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Pyridinium N-2′-pyridylaminide: synthesis of 3-aryl-2-aminopyridines through an intramolecular radical process

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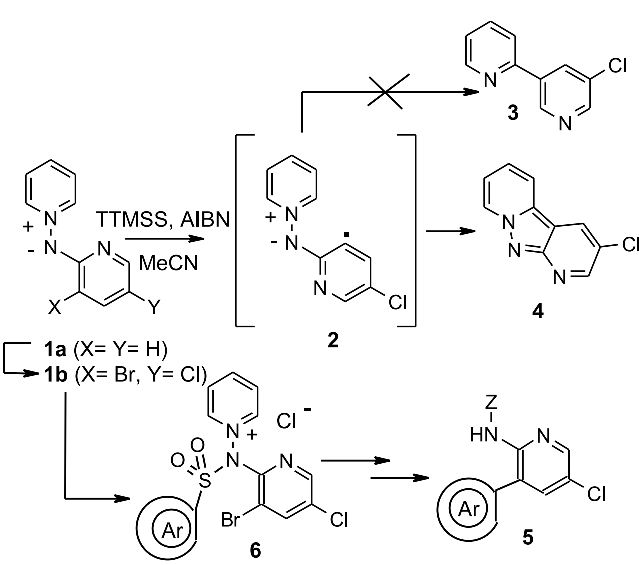
Abstract—Tris(trimethylsilyl)silane (TTMSS) and azobisisobutironitrile (AIBN) promote the intramolecular heteroarylation of arenesulfonamides with pyridyl radicals under thermal conditions. The arenesulfonamides are easily prepared from pyridinium N-2′-pyridylaminide. The heteroarylation process involves pyridyl radical cyclization and *ipso* substitution.

1. Introduction

Azinium N-ylides, a subgroup of mesomeric betaines, are interesting compounds due to their dipolar character, as well as to their biological properties and synthetic applications.[1,2] During the past few years our research group has been interested in the chemistry of pyridinium N-2′-pyridylaminide, **1a** (Scheme 1), a stable heterocyclic betaine, that has a π-deficient pyridinium fragment attached to a π-excessive 2-iminopyridine moiety. This compound has proven to be a versatile scaffold in a wide range of transformations. Thus, for example, the preparation of 3-or 3,5-halogenated 2-alkyl aminopyridines from **1a** can be carried out by an easy and selective halogenation at the iminopyridine moiety (for supply, for example **1b**, Scheme 1), followed by regioselective N-alkylation at the aminide nitrogen and final reduction of N–N bond.[3]



Scheme 1.

During the course of our studies on the intramolecular arylation of **1b**, we evaluated the behavior of the pyridyl radical **2** (Scheme 1). The ultimate goal was the preparation of bipyridine **3** by a reaction pathway involving a exo/endo-*trig* cyclization, followed by N–N bond breaking, as previously described.[3d] Compound **3**, however, was not detected and instead, the tricyclic derivative **4** was obtained in moderate yield.[4] Following the same target in the development of a preparation of bipyridines and related biaryls by intramolecular radical arylation (i.e., **5**, Scheme 1), we decided to prepare salt **6** in order to explore the feasibility of an intramolecular free radical *ipso*-substitution of the corresponding arenesulfonamides by pyridyl radicals, according to the methodology described by Motherwell and col.[5] This well-established method, based on aryl radical cyclizations, has been applied to the synthesis of biaryls and arylheterocycles. However, to the best of our knowledge, references concerning the use of heteroaryl radicals in such a method have not been published to date. Indeed, from a general point of view, the cyclization of pyridyl radicals has scarcely been exploited in synthesis.[6]

Keywords: Arylation; Biaryls; *Ipso*-substitution mechanism; Radicals and radical reaction; Tris(trimethylsilyl)silane.
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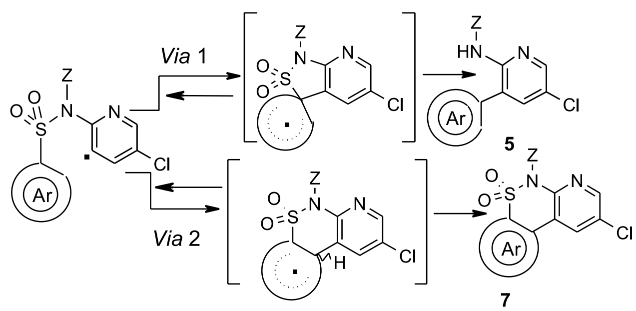
On the other hand, reductive cyclization of *N*-(2-haloaryl)arenesulfonamides has been studied by Motherwell in the first instance, in the presence of tributyltin hydride/AIBN,[5] which later obviated the need for tin derivatives by using arenesulfonylaminobenzene-diazonium salts and $TiCl_3$.[7] More recently, Togo and Ryokawa reported a similar tin-free cyclization of bromoaryl arenesulfonamides, using 1,1,2,2 tetraphenyl disilane, in the presence of AIBN.[8]

The 1,5-*ipso*-substitution approach to biaryls compounds **5** is shown in Scheme 2, via 1, while via 2, shows the alternative 1,6-cyclization to yield the by-products **7**. Both of processes occur according to the reaction mechanism described by Motherwell and colleagues.[5]

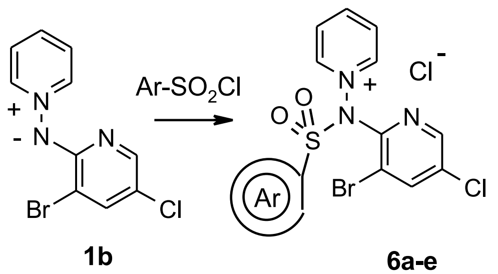


Scheme 2.

As a continuation of our interest in inter- and intramolecular radical heteroarylations of aromatic substrates, using Tris(trimethylsilyl)silane (TTMSS)/AIBN, under reductive conditions, we wish to report our preliminary results concerning pyridyl radical cyclizations, onto arenesulfonamide derivatives, using *N*-2′-pyridylaminide, **1a**, as starting material.

2. Results and discussion

Pyridyl-substituted aminide **1b** (Scheme 3),[3c] was reacted with the corresponding aryl sulfonyl chlorides to produce *N*-[(3-bromo-5-chloro-pyridin-2-yl)arenesulfonamido] pyridinium chlorides **6**. Best results were obtained for compounds **6a–e** (Table 1, entries 1–5) by addition, at room temperature, of a solution of corresponding aryl sulfonyl chloride (3 equiv) in acetone (15 mL) to a stirred solution of **1b** (1 equiv) in acetone (5 mL). Stirring was then maintained for 24 h (method A). The method, however, did not produce detectable yields of **6** with other aryl sulfonyl chlorides such as 2,4,6-trimethylbenzenesulfonyl chloride,



Scheme 3.

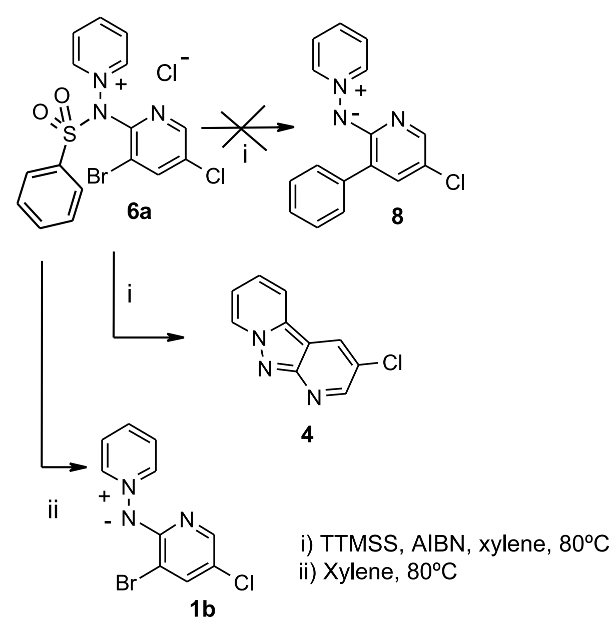
Table 1. Arenosulfonamides salts **6** were obtained

Entry	Compound	Ar[a]	Yield (%)
1	**6a**	C_6H_5	79
2	**6b**	4-Me–C_6H_4	66
3	**6c**	4-MeO–C_6H_4	46
4	**6d**	4-Cl–C_6H_4	53
5	**6e**	4-NO_2–C_6H_4	65

[a] Method A: aryl sulfonyl chloride (3 equiv) in acetone (15 mL) to a stirred solution of **1b** (1 equiv) in acetone (5 mL), stirring was then maintained for 24 h.

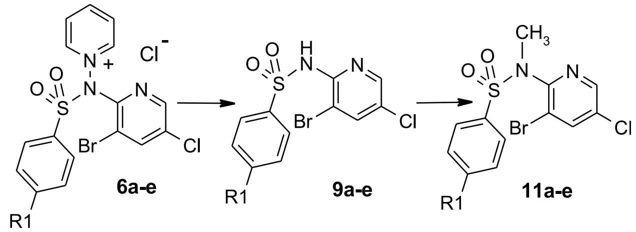
quinoline 8-sulfonyl chloride or thiophene-2-sulfonyl chloride, even refluxing toluene for 48 h (method B).

Having obtained substrates **6**, initial experiments on pyridyl radical cyclization were undertaken on **6a**, bearing in mind the results of previous work on the intramolecular process.[4] Thus, as indicated in Scheme 4, the very slow dropwise addition (syringe pump) of a solution of TTMSS (2 equiv) and AIBN (2 equiv) to a solution of **6a** in benzene/acetonitrile did not generate detectable yields of **8** and only poor yields of tricyclic derivative **4** could be obtained. Similar results were found when the reaction was carried out in *m*-xylene, which was used as an alternative to avoid the use of benzene.[8] As a result, the suggested reaction mechanism would involve N–S fission and subsequent 5-*exo*/*endo*-*trig* cyclization, or alternatively radical cyclization followed by desulfonylation, both consistent with the formation of ylide **1b** in the absence of TTMSS and AIBN (Scheme 4).[4]



Scheme 4.

Cyclization of compound **6a** did not seem to be an efficient process, so N–N reduction of **6** was performed. The use of a two molar excess of reducing agents [method C, **6** (0.5 mmol), Pt/C 5% (240 mg), formic acid 96% (1.6 mL, 40 mmol), triethylamine (15 mL, 108 mmol)] on the previously described method,[3c] gave *N*-unsubstituted compounds **9**. These results are shown in Scheme 5 and Table 2. The process, when applied to pyridinium salts **6a–d**,



Scheme 5.

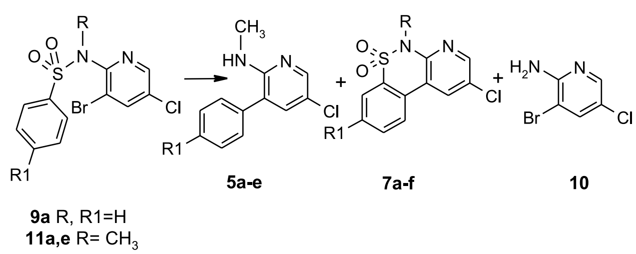
Once again, application of the radical cyclization process, under similar experimental conditions, to **9a**, which has a N–H free sulfonamide, did not generate the rearranged biaryl **5**. In this case, only the cyclization **7f** and the reduction products **10** were obtained in moderate yields, a situation in agreement with the results reported for other radical arylations,[5,8] (see Scheme 6 and Table 3, entry 10). As an alternative, compounds **11** were prepared by *N*-methylation with methyl iodide/potassium carbonate (method E). Results are summarized in Scheme 5 and Table 2.

Table 2. Compounds **9** and **11** were obtained

Entry	R_1	Starting material	**9**, Yield (%)	Method	**11**, Yield (%)	Method
1	H	**6a**	70	C[a]	72	E[b]
2	CH_3	**6b**	82	C[a]	60	E[b]
3	OCH_3	**6c**	54	C[a]	96	E[b]
4	Cl	**6d**	54	C[a]	71	E[b]
5	NO_2	**6e**	4	C[a]	61	E[b]
6	NO_2	**6e**	70	D[c]		

[a] Method C: **6** (0.5 mmol), Pt/C 5% (240 mg), formic acid 96% (1.6 mL,40 mmol), triethylamine (15 mL, 108 mmol)), 0–4 °C.
[b] Method E: **9** (5 mmol), K_2CO_3 (10 mmol), MeI (15 mmol) in acetone (20 mL), RT, 24 h.
[c] Method D: **6e** (0.5 mmol) in EtOH (6 mL), Et_3B (1 M, 0.85 mL), RT, 24 h.

produced arenesulfonamides **9a–d** (Table 2, entries 1–4) in good yields. As expected, reduction of **6e**, ($R_1=NO_2$) produced simultaneous reduction of the nitro group and only 4% of compound **9e** was isolated (entry 5). Finally, the product **9e** was satisfactorily obtained (70%), in the presence of BEt_3/EtOH, at room temperature (entry 6, method D). The process, probably, involves in situ generation of ethoxydiethylborane as previously described.[9]



Scheme 6.

Optimal conditions for radical *ipso*-substitution with TTMSS and AIBN were studied and the results are shown in Scheme 6 and Table 3. AIBN (2 mmol) in *m*-xylene (10 mL) was added dropwise over 20 h to a stirred solution, at 80 °C, of **11a** (0.5 mmol) and TTMSS (2 mmol) in *m*-xylene (2 mL). After 7 h, additional TTMSS (2 mmol) was added in one portion. When the addition was complete, the mixture was stirred at the same temperature, for a further 24 h. In this case, cyclized **7a** (48%) and the desired compound **5a** (25%) were obtained (Table 3, entry 1, method F). Similar results were observed on slow addition of TTMSS (entry 2, method G). The best results were obtained by slow addition (29 h) of a solution of AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) to a stirred solution, at 80 °C, of **11a** (0.5 mmol) in *m*-xylene (2 mL) (entry 3, method H). The reaction did not go to completion (40% starting material was recovered

Table 3. Compounds **5** and 7 were obtained

Entry	R_1	Starting material	**5**, Yield (%)	**7**, Yield (%)	**10**, Yield (%)	Method
1	H	**11a**	25	48	—	F[a]
2	H	**11a**	28	34		G[b]
3	H	**11a**	67	20	—	H[c]
4	H	**11a**	11	40		I[d]
5	H	**11a**	17	57		J[e]
6	CH_3	**11b**	63	18		H[c]
7	OCH_3	**11c**	60	13		H[c]
8	Cl	**11d**	50	20		H[c]
9	NO_2	**11e**	33	—		H[c]
10	H	**9a**		33	7	H[c]

[a] Method F: AIBN (2 mmol) in *m*-xylene (10 mL) was added over 20 h to a stirred solution at 80 °C, of **11a** (0.5 mmol) and TTMSS (2 mmol) in *m*-xylene (2 mL); after 7 h, TTMSS (2 mmol) in one portion was added, 80 °C for futher 24 h.
[b] Method G: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) was added over 20 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[c] Method H: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (10 mL) was added over 29 h to a stirred solution at 80 °C of **11** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[d] Method I: AIBN (2 mmol) and TTMSS (2 mmol) in *m*-xylene (10 mL) was added over 29 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.
[e] Method J: AIBN (2 mmol) and TTMSS (4 mmol) in *m*-xylene (20 mL) was added over 29 h to a stirred solution at 80 °C of **11a** (0.5 mmol) in *m*-xylene (2 mL), 80 °C for futher 24 h.

unchanged) when only 2 equiv of TTMSS (1 mmol) were used (entry 4, method I). When the reaction was carried out in more diluted conditions (entry 5, method J) only 17% yield of substituted compound **5a** was detected.

Method H was also applied to compounds **11b–e** and the results are summarized in Table 3 (entries 6–9). When the reaction was carried out using **11e** as the starting material (entry 9), the reaction mixture appeared very complex and only **5e** was obtained, albeit in poor yield. In general terms, the presence of an electron-withdrawing substituents in the *para*-position of the sulfonyl group led to lower yields in the *ipso*-substitution product (entries 8 and 9, Table 3). In contrast, an electron-donating substituent on the benzene-sulfonyl moiety produced higher yields of derivatives **5**. Additionally, the π-excessive character of 2-azinylimino-pyridine moiety on the heterocyclic side, seems to facilitate the rearrangement to biaryls, both effects being in agreement with previously reported *ipso*-substitutions in arenesulfonamides.[8]

3. Conclusions

Pyridinium *N*-2′-pyridylaminide is a suitable starting material to produce halo pyridin-2-yl benzenesulfonamides through halogenation, sulfonylation and N–N reduction in very mild conditions. The method, combined with *N*-methylation and cyclization, by a radical *ipso*-substitution mechanism, in the presence of TTMSS/AIBN, yields 3-aryl-2-aminopyridines in good yield. In agreement with previously reported observations, the presence of electron-donating substituents on both aromatics rings seems to facilitate the rearrangement to biaryls.

4. Experimental

General methods. 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. Pyridinium *N*-aminides **1a**[3b] and **1b**[3c] have been previously described.

4.1. Reaction de aminide 1b with arene sulfonyl chlorides

General method, method A. To a solution of aminide **1b** (0.285 g, 1 mmol) in acetone (5 mL) was added the corresponding sulfonyl chloride (3 mmol for compounds **6a**,**b**,**d**,**e** and 6 mmol for compound **6c**) The mixture was stirred at room temperature until starting material could not be detected by TLC (24 h for compounds **6a–d** and only 1 h for compound **6e**). The resulting solid was filtered off and washed with dry acetone.

4.1.1. *N*-[Benzenesulfonyl-(3′-bromo-5′-chloro-pyridin-2-yl)amino] pyridinium chloride 6a. White solid (364 mg, 79%), mp 170–175 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.34 (d, 2H, *J*=6.2 Hz), 8.90 (t, 1H, *J*=8.0 Hz), 8.65 (d, 1H, *J*=1.8 Hz), 8.58 (d, 1H, *J*=1.8 Hz), 8.45 (at, 2H, *J*=7.7 Hz), 7.98 (t, 1H, *J*=7.6 Hz), 7.82 (d, 2H, *J*=7.6 Hz), 7.76 (at, 2H, *J*=7.6 Hz); MS (ESI) *m*/*z* (relative intensity) 424, 426, 428 [(M^+) 92, 100, 41], 284, 286, 288 (23, 30, 8); Anal. Calcd for $C_{16}H_{12}BrCl_2N_3O_2S$ 461.17: C, 41.67; H, 2.62; N, 9.11; S, 6.95%. Found: C, 41.93; H, 2.77; N, 9.41; S, 6.84%.

4.1.2. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(toluene-4″-sulfonyl)-amino] pyridinium chloride 6b. White solid (314 mg, 66%), mp 175–180 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.18 (d, 2H, *J*=5.5 Hz), 8.76 (t, 1H, *J*=7.8 Hz), 8.52 (d, 1H, *J*=2.2 Hz), 8.44 (d, 1H, *J*=2.2 Hz), 8.12 (dd, 2H, *J*=7.8, 5.5 Hz), 7.56 (d, 2H, *J*=8.4 Hz), 7.44 (d, 2H, *J*=8.4 Hz) 2.43 (s, 3H); MS (ESI) *m*/*z* (relative intensity) 438, 440, 442 [(M^+) 96, 100, 41], 284, 286, 288 (16, 21, 5); Anal. Calcd for $C_{17}H_{14}BrCl_2N_3O_2S$ 475.19: C, 42.97; H, 2.97; N, 8.84; S, 6.75%. Found: C, 42.93; H, 2.78; N, 8.61; S, 6.84%.

4.1.3. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-methoxy-benzenesulfonyl)-amino] pyridinium chloride 6c. White solid (319 mg, 65%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.31 (dd, 2H, *J*=5.5, 1.2 Hz), 8.88 (tt, 1H, *J*=6.7, 1.2 Hz), 8.65 (d, 1H, *J*=2.2 Hz), 8.56 (d, 1H, *J*=2.2 Hz), 8.26 (dd, 2H, *J*=6.7, 5.5 Hz), 7.74 (d, 2H, *J*=7.1 Hz), 7.22 (d, 2H, *J*=7.1 Hz), 4.00 (s, 3H); MS (ESI) *m*/*z* (relative intensity) 454, 456, 458 [(M^+) 73, 100, 31], 284, 286, 288 (9, 11, 3); Anal. Calcd for $C_{17}H_{14}BrCl_2N_3O_3S$ 491.19: C, 41.57; H, 2.87; N, 8.55; S, 6.82%. Found: C, 41.63; H, 2.70; N, 8.31; S, 6.85%.

4.1.4. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-chloro-benzenesulfonyl)-amino] pyridinium chloride 6d. White solid (263 mg, 53%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.36 (d, 2H, *J*=6.3 Hz), 8.92 (t, 1H, *J*=7.7 Hz), 8.66 (d, 1H, *J*=1.3 Hz), 8.58 (d, 1H, *J*=1.3 Hz), 8.30 (dd, 2H, *J*=7.7, 6.3 Hz), 7.80 (m, 4H); MS (ESI) *m*/*z* (relative intensity) 458, 460, 462 [(M^+) 83, 100, 76], 284, 286, 288 (16, 21, 5); Anal. Calcd for $C_{16}H_{11}BrCl_3N_3O_2S$ 495.61: C, 38.78; H, 2.24; N, 8.48; S, 6.47%. Found: C, 38.68; H, 2.50; N, 8.38; S, 6.66%.

4.1.5. *N*-[(3′-Bromo-5′-chloro-pyridin-2-yl)(4″-nitro-benzenesulfonyl)-amino] pyridinium chloride 6e. White solid (329 mg, 65%), mp 115–120 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.40 (dd, 2H, *J*=6.6, 1.1 Hz), 8.94 (tt, 1H, *J*=7.8, 1.1 Hz), 8.66 (d, 1H, *J*=2.1 Hz), 8.62 (d, 1H, *J*=2.1 Hz), 8.56 (d, 2H, *J*=6.9 Hz), 8.30 (dd, 2H, *J*=7.8, 6.6 Hz), 8.10 (d, 2H, *J*=6.9 Hz); MS (ESI) *m*/*z* (relative intensity) 469, 471, 473 [(M^+) 72, 100, 35], 284, 286, 288 (26, 33, 10); Anal. Calcd for $C_{16}H_{11}BrCl_2N_4O_4S$ 506.16: C, 37.97; H, 2.19; N, 11.07; S, 6.34%. Found: C, 38.09; H, 2.26; N, 11.38; S, 6.55%.

4.2. Reduction of substituted *N*-arenesulfonyl *N*-(3′-bromo-5′-chloro-pyridin-2-yl) pyridinium chlorides

General method, method C. Platinum on charcoal (5%) (240 mg) was suspended in a solution of the pyridinium salts (0.5 mmol) in CH_3CN (12 mL) and cooled in an ice bath. A solution of formic acid (96%, 1.6 mL) in CH_3CN (5 mL) and then triethylamine (15 mL) in the same solvent (12 mL) were added dropwise. The resulting suspension was allowed to warm up to room temperature and filtered through Celite. The filtrate was evaporated and the residue dissolved in water, made basic with solid K_2CO_3 and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The corresponding benzenesulfonamide was purified by flash chromatography and crystallization from diethyl ether/hexanes.

4.2.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)benzenesulfonamide 9a. The general procedure (method C) using **6a** (231 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (80:20), $R_f \approx 0.48$], a white solid (122 mg, 70%), mp 146–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 2H, $J=7.4$ Hz), 8.10 (d, 1H, $J=2.1$ Hz), 7.75 (d, 1H, $J=2.1$ Hz), 7.58 (t, 1H, $J=8.0$ Hz), 7.48 (dd, 2H, $J=8.0$, 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 145.2, 141.8, 140.1, 133.4, 133.0, 128.6, 128.4, 107.0; MS (EI) *m*/*z* (relative intensity) 346, 348, 350 [(M^+), 0.4, 0.6, 0.2], 281, 283, 285 (27, 35, 9), 77 (100); Anal. Calcd for $C_{11}H_8BrClN_2O_2S$ 347.62: C, 38.01; H, 2.32; N, 8.06; S, 9.22%. Found: C, 37.72; H, 2.56; N, 7.88; S, 9.16%.

4.2.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methyl-benzenesulfonamide 9b. The general procedure (method C) using **6b** (238 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.28$], a white solid (148 mg, 82%), mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, $J=2.1$ Hz), 7.98 (d, 2H, $J=8.2$ Hz), 7.74 (d, 1H, $J=2.1$ Hz), 7.62 (bs, 1H), 7.28 (d, 2H, $J=8.2$ Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.2, 144.3, 140.0, 136.0, 129.2, 128.5, 125.1, 106.7, 21.7; MS (EI) *m*/*z* (relative intensity) 360, 362, 364 [(M^+), 0.4, 0.6, 0.1], 295, 297, 299 (57, 74, 18), 91 (100); Anal. Calcd for $C_{12}H_{10}BrClN_2O_2S$ 361.65: C, 39.85; H, 2.79; N, 7.75; S, 8.87%. Found: C, 39.65; H, 2.83; N, 7.48; S, 8.40%.

4.2.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methoxy-benzenesulfonamide 9c. The general procedure (method C) using **6c** (246 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.45$], a white solid (102 mg, 54%), mp 155–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, $J=2.0$ Hz), 8.02 (d, 2H, $J=8.9$ Hz), 7.70 (d, 1H, $J=2.0$ Hz), 6.92 (d, 2H, $J=8.9$ Hz), 5.00 (bs, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 163.4, 146.5, 145.2, 140.0, 134.6, 130.7, 125.5, 113.7, 106.6, 55.5; MS (EI) *m*/*z* (relative intensity) 311, 313, 315 (74, 100, 27), 171 (27), 107 (11), 77 (86); Anal. Calcd for $C_{12}H_{10}BrClN_2O_3S$ 377.65: C, 38.17; H, 2.67; N, 7.42; S, 8.49%. Found: C, 38.33; H, 2.77; N, 7.41; S, 8.24%.

4.2.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-chloro-benzenesulfonamide 9d. The general procedure (method C) using **6d** (248 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization [silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.37$], a white solid (103 mg, 54%) mp 145–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, $J=2.0$ Hz), 8.05 (d, 2H, $J=8.5$ Hz), 7.74 (d, 1H, $J=2.0$ Hz), 7.44 (d, 2H, $J=8.5$ Hz), 5.00 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.2, 140.3, 139.9, 137.7, 130.0, 128.9, 126.0, 106.9; MS (EI) *m*/*z* (relative intensity) 315, 317, 319 (61, 100, 46), 111 (73), 75 (43); Anal. Calcd for $C_{11}H_7BrCl_2N_2O_2S$ 382. 06: C, 34.58; H, 1.85; N, 7.33; S, 8.39%. Found: C, 34.75; H, 1.90; N, 7.37; S, 8.01%.

4.2.5. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-nitro-benzenesulfonamide 9e. The general procedure (method C) using **6e** (253 mg) as the starting pyridinium salt gave, after flash chromatography and crystallization (silica gel, hexanes/ethyl acetate (70:30), $R_f \approx 0.31$), a white solid (8 mg, 4%). *Method D*. Compound **6e** (0.5 mmol, 253 mg) was dissolved in EtOH (6 mL). The solution was flushed with argon and stirred at room temperature. A solution of triethylborane in hexane (1.0 M, 0.85 mL, 0.85 mmol) was then added dropwise. After stirring for 2 h at room temperature, air (0.85 mL) was added with a syringe and stirring was maintained at the same temperature for further 24 h. Purification by flash chromatography and crystallization furnished **9e** (137 mg, 70%), mp 202–203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, 2H, $J=6.8$ Hz), 8.32 (d, 2H, $J=6.8$ Hz), 8.11 (d, 1H, $J=2.4$ Hz), 7.79 (d, 1H, $J=2.4$ Hz), 7.68 (bs, 1H); MS (EI) *m*/*z* (relative intensity) 326, 328, 330 (76, 100, 26), 282 (35), 248 (23), 208 (53), 76 (41); Anal. Calcd for $C_{11}H_7BrClN_3O_4S$ 392.62: C, 33.65; H, 1.80; N, 10.70; S, 8.17%. Found: C, 33.32; H, 1.84; N, 10.47; S, 7.98%.

4.3. Reaction of arenesulfonamides with iodomethane

General method, method E: To a dispersion of corresponding *N*-unsubstituted arenesulfonamide **9a–e** (5 mmol) and potassium carbonate (10 mmol, 1.38 g) in acetone (20 mL), was added iodomethane (15 mmol, 0.93 mL). The mixture was stirred at room for 24 h and all starting material was consumed (TLC analysis). Purification by flash chromatography furnished a white solid, which was crystallized from hexanes.

4.3.1. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-methyl-benzenesulfonamide 11a. The general procedure (method E) using **9a** (1.738 g) as starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.86$], a white solid (1.310 g, 72%), mp 145–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 1H, $J=2.3$ Hz), 8.02 (d, 1H, $J=2.3$ Hz), 7.83 (d, 2H, $J=7.5$ Hz), 7.62 (t, 1H, $J=7.3$ Hz), 7.52 (dd, 2H, $J=7.5$, 7.3 Hz), 3.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 144.1, 139.7, 135.3, 131.0, 129.6, 126.6, 126.4, 119.9, 34.8; MS (EI) *m*/*z* (relative intensity) 295, 297, 299 (61, 80, 20), 221 (25), 77 (100); Anal. Calcd for $C_{12}H_{10}BrClN_2O_2S$ 361.65: C, 39.85; H, 2.79; N, 7.75; S, 8.87%. Found: C, 40.10; H, 2.97; N, 7.70; S, 8.64%.

4.3.2. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′,*N*-dimethyl-benzene sulfonamide 11b. The general procedure (method E) using **9b** (1.808 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.90$], a white solid (1.126 g, 60%), mp 120–125 °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), 7.69 (d, 2H, $J=8.2$ Hz), 7.30 (d, 2H, $J=8.2$ Hz), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 145.9, 143.7, 141.5, 134.1, 131.3, 129.2, 128.4, 121.8, 36.7, 21.6; MS (EI) *m/z* (relative intensity) 309, 311, 313 (50, 66, 17), 91 (100); Anal. Calcd for $C_{13}H_{12}BrClN_2O_2S$ 375.67: C, 41.56; H, 3.22; N, 7.46; S, 8.54%. Found: C, 41.40; H, 3.39; N, 7.20; S, 8.71%.

4.3.3. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-methoxy-*N*-methyl-benzenesulfonamide 11c. The general procedure (method E) using **9c** (1.888 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.40$], a white solid (1.194 g, 61%), mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, 1H, $J=2.2$ Hz), 7.99 (d, 1H, $J=2.2$ Hz), 7.72 (d, 2H, $J=8.8$ Hz), 6.95 (d, 2H, $J=8.8$ Hz), 3.84 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 151.2, 146.1, 141.6, 131.3, 130.6, 121.8, 113.8, 109.0, 55.4, 36.6; MS (EI) *m/z* (relative intensity) 325, 327, 329 (67, 96, 33), 171 (56), 107 (99), 92 (71), 77 (100); Anal. Calcd for $C_{13}H_{12}BrClN_2O_3S$ 391.67: C, 39.87; H, 3.09; N, 7.15; S, 8.19%. Found: C, 40.06; H, 3.13; N, 7.12; S, 7.92%.

4.3.4. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-4′-chloro-*N*-methyl-benzenesulfonamide 11d. The general procedure (method E) using **9d** (1.910 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.64$], a white solid (1.406 g, 71%), mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, 1H, $J=2.2$ Hz), 7.98 (d, 1H, $J=2.2$ Hz), 7.75 (d, 2H, $J=8.5$ Hz), 7.46 (d, 2H, $J=8.5$ Hz), 3.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.1, 141.7, 139.4, 135.9, 131.6, 129.8, 128.9, 121.7, 36.6; MS (EI) *m/z* (relative intensity) 329, 331, 333 (53, 86, 40), 111 (100), 75 (90); Anal. Calcd for $C_{12}H_9BrCl_2N_2O_2S$ 396.09: C, 36.39; H, 2.29; N, 7.07; S, 8.10%. Found: C, 36.07; H, 2.37; N, 7.06; S, 7.10%.

4.3.5. *N*-(3-Bromo-5-chloro-pyridin-2-yl)-*N*-methyl-4′-nitro-benzenesulfonamide 11e. The general procedure (method E) using **9e** (1.910 g) as the starting material gave, after flash chromatography and crystallization [silicagel, hexanes/ethyl acetate (70:30), $R_f \approx 0.83$], a white solid (1.951 g, 96%), mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, 2H, $J=8.7$ Hz), 8.26 (d, 1H, $J=2.2$ Hz), 8.02 (m, 3H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 150.2, 146.4, 143.4, 142.1, 132.3, 129.8, 123.9, 121.8, 37.0; MS (EI) *m/z* (relative intensity) 340, 342, 344 (78, 100, 29), 219, 221, 22 (63, 75, 19), 190, 192, 194 (30, 44, 17); Anal. Calcd for $C_{12}H_9BrClN_3O_4S$ 406.64: C, 35.44; H, 2.23; N, 10.33; S, 7.89%. Found: C, 35.27; H, 2.33; N, 10.12; S, 7.91%.

4.4. Radical reaction of arenesulfonamides

General method, method H. A solution of TTMSS (0.498 g, 2 mmol) and AIBN (0.328 g, 2 mmol) in *m*-xylene (10 mL) was added dropwise by a syringe pump during 29 h to a stirred solution of appropriate arenesulfonamide (**9a** or **11a–e**, 0.5 mmol) in *m*-xylene (2 mL), at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 24 h, after which the starting material had been consumed (TLC analysis). The solution was concentrated and the crude mixture was separated by flash chromatography [silicagel, hexanes/ethyl acetate (70:30)], yielding the pure compounds.

4.4.1. (5-Chloro-3-phenyl-pyridin-2-yl)-methyl amine 5a and 3-chloro-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7a. The general procedure (method H) using **11a** as the starting sulfonamide (181 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5a** and **7a** were obtained. **5a** yellow oil, $R_f \approx 0.39$ (73 mg, 67%); ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (d, 1H, $J=2.5$ Hz), 7.51 (dd, 1H, $J=7.8$, 7.3 Hz), 7.44 (tt, 1H, $J=7.3$, 1.4 Hz), 7.42 (dd, 1H, $J=7.8$, 1.4 Hz), 2.87 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 155.2, 144.0, 136.6, 136.5, 130.1, 129.1, 128.7, 128.1, 124.4, 118.7, 28.9; MS (EI) *m/z* (relative intensity) 218, 220 [(M^+) 11, 4], 202 (2), 217, 219 (20, 4), 128 (31), 111 (24), 82 (66), 58 (100). **7a** White solid, $R_f \approx 0.61$ (28 mg, 20%, diethyl ether/hexanes), mp 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, $J=2.4$ Hz), 8.28 (d, 1H, $J=2.4$ Hz), 8.09 (dd, 1H, $J=7.9$, 1.3 Hz), 7.94 (d, 1H, $J=8.1$ Hz), 7.77 (ddd, 1H, $J=8.1$, 7.1, 1.3 Hz), 7.67 (dd, 1H, $J=7.9$, 7.1 Hz) 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.3, 133.8, 132.6, 132.4, 129.4, 128.8, 126.7, 125.1, 122.4, 118.5, 28.7; MS (EI) *m/z* (relative intensity) 280, 282 (16, 6), 215, 217 (100, 37), 73 (16); Anal. Calcd for $C_{12}H_9ClN_2O_2S$ 280.73: C, 51.34; H, 3.23; N, 9.98; S, 11.42%. Found: C, 51.33; H, 2.95; N, 10.06; S, 11.56%.

4.4.2. (5-Chloro-3-*p*-tolyl-pyridin-2-yl)-methyl-amine 5b and 3-chloro-6,10-dimethyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7b. The general procedure (method H) using **11b** as the starting sulfonamide (188 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5b** and **7b** were obtained. **5b** yellow oil, $R_f \approx 0.73$ (74 mg, 63%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.92 (d, 1H, $J=2.5$ Hz), 7.27 (m, 4H), 7.24 (d, 1H, $J=2.5$ Hz), 2.83 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 149.1, 144.8, 139.3, 137.5, 134.7, 130.8, 129.6, 121.9, 119.8, 28.9, 21.2; MS (EI) *m/z* (relative intensity) 231, 232 [(M^+) 26, 11], 231, 233 (44, 21), 103 (13). **7b** White solid, $R_f \approx 0.65$ (26 mg, 18%, diethyl ether/hexanes), mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, 1H, $J=2.4$ Hz), 8.25 (d, 1H, $J=2.4$ Hz), 7.96 (d, 1H, $J=8.1$ Hz), 7.71 (bs, 1H, w ½=2 Hz), 7.45 (dd, 1H, $J=8.1$, 2.0 Hz), 3.60 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.1, 143.5, 132.3, 131.3, 130.2, 128.8, 126.6, 125.4, 122.5, 118.5, 28.4, 21.9; MS (EI) *m/z* (relative intensity) 294, 296 [(M^+) 17, 3], 229, 231 (100, 30); Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$ 294.76: C, 52.97; H, 3.76; N, 9.50; S, 10.88%. Found: C, 52.76; H, 4.01; N, 9.55; S, 10.83%.

4.4.3. [5-Chloro-3-(4-methoxy-phenyl)-pyridin-2-yl]-methyl-amine 5c and 3-chloro-6-methoxy-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7c. The general procedure (method H) using **11c** as the starting sulfonamide (196 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5c** and **7c** were obtained. **5c** yellow oil, $R_f \approx 0.55$ (75 mg, 60%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (d, 1H, $J=$

2.5 Hz), 7.29 (d, 2H, J=8.8 Hz), 7.22 (d, 1H, J=2.5 Hz), 7.01 (d, 2H, J=8.8 Hz), 3.82 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.2, 156.8, 144.8, 137.6, 131.1, 129.8, 125.5, 119.9, 115.7, 30.6, 24.2; MS (EI) m/z (relative intensity) 248, 250 [(M^++1) 73, 24], 247, 249 [(M^+) 100, 41]. **7c** White solid, R_f≈0.39 (20 mg, 13%, diethyl ether/hexanes), mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 1H, J=2.4 Hz), 8.21 (d, 1H, J=2.4 Hz), 8.00 (d, 1H, J=8.8 Hz), 7.33 (d, 1H, J=2.4 Hz), 7.15 (dd, 1H, J=8.8, 2.4 Hz), 3.97 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 148.2, 147.5, 132.5, 132.4, 130.9, 126.6, 124.7, 118.4, 115.2, 109.9, 55.8, 28.3; MS (EI) m/z (relative intensity) 311, 313 [(M^++1) 4, 2], 310, 312 [(M^+) 23, 9], 246, 248 (16, 5), 245, 247 (100, 34), 231 (21), 202 (22); Anal. Calcd for $C_{13}H_{11}ClN_2O_3S$ 310.76: C, 50.24; H, 3.57; N, 9.01; S, 10.32%. Found: C, 50.40; H, 3.64; N, 9.22; S, 10.56%.

4.4.4. [5-Chloro-3-(4-chloro-phenyl)-pyridin-2-yl]-methyl-amine 5d and 3,6-dichloro-10-methyl-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7d. The general procedure (method H) using **11d** as the starting sulfonamide (198 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **5d** and **7d** were obtained. **5d** yellow oil, R_f≈0.71 (58 mg, 46%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (d, 1H, J=2.4 Hz), 7.48 (d, 2H, J=8.5 Hz), 7.38 (d, 2H, J=8.5 Hz), 7.28 (d, 1H, J=2.4 Hz), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 145.6, 137.7, 136.4, 135.2, 131.5, 130.3, 124.1, 119.9, 28.9; MS (EI) m/z (relative intensity) 252, 254 [(M^+) 15, 10], 251, 253 (25, 11), 71 (64), 69 (100), 73 (63). **7d** White solid, R_f≈0.68 (34 mg, 21%, diethyl ether/hexanes), mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ 8.44 (d, 1H, J=1.2 Hz), 8.21 (d, 1H, J=1.4 Hz), 7.98 (d, 1H, J=8.4 Hz), 7.87 (d, 1H, J=1.2 Hz), 7.61 (dd, 1H, J=8.4, 1.4 Hz), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 148.0, 139.3, 132.6, 132.3, 130.7, 129.6, 127.0, 125.2, 124.2, 117.6, 28.6; MS (EI) m/z (relative intensity) 314, 316 [(M^+) 13, 10], 249, 251 (100, 65); Anal. Calcd for $C_{12}H_8Cl_2N_2O_2S$ 315.18: C, 45.73; H, 2.56; N, 8.89; S, 10.17%. Found: C, 45.94; H, 2.66; N, 8.79; S, 9.98%.

4.4.5. [5-Chloro-3-(4-nitro-phenyl)-pyridin-2-yl]-methyl-amine 5e. The general procedure (method H) using **11e** as the starting sulfonamide (203 mg) gave a after purification by flash chromatography, only pure compound **5e**. Yellow solid, R_f≈0.54 (43.5 mg, 33%, hexanes), mp 128–130 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.00 (d, 1H, J=2.5 Hz), 7.62 (d, 2H, J=8.4 Hz), 7.49 (d, 2H, J=8.4 Hz), 7.36 (d, 1H, J=2.5 Hz), 2.88 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.3, 148.6, 145.6, 137.9, 137.7, 130.3, 127.4, 121.7, 120.0, 28.9; MS (EI) m/z (relative intensity) 263, 265 [(M^+) 3, 1], 248 (100), 247 (55); Anal. Calcd for $C_{12}H_{10}ClN_3O_2$ 263.69: C, 54.66; H, 3.82; N, 15.94%. Found C, 54.94; H, 3.88; N, 16.17%.

4.4.6. 3-Chloro-10H-9-thia-1,10-diaza-phenanthrene 9,9-dioxide 7f and *N*-(5-chloro-pyridin-2-yl)benzene-sulfonamide 10. The general procedure (method H) using **9a** as unsubstituted sulfonamide (174 mg) gave a mixture of products. After separation by flash chromatography, pure compounds **7f** and **10** were obtained. **7f** pale yellow solid, R_f≈0.66 (44 mg, 33%, diethyl ether/hexanes), mp >250 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (d, 1H, J=2.3 Hz), 8.37 (d, 1H, J=7.1 Hz), 8.36 (d, 1H, J=2.3 Hz), 7.94 (dd, 1H, J=7.4, 1.8 Hz), 7.75 (m, 2H), 4.50 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 148.8, 135.2, 133.0, 131.3, 129.6, 127.5, 124.7, 121.9, 117.0, 108.2; MS (EI) m/z (relative intensity) 267, 269 [(M^++1) 9, 4], 266, 268 [(M^+) 62, 24], 203, 205 (19, 9), 202, 204 (100, 52), 140 (69), 113 (31); Anal. Calcd for $C_{11}H_7ClN_2SO_2$ 266.71: C, 49.54; H, 2.65; N, 10.50, S, 12.02%. Found C, 49.66; H, 2.84; N, 10.71; S, 11.86%. **10** white solid, R_f≈0.62 (10 mg, 7%, hexanes), mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H, J=2.3 Hz), 8.20 (bs, 1H), 7.81 (d, 2H, J=7.1 Hz), 7.62 (dd, 1H, J=8.5, 2.3 Hz), 7.55 (d, 1H, J=8.5 Hz), 7.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 146.9, 139.5, 138.7, 133.3, 133.0, 129.2, 127.0, 113.0; MS (EI) m/z (relative intensity) 268, 270 [(M^+) 3, 1], 203, 205 (60, 21), 77 (100); Anal. Calcd for $C_{11}H_9ClN_2O_2S$ 268.72: C, 49.17; H, 3.38; N, 10.42; S, 11.93%. Found: C, 48.97; H, 3.65; N, 10.46; S, 12.07%.

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