N-Azinylpyridinium *N*-Aminides: An Approach to Pyrazolopyridines via an Intramolecular Radical Pathway

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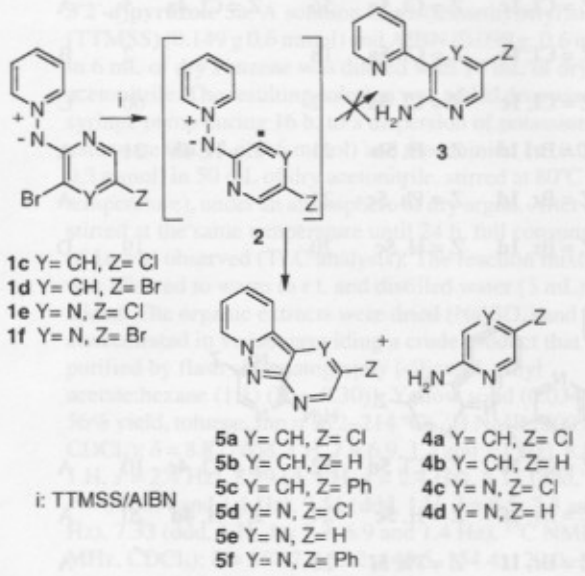
Abstract: Intramolecular radical arylation, under thermal conditions, to a π-deficient pyridinium, linked to a π-excessive 2-azinyliminopyridine moiety is described. The method allows a new entry to pyrazolo[1,5-*a*]pyridine nucleus.

Key words: aminides, pyrazolopyridines, intramolecular radical reactions, ylides

The generation and subsequent reactions of aryl radicals, derived from aryl halides using *tri-n*-butyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) is now well documented, and several syntheses, based on aryl radical cyclisations have been reported.[1] Few examples of heteroaryl radicals are known, and presumably they would behave similarly to aryl radicals, since the lone electron would be in an orbital orthogonal to the aromatic π-system and hence, its nature (π-excessive or π-deficient) should have little or no effect on the reactivity of such radicals.[2] Particular attention has been devoted to pyridyl radicals; both Snieckus[3] and Nadin[4] have reported pyridyl radical cyclisations. Harrowven[5] has published some papers, which include pyridyl radical cyclisations and aryl radical cyclisations onto pyridines. Jones[6] has disclosed the use of radicals derived from 3-bromopyridine and the extension of this chemistry to pyridinium radicals.[7] However, to the best of our knowledge, pyrazinyl radical cyclisations have not been reported before.

On the other hand, alkylation of heteroaromatic bases via a radical pathway is an useful synthetic method with a broad potential. Radical alkylations onto heteroaromatic systems, under oxidative conditions, were initially studied by Minisci's group,[8] but more recently, Minisci and co-workers[9] and Togo and co-workers[10] have reported intermolecular radical alkylations onto heteroaromatic substrates by alkyl halides, using tris(trimethylsilyl)silane (TTMSS) as mediator of the radical process. These authors have shown that the heterocyclic ring needs to bear a positive charge for successful attack by the nucleophilic carbon radicals.

The first example of intramolecular radical addition to quaternized pyridinium salts was described by Murphy and co-workers[11] who exploited the non oxidative chemistry of Bu_3SnH. Although arylations of aromatic and heteroaromatic compounds, via an *ipso* substitution radical mechanism are known,[12] to our knowledge, only one method of arylation of quaternized heteroaryl substrates has been published. In this case, a pyridinium radical was added onto another aromatic nucleus, with subsequent rearomatisation of the aryl ring.[7]



Scheme 1

In the course of our studies on the reactivity of heteroaryl-stabilized cycloimonium ylides [i.e. pyridinium *N*-(2′-azinyl)aminides **1**, (Scheme 1)],[13] we attempted the intramolecular arylation of ylide **1**, through the radical **2**. We expected to obtain the bipyridine **3**, by a reaction pathway involving a 5-*exo-trig* cyclisation, and then, rupture of N-N bond, as previously described.[13c] To our surprise, product **3** was not detected, and only reduction compounds **4** and cyclisation products **5** were observed, the last ones corresponding either to dipyrido[1,2-*b*; 3′, 2′-*d*]pyrazole nucleus (compounds **5a–c**, Y = CH) or pyrido[1′,2′:2,3]pyrazole[5,4-*b*]pyrazine derivatives (compounds **5d–f**, Y = N), obtained from ylides **1c,d** or **1e,f**, respectively (Scheme 1). The reaction could follow a similar course to those postulated by Murphy[11] to generate the final product. For the dipyridopyrazole nucleus, only few examples, obtained by alternative ways, are known.[14] The preparation of the unsubstituted nucleus, however, (compound **5b**, Z = H) has not been reported to date. No references have been found for the pyrazino derivatives (compounds

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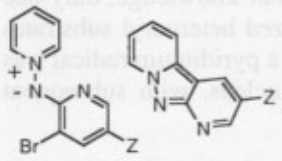
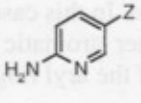
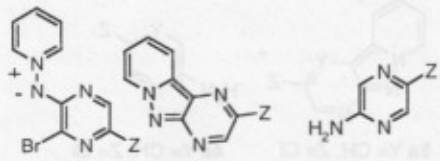
5d–f). In this paper we wish to report our preliminary results on the intramolecular radical arylation of stable heterocyclic betaine systems, using TTMSS/AIBN under thermal conditions to supply this kind of pyridopyrazole derivatives. This study represents the first example of an aryl radical addition to a π-deficient pyridinium fragment linked to a π-excessive 2-azinyliminopyridine moiety.

Table Radical Cyclisation for Compound **1c–f**

Entry	Starting amidine	Cyclizated product	Yield[a] (%)	Reduced product	Yield[a] (%)	Method
						
1	Z = Cl, **1c**	Z = Cl, **5a**	56	Z = Cl, **4a**	5	A
2	Z = Cl, **1c**	Z = Cl, **5a**	18		2	B
3	Z = Cl, **1c**	Z = Cl, **5a**	2		60	C
4	Z = Br, **1d**	Z = H, **5b**	21	Z = H, **4b**	21	A
5	Z = Br, **1d**	Z = Ph, **5c**	23			A
6	Z = Br, **1d**	Z = H, **5c**	20		19	D
						
7	Z = Cl, **1e**	Z = Cl, **5d**	52	Z = Cl, **4c**	10	A
8	Z = Br, **1f**	Z = H, **5e**	24	Z = H, **4d**	20	A
9	Z = Br, **1f**	Z = Ph, **5f**	20			A

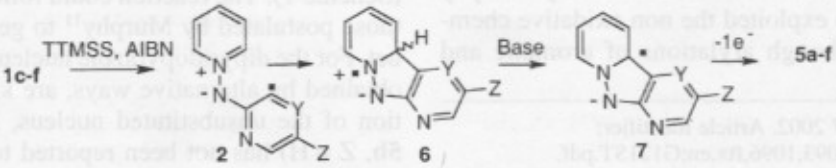
[a] Yields refer to isolated pure product. All the products were identified by spectroscopic and literature data. **Method A**: TTMSS (2 equiv), AIBN (2 equiv) in 40 mL of dry (acetonitrile:benzene, 7:3) were added during 16 h to a dispersion of potassium carbonate (2 equiv) and the corresponding aminide **1c–f** (1 equiv) in 50 mL of dry acetonitrile, 80 °C, 24 h. **Method B**: TTMSS (1 equiv), AIBN (1 equiv) in 20 mL of dry (acetonitrile:benzene, 7:3) were added during 8 h to a dispersion of potassium carbonate (2 equiv) and the aminide **1c** (1 equiv) in 50 mL of dry acetonitrile, 80 °C, 24 h. **Method C**: TTMSS (2 equiv), AIBN (2 equiv) in 40 mL of dry (acetonitrile:benzene, 7:3) were added during 16 h to a solution of aminide **1c** (1 equiv) in 50 mL of acetonitrile, 80 °C, 24 h. **Method D**: TTMSS (2 equiv), AIBN (2 equiv) in 40 mL of dry (acetonitrile:THF, 7:3) were added during 16 h to a dispersion of potassium carbonate (2 equiv) and the aminide **1d** (1 equiv) in 50 mL of dry acetonitrile, 80 °C, 24 h.

As indicated in Scheme 1 and the Table, the dipyridopyrazole **5a** was satisfactorily obtained by slow dropwise addition, by a syringe pump, of a solution of TTMSS and AIBN in a mixture of dry benzene/acetonitrile, to a dispersion, at 80 °C, of potassium carbonate and the halogenated aminide **1c** in dry acetonitrile (entry 1, Method A).[15] The reaction did not go to completion when only 1 equivalent of each TTMSS and AIBN were employed (entry 2, Method B), as previously reported.[11a] When the reaction was carried out in the absence of potassium carbonate, poor yields of pyrazolo[1,5-*a*]pyridine **5a** were observed, and the direct reduction of aminide **1c** (to give **4a**) appeared as the main process (entry 3, Method C).[16] Although several reaction mechanisms could explain this transformation, we suggest what appears as the simplest pathway, involving a 5-exo/*endo-trig* cyclisation, as described in Scheme 2, which agrees with the role of potassium carbonate and with the production of arylated compound **5** during the reaction process.[17]

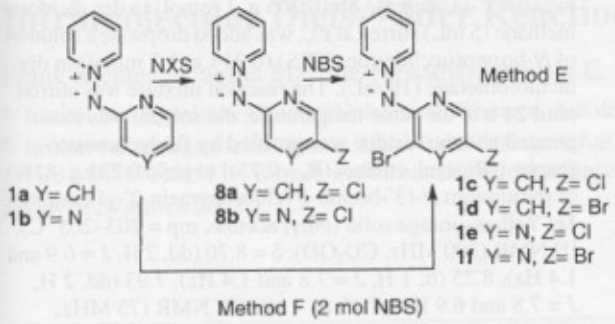
When the reaction was carried out in benzene and the starting aminide has an additional bromine (e.g. *N*-aminides **1d** and **1f**, entries 4, 5 and 8, 9 respectively) a concomitant phenylation was observed.[18] However, when the reaction was performed in THF/acetonitrile (entry 6, Method D), only poor yields of the cyclised compounds were obtained, probably due to H abstraction from the solvent. In similar manner, aminides **1e,f** reacted using Method A, to afford pyridopyrazolepyrazine derivatives **5d–f** (entries 7–9, Table).

Preparation of starting aminides **1a,b** (Scheme 3) has been previously described from 2,4-dinitrophenyl pyridinium chloride and the corresponding 2-heteroaryl hydrazine, producing the corresponding hydrazones. Then, cyclisation in acetic acid and treatment with potassium carbonate provides the stable aminides **1a,b** in good yields.[13a] Halogenation of **1a** under very mild conditions, with *N*-chlorosuccinimide (NCS), provides the chloro derivative **8a**,[13b] which was halogenated again by treatment with *N*-bromosuccinimide (NBS), yielding the dihalo derivative **1c** (Z = Cl, Method E, Scheme 3). When this process was carried out using a two molar excess of NBS, the dibromoaminide **1d** was obtained in one step (Z = Br, Method F, Scheme 3). In a similar way, halogenation of aminide **1b** yielded the halo derivatives **1e,f**.[19]

In conclusion, it has been shown that it is possible to generate the pyrazolepyridine nucleus from *N*-azynilpyridinium *N*-aminides through a radical pathway, using TTMSS/AIBN under thermal conditions. Further experiments are in progress to extend the process as a general methodology to other azine derivatives.



Scheme 2



Scheme 3

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(15) **Typical Procedure, Method A: 3-Chloro-dipyrido[1,2-*b*; 3′2′-*d*]pyrazole 5a**: A solution of tris(trimethylsilyl)silane (TTMSS) (0.149 g 0.6 mmol) and AIBN (0.099 g, 0.6 mmol) in 6 mL of dry benzene was diluted with 14 mL of dry acetonitrile. The resulting solution was added dropwise by a syringe pump during 16 h, to a dispersion of potassium carbonate (0.083 g, 0.6 mmol) and the aminide **1c** (0.062 g, 0.3 mmol) in 50 mL of dry acetonitrile, stirred at 80°C (bath temperature), under an atmosphere of dry argon. After being stirred at the same temperature until 24 h, full consumption of **1c** was observed (TLC analysis). The reaction mixture was allowed to warm to r.t. and distilled water (5 mL) was added. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo, providing a crude product that was purified by flash chromatography [silicagel, ethyl acetate:hexane (1:1) (R_f = 0.30)]. Yellow solid (0.034 g, 56% yield, toluene, mp = 212–214 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (ddd, 1 H, *J* = 6.9, 1.2 and 1.1 Hz), 8.80 (d, 1 H, *J* = 2.4 Hz), 8.39 (d, 1 H, *J* = 2.4 Hz), 8.11 (ddd, 1 H, *J* = 8.5, 1.4 and 1.1 Hz), 7.51 (ddd, 1 H, *J* = 8.5, 7.3 and 1.2 Hz), 7.33 (ddd, 1 H, *J* = 7.3, 6.9 and 1.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 152.2, 146.5, 134.4, 129.0, 127.7, 124.0, 122.8, 118.5, 117.8. IR (KBr): 2922, 1706, 1641, 1437 cm^{-1}. MS (CI): *m/z* = 204, 206 ([M$^+$ + 1], 100, 32). EIMS HR: calcd for $C_{10}H_6{}^{35}ClN_3$: [M$^+$] 203.0246. Found: 203.0240.

(16) (a) Loss of a proton from a dihydropyridine radical cation is a key step in the oxidative homolytic alkylation of pyridinium salts, in aqueous or Me_2SO solutions: Minisci, F.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1987**, *52*, 730. (b) Rusell and co-workers have reported previously the use of bases to promote the substitutive reactions of aromatics: Rusell, G. A.; Chen, P.; Kim, B. H.; Rajaratnam, R. *J. Am. Chem. Soc.* **1997**, *119*, 8795. (c) Wang, C.; Rusell, G. A.; Trahanovsky, W. S. *J. Org. Chem.* **1998**, *63*, 9956.

(17) Potassium carbonate could abstract a proton from the substituted dihydropyridine radical **6** (Scheme 2), to form the radical **7**, that would be converted in the arylated compound **5** (see ref.[15b,c]). In the absence of potassium carbonate, dihydropyridine radical **6** did not evolve to **5**, and only decomposition products and N-N reduction compounds were observed.

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(19) **Typical Procedure, Method E: Pyridinium *N*-(3′-bromo-5′-chloropyrazin-2′-yl)aminide 1e**: To a solution of pyridinium (N-(2′-pyrazinyl)aminide **1b** (0.172 g, 1 mmol)

in dry dichloromethane (5 mL) stirred at 0 °C was added dropwise a solution of *N*-chlorosuccinimide (NCS) (0.160 g, 1.2 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 1 h at the same temperature, allowed to warm up to r.t. and stirring for a further 24 h. The solvent was evaporated and the residue was purified by flash chromatography [silicagel, ethanol, ($R_f \approx 0.25$)] to yield 0.149 g (72%) of pyridinium *N*-(5′-chloropyrazin-2′-yl)aminide **8b**: Yellow solid (ethyl acetate, mp = 158–161 °C). ^{1}H NMR (300 MHz, CD_3OD): δ = 8.76 (dd, 2 H, *J* = 5.7 and 1.3 Hz), 8.13 (tt, 1 H, *J* = 8.2 and 1.3 Hz), 7.86 (dd, 2 H, *J* = 8.2 and 5.7 Hz), 7.62 (d, 1 H, *J* = 1.4 Hz), 7.60 (d, 1 H, *J* = 1.4 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ = 160.8, 145.0, 140.3, 139.5, 135.4, 132.1, 128.7. Anal. Calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.32; H, 3.69; N, 27.31. To a solution of pyridinium *N*-(5′-chloropyrazin-2′-yl)aminide **8b** (0.206 g, 1 mmol) in dry dichloromethane (5 mL) stirred at r.t., was added dropwise a solution of *N*-bromosuccinimide (NBS) (0.214 g, 1.2 mmol) in dry dichlorometane (10 mL). The reaction mixture was stirred until 24 h at the same temperature, the solvent was evaporated and the residue was purified by flash chromatography [silicagel, ethanol ($R_f \approx 0.75$)] to yield 0.231 g (81%) of pyridinium *N*-(3′-bromo-5′-chloropyrazin-2′-yl)aminide **1e**: Yellow-orange solid (ethyl acetate, mp = 203–205 °C). ^{1}H NMR (300 MHz, CD_3OD): δ = 8.70 (dd, 2 H, *J* = 6.9 and 1.4 Hz), 8.25 (tt, 1 H, *J* = 7.8 and 1.4 Hz), 7.93 (dd, 2 H, *J* = 7.8 and 6.9 Hz), 7.60 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 158.4, 146.2, 141.4, 139.6, 130.8, 129.0, 126.0; Anal. Calcd for $C_9H_6BrClN_4$: C, 37.86; H, 2.12; N, 19.62. Found: C, 38.01; H, 2.43; N, 19.31.