Synthesis Y. Jeong et al. Paper

A Novel Synthesis of *N*-Sulfonylformamidines from *N*-Sulfonylsulfonamides

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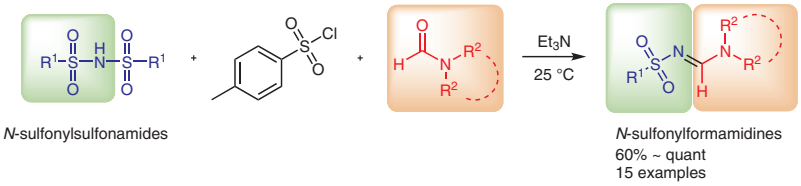

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Abstract *N*-Sulfonylformamidines were synthesized from *N*-sulfonylsulfonamides by reacting with *p*-toluenesulfonyl chloride (TsCl) and *N*,*N*-disubstituted formamides. In this reaction, it was expected that mixing TsCl with the *N*,*N*-disubstituted formamide would generate an iminium salt (Vilsmeier reagent). The reaction avoids the use of metal catalysts and hazardous reagents, and the desired *N*-sulfonylformamidines were obtained in 60% to quantitative yields.

Key words *N*-sulfonylformamidine, *N*-sulfonylsulfonamide, sulfonamide, sulfonyl chloride, Vilsmeier reagent

N-Sulfonylformamidines are widely used synthetic intermediates for medicinal compounds with immense biological importance. These compounds have emerged as bioactive pharmacophores with antiresorptive, antitumor, and antiproliferative properties.[1] In addition, *N*-sulfonylformamidines, shown in Figure 1, are efficient inhibitors of gastric acid incretion.[2] Furthermore, *N*-sulfonylformamidines have served as useful coordinating ligands.[3]

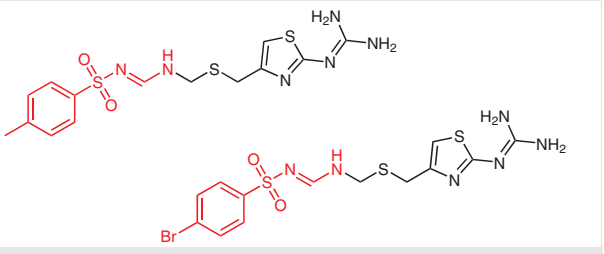
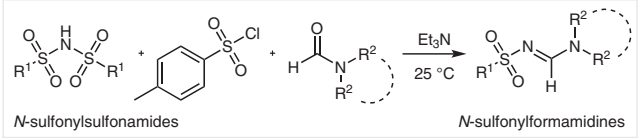


Figure 1 Examples of compounds containing the *N*-sulfonylformamidine moiety

Several synthetic methods to generate *N*-sulfonylformamidines from *N*-sulfonamides,[4] azides,[5] and isocyanates[6] have previously been reported. In particular, direct condensation of sulfonamide and formamide with Vilsmeier reagent by phosphoryl chloride,[7] thionyl chloride,[8] or oxalyl chloride[9] is the most straightforward and atom-economic method for the synthesis of *N*-sulfonylformamidines. However, the reported methods require high temperatures, anhydrous conditions, corrosive reagents, and metal catalysts,[10] which are drawbacks to their utility. Polanc and coworkers reported the transformation of *N*-acylsulfonamides into *N*-sulfonylformamidines using oxalyl chloride.[9] The reaction can be performed in the presence of various functional groups, and it is a very selective procedure for the preparation of *N*-sulfonylformamidines. But this method requires 2.5 equivalent of oxalyl chloride to complete the reaction. We were interested in finding a better route for the synthesis of *N*-sulfonylformamidines under mild reaction conditions that would be more convenient and efficient. It was inquisitive to find out whether *N*-sulfonylsulfonamides can be converted to *N*-sulfonylformamidines or not. Here, we report a novel method for the synthesis of *N*-sulfonylformamidines starting from *N*-sulfonylsulfonamides using *p*-toluenesulfonyl chloride (TsCl) and various *N*,*N*-disubstituted formamides (Scheme 1). To date, there has been no report on the synthesis of *N*-sulfonylformamidines from *N*-sulfonylsulfonamides.



Scheme 1 Synthesis of *N*-sulfonylformamidines from various substituted *N*-sulfonylsulfonamides

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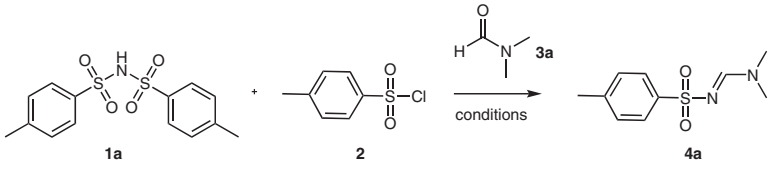
Prior to the *N*-sulfonylformamidine synthesis, we synthesized various *N*-sulfonylsulfonamide derivatives from sulfonamide and sulfonyl chloride. Interestingly, when $TsNH_2$ (1.0 equiv) was reacted with TsCl (1.2 equiv) and base in DMF, *N*-sulfonylformamidine was obtained along with *N*-sulfonylsulfonamide. It was anticipated that the use of slightly excess TsCl participated in the formation of *N*-sulfonylformamidine from *N*-sulfonylsulfonamide.

The reaction conditions were optimized with 4-methyl-*N*-[(4-methylphenyl)sulfonyl]benzenesulfonamide (**1a**) and TsCl as reagents to form the iminium salt in DMF (Table 1). First, the reaction was optimized using NaH, triethylamine, or without base and varying the amount of TsCl. The amount of reagent was critical for reaction efficiency; thus, the reactivity related to the amount of TsCl was tested. Unexpectedly, it was confirmed that the reaction proceeded with just 0.2 equivalent of TsCl (Table 1, entry 3). However, to form sufficient iminium salt to complete the reaction, it was necessary to use 0.5 equivalent of TsCl (entry 2). In the absence of base, the desired product was obtained in 86% yield, but when using a base, the product was obtained in quantitative and 96% yield (entries 4, 5). Using either NaH or triethylamine as base, the reaction gave similar results; therefore, we chose the milder triethylamine base for the synthesis of *N*-sulfonylformamidines. The reactivity was excellent regardless of reaction temperature.

At either 60 °C or room temperature, the reaction gave an excellent yield within 4 hours (Table 1, entries 5, 7). The reaction time was determined based on the disappearance of the starting material by thin layer chromatography analysis. Furthermore, the reactivity of oxalyl chloride as another reagent capable of forming the iminium salt was tested. Oxalyl chloride is known to be a good reagent for making iminium salts; however, when the sulfonylsulfonamide **1a** was reacted with oxalyl chloride (0.5 equiv) and Et_3N in DMF, the product was obtained in 64% yield. Under the optimized reaction conditions, we investigated the substrate scope of the transformation with various *N*-sulfonylsulfonamides **1** and formamide derivatives **3** at 25 °C (Table 2). The desired products **4** were obtained in 60% to quantitative yield. In the cases of *tert*-butyl group and electron-withdrawing groups, such as acetyl, nitro, and chloro substituents on the aromatic ring of the sulfonyl group (Table 2, entries 4–7), the yields were low at 25 °C. In these cases, an increase to 1.5 equivalent of TsCl and to a temperature of 100 °C led to the desired products in 61% to quantitative yields. *N*-Sulfonylformamidines with an aliphatic moiety were also obtained in excellent yields except with a benzyl substituent (Table 2, entries 9–11). Upon increasing the reaction temperature to 100 °C, *N*-sulfonylformamidine **4k** was obtained in 77% yield (entry 11). We also tried the reaction using various substituted formamides **3**. Formamides including *N*,*N*-diethylformamide, 1-pyrrolidinecarboxaldehyde, 1-piperidinecarboxaldehyde, and 4-morpholinecarboxaldehyde gave the corresponding *N*-sulfonylformamidines **4** in 66 to 97% yield (entries 12–15).

Table 1 Optimization Study for the Synthesis of *N*-Sulfonylformamidine **4a**[a]



1a 2 4a

Entry	Base	TsCl (**2**) (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	NaH	1.0	60	4	quant
2	NaH	0.5	60	4	quant
3	NaH	0.2	60	4	62
4	Et_3N	1.0	60	4	quant
5	Et_3N	0.5	60	4	96
6	–	0.5	60	4	86
7	**Et_3N**	**0.5**	**r.t.**	**4**	**97**

[a] Reaction conditions: *N*-sulfonylsulfonamide **1a** (1.68 mmol), base (2.10 mmol), DMF (**3a**; 3.0 mL).
[b] Isolated yield calculated from the equimolar amount of *N*-sulfonylsulfonamide.

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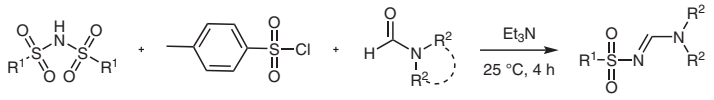
Table 2 Synthesis of Various *N*-Sulfonylformamidines[a]



1 2 3 4

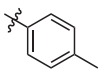
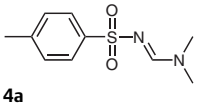
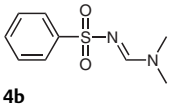
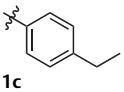
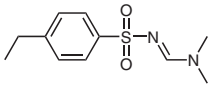
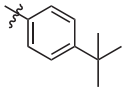
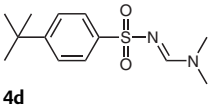
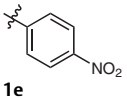
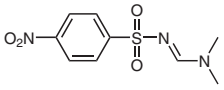
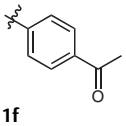
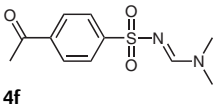
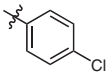
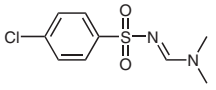
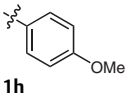
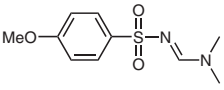
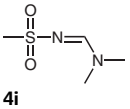
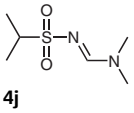
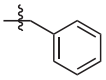
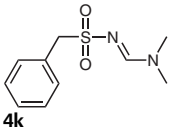
Entry	R^1	Formamide **3**	Product **4**	TsCl (**2**) (equiv)	Yield (%)[b]
1	 **1a**	 **3a**	 **4a**	0.5	97
2	 **1b**	**3a**	 **4b**	0.5	90
3	 **1c**	**3a**	 **4c**	0.5	60
4	 **1d**	**3a**	 **4d**	1.5	88[c]
5	 **1e**	**3a**	 **4e**	1.5	61[c]
6	 **1f**	**3a**	 **4f**	1.5	76[c]
7	 **1g**	**3a**	 **4g**	1.5	quant[c]
8	 **1h**	**3a**	 **4h**	0.5	88
9	 **1i**	**3a**	 **4i**	0.5	quant
10	 **1j**	**3a**	 **4j**	0.5	84
11	 **1k**	**3a**	 **4k**	0.5	77[c]

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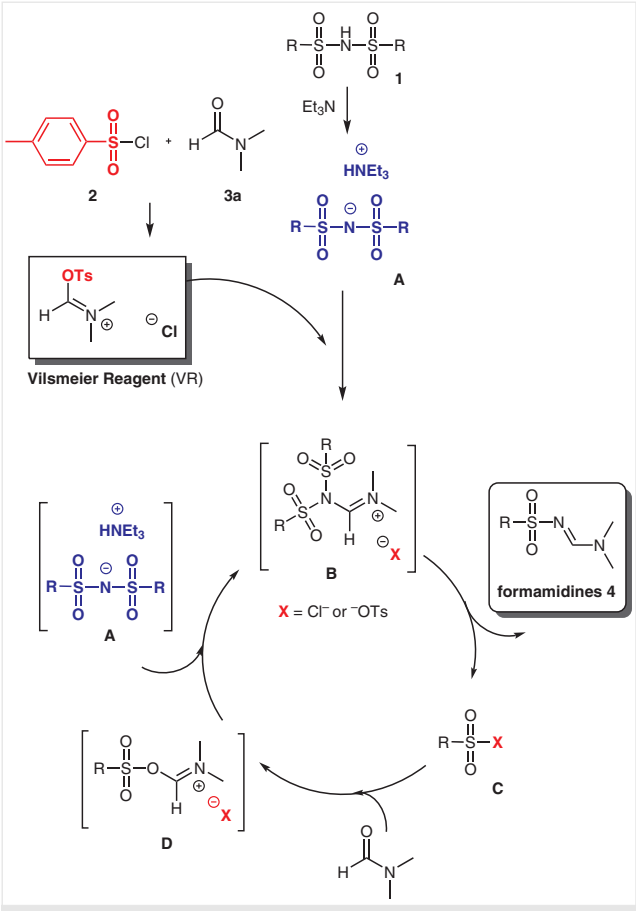
Table 2 (continued)

Entry	R^1	Formamide **3**	Product **4**	TsCl (**2**) (equiv)	Yield (%)[b]
12	**1a**	**3b**	**4l**	0.5	82
13	**1a**	**3c**	**4m**	0.5	97
14	**1a**	**3d**	**4n**	0.5	90
15	**1a**	**3e**	**4o**	0.5	66

[a] Reaction conditions: *N*-sulfonylsulfonamide **1** (1.68 mmol), Et_3N (2.10 mmol), *N*,*N*-disubstituted formamide **3** (3.0 mL), 25 °C.
[b] Isolated yield calculated from the equimolar amount of *N*-sulfonylsulfonamide.
[c] Reaction was carried out at 100 °C.

Based on the results, a plausible mechanism for the synthesis of *N*-sulfonylformamidine is proposed, as shown in Scheme 2. In situ iminium salt formed with TsCl (**2**) in DMF (**3a**)[11] reacts with *N*-sulfonylsulfonamide anion **A** to form intermediate **B**. The counterion X^- in **B** attacks the sulfonyl group to release **C**, generating the desired product **4**. Another DMF reacts with **C** to form intermediate **D**, which can react with *N*-sulfonylsulfonamide anion **A** to complete the reaction cycle. Using 0.5 equivalent of TsCl, the reaction could proceed to completion as suggested by this mechanism.

In summary, reactions were carried out under aerobic conditions at room temperature using TsCl as a reagent to form the iminium salt. In particular, the reactions were carried out with 0.5 equivalent of TsCl and reached to completion in a short reaction time. In addition, a plausible mechanism based on the optimized conditions is presented. Furthermore, the reactions proceeded well with a variety of *N*-sulfonylsulfonamides **1** and formamides **3**. Yields of the reactions with various *N*-sulfonylsulfonamides **1** affected by electronic or steric effects could be improved by controlling the amount of TsCl and the reaction temperature. As a result, *N*-sulfonylsulfonamides **1** with electron-withdrawing groups were obtained in yields ranging from 61 to quantitative, while compounds with electron-donating groups were obtained in yields ranging from 60–97%. In addition, reactions with various substituted formamides proceeded in yields ranging from 66–97%.



Scheme 2 Plausible mechanism for the synthesis of *N*-sulfonylformamidines

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Solvents such as anhydrous DMF and toluene in sure-seal bottles were purchased from Sigma-Aldrich. All reagents including sulfonamides and sulfonyl chlorides were purchased from Sigma-Aldrich or TCI and were used as received. Reaction progress was monitored by TLC. The products *N*-sulfonylsulfonamides and *N*-sulfonylformamidines were characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy. NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 with a Bruker 400 MHz instrument (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). IR spectra were recorded on a Bruker Alpha FT-IR spectrometer. Melting points were determined with a Sanyo Gallenkamp melting point apparatus. HRMS were obtained on a JMS 700 spectrometer and were recorded in EI or FAB mode. *N*-Sulfonylsulfonamides were purified by recrystallization (using hot $CHCl_3$/hexane), and *N*-sulfonylformamidine products were purified by silica gel flash column chromatography.

N-Sulfonylsulfonamides 1; General Procedure

*Method A (for **1a–h**)*: A mixture of the appropriate arylsulfonyl chloride (11.2 mmol), the corresponding arylsulfonamide (12.3 mmol), DMAP (0.274 g, 2.24 mmol), and Et_3N (1.95 mL, 14.0 mmol) in toluene (0.5 M) was kept at 70 °C for 12 h (monitored by TLC). The reaction was quenched with aq 2 M HCl (30 mL) to pH 1. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried (anhydrous $MgSO_4$). The solvent was evaporated, and the crude product mixture was purified by recrystallization using hot $CHCl_3$/hexane to afford the desired product.

*Method B (for **1i–k**)*: The respective alkylsulfonamide (11.2 mmol) and KOH (1.26 g, 22.4 mmol) were added to H_2O (0.2 M), and the mixture was cooled to 0 °C. The appropriate alkylsulfonyl chloride (12.3 mmol) was added dropwise, and the stirred solution was slowly warmed to 60 °C and stirred for 12 h. The solution was then acidified with HCl and kept at low temperature for 12 h to produce a white precipitate, which was collected by filtration. The product obtained was pure enough for direct use in the next step.

4-Methyl-*N*-[(4-methylphenyl)sulfonyl]benzenesulfonamide (1a)[12] CAS Reg. No. 3695-120-9

White solid; yield: 1.53 g (42%); mp 171–172 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.4 (br s, 1 H), 7.56 (d, *J* = 8.0 Hz, 4 H), 7.23 (d, *J* = 8.0 Hz, 4 H), 2.34 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 141.6, 140.9, 128.8, 126.5, 20.9.

N-(Phenylsulfonyl)benzenesulfonamide (1b)[13] CAS Reg. No. 2618-96-4

White solid; yield: 0.699 g (21%); mp 270–271 °C.

IR (neat): 3072, 1360, 1153, 1082, 861, 755 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.44 (br s, 1 H), 7.68 (d, *J* = 7.2 Hz, 4 H), 7.46 (t, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.5, 131.2, 128.6, 126.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{11}NO_4S_2$: 297.0129; found: 297.0131.

4-Ethyl-*N*-[(4-ethylphenyl)sulfonyl]benzenesulfonamide (1c)

White solid; yield: 3.13 g (79%); mp 144–145 °C.

IR (neat): 3153, 2791, 1594, 1361, 1165, 833, 650, 538 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.13 (br s, 1 H), 7.57 (d, *J* = 8.0 Hz, 4 H), 7.24 (d, *J* = 8.0 Hz, 4 H), 2.49 (q, *J* = 7.6 Hz, 4 H), 1.18 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.9, 141.8, 128.1, 127.0, 28.5, 15.8.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{19}NO_4S_2$ + H: 354.0834; found: 354.0836.

4-*tert*-Butyl-*N*-[(4-*tert*-butylphenyl)sulfonyl]benzenesulfonamide (1d) CAS Reg. No. 1355251-10-3

White solid; yield: 1.28 g (28%); mp 207–208 °C.

IR (neat): 3168, 3970, 1593, 1362, 1164, 864, 624, 549 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.5 (br s, 1 H), 7.62 (d, *J* = 8.4 Hz, 4 H), 7.46 (d, *J* = 8.4 Hz, 4 H), 1.29 (s, 18 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.7, 141.6, 126.7, 125.6, 35.2, 31.4.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}NO_4S_2$ + H: 410.1460; found: 410.1458.

4-Nitro-*N*-[(4-nitrophenyl)sulfonyl]benzenesulfonamide (1e)[14] CAS Reg. No. 4009-06-7

White solid; yield: 1.30 g (30%); mp 242–243 °C.

IR (neat): 3192, 1530, 1366, 1159, 874, 739 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.9 (br s, 1 H), 8.24 (d, *J* = 8.8 Hz, 4 H), 7.89 (d, *J* = 8.8 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.9, 148.7, 128.2, 124.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_9N_3O_8S_2$: 386.9831; found: 386.9828.

4-Acetyl-*N*-[(4-acetylphenyl)sulfonyl]benzenesulfonamide (1f) CAS Reg. No. 185117-45-7

Pale yellow solid; yield: 1.45 g (34%); mp 220–221 °C.

IR (neat): 3187, 2965, 1667, 1363, 1164, 868 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.28 (br s, 1 H), 7.92 (d, *J* = 8.8 Hz, 4 H), 7.74 (d, *J* = 8.8 Hz, 4 H), 2.59 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 198.0, 150.3, 138.2, 128.4, 126.9, 27.4.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}NO_6S_2$ + H: 382.0419; found: 382.0417.

4-Chloro-*N*-[(4-chlorophenyl)sulfonyl]benzenesulfonamide (1g)[15] CAS Reg. No. 2725-55-5

White solid; yield: 2.05 g (50%); mp 207–208 °C.

IR (neat): 3514, 1400, 1159, 880 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.74 (br s, 1 H), 7.63 (d, *J* = 8.4 Hz, 4 H), 7.43 (d, *J* = 8.4 Hz, 4 H).

^{13}C NMR (100 Hz, DMSO-d_6): δ = 144.8, 135.0, 128.2, 128.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_9Cl_2NO_4S_2$: 364.9350; found: 364.9353.

4-Methoxy-*N*-[(4-methoxyphenyl)sulfonyl]benzenesulfonamide (1h) CAS Reg. No. 185117-44-6

White solid; yield: 3.20 g (80%); mp 170–171 °C.

IR (neat): 3078, 1592, 1367, 1157, 824 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.06 (br s, 1 H), 7.58 (d, *J* = 8.8 Hz, 4 H), 6.95 (d, *J* = 8.8 Hz, 4 H), 3.81 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.2, 135.1, 129.1, 114.1, 56.0.

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HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{15}NO_6S_2$: 357.0341; found: 357.0343.

***N*-(Methylsulfonyl)methanesulfonamide (1i)[16] CAS Reg. No. 5347-82-0**

White solid; yield: 1.75 g (90%); mp 152–153 °C.

IR (neat): 3156, 3027, 1347, 1146, 946, 864 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.4 (br s, 1 H), 3.08 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.2.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_2H_7NO_4S_2$: 172.9816; found: 172.9818.

***N*-(Isopropylsulfonyl)isopropanesulfonamide (1j) CAS Reg. No. 1416768-55-2**

White solid; yield: 2.00 g (78%); mp 140–141 °C.

IR (neat): 3185, 2967, 1350, 1135, 843 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.35 (br s, 1 H), 3.48 (sept, *J* = 6.8 Hz, 2 H), 1.29 (d, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.2, 16.4.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_6H_{15}NO_4S_2$ + H: 230.0521; found: 230.0523.

***N*-[(Phenylmethyl)sulfonyl]benzylsulfonamide (1k) CAS Reg. No. 856359-56-3**

White solid; yield: 2.19 g (60%); mp 160–161 °C.

IR (neat): 3095, 1356, 1134, 850 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38–7.27(m, 10 H), 6.14 (br s, 1 H), 4.36 (s, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 132.1, 131.4, 128.4, 127.9, 59.8.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_4S_2$ + H: 326.0521; found: 326.0519.

***N*-Sulfonylformamidines 4; General Procedure**

To a solution of *N*-sulfonylsulfonamide **1** (1.68 mmol) in N,N-disubstituted formamide **3** (3.0 mL) was added TsCl (**2**; 0.160 g, 0.840 mmol; 0.480 g, 2.52 mmol for products **4d–g**) and Et_3N (0.29 mL, 2.10 mmol). The mixture was stirred at r.t. (or heated to 100 °C in the cases of **4d–g**,**k**). After the starting material was consumed as indicated by TLC, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The combined organic phases were washed with H_2O, dried (anhydrous $MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified, if necessary, by silica gel flash column chromatography (hexane/EtOAc) to give the desired product as a white solid (Table 2).

***N*,*N*-Dimethyl-*N*′-tosylformimidamide (4a)[4b] CAS Reg. No. 25770-53-0**

White solid; yield: 0.369 g (97%); mp 136–137 °C; R_f = 0.15 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 3.12 (s, 3 H), 3.01 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 142.5, 139.6, 129.3, 126.5, 41.5, 35.5, 21.5.

***N*,*N*-Dimethyl-*N*′-(phenylsulfonyl)formimidamide (4b)[17] CAS Reg. No. 13707-43-2**

White solid; yield: 0.321 g (90%); mp 189–190 °C; R_f = 0.45 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.90 (d, *J* = 8.0 Hz, 2 H), 7.54–7.44 (m, 3 H), 3.13 (s, 3 H), 3.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 142.4, 131.9, 128.7, 126.5, 41.5, 35.6.

***N*,*N*-Dimethyl-*N*′-(4-ethylphenylsulfonyl)formimidamide (4c) CAS Reg. No. 57603-97-1**

White solid; yield: 0.242 g (60%); mp 118–119 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

IR (neat): 2968, 2934, 1625, 1084, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 3.12 (s, 3 H), 3.01 (s, 3 H), 2.69 (q, *J* = 7.6 Hz, 2 H), 1.24 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 148.6, 139.7, 128.2, 126.6, 41.5, 35.5, 28.8, 15.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{16}N_2O_2S$: 240.0932; found: 240.0934.

***N*,*N*-Dimethyl-*N*′-(4-*tert*-butylphenylsulfonyl)formimidamide (4d) CAS Reg. No. 2089434-81-9**

White solid; yield: 0.397 g (88%); mp 160–161 °C; R_f = 0.45 (hexane/EtOAc 1:1, v/v).

IR (neat): 2960, 1629, 1297, 1152, 1107, 915, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 3.12 (s, 3 H), 3.02 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 155.5, 139.4, 126.3, 125.7, 41.5, 35.5, 35.0, 31.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{20}N_2O_2S$: 268.1245; found: 268.1243.

***N*,*N*-Dimethyl-*N*′-(4-nitrophenylsulfonyl)formimidamide (4e)[4b] CAS Reg. No. 29912-59-2**

White solid; yield: 0.264 g (61%); mp 186.5–187.5 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 8.8 Hz, 2 H), 8.27 (s, 1 H), 8.03 (d, *J* = 8.8 Hz, 2 H), 3.17 (s, 3 H), 2.93 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 149.6, 149.0, 128.0, 124.9, 41.6, 35.7.

***N*,*N*-Dimethyl-*N*′-(4-acetylphenylsulfonyl)formimidamide (4f)**

White solid; yield: 0.325 g (76%); mp 154–155 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

IR (neat): 2929, 1691, 1632, 1246, 1149, 907, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 8.03 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 8.8 Hz, 2 H), 3.16 (s, 3 H), 3.04 (s, 3 H), 2.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 159.4, 146.3, 139.4, 128.7, 126.8, 41.7, 35.7, 26.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{14}N_2O_3S$: 254.0725; found: 254.0723.

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***N*,*N*-Dimethyl-*N*′-(4-chlorophenylsulfonyl)formimidamide (4g)[4b] CAS Reg. No. 29619-30-5**

White solid; yield: 0.414 g (quant); mp 109–110 °C; R_f = 0.35 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 3.15 (s, 3 H), 3.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 141.0, 138.1, 129.0, 128.0, 41.6, 35.6.

***N*,*N*-Dimethyl-*N*′-(4-methoxyphenylsulfonyl)formimidamide (4h)[4b] CAS Reg. No. 1344029-97-5**

White solid, yield: 0.358 g (88%); mp 152–153 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 3.12 (s, 3 H), 3.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 158.9, 134.4, 128.5, 113.9, 55.6, 41.4, 35.5.

***N*,*N*-Dimethyl-*N*′-(methylsulfonyl)formimidamide (4i) CAS Reg. No. 52776-60-0**

White solid; yield: 0.252 g (quant); mp 80–81 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

IR (neat): 2391, 1627, 1270, 1110, 964 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 3.05 (s, 3 H), 2.94 (s, 3 H), 2.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 42.0, 41.4, 35.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4H_{10}N_2O_2S$: 150.0463; found: 150.0464.

***N*,*N*-Dimethyl-*N*′-(isopropylsulfonyl)formimidamide (4j)**

Colorless oil; yield: 0.252 g (84%); R_f= 0.20 (hexane/EtOAc 1:2, v/v).

IR (neat): 2977, 2937, 1619, 1250, 1108, 902, 843 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 3.11 (s, 1 H), 3.10 (sept, *J* = 6.8 Hz, 3 H), 3.03 (s, 3 H), 1.32 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 53.4, 41.3, 35.4, 16.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_6H_{14}N_2O_2S$: 178.0776; found: 178.0777.

***N*,*N*-Dimethyl-*N*′-[(phenylmethyl)sulfonyl]formimidamide (4k)[4b] CAS Reg. No. 90873-49-7**

White solid, yield: 0.293 g (77%); mp 136–137 °C; R_f = 0.20 (hexane/EtOAc 1:2, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 7.37–7.32 (m, 5 H), 4.26 (s, 2 H), 2.99 (s, 3 H), 2.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 130.9, 130.3, 128.4, 128.3, 59.7, 41.1, 35.3.

***N*,*N*-Diethyl-*N*′-tosylformimidamide (4l)[4b] CAS Reg. No. 29397-20-4**

White solid; yield: 0.350 g (82%); mp 75–76 °C; R_f = 0.40 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 3.47 (q, *J* = 7.2 Hz, 2 H), 3.37 (q, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 142.3, 139.8, 129.3, 126.4, 47.0, 40.9, 21.5, 14.5, 12.1.

4-Methyl-*N*-(pyrrolidinomethylene)benzenesulfonamide (4m)[4b] CAS Reg. No. 57988-74-6

White solid; yield: 0.411 g (97%); mp 139–140 °C; R_f = 0.20 (hexane/EtOAc 1:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 3.60–3.57 (m, 2H), 3.48–3.45 (m, 2H), 2.40 (s, 3 H), 1.97–1.94 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 142.4, 139.7, 129.3, 126.6, 50.0, 46.5, 25.0, 24.4, 21.5.

4-Methyl-*N*-(piperidinomethylene)benzenesulfonamide (4n)[4b] CAS Reg. No. 27049-60-1

White solid; yield: 0.403 g (90%); mp 148–149 °C; R_f = 0.13 (hexane/EtOAc 1:2, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 3.61–3.58 (m, 2H), 3.42–3.40 (m, 2H), 2.40 (s, 3 H), 1.71–1.63 (m, 4 H), 1.61–1.56 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 142.4, 139.7, 129.3, 126.5, 51.9, 44.7, 26.4, 24.9, 24.0, 21.6.

4-Methyl-*N*-(morpholinomethylene)benzenesulfonamide (4o)[4b] CAS Reg. No. 15294-84-5

White solid; yield: 0.298 g (66%); mp 169–170 °C; R_f = 0.30 (hexane/EtOAc 1:2, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.77 (d, *J* = 7.6 Hz, 2 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 3.76–3.74 (m, 2H), 3.68–3.67 (m, 4 H), 3.50–3.48 (m, 2H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 142.7, 139.2, 129.4, 126.6, 66.8, 65.9, 50.3, 44.2, 21.5.

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Supporting Information

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References

(1) (a) Suja, T. D.; Divya, K. V. L.; Naik, L. V.; Kumar, A. R.; Kamal, A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2072. (b) Song, Z. L.; Chen, H. L.; Wang, Y. H.; Goto, M.; Gao, W. J.; Cheng, P. L.; Cheng Morris-Natschke, S. L.; Liu, Y. Q.; Zhu, G. X.; Wang, M. J.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2690.
(2) Anglada, L.; Marquez, M.; Sacristan, A.; Ortiz, J. *Eur. J. Med. Chem.* **1988**, *23*, 97.

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(3) Andersen, N. K.; Chandak, N.; Brulikova, L.; Kumar, P.; Jensen, M. D. F.; Sharma, P. K.; Nielsen, P. *Bioorg. Med. Chem.* **2010**, *18*, 4702.
(4) (a) Niu, Z.; Lin, S.; Dong, Z.; Sun, H.; Liang, F.; Zhang, J. *Org. Biomol. Chem.* **2013**, *11*, 2460. (b) Chen, S.; Xu, Y.; Wan, X. *Org. Lett.* **2011**, *13*, 6152.
(5) (a) Zhang, L.; Su, J. H.; Wang, S.; Wan, C.; Zha, Z.; Du, J.; Wang, Z. *Chem. Commun.* **2011**, *47*, 5488. (b) Wang, S.; Wang, Z.; Zheng, X. *Chem. Commun.* **2009**, 7372. (c) Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2836. (d) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048. (e) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520. (f) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038.
(6) King, C. *J. Org. Chem.* **1960**, *25*, 352.
(7) (a) Tosolini, G. *Chem. Ber.* **1961**, *94*, 2731. (b) Kumar, P.; Chandak, N.; Nielsen, P.; Sharma, P. K. *Bioorg. Med. Chem.* **2012**, *20*, 3843. (c) Sharma, P. K.; Chandak, N.; Kumar, P.; Sharma, C.; Aneja, K. R. *Eur. J. Med. Chem.* **2011**, *46*, 1425.
(8) (a) Hudabaierdi, R.; Wusiman, A.; Mulati, A. *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 485. (b) Pettit, G. R.; Kadunce, R. E. *J. Org. Chem.* **1962**, *27*, 4566.
(9) Gazvoda, M.; Kočevar, M.; Polanc, S. *Eur. J. Org. Chem.* **2013**, 5381.
(10) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. *Org. Lett.* **2010**, *12*, 897.
(11) Golten, S.; Fontenelle, C. Q.; Timofte, R. S.; Bailac, L.; Light, M.; Sebban, M.; Oulyadi, H.; Linclau, B. *J. Org. Chem.* **2016**, *81*, 4434.
(12) Li, J.; Cai, W.; Zhang, Y.; Chen, Z.; Xu, G.; Cheng, H. *Electrochimica Acta* **2015**, *151*, 168.
(13) Weng, S.-S.; Hsieh, K.-Y.; Zeng, Z.-J.; Zhang, J.-W. *Tetrahedron Lett.* **2017**, *58*, 670.
(14) Curtis, V. A.; Knutson, F. J.; Baumgarten, R. J. *Tetrahedron Lett.* **1981**, *22*, 199.
(15) Chen, G.; Chen, F.; Zhang, Y.; Yang, X.; Yuan, X.; Wu, F.; Yang, X. *J. Fluorine Chem.* **2012**, *133*, 155.
(16) Pringle, J. M.; Golding, J.; Baranyai, K.; Forsyth, C. M.; Deacon, G. B.; Scott, J. L.; MacFarlane, D. R. *New J. Chem.* **2003**, *27*, 1504.
(17) Chandna, N.; Chandak, N.; Kumar, P.; Kapoor, J. K.; Sharma, P. K. *Green Chem.* **2013**, *15*, 2294.

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