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A New Class of Pyrazolopyridine Nucleus with Fluorescent Properties, Obtained through Either a Radical or a Pd Arylation Pathway from *N*-Azinylpyridinium *N*-Aminides

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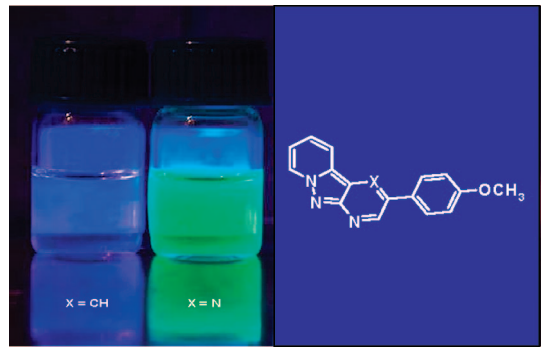

The synthesis of dipyridopyrazole and pyridopyrazolopyrazine derivatives—both of which incorporate a 3-aryl moiety—can be achieved in moderate yields by intramolecular radical arylation of pyridinium *N*-aminides using tris(trimethylsilyl)silane and azobisisobutyronitrile. Improved results were obtained on using Pd direct arylation in conjunction with microwave irradiation. A preliminary study into the fluorescent properties of the target compounds is also reported.

Introduction

Azaindolizines (e.g., **II**−**IV**, Figure 1) with additional nitrogens in either the azine ring (**II**) or the azole ring (**III**) or both (**IV**) are rare systems in nature, and their similarity to both indoles and purines has triggered recent interest in their study. Some remarkable members of these families are the biologically relevant variolins[1] and luciferins,[2] which are related to classes **II** and **IV**, respectively (Figure 1). Examples of type **III** systems include the antiallergic and cerebroactive agent ibudilast and the highly selective D_4 receptor partial agonist FAUC 113 (Figure 2), which have been prepared for assessment of their pharmacological activity.[3]

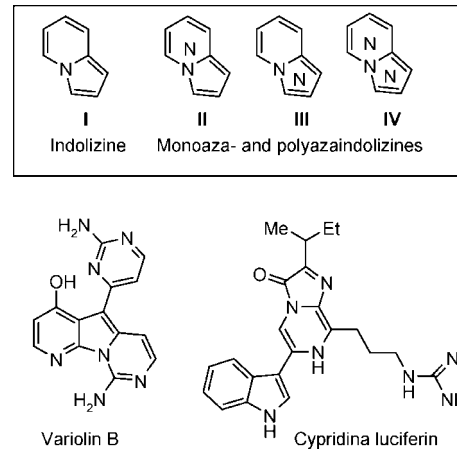

FIGURE 1. General structure of indolizine and azaindolizines and some related natural products.

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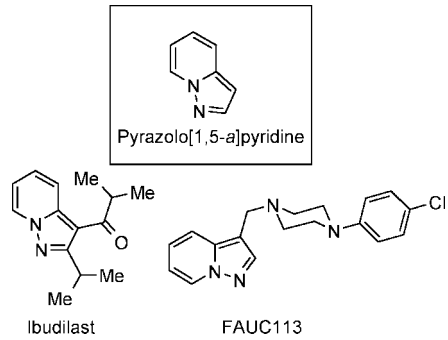
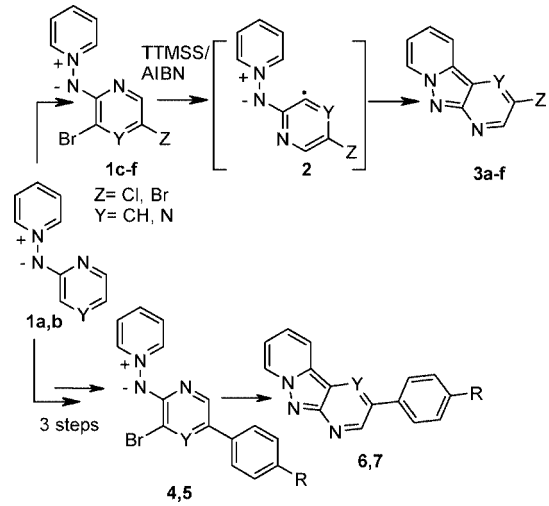


FIGURE 2. Structure of pyrazolo[1,5-*a*]pyridine and some examples of products with interesting pharmacological activity.

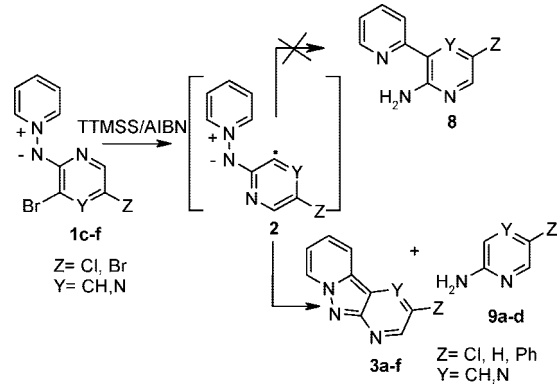
In recent years our research group has been developing a project centered on the study of the type **II** azaindolizines[4] (Figure 1). Our initial interest in these systems resulted from the scarce precedents on their basic chemistry and the absence of viable synthetic methods for some of these compounds. Bearing in mind the interest in azaindolizines, in which the additional nitrogen is located on the azole ring (i.e., type **III**), the work described here focused on the synthesis of a new class of pyrazolo[1,5-*a*]pyridine, a type **III** azaindolizine.

During the course of our studies into the reactivity of pyridinium *N*-aminides[5] (i.e., **1**, Scheme 1), it was shown that it is possible to generate the pyrazolopyridine nucleus **3** from **1**, through the radical intermediate **2**, using tris(trimethylsilyl-)silane and azobisisobutyronitrile (TTMSS/AIBN).[6] This study represented the first example of the intramolecular addition of an aryl radical to a π-deficient pyridinium fragment linked to a π-excessive 2-azinyliminopyridine moiety. This process gave dipyridopyrazoles **3a**−**c** and pyridopyrazolopyrazines **3d**−**f**, all of which contain the pyrazolopyridine nucleus. Although a few examples of the synthesis of dipyridopyrazole derivatives by alternative routes were already known,[7] our approach allowed the preparation of the fully aromatic and unsubstituted nucleus, as well as the previously unreported pyrazine structures.

SCHEME 1. Preparation of Compounds 3 and the Planned Extension of the Process to 6 and 7



SCHEME 2. Previously Described Route



Moreover, these chromophores exhibit a high degree of conjugation and display bright color and strong fluorescence properties.

The intramolecular arylation method has now been extended to the preparation of aryl derivatives **6** and **7**, both of which have a more extended π-system and, consequently, a higher degree of conjugation. The synthesis of **6** and **7** was achieved through the bromo ylides **4** and **5** using either radical- or palladium-catalyzed methodologies. A preliminary study of the fluorescence properties of these compounds is also described.

Results and Discussion

As shown in Scheme 2 and Table 1, and bearing in mind previous literature data,[8] the intramolecular arylation was attempted on ylides **1** via radical **2**. It was expected that bipyridine **8** would be obtained through a reaction pathway involving a 5-*exo*/*endo*-trig cyclization followed by cleavage of the N−N bond, as described previously.[5e] To our surprise, compound **8** was not detected and only reduction compounds **9**

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TABLE 1. Preliminary Results for the Radical Cyclization

entry	starting material	3	yield (%)	9	yield (%)	method
1	Y = CH, Z = Cl, **1c**	Y = CH, Z = Cl, **3a**	2	Y = CH, Z = Cl, **9a**	60	A[a]
2	Y = CH, Z = Cl, **1c**	Y = CH, Z = Cl, **3a**	56	Y = CH, Z = Cl, **9a**	5	B[b]
3	Y = CH, Z = Br, **1d**	Y = CH, Z = H, **3b**	21	Y = CH, Z = H, **9b**	21	B
4		Y = CH, Z = Ph, **3c**	23			
5	Y = N, Z = Cl, **1e**	Y = N, Z = Cl, **3d**	52	Y = N, Z = Cl, **9c**	10	B
6	Y = N, Z = Br, **1f**	Y = N, Z = H, **3e**	24	Y = N, Z = H, **9d**	20	B
7		Y = N, Z = Ph, **3f**	20			

[a] Method A: TTMSS (2 equiv) and AIBN (2 equiv) in 40 mL of dry acetonitrile/benzene (7:3) were added during 32 h to a solution of aminide **1c** (1 equiv) in 50 mL of acetonitrile, 80 °C, 24 h. [b] Method B: TTMSS (2 equiv) and AIBN (2 equiv) in 40 mL of dry acetonitrile/benzene (7:3) were added during 32 h to a dispersion of potassium carbonate (2 equiv) and the corresponding aminide **1c**−**f** (1 equiv) in 50 mL of dry acetonitrile, 80 °C, 24 h.

and tricyclic products **3** were observed, the latter corresponding to the dipyrido[1,2-*b*:3′,2′-*d*]pyrazole nucleus obtained from ylides **1c**,**d**. When the reaction was carried out on ylides **1e**,**f**, pyrido[1′,2′:2,3]pyrazolo[5,4-*b*]pyrazine derivatives (compounds **3d**−**f**, Y = N) were obtained.

The results obtained are summarized in Table 1. In initial experiments only poor yields of **3a** were obtained in the absence of potassium carbonate (entry 1, method A), a finding consistent with the reaction pathway previously reported.[6] Indeed, only when the reaction was carried out in benzene/acetonitrile in the presence of 2 equiv each of TTMSS, AIBN, and potassium carbonate did the reaction go to completion in satisfactory yield (entry 2, method B). When the reaction was performed on the amidine **1d**, which has an additional bromo substituent, two tricyclic derivatives were observed (**3b** and **3c**) as a result of bromoreduction or concomitant phenylation, respectively, as reported previously (entries 3 and 4).[6] Similar results were obtained under comparable experimental conditions on using the pyrazino aminides **1e**,**f** as starting materials. All of the compounds obtained showed moderate fluorescence under visible light, probably due to the presence of three conjugated aromatic rings and the bathochromic effect exerted by the endocyclic imino moiety.[9]

To explore the general utility of the method, and taking into consideration the remarkable fluorescence properties, a broader study of the process was planned to include more complex systems. In this context, compounds **4** and **5** (Scheme 3) would meet the requirements as starting materials for the radical cyclization process to generate the tricyclic systems **6** and **7**.

For many years, part of our research has been dedicated to heteroaryl-stabilized cycloiminium ylides (e.g., **1a**,**b**, Scheme 3) as building blocks for the synthesis of heterocyclic derivatives and, more recently, in relation to their synthetic utility in palladium-catalyzed cross-coupling processes—particularly in the Suzuki−Miyaura reaction.[10] Due to their peculiar structures, these compounds show a clearly defined reactivity. Thus, for example, the dibromo derivatives **1d** and **1f** (Scheme 3) show regioselectivity in the coupling reaction at the 3′-position to give compound **10**. In addition, this type of structure (i.e., **1a**,**b**, Scheme 3) only undergoes bromination at the 3′-position if the 5′-position has previously been substituted (i.e., to yield **1c**,**e**, Scheme 3)′.[5f] Bearing these findings in mind, a strategy to build the tricyclic systems **6** and **7** was envisaged. This approach involved the use of 5′-bromo derivatives **12** and 5′-aryl derivatives **13** and **14** to provide **4** and **5**, which would then be cyclized through the radical process described above.

SCHEME 3. Reactivity of Azinylpyridinium *N*-Aminides

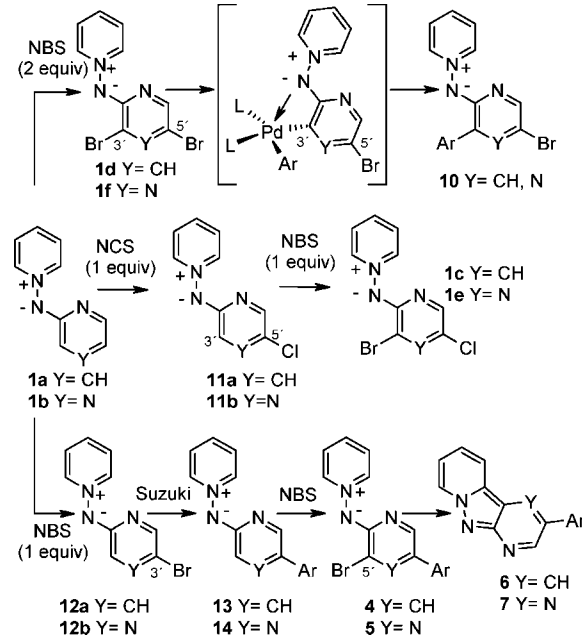
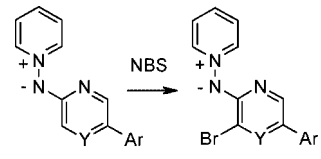


TABLE 2. Synthesis of 4 and 5



entry	starting material	Y	Ar	4, 5	yield[a] (%)
1	**13a**	CH	C_6H_5	**4a**	76
2	**13b**	CH	4-MeC_6H_4	**4b**	89
3	**13c**	CH	4-$MeOC_6H_4$	**4c**	87
4	**13d**	CH	4-$MeCOC_6H_4$	**4d**	86
5	**13e**	CH	4-$Me_2NC_6H_4$	**4e**	
6	**14a**	N	C_6H_5	**5a**	91
7	**14b**	N	4-MeC_6H_4	**5b**	93
8	**14c**	N	4-$MeOC_6H_4$	**5c**	84
9	**14d**	N	4-$MeCOC_6H_4$	**5d**	86

[a] Isolated pure product.

The preparation of intermediates **13** and **14**[10] has previously been reported from **12a**,**b**.[5f] Subsequent halogenation under mild conditions with *N*-bromosuccinimide (NBS) provided **4** and **5** in excellent yields. The results are summarized in Table 2. However, *N*-aminide **13e**, which is an electron-rich substrate

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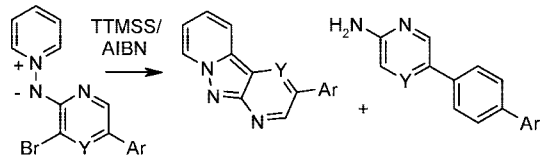
TABLE 3. Results for the Radical Arylation from *N*-Aminides 4 and 5



4 Y= CH, **5** Y= N — **3c**, **6** Y= CH, **3f**, **7** Y= N — **15** Y= CH, **16** Y= N

entry	starting material	Ar	**3**, **6**, **7**	yield[a] (%)	**15**, **16**	yield[a] (%)
1	**4a**,Y=CH	C_6H_5	**3c**	29	**15a**	44
2	**4b**,Y=CH	4-MeC_6H_4	**6b**	32	**15b**	63
3	**4c**,Y=CH	4-$MeOC_6H_4$	**6c**	30	**15c**	50
4	**4d**,Y=CH	4-$MeCOC_6H_4$	**6d**	9	**15d**	79
5	**5a**,Y= N	C_6H_5	**3f**	34	**16a**	31
6	**5b**,Y= N	4-MeC_6H_4	**7b**	35	**16b**	58
7	**5c**,Y= N	4-$MeOC_6H_4$	**7c**	45	**16c**	17
8	**5d**,Y= N	4-$MeCOC_6H_4$	**7d**	32	**16d**	56

[a] Isolated pure product.

(entry 5, Table 2, Y = CH, Ar = 4-$Me_2NC_6H_4$), did not generate the expected product **4e**, probably due to competition between the bromo substitution and oxidation processes. Indeed, only small amounts of highly colored products were isolated.

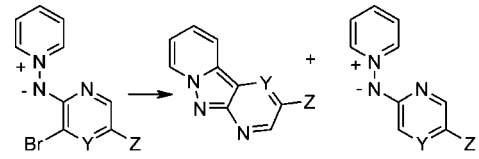
Having obtained substrates **4** and **5**, initial radical cyclization experiments were undertaken on the basis of our previous experience in this area.[6] The slow dropwise addition (32 h, syringe pump) of a solution of TTMSS (2 equiv) and AIBN (2 equiv) to a solution of the corresponding substrate **4** or **5** in benzene/acetonitrile gave only poor yields of **6** or **7**. The best results are summarized in Table 3. Other catalysts (such as SmI_2[11] or $InCl_3$[12]) or experimental conditions proved unsuccessful. Although this radical methodology seems to be efficient in the preparation of the chloro-substituted nuclei **3a** and **3d** (Scheme 2, Table 1, entries 2 and 5), 3-aryldipyridopyrazole derivatives **3c** and **6b**−**d** (Y = CH) were only obtained in low yields (Table 3, entries 1−4). In particular, **6d** was obtained in only 9% yield as practically all of the starting material had been reduced and dehalogenated to **15d**.

The best results were achieved with electron-rich substrates, an observation consistent with previous reports,[13] although the increases in the reaction yields were only moderate. The results obtained were slightly better for the 3-arylpyridopyrazolopyrazine derivatives **3f** and **7b**−**d** (Y = N) (Table 3, entries 5−8). It is possible, however, that this effect could only be due to the easier isolation of the products. Once again, the electron-rich substituents seem to favor the cyclization process.

The poor results obtained in the radical cyclization led us to turn our attention to palladium-promoted C−C bond formation. However, in the case of 2-pyridyl derivatives, the precursors required (i.e., 2-pyridylboronic acids or 2-pyridylstannanes) limit the utility of the process due to their low stability, high price, and difficult synthesis.

On the other hand, in recent years direct arylation reactions have emerged as an attractive alternative to typical cross-coupling reactions.[14] In direct arylation, one of the preactivated partners (typically the organometallic species) is replaced by a nonfunctionalized arene. However, there has been considerable debate concerning the possible mechanism for the formation of biaryl bonds on electron-deficient aromatics and heteroaromatics, and in this context, works by Echavarren[15] and Fagnou[14,16] suggest a reaction course that is incompatible with a classical electrophilic aromatic substitution. Bearing in mind the papers cited above, as well as the study reported by Dominguez et al.[17] concerning Heck-like processes, our initial studies in this area concerned the feasibility of this reaction on **1c**, as a readily available model, using experimental conditions similar to those reported previously.[17] Thus, the reaction of **1c** (0.5 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol, 22 mg), K_2CO_3 (2.5 mmol, 0.345 g), LiCl (0.75 mmol, 31 mg), and *n*-Bu_4NBr (0.33 mmol, 106 mg) in DMF in a sealed tube (110 °C, 48 h) furnished moderate yields of cyclized product **3a** together with some unreacted starting material (Table 4, entry 1, method C). Changes in the catalyst [$Pd_2(dba)_3$, $PdCl_2$], base (K_2CO_3, 2.5−5.0 mmol; Cs_2CO_3, 2.5−5.0 mmol), ammonium salt, and amount of LiCl (0.5−1.5 mmol) or solvent (acetonitrile, THF) did not improve the reaction yield. In an effort to find

TABLE 4. Results for the Palladium Arylation from *N*-Aminides 1, 4, and 5



1c Y= CH, Z= Cl; **1e** Y= N, Z= Cl; **4** Y= CH, Z= Ar; **5** Y= N, Z= Ar — **3a** Y= CH, Z= Cl; **3d** Y= N, Z= Cl; **6** Y= CH, Z= Ar; **7** Y= N, Z= Ar — **11a** Y=CH, Z= Cl; **11b** Y= CH, Z= Cl; **13** Y= CH, Z= Ar; **14** Y= N, Z= Ar

entry	starting material	Y	Z	**3**, **6**, **7**	yield (%)	method
1	**1c**	CH	Cl	**3a**	47	C[a]
2	**1c**	CH	Cl	**3a**	72	D[b]
3	**4a**	CH	C_6H_5	**3c**	73	D
4	**4b**	CH	4-MeC_6H_4	**6b**	40	D
5	**4c**	CH	4-$MeOC_6H_4$	**6c**	37	D
6	**4d**	CH	4-$MeCOC_6H_4$	**6d**	53	D
7	**1e**	N	Cl	**3d**		D
8	**1e**	N	Cl	**3d**		E[c]
9	**5a**	N	C_6H_5	**3f**	50	D
10	**5a**	N	C_6H_5	**3f**	78	E
11	**5b**	N	4-MeC_6H_4	**7b**	31	D
12	**5b**	N	4-MeC_6H_4	**7b**	41	E
13	**5c**	N	4-$MeOC_6H_4$	**7c**	27	D
14	**5c**	N	4-$MeOC_6H_4$	**7c**	39	E
15	**5d**	N	4-$MeCOC_6H_4$	**7d**	24	D
16	**5d**	N	4-$MeCOC_6H_4$	**7d**	31	E

[a] Method C: **1c** (1 equiv), $Pd(OAc)_2$ (20% mol), K_2CO_3 (5 equiv), LiCl (1.5 equiv), and *n*-Bu_4Br (1 equiv) in DMF in a sealed tube (110 °C, 48 h). [b] Method D: *N*-amidine (1 equiv), $Pd(OAc)_2$ (20 mol %), K_2CO_3 (5 equiv), LiCl (1.5 equiv), and *n*-Bu_4NBr (1 equiv) in DMF in a sealed tube, MW (170 °C, 10 min). [c] Method E: *N*-amidine (1 equiv), $Pd(OAc)_2$ (20 mol %), K_2CO_3 (5 equiv), LiCl (1.5 equiv), and *n*-Bu_4NBr (1 equiv) in DMF in a sealed tube, MW (150 °C, 80 min).

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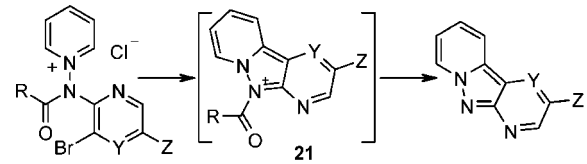
milder conditions that would be more appropriate for this nucleus, direct arylation using microwave (MW) heating was investigated. Microwave experiments were performed in sealed reaction vessels using a CEM-Discover microwave unit (IR monitoring of temperature), working at 200−250 W power (170 °C) and using experimental conditions similar to those reported previously [**1c** (0.5 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol, 22 mg), K_2CO_3 (2.5 mmol, 0.345 g), LiCl (0.75 mmol, 31 mg), and *n*-Bu_4NBr (0.33 mmol, 106 mg) in DMF in a sealed tube, 170 °C, 10 min]. Under these conditions compound **3a** (Table 4, entry 2, method D) was obtained in satisfactory yield (72%). When the same cyclization was applied to substrate **4a** (Y = CH, Z = C_6H_5, Table 4, entry 3), **3c** was obtained in 73% yield without traces of debrominated **13**. However, with the substrates **4b** and **4c** (entries 4 and 5), both of which have electron-donating ring substituents, only poor yields of the corresponding tricyclic derivatives **6b** and **6c** were obtained, probably due to the destabilizing effect exerted by the negatively charged exocyclic nitrogen. In contrast, when the arylation process was tried on **4d** (R = 4-$MeCOC_6H_4$) (entry 6), compound **6d** was obtained in 53% yield—a finding consistent with the π-stabilizing effect exerted by the aryl substituent. In addition, for compounds **4b**−**d**, small amounts of debrominated derivatives **13b**−**d**, respectively, were characterized. In the case of the pyrazine series (compounds **1e** and **5a**−**d**, entries 7−16), however, controversial results were obtained. Attempts to prepare the tricyclic compound **3d** from **1e** using different experimental conditions [methods D (170 °C, 10 min) and E (150 °C, 80 min), entries 7 and 8, Table 4] did not generate any cyclized product at all. Once again, the best result was obtained with the phenyl derivative **5a** (entries 9 and 10, methods D and E, respectively), while the electronic effect of the 4-aryl substituent seems to have only a small effect on the cyclization process (entries 11−16). A number of questions arise from the results of these experiments.

In the first place, some authors have found that an azine nitrogen on pyridine or pyrazine rings could function as an effective poison for the palladium catalyst.[16] This effect could be increased by the negatively charged aminide nitrogen and its mesomeric resonance forms on the azine nitrogen for both pyridine and pyrazine derivatives. In addition, pyrazine derivatives possess a second free nitrogen atom that could bind and poison the catalyst, thus reducing the efficiency of the process. To overcome catalyst inhibition, an excess of palladium catalyst (20 mol %) was required in these experiments and in all cases the use of LiCl as an additive was found to be necessary. When the reaction was carried out in the absence of LiCl, poor yields of pyrazolo[1,5-*a*]pyridine were obtained and the direct reduction of the starting aminide was observed as the main process.[18]

Second, Fagnou described competitive experiments on *N*-oxides in which direct arylation arises from the reaction of the more electron-deficient pyridine *N*-oxide.[16b] It is noteworthy that in these species (**4** and **5**, Table 4) resonance contributions from the 4-aryl substituent induce a different stabilizing−destabilizing effect on the negatively charged *N*-exocyclic nitrogen. This nitrogen in turn induces a partial negative charge on the pyridinium ring, thus reducing its electron-poor character. Taking into account these premises and the previously reported work on the synthesis and reactivity of *N*-acylaminides,[5a,19]

TABLE 5. Results for the Palladium Arylation from Pyridinium *N*-Acyl Derivatives 17−20



17 Y= CH, Z= Cl, R= 4-MeC_6H_4
19 Y= N, Z= Cl, R= 4-MeC_6H_4
18 Y= CH, Z= Ar, R= 4-MeC_6H_4
20 Y= N, Z= Ar, R= 4-MeC_6H_4

3a Y= CH, Z= Cl
3d Y= N, Z= Cl
6 Y= CH, Z= Ar
7 Y= N, Z= Ar

entry	starting material	Y	Z	**3**, **6**, **7**	yield[a] (%)
1	**17**	CH	Cl	**3a**	81
2	**18a**	CH	C_6H_5	**3c**	59
3	**18b**	CH	4-MeC_6H_4	**6b**	63
4	**18c**	CH	4-$MeOC_6H_4$	**6c**	70
5	**18d**	CH	4-$MeCOC_6H_4$	**6d**	51
6	**19**	N	Cl	**3d**	22
7	**20a**	N	C_6H_5	**3f**	59
8	**20b**	N	4-MeC_6H_4	**7b**	74
9	**20c**	N	4-$MeOC_6H_4$	**7c**	74
10	**20d**	N	4-$MeCOC_6H_4$	**7d**	66

[a] Method F: *N*-amidine (1 equiv), $Pd(OAc)_2$ (20 mol %), K_2CO_3 (5 equiv), LiCl (1.5 equiv), and *n*-Bu_4NBr (1 equiv) in DMF in a sealed tube, MW (170 °C, 10 min).

additional experiments were carried out on the *N*-acyl salts **17**−**20**. Acylation on the *N*-exocyclic nitrogen could partially neutralize its electron-donating effect on both the pyridinium and 2-aminopyridine rings. This class of pyridinium salt was obtained in excellent yield by benzoylation of the corresponding *N*-aminides **1c**, **1e**, **4**, and **5**, but these compounds were only moderately stable due to the leaving group behavior of *N*-aminides. In particular, compound **19**, prepared from *N*-[(3′-bromo-5′-chloropyrazin-2-yl]pyridinium aminide **1e**, is a stable yellow solid, but in solution it evolves to the starting aminide **1e** through *N*-acyl bond fission.

Pd arylation experiments on *N*-acylaminides were performed using method F (MW, 170 °C, 10 min). In these cases a variety of substituents are tolerated on the aryl residue, including electron-donating and electron-withdrawing groups. The results are shown in Table 5. Although several reaction mechanisms could be used to explain this transformation, we suggest a cyclization involving intermediates **21** and in situ N−acyl bond fission. This mechanism is consistent with the poor yield obtained for compound **3d** from the highly unstable *N*-acylaminide **19** because, bearing in mind previous experimental results (see Table 4, entries 7 and 8), only a fraction of *N*-acylaminide **19** present could furnish the tricyclic derivative **3d**. However, other tricyclic derivatives were obtained in satisfactory yields in most of the cases studied.

As far as spectroscopic studies are concerned, the absorption spectra of dipyridopyrazole derivatives **3a**, **6b**, and **6d** are shown in Figure 3a. The spectrum of **3a** exhibits peaks centered at 324, 364, 382, and 402 nm in THF at 25 °C. The peak located at 364 nm becomes a shoulder in **6b**,**d**. This red shift increases in the order **3a**, **3c**, **6b**, **6c**, and **6d**. This shift is particularly significant for the most energetic band. The presence of an aryl-containing π-electron moiety on the dipyridopyrazole nucleus contributes to extension of the π-delocalization by stabilizing the system, thus inducing a shift in the $\pi^*-\pi$ transitions responsible for such bands to higher wavelength.

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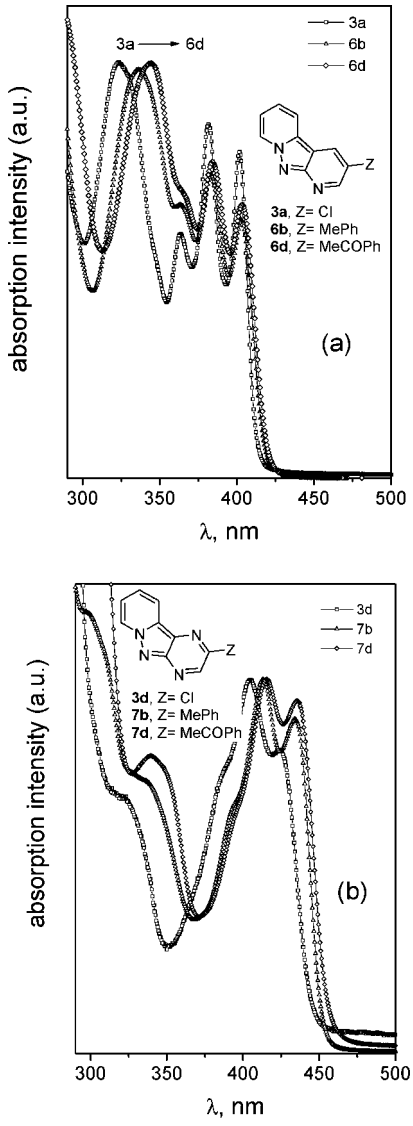

FIGURE 3. Absorption spectra of tricyclic derivatives in THF at 25 °C in the 280−500 nm range: (a) dipyridopyrazole and (b) pyridopyrazolopyrazine derivatives.

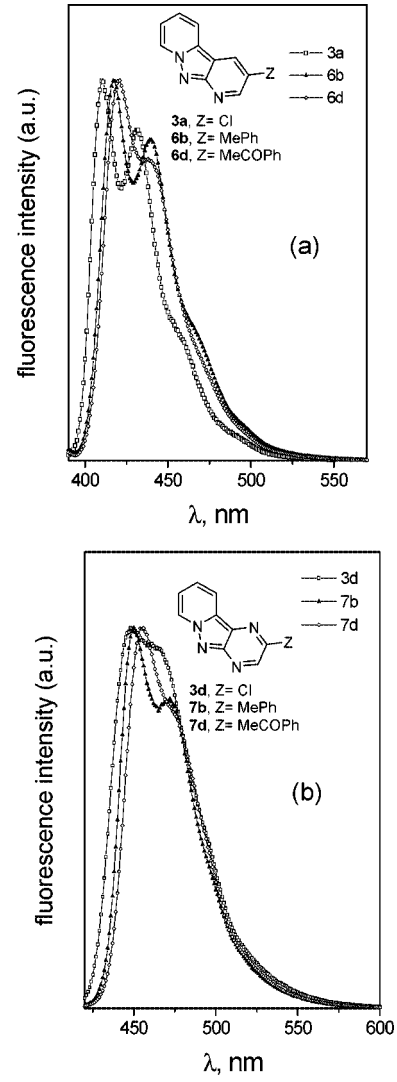

FIGURE 4. Emission spectra of tricyclic derivatives in THF at 25 °C: (a) dipyridopyrazole and (b) pyridopyrazolopyrazine derivatives. Excitation wavelengths are collected in Table 6.

On the other hand, the absorption spectra displayed by some of the pyridopyrazolopyrazine derivatives (e.g., **3d**, **7b**, and **7d**, Figure 3b) are quite similar to the dipyridopyrazole spectra, although the bands are significantly displaced to higher wavelengths. The bathochromic effect exerted by the pyrazinylamino moiety that forms part of the conjugated aromatic system is known.[9] Thus, the spectrum of **3d** shows bands centered at 405 and 424 nm and shoulders at 321 and 385 nm, which were also displaced to the red with increasing degree of conjugation from **3d** to **7d**.

The fluorescence emission spectra of both types of pyrazolopyridine (see Figure 4) exhibit features similar to those of the absorption spectra. This is a consequence of the change in the conjugation upon attaching a π-electron-containing substituent to the dipyridopyrazole or pyridopyrazolopyrazine rings and/or on passing from the dipyridopyrazole to pyridopyrazolopyrazine series.

The emission spectrum of **3a** shows two peaks at 410 and 432 nm and a shoulder at approximately 460 nm. Compound **3d**, however, exhibits two bands centered at 448 and 468 nm. Shifts to the red are observed in other members of both series.

The fluorescence quantum yields (Φ_f) and lifetimes (τ) for all of the systems were determined in THF at 25 °C upon excitation at the selected wavelengths, and the results are given in Table 6. The Φ_f values for all the systems cover a wide range—from **3a**, which only fluoresces slightly (0.05), to **3f**, where almost all deactivation takes place in a radiative way (0.96). Other samples exhibit quite reasonable fluorescence levels. In general, pyridopyrazolopyrazine derivatives seem to have higher fluorescence quantum yields than dipyridopyrazole systems. The fluorescence intensity decays for all samples were reasonably fitted to a monoexponential, indicating emission from the singlet excited state in each case. Several photophysical parameters such as rate constants for radiative (k°_r) and nonradiative (k_{nr}) deactivation processes and radiative lifetime (τ°) are also gathered in Table 6. Fluorescence lifetimes for pyridopyrazolopyrazines are longer than those of the dipyridopyrazole derivatives. As a consequence, and broadly speaking, the nonradiative rates of the singlet state are higher for dipyridopyrazole derivatives than for the pyridopyrazolopyrazines ones. This fact is clearly related to the influence of the additional amino moiety on the spectroscopic properties of conjugated aromatic systems.[9]

TABLE 6. Selected Photophysical Properties of the Tricyclic Derivatives

sample	Y	Z	ε^a (M^{-1} cm^{-1})	λ_{exc} (nm)	λ_{em} (nm)	$\Phi_f{}^b$	τ (10^{-9}s)	$k^\circ_r{}^c$ (10^8 s^{-1})	$k_{nr}{}^c$ (10^8 s^{-1})	$\tau^{\circ\,c}$ (10^{-9} s)
3a	CH	Cl	8.260	373	410	0.05	2.7	0.19	3.52	54.0
3c	CH	C_6H_5	8.930	383	415	0.38	4.7	0.81	1.32	12.4
6b	CH	4-MeC_6H_4	8.425	386	418	0.29	4.6	0.63	1.54	15.9
6c	CH	4-MeOC_6H_4	7.790	386	423	0.39	4.8	0.81	1.27	12.3
6d	CH	4-MeCOC_6H_4	11.990	386	420	0.63	3.4	1.85	1.09	5.4
3d	N	Cl	4.045	404	448	0.38	6.2	0.61	0.10	16.3
3f	N	C_6H_5	9.990	400	449	0.96	5.3	1.81	0.08	5.5
7b	N	4-MeC_6H_4	9.875	400	450	0.26	5.2	0.50	1.42	20.0
7c	N	4-MeOC_6H_4	11.475	400	455	0.83	5.4	1.54	0.32	6.5
7d	N	4-MeCOC_6H_4	14.960	400	455	0.50	5.1	0.98	0.98	10.2

[a] Measured at the λ_{max} of the excitation band. [b] Fluorescence quantum yields (Φ_f) were determined in THF at 25 °C, using quinine sulfate/0.1 M sulfuric acid as the standard, upon selection of λ_{exc} and λ_{em} (maximum of emission) as the excitation and emission wavelengths. [c] Some photophysical parameters: rate constants for radiative (k°_r) and nonradiative (k_{nr}) deactivation processes and radiative lifetime (τ°).

Conclusion

Some results on the synthesis of substituted dipyridopyrazoles and pyridopyrazolopyrazines, obtained through an intramolecular radical pathway from pyridinium *N*-aminides, are described. The methodology seems to be efficient for the preparation of 3-chloro derivatives. The method does, however, produce poor yields of 3-aryl derivatives. In these cases, Pd direct arylation of 3-aryl *N*-aminides or their *N*-acyl derivatives using microwave irradiation furnished better results. A preliminary study of the fluorescence properties of the materials is also reported.

Experimental Section

General Procedure for the Preparation of *N*-[(5′-Aryl-3′-bromo-)azin-2′-yl]pyridinium Aminide Derivatives 4 and 5. A solution of NBS (0.213 g, 1.2 mmol) in CH_2Cl_2 (14 mL) was added dropwise to a stirred solution of *N*-[(5′-aryl)azin-2′-yl]pyridinium aminide **13** or **14** (1 mmol) in CH_2Cl_2 (14 mL) at room temperature. The reaction mixture was stirred at room temperature until the starting material had been consumed (TLC analysis). The solvent was evaporated, and the residue was purified by flash chromatography on silica gel followed by crystallization, yielding the corresponding products **4** and **5**.

Data for *N*-[(3′-bromo-5-phenyl)pyridin-2′-yl]pyridinium Aminide (4a): reaction time 10 min; chromatography, EtOH; 76%; orange solid (EtOAc); mp 154−156 °C; IR (KBr) ν_{max} 1586, 1469, 1435, 1384, 1154, 1032, 789 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 8.73 (d, 2H, J = 5.1 and 1.3 Hz), 8.18 (tt, 1H, J = 7.9 and 1.3 Hz), 7.97 (d, 1H, J = 2.2 Hz), 7.91 (m, 3H), 7.49 (dd, 2H, J = 8.1 and 1.4 Hz), 7.40 (dd, 2H, J = 8.1 and 7.3 Hz), 7.26 (tt, 1H, J = 7.3 and 1.4 Hz); ^{13}C NMR (75 MHz CD_3OD) δ 161.8, 145.9, 143.9, 139.6, 139.3, 138.6, 129.8, 128.5, 127.4, 126.3, 126.0, 106.6; MS (EI) *m*/*z* (relative intensity) 327, 325 (M^+, 52.3, 52.4), 326 (100), 246, 244 (4.5, 4.7), 167(22), 140 (97), 79 (23). Anal. Calcd for $C_{16}H_{12}BrN_3$ (326.20): C, 58.91; H, 3.71; N, 12.88. Found: C, 58.54; H, 3.66; N, 12.97.

General Procedure for the Preparation of *N*-acylpyridinium Salts 17−20. 4-Methylbenzoyl chloride (0.170 g, 1.1 mmol) was added dropwise to a stirred solution of *N*-[(5′-substituted-3′-bromo)azin-2′-yl]pyridinium aminide derivatives **1c**,**e**, **4**, and **5** (1 mmol) in dry acetone (7 mL) at room temperature. The reaction mixture was stirred at room temperature until all the starting material had been consumed (TLC analysis). The suspension was filtered, and the solid was washed with EtOAc and crystallized from ethanol, yielding compounds **17**−**20**.

Data for *N*-[(3′-bromo-5′-phenylpyridin-2′-yl)(4″-methylbenzoyl)amino]pyridinium Chloride (18a): yellow solid; 98%; mp 165−167 °C; IR (KBr) ν_{max}, 3414, 3057, 1701, 1610, 1475, 1260, 1084, 831, 767 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 9.56 (d, 2H, J = 5.8 Hz), 8.93 (t, 1H, J = 7.7 Hz), 8.82 (d, 1H, J = 1.5 Hz), 8.55 (d, 1H, J = 1.5 Hz), 8.41 (at, 2H, J = 7.1 Hz), 7.70 (m, 4H), 7.53 (m, 3H), 7.28 (d, 2H, J = 7.9 Hz), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.1, 150.2, 150.0, 148.8, 148.3, 146.2, 142.9, 141.9, 135.4, 130.8, 130.7, 130.6, 130.5, 130.4, 129.3, 128.5, 121.0, 21.6. HRMS: *m*/*z* calcd for $C_{24}H_{19}BrN_3OCl$ (M^+) 444.0708, found 444.0694.

General Procedure for the Preparation of Tricyclic Derivatives 3, 6, and 7 through a Radical Pathway. Method B. A solution of TTMSS (0.149 g 0.6 mmol) and AIBN (0.099 g, 0.6 mmol) in dry benzene (12 mL) was diluted with dry acetonitrile (28 mL). The resulting solution was added dropwise by a syringe pump during 32 h to a stirred dispersion of potassium carbonate (0.083 g, 0.6 mmol) and the corresponding aminide (0.3 mmol) in dry acetonitrile (50 mL) at 80 °C (bath temperature), under an atmosphere of dry argon. The mixture was stirred for 48 h at 80 °C, and all of the aminide had been consumed (TLC analysis). The reaction mixture was allowed to cool to room temperature and concentrated. The crude product was purified by flash chromatography and crystallization.

General Procedure for the Preparation of Tricyclic Derivatives 3, 6, and 7 by Pd Arylation−Microwave Irradiation. Methods D and E. A suspension of the corresponding *N*-amidine (0.5 mmol), $Pd(OAc)_2$ (0.1 mmol, 22 mg), K_2CO_3 (2.5 mmol, 0.345 g), LiCl (0.75 mmol, 31 mg), and *n*-Bu_4NBr (0.33 mmol) in degassed dry DMF (4.20 mL), in a sealed tube under an atmosphere of dry argon, was irradiated in a microwave oven (CEM-Discover, IR temperature monitoring) working at 250−200 W power [170 °C, 10 min (method D), 150 °C, 80 min (method E)]. The reaction mixture was allowed to cool to room temperature, and distilled water (5 mL) was added. After extraction with EtOAc the organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel followed by crystallization.

General Procedure for the Preparation of Tricyclic Derivatives 3, 6, and 7 by Pd Arylation−Microwave Irradiation. Method F. A suspension of the corresponding pyridinium salt **17**−**20** (0.5 mmol), $Pd(OAc)_2$ (0.1 mmol, 22 mg), K_2CO_3 (2.5 mmol, 0.345 g), LiCl (0.75 mmol, 31 mg), and *n*-Bu_4NBr (0.33 mmol) in degassed dry DMF (4.20 mL), in a sealed tube under an atmosphere of dry argon, was irradiated in a microwave oven (CEM-Discover, IR monitoring temperature), working at 250−200 W power (170 °C, 10 min). The reaction mixture was allowed to warm to room temperature, and distilled water (5 mL) was added. After extraction with EtOAc, the organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel followed by crystallization.

Data for 3-(4″-methylphenyl)dipyrido[1,2-*b*:3′,2′-*d*]pyrazole (6b): chromatography, hexane/EtOAc (1:1), 32% (method B), 40% (method D), 63% (method F); yellow solid (EtOAc); mp 213−214 °C; IR (KBr) ν_{max} 2918, 1642, 1504, 1437, 1288, 1258, 823, 741. cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, 1H, J = 2.4 Hz), 8.86 (d, 1H, J = 6.9 Hz), 8.50 (d, 1H, J = 2.4 Hz), 8.13 (d, 1H, J = 8.6 Hz), 7.56 (d, 2H, J = 8.2 Hz), 7.46 (dd, 1H, J =

8.6 and 7.0 Hz), 7.28 (m, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 152.9, 137.1, 135.7, 135.0, 129.7, 128.9, 128.8, 127.0, 126.1, 123.4, 118.4, 117.2, 21.2; MS (EI) *m*/*z* (relative intensity) 259 (M^+, 100), 231 (11) 216 (5) 129 (3) 78 (6). Anal. Calcd for $C_{17}H_{13}N_3$ (259.31): C, 78.74; H, 5.05; N, 16.20. Found: C, 78.61; H, 5.52; N, 15.99.

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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