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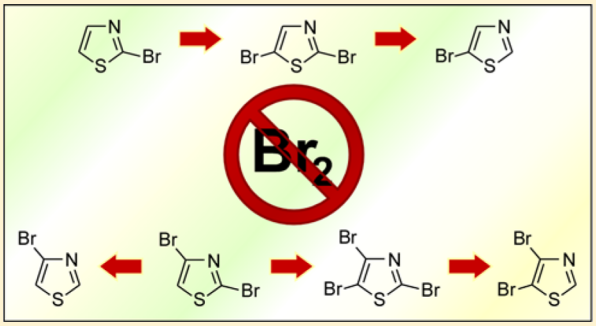
Synthesis of Brominated Thiazoles via Sequential Bromination–Debromination Methods

Eric J. Uzelac and Seth C. Rasmussen*

Department of Chemistry and Biochemistry, North Dakota State University, NDSU Department 2735, P.O. Box 6050, Fargo, North Dakota 58108-6050, United States

Supporting Information

ABSTRACT: The synthesis of the full family of bromothiazoles has been revisited in order to update and optimize their production. The species reported include 2-bromothiazole, 4-bromothiazole, 5-bromothiazole, 2,4-dibromothiazole, 2,5-dibromothiazole, 4,5-dibromothiazole, and 2,4,5-tribromothiazole, the majority of which are produced via sequential bromination and debromination steps. This complete family can now be produced without the use of elemental bromine, and the presented methods have allowed the physical and NMR spectroscopic characterization of the full family to be reported for the first time.



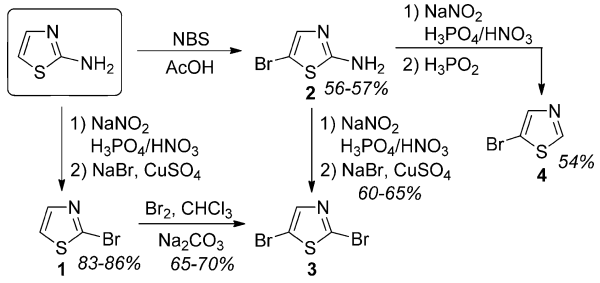
Bromothiophenes are the most common synthetic precursors for the production of functionalized thiophenes,[1] which in turn provide critical building blocks for the synthesis of large families of materials,[2] natural products,[3] and pharmaceuticals.[4] In efforts to modulate and fine-tune the properties of such thiophene species, recent efforts have focused on the replacement of thiophene units with the close heterocyclic analogue thiazole.[5−9] As a consequence, this has led to a current need for convenient access to various bromothiazoles.

Although one would assume that such bromothiazoles could be efficiently produced via analogous methods to the more commonly applied bromothiophenes, there are some important differences between the two sulfur-based heterocycles. Bromothiophenes are typically generated by various sequential bromination and debromination steps in which bromination is accomplished via electrophilic aromatic substitution using either Br_2 or *N*-bromosuccinimide (NBS).[10] While bromothiazoles can also be produced via direct bromination, thiazole is both less aromatic[11] and considerably less electron rich than thiophene. As a consequence, electrophilic aromatic substitution of thiazole is much less facile, typically requiring much more aggressive reaction conditions. The other complicating factor is that the addition of the nitrogen atom breaks the symmetry of the heterocycle, resulting in three inequivalent points of substitution,[12,13] which complicate the synthetic steps required to access particular members of the bromothiazole family.

The full family of simple bromothiazoles include 2-bromothiazole,[14−16] 4-bromothiazole,[17−19] 5-bromothiazole,[15,17,20] 2,4-dibromothiazole,[16,17,19,21,22] 2,5-dibromothiazole,[15−17,20,23] 4,5-dibromothiazole,[19,21] and 2,4,5-tribromothiazole,[19,24,25] all of which have been previously reported in the literature. However, it should be noted that 4,5-dibromothiazole has only been previously produced in either trace amounts[21] or as part of inseparable mixtures.[19] In addition, with the exception of a few recent reports,[16,17] the bulk of these previous studies are significantly dated, thus providing limited characterization and utilizing less than ideal reaction conditions. As such, it was deemed worthy to revisit the synthesis and characterization of this family of important precursors in order to make them more readily available to modern efforts.

2-Bromothiazole (1). Due to the low reactivity of the parent thiazole to direct bromination, 2-bromothiazole is commonly produced from the inexpensive and readily available 2-aminothiazole (Scheme 1). The currently applied methods find their origins in a 1945 report by Ganapathi and Venkataraman,[14] in which the amino group is first converted to a diazonium compound before being converted to the bromide by a $NaBr/CuSO_4$ mixture. Although this method gave **1** in reasonable yields (75%), a modified procedure was

Scheme 1. Synthesis of Bromothiazoles 1, 3, and 4 from 2-Aminothiazole



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then reported by Roussel and Metzger in 1962.[15] The reported modifications focused primarily on strict temperature control and longer reaction times, resulting in a reported increase in yield to 80% (although papers[13,26] utilizing these methods report effective yields of 90%). Sampson and co-workers reported a more recent update of the original 1945 methods in 2012,[16] although their most significant modifications are essentially the same as those reported in 1962 and provide no additional increases in yield. As such, the methods of Roussel and Metzger represent the most simple and efficient route to **1**, and a simplified version of their methods are reported here to give yields of 83−86%.

2,5-Dibromothiazole (3). This dibromothiazole was first reported by Erlenmeyer and Kiefer in 1945,[23] in which 2-aminothiazole was first treated with Br_2 to give the intermediate 2-amino-5-bromothiazole (**2**) in unspecified yields. The intermediate **2** was then converted to the corresponding diazonium compound and treated with a copper/HBr mixture to generate **3** in a 40% yield. Beyerman and co-workers[20] modified these methods in 1954 by replacing the copper/HBr mixture with a $NaBr/CuSO_4$ combination to give **3** in an overall yield of 24% from 2-aminothiazole. Roussel and Metzger then reported further modifications of these methods in 1962,[15] resulting in an overall yield of ca. 38%.

The production of **3** from **1** was first reported in 2006 by Stanetty and co-workers,[17] in which an aqueous mixture of HBr and Br_2 was used to prepare **3** in a yield of 55%. Although the monobromo **1** is more reactive to electrophilic aromatic substitution than the parent thiazole, its reactivity is still quite low, thus requiring the application of a large excess (4.7 equiv) of Br_2 in order to increase the reaction rate to a point that significant product could be generated. In 2012, Sampson and co-workers improved on these methods by carrying out the bromination in a mixture of $CHCl_3$ and solid $NaHCO_3$, while also increasing the reaction time from 3 to 96 h, resulting in an increase in yield to 79%.[16] Although this yield was respectable, these methods still required nearly a 5-fold excess of Br_2. Attempts to improve routes to **3** therefore began with efforts to reduce the amount of Br_2 applied.

Limiting the amount of Br_2 is not only important in terms of atom efficiency and reducing waste, but the recognized toxic nature of Br_2 is also a critical factor. Bromine is a potent respiratory irritant, and accidental exposure may result in burns, irritation of the eyes and mucous membranes, as well as the development of bronchospasm or chemical pneumonitis.[27] The median lethal toxicity (LD_{50}) of Br_2 for a 10 min exposure has been estimated at 546 ppm,[28,29] with death resulting from pulmonary edema or asphyxiation due to damage of the respiratory tract. Even nonlethal exposure can lead to severe pulmonary complications.[27] Such hazards can be reduced by either reducing exposure to Br_2 or utilizing an alternate brominating reagent such as NBS.

Although NBS is easier and safer to handle than Br_2, it is also typically a less powerful brominating agent. Thus, attempts to replace Br_2 with NBS in the bromination of **1** were unsuccessful, even when applying large excesses of NBS. Efforts thus focused on limiting the amount of Br_2 necessary for the successful production of **3**. It was found that modification of the conditions allowed dropping the Br_2 to 2.5 equiv while also reducing the overall reaction time from 96 to 24 h to give **3** in yields of 65−70%. Although this is a ca. 5−10% reduction in yield compared to the previous methods of Sampson and co-workers,[16] this minor loss in yield is worth cutting the costliest (and most toxic) reagent in half while also significantly reducing the overall prep time.

Of course, it would be even better to completely remove the need to utilize Br_2 to produce **3**. As increasing the electron-rich nature of the thiazole should increase its ease of bromination, it was felt that access to **3** via the direct bromination of 2-aminothiazole may allow greater flexibility in the bromination conditions utilized. Thus, it was found that 2-aminothiazole could be efficiently brominated via NBS to give **2** in 56−57% yields (Scheme 1). As stated by previous authors,[16] the stability of this intermediate is limited and decomposition was observed within 24 h, even when stored under N_2 at low temperatures. However, both the production of **2** and its sequential conversion to **3** can be each be done in a matter of hours and thus **3** can easily be generated from 2-aminothiazole in a single day. Conversion of **2** to **3** can be accomplished in yields of 60−65% (Scheme 1), thus giving overall yields of ca. 37% for this route. Although the overall yield from via **2** is about 20% lower than the overall yield for the route via **1**, this alternate method does allow access to **3** with no use of Br_2.

5-Bromothiazole (4). This second monobromothiazole was first reported by Beyerman and co-workers in 1954,[20] who prepared it either by reduction of the diazonium derivative of **2** in 41% yield or by treatment of **3** with sodium ethoxide followed by hydrogenation over Raney nickel. The efficiency of this second method was not reported. In 1962, Roussel and Metzger again reported the preparation of **4** from **2**, but with no real increase in yield.[15] An alternate method to **4** via the debromination of **3** was reported by Stanetty and co-workers in 2006.[17] In this case, isopropylmagnesium chloride was used to isolate **4** in 20% yield. Efforts to improve the production of **4** thus began with an attempt to optimize the debromination of **3**. It was found, however, that the application of butyllithium, Grignard reagents, or $NaBH_4$ all resulted in the nearly exclusive production of **1** over the desired isomer **4**. These results were somewhat surprising as the regioselectivity of the thiazole positions are generally regarded as following the recognized acidity of the thiazole protons, H2 > H5 ≫ H4.[30] In addition, photolysis of bromothiazoles have shown that the C−Br bond at the 2-position of thiazole undergoes selective cleavage more rapidly and efficiently than the corresponding C−Br bond at the 5-position.[13] However, it has also been shown that 5-bromothiazole reacts more quickly with sodium methoxide than 2-bromothiazole, which has led to the conclusion that the electron density at C-5 of the thiazole ring must be relatively close to that at C-2, at least in the transition state.[12] Thus, even if thermodynamics favored the production of **4** via debromination of **3**, the kinetically favored product could still be **1**.

With this in mind, attempts to reduce the reactivity of the debromination reaction were investigated by treating **3** with butyllithium in hexanes. As the butyllithium is more aggregated in this noncoordinating solvent,[31] the reactivity of the reagent should be reduced, and thus, enhanced selectivity for the thermodynamic product may be favored. This approach also appeared promising as it had been previously reported to selectively generate the 5-bromo-2-thiazolyllithium intermediate.[32] Application of this approach to **3** did successfully produce the desired isomer **4**, but as one component of a complex mixture and only in 28% yield.

Due to the difficulties with regioselectivity for the debromination of **3**, it was decided to revisit the original route to **4** via the 2-amino-5-bromothiazole (**2**), particularly as the synthesis of **2** had already been optimized as an

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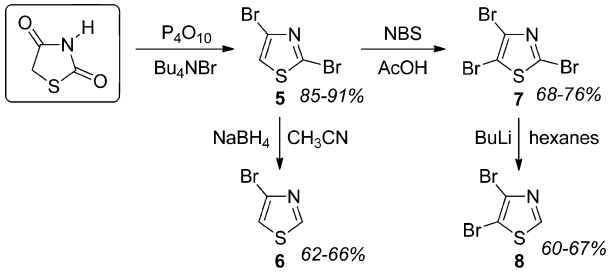
intermediate to **3**. Here, **2** was converted to the corresponding diazonium compound and treated with H_3PO_2 to give the desired isomer **4** in 54% yield (Scheme 1). Not only did this produce **4** in considerably higher yield than via debromination of **3**, but the initially isolated crude material was relatively clean and required little purification.

2,4-Dibromothiazole (5). As with 2-bromothiazole (**1**), this dibromothiazole is not produced via either the parent heterocycle or its brominated derivatives but via simultaneous aromatization and bromination of 2,4-thiazolidinedione (Scheme 2). This approach finds its origins in 1962, where

Scheme 2. Synthesis of Bromothiazoles 5-8 from 2,4-Thiazolidinedione



Reynaud et al. produced **5** via the treatment of 2,4-dihydroxythiazole with $POBr_3$ in 60% yield.[21] Stanetty and co-workers then revisited the process in early 2006,[17] where the more readily available 2,4-thiazolidinedione was substituted for the oxidized form and ca. 2.3 times the quantity of $POBr_3$ was used, resulting in a near-quantitative yield. Later that same year, Cossy and co-workers reported a nearly identical procedure, but using $POBr_3$ quantities similar to that originally reported by in 1962.[22] Here, the lesser equivalents of $POBr_3$ produced a lower yield of only 68%. Sampson and co-workers then reported another modification of the process in 2012,[16] where the costly $POBr_3$ was replaced with a mixture of P_4O_{10} (commonly referred to by its empirical formula P_2O_5)[33] and tetrabutylammonium bromide to give yields of 95%. The crystal structure of **5** has also been recently reported.[34]

Although other phosphorus reagents such as PBr_5 also resulted in the production of **5**, none of these alternate methods can compete with the cost and efficiency of the methods reported by Sampson and co-workers. As such, reported here (Scheme 1) are minor modifications of those methods, primarily utilizing a simple silica plug for purification, rather than sublimation. It should be pointed out that this procedure does seem to be somewhat scale dependent in terms of yield, and thus, while yields of 95% are possible at the larger scale reported by Sampson and co-workers, the scales reported here are typically 85−91% (Scheme 2).

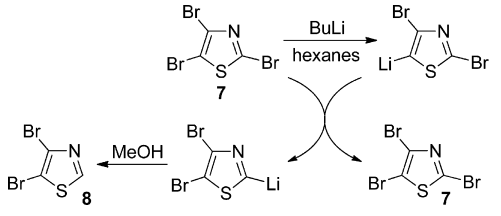
4-Bromothiazole (6). The last monobromothiazole is typically produced via debromination of **5**, which has been accomplished using butyllithium[18,19] or Grignard reagents[17] in yields of ca. 70%. However, these reagents are pyrophoric and require the application of cryogenic reaction conditions, thus adding to the difficulty and cost of the applied methods. A simple alternative is the application of $NaBH_4$ in CH_3CN at reflux temperature (ca. 80 °C) to give **6** in 62−66% yields.

2,4,5-Tribromothiazole (7). The perbrominated analogue **7** was first reported in 1964 by Robba and Moreau via the exhaustive bromination of 2,4-dihydroxythiazole in 85% yield.[24] An alternate approach via the bromination of **5** was then reported by Herkes and Blazer in 1976 to give **7** in 87%.[25] Of course, both of these methods utilized Br_2, which includes all of the issues discussed above. Thus, efforts were undertaken to investigate the bromination of **5** via NBS. Although the NBS bromination of the monobromothiazole **1** was unsuccessful, it was felt that the second bromo group of **5** should provide enough additional electron density to allow its successful bromination via NBS. Thus, treatment of **5** with 1.5 equiv of NBS in glacial acetic acid successfully afforded **7** in 68−76% yields. Again, while this is a ca. 10% reduction in yield from the previous methods, the reduced toxicity of NBS vs Br_2 is a significant benefit. Attempts to access **7** via the treatment of the dibromothiazole **3** with NBS were unsuccessful, which is consistent with the lower reactivity of the 4-position in relation to either of the thiazole α-positions.

4,5-Dibromothiazole (8). The final bromothiazole **8** is the only member of this family that has never been fully reported as an isolated and pure material. The first attempt to produce **8** was in 1962, when Moreau and co-workers treated sodium acetylaminomethanesulfonate with thionyl bromide.[21] However, this approach produced **8** in only trace amounts (ca. 2% yield). A second attempt was then made in 1992 by Iddon and co-workers,[19] who treated tribromothiazole **7** with 1 equiv of butyllithium under standard conditions, followed by quenching with HCl. The resulting inseparable mixture was found to contain **5** (50.0%), **6** (27.25%), and **8** (22.75%).

As **8** should be accessible via the debromination of **7**, efforts began with repeating its treatment with a range of species, including butyllithium, various Grignard reagents, and $NaBH_4$. In all cases, however, the primary product was the 2,4-dibromothiazole **5**. As this reactivity appeared similar to that discussed for the debromination of **3** above, the treatment of **7** with butyllithium in hexanes was then investigated. Although this approach had been only marginally successful in the case of **3**, its application to **7** successfully produced **8** in 60−67% yield (Scheme 2). Under these conditions, it was found that metal−halogen exchange initially occurred at the 5-position but slowly interconverted to the desired 2-lithium derivative via the halogen dance[35] (Scheme 3). In this case, the reduced reactivity

Scheme 3. Halogen Dance in the Production of 8 from 7



of the butyllithium in hexanes slows the rate of the overall reaction and allows the needed time for the halogen dance to generate the thermodynamic product.

In conclusion, although the preparation of bromothiazoles require a bit more effort than the analogous bromothiophenes, the full family of bromothiazoles can be prepared in moderate to good yields without the use of toxic Br_2. In addition, only the production of the final dibromothiazole **8** requires pyrophoric reagents or cryogenic reaction conditions. As such, the methods reported here represent the most practical and environmentally friendly conditions reported to date for the preparation of these increasingly important synthetic precursors as well as the first

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full report of the NMR characterization of all seven bromothiazoles.

EXPERIMENTAL SECTION

General Information. 2-Aminothiazole and 2,4-thiazolidinedione were purchased from Alfa Aesar. NBS was recrystallized from water as previously described.[36] Dry CH_3CN was treated with CaH_2 and distilled prior to use. Dry toluene was obtained via distillation over sodium benzophenone. The solvents $CHCl_3$ and hexanes used as reaction media were dried over $MgSO_4$ prior to use. All other materials were reagent grade and used without further purification. With the exception of the Sandmeyer reactions, all reactions were carried out under a nitrogen atmosphere. All glassware was oven-dried, assembled hot, and cooled under a dry nitrogen stream before use. Chromatographic separations were performed using standard column chromatography methods with silica gel (230−400 mesh) in 1 in. diameter columns. Melting points were determined using a digital thermocouple with a 0.1 °C resolution. All NMR data were obtained in $CDCl_3$ on a 400 MHz spectrometer and referenced to the $CHCl_3$ signal. Peak multiplicity is reported as follows: s = singlet, d = doublet, and br = broad. HRMS (ESI-TOF) was performed in house.

*2-Bromothiazole (**1**).* 2-Aminothiazole (5.01 g, 50.0 mmol) was added to 85% H_3PO_4 (20 mL) and sonicated to dissolve the amine. The red solution was added to a 500 mL, round-bottom flask submerged in an ice−NaCl bath, and the temperature lowered to 0 °C. Concentrated HNO_3 (10 mL) was then added, and the stirred mixture was again cooled to a constant 0 °C. $NaNO_2$ (4.48 g, 65.0 mmol) was dissolved in 10 mL of deionized H_2O and added dropwise to the acids over 1 h, keeping the temperature below 5 °C. The reaction was stirred for an additional 1 h at 0 °C. Meanwhile, a solution of NaBr (13.2 g, 130 mmol) and $CuSO_4{\cdot}5H_2O$ (10.37 g, 41.0 mmol) in 100 mL of H_2O was prepared in a 1 L beaker and cooled to 0 °C in a second ice−NaCl bath. The red diazonium solution was pipetted dropwise into the beaker, keeping the temperature below 5 °C. The blue solution gradually turned green, with vigorous effervescence and a gradual buildup of film on the sides of the beaker. After complete addition of the acid solution, the dark-green mixture was stirred for an additional 30 min, during which bubbling ceased. The solution was adjusted to pH 8 with solid Na_2CO_3 and extracted with diethyl ether to yield an orange-red oil. This crude product was run through a short silica plug (ca. 3 cm) (5% Et_2O in hexanes) to yield a colorless to faint-yellow oil in 83−86% yield (6.81−7.05 g). ^{1}H NMR: δ 7.61 (d, 1H, J = 3.56 Hz), 7.30 (d, 1H, J = 3.56 Hz). ^{13}C NMR: δ 143.1, 136.1, 123.0. NMR data agree well with previously reported values.[16]

*2-Amino-5-bromothiazole (**2**).* 2-Aminothiazole (1.02 g, 10.0 mmol) was dissolved in 10 mL of glacial acetic acid and heated to 40−50 °C. After the mixture was stirred for 10 min, NBS (2.31 g, 13.0 mmol) was added, and the clear, tan solution turned dark red, with a corresponding increase in temperature to 60−65 °C. The reaction was stirred for 1 h at 50 °C, after which 50 mL of water was added and the solution transferred to a 400 mL beaker. Diethyl ether (100 mL) was added, and solid Na_2CO_3 was used to adjust the solution to pH 8. The mixture was extracted with ethyl acetate, and the combined organic layers were washed three times with water to remove residual succinimide. The orange-red organic layer was evaporated in vacuo to give a red solid in 56−57% yield (1.00−1.02 g). The solid was not further purified but used immediately due to limited stability. Mp: 77.4 °C dec (lit.[20] mp 78 °C dec). ^{1}H NMR: δ 6.98 (s, 1H), 5.06 (br s, 2H). ^{13}C NMR: δ 168.3, 139.5, 95.8. HRMS: calcd for $C_3H_4{}^{79}BrN_2S$ $[M + H]^+$ 178.9279, found 178.9272.

*2,5-Dibromothiazole (**3**).* Via bromination of **1**: Na_2CO_3 (3.18 g, 30.0 mmol) was added to N_2-sparged $CHCl_3$ (15 mL) in a 125 mL three-neck flask. Thiazole **1** (2.46 g, 15 mmol) was added to the solution, followed by the dropwise addition of Br_2 (1.92 mL, 37.5 mmol). The reaction was stirred until **1** could no longer be detected by thin-layer chromatography, which took ca. 24 h. Saturated $Na_2S_2O_3$ (15 mL) was then added, and the solution was stirred for 30 min. The solution was made basic with solid Na_2CO_3 and the organic layer extracted with CH_2Cl_2, washed with brine, concentrated in vacuo, and dried over $MgSO_4$. The yellow oil was purified via column chromatography (10% Et_2O in hexanes) to give the product in 65% yield (4.73 g).

Via Sandmeyer reaction of **2**: Compound **2** (0.984 g, 5.50 mmol) was added to 10 mL of 85% H_3PO_4 and added to a 250 mL three-neck flask equipped with a thermometer. Concentrated HNO_3 (5 mL) was added to give a clear solution, which was then cooled to 0 °C with an ice−NaCl bath. A solution of $NaNO_2$ (0.493 g, 7.15 mmol) in 3 mL of deionized H_2O was then added dropwise over 30 min, keeping the temperature below 5 °C. The mixture was stirred for an additional 30 min. NaBr (1.45 g, 14.3 mmol) and $CuSO_4{\cdot}5H_2O$ (1.78 g, 7.15 mmol) were added to 30 mL of deionized water in a 400 mL beaker submerged in a second ice−NaCl bath and cooled to 0 °C. The diazonium solution was added dropwise into the beaker over 30 min, keeping the temperature below 5 °C. The blue solution gradually turned green, with vigorous effervescence. The solution was stirred for an additional 30 min, after which diethyl ether was added. The mixture was neutralized with solid Na_2CO_3, extracted with diethyl ether, and evaporated in vacuo to give the product in 60−65% yield (0.80−0.86 g). Mp: 46.5−47.1 °C (lit.[23] mp 46−47 °C). ^{1}H NMR: δ. 7.52 (s, 1H). ^{13}C NMR: δ 144.0, 135.8, 110.7. NMR data agree well with previously reported values.[16,17]

*5-Bromothiazole (**4**).* Compound **2** (1.25 g, 7.0 mmol) was dissolved in 10 mL of 85% H_3PO_4. Concentrated HNO_3 (5 mL) was added, and the solution was cooled to 0 °C in an ice−NaCl bath. $NaNO_2$ (0.77 g, 11.2 mmol) was dissolved in 3 mL of deionized H_2O and pipetted into the acid solution over the course of 30 min, keeping the temperature below 5 °C. The reaction was stirred for an additional 30 min, during which time the red-orange gas no longer evolved. H_3PO_2 (50% by mass, 3.8 mL, 35 mmol) was added dropwise, keeping the temperature below 5 °C. After the addition was complete, the reaction was stirred for 3 h at 0 °C and then brought to room temperature. Solid Na_2CO_3 was used to adjust the pH to 8, and the organic layer was extracted with diethyl ether. The organic layer was dried with $MgSO_4$ and the resulting oil purified via column chromatography (5% diethyl ether in hexanes) to give the product in 54% yield (0.62 g). ^{1}H NMR: δ 8.76 (s, 1H), 7.81 (s, 1H). ^{13}C NMR: δ 154.5, 144.8, 109.5. NMR data agree well with previously reported values.[17]

*2,4-Dibromothiazole (**5**).* To a 500 mL, round-bottom flask equipped with a reflux condenser were added 2,4-thiazolidinedione (3.51 g, 30 mmol), phosphorus pentoxide, (21.29 g, 150 mmol), and tetrabutylammonium bromide (20.56 g, 70 mmol). The solids were dissolved in 60 mL of toluene and heated to a gentle reflux for 20 h. The solution was cooled to room temperature, and 100 mL of saturated Na_2CO_3 was added. The solution was adjusted to pH 8 with solid Na_2CO_3 and extracted with diethyl ether, and the organic layer dried over $MgSO_4$. The resulting residue was purified via a short silica plug (ca. 3 cm) in pure hexanes to afford a white solid in 85−91% yield (6.20−6.53 g). Mp: 81.4−82.1 °C (lit.[21] mp 82 °C). ^{1}H NMR: δ 7.21 (s, 1H). ^{13}C NMR: δ 136.3, 124.3, 120.8. NMR data agree well with previously reported values.[16,17]

*4-Bromothiazole (**6**).* To a 50 mL, round-bottom flask equipped with reflux condenser were added **5** (0.243 g, 1.0 mmol) and $NaBH_4$ (0.076 g, 2.0 mmol). The solids were dissolved in acetonitrile, and the solution was refluxed overnight. Water (50 mL) was added to the yellow, opaque mixture, extracted with diethyl ether, and dried over $MgSO_4$. The residue was purified via column chromatography (1:1 $CHCl_3$/hexanes) to give a faint yellow oil in 62−66% yield (0.10−0.11 g). ^{1}H NMR: δ 8.75 (d, 1H, J = 2.26 Hz), 7.30 (d, 1H, J = 2.26 Hz). ^{13}C NMR: δ 153.9, 126.6, 116.9. NMR data agree well with previously reported values.[17]

*2,4,5-Tribromothiazole (**7**).* To an oven-dried, round-bottom flask were added **5** (4.8 g, 20 mmol) and NBS (4.3 g, 24 mmol). Glacial acetic acid (20 mL) was added via syringe and the reaction mixture heated at reflux. The reaction progress was monitored via thin-layer chromatography and allowed to proceed until product formation was complete (ca. 1−2 h). The reaction mixture was then cooled, made basic with solid Na_2CO_3, and extracted with diethyl ether. Purification of the crude product via silica gel chromatography in hexanes gave the

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product as a white solid in 68−76% yield (4.4−4.9 g). Mp: 33.2−33.5 °C (lit.[19,25] mp 36 °C). ^{13}C NMR: δ 136.0, 127.8, 109.5. HRMS: calcd for $C_3H^{79}Br_2{}^{81}BrNS$ $[M + H]^+$ 321.7359, found 321.7357.

*4,5-Dibromothiazole (**8**).* Compound **7** (0.646 g, 2 mmol) was dissolved in N_2-sparged hexane (100 mL) in a 250 mL round-bottom flask. The solution was cooled to −78 °C, and butyllithium (2.5 M in hexane, 0.88 mL, 2.2 mmol) was added dropwise. The solution was stirred at −78 °C for 3 h, quenched with methanol, and then warmed to room temperature. Brine was added, the mixture was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$. The dried organic fraction was then concentrated in vacuo and purified via column chromatography in hexanes to give the product as a white solid in 60−67% yield (0.29−0.36 g). Mp: 74.1−74.8 °C. ^{1}H NMR: δ 8.75 (s, 1H). ^{13}C NMR: δ 154.3, 130.0, 108.2. HRMS: calcd for $C_3H_2{}^{79}Br_2NS$ $[M + H]^+$ 241.8275, found 241.8251.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00495.

^{1}H and ^{13}C NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seth.rasmussen@ndsu.edu.

ORCID

Seth C. Rasmussen: 0000-0003-3456-2864

Notes

The authors declare no competing financial interest.

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