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Regioselective Reaction of Heterocyclic *N*-Oxides, an Acyl Chloride, and Cyclic Thioethers

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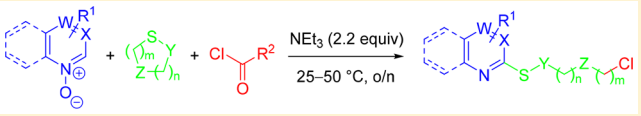
Supporting Information

ABSTRACT: Treatment of electron deficient pyridine *N*-oxides with 4-nitrobenzoyl chloride and a cyclic thioether in the presence of triethylamine leads to the corresponding 2-functionalized product in up to a 74% isolated yield. The transformation can also be accomplished with alternative nitrogen containing heterocycles, including quinolines, pyrimidines, and pyrazines. To expand the scope of the transformation, diisopropyl ether can be used as the reaction medium to allow for the use of solid thioether substrates.



Nitrogen containing heterocycles including pyridines, quinolines, pyrazines, and pyrimidines are embedded in many molecules of agrochemical and pharmaceutical significance.[1] Methods for either the generation or selective functionalization of these heterocycles are therefore of great interest.[2−4] 2-Substituted derivatives represent an important subset of this family that show a broad spectrum of biological activities as exemplified by nexium, pirfenidone, boscalid, and lunesta (Figure 1), which

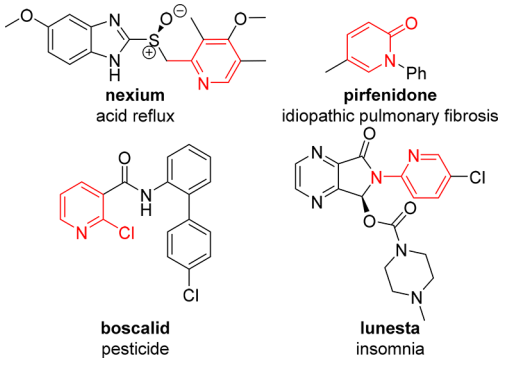


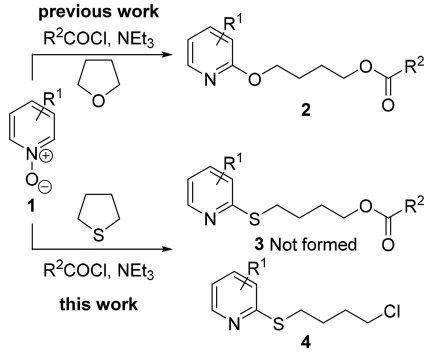
Figure 1. Examples of 2-heteroatom-substituted pyridine derivatives with biological activity.

contain carbon, oxygen, chlorine, and nitrogen substitution at the 2-position, respectively.

When compared to the introduction of nitrogen[5] and oxygen[6] heteroatoms at the 2-position of nitrogen containing heterocycles, the addition of a sulfur atom is a substantially less developed area. Two principal approaches have been developed for the introduction of a sulfur heteroatom: (1) an S_NAr reaction on a 2-halo derivative, which is an effective strategy for electron deficient substrates,[7] and (2) the activation of heterocyclic *N*-oxides in the presence of a nucleophile. For example, PyBroP has been shown to be an excellent reagent in facilitating the addition of a thiol to the 2-position of a pyridine *N*-oxide.[8] More recent methods for the sulfonylation of quinoline and pyridine *N*-oxides through reaction with sodium sulfonates,[9] sulfonyl hydrazides,[10] or sulfonyl chlorides[11] have further expanded this toolbox.

We recently described a simple and effective regioselective three-component coupling reaction of a pyridine *N*-oxide **1**, an acyl chloride, and THF, which led to the corresponding 2-functionalized pyridine **2** (Scheme 1).[12] We were interested

Scheme 1. Different Reactivity of Ethers and Thioethers



in discovering if a similar transformation could be performed using tetrahydrothiophene as a method for preparing 2-thio-substituted pyridine derivatives. The reaction of 3-cyanopyridine *N*-oxide **1a** (R^1 = 3-CN) with 4-nitrobenzoyl chloride

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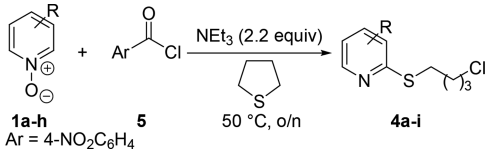
(R^2 = 4-$NO_2C_6H_4$, 2.2 equiv) and triethylamine (2.2 equiv) in tetrahydrothiophene (0.2 M) at 50 °C overnight did not give **3**, the product analogous to that observed using THF. Instead, the 2-substituted pyridine **4a** (R^1 = 3-CN) was isolated in an excellent 74% yield. With this transformation, a chloride had been incorporated into the product rather than a molecule of 4-nitrobenzoate. Introduction of the chloride group provided greater potential for further functionalization, and we believed this represented a promising new transformation. Within this manuscript we describe the scope and limitations of this process, expand the transformation to encompass alternative nitrogen containing heterocycles, and show that the reaction can be performed effectively in ethereal solvents, allowing a significant reduction in the amount of sulfide nucleophile used.

Having showed the reaction was effective using 3-cyanopyridine *N*-oxide **1a** as the substrate under the same conditions developed for the reaction of THF,[12] we went on to examine alternative pyridine *N*-oxide substrates (Table 1). While 4-cyanopyridine

Table 1. Reaction of Pyridine *N*-Oxide Substrates[a]



1a-h **5** **4a-i**
Ar = 4-$NO_2C_6H_4$

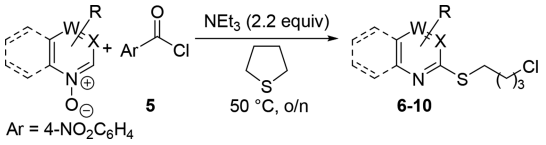
entry	*N*-oxide	R	product	yield (%)[b]
1	**1a**	3-CN	**4a**	74
2	**1b**	4-CN	**4b**	28
3	**1c**	3-Cl	**4c**	51
4	**1d**	4-Cl	**4d**	39
5	**1e**	3-NO_2	**4e**	37
6	**1f**	4-NO_2	**4f**	0[c]
7	**1g**	2-CF_3, 5-CN	**4g**	60
8	**1h**	H	**4h**	0[d]
9	**1i**	2-Cl, 6-Cl	**4i**	0[d]

[a]Reactions carried out at 0.2 M with 2.2 equiv of 4-nitrobenzoyl chloride. [b]Isolated yield. [c]Starting material recovered. [d]Product of *O*-benzoylation observed.

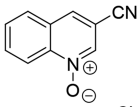
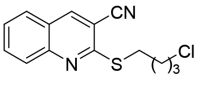
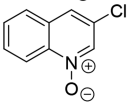
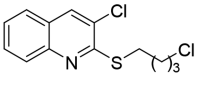
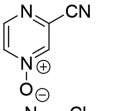
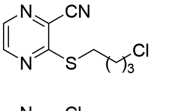
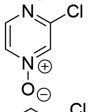
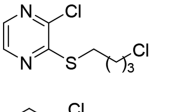
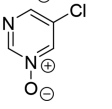
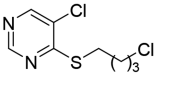
N-oxide **1b** was a less effective substrate, the product was easily purified by column chromatography (entry 2, 28%). 3-Chloro- and 4-chloropyridine *N*-oxide **1c** and **1d** also gave the expected products in 51% and 39% yields, respectively (entries 3 and 4). In addition, the disubstituted substrate **1g** gave **4g** in an excellent 60% yield (entry 7), providing an improved entry to a scaffold known to be a potent TRPV1 antagonist.[13] The transformation requires an electron withdrawing group on the pyridine to proceed (**1h**, entry 8), although in an extreme case (**4f**, entry 6) this prevents *O*-benzoylation, presumably due to the reduced nucleophilicity of the *N*-oxide. Blocking the 2-position of the pyridine ring resulted in *O*-benzoylation, but this product did not lead to the 4-substituted derivative (entry 9).

Encouraged by the excellent reactivity shown by pyridine *N*-oxide substrates, we went on to examine alternative nitrogen containing heterocycles within the transformation (Table 2). Electron deficient quinoline *N*-oxides smoothly delivered the 2-substituted products (entries 1 and 2). 1,4-Pyrazine *N*-oxides (entries 3 and 4) and a pyrimidine *N*-oxide (entry 5, 63%) were also effective substrates. The transformation therefore appears to be effective across a range of heterocyclic *N*-oxides, leading to functionalized products with excellent opportunities for further elaboration.

Table 2. Reaction of Alternative Heterocyclic *N*-Oxides

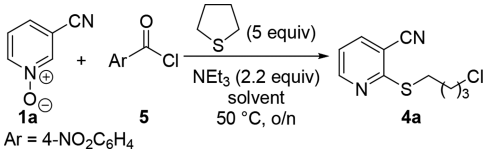


Ar = 4-$NO_2C_6H_4$ **5** **6-10**

entry	substrate	product		yield (%)
1			**6**	63
2			**7**	62
3			**8**	56
4			**9**	54
5			**10**	63

Despite the success observed in the reaction of the *N*-oxide substrates shown in Tables 1 and 2, a drawback of the overall transformation was using sulfide as the reaction medium. This presented two distinct disadvantages to the process. First, the sulfide was used in vast excess; for example, in the reaction of tetrahydrothiophene with 3-cyanopyridine *N*-oxide **1a** the sulfide was present in a 57 equiv excess (Table 1, entry 1). Second, the transformation was limited to sulfides which were liquids at 50 °C. We therefore sought to discover if a suitable solvent could be found to overcome these challenges (Table 3).

Table 3. Optimization of the Reaction Solvent[a]



1a **5** **4a**
Ar = 4-$NO_2C_6H_4$

entry	solvent	yield (%)[b]
1	toluene	0
2	acetonitrile	not isolated
3	THF	not isolated
4	acetone	14
5	eucalyptol	26
6	*t*-butylmethyl ether	44
7	diethyl ether	51
8	dibutyl ether	42
9	diisopropyl ether	53

[a]Reactions carried out at 0.2 M with 2.2 equiv of 4-nitrobenzoyl chloride. [b]Isolated yield.

Toluene proved ineffective, returning only starting material after reaction at 50 °C overnight. Both acetonitrile (entry 2) and THF (entry 3) showed the presence of the desired product **4a** in the crude reaction mixture along with a number of unidentified co-products that incorporated the solvent.[14] Given

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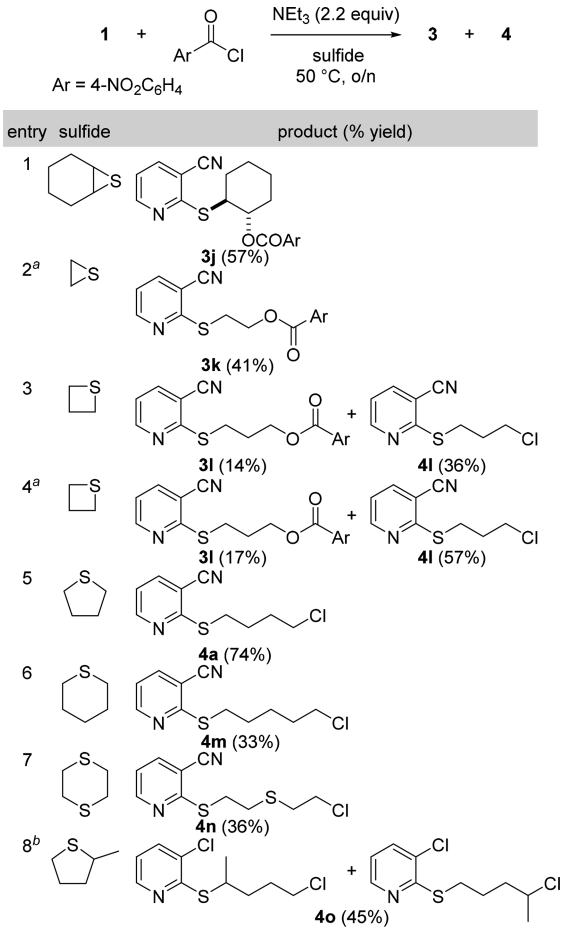
the promise of THF, we postulated that a more hindered ether may prove effective as the solvent. We initially examined eucalyptol which gave the product in a 26% isolated yield (entry 5). We also examined a series of acyclic ethers with different steric demands (entries 6–9). From this study, diisopropyl ether emerged as the most effective solvent, which was easy to handle at the operating temperature of the reaction (entry 9, 53%). While this gave the product in a yield lower than when using the sulfide as the reaction solvent (Table 1, entry 1, 74%), the reduction to 5 equiv of sulfide provided distinct benefits.

Having discovered a suitable solvent with which to undertake the reaction, we were able to explore the effect of changing the thioether substrate (Table 4). Crucially, adoption of a solvent allowed the use of solid thioether substrates (e.g., entry 7). Two key findings came from this part of the investigation. We were able to isolate products from the reaction of 3- and 4-membered thioethers which provided 2-substituted pyridine products (entries 1–3). This was in stark contrast to previous investigations where we were unable to isolate a product from the reaction using either epoxides or oxiranes.[12] In addition, the ring size of the nucleophilic sulfide dictated which product was obtained from the reaction. Using the strained cyclohexene sulfide (entry 1) and thiirane (entry 2), the product from the transformation was 4-nitrobenzoate **3**. With less strained 5- and 6-membered ring sulfides as substrates the product was the corresponding chloride **4** (entries 5–8). Using thietane as the substrate gave mixtures of both the 4-nitrobenzoate **3** and the chloride product **4**, the ratio of which could be altered by changing the reaction temperature (entries 3 and 4).

Table 4. Alternative Thioether Substrates



[a]Reaction carried out at 25 °C. [b]Product isolated as an inseparable 1:1 mixture of regioisomers.

The unexpected change in reaction outcome based upon the structure of the sulfide is intriguing and provides insight into the reaction mechanism. A potential mechanistic course for the process is presented in Scheme 2. *O*-Benzoylation of **1a** followed by deprotonation leads to the carbene intermediate **13** which can combine with the sulfide to generate the ylide **14**. Sulfur ylides are more stable than their corresponding oxygen variants,[15] which could provide the reason for the product divergence when changing from cyclic ethers to cyclic thioethers and for the effect of different thioether substrates. Ylides derived from more strained sulfur nucleophiles will be less stable. Therefore, the reaction follows path A, eliminating 4-nitrobenzoate followed by recombination through ring opening to give the product **3a**. Increasing the stability of the ylide through use of a less strained sulfide (Table 4, entries 5–8) slows the elimination of 4-nitrobenzoate and allows for selective ring opening with the more nucleophilic chloride ion which leads to **4a** (path B).[16] Consistent with this proposal, in reactions where mixtures of **3a** and **4a** are observed, reducing the temperature provides increased amounts of **4a** (Table 4, entries 3 and 4).

The introduction of a chloride instead of a 4-nitrobenzoate in the reaction products was unexpected at the start of this work; however, chloride is an extremely versatile functional group (Table 5). We examined the addition of a series of nitrogen (entry 1, 97%, and entry 2, 36%), oxygen (entry 3, 97%), sulfur (entry 4, 96%, and entry 5, 34%), phosphorus (entry 6, 32%), and carbon nucleophiles (entry 7, 88%) to **4a** to explore the flexibility of the transformation in synthesis. Overall, the product from this novel coupling process provides an effective substrate for further transformations to introduce diversity.

In summary, we have developed a simple and effective method for the regioselective functionalization of heterocyclic *N*-oxides through the reaction with 4-nitrobenzoyl chloride and

Scheme 2. Potential Mechanism for the Pyridine *N*-Oxide Functionalization

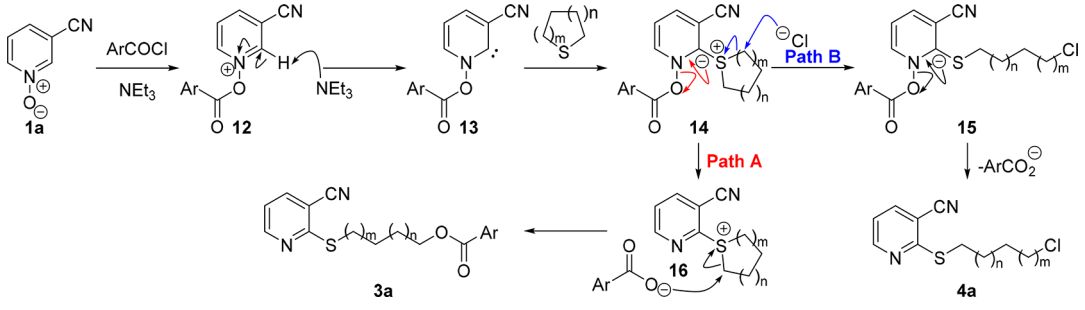


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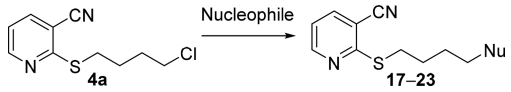
Table 5. Functionalization of Pyridine Products



entry	nucleophile	product	yield (%)
1[a]	NaN_3	**17**	97
2[b]	morpholine	**18**	36
3[c]	NaOAc	**19**	97
4[d]	KSAc	**20**	96
5[e]	4-$MeOC_6H_4SH$	**21**	34
6[f]	$P(OEt)_3$	**22**	32
7[g]	KCN	**23**	88

[a]NaN_3, DMF, 80 °C, 48 h. [b]Morpholine, rt, 48 h. [c]NaOAc, DMF, 80 °C, 48 h. [d]KSAc, KI, DMF, 80 °C, 48 h. [e]4-$MeOC_6H_4CH_2SH$, Cs_2CO_3, DMF, 80 °C, 48 h. [f]$P(OEt)_3$, 160 °C, 48 h. [g]KCN, KI, DMF, rt, 18 h.

cyclic sulfide under basic conditions. The transformation results in yields higher than that of the related process involving cyclic ethers and is tolerant of a greater range of substrates. Thioethers within a strained 3- or 4-membered ring provide access to an alternative ester product. It is believed the divergence in the reaction pathways is due to the formation of a less-stable ylide intermediate when using thiirane or thietane derivatives as the reactive sulfide. Thioethers are significantly more reactive than ethers within this transformation such that ethers are effective solvents for the reaction, allowing the use of solid sulfides within the process. The products can be used in a variety of substitution reactions, suggesting they could be useful in the formation of nitrogen containing heterocycles of pharmaceutical and agrochemical interest. For example, 2-thio-substituted pyridine *N*-oxides have been shown to have antibiotic activity.[17] We are currently engaged in exploiting this transformation in discovery research and will report on our findings in due course.

EXPERIMENTAL SECTION

General Procedure A. The appropriate pyridine *N*-oxide (1.0 equiv) and 4-nitrobenzoyl chloride (2.2 equiv) were added to a 20 mL flame-dried microwave vial. The pressure was carefully restored using a nitrogen/argon balloon. The appropriate cyclic thioether (0.2 M) was introduced, and the mixture was cooled to 0 °C. Triethylamine (2.2 equiv) was added during rapid stirring of the reaction mixture. Following completion of the addition, the cooling bath was removed and the mixture was stirred for 5 min at room temperature before being heated to 50 °C overnight. Ethyl acetate (EtOAc) (5 mL) was added to the mixture, and the mixture was transferred to a round-bottomed flask. The volatiles were removed under reduced pressure. The compounds were purified by flash column chromatography eluted with the stated solvent systems.

General Procedure B. The appropriate pyridine *N*-oxide (1.0 equiv) and 4-nitrobenzoyl chloride (2.2 equiv) were added to a 20 mL flame-dried microwave vial. The pressure was carefully restored using a nitrogen/argon balloon. Diisopropyl ether (0.4 M) and the appropriate cyclic thioether (5.0 equiv) were introduced, and the mixture was cooled to 0 °C. Triethylamine (2.2 equiv) was added during rapid stirring of the reaction mixture. Following completion of the addition, the cooling bath was removed and the mixture was stirred for 5 min at room temperature before being heated to 50 °C overnight. EtOAc (5 mL) was added to the mixture, and the mixture was transferred to a round-bottomed flask. The volatiles were removed under reduced pressure.The compounds were purified by flash column chromatography eluted with the stated solvent systems.

*2-((4-Chlorobutyl)thio)nicotinonitrile (**4a**).* Following General Procedure A, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in tetrahydrothiophene (THT) (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **4a** (138 mg, 0.61 mmol, 74%) as a yellow oil: IR (ATR)/cm^{-1} 3061, 2936, 2864, 2222, 1571, 1549, 1443, 1391; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 7.79 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.07 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 3.58 (t, J = 6.3 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H), 1.99−1.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.2, 140.7, 118.6, 115.6, 107.7, 44.5, 31.6, 29.4, 26.6; LRMS (ES + APCI) m/z calcd for $C_{10}H_{11}{}^{35}ClN_2S$ 226.0, found 227.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{12}{}^{35}ClN_2S$ 227.0410, found 227.0408.

*2-((4-Chlorobutyl)thio)isonicotinonitrile (**4b**).* Following General Procedure A, 4-cyanopyridine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **4b** (52 mg, 0.23 mmol, 28%) as a yellow oil: IR (ATR)/cm^{-1} 3050, 2925, 2853, 2237, 1584, 1530, 1458, 1365; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 5.1 Hz, 1H), 7.38−7.36 (m, 1H), 7.15 (dd, J = 5.1 Hz, J = 1.4 Hz, 1H), 3.57 (t, J = 6.3 Hz, 2H), 3.22 (t, J = 7.0 Hz, 2H), 1.97−1.83 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 150.3, 124.0, 120.4, 120.0, 116.4, 44.5, 31.6, 29.3, 26.7; LRMS (ES + APCI) m/z calcd for $C_{10}H_{11}{}^{35}ClN_2S$ 226.0, found 226.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{12}{}^{35}ClN_2S$ 227.0410, found 227.0406.

*3-Chloro-2-((4-chlorobutyl)thio)pyridine (**4c**).* Following General Procedure A, 3-chloropyridine *N*-oxide (108 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **4c** (100 mg, 0.42 mmol, 51%) as a yellow oil: IR (ATR)/cm^{-1} 3044, 2929, 2864, 1566, 1434, 1387; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H), 7.53 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 6.95 (dd, J = 7.8 Hz, J = 4.7 Hz, 1H), 3.58 (t, J = 7.0 Hz, 2H), 3.23 (t, J = 7.0 Hz, 2H), 1.99−1.84 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 147.1, 135.9, 129.3, 119.7, 44.6, 31.8, 29.3, 26.7; LRMS (ES + APCI) m/z calcd for $C_9H_{11}{}^{35}Cl_2NS$ 235.0, found 235.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}{}^{35}Cl_2NS$ 236.0067, found 236.0063.

*4-Chloro-2-((4-chlorobutyl)thio)pyridine (**4d**).* Following General Procedure A, 4-chloropyridine *N*-oxide (108 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **4d** (77 mg, 0.33 mmol, 39%) as a yellow oil: IR (ATR)/cm^{-1} 3042, 2933, 2864, 1562, 1540, 1452, 1355; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 5.4 Hz, 1H), 7.18−7.16 (m, 1H), 6.97 (dd, J = 5.4 Hz, J = 1.9 Hz, 1H), 3.57 (t, J = 7.0 Hz, 2H), 3.20 (t, J = 7.0 Hz, 2H), 1.97−1.82 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 150.1, 143.9, 122.0, 120.0, 44.6, 31.7, 29.4, 26.8; LRMS (ES + APCI) m/z calcd for $C_9H_{11}{}^{35}Cl_2NS$ 235.0, found 235.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}{}^{35}Cl_2NS$ 236.0067, found 236.0063.

*2-((4-Chlorobutyl)thio)-3-nitropyridine (**4e**).* Following General Procedure A, 3-nitropyridine *N*-oxide (116 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 8:1 isocratic), afforded the title compound **4e** (75 mg, 0.30 mmol, 37%) as a yellow oil: IR (ATR)/cm^{-1} 3076, 2931, 2860, 1584, 1554, 1510, 1396, 1329; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.6 Hz, J = 1.7 Hz, 1H), 8.48 (dd, J = 8.2 Hz, J = 1.7 Hz, 1H), 7.19 (dd, J = 8.2 Hz, J = 4.6 Hz, 1H), 3.59 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H), 2.01−1.85 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 153.2, 142.3, 133.9, 118.7, 44.6, 31.9, 29.8, 26.2; LRMS (ES + APCI) m/z calcd for $C_9H_{11}{}^{35}ClN_2O_2S$ 246.0, found 246.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}{}^{35}ClN_2O_2S$ 247.0308, found 247.0310.

*5-Cyano-2-(trifluoromethyl)pyridine 1-Oxide (**1g**).*[19] To a stirred mixture of 6-(trifluoromethyl)nicotinonitrile (1.00 g, 5.81 mmol) and urea-hydrogen peroxide addition complex (UHP) (1.15 g, 12.21 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic anhydride (TFAA) (1.7 mL, 12.21 mmol) at 0 °C under an argon atmosphere. The reaction

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mixture was allowed to stir at room temperature for 0.5 h. Excess peroxide was destroyed by the addition of 10% aqueous potassium iodide solution (50 mL). The organic phase was washed with saturated 10% aqueous $Na_2S_2O_3$ solution (50 mL) and water (50 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure before the residue was triturated by diethyl ether to afford the title compound **1g** as an off-white solid (571 mg, 3.04 mmol, 52%): mp 94−96 °C; IR (ATR)/cm^{-1} 3031, 2988, 2243, 1605, 1549, 1389, 1277, 1155; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 126.0, 125.9−125.8 (m, 1C), 122.6, 119.2 (q, J_{FC} = 271.6 Hz), 115.8, 113.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ −69.6 (s, 3F); LRMS (ES + APCI) m/z calcd for $C_7H_3F_3N_2O$ 188.0, found 187.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_7H_4F_3N_2O$ 189.0276, found 189.0274.

*2-((4-Chlorobutyl)thio)-6-(trifluoromethyl)nicotinonitrile (**4g**).* Following General Procedure A, compound **1g** (100 mg, 0.53 mmol) and 4-nitrobenzoyl chloride (218 mg, 1.17 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/CH_2Cl_2 3:1 isocratic), afforded the title compound **4g** (94 mg, 0.32 mmol, 60%) as a yellow oil: IR (ATR)/cm^{-1} 3079, 2940, 2869, 2230, 1579, 1361, 1333, 1143; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.33 (t, J = 6.5 Hz, 2H), 1.98−1.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 150.2 (q, J_{FC} = 36.1 Hz, 1C), 142.3, 120.7 (q, J_{FC} = 273.9 Hz, 1C), 115.1 (q, J_{FC} = 2.8 Hz, 1C), 114.5, 110.4, 44.3, 31.6, 29.9, 26.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ −69.1 (s, 3F); LRMS (ES + APCI) m/z calcd for $C_{11}H_{10}{}^{35}ClF_3N_2S$ 294.0, found 295.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{11}{}^{35}ClF_3N_2S$ 295.0284, found 295.0280.

*2-((3-Cyanopyridin-2-yl)thio)cyclohexyl 4-Nitrobenzoate (**3j**).* Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and 7-thiabicyclo[4.1.0]heptane (476 mg, 4.17 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the title compound **3j** (182 mg, 0.48 mmol, 57%) as a yellow oil: IR (ATR)/cm^{-1} 3050, 2933, 2856, 2224, 1720, 1571, 1525, 1391, 1346, 1264; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, J = 5.0 Hz, J = 1.5 Hz, 1H), 8.18 (d, J = 9.0 Hz, 2H), 8.03 (d, J = 9.0 Hz, 2H), 7.73 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.08 (dd, J = 8.0 Hz, J = 5.0 Hz, 1H), 5.19 (td, J = 9.0 Hz, J = 4.0 Hz, 1H), 4.43 (td, J = 9.0 Hz, J = 4.0 Hz, 1H), 2.37−2.23 (m, 2H), 1.90−1.66 (m, 4H), 1.61−1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 162.4, 152.1, 150.6, 140.9, 135.8, 130.8, 123.5, 119.0, 115.4, 108.1, 77.4, 75.9, 46.5, 31.3, 25.1, 23.4; LRMS (ES + APCI) m/z calcd for $C_{19}H_{17}N_3O_4S$ 383.1, found 384.2 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{18}N_3O_4S$ 384.1018, found 384.1019.

*2-((3-Cyanopyridin-2-yl)thio)ethyl 4-Nitrobenzoate (**3k**).* Following General Procedure B, with stirring at 25 °C overnight, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and thiirane (250 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the title compound **3k** (112 mg, 0.34 mmol, 41%) as an off-white solid: mp 132−134 °C; IR (ATR)/cm^{-1} 3109, 3078, 2921, 2853, 2224, 1714, 1608, 1569, 1525, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 8.28 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H), 7.83 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.11 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 4.65 (t, J = 6.4 Hz, 2H), 3.70 (t, J = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 161.8, 152.3, 150.8, 141.0, 135.4, 130.9, 123.7, 119.2, 115.3, 107.9, 64.1, 28.7; LRMS (ES + APCI) m/z calcd for $C_{15}H_{11}N_3O_4S$ 329.0, found 330.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_3O_4S$ 330.0543, found 330.0545.

*3-((3-Cyanopyridin-2-yl)thio)propyl 4-Nitrobenzoate (**3l**).* Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and thietane (308 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the title compound **3l** (48 mg, 0.14 mmol, 17%) as a yellow solid: mp 123−125 °C; IR (ATR)/cm^{-1} 3113, 3081, 2957, 2933, 2220, 1716, 1607, 1567, 1519, 1385; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 8.34−8.22 (m, 2H), 8.27−8.22 (m, 2H) 7.80 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.08 (dd, J = 7.7 Hz, 4.9 Hz, 1H), 4.52 (t, J = 7.0 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 2.26 (app quint, J = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 162.6, 152.2, 150.8, 140.8, 135.7, 130.9, 123.8, 118.8, 115.5, 107.8, 64.6, 28.6, 26.8; LRMS (ES + APCI) m/z calcd for $C_{16}H_{13}N_3O_4S$ 343.1, found 344.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O_4S$ 344.0705, found 344.0708.

*2-((3-Chloropropyl)thio)nicotinonitrile (**4l**).* Following General Procedure B, with stirring at 25 °C overnight, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and thietane (308 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the title compound **4l** (100 mg, 0.47 mmol, 57%) as a yellow oil: IR (ATR)/cm^{-1} 3063, 2955, 2222, 1571, 1551, 1441, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 7.79 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.08 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 3.60 (t, J = 7.0 Hz, 2H), 3.42 (t, J = 7.0 Hz, 2H), 2.20 (app quint, J = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.3, 140.7, 118.7, 115.5, 107.7, 43.5, 32.0, 27.4; LRMS (ES + APCI) m/z calcd for $C_9H_9{}^{35}ClN_2S$ 212.0, found 212.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{10}{}^{35}ClN_2S$ 213.0248, found 213.0248.

*2-((5-Chloropentyl)thio)nicotinonitrile (**4m**).* Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and thiane (424 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 8:1 isocratic), afforded the title compound **4m** (66 mg, 0.28 mmol, 33%) as a yellow solid: mp 28−30 °C; IR (ATR)/cm^{-1} 3059, 2988, 2949, 2925, 2853, 2224, 1571, 1545, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 7.79 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.07 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 3.55 (t, J = 7.0 Hz, 2H), 3.28 (t, J = 7.0 Hz, 2H), 1.88−1.73 (m, 4H), 1.66−1.57 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 152.2, 140.7, 118.5, 115.7, 107.7, 44.9, 32.2, 30.0, 28.6, 26.2; LRMS (ES + APCI) m/z calcd for $C_{11}H_{13}{}^{35}ClN_2S$ 240.0, found 241.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{14}{}^{35}ClN_2S$ 241.0566, found 241.0567.

*2-((2-((2-Chloroethyl)thio)ethyl)thio)nicotinonitrile (**4n**).* Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and 1,4-dithiane (500 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 7:1 isocratic), afforded the title compound **4n** (78 mg, 0.30 mmol, 36%) as an off-white solid: mp 58−60 °C; IR (ATR)/cm^{-1} 3057, 2964, 2946, 2929, 2222, 1571, 1553, 1437, 1393; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.9 Hz, J = 1.8 Hz, 1H), 7.82 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.11 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 3.75−3.69 (m, 2H), 3.48−3.42 (m, 2H), 3.04−2.98 (m, 2H), 2.90−2.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 152.4, 140.9, 119.0, 115.4, 107.8, 43.1, 34.0, 31.6, 30.1; LRMS (ES + APCI) m/z calcd for $C_{10}H_{11}{}^{35}ClN_2S_2$ 258.0, found 259.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{12}{}^{35}ClN_2S_2$ 259.0130, found 259.0129.

*2-((5-Chloropentan-2-yl)thio)nicotinonitrile and 2-((4-Chloropentyl)-thio)nicotinonitrile (**4o**).* Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol), and 2-methyltetrahydrothiophene (426 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **4o** (90 mg, 0.38 mmol, 45%) as a yellow oil in a 1:1 mixture of regioisomers: IR (ATR)/cm^{-1} 3056, 2959, 2925, 2224, 1573, 1551, 1443, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.54 (m, 2H), 7.80−7.76 (m, 2H), 7.09−7.03 (m, 2H), 4.18−4.01 (m, 2H), 3.57 (t, J = 6.4 Hz, 1H), 3.32−3.26 (m, 3H), 2.04−1.80 (m, 8H), 1.52 (d, J = 6.4 Hz, 4H), 1.45 (d, J = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 163.1, 152.2, 140.8, 140.7, 118.6, 118.5, 115.7, 107.7, 107.6, 58.2, 44.8, 39.8, 39.2, 33.8, 30.1, 29.7, 26.4, 25.5, 21.3 (2 C missing); LRMS (ES + APCI) m/z calcd for $C_{11}H_{13}{}^{35}ClN_2S$ 240.0,

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found 241.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{14}{}^{35}ClN_2S$ 241.0561, found 241.0562.

3-Cyanoquinoline N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.35 g, 7.79 mmol) was added portion-wise to a solution of 3-cyanoquinoline (1.00 g, 6.49 mmol) in CH_2Cl_2 (17 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and the reaction was subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic) afforded the title compound as an off-white solid (473 mg, 2.78 mmol, 43%): mp 156−158 °C; IR (ATR)/cm^{-1} 3042, 2936, 2237, 1580, 1495, 1372, 1331, 1229; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 8.5 Hz, 1H), 8.60 (s, 1H), 8.05 (s, 1H), 7.98−7.90 (m, 2H), 7.78 (app t, J = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 143.5, 134.9, 133.5, 130.6, 129.9, 129.2, 129.1, 120.2, 115.1, 107.3; LRMS (ES + APCI) m/z calcd for $C_{10}H_6N_2O$ 170.1, found 171.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_7N_2O$ 171.0558, found 171.0560.

*2-((4-Chlorobutyl)thio)quinoline-3-carbonitrile (**6**).* Following General Procedure A, 3-cyanoquinoline *N*-oxide (100 mg, 0.59 mmol) and 4-nitrobenzoyl chloride (241 mg, 1.29 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the title compound **6** (102 mg, 0.37 mmol, 63%) as a yellow oil: IR (ATR)/cm^{-1} 3050, 2933, 2860, 2224, 1614, 1584, 1556, 1333; ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.82−7.74 (m, 2H), 7.52 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 3.43 (t, J = 6.5 Hz, 2H), 2.05−1.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 148.7, 142.6, 133.0, 128.4, 128.3, 126.8, 123.9, 115.9, 106.3, 44.5, 31.7, 29.5, 26.5; LRMS (ES + APCI) m/z calcd for $C_{14}H_{13}{}^{35}ClN_2S$ 276.0, found 277.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{14}{}^{35}ClN_2S$ 277.0566, found 277.0570.

3-Chloroquinoline N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.27 g, 7.36 mmol) was added portion-wise to a solution of 3-chloroquinoline (1.00 g, 6.13 mmol) in CH_2Cl_2 (16 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and the reaction was subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure to afford the title compound as a pale yellow solid (1.04 g, 5.81 mmol, 95%): mp 118−120 °C; IR (ATR)/cm^{-1} 3066, 2921, 2851, 1580, 1556, 1361, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 1.2 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.76−7.70 (m, 2H), 7.69−7.63 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 135.5, 130.5, 129.9, 129.8, 127.6, 127.5, 124.5, 119.9; LRMS (ES + APCI) m/z calcd for $C_9H_6{}^{35}ClNO$ 179.0, found 179.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_7{}^{35}ClNO$ 179.0132, found 179.0133.

*3-Chloro-2-((4-chlorobutyl)thio)quinoline (**7**).* Following General Procedure A, 3-chloroquinoline *N*-oxide (100 mg, 0.56 mmol) and 4-nitrobenzoyl chloride (229 mg, 1.23 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/CH_2Cl_2 2:1 isocratic), afforded the title compound **7** (99 mg, 0.35 mmol, 62%) as a yellow oil: IR (ATR)/cm^{-1} 3053, 2914, 2847, 1579, 1523, 1469, 1383; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.68−7.62 (m, 2H), 7.45 (app t, J = 7.0 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 3.38 (t, J = 6.5 Hz, 2H), 2.05−1.94 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 146.4, 133.9, 129.8, 128.0, 127.2, 126.9, 126.4, 126.1, 44.7, 31.9, 29.6, 26.6; LRMS (ES + APCI) m/z calcd for $C_{13}H_{13}{}^{35}Cl_2NS$ 285.0, found 285.9 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{14}{}^{35}Cl_2NS$ 286.0224, found 286.0227.

3-Cyanopyrazine N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.97 g, 11.42 mmol) was added portion-wise to a solution of pyrazine-2-carbonitrile (1.00 g, 9.51 mmol) in CH_2Cl_2 (25 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and the reaction was subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic) afforded the title compound as an off-white solid (240 mg, 1.98 mmol, 21%): mp 140−142 °C; IR (ATR)/cm^{-1} 3059, 3013, 2903, 2200, 1579, 1456, 1415, 1279; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.0 Hz, 1H), 8.37 (d, J = 1.5 Hz, 1H), 8.22 (dd, J = 4.0 Hz, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 138.3, 136.7, 134.2, 113.7; LRMS (ES + APCI) m/z calcd for $C_5H_3N_3O$ 121.0, found 122.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_5H_4N_3O$ 121.0271, found 121.0270.

*3-((4-Chlorobutyl)thio)pyrazine-2-carbonitrile (**8**).* Following General Procedure A, 3-cyanopyrazine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (338 mg, 1.82 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/EtOAc 6:1 isocratic), afforded the title compound **8** (105 mg, 0.46 mmol, 56%) as a yellow oil: IR (ATR)/cm^{-1} 3070, 2927, 2864, 2230, 1514, 1430, 1357, 1196; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.29 (t, J = 6.5 Hz, 2H), 1.98−1.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 146.0, 139.6, 128.4, 114.5, 44.3, 31.5, 29.4, 26.4; LRMS (ES + APCI) m/z calcd for $C_9H_{10}{}^{35}ClN_3S$ 227.0, found 228.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{11}{}^{35}ClN_3S$ 228.0362, found 228.0366.

3-Chloropyrazine N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.80 g, 10.50 mmol) was added portion-wise to a solution of 2-chloropyrazine (1.00 g, 8.73 mmol) in CH_2Cl_2 (23 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and the reaction was subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic) afforded the title compound as an off-white solid (970 mg, 7.46 mmol, 85%): mp 97−99 °C; IR (ATR)/cm^{-1} 3053, 3005, 2979, 1582, 1445, 1409, 1272; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 4.0 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.01 (dd, J = 4.0 Hz, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.1, 133.7, 133.3; LRMS (ES + APCI) m/z calcd for $C_4H_3{}^{35}ClN_2O$ 130.0, found 131.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_4H_4{}^{35}ClN_2O$ 130.9914, found 130.9915.

*2-Chloro-3-((4-chlorobutyl)thio)pyrazine (**9**).* Following General Procedure A, 3-chloropyrazine *N*-oxide (100 mg, 0.77 mmol) and 4-nitrobenzoyl chloride (315 mg, 1.69 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/CH_2Cl_2 3:1 isocratic), afforded the title compound **9** (98 mg, 0.42 mmol, 54%) as a yellow oil: IR (ATR)/cm^{-1} 3046, 2927, 2866, 1528, 1497, 1432, 1337, 1143; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H), 1.99−1.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 146.5, 141.8, 137.9, 44.5, 31.7, 29.6, 26.3; LRMS (ES + APCI) m/z calcd for $C_8H_{10}{}^{35}Cl_2N_2S$ 236.0, found 236.4 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{11}{}^{35}Cl_2N_2S$ 237.0020, found 237.0024.

5-Chloropyrimidine N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.81 g, 10.50 mmol) was added portion-wise to a solution of 5-chloropyrimidine (1.00 g, 8.73 mmol) in CH_2Cl_2 (23 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and subsequently the reaction was quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer

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was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic) afforded the title compound as an off-white solid (874 mg, 6.72 mmol, 77%): mp 108−109 °C; IR (ATR)/cm^{-1} 3026, 3003, 2879, 1569, 1519, 1406, 1249; ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.39 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 143.6, 142.2, 130.8; LRMS (ES + APCI) m/z calcd for $C_4H_3{}^{35}ClN_2O$ 130.0, found 130.8 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_4H_4{}^{35}ClN_2O$ 131.0007, found 130.9996.

*5-Chloro-4-((4-chlorobutyl)thio)pyrimidine (**10**).* Following General Procedure A, 5-chloropyrimidine *N*-oxide (100 mg, 0.77 mmol) and 4-nitrobenzoyl chloride (315 mg, 1.69 mmol) in THT (0.2 M), after purification via flash column chromatography (dry loading, petroleum ether/CH_2Cl_2 1:1 isocratic), afforded the title compound **10** (114 mg, 0.48 mmol, 63%) as a yellow oil: IR (ATR)/cm^{-1} 3040, 2936, 2866, 1543, 1415, 1370, 1132; ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.38 (s, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H), 1.99−1.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 155.3, 152.8, 128.9, 44.4, 31.7, 29.1, 26.5; LRMS (ES + APCI) m/z calcd for $C_8H_{10}{}^{35}Cl_2N_2S$ 236.0, found 237.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{11}{}^{35}Cl_2N_2S$ 237.0020, found 237.0025.

2,6-Dichloropyridine N-Oxide.[18] *m*-Chloroperoxybenzoic acid (<77%, 1.40 g, 8.10 mmol) was added portion-wise to a solution of 2,6-dichloropyridine (1.00 g, 6.76 mmol) in CH_2Cl_2 (18 mL) at 0 °C. Following completion of the addition, the reaction mixture was stirred overnight at room temperature, and subsequently the reaction was quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic) afforded the title compound as an off-white solid (420 mg, 2.58 mmol, 38%): mp 135−137 °C; IR (ATR)/cm^{-1} 3081, 2960, 2866, 1532, 1447, 1365, 1264, 1143; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 125.2, 124.6; LRMS (ES + APCI) m/z calcd for $C_5H_3{}^{35}Cl_2NO$ 163.0, found 164.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_5H_4{}^{35}Cl_2NO$ 163.9664, found 163.9662.

*2-((4-Azidobutyl)thio)nicotinonitrile (**17**).* A microwave vial, placed under an inert atmosphere, was charged with a solution of **4a** (50 mg, 0.22 mmol) in dimethylformamide (DMF) (0.9 mL). Sodium azide (86 mg, 1.33 mmol) was added to this solution. The reaction mixture was stirred at 80 °C for 48 h before being cooled to room temperature. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound **17** (50 mg, 0.21 mmol, 97%) as a yellow oil: IR (ATR)/cm^{-1} 3057, 2931, 2862, 2224, 1573, 1551, 1391; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, J = 5.0 Hz, J = 2.0 Hz, 1H), 7.79 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.0 Hz, J = 5.0 Hz, 1H), 3.33 (t, J = 7.0 Hz, 2H), 3.29 (t, J = 7.0 Hz, 2H), 1.87−1.80 (m, 2H), 1.79−1.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 152.2, 140.7, 118.6, 115.6, 107.7, 51.1, 29.6, 28.1, 26.6; LRMS (ES + APCI) m/z calcd for $C_{10}H_{11}N_5S$ 233.1, found 234.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{12}N_5S$ 234.0808, found 234.0809.

*2-((4-Morpholinobutyl)thio)nicotinonitrile (**18**).* To a microwave vial charged with compound **4a** (95 mg, 0.38 mmol) was added morpholine (60 μL, 0.66 mmol). The reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Further purification was performed via flash column chromatography (petroleum ether/EtOAc 1:1 isocratic) to afford the title compound **18** (38 mg, 0.14 mmol, 36%) as a yellow oil: IR (ATR)/cm^{-1} 3072, 2934, 2853, 2804, 2222, 1573, 1549, 1391, 1166; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J = 5.0 Hz, J = 1.5 Hz, 1H), 7.77 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.05 (dd, J = 7.5 Hz, J = 5.0 Hz, 1H), 3.70 (t, J = 5.0 Hz, 4H), 3.29 (t, J = 7.5 Hz, 2H), 2.46−2.40 (m, 4H), 2.37 (t, J = 7.5 Hz, 2H), 1.81−1.73 (m, 2H), 1.69−1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 152.2, 140.7, 118.5, 115.7, 107.6, 67.1, 58.5, 53.8, 30.2, 27.2, 25.8; LRMS (ES + APCI) m/z calcd for $C_{14}H_{19}N_3OS$ 277.1, found 278.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{20}N_3OS$ 278.1322, found 278.1323.

*4-((3-Cyanopyridin-2-yl)thio)butyl Acetate (**19**).* To a microwave vial charged with compound **4a** (100 mg, 0.44 mmol) in a solution of DMF (1.8 mL) was added sodium acetate (218 mg, 2.65 mmol). The reaction mixture was heated to 80 °C for 48 h before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound **19** (107 mg, 0.43 mmol, 97%) as a yellow oil: IR (ATR)/cm^{-1} 3065, 2946, 2864, 2224, 1731, 1573, 1549, 1391, 1233; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.8 Hz, J = 1.6 Hz, 1H), 7.78 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.06 (dd, J = 8.0 Hz, J = 4.8 Hz, 1H), 4.13−4.08 (m, 2H), 3.32−3.28 (m, 2H), 2.05 (s, 3H), 1.84−1.77 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 163.2, 152.2, 140.7, 118.6, 115.7, 107.7, 63.9, 29.8, 27.9, 25.9, 21.1; LRMS (ES + APCI) m/z calcd for $C_{12}H_{14}N_2O_2S$ 250.1, found 251.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2S$ 251.0849, found 251.0850.

*S-(4-((3-Cyanopyridin-2-yl)thio)butyl) Ethanethioate (**20**).* To a microwave vial charged with compound **4a** (50 mg, 0.22 mmol) in a solution of DMF (1.1 mL) were added potassium thioacetate (152 mg, 1.32 mmol) and potassium iodide (8.2 mg, 0.04 mmol). The reaction mixture was heated to 80 °C for 48 h before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound **21** (56 mg, 0.21 mmol, 96%) as a yellow oil: IR (ATR)/cm^{-1} 3063, 2923, 2851, 2222, 1683, 1571, 1549, 1391, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.8 Hz, J = 1.6 Hz, 1H), 7.78 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.06 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 3.27 (t, J = 7.2 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.85−1.69 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 163.1, 152.2, 140.7, 118.6, 115.7, 107.6, 30.8, 29.6, 28.8, 28.6, 28.4; LRMS (ES + APCI) m/z calcd for $C_{12}H_{14}N_2OS_2$ 266.1, found 267.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2OS_2$ 267.0620, found 267.0621.

*2-((4-((4-Methoxyphenyl)thio)butyl)thio)nicotinonitrile (**21**).* To a microwave vial charged with compound **4a** (50 mg, 0.22 mmol) in a solution of DMF (1.1 mL) was added 4-methoxybenzenethiol (63 mg, 0.44 mmol) and cesium carbonate (216 mg, 0.66 mmol). The reaction mixture was heated to 80 °C for 48 h before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound **23** (25 mg, 0.08 mmol, 34%) as an off-white solid: mp 38−40 °C; IR (ATR)/cm^{-1} 3066, 2949, 2830, 2220, 1571, 1553, 1493, 1395, 1235; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J = 5.2 Hz, J = 1.6 Hz, 1H), 7.77 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.05 (dd, J = 7.6 Hz, J = 5.2 Hz, 1H), 6.83, (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.25 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 1.90−1.81 (m, 2H), 1.77−1.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 159.1, 152.2, 140.7, 133.5, 126.4, 118.5, 115.7, 114.7, 107.6, 55.5, 35.5, 29.8, 28.4, 28.1; LRMS (ES + APCI) m/z calcd for $C_{17}H_{18}N_2OS_2$ 330.1, found 331.0 $[M + H]^+$; HRMS

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(ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{19}N_2OS_2$ 331.0939, found 331.0936.

*Diethyl (4-((3-Cyanopyridin-2-yl)thio)butyl)phosphonate (**22**).* To a microwave vial charged with compound **4a** (50 mg, 0.22 mmol) was added triethyl phosphite (484 mg, 2.92 mmol). The reaction mixture was heated to 160 °C for 48 h before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Further purification via flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic) afforded the title compound **24** (23 mg, 0.07 mmol, 32%) as an orange oil: IR (ATR)/cm^{-1} 3047, 2931, 2867, 2222, 1573, 1551, 1391, 1231, 1017, 956; ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 4.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.5 Hz, J = 4.0 Hz, 1H), 4.18−4.02 (m, 4H), 3.27 (t, J = 6.0 Hz, 2H), 1.88−1.72 (m, 6H), 1.32 (t, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 152.2 (d, J_{PC} = 18.5 Hz, 1C), 140.7 (d, J_{PC} = 9.0 Hz, 1C), 118.6, 115.6, 107.6, 62.0−60.4 (m, 2C), 31.2−28.3 (m, 3C), 22.3 (d, J_{PC} = 107.5 Hz, 1C), 16.6 (d, J_{PC} = 66.8 Hz, 2C); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.2−28.5 (m, 1P); LRMS (ES + APCI) m/z calcd for $C_{14}H_{21}N_2O_3PS$ 328.1, found 328.7 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{22}N_2O_3PS$ 329.1089, found 329.1087.

*2-((4-Cyanobutyl)thio)nicotinonitrile (**23**).* A microwave vial placed under an inert atmosphere was charged with a solution of **4a** (50 mg, 0.22 mmol) in DMF (0.8 mL). To this solution were added potassium cyanide (29 mg, 0.44 mmol) and potassium iodide (2.2 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 18 h. A 1:1 mixture of EtOAc/H_2O (10 mL) was added; the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound **25** (42 mg, 0.19 mmol, 88%) as a yellow oil: IR (ATR)/cm^{-1} 3055, 2936, 2856, 2243, 2222, 1571, 1551, 1391; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.8 Hz, J = 1.6 Hz, 1H), 7.79 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.08 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 3.30 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 1.95−1.78 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 152.3, 140.8, 119.4, 118.8, 115.5, 107.7, 29.0, 28.4, 24.5, 16.9; LRMS (ES + APCI) m/z calcd for $C_{11}H_{11}N_3S$ 217.1, found 218.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3S$ 218.0746, found 218.0744.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02457.

NMR spectra for all reported compounds (PDF)

X-ray data for 3-chloropyrazine 1-oxide (CIF)

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Notes

The authors declare no competing financial interest.

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