Pyridinium *N*-heteroarylaminides: a brief study of the synthesis and reactivity under solvent-free mechanochemical conditions

Marta Cordoba, Valentina Abet, Maria Moron, Rafael R. Castillo, Carolina Burgos,* and M. Luisa Izquierdo*

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Spain
E-mail: mluisa.izquierdo@uah.es, carolina.burgos@uah.es

Dedicated to Professor Julio Alvarez-Builla on the occasion of his 65th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.312

Abstract
The first example of a heterocyclic aromatic substitution by an *N*-ylide and the first examples of heteroaromatic halogenations in the presence of *N*-halosuccinimides using mechanochemical conditions are described.

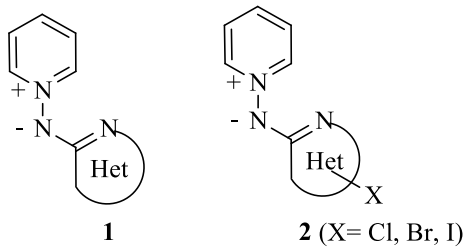
Keywords: Pyridinium *N*-aminides, halogenation, mechanochemical conditions

Introduction

Over the past few decades, environmentally friendly processes based on the replacement of volatile organic solvents by other non-toxic and/or non-volatile solvents such as water, ionic liquids and supercritical fluids have attracted considerable attention.[1] In this context, solvent-free conditions give rise to interesting alternatives.[2] There are various approaches to carry out solvent-free reactions. For example, in solid-state reactions the use of ball mills leads to more reproducible processes whereas the mechanochemical approach, which is based on manually grinding together solid starting materials with a mortar and a pestle, provides the simplest and easiest method.[3] Another attractive aspect is that in some cases these reactions are faster than the original solvent-based processes.

For several years our research program has to some extent focused on the study of pyridinium heteroaryl-stabilized aminides **1** (Figure 1).[4] These compounds have proven to be useful intermediates in heterocyclic synthesis, particularly in radical chemistry[5] and in Pd cross-coupling[6] and other metal-catalyzed methods.[7] The presence of an electronegative substituent in the *N*-aminide nucleus can effectively assist the site-selective functionalization of the heterocyclic core and, as a result, halogenated species **2** (Figure 1) are our preferred starting

materials for this kind of chemistry. Accordingly, some of our work has been dedicated to finding a set of appropriate conditions to obtain both *N*-aminides **1** and halogenated *N*-aminides **2** under clean, facile and non-polluting conditions and in synthetically useful yields. In this context, mechanochemical methods could provide an interesting alternative. In this paper we report our preliminary results on the preparation of stable heterocyclic betaine systems **1** and **2** using this methodology. To the best of our knowledge, this study represents the first example of a heterocyclic aromatic substitution by an *N*-ylide and the first example of heteroaromatic halogenations in the presence of *N*-halosuccinimides using mechanochemical conditions.

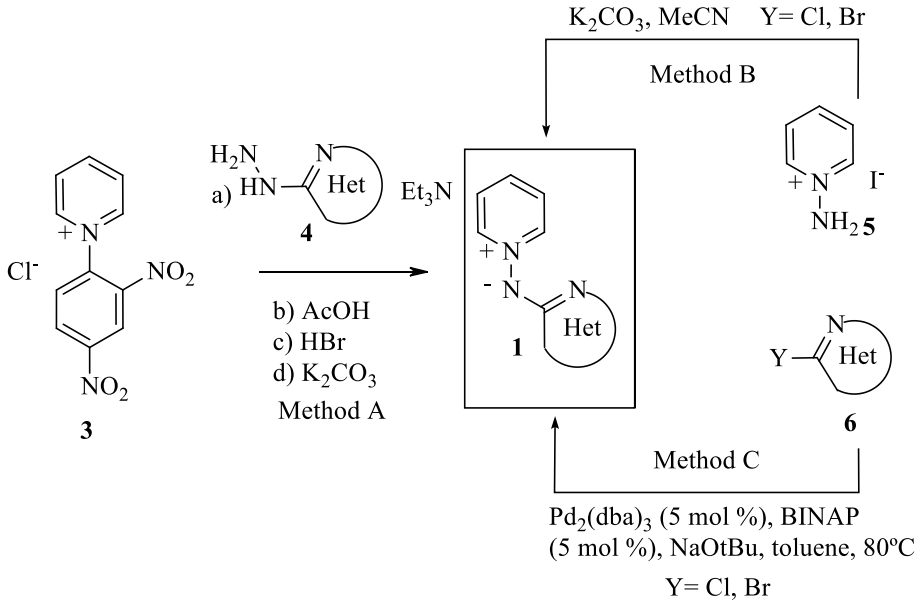


1 **2** (X= Cl, Br, I)

Figure 1. General structures of pyridinium *N*-aminides **1** and halogenated pyridinium *N*-aminides **2**.

Results and Discussion

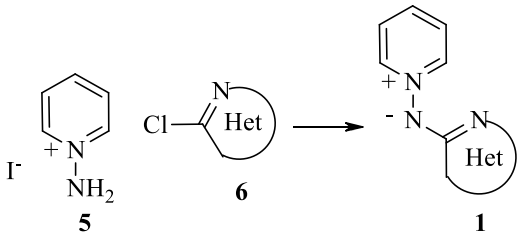
The classical synthesis of pyridinium *N*-aminides **1** is an adapted version of the method previously described by Beyer and Thieme[8] and it involves the reaction of Zincke salt (2,4-dinitrophenylpyridinium chloride) **3** with the corresponding 2-heteroaryl hydrazine **4** in a typical ANRORC process to give the corresponding hydrazones. Acid catalysis then produces the pyridinium salts, which are transformed into the *N*-aminides **1** by treatment with base (Scheme 1, method A). Alternatively, an easy method can be used for various π-deficient heterocycles and it simply involves treating the commercially available *N*-aminopyridinium iodide **5** with the corresponding haloheteroaryls **6** (Y = Cl, Br) in the presence of base (Scheme 1, method B).[9,10] This method generates the pyridinium *N*-aminides **1** in a single step and is a suitable alternative to prepare a diverse range of these useful intermediates. More recently,[10] in an attempt to expand this simple methodology for the synthesis of pyridinium *N*-heteroarylaminides **1** and bearing in mind the palladium-promoted C–N bond formation developed by Buchwald and Hartwig,[11] we accomplished the formation of a C–N bond between several haloheterocycles **6** (Y = Cl, Br) and *N*-aminopyridinium iodide **5** using a palladium-catalyzed amination process (Scheme 1, method C).

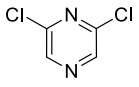
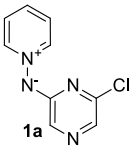
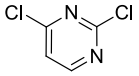
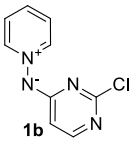
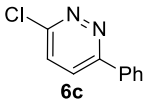
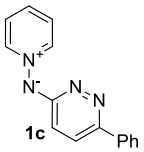
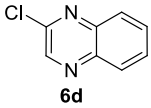
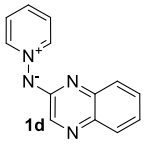


Scheme 1

On considering the easier method (Method B, Scheme 1), we envisaged that the strategy for building up the *N*-aminide nucleus could involve a mechanochemical approach if it was possible to find suitable experimental conditions. Taking into account previous reports,[9] the nucleophilic substitution process could work well using chlorodiazines, in accordance with their more π-deficient character, whereas the reaction could not take place using simpler haloazines. Additionally, a nucleophilic substitution process could also work well in the presence of electron-withdrawing substituents (such as halogens), which would make the heterocyclic ring more π-deficient and facilitate attack by the nucleophile. Our initial results showed that a mixture of *N*-aminopyridinium iodide **5** and **6a** (2,6-dichloropyrazine) can be converted into *N*-(6-chloropyrazin-2-yl)pyridinium aminide **1a** using potassium carbonate as the base. The best yield (70%) was obtained using a slight excess of the chloroheterocycle **6a** (1.2 equiv) and excess base (3 equiv) at room temperature, with the solid starting materials ground manually with a mortar and pestle for 2–5 min (Entry 1, Table 1). Similar satisfactory results were obtained using 2,4-dichloropyrimidine **6b** as starting material, a reaction that yielded *N*-(2-chloropyrimidin-4-yl)pyridinium aminide **1b** in 82% yield without traces of the corresponding isomeric *N*-(4-chloropyrimidin-2-yl)pyridinium aminide (Entry 2, Table 1). However, poor results were obtained starting from the monohalodiazines 3-chloro-6-phenylpyridazine **6c** and 2-chloroquinoxaline **6d**, which have an additional π-system as a substituent or as a condensed ring. The corresponding *N*-(6-phenylpyridazin-3-yl)pyridinium aminide **1c** and *N*-(quinoxalin-2-yl)pyridinium aminide **1d** were obtained in low yields (12 and 37%, respectively) (Entries 3 and 4, Table 1). Although all of the products have been reported previously with similar or better yields,[9,10] the method described here proved to be very convenient for multigram-scale synthesis, it avoids the use of solvent and it is considerably faster and cleaner than classical solvent-based methods.[12]

Table 1. Synthesis of pyridinium *N*-heteroarylaminides by a mechanochemical approach

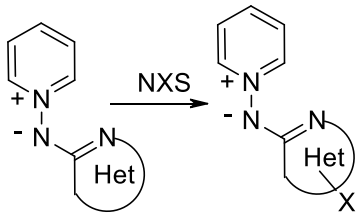


Entry	Starting chloro diazine **6**	*N*-Aminide **1**	Yield %[a]
1	 **6a**	 **1a**	70
2	 **6b**	 **1b**	82
3	 **6c**	 **1c**	12
4	 **6d**	 **1d**	37

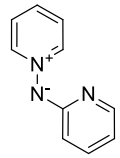
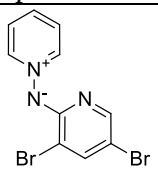
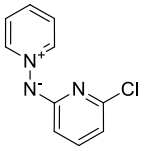
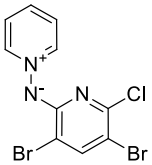
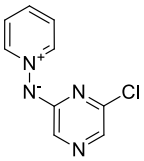
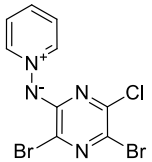
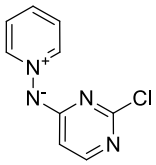
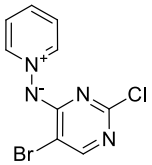
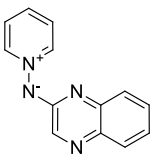
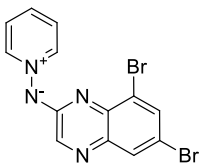
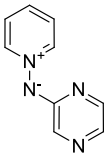
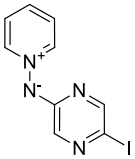
[a]Yields are given for isolated products.

On the other hand, halogenation reactions in the presence of *N*-halosuccinimides – one of the mildest sources of X^+ – have grown in importance in modern organic synthesis. For example, Santi and co-workers[13a] reported the use of *N*-halosuccinimides in organoselenium-catalyzed oxidative halogenations. Bengtsson and Almqvis[13b] communicated the iodination of 2-pyridones in the presence of NIS. The aromatic halogenation of benzo- and dibenzocrown ethers in the presence of *N*-halosuccinimides and under mechanochemical activation has recently been studied.[14] In a similar way, some of our work has concerned the use of different *N*-halosuccinimides (NXS) – a safe alternative to the use of molecular halogens – in the preparation of a wide range of halogenated *N*-aminides.[15] Taking into account the remarkable advantages of solvent-free approaches, we contemplated the possibility of attempting this kind of reaction under mechanochemical conditions.

Table 2. Synthesis of halo pyridinium *N*-heteroarylaminides **2** by a mechanochemical approach from *N*-heteroarylaminides **1**



1 **2**

Entry	*Starting N-aminide **1***	*Halogenation product **2***	*Yield %*[a]
1	 **1e**	 **2a**	89
2	 **1f**	 **2b**	64
3	 **1a**	 **2c**	66
4	 **1b**	 **2d**	77
5	 **1d**	 **2e**	88
6	 **1g**	 **2f**	51

[a]Yields are given for isolated products

Initial experiments showed that a mixture of *N*-(pyridin-2-yl)pyridinium aminide **1e**[4a,b] (1 equiv) in the presence of *N*-bromosuccinimide (1.2 equiv) gave only poor yields of dibromo-derivative **2a** and monobromo-derivatives were not detected at all. Better results were obtained using a 2.2 molar excess of NBS and in this case **2a** was obtained in 89% yield, which is an improvement on previously described yields[4a,4b,15] (Entry 1, Table 2).

Similar results were obtained using **1f**, which contains an additional chloro-substituent in the 6-position, as the starting *N*-aminide[9] or when the reaction was attempted on the more π-deficient *N*-(6-chloropyrazin-2-yl)pyridinium aminide **1a**, which gave dibromo derivatives **2b** and **2c**, respectively, as the only detectable products (Entries 2 and 3, Table 2).

As expected, when the reaction was carried out on *N*-(2-chloropyrimidin-4-yl)pyridinium aminide **1b**, in which there is only one position susceptible to SEAr, in the presence of *N*-bromosuccinimide, a good yield of *N*-(5-bromo-2-chloropyrimidin-4-yl)pyridinium aminide **2d** was obtained (Entry 4, Table 2). However, a similar process with *N*-(quinoxalin-2-yl)pyridinium aminide **1d** gave only electrophilic substitution on the carbocyclic ring and no traces of 3-bromo derivative were detected, according to a pseudo-quinoline pattern (Entry 5, Table 2).[16]

Iodination in the presence of *N*-iodosuccinimide was also tested on the *N*-(pyrazin-2-yl)pyridinium aminide **1g**.[4b,9] In this case only selective monoiodination at the 5-position was observed (Entry 6, Table 2) and all attempts to transform **2f** into the diiodo-derivative were unsuccessful.[17]

Conclusions

Differently substituted pyridinium *N*-heteroarylaminides have been prepared in one step under mechanochemical conditions. The reactions were carried out from *N*-aminopyridinium iodide and the corresponding heteroaryl chloride using potassium carbonate as the base. In a similar way, the regioselective halogenation of pyridinium *N*-heteroarylaminides was achieved in the presence of *N*-halosuccinimides. For both processes, the method proved to be very convenient for multigram-scale syntheses,[18] it avoids the use of solvent and is considerably faster and cleaner than classical solvent-based methods.

Experimental Section

General. Column chromatography was performed on silica gel (60 F_{254}, 70–200 μm) as the stationary phase. All melting points are uncorrected. NMR spectra were obtained at 300 (^{1}H) and 75 (^{13}C) MHz. Chemical shifts are reported in ppm relative to tetramethylsilane.

Compounds **1e**,[4a,b] **1f**[9] and **1g**[4b,9] were synthesized according to the previously reported procedures. The following compounds have been described previously: **1a**,[9] **1b**,[9] **1c**,[9] **1d**[10] and **2a**.[4a,4b,15]

General procedure for the preparation of pyridinium *N*-heteroarylaminides (1a–d)

Potassium carbonate (0.153 g, 1.11 mmol), *N*-aminopyridinium iodide (0.083 g, 0.37 mmol) and the corresponding haloheterocycle (0.37 mmol) were added to a mortar. The mixture was ground with a pestle at room temperature and it acquired a yellow color. The reaction was completed in 2–5 min and the reaction mixture was dissolved in ethanol. The solution was filtered and the solvent was removed *in vacuo*. The product was purified by chromatography on silica gel using ethanol as eluent. Finally, the products were crystallized from the appropriate solvent and identified.

***N*-(6-Chloropyrazin-2-yl)pyridinium aminide (1a).** Yield 70%; yellow solid (from EtOH/EtOAc); mp 184–186 ºC (lit.[9] mp 184–186 ºC).

***N*-(2-Chloropyrimidin-4-yl)pyridinium aminide (1b).** Yield 82%; yellow solid (from EtOH/EtOAc); mp 133–136 ºC (lit.[9] mp 134–136 ºC).

***N*-(6-Phenylpyridazin-3-yl)pyridinium aminide (1c).** Yield 12%; yellow solid (from EtOH/EtOAc); mp 159–161 ºC (lit.[9] mp 160–161 ºC).

***N*-(Quinoxalin-2-yl)pyridinium aminide (1d).** Yield 37%; yellow solid (from EtOH/EtOAc); mp 132–134 ºC (lit.[10] mp 132–134 ºC).

General procedure for the preparation of halo pyridinium *N*-(heteroaryl) aminides (2a–f)

The corresponding *N*-aminide **1** (1 mmol) and NXS (2.2 mmol for *N*-aminides **1a**, **1d**, **1e** and **1f**, and 1.1 mmol for *N*-aminides **1b** and **1g**) were added to a mortar. The mixture was ground with a pestle at room temperature. The reaction was completed in 2–5 min and the reaction mixture was dissolved in ethanol. The solvent was removed *in vacuo* and the product was purified by chromatography on silica gel using ethanol as eluent. Finally the compounds were crystallized from the appropriate solvent and identified.

***N*-(3,5-Dibromopyridin-2-yl)pyridinium aminide (2a).** Yield 89%; yellow solid (from acetone); mp 148–149 ºC (lit.[4b] mp 148–149 ºC).

***N*-(6-Chloro-3,5-dibromopyridin-2-yl)pyridinium aminide (2b).** Yield 64%; yellow solid (from CH_2Cl_2/Et_2O); mp 207–210 ºC; ^{1}H NMR (300 MHz, CD_3OD), δ 7.78 (s, 1H), 7.93 (dd, *J* = 7.7 and 6.9 Hz, 2H), 8.24 (tt, *J* = 7.7 and 1.3 Hz, 1H), 8.69 (dd, *J* = 6.9 and 1.3 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD), δ 100.0, 104.0, 128.6, 140.4, 144.9, 146.0, 147.1, 161.3; MS (EI, m/z); 367/365/363/361 (11/51/73/32, M^+), 366/364/362/360 (19/72/93/39), 205 (53), 203 (100), 168 (31), 142 (30), 79 (34), 52 (50); HRMS (ESI-TOF): calcd for $C_{10}H_7{}^{79}Br_2{}^{35}ClN_3$: $[M + H]^+$ 361.8695 found: 361.8830. Anal. Calcd for $C_{10}H_6Br_2ClN_3$: C, 33.05; H, 1.66; N, 11.56. Found: C, 33.14; H, 1.33; N: 11.56.

***N*-(6-Chloro-3,5-dibromopyrazin-2–yl)pyridinium aminide (2c).** Yield 66%; yellow solid (from MeOH); mp 199–201 ºC; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.71 (dd, *J* = 7.7 and 6.9 Hz, 2H), 7.95 (tt, *J* = 7.7 and 1.3 Hz, 1H), 8.66 (dd, *J* = 6.9 and 1.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 114.8, 123.9, 126.7, 137.2, 143.0, 144.3, 155.9; MS (EI, m/z); 368/366/364/362 (15/71/100/49, M^+), 367/365/363/361 (21/45/37/5), 287/285/283 (24/74/52), 204 (36), 169 (45),

79 (22); HRMS (ESI-TOF): calcd for $C_9H_6{}^{79}Br_2{}^{35}ClN_4$: $[M + H]^+$ 362.8648 found: 362.8647. Anal. Calcd for $C_9H_5Br_2ClN_4$: C, 29.66; H, 1.38; N, 15.37. Found: C, 29.59; H, 1.75; N: 15.46.

***N*-(5-Bromo-2-chloropyrimidin-4-yl)pyridinium aminide (2d).** Yield 77%; yellow solid (from CH_2Cl_2/Et_2O); mp 118–120 ºC; ^{1}H NMR (300 MHz, CD_3OD), δ 7.94 (s, 1H), 8.02 (dd, *J* = 7.7 and 6.9 Hz, 2H), 8.36 (tt, *J* = 7.7 and 1.3 Hz, 1H), 8.70 (dd, *J* = 6.9 and 1.3 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD), δ 103.5, 128.9, 141.8, 145.4, 155.1, 159.5, 165.5; MS (EI, m/z); MS (EI, m/z); 288/286/284 (10/40/31, M^+), 287/285/283 (26/95/71), 204 (19), 169 (16), 143 (23), 79 (100), 52 (67); HRMS (ESI-TOF): calcd for $C_9H_7{}^{79}Br{}^{35}ClN_4$: $[M + H]^+$ 284.9543, found 284.9566**.** Anal. Calcd for $C_9H_6BrClN_4$: C, 37.86; H, 2.12; N, 19.62. Found: C, 38.14; H, 2.33; N: 19.56.

***N*-(6,8-Dibromoquinoxalin-2-yl)pyridinium aminide (2e).** Yield 88%; yellow solid (from CH_2Cl_2/Et_2O); mp 215–217 ºC; ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.77 (d, *J* = 2.1 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.93 (at, *J* = 7.0 Hz, 2H), 8.14 (m, 2H), 9.25 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 111.2, 118.6, 126.5, 129.3, 133.3, 136.5, 137.4, 138.8; 141.9, 146.2, 156.9; MS (ESI, m/z); 383/381/379 (46/100/47, M^++1). Anal. Calcd for $C_{13}H_8Br_2N_4$: C, 41.09; H, 2.12; N, 14.74. Found: C, 41.00; H, 2.43; N: 14.70.

***N*-(5-Iodopyrazin-2-yl)pyridinium aminide (2f).** Yield 51%; orange solid (from CH_2Cl_2/Et_2O); mp 132–134 ºC; ^{1}H NMR (300 MHz, CD_3OD), δ 7.76 (d, *J* = 1.5 Hz, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.94 (dd, *J* = 7.7 and 7.2 Hz, 2H), 8.24 (tt, *J* = 7.7 and 1.3 Hz, 1H), 8.83 (dd, *J* = 7.2 and 1.3 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD), δ 94.4, 128.9, 137.9, 140.6, 145.4, 149.2, 160.1; MS (EI, m/z); 298 (100, M^+), 297 (90), 170 (44), 80 (33), 79 (91); HRMS (ESI-TOF): calcd for $C_9H_8IN_4$: $[M + H]^+$ 298.9794 found: 298.9777. Anal. Calcd for $C_9H_7IN_4$: C, 36.26; H, 2.37; N, 18.80. Found: C, 35.97; H, 2.56; N: 18.45.

Acknowledgements

The authors acknowledge support of this work from Ministerio de Ciencia e Innovación (project CTQ2008-05027/BQU2) and Instituto de Salud Carlos III (Red de Investigación Renal, REDinREN, RD06/0016/0016) and grants from the Ministerio de Educación y Ciencia and from Universidad de Alcalá (V.A and M.M., respectively).

References and Notes

1. Tundo, P. Anastas, P. T. *Green Chemistry: Challenging Perpectives*; Oxford University Press: Oxford, 2000.
2. (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (b) Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003.

3. (a) Pichon, A.; James, S. *Chemistry World* **2007**, *4*, 35. (b) Pichon, A.; James, S. *CrystEngComm* **2008**, *10*, 1839.
4. (a) Carceller, R.; Garcia-Navio, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2019. (b) Carceller, R.; Garcia-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J.; Fajardo, M.; Gomez-Sal, P.; Gago, F. *Tetrahedron* **1994**, *50*, 4995. (c) Garcia de Viedma, A.; Martinez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *J. Org. Chem.* **1999**, *64*, 1007. (d) Martinez-Barrasa, V.; Delgado, F.; Burgos, C.; Garcia-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2000**, *56*, 2481. (e) De la Rosa, R.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2000**, *41*, 5837. (f) Reyes, M. J.; Delgado, F.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2002**, *58*, 8573. (g) Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2007**, *48*, 5899. (h) Castillo, R.; Cordoba, M. J.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2009**, 65, 9782.
5. (a) Martinez-Barrasa, V.; Garcia de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933. (b) Nuñez, A.; Garcia de Viedma, A.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, 1093. (c) Sanchez, A.; Nuñez, A.; Alvarez-Builla, J.; Burgos, C. *Tetrahedron* **2004**, *60*, 11843. (d) Sanchez, A.; Nuñez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006**, *47*, 8343. (e) Nuñez, A.; Sanchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2007**, *63*, 6774. (f) Abet, V.; Nuñez, A.; Mendicuti, F.; Burgos, C.; Alvarez-Builla, J. *J. Org. Chem.* **2008**, *73*, 8800.
6. (a) Reyes, M. J.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2004**, *45*, 8713. (b) Reyes, M. J.; Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006**, *47*, 6457. (c) Castillo, R.; Reyes, M. J.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2008**, *64*, 1351. (d) Cordoba, M. J.; Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2010**, *66*, 2624.
7. (a) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org.Lett*. **2004**, *6*, 4125. (b) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. *Chem. Commun.* **2006**, 2690. (c) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org.Lett*. **2007**, *9*, 2977. (d) Nuñez, A.; Abarca, B.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2009**, *74*, 4166.
8. Beyer, H.; Thieme, E. *J. Prakt. Chem.* **1966**, *31*, 293.
9. Reyes, M. J.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 1093.
10. Córdoba, M. J.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2008**, *64*, 7914.
11. (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417. (c) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729. (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (e) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166 and references therein.
12. However, the reaction failed for 2-chloroquinoline, a finding consistent with its less marked π-deficient character. Similar negative results were obtained using liquid starting materials, e.g. 2-chloropyrazine (bp 153–154 ºC).

13. (a) Freudendahl, D. M.; Santoro, S.; Shahzad, S. A.; Santi, C.; Wirth, T. *Angew. Chem., Int. Ed. Engl*. **2009**, *48*, 8409. (b) Bengtsson, C.; Almqvist, F. *J. Org. Chem.* **2010**, *75*, 972.
14. Pluzhnik-Gladyr, S. M.; Rakipov, I. M.; Kotlyar, S. A. *Bash. Khim. Zhur.* **2008**, *15*, 72.
15. Burgos, C.; Delgado, F.; Garcia-Navio, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **1995**, *51*, 8649.
16. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; 4th Edn.; Blackwell Science: Oxford, 2000; p 68.
17. Several attempts to obtain the diiododerivative, starting from either, *N*-(pyrazin-2-yl)pyridinium aminide **1g** or *N*-(5-iodopyrazin-2-yl)pyridinium aminide **2f** and using a large excess of NIS or in the presence of large excess of NIS and potassium carbonate, were unsuccessful. On the other hand, the reaction of **2f** with NIS also failed under different homogeneous conditions.
18. Typical procedure for a multigram-scale process: Powdered potassium carbonate (3.726 g, 27.0 mmol), powdered *N*-aminopyridinium iodide (2.0 g, 9.0 mmol) and powdered 2,4-dichloropyrimidine **6b** (1.341 g, 9.0 mmol) were added to a mortar. The mixture was ground with a pestle at room temperature for 15–20 min (TLC analysis). The reaction was worked-up as indicated above to afford **1b** (1.430 g, 77 %).

