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Blue LED Mediated Intramolecular C−H Functionalization and Cyclopropanation of Tryptamines: Synthesis of Azepino[4, 5-b]indoles and Natural Product Inspired Polycyclic Indoles

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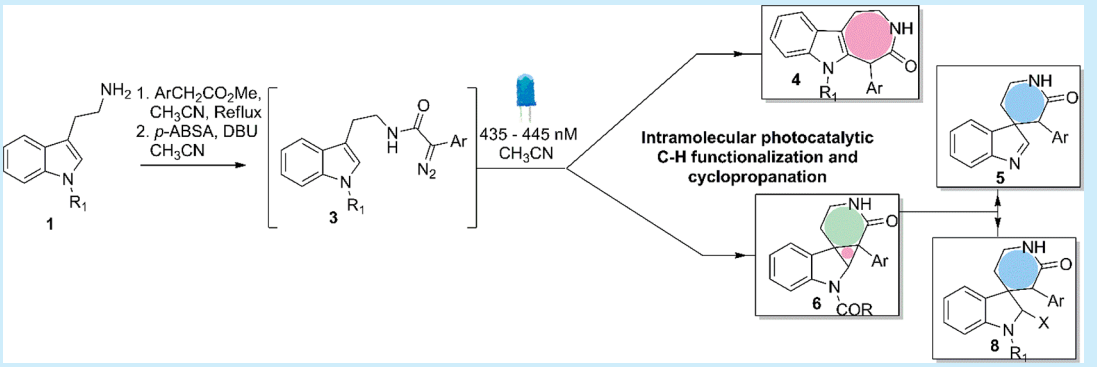

ABSTRACT: We report a novel blue LED mediated intramolecular C−H functionalization of tryptamine derivatives to generate azepino[4, 5-b]indoles (**4**) in moderate to good yields. By altering the substitution at the tryptamine nitrogen, intramolecular cyclopropanation is achieved in high yields under the same reactions condition to provide natural product inspired polycyclic indoles (**6**), which are further transformed to spiropiperidino (**5** and **8**) indoles in decent yields. The mechanism of formation of the compounds was investigated through DFT studies.

By virtue of their ubiquitous presence in various natural products, receptors, proteins, and drug molecules, indole derivatives are essential building blocks and hold a niche position among the synthetic organic chemists and pharmaceutical scientists.[1,2] Transition metal catalyzed C2/C3−H activation and cyclopropanation of indoles are robust synthetic strategies to afford functionalized indoles from simple substrates (Scheme 1a).[3−5] However, there are only few reports involving the photocatalytic version of this reaction on indoles (Scheme 1b,c).[6,7] Among them there is an *in situ* generation of diazoalkane via Bamford-Stevens reaction of tosyl hydrazone (in Cs_2CO_3), which reacts with various *N*-substituted indoles in the presence of blue LED to provide either C3 substituted or cyclopropanated product based on the *N*-substitution (Scheme 1b).[6] A ruthenium ($Ru(bpy)_3Cl_2$) catalyzed blue LED reaction of diazoalkanes with substituted indole was also reported to afford mixtures of C2/C3 substituted products (Scheme 1c).[7] Amidst these efforts, it was also interesting to observe that there is a dearth of similar experiments on C2/C3 substituted indoles or on indole derivatives like tryptamine and the application of this methodology (be it transition metal or blue LED catalyzed) to generate biologically active molecular scaffolds. It is noteworthy that despite being biologically interesting there is a lack of efficient strategies to access azepino[4, 5-b]-indoles.[8−10] As a part of our ongoing investigation on blue LED catalyzed carbene reactions, we herein report the first intramolecular C−H functionalization of unsubstituted or *N*-methyl tryptamines to afford azepino[4, 5-b]indole (Scheme 1d). This was achieved through blue LED (5−6 W Micro Photochemical Reactor (ALDKIT001) with blue LED lights [435−445 nm] source). Acyl substitution on the tryptamine nitrogen (**1c,d**) facilitated intramolecular cyclopropanation to provide polycyclic indole molecules (**6a−h**).

We began by the proof of concept study where tryptamine **1a** was reacted with phenyl acetate in acetonitrile under reflux (Scheme 1d). Once **1a** was completely consumed, the reaction mixture was cooled to room temperature followed by sequential addition of *p*-acetamido benzenesulfonyl azide (*p*-ABSA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction was stirred for three more hours at room temperature,

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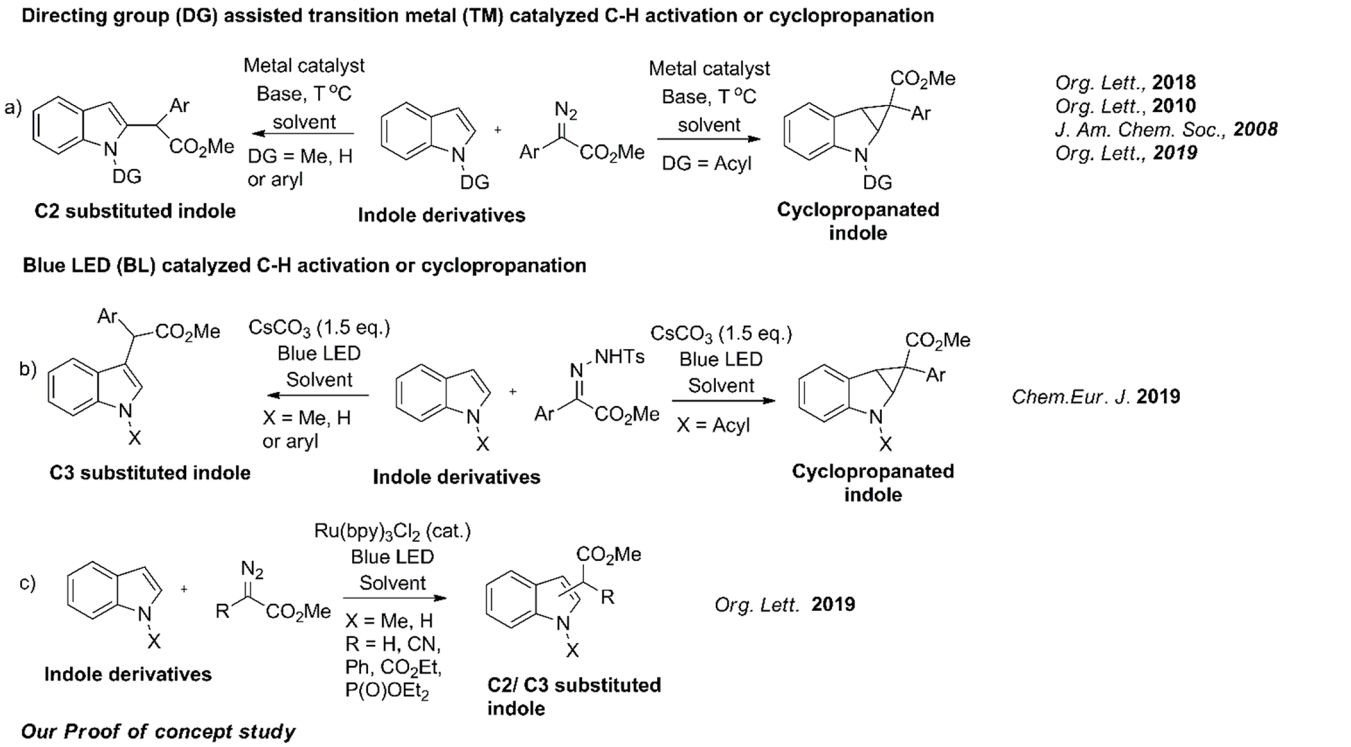
Scheme 1. Previous Reports for C2/C3 Functionalization of Indoles and Our Proof of Concept Study



after which the TLC indicated complete formation of the diazo intermediate **3a**. At this point, any effort (precipitation, column chromatography, or crystallization) to isolate **3a** from the reaction mixture led to its decomposition. We realized that maybe **3a** is unstable under standard condition; hence, the reaction mixture was immediately subjected to blue LED. The reaction was monitored by LC−MS, and both the carbene **2a′** and final product **4a** were detected (Scheme 1d and related mass spectrum). After nearly 24 h, intermediates were completely consumed. The reaction mixture was diluted with water and extracted with ethyl acetate to provide the crude product, which was further purified to afford compound **4a** in 61% overall yield. Further screening of the reaction in various solvents (viz. ethanol, dichloroethane, trifluoroethanol, etc.) and in a range of LEDs (such as green, red, white) (see et al.) established that reaction in acetonitrile and blue LED at r.t. is currently the most appropriate condition to generate the desired azepino[4, 5-b]indoles **4**.

Utilizing the optimal reaction condition, we assessed tryptamine **1a**, *N*-methyl tryptamine **1b**, and serotonin **1c** in the intramolecular C2−H functionalization under blue LED to provide azepino[4, 5-b]indole compounds **4b−g** by reacting with a bevy of alkyl aryl acetates **7a−e** containing electron withdrawing and electron donating groups at the *ortho*-, *meta*-, and *para*-position of the aryl moiety (Scheme 2). The average yield of the products obtained from this one pot sequence of amidation-diazotization−C2-H functionalization ranged from 52 → 71% (Scheme 2). The amidation and the diazotization reaction went smoothly with complete conversion of the starting material to the product. We envision that the unstable nature of the diazo intermediate may be the reason for the moderate yield of the products. However, the yield remained consistent irrespective of the nature of substitution on the aryl moiety of the alkyl aryl acetates. The reaction condition was also amenable to thiophene substituted diazo moiety to provide **4e** and **4g** in 71 and 69% yield, respectively. Generally simple arenes are higher yielding than hetero arenes. Herein,

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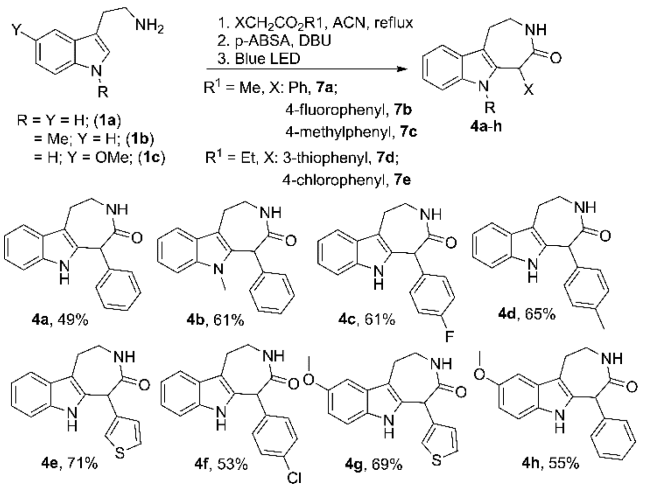
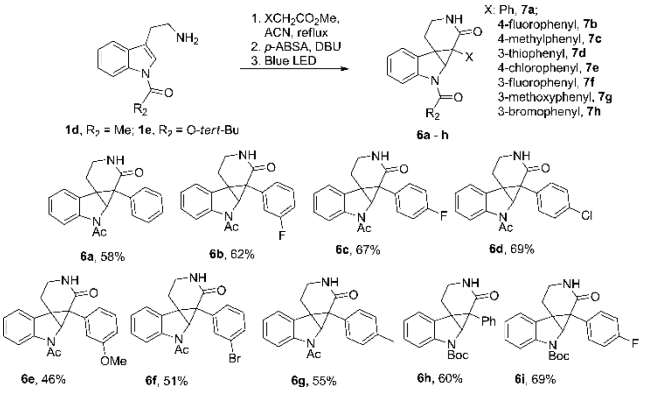
Scheme 2. Synthesis of Azepino Indole Molecules 4a−h



the intermediate carbene **3** (Scheme 5) is electron deficient; hence, the high electron density of the thiophene could have provided stability to it, and consequently, **4e** and **g** were high yielding compared to the arene analogs. The fact that azepino[4, 5-b] indoles were isolated as the desired products indicated exclusive C2 substitution in the indole ring without any. Interestingly, no keto enol tautomerism was observed during the formation of **4**.

Next, intramolecular cyclopropanation of aryl diazoacetates derived from *N*-acetyl and *N*-Boc tryptamine **1d** and **1e** afforded the library of polycyclic indole molecules **6a−i** (Scheme 3). It was remarkable how the alteration in the

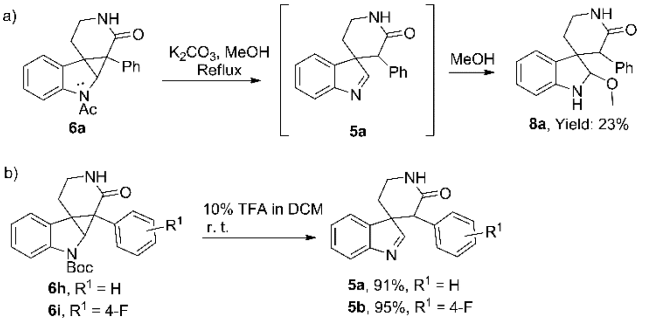
Scheme 3. Synthesis of Cyclopropane Fused Polycyclic Compounds 6a−h



substitution type (from H/methyl → acyl) on the tryptamine nitrogen influenced the change in the course of the reaction, ultimately providing a different product. Typically the aryl diazoester from **1d** and a series of alkyl aryl acetate (**7b−g**) under the blue LED in acetonitrile provided the desired compounds **6a−g** in 48 to 69% yield (Scheme 3). Generally the reactions with electron withdrawing functionalities on the aryl moiety such as 4-fluoro and 3-fluoro (**6b** and **6c**) were better yielding (yield: 62 and 67%) compared to the electron donating substituents such as 4-methyl, 3-methoxy, and 3-bromo (**6e**, **6f**, and **6g**) (yield: 46 → 55%) (Scheme 3). In a similar fashion, *N*-boc tryptamine **1e** afforded **6h** and **6i** in 66 and 69% yield, respectively.

The highly active donor−acceptor type polycyclic compounds **6** provide opportunities for further transformation (Scheme 4). Accordingly, deacetylation of **6a** in the presence

Scheme 4. Synthesis of Spiropiperidino Indoles 8a and 5a,b



of methanol and potassium carbonate afforded the spiropyrrolidinone indole molecule **8a** albeit in a poor yield of 25% (Scheme 4a). We expected indoleamine **5a** but realized that deacetylation prompted the cyclopropane ring opening of **6a** to the indoleamine **5a**, which was subsequently attacked by the methanol to provide **8a**. Despite few other bases (sodium hydroxide, potassium hydroxide) and acid (dilute hydrochloric acid) mediated deacetylation efforts, the reaction yield could not be further improved. To solve this, it was envisaged that deboc of **6h** will be simpler and high yielding and could provide the indoleamine **5a**. Accordingly, Boc-deprotection of **6h** in the presence of 10% trifluoroacetic acid in dichloromethane afforded **5a** in 91% yield (Scheme 4b). Similarly, **6i** afforded **5b**.

On the basis of experimental results and density functional theory calculation, a putative mechanism of transformation is derived (Scheme 5). All optimized geometries of local minima and transition states were optimized using ωB97XD/6-31g(d,p) level of theory, and stationary point geometries of reactants, intermediates, products, and transition states were characterized by harmonic vibrational frequencies. The transition states and corresponding reactants and products they connect were confirmed by following the intrinsic reaction coordinate (IRC) method. All calculations were carried out using Gaussian 16 software package.[11] Mechanistically, the syntheses of compounds **4**, **5**, and **6** are interrelated. Compounds **4** and **6** are generated under blue LED (as depicted in Scheme 5), and the calculated free energies for their formation are depicted in plots a and b of Scheme 5, respectively. Compound **5** is obtained by deprotection of **6** (R = *tert*-BuO) in with 10% TFA-DCM at r.t. According to the mechanism, the diazo intermediate **2** under blue LED provided the carbene **3**, which underwent cyclopropanation with the indole moiety to afford **A** through **TS1** (Scheme 5). The calculated free energy from ωB97XD/6-31g(d,p) level of theory revealed that the process is barrierless and highly exothermic (−58.26 kcal/mol) (plot b, Scheme 5). When R = H or Me, in **A**, the lone pair of electrons on the indole nitrogen destabilizes the cyclopropyl ring, which opens up to provide **B** (plot b, Scheme 5). The hydride transfer from C2 of indole to the adjacent carbocation afforded compound **4** with reaction energy −78 kcal/mol (Scheme 5). With acyl substitution on **A**, the cyclopropane formation is barrierless and highly energonic (−63.2 kcal/mol) (plot a, Scheme 5). Since the lone pair on

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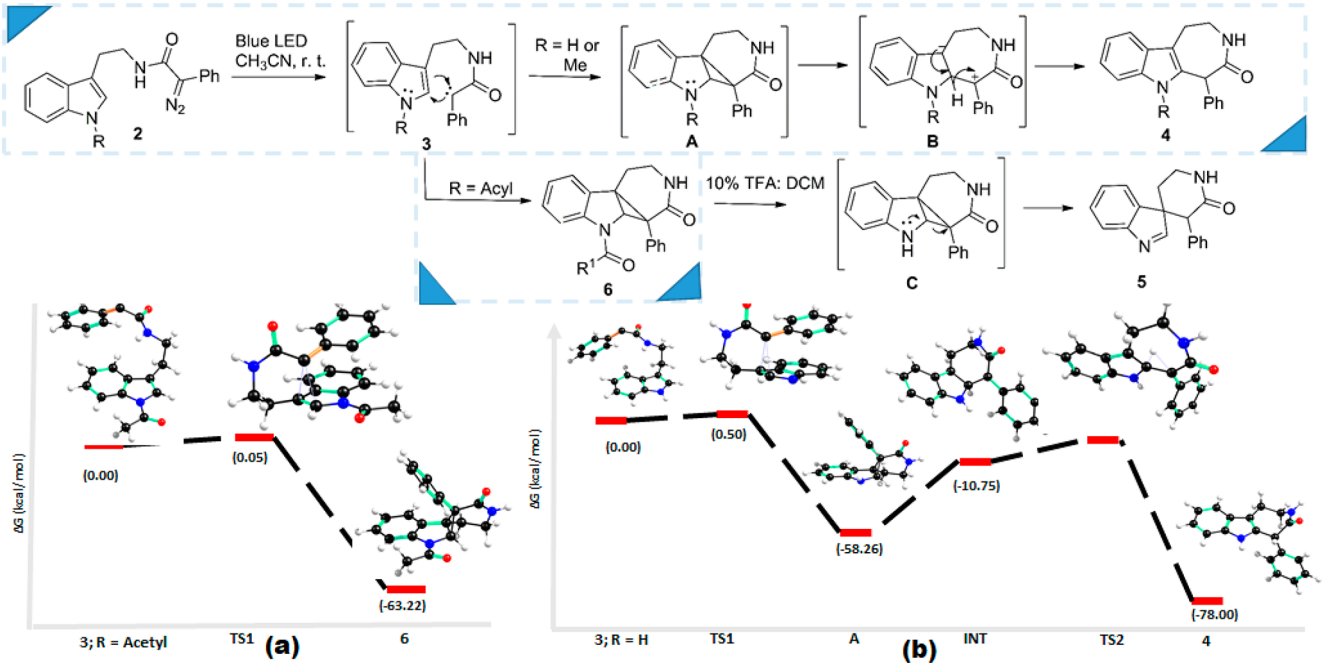
Scheme 5. Mechanism of Formation of 4, 5, and 6[a]



[a]Free energy profile of the reaction (formation of **4a**) calculated at ωB97XD/6-31G(d,p) level of theory. All values are given in kcal/mol.

the indole nitrogen here is in conjugation with the acyl moiety, the cyclopropane ring is more stable to provide **6**.

In summary, we accomplished intramolecular C−H functionalization and cyclopropanation of tryptamine derivatives by blue LED to afford azepino[4, 5-b]indole and polycyclic indoles in moderate to good yields under mild reaction condition. The donor−acceptor type polycycles allowed further transformation to spiropiperidino indoles in excellent yield. These natural product like molecules generated through this strategy are presently being screened against various phenotypes to identify their biological activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01559.

Optimization details, mechanistic experiments, experimental procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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