Tetrahedron 69 (2013) 6088–6094

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A facile synthesis of 3,5-halo and aryl 1*H*-pyridin-2-ones from pyridinium *N*-(pyridin-2-yl)aminide

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ARTICLE INFO

Article history:
Received 10 April 2013
Received in revised form 15 May 2013
Accepted 17 May 2013
Available online 23 May 2013

Keywords:
1*H*-Pyridin-2-ones
Pyridinium *N*-(pyridin-2-yl)aminide
Diazonium salts

ABSTRACT

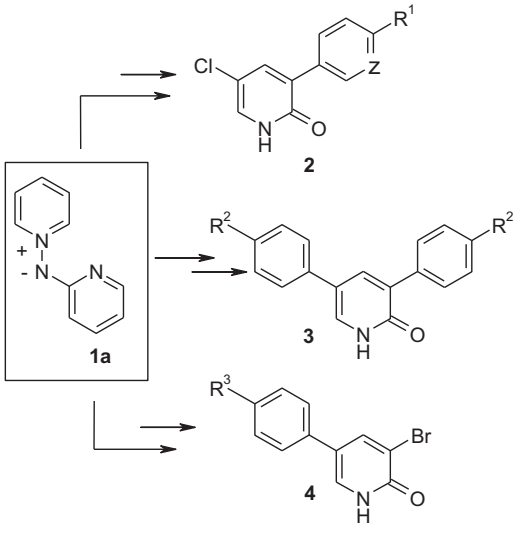
The synthesis of halogenated and arylated 1*H*-pyridin-2-ones starting from pyridinium *N*-(pyridin-2-yl) aminides is described. The synthetic pathway involves the reaction of pyridinium *N*-(5-bromopyridin-2-yl)aminide, *N*-(3-bromo-5-chloropyridin-2-yl)aminide or *N*-(3,5-dibromopyridin-2-yl)aminide with different boronic acids to afford monosubstituted and disubstituted aminides in good yields. An additional bromination in the 3-position of *N*-(5-arylpyridin-2-yl)aminides was performed. Finally, reduction of the N–N bond followed by the reaction of the corresponding 2-aminopyridines with sodium nitrite/sulfuric acid in water yields 3,5-disubstituted 1*H*-pyridin-2-ones in good yields.

1. Introduction

Functionalized 1*H*-pyridin-2-ones have emerged as an important class of organic azaheterocycles due to their presence in numerous natural and synthetic products that have diverse biological activities.[1] In the same way, halogenated 1*H*-pyridin-2-ones are an important subclass of pyridines and they have formed the basis of cardiotonic agents, antiviral drugs and fungicides.[2] Consequently, a wide variety of synthetic methods have been developed for the preparation of 1*H*-pyridin-2-ones, including the construction of the heterocyclic skeleton from acyclic precursors[3] and the modification of the heterocyclic core, frequently through the pyridinium salt or *N*-oxide.[4] Unfortunately, most of the available approaches for the synthesis of pyridones are not general for the preparation of halogenated 1*H*-pyridin-2-ones. In this context, the Vilsmeier reaction of enaminones has recently been applied by Dong and coworkers as an elegant approach to halogenated 1*H*-pyridin-2-ones.[5]

On the other hand, it is a well-known axiom in heterocyclic chemistry[6] that transformation of 2-aminoazines into the corresponding diazonium salts under standard conditions furnishes 2-pyridones in an easy one-pot process.

In recent years our research group has been interested in the chemistry of pyridinium *N*-pyridin-2-ylaminide **1a** (Scheme 1). Compound **1a** is a stable heterocyclic betaine in which the exocyclic nitrogen anion is stabilized by the presence of a pyridinium moiety and also by a pyridine ring in which the charge is delocalized. This compound has proven to be a versatile scaffold in a wide range of transformations, including regioselective halogenations that avoid the use of the aggressive molecular halogen and generate 3,5-mono- or dihalogenated aminides, or in Suzuki cross-coupling



Scheme 1. Substituted 1*H*-pyridin-2-ones **2**–**4** prepared in this work from pyridinium *N*-pyridin-2-ylaminide **1a**.

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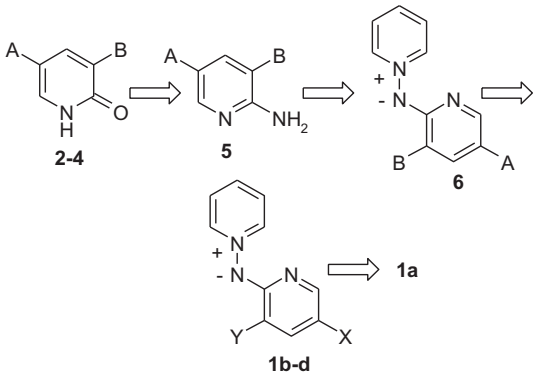
http://dx.doi.org/10.1016/j.tet.2013.05.065

reactions. Moreover, the N–N bond reduction yields the corresponding 2-aminopyridine derivatives.[7] Taking into consideration the versatility of this compound, we report here an easy application of this chemistry to the preparation of compounds **2**–**4** (Scheme 1). Compounds **2** are related to the non-nucleoside compounds described as inhibitors of RNA-dependent RNA viral polymerase and are useful for the treatment of hepatitis C.[2a] In addition, this system has been described by Knochel and co-workers as an intermediate in the preparation of Etoricoxib, using a methodology of directed metalations in the presence of TMPMgCl·LiCl [(2,2,6,6-tetramethylpiperidyl)-derived bases].[8] Compounds **3** have been described very recently in the synthesis of Perampanel, a triaryl 2-pyridone that acts as a selective non-competitive antagonist of AMP-type ionotropic glutamate receptors implicated in the pathogenesis of epilepsy and other neurological diseases.[9] Finally, the 3-bromo-5-aryl derivatives **4** are intermediates in the synthesis of compounds that have a phosphodiesterase 10A inhibitory effect and are useful in the prevention or treatment of schizophrenia.[10]

2. Results and discussion

The general strategy for preparation of compounds **2**–**4** from **1a** is outlined in Scheme 2. This sequence is based on the efficient preparation of substituted amines **5**, obtained by N–N-reduction of arylated pyridinium *N*-aminides **6** whereas compounds **6** were obtained from halogenated pyridinium *N*-aminides using a previously reported methodology.[7]



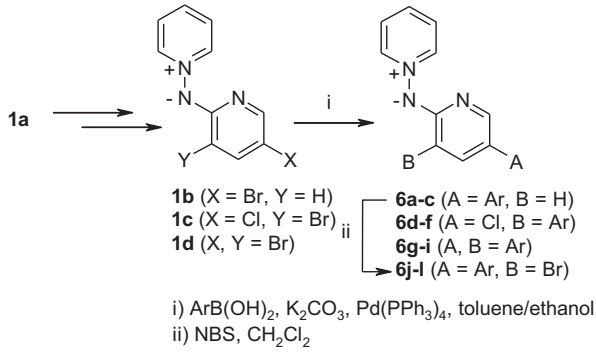
Scheme 2. General strategy for preparation of compounds **2**–**4** from **1a**.

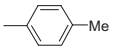
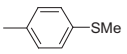
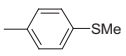
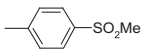
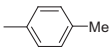
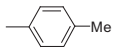
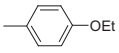
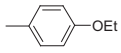
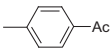
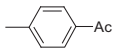
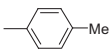
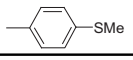
The synthesis began with the *N*-aminides *N*-(5-bromopyridin-2-yl)pyridinium aminide **1b**, *N*-(3-bromo-5-chloropyridin-2-yl)pyridinium aminide **1c** and *N*-(3,5-dibromopyridin-2-yl)pyridinium aminide **1d**. These compounds were obtained by selective halogenation of *N*-(pyridin-2-yl)pyridinium aminide **1a**[7j] and they were coupled with different boronic acids. Under previously reported standard conditions,[7h] the coupling of aminides **1b** and **1c** took place efficiently in the presence of the corresponding boronic acid (1.5 equiv), K_2CO_3 (10 equiv) and $Pd(PPh_3)_4$ (5 mol %) in toluene/ethanol (20:1) (method A) to afford the 5-arylated (entries 1–3, Table 1) or 3-arylated (or heteroarylated) products (entries 4–6, Table 1). Compound **1d** underwent a double Suzuki process (entries 7–9, Table 1) in the presence of boronic acid (3 equiv), K_2CO_3 (20 equiv) and $Pd(PPh_3)_4$ (5 mol %) in toluene/ethanol (4:1) (method B).

In most cases the aryl- or diaryl-aminides were obtained in excellent yields. Only in the reaction involving 3-pyridyl boronic acid in the presence of aminide **1c** was the yield disappointing (entry 6, Table 1). Compounds **6a**–**c** are suitable substrates to undergo a new, chemoselective, bromination in the 3-position of the pyridine ring to afford the corresponding aminides **6j**–**l**.[7b,d] The halogenation was accomplished under previously reported conditions, which involved the use of NBS in dichloromethane at room temperature (entries 10–12, Table 1).

Having the halogenated and arylated substrates **6d**–**l** in hand, the next step was the preparation of the corresponding 2-

Table 1
Arylation and halogenation of *N*-aminides

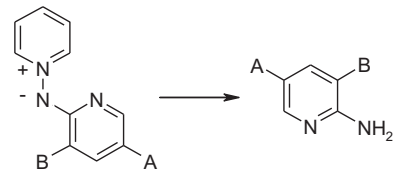


Entry	Method[a]	Starting material	6	A	B	Yield (%)
1	A	**1b** X=Br, Y=H	**6a**			91
2	A	**1b** X=Br, Y=H	**6b**			88
3	A	**1b** X=Br, Y=H	**6c**			87
4	A	**1c** X=Cl, Y=Br	**6d**	Cl		88
5	A	**1c** X=Cl, Y=Br	**6e**	Cl		80
6	A	**1c** X=Cl, Y=Br	**6f**	Cl		51
7	B	**1d** X, Y=Br	**6g**			56
8	B	**1d** X, Y=Br	**6h**			78
9	B	**1d** X, Y=Br	**6i**			81
10	C	**6a** A=Ar, B=H	**6j**		Br	74
11	C	**6b** A=Ar, B=H	**6k**		Br	89
12	C	**6c** A=Ar, B=H	**6l**		Br	91

[a] Method A: aminide (1 mmol), boronic acid (1.5 mmol), K_2CO_3 (10 mmol), $Pd(PPh_3)_4$ (5 mol %), toluene/EtOH (20:1). Method B: aminide (1 mmol), boronic acid (3 mmol), K_2CO_3 (20 mmol), $Pd(PPh_3)_4$ (5 mol %), toluene/EtOH (4:1). Method C: aminide (1 mmol), NBS (1.1 mmol), CH_2Cl_2.

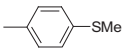
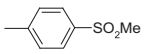
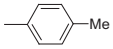
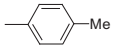
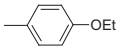
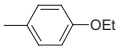
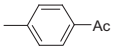
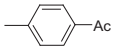
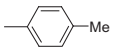
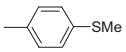
aminopyridines **5** by removing the pyridinium fragment using different methodologies developed in our group.[7] The reduction of the N–N bond was performed using two alternative methods. Thus, 2-aminopyridines **5d**–**i** were satisfactorily obtained using zinc and glacial acetic acid (method D, entries 1–6, Table 2), whereas compounds **5j**–**l** were synthesized using formic acid/triethylamine in the presence of platinum on carbon to avoid a concomitant debromination (method E, Entries 7–9, Table 2).

Table 2
Reduction of aminides **6d**–**l**



6d-f (A = Cl, B = Ar)
6g-i (A, B = Ar)
6j-l (A = Ar, B = Br)

5d-f (A = Cl, B = Ar)
5g-i (A, B = Ar)
5j-l (A = Ar, B = Br)

Entry	Method[a]	Starting material	5	A	B	Yield (%)
1	D	**6d**	**5d**	Cl		70
2	D	**6e**	**5e**	Cl		65
3	D	**6f**	**5f**	Cl		44
4	D	**6g**	**5g**			95
5	D	**6h**	**5h**			91
6	D	**6i**	**5i**			51
7	E	**6j**	**5j**		Br	83
8	E	**6k**	**5k**		Br	98
9	E	**6l**	**5l**		Br	82

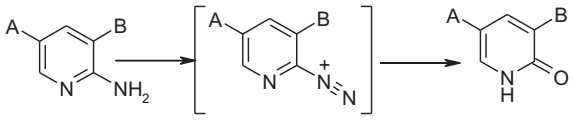
[a] Method D: aminide (1 mmol), Zn (20 mmol), acetic acid (15 mL). Method E: aminide (0.32 mmol), Pt/C (5 mmol %), $HCOOH/Et_3N$.

Once again, the arylated and diarylated amines were obtained in good to excellent yields, especially in the case of compounds **5g** and **5k** (entries 4 and 8, Table 2), which was obtained in almost quantitative yield. The reaction of 3-pyridyl derivative **6f** (entry 3, Table 2) again led to only moderate yield. A similar result was obtained with compound **6i** (entry 6, Table 2), which has an acetyl substituent, and this can be attributed to possible competition of a carbonyl reduction. Attempts to increase this yield by using method E were unsuccessful.

Treatment of 2-aminopyridines with sodium nitrite in an acidic medium affords the corresponding diazonium salts, which easily decompose and react with diverse nucleophilic reagents. However, diazonium salts of 2-aminopyridines decompose particularly rapidly and immediately react with the aqueous solvent to give the corresponding 2-pyridones.[6] Taking this fact into consideration, we planned to prepare the 1*H*-pyridin-2-ones **2**–**4** through a diazotization process, using pyridine as solvent in the presence of sodium nitrite in dilute sulfuric acid followed by displacement by water [method F: 2-aminopyridine (1 mmol) in pyridine, $NaNO_2$ (5 mmol), sulfuric acid (2.6 mL), H_2O (1 mL)].[11]

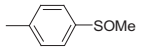
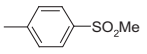
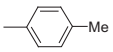
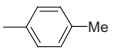
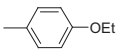
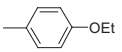
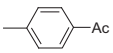
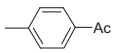
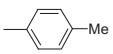
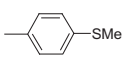
Under optimal conditions, amines **5d**–**f** and **5j**–**l** reacted to give 2-pyridones **2a**–**c** and **4a**–**c** with yields shown in Table 3 (entries 1–3 and 7–9). When these conditions were applied to **5d** (entry 1, Table 3), a concomitant oxidation on the sulfur group was observed to give **2a**, with Ar=4-Me–SO–Ph, as the sole final product. However, this simultaneous oxidation was not observed for the other methylthio derivative **5l** (entry 9, Table 3), from which compound **4c** was obtained (Ar=4-Me–S–Ph)—albeit in only 33% yield. When these conditions were applied to diarylated derivatives **5g**–**i** only poor yields were achieved. Moderate yields of final products could be obtained, however, on employing 10 equiv of sodium nitrite (entries 4–6, method G, Table 3). In order to improve yields for compounds **3**, we explored the possibility of using a different method to generate the diazonium salt, i.e., *tert*-butyl nitrite/CuO in aqueous ethanol (method H).[12] Unfortunately, this method failed and only afforded the desired 2-pyridinones in very low yield. It is worth noting that compounds **2b**, **4a** and **4b** were obtained in excellent yields and that the yields were almost satisfactory in all other cases.

Table 3
Preparation of 2-pyridones **2**–**4**



5d-f, A = Cl, B = Ar
5g-i, A, B = Ar
5j-l, A = Ar, B = Br

2a-c, A = Cl, B = Ar
3a-c, A, B = Ar
4a-c, A = Ar, B = Br

Entry	Method[a]	Starting material	Compound	A	B	Yield (%)
1	F	**5d**	**2a**	Cl		60
2	F	**5e**	**2b**	Cl		80
3	F	**5f**	**2c**	Cl		50
4	G	**5g**	**3a**			50
5	G	**5h**	**3b**			51
6	G	**5i**	**3c**			44
7	F	**5j**	**4a**		Br	87
8	F	**5k**	**4b**		Br	73
9	F	**5l**	**4c**		Br	33

[a] Method F: 2-aminopyridine (1 mmol), $NaNO_2$ (5 mmol), sulfuric acid (2.6 mL), H_2O (1 mL). Method G: 2-aminopyridine (1 mmol), $NaNO_2$ (10 mmol), sulfuric acid (5.2 mL), H_2O (1 mL).

3. Conclusions

A selective, facile and efficient route to prepare a series of 3,5-disubstituted 1*H*-pyridin-2-ones is described. The versatility of *N*-(pyridin-2-yl)aminide **1a** was exploited to synthesize 2-aminopyridines **5** through the prior introduction of halo and/or

different aryl groups to supply compounds **6a**–**l** and subsequent reduction of the *N*–*N* bond. Diazonium salts were then generated under standard conditions and for these reactive substrates the addition of water is very rapid. In this way we obtained 2-pyridones **2**–**4** very easily. This route could prove to be very useful, especially for compounds **2** and **4** given the difficulty in generating halogenated 2-pyridones.

4. Experimental section

4.1. General remarks

All melting points were determined in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer FTIR spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Gemini (200 MHz), Varian Mercury VX-300, Varian Unity 300 or 500 MHz spectrometer at room temperature. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS. Coupling constants (J) are in hertz (Hz) and signals are described as follows: s, singlet; d, doublet; t, triplet; br, broad; m, multiplet; ap, apparent, etc. High-resolution analysis (TOF) was performed on an Agilent 6210 time-of-flight LC/MS system. All reagents were obtained from commercial sources and were used without further purification. Solvents were purified and dried by standard procedures. TLC analyses were performed on silica gel (Kieselgel 60 F_{254}, Macherey-Nagel) and spots were visualized under UV light. Column chromatography was carried out with silica gel 60 (40–63 mm, Merck) columns using the eluent reported in each case.

4.2. General procedures for the preparation of 5-aryl *N*-(pyridin-2-yl)pyridinium aminides (6a–c), 5-chloro-3-aryl *N*-(pyridin-2-yl)pyridinium aminides (6d–f), and 3,5-biaryl *N*-(pyridin-2-yl)pyridinium aminides (6g–i)[7e,g,h]

Method A: A solution of aminide **1b**[7j] or **1c**[7j] (1 mmol), the corresponding boronic acid (1.5 mmol), K_2CO_3 (10 mmol) and $Pd(PPh_3)_4$ (5 mol %) in toluene/ethanol (20:1, 10 mL) was heated under reflux for 12 h under an atmosphere of dry argon. The course of the reaction was followed by TLC. Once the starting material had been consumed, the system was allowed to cool down to room temperature. The mixture was filtered through Celite and washed with acetonitrile until colour was no longer observed in the filtrate. The combined filtrates were evaporated to dryness. The crude product was purified by flash chromatography, with ethanol as the mobile phase, and recrystallized from a suitable solvent.

Method B: *N*-(3,5-Dibromopyridin-2-yl)pyridinium aminide **1d**[7j] (1 mmol) and the corresponding boronic acid (3 mmol) were dissolved in a toluene/ethanol mixture (4:1, 10 mL). K_2CO_3 (20 mmol) was added followed by $Pd(PPh_3)_4$ (5 mol %). After the addition, the mixture was kept under argon with vigorous stirring for 5 min and then heated under reflux for 12 h. As soon as the starting material has been consumed, the mixture was allowed to cool down to room temperature and was filtered through Celite and the residue washed with acetonitrile. The filtrates were combined, the solvent evaporated to dryness and the residue purified by flash chromatography using ethanol as the mobile phase. Finally, the compounds were recrystallized from a suitable solvent.

*4.2.1. N-(5-Phenylpyridin-2-yl)pyridinium aminide (**6a**).* See Ref. 7b.

*4.2.2. N-[5-(4-Methylphenyl)pyridin-2-yl]pyridinium aminide (**6b**).* See Ref. 7e.

*4.2.3. N-[5-(4-Methylthiophenyl)pyridin-2-yl]pyridinium aminide (**6c**).* Orange solid (255 mg, 87%, ethyl acetate), mp 169–171 °C; IR (KBr) ν_{max} (cm^{-1}): 1595, 1465, 1375, 1287, 1134; ^{1}H NMR (300 MHz, CD_3OD): δ 8.80 (2H, d, J=5.5 Hz), 8.07 (1H, t, J=7.6 Hz), 7.96 (1H, d, J=2.3 Hz), 7.85 (2H, ap t, J=6.8 Hz), 7.71 (1H, dd, J=8.7, 2.3 Hz), 7.46 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 6.62 (1H, d, J=8.7), 2.51 (3H, s); ^{13}C NMR (75 MHz, CD_3OD): δ 162.3, 144.7, 144.5, 138.1, 137.8, 136.9, 135.7, 128.6, 128.3, 126.8, 125.2, 112.2, 15.9; HRMS (ESI-TOF, CH_3OH): calcd for $C_{17}H_{16}N_3S$: $[M+H]^+$ 294.1065, found 294.1031.

*4.2.4. N-[5-Chloro-3-(4-methylthiophenyl)pyridin-2-yl]pyridinium aminide (**6d**).* Orange solid (288 mg, 88%, ethyl acetate), mp 163–164 °C; IR (KBr) ν_{max} (cm^{-1}): 1575, 1489, 1425, 1384, 1142; ^{1}H NMR (300 MHz, CD_3OD): δ 8.67 (2H, d, J=5.9 Hz), 8.07 (1H, t, J=7.2 Hz), 7.81 (2H, ap t, J=7.2 Hz), 7.65 (2H, d, J=8.4 Hz), 7.55 (1H, d, J=2.6 Hz), 7.33 (2H, d, J=8.4 Hz), 7.28 (1H, d, J=2.6 Hz), 2.52 (3H, s); ^{13}C NMR (75 MHz, CD_3OD): δ 162.3, 155.2, 145.6, 144.0, 139.1, 138.4, 137.8, 136.5, 130.7, 128.5, 127.3, 125.1, 15.7; HRMS (ESI-TOF, CH_3OH): calcd for $C_{17}H_{15}^{35}ClN_3S$: $[M+H]^+$ 328.0670, found 328.0709.

*4.2.5. N-[5-Chloro-3-(4-methylsulfonylphenyl)pyridin-2-yl]pyridinium aminide (**6e**).* Orange solid (287 mg, 80%, ethyl acetate/hexane), mp 178–180 °C; IR (KBr) ν_{max} (cm^{-1}): 1580, 1515, 1384, 1308, 1190, 1148; ^{1}H NMR (300 MHz, CD_3OD): δ 8.71 (2H, d, J=5.6 Hz), 8.12 (1H, t, J=7.9 Hz), 8.00 (m, 4H), 7.85 (2H, ap t, J=6.9 Hz), 7.65 (1H, d, J=2.6 Hz), 7.40 (1H, d, J=2.6 Hz), 3.17 (3H, s); ^{13}C NMR (75 MHz, CD_3OD): δ 146.2, 145.9, 145.6, 140.4, 139.4, 138.4, 131.3, 129.1, 128.7, 128.6, 128.4, 126.7, 44.4; HRMS (ESI-TOF, CH_3OH): calcd for $C_{17}H_{15}^{35}ClN_3O_2S$: $[M+H]^+$ 360.0568, found 360.0600.

*4.2.6. N-[5-Chloro-3-(3′-pyridin)pyridin-2-yl]pyridinium aminide (**6f**).* Orange solid (144 mg, 51%, ethyl acetate/hexane), mp 54–56 °C; IR (KBr) ν_{max} (cm^{-1}): 1577, 1388, 1144, 1009; ^{1}H NMR (200 MHz, CD_3OD): δ 8.88 (1H, br s), 8.69 (2H, d, J=5.5 Hz), 8.48 (1H, d, J=4.2 Hz), 8.19 (1H, dt, J=7.6, 1.8 Hz), 8.08 (1H, t, J=7.6 Hz), 7.82 (2H, ap t, J=7.0 Hz), 7.62 (1H, d, J=2.5 Hz), 7.50 (1H, dd, J=7.6, 4.5 Hz), 7.36 (1H, d, J=2.5); ^{13}C NMR (75 MHz, CD_3OD): δ 161.1, 149.0, 146.9, 144.2, 144.0, 137.6, 137.2, 136.8, 127.2, 127.1, 123.5, 119.8, 116.5; HRMS (ESI-TOF, CH_3OH): calcd for $C_{15}H_{12}^{35}ClN_4$: $[M+H]^+$ 283.0745, found 283.0744.

*4.2.7. N-[3,5-Bis(4-methylphenyl)pyridin-2-yl]pyridinium aminide (**6g**).* See Ref. 7g.

*4.2.8. N-[3,5-Bis(4-ethoxyphenyl)pyridin-2-yl]pyridinium aminide (**6h**).* Red solid (320 mg, 78%, ethanol), mp 140–142 °C; IR (KBr) ν_{max} (cm^{-1}): 1593, 1506, 1436, 1384, 1236, 1148; ^{1}H NMR (300 MHz, CD_3OD): δ 8.70 (2H, d, J=5.6 Hz), 7.97 (1H, t, J=7.9 Hz), 7.86 (1H, d, J=2.3 Hz), 7.78 (2H, ap t, J=6.9 Hz), 7.65 (2H, d, J=8.6 Hz), 7.54 (1H, d, J=2.3 Hz), 7.45 (2H, d, J=8.6 Hz), 6.99–6.94 (4H, m), 4.13–4.03 (4H, m), 1.46–1.39 (6H, m); ^{13}C NMR (75 MHz, CD_3OD): δ 158.2, 157.9, 149.5, 143.8, 141.6, 136.5, 135.8, 130.9, 130.1, 127.1, 126.9, 126.2, 123.5, 114.5, 113.8, 103.9, 63.1, 15.2; HRMS (ESI-TOF, CH_3OH): calcd for $C_{26}H_{26}N_3O_2$: $[M+H]^+$ 412.2025, found 412.2057.

*4.2.9. N-[3,5-Bis(4-acetylphenyl)pyridin-2-yl]pyridinium aminide (**6i**).* Orange solid (330 mg, 81%, ethanol), mp 101–102 °C; IR (KBr) ν_{max} (cm^{-1}): 3418, 1675, 1587, 1398, 1270, 1145; ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (2H, d, J=5.6 Hz), 8.15 (1H, t, J=7.6 Hz), 8.10 (1H, d, J=2.3 Hz), 8.09–8.07 (4H, m), 7.99 (2H, d, J=8.6 Hz), 7.89 (2H, ap t, J=6.9 Hz), 7.77 (1H, d, J=2.3 Hz), 7.71 (2H, d, J=8.6 Hz), 2.67 (3H, s), 2.63 (3H, s); ^{13}C NMR (75 MHz, CD_3OD): δ 198.8, 198.6, 162.1, 144.9, 144.5, 144.2, 143.4, 137.2, 135.7, 135.3,

134.3, 129.3, 128.9, 127.1, 126.0, 124.5, 121.9, 121.7, 25.3, 25.2; HRMS (ESI-TOF, CH_3OH): calcd for $C_{26}H_{22}N_3O_2$: $[M+H]^+$ 408.1707, found 408.1684.

4.3. Bromination of *N*-5-(4-aryl)pyridin-2-yl]pyridinium aminides 6a–c

Method C: A solution of NBS (1.2 mmol) in dichloromethane (15 mL) was added dropwise to a stirred solution of *N*-(5-arylpyridin-2-yl)pyridinium aminide (1 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred for 3 h and the solvent was evaporated. The residue was purified by column chromatography on silica gel with ethanol as eluent and then recrystallized from the appropriate solvent.

*4.3.1. N-[3-Bromo-5-(phenyl)pyridin-2-yl]pyridinium aminide (**6j**).* See Ref. 7d.

*4.3.2. N-[3-Bromo-5-(4-methylphenyl)pyridin-2-yl]pyridinium aminide (**6k**).* See Ref. 7d.

*4.3.3. N-[3-Bromo-5-(4-methylthiophenyl)pyridin-2-yl]pyridinium aminide (**6l**).* Orange powder (337 mg, 91%, ethyl acetate/hexane), mp 149–151 °C; IR (KBr) ν_{max} (cm^{-1}): 1590, 1469, 1443, 1381, 1247, 1151, 817, 670; ^1H NMR (300 MHz, CD_3OD): δ 8.78 (2H, d, J=7.2 Hz), 8.23 (1H, t, J=8.0 Hz), 8.00 (1H, d, J=2.0 Hz), 7.98–7.93 (3H, m), 7.45 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 2.51 (3H, s); ^{13}C NMR (75 MHz, CD_3OD): δ 162.3, 144.7, 142.5, 141.7, 138.1, 134.3, 127.3, 126.8, 125.4, 117.6, 105.4, 14.5; HRMS (ESI-TOF, CH_3OH): calcd for $C_{17}H_{15}^{79}BrN_3S$: $[M+H]^+$ 372.0171, found 372.0178.

4.4. Reduction of *N*-(pyridin-2-yl)pyridinium aminides 6d–l[7j]

Method D: A suspension of the corresponding *N*-(pyridin-2-yl)pyridinium aminide **6d–i** (1 mmol) in glacial acetic acid (15 mL) and zinc dust (10 mmol) was stirred at room temperature for 5 h. When almost all of the Zn had disappeared, another portion of Zn (10 mmol) was added and the mixture was stirred for a further 24 h. The resulting suspension was filtered through a Celite column and eluted with acetic acid. The eluate was evaporated in vacuo and the product was purified by chromatography on silica gel using ethyl acetate/hexane as eluent. Finally, the compounds were recrystallized from a suitable solvent.

Method E: Platinum on activated carbon (5%) was suspended in a solution of the corresponding aminide (0.32 mmol) in acetonitrile (4 mL) and cooled in an ice bath. Formic acid (98%, 0.5 mL) in acetonitrile (1.5 mL) was added and a solution of triethylamine (4.5 mL) in acetonitrile (3 mL) was added dropwise. The reaction mixture was heated under reflux for 3–4 h. The mixture was allowed to cool down to room temperature and was filtered. The filtrate was evaporated and the residue was dissolved in water, made basic with sodium carbonate and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (EtOAc/hexane) and the compound was recrystallized from a suitable solvent.

*4.4.1. 5-Chloro-3-(4-methylthiophenyl)-2-pyridinamine (**5d**).*[13] White solid (175 mg, 70%, ethyl acetate/hexane), mp 108–110 °C; IR (KBr) ν_{max} (cm^{-1}): 3435, 3286, 3159, 1623, 1566, 1455, 1094; ^1H NMR (75 MHz, $CDCl_3$): δ 7.96 (1H, d, J=2.5 Hz), 7.35 (1H, d, J=2.5 Hz), 7.32 (4H, m), 4.90 (2H, br s), 2.50 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 144.9, 139.3, 137.4, 132.9, 128.8, 127.1, 126.9, 126.8, 15.5; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{12}^{35}ClN_2S$: $[M+H]^+$ 251.0404, found 251.0385.

*4.4.2. 5-Chloro-3-(4-methylsulfonylphenyl)-2-pyridinamine (**5e**).*[13] White solid (183 mg, 65%, ethyl acetate/hexane), mp 103–105 °C; IR (KBr) ν_{max} (cm^{-1}): 3471, 3300, 3182, 1624, 1597, 1146; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06–8.02 (3H, m), 7.65 (2H, d, J=8.5 Hz), 7.35 (1H, d, J=2.1 Hz), 4.62 (2H, br s), 3.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 146.4, 142.3, 140.3, 137.4, 128.3, 128.1, 121.4, 120.6, 44.4; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{12}^{35}ClN_2O_2S$: $[M+H]^+$ 283.0308, found 283.0372.

*4.4.3. 5-Chloro-(3,3′-bipyridin)-2-amine (**5f**).* White solid (90 mg, 44%, ethyl acetate/hexane), mp 153–155 °C; IR (KBr) ν_{max} (cm^{-1}): 3397, 3322, 3202, 1650, 1458, 1244, 1032; ^1H NMR (200 MHz, $CDCl_3$): δ 8.68–8.66 (2H, m), 8.05 (1H, d, J=2.1 Hz), 7.77 (1H, dt, J=7.6, 1.7 Hz), 7.39 (1H, dd, J=7.6, 4.9 Hz), 7.34 (1H, d, J=2.1 Hz), 4.55 (2H, br s); ^{13}C NMR (75 MHz, CD_3OD): δ 154.3, 149.6, 146.4, 137.7, 136.1, 132.7, 123.9, 121.5, 119.2, 102.5; HRMS (ESI-TOF, CH_3OH): calcd for $C_{10}H_9^{35}ClN_3$: $[M+H]^+$ 206.0485, found 206.0488.

*4.4.4. 3,5-Bis(4-methylphenyl)-2-pyridinamine (**5g**).* White solid (260 mg, 95%, ethanol), mp 121–123 °C; IR (KBr) ν_{max} (cm^{-1}): 3491, 3295, 3150, 1631, 1512, 1463, 1246; ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, d, J=2.3 Hz), 7.44 (1H, d, J=2.3 Hz), 7.30–7.24 (4H, m), 7.15–7.08 (4H, m), 4.55 (2H, br s), 2.27 (3H, s), 2.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 145.0, 137.7, 136.6, 136.4, 135.4, 135.0, 129.8, 129.6, 128.6, 127.8, 126.1, 121.7, 21.3, 21.1; HRMS (ESI-TOF, CH_3OH): calcd for $C_{19}H_{19}N_2$: $[M+H]^+$ 275.1548, found 275.1547.

*4.4.5. 3,5-Bis(4-ethoxyphenyl)-2-pyridinamine (**5h**).* Yellow solid (304 mg, 91%, ethanol), mp 135–137 °C; IR (KBr) ν_{max} (cm^{-1}): 3479, 3382, 2976, 1608, 1512, 1462, 1243, 1045; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (1H, d, J=2.3 Hz), 7.53 (1H, d, J=2.3 Hz), 7.44–7.37 (4H, m), 6.99–6.91 (4H, m), 4.64 (2H, br s), 4.07–4.01 (4H, m), 1.45–1.39 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 158.2, 154.7, 144.0, 136.4, 130.5, 129.8, 129.7, 127.7, 127.3, 121.7, 115.0, 114.9, 63.5, 63.4, 14.8; HRMS (ESI-TOF, CH_3OH): calcd for $C_{21}H_{23}N_2O_2$: $[M+H]^+$ 335.1760, found 335.1766.

*4.4.6. 3,5-Bis(4-acetylphenyl)-2-pyridinamine (**5i**).* White solid (168 mg, 51%, ethanol), mp 182–184 °C; IR (KBr) ν_{max} (cm^{-1}): 3482, 3391, 3140, 1678, 1633, 1600, 1472, 1421, 1269; ^1H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J=2.2 Hz), 8.07 (2H, d, J=8.6 Hz), 8.00 (2H, d, J=8.6 Hz), 7.65 (1H, d, J=2.2 Hz), 7.63–7.59 (4H, m), 4.81 (2H, br s), 2.64 (3H, s), 2.61 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 197.3, 155.2, 145.9, 142.3, 142.2, 136.6, 135.6, 129.3, 129.1, 128.9, 128.8, 126.5, 126.1, 120.8, 26.7, 26.6; HRMS (ESI-TOF, CH_3OH): calcd for $C_{21}H_{19}N_2O_2$: $[M+H]^+$ 331.1447, found 331.1450.

*4.4.7. 3-Bromo-5-phenyl-2-pyridinamine (**5j**).*[14] White solid (66 mg, 83%), mp 114–116 °C; IR (KBr) ν_{max} (cm^{-1}): 3469, 3292, 3137, 1639, 1471; ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (1H, d, J=2.1 Hz), 7.89 (1H, d, J=2.1 Hz), 7.48–7.38 (4H, m), 7.34–7.29 (1H, m), 4.98 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 144.9, 138.9, 136.8, 128.9, 127.4, 126.3, 104.9, 104.6; HRMS (ESI-TOF, CH_3OH): calcd for $C_{11}H_{10}^{79}BrN_2$: $[M+H]^+$ 249.0028, found 249.0030.

*4.4.8. 3-Bromo-5-(4-methylphenyl)-2-pyridinamine (**5k**).* White solid (82 mg, 98%), mp 153–155 °C; IR (KBr) ν_{max} (cm^{-1}): 3480, 3289, 3144, 1637, 1603, 1490, 1027; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (1H, d, J=2.0 Hz), 7.85 (1H, d, J=2.0 Hz), 7.35 (2H, d, J=8.1 Hz), 7.21 (2H, d, J=8.1 Hz), 4.90 (2H, br s), 2.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 154.2, 144.7, 141.8, 138.8, 137.3, 133.9, 129.7, 126.2,

21.1; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{12}^{79}BrN_2$: $[M+H]^+$ 263.0178, found 263.0128.

*4.4.9. 3-Bromo-5-(4-methylthiophenyl)-2-pyridinamine (**5l**).* White solid (77 mg, 82%), mp 172–174 °C; IR (KBr) ν_{max} (cm^{-1}): 3450, 3280, 3121, 1630, 1590, 1473; ^1H NMR (300 MHz, $CDCl_3$): δ 8.21 (1H, d, J=1.7 Hz), 7.84 (1H, d, J=1.7 Hz), 7.37 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 4.99 (2H, br s), 2.49 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 144.8, 138.6, 137.9, 133.6, 128.3, 127.1, 126.7, 104.7, 15.9; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{12}^{79}BrN_2S$: $[M+H]^+$ 294.9899, found 294.9892.

4.5. Preparation of 1*H*-pyridin-2-ones 2a–c, 3a–c and 4a–c

Method F: A solution of sodium nitrite (5 mmol) in water (1 mL) was dropped into sulfuric acid (2.6 mL) at 0 °C. This solution was added dropwise to a stirred solution of the corresponding 2-pyridinamine **5d–l** (1 mmol) in a minimal amount of pyridine at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. For the preparation of compounds **3** another portion of sodium nitrite (5 mmol) in water (1 mL) and sulfuric acid (2.6 mL) was dropped into the solution containing the corresponding 2-pyridinamines **5g–i** (*method G*). The reaction mixture was stirred for 2 h at 0 °C. Water (4 mL) was added. After 16 h at room temperature, ice was added. The precipitate was filtered off and washed with cold water to give the corresponding 1*H*-pyridin-2-one. The products **3a–c** were purified by chromatography on silica gel using ethyl acetate/hexane/triethylamine 5.9:4:0.1 as eluent. Analytical samples of compounds **2a–c**, **3a–c** and **4a–c** were recrystallized from a suitable solvent.

*4.5.1. 5-Chloro-3-(4-methylsufinylphenyl)-2(1H)-pyridinone (**2a**).* White solid (160 mg, 60%, ethanol), mp 235–237 °C; IR (KBr) ν_{max} (cm^{-1}): 3128, 3043, 2852, 1640, 1556, 1041; ^1H NMR (300 MHz, DMSO): δ 7.92 (2H, d, J=8.2 Hz), 7.78 (1H, d, J=2.6 Hz), 7.70–7.67 (3H, m), 2.75 (3H, s); ^{13}C NMR (75 MHz, DMSO): δ 159.3, 145.1, 138.8, 137.2, 133.4, 129.0, 128.6, 122.8, 110.9, 42.7; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{11}^{35}ClNO_2S$: $[M+H]^+$ 268.0194, found 268.0183.

*4.5.2. 5-Chloro-3-(4-methylsufonylphenyl)-2(1H)-pyridinone (**2b**).*[8] White solid (227 mg, 80%, ethanol), mp 238–240 °C; IR (KBr) ν_{max} (cm^{-1}): 3418, 3058, 2762, 1642, 1614, 1307, 1155; ^1H NMR (200 MHz, DMSO): δ 8.00 (2H, d, J=8.5 Hz), 7.92 (2H, d, J=8.5 Hz), 7.84 (1H, d, J=2.7 Hz), 7.72 (1H, d, J=2.7 Hz), 3.22 (3H, s); ^{13}C NMR (75 MHz, DMSO): δ 159.2, 139.9, 139.4, 139.2, 134.0, 128.6, 128.2, 127.7, 126.1, 43.0; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{11}^{35}ClNO_3S$: $[M+H]^+$ 284.0148, found 284.0226.

*4.5.3. 5-Chloro-3-(3′-pyridin)-2(1H)-pyridinone (**2c**).*[15] White solid (103 mg, 50%, ethanol), mp 237–239 °C; IR (KBr) ν_{max} (cm^{-1}): 3415, 1649, 1579, 1420; ^1H NMR (500 MHz, CD_3OD): δ 8.92 (1H, br s), 8.56 (1H, br s), 8.20 (1H, d, J=7.8 Hz), 7.86 (1H, d, J=2.8 Hz), 7.61 (1H, d, J=2.8 Hz), 7.53 (1H, dd, J=7.8, 5.3 Hz); ^{13}C NMR (125 MHz, CD_3OD): δ 162.3, 149.7, 149.4, 141.9, 138.1, 134.3, 131.4, 129.9, 124.9, 114.7; HRMS (ESI-TOF, CH_3OH): calcd for $C_{10}H_8^{35}ClN_2O$: $[M+H]^+$ 207.0320, found 207.0323.

*4.5.4. 3,5-Bis(4-methylphenyl)-2(1H)-pyridinone (**3a**).* Yellow solid (137 mg, 50%, ethanol), mp 219–221 °C; IR (KBr) ν_{max} (cm^{-1}): 2918, 1639, 1511, 1478, 1299; ^1H NMR (300 MHz, $CDCl_3$): δ 13.4 (1H, br s), 7.85 (1H, d, J=2.5 Hz), 7.66 (2H, d, J=8.1 Hz), 7.56 (1H, d, J=2.5 Hz), 7.34 (2H, d, J=8.1 Hz), 7.25–7.20 (4H, m), 2.38 (3H, s), 2.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 139.0, 137.8, 137.1, 133.7, 133.6, 131.3, 130.6, 129.8, 129.1, 128.6, 125.7, 121.2, 21.3, 21.1; HRMS (ESI-TOF, CH_3OH): calcd for $C_{19}H_{18}NO$: $[M+H]^+$ 276.1388, found 276.1391.

*4.5.5. 3,5-Bis(4-ethoxyphenyl)-2(1H)-pyridinone (**3b**).* Yellow solid (171 mg, 51%, ethanol), mp 158–160 °C; IR (KBr) ν_{max} (cm^{-1}): 2925, 1650, 1510, 1475, 1246; ^1H NMR (300 MHz, $CDCl_3$): δ 13.3 (1H, br s), 7.79 (1H, d, J=2.4 Hz), 7.71 (2H, d, J=8.7 Hz), 7.53 (1H, d, J=2.4 Hz), 7.35 (2H, d, J=8.7 Hz), 7.00–6.90 (4H, m), 4.13–4.00 (4H, m), 1.42 (6H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 158.8, 158.4, 138.5, 130.8, 130.6, 129.8, 129.0, 128.8, 126.9, 121.2, 114.9, 114.3, 63.5, 63.4, 14.84, 14.82; HRMS (ESI-TOF, CH_3OH): calcd for $C_{21}H_{22}NO_3$: $[M+H]^+$ 336.1594, found 336.1586.

*4.5.6. 3,5-Bis(4-acetylphenyl)-2(1H)-pyridinone (**3c**).* Yellow solid (146 mg, 44%, ethyl acetate/ethanol), mp 274–276 °C; IR (KBr) ν_{max} (cm^{-1}): 2919, 1659, 1602, 1359, 1259; ^1H NMR (300 MHz, $CDCl_3$): δ 12.95 (1H, br s), 8.04 (2H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz), 7.97 (1H, d, J=2.4 Hz), 7.86 (2H, d, J=8.4 Hz), 7.73 (1H, d, J=2.4 Hz), 7.56 (2H, d, J=8.4 Hz), 2.63 (3H, s), 2.62 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 197.3, 162.2, 140.2, 139.7, 136.6, 132.3, 130.5, 129.7, 129.8, 129.3, 128.8, 128.5, 125.8, 114.8, 26.7, 26.6; HRMS (ESI-TOF, CH_3OH): calcd for $C_{21}H_{18}NO_3$: $[M+H]^+$ 332.1287, found 332.1318.

*4.5.7. 3-Bromo-5-(phenyl)-2(1H)-pyridinone (**4a**).*[10] Yellow solid (217 mg, 87%, ethyl acetate/ethanol), mp 205–207 °C; IR (KBr) ν_{max} (cm^{-1}): 2865, 1652, 1597, 1499, 1269; ^1H NMR (300 MHz, $CDCl_3$): δ 13.15 (1H, br s), 8.18 (1H, d, J=2.3 Hz), 7.71 (1H, d, J=2.3 Hz), 7.43–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 143.4, 135.0, 131.3, 129.3, 127.9, 125.8, 122.2, 115.8; HRMS (ESI-TOF, CH_3OH): calcd for $C_{11}H_9^{79}BrNO$: $[M+H]^+$ 249.9862, found 249.9860.

*4.5.8. 3-Bromo-5-(4-methylphenyl)-2(1H)-pyridinone (**4b**).* Yellow solid (192 mg, 73%, ethyl acetate/ethanol), mp 209–211 °C; IR (KBr) ν_{max} (cm^{-1}): 2924, 2854, 2771, 1646, 1617, 1514, 1035; ^1H NMR (300 MHz, $CDCl_3$): δ 13.00 (1H, br s), 8.15 (1H, d, J=2.2 Hz), 7.69 (1H, d, J=2.2 Hz), 7.28 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz), 2.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 143.3, 137.8, 132.1, 130.9, 129.9, 125.7, 122.2, 115.8, 21.1; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{10}^{79}BrNO$: $[M+H]^+$ 264.0019, found 263.9987.

*4.5.9. 3-Bromo-5-(4-methylthiophenyl)-2(1H)-pyridinone (**4c**).* Yellow solid (97 mg, 33%, methanol), mp 240–242 °C; IR (KBr) ν_{max} (cm^{-1}): 2853, 1645, 1495, 1247, 1032; ^1H NMR (300 MHz, CD_3OD): δ 8.35 (1H, d, J=2.3 Hz), 7.73 (1H, d, J=2.3 Hz), 7.47 (2H, d, J=8.6 Hz), 7.35 (2H, d, J=8.6 Hz), 2.50 (3H, s); ^{13}C NMR (75 MHz, DMSO): δ 157.3, 141.0, 136.6, 131.5, 131.1, 125.9, 125.5, 117.7, 115.3, 14.2; HRMS (ESI-TOF, CH_3OH): calcd for $C_{12}H_{11}^{79}BrNOS$: $[M+H]^+$ 295.9745, found 295.9746.

Acknowledgements

Financial support from Instituto de Salud Carlos III (REDinREN, RD6/0016/0016) for University of Alcalá (UAH GC 2012-001 and UAH2011/EXP-027) and a grant from the University of Alcalá (F.F.) are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.065.

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