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Syntheses of phenanthridines and benzophenanthridines by intramolecular *ortho*-arylation of aryl amide ions with aryl halides via $S_{RN}1$ reactions

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Dedicated to Professor Miguel Yus on the occasion of his 60th anniversary

Abstract—The photostimulated reaction of *N*-(2-halo-benzyl)aryl amines with *t*-BuOK in liquid ammonia affords fused azaheterocycles by the $S_{RN}1$ mechanism. The starting materials are easily obtained by the reaction of 2-halo-benzyl chloride and aromatic amines to prepare the secondary amines. Through this approach, phenanthridine (90%), 4-phenylphenanthridine (87%), benzo[*a*]phenanthridine (98%), and benzo[*c*]phenanthridine (84%) were synthesized.

Fused azaheterocycles are a family of biological agents with particularly interesting pharmacological properties related to the planarity of the system and consequently to its DNA-chain intercalating ability, which make them suitable for anti-neoplastic or mutagenic applications.[1]

Due to their significant biological activity, these are an important class of heterocyclic compounds in medicinal chemistry.

Substituted phenanthridines and benzo[*c*]phenanthridines, an important class of heterocyclic compounds in medicinal chemistry, are attractive synthetic targets due to their widespread occurrence in nature and broad range of biological, including anti-tumor and anti-viral activity.[2–4] This has led to the search for new synthetic methods that would facilitate the preparation of an appropriate series of compounds.[5] However, many of the benzophenanthridine synthetic processes have shown certain disadvantages: numerous steps, low yields, or poor generality. Thus, a synthesis suitable for both these compounds and also their analogues is required.

Nitroarylstannanes have been used as intermediates for the preparation of phenanthridine and benzophenanthridine derivatives.[6] Recently it has been reported that aromatic aldehydes reacted with anilines and benzenediazonium-2-carboxylate to afford 6-aryl-phenanthridines via a one-pot cascade process.[7] A method to synthesize benzo[*c*]phenanthridine was then developed using nickel- or palladium catalyzed iminoannulation of an internal alkyne.[8]

In the present study, we explore the synthesis of phenanthridines, benzophenanthridines and related derivatives employing photostimulated coupling of suitable precursors.

The radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which an aromatic nucleophilic substitution is achieved. Since the scope of this process has increased considerably over the last decades, nowadays it serves as an important synthetic strategy.[9] 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 others light, electrons from dissolved alkali metals in liquid ammonia, from a cathode, or inorganic salts (i.e., Fe^{+2} or SmI_2) can initiate the reaction.

Keywords: $S_{RN}1$; Phenanthridine; Benzophenanthridine; Photostimulated reactions.
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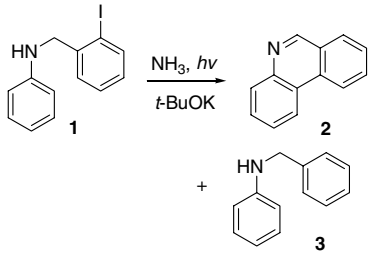
Several nucleophiles such as carbanions and heteroatom anions can be used for $S_{RN}1$ reactions to form new C–C or C-heteroatom bonds in good yields. An exception to this is the reaction of aromatic amide ions with aromatic substrates. In these cases, C–N and C–C bond formation is achieved instead. For instance, the reaction of phenylamide with PhI initiated by K metal in liquid ammonia affords diphenylamine (19%), and 2- (11%) and 4-biphenyl amines (11%).[10]

2-Naphthylamide ions initiate the photo $S_{RN}1$ process of PhI, 4-$MeOC_6H_4I$, and 1-iodonaphthalene in liquid ammonia. Here, 1-aryl 2-naphthylamines are formed regioselectively in 45–63% yields, with 3–6% of *N*-arylation.[11]

When a substrate has both the leaving group and the nucleophilic center, the *intramolecular* reaction affords a cyclic product.[12] This method has been recently applied to the synthesis of 1-phenyl-1-oxazolino-indan derivatives and related compounds,[13] and to the synthesis of aporphine and homoaporphine alkaloids by *ortho*-arylation of phenoxide ions.[14]

So far, there is no instance of the intramolecular arylation of the aromatic amide ions with a pendant aryl moiety to obtain fused azaheterocycles. The starting materials are easily obtained by the reaction of 2-halobenzyl chloride and aromatic amines to prepare the secondary amines.

The substrate *N*-(2-iodobenzyl)benzenamine (**1**) was prepared by standard procedures in 85% yield.[15] In the dark (180 min), there was no reaction of **1** and *t*-BuOK in excess in liquid ammonia under a nitrogen atmosphere. However, under irradiation (30 min), phenanthridine (**2**) was obtained in 56% yield, and the reduced product *N*-benzyl-benzenamine (**3**) was achieved in 2% yield (Eq. 1).



(1)

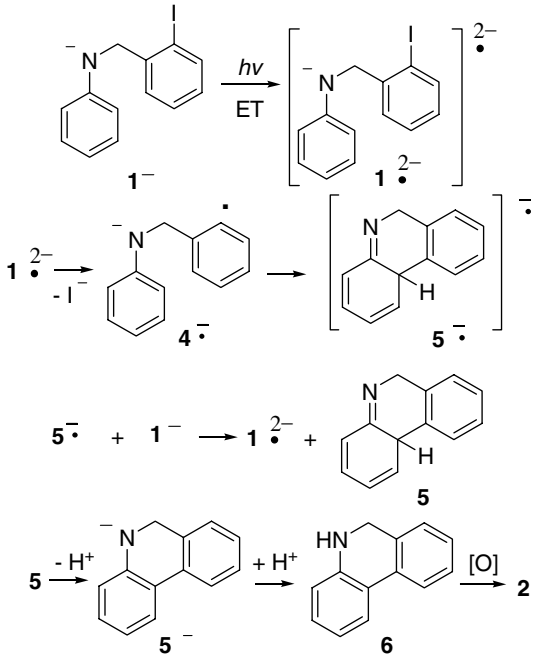
After 120 min of irradiation, **2** and the reduced product **3** were obtained in 90% and 9% yields, respectively. The reaction was partially inhibited by *p*-dinitrobenzene (*p*-DNB), a well-known inhibitor of $S_{RN}1$ processes (Table 1), however, the reaction was not inhibited by radical traps, such as di-*tert*-butyl nitroxide or TEMPO.[16] In DMSO as a solvent, **2** and the reduced product **3** were obtained in 68% and 18% yields, respectively. All these results indicate that the reaction occurs by the $S_{RN}1$ mechanism, as depicted in Scheme 1.

The reaction of **1** with *t*-BuOK in excess affords the amide ions $\mathbf{1}^-$. The initiation step is the photoinduced ET to $\mathbf{1}^-$ yielding the radical dianion $\mathbf{1}^{2-\bullet}$.[17] Fragmentation of the C–I bond of $\mathbf{1}^{2-\bullet}$ gives the distonic radical anion $\mathbf{4}^{-\bullet}$ and I^- ion. The intermediate radical anion $\mathbf{4}^{-\bullet}$, via an intramolecular process, yields the conjugated radical anion $\mathbf{5}^{-\bullet}$.[18] An ET from $\mathbf{5}^{-\bullet}$ to $\mathbf{1}^-$ affords the intermediate **5** and the radical dianion $\mathbf{1}^{2-\bullet}$, which propagates the reaction. The intermediate **5** gives anion $\mathbf{5}^-$ under these basic reaction conditions. Upon acidification of the reaction media and work up, product **6**

Table 1. Synthesis of fused azaheterocycles[a]

Expt[a]	Substrate	Conditions	X^-[b] (%)	Products[c,a] (yield %)
1	**1**	Dark, 180 min	—	[d]
2[e]	**1**	*hv*, 30 min	56	**2** (56), **3** (2)
3	**1**	*hv*, 120 min	97	**2** (90), **3** (9)
4[f]	**1**	*hv*, 120 min	38	**2** (32), **3** (2)
5[g]	**1**	*hv*, 120 min	97	**2** (68), **3** (18)
6[h]	**1**	*hv*, 120 min	89	**2** (85), **3** (8)
7[i]	**1**	*hv*, 120 min	88	**2** (88), **3** (4)
8	**7**	*hv*, 180 min	95	**8** (87), **9** (10)
9	**10**	*hv*, 120 min	101	**11** (98)
10[j]	**12**	*hv*, 180 min	96	**13** (84), **14** (8)

[a] The substrate (1 equiv) and *t*-BuOK (2.5 equiv) in 200 mL of anhydrous liquid ammonia N_2 atmosphere, unless otherwise indicated. Irradiation was conducted in a photochemical reactor equipped with two 400-W Hg lamps emitting maximally at 350 nm (air and water refrigerated).
[b] The halides were determined potentiometrically.
[c] The products were determined by GLC, unless otherwise indicated.
[d] The substrate was recovered almost quantitatively.
[e] The substrate was recovered in 38%.
[f] *p*-DNB was added (27 mol %). The substrate was recovered in 39%.
[g] The solvent was DMSO.
[h] Di-*tert*-butyl nitroxide was added (30 mol %).
[i] TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added (38 mol %).
[j] The reduced product was observed (3%).

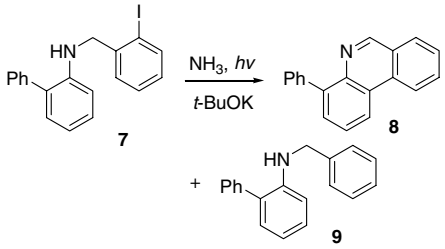


Scheme 1. Mechanism of the cyclization–oxidation processes.

was not isolated, whereas the oxidized aromatized product **2** was.

A reaction that competes with the cyclization of the radical anion $\mathbf{4}^{-\cdot}$ is the reduction of this ion by hydrogen abstraction from the solvent to yield **3**.

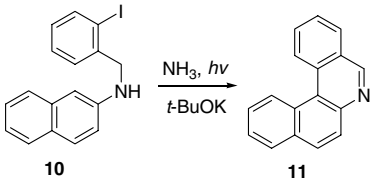
With biphenyl-2-amine, substrate **7** was prepared (82%), and in the photostimulated reaction, it afforded 87% of 4-phenylphenanthridine (**8**) and a small amount of the reduced product **9** (Eq. 2). Employing the same procedure, *N*-(2-iodobenzyl) naphthalen-2-amine (**10**) was prepared (80% yield) with 2-naphthyl amine as a substrate. In the photostimulated reaction (120 min) with an excess of *t*-BuOK in liquid ammonia, benzo[*a*]phenanthridine (**11**) was obtained in 98% yield (Eq. 3).[19]



(2)

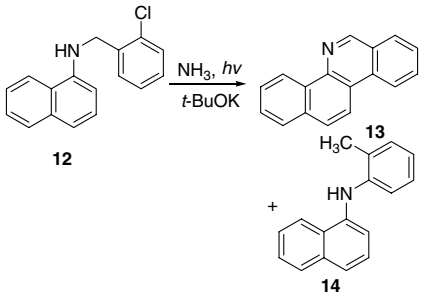
With the substrate *N*-(2-chlorobenzyl)naphthalen-1-amine (**12**), obtained in 91% yield, under 180 min of irradiation, the expected ring closure product benzo[*c*]phenanthridine (**13**) was formed in 84% yield, and rearranged product **14** in a small amount (8%) (Eq. 4). The same result was observed with *N*-(2-iodobenzyl)naphthalen-1-amine.

The rearranged product **14** may be obtained by the reaction of the distonic radical anion intermediate $\mathbf{15}^{-\cdot}$ with the nucleophilic N to form the radical anion $\mathbf{16}^{-\cdot}$, which by ring opening, yields the radical anion $\mathbf{17}^{-\cdot}$, as a result of the stability of the diaryl amide moiety and the benzyl radical (Eq. 5). By H abstraction and after protonation, $\mathbf{17}^{-\cdot}$ affords the product **14** observed. There is a precedent that cyclic radical anions can suffer ring opening to give benzyl radicals and the nucleophilic center.[20]

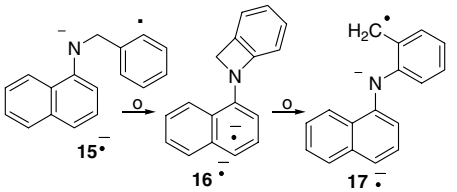


(3)

The occurrence of the coupling reaction on N with substrate **12** rather than **10** may be due to the fact that with **10**, the aromatic radical reacts with the position one of the naphthalene ring, while with substrate **12**, the aromatic radical has to react with the position two of the naphthalene ring, and it is known that the position one is more reactive toward radicals than the position two.



(4)



(5)

We have shown that the photostimulated reactions of several *N*-(2-halo-benzyl)aryl amines with *t*-BuOK in liquid ammonia afford fused azaheterocycles with excellent yields by the $S_{RN}1$ mechanism. The starting materials are easily obtained by the reaction of 2-halobenzyl chloride and aromatic amines to prepare the secondary amines. Considering the availability and/or simplicity of the starting materials, and the readiness and mild conditions of the procedure, we have demonstrated that this can be a general methodology for the synthesis of this family of compounds. Further studies are in progress in order to optimize the synthesis of fused azaheterocycles with aromatic and heteroaromatic amines, and also to examine the possibility of polysubstitution.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.009.

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16. This suggests that the intramolecular reaction of the radical anion $\mathbf{4}^{-\cdot}$ is faster than the intermolecular reaction with radical traps.
17. The possibility of an intramolecular ET from the amide moiety to the iodoarene cannot be ruled out since, without excess of *t*-BuO-ions, the reaction still occurs. The fact that the reaction is inhibited by *p*-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 phenylamide ions (pK_a of $PhNH_2$ is 30.6 in DMSO), see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463, and references cited therein.
18. The conjugated radical anion $\mathbf{5}^{-\cdot}$ is ca. 39 kcal/mol more stable than the distonic radical anion $\mathbf{4}^{-\cdot}$ (AM1/UHF method), this being the driving force of the coupling reaction.
19. Although there are two non-equivalent *ortho*- positions to the amide group, the intramolecular reaction affords **11** regiospecifically. Ab initio calculations are in progress to inspect the electronic and geometric factors responsible for this regiochemistry.
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