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Visible Light Induced, Metal-free Denitrative Formal [3+2] Cycloaddition for Trisubstituted-Pyrrole Synthesis

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Abstract: A metal free regioselective synthesis of trisubstituted pyrroles has been developed through a formal [3+2] cycloaddition reaction between 2H-azirines and nitroalkenes under visible light photoredox catalyzed conditions. The reaction proceeds through 2H-azaallenyl radical addition on β -nitrostyrenes in a Michael fashion followed by base-mediated denitration reaction. The directive group influence of the nitro group controls the regiochemistry of the reaction.

Introduction

The nitrogen-containing heterocycles or aza-heterocycles are ubiquitous in biologically active molecules of natural as well as synthetic origin.1 Among these aza-heterocycles, the pyrrole derivatives register a remarkable presence due to their importance as nature's building blocks, drugs, dyes, insecticides, optoelectronic materials etc (figure 1).² Quite understandably, literature is replete with synthetic strategies to access pyrrole derivatives.³ Despite several elegant methods available, the milder and more efficient synthetic routes are still desired for the synthesis of pyrroles bearing divergent substitution patterns. In this context, the visible light photoredox catalysis has emerged lately as a greener alternative to the conventional synthetic approaches.⁴ The potential of photoredox catalysis has been realized immensely by its application for the construction of various heterocyclic motifs including natural products.5 "Natural'



Figure 1. Pyrrole motif in natural bioactive molecules and synthetic drugs

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In 2014, Lu and Xiao reported pyrrole synthesis through visible light irradiation of 2H-azirines and alkynes in the presence of an organic photosensitizer.⁶ The reaction involves azirine C-C bond cleavage resulting into the generation of 2-azaallenyl radical cation which undergo formal [3+2] cycoaddition with alkynes. Thereafter, a handful of other reports followed employing azirines for the construction of heterocyclic scaffolds such as oxazoles,7 pyrrolidines,8 triazolines and triazoles9 and recently dihydro-oxadiazoles¹⁰ via 2-azaallenyl radical cation formed by the cleavage of azirine C-C bond under visible light irradiation. However, Li and Wang documented a visible light photoredox catalyzed synthesis of oxazoles from azirines that involved azirine C-N bond cleavage.¹¹ Notably, azirines usually undergo C-N bond cleavage under metal catalyzed conditions generating vinyl nitrenoid intermediates and in few cases simultaneous cleavage of both C-C and C-N bonds results into the formation of carbenoids and nitriles. Such behavior of azirines has been well exploited for assembling diverse acyclic as well as heterocyclic scaffolds under metal catalysis.12

Nitroalkenes are versatile building blocks for several target scaffolds including various carbocycles and hetrocycles.¹³ The strong electron withdrawing nature of the nitro group makes them highly electron deficient alkenes, a suitable substrate for numerous organic reactions such as Michael reaction, Mannich reaction, Baylis-Hillman reaction, Rauhut-Currier reaction, cycloadditions and metal-catalyzed coupling reactions.¹⁴ Recently, nitroalkenes have been exploited as the source of alkenyl function in visible light mediated denitrative arylation,¹⁵ trifluoromethylation,¹⁶ carboxylation¹⁷ and alkylation reactions.¹⁸ However, to the best of our knowledge, nitroalkene have never been used as dipolarophiles in visible light mediated cycloadition reactions.

We envisaged that owing to the directive group influence of the nitro group, the nitroalkenes can impart regioselectivity in the dipolar cycloaddition with 2-azaallenyl radical cations generated from 2H-azirines under visible light mediated conditions. Also, the excellent leaving group ability of the nitro group can be exploited for aromatization of the expected cycloaddition products i.e. pyrrolidines. Further, the 2-H azirines usually undergo C-C bond cleavage under visible light irradiation which would install 2- and 3- substituents on azirines on the 2- and 5-position of the pyrroles, which cannot be achieved under metal catalyzed conditions. We herein report our findings on the visible light mediated denitrative formal [3+2] cycloaddition reaction between 2H-azirines and aromatic nitroalkenes for the construction of trisubstituted pyrroles (Scheme 1).





Scheme 1. Formal cycloadditions of 2H-azirines under visible light photoredox catalyzed (VLPC) conditions

Results and Discussion

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The initial experiment was carried out with 2,3-diphenyl-2Hazirine 1a and β -nitrostyrene 2a in the presence of organic dye 9-mesityl-10-methylacridinium tetrafluoroborate (Mes-Acr+BF4)19 or PC-I in DCM under blue light irradiation (Table 1). After 16 h, the light source was removed and 2 equivalents of DBU was added in the reaction mixture and reaction was continued at room temperature for 2 hours. We were delighted to isolate the product 3a in 76% yield after total 18 h of reaction time (Table 1, entry 1).





1a:2a = 1:1.5

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[a] Unless otherwise mentioned, 1a (0.4 mmol) with specified amounts of 2a and photocatalyst was irradiated in solvent (4.0 mL) with a 450 nm blue LED for 16 h followed by light switch-off and addition of DBU (2 equiv.) in the reaction mixture under N2. [b] NMR yields. [c] Isolated yields in parentheses. [d] Green light was used. [e] 4a: 3-Nitro-2,4,5-triphenyl-3,4-dihydro-2H-pyrrole.

After extensive optimization of reaction conditions, we set out to examine the scope of nitroalkenes in the reaction. Several aryl, heteroaryl and alkyl nitroalkenes were reacted with 2,3-diphenyl-2H-azirine 1a under standard reaction conditions (Table 2).

Table 2. Scope of the reaction in terms of nitroalkenes.^a



[a] Unless otherwise mentioned, 1a (0.4 mmol), 2 (0.2 mmol) and PC-I (0.006 mmol) were irradiated in DCM (4.0 mL) with a 450 nm blue LED for 16 h followed by light switch-off and addition of DBU (0.4 mmol) in the reaction mixture under N₂.

The results in Table 2 clearly indicate wide scope of the [3+2] cyclization reaction with respect to nitroalkenes. The aryl nitroalkenes bearing electron-releasing groups such as Me, OMe and SMe reacted efficiently with 1a under optimized reaction conditions allowing swift access to the corresponding trisubstituted pyrroles 3a-3f in good yields. Similarly, the electron-withdrawing groups including CN, CI, CF₃ and NO₂ on nitroalkenes too were well accommodated and the products 3g-3k were isolated in excellent yields. In addition to aryl nitroalkenes, the heteroaryl nitroalkenes also worked well in the [3+2] cyclization with 1a affording heteroarene-substituted pyrroles 3I-3m in high yields. However, a complex mixture was obtained when aliphatic nitroalkenes were employed in the reaction.

Next we aimed to investigate the range of 2H-azirines employable in the reaction with various nitroalkenes (Table 3). Several azirines with diverse substitution patterns were prepared following standard literature procedures. The azirines 1b and 1c bearing electron-releasing groups Me and OMe, respectively reacted well with electron-rich as well as electron-deficient

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nitroalkenes under optimized reaction conditions yielding products 3n-3s in good yields. The CI-substituted azirine 1d too reacted efficiently with nitroalkenes possessing 4-OMe, 4-CN and 4-NO₂ substitution providing corresponding pyrroles in 50%, 87% and 81% yields, respectively. Also, azirine featuring 2thienyl-substitution 1e reacted smoothly with various aryl as well as heteroaryl nitroalkenes affording products 3w-3y under the standard reaction conditions. The alkyl-aryl azirine 1f could also be successfully employed in the reaction, however yield of the product 3z was low. It is especially noteworthy that the reaction exhibited complete regioselectivity in favour of the products obtained through 2-azaallenyl radical cation addition on the β position of nitroalkenes over the other regioisomer expected to form through the α -addition of radical cation (please refer to the plausible mechanism; Scheme 3). The correct structure for the exclusive regioisomer was established by NMR spectroscopy and single crystal X-ray analysis of 3r and the same regiochemistry was assigned to other products on the basis of analogy.20



[a] Unless otherwise mentioned, 1 (0.4 mmol), 2 (0.2 mmol) and PC-I (0.006 mmol) were irradiated in DCM (4.0 mL) with a 450 nm blue LED for 16 h followed by light switch-off and addition of DBU (0.4 mmol) in the reaction mixture under N₂.

Further, the necessity of both visible light and photocatalyst was established through key control experiments since no product formation were noticed in absence of **PC-I** or visible light. Additionally, a test reaction of 3-(4-methoxyphenyl)-2-phenyl-2H-azirine **1c** with the radical trapping agent allyltributyltin in the presence of **PC-I** furnished N-benzyl-1-phenylbut-3-en-1-imine **5** under visible light irradiation (see the Supporting Information for

data), confirming the involvement of 2-azaallenyl radical cation in the reaction, as proposed in the literature⁶⁻¹⁰ (Scheme 2).



The mechanism of 2H-azirine - nitroalkene [3+2] cycloaddition proposed on the basis of control experiments and previous literature reports⁶⁻¹⁰ is depicted in Scheme 3, exemplified by the reaction between substrates **1a** and **2a**.



Scheme 3. Plausible mechanism

The excited photocatalyst **PC-I**^{*} generated upon visible light irradiation undergoes reductive quenching by single electron transfer from strongly reducing 2H-azirine 1a.²¹ This result into the generation of azirine radical cation **A** and the reduced photocatalyst. The radical cation **A** forms 2-azaallenyl radical cation **B/B'** following ring opening through C-C bond cleavage. The radical cation **B'** adds on to the β -position of nitroalkene 2a furnishing intermediate **C**, which oxidizes the reduced photocatalyst and leads to the intermediate species **D**. The intermediate **D** follows cyclization and base-mediated denitration sequence to afford the trisubstituted pyrrole 3a. It is noteworthy that radical addition on the nitroalkene takes place in Michael fashion unlike usual reactions of nitroalkenes under visible light irradiation¹⁵⁻¹⁸ owing to the charge stabilizing capacity of the nitro

group. This in effect accords high level of regioselectivity to the reaction, affording products as a single regioisomer.

Conclusions

In conclusion, an efficient regioselective synthesis of trisubstituted pyrroles has been developed using simple substrates and organic dye as photocatalyst under visible light irradiation. The reaction is reasonably general in nature in terms of 2H-azirines and nitroalkenes employed in the reaction. Further, the complete regioselectivity of the reaction and high yields of product in most of the cases are noteworthy attributes of the reaction.

Experimental Section

General procedure for visible light mediated trisubstituted pyrrole 3 synthesis

In a 5 mL snap vial equipped with magnetic stirring bar, the 2Hazirine 1 (0.4 mmol), nitroalkene 2 (0.2 mmol) and photocatalyst (Mes-Acr⁺BF₄⁻) PC-I (3 mg, 0.006 mmol, 3 mol% w.r.t. 2) were dissolved in anhydrous dichloromethane (4 mL). The resulting reaction mixture was degassed by three "freeze-pump-thaw" cycles via a syringe needle. The vial was irradiated using 450 nm blue LED with a cooling device maintaining a temperature around 25 °C. After 16 h of irradiation (TLC monitoring), the light source was removed and DBU (0.06 mL, 0.4 mmol) was added in the reaction mixture which was stirred at room temperature for additional 2 h (TLC monitoring). The reaction mixture was washed with water (2 x 5 mL) and brine (2 x 5 mL). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the crude product was achieved by column chromatograpy on silica gel using hexane/ethyl acetate as eluent to afford the pure product 3.

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