RECENT DEVELOPMENTS IN THE SYNTHESIS OF AROMATIC HETEROCYCLES BY $S_{RN}1$ AND RELATED MECHANISMS

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Abstract. *Results from recent developments of ring closure reactions that afford heterocycles by the $S_{RN}1$ mechanism are presented. However, in other cases the reaction can occur by related radical mechanisms or undetermined mechanisms, and thus the interpretation of the latter required more investigation.*

Contents

1. Introduction

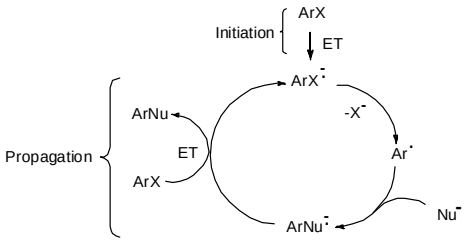
Heterocyclic compounds are abundant in natural products, pharmaceuticals and bioactive molecules, and are widely used in industrial chemistry (agrochemicals, colorants, plastics, etc.), with many pharmacological compounds containing heterocyclic rings, for instance, and approximately 70% of all agrochemicals that have been introduced to the market have at least one heterocyclic ring.[1] These applications make the synthesis of heterocycles of particular interest, especially the search for new and improved methods.

Radical reactions have been more utilized lately, with radical synthesis becoming more common and radical cyclization providing a new pathway in the synthesis of many heterocyclic compounds. In recent years, $S_{RN}1$ and related mechanisms have been shown to be important tools for the synthesis of heterocycles free of transition metals, thereby proving greener and more sustainable techniques. In this chapter, we will describe recent advances in the construction of aromatic heterocycles by radical ring closure reactions using $S_{RN}1$ and related mechanisms. The scope and limitations of these cyclization reactions are discussed, as well as their mechanisms.

The chapter has been organized into intermolecular $S_{RN}1$ reactions followed by a polar ring closure reaction; intramolecular $S_{RN}1$ reactions and ring closure with formation of C-N, C-O or C-S bonds; 5-*exo* or 6-*endo* ring closure reactions followed by a $S_{RN}1$ reaction; and miscellaneous ring closure processes.

Nucleophilic substitution reactions are possible through processes that involve electron transfer (ET) steps, and have been widely used to achieve new C-C or C-heteroatom bonds. The $S_{RN}1$ mechanism was first proposed for the substitution of alkyl halides bearing electron withdrawing groups (EWG) in the α-position and a suitable leaving group,[2,3] and was subsequently extended to unactivated aromatic halides.[4,5] Latter, other substrates were reported to react through this mechanism. Among these, the aromatic $S_{RN}1$ reactions have been by far the most widely utilized approach for the synthesis of heterocycles.

The aromatic $S_{RN}1$ reaction is a chain process. In the initiation step, the radical anion of the substrate $ArX^{\bullet-}$ is formed, which fragments to afford the radical $Ar^{\bullet}$ and the X^- ion. The radical thus formed can then react with the Nu^- to give the radical anion $ArNu^{\bullet-}$, which by ET to the substrate affords the substitution product ArNu and the radical anion $ArX^{\bullet-}$ required for continuing the propagation cycle (Scheme 1).



Scheme 1. The $S_{RN}1$ mechanism.

Few initiation steps are necessary if the propagation cycle is fast and efficient in order to afford a successful process of substitution. Inhibition by radical traps with stable free radicals [2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), di-*t*-butylnitroxide (DTBN), galvinoxyl, O_2, etc.] has been extensively used to provide mechanistic evidence. Inhibition with good electron acceptors such as *p*-

dinitrobenzene is taken as evidence of an ET process. Radical probes have also been used to demonstrate the formation of radicals during the propagation cycle, and products from ring closure, ring opening or from rearrangement of the radicals have been taken as evidence of the presence of these intermediates.

By far, the halides are the most used leaving groups. However, it is important to mention that ArOH and $ArNH_2$ substrates have potential leaving groups by the formation of their phosphate esters $ArOP(O)(OEt)_2$ and ammonium salts $Ar\text{-}NR_3^+$, respectively.

Carbanions are some of the most common nucleophiles through which a new C-C bond can be formed. C-C instead of C-O or C-N bond formation is achieved with nitranion and oxianion nucleophiles in intermolecular reactions. However, in intramolecular processes, C-O and C-N bonds could be formed.

Several reviews have been published with respect to the $S_{RN}1$ mechanism,[6-8] which have described aromatic photoinitiated substitutions and reactions performed under electrochemical catalysis,[9] as well as synthetic applications of the process. The $S_{RN}1$ reaction has become one of the most common methodologies in modern synthesis.[10,11]This chapter covers the basic research performed in the area, the mechanistic studies, and the recent synthetic strategies used for the syntheses of heterocycles by $S_{RN}1$ reactions. We also describe recent developments in this area, covering works published after our previous review on the synthesis of heterocycles by the $S_{RN}1$ mechanism,[11] with emphasis on the scope of the process in terms of synthetic capability and target applications.

2. Mechanism of the $S_{RN}1$ reactions

2.1. Initiation step

In the initiation step, an ET from the Nu^- (or other donors) to the ArX takes place. In some systems, spontaneous or thermal ET is a possible initiation step, which depends on the electron affinity of the substrate and the oxidation potential of the Nu^-.[12]

In most cases, induced ET is necessary to produce $S_{RN}1$ reactions, with different methodologies having been utilized to initiate these reactions, such as: (1) photostimulated reactions, (2) electrochemically induced reactions, (3) using solvated electrons from alkali metal in liquid ammonia, (4) using inorganic salts (usually Fe(II)), and (5) microwave (MW) or conventional heating.

Of these methods, photostimulation is by far the most commonly used method to initiate $S_{RN}1$ reactions. The initiation step by photoinduced ET can be performed using the followings mechanisms (1) homolytic cleavage of the C-X bond in the excited ArX; (2) ET from the Nu^- to the excited ArX (or from the excited Nu^- to the ArX), (3) ET within an excited charge transfer complex (CTC), among others. It is noteworthy that in some systems *t*-BuOK or other strong bases in DMSO can form $[ArX]^{\bullet-}$ by ET under irradiation.[13-15] Depending on the nature of the ArX, the $Nu^-$and the experimental conditions, the most appropriate mechanisms can be considered as the initiation step.

The electrochemical initiation method is applied in a number of cases with aromatic and heteroaromatic substrates. This approach allows a quantitative analysis of the mechanism, by determining the constant rate of fragmentation of anion radicals, and the absolute rate constant for a coupling reaction of the formed radical and the Nu^-; most of these types of reactions having been studied by the Savéant group.[9,16]

Another method of initiation of $S_{RN}1$ reactions is by using alkali metals (Na or K) dissolved in liquid ammonia. This type of initiation is important when substrates are capable of reacting by the benzyne mechanism, which over rides the $S_{RN}1$ reactions.[3,17] However, the main disadvantage of this type of initiation is the formation of the reduction product of the substrate and/or substitution products.

An alternative technique for initiation is the use of inorganic salts. Although to date several inorganic salts have been tested, Fe(II) salts (especially $FeSO_4$ in liquid ammonia and $FeCl_2$ or $FeBr_2$ in DMSO) have provided the best results of substitution.[18]

A few cases of thermally induced $S_{RN}1$ reactions by MW irradiation have been reported for the substitution of activated nitro benzyl derivatives. For example, Vanelle *et al.* observed that $S_{RN}1$ reaction of *p*-nitrobenzyl chloride with 2-nitropropane anion under MW irradiation using a domestic oven, affords very good coupling yields.[19]

Unreactive nucleophiles (Nu^{1-}) can react through *entrainment* conditions.[20] *Entrainment* is useful when Nu^{1-} is unreactive at initiation but quite reactive at propagation. If a nucleophile (here Nu^{2-}) is reactive at both initiation and propagation steps, it gives the substitution product Ar-Nu^2. In the reaction of ArX with Nu^{1-}, the Nu^{2-} could be added to increase the generation of radical intermediates by initiation events, this will allow the less reactive in the initiation step Nu^{1-} to establish its own propagation, managing the reaction condition to make the coupling with Nu^{1-} faster than with Nu^{2-}.[21]

2.2. Propagation steps

Although any of the reactive intermediates can initiate the chain reaction, the formation of the radical anion of the substrate $(ArX)^{\bullet -}$ is by far the more common initiation step. The main steps of the propagation chain are:

1. radical anion fragmentation of the substrate $ArX^{\bullet -}$ to give the $Ar^{\bullet}$ and X^- ions;
2. coupling of the radical with the Nu^- to yield the $ArNu^{\bullet -}$ radical anion;
3. ET from the $ArNu^{\bullet -}$ to the substrate ArX to yields $ArX^{\bullet -}$ to maintain the propagation cycle.

The fragmentation of the radical anion $ArX^{\bullet -}$ occurs through an intramolecular ET from the π^* molecular orbital (MO) to the σ^* MO of the C-X bond. These π^* and σ^* systems are adjacent and orthogonal and the main reaction coordinates for the intramolecular ET from the π^* MO to the σ^* MO, which dissociates into $Ar^{\bullet}$ radical and X^- ions, is the C-X bond elongation and bending with respect to the arene plane.[22]

Once $Ar^{\bullet}$ radicals are formed, they can couple with a variety of nucleophiles. The absolute rate constant of the coupling reaction of the $Ar^{\bullet}$ radical with different Nu^- has been determined electrochemically, and most of these reactions are close to the diffusional rate. For example, the coupling constants of $Ar^{\bullet}$ with the anions PhS^-, $^-PO(OEt)_2$, and $^-CH_2COMe$ in liquid ammonia are within the range 10^7-10^{10} M^{-1} s^{-1}.[23,24]

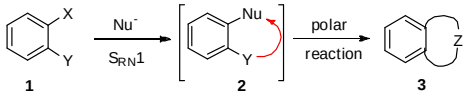
Once the radical anion of the substitution product $ArNu^{\bullet -}$ is formed, it should transfer the odd electron to the substrate to form the substitution product ArNu and the $ArX^{\bullet -}$ radical anion. For this to occur, the condition $E_{ArX/ArX^{\bullet -}} > E°_{ArNu/ArNu^{\bullet -}}$ must be hold, so that the ArX will be a better electron acceptor than ArNu. If the $E_{ArX/ArX^{\bullet -}} < E°_{ArNu/ArNu^{\bullet -}}$, the ET is thermodynamically unfavorable and this becomes the rate determining step. When this condition occurs, the termination steps become more favorable.

2.3. Termination steps

The $S_{RN}1$ mechanism has termination steps that depend on ArX, Nu^- and the experimental conditions. For instance, $Ar^\bullet$ can react with the solvent (S-H) through a hydrogen-atom abstraction reaction to yield Ar-H, or by ET to yield the anion Ar^-, which is protonated by S-H to afford Ar-H. Hydrogen abstraction from the solvent is always a competing reaction and poor hydrogen donor solvents, such as liquid ammonia or DMSO, are used to decrease the reduction products.

3. Intermolecular $S_{RN}1$ reactions followed by a spontaneous polar ring closure reaction

One of the strategies employed for the synthesis of heterocyclic compounds where one of the key steps is the $S_{RN}1$ reaction, is the use of precursors where *ortho* to the leaving group is a suitable substituent Y such as **1**. Precursor **1** by an $S_{RN}1$ reaction with Nu^- affords the substitution product **2**, which by a spontaneous polar reaction gives finally the ring closure product **3** (Scheme 2).

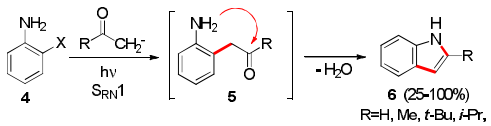


Scheme 2. Synthesis of heterocycles by tandem: $S_{RN}1$- ring closure polar reactions.

This methodology has been widely used in the synthesis of heterocycles with 5, 6 or more members that contain different heteroatoms, such as nitrogen, oxygen, sulfur and phosphorus.

3.1. Synthesis of five member heterocycles

Although numerous examples of synthesis of the indole nucleus are known, the methodology involving a $S_{RN}1$ reaction followed by a polar reaction is a versatile synthetic alternative. One of the most important examples is obtaining indoles **6** by reacting 2-haloanilinas **4** with enolates anions derived from aliphatic ketones and aldehydes (Scheme 3).[25] The reaction of **4** with enolate ions afforded the product **5,** which cyclized spontaneously in the reaction medium by dehydratation to give indoles **6** with different substituents in position two with moderate to high yields. From photostimulated reactions with enolate ions of aromatic ketones, the indoles **7-9** were obtained in good yields (Figure 1),[26] and these reactions can also be induced by Fe(II) in DMSO. When used as nucleophile enolates of cyclic ketones, the fused indoles **10-12** can be synthesized as shown in Scheme 3 and Figure 1, making this a good alternative methodology for preparing these compounds.[27]



Scheme 3. Synthesis of indoles **6**.

Recently 2-aryl indoles were prepared with **4** and the anion methyl aryl ketones under irradiation in DMSO to prepare finally 3-thiocyanato-1*H*-indoles as potential anticancer agents.[28]Azaindole derivatives

were synthesized by the reaction of iodoaminopyridines with ketone enolates ions to afford **13-15** (Figure 1).[29]

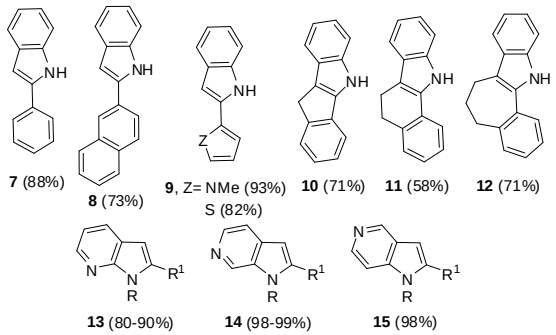
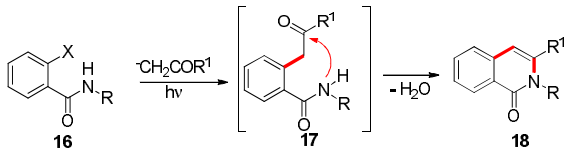


Figure 1. Indoles synthesized by intramolecular $S_{RN}1$ reactions.

3.2. Synthesis of six member heterocycles[30]

The 2-halobenzamides such as **16** react with ketone enolate ions to afford isoquinolones **18** by dehydratation of the substitution product **17** (not isolated). This strategy gave **18** by one-pot type of reaction with both alkyl[31,32] and aryl substituents (R^1= Aryl) in position three of the ring closure product **18** (Scheme 4).



Scheme 4. Synthesis of isoquinolones **18** from **16**.

With enolate ions of cyclic ketones it is then possible to synthesize the family of fused isoquinolones **19-23** as shown in Figure 2.[32]

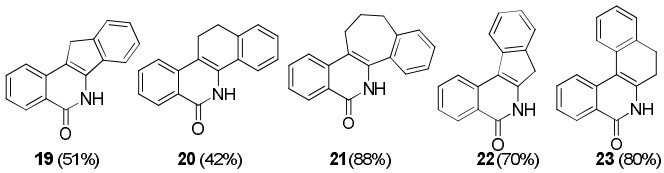
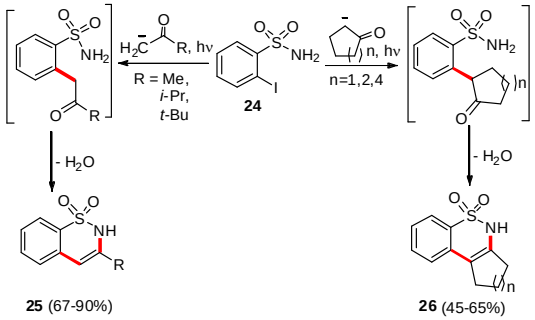


Figure 2. Selected examples of fused isoquinolones.

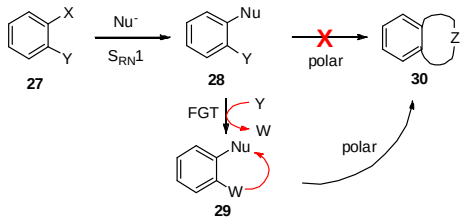
Following the same synthetic strategy, 2-iodobenzenesulfonamide **24** undergoes photostimulated $S_{RN}1$ reactions in liquid ammonia with alkyl and cycloalkyl enolate ions and gives fair to good yields of 3-alkyl 2*H*-1,2-benzothiazine-1,1-dioxides **25** and fused **26** (Scheme 5).[33]



Scheme 5. Synthesis of benzothiazine-1,1-dioxides **25** and fused **26**.

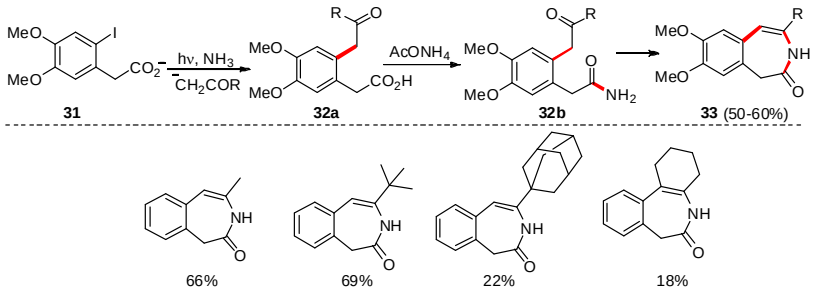
4. $S_{RN}1$ reaction followed by functional group transformation-ring closure reactions

Similar to the strategy showed in section 3, a substrate with an *ortho* substituent Y (**27**) which does not react spontaneously with Nu^- after the $S_{RN}1$ reaction could be used to synthesize heterocycles. In this case, by functional group transformation (FGT) the substituent Y is changed to W (Y→W) to give **29**, reacting this new group with Nu^- moiety to give the ring closure product **30** (Scheme 6).[34]



Scheme 6. Synthesis of heterocycles by tandem: $S_{RN}1$- FGT - ring closure polar reactions.

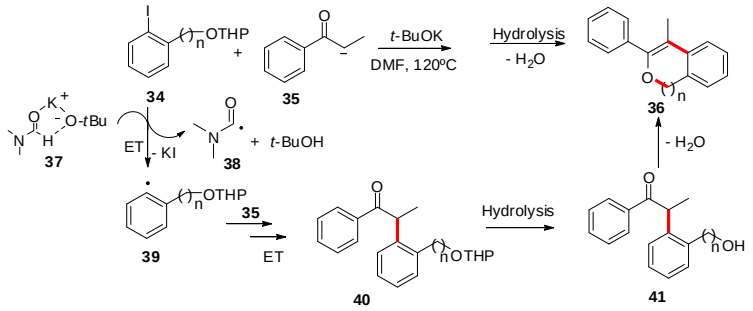
Following this strategy, the photostimulated reaction of (*o*-iodophenyl)acetic acid derivatives **31** with enolate ions from ketones gave the $S_{RN}1$ substitution product **32a**, which by treatment with ammonium acetate lead to the respective product **32b** which finally gave benzazepines **33**.[35] Recently, using the same approach, other benzazapines were also obtained (Scheme 7).[36]



Scheme 7. Synthesis of benzazepines through by tandem: $S_{RN}1$-amonia acylation-cyclization.

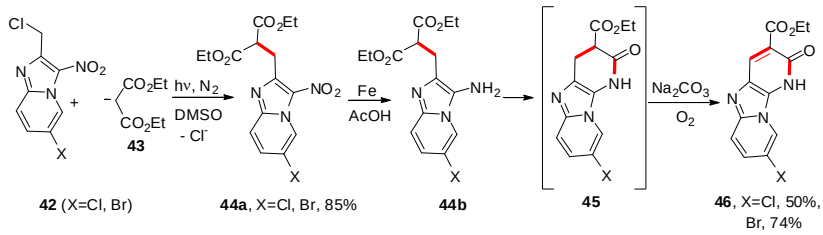
When 2-iodophenol **34** (n=0) or 2-iodobenzyl alcohol **34** (n=1) were protected with tetrahydropyranyl (THP) acetals and then treated with the enolate ion of propiophenone **35** in DMF at 120ºC, the products obtained were hydrolyzed to obtain benzofuran (**36**, n=0) and 1*H*-isochromene (**36**, n=1) in 52% and 50% yields, respectively (Scheme 8).[37]

Based on previous results[38] for the initiation step in these experimental conditions, it was suggested that *t*-BuOK abstracts a proton from DMF, generating carbamoyl anion **37**. Anion **37** by ET to **34** generates the carbamoyl radical **38** along with the radical **39**, which enters in the propagation cycle of the $S_{RN}1$ mechanism to react with **35** to afford the radical anion **40**$^{\bullet-}$. This then loses an electron to give **41**, which after hydrolysis and dehydration affords **36** (Scheme 8). This proposal of the initiation step hypothesis was confirmed at the theoretical level using density functional theory (DFT) and bulk solvent effects were included by means of a polarizable continuum model (PCM).[37]



Scheme 8. Mechanistic proposal of the formation of **36** from **34** in DMF at 120 ºC.

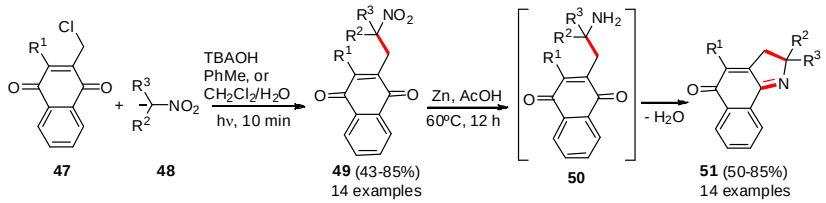
There are not many examples of ring closure reaction using aliphatic substrates with EWG in $S_{RN}1$ reactions. The reaction of 6-halo-2-(chloromethyl)nitroimidazo[1,2-*a*]pyridines **42** with the anion of diethyl malonate **43** under irradiation in DMSO afforded the diesters **44a** with good yields. This diester was reduced with Fe in acetic acid to afford amine derivative **44b**, which gave the ring closure product **45** (not isolated). Then, after treatment of **45** with Na_2CO_3 in air, the tricyclic pyridinones **46** were obtained (Scheme 9).[39]



Scheme 9. Synthesis of the tricyclic pyridinones **46** from **42**.

Recently, Vanelle *et al* reported that the photostimulated $S_{RN}1$ reaction of the 2-(chloromethyl)-3-substituted naphthalene-1,4-diones **47** with various nitronate anions derivatives **48** gave the C-alkylation products **49** in moderate to good yields. The phase-transfer conditions using 40% tetrabutylammonium

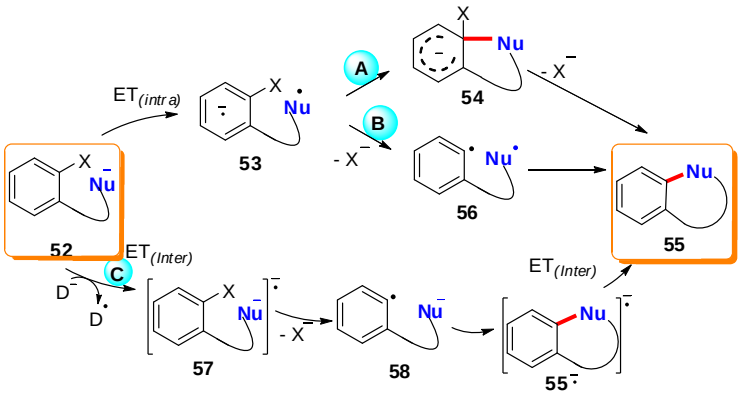
hydroxide (TBAOH) in water and toluene or CH_2Cl_2 as solvent were found to be the best reaction conditions (Scheme 10).[40] Reduction of the nitro group with zinc in acetic acid gave, after cyclization, the substituted 2,3-dihydrobenzo[*g*]indol-5-one derivatives **51** in moderate to good yields.



Scheme 10. Synthesis of 2,3-dihydrobenzo[g]indol-5-one derivatives **51** from **47**.

5. Intramolecular $S_{RN}1$ and related reactions

When a substrate has both the leaving group and a pendant nucleophilic centre, such as **52**, the ET reaction affords the ring closure product **55**,which depends on the distance between the leaving group X and the nucleophilic center Nu^-, the structure of the nucleophile and X, and the flexibility of the chain that connecting them (Scheme 11).



Scheme 11. Intramolecular aromatic substitution mechanisms by ET: Path A) $S_N(ET)Ar^*$; Path B) radical-radical collapse; Path C) the $S_{RN}1$ mechanism.

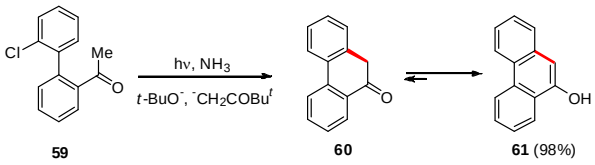
A mechanistic possibility is an intramolecular ET ($ET_{(intra)}$) from the nucleophilic centre to the pendant aryl halide to give the diradical anion **53**, which by coupling of the radical centre to the pendant aryl halides gives the anion **54** (Path A, Scheme 11). Elimination of the X^- ions affords finally the ring closure product **55** ($S_N(ET)Ar^*$). Another possibility is that the diradical anion **53** by fragmentation of the C-X bond (Path B), gives the diradical **56**, which collapses in the ring closure product **55**. In these two paths, there are no chain propagation steps.

When substrate **52** receives an electron by an intermolecular ET ($ET_{(inter)}$) from a donor D^- it forms the radical dianion **57**(Path C), which by fragmentation of the C-X bond gives the distonic radical anion **58**. This

is a high-energy intermediate, and the driving force to afford the ring closure product is the lowest energy of the conjugated radical anion **55**$^{\bullet-}$. Finally, an $ET_{(inter)}$ reaction furnishes **55** (intramolecular $S_{RN}1$). In this case, there are chain propagation steps.

5.1. Ring closure with formation of a C-C bond with carbanions[41]

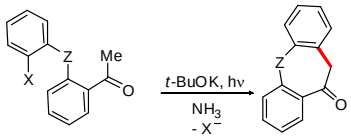
Recently, the use of enolate anion of methyl ketones with a pendant haloarene has been reported to synthesize different heterocycles with excellent yields.[42] Thus, when 2-chlorobiphenyl **59** with an acetyl group in the 2´position was irradiated with an excess of *t*-BuOK and with pinacolone enolate ions as an *entrainment* reagent it afforded **60**, which isomerised to the more stable tautomer phenanthren-9-ol **61** in high yields (Scheme 12).



59 **60** **61** (98%)

Scheme 12. Synthesis of phenanthren-9-ol **61** from **59**.

Following the same strategy, seven-membered heterocycles **63a-b** were obtained with very good yields starting from suitable precursors **62a-b** (Scheme 13).[42]

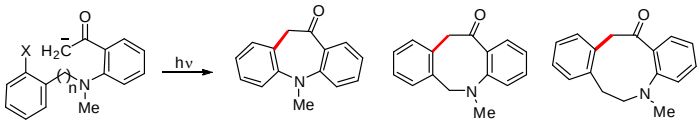


62a, Z=O, X=Br
62b, Z=S, X=Cl

63a (99%)
63b (85%)

Scheme 13. Construction of seven-membered heterocycles **63a-b** from precursors **62a-b**.

By changing the length of the bridge with N-Me moiety linking the nucleophilic center and the leaving group, such as **64**, rings with 7, 8 and up to 9 members are obtained with good yields (Scheme 14).[42]



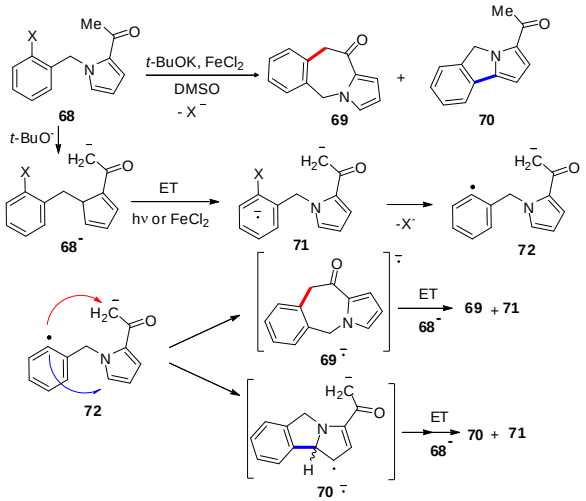
64, n=0,1,2

65 (73%) **66** (78%) **67** (69%)

Scheme 14. Synthesis of 7, 8 and 9 members **65-67** from **64**.

This methodology was extended to pyrrole derivatives **68** (X=Cl, Br, I)**.** By employing conditions of photostimulation, the substitution product **69** was obtained in low yields (31-45%) with traces of product **70** (3-5%) (Scheme 15). The low mass balance in these reactions was attributed to the high sensitivity that the

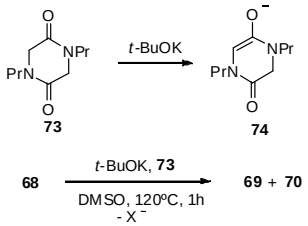
starting materials presented to irradiation. As a synthetic alternative, the reaction of **68** (X=I) was initiated with $FeCl_2$ in DMSO, giving 84% yield of product **69** and 11% yield of product **70** (Scheme 15).[42]



Scheme 15. Proposed reaction mechanism for the formation of **69** and **70**.

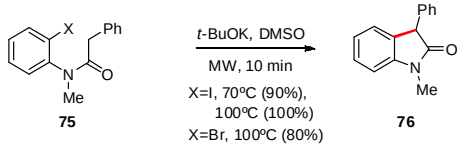
In this basic condition, substrate **68** forms the anion **68**$^{-}$. The initiation step probably occurs by iron or photo-assisted intermolecular ET to **68**$^{-}$ yielding the radical dianion **71**. Fragmentation of the C-X bond of **71** gives the distonic radical anion **72**, which via an intramolecular reaction, affords the conjugated radical anion **69**$^{\cdot-}$. An ET from **69**$^{\cdot-}$ to **68**$^{-}$ anion affords product **69** and the radical dianion**71**, which propagates the reaction. The intermediate distonic radical anion **72** can also couple with the pyrrole moiety to give the distonic radical anion **70**$^{\cdot-}$, which by an ET and acid-base reaction gives the more stable tautomer **70** and radical dianion **71**.

Most of the $S_{RN}1$ reactions need to be induced by light or other methods. However Murphy *et al* have developed a new "super" electron donors to transfer an electron to aryl halides using *N,N'*-dipropyldiketopiperazine **73** with *t*-BuOK to form the enolate ion **74**, that acts as an good electron donor to the aryl halides.[43] The reaction of **68**$^{-}$(X=I) with **74** in DMSO for 1 h at 120 ºC afforded **69** (79%) and **70** (10%), (Scheme 16), at similar yields to the reaction induced by Fe(II) (see Scheme 15). The fact that in both systems the yields of products **69** and **70** are quite similar indicates that the same mechanism is operating.[44]



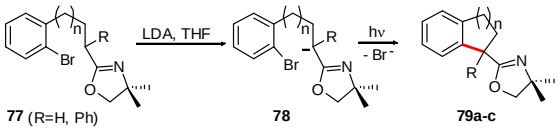
Scheme 16. Reaction induced by electron donor **73**.

Formation of the monoanions of a series of *N*-acyl-*N*-alkyl-*o*-chloroanilines by means of LDA in THF followed by irradiation with near-UV light affords 1,3-dialkyl-phenylindolin-2-ones in fair to good yields.[45] Recently, similar reaction was studied, but was induced by MW heating.[46] The cyclization reaction of the anion of *N*-(2-halophenyl)phenyl acetamides **75** afford 1-methyl-3-phenylindolin-2-one **76** under MW heating with good yields and short reaction times (Scheme 17). This is the first example of an aromatic $S_{RN}1$ reactions induced by MW.



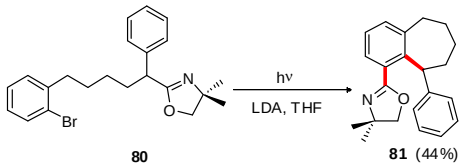
Scheme 17. Synthesis of 1-methyl-3-phenylindolin-2-one **76** under MW heating.

When substrate **77** with a pendant chiral 4,4-dimethyl-4,5-dihydrooxazol-2-yl moiety were treated with LDA in THF the carbanion **78** was formed, which under irradiation led to indanes (**79a** n=1, R=H, 58% yield and **79b** n=1, R=Ph, 57% yield) and tetraline derivatives (**79c** n=2, R=Ph, 50% yield) (Scheme 18).[47]



Scheme 18. Synthesis of indanes and tetralines **79a-c** from **77**.

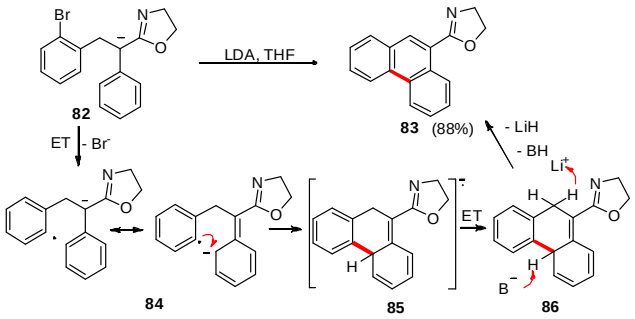
In the same experimental conditions, the substrate **80** gave as a main product the benzocycloheptane **81** in 44% yields, where the oxazolyl group had migrated to the phenyl ring. This migration was unexpected and attributed to the proximity of the 2-oxazolyl group (at its pseudo-equatorial position) with the benzene ring, once the 7-member ring has been formed (Scheme 19).[48]



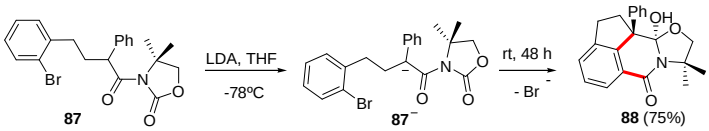
Scheme 19. Synthesis of benzocycloheptane **81** from **80**.

The ring closure of carbanion **82** formed with LDA in THF to afford **83** occurred by an ET reaction, and after C-Br fragmentation afforded a distonic radical anion **84**, which coupled via a six-membered ring $S_{RN}1$-type chain to afford the conjugated radical anion **85**, which finally gives the dihydrophenanthrene derivative **86**. In this strongly basic solution, aromatization of **86** gave the oxazolinophenanthrene derivative **83** in 88% yield. This reaction probably occurred by deprotonation and loss of lithium hydride (Scheme 20).[48] Another possibility is the oxidation of **86** in the work up.

Following a similar approach, the anion of **87**$^{-}$, prepared from **87**, afforded the fused tetracyclic derivative **88** when was treated with an excess of LDA in THF for 48 h via a $S_{RN}1$ reaction followed by 1,3-areneotropic migration (Scheme 21).[49]

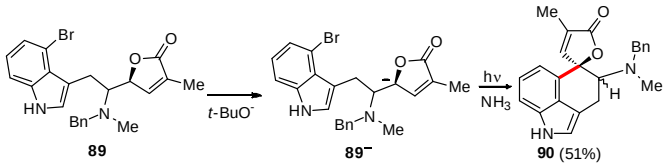


Scheme 20. Mechanistic proposal for the synthesis of **83**.



Scheme 21. Synthesis of **88** from **87**.

When the indole **89** with a pendant 3-methylfuran-2(5*H*)-one moiety was irradiated in refluxing ammonia in the presence of *t*-BuOK to form the carbanion **89**$^{-}$, the photostimulated reaction delivered a mixture (1:2) of the precursors of *N*-benzyl Rugulovasines A (β-H) and B (α-H) **90** (Scheme 22).[50]

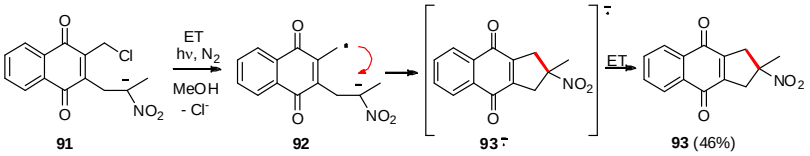


Scheme 22. Synthesis of precursors of Rugulovasines A and B **90** from **89**.

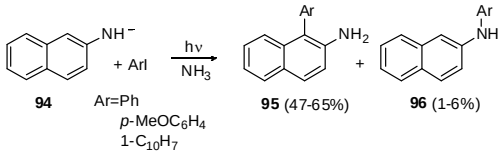
Although the $S_{RN}1$ reaction of aliphatic substrates with EWG, such as 2-(chloromethyl)naphthalene-1,4-dione are well known to react with carbaniones derived from nitroalkanes, there are only a few examples of synthesis of heterocycles via intramolecular reactions. For example, the photostimulated reaction of the carbanion **91** afforded the ring closure product **93** in 46% yield (Scheme 23).[51]

5.2. Ring closure with a C-C bond formation with aromatic nitranions

Photostimulated reactions of the anion of 2-naphthylamine **94** with different ArI mainly gave the product of coupling at position one of the naphthalene ring **95**, together with traces of the product of coupling on nitrogen **96** (Scheme 24).[52]

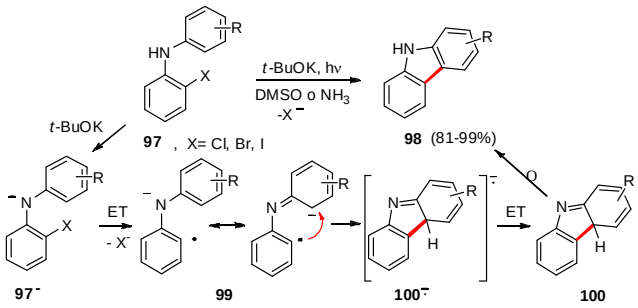


Scheme 23. Synthesis of **93** from the carbanion **91**.



Scheme 24. Formation of products **95** (C-C coupling) and **96** (C-N coupling).

On the other hand, the photostimulated reaction of 2-halo-*N*-phenylaniline derivatives **97** (R=Me, *t*-Bu, Ph, OMe, pyrrolyl) afford the intramolecular C-C bond carbazoles **98** as the only product since a C-N bond formation would afford a highly energetic three member ring (Scheme 25). These reactions took place with both in liquid ammonia and DMSO as solvents to give very good yields of substituted carbazoles **98**. The mechanism proposed is that **97** reacts with *t*-BuOK to gives the diphenylamide **97**$^-$, which by ET forms the dianion radical. Then, C-X bond fragmentation delivers the distonic radical anion **99**, which by a C-C bond formation gives the conjugated radical anion **100**$^{-\cdot}$. By ET, the radical anion **100**$^{-\cdot}$ yielded the substitution product **100**, which finally gives **98**, the more stable tautomer (Scheme 25).[53]



Scheme 25. Mechanism proposed for the synthesis of carbazoles **98** from **97**.

This synthetic strategy was extended to the synthesis of benzocarbazoles (**101** and **102**) and dibenzocarbazol **103** (Figure 3).

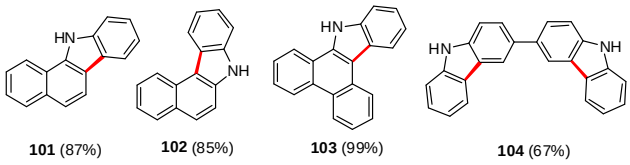
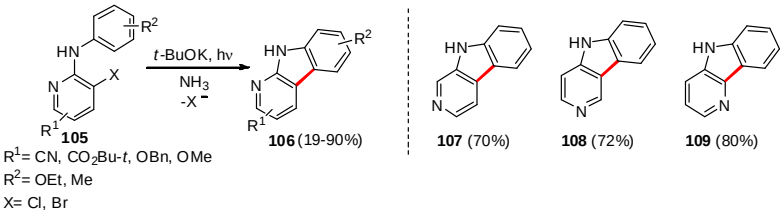


Figure 3. Carbazoles synthesized by intramolecular $S_{RN}1$ reactions.

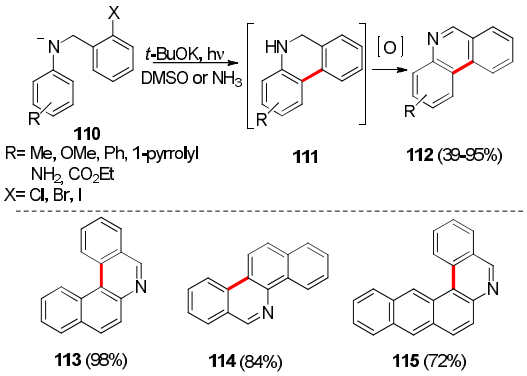
Similarly, a double ring closure was carried out starting from the diamine N^4,$N^{4'}$-bis(2-bromophenyl)biphenyl-4,4'-diamine to gave the corresponding 3,3'-bi(9*H*-carbazole) **104,** with a 67% isolated yield (Figure 3).[53]

Following the same methodology, a family of α-carbolines **106** were synthesized with good to very good yields, starting from the corresponding *o*-halopyridylanilines **105**. The approach could be extended to all regioisomers β, γ and δ carbolines (**107**, **108** and **109** respectively), in both liquid ammonia and DMSO as the solvent (Scheme 26). This is the only synthetic method known so far that can synthesized all carboline regioisomers.[54]



Scheme 26. Synthesis of all the carboline regioisomers.

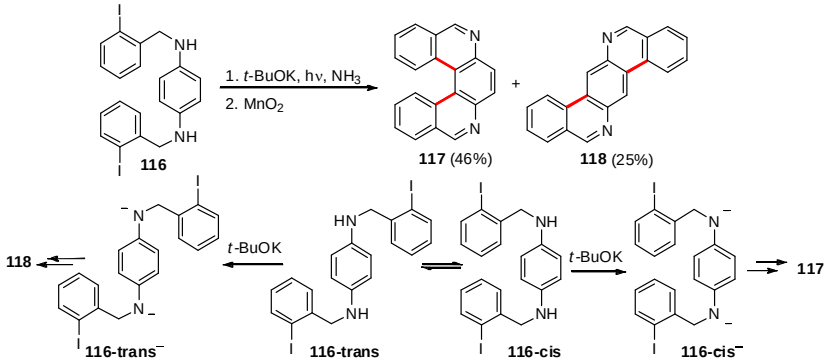
Similar to the anions of diarylamines, other anilines have been used to obtain new heterocycles through the intramolecular C-C bond formation. For instance, the intramolecular arylation of iodobenzyl phenyl amide anion **110** afforded phenanthridines **112** in very good yields; these reactions being carried out under irradiation in liquid ammonia or DMSO. Although **111** were the ring closure products, they oxidized spontaneously in the work-up to finally afford **112** (Scheme 27). Benzo[*a*]phenanthridine **113**, benzo[*c*]phenanthridine **114**, and naphtho[2,3*a*]phenanthridine **115** were obtained following this synthetic strategy.[55]



Scheme 27. Synthesis of phenanthridines **112** and fused phenanthridines **113-115**.

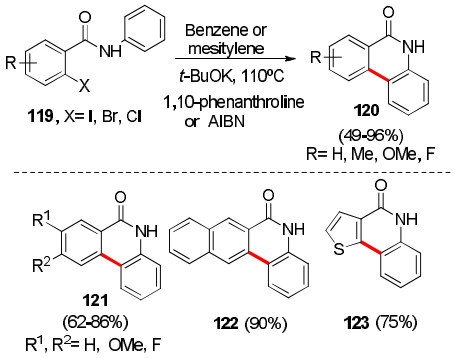
Recently, the photostimulated reaction in liquid ammonia of the bis(2-iodobenzyl)benzene-1,4-diamine **116** was reported to give two isomeric products: dibenzo[*a*,*k*][4,7]phenanthroline **117** and isoquinolino[3,4-*b*]phenanthridine **118**, by two ring closure reactions. This reaction was studied theoretically

using DFT methodology with the B3LYP functional and it was concluded that two conformers **116-cis** and **116-trans** were present. The Boltzmann distribution of conformers revealed a ratio of 1.2:1 for **116-cis**:**116-trans** and in the basic reaction medium, the dianions **116-cis**$^-$ and **116-trans**$^-$ were formed. The **116-cis**$^-$ ⇌ **116-trans**$^-$ isomerization barrier for the anions is high because it involves rotation around C (phenyl) and the N bond, which has a partial double bond character. Thus, the distributions of the anions were directly related to their neutral precursors, which is in agreement to the ratio of the products found.[56]



Scheme 28. Mechanism proposed for the formation of **117** and **118** from **116**.

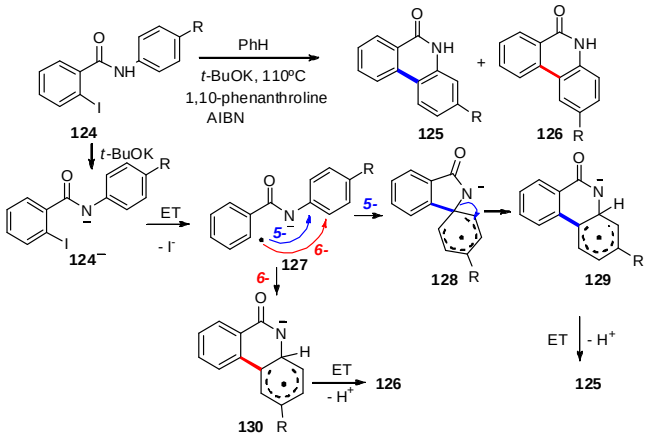
When the anions of 2-halo-phenylbenzamide derivatives **119** were treated with AIBN or 1,10-phenantroline to induce a reaction in benzene (or mesitylene) at 110ºC, phenanthridinones **120** were obtained with good yields (Scheme 29, 6 examples, 49-96% yields). Other phenanthridones **121-122** and a thienoquinolinone **123** were also obtained with good yields.[57]



Scheme 29. Synthesis of phenanthridinones **120-123**.

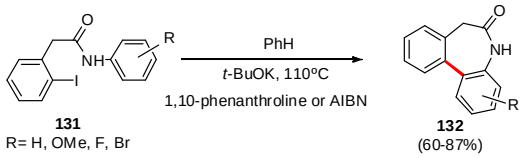
When substituted 2-iodo-*N*-(aryl)benzamides such as **124** were employed as substrates, two isomeric products **125** and **126** were found. A possible reaction mechanism was suggested as depicted in Scheme 30, with C-C coupling occurring in the presence of the radical initiator AIBN or 1,10-phenanthroline. The first step is the deprotonation of **124** to give the anion **124**$^-$, as studied using ^{1}H NMR. The next step with 1,10-phenanthroline is the formation of a radical anion by ET followed by C-X bond fragmentation to afford the

distonic radical anion **127**. With AIBN by abstraction of iodo also forms the radical anion **127**. This radical anion **127** can attack the aryl ring in a 5-*exo*-*trig* or 6-*endo trig* mode, leading to intermediates **128** and **130** respectively. Ring expansion in the intermediate **128** afford the more stable hexadienyl radical **129**, which by deprotonation and ET give the product **125**. Intermediate **130** also by deprotonation and ET give the product **126**. The presence of radicals was confirmed by EPR spectroscopy in the reaction mixture.[57]



Scheme 30. Mechanistic proposal for the formation of isomers **125** and **126**.

There are only a few examples of the synthesis of seven member heterocycles. When 2-(2-iodophenyl)-*N*-phenylacetamides derivatives **131** were treated with *t*-BuOK and AIBN (or 1,10-phenantroline) to induce a reaction in benzene (or mesitylene) at 110ºC, the seven-member dibenzoazepinones **132** were obtained with good yields by a C-C bond formation with high chemoselectively, despite the possibility of a C-N coupling reaction (Scheme 31, with 7 examples). The mechanism proposed is similar to the one depicted in Scheme 30.[57]

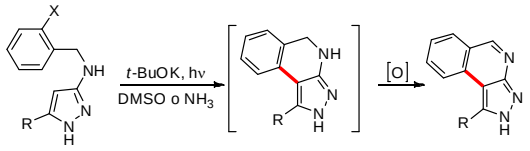


Scheme 31. Synthesis of dibenzoazepinones **132** from **131**.

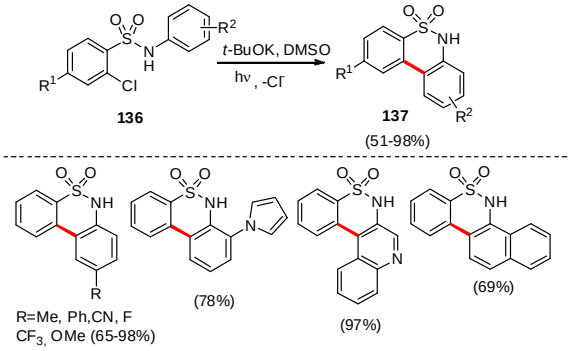
The photostimulated reactions of *N*-(2-halobenzyl)pyrazoles **133a-b**, with excess *t*-BuOK in liquid ammonia or DMSO, afforded the 2*H*-pyrazolo[3,4-*c*]isoquinolines **134a-b** by a cyclization reaction with C-C bond formation in position four of the pyrazole ring, followed by spontaneous oxidation of the substitution products to yield **135a-b** (Scheme 32).[58]

A new and general synthetic route to prepare dibenzosultams has been reported using an intramolecular C-C photoinduced arylation under mild conditions. The substrates **136** were treated with *t*-BuOK in DMSO to give the corresponding anion, that under irradiation led to product **137**, a more stable

tautomer of the ring closure product with good to excellent isolated yields (Scheme 33). It was shown that LED (λ=395 nm) is an efficient light energy source for efficiently initiating the reactions.[59]

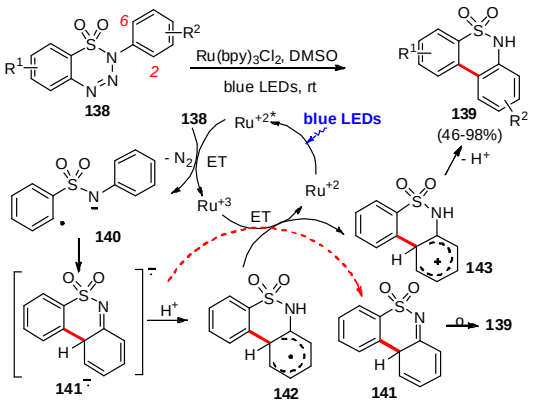


Scheme 32. Synthesis of 2H-pyrazolo[3,4-*c*]isoquinolines **135a-b**.



Scheme 33. Synthesis of dibenzosultams **137** from **136**.

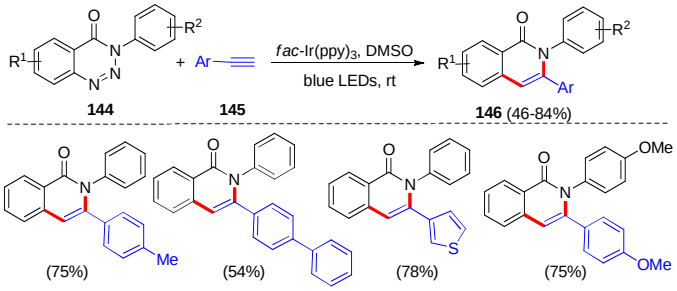
A quite different approach has also been reported for the synthesis of dibenzosultams. A solution of 1,2,3,4-benzothiatriazine-1,1-dioxides **138** in DMSO was irradiated by blue LEDs in the presence of the photocatalyst $Ru(bpy)_3Cl_2$, and dibenzosultams **139** were obtained with 46-98% yield (Scheme 34, 12 examples).



Scheme 34. Synthesis and the proposed mechanism for the formation of **139**.

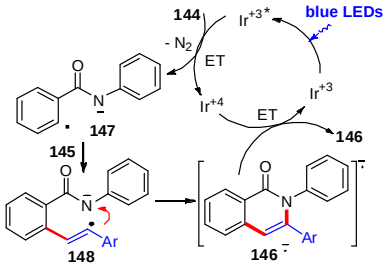
The substrates 1,2,3,4-benzothiatriazine-1,1-dioxides **138** were prepared by diazotization of the corresponding 2-amino-*N*-phenylbenzenesulfonamides, and this procedure was also carried out in a one pot reaction: diazotization with the generation of triazenes *in situ* followed by irradiation, with good yields of ring closure products **139**.[60] When R^2 is in the *m*- position, two isomerics products are formed by attack on positions 2 and 6 of the aryl ring. It was observed that the luminescence of $Ru(bpy)_3Cl_2$ being quenched by **138** following Stern-Volmer kinetics, and this luminescence quenching is probably being due to the photo-induced ET, a plausible mechanism was proposed (Scheme 34). First, the photocatalyst Ru(II) gave the excited state Ru(II)* under blue LEDs irradiation, then by ET to **138** the Ru(III) and the radical anion of **145** were afforded, which by loosing N_2 yielded the distonic radical anion **140**. Then, a C-C bond formation afforded the conjugated radical anion **141**$^{\bullet-}$, which was protonated and then oxidized by Ru(III) to yield cation **143** with regeneration of the photocatalyst Ru(II). Finally, sultam **139** was generated after loss of a proton.[60] Another mechanistic possibility is that the radical anion **141**$^{\bullet-}$ is oxidized by Ru(III) to yield the photocatalyst Ru(II) and the tautomer **141**, and finally the more stable tautomer product **139**.

Using a similar approach, when a solution of 1,2,3-benzotriazinone derivatives **144** and arylacetylenes **145** in DMSO was irradiated using blue LEDs in the presence of the photocatalyst *fac*-$Ir(ppy)_3$ for 15 h, the product substituted isoquinolones **146** were obtained in good yields (Scheme 35, 24 examples). Some representative examples are shown in Scheme 35. Addition of the radical trap TEMPO inhibited the reaction, and furthermore, the luminescence of *fac*-$Ir(ppy)_3$ could be readily quenched by the substrate following Stern−Volmer kinetics. It was proposed that this luminescence quenching was most likely due to photoinduced ET.[61]



Scheme 35. Synthesis of substituted isoquinolones **146** from **144** and **145**.

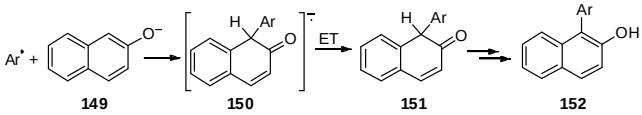
On the basis of the experimental observations and photochemical studies, a plausible mechanism was proposed (Scheme 36). The Ir(III) photocatalyst is irradiated to the excited state Ir(III)*, which is then oxidized by the substrate to give Ir(IV) and radical anion **147** by loss of N_2. Radical anion **147** is then trapped by the alkyne **145** to give the distonic radical anion **148**, which affords the conjugate radical anion **146**$^{\bullet-}$ by intramolecular coupling reaction. Finally, radical anion **146**$^{\bullet-}$ is oxidized by Ir(IV) to yield **146**, with regeneration of the photocatalyst Ir(III).[61]



Scheme 36. Mechanistic proposal for the photochemical reaction of **144** and **145** to obtain **146**.

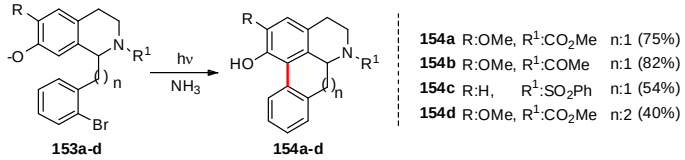
5.3. Ring closure with formation of a C-C bond with aromatic oxianions

Aromatic oxianions are bidentate nucleophiles that can react with radicals through the O- or the C-atoms. However, in intermolecular reactions, only couples on C to give a new C-C bond. For example, 2-naphthoxide ions **149** react with ArX to give substitution only at C-1 of the naphthalene ring.[62] In this reaction, the intermediate radical Ar$^{\bullet}$ couples in C-1 of **149** to yield the radical anion **150**, which by ET gives the product **151** and after tautomerization yields the more stable products **152** (Scheme 37). The rates of reactions of 2- and 4-anisyl and 2-methoxy-1-naphthyl radicals with **149** were founded to be 10^8-10^9 M^{-1} s^{-1}.[63]



Scheme 37. Mechanistic proposal for the formation of product **152** from **149** and Ar$^{\bullet}$ radicals.

The phenoxide ion linked with a pendant bromoarene by *N*-substituted tetrahydroisoquinolines bridge such as **153a-d**, afforded under photostimulation, aporphine alkaloid derivatives **154a-c** (n=1) in good yields (Scheme 38). This approach has been extended for the first time to the synthesis of the homoaporphine alkaloid **154d** (n=2).[64]

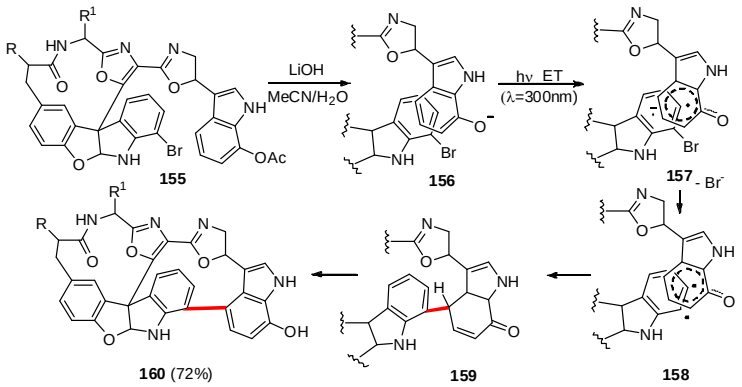


Scheme 38. Synthesis of aporphine alkaloid derivatives **154a-d** from **153a-d**.

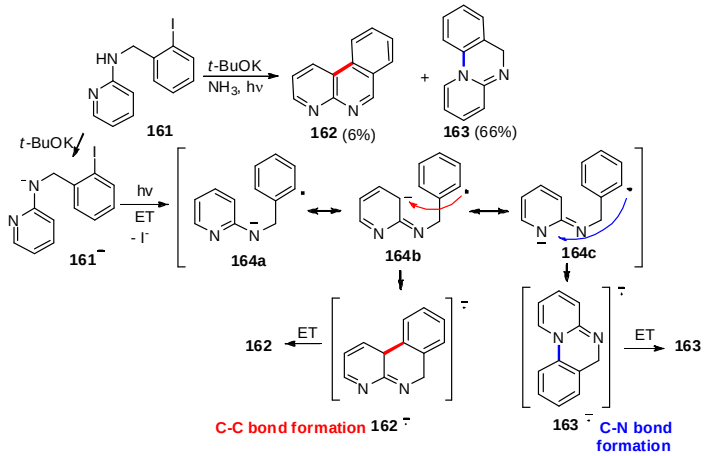
Diazonamida A, which is a potent antimitotic natural product has been synthesized from synthetic precursor **155** by a photoinduced ET reaction (Scheme 39). The deprotection of the phenolic group and ionization occurred in basic medium to give **156**, and under irradiation the intramolecular ET reaction gave the diradical anion **157**. Then, after fragmentation of the C-Br bond a diradical **158** was afforded, which by radical-radical coupling reaction gave **159,** that in basic medium furnished the most stable tautomer **160** in 72% yield (Scheme 39).[65]

5.4. Ring closure with formation of a C-N bond

As we have seen above (section 5.2.), the photostimulated reaction of benzylphenyl amines gave phenanthridines with good yields.[55] In order to expand the applications of this methodology to heteroaromatic amine, the *N*-(2-iodobenzyl)pyridin-2-amine **161** was studied. When **161** was treated with excess *t*-BuOK in liquid ammonia under photostimulation, only 6% of the corresponding benzo[*c*][1,8]naphthyridine **162** was obtained (C-C bond formation), together with the ring closure product 6*H*-pyrido[1,2-*a*]quinazoline **163** (C-N bond formation) in 66% yield (Scheme 40). The reaction was studied in the dark, but only unreacted substrate was found, so polar mechanisms could be discarded.[55b]



Scheme 39. Mechanism proposed for the formation of product **160** from **155**.

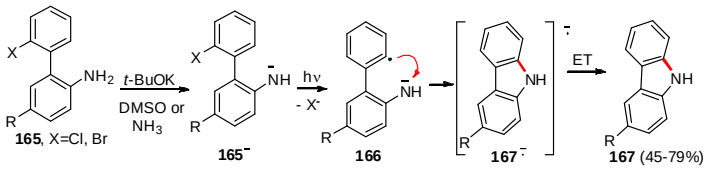


Scheme 40. Mechanism proposed for the formation of products **162** and **163** from **161**.

The proposed mechanism (Scheme 40) starts with formation of amide anion **161**$^{\bullet-}$, with a radical dianion being formed under irradiation by ET to **161**$^{-}$, which fragments in the C-I bond to form the distonic radical anion **164**. The resonance structure **164b** justifies formation of the C-C bond to give the conjugate radical anion **162**$^{\bullet-}$, which by ET affords the product **162**. In addition, the resonance structure of the distonic

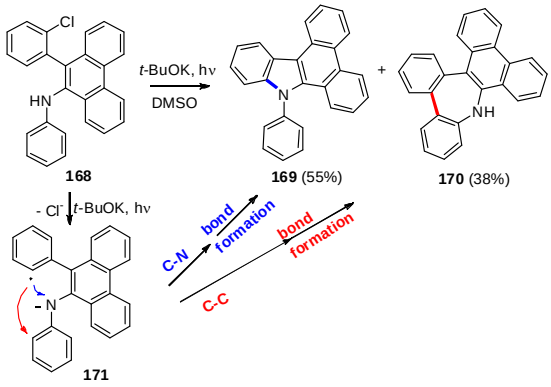
radical **164c** gives the conjugate radical anion **163**$^{\bullet-}$ (via coupling C-N). In order to explain the regiochemical outcome of these reactions, a theoretical analysis was performed using DFT methods and the B3LYP functional.[55b]The activation energy of ring closure to give the radical anion **163**$^{\bullet-}$ is 8 kcal/mol lower than that for the formation of **162**$^{\bullet-}$, with this being the first example of intramolecular coupling reactions giving a C-N bond formation by the $S_{RN}1$ mechanism.

We discuss before that the photostimulated reaction of 2-halo-*N*-phenylaniline derivatives **97** the intramolecular reaction only is possible the C-C bond formation and carbazoles **98** are formed (Scheme 25).[53] However, substituted 9*H*-carbazoles were synthesized in good to excellent yields through an intramolecular C-N bond formation of 2′-halo[1,1′-biphenyl]-2-amines **165** by the photoinitiated $S_{RN}1$ mechanism. Thus when substrates **165** (R=H, Me, OMe, CN, CF_3, CO_2Et) in DMSO or NH_3 with excess of *t*-BuOK, the anion **165**$^{-}$ were formed, and under irradiation, the distonic radical anion **166** were formed after loss of X^-. Then, C-N bond formation afforded the conjugated radical anion **167**$^{\bullet-}$ which finally by ET afforded the carbazoles **167** (Scheme 41).[66]



Scheme 41. Synthesis of carbazoles through a C-N bond formation.

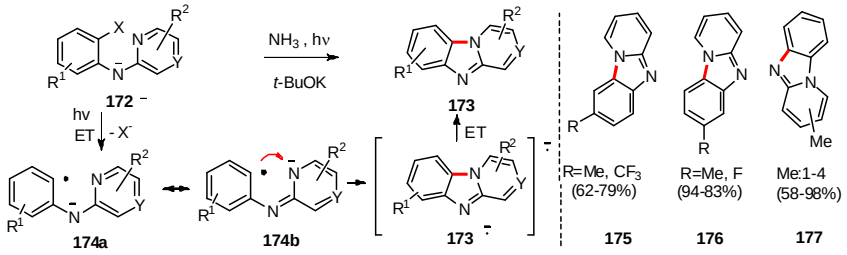
When the photostimulated reaction was carried out with the amide of **168**, 9-phenyl-9*H*-dibenzo[*a*,*c*]carbazole **169** was obtained in 55% yield by an expected C-N bond formation, together with 9*H*-dibenzo[*b*,*d*]phenanthro[9,10-*f*]azepine **170** in 38% yield corresponding to C-C coupling (Scheme 42). To rationalize the experimental results, a computational study with B3LYP DFT functional and the 6-311+G* basis set was carried out. These calculations were able to explain the experimentally observed regiochemistry of C-C vs. C-N cyclization for **168**.[66]



Scheme 42. Mechanism proposed for the formation of **169** and **170** from **168**.

To investigate the mechanism of this photostimulated synthesis of carbazoles, a study of the experimental reaction conditions, photophysical properties, photochemical studies and computational data was carried out. A complete mechanistic picture of the photoinduced ET cyclization reaction was realized and from a comparative study at the initiation level it was concluded that ET process involves a bimolecular interaction ($S_{RN}1$), excluding $ET_{(intra)}$ mechanisms such as $S_N(ET)Ar^*$ and radical-radical collapse.[67]

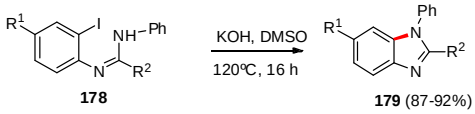
When 2-halophenyl pyridyl amide anion **172**$^-$ were irradiated, pyrido[1,2-*a*]benzimidazoles **173** were obtained with good yields through a new C-N bond formation. The mechanism proposed is that under irradiation by ET and after C-X bond fragmentation the distonic radical anion **174** is formed, and from the resonance structure **174b**, the conjugated radical anion **173**$^{\bullet-}$ is given, which by ET affords the product **173** (Scheme 43, 10 examples in general with good yields, for instances benzimidazoles **175-177**).[68]



172$^-$ **173** **174a** **174b** **173**$^{\bullet-}$ **175** **176** **177**

Scheme 43. Synthesis of pyrido[1,2-*a*]benzimidazoles **173**, **175-177** from **172**.

Benzimidazoles were also prepared by intramolecular *N*-arylations of amidines mediated by KOH in DMSO. In this manner, substituted products were obtained in very good yields. Thus, when *N*'-(2-iodophenyl)-*N*-phenyl formimidamides **178** were treated in DMSO/KOH at 120°C, 1-phenyl-1*H*-benzo[*d*]imidazoles **179** were obtained by the $S_{RN}1$ mechanism [R^1= H, R^2= Me (92%); R^1= H, R^2= Ph (90%); R^1= Cl, R^2= Me (87%)]. In contrast, when the leaving group iodo was changed for Br, Cl or F, the experimental evidences indicates that mechanism proposed being through a typical S_NAr mechanism (Scheme 44).[69]

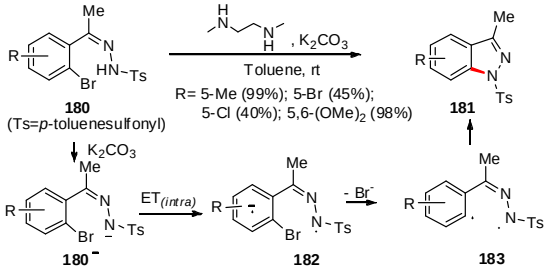


178 **179** (87-92%)

Scheme 44. Synthesis of benzoimidazoles **179** from **178**.

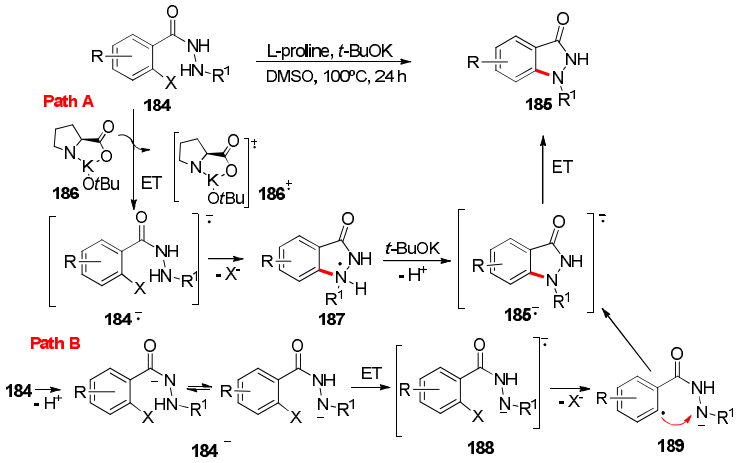
Another system where C-N bond formation was observed is in the synthesis of indazoles **181** (Scheme 45). The synthesis of heterocycles **181** from (*Z*)-2-bromoacetophenone tosylhydrazones **180** involves a catalytic system composed of a diamine as the ligand, such as N^1,N^2-dimethylethane-1,2-diamine, and K_2CO_3 at rt. Various possible mechanisms for this cyclization are possible. The fact that only *N*-arylsulfonyl substituted substrates with relatively acidic NH were able to react indicates that deprotonation is the initial step of the process. Since only Br and I derivatives cyclized well, where as Cl and F compounds were unreactives, indicates that intramolecular as S_NAr is unlikely. Although another possibility is an

electrocyclic ring closure reaction; attempts to detect the intermediates by ^{13}C NMR spectroscopy were unsuccessful. One of the mechanisms proposed is that with K_2CO_3 the anion **180**$^-$ is formed, and by intramolecular ET from the nucleophilic center to the pendant aryl bromide the diradical anion **182** is formed, which after fragmentation of the C-Br bond forms the diradical **183** followed by radical-radical coupling affording **181** (Scheme 45). The formation of radical intermediates was demonstrated by ESR spectroscopy.[70]



Scheme 45. Synthesis of indazoles **181** from **180**.

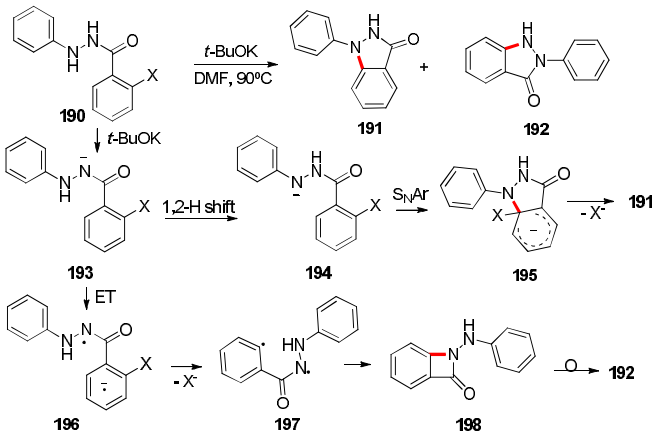
Recently, it has been reported that the reaction of 2-halobenzohydrazides **184** with *t*-BuOK in the presence of proline as catalyst afforded indazolones **185** in moderate to good yields (Scheme 46, with 21 examples up to 84% yields). The reaction was inhibited by TEMPO, which indicated that radicals are intermediates of this reaction. The mechanism proposed is described in Scheme 46: path A, is that *t*-BuOK with proline forms a chelate **186**, which by ET to **184** forms the radical cation **186**$^{+\cdot}$ and the radical anion **184**$^{\cdot-}$. Then, after C-X fragmentation of the radical anion **184**$^{\cdot-}$, the radical thus formed reacts with N affording **187** by intramolecular C-N coupling. The deprotonation of **187** by the base can convert radical **187** to the radical anion **185**$^{\cdot-}$, which then forms the final product **185** by ET to the substrate **184**.[71]



Scheme 46. Mechanistic proposal by the synthesis of indazolones **185** from **184**.

Another mechanistic possibility (path B, Scheme 46) is that with an excess of *t*-BuOK, substrate **184** forms the anion **184**$^{-}$, which by ET from **186** forms the dianion radical **188**. Then, C-X fragmentation forms the distonic radical anion **189** that by intramolecular ring closure reaction affords the conjugated radical anion **185**$^{\bullet-}$ to afford finally the observed products **185**. The pKa of **184** are not known in DMSO, but should be lower than the pKa value of 21.8 of acetohydrazide.[72]

When *N*′-aryl-2-halobenzohydrazides **190** were treated with *t*-BuOK in DMF at 90ºC different products were formed, depending on the halogen. Thus, when X= Cl or F, only 1-phenylindazolone **191** was formed (several examples, 83-99%). When X= Br or I, product **191** (18-33%) and 2-phenylindazolone **192** (56-68%) were formed (Scheme 47).[73]



Scheme 47. Mechanistic proposal for the formation of products **191** and **192**.

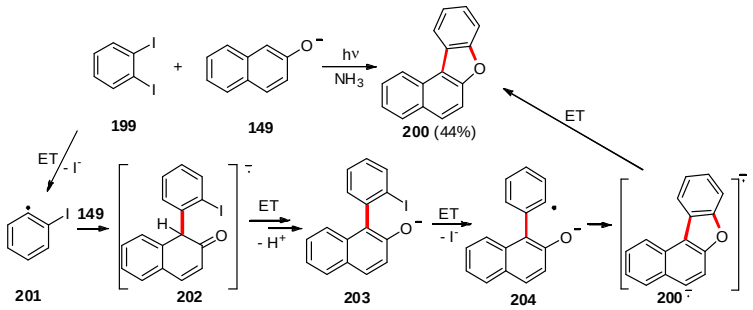
Two different reaction pathways are proposed (Scheme 47). The deprotonation of the substrate **190** generates an amide anion **193**. After 1,2-hydrogen shift, the acyl hydrazine anion **194** is formed, that by a S_NAr reaction with phenyl ring gives a cyclohexadiene anion **195**, which finally afford the product **191** after elimination of the halide anion. The amide anion **193** by an intramolecular ET to the pendant phenyl ring affords the diradical anion **196**. After elimination of the halogen anion, a diradical intermediate **197** is formed. The following radical-radical coupling gives a β-lactam **198**, that by a rearrangement reaction yields finally the product **192**.

5.5. Ring closure with the formation of a C-O or C-S bonds

As discussed above, aromatic oxianions are bidentate nucleophiles and can react with radicals through the O- or the C-atoms. However, in intermolecular reactions, they react only on C to give a new C-C bond (Scheme 37). The photostimulated reaction of *o*-diiodobenzene **199** with 2-naphthoxide ion **149** in liquid ammonia afforded the tetracyclic benzo[*d*]naphtho[2,1-*b*]furan compound **200** (Scheme 48).[74]

When **199** receives an electron, C-I bond fragmentation affords the radical **201**, which reacts with **149** on C to give the radical anion **202**. Then, **202** by ET followed by losing a proton in this basic medium gives the most stable tautomer **203**. Through ET to **203** and after C-I bond fragmentation the distonic radical anion

204 is formed, which by a coupling reaction on O yields the more stable conjugated radical anion **200**$^{\bullet-}$. Finally, by ET, the product **200** is obtained (Scheme 48). This is the first report that an aromatic radical couples with an oxianion by a proximity effect and by an exothermic reaction.



Scheme 48. Synthesis and mechanistic proposal for the formation of **200**.

Similar results were obtained for the photostimulated reaction of the anion of phenanthren-9-ol with diiodobenzene **199**, which gave 35% yield of the ring closure pentacycle **205** using the same approach as Scheme 48 (Figure 4).[75] A photostimulated reaction of 4-hydroxycoumarin and Sesamol (5-benzodioxolol) with a dihalobenzene and *t*-BuOK as the base in DMSO has been reported, and the tetracyclic products 6*H*-benzofuro[3,2-*c*]chromen-6-one **206** were obtained in similar yield (Figure 4).[76,77]

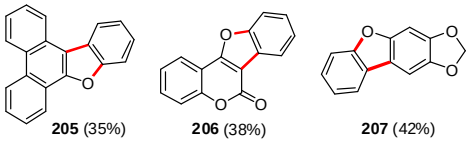
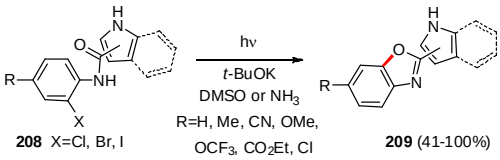


Figure 4. Synthesis of compounds **205-207** by two consecutive $S_{RN}1$ reactions.

The synthesis of a series of 6-substituted 2-pyrrolyl, 2-indolyl benzoxazoles and 3-indolyl benzoxazoles **209** were obtained by photostimulated cyclization of anions from 2-pyrrole carboxamides, 2-indole carboxamides, or 3-indole carboxamides **208** in liquid ammonia or DMSO. It has been reported that these reactions proceed with a C-O bond formation in good to excellent yields (Scheme 49).[78]

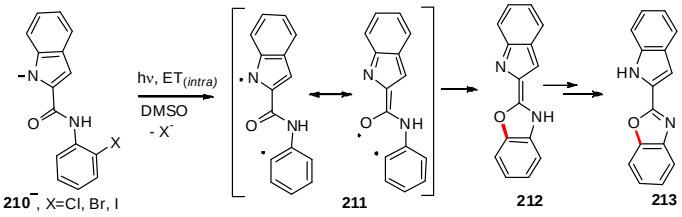


Scheme 49. Synthesis of substituted 2-pyrrolyl and 2-indolyl benzoxazoles **209**.

The pyrrole carboxamides bear two hydrogens, which can be ionized under basic reactions conditions; however, the pKas for these compounds are unknown for liquid ammonia or DMSO. Computational calculations were performed using a DFT method, and it was determined that the pyrrole anion is

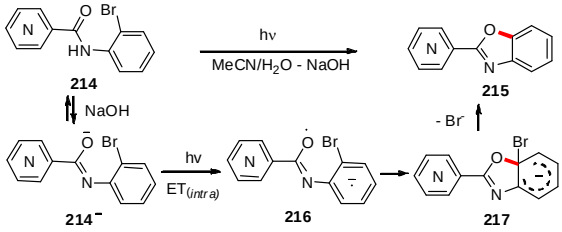
energetically more stable than the amide anion by 2.1 kcal/mol.[78] It was found that (i) this reaction only occurred under photostimulation and (ii) the photostimulated reaction was inhibited by *p*-DNB, which suggests that there are probably ET events taking place. To try to explain the regiochemical outcome of these reactions (C–O arylation *vs* C–N or C–C arylation), a theoretical analysis was performed using DFT methods and the B3LYP functional.[78]

In order to investigate more about the mechanism of reaction of this system, a photochemical study was carried out with the indole carboxamides anion **210**$^{-}$. On the basis of photochemical and photophysical experiments, it was proposed that 2-indolylbenzoxazole product **213** was obtained from anion **210**$^{-}$, by an intramolecular ET similar to Scheme 11 (Path B). Once formed, the diradical **211** collapse to give **212**, which ultimately give the more stable tautomer **212** (Scheme 50).[79]



Scheme 50. Mechanistic proposal for the formation of **213** from **210** $^{-}$.

When the 3-pyridyl and 4-pyridyl carboxamides **214** were irradiated with NaOH in MeCN/H_2O, the pyridyl benzoxazoles **215** were obtained in 34-43% yields (Scheme 51). On the basis of the photokinetic and laser flash photolysis studies, intramolecular photosubstitution of **214** occurred via an intramolecular S_N(ET)Ar* mechanism to afford **215**, similar to Scheme 11, Path A.[80]

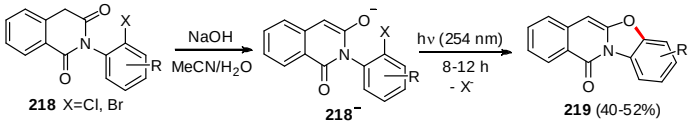


Scheme 51. Synthesis and mechanistic proposal for the formation of pyridyl benzoxazoles **215**.

In the basic medium, the keto form of the amide **214** is in equilibrium with the imidolate anion **214** $^{-}$, and under irradiation, there is an ET from the anion to the pendant phenyl bromide to afford the radical on the oxygen and the radical anion **216** on the phenyl ring. Intramolecular addition of the oxygen radical to bromophenyl moiety produces a cyclohexadienyl anion **217** and finally the product **215** by ejection of the bromide anion (Scheme 51).

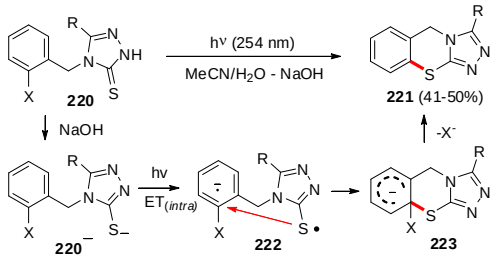
Using a similar approach, irradiation of the tetrahydroisoquinoline-1,3-diones **218** under aqueous basic conditions (MeCN/1 M NaOH, two-phase λ=254 nm), furnished the benzoxazolo[3,2-*b*]isoquinolin-11-ones **219** (Scheme 52). The reaction under dark conditions gave no products. The photosubstitution reaction

described here involves intramolecular replacement of the halogen atom present in the *N*-phenyl moiety of the isoquinoline-1,3-diones by the negatively charged oxygen **218** $^-$ through the same mechanism described in Scheme 51.[81]



Scheme 52. Synthesis of benzoxazolo[3,2-*b*]isoquinolin-11-ones **219** from **218**.

There are few reports of ring closure with formation of a C-S bond.[82] The photostimulated reaction of triazole-3-thiones **220** with NaOH in MeCN/H_2O afforded triazolo[3,4-*b*]-1,3(4*H*)-benzothiazines **221**. In the presence of NaOH, the UV-spectra of **220** (R=Ph, X=Cl) with λ_{max} = 262 nm in MeCN changed to λ_{max}= 300 nm, due to be the formation of an anionic form of the triazole-3-thione **220**$^-$. By irradiation there is an intramolecular ET to form the diradical anion **222**, which produces a cyclohexadienyl anion **223** by the intramolecular addition of the sulfur radical, followed by halide ion expulsion to yield the product **221** (Scheme 53).[83]



Scheme 53. Mechanistic proposal for the synthesis of benzothiazines **221** from **220**.

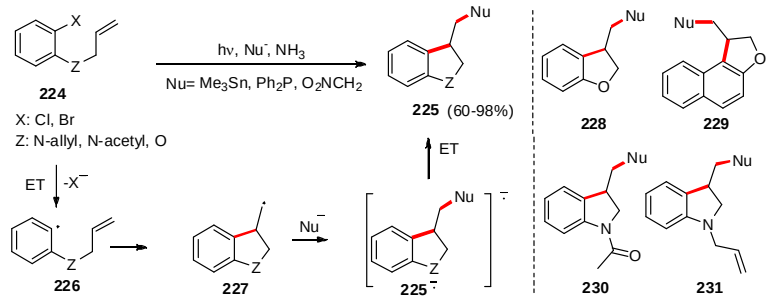
6. *Exo* or *endo* radical ring closure $S_{RN}1$ reaction

The synthesis of carbocyclic and heterocyclic compounds by radical cyclization with a double or triple bond is nowadays a well-known process and has become a preeminent tool in organic synthesis. The advantages of radical cyclization in comparison with ionic process include high functional group tolerance, mild reaction conditions and high levels of regio and stereoselectivities.[84]

Ring closure reactions take place by intramolecular addition of an aromatic radical to a double bond at an appropriate distance. The radical formed after ET and C-X bond fragmentation, can be trapped by the double bond in an *exo* or *endo* ring closure mode, and has been widely studied with regard to both its regio- and stereochemical aspects.

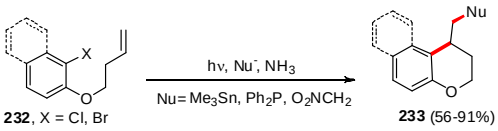
Aryl halides and diazonium salts substituted at the *ortho*-position with an *O*-allyl or *N*-allyl chain have been used for the preparation of substituted and unsubstituted 2,3-dihydrobenzofuranes and 2,3-dihydro-1*H*-indoles under different reaction conditions.[85] For instance, the photostimulated reaction of substrates **224** with Nu$^-$ afforded the ring closure substitution products **225** (Scheme 54). The mechanism proposed for this process is that by ET to **224** and after C-X bond fragmentation the radical **226** is formed, which is trapped by

the double bond in a *5-exo-trig* ring closure mode to afford radical **227**. The resulting alkyl radical **227** is able to react with Nu^- to afford the radical anion **225**$^{\bullet-}$ that finally afforded the ring closure substitution product **225**. In this way, 3-substituted 2,3-dihydrobenzofurans **228,** 1-substituted-1,2-dihydronaphtho[2,1-*b*]furan **229**, and 3-substituted-2,3-dihydro-1-*H*-indoles **230-231**, were obtained in very good yields.[86]



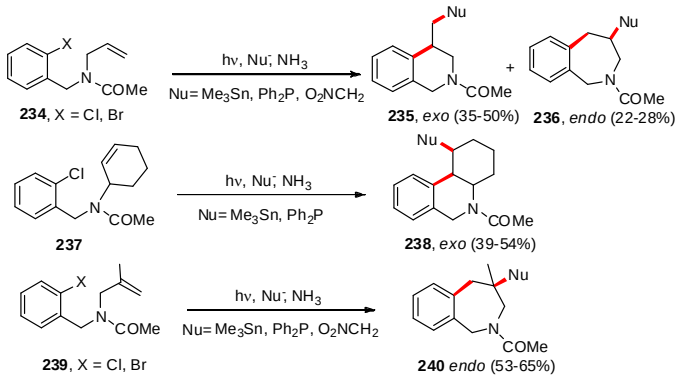
Scheme 54. Mechanism proposed for the synthesis of heterocycles **225, 228-231**.

Moreover, the tandem 6-*exo-trig* cyclization-$S_{RN}1$ reactions with 1-(but-3-enyloxy)-2-halobenzenes and 1-(but-3-enyloxy)-2-halonaphthalenes **232** afford 4-substituted chromanes and benzo(*f*)chromanes **233** in good to excellent yields (Scheme 55).[87]



Scheme 55. Synthesis of 4-substituted chromanes and benzo(*f*)chromanes **233** from **232**.

In a similar way, *N*-allyl-*N*-(2-chlorobenzyl)acetamide **234** reacted with nucleophiles to furnish the cyclized-substituted compounds 6-*exo-trig* **235** (35-50%) and 7-*endo-trig* **236** (22-28%) (Scheme 56).[88] In this sense, the acetamide **237** reacts with nucleophiles to yield only the *6-exo-trig* ring closure p*r*oduct **238**.



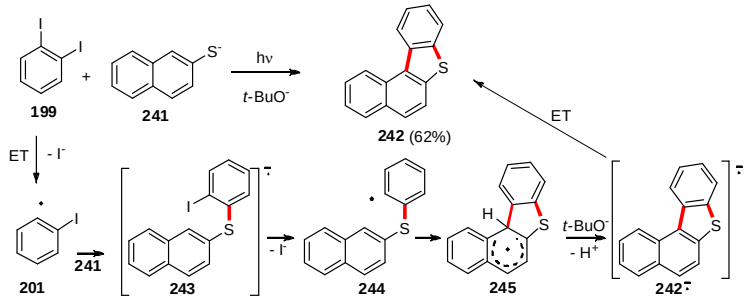
Scheme 56. Radical ring closure reaction followed by an $S_{RN}1$ reaction.

However, changing the *N*-cyclohexene moiety of **237** by *N*-(2-methylallyl)acetamide moiety **239** affords only the *7-endo-trig* ring closure product **240** with good yields. These reactions were modeled using DFT method and related the products distributions to the structure of the aliphatic radical intermediates.

7. Miscellaneous ring closure reactions

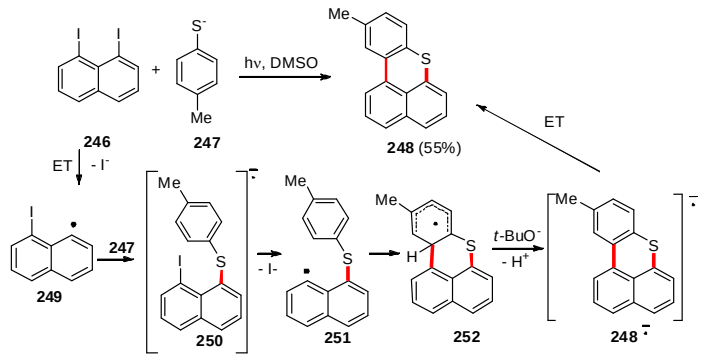
7.1. Heterocyclic synthesis by $S_{RN}1$-BHAS reactions

The photostimulated reaction of *o*-diiodobenzene **199** with naphthalene-2-thiolate ions **241** and an excess of *t*-BuOK afforded benzo[*d*]naphtho[2,1-*b*]thiophene **242** (Scheme 57). When **199** receive an electron, the *o*-iodophenyl radical **201** is formed after C-I bond fragmentation. The radical **201** couples with **241** by the $S_{RN}1$ mechanism to afford radical anion **243**, which after C-I bond fragmentation affords radical **244**. A base promoted homolytic aromatic substitution (BHAS) reaction[89] in the α position of the naphthalene ring leads to the cyclohexadienyl radical **245**, which is deprotonated by *t*-BuOK to form radical anion **242**$^{\bullet-}$, and by ET product **242** is observed.[90]



Scheme 57. Mechanism proposed for the formation of ring closure product **242**.

The photostimulated reaction of 1,8-diiodonaphthalene **246** with 4-methylbenzene tiolate ions **247** in DMSO affords the ring closure product 10-methylbenzo[*k,l*]thioxanthene **248** with moderate yields (Scheme 58).[91] The mechanism proposed is similar to Scheme 57: when **246** receives an electron, the radical **249** is formed after C-I bond fragmentation, which couples with **247** to afford radical anion **250**.

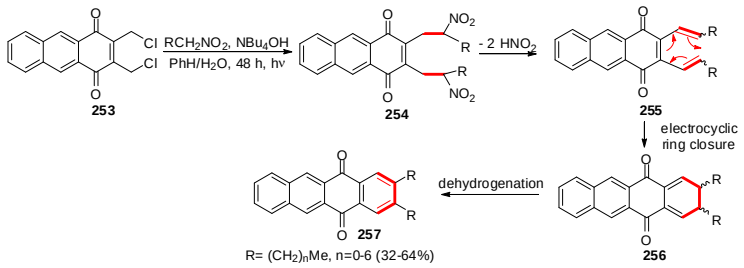


Scheme 58. Mechanistic proposal for the synthesis of thioxanthene **248**.

After C-I bond fragmentation radical **251** is build up and by an BHAS reaction[89] the product **248** is observed.

7.2. Heterocyclic synthesis by $S_{RN}1$ reaction followed by nitrous acid elimination-electrocyclic ring closure reaction

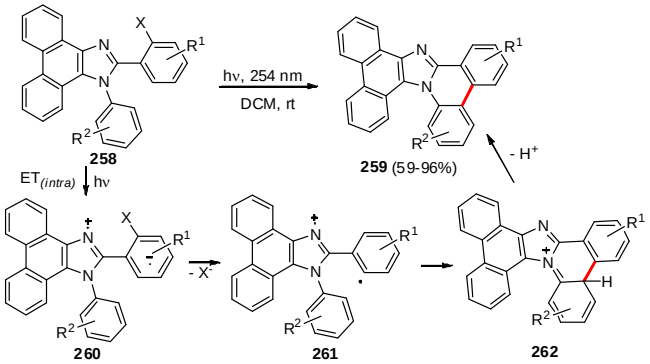
The substrate **253** reacted successfully with the anion of nitroalkanes RCH_2NO_2 under irradiation in phase-transfer conditions with NBu_4OH in PhH/H_2O for 48 h. Two consecutive $S_{RN}1$ reactions led to a bis-C-alkylated product **254**, followed by base-promoted nitrous acid elimination by the base giving the product **255**. Electrocyclic ring closure reaction afforded the dihydro dialkylnaphthacene-5,12-diones **256**, that by dehydrogenation finally gave 2,3-dialkylnaphthacene-5,12-dione **257** (Scheme 59).[92]



Scheme 59. Mechanistic proposal for the formation of 2,3-dialkylnaphthacene-5,12-dione **257** from **253**.

7.3. Ring closure reactions by formation of radical anion-radical cation pair under irradiation

The photostimulated reaction of several of phenanthro[9,10-*d*]imidazoles **258** (λ=254 nm) in CH_2Cl_2 afforded **259** in good yields (Scheme 60, with 17 examples). This reaction also occurred with good yields in other solvents (PhMe, THF, etc), but due to solubility problems, CH_2Cl_2 was chosen. The mechanism proposed is that under irradiation there is an ET from the imidazole moiety to the pendant halobenzene to form a radical cation–radical anion pair **260**. By C-X bond fragmentation, the diradical cation **261** is formed, which collapses by ring closure reaction in the cation **262**, and by losing a proton gives the more stable tautomer **259**.[93]



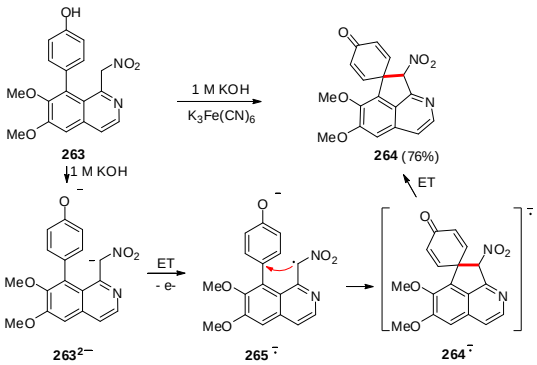
Scheme 60. Mechanism proposed and synthesis of products **259**.

Other structures were also synthesized, and using substrates with two leaving groups some double ring closure reactions were found.

7.4. Heterocyclic synthesis by oxidation of a carbanion followed by a coupling reaction

Several examples of oxidative cyclization of dianions via nitroalkyl radicals have been reported, such as dinitronate anions. The successful synthesis of vic-dinitrocycloalkanes has good synthetic potential because of the simple conversion of nitro groups to other functionalities.[94]

Based on the Kende annulation reaction for the preparation of spiro cycles from the selective oxidation of dicarbanions in general, and also of the phenolic nitronate to give the cyclization product,[95] Cha, Kim *et al* studied the synthesis of a precursor of the alkaloid pareitropone. The dianion phenolic nitronate **263**$^{2-}$ was used as the model of the precursor, prepared from **263** and 1 M solution of KOH, which by oxidation with $K_3Fe(CN)$ afforded the distonic radical anion **265**, which by C-C bond formation gave the ring closure spiro cycle conjugated radical anion **264**$^{\cdot-}$ that by ET yielded the product **264**. This reaction is the type of the $S_{RN}1$ mechanism, in which the radical intermediate **265** is formed by oxidation of an anion, rather than by fragmentation of a radical anion with an adequate leaving group (Scheme 61).[96]



Scheme 61. Mechanistic proposal for the synthesis of **264**.

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