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Transition-Metal-Free Synthesis of 2-Substituted Benzothiazoles from Nitrobenzenes, Methylheteroaryl Compounds, and Elemental Sulfur, Based on Nitro-Methyl Redox-Neutral Cyclization

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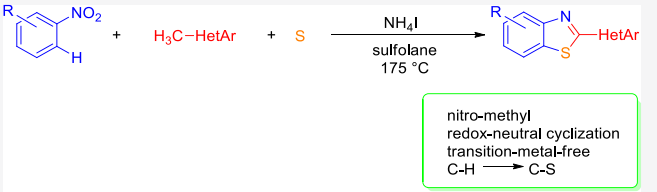
ABSTRACT: Greener and more sustainable chemical processes are required to address increasing environmental pollution and depletion of natural resources. This paper aims to develop greener and more sustainable modern synthetic chemical processes using redox-neutral cyclization. Redox-neutral cyclization has been shown to promote the efficient synthesis of 2-substituted benzothiazoles from easily available nitrobenzenes, methylheteroaryl compounds, and elemental sulfur in the absence of transition-metal catalysts. The 2-substituted benzothiazoles were obtained in reasonable yields through the sulfuration of electron-deficient C−H bonds with elemental sulfur. This synthetic methodology also affords a high atom economy without the use of any external oxidizing and/or reducing reagents.



INTRODUCTION

In order to address depletion of natural resources and environmental pollution, a great deal of effort has been made toward developing greener and more sustainable modern chemical processes, particularly with regard to large-scale production. This study was aimed at developing synthetic processes that meet one or more of the following criteria: (1) employ transition-metal-free reaction conditions, (2) use readily available starting materials, (3) have high atom economy, and (4) involve cascade reactions.

In the nitro-methyl redox-neutral reaction, the starting materials are subjected to two opposite reactions: the reduction of the corresponding nitrobenzenes ($6e^-$ transfer) and the oxidation of methylheteroaryl compounds ($6e^-$ transfer). This type of reaction is highly desirable because three processes (oxidation, reduction, and condensation) are carried out in only one operation.

In 2013, Nguyen and co-workers discovered the synthesis of 2-heteroaryl benzimidazoles and benzoxazoles from 2-amino/hydroxynitrobenzenes and methylheteroaryl compounds as starting materials in the presence of an iron sulfide catalyst.[1] Furthermore, we have previously reported the redox-neutral and high atom-economic transformation of 2-nitrophenols and 2,6-disubstituted *p*-cresols to afford 2-arylbenzoxazoles.[2]

The benzothiazole ring is a notable discovery in drug research because of its diverse pharmacological activities. This ring system is present in numerous marine and terrestrial plants with a wide range of pharmacological activities.[3] Benzothiazoles are also valuable building blocks for the construction of functional materials,[4] agrochemical compounds,[5] and polymers[6] (Scheme 1).

For the synthesis of 2-substituted benzothiazoles using nitro-methyl redox reactions, Nguyen et al. reported the synthesis of 2-heteroarylbenzothiazoles from 2-halonitrobenzenes, elemental sulfur, and methylheteroarenes by redox cyclization (Scheme 2a)[7] and the formation of 2-aroylbenzothiazoles by redox condensation from 2-halonitrobenzenes, elemental sulfur, and acetophenones (Scheme 2b).[8] However, these redox reactions require 2-halonitrobenzenes (which are not readily available) as starting materials.

Recently, the excellent iron-promoted synthesis of 2-substituted benzothiazoles from nitrobenzenes, elemental sulfur, and benzyl alcohol was reported through the conversion of C−H bonds into C−S bonds (Scheme 2c).[9−11] However, because of the relatively low reactivity of electron-deficient C−H bonds, direct sulfuration with elemental sulfur still presents a challenge.

Therefore, this paper focuses on redox reactions using easily available nitrobenzenes to afford the 2-substituted benzothiazoles. Herein, we report the successful redox-neutral and high atom-economic transformation of nitrobenzenes, sulfur, and

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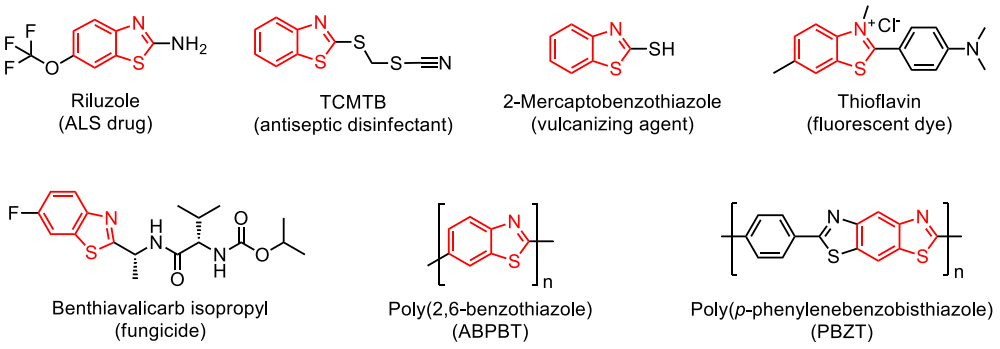
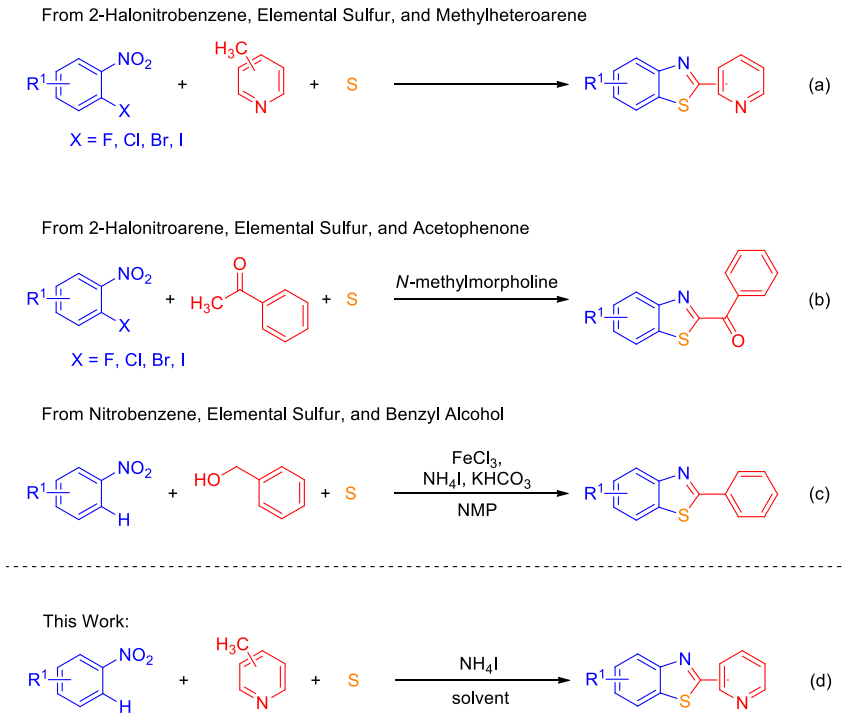
Scheme 1. Benzothiazoles as Building Blocks



Scheme 2. Synthesis of 2-Substituted Benzothiazoles Using Redox Reaction



methylheteroaryl compounds to afford 2-substituted benzothiazoles, without using a transition-metal catalyst (Scheme 2d).

RESULTS AND DISCUSSION

At the outset, reaction conditions for the synthesis of 2-substituted benzothiazoles (**3**) were optimized using nitrobenzene (**1a**) and 4-methylpyridine (**2a**) as a model (Table 1). For a survey of several solvents in the presence of elemental sulfur (5.0 equiv), $FeCl_3$ (10 mol %), and NH_4I (1.0 equiv) as additives, sulfolane was especially effective in affording the desired 2-(pyridine-4′-yl)benzo[*d*]thiazole (**3aa**) in good yield (entries 1−3). Compared with other iron catalysts such as Fe (powder), $Fe(acac)_3$, $FeSO_4$, and $Fe(NO_3)_3$, $FeCl_3$ showed the best catalytic effect (entries 3−7). Surprisingly, 63% yield of **3aa** was obtained (54% isolated yield), even without the use of an iron catalyst (entry 8). This yield was amazing because the multistep reactions such as reduction of the nitro group, functionalization of the aromatic C−H bond, redox reaction, and cyclization were performed all at once, and all reactions proceeded well to form a heterocycle. Furthermore, safety and purity of the synthesized heterocycle are required for pharmaceuticals and electronic materials; the use of transition-metal catalysts requires significant cost and labor to remove residual metals. This transition-metal-free reaction has an advantage as a synthetic method. Moreover, solvent-free reaction was tried; however, yield of **3aa** lowered (entry 9). Next, other iodide compounds and organic bases were examined under similar conditions, and poor results were obtained (entries 10−16). The quantity of elemental sulfur was an important factor in the preparation of **3aa**, and the use of 5.0 equivalents of elemental sulfur led to a good result (entries 8, 17−19). Reactivity decreased significantly at lower reaction temperatures (150 °C) (entry 20). A long reaction time slightly increased the yield of **3aa** (entry 21). When the reaction was carried out under air, the reactivity was lowered (entry 22). Neither increasing nor decreasing NH_4I did not improve the yields of **3aa** (entries 23 and 24).

With the optimized reaction conditions established, the scope and limitations of the synthesis of 2-substituted benzothiazoles **3** from **1a** with various methylheteroarenes **2** were explored (Table 2). The reaction of **1a** with sulfur with 2-methylpyridine (**2b**) afforded **3ab** in moderate yield (entry 1). When 3-methylpyridine (**2c**) was used, the desired **3ac** was not observed and both starting materials **1a** and **2c** were recovered unchanged

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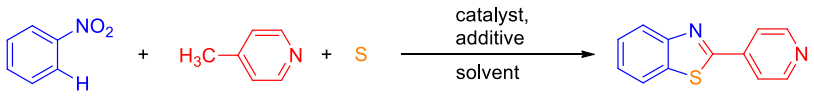
Table 1. Optimization of Synthesis of 3aa[a]



1a 2a 3aa

entry	solvent	catalyst	additive	sulfur (equiv)	yield (%)[b]
1	1,2-dichloro-benzene	$FeCl_3$	NH_4I	5.0	36
2	NMP	$FeCl_3$	NH_4I	5.0	34
3	sulfolane	$FeCl_3$	NH_4I	5.0	57
4	sulfolane	Fe (powder)	NH_4I	5.0	52
5	sulfolane	$Fe(acac)_3$	NH_4I	5.0	37
6	sulfolane	$FeSO_4{\cdot}nH_2O$	NH_4I	5.0	49
7	sulfolane	$Fe(NO_3)_3{\cdot}9H_2O$	NH_4I	5.0	56
8	sulfolane	none	NH_4I	5.0	63(54)[c]
9	none	none	NH_4I	5.0	39
10	sulfolane	none	KI	5.0	19
11	sulfolane	none	I_2	5.0	19
12	sulfolane	none	Me_4NI	5.0	8
13	sulfolane	none	$(NH_4)_2SO_4$	5.0	19
14	sulfolane	none	4-methyl-morpholine	5.0	10
15	sulfolane	none	1-methyl-piperidine	5.0	9
16	sulfolane	none	none	5.0	20
17	sulfolane	none	NH_4I	1.0	36
18	sulfolane	none	NH_4I	3.0	42
19	sulfolane	none	NH_4I	10.0	59
20[d]	sulfolane	none	NH_4I	5.0	4
21[e]	sulfolane	none	NH_4I	5.0	66
22[f]	sulfolane	none	NH_4I	5.0	50
23[g]	sulfolane	none	NH_4I	5.0	59
24[h]	sulfolane	none	NH_4I	5.0	42

[a]Reaction conditions: **1a** (1.5 mmol), **2a** (2.25 mmol), catalyst (0.15 mmol), additive (1.5 mmol), sulfur, and solvent (4 mL) at 175 °C for 24 h under argon atmosphere. [b]GC yields based on **1a**. [c]Isolated yield. [d]Reaction temperature was 150 °C. [e]Reaction time was 48 h. [f]Under air. [g]NH_4I (3.0 mmol) was used. [h]NH_4I (0.75 mmol) was used.

(entry 2). This result was in consistent with previous reports.[1,7] The reaction of 2-methylquinoline (**2d**) with **1a** afforded product **3ad** in good yields (51% isolated yield and 60% GC yield) (entry 3). When 4-methylquinoline (**2e**) was used, the product (**3ae**) was obtained in a slightly low yield (entry 4). The products (**3af** and **3ag**) were obtained in low yields when 2,6-dimethylpyridine (**2f**) and 3,4-dimethylpyridine (**2g**) were used as reactants (entries 5 and 6). In these cases, a complex mixture also formed.

Next, the reactions of 4-methylpyridine (**2a**) or 2-methylquinoline (**2d**) with various nitroarenes **1** were examined (Table 3). The synthesis of 6-methyl-2-(pyridine-4′-yl)-benzo-[*d*]thiazole (**3ba**) from 4-methylnitrobenzene (**1b**) with **2a** was successfully performed. The product (**3ba**) was obtained in moderate yield (entry 1). However, the reaction of 2-methylnitrobenzene (**1c**) with **2a** afforded **3ca** in lower yield (entry 2). It is very interesting that the reaction proceeded despite the steric hindrance of the ortho substituent. 4-Ethylnitrobenzene (**1d**) with **2a** afforded **3da** in 36% yield (entry 3). When the electron-donating methoxy group was substituted, **3ea** was obtained in low yield (entry 4). The electron-donating group deactivates the fission of the electron-deficient C−H bond. Using 3-chloronitrobenzene (**1f**) and **2a** as reactants, products **3fa** and **3fa′** were obtained in reasonable yields (entry 5). When the reactant 2-chloronitrobenzene (**1g**) was used, the sole product **3aa** was obtained in 46% yield (entry 6). This result clearly shows that the sulfuration of the electron-deficient C−Cl bond with elemental sulfur was more reactive than the sulfuration of the electron-deficient C−H bond. A similar reaction has been reported in the literature.[7] The reaction of 1-nitronaphthalene (**1h**) and **2a** gave **3ha** in good yield (57%) (entry 7). Both 4-methylnitrobenzene (**1b**) and 1-nitronaphthalene (**1h**), with 2-methylquinoline (**2d**) afforded **3bd** and **3hd** in satisfactory yields (51 and 50%) (entries 8 and 9).

Next, the gram-scale synthesis of **3aa** was successfully performed under the standard conditions to give **3aa** in useable yield (60%) (Scheme 3).

Finally, control experiments were performed to gain insights into the reaction mechanism. First, the reaction was carried out in the absence of NH_4I at 175 °C for 24 h in sulfolane. Products **3aa** (20%) and **4aa** (26%) were obtained (Scheme 4a).[12] Thioamide (**4aa**) reacted with NH_4I and sulfur under similar reaction conditions to give **3aa** in 36% yield (without S: 28%) (Scheme 4b). However, in the absence of NH_4I, the cyclization reaction hardly occurred (7%) (Scheme 4c). These results clearly indicated that the conversion of C−H to C−S was accelerated by NH_4I.

Furthermore, in the reaction mixture of **3aa** synthesis, aniline (**5a**) was detected by GC−MS analysis. Therefore, **3aa** preparation from **5a**, **2a**, and sulfur was attempted. The product (**3aa**) was obtained successfully in 34% yield (Scheme 4d).

Based on the experimental results and reported literature,[9,13] we proposed a possible reaction mechanism (Scheme 5). Initially, nitrobenzene (**1a**) is subjected to a six-electron reduction to form aniline (**5a**). 4-Methylpyridine (**2a**) is

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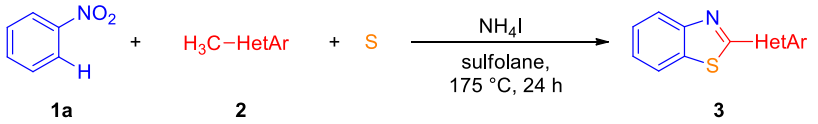
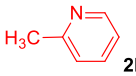
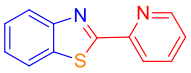
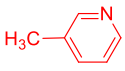
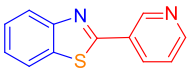
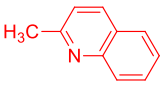
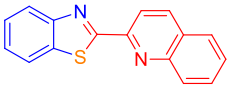
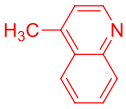
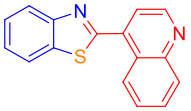
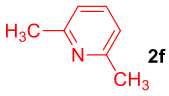
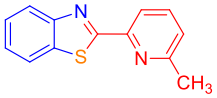
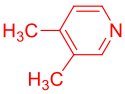
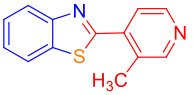
Table 2. Substrate Scope with Various Methylheteroarenes[a]



1a **2** **3**

entry	HetAr	product	yield (%)[b]
1	 **2b**	 **3ab**	44%
2	 **2c**	 **3ac**	0%[c]
3	 **2d**	 **3ad**	51%, 60%[d]
4	 **2e**	 **3ae**	29%
5	 **2f**	 **3af**	10%
6	 **2g**	 **3ag**	26%

[a]Reaction conditions: **1a** (1.5 mmol), **2** (2.25 mmol), NH_4I (1.5 mmol), sulfur (7.5 mmol), and sulfolane (4 mL) at 175 °C for 24 h under argon atmosphere. [b]Isolated yields. [c]Reaction time was 96 h. [d]GC yield based on **1a**.

oxidized to generate aldehyde **A** (four-electron transfer). Next, the condensation of **5a** and **A** affords imine **B**. The imine **B** reacts with sulfur to form thioamide (**4aa**) through intermediate **C**. The cyclization of **4aa** gave intermediate **D**, promoted by NH_4I. Finally, the two-electron oxidation of **D** provides the final product **3aa**.

In summary, we have developed a high atom-economic synthesis of 2-substituted benzothiazoles using readily available nitroarenes, sulfur, and methyl heteroarenes. This reaction provides a transition-metal-free synthetic method for 2-substituted benzothiazoles using a nitro-methyl redox system and the conversion of C–H bonds into C–S bonds with elemental sulfur. Compared to carrying out this reaction sequentially, the work of isolation and purification can be largely saved. This method is superior from the viewpoint of process chemistry and low carbon. Thus, this synthetic method could be regarded as an ideal reaction system. Further investigations of the mechanism and applications are currently underway.

EXPERIMENTAL SECTION

General Information. All starting materials were purchased from commercial sources and used without further purification. FT-IR spectra are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on a 600 or 400 MHz spectrometer using $CDCl_3$ as solvent referenced to TMS (0 ppm) and $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded at 151 or 100 MHz in $CDCl_3$ using $CDCl_3$ (77.2 ppm) as the standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Exact mass spectra were recorded using direct analysis in real time (DART-TOFMS). Analytical thin-layer chromatography was performed on silica gel plates using short-wave (254 nm) UV light. Silica gel (230–400 mesh) was used for column chromatography.

General Procedure for the Synthesis of 2-Arylbenzothiazole 3. In a 15 mL oven-dried reaction vessel, nitrobenzene (**1a**, 153 μL, 1.5 mmol), 4-methylpyridine (**2a**, 221 μL, 2.25 mmol), powdered sulfur (241 mg, 7.5 mmol), NH_4I (217 mg, 1.5 mmol), and sulfolane (4 mL) were charged under argon. The sealed reaction vessel was stirred at 175 °C (oil bath) for 24 h. After cooling to ca. 100 °C, the reaction was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was further purified by column

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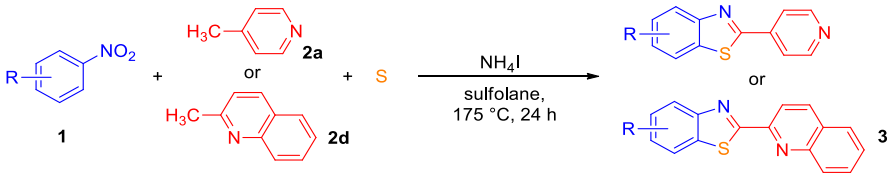
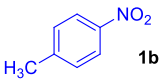
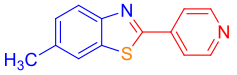
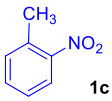
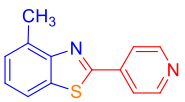
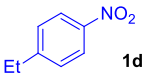
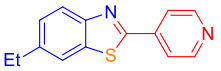
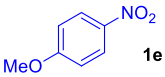
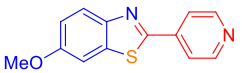
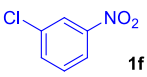
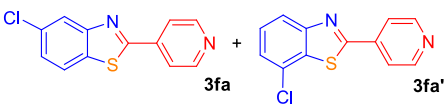
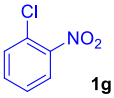
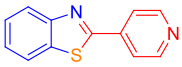
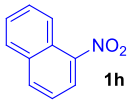
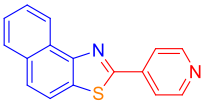
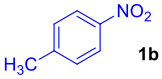
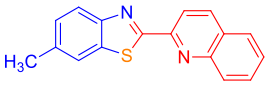
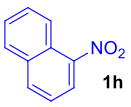
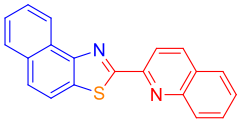
Table 3. Substrate Scope with Various Nitroarenes[a]



entry	nitroarene	product	yield (%)[b]
1	 1b	 3ba	48%
2	 1c	 3ca	16%
3	 1d	 3da	36%
4	 1e	 3ea	9%
5	 1f	 3fa + 3fa'	38%[c]
6	 1g	 3aa	46%
7	 1h	 3ha	57%
8	 1b	 3bd	51%
9	 1h	 3hd	50%

[a]Reaction conditions: **1** (1.5 mmol), **2a** (2.25 mmol), NH_4I (1.5 mmol), sulfur (7.5 mmol), and sulfolane (4 mL) at 175 °C for 24 h under argon atmosphere. [b]Isolated yields. [c]**3fa**:**3fa′** = 58:42.

chromatography on silica gel (hexane/ethyl acetate) to obtain 2-(pyridine-4′-yl)benzo[*d*]thiazole (**3aa**) as a pure form.

2-(Pyridine-4′-yl)benzo[d]thiazole (***3aa***). Eluent, hexane/ethyl acetate = 3:1; pale yellow powder, 170 mg, 54% yield; mp: 133−134 °C (lit.[14] 132−134 °C); FT-IR (diamond ATR): 1591, 1474, 1408, 1254, 1213, 978, 822, 756, 727, 702, 476 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.78 (dd, J = 1.4, 4.1 Hz, 2H), 8.14 (d, J = 7.6 Hz, 1H), 7.96−7.95 (m, 3H), 7.55 (t, J = 7.6, 1H), 7.47 (t, J = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 165.3, 154.1, 150.9, 140.6, 135.4, 127.0, 126.4, 124.1, 122.0, 121.3.

2-(Pyridine-2′-yl)benzo[d]thiazole (***3ab***). Eluent, hexane/ethyl acetate = 4:1; pale yellow powder, 139 mg, 44% yield; mp: 129−131

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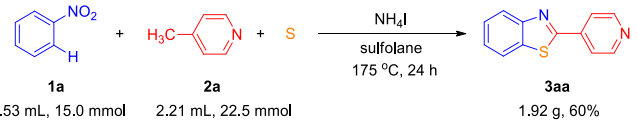
Scheme 3. Large-Scale Reaction



°C (lit.[15] 129−130 °C); FT-IR (diamond ATR): 1454, 1431, 1315, 1261, 976, 779, 723, 617, 424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, J = 1.7, 4.7 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.96 (dd, J = 1.3, 8.0 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.44−7.37 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 154.4, 151.6, 149.8, 137.1, 136.3, 126.4, 125.8, 125.4, 123.7, 122.1, 120.9.

2-(Quinolin-2′-yl)benzo[d]thiazole (***3ad***). Eluent, hexane/ethyl acetate = 7:1; orange-white powder, 200 mg, 51% yield; mp: 197−199 °C (lit.[16] 199−201 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, J = 8.6 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 154.5, 151.5, 148.1, 137.1, 136.7, 130.2, 129.9, 129.1, 127.9, 127.7, 126.4, 126.0, 123.9, 122.2, 118.5.

2-(Quinolin-4′-yl)benzo[d]thiazole (***3ae***).[7] Eluent, hexane/ethyl acetate = 3:1; light brown powder, 115 mg, 29% yield; mp: 175−178 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 9.05 (d, J = 4.1 Hz, 1H), 9.00 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.83−7.80 (m, 2H), 7.70 (t, J = 7.9 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 164.9, 154.3, 149.9, 149.3, 138.5, 135.5, 130.1, 130.1, 128.3, 126.9, 126.3, 126.2, 125.1, 124.3, 122.3, 121.8.

2-(6′-Methylpyridine-2′-yl)benzo[d]thiazole (***3af***).[17] Eluent, hexane/ethyl acetate = 10:1; yellow powder, 34 mg, 10% yield; mp: 143−145 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 2.65 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 170.1, 158.9, 154.5, 150.8, 137.3, 136.3, 126.3, 125.6, 125.1, 123.6, 122.1, 117.9, 24.5.

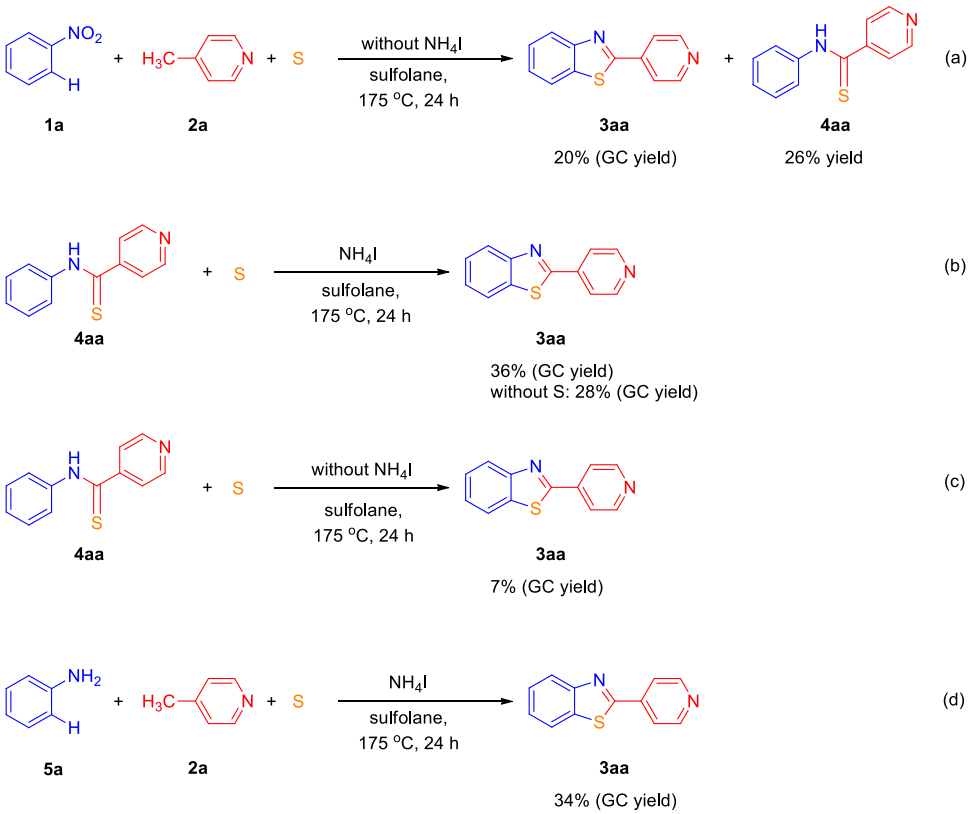
2-(3′-Methylpyridine-4′-yl)benzo[d]thiazole (***3ag***).[7] Eluent, hexane/ethyl acetate = 2:1; light brown oil, 87 mg, 26% yield; ^1H NMR (600 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 2.70 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 165.1, 153.8, 152.9, 148.0, 139.9, 135.6, 131.5, 126.7, 126.1, 124.1, 123.6, 121.7, 18.6.

6-Methyl-2-(pyridine-4′-yl)benzo[d]thiazole (***3ba***). Eluent, hexane/ethyl acetate = 3:1; yellowish brown powder, 162 mg, 48% yield; mp: 167−169 °C (lit.[14] 167−169 °C); ^1H NMR (600 MHz, $CDCl_3$): δ 8.76 (dd, J = 1.7, 4.2 Hz, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.93 (dd, J = 1.7, 4.2 Hz, 2H), 7.74 (s, 1H), 7.36 (d, J = 8.9 Hz, 1H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 164.1, 152.3, 150.8, 140.8, 136.7, 135.6, 128.7, 123.5, 121.7, 121.2, 21.8.

4-Methyl-2-(pyridine-4′-yl)benzo[d]thiazole (***3ca***). Eluent, hexane/ethyl acetate = 3:1; yellow powder, 54 mg, 16% yield; mp: 84−86 °C; FT-IR (KBr): 1595, 1480, 1411, 1329, 1261, 766, 619, 469 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.76 (dd, J = 1.7, 4.2 Hz, 2H), 7.96 (dd, J = 1.7, 4.5 Hz, 2H), 7.77 (dd, J = 2.1, 6.9 Hz, 1H), 7.36−7.32 (m, 2H), 2.82 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 163.7, 153.5, 150.8, 140.9, 135.3, 134.3, 127.3, 126.2, 121.3, 119.3, 18.4; HRMS (DART-TOFMS): calcd for $C_{13}H_{11}N_2S^+$ [M + H^+], 227.0637; found, 227.0613.

6-Ethyl-2-(pyridine-4′-yl)benzo[d]thiazole (***3da***). Eluent, hexane/ethyl acetate = 3:1; yellow powder, 130 mg, 36% yield; mp: 83−84 °C; FT-IR (KBr): 2965, 1593, 1479, 1408, 981, 822, 601 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.76 (dd, J = 1.7, 4.5 Hz, 2H), 8.03 (d, J = 8.3 Hz, 1H), 7.93 (dd, J = 1.7, 4.5 Hz, 2H), 7.76 (s, 1H), 7.39 (dd, J = 1.7, 8.3 Hz, 1H), 2.82 (q, J = 7.6 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 164.2, 152.5, 150.9, 143.1, 140.8, 135.6, 127.6, 123.7, 121.3, 120.5, 29.2, 15.9; HRMS (DART-TOFMS) calcd for $C_{14}H_{13}N_2S^+$ [M + H^+], 241.0794; found, 241.0775.

Scheme 4. Control Experiments



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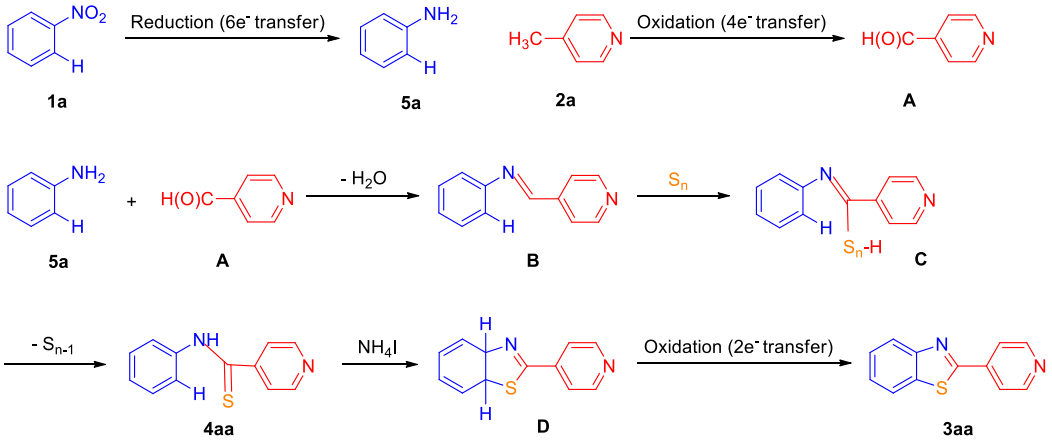
Scheme 5. Proposed Mechanism



*6-Methoxy-2-(pyridine-4′-yl)benzo[d]thiazole (**3ea**).* Eluent, hexane/ethyl acetate = 1:1; yellow-white powder, 34 mg, 9% yield; mp: 153−155 °C (lit.[14] 158−159 °C); FT-IR (diamond ATR): 1590, 1484, 1413, 1263, 1215, 1022, 817, 592, 498 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.74 (dd, J = 1.4, 4.1 Hz, 2H), 8.00 (d, J = 8.9 Hz, 1H), 7.90 (dd, J = 1.7, 4.8 Hz, 2H), 7.38 (d, J = 2.1 Hz, 1H), 7.15 (dd, J = 2.4, 8.4 Hz, 1H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 162.5, 158.7, 150.8, 148.7, 140.8, 136.9, 124.6, 121.1, 116.7, 104.2, 56.0.

*5-Chloro-2-(pyridine-4′-yl)benzo[d]thiazole (**3fa**).* Eluent, hexane/ethyl acetate = 3:1; pale yellow powder, 82 mg, 22% yield; mp: 182−183 °C (lit.[16] 178−179 °C); ^1H NMR (600 MHz, $CDCl_3$): δ 8.79 (dd, J = 2.1, 4.2 Hz, 2H), 8.12 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 1.7, 4.2 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H), 7.44 (dd, J = 1.7, 8.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 167.1, 154.9, 151.0, 140.2, 133.6, 133.1, 126.9, 123.8, 122.7, 121.3.

*7-Chloro-2-(pyridine-4′-yl)benzo[d]thiazole (**3fa′**).*[7] Eluent, hexane/ethyl acetate = 3:1; pale yellow powder, 60 mg, 16% yield; mp: 122−124 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 8.79 (d, J = 6.2 Hz, 2H), 8.02 (d, J = 8.9 Hz, 1H), 7.94 (dd, J = 1.7, 4.2 Hz, 2H), 7.50 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 166.0, 154.7, 151.0, 140.2, 135.7, 127.9, 127.3, 125.9, 122.4, 121.3.

*2-(Pyridine-4′-yl)naphto[1,2-d]thiazole (**3ha**).*[18] Eluent, hexane/ethyl acetate = 1:1; yellowish-brown powder, 225 mg, 57% yield; mp: 144−145 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 8.91 (d, J = 8.3 Hz, 1H), 8.78 (dd, J = 1.4, 4.8 Hz, 2H), 8.03 (dd, J = 1.4, 4.1 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.9 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.72 (t, J = 8.3 Hz, 1H), 7.63 (t, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 164.0, 150.9, 150.7, 140.9, 132.4, 132.3, 129.0, 128.3, 127.5, 127.3, 126.7, 124.1, 121.1, 119.0.

*6-Methyl-2-(quinolin-2′-yl)benzo[d]thiazole (**3bd**).*[19] Eluent, hexane/ethyl acetate = 10:1; brown powder, 212 mg, 51% yield; mp: 207−210 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 8.6 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.78−7.73 (m, 2H), 7.59 (t, J = 8.2 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 152.7, 151.6, 148.1, 137.1, 136.8, 136.3, 130.2, 129.9, 129.1, 128.1, 127.9, 127.6, 123.4, 121.9, 118.5, 21.8.

*2-(Quinolin-2′-yl)naphto[1,2-d]thiazole (**3hd**).*[19] Eluent, hexane/ethyl acetate = 10:1; brown powder, 232 mg, 50% yield; mp: 205−207 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (d, J = 8.2 Hz, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.00 (t, J = 8.6 Hz, 2H), 7.88 (t, J = 8.6 Hz, 2H), 7.80−7.71 (m, 2H), 7.64−7.58 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.7, 151.9, 150.9, 148.1, 137.1, 133.8, 132.2, 130.2, 129.8, 129.2, 129.1, 128.3, 127.9, 127.5, 127.3, 126.9, 126.4, 123.9, 119.5, 118.6.

Large-Scale Synthesis of 3aa (Scheme 3). The 2-(pyridine-4′-yl)benzo[*d*]thiazole (**3aa**) was prepared from a mixture of nitrobenzene (**1a**, 1.53 mL, 15.0 mmol), 4-methylpyridine (**2a**, 2.21 mL, 22.5 mmol), elemental sulfur (2.41 g, 75.0 mmol), and NH_4I (2.17 g, 1.50 mol) in sulfone (40 mL) under argon, according to the general procedure [175 °C (oil bath), 24 h]. After the reaction, the reaction was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was further purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1) to obtain a pure product (**3aa**, 1.92 g, 60%).

*N-Phenyl-4-pyridinecarbothioamide (**4aa**).* Eluent, hexane/ethyl acetate = 3:1; orange powder, 83 mg, 26% yield; mp: 174−176 °C (lit.[14] 180−182 °C); ^1H NMR (600 MHz, $CDCl_3$): δ 9.09 (br s, 1H), 8.73 (d, J = 5.5 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 5.5 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 195.6, 150.7, 149.7, 138.6, 129.4, 127.6, 123.6, 120.5.

Reaction of Thioamide (4aa) with NH_4I (Scheme 4b). Using a 15 mL oven-dried reaction vessel, the reaction of *N*-phenyl-4-pyridinecarbothioamide (**4aa**, 107 mg, 0.50 mmol), powdered sulfur (81 mg, 2.5 mmol), and NH_4I (73 mg, 0.50 mmol) in sulfolane (2 mL) was performed at 175 °C (oil bath) for 24 h under argon. The product (**3aa**) was obtained in 36% GC yield based on **4aa**. When the reaction was carried out without sulfur, **3aa** was obtained in 28% GC yield based on **4aa**.

Reaction of 3aa from Aniline (5a) (Scheme 4d). In a 15 mL oven-dried reaction vessel, aniline (**5a**, 140 μL, 1.5 mmol), 4-methylpyridine (**2a**, 221 μL, 2.25 mmol), powdered sulfur (241 mg, 7.5 mmol), NH_4I (217 mg, 1.5 mmol), and sulfolane (4 mL) were charged under argon. The sealed reaction vessel was stirred at 175 °C (oil bath) for 24 h. The yield of **3aa** was obtained in 34% GC yield based on **5a**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02072.

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

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Notes

The authors declare no competing financial interest.

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