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Synthesis of novel fused azaheterocycles by photostimulated intramolecular $S_{RN}1$ reactions with nitrogen nucleophiles

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ABSTRACT

The synthesis of pyrrole, indole, and pyrazole fused azaheterocycles is presented. The anions of carboxamides (**6** and **12**) and pyrazolylamines (**15a–b**) react under photostimulation by an intramolecular $S_{RN}1$ process to yield fused azaheterocycles with good to excellent yields. We report on an efficient two-step synthesis of new fused azaheterocycles derived from pyrrole, indole, and pyrazole, as well as the synthesis of their precursors. By the reaction of carboxamides (**6** and **12**) and pyrazolylamines (**15a–b**) with a base, the corresponding anion could be formed. Then, by an intramolecular photostimulated $S_{RN}1$ reaction, the fused azaheterocycles were achieved (54–100%).

Nitrogen-containing heterocycles constitute the main structure within a large number of natural products and many pharmacologically active compounds. Primarily, condensed heterocyclic compounds play increasingly important roles as synthetic building blocks, and also as pharmacophores.[1] Fused azaheterocycles comprise a family of biological agents with particularly interesting pharmacological properties related to planarity of the system and consequently to its DNA-chain intercalating ability, which make them suitable for anti-neoplastic or mutagenic applications.[2] Due to their significant biological activity, azaheterocycles are an important class of heterocyclic compounds in medicinal chemistry.

As a result of azaheterocycles intensive application in bio-organic chemistry, the search for new efficient methods for their synthesis represents an active field of interest. Recent synthetic routes to quinolinone heterocycles have involved strategies based on the Baylis–Hillman adduct followed by a Friedel–Crafts cyclization from Baylis–Hillman acid and arylamines[3] or Diels–Alder cyclization of *exo*-diene lactams and followed by aromatization.[4] Alternatively, to obtain heterocycles derived from isoquinolines, aryl iodide with bromoalkyl pirazole in a palladium-catalyzed reaction was used.[5] Triazolo-isoquinolines were synthesized by the reaction of 2,3-diaminoisoquinolinium salts with aldehydes by a ring closure.[6]

On the other hand, the unimolecular radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which an aromatic nucleophilic substitution is achieved by a chain reaction with radical and radical anions as intermediates. Since the scope of this mechanism has broadened considerably over the last decades, nowadays it serves as an important synthetic strategy.[7] The initiation step is an electron transfer (ET) from suitable donors (i.e., the nucleophile or a base) to the substrate to afford a radical anion. In some systems, the ET step is spontaneous. However, in other systems light, electrons from alkali metals dissolved in liquid ammonia or from a cathode, or inorganic salts (i.e., Fe^{+2} or SmI_2) can initiate the reaction. Several nucleophiles such as carbanions and heteroatom anions can be used in $S_{RN}1$ reactions to form new C–C or C-heteroatom bonds in good yields. An exception to this is the reaction of aromatic amide ions with aromatic substrates. In these cases, the formation of both C–N and C–C bonds is achieved instead, and the regiochemistry of the reaction depends on the substrates and nucleophiles.[8,9]

The anion of azaheterocycles such as pyrrole reacted with chloroarenes by a cathode-induced reaction, to give mainly arylation in the position two (52–67%) with a 3–14% arylation in position three of the pyrrole moiety.[10]

Additionally, the anion of 4-methylimidazole also reacted with chloroarenes in similar experimental conditions to afford 4-methyl-5-aryl-1*H*-imidazole and 4-methyl-2-aryl-1*H*-imidazole in a ratio of 4:1.[11]

Furthermore, to synthesize heterocyclic compounds by the $S_{RN}1$ reaction, a straightforward synthetic strategy was developed. Cyclic products could be obtained by an intramolecular reaction, when a substrate having both, the leaving group and the nucleophilic center, was used.[12] This method has been recently applied to the synthesis of 1-phenyl-1-oxazolino-indan derivatives and related compounds,[13] to the synthesis of aporphine and homoaporphine alkaloids by *ortho*-arylation of phenoxide ions,[14] and to the synthesis of phenanthridines and benzophenanthridines by intramolecular *ortho*-arylation of aryl amide ions with aryl halides.[15]

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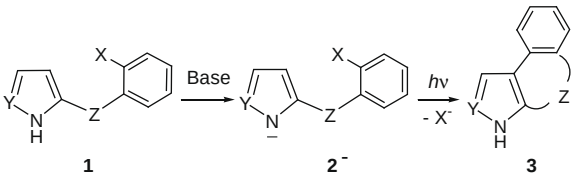
So far, there has been no instance of the intramolecular arylation of pyrrole anion and related azaheterocycle ions with a pendant aryl moiety which contain an appropriate leaving group to obtain fused azaheterocycles through the $S_{RN}1$ mechanism. The methodology could be a useful tool for the preparation of novel condensed azaheterocyles. The synthetic strategy involves the reaction of suitable pyrrole containing substrate **1** with a base to yield nitrogen anion **2**$^{-}$. Upon photostimulation and work-up in acidic conditions, fused azaheterocyles may be obtained (compound **3**, Eq. 1).

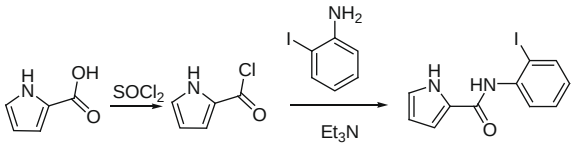


1 **2**$^{-}$ **3** (1)

Thus, herein we report on an efficient two-step synthesis of new fused azaheterocycles derived from pyrrole, indole, and pyrazole, and the synthesis of the precursors required.

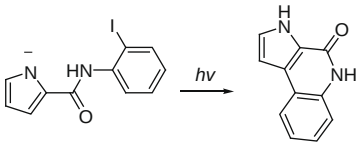
As the pyrrole nucleus is present in many compounds with biological activities,[16] we chose a derivative of this azaheterocycle with suitable substituents to probe the synthetic strategy. In a one-pot, two-step process, the precursor *N*-(2-iodophenyl)-1*H*-pyrrole-2-carboxamide (**6**) was synthesized. From the commercial 1*H*-pyrrole-2-carboxylic acid (**4**) we prepared the 1*H*-pyrrole-2-carbonyl chloride (**5**). After this, and by the reaction of **5** with 2-iodoaniline, carboxamide **6** was obtained with 60% overall isolated yield (Eq. 2).

Amide **6** has two acidic hydrogens, and since it is a new compound, we did not know the pK_a in liquid ammonia. However, considering that pyrrole has a pK_a of 17.5 in DMSO, and taking 3,4-dihydroquinolin-2(1*H*)-one, which has a pK_a of 20.7 in DMSO,[17] as a model of carboxamide **6**, we can assume that the pyrrole hydrogen will be the first to be deprotonated by the base.



4 **5** **6** 60 % overall yield (2)

Therefore, when substrate **6** (1 equiv) was treated with *t*-BuOK (2 equiv), anion **6**$^{-}$ was formed, and under irradiation (2 h) the new azaheterocycle 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one (**7**) was obtained in 68% isolated yield (Eq. 3) (Table 1, entry 1). In the same experimental conditions, however, after a 3 h irradiation, **7** was obtained in 100% yield (Table 1, entry 2).

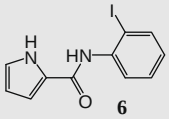
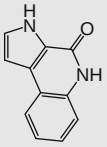
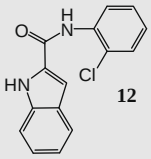
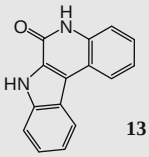
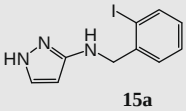
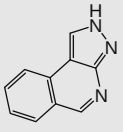
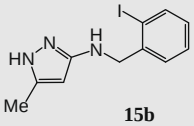
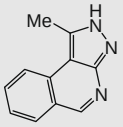


6^{-} **7** (3)

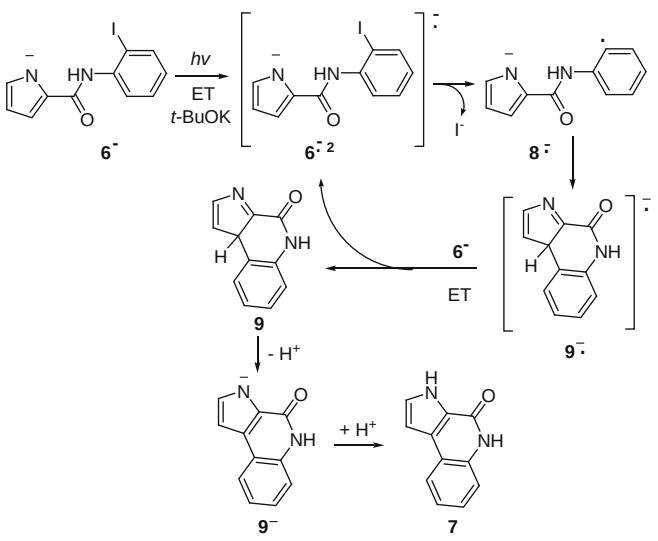
When the reaction was carried out in DMSO, azaheterocycle **7** was obtained in 53% isolated yield (2 h) and 83% yield after 3 h of irradiation (Table 1, entries 3 and 4). The reaction did not occur in the dark, and the photostimulated reaction was inhibited by 1,4-dinitrobenzene, a well-known inhibitor of $S_{RN}1$ reactions (Table 1, entries 5 and 6). On the basis of the lack of formation of product **7** in dark conditions, as well as, when the irradiated reaction was carried out in the presence of 1,4-dinitrobenzene, a $S_{RN}1$ mechanism can be proposed for this reaction (Scheme 1).

This reaction mechanism involved, in the first place, the reaction of **6** with *t*-BuOK in excess, which afforded amide ions **6**$^{-}$.

Table 1
Intramolecular photostimulated reactions of carboxamides (**6** and **12**) and pyrazolylamines (**15a–b**)[a]

Entry	Substrate	Solvent	Substrate recovered[b] (%)	Conditions	Product	Yield[b] (%)
1	 **6**	NH_3	25	*hv*, 2 h	 **7**	75 (68)
2		NH_3	–	*hv*, 3 h		100
3		DMSO	27	*hv*, 2 h		72 (53)
4		DMSO	–	*hv*, 3 h		83
5		DMSO	95	Dark, 2 h		–
6[c]		DMSO	100	*hv*, 2 h		–
7[d]	 **12**	NH_3	–	*hv*, 2.5 h	 **13**	83
8[d]		DMSO	–	*hv*, 2.5 h		94
9	 **15a**	NH_3	–	*hv*, 3 h	 **17a**	54
10	 **15b**	NH_3	–	*hv*, 3 h	 **17b**	56
11		DMSO	–	*hv*, 3 h		25

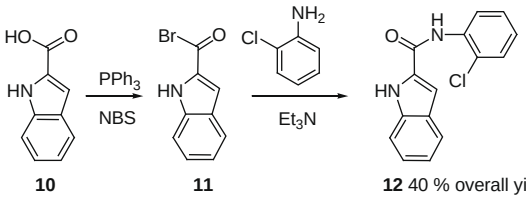
[a] The reactions were run in 200 mL of liquid ammonia or 7 mL of DMSO, with 1 equiv of the substrate (0.25 mmol) and 2 equiv of *t*-BuOK (0.5 mmol) and irradiated.
[b] Yields were determined by GC (internal standard method). Isolated yields are given in parentheses.
[c] 20 mol % of 1.4-dinitrobenzene was added. The substrate was 100% recovered.
[d] 1 equiv of **12** and 2.5 equiv of *t*-BuOK were used.



Scheme 1.

The initiation step of the $S_{RN}1$ reaction was the photoinduced ET to $\mathbf{6}^-$ yielding the radical dianion $\mathbf{6}^{2-\cdot}$.[18] The subsequent fragmentation of the C–I bond of $\mathbf{6}^{2-\cdot}$ gave the distonic radical anion $\mathbf{8}^-$and I^- ion. The intermediate radical anion $\mathbf{8}^-$, via an intramolecular process, yields the conjugated radical anion $\mathbf{9}^-$.[19] An ET from $\mathbf{9}^-$ to $\mathbf{6}^-$ affords the intermediate **9** and the radical dianion $\mathbf{6}^{2-\cdot}$, which propagates the chain reaction. Therefore, under the basic reaction conditions, intermediate **9** led to anion $\mathbf{9}^-$, which upon acidification of the reaction media and work-up gives product **7**.

With similar approach, from the commercial 1*H*-indole-2-carboxylic acid (**10**) bromide acid **11** was prepared. Then, by the reaction of **11** with 2-chloroaniline in a one-pot two-step process, *N*-(2-chlorophenyl)-1*H*-indole-2 (**12**) was obtained in 40% overall isolated yield (Eq. 4).

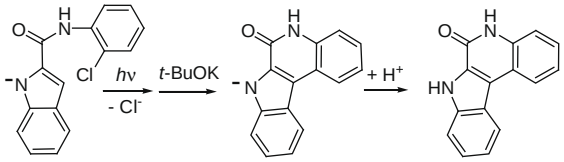


(4)

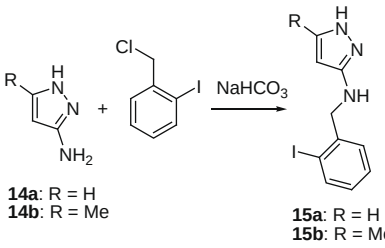
As with the pyrrole precursor **6**, the pK_a of the indole (pK_a = 16.9 in DMSO)[17] seems to be smaller than the pK_a of the corresponding amide. Thus, the indole hydrogen will be the first to be deprotonated by the base. In the photostimulated reaction of anion $\mathbf{12}^-$ (2.5 h), formed by the acid base reaction of **12** with *t*-BuOK (2.5 equiv) in liquid ammonia, 83% of the ring closure product 5*H*-indolo[2,3-*c*]quinolin-6(7*H*)-one (**13**) was formed after the acidification of the reaction mixture (Eq. 5) (Table 1, entry 7). Similarly, the photostimulated reaction of anion $\mathbf{12}^-$ in DMSO (2.5 h) afforded 94% yield of fused heterocycle **13** (Table 1, entry 8).

Since the pyrazole nucleus is an important heterocyclic system with a wide variety of biological activities,[20] we extended the application of the synthetic strategy developed to fused heterocycle derivatives of pyrazole. The approach involved the reaction of the commercial 1*H*-pyrazol-3-amine (**14a**) and 5-methyl-1*H*-pyrazol-3-amine (**14b**) with 1-(chloromethyl)-2-iodobenzene to give *N*-(2-iodobenzyl)-1*H*-pyrazol-3-amines **15** (Eq. 6), but with an isolated yield of 30% for both.

The pK_a of pyrazole is 28.8 in DMSO,[17] and probably more acidic than the benzyl-pyrrolylamine moiety. Thus, when substrates **15** were treated with 2 equiv of *t*-BuOK in liquid ammonia, anions $\mathbf{15}^-$ were formed (Eq. 7).

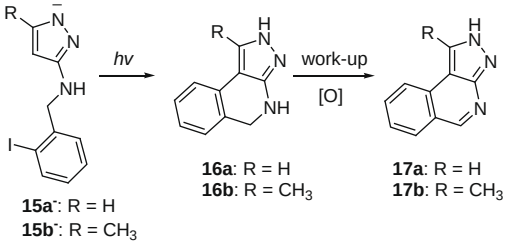


(5)



(6)

When the reaction mixtures were irradiated (3 h), the fused 2*H*-pyrazolo[3,4-*c*]isoquinoline (**17a**) and 1-methyl-2*H*-pyrazolo[3,4-*c*]isoquinoline (**17b**) were obtained (Table 1, entries 9 and 10). Upon acidification of the reaction media and after the work-up, products **16** were not isolated, whereas the spontaneously oxidized aromatized products **17** were obtained (Eq. 7).



(7)

When the photostimulated reaction of **15b** was carried out in DMSO, the yield was only 25% (Table 1, entry 11). It is important to notice that in all reactions with pyrazole derivatives remained substrate were not found, and the dehalogenation was complete (100% of I^- ions), which indicated the total conversion of the substrate. As the nucleus of pyrazole is quite sensitive to light,[21] we believe that precursor $\mathbf{15}^-$ and/or products **16** are partially destroyed by the irradiation. Nevertheless, yields of 54–56% of fused azaheterocycles **17** were obtained.

We have shown that the photostimulated intramolecular reactions of anions derived from pyrrole, indole, and pyrazole with a pendant aromatic moiety with a suitable leaving group in liquid ammonia afford novel fused azaheterocycles in good to excellent yields by the $S_{RN}1$ mechanism. The starting materials to prepare the precursors of the fused azaheterocycle products are easily obtained. Considering the availability and/or simplicity of the starting materials, and the readiness and mild conditions of the procedures, we have demonstrated that this can be a general methodology for the synthesis of this family of compounds.

Acknowledgments

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Supplementary data

Supplementary data (general experimental details and procedures, and also characterization of **6**, **7**, **12**, **13**, **15** and **17**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.042.

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18. The possibility of an intramolecular ET from the pyrrole anion to the iodoarene cannot be ruled out. The fact that the reaction is inhibited by 1,4-DNB indicates that radical anions are intermediates. Probably *t*-BuO$^-$ ion (pK_a of *t*-BuOH is 32.2 in DMSO) is a better electron donor than pyrrole ion of lower pK_a, see Ref. 17.
19. The conjugated radical anion **9**$^-$ is ca 43 kcal/mol more stable than the distonic radical anion **8**$^-$ (AM1/UHF method), this being the driving force of the coupling reaction.
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