www.thieme.com

SYNTHESIS
Reviews and Full Papers in Chemical Synthesis

Publishing House and Copyright:
© 2015 by
Georg Thieme Verlag KG
Rüdigerstraße 14
70469 Stuttgart
ISSN 0039-7881

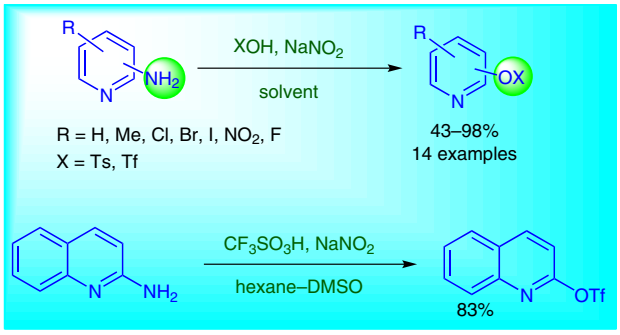
Thieme

Synthesis A. Z. Kassanova et al. Paper

A Novel Convenient Synthesis of Pyridinyl and Quinolinyl Triflates and Tosylates via One-Pot Diazotization of Aminopyridines and Aminoquinolines in Solution

Assiya Zh. Kassanova
Elena A. Krasnokutskaya*
Perizat S. Beisembai
Victor D. Filimonov*

Department of Biotechnology and Organic Chemistry,
National Research Tomsk Polytechnic University,
634050 Tomsk, Russian Federation
eak@tpu.ru
filimonov@tpu.ru



Received: 01.10.2015
Accepted after revision: 04.11.2015
Published online: 02.12.2015
DOI: 10.1055/s-0035-1560392; Art ID: ss-2015-z0565-op

Abstract The first effective and simple method for the direct one-pot transformation of 2-, 3-, and 4-aminopyridines, 2,6-diaminopyridines, and 2-aminoquinoline into the corresponding pyridinyl and quinolinyl trifluoromethanesulfonates and tosylates in solvents was developed. The procedure involves diazotization of the heterocyclic amines with sodium nitrite in mixed hexane–DMSO or hexane–DMF solutions in the presence of trifluoromethanesulfonic acid or *p*-toluenesulfonic acid.

Key words diazotization, pyridine, quinoline, triflate, tosylate

Pyridine and quinoline derivatives containing trifluoromethanesulfonates[1] or 4-methylbenzenesulfonates[2] as a good leaving group are valuable blocks for the synthesis of highly functionalized heterocycles with broader applications in medicinal and other fields of chemistry.

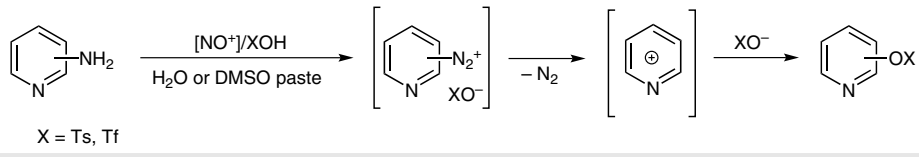
So far the only method for the synthesis of such compounds was the acylation of hydroxypyridines and hydroxyquinoline by TsCl, TfCl, $(Tf)_2O$, or $(Tf)_2NR$.[1–3] In general, these methods provide good yields, but the high cost of reagents and the requirements for an inert atmosphere and low temperature (down to –78 °C) in some cases make the target products fairly expensive.

Recently we have reported an alternative approach to the synthesis of pyridinyl tosylates and pyridinyl triflates through diazotization of available aminopyridines in the presence of TsOH[4] or TfOH[5] by grinding reagents in water or DMSO pastes, respectively, at room temperature (Scheme 1).

These reactions are unknown for aromatic amines, which form stable arenediazonium tosylates at the diazotization step in the presence of *p*-toluenesulfonic acid.[6] However, the reaction takes place due to the known instability of intermediate pyridinediazonium salts (especially with 2- and 4-pyridinediazonium cations) in comparison with arenediazonium salts.[7]

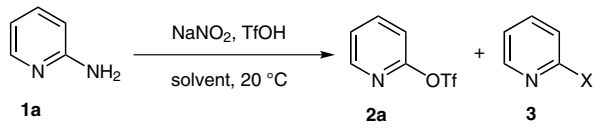
The grinding methods[4,5] are simple and are realized using cheap reagents. However, the grinding reactions in the paste forms are difficult to implement on a large scale, and they cannot be used in flow[8] or combinatorial chemistry. Thus, it is important to develop a more versatile and scalable method for the synthesis of pyridinyl and quinolinyl triflates and tosylates through aminopyridines and aminoquinolines by the diazotization in the presence of TsOH and TfOH in solution.

The selection of the optimal solvents for the diazotization reaction in the presence of $NaNO_2$ and TfOH was conducted using 2-aminopyridine (**1a**). It was found that

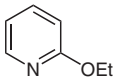
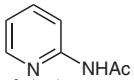
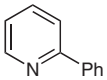
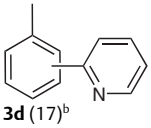
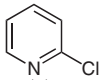
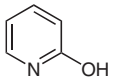


Scheme 1 The one-pot transformation of aminopyridines in pyridinyl tosylates and triflates via the diazotization in the presence of *p*-toluenesulfonic acid and trifluoromethanesulfonic acid[4,5]

Table 1 Diazotization of Pyridine-2-amine (**1a**) by $NaNO_2$ in the Presence of TfOH in Solvents at Room Temperature[a]



1a **2a** **3**

Entry	Solvent	Composition of the reaction mass (GC/MS), %		
		2a	**3**	**1a**
1	EtOH	5	 **3a** (5)	90
2	MeCN	40	 **3b** (45)	2.5
3	benzene	52	 **3c** (20)	28
4	toluene	55	 **3d** (17)[b]	28
5	CH_2Cl_2	89	 **3e** (8)	0
6	DMSO	90	 **3f** (10)	0
7	DMF	100	0	0
8	hexane–DMSO	100	0	0

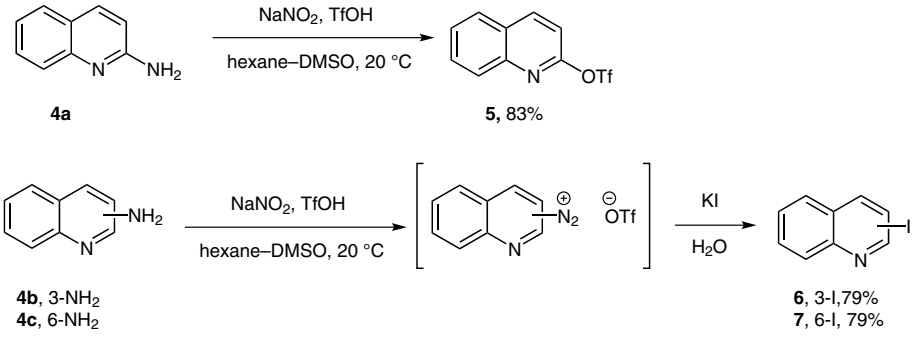
[a] Mole ratio of **1a**/$NaNO_2$/TfOH = 1:2.5:3; reaction time: 1 h.
[b] Mixture of *o*-, *m*-, and *p*-isomers.

during diazotization in EtOH, MeCN, CH_2Cl_2, benzene, and toluene, the formation of target pyridinyl-2-trifluoromethanesulfonate (**2a**) is accompanied by the formation of by-products **3a**–**e** occurring as a result of substitution of the amino group by solvent residues with incomplete conversion of the starting amine **1a** (Table 1).

The best results were obtained using DMSO and DMF (Table 1, entries 6 and 7), but in the case of DMSO, the formation of 2-pyridinol (**3f**) was observed, perhaps, because of the residual water present in the solvent. The full conversion of starting amine **1a** after 20–30 minutes with an absence of by-products was observed in DMF, but in this case unexpected difficulties arose in the separation of 2-pyridinyl triflate (**2a**) from residual amounts of the solvent. Probably, DMF forms strong complexes with pyridine **2a** as significant amounts of DMF (up to 44%) can be found in the NMR spectrum after multiple washings of the extract of **2a** in ethyl acetate or CH_2Cl_2 with water or even after chromatographic purification on silica gel.

For these reasons, inert hexane supplemented with 10% DMSO was tested for better solubility of the reaction components (Table 1, entry 8) and it was found that there were no by-products upon complete conversion of amine **1a**. This solvent system was used for the further preparative syntheses of pyridinyl triflates **2a**–**n** (Table 2). The reactions were conducted as follows. Trifluoromethanesulfonic acid was added to a cooled (5 °C) mixture of hexane–DMSO (10:1 vol%), then the pre-ground mixture of the corresponding aminopyridine **1a**–**n** and sodium nitrite was added at several stages to the reaction mass. After loading of the reagents, the reaction mass was stirred at 5 °C for 10 minutes and then for 50 minutes at room temperature.

It is important to note that formation of pyridinyl triflates **2a**–**n** under the $NaNO_2$/TfOH treatment in hexane–DMSO system takes place within 1 hour, that is, it is significantly faster than in DMSO paste (2.5–38 h).[5] Yields of the target pyridinyl triflates **2a**–**n** during diazotization in solution are also higher than in DMSO paste.[5] The proposed synthetic method has a general character, allowing the preparation of 2-, 3-, and 4-pyridinyl trifluoromethanesulfonates as well as the almost unknown 2,6-pyridinyl ditri-



4a **5**, 83%

4b, 3-NH_2 **6**, 3-I,79%
4c, 6-NH_2 **7**, 6-I, 79%

Scheme 2 Diazotization of aminoquinolines **4a**–**c** in the presence of trifluoromethanesulfonic acid

flates **2k**–**n**.[5] At the same time, pyridine-3,4-diamine and 3-nitropyridine-4-amine are inert under the described conditions and are isolated unchanged from the reaction mixture.

Table 2 Synthesis of Pyridinyl Trifluoromethanesulfonates **2a**–**n**[a]

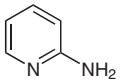
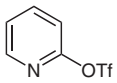
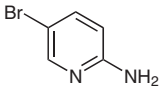
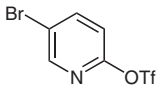
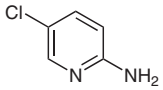
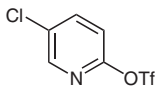
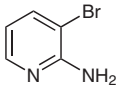
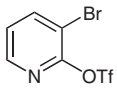
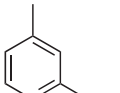
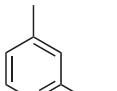
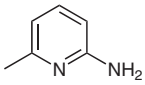
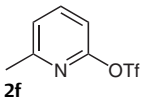
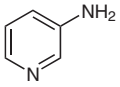
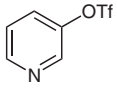
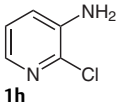
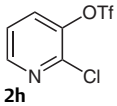
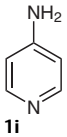
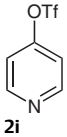
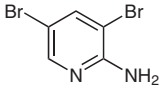
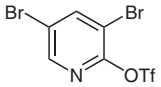
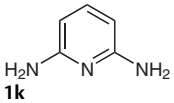
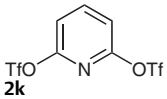
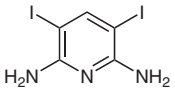
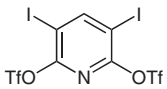
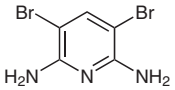
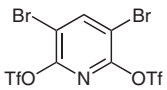
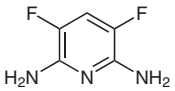
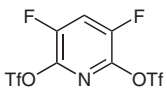
Substrate	Product	Yield (%)[b]
 **1a**	 **2a**	96
 **1b**	 **2b**	92
 **1c**	 **2c**	86
 **1d**	 **2d**	60
 **1e**	 **2e**	75
 **1f**	 **2f**	78
 **1g**	 **2g**	98
 **1h**	 **2h**	90
 **1i**	 **2i**	73
 **1j**	 **2j**	75
 **1k**	 **2k**	61

Table 2 (continued)

Substrate	Product	Yield (%)[b]
 **1l**	 **2l**	56
 **1m**	 **2m**	43
 **1n**	 **2n**	50[c]

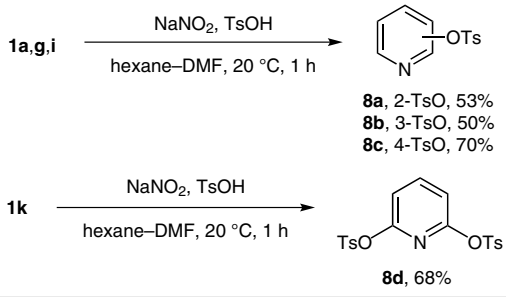
[a] The diazotization of aminopyridines **1a**–**n** by $NaNO_2$ was conducted in the presence of TfOH in hexane–DMSO mixture. Mole ratio of **1a**–**j**/$NaNO_2$/TfOH = 1:2.5:3, for **1k**–**n** mole ratio = 1:5:6.
[b] Isolated yields.
[c] Inseparable mixture with 3,5-difluoropyridin-2-yl trifluoromethanesulfonate in a ratio of 95:5.

It is important to note also that the reaction of 3,5-difluoropyridine-2,6-diamine (**1n**) is accompanied by a partial hydro-dediazoniation and an inseparable mixture of the target product **2n** together with about 5% of 3,5-difluoropyridin-2-yl trifluoromethanesulfonate was formed (GC/MS data).

The found conditions were used in attempts to the first direct conversion of 2-, 3- and 6-aminoquinolines **4a**–**c** into the corresponding triflate derivatives via diazotization in the presence of TfOH. However, it was found that only 2-aminoquinoline (**4a**) was converted into quinolin-2-yl trifluoromethanesulfonate (**5**) in good yield similar to aminopyridines **1**. At the same time, 3- and 6-aminoquinolines **4b**,**c** form only relatively stable diazonium salts, which even when heated were not converted into the 3- and 6-quinolinyl triflates, but quickly gave 3- and 6-iodoquinolines **6** and **7** in 79% yield under the treatment of aqueous KI at room temperature (Scheme 2).

We have also used this approach for obtaining 2-, 3-, and 4-pyridinyl-4-methylbenzenesulfonates **8a**–**c** and pyridine-2,6-diyl bis(4-methylbenzenesulfonate) (**8d**) via the solution diazotization of 2-, 3-, and 4-aminopyridines **1a**,**g**,**i** or pyridine-2,6-diamine (**1k**) in the presence of TsOH (Scheme 3) as well. However, in this case it is preferred to use DMF instead of DMSO for better dissolution of TsOH. This solution reaction takes place slightly faster than the diazotization in the presence of TsOH in the aqueous paste.[4]

The possibility of scaling up the developed method was confirmed by the experiment in which 2-pyridinyl triflate (**2a**) and 2-pyridinyl tosylate (**8a**) were obtained with an increased load of pyridin-2-amine up to 10 mmol without a reduction in target product yields.



Scheme 3 Synthesis of pyridinyl tosylates **8a–d** via the diazotization in hexane–DMF solution in the presence of *p*-toluenesulfonic acid

In summary, we have presented a simple and scalable method for the synthesis of pyridinyl triflates and tosylates as well as quinolin-2-yl triflate from the available aminopyridines and 2-aminoquinoline via the diazotization by sodium nitrite in the presence of TsOH or TfOH in hexane solution with the addition of DMF or DMSO. Under the same conditions, 3- and 6-aminoquinolines form relatively stable diazonium salts, which can be easily converted into 3- and 6-iodoquinolines.

All starting materials **1a–j** were ACS grade and used without further purification except pyridine-2,6-diamine (**1k**) (Sigma Aldrich), which was purified by recrystallization from benzene. Compound **1l** was prepared by the iodination of **1k** with NIS.[9] HPLC analyses were conducted with an Agilent 1200 instrument fitted with an Eclipse Plus C18 column (5 µm, 4.6 × 150 mm) and UV detector. GC/MS measurements were obtained with an Agilent 7890/5975C instrument. ^{1}H, ^{13}C NMR, and IR spectra were recorded on a Bruker and PerkinElmer BXII instruments. Melting points (uncorrected) were obtained with a melting point system MP50, Mettler, Toledo. Elemental analyses were performed with a Vario MACRO cube CHNS instrument (Elementar Analysensysteme GmbH, Germany). All the known compounds, **2a–c**,**e–i**,**k**,**l**, **5**, and **8a–d**, were characterized by comparison of melting points and NMR spectra with the literature data and authentic samples.

Pyridinyl and Quinolinyl Trifluoromethanesulfonates 2a–n, 5; General Procedure

To a solution of hexane (5 mL), DMSO (0.5 mL), and trifluoromethanesulfonic acid (0.54 mL, 6 mmol) at 5 °C were sequentially added the respective aminopyridine **1a–j** (2 mmol) and $NaNO_2$ (0.35 g, 5 mmol) under stirring and the mixture was stirred for 10 min. An immediate emission of N_2 bubbles was observed. In the case of diamino derivatives **1k–n**, double amounts of $NaNO_2$ and TfOH were used. The resulting mixture was then stirred for 50 min at r.t. until the starting amine had been consumed as monitored by TLC. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure on a rotary evaporator. The product was purified by silica gel flash chromatography (eluent: CH_2Cl_2).

Pyridin-2-yl Trifluoromethanesulfonate (2a)[5]

Yield: 436 mg (96%, 1.92 mmol); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2 (d, *J* = 8.1 Hz, 1 H), 7.4 (m, 1 H), 7.9 (m, 1 H), 8.4 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.3, 118.6 (q, *J* = 300 Hz), 124.3, 141.1, 148.8, 155.9.

MS (EI): *m*/*z* (%) = 227 (38, $[M]^+$), 199 (2), 163 (4), 135 (100), 116 (9), 96 (13), 69 (60), 39 (45).

5-Bromopyridin-2-yl Trifluoromethanesulfonate (2b)[5]

Yield: 563 mg (92%, 1.84 mmol); light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.1 (d, *J* = 8.7 Hz, 1 H), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1 H), 8.5 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.8, 118.5 (q, *J* = 300 Hz), 120.5, 143.6, 149.7, 154.5.

MS (EI): *m*/*z* (%) = 307 (15, $[^{81}Br, M]^+$), 243 (4), 213 (62), 174 (4), 144 (29), 117 (46), 96 (10), 69 (100), 38 (46).

5-Chloropyridin-2-yl Trifluoromethanesulfonate (2c)

Yield: 449 mg (86%, 1.72 mmol); white solid; mp 67 °C (Lit.[5] mp 67 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.1 (d, *J* = 8.7 Hz, 1 H), 7.85 (dd, *J* = 8.7, 2.4 Hz, 1 H), 8.3 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.3, 118.4 (q, *J* = 317 Hz), 132.3, 140.6, 147.2, 153.7.

MS (EI): *m*/*z* (%) = 261 (30, $[^{35}Cl, M]^+$), 233 (2), 197 (4), 169 (100), 134 (9), 100 (30), 69 (53), 38 (9).

3-Bromopyridin-2-yl Trifluoromethanesulfonate (2d)

Yield: 367 mg (60%, 1.2 mmol); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.29 (m, 1 H), 8.06–8.09 (dd, $J_{3,2}$ = 7.95 Hz, $J_{3,1}$ = 1.5 Hz, 1 H), 8.31–8.33 (dd, $J_{1,2}$ = 4.8 Hz, $J_{1,3}$ = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.1, 120.6 (q, *J* = 318.0 Hz), 125.3, 144.3, 146.5, 152.9.

MS (EI): *m*/*z* (%) = 307 (66, $[^{81}Br, M]^+$), 241 (10), 213 (100), 193 (3), 162 (64), 144 (60), 117 (26), 93 (21), 69 (91), 38 (29).

Anal. Calcd for $C_6H_3BrF_3NO_3S$: C, 23.55; H, 0.99; N, 4.58; S, 10.48. Found: C, 23.55; H, 1.07; N, 5.08; S, 10.48.

4-Methylpyridin-2-yl Trifluoromethanesulfonate (2e)[5]

Yield: 361 mg (75%, 1.5 mmol); light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.4 (s, 3 H), 6.9 (s, 1 H), 7.2 (d, *J* = 4.8 Hz, 1 H), 8.2 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 115.5, 118.6 (q, *J* = 318 Hz), 125.3, 148.0, 153.4, 156.2.

MS (EI): *m*/*z* (%) = 241 (45, $[M]^+$), 213 (9), 177 (6), 148 (100), 128 (3), 108 (9), 96 (1), 92 (20), 80 (30), 69 (38), 65 (15), 53 (52), 39 (13).

6-Methylpyridin-2-yl Trifluoromethanesulfonate (2f)[5]

Yield: 376 mg (78%, 1.6 mmol); light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.5 (s, 3 H), 6.9 (d, *J* = 7.8 Hz, 1 H), 7.2 (d, *J* = 7.5 Hz, 1 H), 7.7 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 111.7, 118.6 (q, *J* = 319 Hz), 123.7, 140.9, 155.1, 159.0.

MS (EI): *m*/*z* (%) = 241 (65, [M]$^+$), 213 (13), 177 (6), 158 (1), 148 (55), 142 (1), 128 (1), 108 (6), 91 (100), 80 (35), 69 (41), 65 (20), 53 (33), 39 (68).

Pyridin-3-yl Trifluoromethanesulfonate (2g)[5]

Yield: 445 mg (98%, 1.9 mmol); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (dd, *J* = 8.4, 4.8 Hz, 1 H), 8.0 (dd, *J* = 8.4, 1.2 Hz, 1 H), 9.0 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.5 (q, *J* = 319 Hz), 124.6, 128.9, 142.7, 146.6, 149.4.

MS (EI): *m*/*z* (%) = 227 (100, [M]$^+$), 163 (36), 135 (5), 116 (4), 94 (25), 78 (20), 69 (69), 39 (64).

2-Chloropyridin-3-yl Trifluoromethanesulfonate (2h)[5]

Yield: 472 mg (90%, 1.8 mmol); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4 (dd, *J* = 8.3, 4.5 Hz, 1 H), 7.7 (d, *J* = 8.1 Hz, 1 H), 8.4 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.4 (q, *J* = 319 Hz), 123.8, 131.4, 142.7, 144.1, 148.7.

MS (EI): *m*/*z* (%) = 261 (50, [^{35}Cl, M]$^+$), 197 (23), 169 (4), 150 (2), 128 (11), 100 (100), 69 (68), 39 (48).

Pyridin-4-yl Trifluoromethanesulfonate (2i)[5]

Yield: 331 mg (73%, 1.46 mmol); light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2 (d, *J* = 5.7 Hz, 2 H), 8.7 (d, *J* = 5.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.1, 118.3 (q, *J* = 334 Hz), 152.3, 155.9.

MS (EI): *m*/*z* (%) = 227 (100, [M]$^+$), 163 (18), 136 (5), 109(2), 94 (17), 77 (13), 69 (87), 39 (25).

3,5-Dibromopyridin-2-yl Trifluoromethanesulfonate (2j)

Yield: 573 mg (75%, 1.4 mmol); yellow solid; mp 100–101 °C (Lit.[5] mp 100 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.2 (d, *J* = 2.1 Hz, 1 H), 8.4 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.7, 118.3 (q, *J* = 319 Hz), 120.1, 145.9, 147.6, 151.7.

MS (EI): *m*/*z* (%) = 385 (35, [^{81}Br, M]$^+$), 321 (8), 293 (75), 252 (10), 224 (67), 197 (25), 172 (12), 144 (10), 118 (35), 69 (100), 37 (25).

Pyridine-2,6-diyl Bis(trifluoromethanesulfonate) (2k)

Yield: 457 mg (61%, 1.22 mmol); yellow solid; mp 32–33 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.1 Hz, 2 H), 8.11–8.15 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.1, 118.7 (q, *J* = 319.0 Hz), 145.4, 153.4.

MS (EI): *m*/*z* (%) = 375 (11, [M]$^+$), 283 (2), 247 (2), 219 (10), 180 (7), 150 (82), 122 (8), 93 (54), 69 (100), 39 (12).

Anal. Calcd for $C_7H_3F_6NO_6S_2$: C, 22.41; H, 0.81; N, 3.73; S, 17.09. Found: C, 22.9; H, 0.79; N, 4.06; S, 17.90.

3,5-Diiodopyridine-2,6-diyl Bis(trifluoromethanesulfonate) (2l)

Yield: 702 mg (56%, 1.12 mmol); white solid; mp 128 °C (Lit.[5] mp 128 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.8 (s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.5, 118.5 (q, *J* = 319 Hz), 154.5, 162.2.

MS (EI): *m*/*z* (%) = 627 (52, [M]$^+$), 494 (7), 466 (2), 430 (4), 402 (31), 374 (9), 345 (27), 325 (2), 303 (18), 275 (21), 254 (2), 234 (17), 206 (45), 178 (27), 163 (16), 148 (11), 127 (32), 69 (100), 39 (5).

3,5-Dibromopyridine-2,6-diyl Bis(trifluoromethanesulfonate) (2m)

Yield: 458 mg (43%, 0.86 mmol); white solid; mp 64–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 112.2, 118.5 (q, *J* = 321.1 Hz), 149.3, 150.4.

MS (EI): *m*/*z* (%) = 533 (24, [^{81}Br, M]$^+$), 455 (2), 405 (4), 368 (2), 324 (14), 308 (41), 280 (22), 251 (31), 213 (17), 160 (18), 144 (12), 130 (14), 116 (8), 69 (100), 51 (8), 37 92).

Anal. Calcd for $C_7HBr_2F_6NO_6S_2$: C, 15.77; H, 0.19; N, 2.63; S, 12.03. Found: C, 16.03; H, 0.33; N, 2.63; S, 12.20.

3,5-Difluoropyridine-2,6-diyl Bis(trifluoromethanesulfonate) (2n)

Yield: 411 mg (50%, 1 mmol); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.80 (m).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 118.6 (q, *J* = 321 Hz), 119.18–119.61 (m), 135.68–135.89 (m), 149.4 (dd, *J* = 272.6, 5.2 Hz).

MS (EI): *m*/*z* (%) = 411 (7, [M]$^+$), 379 (1), 342 (1), 326 (1), 300 (1), 283 (3), 262 (3), 236 (1), 214 (1), 198 (5), 198 (43), 167 (5), 154 (10, 141 (2), 129 (24), 117 (7), 101 (17), 89 (9), 69 (100), 48 (2), 31 (2).

Compound **2n** according to GC/MS data was contaminated with about 5% of 3,5-difluoropyridin-2-yl trifluoromethanesulfonate [MS (EI): *m*/*z* (%) = 411 (7, [M]$^+$), 379 (1), 342 (1), 326 (1), 300 (1), 283 (3), 262 (3), 236 (1), 214 (1), 198 (5), 198 (43), 167 (5), 154 (10, 141 (2), 129 (24), 117 (7), 101 (17), 89 (9), 69 (100), 48 (2), 31 (2)].

Quinolin-2-yl Trifluoromethanesulfonate (5)[2h]

Yield: 460 mg (83%, 1.66 mmol); light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.7 Hz, 1 H), 7.54–7.59 (m, 1 H), 7.71–7.76 (m, 1 H), 7.81 (d, *J* = 8.1 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.25 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.9, 120.8 (q, *J* = 318 Hz), 127.5, 128.5, 131.1, 141.9, 145.6, 153.5.

MS (EI): *m*/*z* (%) = 277 (26, [M]$^+$), 249 (1), 213 (14), 185 (32), 166 (4), 144 (16), 128 (20), 116 (100), 101 (5), 89 (23), 75 (5), 69 (27), 64 (18), 51 (5), 39 (7).

Diazotization-Iodination of 3- and 6-Quinoline Amines 4b,c; General Procedure

To a solution of hexane (5 mL), DMSO (0.5 mL), and trifluoromethanesulfonic acid (0.54 mL, 6 mmol) at 5 °C were sequentially added the quinoline amine **4b** or **4c** (2 mmol) and $NaNO_2$ (350 mg, 5 mmol) under stirring, and the mixture was stirred for 10 min. The resulting mixture was then stirred for 50 min at r.t. until the starting amine had been consumed as monitored by TLC. An emission of N_2 bubbles was not observed and the reaction solution gave the positive probe on diazonium salts with β-naphthol. Next, KI (2.4 mmol) in H_2O (0.5 mL) was added and the mixture was stirred 10 min at r.t. until evolution of N_2 bubbles ceased. In the case of **4b**, the solid 3-iodoquinoline **6** obtained was filtered, washed with H_2O, and dried. In the case of **3c**, the reaction mixture was poured into H_2O and the oily product **7** was

extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure on a rotary evaporator. The product **7** was purified by silica gel flash chromatography (eluent: CH_2Cl_2).

3-Iodoquinoline (6)

Yield: 403 mg (79%, 1.27 mmol); white solid; mp 58–59 °C (Lit.[10] mp 56–58 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.58 (m, 1 H), 7.68–7.75 (m, 2 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 8.53 (s, 1 H), 9.03 (s, 1 H).

MS (EI): *m*/*z* (%) = 255 (100, $[M]^+$), 128 (80), 101 (36), 75 (21), 51 (9).

6-Iodoquinoline (7)

Yield: 403 mg (79%, 1.27 mmol); yellow solid; mp 91–92 °C (Lit.[11] mp 91 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 7.8, 4.2 Hz, 1 H), 7.81 (d, *J* = 8.7 Hz, 1 H), 7.92 (d, *J* = 9 Hz, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H), 8.18 (s, 1 H), 8.89 (d, *J* = 4.2 Hz, 1 H).

MS (EI): *m*/*z* (%) = 255 (100, $[M]^+$), 128 (54), 101 (25), 75 (13), 51 (7).

Pyridinyl 4-Methylbenzenesulfonates 8a–d: General Procedure

To a solution of hexane (5 mL), DMF (0.5 mL), and *p*-toluenesulfonic acid (1.14 g, 6 mmol) at 5 °C were sequentially added the respective aminopyridine **1a**,**g**,**i** (2 mmol) and $NaNO_2$ (350 mg, 5 mmol) under stirring and the mixture was stirred for 10 min. An immediate emission of N_2 bubbles was observed. In the case of diamino derivative **1k**, double amounts of $NaNO_2$ and TsOH were used. The resulting mixture was then stirred for 50 min at r.t. until the starting amines had been consumed as monitored by TLC. The reaction mixture was poured into H_2O and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed on a rotary evaporator under reduced pressure. The products **8a**–**d** were purified by crystallization from hexane.

Pyridin-2-yl 4-Methylbenzenesulfonate (8a)[4]

Yield: 264 mg (53%, 1.06 mmol); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 7.1 (d, *J* = 8.1 Hz, 1 H), 7.19–7.23 (m, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.74–7.79 (m, 1 H), 7.89 (d, *J* = 7.8 Hz, 2 H), 8.26 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 115.8, 122.5, 128.4, 129.5, 133.4, 140.0, 145.1, 148.2, 156.7.

MS (EI): *m*/*z* (%) = 249 (2, $[M]^+$), 184 (78), 166 (2), 157 (31), 139 (3), 129 (3), 115 (3), 102 (1.5), 91 (100), 78 (9), 65 (25), 57 (2), 51 (3), 39 (13).

Pyridin-3-yl 4-Methylbenzenesulfonate (8b)

Yield: 250 mg (50%, 1.0 mmol); white solid; mp 79–80 °C (Lit.[4] mp 80 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 7.25–7.32 (m, 3 H), 7.42–7.46 (m, 1 H), 7.68 (d, *J* = 7.8 Hz, 2 H), 8.1 (d, *J* = 1.8 Hz, 1 H), 8.47 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 124.2, 128.4, 130.0, 130.2, 131.4, 143.9, 145.9, 146.3, 148.2.

MS (EI): *m*/*z* (%) = 249 (34, $[M]^+$), 182 (2), 167 (2), 155 (78), 149 (2), 139 (2), 102 (2), 91 (100), 83 (2), 77 (3), 65 (25), 57 (2), 51 (3), 39 (17).

Pyridin-4-yl 4-Methylbenzenesulfonate (8c)

Yield: 349 mg (70%, 1.4 mmol); white solid; mp 152–153 °C (Lit.[4] mp 150–154 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 7.0 (d, *J* = 4.9 Hz, 2 H), 7.3 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 8.55 (d, *J* = 3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 116.9, 128.2, 129.9, 131.7, 145.9, 151.6, 156.2.

MS (EI): *m*/*z* = 249 (44, $[M]^+$), 185 (13), 169 (2), 155 (75), 149 (2), 139 (2), 129 (2), 115 (2), 107 (2), 91 (100), 82 (2), 77 (3), 65 (25), 57 (2), 51 (3), 39 (9).

Pyridine-2,6-diyl Bis(4-methylbenzenesulfonate) (8d)

Yield: 567 mg (68%, 1.48 mmol); white solid; mp 80–81 °C (Lit.[4] mp 80 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 6 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 4 H), 7.79–7.84 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 114.2, 128.7, 129.8, 133.1, 143.4, 145.6, 154.8.

MS (EI): *m*/*z* (%) = 355 (6, $M^+ - SO_2$), 327 (2), 291 (3), 274 (2), 263 (2), 200 (25), 184 (3), 165 (2), 155 (59), 139 (5), 129 (1), 107 (2), 91 (100), 77 (2), 65 (16), 39 (5).

Acknowledgment

The authors gratefully acknowledge the Russian Scientific Fund (Project No. 15-13-10023) supported the synthesis of pyridine derivatives **2a**–**n**. Part of this work was supported by the Russian Foundation for Basic Research (Project No. 14-03-00743a). E.A.K. acknowledges the Scientific Program 'Nauka' (No 2387), V.F. acknowledges the Scientific Program 'Nauka' (No 4.1991.2014 K). The analytical experiments were performed by the scientific equipment network center of TPU.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561272.

References

(1) (a) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (b) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (d) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (e) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848. (f) Pschierer, J.; Plenio, H. *Eur. J. Org. Chem.* **2010**, 2934. (g) Lin, W.; Chen, L.; Knochel, P. *Tetrahedron* **2007**, *63*, 2787. (h) Sergeev, M. E.; Morgia, F.; Lazari, M.; Wang, C.; van Dam, R. M. *J. Am. Chem. Soc.* **2015**, *137*, 5686. (i) Lin, C.-P.; Florio, P.; Campi, E. M.; Zhang, C.; Fredericks, D. P.; Saito, K.; Jackson, W. R.; Hearn, M. T. W. *Tetrahedron* **2014**, *70*, 8520.

(2) (a) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048. (b) Kim, H.; Lee, K.; Lee, P. H.; Kim, S. *Chem. Commun.* **2010**, 6341. (c) Nicolaou, K. C.; Kiappes, J. L.; Tian, W.; Gondi, V. B.; Becker, J. *Org. Lett.* **2011**, *13*, 3924. (d) Seganish, W. M.; DeShong, Ph. *J. Org. Chem.* **2004**, *69*, 1137. (e) Hammoud, H.; Schmitt, M.; Bihel, F.; Antheaume, C.; Bourguignon, J.-J. *J. Org. Chem.* **2012**, *77*, 417. (f) Du, G.; Moulin, E.; Jouault, N.; Buhler,

E.; Guiseppone, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 12504. (g) Maloney, K. M.; Nwakpuda, E.; Kuethe, J. T.; Yin, J. *J. Org. Chem.* **2009**, *74*, 5111. (h) Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 4893.

(3) Wentworth, A. D.; Wentworth, P.; Mansoor, U. F.; Janda, K. D. *Org. Lett.* **2000**, *2*, 477.

(4) Tretyakov, A. N.; Krasnokutskaya, E. A.; Gorlushko, D. A.; Ogorodnikov, V. D.; Filimonov, V. D. *Tetrahedron Lett.* **2011**, *52*, 85.

(5) Krasnokutskaya, E. A.; Kassanova, A. Z.; Estaeva, M. T.; Filimonov, V. D. *Tetrahedron Lett.* **2014**, *55*, 3771.

(6) (a) Filimonov, V. D.; Trusova, M. E.; Postnikov, P. S.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Ki-Whan, C. *Org. Lett.* **2008**, *10*, 3961. (b) Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis* **2007**, 81. (c) Kutonova, K. V.; Trusova, M. E.; Postnikov, P. S.; Filimonov, V. D.; Parello, J. *Synthesis* **2013**, *45*, 2706.

(7) Butler, R. N. *Chem. Rev.* **1975**, *75*, 241.

(8) Oger, N.; Le Grognec, E.; Felpin, F.-X. *J. Org. Chem.* **2014**, *79*, 8255.

(9) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

(10) Boganyi, B.; Kaman, J. *Tetrahedron* **2013**, *69*, 9512.

(11) Ullmann, F. *Justus Liebigs Ann. Chem.* **1904**, *332*, 38.