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Pyridinium *N*-2′-pyridylaminide: radical cyclization for the synthesis of benzonaphthyridine derivatives

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Abstract—The synthesis of benzonaphthyridine derivatives that incorporate a 2-aminopyridine moiety can be performed by intramolecular radical pyridylation of the appropriate substrates, obtained from pyridinium *N*-2′-pyridylaminide, using TTMSS and AIBN.

1. Introduction

Benzonaphthyridine derivatives are compounds of current interest due to their diverse biological activities.[1] These compounds can also be considered as '*aza*-analogues' of phenanthridine derivatives, which are widely studied in the field of medicinal chemistry.[2]

Among the different benzonaphthyridine isomers, we are specifically interested in those that contain a 2-aminopyridine moiety (see structures in Fig. 1). In recent years, particular attention has been devoted to the study of this class of derivatives. For example, Ferraris and co-workers[3] reported the preparation and biological evaluation of a series of *aza*-5[*H*]phenanthridin-6-ones, e.g., compound **I** (Fig. 1), as potent, water-soluble inhibitors of poly ADP-ribose polymerase 1 (PARP1) for the treatment of ischemic injuries. The preparation of these compounds, however, remains a difficult area. The synthesis of 5*H*-benzo[*c*][1,8]naphthyridin-6-one nucleus **I** (Fig. 1) has been performed by photoreaction of 2-halo-*N*-pyridinylbenzamides[4] or, alternatively, under standard Suzuki conditions.[3] Other related heterocyclic structures have recently been synthesized through palladium-catalyzed sequential aryl–aryl and *N*-aryl coupling,[5] or by a two-step procedure that involves an anionic ring closure and, once again, Suzuki cross-coupling.[6] Some 5,6-dihydrobenzo[*c*][1,8]naphthyridines **II** (Fig. 1) have been prepared by thermolysis of the corresponding benzoannulated enyne-carbodiimides through a biradical intermediate.[7] Finally, benzo[*c*][1,8]naphthyridines **III** have been synthesized by a variation of the classical Skraup method.[8]

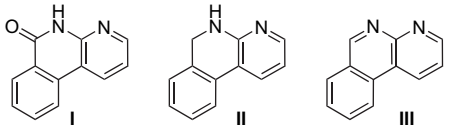
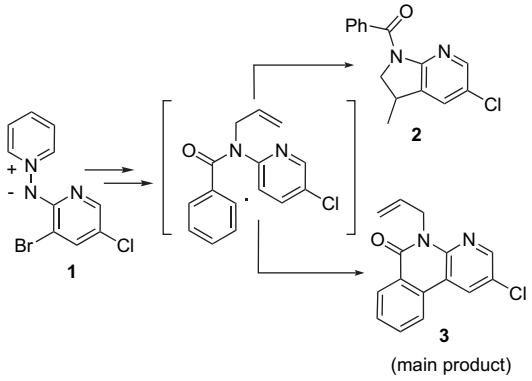


Figure 1. Some benzonaphthyridine derivatives containing a 2-aminopyridine nucleus. **I**: 5*H*-benzo[*c*][1,8]naphthyridin-6-one; **II**: 5*H*-5,6-dihydrobenzo[*c*][1,8]naphthyridine; **III**: benzo[*c*][1,8]naphthyridine.

As part of our work on free-radical heteroarylations,[9] using halogenated pyridinium *N*-2′-pyridylaminides (i.e. **1**, Scheme 1) as starting materials, tris(trimethylsilyl)silane and azobisisobutyronitrile (TTMSS/AIBN) under reductive conditions we described an approach to 7-azaindoline derivatives (i.e. **2**, Scheme 1) via an intramolecular radical process in which a pyridyl radical was added to an alkenyl fragment.[10] However, in the case outlined in Scheme 1, the main product of the process was *N*-allyl-2-chloro-5*H*-benzo[*c*][1,8]naphthyridin-6-one **3**, thus showing the preference of the pyridyl radical, in this case, to take part in a homolytic aromatic substitution.



Scheme 1. Preliminary results in the synthesis of benzo[*c*][1,8]naphthyridin-6-one derivatives.

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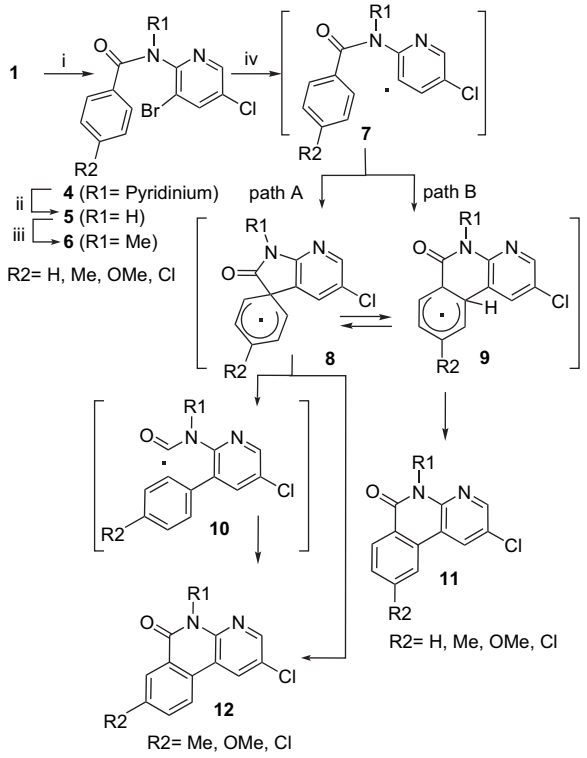
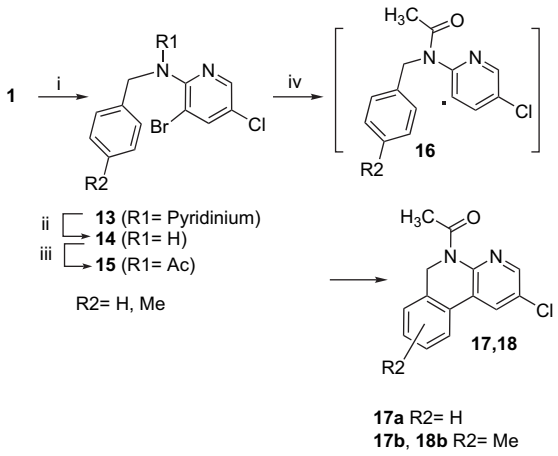
Despite the fact that homolytic aromatic substitution has been studied by various research groups,[11] we wish to report here the preparation of a series of compounds containing a 2-aminopyridine fragment fused to a benzene ring. The route starts from the appropriate pyridinium *N*-2′-pyridylaminide **1** and proceeds through a pyridyl radical cyclization. It should be borne in mind that electrophilic substitution on the *N*-exocycle in 2-aminopyridine, using conventional methods, to obtain suitable 2-aminopyridine derivatives, occurs with difficulty—if at all.[12]

2. Results and discussion

Our initial studies in this area started from the salts **4** (Scheme 2) obtained from *N*-aminide **1** by reaction with different acyl chlorides (R2=H, CH_3, OCH_3, Cl). Reduction of the N–N bond furnished unsubstituted amides **5** and methylation on the exocyclic nitrogen provided methylbenzamides **6**, which are starting materials for the radical cyclization process. Bearing in mind previous reports from Curran[13] and Ganguly,[11c,14] and our own previous results,[9] aryl radical **7**, derived from **6**, can cyclize at the *ipso*-position (path A) to supply radical **8** or at the *ortho*-position (path B) to give radical **9**. Both radicals could be in equilibrium through a formal 1,2-shift.[13] Whereas oxidation of radical **9** could provide 9-substituted 5*H*-benzo[*c*][1,8]naphthyridin-6-ones **11** (R1=CH_3, R2=H, CH_3, OCH_3, Cl), the other isomeric 5*H*-benzo[*c*][1,8]naphthyridin-6-ones **12** were observed in all cases. The latter species should arise from the β-fragmentation of spirocyclic radical **8** to provide, through a 1,4-aryl migration, an amidoyl radical **10**, which would eventually



Scheme 2. Preparation of starting material and radical cyclization from **6**. Reagents: (i) ArCOCl/acetone 80–95%; (ii) Et_3B/EtOH 41–56%; (iii) CH_3I/acetone, K_2CO_3 78–90%; (iv) TTMSS/AIBN/*m*-xylene, 69–79%.



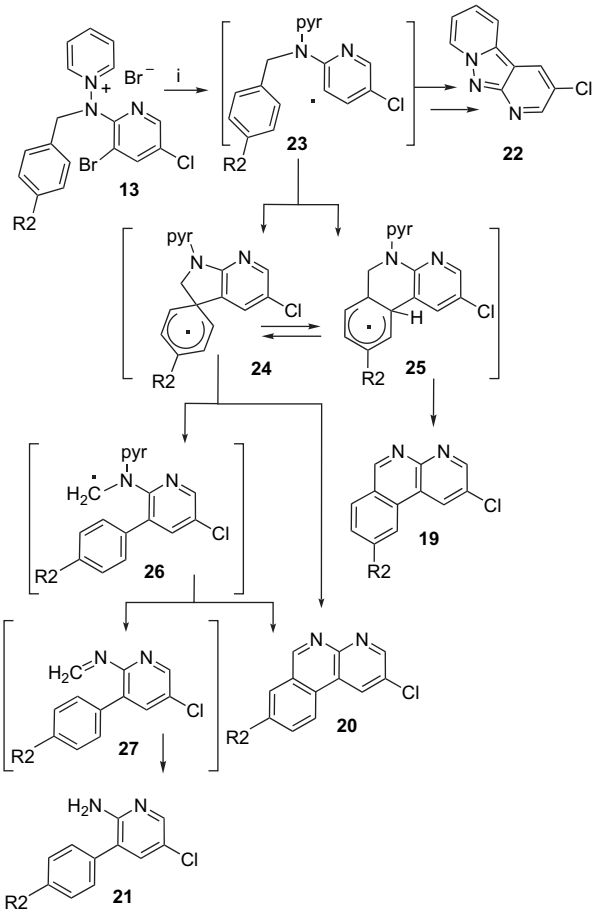
Scheme 3. Preparation of starting material and radical cyclization from **15**. Reagents: (i) $ArCH_2Br$/acetone 73–93%; (ii) TEAF/Pt/C 57–90%; (iii) AcCl/Et_3N, CH_2Cl_2 55–87%; (iv) TTMSS/AIBN/*m*-xylene, 21–32%.

afford the 8-substituted 5*H*-benzo[*c*][1,8]naphthyridin-6-ones **12** (R1=CH_3, R2=CH_3, OCH_3, Cl), or alternatively, from the spirocyclic radical **8**, through a formal 1,2-shift.[11c] This class of 1,4-aryl migration has been previously reported by Chuang et al.[15] and by Ganguly et al.,[11c,14b] and has been extensively studied by Studer[16] on related substrates. However, when the cyclization process was tried on **4** (R1=pyridinium, R2=H, OCH_3, Scheme 2) under similar experimental conditions, only poor yields of **11** (R1=H, R2=H, OCH_3) were obtained (**11e** and **11f** in 18% and 25%, respectively). When the procedure was attempted on the benzyl derivative **15** (R1=Ac, R2=H, CH_3) (Scheme 3)—obtained from amidine **1** by reaction with the corresponding benzyl bromide, N–N fission and acetylation in the presence of a base[17]—cyclized compounds were obtained but only in low yield (21–32%).

Once again, when R2≠H (for **15b** R1=Ac, R2=CH_3), two isomeric compounds **17b** and **18b** were characterized, presumably due to 6-cyclization and 5-cyclization processes, respectively.

Unexpectedly, when the cyclization reaction was carried out from **13** (R2=H, CH_3, OCH_3, Cl), a complex mixture of products was identified [**19**, **20**, and **21**, with a small amount of tricyclic derivative **22** (≈3%)] (Scheme 4 and Table 1), a situation in agreement with previous reports.[9b,c] It would seem that in **13**, which is less reactive than **4**, the N–N bond reduction would occur at a slower rate and the formation of compounds **19** can be explained in terms of the expected reaction pathway and subsequent elimination of pyridine, as described for a related process.[18] Additionally, the well-documented stabilized radical **26**, produced by *ipso*-substitution of an aminomethyl group by an aryl radical, according to previous report by Renaud et al.,[19] could evolve to imine **27** or, alternatively, supply **20** by cyclization at the *ortho*-position. Once again, the formation of **20** could be explained also from **24** through a formal 1,2-shift.[11c] However, compounds **21** were identified as 3-aryl-5-chloropyridin-2-yl amines and imino derivatives were not detected: probably **27** was converted into **21** in the chromatographic process. In order to shed some light on this issue, a molar

excess of sodium borohydride was added to the crude reaction mixture, and the reaction was investigated by ^{1}H NMR spectroscopy and mass spectrometry. In this case, 3-aryl-2-methylaminopyridines, corresponding to the reduction of **27**, were identified. Other experiments are in progress to clarify this unusual behavior.



Scheme 4. Preparation of **19**, **20**, and **21** and suggested reaction pathway. Reagents: (i) TTMSS/AIBN/*m*-xylene, 31–59%.

In conclusion, some results on the synthesis of benzo[*c*][1,8]naphthyridine derivatives by intramolecular radical pyridylation of suitable substrates, obtained from pyridinium *N*-2′-pyridylaminide, through an easy, mild, and selective approach are described. The methodology generally seems to be more flexible and efficient in the preparation of 5*H*-benzo[*c*][1,8]naphthyridin-6-one derivatives and should be complementary to conventional routes in the preparation of fused pyridines. The method does, however, produce complex reaction mixtures and/or poor yields for other derivatives. Although several reaction mechanisms can explain these transformations, reasonable pathways involving the formation of the observed products are suggested.

Table 1. Results of the cyclization from compounds **13**

Starting material	**19** (%)	**20** (%)	**21** (%)	**22** (%)
R2=H, **13a**	19	—	27	3
R2=Me, **13b**	31	—	27	3
R2=OMe, **13c**	39	—	—	3
R2=Cl, **13d**	15	8	8	3

3. Experimental section

3.1. General

All experiments were carried out under a dry argon atmosphere, with solvents freshly distilled under anhydrous conditions, unless stated otherwise. All chemicals were purchased from the Aldrich Chemical Company and Fluka, and were used without further purification. ^{1}H, ^{13}C NMR, and decoupled spectra were recorded on a Varian UNITY 300 MHz or VARIAN UNITY PLUS 500 MHz spectrometer. Mass spectra were recorded on a VG AutoSpec (Micromass Instruments). Elemental analysis was performed on a LECO instruments CHNS-932. Compounds **1**,[17c] **21a**,[20] and **22**[9c] have been described previously.

3.2. General procedure for the preparation of pyridinium salts 4

To a stirred solution of aminide **1** (284 mg, 1 mmol) in dry acetone (7 mL), at room temperature, was added dropwise the corresponding benzoyl chloride (1.1 mmol). The mixture was stirred at the same temperature until all the starting material had been consumed (TLC). The mixture was filtered and the solid was washed with acetone and crystallized from ethanol, yielding compounds **4a–d**.

3.2.1. *N*-[Benzoyl-(3-bromo-5-chloro-pyridin-2-yl)-amino]-pyridinium chloride 4a. The general procedure using 155 mg of benzoyl chloride gave a white solid (388 mg, 91%), mp 195–197 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.54 (d, 2H, J=5.9 Hz), 8.94 (t, 1H, J=7.8 Hz), 8.56 (d, 1H, J=2.2 Hz), 8.47 (d, 1H, J=2.2 Hz), 8.41 (at, 2H, J=7.6 Hz), 7.75 (d, 2H, J=8.6 Hz), 7.62 (t, 1H, J=7.5 Hz), 7.47 (at, 2H, J=7.8 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 169.8, 150.4, 149.5, 149.2, 148.9, 144.8, 136.0, 134.7, 132.0, 130.7, 130.2, 130.0, 121.4; MS (ESI), *m*/*z* (relative intensity): 392, 390, 388 (M^+, 35, 100, 91), 345, 343, 341 (1, 3.4, 2.6); Anal. Calcd for $C_{17}H_{12}BrCl_2N_3O$: C, 48.03; H, 2.85; N, 9.88%. Found: C, 48.40; H, 2.63; N, 9.91%.

3.2.2. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-methylbenzoyl)-amino]-pyridinium chloride 4b. The general procedure using 170 mg of 4-methylbenzoyl chloride gave a white solid (416 mg, 95%), mp 135–136 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.51 (d, 2H, J=5.8 Hz), 8.92 (t, 1H, J=7.7 Hz), 8.56 (d, 1H, J=2.2 Hz), 8.47 (d, 1H, J=2.2 Hz), 8.39 (at, 2H, J=7.1 Hz), 7.63 (d, 2H, J=8.2 Hz), 7.29 (d, 2H, J=8.2 Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.6, 150.2, 149.6, 149.1, 148.7, 146.2, 144.7, 135.8, 130.6, 130.5, 130.2, 128.9, 121.2, 24.2; MS (ESI), *m*/*z* (relative intensity): 406, 404, 402 (M^+, 34, 100, 91), 359, 357, 355 (0.7, 2.6, 1.9); Anal. Calcd for $C_{18}H_{14}BrCl_2N_3O$: C, 44.71; H, 2.92; N, 8.69%. Found: C, 44.53; H, 2.81; N, 8.30%.

3.2.3. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-methoxybenzoyl)-amino]-pyridinium chloride 4c. The general

procedure using 188 mg of 4-methoxybenzoyl chloride gave a white solid (364 mg, 80%), mp 185–187 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.48 (d, 2H, J=5.5 Hz), 8.92 (t, 1H, J=7.9 Hz), 8.57 (d, 1H, J=2.4 Hz), 8.48 (d, 1H, J=2.4 Hz), 8.39 (at, 2H, J=7.1 Hz), 7.72 (d, 2H, J=8.9 Hz), 7.00 (d, 2H, J=8.9 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.3, 165.6, 150.2, 150.0, 149.2, 148.9, 144.8, 135.8, 132.7, 130.6, 123.6, 121.2, 115.4, 56.2; MS (ESI), m/z (relative intensity): 422, 420, 418 (M^+, 29, 100, 71), 288, 286, 284 (2.5, 10, 7.5); Anal. Calcd for $C_{18}H_{14}BrCl_2N_3O_2$: C, 47.50; H, 3.10; N, 9.23%. Found: C, 47.40; H, 2.73; N, 9.41%.

3.2.4. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-chlorobenzoyl)-amino]-pyridinium chloride 4d. The general procedure using 193 mg of 4-chlorobenzoyl chloride gave a white solid (391 mg, 85%), mp 51–52 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.53 (dd, 2H, J=5.7, 1.1 Hz), 8.82 (tt, 1H, J=7.9, 1.1 Hz), 8.58 (d, 1H, J=2.2 Hz), 8.48 (d, 1H, J=2.2 Hz), 8.41 (at, 2H, J=7.5 Hz), 7.73 (d, 2H, J=8.8 Hz), 7.51 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 168.7, 150.4, 149.2, 148.6, 144.8, 140.8, 136.0, 131.7, 130.6, 130.5, 130.2, 129.6, 121.2; MS (ESI), m/z (relative intensity): 428, 426, 424, 422 (M^+, 13, 82, 100, 93), 379, 379, 377, 375 (1.5, 3.3, 2.2), 288, 286, 284 (3.4, 13.9, 10.8); Anal. Calcd for $C_{17}H_{11}BrCl_3N_3O$: C, 44.43; H, 2.41; N, 9.14%. Found: C, 44.06; H, 2.31; N, 9.22%.

3.3. General procedure for the preparation of unsubstituted benzamides 5

To a stirred solution of the corresponding pyridinium salt **4** (0.5 mmol) in ethanol (20 mL), at room temperature, was added dropwise a solution of triethylborane in hexane (1 mL, 1.0 M, 1 mmol). After stirring for 3 h at the same temperature, air (1 mL) was passed with a syringe. After stirring at the same temperature for a further 24 h, the same amount of triethylborane and air were added again, until the starting material had been consumed (TLC). Purification by flash chromatography and crystallization from EtOAc/hexanes furnished compounds **5a–d**.

3.3.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-benzamide 5a. The general procedure starting from 213 mg of the corresponding pyridinium salt **4a** gave, after flash chromatography [silica gel, hexanes/EtOAc (90:10), $R_f \approx 0.15$] and crystallization, a white solid (87 mg, 56%), mp 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, 2H, J=2.4 Hz), 7.92 (m, 3H), 7.66 (tt, 1H, J=7.3, 1.3 Hz), 7.50 (at, 2H, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 147.1, 146.0, 140.6, 133.7, 132.5, 128.8, 128.0, 127.4, 112.6; MS (EI) m/z (relative intensity): 314, 312, 310 (M^+, 0.4, 2, 1.4), 231 (22), 105 (100), 77 (43); Anal. Calcd for $C_{12}H_8BrClN_2O$: C, 46.26; H, 2.59; N, 8.99%. Found: C, 46.26; H, 2.57; N, 8.88%.

3.3.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4-methyl-benzamide 5b. The general procedure starting from 219 mg of the corresponding pyridinium salt **4b** gave, after flash chromatography [silica gel, hexanes/EtOAc (90:10), $R_f \approx 0.11$] and crystallization, a white solid (75 mg, 46%), mp 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 8.37 (d, 1H, J=2.2 Hz), 7.90 (d, 1H, J=2.2 Hz), 7.82 (d, 2H, J=8.2 Hz), 7.27 (d, 2H, J=8.2 Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 147.2, 146.0, 143.2, 140.5, 130.9, 129.4, 127.7, 127.5, 112.3, 21.5; MS (EI) m/z (relative intensity): 328, 326, 324 (M^+, 0.2, 1, 0.8), 247, 245 (4, 12), 119 (100), 91 (29); Anal. Calcd for $C_{13}H_{10}BrClN_2O$: C, 47.96; H, 3.10; N, 8.60%. Found: C, 47.67; H, 2.94; N, 8.42%.

3.3.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4-methoxy-benzamide 5c. The general procedure starting from 227 mg of the corresponding pyridinium salt **4c** gave, after flash chromatography [silica gel, hexanes/EtOAc (80:20), $R_f \approx 0.11$] and crystallization, a white solid (70 mg, 41%), mp 161–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 8.36 (d, 1H, J=2.2 Hz), 7.90 (d, 1H, J=2.2 Hz), 7.88 (d, 2H, J=8.8 Hz), 6.96 (d, 2H, J=8.8 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 163.2, 147.6, 146.3, 140.8, 129.7, 127.9, 126.1, 114.3, 112.7, 55.7; MS (EI) m/z (relative intensity): 344, 342, 340 (M^+, 0.3, 1.1, 0.9), 263, 261 (2.3, 6.8), 135 (100); Anal. Calcd for $C_{13}H_{10}BrClN_2O_2$: C, 45.71; H, 2.95; N, 8.20%. Found: C, 45.65; H, 2.82; N, 8.09%.

3.3.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4-chloro-benzamide 5d. The general procedure starting from 229 mg of the corresponding pyridinium salt **4d** gave, after flash chromatography [silica gel, hexanes/EtOAc (85:15), $R_f \approx 0.15$] and crystallization, a white solid (76 mg, 44%), mp 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 8.34 (d, 1H, J=2.3 Hz), 7.91 (d, 1H, J=2.3 Hz), 7.85 (d, 2H, J=8.5 Hz), 7.44 (d, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 146.9, 146.2, 140.7, 138.7, 132.1, 129.2, 128.9, 128.2, 112.5; MS (EI) m/z (relative intensity): 350, 348, 346, 344 (M^+, 0.6, 1, 0.8, 0.3), 319, 317, 315, 313 (2, 3.6, 2.2, 6.8), 139 (100), 111 (42); Anal. Calcd for $C_{12}H_7BrCl_2N_2O$: C, 41.66; H, 2.04; N, 8.10%. Found: C, 41.62; H, 1.97; N, 8.04%.

3.4. General procedure for the preparation of methylbenzamides 6

To a stirred dispersion of the corresponding unsubstituted benzamide **5** (0.4 mmol) and potassium carbonate (110 mg, 0.8 mmol) in acetone (10 mL), at room temperature, was added iodomethane (4 mmol, 0.25 mL). The mixture was stirred at the same temperature for 24 h until the starting material had been consumed (TLC). Purification by flash chromatography furnished products **6a–d**.

3.4.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-methyl-benzamide 6a. The general procedure using **5a** (125 mg) as starting material gave, after flash chromatography [silica gel, hexanes/EtOAc (90:10), $R_f \approx 0.12$], a yellow oil (117 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H, J=2.4 Hz), 7.79 (d, 1H, J=2.4 Hz), 7.37 (d, 2H, J=7.4 Hz), 7.27 (t, 1H, J=7.4 Hz), 7.18 (t, 2H, J=7.4 Hz), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 153.5, 146.7, 141.5, 135.4, 130.7, 130.3, 128.2, 127.7, 119.0, 35.7; MS (EI) m/z (relative intensity): 328, 326, 324 (M^+, 0.1, 0.3, 0.2), 247, 245 (8, 25), 105 (100), 77 (35).

3.4.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4,*N*-dimethyl-benzamide 6b. The general procedure using **5b** (130 mg)

as starting material gave, after flash chromatography [silica gel, hexanes/EtOAc (85:15), $R_f \approx 0.16$], a white solid (117 mg, 90%), mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H, J=2.4 Hz), 7.78 (d, 1H, J=2.4 Hz), 7.25 (d, 2H, J=7.9 Hz), 6.97 (d, 2H, J=7.9 Hz), 3.36 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 153.5, 146.6, 141.5, 140.5, 132.5, 130.4, 128.4, 128.3, 118.9, 35.6; MS (EI) *m*/*z* (relative intensity): 342, 340, 338 (M^+, 0.1, 0.3, 0.2), 261, 259 (4, 13), 119 (100), 91 (25); Anal. Calcd for $C_{14}H_{12}BrClN_2O$: C, 49.51; H, 3.56; N, 8.25%. Found: C, 49.87; H, 3.52; N, 8.17%.

3.4.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4-methoxy-*N*-methyl-benzamide 6c. The general procedure using **5c** (137 mg) as starting material gave, after flash chromatography [silica gel, hexanes/EtOAc (80:20), $R_f \approx 0.23$], a white solid (128 mg, 90%), mp 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, 1H, J=2.3 Hz), 7.78 (d, 1H, J=2.3 Hz), 7.30 (d, 2H, J=8.8 Hz), 6.66 (d, 2H, J=8.8 Hz), 3.72 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 161.0, 153.9, 146.7, 141.6, 130.4, 130.3, 127.7, 119.0, 113.0, 55.1, 35.8; MS (EI) *m*/*z* (relative intensity): 358, 356, 354 (M^+, 0.2, 0.9, 0.7), 277, 275 (4, 11), 135 (100); Anal. Calcd for $C_{14}H_{12}BrClN_2O_2$: C, 47.29; H, 3.40; N, 7.88%. Found: C, 47.49; H, 3.34; N, 7.77%.

3.4.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4-chloro-*N*-methyl-benzamide 6d. The general procedure using **5d** (138 mg) as starting material gave, after flash chromatography [silica gel, hexanes/EtOAc (85:15), $R_f \approx 0.33$], a yellow oil (112 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, 1H, J=2.4 Hz), 7.78 (d, 1H, J=2.4 Hz), 7.28 (d, 2H, J=8.4 Hz), 7.13 (d, 2H, J=8.4 Hz), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 153.2, 146.8, 141.6, 136.3, 133.8, 130.9, 129.6, 128.0, 118.8, 35.6; MS (EI) *m*/*z* (relative intensity): 364, 362, 360, 358 (M^+, 0.3, 0.6, 0.2, 0.4), 279 (27), 141, 139 (33, 100).

3.5. Radical reaction on methylbenzamides 6: general procedure for the preparation of 11a–d and 12b–d

A solution of TTMSS (248 mg, 1 mmol) and AIBN (164 mg, 1 mmol) in *m*-xylene (10 mL) was added dropwise by a syringe pump, during 13 h, to a stirred solution of the corresponding methylbenzamide **6** (0.5 mmol) in *m*-xylene (2 mL) at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 12 h. The solution was concentrated and the crude mixture separated by flash chromatography, yielding the pure compounds **11a–d** and **12b–d**.

3.5.1. 2-Chloro-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11a. The general procedure using **6a** (163 mg) as the starting material gave, after flash chromatography [silica gel, hexanes/EtOAc (90:10), $R_f \approx 0.30$] and crystallization, a white solid (97 mg, 79%, EtOAc/hexanes), mp 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, 1H, J=8.0, 1.3 Hz), 8.49 (d, 1H, J=2.4 Hz), 8.43 (d, 1H, J=2.4 Hz), 8.14 (dd, 1H, J=8.0, 1.1 Hz), 7.78 (dt, 1H, J=8.0, 1.3 Hz), 7.65 (dt, 1H, J=8.0, 1.1 Hz), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 146.8, 146.7, 132.7, 130.6, 130.4, 129.3, 129.0, 125.9, 125.8, 121.7, 115.6, 28.9; MS (EI) *m*/*z* (relative intensity): 246, 244 (M^+, 33, 100), 218, 216 (27, 84); Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.82; H, 3.71; N, 11.45%. Found: C, 63.50; H, 3.54; N, 11.12%.

3.5.2. 2-Chloro-5,9-dimethyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11b and 2-chloro-5,8-dimethyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 12b. The general procedure using **6b** (170 mg) as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (90:10)], pure compounds **11b** and **12b** were obtained (73%, 1.2:1). Analysis of the structures was performed using NOE experiments.

3.5.2.1. 2-Chloro-5,9-dimethyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11b. White solid, $R_f \approx 0.27$ (51 mg, EtOAc/hexanes), mp 204–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, 1H, J=2.4 Hz), 8.43 (d, 1H, J=2.4 Hz), 8.42 (d, 1H, J=8.2 Hz), 7.93 (s, 1H), 7.46 (dd, 1H, J=8.2, 1.6 Hz), 3.86 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 146.7, 143.5, 130.8, 130.7, 130.4, 129.1, 129.0, 125.7, 123.7, 121.8, 115.7, 28.9, 22.0; MS (EI) *m*/*z* (relative intensity): 260, 258 (M^+, 31, 93), 232, 230 (32, 100), 166 (66); Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83%. Found: C, 65.21; H, 4.30; N, 10.51%.

3.5.2.2. 2-Chloro-5,8-dimethyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 12b. White solid, $R_f \approx 0.30$ (42 mg, EtOAc/hexanes), mp 223–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, 1H, J=2.3 Hz), 8.40 (d, 1H, J=2.3 Hz), 8.34 (br s, 1H), 8.03 (d, 1H, J=8.2 Hz), 7.60 (dd, 1H, J=8.2, 1.9 Hz), 3.87 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 146.7, 146.3, 139.9, 134.1, 130.2, 128.8, 128.2, 125.8, 125.7, 121.8, 115.9, 29.0, 21.6; MS (EI) *m*/*z* (relative intensity): 260, 258 (M^+, 33, 100), 232, 230 (25, 80), 135 (36); Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83%. Found: C, 64.95; H, 4.14; N, 10.56%.

3.5.3. 2-Chloro-9-methoxy-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11c and 2-chloro-8-methoxy-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 12c. The general procedure using **6c** (178 mg) as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (90:10)], pure compounds **11c** and **12c** were obtained (73%, 1.1:1). Analysis of the structures was performed using NOE experiments.

3.5.3.1. 2-Chloro-9-methoxy-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11c. White solid, $R_f \approx 0.13$ (52 mg, CH_2Cl_2), mp 217–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, 1H, J=2.3 Hz), 8.46 (d, 1H, J=8.8 Hz), 8.36 (d, 1H, J=2.3 Hz), 7.48 (d, 1H, J=2.4 Hz), 7.20 (dd, 1H, J=8.8, 2.4 Hz), 3.97 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 161.8, 147.3, 146.9, 132.5, 131.1, 130.4, 125.5, 119.5, 117.1, 115.5, 104.6, 55.6, 28.7; MS (EI) *m*/*z* (relative intensity): 276, 274 (M^+, 33, 99), 248, 246 (33, 99), 202 (24), 168 (12), 140 (14); Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20%. Found: C, 61.60; H, 3.91; N, 10.17%.

3.5.3.2. 2-Chloro-8-methoxy-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 12c. White solid, $R_f \approx 0.18$ (48 mg, CH_2Cl_2), mp 219–220 °C; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.43 (d, 1H, J=2.4 Hz), 8.33 (d, 1H, J=2.4 Hz), 8.04 (d, 1H, J=8.8 Hz), 7.94 (d, 1H, J=2.8 Hz), 7.35 (dd, 1H, J=8.8, 2.8 Hz), 3.96 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 160.8, 146.2, 145.8, 129.8, 127.6, 126.1, 124.1, 123.7, 122.8, 116.0, 109.7, 56.0, 29.3; MS (EI) m/z (relative intensity): 276, 274 (M^+, 34, 100), 248, 246 (12, 36), 202 (17); Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20%. Found: C, 61.60; H, 3.91; N, 10.17%.

3.5.4. 2,9-Dichloro-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11d and 2,8-dichloro-5-methyl-5*H*-benzo-[*c*][1,8]naphthyridin-6-one 12d. The general procedure using **6d** (180 mg) as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (95:5)], pure compounds **11d** and **12d** were obtained (69%, 1.4:1). Assignment and analysis of the structures were performed using NOE experiments.

3.5.4.1. 2,9-Dichloro-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11d. White solid, $R_f \approx 0.15$ (56 mg, CH_2Cl_2), mp 237–240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, 1H, J=2.3 Hz), 8.48 (d, 1H, J=8.6 Hz), 8.37 (d, 1H, J=2.3 Hz), 8.11 (d, 1H, J=1.9 Hz), 7.60 (dd, 1H, J=8.6, 1.9 Hz), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 147.9, 139.9, 132.4, 131.1, 131.0, 130.0, 126.3, 124.6, 122.0, 114.9, 104.6, 29.3; MS (EI) m/z (relative intensity): 282, 280, 278 (M^+, 11, 66, 100), 253, 251, 249 (14, 66, 88); Anal. Calcd for $C_{13}H_8Cl_2N_2O_2$: C, 55.94; H, 2.89; N, 10.04%. Found: C, 55.60; H, 2.98; N, 10.18%.

3.5.4.2. 2,8-Dichloro-5-methyl-5*H*-benzo[*c*][1,8]naphthyridin-6-one 12d. White solid, $R_f \approx 0.16$ (40 mg, CH_2Cl_2), mp 257–259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, 1H, J=2.2 Hz), 8.50 (d, 1H, J=2.2 Hz), 8.39 (d, 1H, J=2.2 Hz), 8.08 (d, 1H, J=8.6 Hz), 7.73 (dd, 1H, J=8.6, 2.2 Hz), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 147.4, 147.0, 136.0, 133.5, 130.8, 129.3, 128.9, 127.5, 126.3, 123.8, 115.3, 29.4; MS (EI) m/z (relative intensity): 282, 280, 278 (M^+, 11, 65, 100), 253, 251, 249 (13, 57, 79); Anal. Calcd for $C_{13}H_8Cl_2N_2O_2$: C, 55.94; H, 2.89; N, 10.04%. Found: C, 56.00; H, 2.98; N, 10.22%.

3.6. Radical reaction of pyridinium salts 4: general procedure for the preparation of 11e,f

A solution of TTMSS (248 mg, 1 mmol) and AIBN (164 mg, 1 mmol) in *m*-xylene (1 mL) and MeCN (9 mL) was added dropwise by a syringe pump, during 13 h, to a stirred solution of the corresponding salt **4** (0.5 mmol) in MeCN (2 mL) at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 12 h. The resulting solid was filtered off and washed with cold MeCN. Purification by flash chromatography and crystallization furnished products **11e**,**f**.

3.6.1. 2-Chloro-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11e. The general procedure using **4a** (213 mg) as the starting material gave, after purification by flash chromatography [silica gel, hexanes/EtOAc (90:10)], a white solid (21 mg, 18%, EtOAc/hexanes), mp>300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.97 (d, 1H, J=1.9 Hz), 8.60 (d, 1H, J=7.9 Hz), 8.51 (d, 1H, J=1.9 Hz), 8.31 (d, 1H, J=7.9 Hz), 7.89 (t, 1H, J=7.9 Hz), 7.72 (t, 1H, J=7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 148.1, 147.5, 133.9, 132.6, 132.1, 130.0, 128.2, 126.5, 125.5, 124.4, 115.2; MS (EI) m/z (relative intensity): 232, 230 (M^+, 33, 100), 204, 202 (18, 58), 140 (34); Anal. Calcd for $C_{12}H_7ClN_2O$: C, 62.49; H, 3.06; N, 12.15%. Found: C, 62.61; H, 3.21; N, 12.88%.

3.6.2. 2-Chloro-9-methoxy-5*H*-benzo[*c*][1,8]naphthyridin-6-one 11f. The general procedure using **4c** (227 mg) as the starting material gave, after purification by flash chromatography [silica gel, hexanes/EtOAc (80:20)], a white solid (32 mg, 25%, EtOAc/hexanes), mp>300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (s, 1H), 9.05 (br s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.21 (d, 1H, J=8.8 Hz), 7.99 (br s, 1H), 7.26 (dd, 1H, J=8.8, 1.8 Hz), 3.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 160.7, 146.9, 146.6, 133.6, 131.2, 129.0, 124.0, 118.7, 117.3, 113.9, 105.5, 55.5; MS (EI) m/z (relative intensity): 262, 260 (M^+, 33, 100), 219, 217 (10, 30), 189 (17); Anal. Calcd for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75%. Found: C, 60.10; H, 3.11; N, 10.79%.

3.7. General procedure for the preparation of pyridinium salts 13

The corresponding benzyl bromide (3.5 mmol) was added dropwise to a stirred solution of aminide **1b** (284 mg, 1 mmol) in dry acetone (11 mL) at room temperature. The mixture was stirred at the same temperature until the starting material had been consumed (TLC). The resulting solid was filtered off, washed with EtOAc, and crystallized from ethanol, yielding compounds **13a**–**d**.

3.7.1. *N*-[Benzyl-(3-bromo-5-chloro-pyridin-2-yl)-amino]-pyridinium bromide 13a. The general procedure using 598 mg of benzyl bromide furnished **13a** as a white solid (374 mg, 82%), mp 140–141 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.28 (d, 2H, J=5.7 Hz), 8.66 (t, 1H, J=7.8 Hz), 8.55 (d, 1H, J=2.2 Hz), 8.40 (d, 1H, J=2.2 Hz), 8.13 (at, 1H, J=7.3 Hz), 7.50 (m, 2H), 7.35 (m, 3H), 5.21 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 153.3, 148.8, 148.2, 147.3, 144.5, 134.3, 132.9, 130.6, 130.2, 130.1, 129.9, 116.9, 61.4; MS (ESI) m/z (relative intensity): 378, 376, 374 (M^+, 21, 77, 55), 331, 329, 327 (25, 100, 76); Anal. Calcd for $C_{17}H_{14}Br_2ClN_3$: C, 44.82; H, 3.10; N, 9.22%. Found: C, 45.11; H, 3.43; N, 9.16%.

3.7.2. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-methylbenzyl)-amino]-pyridinium bromide 13b. The general procedure using 647 mg of 4-methylbenzyl bromide gave a white solid (436 mg, 93%), mp 169–170 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.26 (dd, 2H, J=7.0, 1.2 Hz), 8.66 (tt, 1H, J=7.8, 1.2 Hz), 8.54 (d, 1H, J=2.3 Hz), 8.38 (d, 1H, J=2.3 Hz), 8.13 (dd, 2H, J=7.8, 7.0 Hz), 7.36 (d, 2H, J=7.9 Hz), 7.16 (d, 2H, J=7.9 Hz), 5.16 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 153.2, 148.6, 148.1, 147.1, 144.3, 140.3, 132.7, 131.1, 130.6, 130.5, 129.8, 116.7, 61.2, 21.2; MS (ESI), m/z (relative intensity): 392, 390, 388 (M^+, 43, 100, 96), 345, 343, 341 (2, 9, 6); Anal. Calcd for $C_{18}H_{16}Br_2ClN_3$: C, 46.04; H, 3.43; N, 8.95%. Found: C, 46.21; H, 3.52; N, 8.81%.

3.7.3. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-methoxybenzyl)-amino]-pyridinium bromide 13c. The general procedure using 703 mg of 4-methoxybenzyl bromide gave a white solid (354 mg, 73%), mp 168–169 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.22 (dd, 2H, J=6.9, 1.3 Hz), 8.66 (tt, 1H, J=7.8, 1.3 Hz), 8.55 (d, 1H, J=2.2 Hz), 8.39 (d, 1H, J=2.2 Hz), 8.12 (dd, 2H, J=7.8, 6.9 Hz), 7.37 (d, 2H, J=8.6 Hz), 6.88 (d, 2H, J=8.6 Hz), 5.13 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.8, 153.4, 148.7, 148.2, 147.3, 144.5, 132.8, 132.1, 129.9, 125.9, 116.8, 115.4, 61.1, 55.7; MS (ESI) *m*/*z* (relative intensity): 408, 406, 404 (M^+, 19, 69, 52), 361, 359, 357 (11, 44, 34), 329, 327, 325 (25, 100, 75); Anal. Calcd for $C_{18}H_{16}Br_2ClN_3O$: C, 44.52; H, 3.32; N, 8.65%. Found: C, 44.11; H, 3.00; N, 8.78%.

3.7.4. *N*-[(3-Bromo-5-chloro-pyridin-2-yl)-(4-chlorobenzyl)-amino]-pyridinium bromide 13d. The general procedure using 719 mg of 4-methoxybenzyl bromide gave a white solid (441 mg, 90%), mp 156–157 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.34 (d, 2H, J=5.7 Hz), 8.70 (t, 1H, J=7.8 Hz), 8.54 (d, 1H, J=2.2 Hz), 8.38 (d, 1H, J= 2.2 Hz), 8.18 (at, 2H, J=7.3 Hz), 7.53 (d, 2H, J=8.2 Hz), 7.36 (d, 2H, J=8.2 Hz), 5.23 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 153.0, 148.9, 148.1, 147.4, 144.5, 136.0, 133.2, 133.0, 132.3, 130.2, 130.1, 117.1, 60.6; MS (ESI) *m*/*z* (relative intensity): 414, 412, 410, 408 (M^+, 8, 52, 100, 68), 365, 363, 361 (12, 44, 34); Anal. Calcd for $C_{17}H_{13}BrCl_2N_3$: C, 41.67; H, 2.67; N, 8.58%. Found: C, 42.01; H, 3.02; N, 8.38%.

3.8. General procedure for the preparation of unsubstituted benzylaminopyridines 14

Platinum on charcoal (5%) (75 mg) was suspended in a stirred solution of the corresponding pyridinium salt **13** (0.31 mmol) in MeCN (3 mL) and cooled in an ice bath. Formic acid (96%, 1.5 mL) in MeCN (1.5 mL) and then triethylamine (4.5 mL) in the same solvent (3 mL) were added dropwise. The resulting suspension was stirred at room temperature and filtered through Celite. The filtrate was evaporated and the residue dissolved in water, made basic with solid potassium carbonate, and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The corresponding *N*-benzylaminopyridine was purified by flash chromatography [silica gel, hexanes/EtOAc (95:5)].

3.8.1. *N*-Benzyl-(3-bromo-5-chloro-pyridin-2-yl)-amine 14a. The general procedure using 141 mg of **13a** as the starting material gave a yellow oil (R_f≈0.35, 83 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 1H, J=2.3 Hz), 7.64 (d, 1H, J=2.3 Hz), 7.32 (m, 5 H), 5.34 (br s, 1H), 4.65 (d, 2H, J=5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 152.0, 145.0, 138.9, 128.6, 127.5, 127.3, 119.0, 104.9, 45.8; MS (EI) *m*/*z* (relative intensity): 300, 298, 296 (M^+, 9, 37, 28), 263, 261 (3, 3), 106 (49), 91 (100); Anal. Calcd for $C_{12}H_{10}BrClN_2$: C, 48.43; H, 3.39; N, 9.41%. Found: C, 48.21; H, 3.55; N, 9.37%.

3.8.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-(4-methylbenzyl)-amine 14b. The general procedure using 146 mg of **13b** as the starting material gave a white solid (R_f≈0.39, 55 mg, 57%), mp 47–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, J=2.2 Hz), 7.62 (d, 1H, J=2.2 Hz), 7.24 (d, 2H, J=8.0 Hz), 7.10 (d, 2H, J=8.0 Hz), 5.28 (br s, 1H), 4.59 (d, 2H, J=5.5 Hz), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 145.0, 138.4, 137.0, 135.8, 129.3, 127.6, 118.9, 104.9, 45.6, 21.1; MS (EI) *m*/*z* (relative intensity): 314, 312, 310 (M^+, 4, 15, 12), 299, 297, 295 (2, 6, 5), 105 (100), 77 (13); Anal. Calcd for $C_{13}H_{12}BrClN_2$: C, 50.11; H, 3.88; N, 8.99%. Found: C, 50.21; H, 3.65; N, 9.17%.

3.9. General procedure for the preparation of benzylacetamidopyridines 15

Et_3N (1.1 mmol, 0.15 mL) and then acetyl chloride (1 mmol, 71 μL) were added to a stirred solution of the corresponding unsubstituted benzylaminopyridine **14** (1 mmol) in dry CH_2Cl_2 (15 mL) at room temperature. After stirring for 8 h at the same temperature, further quantities of Et_3N (0.5 mmol, 70 μL) and acetyl chloride (0.5 mmol, 35 μL) were added. The mixture was stirred at the same temperature for further 12 h until the starting material had been consumed (TLC). Purification by flash chromatography [silica gel, hexanes/EtOAc (80:20)] furnished products **15a**,**b**.

3.9.1. *N*-Benzyl-*N*-(3-bromo-5-chloro-pyridin-2-yl)-acetamide 15a. The general procedure using **14a** (297 mg) as starting material gave, after flash chromatography, a white solid (R_f≈0.40, 187 mg, 55%), mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 1H, J=2.2 Hz), 7.92 (d, 1H, J=2.2 Hz), 7.20 (s, 5H), 5.00 (br s, 2H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 151.9, 147.1, 141.7, 136.1, 131.5, 129.0, 128.2, 127.5, 120.5, 50.9, 22.5; MS (EI) *m*/*z* (relative intensity): 342, 340, 338 (M^+, 1.5, 5.8, 4.4), 299, 297, 295 (16, 64, 48), 190 (8), 91 (100); Anal. Calcd for $C_{14}H_{12}BrClN_2O$: C, 49.51; H, 3.56; N, 8.25%. Found: C, 49.21; H, 3.55; N, 8.37%.

3.9.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-(4-methylbenzyl)-acetamide 15b. The general procedure using **14b** (311 mg) as starting material gave, after flash chromatography, a yellow oil (R_f≈0.24, 307 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 1H, J=2.2 Hz), 7.93 (d, 1H, J=2.2 Hz), 7.10 (d, 2H, J=7.8 Hz), 7.01 (d, 2H, J=7.8 Hz), 4.95 (br s, 2H), 2.03 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 151.8, 146.9, 141.6, 136.9, 132.9, 131.3, 128.9, 128.8, 120.4, 50.4, 22.4, 21.0; MS (EI) *m*/*z* (relative intensity): 342, 340, 338 (M^+, 1.5, 5.8, 4.4), 299, 297, 295 (16, 64, 48), 190 (8).

3.10. Radical reaction on methylbenzamides 15: general procedure for the preparation of 17a,b and 18b

A solution of TTMSS (248 mg, 1 mmol) and AIBN (164 mg, 1 mmol) in *m*-xylene (10 mL) was added dropwise by a syringe pump, during 13 h, to a stirred solution of the corresponding benzyl acetamidopyridine **15** (0.5 mmol) in *m*-xylene (2 mL) at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 12 h. The solution was concentrated and the crude mixture was separated by flash chromatography [silica gel, hexanes/EtOAc (80:20)], yielding the pure compounds **17** and **18**.

3.10.1. 1-(2-Chloro-6*H*-benzo[*c*][1,8]naphthyridin-5-yl)-ethanone 17a. The general procedure using **15a** (170 mg) as starting material gave a white solid ($R_f \approx 0.47$, 41 mg, 32%), mp 150–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 1H, J=2.4 Hz), 8.02 (d, 1H, J=2.4 Hz), 7.65 (dd, 1H, J=6.6, 2.2 Hz), 7.35 (m, 3H), 5.02 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 148.9, 145.2, 134.2, 131.6, 129.4, 129.2, 128.6, 128.2, 126.4, 124.4, 123.3, 44.7, 24.0; MS (EI) *m*/*z* (relative intensity): 260, 258 (M^+, 2, 6), 217, 215 (35, 100), 179 (8), 152 (16). Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83%. Found: C, 64.63; H, 4.42; N, 10.49%.

3.10.2. 1-(2-Chloro-9-methyl-6*H*-benzo[*c*][1,8]naphthyridin-5-yl)-ethanone 17b and 1-(2-chloro-8-methyl-6*H*-benzo[*c*][1,8]naphthyridin-5-yl)-ethanone 18b. The general procedure using **15b** (176 mg) as starting material gave a mixture of products (**17b** and **18b**) as a white solid ($R_f \approx 0.30$, 28 mg, 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, 1H, J=2.3 Hz), 8.25 (d, 1H, J=2.4 Hz), 8.02 (d, 1H, J=2.3 Hz), 7.99 (d, 1H, J=2.4 Hz), 7.53 (d, 1H, J=7.8 Hz), 7.50 (br s, 1H), 7.20 (m, 3H), 7.13 (br s, 1H), 4.98 (s, 4H), 2.38 (s, 3H), 2.36 (s, 3H).

3.11. Radical reaction on pyridinium salts 13: general procedure for the preparation of 19, 20, and 21

A solution of TTMSS (0.248 g, 1 mmol) and AIBN (0.164 g, 1 mmol) in *m*-xylene (1 mL) and MeCN (9 mL) was added dropwise by a syringe pump, during 13 h, to a stirred solution of the corresponding pyridinium salt **13** (0.5 mmol) in MeCN (2 mL) at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 12 h. The solution was concentrated and the crude mixture was separated by flash chromatography, yielding the pure compounds **19**, **20**, and **21**. Assignments and analysis of the structures were performed using NOE experiments.

3.11.1. 2-Chloro-benzo[*c*][1,8]naphthyridine 19a and 5-chloro-3-phenyl-pyridin-2-ylamine 21a. The general procedure using 228 mg of **13a** as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (70:30)], pure compounds **19a** and **21a** were obtained (46%, 1:1.4) together with a small amount (3%) of tricyclic derivative **22**.[9c]

3.11.1.1. 2-Chloro-benzo[*c*][1,8]naphthyridine 19a. Yellow solid, $R_f \approx 0.10$ (20 mg), mp 231–233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 8.98 (d, 1H, J=2.4 Hz), 8.84 (d, 1H, J=2.4 Hz), 8.51 (d, 1H, J=8.1 Hz), 8.12 (d, 1H, J=8.1 Hz), 7.93 (t, 1H, J=8.1 Hz), 7.80 (t, 1H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 152.0, 150.3, 131.8, 131.7, 130.4, 130.0, 129.1, 129.0, 128.5, 122.1, 119.6; MS (EI) *m*/*z* (relative intensity): 216, 214 (M^+, 32, 100), 179 (24); Anal. Calcd for $C_{12}H_7ClN_2$: C, 67.15; H, 3.29; N, 13.05%. Found: C, 67.29; H, 2.91; N, 12.86%.

3.11.1.2. 5-Chloro-3-phenyl-pyridin-2-ylamine 21a.[20] Yellow solid, $R_f \approx 0.45$ (28 mg), mp 93–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 1H, J=2.4 Hz), 7.42 (m, 5H), 7.34 (d, 1H, J=2.4 Hz), 4.68 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 144.9, 137.5, 136.5, 129.3, 128.5, 128.4, 123.1, 121.1; MS (EI) *m*/*z* (relative intensity): 206, 204 (M^+, 21, 65), 205, 203 (33, 100), 168 (30); Anal. Calcd for $C_{11}H_9ClN_2$: C, 65.56; H, 4.43; N, 13.69%. Found: C, 64.31; H, 4.15; N, 13.87%.

3.11.2. 2-Chloro-9-methyl-benzo[*c*][1,8]naphthyridine 19b and 5-chloro-3-*p*-tolyl-pyridin-2-ylamine 21b. The general procedure using 235 mg of **13b** as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (1:1)], pure compounds **19b** and **21b** were obtained (59%, 1.1:1), together with a small amount (3%) of tricyclic derivative **22**. In this case, no traces of 5-cyclization compound **20b** were detected. Assignment and analysis of the structures were performed using NOE experiments.

3.11.2.1. 2-Chloro-9-methyl-benzo[*c*][1,8]naphthyridine 19b. Yellow solid, $R_f \approx 0.15$ (35 mg), mp 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.96 (d, 1H, J=2.6 Hz), 8.82 (d, 1H, J=2.6 Hz), 8.28 (br s, w½=0.9 Hz), 8.01 (d, 1H, J=8.1 Hz), 7.63 (dd, 1H, J=8.1, 0.9 Hz), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 152.1, 150.1, 142.7, 131.8, 130.7, 130.3, 129.7, 128.9, 124.7, 121.7, 119.4, 22.4; MS (EI) *m*/*z* (relative intensity): 230, 228 (M^+, 33, 100); Anal. Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25%. Found: C, 67.97; H, 3.86; N, 12.36%.

3.11.2.2. 5-Chloro-3-*p*-tolyl-pyridin-2-ylamine 21b. White solid, $R_f \approx 0.67$ (31 mg), mp 157–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 1H, J=2.4 Hz), 7.34 (d, 1H, J=2.4 Hz), 7.32 (d, 2H, J=8.2 Hz), 7.26 (d, 2H, J=8.2 Hz), 4.64 (br s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 144.7, 138.2, 137.4, 133.6, 129.9, 128.3, 123.1, 121.1, 21.2; MS (EI) *m*/*z* (relative intensity): 220, 218 (M^+, 22, 69), 219, 217 (41, 100), 182 (18); Anal. Calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81%. Found: C, 65.71; H, 5.38; N, 12.68%.

3.11.3. 2-Chloro-9-methoxy-benzo[*c*][1,8]naphthyridine 19c. The general procedure using 243 mg of **13c** as the starting material gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (1:1)], pure compound **19c** was obtained (39%) together with a small amount (3%) of tricyclic derivative **22**. In this case, neither **20c** nor **21c** was detected. Assignment and analysis of the structures were performed using NOE experiments. Yellow solid, $R_f \approx 0.15$ (48 mg), mp 205–207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.42 (s, 1H), 9.31 (br s, 1H), 8.91 (br s, 1H), 8.24 (d, 1H, J=8.5 Hz), 8.10 (br s, 1H), 7.43 (d, 1H, J=8.5 Hz), 4.07 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.8, 154.1, 150.1, 147.2, 134.8, 132.1, 132.0, 129.3, 120.2, 119.6, 119.3, 104.1, 56.2; MS (EI) *m*/*z* (relative intensity): 246, 244 (M^+, 33, 100), 203, 201 (13, 40); Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.82; H, 3.71; N, 11.45%. Found: C, 64.12; H, 3.51; N, 11.53%.

3.11.4. 2,9-Dichloro-benzo[*c*][1,8]naphthyridine 19d, 2,8-dichloro-benzo[*c*][1,8]naphthyridine 20d, and 5-chloro-3-(4-chlorophenyl)-pyridin-2-ylamine 21d. The general procedure using 245 mg of **13d** as the starting material

gave a mixture of products. After separation by flash chromatography [silica gel, hexanes/EtOAc (60:40)], pure compounds **19d**, **20d**, and **21d** were obtained (31%, 2:1:1) together with a small amount (3%) of tricyclic derivative **22**. Assignment and analysis of the structures were performed using NOE experiments.

3.11.4.1. 2,9-Dichloro-benzo[*c*][1,8]naphthyridine 19d. White solid, $R_f \approx 0.10$ (19 mg), mp 242–243 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.01 (d, 1H, J=2.5 Hz), 8.78 (d, 1H, J=2.5 Hz), 8.48 (d, 1H, J=1.8 Hz), 8.06 (d, 1H, J=8.4 Hz), 7.75 (dd, 1H, J=8.4, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 152.1, 151.0, 138.6, 132.9, 130.5, 130.4, 130.3, 129.8, 124.2, 121.9, 118.5; MS (EI) *m*/*z* (relative intensity): 252, 250, 248 (M^+, 11, 64, 100), 215, 213 (10, 30); Anal. Calcd for $C_{12}H_6Cl_2N_2$: C, 57.86; H, 2.43; N, 11.25%. Found: C, 57.57; H, 2.39; N, 11.57%.

3.11.4.2. 2,8-Dichloro-benzo[*c*][1,8]naphthyridine 20d. White solid, $R_f \approx 0.15$ (10 mg), mp 262–243 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 9.00 (d, 1H, J=2.4 Hz), 8.80 (d, 1H, J=2.4 Hz), 8.45 (d, 1H, J=8.7 Hz), 8.10 (d, 1H, J=2.0 Hz), 7.87 (dd, 1H, J=8.7, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 152.1, 150.9, 135.4, 132.7, 130.8, 130.6, 130.3, 128.4, 127.6, 124.1, 119.4; MS (EI) *m*/*z* (relative intensity): 252, 250, 248 (M^+, 11, 64, 100), 215, 213 (10, 29); Anal. Calcd for $C_{12}H_6Cl_2N_2$: C, 57.86; H, 2.43; N, 11.25%. Found: C, 57.99; H, 2.22; N, 10.85%.

3.11.4.3. 5-Chloro-3-(4-chlorophenyl)-pyridin-2-ylamine 21d. Yellow solid, $R_f \approx 0.36$ (10 mg), mp 140–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, 1H, J=2.4 Hz), 7.45 (d, 2H, J=8.6 Hz), 7.37 (d, 2H, J=8.6 Hz), 7.32 (d, 1H, J=2.4 Hz), 4.56 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 145.2, 137.6, 135.2, 134.7, 130.1, 129.7, 121.9, 121.5; MS (EI) *m*/*z* (relative intensity): 242, 240, 238 (M^+, 7, 41, 64), 204, 202 (11, 32), 168 (18); Anal. Calcd for $C_{11}H_8Cl_2N_2$: C, 55.26; H, 3.37; N, 11.72%. Found: C, 55.60; H, 3.01; N, 11.91%.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2007.04.077.

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