pyrrole **4**.

Next, we thought of further exploring the scope of pyrrole synthesis by attempting a similar 1,3-migration of an alkoxy group of vinyl azide **VIII** (Scheme 1d) under similar reaction conditions. We, therefore, prepared vinyl azide **11** *via* Knoevenagel condensation reaction of 2-azido-1-(*p*-tolyl)ethanone **3c** with 4-chloro-2-oxo-*2H*-chromene-3-carbaldehyde **2f**. The UV-Visible absorption spectrum of vinyl azide **11** showed strong absorption of light in 287–430 nm with absorption maxima at 339 nm. The photodecomposition of **11** was studied under various conditions including blue LED light, CFL light, heating, and exposure of light in the presence catalytic $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ (For details, see electronic supporting information). However, in all the cases we ended up with a reaction mixture with multiple spots on TLC which could not be purified using silica-gel column chromatography. To our surprise, when **11** was exposed to blue LED light in the presence of piperidine, the reaction gave a prominent spot on TLC with very little side products. After work-up and purification, compound **4d** was isolated in 78% yield (Scheme 4).

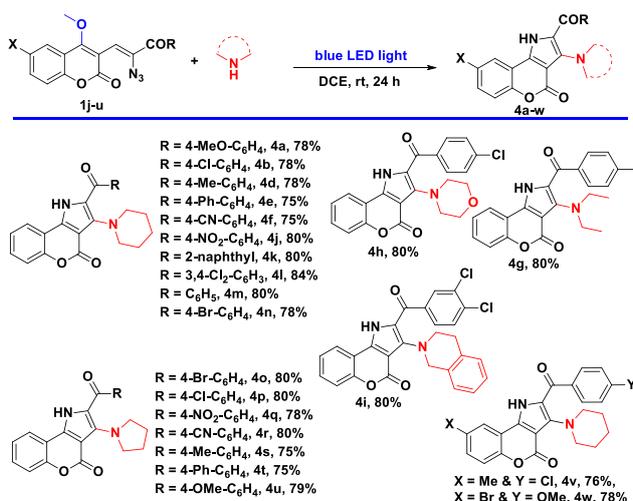


Scheme 4. Photochemical coupling of **11** with piperidine to yield pyrrole **4d**.

Mechanistic rationalization for the smooth formation of **4d** from the coupling of piperidine and vinyl azide **11** is depicted in Scheme 4. After absorption of light, the vinyl azide **11** undergoes denitrogenative decomposition into a *2H*-azirine followed by its ring opening and annulations to intermediate **10**, in a similar fashion depicted in Scheme 3. The methoxy group of the intermediate **10** is not as good nucleophile as the amino group of the intermediate **7**. Therefore, it does not lead to the anticipated 1,3-methoxy group migration. The intermediate **10** is attacked by piperidine to give intermediate **11**, which after elimination of a

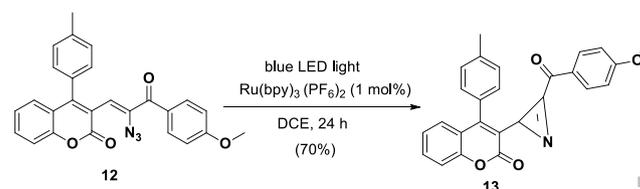
molecule of methanol and isomerisation yields pyrrole **4d**.

The successful coupling of vinyl azide **1l** with piperidine prompted us to explore the scope of the reaction. Several vinyl azides **1j-u** were prepared and coupled with amines to yield pyrroles under same reaction conditions (Scheme 5). Vinyl azides (**1j-u**) bearing electron withdrawing groups (CN, NO₂), electron donating groups (OMe, Me, 4-Phenyl, 2-Naphthyl) and halogens (Br and Cl) in their aryl residue were coupled efficiently with piperidine to afford fused pyrrole (**4a-b**, **4d-f**, **4j-n**) in good yields (75-80%). The photochemical coupling reaction was successfully generalized with piperidine, morpholine, pyrrolidine, *N,N*-diethylamine, and 1,2,3,4-tetrahydroisoquinoline. In all these cases, good yield of desired pyrrole derivatives (**4a-w**) were obtained. The coupling of vinyl azide with primary amines (methylamine and 4-toluidine) gave inseparable multiple spots on TLC which were not purified. In another experiment, a photochemical coupling of vinyl azide **1j** with a secondary aromatic amine (*N*-methylaniline) was attempted. Analysis of the reaction mixture revealed the formation of desired pyrrole among with the several by-products (for details, see the electronic supporting information). Next, we investigated the possibility of a thermal coupling of vinyl azide **1j** with piperidine. In an experiment that was performed at ambient temperature in dark, both the starting materials (vinyl azide **1j** and piperidine) remained un-reacted even after 12 h. Further heating the same reaction mixture at 60 °C led to complete decomposition of the vinyl azide with the formation of many spots on TLC. The desired pyrrole **4a** could not be isolated from the thermal coupling of vinyl azide **1j** with piperidine. These results clearly demonstrate the superiority of photochemical coupling of the vinyl azides with secondary amines (Scheme 5).



Scheme 5. Photochemical coupling of vinyl azides **1** with secondary amines to yield pyrroles **4**.

In order to explore the scope of the reaction and study the similar migration of a carbon substituent (aryl), vinyl azide **12** was prepared and its photodecomposition was studied. Vinyl azide **12** remained un-decomposed when its solution in DCE (0.1 M) was irradiated with a blue LED light (7W) for a period of 12 h. Therefore, a photosensitized decomposition of vinyl azide **12** was performed using Ru(bpy)₃(PF₆)₂ (1 mol%) as a photocatalyst (Scheme 6). Vinyl azide **12** was completely decomposed in 24 h giving multiple spots on TLC. The major product of the reaction was characterized as 2*H*-azirine **13**.



Scheme 6. Photosensitized decomposition of vinyl azide **12** into 2*H*-azirine **13**.

In conclusion, a novel visible light enabled photocatalyst-free synthetic method to construct pyrroles from α -keto vinyl azides was developed. Vinyl azides having amino group in conjugation with the azide underwent denitrogenative photodecomposition and 1,3-amino group migration to yield pyrroles. On the other hand, vinyl azides having methoxy group in conjugation with the azide were smoothly coupled with secondary amines to give pyrroles in good yields. Several control experiments were carried out to get mechanistic insight of the reaction. As this photochemical transformation does not require external photocatalyst or additive, it reduces chemical wastes and the manufacturing costs. The reaction opens up the possibility of studying further photochemical rearrangements and coupling of nucleophiles with vinyl azides to construct complex molecular scaffolds.

Experimental Section

General procedure for decomposition of vinyl azides (1a-i) in the presence of blue LEDs to yield substituted pyrroles 4a-i: In a 25 mL round bottom flask, the corresponding vinyl azide (0.5 mmol) was taken in DCE (5 mL). Next, the reaction mixture was stirred and irradiated with a 7W blue LED light placed in close contact to the reaction vessel till completion (24 h). Next, the reaction mixture was concentrated to obtain a crude product which was purified by silica-gel (100-200 mesh) column chromatography using ethyl acetate / *n*-hexane in increasing polarity to yield compounds **4a-i**.

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