# Oxidative Ring-Opening of Benzothiazole Derivatives

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Oxidative Ring-Opening of Benzothiazole Derivatives

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Abstract

An oxidative ring opening of benzothiazole to an acylamidobenzene sulfonate ester using alcohol solvents and magnesium monoperxoyphthalate hexahydrate has been described. Under the established conditions, the reaction produces synthetically significant yields with a variety of benzothiazole derivatives. A sulfonate ester intermediate suggests that the reaction proceeds via thiazole ring opening followed by thiol oxidation.

Key words: heterocycles, oxidation, ring-opening, thiazoles, sulfonate esters
Introduction

The ring-opening of heterocyclic systems has long been used as a facile synthetic method for unlocking complex organic structures.\(^1\) While these transformations may be simple for many common heterocycles, they often require a release of ring-strain\(^2\) or proceed via transition-metal catalysis.\(^3\) Only a few reported instances have shown the possibility of ring-opening of thiazole and benzothiazole derivatives under mild, metal-free conditions.\(^4,5\) Facilitated by nucleophilic action, irreversible ring cleavage of a benzothiazole is induced in order to reveal two new handles for subsequent synthetic transformations: a free thiol and acyl amide functional groups. In addition to these 2-aminoarylthiols commonly found in natural products and biologically active compounds, the oxidized sulfur form, orthanilic acid, and its ester and amide derivatives are extremely prevalent, however, they are synthetically difficult to access from the thiol.\(^6,7\)

Currently, aryl sulfonamides and sulfonate esters derived from thiols must be prepared through a tedious multi-step synthesis. First, the thiol must be oxidized to the sulfonic acid, which, while often simple, can require harsh or costly oxidation conditions.\(^8\) To yield the corresponding sulfonyl chloride, the sulfonic acid must be subjected to chlorination conditions such as thionyl chloride, phosphoryl chloride or phosphorous pentachloride, which can be problematic due to the generally high reactivity of these chlorinating agents.\(^9\) Alkoxide or amine nucleophiles are then allowed to react with the sulfonyl chloride to produce a sulfonate ester or sulfonamide respectively.\(^10\) This synthetic route can be vastly improved as it requires many steps for a small transformation, where each added step increases temporal inefficiency, adds costs of solvents, reagents, purifications and labour, as well as allows for additional issues to arise.\(^11\) Thus, a synthetic strategy that is able to couple the ring-opening of a thiazole with subsequent conversion of the liberated thiol to a sulfonate ester is of high interest.\(^12\)
Herein, we describe a novel and facile ring-opening of commercially available benzothiazole derivatives to yield an array of acyl aminobenzene sulfonate esters (Scheme 1). The reaction is technically simple and is performed under mild oxidative conditions in alcohol solvents. This method also offers a rare example of tandem reactivity of functional groups following a heterocyclic ring opening reaction.

**Results and Discussion**

Our investigations commenced with the screening of a various oxidants and conditions in the attempt to oxidize benzothiazole to benzothiazole \(\text{N-oxide}\). We found that under the action of mild oxidant magnesium monoperoxyphthalate hexahydrate (MMPP) \(^{13}\) in alcohol \(\text{MeOH}\) (2a), benzothiazole (1a) undergoes an oxidative ring-opening to yield methyl sulfonate ester 3a after a reaction time of 22 h at room temperature. The product 3a was identified and characterized by single-crystal X-ray crystallography (Figure 1).

In order to maximize the yield of obtained sulfonate ester 3a from the initial discovery conditions (Table 1, Entry 1), we proceeded with a series of reactions to determine the optimal conditions. An initial screen showed that applying 1.6 equiv of MMPP resulted in a significant increase in yield (Table 1, Entry 2). Another major increase in yield was observed by first incubating the reaction mixture at \(-78^\circ\text{C}\) for 8 hours of the 22-hour reaction duration (Table 1, Entry 3) and again by incubating at \(0^\circ\text{C}\) for the same duration (Table 1, Entry 4). It was speculated that the increase in yield could be attributed to a reduced rate of product degradation at a lower temperature based on the known lability of sulfonate esters. This ultimately led us to reduce the room temperature reaction time to 4 hours, allowing for less degradation to occur, where a similar yield of 45% was observed (Table 1, Entry 5).
The low yields obtained in these reactions are attributed to the incomplete reaction of starting material (approximately 20% in the formation of 3b) combined with potential ester hydrolysis and deformylation of the desired product to orthanilic acid. This decomposition was confirmed by the isolation of the dealkylated and deformylated product (4) by continued exposure of 3a to the reaction conditions. Thus, we determined that there is an optimal window to obtain a maximum yield of product before further undesired reactions can occur.

Upon obtaining the optimized reaction conditions, the scope of alcohol reactants was investigated, the results of which are found in Figure 2. With the reaction having been initially explored with benzothiazole (1a) and methanol (2a) as a solvent, which yielded 3a in a 45% yield, we proceeded to investigate other alcohols including: ethanol (2b), 2-propanol (2c), and n-butanol (2d) to yield 3b-3d (25 – 55% yield). We observed that the products obtained in longer alkyl chain alcohol solvents did not suffer from product degradation as the methyl sulfonate ester 3a and as such the reactions were run for the full 22 h at room temperature. The reaction was also able to succeed using fluorinated alcohol 2,2,2-trifluoroethanol (2e) to yield the corresponding trifluoroethyl sulfonate ester 3e in an 11% yield. We suspected that the formation of products 3b-3e also proceeded more slowly due to a reduced solubility of the oxidant MMPP in the longer chain alcohols. The reaction was unable to proceed in benzyl (2f) and longer chain alcohols as they are not polar enough to solubilize the MMPP. We further explored the scope of the oxidative ring-opening reaction by investigating various commercially available derivatives of the benzothiazole core in ethanol (2b) (Figure 3). These benzothiazole derivatives comprised of substituents at the 2-, 5- and 6-positions including; 2-methyl (1b), 2-amino (1c), 5-bromo (1d), 5-nitro (1e), 6-nitro (1f) and 6-bromo benzothiazole (1g), which produced sulfonate esters 3h – 3l in yields ranging from 18 – 33%. It was satisfying that the reaction occurs with a
substituent at the 2-position as demonstrated by the reaction of 2-methylbenzothiazole (1) and 2-aminobenzothiazole (1c) which ultimately rendered acetamide 3h and carbamide 3i respectively. While this suggests the possibility that further functionalization required on the amide group can be built-in at the 2-position of the benzothiazole prior to ring-opening, we found that derivatives possessing larger substituents were unable to afford the ring-opening product. Additionally, while the product of the 5-bromo substrate (3j) could be formed in a 33% yield, the 6-bromo substrate did not undergo the ring-opening oxidation to yield 3m. Conversely, there seemed to be no effect of the nitro substituent position as both compounds 3k and 3l were formed in similar yields of 19% and 21%. The substrate tolerance of the reaction in 2-propanol (2c) was less than that of ethanol (2b) mainly due to reduced solubility; however, compounds 3n and 3o were able to be produced from the 2-methyl (1b) and 5-bromo (1d) substrates respectively.

In order to explore the operative mechanism for this ring-opening transformation a kinetic experiment was performed. By monitoring the reaction by $^1$H NMR over time we observed that in addition to the disappearance of starting material (1a) and the formation of product (3a), a stable intermediate was being formed in significant amounts (Figure 4). This intermediate was isolated and, by a combination of NMR and crystallographic characterization (Figure 5), was revealed to be the methyl sulfonate ester 5. This suggested that the ring opening of the thiazole occurred prior to oxidation of the sulfur to the sulfonate ester and finally to the sulfonate ester.

During our investigations, we noted that performing this reaction with 1a and alternate oxidant: 3-chloroperoxybenzoic acid (mCPBA) in ethanol only produced a low 24% yield of sulfonate ester 3b (compared to 55% with MMPP) despite the typically similar reactivity (Scheme 2, eq 1b). This indicated that the magnesium and/or water associated with MMPP may be facilitating this reaction. The reaction of 1a with mCPBA and 2b was then performed in the presence of
magnesium metal (presumably oxidized \textit{in situ} to Mg$^{2+}$) which amplified the yield of 3b to 49%, indicating that the magnesium is essential for the reaction to proceed (Scheme 2, eq 1c). In order to evaluate the water dependence of this reaction, an experiment was performed on benzothiazole (1a) using a solution of methanol:MMPP that had been dried over molecular sieves. We observed from this experiment that only trace amounts of 3a had been formed indicating that water was indeed necessary for this reaction (Scheme 2, eq 2).

Although the precise mechanism of this reaction is unclear, we have proposed a potential pathway in which the oxidative ring-opening of benzothiazole (1a) may proceed (Scheme 3). Firstly, the magnesium found in MMPP could act as a Lewis acid catalyst by coordinating to the nitrogen of the thiazole ring, increasing the electrophilicity at the 2-position. Nucleophilic attack by water could then occur to liberate the thiol and amide groups. Oxidation of the thiol by the first 0.5 equiv of MMPP (1 equiv of active oxidant) would render the sulfenic acid, which can undergo nucleophilic addition by the alcohol solvent yielding the methoxy sulfane, or simply oxidized to the sulfinic acid. The methoxy compound can continue to be oxidized to the methyl sulfinate 5 and finally to the methyl sulfonate 3a. Additionally, it is possible that the sulfinic acid intermediate could be directly oxidized to the sulfonic acid, which may lead to reduced yields of desired product.

\textbf{Conclusions}

In summary, we have realized an oxidative ring-opening reaction of benzothiazoles with MMPP and alcohol reactants to yield synthetically useful amounts of acylamidobenzene sulfonate ester products. The protocol is facile, has been shown to work in familiar alcohols, uses an inexpensive oxidant, and proceeds on a number of commonly used and commercially available
benzothiazole derivatives. Moreover, we have proposed a pathway in which the ring-opening of benzothiazole happens prior to oxidation based on our mechanistic evidence. Finally, this established synthetic method should prove valuable as an efficient means of accessing substituted aryl sulfonate esters due to the greatly reduced number of steps when compared to traditional methods.

**Experimental**

**General Methods**

Solvents were either reagent grade and/or HPLC grade. Chemical reagents were purchased from Sigma-Aldrich. Flash chromatography was performed using 230–400 mesh silica gel. $^1$H-NMR spectra were recorded on a Brüker AVANCE300 (300 MHz) δ or Brüker AC300 (300 MHz) δ NMR spectrometers. $^{13}$C-NMR spectra were broad band decoupled and recorded on a Brüker AVANCE300 (75.5 MHz) δ or Brüker AC300 (75.5 MHz) δ NMR spectrometers using the carbon signal of the deuterated solvent as the internal standard. The following abbreviations are used for NMR peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Chemical shifts are reported in parts per million (ppm) relative to either TMS (δ 0.0) or chloroform (δ 7.25) for $^1$H-NMR, and chloroform (δ 77.0) for $^{13}$CNMR. High resolution mass spectra (HRMS) were obtained via electrospray ionization (ESI) or direct analysis in real time (DART), which were measured on a Thermo Scientific Q ExactiveTM Plus Hybrid Quadrupole-OrbitrapTM at the University of Waterloo Mass Spectrometry Facility. X-ray crystal structure was determined by Dr. Jalil Assoud.

**General Procedure A**
A 0.2 M solution of benzothiazole 1 (1.00 mmol, 1.0 equiv) in alcohol 2 (5 mL) was stirred vigorously, at which point MMPP (1.00 g, 1.60 mmol, 1.6 equiv) was added. The reaction mixture was stirred at room temperature for 4 hours. After the reaction time, H₂O (10 mL) was added to the reaction vessel and the solution was extracted with 3 x CH₂Cl₂ (10 mL). The organic layers were collected, dried over anhydrous MgSO₄, filtered and concentrated to yield the crude product. The product was purified by silica gel column chromatography (1:4 EtOAc/hexanes → 2:3 EtOAc/hexanes) to yield purified product 3.

**methyl 2-formamidobenzenesulfonate (3a)**

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg) and MeOH (2a). This yielded 3a as a light yellow, waxy solid (97 mg, 0.45 mmol, 45% yield). Rf = 0.4 (2:3 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) (Rotamer ratio: 2.2:1, Asterisk denotes minor peak) δ 8.97 (br. s, 1H) *8.53 (br. s, 1H) 8.59 (d, 1H, J = 8.58 Hz) 8.50 (s, 1H) 7.93 (d, 1H, J = 7.99 Hz) 7.67 (t, 1H, J = 7.81 Hz) 7.28 (t, 1H, J = 7.80 Hz) 3.76 (s, 3H).

¹³C NMR (CDCl₃, 100 MHz) δ 161.6, 138.2, 137.7, 132.3, 126.3, 125.5, 124.2, 59.1. HRMS calculated for C₈H₁₀NO₄S (M+H) 216.0325; Found 216.0326.

**ethyl 2-formamidobenzenesulfonate (3b)**

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg), EtOH (2b) and a reaction time of 22 h. This yielded 3b as a dull yellow solid (105 mg, 0.46 mmol, 46% yield). Rf = 0.28 (1:4 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) (Rotamer ratio: 2.1:1, Asterisk denotes minor peak) δ 8.97 (br. s, 1H) *8.80 (br. s, 1H) 8.57 (d, 1H, J = 8.67 Hz) 8.48 (s, 1H) 7.93 (d, 1H, J = 7.93 Hz) 7.66 (t, 1H, J = 7.92 Hz) 7.29 (t, 1H, J = 7.84 Hz) 4.11 (q, 2H, J = 6.89 Hz) 1.31 (t, 3H, J = 7.02). ¹³C NMR (CDCl₃, 100 MHz) δ 159.3, 135.8,
isopropyl 2-formamidobenzenesulfonate (3c)

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg), i-PrOH (2c) and a reaction time of 22 h. This yielded 3c as a white solid (57 mg, 0.24 mmol, 25% yield). Rf = 0.38 (2:3 EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 300 MHz) (Rotamer ratio: 3.1:1, Asterisk denotes minor peak) $\delta$ 8.95 (br. s, 1H) $^*8.77$ (br. s, 1H) 8.55 (d, 1H, $J = 9.00$ Hz) 7.94 (d, 1H, $J = 7.50$ Hz) 7.65 (t, 1H, $J = 7.81$ Hz) 7.28 (m, 1H) 4.70 (sept., 1H, $J = 6.38$ Hz) 1.26 (d, 6H, $J = 6.12$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 159.2, 135.6, 135.3, 129.8, 124.8, 124.4, 123.5, 79.0, 22.8. HRMS calculated for C$_{10}$H$_{13}$NO$_4$S (M+H) 244.0638; Found 244.0638.

butyl 2-formamidobenzenesulfonate (3d)

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg), n-BuOH (2d) and a reaction time of 22 h. The n-butanol was removed in-vacuo using a toluene:n-butanol (1:1) azeotrope. This yielded 3d as a bright yellow solid (77 mg, 0.30 mmol, 30% yield). Rf = 0.30 (1:5 EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 300 MHz) (Rotamer ratio: 2.0:1, Asterisk denotes minor peak) $\delta$ 9.00 (br. s, 1H) $^*8.79$ (br. s, 1H) 8.57 (d, 1H, $J = 8.69$ Hz) 8.50 (s, 1H) 7.92 (d, 1H, $J = 7.72$ Hz) 7.66 (t, 1H, $J = 7.93$ Hz) 7.28 (t, 1H, $J = 7.72$ Hz) $^*4.10$ (m, 2H) 4.03 (t, 2H, $J = 6.74$ Hz) 1.61 (quint, 2H, $J = 6.74$ Hz) 1.31 (sext, 2H, $J = 7.38$ Hz) 0.84 (t, 3H, $J = 7.34$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 159.2, 135.9, 135.5, 130.2, 124.4, 123.4, 123.3, 71.7, 30.8, 18.7, 13.5. HRMS calculated for C$_{11}$H$_{16}$NO$_4$S (M+H) 258.0795; Found 258.0796.
**2,2,2-trifluoroethyl 2-formamidobenzenesulfonate (3e)**

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg), 2,2,2-trifluoroethanol (2e) and a reaction time of 22 h. This yielded 3e as a light yellow solid (29 mg, 0.11 mmol, **11% yield**). Rf = 0.38 (2:3 EtOAc/hexanes). \(^1\)H NMR (CDCl\(_3\), 300 MHz) (Rotamer ratio: 5.4:1, Asterisk denotes minor peak) \(\delta\) 8.82 (br. s, 1H) *8.76 (br. s, 1H) 8.62 (d, 1H, \(J = 8.36\ Hz\)) 8.51 (s, 1H) *8.037 (m, 1H) 7.93 (d, 1H, \(J = 8.07\ Hz\)) 7.72 (t, 1H, \(J = 7.82\ Hz\)) *7.44 (m, 1H) 7.31 (t, 1H, \(J = 7.83\ Hz\)) *4.43 (m, 2H) 4.36 (q, 2H, \(J = 8.39\ Hz\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 158.9, 136.4, 136.1, 130.0, 125.7, 124.4, 123.6, 122.6, 121.7, 120.4, 118.2, 65.4, 65.1, 64.8, 64.5. \(^{19}\)F NMR (CDCl\(_3\), 280 MHz) \(\delta\) -73.8. HRMS calculated for C\(_9\)H\(_9\)NO\(_4\)SF\(_3\) (M+H) 284.0199; Found 284.0198.

**ethyl 2-acetamidobenzenesulfonate (3h)**

This compound was synthesized following the General Procedure A with 2-methylbenzothiazole 1b (149 mg), ethanol (2b) and a reaction time of 22 h. This yielded 3h as a pale yellow solid (43 mg, 0.18 mmol, **18% yield**). Rf = 0.24 (1:4 EtOAc/hexanes). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.96 (br. s, 1H) 8.46 (d, 1H, \(J = 8.38\ Hz\)) 7.88 (dd, 1H, \(J = 7.98, 1.45\ Hz\)) 7.65-7.59 (m, 1H) 7.21 (t, 1H, \(J = 7.68\ Hz\)) 4.08 (q, 2H, \(J = 7.11\ Hz\)) 2.22 (s, 3H) 1.27 (t, 3H, \(J = 7.12\ Hz\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 168.8, 137.0, 135.3, 129.9, 123.7, 123.4, 123.2, 68.0, 25.2, 14.8. HRMS calculated for C\(_{10}\)H\(_{14}\)NO\(_4\)S (M+H) 244.0644; Found 244.0639.

**ethyl 2-ureidobenzenesulfonate (3i)**

This compound was synthesized following the General Procedure A with 2-aminobenzothiazole 1c (149 mg), ethanol (2b), MMPP (3.2 equiv), and a reaction time of 22 h. This yielded 3i as an orange solid (40mg, 0.16 mmol, **16% yield**). Rf = 0.25 (1:1 EtOAc/hexanes). \(^1\)H NMR (CDCl\(_3\),
300 MHz) δ 7.90 (d, 1H, \( J = 7.1 \text{ Hz} \)) 7.70 (d, 1H, \( J = 6.8 \text{ Hz} \)) 7.59-7.55 (m, 2H) 5.98 (br, 3H), 4.38 (q, 2H, \( J = 7.2 \text{ Hz} \)) 1.37 (t, 3H, \( J = 7.1 \text{ Hz} \)). \(^{13}\text{C NMR (CDCl}_3\), 100 MHz} \delta 171.9, 168.2, 133.3, 132.0, 130.9, 130.3, 129.9, 128.8, 62.0, 13.9. HRMS calculated for \( \text{C}_9\text{H}_{13}\text{N}_2\text{O}_4\text{S} \) (M+H) 245.05905; Found 245.05909.

**ethyl 4-bromo-2-formamidobenzenesulfonate (3j)**

This compound was synthesized following the General Procedure A with 5-bromobenzothiazole \( \text{1d} \) (214 mg), ethanol \( \text{2b} \) and a reaction time of 22 h. This yielded \( \text{3j} \) as a pale yellow solid (100 mg, 0.33 mmol, **33% yield**). Rf = 0.25 (1:4 EtOAc/hexanes). \(^1\text{H NMR (CDCl}_3\), 300 MHz} \delta 9.01 (br. s, 1H) 8.82 (s, 1H) 8.45 (s, 1H) 7.75 (d, 1H, \( J = 8.44 \text{ Hz} \)) 7.40 (d, 1H, \( J = 8.44 \text{ Hz} \)) 4.11 (q, 2H, \( J = 7.02 \text{ Hz} \)) 1.30 (t, 3H, \( J = 7.06 \text{ Hz} \)). \(^{13}\text{C NMR (CDCl}_3\), 100 MHz} \delta 159.2, 136.7, 131.1, 130.5, 127.5, 126.0, 122.0, 68.4, 14.8. HRMS calculated for \( \text{C}_9\text{H}_{10}\text{BrNO}_4\text{S} \) (M+H) 307.9587; Found 307.9586.

**ethyl 2-formamido-4-nitrobenzenesulfonate (3k)**

This compound was synthesized following the General Procedure A with 5-nitrobenzothiazole \( \text{1e} \) (180 mg), ethanol \( \text{2b} \) and a reaction time of 22 h. This yielded \( \text{3k} \) as a bright yellow solid (52 mg, 0.19 mmol, **19% yield**). Rf = 0.42 (2:3 EtOAc/hexanes). \(^1\text{H NMR (CDCl}_3\), 300 MHz} \delta 9.31 (br. s, 1H) 8.91-8.89 (m, 1H) 8.80 (d, 1H, \( J = 2.62 \text{ Hz} \)) 8.60 (br. s, 1H) 8.49 (dd, 1H, \( J = 9.18, 2.61 \text{ Hz} \)) 4.25 (q, 2H, \( J = 7.11 \text{ Hz} \)) 1.37 (t, 3H, \( J = 7.10 \text{ Hz} \)). \(^{13}\text{C NMR (CDCl}_3\), 100 MHz} \delta 159.1, 142.6, 140.8, 130.1, 125.7, 123.7, 123.0, 69.1, 14.7. HRMS calculated for \( \text{C}_9\text{H}_{11}\text{N}_2\text{O}_6\text{S} \) (M+H) 275.0338; Found 275.0333.

**ethyl 2-formamido-5-nitrobenzenesulfonate (3l)**

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This compound was synthesized following the General Procedure A with 6-nitrobenzothiazole 1f (180 mg), ethanol (2b) and a reaction time of 22 h. This yielded 3l as a bright yellow solid (57 mg, 0.21 mmol, 21% yield). Rf = 0.42 (2:3 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 9.32 (br. s, 1H) 8.90 (d, 1H, J = 8.04 Hz) 8.80 (d, 1H, J = 2.05 Hz) 8.59 (br. s, 1H) 8.49 (dd, 1H, J = 9.18, 2.55 Hz) 4.24 (q, 2H, J = 7.05 Hz) 1.37 (t, 3H, J = 7.08 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ 159.1, 142.6, 140.8, 130.1, 125.7, 123.7, 123.0, 69.2, 14.7. HRMS calculated for C₉H₁₁N₂O₆S (M+H) 275.03323; Found 275.03350.

**isopropyl 2-acetamidobenzenesulfonate (3n)**

This compound was synthesized following the General Procedure A with 2-methylbenzothiazole 1b (149 mg), isopropanol (2c) and a reaction time of 22 h. This yielded 3n as a dull yellow solid (17 mg, 0.07 mmol, 7% yield). Rf = 0.17 (1:4 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) (Rotamer ratio: 7.8:1, Asterisk denotes minor peak) 8.92 (br. s, 1H) 8.43 (d, 1H, J = 8.44 Hz) *8.01 (d, 1H, J = 7.94 Hz) 7.90 (d, 1H, J = 8.04 Hz) *7.75 (m, 1H) 7.62 (t, 1H, J = 8.44 Hz) *7.42 (m, 1H) 7.22 (t, 1H, J = 7.65 Hz) 4.66 (sept., 1H, J = 6.28 Hz) 2.23 (s, 3H) 1.24 (d, 6H, J = 6.23 Hz). ¹³C NMR (CDCl₃, 100 MHz) 168.8, 136.8, 135.2, 129.7, 124.7, 123.8, 78.7, 25.2, 22.8. HRMS calculated for C₁₁H₁₆NO₄S (M+H) 258.0795; Found 258.0795.

**isopropyl 4-bromo-2-formamidobenzenesulfonate (3o)**

This compound was synthesized following the General Procedure A with 5-bromobenzothiazole 1d (214 mg), ethanol (2c) and a reaction time of 22 h. This yielded 3o as a dull yellow solid (87 mg, 0.19 mmol, 19% yield). Rf = 0.38 (1:4 EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) (Rotamer ratio: 8.5:1, Asterisk denotes minor peak) δ 8.97 (br. s, 1H) 8.81 (s, 1H) *8.79 (br. s, 1H) 8.49 (s, 1H) 7.77 (d, 1H, J = 8.43 Hz) *7.57 (m, 1H) 7.41 (d, 1H, J = 8.26 Hz) *4.82 (m,
1H) 4.71 (sept., 1H, J = 5.4 Hz) 1.27 (d, 6H, J = 6.18 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) 159.1, 136.5, 130.8, 130.2, 127.6, 126.1, 123.4, 79.4, 22.8. HRMS calculated for C$_{10}$H$_{13}$NO$_4$SBr (M+H) 321.9749; Found 321.9743.

2-aminobenzenesulfonic acid (4)

Sulfonate ester 3a (100 mg, 0.47 mmol) was stirred in MeOH (8 mL) and refluxed for 3 h. Removal of solvent yielded complete conversion to product 4. $^1$H NMR (CD$_3$OD, 300 MHz) $\delta$ 7.82 (d, 1H, J = 7.8 Hz) 7.54 (t, 1H, J = 7.7 Hz) 7.45 (t, 1H, J = 7.2 Hz) 7.35 (d, 1H, J = 7.9 Hz). $^{13}$C NMR (CD$_3$OD, 100 MHz) $\delta$ 138.1, 135.8, 131.7, 131.0, 130.5, 126.9. Characterization data is consistent with authentic samples.

methyl 2-formamidobenzenesulfinic (5)

This compound was synthesized following the General Procedure A with benzothiazole 1a (135 mg), MeOH (2a) and a reaction time of 2 h. This yielded 5 as a light yellow, flakey solid (8.2 mg, 0.04 mmol, 4% yield). Rf = 0.31 (2:3 EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 300 MHz) (Rotamer ratio: 4.2:1, Asterisk denotes minor peak) $\delta$ 10.11 (br. s, 1H) *9.00 (br. s, 1H) *8.75 (d, 1H, J = 10.81 Hz) 8.57 (d, 1H, J = 8.42 Hz) 8.46 (s, 1H) *7.66 (d, 1H, J = 7.47 Hz) 7.54 (t, 1H, J = 7.79 Hz) 7.45 (d, 1H, J = 7.75 Hz) *7.35 (m, 1H) 7.23 (t, 1H, J = 7.59 Hz) 3.66 (s, 3H) *3.64 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 159.6, 138.4, 133.7, 128.1, 127.6, 124.3, 122.9, 51.6. HRMS calculated for C$_8$H$_9$NO$_3$SLi (M+Li) 206.0458; Found 206.0459.

Procedure for NMR kinetic Analysis

A room temperature round bottom flask was charged with benzothiazole (0.22 mL, 2.00 mmol, 1.0 equiv) and methanol (10 mL). Dodecane (45 µL, 0.2 mmol, 0.1 eq) was then added to the
reaction mixture. The reaction mixture was stirred vigorously at which point MMPP (2.00 g, 3.20 mmol, 1.6 eq) was added. After 5 min, a 0.5 mL aliquot of the reaction mixture was removed, DI H₂O (0.5 mL) was added to the aliquot and the solution was extracted with CH₂Cl₂ (1 mL) 3 times. The organic layers were collected, dried over MgSO₄ and concentrated to yield the crude product. This process was repeated at the following times: 5 min, 20 min, 1 hour, 2 hours, 4 hours, 10 hours. After the data was collected, the relative concentrations of product and intermediate were determined by integrating δ 3.64 (2) and δ 3.76 (1) relative to δ 0.86 (dodecane).

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(15) Including 2-hydroxymethyl benzothiazole and 2-ethylcarboxylate benzothiazole.

(16) See the Supporting Information for more details.

(17) The single crystal x-ray structure could not be completely solved due to weak crystal data; however, the suggested structure of 5 was confirmed when combined with ¹H and ¹³C NMR characterization data.
Captions

Scheme 1 Oxidative ring opening of benzothiazole derivatives.

Figure 1 Single crystal x-ray structure of 3a.

Table 1 Optimization of reaction conditions.

Figure 2 Scope of alcohol solvents in benzothiazole oxidative ring-opening. All reactions were carried out in the presence of 1 mmol of 1a, 1.6 mmol of MMPP in 5 mL of 2. a Reaction duration of 4 h. b Reaction duration of 22 h.

Figure 3 Scope of benzothiazole derivatives in the oxidative ring-opening. All reactions were carried out in the presence of 1 mmol of 1, 1.6 mmol of MMPP in 5 mL of 2 for 22 h. a Used MMPP (3.2 equiv).

Figure 4 Reaction kinetic profile for the formation of 3a and 5 from 1a. Peak integrations are reported relative to an internal standard.

Figure 5 X-ray crystal data of 5.

Scheme 2 Effects of Mg and H$_2$O on the oxidative ring-opening.

Scheme 3 Proposed reaction pathway.
Table 1 Optimization of reaction conditions\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>MMPP (equiv)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>% yield of 3\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>rt</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>rt</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>-78 → rt</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1.6</td>
<td>0 → rt</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>1.6</td>
<td>rt</td>
<td>4</td>
<td>45</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were carried out in the presence of 1.0 mmol of 1\textsuperscript{a} and 5mL MeOH 2\textsuperscript{a}.

\textsuperscript{b} NMR yield.
1a + MMPP+6H2O (1.6 equiv) → R

<table>
<thead>
<tr>
<th>R</th>
<th>ROH (2)</th>
<th>rt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>3a</td>
<td>45%</td>
</tr>
<tr>
<td>Et</td>
<td>3b</td>
<td>55%</td>
</tr>
<tr>
<td>i-Pr</td>
<td>3c</td>
<td>25%</td>
</tr>
<tr>
<td>n-Bu</td>
<td>3d</td>
<td>30%</td>
</tr>
<tr>
<td>CF3</td>
<td>3e</td>
<td>11%</td>
</tr>
<tr>
<td>Bn</td>
<td>3f</td>
<td>11%</td>
</tr>
</tbody>
</table>

45% 55% 25%
30% 11% --%
MMPP•6H₂O (1.6 equiv) → R¹OH (2b) → rt, 22h

R¹NH

3h 18 %
3i 16 %
3j 33 %
3k 19 %
3l 21 %
3m --
3n 11 %
3o 7 %
Kinetic Profile of 3a and 5

H NMR Peak Integration

Time (h)
this work:

\[
\begin{align*}
\text{1} & \xrightarrow{\text{MMPP} \cdot 6\text{H}_{2}\text{O}, \text{rt}} \text{2} \\
\text{2} & \xrightarrow{\text{R}^1\text{OH}, \text{rt}} \text{3}
\end{align*}
\]
(1) $\text{SNOS} \xrightarrow{\text{oxidant (1.6 equiv)}} \xrightarrow{\text{EtOH, rt, 22h}} \text{EtO}

\text{a) MMPP-H$_2$O: 55 %}
\text{b) mCPBA: 24 %}
\text{c) mCPBA + Mg: 49 %}

(2) $\text{SNOS} \xrightarrow{\text{MMPP (1.6 equiv)}} \xrightarrow{\text{MeOH (dry), rt, 22h}} \text{Me}
\text{trace}