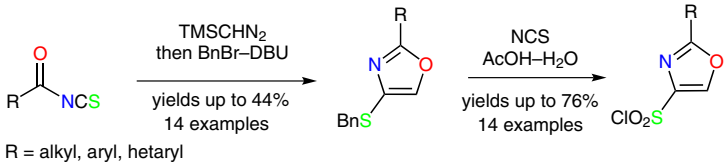
Synlett J. I. Trujillo et al. Letter

Facile Synthesis of 2,4-Disubstituted Thiooxazoles and 2,4-Disubstituted Oxazole Sulfonyl Chlorides via Acyl Isothiocyanates and TMS-Diazomethane

John I. Trujillo*
Eric P. Arnold
Steve Kortum
Ralph P. Robinson

Pfizer Worldwide R&D, Eastern Point Road, Groton, CT 06340, USA
john.i.trujillo@pfizer.com



Received: 18.03.2015
Accepted after revision: 23.04.2015
Published online: 01.06.2015
DOI: 10.1055/s-0034-1380218; Art ID: st-2015-r0193-l

Abstract An expedient method for the direct conversion of acyl isothiocyanates to 2,4-disubstitued thiooxazoles and 2,4-disubstituted oxazole sulfonyl chlorides is described. The method takes advantage of an early observation by Sheehan and the reaction of diazomethane with isocyanates to form oxazolones. However, in this case an acyl isothiocyanate is utilized as well as the readily available TMS-diazomethane to provide access to the desired 4-substituted sulfur derivatives. The 2,4-disubstituted oxazole systems synthesized represent novel thiooxazoles and oxazole sulfonyl chlorides not previously described.

Key words medicinal chemistry, heterocycles, sulfonamides, diazo compounds, sulfur

As a part of a recent drug discovery effort to expand the chemical space around a lead compound and modify its biological and physical properties, we sought the synthesis of various sulfonyl chlorides to append to our core structure. After extensive docking experiments and calculation of key physiochemical properties several novel ring systems were considered.[1] Of the novel ring systems considered, the 2,4-disubstituted oxazole sulfonyl chlorides **1** were identified as key targets for further exploration (Figure 1). The sulfonamide moiety and oxazole ring system serve to reduce the overall logD (Δ = ca. 1.1) and increase the TPSA (Δ = ca. 43) vs. the parent carboxamide and aryl-ring parent system.

Indeed, the oxazole ring system is found in various molecules that display biological activity (antiviral, antifungal, antibacterial, and antiproliferative). The biological activity and presence of oxazoles in natural products and drugs have generated interest in the synthesis of these ring systems.[2] In particular, 2,4-disubstituted oxazole sulfonyl chlorides (**1**, Figure 1) represent a novel variation of the

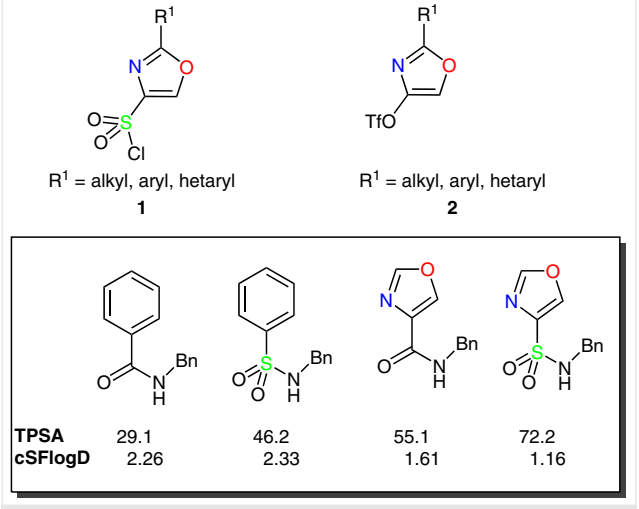
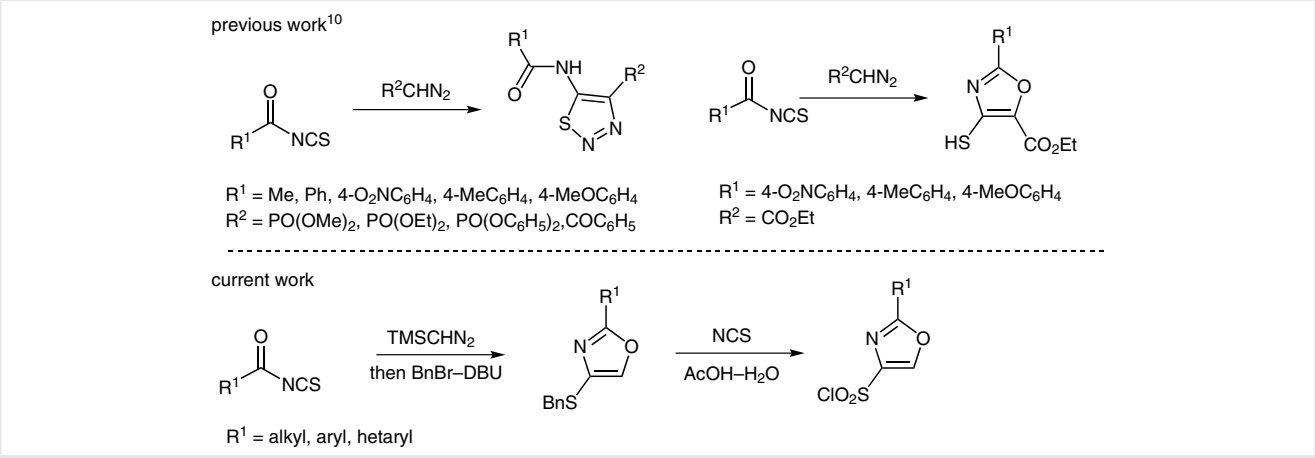


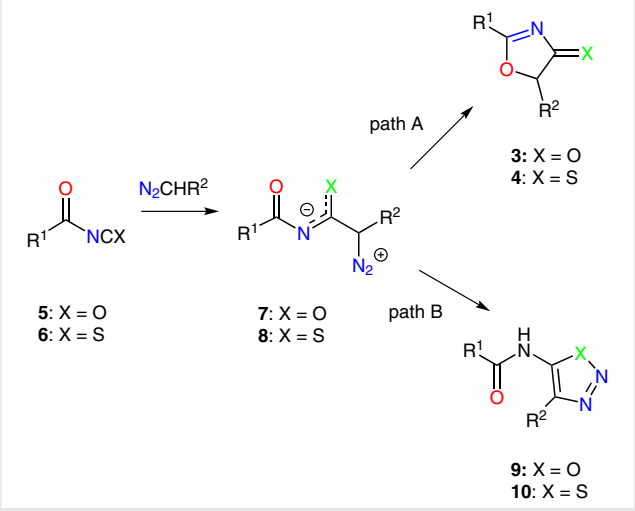
Figure 1 Desired sulfonyl chlorides **1**, oxazole triflate **2**, and calculated properties for aryl and oxazole carboxamides/sulfonamides

core oxazole ring system and no synthesis of these structures has been described in the literature to the best of our knowledge (Scheme 1).[3,4]

A survey of the literature revealed the synthesis of oxazolones **3** (Scheme 2), which are the oxygen homologues of our desired oxazolethiones **4**, as being accessible from isocyanates and diazomethane.[5] Indeed conversion of the oxazolone **3** to the triflate **2** (Scheme 1) has been well utilized by various investigators to prepare oxazole-containing natural products[6] and various 2,4-disubstituted oxazole derivatives.[7,8] Initial routes considered for the preparation of the desired oxazole sulfonyl chlorides sought to utilize the known triflate derivative **2** as a precursor, followed by sulfur incorporation via transition-metal catalysis.[9]



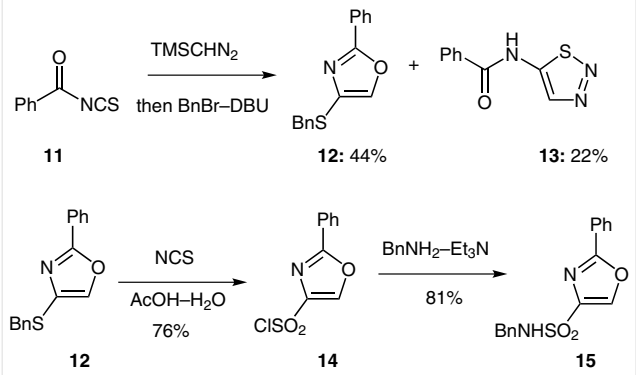
Scheme 1 Previous work by Regitz and current work



Scheme 2 Pathway for the formation of oxazoles **3**, **4** and thiadiazoles **9**, **10**

However, comparison of the initial report by Sheehan[5] pointed to a more direct route to the desired oxazole sulfonyl chloride by simply substituting the acyl isocyanate **5** with an acyl isothiocyanate **6**. Although this appeared to be an obvious variation, an investigation of the literature suggested that acyl isothiocyanates may not be good substrates for oxazole formation when reacted with diazo species [e.g., dimethyl(diazomethyl)phosphonate (R^2 = $PO(OMe)_2$], 2-diazo-1-phenylethan-1-one (R^2 = COPh)] but rather favored the formation of the thiadiazole ring system[10] (Scheme 1 and Scheme 2, path B, **10**). However, in the publication by Regitz[10a] it was reported that 4-substituted benzoyl isothiocyanates were observed to react with ethyl diazoacetate (R^2 = CO_2Et) to form ethyl 4-mercapto-2-phenyloxazole-5-carboxylate derivatives in modest yields (13–20%, via path A, **4**, Scheme 2). With this precedence we decided to further investigate the formation of our desired ring system from acyl isothiocyanates and TMS-diazomethane.[11]

For pilot studies, we explored the synthesis of 2-phenyloxazole-4-sulfonyl chloride (**14**, Scheme 3). Thus benzoyl isothiocyanate (**11**) was combined with TMS-diazomethane (2 M solution in hexanes) in dichloromethane at 0 °C. Although it was not isolated or characterized, this presumably formed the oxazolethione (**4** R^1 = Ph, R^2 = TMS, X = S), which was then treated with DBU–BnBr to provide the 4-(benzylthio)-2-phenyloxazole (**12**) after acidic workup[12a] and chromatography in a 44% yield. In addition to the desired oxazole **12**, the product from path B (Scheme 2), the *N*-(1,2,3-thidiazol-5-yl)benzamide (**13**) was isolated in 22% yield.[12b] The compound **12** was taken forward and treated with NCS in AcOH–H_2O to provide, as desired, the sulfonyl chloride **14** in 76% yield. Reaction of **15** with benzylamine provided sulfonamide **15** (81%), which was then crystallized. Single-crystal X-ray crystallography was performed (Figure 2) to confirm the proposed structure.



Scheme 3 Synthesis of oxazole **12**, thiadiazole **13**, oxazolesulfonyl chloride **14**, and sulfonamide **15**

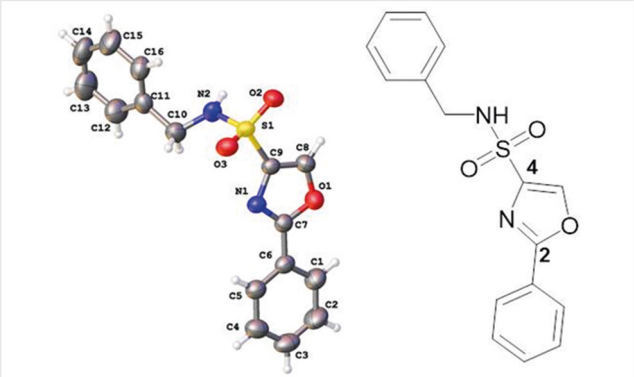


Figure 2 X-ray crystallography of sulfonamide **15**

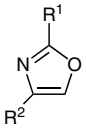
With this result, attempts at increasing the yield of the reaction (conversion of acyl isothiocyanate **11** to the SBn derivative **12**) were investigated (solvent, temperature, and time.) The results of these investigations are summarized in Table 1. It was observed that the conversion was generally best at lower temperatures. The preferred solvents are nonpolar (e.g., CH_2Cl_2, toluene, and cyclohexane). However, use of the more polar solvent (MeCN) resulted in similar yields. Lower conversions were observed with dioxane, while use of ethanol was detrimental to the desired product formation.

Table 1 Solvent, Temperature, and Time Variation

Entry	Solvent	Temp (°C)	Time (h)	Yield of **12** (%)
1	CH_2Cl_2	0	1	44
2	CH_2Cl_2	r.t.	1	38
3	CH_2Cl_2	0	12	37
4	PhMe	0	1	41
5	PhMe	r.t.	1	38
6	PhMe	0	12	41
7	MeCN	0	1	31
8	MeCN	–45	1	36
9	MeCN	r.t.	1	41
10	dioxane	0	1	27
11	*c*-hexane	0	1	43
12	EtOH	0	1	5

The scope of the reaction was investigated by varying the nature of the acyl isothiocyanate. Alkyl, aryl, substituted aryl and heteroaryl acyl isothiocyanates were explored, and the results are described in Table 2. The acyl isothiocyanates not obtained from commercial sources were prepared from the corresponding acid chloride and KSCN by standard methods.[13] The oxazole formation proceeds in modest yields for alkyl isothiocyanates **16**–**18** (>30% yield, Table 2, entries 2–4). In the cases of aryl-substituted acyl isothiocyanates electron-withdrawing (**22**–**24**; Table 2, entries 8–10) and electron-donating substituents (**19**–**21** and **26**; Table 2, entries 5–7 and 12) provide moderate yields, with the exception of the 4-NO_2 derivative (**25**; Table 2, entry 11). Furthermore, the reaction proceeds well regardless of the substitution pattern (**19**–**21** and **22**–**24**; Table 2, entries 5–7 and 8–10) and similar yields were obtained. Finally, the reaction proceeds in modest yields with heterocyclic acyl isothiocyanates (**27**, **28**; Table 2, entries 13 and 14). For the conversion of the SBn derivatives to the corresponding sulfonyl chlorides, the conversions were normally >40% (**14b**, **16b**–**26b**, **28b**; Table 2, entries 1–12 and 14) with the exception of **27b**.

Table 2 Scope of Reaction: Variation of Acyl Isothiocyanate and Synthesis of Thiooxazoles and Oxazole Sulfonyl Chlorides



Enty	Compd	R^1	Yield of **a** (R^2 = SBn) (%)[17]	Yield of **b** (R^2 = SO_2Cl) (%)[18]
1	**14**	Ph	44	76
2	**16**	Me	30	41
3	**17**	*i*-Pr	28	50
4	**18**	*t*-Bu	35	53
5	**19**	2-MeC_6H_4	37	53
6	**20**	3-MeC_6H_4	39	56
7	**21**	4-MeC_6H_4	42	44
8	**22**	2-ClC_6H_4	27	66
9	**23**	3-ClC_6H_4	25	66
10	**24**	4-ClC_6H_4	33	75
11	**25**	4-$O_2NC_6H_4$	16	72
12	**26**	4-$MeOC_6H_4$	30	74
13	**27**	2-pyridyl	20	18
14	**28**	3-Me-4-pyridyl	30	54

In conclusion, a facile method for the synthesis of 2,4-disubstituted thiooxazoles and oxazole sulfonyl chlorides is described. The method utilizes readily accessible acyl isothiocyanates and commercially available TMS-diazomethane to form the desired ring system in useful yields. Our results contrast earlier reports in the literature that the reaction of acyl isothiocyanates and certain diazospecies give 1,2,3-thiadiazoles almost exclusively.[10a] The oxazole sulfonyl chlorides and thiooxazoles represent novel 2,4-substituted oxazoles not previously described in the literature. As small polar monomers we anticipate these will find utility in medicinal chemistry applications seeking to explore chemical space while maintaining druglike physicochemical properties.[14–16]

Acknowledgment

The authors acknowledge Pfizer Research Laboratories for supporting this research. We thank Brian Samas (MatSci, PGRD-Groton) for X-ray structure determination of sulfonamide **15** and Justin Stroh (PGRD-Groton) for acquisition of high-resolution mass spectrometry.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380218.

References and Notes

(1) (a) Ortwine, D. F.; Aliagas, I. *Mol. Pharmaceutics* **2013**, *10*, 1153. (b) Meanwell, N. *Chem. Res. Toxicol.* **2011**, *24*, 1420. (c) *Metabolism, Pharmacokinetics and Toxicity of Functional Groups*; Smith, D., Ed.; RSC Publishing: Cambridge, **2010**. (d) TPSA (Topical Polar Surface Area) PropCalc v2.41. (e) cSFlogD (prediction of distribution coefficient (logD) in octanol/buffer at pH 7.4) Pfizer Internal Model.

(2) (a) Azman, A. M.; Mullins, R. J. In *Heterocyclic Chemistry in Drug Discovery*; Li, J. J., Ed.; Wiley: New York, **2013**, 231–281. (b) Khartulyari, A.; Maier, M. E. *Knowledge Updates*, In *Science of Synthesis Vol. 3*; Thieme: Stuttgart, **2011**, 57.

(3) For the preparation of 2,4-disubstituted oxazole carboxylate derivatives, see: Graham, T. *Org. Lett.* **2010**, *12*, 3614; and references cited therein.

(4) For previous reports of 2,4-disubstituted oxazole thio derivatives [SO_2Ar, SMe, and SAr (c,d), respectively], see: (a) Mortensen, D. S.; Perrin-Ninkovic, S. M.; Harris, R.; Lee, B. G. S.; Shevlin, G.; Hickman, M.; Khambatta, G.; Bisonette, R. R.; Fultz, K. E.; Sankar, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6793. (b) DeMartino, J. K.; Garfunkle, J.; Hochstatter, D. G.; Cravatt, B. F.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5842. (c) Schroeder, R.; Schoellkopf, U.; Blume, E.; Hoppe, I. *Justus Liebigs. Ann. Chem.* **1975**, *3*, 533. (d) Schoellkopf, U.; Blume, E. *Tetrahedron Lett.* **1973**, *9*, 629.

(5) Sheehan, J. C.; Izzo, P. T. *J. Am. Chem. Soc.* **1949**, *71*, 4059.

(6) For examples in the synthesis of oxazole-containing natural products, see: (a) Smith, A. B. III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834. (b) Smith, A. B. III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942.

(7) For synthesis of 2,4-substituted oxazole derivatives using triflate, see: (a) Hoffman, T. J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 2400. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495. (c) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485. (d) Smith, A. B. III; Minbiole, K. P.; Freeze, S. *Synlett* **2001**, 1739. (e) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415.

(8) For applications of triflate in the synthesis of druglike compounds, see: (a) Chobanian, H.; Lin, L.; Liu, P.; Chioda, M. D.; Devita, R. J.; Nargund, R. P.; Guo, Y. US 20110021531, **2011**. (b) Huang, Z.; Jin, J.; Machajewski, T. D.; Antonious-McCrea, W. R.; McKenna, M.; Poon, D.; Renhowe, P. A.; Sendzik, M.; Shafer, C. M.; Smith, A.; Xu, Y.; Zhang, Q. WO 2009115572, **2009**. (c) Reiter, L. A.; Freeman-Cook, K. D. PCT 2003090752, **2003**.

(9) For representative examples of aryl triflate to aryl-SR, see: (a) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (b) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D. III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606; Note: To our knowledge, no reactions of oxazole triflate/halo to oxazole-SR have been described in the literature.

(10) For reactions of diazospecies with acyl isothiocyanates and isothiocyanates, respectively, see: (a) Regitz, M.; Weber, B.; Heydt, A. *Liebigs Ann. Chem.* **1980**, 305. (b) Martin, D.; Mucke, W. *Justus Liebigs Ann. Chem.* **1965**, *682*, 90.

(11) (a) Shiori, T.; Aoyama, T.; Snowden, T. In *Handbook of Reagents for Organic Synthesis: Reagents for Silicon-Mediated Organic Synthesis*; Fuchs, P. L., Ed.; Wiley: New York, **2011**, 590–598. (b) Heydt, H. *Science of Synthesis*; Vol. 27; Thieme: Stuttgart, **2014**, 843.

(12) (a) Alternatively, an aqueous workup followed by treatment of crude material with 1 M TBAF in THF (1.0 equiv) facilitated removal of TMS group at 5-position of the oxazole. (b) A portion of the remaining mass balance is 5-silyl derivative (ca. 5%), while the remainder is undetermined.

(13) Skinner, G. S.; Vogt, H. C. *J. Am. Chem. Soc.* **1955**, *77*, 5440.

(14) (a) Lowe, D. *Med. Chem. Commun.* **2015**, *6*, 12. (b) Reymond, J. L.; Ruddigkeit, L.; Awale, M. *Comput. Chemogenomics* **2014**, 39.

(15) For recent reports of Ar/HetAr-SO_2NHR/SO_2Cl, see: (a) Emmet, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10204. (b) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 4404. (c) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226. (d) DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10638.

(16) For a recent report of 2,4,5-trisubstituted oxazole sulfonyl chloride, see: Kornienko, A. N.; Pil'o, S. G.; Prokopenko, V. M.; Brovarets, V. S. *Russ. J. Gen. Chem.* **2014**, *84*, 686.

(17) **General Procedure for Preparation of SBn Derivatives**

To a solution of benzoylisothiocyanate (500 mg, 3.06 mmol) in CH_2Cl_2 (15.0 mL, 0.12 M) cooled to 0 °C (ice-water bath) for 15 min was added $TMSCHN_2$ (2 M in hexanes, 2.30 mL, 4.60 mmol, 1.5 equiv) slowly. The mixture became orange upon addition. After stirring for 1 h at 0 °C a yellow suspension was evident. To the mixture was slowly added DBU (0.92 mL, 6.13 mmol, 2.0 equiv), followed by the addition of BnBr (0.36 mL, 3.06 mmol) at which time the color dissipated. The reaction allowed to warm to ambient temperature and stirred overnight. The reaction was diluted with CH_2Cl_2 (10 mL) and then washed with brine, dried (Na_2SO_4), and the solvent removed to give a residue. The residue was diluted with CH_2Cl_2 (10 mL) and HCl in Et_2O (2 M) was added (5 mL). Note: This was done to ensure removal of TMS group at the 5-position, which was approximately 20% by GC–MS. Alternatively, use of TBAF (2 M in THF was also used). The mixture was stirred for 3 h and then portioned between brine and CH_2Cl_2. The layers were separated and organic phase washed with brine, dried (Na_2SO_4), and the solvent removed to give a residue, which was purified by chromatography (silica, 12 g RediSep Column Gold, EtOAc–heptane, 0–40%, 15 CVs) to give the desired product 4-(benzylthio)-2-phenyloxazole (362 mg, 44%) as an oil and *N*-(1,2,3-thiadiazol-5-yl)benzamide (138 mg, 22%).

4-(Benzylthio)-2-phenyloxazole (12, Table 1 and 14a, Table 2, entry 1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–8.09 (m, 2 H), 7.44–7.52 (m, 3 H), 7.43 (s, 1 H), 7.20–7.33 (m, 5 H), 4.12 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2, 139.4, 137.7, 134.3, 130.7, 130.2, 129.1, 128.9, 128.8, 128.4, 127.2, 127.1, 126.5, 38.6 ppm. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}NOS$ $[M + H]^+$: 268.0791; found: 268.0791

***N*-(1,2,3-thiadiazol-5-yl)benzamide (13)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.76 (br s, 1 H) 8.85 (s, 1 H) 8.08 (d, *J* = 7.81 Hz, 2 H) 7.50–7.81 (m, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.7, 151.1, 136.2, 133.2, 130.9, 128.9, 128.1 ppm. ESI-HRMS: *m/z* calcd for $C_9H_7N_3OS$ [M + H]$^+$: 206.0388; found: 206.0382.

(18) **General Procedure for Preparation of SO_2Cl Derivatives**

To a solution of 4-(benzylthio)-2-phenyloxazole (347.2 mg, 1.3 mmol) in AcOH (2 mL) was added H_2O (0.5 mL). The reaction was cooled with an ice-water bath. After 10 min, NCS (538 mg, 4.03 mmol) was added in three portions. The reaction was stirred for 15 min at 0 °C and then allowed to stir at ambient temperature for 2 h. Solids were present when the flask was removed from the cooling bath, which subsequently dissolved upon warming. The yellow homogeneous solution was partitioned between brine and EtOAc. The layers were separated, and the organic phase washed with brine, dried (Na_2SO_4), and the solvent removed to give a residue. The residue was purified by chromatography (silica, 4 g Redisep Gold, EtOAc–heptane, 0–55%, 48 CVs) to give the desired product 2-phenyloxazole-4-sulfonyl chloride (240 mg, 76%) as a solid.

2-Phenyloxazole-4-sulfonyl Chloride (14b, Table 2, entry 1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 8.12–8.19 (m, 2 H), 7.52–7.65 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5, 144.8, 141.7, 133.7, 132.4, 130.2, 129.1, 128.5, 128.2, 127.3, 125.1. ESI-HRMS: *m/z* calcd for $C_9H_6ClNO_3S$ [M + H]$^+$: 243.983; found: 243.9829.