Improved Synthesis of *N*-Sulfonylformamidine Derivatives Promoted by Thionyl Chloride

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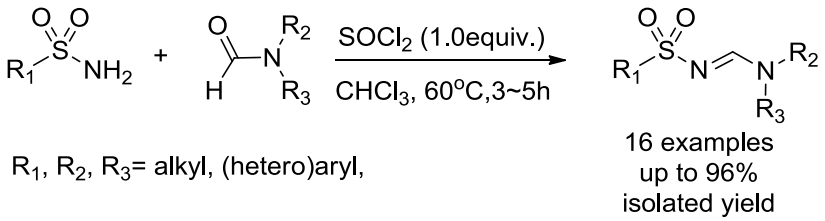

Abstract: An improved synthesis of *N*-sulfonylformamidine derivatives has been developed involving direct condensation of various sulfonamides and formamides in the presence of thionyl chloride using chloroform as solvent. Detailed synthetic studies indicate that this procedure gives the desired products in high yields under mild conditions.

Keywords: Sulfonamide, formamidine, thionyl chloride, Vilsmeier reaction

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Introduction

N-Sulfonylformamidines are a unique structural motif with fascinating chemical properties and are widely used as efficient coordinating ligands [1] and synthetic intermediates[2] to generate compounds of immense biological and pharmacological importance.[3]

Traditional methods for preparing *N*-sulfonylformamidines have been supplemented in recent years[4] with several new protocols based, for example, on Cu-catalyzed imidation of tertiary amines with sulfonyl azides,[5] oxidative dehydration of tertiary amines and tandem reaction with sulfonylazides,[6] selective haloform reaction of tertiary amines with *N*,*N*-dibromosulfonamides or NBS/sulfonamides,[7] direct condensation of sulfonamides with DMF in the presence of NaI/TBHP,[8] NaI-catalyzed oxidative tetrahydrogenative cross-coupling between *N*,*N*-dimethylaniline and sulfonamides,[9] as well as other approaches.[10] All these reactions have drawbacks, which can include limited substrate scope; a requirement for special reactants or catalysts such as sulfonyl azides, diethyl azodicarboxylate (DEAD) and transition-metal catalysts or oxidants (TBHP); and/or elevated temperature and longer reaction time.

In theory, direct condensation of sulfonamide and formamide should provide the most straightforward and atom-economic method for the synthesis of

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N-sulfonylformamidines. But reported syntheses following this approach, based on $POCl_3$,[4b] $(COCl)_2$[4i] or $SOCl_2$[4c] show the same drawbacks as the above mentioned protocols. *N*-Sulfonylformamidine, for instance, can be obtained by condensation of sulfonamide and formamide in the presence of corrosive $POCl_3$, but only in 26% yield. The $(COCl)_2$-mediated reaction is convenient and provides good yields, but it requires 2.5 equiv. of $(COCl)_2$ and formamidine. The $SOCl_2$-triggered reaction requires heating the reaction partners in toluene or xylene at higher temperature, and it provides products in only low to moderate yields. Recently, our group reported a facile one-pot procedure for synthesizing cyclic *N*-sulfonyl amidines.[11] We found that most sulfonamides showed poor solubility in toluene or xylene even at higher temperatures, suggesting that more polar solvents are needed to improve the sulfonamide reactivity and to increase the product yield in this approach. Herein we describe our efforts to achieve a gentle, simple, cheap and very efficient procedure for the preparation of *N*-sulfonylformamidines in chloroform by use the of common and cheap reagent thionyl chloride. Our newly improved procedure does not involve any transition metal catalyst/oxidants or potentially explosive materials, and can be carried out under mild conditions.

Results and discussion

Reaction conditions were explored by use of the model reaction of tosylamide (**1a**) with DMF (**2a**) (Table 1). In the presence of 1.0 equiv. of phosphoryl chloride in chlorobenzene, the desired product **3a** was

obtained in 90% yield at 80 °C after 2 h (entry 1). To our delight, using $SOCl_2$ under the same conditions gave **3a** in 88% yield (entry 2). Oxalyl chloride gave lower yield (entry 3). Lowering the reaction temperature to 60 °C and changing the solvent to chloroform gave the highest yield of 95% after 2 h (entry 6). Changing the solvent to DMF without changing the other reaction conditions led to only a trace amount of desired product (entry 6). We attribute this result to a reaction between the electrophilic Vilsmeier complex and DMF itself, which formed an inactive complex.[12] Decreasing the temperature reduced the yield of **3a** and necessitated longer reaction times (entries 8 and 9). Exposure to air did not affect the reaction (entry 10), while the desired product were be obtained in comparable yields (entries 11 and 12) by use of 2 mL or 5mL of solvent. After removal of the chlorinating agent, no reaction at all occurred (entry 13).

Using the optimized conditions (Table 1, entry 12), we conducted $SOCl_2$-mediated direct condensation of various substituted sulfonamides and formamides (Table 2). Sulfonamides with electron-neutral or electron-donating groups on aryl rings such as methyl, *tert*-butyl and methoxy groups reacted with DMF to form the corresponding sulfonylamidines **3a−3d** in excellent yield (Table 2, entries 1-4). While electron-withdrawing groups such as chloro and nitro substituents on the aromatic ring had varying influence, and yields ranging from 50% to 75% (entries 5-7) of the corresponding products **3** were obtained. These results indicate that the electronic nature of the sulfonamide

obviously effects the reaction. In addition, heterocyclic derivatives such as thiophene-2-sulfonamide and 5-methylpyridine-2-sulfonamide also participated in the reaction under the optimized conditions and provided the corresponding amidines **3h** and **3i** in 70% and 50% respectively (entries 8 and 9). Various formamides including *N*,*N*-diethylformamide, *N*,*N*-diisopropylformamide, *N*-methyl-*N*-phenylformamide, *N*-formyl-piperidine, and 4-formylmorpholine were examined and gave products in excellent yield (entries 10-14). Methane sulfonamide reacted smoothly to afford the desired **3o** in 80% yield (entry 15). Using chiral substrates such as (1*S*)-10-camphorsulfonamide (**1k**) led to the corresponding amidine enantiomer **3p** in 84% yield (entry 16), together with (1*S*)-camphorsulfonylimine as byproduct in 13% yield.[13] In contrast, the reaction of tosylamide with formanilide (**1l)** gave a complex product mixture (entry 17).

The structure of **3p** was confirmed by a single-crystal X-ray diffraction analysis (Figure 1). The structural features of **3p** are the same as observed in the previously cited *N*-sulfonylformamidine derivative.[10c] The lengths of the two C-N bonds [N1-C11, 1.316(3) Å; N2-C11, 1.320(2) Å] are similar, which is indicative of the delocalized nature of the C=N double bond. The N1-C11-N2 angle is 122.11° which discloses an *E*-isomer of the generated C=N double bond.[14]

To confirm the reaction pathway of the described transformations, we treated **1a** with the commercially accessible Vilsmeier reagent chloromethylenedimethyliminium chloride (Scheme 1) under the standard reaction conditions. As we had anticipated, the reactions led to the same product **3a** with 96% isolated yield. This result indicates that the formation of **3a** presumably underwent a Vilsmeier reaction pathway.[15]

Conclusion

In summary, we have improved an efficient procedure for synthesizing *N*-sulfonylformamidines under mild conditions. Aliphatic and (hetero)aromatic sulfonamides are well tolerated in this transformation and the desired products were obtained in good to excellent yields.

Experimental

Reagents were purchased from commercial sources and used without further purification unless otherwise specified. Dichloromethane (DCM), chlorobenzene (PhCl), 1,2-dichloroethane (DCE) and chloroform ($CHCl_3$) were distilled from CaH_2.

Other solvents were used without additional purification. Purification of the reaction products was carried out by flash column chromatography using 200-300 mesh silica gel. Visualization on TLC (analytical thin layer chromatography) was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid or anisaldehyde stain followed by heating. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.27 ppm; ^{13}C NMR: $CDCl_3$ at 77.23 ppm). ^{1}H NMR data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet), coupling constant(s) in Hz, integration. Single-crystal X-ray diffraction was carried out on a diffractometer using a Rigaku AFC12/Saturn 724 CCD fitted with Mo Kα radiation (λ = 0.71073 Å) at 298 K. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for the products 3 (Figures S 1 – S 34).

***General procedure for the preparation of N-sulfonylformamidines* 3a–3p.**

A mixture of sulfonamide **1** (2.0 mmol, 1.0 equiv.), formamide 2 (2.0 mmol, 1.0 equiv.) and thionyl chloride (0.236g, 145 µL, 2.0 mmol) in $CHCl_3$ (10 mL) was stirred at 60°C for the indicated reaction time (see Table 2). Then, the solvent was evaporated under vacuum to give the products in excellent yields or the residue was purified by silica gel column chromatography (petroleum

ether and ethyl acetate) to give the desired products.

***(E)-N,N-dimethyl-N'-tosylformimidamide* (3a)**:[8] White powder; mp: 131-132°C; ^{1}H NMR: δ 8.13 (s, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 3.12 (s, 3H), 3.01 (s, 3H), 2.40 (s, 3H); ^{13}C NMR: δ 158.2, 141.6, 138.7, 128.5, 125.7, 40.6, 34.7, 20.6.

***(E)-N,N-dimethyl-N'-(phenylsulfonyl)-formimidamide* (3b)**: White powder; mp: 134-136°C; ^{1}H NMR: δ 8.14 (s, 1H), 7.89 (d, J = 6.8 Hz, 2H), 7.52-42 (m, 3H), 3.13 (s, 3H), 3.02 (s, 3H); ^{13}C NMR: δ 159.3, 142.5, 131.9, 128.8, 126.6, 41.6, 35.7.

***(E)-N'-(4-methoxyphenylsulfonyl)-N,N-dimethylformimidamide* (3c):**[8] White powder; mp: 155-156°C; ^{1}H NMR: δ 8.11 (s, 1H), 7.81 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H) 3.12 (s, 3H), 3.00 (s, 3H); ^{13}C NMR: δ 162.3, 159.0, 134.4, 128.6, 113.9, 55.6, 41.5, 35.5.

***(E)-N'-(4-tert-butylphenylsulfonyl)-N,N-dimethylformimidamide* (3d):** White powder; mp: 166-167°C; ^{1}H NMR: δ 8.14 (s, 1H), 7.81 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 3.12 (s, 3H), 3.02 (s, 3H), 1.32 (s, 9H); ^{13}C NMR: δ 159.2, 155.5, 139.5, 126.4, 125.8, 41.5, 35.6, 35.1, 31.2; HRMS calcd. for $C_{13}H_{20}N_2NaO_2S$ $[M+Na]^+$; 291.1143; found 291.1138.

***(E)-N,N-dimethyl-N'-(4-nitrophenylsulfonyl) formimidamide* (3e)**: [8] White powder; mp: 193-194°C; ^{1}H NMR: δ 8.30 (d, J = 8.6 Hz, 2H), 8.15 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 3.17 (s, 3H), 3.04 (s, 3H); ^{13}C NMR: δ 159.5, 149.7, 148.3, 127.9, 124.1, 41.6, 35.9.

***(E)-N,N-dimethyl-N'-(2-nitrophenylsulfonyl) formimidamide* (3f)**: White powder; mp:

135-136°C; ^{1}H NMR: δ 8.27 (d, J = 7.6 Hz, 1H), 8.10 (s, 1H), 7.65 (m, 3H), 3.21 (s, 3H), 3.05 (s, 3H); ^{13}C NMR: δ 160.8, 132.7, 132.0, 130.7, 123.9, 41.8, 35.7; HRMS calcd. for $C_9H_{11}N_3NaO_4S$ $[M+Na]^+$; 280.0368; found 280.0361.

***(E)-N'-(4-chlorophenylsulfonyl)-N,N-dimethylformimidamide* (3g)**:[8] White powder; mp: 122-123°C; ^{1}H NMR: δ 8.13 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 3.14 (s, 3H), 3.03 (s, 3H); ^{13}C NMR: δ 159.3, 141.1, 138.2, 129.0, 128.1, 41.6, 35.7.

***(E)-N,N-dimethyl-N'-(thiophen-2-ylsulfonyl)formimidamide* (3h):** White powder; mp: 95-96°C; ^{1}H NMR: δ 8.13 (s, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.02 (t, J = 4.4 Hz, 1H), 3.15 (s, 3H), 3.05 (s, 3H); ^{13}C NMR: δ 159.2, 143.9, 130.67, 130.63, 126.9, 41.5, 35.6; HRMS calcd. for $C_7H_{10}N_2NaO_2S_2$ $[M+Na]^+$; 241.0081; found 241.0088.

***(E)-N,N-dimethyl-N'-[(5-methylpyridin-2-yl)sulfonyl]formimidamide* (3i):** White powder; mp: 183-184°C; ^{1}H NMR: δ 8.50 (s, 1H), 8.36 (s, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H), 3.20 (s, 3H), 3.03 (s, 3H), 2.42 (s, 3H); ^{13}C NMR: δ 161.9, 154.2, 147.7, 140.7, 137.5, 122.6，42.0, 35.8, 18.5；HRMS calcd. for $C_9H_{13}N_3NaO_2S$ $[M+Na]^+$; 250.0626; found 250.0620.

***(E)-N,N-diethyl-N'-tosylformimidamide* (3j):**[8] White powder; mp: 71-72°C; ^{1}H NMR: δ 8.14 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.25 (d, J= 8.0, 2H), 3.47 (q, J = 7.2 Hz, 2H), 3.37 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR: δ 158.1, 142.3, 139.9, 129.3, 126.4, 47.1, 41.0, 29.8, 21.5, 14.6 12.2.

(E)-N,N-diisopropyl-N'-tosylformimidamide **(3k):**[10b] White powder; mp: 112-113°C; ^{1}H NMR: δ 8.24 (s, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 4.52 (dt, J = 13.6, 6.8 Hz, 1H), 3.67 (dt, J = 13.6, 6.8 Hz, 1H), 2.38 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 6H); ^{13}C NMR: δ 156.2, 142.0.4, 139.9, 129.2, 126.2, 48.4, 47.8, 23.6, 21.4, 19.6.

(E/Z)-N-methyl-N-phenyl-N'-tosylformimidamide **(3l):**[9] White powder; mp: 64-65°C; ^{1}H NMR: δ 8.57 (s, 0.5H), 8.48 (s, 0.5H), 7.82 (dd, J = 8.1, 4.6 Hz, 1H), 7.43 (dd, J = 14.6, 7.2 Hz, 2H), 7.3-7.28 (m, 2H), 7.19 (t, J = 8.4 Hz, 2H), 3.44 (s, 1.5H), 3.33 (s, 1.5H), 2.43 (d, J = 5.8 Hz, 3H); ^{13}C NMR: δ 162.5, 158.52, 143.7, 143.4, 143.0, 139.0, 133.1, 131.4, 130.0, 129.8, 129.7, 129.5, 127.4, 126.9, 126.6, 126.5, 122.5, 122.2, 36.2, 33.2, 21.6.

(E)-4-methyl-N-(piperidin-1-ylmethylene)benzenesulfonamide **(3m)**:[8] White powder; mp: 152-153°C; ^{1}H NMR: δ 8.11 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.6 Hz, 3H), 3.59 (t, J = 5.6 Hz, 2H), 3.40 (t, J = 5.2 Hz, 2H), 2.40 (s, 3H), 1.73-1.58 (m, 6H); ^{13}C NMR: δ 157.3, 142.4, 139.8, 129.4, 126.6, 52.0, 44.8, 26.5, 25.0, 24.1, 21.6.

(E)-4-methyl-N-(morpholinomethylene)benzenesulfonamide **(3n):**[8] White powder; mp: 178-179°C; ^{1}H NMR: δ 8.17 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 3.74 (t, J = 4.8 Hz, 2H), 3.67 (s, 4H), 3.47 (t, J = 4.8 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR: δ 157.4, 142.6, 139.0, 129.3, 125.6, 66.7, 65.9, 50.2, 44.2, 21.4.

(E)-N-methyl-N'-(methylsulfonyl)-N-phenylformimidamide **(3o):**[4i] White powder;

mp: 69-70°C; ^{1}H NMR: δ 8.43 (s, 1H), 7.39 (t, J = 8.0, Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 3.43 (s, 3H), 2.99 (s, 3H); ^{13}C NMR: δ 158.4, 142.9, 129.6, 127.1, 121.9, 41.7, 35.8.

(E)-N'-{[(1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-an-1-yl]methylsulfonyl}-N,N-dimethylformimidamide **(3p):** White powder; mp: 172-173°C; ^{1}H NMR (500 MHz): δ 8.02 (s, 1H), 3.49-3.40 (m, 1H), 3.13 (d, J = 0.6 Hz, 3H), 3.00 (dd, J = 1.8, 1.1 Hz, 3H), 2.98-2.92 (m, 1H), 2.62 (t, J = 13.0 Hz, 1H), 2.33 (dd, J = 18.4, 2.9 Hz, 1H), 2.11-1.98 (m, 2H), 1.89 (d, J = 18.3 Hz, 1H), 1.77-1.72 (m, 1H), 1.45-1.37 (m, 1H), 1.11 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz): δ 215.39, 159.77, 58.51, 50.82, 48.03, 42.66 (d, J = 9.7 Hz), 41.35, 35.38, 26.99, 24.76, 19.94, 19.76; HRMS calcd. for $C_{13}H_{22}N_2NaO_3S$ $[M+Na]^+$; 309.1249; found 309.1243.

***(1S)-Camphorsulfonylimine*:**[16] White powder; mp: 224-226°C; ^{1}H NMR (500 MHz): δ 3.18 (d, J = 13.3 Hz, 1H), 2.97 (d, J = 13.3 Hz, 1H), 2.76 (ddd, J = 19.3, 4.4, 2.2 Hz, 1H), 2.38 (d, J = 19.3 Hz, 1H), 2.25 (t, J = 4.2 Hz, 1H), 2.06 (ddd, J = 5.7, 4.7, 2.1 Hz, 2H), 1.76 (t, J = 9.1 Hz, 1H), 1.50-1.42 (m, 1H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz): δ 195.56, 77.33, 77.08 (s), 76.82, 64.50, 49.39, 47.95, 44.58, 35.87, 28.36, 26.57, 19.40, 18.93.

Acknowledgments

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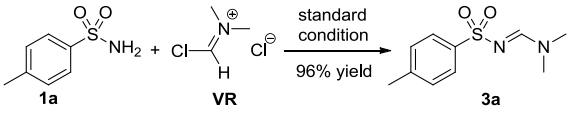


Scheme 1. The reaction between **1a** and Vilsmeier reagent

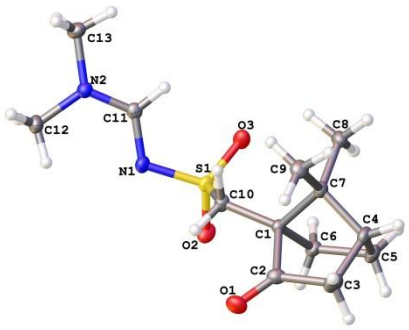
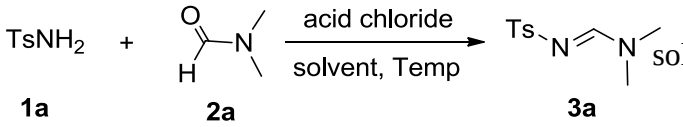


Figure 1. X-Ray crystal structure of **3p**

Table 1. Optimization of the reaction conditions [a]

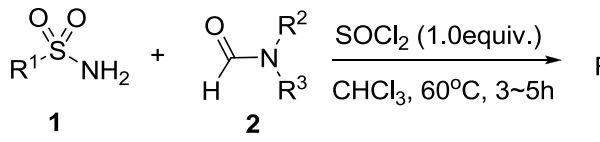


1a 2a 3a

Entry	Acid chloride	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$POCl_3$	PhCl	80	2	90
2	$SOCl_2$	PhCl	80	2	88
3	$(COCl)_2$	PhCl	80	8	50
4	$SOCl_2$	DCM	40	5	70
5	$SOCl_2$	DCE	60	5	60
6	$SOCl_2$	$CHCl_3$	60	2	95
7	$SOCl_2$	DMF	60	5	trace
8	$SOCl_2$	$CHCl_3$	40	5	70
9	$SOCl_2$	$CHCl_3$	rt	8	50
10[c]	$SOCl_2$	$CHCl_3$	60	2	95
11[d]	$SOCl_2$	$CHCl_3$	60	2	96
12[e]	$SOCl_2$	$CHCl_3$	60	2	93
13	--	$CHCl_3$	60	8	NR[f]

[a] Reactions were performed with 2.0 mmol of $TsNH_2$ (1.0 equiv.), 2.0 mmol DMF (1.0 equiv.) and 2.0 mmol, (1.0 equiv.) of acid chloride in 10 mL of solvent, unless otherwise noted. [b] Isolated yield after column chromatography. [c] Reaction was performed with a drying tube on top of the condenser. [d] 5.0 mL of solvent was used. [e] 2.0 mL of solvent was used. [f] No reaction.

Table 2. Preparation of *N*-sulfonylformamidines[a]



1 **2** **3**

Entry	**1**	R^1	**2**	R^2	R^3	Time (h)	**3**	Yield (%)[b]
1	**1a**	4-MeC_6H_4	**2a**	Me	Me	2	**3a**	93
2	**1b**	C_6H_5	**2a**	Me	Me	3	**3b**	93
3	**1c**	4-$MeOC_6H_4$	**2a**	Me	Me	3	**3c**	90
4	**1d**	4-*t*-BuC_6H_4	**2a**	Me	Me	3	**3d**	91
5	**1e**	4-$NO_2C_6H_4$	**2a**	Me	Me	6	**3e**	62[c]
6	**1f**	2-$NO_2C_6H_4$	**2a**	Me	Me	6	**3f**	50[d]
7	**1g**	4-ClC_6H_4	**2a**	Me	Me	5	**3g**	75
8	**1h**	2-thienyl	**2a**	Me	Me	8	**3h**	70[e]
9	**1i**	5-methyl-2-pyridinyl	**2a**	Me	Me	8	**3i**	51[f]
10	**1a**	4-MeC_6H_4	**2b**	Et	Et	3	**3j**	96
11	**1a**	4-MeC_6H_4	**2c**	*i*-Pr	*i*-Pr	3	**3k**	95
12	**1a**	4-MeC_6H_4	**2d**	Me	Ph	4	**3l**	95[g]
13	**1a**	4-MeC_6H_4	**2e**	$(CH_2)_5$		4	**3m**	93
14	**1a**	4-MeC_6H_4	**2f**	$(C_2H_4)_2O$		3	**3n**	87
15	**1j**	Me	**2d**	Me	Ph	4	**3o**	80
16	**1k**	(1*S*)-10-camphoryl	**2a**	Me	Me	3	**3p**	84[h]
17	**1l**	4-MeC_6H_4	**2g**	H	Ph	5	**3q**	0

[a] Reactions were performed with 2.0 mmol of sulfonamide **1** (1.0 equiv.) and 2.0 mmol formamide **2** (1 equiv.) in 2.0 mL of chloroform, unless otherwise noted. [b] Isolated yield after column chromatography. [c] 28 % **1e** was recovered. [d] 37% **1f** was recovered. [e] 23% **1h** was recovered. [f] 33% **1i** was recovered. [g] The *E* and *Z* isomers ratio was 1:1. [h] 13% (1*S*)-camphorsulfonylimine was isolated.