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Iterative double cyclization reaction by $S_{RN1}$ mechanism. A theoretical interpretation of the regiochemical outcome of diazaheterocycles

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In this report, we present a synthetic and mechanistic study of novel iterative double cyclization intramolecular $S_{RN1}$ reactions from diamides bearing two aryl iodide moieties. This cyclization affords aromatic diazaheterocyclic compounds in good yields. Two synthetic strategies were employed for their preparation: intramolecular $S_{RN1}$ and Homolytic Aromatic Substitution. The mechanism is non-trivial and we propose that radicals are intermediates. The regiochemistry was studied using computational calculations, employing the DFT method and B3LYP functional. It was found that the distribution of products depends on the cyclization activation energies, proportion of neutral conformers, and the type of the electron transfer reaction.

1 Introduction

Aromatic azaheterocycles present interesting pharmacological properties related to the planarity of the system and consequently to their DNA-chain intercalating abilities, which make them suitable for anti-neoplastic or mutagenic applications.$^{1-4}$ Due to their significant biological activity, they are an important class of heterocyclic compounds in medicinal chemistry, being able to bind with high affinities to the aryl hydrocarbon receptor (AhR), which activates the regulatory protein. This effect was studied experimentally and using QSAR methods.$^5$–$^8$

In another context, N-containing aromatic heterocycles having more than one nitrogen atom have received an increasing interest owing to the fact that their complexes with transition-metal ions show interesting properties in harvesting light and reemitting it at a wavelength that depends on the metal ion used.$^9$–$^{10}$

The radical nucleophilic substitution, or $S_{RN1}$ reaction, is a process through which an aromatic nucleophilic substitution is achieved. Since the scope of this process has been increased considerably over recent decades, it has become an important synthetic strategy.$^{11}$ The initiation step is by 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$_2$) are needed to initiate the reaction.$^{12}$

Several nucleophiles, for example carbanions and heteroatomic anions, can be used for $S_{RN1}$ reactions to form new C–C or C–heteroatom bonds in good yields. However, an exception to these is the reaction of phenyl amide anions with haloaromatic substrates, where C–N and C–C bond formations were achieved instead.$^{13}$ 2-Naphthylamide anions can react by the photo $S_{RN1}$ process with PhI, 4-MeOC$_6$H$_4$I and 1-iodonaphthalene in liquid ammonia. Here, 1-aryl 2-naphthylamines were formed regioselectively in 45–63% yields, with only 3–6% of N-arylation.$^{14}$ Moreover, double arylation has been previously achieved using $p$-dihalobenzene as a substrate with the anions of 2-naphthylamine and 9-phenanthrylamine under irradiation in liquid ammonia.$^{15}$

An $S_{RN1}$ synthetic strategy to obtain heterocyclic compounds was previously developed based on the intramolecular cyclization of substrates bearing both the leaving group and the nucleophilic center.$^{16}$ This methodology has been recently applied to the synthesis of 1-phenyl-1-oxazolinoindan derivatives and their related compounds.$^{17}$
tetracyclic isoquinoline derivatives; a series of substituted 9H-carbazoles and carbolines; aporphine and homoaporphine alkaloids; pyroles, indoles, and pyrazoles; indazoles; pyrido[1,2-a]benzimidazoles; 2- pyryrolyl and 2-indoly 1 benzoxazoles, among others. Moreover, an intramolecular \(S_{RN1}\) reaction of substituted iodobenzylamines with several tetratones afforded a series of benz[c]phenanthridines with modest overall yields after several steps.

Recently, Rossi et. al. proposed a new approach for the syntheses of phenanthridines and benzophenanthridines (2) by intramolecular \(ortho\)-arylation of (2-halobenzyl)-N-aryl amines (1) (eq 1). In these reactions, the cyclization of compounds such as 1 gives very good yields of the phenanthidine derivatives (2 (44-85%). On other hand, by direct photolysis of the C–I bond of 1, the synthesis of 2 was achieved with 30-95% yields via Homolytic Aromatic Substitution (HAS).

It is worth noting in the literature an example reported of double ring closure reactions by \(S_{RN1}\) where two 5-membered rings are formed. In this case, two intramolecular consecutive \(S_{RN1}\) of substrate 3 were reported to give dicarbazol 4 in 67% yield (eq 2). However, there is no other reported example where a double closure afforded two 6-membered rings. With this in mind, in the present article we report a double cyclization reaction to give 6-membered diazaheterocyclic compounds. In order to explain their regiochemical outcome, a computational study of the non-trivial mechanism is presented.

### Scheme 1 Synthesis of diamine 8

Following the same procedure, substrates 9 and 11 were obtained in 26% and 65% isolated yields, from 4,4′-diaminobiphenyl and 1,3-diaminopyridine, respectively (Scheme 2), using the new synthetic intermediates 10 and 12.

### Scheme 2 Retrosynthetic preparation of diamines 9 and 11

#### 2.1 Intramolecular \(S_{RN1}\) Reactions

The results of the photostimulated reaction (180 min) of the diamines 8, 9 and 11 in the presence of excess \(t\)-BuOK (5 equiv) under a nitrogen atmosphere are presented in Table 1. Under these reaction conditions, and after oxidation with \(\text{MnO}_2/\text{CHCl}_3\), the diamine 8 afforded good yields of diphenanthridines 13 (46%) and 14 (25%) using liquid ammonia as the solvent (Table 1, entries 1-3 and eq 3).
hydrogen–donor capacity of the media. For instance in DMF, the second cyclization reaction competed with the hydrogen–reduction product and the presence of t-BuOK.

In dark conditions, there was no reaction of the reaction was partially inhibited by m-dinitrobenzene (m-DNB), a well-known inhibitor of the S_{DNB} processes (Table 1, entry 5), as well as being inhibited by radical traps such as TEMPO (Table 1, entry 6). This indicates, for this system, that the double cyclization is slow with respect to the single ring closures previously reported, in which TEMPO caused no inhibition.

The reaction was tested in the organic solvents DMF, diphenylmethane and DMSO. However, the yields of diphenanthridines 13 and 14 were lower than in NH\textsubscript{3}.

In the HPLC/MS chromatogram profile of the selected reaction (Table 1, entry 7; see ESI), the double-cyclization products 13 and 14 were observed, together with the monocyclization–reduction product 15, monocyclization with iodo retention 16 and the monocyclization–fragmentation (C\textsubscript{benzylic–N}) product 17 (Figure 1). The absence of a double–reduction product and the presence of 15 and 16 indicate that the first cyclization was favored with respect to the second one. The second cyclization reaction competed with the hydrogen– abstraction from the solvent to afford 15, and with the C\textsubscript{benzylic–N} fragmentation to give 17.

In this work, the product yield of 13 was 46% (24% overall yield) which is comparable, and in some cases better, than those obtained by other synthetic strategies. Starting from analog chloride derivative type 8, a 4% yield of 13 was obtained through a benzyne type mechanism using NaNH\textsubscript{4}/THF\textsuperscript{33} and 40% yield using KNH\textsubscript{2}/NH\textsubscript{3}\textsubscript{aq}\textsuperscript{34}. However, there is no specification for the preparation of the chloride derivative type 8, which is not a single molecule. Furthermore, a comparable yield of 13 (49% yield) was also reported using photochemical methodology. However, these reactions were irradiated for 24-36 hours.

Concerning the synthesis of 14, there is only one report in which, after four consecutive reactions, the product was obtained in 14% yield.\textsuperscript{26} This value is comparable to that obtained by the route where 14 was afforded with 9% overall yield.

Following the same methodology, the photostimulated reaction of diamine 9 was carried out in NH\textsubscript{3} as the solvent, and the diphenanthridine 18 was obtained in 17% yield (Table 1, entry 9 and eq 4). In this case, a 48% yield of unreacted substrate 9 was achieved, due to its very low solubility in the reaction media. When the reaction was carried out in organic solvents such as diglyme and DMF, diazaheterocycle 18 was formed, with only a reduced product being observed (results not tabulated). Despite its regular yield, diazaheterocycle 18 has not been described in the literature.

In the same way, the photostimulated reaction of diamine 11 was carried out in NH\textsubscript{3} and the double cyclization products 19 (C–C coupling) and 20 (C–N coupling) were both afforded in 13%, together with the monocyclization–reduction product 21 in 22% yield (Table 1, entry 10 and eq 5). However, when the reaction was carried out in DMF as the solvent, the yields of the cyclic products 19 and 20 did not improve (results not tabulated).

Table 1 Photochemical reactions of compounds 8, 9, and 11 in the presence of t-BuOK.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substr</th>
<th>Solvent</th>
<th>Product Yields (%)</th>
<th>( \Gamma ) (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (42)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (46)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (46)\textsuperscript{c}</td>
<td>14 (17)\textsuperscript{d}</td>
</tr>
<tr>
<td>4\textsuperscript{e}</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (--)</td>
<td>14 (--)</td>
</tr>
<tr>
<td>5\textsuperscript{f}</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (3)</td>
<td>14 (&lt;1)</td>
</tr>
<tr>
<td>6\textsuperscript{g}</td>
<td>8</td>
<td>NH\textsubscript{3}</td>
<td>13 (18)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>7\textsuperscript{h}</td>
<td>8</td>
<td>DMF</td>
<td>13 (21)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>8\textsuperscript{i}</td>
<td>8</td>
<td>Diglyme</td>
<td>13 (11)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>9\textsuperscript{j}</td>
<td>9</td>
<td>NH\textsubscript{3}</td>
<td>18 (17)</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>NH\textsubscript{3}</td>
<td>19 (13)</td>
<td>20 (13)</td>
</tr>
</tbody>
</table>

\( ^{a} \) Photostimulated reactions were performed with [substrate]=1.33 \times 10^{-3} M and five times with [t-BuOK]. The substrate was previously dissolved in DMSO. Reaction times were 180 min, unless indicated otherwise. Irradiation was conducted in a reactor equipped with two high pressure lamps of model Phillips HPI-T plus 406-W (air- and water-refrigerated) with a maximum emission at 530 nm. Oxidation reactions were carried out by stirring the crude reaction with MnO\textsubscript{2} in CHCl\textsubscript{3}. Yields of the products was determined by \( ^{1} \text{H}-\text{NMR}.\)

\( ^{b} \) The halides were determined potentiometrically.

\( ^{c} \) The substrate was not dissolved in DMSO.

\( ^{d} \) Isolated yield.

\( ^{e} \) Dark conditions. Only the substrate was detected (95% yield).

\( ^{f} \) m-dinitrobenzene was added (30 mol%).

\( ^{g} \) TEMPO was added (30 mol%).

\( ^{h} \) [substrate] = 100 \times 10^{-3} M and [t-BuOK] = 70 \times 10^{-2} M.

\( ^{i} \) [substrate] = 20 \times 10^{-3} M and [t-BuOK] = 140 \times 10^{-3} M.

\( ^{j} \) Reaction time 240 min. Substrate was detected (48% yield).
Although, diazaheterocycle 19 was obtained in 68% yield in two consecutive reactions (diodination of 2,6-diaminopyridine followed by a double Suzuki coupling with 2-formylphenyl boronic acid and spontaneous cyclization and aromatization), our strategy did not include the use of a transition metal. This is important because impurities can be avoided and the products used directly in pharmaceutical and other industries. In addition, for compounds 20 and 21 there are no precedent in the literature of their preparation.

Taking into account that in all reactions double cyclization products were formed, and considering the results presented in Table 1 and those previously reported, we suggest that S_{RN1} is the operating mechanism. Furthermore, the results in dark conditions, the inhibitor exerted by TEMPO and another inhibitor (m-DNB), and the presence of monocyclization–reduction product 15, are consistent with aryl radicals and radical anions as intermediates.

### 2.2 Intramolecular HAS Reactions

In order to explore other possible reaction patterns of the substrates described above, we used the direct photolysis reaction of compounds 8, 9 and 11 to obtain the diazaheterocycles. These reactions were carried out in a quartz tube using anhydrous acetonitrile as the solvent. Photostimulation was achieved by irradiating with a wavelength of 254 nm. In this cyclization reaction, the presence of a base is not required because initiation takes place through the homolytic C–I breaking bond. The aryl radicals thus formed can be added to the π system of the central aromatic ring to yield a cyclohexadienyl radical. Possibly, this radical transfers the tertiary hydrogen atom to other radical intermediates present in the reaction media (i.e. iodine atom) to give the neutral cyclic product.

After a screening of conditions, the best results were found to be obtained when degassing the reaction media by nitrogen bubbling and sonication. Results of photolysis reactions in these conditions for the three substrates studied are presented in Table 2. In the photostimulated reaction (120 minutes) of 8, the cyclic product 13 was obtained in 36% yield, and traces of isomer 14 were also obtained (Table 2, entry 2). Although the S_{RN1} reaction gave a higher yield of both products (Table 1, entry 2), the direct photolysis was more selective towards product 13.

In contrast with the S_{RN1} conditions (Table 1, entry 9), substrate 9 was completely soluble in the direct photolysis conditions. However, the yield of the double-cyclization product 18 was less than 10% (Table 2, entries 3-5). A similar behavior was observed in the reaction of 11, where the double-cyclization products (19 and 20) were not obtained and only the monocyclization–reduction product 21 was detected (Table 2, entry 6).

### Table 2 Photolysis reaction of compounds 8, 9 and 11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>60</td>
<td>13 (28) 14 (&lt;5)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>120</td>
<td>13 (36) 14 (5)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>60</td>
<td>18 (6)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>120</td>
<td>18 (6)</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>180</td>
<td>18 (6)</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>60</td>
<td>19 (36) 20 (&lt;5) 21 (32)</td>
</tr>
</tbody>
</table>

* Photostimulated reactions were performed with [substrate] = 1 mg/mL with acetonitrile as solvent (7 mL) in a quartz tube, under a nitrogen atmosphere and bubbling during all the reaction time. The reaction mixture was previously degassed by nitrogen bubbling and sonication for 20 minutes. Irradiation was conducted in a photochemical reactor equipped with nine Hg high pressure lamps (254 nm). Oxidation reactions were carried out by stirring the crude reaction with MnO2 in CHCl3. Product yields were determined by 1H-NMR.

### 2.3 Mechanism and Theoretical Calculations

#### 2.3.1 Diamine 8

The experimental behavior of the system was modeled using the DFT methodology and the B3LYP functional. A systematic inspection of the conformational potential energy surface (PES) of diamine 8 led us to conclude that principally two conformers, 8 s-cis and 8 s-trans, are present under the conformational equilibrium (eq 6). The Boltzmann distribution of conformers (T =240 K) showed that their conformer distribution ratio is 1.2:1 for 8 s-cis:8 s-trans.

In the superbasic reaction medium, the dianions 8 s-cis² and 8 s-trans² can be formed. The s-cis/s-trans isomerization barrier for the anions is high, because it involves rotation around C_{aryl} and the N2 bond, which has a partial double-bond character. Thus, the distribution of the anions 8 s-cis²:8 s-trans² is directly related to its neutrals (8 s-cis:8 s-trans). The initiation step involves a photoinduced ET to 8²⁺ followed by fragmentation of a C–I bond to give the distonic radical diamion [8]²⁻ (s-cis and s-trans) and τ anion (Scheme 3). The intermediate radical diamion [8]²⁻ adds quickly, via intramolecular C–C cyclization, to afford the monocyclic conjugated radical diamion [22]⁻ (s-cis and s-trans), which is separated from the second o-iodoaryl moiety by a C_{aryl} atom. The radical diamion [22]⁻ may follow either an intramolecular (Scheme 4) or an intermolecular ET reaction pathway (Scheme 5).
Scheme 3 Possible initiation step and first ring closure reaction of $8^2$-

Following the intramolecular pathway, $23^-$ (s-cis and s-trans) can be formed (Scheme 4). However, cyclization to give radical anion $24^-$ is favored from $23^-$ s-cis because in $23^-$ the negative charge is localized in the C vicinal to C$_{sp3}$ of the central ring (Figure 2). After ring closure radical anion $24^-$ is yielded. This transfers the extra electron to $8^2$ to afford $24$ and $[8^2]^+$, with the latter propagating the reaction cycle. Ultimate tautomerization of $24$ in the basic media, and subsequent oxidation will afford $13$. Thus, the $23^-$ s-trans isomer cannot cyclize, and reduction of this radical anion by hydrogen-abstraction from the solvent occurs to finally yield the monocyclization–reduction product $15$ (Scheme 4). Under this intramolecular ET pathway, only the cis product $13$ and reduced product $15$ will be observed.

On the other hand, if intermolecular ET from $[22^+]^-$ to $8^2$- is followed, $22$ (s-cis and s-trans) and $[8^2]^+$ can be afforded (Scheme 5). The anion $22^-$ in the basic medium rearomatizes the central ring to give $25^-$ (s-cis and s-trans), which can initiate a second S$_{RN1}$ cycle through the formation of the distonic radical anion $[26^+]^-$ (s-cis and s-trans). Given the electronic distribution of $[26^+]^-$, both ortho positions to the amide group are favored to couple with aryl radicals (Figure 2B). Following this reactive pathway, $[26^+]^-$ and $26$ s-trans $^-$ can cyclize to give products $13$ and $14$. Experimentally, we observed that both products are formed together with products $15$ and $16$ (Figure 1). Moreover, product $16$ is formed through intermediate $25^-$, via protonation–oxidation reactions. Therefore, intermolecular ET is operating in the cyclization of $8^2$. 

Figure 2 A) Resonance structures for radical anion $23^-$. B) Electrostatic potential of radical anions $23^-$ and $[26^+]^-$. 

Scheme 4 Intramolecular ET from $[22^+]^-$. 

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Considering that the electronic structure of radical dianion \([26]^-\) (s-cis and s-trans) corresponds to a conjugated species and that the evaluated energy for its cyclization is high (see ESI), we propose that cyclization to occurs via the distonic radical anion \([26]^-\) (s-cis and s-trans), which can be present under the reaction conditions (eq 7).

The PES for cyclization of radical anions \([26]^-\) (s-cis and s-trans) presented in Figure 3 shows that both conformers cyclize with similar energies to give the s-cis and s-trans cyclic products. Considering that the kinetics of ring closure are similar and that the interconversion between the s-cis and s-trans conformers is very slow because it implies a rotation around C-N bond with a double-bond character,§ then the product distribution for this path is governed by this conformational distribution and should be close to 1.2:1. Taking into account that the experimental ratio of s-cis:s-trans products is 1.8:1, we propose that not only the intermolecular ET pathway, but also the intramolecular ET pathway is taking place in this system.

![Scheme 5 Intermolecular ET from \([22]^-\) (s-cis and s-trans) are present under conformational equilibrium (eq 8) in a relationship 1:1.8, respectively (T = 240 K).](image)

**Figure 3** PES to cyclization of \([26]^-\) radical anion.

### 2.3.2 Diamine 11

Following the same procedure as that for diamine 8, the reaction mechanisms for diamine 11 were analyzed. A systematic inspection of the conformational PES of 11 led us to conclude that principally the two conformers 11 s-cis and 11 s-trans are present under conformational equilibrium (eq 8) in a relationship 1:1.8, respectively (T = 240 K).

As mentioned above, the presence of product 21 (see eq 5) indicate that the first cyclization (C–C coupling) is favored with respect to the second one (C–C or C–N coupling).

In principle, once radical dianion \([28]^-\) is formed, two reactive pathways may be followed: intramolecular ET (Scheme 6) and intermolecular ET (Scheme 7).

Similar to 8, if the reaction takes place by intramolecular ET (Scheme 6), only product 20 (C–N coupling) will be obtained from the 29 s-trans. This behavior can be explained due to the negative charge being localized on the N atom of the pyridine central ring for the radical anion 29 (Figure 4). Thus, the 29 s-cis isomer cannot cyclize, and reduction of this radical anion (by hydrogen-abstraction from the solvent) will occur to finally yield the monocyclization–reduction product 21. Under this intramolecular pathway, product 19 will not be formed.

![Scheme 6 Intramolecular ET](image)

**Scheme 6** Intramolecular ET (Scheme 6) and intermolecular ET (Scheme 7).

### References

1. Section 2.3.1
2. Section 2.3.2

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If intermolecular ET is in play (Scheme 7), the formation of both products 19 and 20 is possible. As the relationship of 11$^{−}$, $s$-cis:$s$-trans conformers is 1:1.8, the ratio of the radical anions $32$ $s$-cis$^{−}$ to $32$ $s$-trans$^{−}$ will remain constant as well as the ratio of products.

Taking this into account, the second cyclization path was theoretically investigated. The PES for this system shows that the activation energy for C–N coupling is 10.4 kcal/mol, while for the C–C coupling is only 2.0 kcal/mol (Figure 5). On the other hand, the activation energy for hydrogen–abstraction of $32$ to yield 21 is 6.5 kcal/mol. This indicates that hydrogen–abstraction competes with C–N coupling, and thus only the monocyclization–reduction product 21 is obtained from $32$ $s$-trans$^{−}$ and only product 19 is formed from $32$ $s$-cis$^{−}$. Accordingly, product 20 is formed by the intramolecular ET pathway (Scheme 6). Similarly to 8, in this system both ET pathways are present.
3 Conclusions

In this article, we have presented the synthesis of novel diazaheterocycles by intramolecular $S_{RN1}$ reactions. This is the first study that explores in detail reactions where two ring closures occur consecutively. Considering that during the reaction two new junctions C–C or C–N are formed to result in the formation of two new heterocycles within the same molecule, it is ensured that the diazaheterocycles have good yields. Direct photolysis reactions of the amines were carried out and dual-closure rings were observed. However, a lower percentage of products than that obtained by $S_{RN1}$ were found. This may have been due to the instability of intermediates and products formed under the irradiation conditions used in the photolysis reactions.

Radicals and radical anions are intermediates of these reactions. The mechanism in the presence of a base was studied using DFT calculations, with the product distribution depending not only on the ratio of conformers of the neutral species, but also on the type of the ET reaction and the relative energies of the coupling. After the first cyclization, the reduction of the aryl radical was always in competition with the second cyclization reaction. Finally, we suggest that for these systems both intramolecular and intermolecular ET were present.

4 Experimental

4.1 Computational Procedure

The conformational search was carried out using a Vconf program. Calculations were performed using the Gaussian09 program, the B3LYP[38,39] DFT functional and the 6-31+G** basis set. The B3LYP functional and the 6-31+G**, 6-311+G*, and 6-311+G** basis sets have been previously tested for similar systems. All determinations were carried out with full geometry optimization, including for all cases the effect of the solvent through Tomasi’s polarized continuum model (PCM)[42,44] as implemented in Gaussian09. The effect of $NH_2(1)$ was evaluated using methanol as the model polar solvent.[38] The TS and intermediates were localized by a scan of the distinguished reaction coordinate. Then, after refinement, a characterization of stationary points was made by Hessian matrix calculations, with all positive eigenvalues for a minimum and only one negative eigenvalue for the TSs. The energy reported for all species includes zero-point corrections.

4.2 General Methods

The products were quantified by $^1$H-NMR. All NMR spectra were obtained on a 400 MHz Spectrometer ($^1$H-NMR (400 MHz), $^{13}$C-NMR (100 MHz), COSY, HSQC, HMBC and NOE) using CDCl$_3$ as the solvent unless otherwise indicated. The coupling constants ($J$) are given in hertz. The HPLC/MS analyses were carried out on a HPLC equipment with a reverse C-18 stationary phase (15 cm x 4.6 x 5 micron) and MeCN:water mixtures as the mobile phase; coupled to high-resolution mass spectra on a TOF analyzer, using an ESI ion source, with nitrogen as the nebulizing and drying gas. High-resolution mass spectra were recorded on a TOF analyzer, using an ESI source in a positive mode, with nitrogen as the nebulizing and drying gas, and sodium formiate (10 mM) as the internal calibrant.

4.3 Materials

Acetic anhydride, sodium hydride (60% on mineral oil), 2-iodobenzyl chloride and potassium tert-butoxide were obtained from commercial sources. DMSO was stored over 4 Å molecular sieves. DMF was distilled from Na metal and stored under nitrogen over 4 Å molecular sieves. Diglyme was distilled from Na metal and stored with Na wires. To prepare the substrates, commercially available 1,4-diaminobenzene, 4,4'-diaminobiphenyl and 2,6-diaminopyridine were used. Silica gel (0.063-0.200 mm) was used in column chromatography and on 2 mm plates (silica gel 60 PF254) in radial thin-layer chromatography purification. All solvents were of analytical grade and used as received from the supplier.

$N^2,N^4$-bis(2-iodobenzyl)benzene,1,4-diamine (8). 1,4-Diaminobenzene (9.25 mmol, 1g) was added to a round-bottomed flask equipped with a reflux condenser and magnetic stirring. Next, an excess of acetic anhydride was added to give the diacetylated intermediate 6, and this mixture was stirred for 15 minutes. Then, water was added and the reaction was refluxed for one hour before the mixture was left to cool at rt. The solid was filtered off, washed with cold water and dried. DMSO (10 mL) and compound 6 (5.2 mmol) were added to a dried shilenk tube (50 mL) with an N$_2$ atmosphere and magnetic stirrer. NaH (10.5 mmol) was then added in small parts, and between each addition, a vacuum was applied to the reaction to favor gas evolution. When an anion was formed, 2-iodobenzyl chloride (1 mmol) was added and the mixture was stirred for 24 hours. The precipitated 7 was favored by water addition, which was filtered off and washed with cold water. To carry out hydrolysis of the acetyl group, 7 (1 mmol) was poured into a round-bottomed flask equipped with a reflux condenser and magnetic stirring. Then, ethanol (20 mL), 37% hydrochloric acid (10 mL) and 98% sulphuric acid (10 drops) were added, and the mixture was boiled for 24 hours. The mixture was left to cool at rt and the precipitated hydrochloride was filtered off and washed with cold ethanol. To obtain free amine 8 (53% global yield), basic medium extractions were carried out. The
products 7 and 8 were characterized by standard spectroscopic techniques as follows.

The compound 8 was isolated by crystallization as hydrochloride from acid ethanol and basic medium extraction. \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta\)H: 3.82 (br s, 2H); 4.24 (s, 4H); 6.53 (s, 4H); 6.95 (td, 2H, \(J = 7.5\) Hz, 1.6Hz); 7.29 (td, 2H, \(J = 7.5\) Hz, 1.1Hz). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta\)C: 51.1; 95.6; 127.2; 128.4; 128.8; 139.1; 142.6; 154.9. ESI-HRMS m/z [M + H]\(^{+}\) calcd for C\(_{27}\)H\(_{23}\)N\(_{2}\)O\(_{3}\) 541.9638, found 541.9630.

\(N,\text{N}-(1,4\text{-phenylene})\text{bis(N-(2-iodobenzoyl)acetamide)} \quad (7)\): white solid. Isolated by precipitation from the reaction media as intermediate. \(^{1}H\)-NMR (400 MHz, DMSO-d\(_6\), \(\delta\)H: 1.83 (s, 6H); 4.81 (s, 4H); 6.97 (td, 2H, \(J = 7.8\) Hz, 4.6Hz); 7.26 (s, 4H); 7.32 (br d, 4H, \(J = 4.3\)Hz); 7.77 (d, 2H, \(J = 7.7\) Hz, 1.1Hz). \(^{13}C\)-NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)C: 22.9; 56.9; 99.5; 128.8; 129.4; 139.6; 139.9; 142.0; 146.2; 169.8. ESI-HRMS m/z [M + Na]\(^{+}\) calcd for C\(_{32}\)H\(_{29}\)N\(_{4}\)O\(_{2}\)Na 646.9684, found 646.9689.

\(N,\text{N}-(\text{bis-(2-iodobenzoyl)}-[1,1'\text{-biphenyl}]-4,4'\text{-diamine}) \quad (9)\): this reaction was carried out using a procedure similar to that described for 8, but the substrate utilized was 4,4'-diaminobiphenyl (10 mmol). Compound 9 (430 mg, 26% global yield) was separated as a yellow solid by column chromatography using petroleum ether:dichloromethane, 10:70.

\(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta\)H: 4.21 (br s, 2H); 4.35 (s, 4H); 6.64 (br d, 4H, \(J = 6.5\)Hz); 6.98 (td, 2H, \(J = 7.6\)Hz, 1.6Hz); 7.31 (td, 2H, \(J = 7.6\)Hz, 1.1Hz). 7.35 (br d, 4H, \(J = 8.0\)Hz). 7.1 (dd, 2H, \(J = 7.1\)Hz, 1.6Hz). 7.86 (dd, 2H, \(J = 7.9\)Hz, 1.1Hz). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta\)C: 53.4; 98.6; 113.3; 127.2; 128.4; 128.8; 129.6; 139.4; 139.5; 142.0; 169.8. ESI-HRMS m/z [M + Na]\(^{+}\) calcd for C\(_{27}\)H\(_{23}\)N\(_{2}\)O\(_{3}\)Na 646.9684, found 646.9950.

\(N,\text{N}-(\text{bis-(2-iodobenzoyl)}-[1,1',1'\text{-tridentate})]-4,4'-\text{diamine}) \quad (10)\): white solid. Isolated by extraction with CH\(_{2}\)Cl\(_2\) (3 x 75 mL) from reaction crude as intermediate. \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta\)H: 1.98 (s, 6H); 5.02 (s, 4H); 6.92 (t, 2H, \(J = 7.5\)Hz); 7.13 (d, 4H, \(J = 7.8\)Hz); 7.30 (t, 2H, \(J = 7.5\)Hz); 7.37 (dd, 2H, \(J = 7.6\)Hz, 1.6Hz); 7.50 (d, 4H, \(J = 8.5\)Hz). 7.74 (d, 2H, \(J = 8.7\)Hz). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta\)C: 22.7; 57.0; 99.2; 128.1; 128.4; 128.5; 129.0; 139.3; 139.4; 142.1; 146.3; 170.5. ESI-HRMS m/z [M + H]\(^{+}\) calcd for C\(_{27}\)H\(_{22}\)N\(_{2}\)O\(_{2}\) 701.0156, found 701.0170.

\(N,\text{N}-(\text{bis-(2-iodobenzoyl)}\text{pyridine-2,6-diamine}) \quad (11)\): this reaction was carried out using a procedure similar to that described for 8, but the substrate utilized was 2,6-diaminopyridine (10 mmol). Compound 11 (1.2 g, 65% global yield) was isolated as a yellow solid by crystallization as hydrochloride from acid ethanol and subsequent basic extraction. \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta\)H: 4.44 (d, 4H, \(J = 6.3\)Hz); 4.81 (t, 2H, \(J = 6.2\)Hz); 5.71 (d, 2H, \(J = 7.9\)Hz). 6.94 (td, 2H, \(J = 7.6\)Hz, 1.7Hz). 7.18 (t, 1H, \(J = 7.9\)Hz). 7.25 (td, 2H, \(J = 7.5\)Hz, 1.1Hz). 7.35 (br d, 2H, \(J = 7.7\)Hz). 7.82 (dd, 2D, \(J = 7.9\)Hz, 1.2Hz). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta\)C: 51.1; 95.6; 98.6; 128.3; 128.7; 128.9; 139.1; 139.3; 143.6; 157.5. ESI-HRMS m/z [M + H]\(^{+}\) calcd for C\(_{26}\)H\(_{22}\)N\(_{2}\)O\(_{2}\) 541.9635, found 541.9600.

\(N,\text{N}-(\text{pyridine-2,6-diyil})\text{bis(N-(2-iodobenzoyl)acetamide}) \quad (12)\): yellow solid. Isolated by precipitation from the reaction media as intermediate. \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta\)H: 2.05 (s, 6H); 4.97 (s, 4H); 6.89 (td, 2H, \(J = 7.6\)Hz, 1.4Hz); 7.10 (br d, 2H, \(J = 8.6\)Hz). 7.19 (td, 2H, \(J = 7.8\)Hz, 1.5Hz). 7.90 (t, 1H, \(J = 8.0\)Hz). 7.73 (br d, 2H, \(J = 7.7\)Hz). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta\)C: 23.5; 56.4; 97.7; 117.9; 127.8; 128.4; 128.9; 138.9; 139.4; 153.3; 171.0. ESI-HRMS m/z [M + Na\(^{+}\)] calcd for C\(_{27}\)H\(_{20}\)N\(_{3}\)O\(_{4}\) 647.9615, found 647.9644.
Benzo[\textit{f}]isoquinolino[3,4-\textit{b}] [1,8]naftiridin (19): \cite{a} purple solid. Isolated (3 mg) by radial thin-layer chromatography eluted with dichloromethane:methanol, 99:1 to 91:9. \textit{\textit{\textit{1H\textit{N}}MR (400 MHz, CDCl\textsubscript{3}),} $\delta$: 8.77 (2H, J = 7.5 Hz); 8.05 (t, 1H, J = 7.6 Hz); 6.80 (d, 2H, J = 8.3 Hz); 6.97 (s, 1H). \textit{\textit{13C\textit{N}}MR (100 MHz, CDCl\textsubscript{3}) $\delta$:} 121.1; 122.0; 124.5; 126.7; 127.8; 129.0; 130.8; 131.2; 153.6; 154.1; 155.8. ESI-HRMS $m/z$ [M + H$^+$] called for C$_{28}$H$_{21}$N$_3$ 357.1386, found 357.1399.

2\textit{H}-Benzo[6\textit{f},5\textit{e}][1,8]naftiridin[1,2-\textit{a}]quinazoline (20): orange solid. Isolated (3 mg) by preparative thin-layer chromatography eluted with dichloromethane:methanol, 98:2 to 97:3. \textit{\textit{\textit{1H\textit{N}}MR (400 MHz, acetone-d$_{6}$),} $\delta$:} 5.30 (2H, J = 8.5 Hz); 8.05 (br d, 1H, J = 8.3 Hz); 7.30 (br d, 1H, J = 8.6 Hz); 7.13 (d, 1H, J = 8.1 Hz); 7.43 (br d, 1H, J = 7.3 Hz); 7.45 (br d, 1H, J = 8.1 Hz); 7.62 (t, 1H, J = 7.8 Hz); 7.92 (cpxl, t, 1H, J = 7.7 Hz); 8.17 (br d, 1H, J = 8.7 Hz); 8.46 (br d, 1H, J = 9.7 Hz); 9.67 (s, 1H). \textit{\textit{13C\textit{N}}MR (100 MHz, CDCl$_{3}$) $\delta$:} 117.8; 122.4; 126.3; 127.4; 128.9; 131.2; 132.4; 153.7; 157.9. ESI-HRMS $m/z$ [M + H$^+$] called for C$_{28}$H$_{18}$N$_4$Na 304.0845, found 304.0845.

N-Benzybenzo[c][1,8]naftiridin-3-amine (21): yellow solid. Isolated (6 mg) by preparative thin-layer chromatography eluted with dichloromethane:methanol, 98:2 to 97.3. \textit{\textit{\textit{1H\textit{N}}MR (400 MHz, acetone-d$_{6}$),} $\delta$:} 5.30 (2H, J = 8.5 Hz); 7.00 (br t, 1H, J = 7.5 Hz); 7.28 (d, 1H, J = 7.2 Hz); 7.33 (br d, 1H, J = 8.6 Hz); 7.34 (br t, 1H, J = 7.9 Hz); 7.43 (br d, 1H, J = 7.3 Hz); 7.45 (br d, 1H, J = 7.7 Hz); 7.51 (br t, 1H, J = 7.1 Hz); 7.52 (cpxl, t, 1H, J = 7.7 Hz); 8.22 (br d, 1H, J = 8.1 Hz); 8.67 (br d, 1H, J = 8.3 Hz); 9.04 (d, 1H, J = 8.9 Hz); 9.47 (s, 1H). \textit{\textit{13C\textit{N}}MR from HSQC and HMBC, acetone-d$_{6}$) $\delta$:} 59.6; 109.0; 109.4; 112.0; 120.9; 121.0; 121.3; 125.3; 126.0; 128.0; 128.7; 130.9; 131.3; 133.5; 153.1; 153.9; 154.0; 155.2; 156.3. ESI-HRMS $m/z$ [M + H$^+$] called for C$_{28}$H$_{21}$N$_3$ 284.1182, found 284.1181.

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Notes and references
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\footnote{** In DMSO and DMF several concentrations of diamine 8 and base were explored, but the yield of cyclic products does not improve.}
\footnote{† For full optimization reaction see ESI.}
\footnote{‡ In the distonic specie, the negative charge is in π system meanwhile the radical is in σ system.}
\footnote{§ The rotation barrier is ca. 23 kcal/mol, from AM1 calculations.}
\footnote{†† http://www.verachem.com/products/vconf/}

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/


