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PHOTOINDUCED INTRAMOLECULAR C–N COUPLING FOR THE SYNTHESIS OF AZOLO[1,2,4]BENZOTHIADIAZINES DERIVATIVES

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Dedicated to Emeritus Professor Roberto Arturo Rossi

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Supporting information for this article is given via a link at the end of the document.

Abstract: This paper explores an original synthesis of novel heterocyclic compounds derived from photoinduced intramolecular coupling reactions, involving the formation of C-N and C-C bonds. Specifically, two classes of compounds were targeted: 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazines and 5-amino-6-thia-4,5*a*-diazaacephenanthrylenes. The synthetic strategy involved nucleophilic substitution reactions to prepare key sulfonamide starting substrates, followed by photoinduced cyclization (via the Substitution Radical Nucleophilic Unimolecular, $S_{RN}1$) under mild conditions using visible light. The scope of the reaction was explored with different substituent groups on the starting materials, which demonstrated moderate to very good product yields, with 13 examples and yields of up to 78%. Moreover, this strategy represents the first synthetic approach to obtain 5-amino-6-thia-4,5*a*-diazaphenanthrylenes.

Introduction

1,2,4-Benzothiadiazines (**1**, Figure 1) is a group of cyclic sulfonamides that have significant pharmacological applications, with antimicrobial, antitumor, antiviral and antidiabetic activities and AMPA receptor modulation, among others.[1] In particular, 5,5-dioxo-5,1-dihydro[1,2,4]triazolo[1,5-*b*]-[1,2,4]benzothiadiazine arylsulfonamide (**2**, Figure 1) and 5,5-dioxo-5,10-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]benzothiadiazines derivatives (**3**, Figure 1) have been reported as potent antibacterial agents and antiproliferative agents, respectively. [2 3]

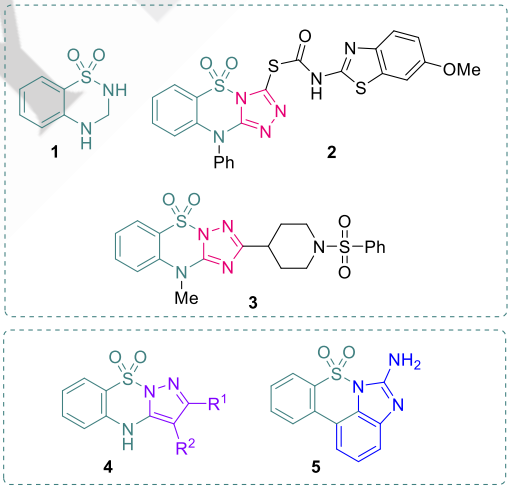

Figure 1. Examples of different cyclic sulfonamide moieties.

Recognizing the importance of these heterocycles, we are interested in preparing derivatives of 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]-thiadiazine 9,9-dioxide derivatives (**4**, Figure 1) and 5-amino-6-thia-4,5*a*-diazaacephenanthrylene 6,6-dioxide (**5**, Figure 1). In 1975, the synthesis of **4** was described through consecutive reduction-cyclization reactions of 1-((2-nitrophenyl)sulfonyl)-1*H*-pyrazole-5-amines (**6**, Scheme 1) with Fe(s) powder and glacial acetic acid at 70 °C for 120 min.[4] Other strategies described the intramolecular formation of the C-N bond from 1-((2-aminophenyl)sulfonyl)-1*H*-pyrazole-5-ol (**7a**) and 1-((2-aminophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrazole-5-ol (**7b**) (Scheme 1).[5] While these latter methods yield acceptable results, they require the use of strong reaction conditions, such as high temperatures (70°C) and the presence of strong acids (HCl). In

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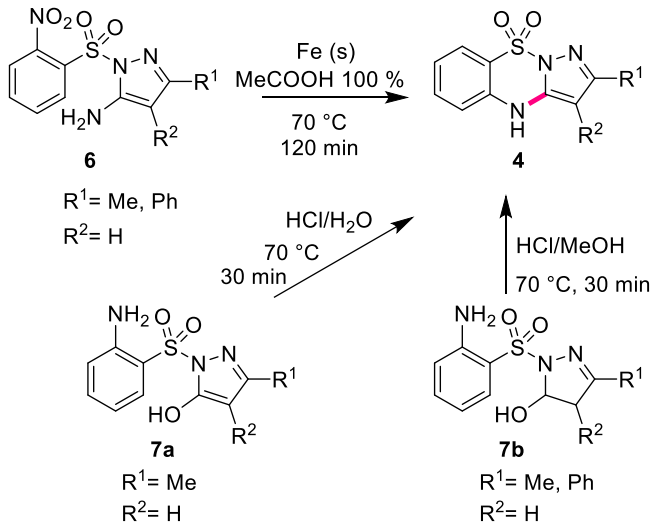
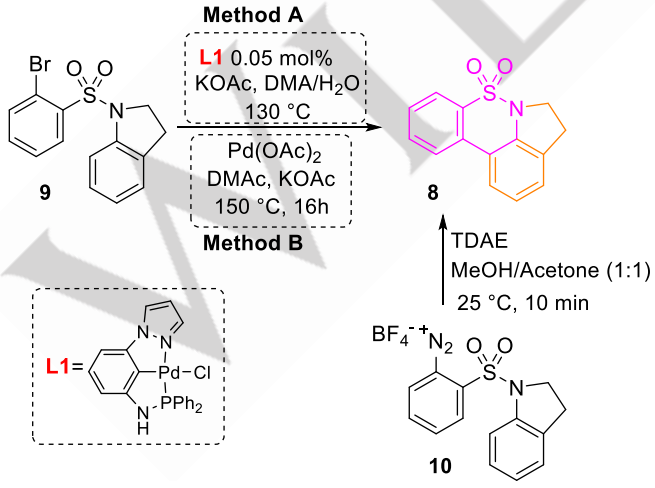
this context, the development of a general, versatile synthetic strategy under milder reaction conditions is desirable.



Scheme 1. Strategies to synthetize benzopyrazolothiadiazines **4**.

Currently, there are no bibliographic reports related to the biological activity or synthesis of **5**. However, tetracyclic systems similar to **5,** such as benzothiazinoindoline **8** (Scheme 2), have been synthesized. For example, **8** was prepared via palladium-catalyzed intramolecular arylation of *N*-(o-bromobenzenesulfonyl)indoline **9** at high temperatures and over extended reaction times (Methods A and B, Scheme 2).[6] Another approach involves intramolecular arylation through the generation of aryl radicals from 2-(2,3-dihydroindol-1-sulfonyl)-benzenediazonium tetrafluoroborate (**10**) using tetrakis-(dimethylamino)ethylene (TDAE) as a reducing agent. Although this methodology was carried out at room temperature, several reaction byproducts were produced (Scheme 2).[7]



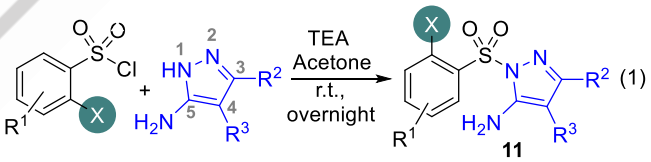
Scheme 2. Strategies to synthetize **8**.

Chemical reactions that use visible light have aroused significant scientific interest in the search for more sustainable synthetic methodologies. [8] Among the various synthetic alternatives that involve electron transfer (ET) and visible light processes, $S_{RN}1$ reactions are some of the most noteworthy.[9] In particular, such as $S_{RN}1$ intramolecular reaction, is a strategy with which a wide diversity of heterocycles have been obtained. [10] This methodology involves designing the substrate with the leaving group and the nucleophilic center on the same molecule at a suitable distance from each other, in order to generate the desired cyclic product through an intramolecular C-C or C-N coupling. Using these intramolecular arylation reactions, alkaloids such as aporphine and homoporphine (C-C),[11] 9*H*-carbazoles (C-N[12] y C-C[13]), carbolines (C-C),[14] pyrido-1,2-benzimidazoles (C-N),[15] and dibenzothiazines (C-C),[16] among others, have been efficiently synthesized.

In this context, we have developed a mild and general protocol for the synthesis of 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazines (**4**) and 5-amino-6-thia-4,5*a*-diazaacephenanthrylenes (**5**), derived from the photoinduced intramolecular coupling of 1-((2-halophenyl)sulfonyl)-3-alkyl-1*H*-pyrazol-5-amines and 1-((2-halophenyl)sulfonyl)-1*H*-benzo[*d*]imidazol-2-amines, respectively. Both these protocols involve the synthesis of precursors that can be easily obtained from commercial and accessible sources.

Results and Discussion

The synthetic strategy involves, as first step, the construction of sulfonamides **11** via a nucleophilic substitution reaction. The compounds **11** were obtained starting from 2-halobenzenesulfonyl chloride substituted with different 5-aminopyrazoles, using triethyl amine (TEA) as base in acetone at room temperature, with stirring performed overnight (eq 1).



It is important to note that 5-aminopyrazoles are bidentate nucleophiles, implying that they have two possible sites, for forming new bonds when reacting with various electrophiles: on the nitrogen at position 1, and the amino group at position 5. In this way, unknown 16 sulfonamides were prepared (**11a-n**) from the formation of the N-S bond at 1-position of the 5-aminopyrazole, with regular to very good yields (13-74% isolated yield, Table S2). Furthermore, sulfonamides resulting from the formation of the N-S bond at the 5-position of the 5-aminopyrazole were also observed as secondary products (with yields between 10 and 40% depending on the starting reagents).[4,17]

First, the photostimulated reaction was studied using 1-((2-bromophenyl)sulfonyl)-3-methyl-1*H*-pyrazol-5-amine (**11a**) as the model substrate. The desired product **4a** was obtained in 24% yield together with unreacted substrate when the reaction was carried out using 3 equiv. of KO^{t}Bu in dry dimethyl sulfoxide (DMSO) after 5 minutes of irradiation using green-LEDs (entry 1, Table 1). Then, motivated by this result, different reaction times were evaluated. When the reaction was irradiated for 15 minutes

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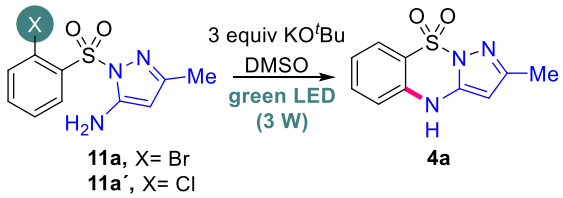
under the same conditions, **4a** was obtained in a similar yield of 28% (entry 2, Table 1). In this case, the conversion was also incomplete. Complete conversion with a 53% yield of **4a** was achieved when the reaction was irradiated for 30 minutes (entry 3, Table 1). Moreover, a detriment to the yield was observed when the reaction was carried out with 2 or 1 equiv. of base (entries 4-5 vs 3, Table 1). Furthermore, an increase in the amount of base (4 and 5 equiv. of KO^{t}Bu) did not improve the yield of product **4a** (entries 6-7, Table1), probably due to the *N*-desulfonylation reaction of the starting substrate **4a** with the excess base.[18] Next, other bases were examined (entries 8-10, Table 1). When NaH and KOH were employed, lower yields of **4a** were observed, (45% and 39% yield, respectively, entries 8-9, Table 1). The reaction did not proceed when KO^{t}Bu was replaced with K_2CO_3, and the unreacted substrate was recovered (entry 10, Table 1). It is well established that the KO^{t}Bu anion is an efficient electron donor in photostimulated ET reactions.[19] However, when the reaction was carried out in the absence of KO^{t}Bu anions, using NaH as a base, the product **4a** was obtained in a 45% yield (entry 8, Table 1). This indicates that the cyclized product is not generated by ET from KO^{t}Bu anions.

The evaluation of a variety of solvents revealed that the reaction medium has a significant impact on the yield of **4a**. For example, **4a** was obtained in only 26% yield when the reaction was carried out in dimethylformamide (DMF), with the presence of unreacted substrate not being observed (entry 11, Table 1). Furthermore, another solvent, tetrahydrofuran (THF), was also examined, and no conversion to the cyclization product was obtained, with **11a** recovered in 44% yield (entry 12, Table 1).

Moreover, no product was obtained in the photostimulated reaction when no base was used (entry 13, Table 1), indicating that a photoinduced homolytic C-X cleavage is not involved in the reaction mechanism. The reaction was partially inhibited by radical traps, such as di-*tert*-butyl nitroxide (DTBN) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (entries 14-15, Table 1). The addition of 30 mol% of DTBN and TEMPO resulted in the inhibition of 47% and 32% of the reaction, respectively.[20] Also, when the reaction was carried out with the addition of 30 mol % of the electron acceptor, such *p*-dinitrobenzene (*p*-DNB), an inhibition of 25% was observed (40% of **4a**, entry 16, Table 1). Similarly, the addition of 60 mol% of *p*-DNB inhibited the reaction by 64% (19% of **4a**, entry 17, Table 1). The Nucleophilic Aromatic Substitution (S_NAr) displacement of a nitro group can be observed with different nucleophiles due to their strong electron-accepting character.[21] Consequently, the reaction was carried out with the addition of 60 mol% of *m*-DNB, which is a substrate that has the same electron affinity (same electron acceptor character as *p*-DNB) but is less reactive towards S_NAr. A similar behavior was observed, with the reaction being inhibited by 77% (12% of **4a**, entry 18, Table 1). These results suggest that radicals (as evidenced by inhibition in the presence of DTBN and TEMPO) and ET processes (as evidenced by inhibition in the presence of *p*-DNB and *m*-DNB) are involved in the reaction mechanism, leading to the formation of **4a**. All this indicates that cyclized product is not generated through a benzyne mechanism or polar reactions.

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



11a, X= Br
11a´, X= Cl

4a

Entry	Conditions	Yield of 4a (%)[b]
1	3 equiv. KO^{t}Bu, DMSO, 5 min,	24
2	3 equiv. KO^{t}Bu, DMSO, 15 min	28
3[c]	**3 equiv. KO^{t}Bu, DMSO, 30 min**	**53**
4	2 equiv. KO^{t}Bu, DMSO, 30 min	45
5	1 equiv. KO^{t}Bu, DMSO, 30 min	26
6	4 equiv. KO^{t}Bu, DMSO, 30 min	25
7	5 equiv. KO^{t}Bu, DMSO, 30 min	14
8	3 equiv. NaH, DMSO, 30 min	45
9	3 equiv. KOH, DMSO, 30 min	39
10[d]	3 equiv. K_2CO_3, DMSO, 30 min	--
11	3 equiv. KO^{t}Bu, DMF, 30 min	26
12[e]	3 equiv. KO^{t}Bu, THF, 30 min	--
13	DMSO, 30 min	--
14	3 equiv. KO^{t}Bu, DMSO, 30 min, 30 mol % TEMPO	28
15	3 equiv. KO^{t}Bu, DMSO, 30 min, 30 mol % DTBN	36
16	3 equiv. KO^{t}Bu, DMSO, 30 min, 30 mol % *p*-DNB	40
17	3 equiv. KO^{t}Bu, DMSO, 30 min, 60 mol % *p*-DNB	19
18	3 equiv. KOtBu, DMSO, 30 min, 60 mol % *m*-DNB	12
19[f]	3 equiv. KO^{t}Bu, DMSO, 30 min	30
20	3 equiv. KO^{t}Bu, DMSO, 30 min, without irradiation	-
21	3 equiv. KO^{t}Bu, DMSO, 30 min, **white LED**	43
22	3 equiv. KO^{t}Bu, DMSO, 30 min, blue LED	50
23	3 equiv. KO^{t}Bu, DMSO, 30 min, **HPI-T**	43
24	3 equiv. KO^{t}Bu, DMSO, 30 min, **green LEDs (40W)**	43

[a] Reactions were carried out under an N_2 atmosphere using **11a** (1 equiv, 0.05 mmol), base and solvent (0.8 mL). Samples were irradiated using green-LED (3 W, 522 nm), unless otherwise stated. [b] Yields were quantified by ^{1}H NMR using 4-nitroacetophenone as standard. [c] Complete conversion. [d] Substrate

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11a recovered in c.a. 100% yield. [e] Substrate **11a** recovered in 44% yield. [f] Substrate **11a´** was employed instead of **11a**.

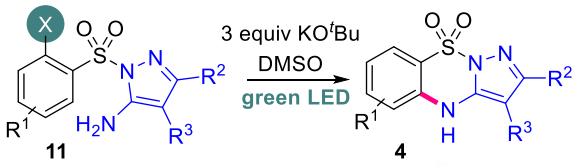
When the leaving group was changed to chlorine (substrate **11a´**), a lower yield of **4a** was obtained under the same reaction conditions (30%, entry 19 vs 3, Table 1), which is consistent with the reactivity order observed for ET reactions (Br > Cl).

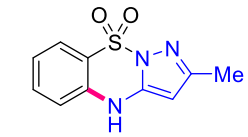
Finally, to study the impact of the light properties on the photocyclization reaction, the reaction was carried out using different irradiation sources under the optimal reaction conditions previously found using green LED (entry 3, Table 1). First, no reaction occurred under dark conditions (without irradiation, entry 20), showing that light is a key reactant for the reaction to proceed at room temperature. In addition, white (λ=350 nm, 3 W) and blue LEDs (λ= 467 nm, 3 W) were also effective and resulted in 43% and 50% yields of **4a**, respectively (entries 21-22 vs 3, Table 1). Furthermore, for irradiation with high-power lamps such as HPI-T metal iodide (400 W, λ ≥ 350 nm) or several green LED lamps in series with a final power of 40 W (see Figure S3 of the supporting information), a yield of 43% of **4a** was observed in both reactions (entries 23-24, Table 1). It should be noted that all the irradiation sources evaluated (blue-, green-, white-LEDs) and the different lamp powers (3 W, 40 W and 400 W) resulted in similar yields of **4a**.

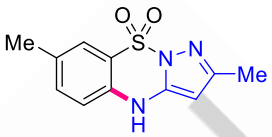
Once the optimal reaction conditions were determined (Table 1, entry 3), we focused on exploring the scope of C-N intramolecular coupling to synthesize the 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazine 9,9-dioxide core. As shown in Table 2, the nature of functional groups on the sulfonyl ring (R^1) and pyrazole ring (R^2 – R^3) were evaluated. Under the explored reaction conditions, both electron-withdrawing groups (EWG) and the electron-donating group (EDG) were examined, and yields were affected by the electronic properties of these substituents. In particular, the reaction worked well when the R^1 group on the sulfonyl ring was a hydrogen or an EWG and with R^2 and R^3 being EDG (Table 2, **4a**, and **4c-l**), giving the cyclization products in 26% to 78% yields. However, when R^1 was an EDG, the reaction did not occur and the product **4b** (R^1 = 7-Me) was not formed. In the same way, when R^2 and R^3 were EWG by a resonance effect, such as a phenyl substituent (**4m**) or Br substituent (**4n**), the reaction did not occur and decomposition products were obtained.

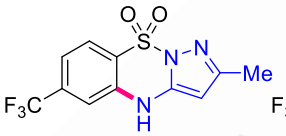
Based on the experimental results, two possible mechanisms involving electron transfer reactions are conceivable for this intramolecular C−N arylation. The reaction of substrate **11** with KO^{t}Bu in excess would afford anion **11**$^-$ (Scheme 3). Then, depending on the initiation step, two pathways are possible (Paths **A** or **B**). The first possibility is an intermolecular ET (Path **A**), which yields product **4** by an $S_{RN}1$ mechanism,[9] with the second possibility being an intramolecular ET (Path **B**) that gives the pyrazolothiadiazine product **4** through nucleophilic aromatic substitution via electron transfer, S_N(ET)Ar.[22,23] If $S_{RN}1$ reaction takes place, the photoinduced ET from donor to anion **11**$^-$ produces a radical dianion (**11**$^-$)$^{\bullet-}$. The donor species could be the photoexcited anion (**11**$^-$)* or dimsyl anion.[24] Fragmentation of the C-X bond of (**11**$^-$)$^{\bullet-}$ produces the distonic radical anion **12**$^{\bullet-}$ and the X$^-$ anion. The intermediate radical anion **12**$^{\bullet-}$, via an intramolecular C-N arylation, yields the conjugated radical anion

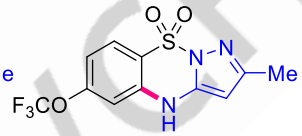
Table 2. Synthesis of **4a–n** under the optimized reaction conditions.[a,b]



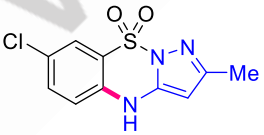

4a, (X = Br, 53 %)
4a, (X = Cl, 30%)

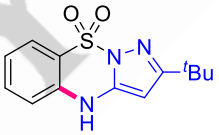

4b, (X = Br, n.d.%)

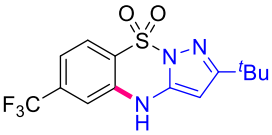

4c, (X = Br, 50 %)

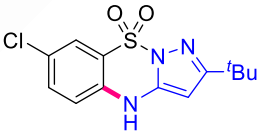

4d, (X = Br, 51%)

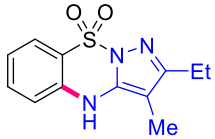

4e, (X = Cl, 47%)
4e, (X = Br, 45%)[c]

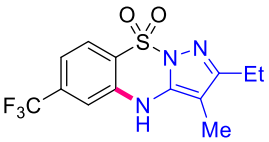

4f, (X = Cl, 30%)

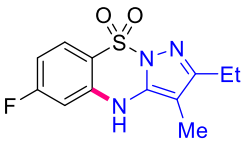

4g, (X = Br, 43%)

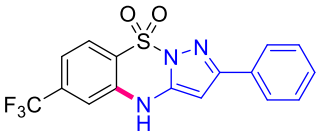

4h, (X = Br, 29%)

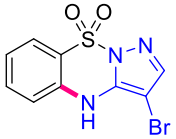

4i, (X = Cl, 36%)


4j, (X = Br, 40%)
4j, (X = Cl, 26%)


4k, (X = Br, 55%)


4l, (X = Cl, 78%)


4m, (X = Br, n.d.%)


4n, (X = Br, n.d.%)

[a] Reactions were carried out under an N_2 atmosphere using **11** (1 equiv, 0.2 mmol), KO^{t}Bu (3 equiv, 0.6 mmol) in DMSO (4 mL) and by irradiation with green LED. The isolated yields are presented in the experimental section. [b] Yields were quantified by ^{1}H NMR using 4-nitroacetophenone as standard. n.d.: not detected. [c] Isolated yields

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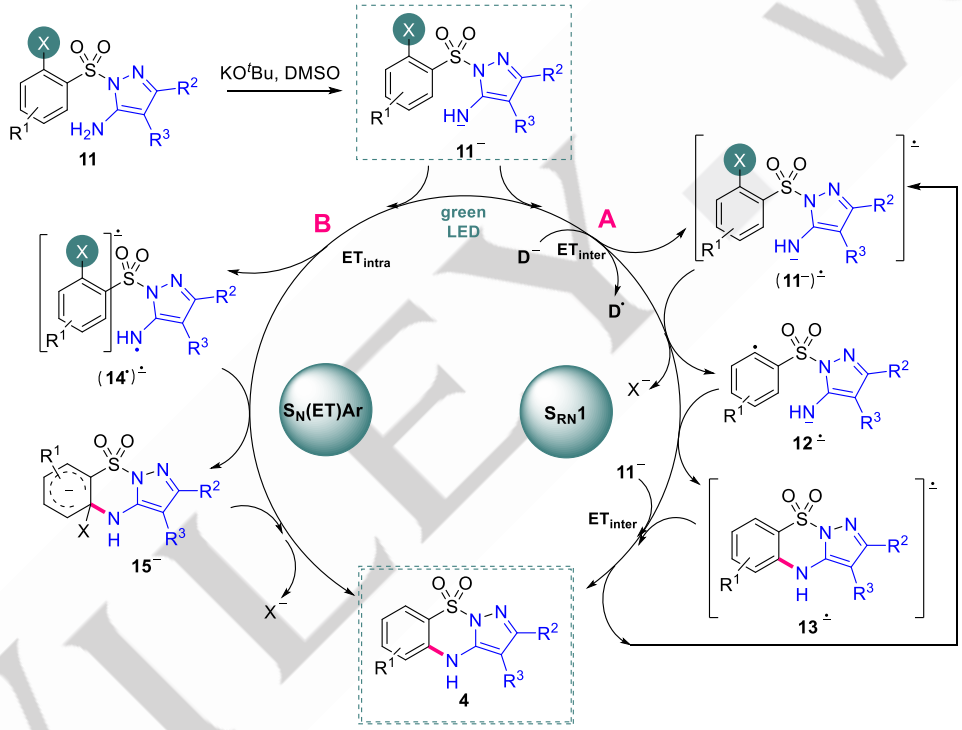
13$^{\bullet-}$. An ET from **13**$^{\bullet-}$ to **11**$^{-}$ produces product **4** and radical dianion (**11**$^{-}$)$^{\bullet-}$, propagating a chain reaction (Scheme 3, Path **A**).

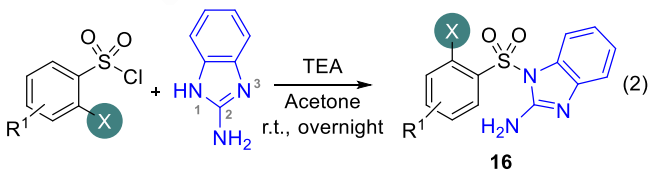
On the other hand, if S_N(ET)Ar takes place, an intramolecular ET from anion **11**$^{-}$ occurs, and the pyrazolyl radical and the sulfonyl aryl halide radical anion are formed (**14**$^{\bullet}$)$^{\bullet-}$ (Scheme 3, Path **B**). This intermediate quickly reacts through radical-radical coupling, yielding a discrete nonaromatic Meisenheimer complex intermediate **15**$^{-}$, which finally undergoes C-X fragmentation to give product **4**. Unlike the $S_{RN}1$ mechanism, the S_N(ET)Ar mechanism does not occur through a chain mechanism.

Taking into account that the reaction requires a short time (30 min) and that similar yields were obtained when different irradiation sources were used, it is likely that a chain mechanism such as $S_{RN}1$ is taking place. In efficient chain processes (with chains longer than 1), yields depend on the chain length. While a propagating radical molecule forms, a specific yield is obtained. In these processes, an efficient initiation step is not necessary since small amounts of initiator radicals allow the chain cycle to start.[9] This implies that different irradiation sources can be used because irradiation at the maximum wavelength of a species is not critical. Conversely, in a non-chain mechanism such as the S_N(ET)Ar mechanism, the source wavelength used must irradiate the substrate anion (**11**$^{-}$). On the other hand, the absorption spectrum of anion **4a** shows an absorption maximum at λ = 349 nm (Figure S4), while the dimsyl anion (formed from the acid-base reaction between DMSO and a strong base such as KO^{t}Bu or NaH, eq S2) absorbs throughout the visible spectrum (Figure S5). This suggests that the dimsyl anion is the electron donor species in the initiation step leading to the cyclized product.[24]



Scheme 3. Different Possible Mechanisms for C-N arylation reaction of **11.**

To expand the scope of this synthetic approach, the reactivity of 1*H*-benzo[*d*]imidazole-2-amine to obtain the sulfonylation products **16** in position 1 (N-1) was examined (eq 2).[25] Consequently, by employing the same methodology used for the synthesis of precursor **11**, the sulfonamides **16a-c** were obtained starting from different substituted 2-halobenzenesulfonyl chloride and 1*H*-benzo[*d*]imidazol-2-amine, resulting in very good to excellent isolated yields (73-96%, eq 2, Table S3).



Likewise, 1-((2-halophenyl)sulfonyl)-1*H*-benzo[*d*]imidazol-2-amine **16a-c** were evaluated as substrates using the methodology described above (Table 3). When 1-((2-bromophenyl)sulfonyl)-1*H*-benzo[*d*]imidazol-2-amine (**16a**) or 1-((2-bromo-4-(trifluoromethyl)phenyl)sulfonyl)-1*H*-benzo[*d*] imidazole-2-amine (**16b**) were employed as substrates, C-C bond cyclization products were obtained, yielding 5-amino-6-thia-4,5*a*-diazaacephenanthrylene 6,6-dioxide (**5a**) and 5-amino-9-(trifluoromethyl)-6-thia-4,5*a*-diazaacephenan-thrylene 6,6-dioxide (**5b**) in yields of 69% and 32%, respectively, after 6 hours of reaction. In addition, when the substituent in the sulfonyl rings was R^1 = 5-Cl (**16c**), the dehalogenated cyclization product **5a** was obtained in 32%.

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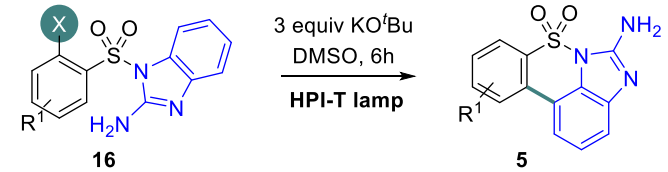
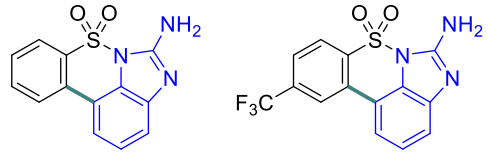
Table 3. Synthesis of 5-amino-6-thia-4,5*a*-diazaacephenanthrylene 6,6-dioxide derivatives (**5a–b**) under the optimized reaction conditions.[a,b]





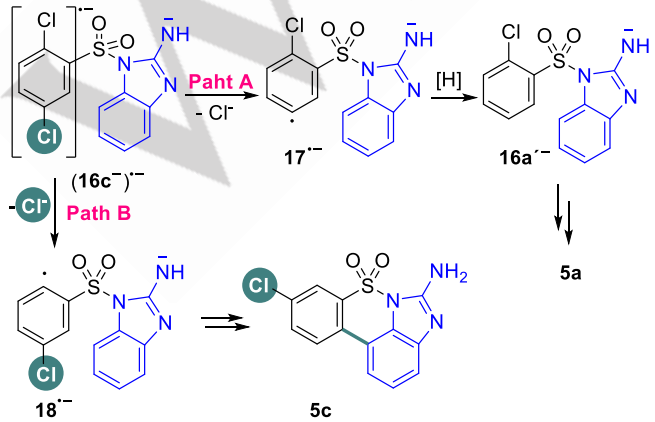
5a (X= Br, 69% from **16a**)
(X= Cl, 42% from **16c**)

5b, 32%

[a] Reactions were carried out under an N_2 atmosphere using **16a-c** (1 equiv., 0.2 mmol), KO^{t}Bu (3 equiv., 0.6 mmol) in DMSO (4 mL) and irradiated with an HPI-T lamp for 6 hours at room temperature. [b] Yields were quantified by ^{1}H NMR using 4-nitroacetophenone as standard.

In contrast with the reactivity observed in sulfonamides derived from aminopyrazole (**11**), which produces the cyclization product **4** through the formation of the C–N bond, amines derived from benzimidazole (**16**) formed the product **5** through C–C coupling. This behavior was observed in similar systems, where the C-N or C-C bond was formed via intramolecular $S_{RN}1$, depending on the conformer structure of the starting anion.[26]

Furthermore, when the substituent in the sulfonyl rings was R^1 = 5-Cl (**16c**), the dehalogenated cyclization product **5a** was obtained in 32% (Table 3). Once the dianion radical (**16c**$^-$)$^{\bullet-}$ is formed, it can cleave either of its two C-Cl bonds: the one *meta* to the sulfonyl group to form radical anion **17**$^{\bullet-}$ (Path **A**, Scheme 4), or the one *ortho* to the sulfonyl group to form radical anion **18**$^{\bullet-}$ (Path **B**, Scheme 4). Radical anion **17**$^{\bullet-}$, upon reduction in the reaction medium, produces anion **16´a**$^-$, which ultimately yields cyclic product **5a**. Alternatively, if the formation of radical anion **18**$^{\bullet-}$ is faster than that the formation of radical anion **17**$^{\bullet-}$, we would expect to observe the halogen-retaining product **5c**. Taking into account that only the formation of product **5a** was observed, we suspect that Path **A** is the one that is operating.



Scheme 4. Proposed mechanism for the formation of product **5a** from **16c.**

Conclusions

To conclude, a novel synthetic strategy using intramolecular reactions induced by visible light has been developed, which has proven to be effective for the synthesis of 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazines and 5-amino-6-thia-4,5*a*-diazaacephenanthrylenes. This process employs *N*-heteroarylbenzenesulfonamides as starting substrates, does not require the use of transition metals, and is promoted by KO^{t}Bu in DMSO as solvent, operating at room temperature with short reaction times. In addition, it demonstrates good tolerance to different functional groups and achieves yields of up to 78%. This methodology provides a milder and more sustainable approach to the synthesis of 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazines compared to traditional methods, thus making it an attractive synthetic alternative. Furthermore, to the best of our knowledge, this strategy represents the first synthetic report for obtaining 5-amino-6-thia-4,5*a*-diazaacephenanthrylenes, a tetracyclic heterocycle, in only two reaction steps from accessible and commercially available substrates.

Experimental Section

1.1 General Considerations

Purification of the synthesized compounds was made by column chromatography on silica gel or by High Performance Liquid Chromatography (HPLC) preparative. Gas Chromatographic (GC) analysis was conducted using a flame-ionization detector and a 30 m capillary column with dimensions of a 0.32 mm x 0.25 µm film thickness, with a 5% phenylpolysiloxane phase. Gas Chromatography-Mass Spectroscopy (GC-MS) analysis utilized an Electronic Impact (EI) ionization method and 30 m capillary column of a 0.32 mm×0.25 µm film thickness, with a 5% phenylpolysiloxane phase. Melting points were measured with an Electrothemal IA9000 melting point apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 400.16 MHz spectrometer using acetone-d_6 (CD_3COCD_3), dimethyl sulfoxide-d_6 (CD_3SOCD_3) or chloroform-*d* ($CDCl_3$, TMS as internal standard) as solvents. Coupling constants are given in Hz, and chemical shifts are reported in δ values in ppm. The data are presented as follows: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, ddd = double double doublet, m = multiplet), coupling constants (Hz), and integration. The unknown products were characterized using high-resolution mass spectrometry (HRMS). HRMS analyses were carried out using a time-of-flight mass spectrometry (TOF-MS) instrument with an electrospray ionization (ESI) source. Photostimulated reactions were carried out with blue LED (λ= (467 ± 20) nm), green LED (λ= (522 ± 20) nm) and white LED (λ=350 nm ± 20) nm) lights functioning at 3 W of potency and 700 mV (Figure S1), or HPI-T 400 W lamps of metallic iodide (λ ≥ 350 nm) cooled with water (Figure S2). The apparatus and irradiation setup are shown in Figure S3.

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Materials

2-Chlorobenzenesulfonyl chloride, 2-bromobenzenesulfonyl chloride, 2-chloro-4-fluorobenzenesulfonyl chloride, 2,5-dichlorobenzenesulfonyl chloride, 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride, 3-methyl-1*H*-pyrazol-5-amine, 3-(*tert*-butyl)-1*H*-pyrazol-5-amine, 3-ethyl-4-methyl-1*H*-pyrazol-5-amine, 3-phenyl-1*H*-pyrazol-5-amine, 4-bromo-1*H*-pyrazol-5-amine, 2-bromo-4-(trifluoromethoxy)aniline, *m*-toluidine, 2-aminobenzimidazole, pyridine, *N*-bromo succinimide (NBS), potassium ethyl xanthate (KEX), KO^{t}Bu, NaH, K_2CO_3, KOH, NH_4NO_3, $NaNO_2$, HCl, EtOH, anhydrous Na_2SO_4, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), *p*-dinitrobenzene (*p*-DNB), *m*-dinitrobenzene (*m*-DNB), di-*tert*-butyl nitroxide (DTBN), triethylamine (TEA), and 4-nitroacetophenone were purchased from commercial suppliers and used without further purification. Acetone, ethyl acetate and dichloromethane (DCM) were previously distilled. DMSO, DMF (dimethylformamide), THF (tetrahydrofuran), MeCN (acetonitrile) and ethyl acetate were distilled and dried under molecular sieves (4 Å). MeOH and MeCN HPLC were previously filtered. All solvents were of analytical grade. The silica used in the column chromatography corresponds to silica gel 60 (0.063–0.200 mm). 2-Bromo-5-methylaniline was prepared according to a procedure in the literature.[27]

General procedures for the synthesis of substrates.

Synthesis of 1-((2-halophenyl)sulfonyl)-1*H*-pyrazol-5-amines 11a-n: Acetone (5 mL) and 2-halobenzenesulfonyl chloride (1.0 equiv., 1.0 mmol) were placed in a Schlenk tube. After purging the system with N_2, 1*H*-pyrazol-5-amine (1.0 equiv., 1.0 mmol) and triethylamine (1.0 equiv., 1.0 mmol) were added. The reaction mixture was stirred for 12 hours at room temperature. Once the reaction time was completed, the mixture was extracted with DCM (3 x 30 mL) and washed with distilled water (2 x 20 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, and filtered. The resulting organic phase was concentrated under reduced pressure to remove volatile compounds. The crude product was then purified by column chromatography on silica gel and subsequently recrystallized from an appropriate solvent.

Synthesis of 1-((2-halophenyl)sulfonyl)-1*H*-benzo[*d*]imidazol-2-amine substituted 16a-c: A solution of 2-aminobenzimidazole (1.0 equiv., 0.5 mmol) and triethylamine (1.0 equiv., 0.5 mmol) in 1.5 mL of acetone was added dropwise to a solution of 2-halobenzenesulfonyl chloride (1.0 equiv., 0.5 mmol) in 1.0 mL of acetone. The mixture was stirred for 12 hours at room temperature, the solvent was distilled off, and the crude was extracted with ethyl acetate (3 x 30 mL) and washed with distilled water. The organic phases were combined, dried over anhydrous Na_2SO_4, and filtered. The resulting organic phase was concentrated under reduced pressure to remove volatile compounds. The crude product was then purified by recrystallization from an appropriate solvent.

General procedures for the synthesis of products in DMSO.

Synthesis of 4*H*-benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazine 9,9-dioxide 4a,c-l and 12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*b*][1,2,4]thiadiazine 5,5-dioxide substituted 5a-b.

The reactions were carried out in a vial under an N_2 atmosphere, equipped with magnetic stirring at room temperature, and irradiated with green LEDs for 3 hours (compounds **11a-n**) or HPI-T lamps for 6 hours (compounds **16a-c**). Each reaction used 1.0 equivalent (0.1 mmol) of the appropriate sulfonamide (**11a-n** or **16a-c**) and 3.0 equivalents of KO^{t}Bu (0.3 mmol) in DMSO (2.0 mL, previously dried and deoxygenated). Once the reaction was complete, it was quenched with NH_4NO_3 and water in excess. The residue was then extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with distilled water (2 x 20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude products. These products were then purified by column chromatography on silica gel or preparative HPLC. Yields were quantified by ^{1}H NMR using 4-nitroacetophenone as the internal standard.

Supporting Information

The General Procedures and Equipment, materials, characterization data, UV-vis spectra for substrate **11a**, the corresponding anion **11a**$^-$, and dimsyl anion, copies of ^{1}H and ^{13}C NMR spectra of compounds **11a-n**, **4a**, **4c-l**, **16a-c** and **5a-b**, as well as the spectroscopic studies, Table S1-S5 and Figures S1-S5 are presented in the Supporting Information, where the authors have cited additional references.[28-29]

Acknowledgements

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Keywords: electron transfer • heterocylces • photoinduced cyclization • sulfonamides • visible light

References and Notes

§ Both authors contributed equally to this study.

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$$\%\ inhibition = \left(1 - \frac{yield\ in\ presence\ of\ the\ inhibitor}{yield\ in\ absence\ of\ the\ inhibitor}\right) \times 100$$

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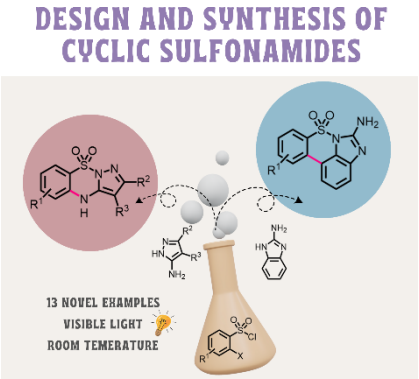

The synthesis of 4*H*-Benzo[*e*]pyrazolo[1,5-*b*][1,2,4]thiadiazines and 5-Amino-6-thia-4,5*a*-diazaacephenanthrylenes derivatives by photoinduced intramolecular coupling from of 1-((2-halophenyl)sulfonyl)-3-alkyl-1*H*-pyrazol-5-amines and 1-((2-halophenyl)sulfonyl)-1*H*-benzo[*d*]imidazol-2-amines is presented. The synthetic protocol uses only KO^{t}Bu and DMSO to generate aryl radicals at room temperature. The reaction was explored with different substituents groups on the starting materials, demonstrating moderate to good products yields, with 13 examples and yields of up to 78%.

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