Note

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Promoting Effect of Crystal Water Leading to Catalyst-Free Synthesis of Heteroaryl Thioether from Heteroaryl Chloride, Sodium Thiosulfate Pentahydrate, and Alcohol

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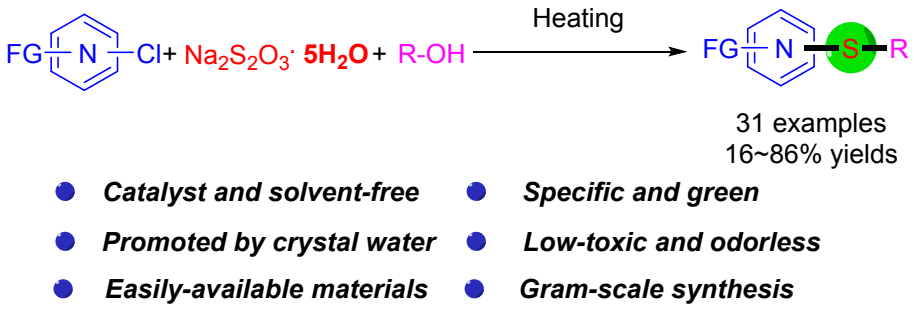
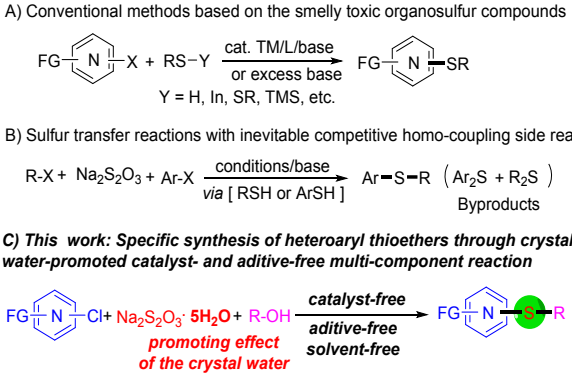
Supporting Information Placeholder



ABSTRACT: It is observed the crystal water in sodium thiosulfate pentahydrate ($Na_2S_2O_3·5H_2O$) can promote its multi-component reaction with heteroaryl chlorides and alcohols, providing a facile, green and specific synthesis of unsymmetrical heteroaryl thioethers *via* one-step formation of two C-S bonds under catalyst-, additive-, and solvent-free conditions. Mechanistic studies suggest that the crystal water in $Na_2S_2O_3·5H_2O$ is crucial in generating the key thiol intermediates and byproduct $NaHSO_4$, which then catalyzes the dehydrative substitution of alcohols with thiols to afford thioethers.

Owing to their unique antibacterial, antimycobacterial, anticancer and anti-inflammatory activities, synthesis and applications of heteroaryl thioethers are always attractive topics among the synthetic and pharmaceutical chemists.[1] However, known methods for heteroaryl thioethers synthesis are mostly cross-coupling reactions starting from the smelly, toxic, sensitive, and commercially less available organosulfur compounds (such as thiols, $In(SR)_3$, disulfides or $PhSSiMe_3$) under TM-catalyzed[2] or non-catalytic[3-4] conditions (Scheme 1A). Therefore, developing eco-friendly and metal-free methods that can employ some cheaper, greener, odorless, more stable, and low-toxic sulfur surrogates instead of the conventional organosulfur reagents is still highly desired in the field.

In recent years, the cheap, lowly toxic, odorless and stable $Na_2S_2O_3$ has been widely used in sulfur-transfer reactions for synthesis of organosulfur compounds.[5] These methods are rather attractive as the use of smelly, toxic and sensitive thiols can be avoided. [5] However, owing to the competitive homo-coupling side reactions of the two *in situ* generated thiol intermediates in MCR sulfur-transfer reactions,[5a,5e] the synthesis of unsymmetrical thioethers is still challenging[5,6] and the known methods were mainly limited to step-wise or muti-step reactions through formation of Bunte salt intermediates via the reaction of one organohalide with $Na_2S_2O_3$ (Scheme 1B).[5e,7] In comparison, successful examples of direct intermolecular muti-component

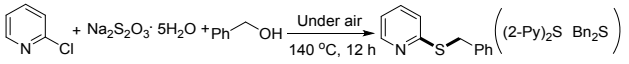


Scheme 1. Methods for unsymmetrical thioether synthesis.

reactions (MCR) of two different carbon sources with $Na_2S_2O_3$ for efficient one-step construction of two C-S bonds are still rare and a catalyst or promoter is generally required to facilitate the *in-situ* liberation of thiol intermediate from Bunte salt.[8] To our knowledge, highly selective and step-economic MCRs of $Na_2S_2O_3$ for direct and efficient synthesis of unsymmetrical heteroaryl thioethers were not known yet.

We have been interested in thioether synthesis for a long time.[9] We have also observed that thiourea can be used as the inorganic sulfur source in the synthesis of heteroaryl thioethers.[9d] However, to obtain satisfactory results, the more expensive heteroaryl bromides are usually required in the method because byproduct HBr-mediated transformation of ROH to the more reactive RBr is a key step in the reaction. To develop a greener and more useful method that can employ the more economic heteroaryl chlorides and an alternative sulfur surrogate that can replace the relatively more toxic thiourea, herein, we describe a direct MCR of heteroaryl chlorides, $Na_2S_2O_3{\cdot}5H_2O$, and alcohols (Scheme 1C). Interestingly, it was observed the crystal water in $Na_2S_2O_3{\cdot}5H_2O$ can promote the reaction greatly. In this MCR, simply replacing the commonly used alkyl halides with alcohols, sequencial C-S bond formations can occur in one-pot to provide an efficient and specific synthesis of heteroaryl thioethers under catalyst-, additive-, and solvent-free conditions.

Table 1. Conditions screening for heteroaryl thioethers synthesis.[a]



1a 2a 3aa 4a 5a

run	Solvent	**3aa**%[b]	**3aa**/**4a**/**5a**[c]
1	none	83	>99/0/0
2	dioxane	32	60/40/0
3	DMSO	0	0/0/>99
4	toluene	0	0/0/0
5	H_2O	82	>99/0/0
6	H_2O[d]	8	18/82/0
7[e]	none	86	>99/0/0
8[f]	none	trace	---
9[f]	H_2O[g]	80	>99/0/0
10[f]	DMF	trace	---
11[f]	DMSO	trace	---
12[h]	none	65	91/9/0

[a] Unlesss otherwise noted, the mixture of 2-pyridyl chloride **1a** (0.50 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (1.0 mmol), benzyl alcohol **2a** (0.50 mmol), and a solvent (0.25 mL) was heated at 140 °C (oil bath) for 12 h in a 10 mL sealed Schlenk tube under air, and then monitored by TLC/GC-MS. [b] Isolated yields based on **1a**. [c] Determined by GC-MS. [d] H_2O (1.0 mL). [e] Under N_2. [f] 1 mmol anhydrous $Na_2S_2O_3$ of 4N grade (99.99% trace metals basis) was used instead of $Na_2S_2O_3{\cdot}5H_2O$. [g] H_2O (0.090 mL, ca. 5 mmol, 5 equiv. to $Na_2S_2O_3$). [h] 120 °C

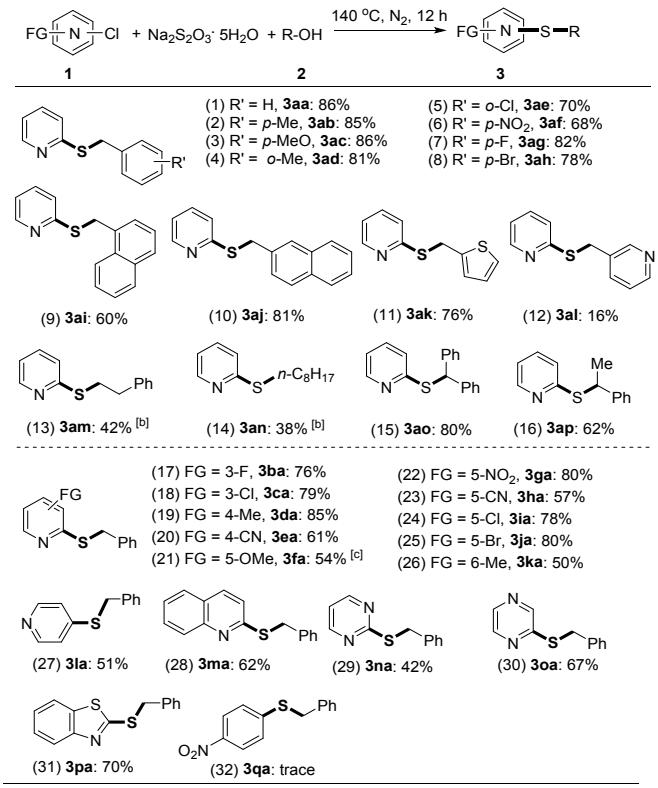
Initially, a neat mixture of 2-pyridyl chloride (**1a**), $Na_2S_2O_3{\cdot}5H_2O$, and benzyl alcohol (**2a**) was directly heated under air. To our delight, even at 140 °C, 2-pyridyl benzyl thioether (**3aa**) could be obtained in 83% isolated yield and >99% selectivity without observing the possible homo-coupling by-products di-(2-pyridyl)thioether (**4a**) and di-(benzyl) thioether (**5a**) (Table 1, run 1). Then various solvents were screened, showing that the reaction is rather sluggish in solvents with detection of by-products **4a** and **5a** (runs 2-4).[10] In great contrast, a control reaction in water successfully afforded a comparable yield (82%) of **3aa** (run 5) with that of the neat reaction (run 1). This may suggest that the reaction is tolerant with water and water a better solvent.[11] However, another control reaction with more water gave only an inferior yield of **3aa** in a low selectivity (run 6). The reaction was then returned to the solvent-free condition and investigated under nitrogen to avoid oxidative side reactions of the thiol intermediates. Indeed, the reaction gave a slightly improved yield of **3aa** (86%) with >99% selectivity (run 7). Anhydrous $Na_2S_2O_3$ (**2a'**)[12] was then investigated for comparison with $Na_2S_2O_3{\cdot}5H_2O$. To our great surprise, only trace amount of **3aa** was observed in the reaction (run 8). Then, ca. 5 mmol water (equals to the amount of crystal water in the added $Na_2S_2O_3{\cdot}5H_2O$) was added to the reaction. To our surprise again, once the water was added, the reaction effectively gave a comparable yield (80%) of **3aa** with that of the neat reaction of $Na_2S_2O_3{\cdot}5H_2O$ (run 1).[13] However, some control experiments using other strongly solvating solvents such as DMSO and DMF only gave trace amount of target **3aa** (runs 10-11). These results implies that the crystal water in $Na_2S_2O_3{\cdot}5H_2O$ may play a significant role in the reaction (*vide infra*). However, running the reaction at temperatures below 140 °C led to lower selectivity of **3aa** with increased yields of **4a** (run 12). Usually, higher temperatures can lead to less difference of the activation barriers between competing reactions and consequently lower selectivities of the products and byproducts. Hence, to improve the product's selectivity, reducing the reaction temperature is usually the mean of choice. On the contrary, the above observed beneficial effect of higher temperature on the product's selectivity is unusual and interesting in organic reactions.

With the optimized conditions in hand (Table 1, run 7), various alcohols and heteroaryl chlorides were then investigated to extend the scope of this method. As shown in Table 2, like the model reaction (run 1), both electron-rich and -deficient primary benzylic alcohols including the sterically more bulky *ortho*-substituted ones reacted effectively with **1a** and $Na_2S_2O_3{\cdot}5H_2O$ to afford moderate to high yields of the correspoding thioethers (runs 2-10). As to heteroaryl methanols, the reaction of 2-thiophenemethanol gave a good yield of the product (run 11); while 3-pyridylmethanol only afforded a low yield of the product (run 12), very possibly due to the interaction of the alcohol's basic pyridyl moiety with the generated intermediate $NaHSO_4$ (*vide infra*). The method can also

be applied to more challenging primary aliphatic alcohols under the standard catalyst- and additive-free conditions, affording moderate yields of the products (runs 13-14).[14] Moreover, sterically more bulky secondary alcohols such as benzhydrol, 2-phenylethanol also afforded the target products in satisfactory yields (runs 15-16).[15]

For substituted 2-pyridyl chlorides, both electron-rich and -deficient 2-pyridyl chlorides, including the dichlorides and those with reactive CN, F, Br and NO_2 groups, reacted smoothly under the standard conditions to give moderate to good yields of the target products (Table 2, runs 17-26). 4-Pyridyl chloride also reacted smoothly to afford the target **3la** in an acceptable yield (run 27). Similarly, other activated heteroaryl halides such as 2-quinolyl, 2-pyrimidyl, 2-pyrazinyl and 2-benzothiazolyl halides mostly reacted smoothly with $Na_2S_2O_3{\cdot}5H_2O$ and **2a** to give the target products in moderate yields (runs 28-31), revealing that the substrate scope of this method can be rather broad. However, the present method is not suitable for electron-deficient aryl chlorides, such as 4-nitrochlorobenzene (run 32).

Table 2. Substrate extension of the catalyst- and additive-free heteroaryl thioether synthesis.[a]



[a] See Table 1 run 7 for details, isolated yield based on **1**. [b] 150 °C. [c] 170 °C.

The above method is also easily scalable. As shown in Figure 1, heating an 8 mmol reaction of **1a**, $Na_2S_2O_3{\cdot}5H_2O$, and **2a** afforded a two-phase mixture, which led to an easy purification of **3aa** without the need of column chromatography. Thus, **3aa** could be obtained in 67% isolated yield (1.08 g, 99% purity) by simple extraction and filtration.[10]

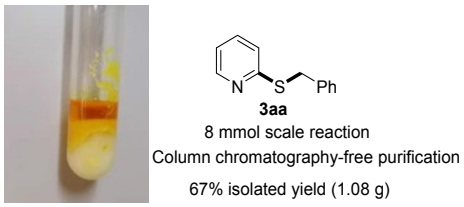
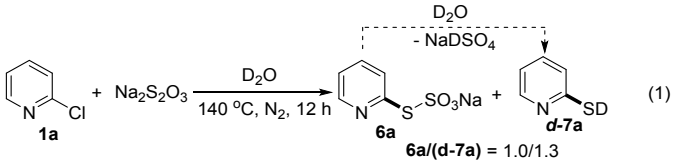
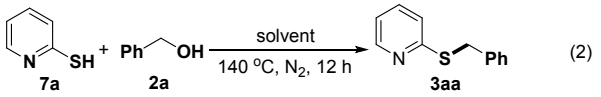


Figure 1. Gram scale synthesis of **2a**.

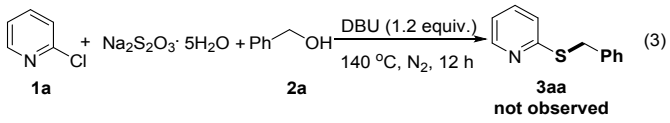
Control experiments were then carried out to investigate the reaction mechanism. As shown in eq. 1, *in situ* ^{1}H NMR analysis of the reaction mixture of 2-pyridyl chloride (**1a**) and anhydrous sodium thiosulfate in the presence of deuteroxide showed that 2-pyridyl Bunte salt (**6a**) and d-2-pyridinethiol (***d*-7a**) were generated during the progress of the reaction.[16] Most likely, an S_NAr reaction of 2-pyridyl chloride (**1a**) and sodium thiosulfate may occur to afford **6a** first, which then hydrolyzed with deuteroxide to afford *d*-2-pyridinethiol (***d*-7a**) and byproduct $NaDSO_4$.[17]



Further reaction of 2-pyridinethiol (**7a**) with the alcohol **2a** was then investigated. Without any additive, the blank reaction of **7a** and **2a** afforded only 13% yield of **3aa** in water (eq. 2, run 1). Then, with addition of only catalytic amount of $NaHSO_4$ (the byproduct), the reaction was greatly promoted to give 94% yield of **3aa** under the same conditions (run 2). This result could be easily repeated by using other solvents (runs 3-4). In contrast, addition of a base (DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene) to the model reaction could quickly terminate the reaction (eq. 3). These results suggest that the generated byproduct $NaHSO_4$ is not useless in the reaction but crucial in the efficient production of the target thiothers. Since water is indispensable in the generation of both the heteroaryl thiols **7** and byproduct $NaHSO_4$ (eq. 1), the above results further revealed the crucial role of water in the present MCR, which is clearly consistent with the preceding experimental findings during condition screening. For example, water is found to be a better solvent for the reaction (Table 1, run 5), and, without water, the reaction of anhydrous sodium thiosulfate could not occur to give the product (Table 1, run 8).

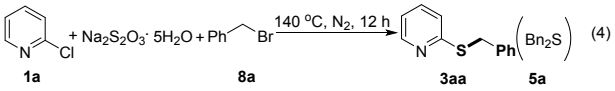


1) blank, H_2O (0.25 mL), 13%
2) $NaHSO_4$ (10 mol%), H_2O (0.25 mL), 94%
3) $NaHSO_4$ (10 mol%), toluene (0.25 mL), 90%
4) $NaHSO_4$ (10 mol%), dioxane (0.25 mL), 80%



(3)

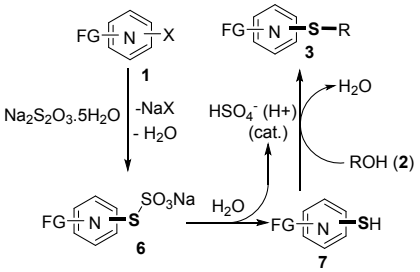
Control reactions using benzyl bromide (**8a**) instead of benzyl alcohol (**2a**) were also investigated to get more information. As shown in Eq. (4), the target **3aa** could only be obtained in low to moderate yields with or without a base; whereas, the homo-coupled di-(benzyl) thioether (**5a**) was also obtained as main product. These results suggest that alkyl halides **8** can compete with the heteroaryl chlorides **1** and lead to low selectivity of the target prouduct, being a disadvantage of using common alkyl halides. In comparison, in the present method, most likely due to inert reactivity of alcohols, $Na_2S_2O_3{\cdot}5H_2O$ may sequentially react with heteroaryl chlorides **1** first and then with alcohols, which then leads to the high selectivity of the target thioethers. Therefore, using alcohols as the alkyl sources is not only an advantage of the mothod for replacing the alkyl halides, the reasults also showed that alcohols are indispensible alkyl sources for the high selectivity of the reaction.



(4)

1) none: **3aa**, 52%; **5a**, 10% isolated yield
2) K_2CO_3 (2.0 equiv.): **3aa**, 31%; **5a**, 22% isolated yield

A plausible mechanism was then proposed as shown in Scheme 2. Initially, heteroaryl chlorides **1** may react with sodium thiosulfate pentahydrate to afford heteroaryl Bunte salts **6**, which then hydrolyze with water to give the key intermediates heteroaryl thiols **7** and bisulfate anion (or a proton).[8] Finally, catalyzed by the in situ generated bisulfate anion (or a proton), the dehydrative substitution reaction of alcohols **2** with heteroaryl thiols **7** may occur to give the target products **3**.[18]



Scheme 2. Possible reaction path way.

In summary, the crystal water in $Na_2S_2O_3{\cdot}5H_2O$ was found able to promote a MCR of heteroaryl chlorides, $Na_2S_2O_3{\cdot}5H_2O$, and alcohols. Thus, a one-pot catalyst-, additive-, and solvent-free method for specific synthesis of the useful unsymmetrical heteroaryl thioethers was developed by using the odorless and lowly toxic $Na_2S_2O_3{\cdot}5H_2O$ as the sulfur surrogate and alcohols the greener alkyl source. Mechanistic studies revealed that the crystal water in $Na_2S_2O_3{\cdot}5H_2O$ is crucial in generating the key thiol intermediates and byproduct $NaHSO_4$, which can then catalyze the dehydrative substitution reaction of thiol intermediates and alcohols to finally afford the unsymmetrical heteroaryl thioethers. This method is suitable for a wide range of substrates and can be easily scaled up to gram scale preparation of the thioethers under column chromatography-free conditions.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all chemicals were purchased and used without further purification. Unless otherwise specified, all reactions were carried out in sealed Schlenk tubes under N_2 and then monitored by TLC and/or GC-MS. Products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as the eluent. Unless otherwise noted, ^1H and ^{13}C $\{^1H\}$ NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz and 125 MHz, respectively) or JNM-ECZ600R/S3 (Jeol, Japan) (600 MHz and 150 MHz, respectively) using $CDCl_3$ as the solvent. Chemical shifts for ^1H and ^{13}C $\{^1H\}$ NMR were referred to internal Me_4Si (0 ppm) as the standard. Mass spectra were measured on an Agilent GC-MS-5890A/5975C Plus spectrometer (EI). HRMS were recorded on a LC-TOF spectrometer (Xevo G2-XS QTof) using ESI techniques.

General Procedure for the Catalyst- and Additive-Free MCR of Heteroaryl Chlorides, Sodium Thiosulfate Pentahydrate and Alcohols. A mixture of 2-pyridyl chloride **1a** (56.5 mg, 0.50 mmol), Sodium thiosulfate pentahydrate (248.0 mg, 1.0 mmol, 2.0 equiv.) and benzyl alcohol **2a** (54.0 mg, 0.50 mmol, 1.0 equiv.) was sealed in a Schlenk tube (20 mL) under N_2, and stirred at 140 °C (oil bath) for 12 h. The reaction was then monitored by TLC and/or GC-MS. After completion of the reaction, the reaction mixture was purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0~ 1/50) as the eluent, giving **3aa** in 86% isolated yield.

2-(Benzylthio)pyridine **(3aa).** Colorless oil, (86.3 mg, 86%).[9b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.31 (m, 1H), 7.44 – 7.34 (m, 3H), 7.26 (dd, J = 10.0, 4.5 Hz, 2H), 7.20 (dd, J = 9.5, 5.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.99 – 6.84 (m, 1H), 4.43 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.9, 149.3, 138.0, 136.1, 129.0, 128.5, 127.1, 122.2, 119.6, 34.6; MS (EI): m/z (%) 201 (48), 168 (100), 154 (2), 124 (10), 121 (4), 91 (58), 65 (24), 51 (8).

2-((4-Methylbenzyl)thio)pyridine **(3ab).** Colorless oil (91.3 mg, 85%).[9d] ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.0 Hz, 2H), 7.16 – 7.07 (m, 3H), 6.98 (t, J = 5.5 Hz, 1H), 4.42 (d, J = 8.5 Hz, 2H), 2.30 (s, 3H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.0, 149.1, 136.8, 136.2, 134.7, 129.2, 128.9, 122.3, 119.6, 34.4, 21.1.

2-((4-Methoxybenzyl)thio)pyridine **(3ac).** Colorless oil (99.3 mg, 86%).[19] ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 4.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.82 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 3.77 (s, 3H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.9, 148.7, 136.6, 130.1, 129.5, 122.5, 119.7, 114.0, 55.3, 34.4.

2-((2-methoxybenzyl)thio)pyridine (**3ad**). Colorless oil (87.0 mg, 81%).[9d] ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J =

4.2 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.11 – 6.98 (m, 4H), 6.95 – 6.79 (m, 1H), 4.37 (s, 2H), 2.33 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.2, 149.3, 137.0, 136.1, 135.4, 130.4, 130.0, 127.5, 126.1, 122.3, 119.5, 32.8, 19.3.

2-((2-Chlorobenzyl)thio)pyridine **(3ae).** Colorless oil (82.4 mg, 70%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.5 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.39 – 7.30 (m, 1H), 7.22 – 7.09 (m, 3H), 7.11 – 6.94 (m, 1H), 4.59 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.3, 149.1, 136.3 135.8, 134.3, 131.0, 129.6, 128.5, 126.8, 122.5, 119.7, 32.1.

2-((4-nitrobenzyl)thio)pyridine (**3af**). Colorless oil (84.0 mg, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.09 – 6.93 (m, 1H), 4.52 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.1, 149.3, 147.0, 146.5, 136.3, 129.8, 123.6, 122.4, 120.1, 33.4. HRMS (ESI) for $C_{12}H_{11}N_2O_2S$ (M+H) Calcd: 247.0541; found: 247.0520.

2-((4-fluorobenzyl)thio)pyridine **(3ag).** Colorless oil (89.8 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 6.0 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.96 (dt, *J* = 13.2, 7.8 Hz, 3H), 4.40 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.0 (d, *J* = 245.3 Hz), 158.4 (s), 149.4 (s), 136.1 (s), 133.9 (d, *J* = 3.2 Hz), 130.5 (d, *J* = 8.1 Hz), 122.2 (s), 119.7 (s), 115.3 (d, *J* = 21.4 Hz), 33.6 (s). HRMS (ESI) for $C_{12}H_{11}FNS$ (M+H) Calcd: 220.0596; found: 220.0608.

2-((4-Bromobenzyl)thio)pyridine **(3ah).** Colorless oil (109.0 mg, 78%).[20] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.03 – 6.93 (m, 1H), 4.39 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.1, 149.2, 137.3, 136.3, 131.5, 130.7, 122.4, 121.0, 119.8, 33.8.

1-((Naphthalen-1-ylmethyl)thio)pyridine **(3ai).** White solid, 113-115 °C (75.0 mg, 60%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.03 – 6.94 (m, 1H), 4.93 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.0, 149.2, 136.2, 134.0, 133.2, 131.8, 128.8, 128.2, 127.6, 126.3, 125.8, 125.4, 124.0, 122.4, 119.7, 32.4.

2-((Naphthalen-1-ylmethyl)thio)pyridine **(3aj).** White solid, 124-125 °C, (101.5 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.2 Hz, 1H), 7.83 (s, 1H), 7.76 (t, *J* = 7.8 Hz, 3H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.00 – 6.84 (m, 1H), 4.60 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 158.7, 149.3, 136.2, 135.4, 133.4, 132.7, 128.3, 127.8, 127.7, 127.6, 127.2, 126.2, 125.8, 122.3, 119.7, 34.8. HRMS (ESI) for $C_{16}H_{14}NS$ (M+H) Calcd: 252.0847; found: 252.0864.

2-((Thiophen-2-ylmethyl)thio)pyridine **(3ak).** Colorless oil, (79.0, 76%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.0 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.09 – 6.97 (m, 2H), 6.89 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.70 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.9, 148.8, 140.7, 136.8, 126.7, 126.6, 125.0, 122.8, 120.0, 29.3.

2-((pyridin-3-ylmethyl)thio)pyridine (**3al**). Colorless oil, (16.0 mg, 16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.8 Hz, 1H), 8.42 – 8.32 (m, 2H), 7.68 – 7.64 (m, 1H), 7.45 – 7.34 (m, 1H), 7.13 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.95 – 6.90 (m, 1H), 4.35 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.6, 150.3, 149.5, 148.3, 136.5, 136.1, 134.4, 123.3, 122.3, 119.9, 31.3;. HRMS (ESI) for $C_{11}H_{11}N_2S$ (M+H) Calcd: 203.0643; found: 203.0666.

2-(Phenethylthio)pyridine **(3am)**. Colorless oil (44.8 mg, 42%).[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.5 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.37 – 7.09 (m, 6H), 7.04 – 6.84 (m, 1H), 3.43 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H) ; ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.0, 149.4, 140.6, 135.9, 128.6, 128.4, 126.4, 122.4, 119.3, 35.9, 31.5.

2-(Octylthio)pyridine **(3an).** Colorless oil, (42.1 mg, 38%).[22] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (t, *J* = 4.5 Hz, 1H), 7.47 (dt, *J* = 7.5, 5.5 Hz, 1H), 7.25 – 7.11 (m, 1H), 7.07 – 6.85 (m, 1H), 3.20 – 3.13 (m, 2H), 1.75 – 1.65 (m, 2H), 1.50 – 1.40 (m, 2H), 1.37 – 1.15 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, CDCl3) δ 159.7, 149.2, 136.0, 122.2, 119.2, 31.8, 30.3, 29.3, 29.1, 28.9, 22.6, 14.0.

2-(Benzhydrylthio)pyridine **(3ao).** White solid, m.p. 69-70 °C, (111.0 mg, 80%).[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.51 – 7.36 (m, 5H), 7.33 – 7.16 (m, 6H), 7.11 (dd, *J* = 7.5, 4.5 Hz, 1H), 6.98 – 6.90 (m, 1H), 6.35 (d, *J* = 4.5 Hz, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.3, 149.2, 141.3, 136.3, 128.6, 128.5, 127.1, 122.5, 119.9, 52.9.

2-((1-Phenylethyl)thio)pyridine **(3ap).** White solid, 47-49 °C, (66.1 mg, 62%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.5 Hz, 1H), 7.44 (t, *J* = 6.5 Hz, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.06 – 6.85 (m, 1H), 5.13 (q, *J* = 7.0 Hz, 1H), 1.74 (d, *J* = 7.0 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.8, 149.2, 143.2, 136.3, 128.5, 127.4, 127.2, 123.1, 119.7, 43.8, 22.6.

2-(Benzylthio)-3-fluoropyridine **(3ba).** Colorless oil, (83.5 mg, 76%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.31 – 7.31 (m, 4H), 7.01 (dd, *J* = 7.5, 4.0 Hz, 1H), 4.48 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.1 (d, *J* = 256.0 Hz), 147.5 (d, *J* = 17.8 Hz), 144.8 (d, *J* = 5.0 Hz), 129.1 (s), 128.5 (s), 127.2 (s), 121.1 (d, *J* = 18.0 Hz), 120.1 (d, *J* = 2.8 Hz), 33.3 (s).

2-(Benzylthio)-3-chloropyridine **(3ca).** Colorless oil, (93.0 mg, 79%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.5 Hz, 1H), 7.52 (d, *J* = 80 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.17 (m, 3H), 6.95 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.46 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.3, 146.8, 137.5, 135.9, 129.2, 129.0, 128.5, 127.2, 119.8, 34.7.

2-(Benzylthio)-4-methylpyridine **(3da).** Colorless oil, (91.5 mg, 85%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.1 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.32 – 7.17 (m, 3H), 6.98 (s, 1H), 6.80 (d, *J* = 5.0 Hz, 1H), 4.42 (s, 2H), 2.24 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.6, 149.1, 147.3, 138.2, 129.1, 128.6, 127.1, 122.7, 121.1, 34.5, 20.9.

2-(Benzylthio)isonicotinonitrile **(3ea).** White solid, 78-79 °C, (69.5 mg, 61%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.0 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.19 (m, 4H), 7.14 (d, *J* = 5.0 Hz, 1H), 4.44 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.3, 150.1, 137.0, 129.0, 128.6, 127.4, 123.7, 120.4, 120.2, 116.2, 34.5.

2-(Benzylthio)-5-methoxypyridine **(3fa).** Colorless oil, (62.5 mg, 54%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.26 – 7.09 (m, 6H), 4.42 (s, 2H), 3.79 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.3, 148.5, 137.2, 133.9, 129.0, 128.5, 127.3, 125.3, 124.9, 56.2, 36.6.

2-(Benzylthio)-5-nitropyridine **(3ga).** Light yellow solid, 92-93 °C, (98.9 mg, 80%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, J = 2.5 Hz, 1H), 8.21 (dd, J = 9.0, 2.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 4.52 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.3, 145.0, 141.3, 136.7, 130.4, 129.0, 128.7, 127.6, 121.3, 34.8.

6-(Benzylthio)nicotinonitrile **(3ha).** White solid, 79-81 °C, (64.0 mg, 57%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26 – 7.20 (m, 2H), 4.47 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.9, 152.2, 137.8, 136.9, 129.0, 128.6, 127.5, 121.6, 117.0, 105.0, 34.4.

2-(Benzylthio)-5-chloropyridine **(3ia).** Colorless oil, (92.0 mg, 78%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.5, 2.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.18 – 7.10 (m, 1H), 7.03 (d, J = 8.5 Hz, 1H), 4.35 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.0, 147.8, 137.5, 136.1, 128.9, 128.5, 128.1, 127.3, 122.9, 34.9.

2-(Benzylthio)-5-bromopyridine **(3ja).** White solid, 86-88 °C, (112.0 mg, 80%).[1a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.56 (dd, J = 8.5, 2.0 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.32 – 7.18 (m, 3H), 7.05 (d, J = 8.5 Hz, 1H), 4.41 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.6, 150.1, 138.6, 137.6, 128.9, 128.5, 127.2, 123.3, 116.2, 34.8.

2-(Benzylthio)-6-methylpyridine **(3ka).** Colorless oil, (53.4mg, 50%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 2H), 7.22 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 4.42 (s, 2H), 2.52 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.3, 157.7, 138.4, 136.4, 129.0, 128.4, 127.0, 119.0, 34.6, 24.3.

4-(Benzylthio)pyridine **(3la).** White solid, 55-57 °C, (52.0 mg, 51%).[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.12 (d, J = 4.0 Hz, 1H), 4.20 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.5, 148.9, 135.5, 128.8, 128.7, 127.7, 120.9, 35.8.

2-(Benzylthio)quinoline **(3ma).** White solid, 123-125 °C, (77.5 mg, 62%).[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 10.0 Hz, 1H), 7.78 – 7.62 (m, 2H), 7.55 – 7.40 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H), 7.26 – 7.13 (m, 2H), 4.65 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.0, 147.6, 138.0, 136.0, 130.1, 129.2, 128.5, 127.6, 127.5, 127.2, 126.1, 125.6, 120.7, 34.4.

2-(Benzylthio)pyrimidine **(3na).** Colorless oil, (42.5 mg, 42%).[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 5.0 Hz, 2H), 7.43 (d, J = 7.5 Hz, 2H), 7.35 – 7.18 (m, 3H), 6.97 (t, J = 5.0 Hz, 1H), 4.43 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.2, 157.2, 137.4, 129.1, 128.5, 127.2, 116.5, 35.3.

2-(Benzylthio)pyrazine **(3oa).** White solid, 56-58 °C, (66.8 mg, 67%).[9d] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.38 (s, 1H), 8.20 (d, J = 1.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 7.0 Hz, 1H), 4.42 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.8, 143.9, 143.6, 139.5, 137.2, 129.0, 128.6, 127.4, 34.0.

2-(Benzylthio)benzo[d]thiazole **(3pa).** White solid, 180-181 °C, (90.0 mg, 70%).[26] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.38 – 7.20 (m, 4H), 4.62 (s, 2H).; ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.7, 152.8, 136.1, 135.2, 129.1, 128.7, 127.8, 126.2, 124.4, 121.5, 121.0, 37.9.

Di(pyridin-2-yl) thioether **(4a).** Colorless solid, 215-216 °C.[9d] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.59 (td, J = 7.8, 1.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.14 (dd, J = 6.6, 5.4 Hz, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.9, 150.3, 137.2, 126.0, 121.9.

Dibenzylsulfane **(5a).** Colorless solid, 45-46 °C.[27] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 – 7.26 (m, 10H), 3.66 (s, 4H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 138.3, 129.2, 128.7, 127.2, 35.7.

General Procedure for Gram scale synthesis of 3aa.

The mixture of 2-pyridyl chloride **1a** (904 mg, 8.0 mmol), sodium thiosulfate pentahydrate (3968 mg, 16.0 mmol, 2.0 equiv.) and benzyl alcohol **2a** (1037 mg, 9.6 mmol, 1.2 equiv.) was sealed in a Schlenk tube (20 mL) under N2, and stirred at 140 °C (oil bath) for 24 h. After the reaction mixture cooled down to room temperature, 30 mL water was added to the reaction mixture. Then the reaction mixture was extracted with ethyl acetate (30*3 mL) for three times. The organic layer was combined, and washed with sodium hydroxide solution (1N, 20 mL), saturated sodium chloride solution, then dried with anhydrous sodium sulfate. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was acidized with HCl solution (6N, 6.0 mL) and some precipitate was generated (possibly **3aa•mHCl**). The mixture was filtered and the residue was then alkalified with NaOH (1N, 30 mL) and then extracted with ethyl acetate for three times (50*3 mL). The organic layer was combined, and washed with saturated sodium chloride solution, then dried with anhydrous sodium sulfate. The mixture was filtered, and the solvent was evaporated under reduced pressure to afford the de-sired **3aa**. Owing to the incomplete salifying with HCl solution, the filtrate of the previous HCl solution was then extracted with ethyl acetate (50*3 mL) for three times again and then dried with anhydrous sodium sulfate. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was handled following the above acidification and alkalization procedures again. And the obtained **3aa** was combined with a total yield of 67% (1.08 g, 99% purity).

ASSOCIATED CONTENT

Supporting Information

Details of the control experiments for mechanistic studies and ^{1}H and ^{13}C {^{1}H} NMR spectra of products are supplied as Supporting Information (i.e., PDF) and this material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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12. Anhydrous $Na_2S_2O_3$ (99.99% trace metals basis) was purchased from SIGMA-ALDRICH. See SI for the details of the certificate of analysis.

13. The effects of water to the reaction were carefully investigated, showing that the reaction can bentical from appropriate amount of water (ca. 5 ~50 equiv.), see SI for details.

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15. The present conditions are currently not suitable for less reactive secondary aliphatic alcohols (such as cyclohexanol) and sterically more bulky tertiary aliphatic alcohols (such as 2-methylpropan-2-ol, and only trace amount of target products were obtained).

16. It is difficult to isolate the heteroaryl Bunte salt **6a** from the reaction mixture. Hence, *in situ* ^{1}H NMR and ESI-HRMS analysis was performed, see SI for details.

17. The pH value of the reaction mixture of **1a**, $Na_2S_2O_3{\cdot}5H_2O$ and **2a** was measured by a pH meter to be 1.87. This is consistent with the generation of $NaHSO_4$ in the reaction. Besides, typical titration experiments of HSO_4^- were also performed, suggesting the possible generation of HSO_4^- during the reaction, see SI for details.

18. Thanks to one of the reviews's kind suggestions, the dehydrative substitution of alcohols may also be catalyzed by thiosulfuric acid – the conjugated acid of thiosulfate.

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