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Unusual Approach to 3-Aryl-2-aminopyridines through a Radical Mechanism: Synthesis and Theoretical Rationale from Quantum Mechanical Calculations†

Marta Camacho-Artacho,‡ Valentina Abet,§ Luis M. Frutos,∥ Federico Gago,*,‡ Julio Alvarez-Builla,§ and Carolina Burgos*,§

‡Departamentos de Farmacología, §Química Orgánica, and ∥Química Física, Universidad de Alcalá, E-28871 Alcalá de Henares, Madrid, Spain

federico.gago@uah.es; carolina.burgos@uah.es

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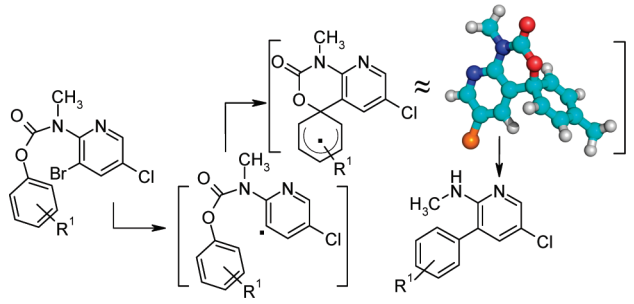

Tris(trimethylsilyl)silane and azobis(cyclohexanenitrile) promoted the easy intramolecular arylation of aryl bromopyridine carbamates through a radical [1,6] ipso substitution process. These substrates showed a preference for this type of reaction over the alternative [1,7] addition. The results were rationalized by making use of quantum mechanical calculations and computer graphics.

The addition of an aryl radical onto another aromatic nucleus has become an important tool in organic synthesis, and consequently, some examples of biaryls and their homologues, such as oligo- and polyaryls, have been prepared from monoaryl precursors.

The process can be considered as a substitution procedure that can be defined as the replacement of a leaving group X by the attacking radical. Since hydrogen is not a feasible leaving group (X = H), one of the possible methods for the homolytic process consists of using a good radical leaving group.[1]

Despite recent progress concerning the intermolecular approach,[2] the use of intramolecular reactions largely overcomes the problems of poor regioselectivity obtained in intermolecular reactions and is therefore much more useful in synthesis.[3] In addition, one of the possible methods for the intramolecular reaction involves the use of a good radical leaving group as part of a linker connecting the aryl radical to the arene under attack. According to previous publications,[4] and as shown in Scheme 1, the intramolecular addition of the aryl radical **I** can take place at two different carbons. The reaction at the ortho position (pathway A, Scheme 1) forms the radical intermediate **II**, which is converted into the fused ring **III** by hydrogen abstraction. Attack at the ipso carbon (pathway B, Scheme 1) produces the unstable spirocyclodienyl radical intermediate **IV**. There are several possible reactions for radical **IV**, but rearomatization by β-scission (ipso substitution) is generally the fastest alternative if a good leaving group is present. This reaction sometimes involves the extrusion of a small, stable fragment and/or molecule to generate the biaryl derivative, depending on the nature of substituents W and X.

In this context, intramolecular arylations, by ipso substitution of suitable sulfonyl,[5] phosphinate,[6] silyl,[7] and benzylic ether derivatives,[8] under reductive conditions, have been widely reported for the preparation of both biaryls and arylheterocyclic derivatives.

In a previous paper[9] and following on Motherwell's work,[5] we reported the preparation of 3-aryl-2-aminopyridines **1** through a radical process based on the intramolecular heteroarylation of arenesulfonamides in the presence of tris(trimethylsilyl)silane (TTMSS) and azobis(isobutyronitrile) (AIBN) under thermal conditions. The heteroarylation process involves the generation of a pyridyl radical, ipso substitution, and rearomatization through the loss of sulfur dioxide. However, in all cases the [1,5] ipso substitution process competes with the alternative [1,6] direct addition, and the corresponding pyrido[2,3-*c*][1,2]benzothiazine dioxides have been isolated as side products.

Taking the above observations into consideration, and since the nature, geometry, and number of atoms in the connecting chain can play an important role in the aromatic

† Dedicated to Prof. Rafael Suau, "in memoriam".

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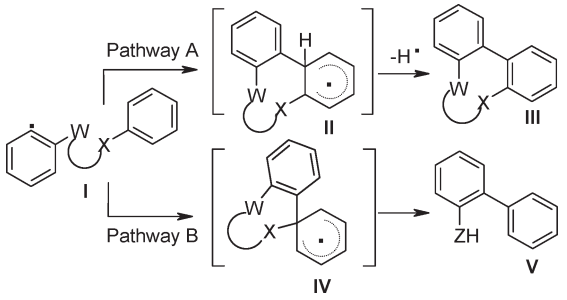
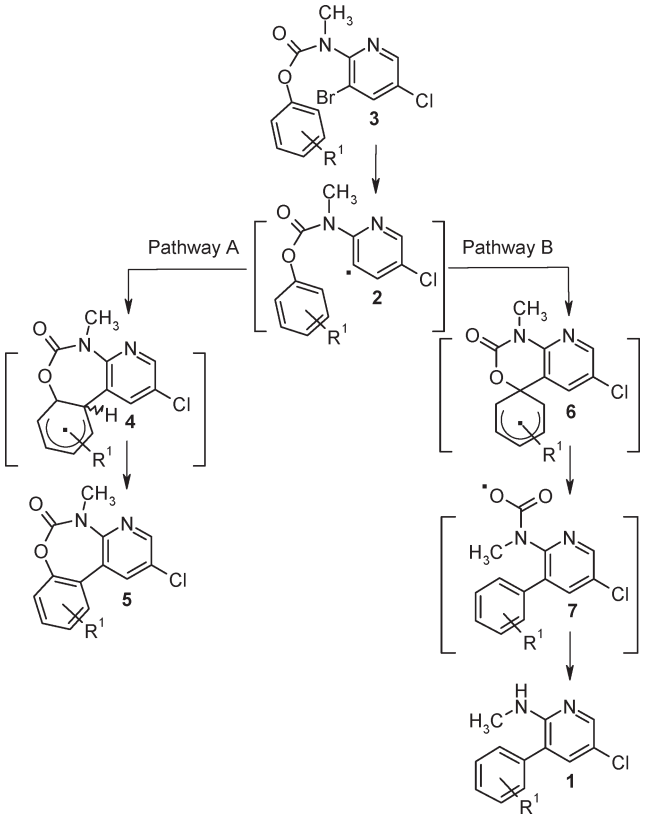
SCHEME 1. Intramolecular Addition of Aryl Radicals onto Arenes



SCHEME 2. Two Plausible Pathways for the Intramolecular Arylation of Carbamate Derivatives through a Radical Process



substitution,[3] we turned our attention to the studies of Newcomb and co-workers[10] concerning carbamate derivatives and the corresponding carbamoyloxyl radicals $R_2NCO_2^{\bullet}$. The authors reported that these kinds of compounds can afford aminyl radicals by decarboxylation of the initially formed $R_2NCO_2^{\bullet}$ radicals. In this context, the pyridyl radical **2** (Scheme 2), obtained from the bromopyridine **3**, could evolve through a [1,7] addition (pathway A), to yield **4** and **5**. Alternatively, **2** could be cyclized onto the aryl moiety through an intramolecular [1,6] process to yield the spirocyclic radical **6**. This intermediate could rearomatize by β-scission and decarboxylation of the initially obtained carbamoyloxyl radical **7** to produce **1**.

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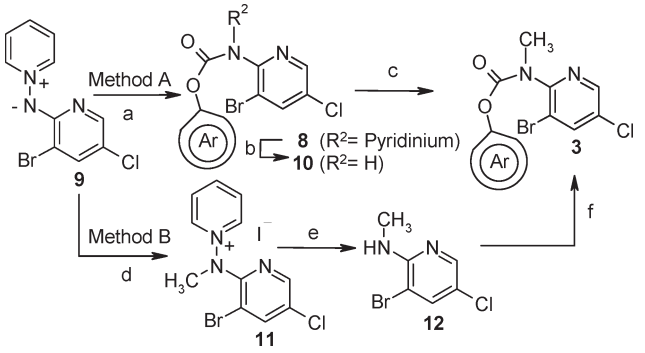
SCHEME 3. Preparation of Starting Materials[a]



[a]Legend: (a) aryl chloroformate in dry acetone, room temperature, 10 min; (b) Et_3B in EtOH, room temperature, 24 h; (c) NaH in dry DMF, 0−5 °C, 30 min, MeI, room temperature, 1 h; (d) MeI in dry acetone, room temperature, 36 h; (e) Pt/C, HCO_2H, Et_3N in MeCN, room temperature, 4 h; (f) NaH in dry CH_2Cl_2, aryl chloroformate, reflux 24 h.

TABLE 1. Preparation of Starting Material 3 from *N*-Aminide 9

			product, yield (%)		
entry	Ar	method	**8**	**10**	**3**
1	Ph	A	**8a**, 98	**10a**, 29	
2	Ph	B			**3a**, 39
3	4-Me-C_6H_4	A	**8b**, 98	**10b**, 60	**3b**, 60
4	4-MeO-C_6H_4	A	**8c**, 78	**10c**, 65	**3c**, 67
5	4-Cl-C_6H_4	A	**8d**, 75	**10d**, −	
6	4-Cl-C_6H_4	B			**3d**, 60
7	4-NO_2-C_6H_4	A	**8e**, 88	**10e**, −	
8	4-NO_2-C_6H_4	B			**3e**, 71
9	1-naphthyl	A	**8f**, 90	**10f**, 25	
10	1-naphthyl	B			**3f**, 65

Previous studies[5] seem to demonstrate that simplistic ideas related to a kinetically driven pathway and a preference for the formation of six- over seven-membered rings are invalid.[11,12] Thus, to explain the regiochemistry of ring closure, we turned to quantum mechanical calculations. Prior work in this area has been communicated by Ganguly and co-workers.[12]

Our initial work in this field started from the salts **8** (R^2 = pyridinium; Scheme 3), obtained from *N*-aminide **9** by reaction with different aryl chloroformates (method A). Reduction of the N−N bond furnished the unsubstituted carbamates **10** (R^2 = H), and methylation on the exocyclic nitrogen provided methyl carbamates **3**, which are starting materials for the radical cyclization process. However, this pathway only gave satisfactory results in some cases (entries 3 and 4 in Table 1; Ar = 4-Me-C_6H_4, 4-MeO-C_6H_4, respectively), and an alternative route (method B) was chosen, starting from *N*-aminide **9**, to prepare **3** in good yields through compounds **11** and **12**, using a previously described method.[13]

(11) For some examples of 7-*trig* cyclization see: (a) De la Fuente, M. C.; Dominguez, D. *J. Org. Chem.* **2007**, *72*, 8804–8810. and references cited therein. (b) Ishibashi, H. *Chem. Rec.* **2006**, *6*, 23–31.

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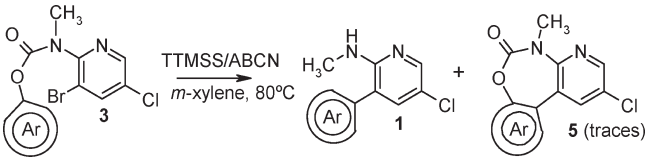
TABLE 2. Preparation of Biaryls 1 from Carbamates 3



entry	Ar	product, yield (%) 1	5
1	Ph	**1a**, 67	**5a**, traces
2	4-Me-C_6H_4	**1b**, 75	**5b**, traces
3	4-MeO-C_6H_4	**1c**, 35	**5c**, –
4	4–Cl-C_6H_4	**1d**, 47	**5d**, –
5	4-NO_2-C_6H_4	**1e**, 45	**5e**, –
7	1-naphthyl	**1f**, 45	**5f**, –

Therefore compounds **3** were prepared by two alternative routes: method A, **9** → **8** → **10** → **3**; method B, **9** → **11** → **12** → **3**. Method A works only for Ar = 4-Me-C_6H_4 and 4-MeO-C_6H_4.

Bearing in mind previous reports from Motherwell[5] and Ganguly,[12] and our own previous results,[13] the radical reaction was attempted in the presence of TTMSS and azobis(cyclohexanenitrile) (ABCN) under thermal conditions.

However, in the course of our experiments to improve the initial yields, we were able to detect only traces of compounds **5** (if at all) and only biaryl derivatives **1** could be isolated in moderate yields (see Table 2).

In order to shed some light on this striking result, the optimized geometries and electronic structures of radicals **2**, **4**, and **6** (R^1 = Me), as well as those of the corresponding transition states (TS_1 and TS_2), were calculated by means of the unrestricted density functional theory (DFT) method B3LYP and a 6-31G(d) basis set, as implemented in Gaussian 03.[14] Vibrational frequencies were computed on the stationary points to identify them as a TS (one imaginary frequency corresponding to the intramolecular bond to be created) or an energy minimum (all frequencies positive) on the potential energy surface. TS were located using the synchronous transit-guided quasi-Newton (STQN) method, and IRC (intrinsic reaction coordinate) calculations in both directions were also performed using 30 steps of 0.1 amu$^{1/2}$ Bohr increments along the reaction pathway. Molden 4.7[15] was used to visualize molecular structures and orbitals. To compare the relative accessibility of each TS, we computed

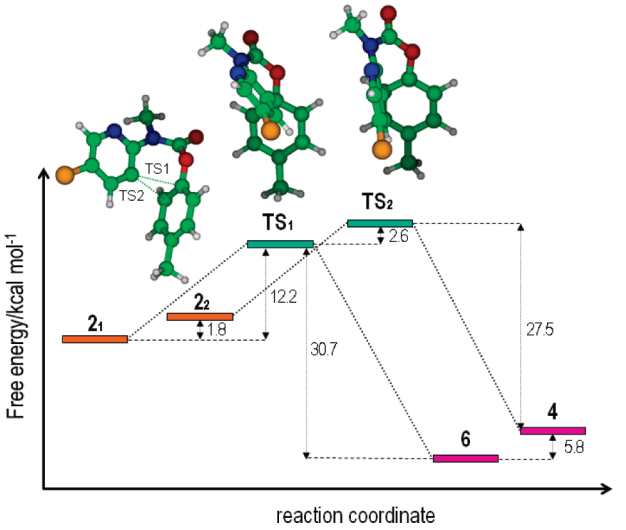


FIGURE 1. Free energy profile for the intramolecular cyclization reaction leading from the starting radical (**2**) to the cyclic radicals **6** and **4** by way of transition states TS_1 and TS_2, respectively. Note that conformation $\mathbf{2_1}$ leads to TS_1 and conformation $\mathbf{2_2}$ leads to TS_2 and also that an additional barrier of ~13–14 kcal mol^{-1} separates the more stable trans conformation of **2** from the reactive cis conformation shown here (Supporting Information, Figure S1).

the free energy of activation for each optimized structure at 298.15 K, their relative equilibrium population being given by

$$\frac{p_{TS_1}}{p_{TS_2}} \propto e^{-\Delta\Delta G^{\ddagger}/RT}$$

where p is the equilibrium population and $\Delta\Delta G^{\ddagger}$ is the difference in the free energy of activation. It is important to realize that, for cyclization to take place, the amide bond of radical **2** must adopt a cis conformation and also that the reactive conformation leading to TS_2 (236.66i cm^{-1}) and **4** is achieved only after visiting that leading to TS_1 (284.01i cm^{-1}) and **6** upon rotation of the pyridine ring relative to the phenyl ring (Figure 1). Furthermore, TS_1 turns out to be ~2.6 kcal mol^{-1} more stable than TS_2, which translates into an expected ratio for both species of 96% and 4%, respectively, in good agreement with the experimental findings, and radical **6** is stabilized through hyperconjugation due to delocalization of the spin density on the phenyl ring (Scheme 2 and Figure 1; see also Figure S2 in the Supporting Information).

With regard to the molecular orbital (MO) containing the electron that will pair up with that present in the SOMO (#72) to form the new bond, we focused on the HOMO (#71) and HOMO-1 (#70), each of which lodges a pair of electrons (one in orbital α and the other in orbital β). The HOMO contributions in **2** emanate from atoms that are not directly involved in the reaction mechanism but instead participate in the π cloud of the pyridine ring and are conjugated with the lone pairs of the heteroatoms that form the carbamate amide bond. In contrast, representation of the HOMO-1, in both **2** and TS_1, showed the important contribution to this orbital of the atoms involved in the formation of the new bond (Supporting Information, Figure S3). A succinct graphical overview of the frontier orbital energy levels for the starting radical, for the reactive conformation (**2**) TS_1, and for the

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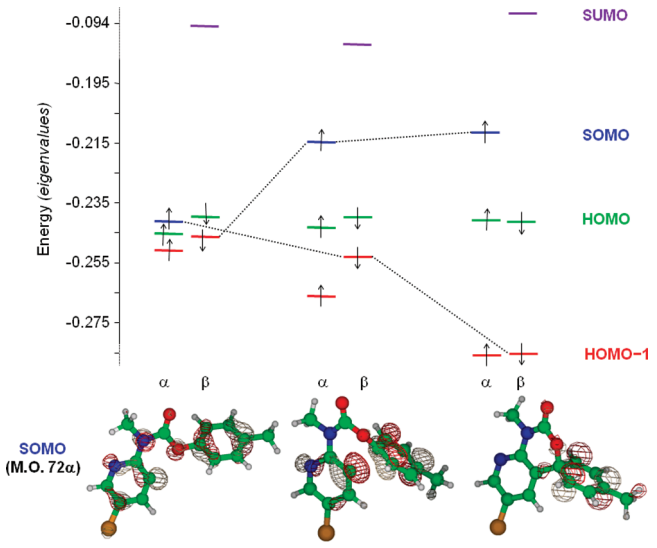

FIGURE 2. Simplified molecular orbital correlation diagram showing the occupation and energies of the frontier orbitals (SOMO [72α] and SUMO [72*β*], HOMO [71α and 71*β*] and HOMO-1 [70α and 70*β*]) of (from left to right) the "reactant" (starting radical, **2**), the major TS (TS_1), and the "product" (cyclic radical, **6**). Orbital numbering is referred to product **6**. The dotted lines show the evolution of the SOMO, with radical character in **2** to HOMO-1 corresponding to a σ bond in **6**, as well as the evolution of HOMO-1 with π character in **2** to radical character in **6**.

cyclic radical **6** (Figure 2) shows the closeness (and even overlap) of the energy levels of the SOMO, HOMO, and HOMO-1 in **2**, and also how far they are from the SUMO. In summary, the single electron in the low-energy SOMO pairs with one of the electrons in HOMO-1 to create a new bonding orbital, which is very low in energy, and the new radical **6**, which contains the unpaired electron in a SOMO higher in energy than in the original radical species. This radical evolves, through the loss of a CO_2 molecule, toward the final major product **1**.

Experimental Section

General Procedure for the Preparation of *N*-Methylcarbamates 3b,c: Method A. The corresponding compound **10** (see the Supporting Information) (1.0 mmol) was dissolved in anhydrous DMF (3 mL), and the solution was cooled to 0 °C in an ice/water bath. Sodium hydride (50 mg, 60% suspension in oil, 1.25 mmol) was added in portions such that the internal temperature was maintained at < 5 °C (vigorous stirring is required to keep the suspension fluid). Upon complete addition, the suspension was stirred vigorously for an additional 20 min while the temperature was maintained below 5 °C, and then methyl iodide (1.15 mmol) was added dropwise. After it was stirred for 30 min, the reaction mixture was brought to room temperature over a 1 h period, before water (0.5 mL) was added. The mixture was then diluted with water (2 mL) and Et_2O (10 mL). The organic layer was separated and extracted with water, 0.1 M HCl, saturated aqueous $NaHCO_3$ solution, and brine, before being dried and concentrated. The resulting residue was then purified by chromatography (silica gel, hexane/ethyl acetate (80/20)), furnishing products **3b**,**c**.

General Procedure for the Preparation of *N*-Methylcarbamates 3a,d−f: Method B. To a suspension of **12** (1 mmol) and NaH (2 mmol) in anhydrous CH_2Cl_2 (6 mL) was added the corresponding chloroformate (1.1 mmol), and the reaction mixture was heated to reflux. Stirring was maintained at the same temperature for a further 24 h. The reaction mixture was brought to room temperature, and water (1 mL) was added. The mixture was then diluted with water (2 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with water, dried, and concentrated. The resulting residue was then purified by chromatography (hexane/ethyl acetate (90/10)).

General Procedure for the Preparation of *N*-Methylamines 1a−f. A solution of TTMSS (248 mg, 1 mmol) and ABCN (164 mg, 1 mmol) in *m*-xylene (10 mL) was added dropwise by syringe pump, over 13 h, to a stirred solution of the corresponding *N*-methylcarbamate **3** (0.5 mmol) in *m*-xylene (2 mL) at 80 °C (bath temperature). After the mixture was stirred for a further 12 h, the same amount of ABCN and TTMSS was added dropwise by syringe pump, over 13 h. Stirring was maintained at the same temperature for a further 12 h. The solution was concentrated and the crude mixture separated by flash chromatography on silica gel (hexane/ethyl acetate).

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Supporting Information Available: Text, tables, and figures giving (1) supplementary graphics, (2) experimental details and characterization data, (3) copies of ^1H and ^{13}C spectra, (4) tables of atom coordinates, and (5) absolute energies for TS_1 and TS_2. This material is available free of charge via the Internet at http://pubs.acs.org.