Sulfonimidation via ring-opening of 2-oxazolines with acidic sulfonimide nucleophiles

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Abstract

Acidic sulfonimide nucleophiles including dibenzenesulfonimide, *o*-benzenesulfonimide, dimethanesulfonimide, and *N*-(methylsulfonyl)-benzenesulfonamide are discovered to open a variety of alkyl-, aryl- and heteroaryl-2-oxazoline rings to provide the sulfonimidation products in refluxing 1,4-dioxane. The electron-rich 2-oxazoline substrates worked well for the nucleophilic ring-opening reactions while no reaction took place for the electron-poor 2-oxazoline substrates.

Keywords: Oxazolines, sulfonimides, ring-opening, nucleophilic substitution

Introduction

Oxazolines are versatile ligands and directing groups in organic synthesis. Chiral bis-oxazolines have been extensively used as chiral ligands for asymmetric synthesis.^{1,2} Aryl-2-oxazolines have served as an important class of directing groups for metalation via complex-induced proximity effect (CIPE), also known as directed *ortho*-metalation (DoM), pioneered by Meyers, Beak, and Snieckus, *et al.*^{3,4} On the other hand, oxazolines are also useful building blocks. For example, 2-substituted 1,3-oxazolines, have been used as starting monomers in the cationic polymerization reactions intended for making poly(ethylene imines) of various compositions and molecular weights.^{5,6}

Another approaches is through nucleophilic ring-opening of oxazolines such as 2-phenyl-2-oxazoline (**1**) to give products **2** as depicted in Scheme 1. A variety of nucleophiles have been applied in this type of transformation. Thiophenols⁷ and thiols⁸ have been used as *S*-nucleophiles; and phenols⁹ as *O*-nucleophiles. *C*-Nucleophiles in the form of stabilized carbanions have been used to open oxazoline rings with the aid of methyl triflate.¹⁰ Halides as

nucleophiles generally react with oxazolines in the form of TMS-X.¹¹ Other nucleophiles that have been used to open oxazoline rings also include selenium-¹² and tellurium-¹³ -containing nucleophiles.

Scheme 1. Nucleophilic ring-opening of the oxazolines.

More interestingly, *N*-nucleophiles have found synthetic utility in opening oxazoline rings. For instance, imidazole was used to open the oxazoline ring,¹⁴ as was azide in form of TMS-N₃.¹⁵ In the presence of a Brønsted–Lowry or Lewis acid, amines such as diphenylamine bring about a nucleophilic ring-opening of 2-ethyl-2-oxazoline (**3**) at high temperature (180 °C), offering a synthesis of unsymmetrically substituted ethylenediamines such as **4**.¹⁶

Results and Discussion

In the process of pursuing our on-going interest in fluorination via C–H activation, we fortuitously discovered that *N*-fluorobenzenesulfonimide (NFSI) was able to open the oxazoline ring on **1** to afford sulfonimide **5** in 15% yield. It was quickly realized that fluorine was not actually required for the manipulation and dibenzenesulfonimide [HN(SO₂Ph)₂] was able to serve as an acidic nucleophile to convert **1** into **5** in 93% yield in refluxing 1,4-dioxane (Scheme 2). To the best of our knowledge, this type of sulfonimidation has not been reported previously. Considering the importance of sulfonimides as important bioisosteres of carboxylic acids in medicinal chemistry,^{17–20} we decided to explore the scope and limitation of such a ring-opening reactions.

Scheme 2. Ring-opening 2-oxazoline with dibenzenesulfonimide.

Our accidental discovery of sulfonimidation of 2-phenyl-2-oxazoline (**1**) to give sulfonimide **5** using $\text{HN}(\text{SO}_2\text{Ph})_2$ prompted us to more closely scrutinize this unique nucleophile. Sandwiched between two powerful electron-withdrawing phenylsulfonyl groups, the NH proton on the molecule is exceptionally acidic with a $\text{p}K_{\text{a}}$ value of 1.45,²¹ with a calculated value of 3.24,²² approximately as strong as phosphoric acid. As a result, we suspected that dibenzenesulfonimide is acidic enough to protonate the nitrogen atom on **1**. Indeed, **1** moved to the baseline on TLC upon contact with $\text{HN}(\text{SO}_2\text{Ph})_2$.

We initially surveyed the solvent effect on transformation **1**→**5**. When **1** was heated with dibenzenesulfonimide in polar solvents including DMF and DMSO, no reaction was observed even at 150 °C for a prolonged time. The reaction took place in alcoholic solvents such as EtOH, *n*-BuOH, and isopentanol, but stalled at approximately 70% conversion. The reaction went to completion cleanly in ethereal solvents such as methyl *t*-butyl ether (MTBE), THF, and 1,4-dioxane. At the end, 1,4-dioxane was chosen because it has the highest boiling point. Meanwhile, the optimal stoichiometry for $\text{HN}(\text{SO}_2\text{Ph})_2$ was found to be 1.5 equivalents.

With reaction conditions optimized, we investigated the scope and limitations of this methodology with regard to different oxazoline substrates **7**. Most of them were prepared via a 2-step sequence consisting of amide formation from carboxylic acid **6** with 2-chloroethylamine•HCl,²³ followed by ring closure of the resulting amido-chloride with the aid of NaOH (Scheme 3).²⁴

Scheme 3. Preparation of 2-oxazoline substrates.

For different substrates, stark differences were observed for electron-rich and electron-poor 2-oxazoline substrates (Table 1). For instance, the reaction between 2-phenyl-2-oxazoline (**1**) and dibenzenesulfonimide in refluxing 1,4-dioxane was complete in 45 minutes while the same reaction for 2-(*p*-methoxyphenyl)-2-oxazoline (**8**) took 1.5 hours. 2-Alkyl-2-oxazolines as represented by 2-ethyl-2-oxazoline (**3**) behaved similarly to 2-phenyl-2-oxazoline (**1**). The

reaction was complete in 30 minutes in refluxing 1,4-dioxane to deliver product **15**. Substrates containing thiophene (**9**, **10**) and furan (**11**, **12**) reacted smoothly with $\text{HN}(\text{SO}_2\text{Ph})_2$ in refluxing 1,4-dioxane and reactions were all completed within 2 hours. This is a reflection that both thiophene and furan are electron-rich heterocycles.

Not surprisingly, the corresponding cyclic aryl-sulfonimide, *o*-benzenesulfonimide,²⁵ worked similarly to dibenzenesulfonimide. As shown in Table 1, *o*-benzenesulfonimide was able to open the aryl-, alkyl-, and heteroaryl-oxazoline rings on substrates **1**, **3**, **8**, **9**, and **11**, respectively, with yields ranging from 72% to 95%.

However, this methodology did not work for electron-poor substrates. For example, no reaction was observed when 2-(4-nitrophenyl)-2-oxazoline (**13**) and $\text{HN}(\text{SO}_2\text{Ph})_2$ were heated together at reflux in 1,4-dioxane. Further, addition of 0.5 equiv of sodium hydride to boost the nucleophilicity and heating up to 150 °C for six hours did not provide any ring-opened product either. The same phenomenon was observed for another electron-poor substrate 2-(pyridin-4-yl)-2-oxazoline (**14**), derived from isonicotinic acid.

Table 1. Imidation via nucleophilic ring-opening of 2-oxazoline with dibenzenesulfonimide and *o*-benzenesulfonimide

Substrates	Products	Reaction Time (min)	Yield (%)
		45	93
		30	75
		90	72
		120	93
		120	94
		120	73

		120	90
		45	95

Table 1 (continued)

Substrates	Products	Reaction Time (min)	Yield (%)
		30	89
		120	95
		120	80
		360	0
		360	0

The aforementioned observations are readily explained by invoking the intermediacy of protonated oxazoline **1'** (*vide infra*, Scheme 4). Electron-rich 2-oxazoline substrates such as **3**, **8**, **9**, **10**, **11** and **12** donate electrons to the oxazoline ring, promoting protonation.²⁶ On the other hand, electron-poor 2-substituents withdraw electrons from the oxazoline ring so that the nitrogen is no longer basic enough to be protonated by $\text{HN}(\text{SO}_2\text{Ph})_2$ and the reaction does not proceed.

As far as the reaction mechanism is concerned, we speculate that the nitrogen atom is protonated by $\text{HN}(\text{SO}_2\text{Ph})_2$, furnishing ammonium intermediate **1'** and $(\text{PhSO}_2)_2\text{N}^\ominus$ anion.²⁷ This was derived from the fact that **1** was protonated upon contact with Brønsted–Lowry acid $\text{HN}(\text{SO}_2\text{Ph})_2$ to form **1'**. Meanwhile, the $(\text{PhSO}_2)_2\text{N}^\ominus$ anion serves as a nucleophile to open the oxazoline ring in an $\text{S}_\text{N}2$ fashion to furnish the imidation product **5**.

Scheme 4. Proposed reaction mechanism.

We then proceeded to explore additional viable acidic sulfonamide nucleophiles for this ring-opening reaction. Three additional nucleophiles were prepared. As shown in Scheme 5, *N*-(phenylsulfonyl)acetamide (**27**) was prepared by treating a suspension of benzenesulfonamide in CH_2Cl_2 with acetic anhydride in the presence of a catalytic amount of TiCl_4 .²⁸ 2,2,2-Trifluoro-*N*-(phenylsulfonyl)acetamide (**28**) was synthesized in the same manner using trifluoroacetic anhydride. Finally, *N*-(methylsulfonyl)benzenesulfonamide (**29**) was assembled in 35% yield by the reaction between benzenesulfonamide and methanesulfonyl chloride in the presence of Et_3N and a catalytic amount of DMAP.²⁹

Scheme 5. Preparation of additional acidic sulfonimide nucleophiles.

We then proceeded to examine a variety of nucleophiles for the oxazoline-opening reaction. With a pK_a of 14.7, phthalimide was not acidic enough to open the 2-oxazoline ring under optimized reaction conditions; neither was benzenesulfonamide, with a pK_a of 10.1.³⁰ When acylsulfonamide **27** (calculated pK_a , 5.51) also failed to open the oxazoline ring,³¹ we began to suspect that a nucleophile with similar acidity to $\text{HN}(\text{SO}_2\text{Ph})_2$ would be more amenable to such transformations. Indeed, heating **1** with triflimide [$\text{HN}(\text{COCF}_3)_2$, pK_a , 2.95) and trifluoroacetylsulfonamide **28** (calculated pK_a , 3.52) in refluxing 1,4-dioxane provided the

desired ring-opening products. Unfortunately, the resulting products were not stable on silica gel and less than 27% of the products were isolated.

Thankfully, dimethanesulfonimide (calculated pK_a , 3.43),²² and mixed sulfonimide **29** (calculated pK_a , 3.63),²² worked well in the ring-opening reaction. Further, both nucleophiles – dimethanesulfonimide and mixed sulfonimide **29** – worked on alkyl-, aryl- and heteroaryl-oxazolines to produce the ring-opening products with yields ranging from 56% to 84% (Table 2). The relatively moderate yields for reactions (Table 2) can be attributed to the fact that alkyl-sulfonimides are less acidic than aryl-sulfonimides.

Table 2. Imidation via nucleophilic ring-opening of 2-oxazolines with additional acidic sulfonimides

Substrates	Products	Yield (%)
56
62
70
61
84
78
70
59

Regrettably, sterically hindered oxazolines **38** and **39** (Figure 1) did not react in attempted ring openings using this methodology. This is most likely due to the fact that steric hindrance of the α -neopentyl cannot accommodate the bulky nucleophile $(\text{PhSO}_2)_2\text{N}^\ominus$ anion.

Figure 1. Sterically hindered oxazolines.

Many efforts were made to react the sulfonimides with other nucleophiles such as azide, but these invariably produced the ring-closure products, the very starting materials to make those linear amide-sulfonimides. This is not completely surprising because once the NH bond on the amide encounters even weak basic conditions, the *intramolecular* ring-closure prevails because it is very much more kinetically favored than the *intermolecular* $\text{S}_\text{N}2$ substitution, especially considering that sulfonimides are such good leaving groups. Therefore, the synthetic utility of the linear ring-opening products are limited to their corresponding linear forms.

Conclusions

We have discovered that acidic sulfonimides can serve as nucleophiles to open 2-substituted oxazolines. This methodology of sulfonimidation works more efficiently for oxazoline substrates with an electron-rich 2-substituent, while no reaction took place for oxazolines with electron-poor 2-substituents. The resulting linear amide-sulfonimides may serve as bioisosteres of carboxylic acids in drug discovery.

Experimental Section

General. All reactions were performed in anhydrous solvents under a N_2 atmosphere. Solvents were purchased from Alfa Aesar and utilized without further purifications. 2-Phenyl-2-oxazoline (**1**), 2-ethyl-2-oxazoline (**3**), dibenzenesulfonimide, bistrifluoroacetamide, and dimethanesulfonimide are commercially available and were used without further purifications. Analytical thin-layer chromatography (TLC) was carried out using Silica G TLC plates, 200 μM with UV254 (SORBENT Technologies), with visualization by UV or iodine. Flash chromatography was performed using standard grade silica gel (60 Å, 230–400 mesh; SORBENT Technologies). Melting Points were taken using Vernier Melt Station LabQuest 2

and were not corrected. NMR spectra were acquired using an Agilent VNMRs spectrometer equipped with one NMR probe (500 MHz for ^1H , 125 MHz for ^{13}C , 470 MHz for ^{19}F). Spectra were processed using MNova software (Mestrelab). Chemical shifts are reported in parts per million (ppm), coupling constants (J) in Hz and are calibrated to residual protonated solvent. Infrared spectra of neat samples were acquired using a PerkinElmer Spectrum 100 FT-IR spectrometer, with solid samples analyzed using a Universal ATR (attenuated total reflectance) sampling accessory. GC-MS was performed on a Hewlett Packard HP6890 Series GC System and a 5973 Mass Selective Detector.

Representative procedures for substrate preparation

Step 1

2-Thiophene carboxylic acid (1 g 7.8 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2 and cooled to $0\text{ }^\circ\text{C}$; 5 drops of DMF was added to the suspension. Oxalyl chloride (1.98 g, 15.8 mmol) was added dropwise to the reaction mixture. The reaction was warmed to rt and stirred for 3 h. The solvent was removed *in vacuo* and the residue was dried for 1 h in high vacuum. The residue was dissolved in 5 mL of CH_2Cl_2 and added dropwise to a suspension of chloroethylamine•HCl (1.08 g, 9.4 mmol), Et_3N (2.52 g, 24 mmol) in 7 mL of CH_2Cl_2 at $0\text{ }^\circ\text{C}$. The reaction stirred for 3 h and was warmed to rt. The reaction was diluted with CH_2Cl_2 and washed once with sat. aq. ammonium NH_4Cl then concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography in a solvent system of hexane:ethyl acetate 2/1, respectively, to afford *N*-(2-chloroethyl)thiophene-2-carboxamide.

Step 2

N-(2-Chloroethyl)thiophene-2-carboxamide, (1.07 g 5.7 mmol) was added to a solution of NaOH (0.286 g 7.2 mmol) dissolved in EtOH. The reaction was heated at $50\text{ }^\circ\text{C}$ for 1 h and cooled to rt. The reaction was diluted with EtOAc and washed twice with brine. The organic layer was dried over MgSO_4 , filtered, and then concentrated.

2-(Thien-2-yl)-4,5-dihydrooxazole (9). White solid, mp $59\text{--}60\text{ }^\circ\text{C}$; FTIR (neat, ATR, cm^{-1}) 1643, 1430, 1246, 1051, 1013, 925, 851, 729, 692; ^1H NMR (500 MHz, CDCl_3) δ 7.58 (dd, J 3.6, 1.2 Hz, 1H), 7.44 (dd, J 5.0, 1.2 Hz, 1H), 7.07 (dd, J 5.0, 3.7 Hz, 1H), 4.42 (t, J 9.4 Hz, 2H), 4.03 (t, J 9.4 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 160.51, 130.49, 130.25, 129.83, 127.68, 68.16, 55.12.

2-(4-Methoxyphenyl)-4,5-dihydrooxazole (8). White solid, mp 40.8–42.3 °C; FTIR (neat, ATR, cm^{-1}) 1644, 1606, 1510, 1253, 1166, 1068, 1021, 939, 844, 672; ^1H NMR (500 MHz, CDCl_3) δ 7.88 (d, J 8.9 Hz, 2H), 6.90 (d, J 8.8 Hz, 2H), 4.39 (t, J 9.5 Hz, 2H), 4.02 (t, J 9.4 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.15, 129.99, 128.94, 120.35, 113.80, 67.64, 55.45, 54.92.

2-(Thien-3-yl)-4,5-dihydrooxazole (10). White solid, mp 73–74 °C; FTIR (neat, ATR, cm^{-1}) 3107, 3070, 1651, 1421, 1317, 1258, 1064, 951, 702; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (d, J 3.3 Hz, 1H), 7.51 (d, J 5.1 Hz, 1H), 7.31 (dd, J 5.1, 3.0 Hz, 1H), 4.38 (t, J 9.4 Hz, 2H), 4.02 (t, J 9.5 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.16, 130.06, 128.66, 127.30, 126.24, 67.55, 54.91.

2-(Furan-2-yl)-4,5-dihydrooxazole (11). White solid, mp 76–79 °C; FTIR (neat, ATR, cm^{-1}) 3099, 1673, 1563, 1480, 1352, 1172, 1096, 1013, 954, 774, 706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.54 (dd, J 1.8, 0.8 Hz, 1H), 6.94 (d, J 3.4 Hz, 1H), 6.48 (dd, J 3.5, 1.8 Hz, 1H), 4.41 (t, J 9.6 Hz, 2H), 4.06 (t, J 9.4 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.09, 145.26, 143.24, 114.27, 111.60, 67.87, 55.04.

2-(Furan-3-yl)-4,5-dihydrooxazole (12). Yellow oil (73% yield), mp 36–39 °C; FTIR (neat, ATR, cm^{-1}) 3091, 1668, 1517, 1353, 1272, 1151, 1113, 1063, 976, 927 869, 843, 750; ^1H NMR (500 MHz, CDCl_3) δ 7.88 (s, 1H), 7.43 (t, J 1.7 Hz, 1H), 6.76 (dd, J 1.8, 0.8 Hz, 1H), 4.36 (t, J 9.4 Hz, 2H), 3.99 (t, J 9.4 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.98, 144.77, 143.80, 115.68, 109.53, 67.42, 54.76; HRMS (ESI, m/z) calcd for $\text{C}_7\text{H}_7\text{N}_1\text{O}_2$: 137.0477, found: 137.0476.

Preparation of sulfonimides

Representative procedure for preparation of N-(2-(N-(phenylsulfonyl)phenyl)sulfonamido)benzamide (5)

2-Phenyl-2-oxazoline (**1**, 0.441 g, 3.0 mmol) was dissolved in 1,4-dioxane (30 mL). After addition of dibenzenesulfonimide (1.336 g, 0.45 mmol), the resulting solution was refluxed for 30 min to 2 h until reaction was judged complete by TLC (hexanes:ethyl acetate). The reaction

was cooled, diluted with ethyl acetate, washed once with saturated aq NH_4Cl , and twice with brine. The organic layer was concentrated *in vacuo*. The residue was purified using flash chromatography (hexane: ethyl acetate) to obtain the desired ring opened product, *N*-(2-(*N*-(phenylsulfonyl)phenylsulfonamido)ethyl)benzamide (**5**), as a white solid (1.241 g, 93%). mp 81.2–83.3 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (dd, J 8.5, 1.3 Hz, 4H), 7.74 (dd, J 8.2, 1.1 Hz, 2H), 7.65–7.56 (m, 2H), 7.53–7.43 (m, 5H), 7.41–7.34 (m, 2H), 6.91 (s, 1H), 3.98 (t, J 5.8 Hz, 2H), 3.72 (q, J 5.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.69, 139.19, 134.26, 133.98, 131.64, 129.34, 128.62, 128.28, 127.06, 47.51, 39.52; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$: 444.0814, found: 444.0815; FTIR (neat, ATR, cm^{-1}) 3312, 3071, 2990, 1725, 1737, 1642, 1544, 1492 1448, 1371, 1353, 1160, 1169, 882, 825.

***N*-(2-(*N*-(Phenylsulfonyl)phenylsulfonamido)ethyl)propionamide (15).** White solid (75% yield), mp 113.3–119.5 °C; FTIR (neat, ATR, cm^{-1}) 3274, 1644, 1539, 1447, 1368, 1166, 1083, 833 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (dd, J 8.4, 1.1 Hz, 4H), 7.70–7.63 (m, 2H), 7.59–7.51 (m, 4H), 5.97 (s, 1H), 3.87 (t, J 5.8 Hz, 2H), 3.54 (q, J 5.7 Hz, 2H), 2.16 (q, J 7.6 Hz, 2H), 1.09 (t, J 7.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.19, 139.21, 134.14, 129.24, 128.24, 47.53, 38.80, 29.55, 9.58; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$: 396.0814, found: 396.08084.

4-Methoxy-*N*-(2-(*N*-(phenylsulfonyl)phenylsulfonamido)ethyl)benzamide (16). White solid (72% yield), mp 139.2–140.0 °C; FTIR (neat, ATR, cm^{-1}) 3317, 1634, 1605, 1548, 1447, 1372, 1260, 1128, 1084, 883, 834; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, J 7.8 Hz, 4H), 7.71 (d, J 8.3 Hz, 2H), 7.62 (t, J 7.5 Hz, 2H), 7.51 (t, J 7.7 Hz, 4H), 6.89 (d, J 8.4 Hz, 2H), 6.76 (s, 1H), 3.97 (t, J 5.7 Hz, 2H), 3.82 (s, 3H), 3.71 (q, J 5.6 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.22, 162.34, 139.26, 134.29, 129.38, 128.91, 128.33, 126.36, 113.85, 55.50, 47.62, 39.47; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S}_2$: 474.0919, found: 474.0912.

***N*-(2-(*N*-(Phenylsulfonyl)phenylsulfonamido)ethyl)thiophene-2-carboxamide (17).** White solid (93% yield), mp 117.3–119.8 °C; FTIR (neat, ATR, cm^{-1}) 3270, 2259, 1626, 1563, 1448, 1372, 1167, 1127, 1083, 870, 857, 809; ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J 7.2 Hz, 4H), 7.67–7.62 (m, 2H), 7.54 (t, J 7.9 Hz, 4H), 7.46 (dd, J 5.0, 1.1 Hz, 1H), 7.43 (dd, J 3.8, 1.2 Hz, 1H), 7.04 (dd, J 5.0, 3.7 Hz, 1H), 6.67 (s, 1H), 3.97 (t, J 5.8 Hz, 2H), 3.71 (q, J 5.5 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.21, 139.25, 138.75, 134.36, 130.31, 129.45, 128.38, 128.23, 127.79, 47.50, 39.40; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_3$: 450.0378, found: 450.0373.

***N*-(2-(*N*-(Phenylsulfonyl)phenylsulfonamido)ethyl)thiophene-3-carboxamide (18).** White solid (94% yield), mp 145.1–145.9 °C; FTIR (neat, ATR, cm^{-1}) 3294, 1633, 1551, 1448, 1369, 1295, 1166, 1083, 861, 830; ^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, J 7.8 Hz, 4H), 7.83 (s, 1H), 7.64 (t, J 7.5 Hz, 2H), 7.53 (t, J 7.7 Hz, 4H), 7.36 (d, J 5.0 Hz, 1H), 7.30 (s, 1H), 6.70 (s, 1H), 3.97 (t, J 5.7 Hz, 2H), 3.70 (d, J 5.7 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.30, 139.20, 137.19, 134.35, 129.42, 128.56, 128.35, 126.55, 126.24, 47.54, 39.21; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_3$: 450.0378, found: 450.0372.

***N*-(2-(*N*-(Phenylsulfonyl)phenylsulfonamido)ethyl)furan-2-carboxamide (19).** White solid (73% yield), mp 124.1–125.3 °C; FTIR (neat, ATR, cm^{-1}) 3269, 1647, 1597, 1537, 1446, 1368,

1350, 1323, 1300, 1177, 1167, 1129, 1077, 1010, 873, 810; ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.99 (m, 4H), 7.67–7.61 (m, 2H), 7.57–7.49 (m, 4H), 7.42 (dd, J 1.8, 0.8 Hz, 1H), 7.08 (dd, J 3.4, 0.8 Hz, 1H), 6.75 (s, 1H), 6.48 (dd, J 3.5, 1.8 Hz, 1H), 3.96 (t, J 6.1 Hz, 2H), 3.68 (q, J 6.0 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.75, 147.74, 144.28, 139.40, 134.24, 129.37, 128.39, 114.46, 112.17, 47.70, 38.95; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_6\text{S}_2$: 434.0606, found: 434.0599

***N*-(2-(*N*-(Phenylsulfonyl)phenylsulfonamido)ethyl)furan-3-carboxamide (20).** White solid (90% yield), mp 121.8–125.3 °C; FTIR (neat, ATR, cm^{-1}) 3254, 2261, 1638, 1589, 1542, 1449, 1373, 1350, 1169, 1127, 1084, 1024, 864; ^1H NMR (500 MHz, CDCl_3) δ 8.03–7.97 (m, 4H), 7.89 (dd, J 1.6, 0.9 Hz, 1H), 7.69–7.62 (m, 2H), 7.57–7.51 (m, 4H), 7.39 (t, J 1.8 Hz, 1H), 6.59 (dd, J 1.9, 0.9 Hz, 1H), 6.52 (s, 1H), 3.95 (t, J 5.4 Hz, 2H), 3.67 (q, J 5.3 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.94, 144.97, 143.86, 139.20, 134.38, 129.44, 128.37, 122.38, 108.41, 47.50, 38.96; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_6\text{S}_2$: 434.0606, found: 434.0602.

***N*-(2-(1,1,3,3-Tetraoxidobenzo[*d*][1,3,2]dithiazol-2-yl)ethyl)benzamide (21).** White solid (95% yield), mp 162–164 °C; FTIR (neat, ATR, cm^{-1}) 3337, 1635, 1536, 1337, 1320, 1203, 1139, 1125, 1069, 947, 797, 761, 721; ^1H NMR (500 MHz, CDCl_3) δ 8.08–7.73 (m, 5H), 7.55–7.32 (m, 3H), 6.81 (s, 1H), 4.06 (br. s, 2H), 3.91 (br. s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.93, 135.21, 135.14, 134.12, 131.77, 128.69, 127.23, 122.47, 42.03, 39.15; HRMS (ESI, m/z) calcd for, $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5\text{S}_2$: 366.0344, found: 366.0340.

***N*-(2-(1,1,3,3-Tetraoxidobenzo[*d*][1,3,2]dithiazol-2-yl)ethyl)propionamide (22).** White solid (89% yield), mp 114–117 °C; FTIR (neat, ATR, cm^{-1}) 3270, 1638, 1551, 1335, 1198, 1167, 1091, 811, 764, 730; ^1H NMR (500 MHz, CDCl_3) δ 8.05–8.00 (m, 2H), 7.99–7.91 (m, 2H), 6.04 (s, 1H), 4.00–3.86 (m, 2H), 3.78–3.55 (m, 2H), 2.27 (q, J 7.6 Hz, 2H), 1.18 (t, J 7.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.45, 135.33, 135.11, 122.45, 42.17, 38.57, 29.72, 9.64; HRMS (ESI, m/z) calcd for, $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5\text{S}_2$: 318.0344, found: 318.0339.

***N*-(2-(1,1,3,3-Tetraoxidobenzo[*d*][1,3,2]dithiazol-2-yl)ethyl)thiophene-2-carboxamide (23).** White solid (95% yield), mp 158–162 °C; FTIR (neat, ATR, cm^{-1}) 3318, 1629, 1547, 1442, 1336, 1203, 1138, 1072, 969, 788, 766, 723; ^1H NMR (500 MHz, CDCl_3) δ 8.07–8.00 (m, 2H), 7.98–7.90 (m, 2H), 7.56 (dd, J 3.8, 1.2 Hz, 1H), 7.48 (dd, J 5.0, 1.1 Hz, 1H), 7.06 (dd, J 5.0, 3.7 Hz, 1H), 6.66 (s, 1H), 4.08–4.02 (m, 2H), 3.93–3.86 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.29, 138.56, 135.22, 135.17, 130.53, 128.58, 127.79, 122.51, 42.10, 39.07; HRMS (ESI, m/z) calcd for, $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_5\text{S}_3$: 371.9908, found: 371.9903.

***N*-(2-(1,1,3,3-Tetraoxidobenzo[*d*][1,3,2]dithiazol-2-yl)ethyl)furan-2-carboxamide (24).** White solid (80% yield), mp 108–110 °C; FTIR (neat, ATR, cm^{-1}) 3314, 1647, 1569, 1532, 1443, 1336, 1202, 1140, 1075, 1046, 1021, 794, 753, 727; ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.99 (m, 2H), 7.97–7.88 (m, 2H), 7.44 (dd, J 1.8, 0.8 Hz, 1H), 7.13 (dd, J 3.5, 0.8 Hz, 1H), 6.91 (s, 1H), 6.48 (dd, J 3.5, 1.7 Hz, 1H), 4.03–3.99 (m, 2H), 3.92–3.86 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.80, 147.70, 144.44, 135.29, 135.11, 122.51, 114.77, 112.20, 41.92, 38.28; HRMS (ESI, m/z) calcd for, $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_6\text{S}_2$: 356.0137, found: 356.0131.

***N*-(2-(*N*-(Methylsulfonyl)methylsulfonamido)ethyl)benzamide (30).** White solid (56%). mp 167–169 °C; FTIR (neat, ATR, cm^{-1}) 3271, 1628, 1543, 1353, 1152, 1068, 967, 900, 795, 759, 671; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J 7.6 Hz, 2H), 7.51 (t, J 7.3 Hz, 1H), 7.45 (t, J 7.6 Hz, 2H), 6.61 (s, 1H), 4.05 (t, J 5.5 Hz, 2H), 3.79 (q, J 5.6 Hz, 2H), 3.33 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.13, 134.05, 131.90, 128.85, 127.10, 47.32, 43.84, 38.93; HRMS (ESI, m/z) calcd for, $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5\text{S}_2$: 320.0501, found: 320.0498.

4-Methoxy-*N*-(2-(*N*-(methylsulfonyl)methylsulfonamido)ethyl)benzamide (31). White solid (62%), mp 128–130 °C; FTIR (neat, ATR, cm^{-1}) 3218, 1626, 1605, 1507, 1344, 1324, 1256, 1153, 1071, 1028, 961, 851, 802, 786, 757; ^1H NMR (500 MHz, CDCl_3) δ 7.80–7.78 (m, 1H), 7.78–7.76 (m, 1H), 6.94–6.93 (m, 1H), 6.92–6.90 (m, 1H), 6.56 (s, 1H), 4.03 (t, J 5.4 Hz, 2H), 3.84 (s, 3H), 3.76 (q, J 5.5 Hz, 2H), 3.32 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.60, 162.52, 128.94, 126.30, 114.03, 55.54, 47.37, 43.81, 38.88; HRMS (ESI, m/z) calcd for, $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_6\text{S}_2$: 350.0606, found: 350.0600.

***N*-(2-(*N*-(Methylsulfonyl)methylsulfonamido)ethyl)thiophene-3-carboxamide (32).** White solid (70%). mp 197–199 °C; FTIR (neat, ATR, cm^{-1}) 3249, 1619, 1546, 1350, 1309, 1151, 1073, 959, 893, 790, 698; ^1H NMR (500 MHz, CDCl_3) δ 7.54 (dd, J 3.8, 1.1 Hz, 1H), 7.50 (dd, J 4.9, 1.2 Hz, 1H), 7.09 (dd, J 5.0, 3.7 Hz, 1H), 6.47 (s, 1H), 4.03 (t, J 5.4 Hz, 2H), 3.76 (q, J 5.6 Hz, 2H), 3.33 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.54, 138.48, 130.61, 128.49, 127.93, 47.18, 43.84, 38.95. HRMS (ESI, m/z) calcd for, $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_5\text{S}_3$: 326.0065, found: 326.0062.

***N*-(2-(*N*-(Methylsulfonyl)methylsulfonamido)ethyl)furan-2-carboxamide (33).** White solid (61%), mp 166–169 °C; FTIR (neat, ATR, cm^{-1}) 3235, 1641, 1569, 1538, 1352, 1319, 1153, 1073, 959, 868, 794; ^1H NMR (500 MHz, CDCl_3) δ 7.47 (dd, J 1.8, 0.8 Hz, 1H), 7.12 (dd, J 3.5, 0.8 Hz, 1H), 6.72 (s, 1H), 6.50 (dd, J 3.5, 1.7 Hz, 1H), 4.00 (t, J 6.2 Hz, 2H), 3.74 (q, J 5.8 Hz, 2H), 3.33 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.98, 147.62, 144.54, 114.80, 112.28, 47.25, 43.67, 38.54; HRMS (ESI, m/z) calcd for, $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_6\text{S}_2$: 310.0293, found: 310.0289.

***N*-(2-(*N*-(Methylsulfonyl)phenylsulfonamido)ethyl)benzamide (34).** White solid (84%), mp 138–141 °C; FTIR (neat, ATR, cm^{-1}) 3364, 1643, 1541, 1369, 1362, 1314, 1290, 1152, 1086, 976, 899, 791, 781, 723; ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.99 (m, 2H), 7.85–7.79 (m, 2H), 7.68–7.61 (m, 1H), 7.58–7.47 (m, 3H), 7.47–7.40 (m, 2H), 6.79 (s, 1H), 3.98 (d, J 6.0 Hz, 2H), 3.75 (q, J 5.5 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.93, 138.75, 134.45, 134.03, 131.83, 129.41, 128.80, 128.39, 127.11, 47.37, 44.95, 39.22; HRMS (ESI, m/z) calcd for, $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_2$: 382.0657, found: 382.0653.

***N*-(2-(*N*-(Methylsulfonyl)phenylsulfonamido)ethyl)propionamide (35).** White solid (78%), m.p. 130–133 °C; FTIR (neat, ATR, cm^{-1}) 3282, 1647, 1539, 1448, 1431, 1360, 1346, 1164, 1070, 964, 900, 796, 725, 681; ^1H NMR (500 MHz, CDCl_3) δ 8.01 (dd, J 8.4, 1.2 Hz, 2H), 7.69–7.64 (m, 1H), 7.59–7.53 (m, 2H), 5.88 (s, 1H), 3.85 (t, J 5.7 Hz, 2H), 3.56 (q, J 5.6 Hz, 2H), 3.43 (s, 3H), 2.24 (q, J 7.6 Hz, 2H), 1.16 (t, J 7.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.49, 138.94, 134.40, 129.40, 128.41, 47.55, 44.89, 38.48, 29.90, 9.82; HRMS (ESI, m/z) calcd for, $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_2$: 334.0657, found: 334.0653.

***N*-(2-(*N*-(Methylsulfonyl)phenylsulfonamido)ethyl)thiophene-2-carboxamide (36).** White solid (70%), mp 123–125 °C; FTIR (neat, ATR, cm⁻¹) 3269, 1610.1549, 1361, 1347, 1320, 1265, 1085, 1065, 967, 895, 853, 819, 783, 735, 728; ¹H NMR (500 MHz, CDCl₃) δ 8.02 (dd, *J* 8.7, 1.5 Hz, 2H), 7.68–7.61 (m, 1H), 7.57–7.50 (m, 3H), 7.48 (dd, *J* 5.0, 1.1 Hz, 1H), 7.07 (dd, *J* 5.0, 3.7 Hz, 1H), 6.71 (s, 1H), 3.95 (t, *J* 5.7 Hz, 2H), 3.71 (q, *J* 5.5 Hz, 2H), 3.42 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 162.28, 138.52, 138.49, 134.31, 130.36, 129.27, 128.25, 128.24, 127.74, 47.08, 44.81, 39.07; HRMS (ESI, *m/z*) calcd for, C₁₄H₁₆N₂O₅S₃: 388.0221, found: 388.0218.

***N*-(2-(*N*-(Methylsulfonyl)phenylsulfonamido)ethyl)furan-3-carboxamide (37).** White solid (70%), mp 123–125 °C; FTIR (neat, ATR, cm⁻¹) 3254, 3150, 1637, 1585, 1539, 1449, 1361, 1348, 1338, 1318, 1128, 1088, 1069, 1031, 965, 873, 809, 753, 725, 682, 674; ¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* 7.4 Hz, 2H), 7.96 (s, 1H), 7.65 (t, *J* 7.5 Hz, 1H), 7.54 (t, *J* 7.8 Hz, 2H), 7.42 (s, 1H), 6.66 (d, *J* 1.9 Hz, 1H), 6.55 (s, 1H), 3.92 (t, *J* 5.7 Hz, 2H), 3.67 (q, *J* 5.5 Hz, 2H), 3.41 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.13, 145.06, 143.97, 138.66, 134.46, 129.41, 128.35, 122.37, 108.41, 47.24, 44.92, 38.66; HRMS (ESI, *m/z*) calcd for, C₁₄H₁₆N₂O₆S₂: 372.0450, found: 372.0446.

***N*-(Phenylsulfonyl)acetamide (27).** White solid, mp 128–131 °C; FTIR (neat, ATR, cm⁻¹) 3112, 2902, 1702, 1686, 1459, 1352, 1160, 1090, 934, 858, 762, 687; ¹H NMR (500 MHz, CDCl₃) δ 9.38 (s, 1H), 8.11–7.99 (m, 2H), 7.68–7.60 (m, 1H), 7.57–7.51 (m, 2H), 2.07 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.00, 138.54, 134.17, 129.16, 128.29, 23.60.

2,2,2-Trifluoro-*N*-(phenylsulfonyl)acetamide (28). White solid, mp 139–142 °C; FTIR (neat, ATR, cm⁻¹) 3223, 1772, 1467, 1360, 1154, 1116, 1081, 887, 826, 757, 679; ¹H NMR (500 MHz, CDCl₃) δ 8.79 (br. s, 1H), 8.14–8.10 (m, 2H), 7.78–7.71 (m, 1H), 7.65–7.56 (m, 2H); ¹³C NMR (126 MHz, cdcl₃) δ 154.20, 153.87, 136.88, 135.38, 129.57, 128.97; ¹⁹F NMR (470 MHz, CDCl₃) δ -75.64.

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