JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02543 • Publication Date (Web): 17 Dec 2019

A Mild Synthesis of 2-Substituted Benzothiazoles *via* Nickel-Catalyzed Intramolecular Oxidative C-H Functionalization

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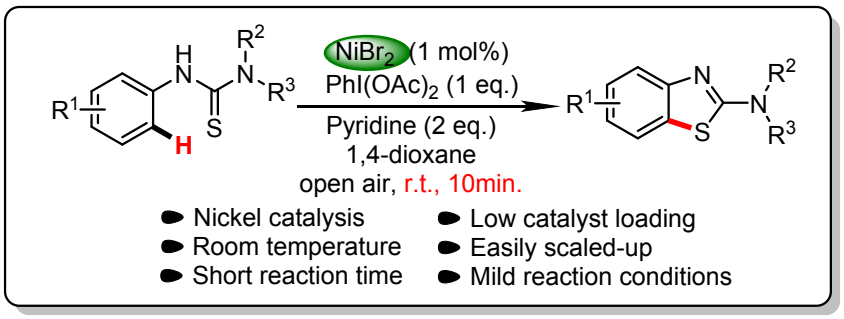


ABSTRACT

A highly-efficient synthetic method for the preparation of 2-aminobenzothiazoles starting from arylthioureas has been reported. By using a nickel catalyst, arylthioureas undergo intramolecular oxidative C-H bond functionalization, giving the desired 2-aminobenzothiazoles in good to excellent yields. This protocol features inexpensive catalyst, low catalyst loading, mild reaction conditions, short reaction time, good to

excellent yields and can be scaled up easily to gram-scale with almost no yields decreasing.

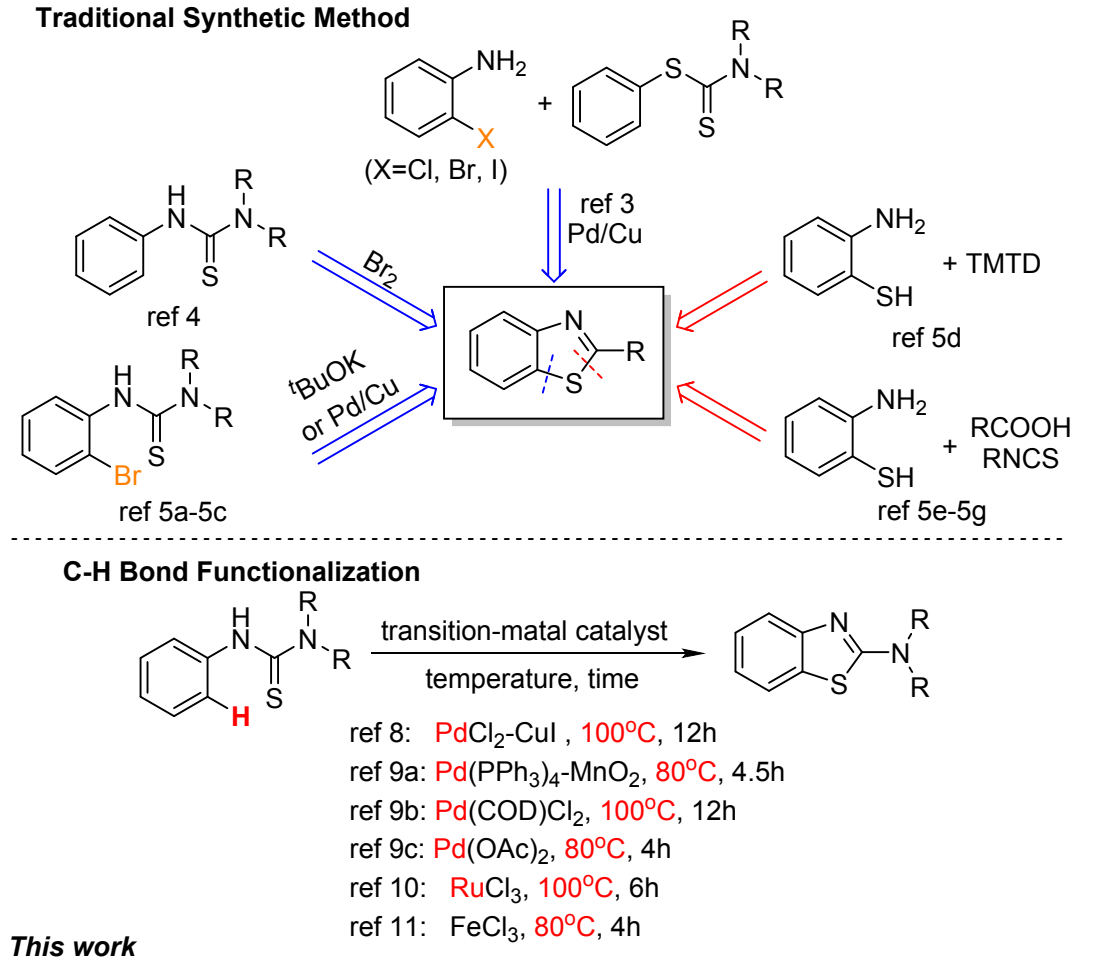
INTRODUCTION

In the last few years, great achievements in synthetic chemistry have been made due to the advances in the oxidative cross-coupling area. As a result, oxidative cross-couplings have long been highly advocated, and one of these powerful applications is C-H bond functionalization.[1] First raw transition metal (Pd, Ru, etc.) and non-first raw transition metal catalysts (Fe, Cu, etc.) have been widely used in cross-coupling, while the reaction conditions are not mild enough and reaction efficiency still needs improving.[2] In oxidative cross coupling, the direct C(sp^2)−H functionalization is particularly promising, primarily because construction of intramolecular C-heteroatom (N, O and S etc.) bond can be achieved in a novel approach. However, most methods involved relatively expensive metal catalysts,[3] less user-friendly strong oxidants[4] or pre-activation designs,[5] which not only bring large amounts of residual metal impurities, but also render unnecessary process and costs. Therefore, it would be quite attractive to explore more effective and mild conditions for direct C(sp^2)−H functionalization. Nevertheless, there are only a few examples where mild conditions are able to be applied to the construction of C-heteroatom bonds.

Benzothiazole-related structures are widely existent in medical and agricultural chemicals,[6] bioactive natural products and organic optoelectronic materials.[7] Thus, organic chemists are devoted to achieve their synthesis mildly and effectively, and choosing readily and commercially available *N*-arylthioureas as starting materials to form 2-aminobenzo-thiazoles is widely accepted (Scheme 1). In 2008, Inamoto

reported that the Pd-catalyzed strategy was suitable for the synthesis of 2-aminobenzothiazoles,[8] Batey, Liu and Pardasani lately re-explored the reaction conditions by using different transition metals such as Pd[9] and Ru.[10a] However, all these reactions used expensive transition metals as catalysts and required high temperature and long reaction time. Thus, a milder and more effective way to access the fast synthesis of 2-aminobenzothiazoles is highly desired.[10b] In 2012, Lei developed iron-promoted cyclization to furnish 2-aminobenzothiazoles,[11] in which only a few arylthioureas were chosen as substances. Though the iron catalysts have the characteristics of low cost and easy availability, the yields of obtained 2-aminobenzo-thiazoles were not satisfactory.

Scheme 1. Protocols for the Synthesis of 2-Aminobenzothiazoles



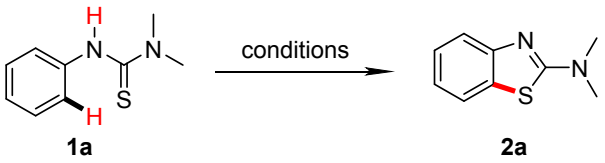
It is worthy to note that, nickel salts boast low cost and relative low toxicity (unlike most expensive metal catalysts), and have been reported as powerful catalysts in the cross-coupling reactions.[12] To our best knowledge, there were almost no reports on the nickel-catalyzed synthesis of 2-aminobenzothiazoles at mild conditions (eg. room temperature, low loading, et. al). As a part of our continued efforts[13] to explore modified protocols for the C-S formation reactions, we report herein an efficient

protocol for the preparation of 2-aminobenzothiazoles *via* nickel-catalyzed intramolecular oxidative C-H functionalization, particularly with *N*-arylthioureas as the starting substances.

RESULTS AND DISCUSSION

N,N-dimethyl-*N'*-phenylthiourea **1a** was chosen as the substrate for the model reaction, aiming at fast and efficient nickel-catalyzed oxidative coupling (Table 1). The reaction was performed in 1,4-dioxane by using 1 equiv. of $PhI(OAc)_2$ (PIDA: Phenyliodine(III) diacetate) as oxidant and 2 equiv. of pyridine as base, the target product **2a** could not be detected even after 6 hours (entry 1). Then 10 mol% $NiCl_2$ was added as the catalyst in the system and it helped to furnish **2a** in 28% isolated yield (entry 2). Encouraged by this initial trial, other nickel catalysts including $(dppp)NiCl_2$, $NiBr_2$ and $Ni(OAc)_2$ were tested (entry 2-5) and results of the experiments indicated that $NiBr_2$ gained the best catalytic result in all studies (entry 4, yield: 83%). Subsequently, various oxidants (entries 4, 6-8) were examined and it was found that only PIDA could promote the reaction. The base screening (entries 4, 9-11) and the solvent screening (entries 4, 12-14) revealed that pyridine was the optimal base, and 1,4-dioxane was the most suitable solvent for the model reaction. To our delight, by reducing the catalyst loading and shortening the reaction time, the reaction could undergo smoothly even by adding 1 mol% equiv. of $NiBr_2$ in 10 minutes (entry 16). Trace of 2-substituted benzothiazole was obtained when the amount of PIDA was decreased to 50 mol% (entry 17). Thus, we believe that the PIDA is crucial for the reaction, and the air might not be the co-oxidant in this reaction.

Table 1. The Reaction Conditions Optimization [a].



1a **2a**

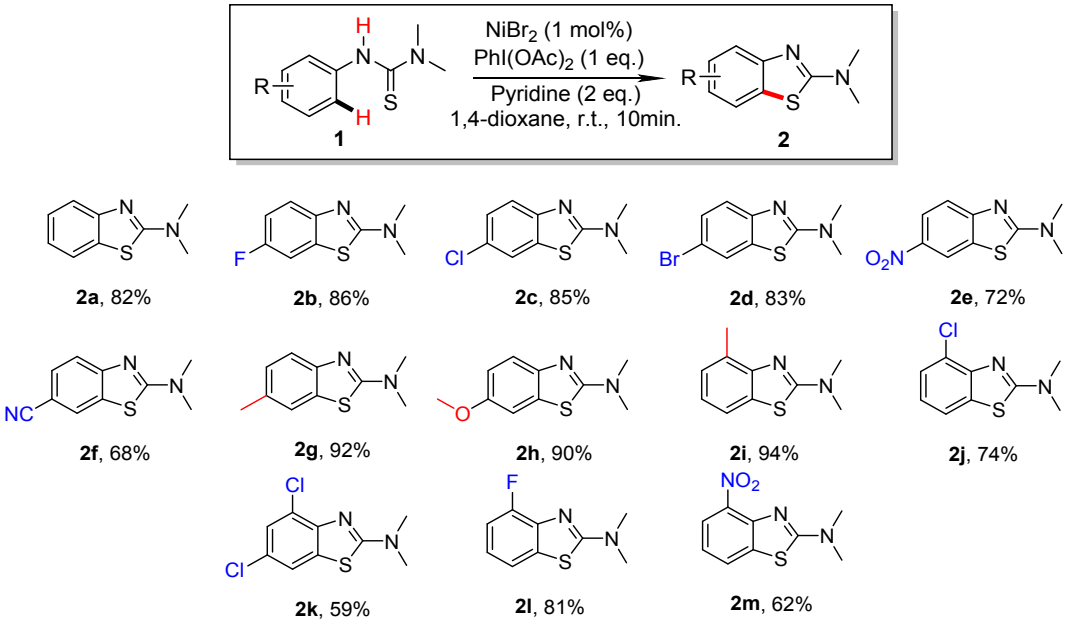
Entry	Cat. (mol %)	Oxidant	Base	Solvent	Time (min)	Yield[b] (%)
1	-	PIDA	Py	dioxane	360	trace
2	$NiCl_2$ (10)	PIDA	Py	dioxane	90	28
3	(dppp)$NiCl_2$ (10)	PIDA	Py	dioxane	90	26
4	$NiBr_2$ (10)	PIDA	Py	dioxane	90	83
5	$Ni(OAc)_2$ (10)	PIDA	Py	dioxane	90	0
6	$NiBr_2$ (10)	$K_2S_2O_8$	Py	dioxane	90	N.R.
7	$NiBr_2$ (10)	PIFA	Py	dioxane	90	0
8	$NiBr_2$ (10)	DDQ	Py	dioxane	90	0
9	$NiBr_2$ (10)	PIDA	Cs_2CO_3	dioxane	90	0
10	$NiBr_2$ (10)	PIDA	Et_3N	dioxane	90	0
11	$NiBr_2$ (10)	PIDA	^{t}BuOK	dioxane	90	0
12	$NiBr_2$ (10)	PIDA	Py	THF	90	56
13	$NiBr_2$ (10)	PIDA	Py	DMSO	90	30
14	$NiBr_2$ (10)	PIDA	Py	DCM	90	20
15	$NiBr_2$ (1)	PIDA	Py	dioxane	90	82
16	**$NiBr_2$ (1)**	**PIDA**	**Py**	**dioxane**	**10**	**82**
17[c]	$NiBr_2$ (1)	PIDA	Py	dioxane	10	trace

[a]Reaction conditions: **1a** (0.5 mmol), oxidant (1 eq.), base (2 eq.), room temperature, open air. [b]Isolated yield. [c]PIDA loading: 50 mol%.

After the optimized reaction conditions were obtained, the substrate generality to furnish 2-dimethylamino-benzothiazoles **2** (**Scheme 2**) was explored. As shown in **Scheme 2**, various substrates, whenever with electron withdrawing groups or electron

donating groups, can be synthesized efficiently and rapidly. Initially, various substituents on phenyl rings were tested. The phenylthioureas with halogen atoms in the para-position (Scheme 2, **2b-2d**) were smoothly transformed to the intended products in excellent yields (86-83%), but the stronger electron-withdrawing groups, such as nitro and cyano groups slightly and negatively influenced the yields (Scheme 2, **2e-2f**). Subsequently, the substrates with electron donating groups were explored (**Scheme 2**, **2g-2i**), and excellent yields were achieved (90-94%). Substrates containing ortho halogens or nitro groups (Scheme 2, **2j-2m**) were also compatible for the reaction, giving the target cyclization products in moderate to good yields (59-81%).

Scheme 2. Substrate Generality to Afford 2-Dimethylamino-benzothiazoles **2** [a]

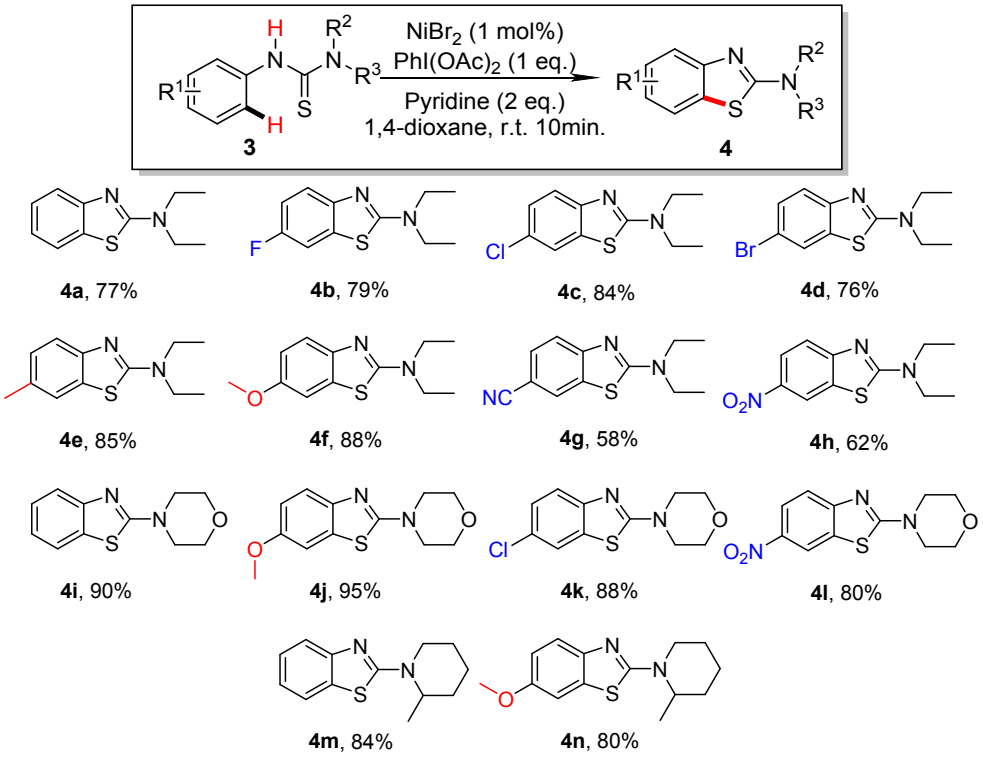


[a]Reaction conditions: **1** (0.5 mmol), open air, isolated yields.

Encouraged by above results, a series of *N*-substituted arylthioureas were explored (Scheme 3). Firstly, 2-diethylamino-benzothiazole (Scheme 3, **4a**) was furnished with

good yield (77%), and para-halogen substituted arylthioureas (Scheme 3, **4b-4d**) were also synthesized in good to excellent yields (76-84%). Stronger electron-withdrawing groups, such as cyano or nitro (Scheme 3, **4g, 4h**) decreased the yields of the product (58-62%). In remarkable contrast, electron-donating groups (Scheme 3, **4e, 4f**) improved the yields (85-88%). Next, 2-N-containing heterocyclic benzothiazoles were synthesized successfully (Scheme 3, **4i-4n**), and we were pleased to find that they all showed excellent yields (80-95%).

Scheme 3. Substrate Scope for *N*-substituted Arylthioureas [a]

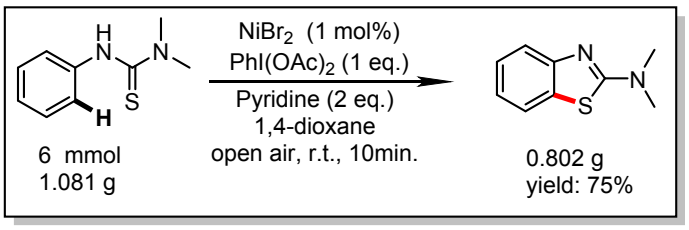


[a]Reaction conditions: **1** (0.5 mmol), open air, isolated yield.

In organic synthesis (especially total synthesis), most natural products have elaborate structures and sensitive functional groups, which means that the harsh reaction conditions, such as strong oxidants or high temperatures should be avoid.[14]

Furthermore, to access fast and promising preparations, organic chemists are devoted to explore various approaches which could be extended to gram-scale production in short time.[15] To illustrate the easy performance and the potential application, we scaled up the reaction in a gram-scale level at standard reaction conditions (room temperature, within 15 minutes). Much to our excitement, the model reaction proceeded quite well with very limited yield loss (around 5%, Scheme 4).

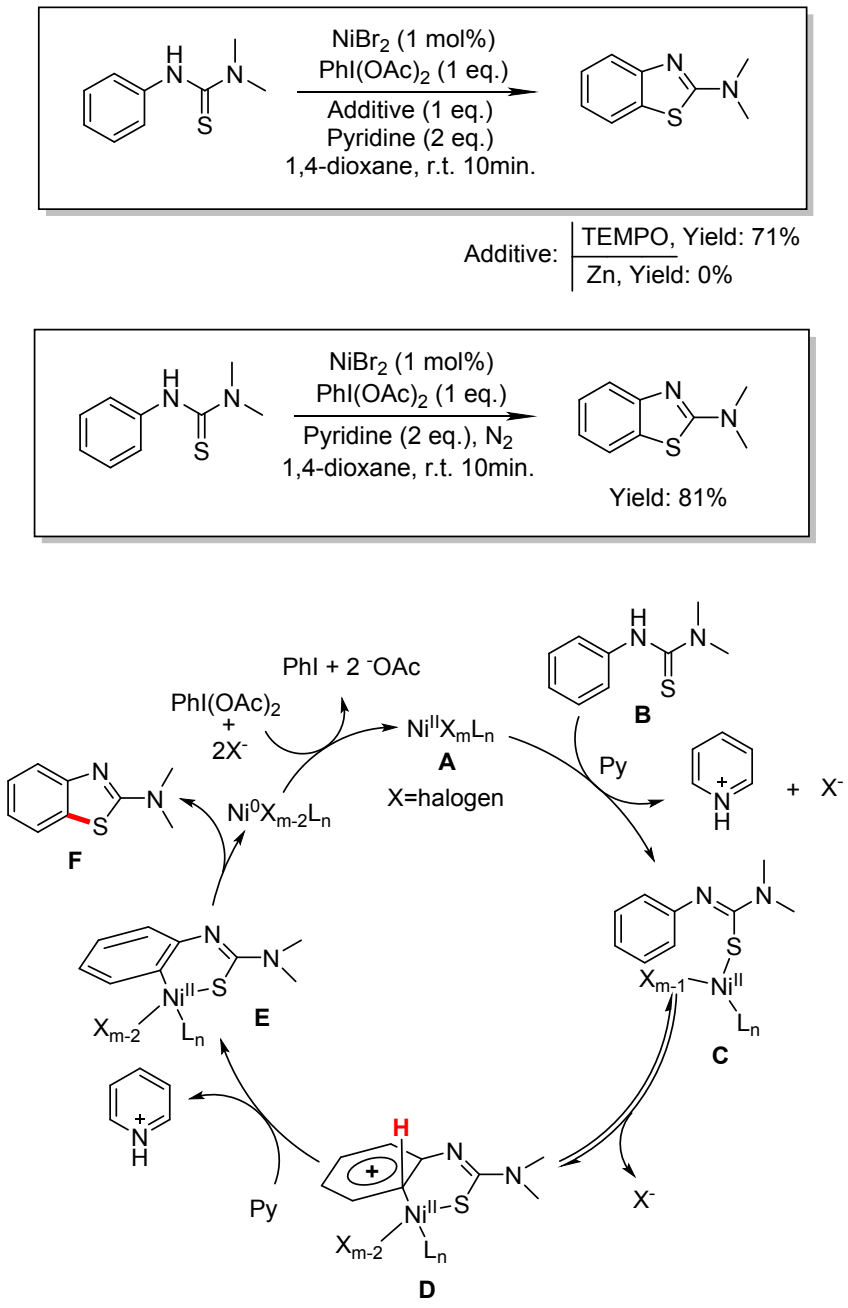
Scheme 4. Gram-scale Synthesis of 2-Dimethylamino-Benzothiazole.



In order to figure out the reaction mechanism, 1 equivalent of TEMPO and zinc powder was added respectively in the control experiments. The results showed that when TEMPO was added, the yield of the product did not decrease significantly, indicating that this reaction does not proceed in a radical pathway. In contrast, when zinc powder was added, the reaction was drastically suppressed, showing that an oxidative step was involved. Besides, the reaction could also be carried out under a nitrogen atmosphere. Based on above experimental results and previously reported literatures,[10,16] the reaction mechanism is proposed (Scheme 5). Firstly, arylthiourea **B** is transformed to isothiourea under the action of pyridine and then complexed with the Ni(II) catalyst **A** to form the intermediate **C** (pyridine might play the role as a ligand to stabilize the intermediate C). Subsequently, a π-complex is formed through Ni-centered electrophilic attacking the benzene, which is rapidly transformed to σ-complex **D**. With the action of pyridine, **D** is deprotonated to give intermediate **E**, which undergoes reductive elimination to give the intended molecule **F** along with Ni^0

catalyst. Finally, the Ni^0 catalyst is oxidized by $PhI(OAc)_2$ to proceed the next catalytic cycle.

Scheme 5. Control Experiments and Proposed Mechanism.



CONCLUSION

In summary, we introduce here an efficient and mild protocol for the easy synthesis of 2-substituted benzothiazoles. By using readily available arylthioureas as starting materials and $NiBr_2$ as catalyst, the target 2-substituted benzothiazoles could be synthesized in good to excellent yields. Compared with former methods, this reaction features lower cost, easier performance and shorter time. Furthermore, the reaction can be scaled up easily with almost no yield loss, illustrating its potential values in pharmaceutical and industrial production.

EXPERIMENTAL SECTION

General Information

In terms of the starting materials (arylthiourea derivatives), **1k** (to give **2k**), **3m** (to give **4m**) and **3a** (to give **4a**) are all commercially available, the rest arylthioureas are obtained according to ref. 17. Flash column chromatography was operated on silica gel with petroleum ether-EtOAc (PE-EA) as the eluent. Thin layer Chromatography was adopted and visualized under UV light. The RY-1G instrument was adopted to determine melting points of target compounds. The HRMS (high-resolution mass spectra) was recorded from a Finnigan MAT 95Q mass instrument (ESI). A Bruker AM400 NMR instrument was operated in $CDCl_3$ to record NMR spectra.

Typical procedure for the synthesis of 2-substitutedbenzothiazole 2 or 4

Arylthiourea derivative **1** or **3** (0.5 mmol), $PhI(OAc)_2$ (PIDA) (1eq., 0.5 mmol, 0.1611g), $NiBr_2$ (1mol%, 0.005 mmol, 0.0011g), 1,4-dioxane (2.5 mL) were mixed in a dried tube with a magnetic stirring bar (open to air), and then pyridine (2eq., 1.0 mmol) was added. The reaction was conducted at 25 ^oC and detected by TLC. After the reaction was finished, it was then quenched with water and extracted with ethyl acetate. The preliminary solution was dried over Na_2SO_4 and evaporated. The crude

material was further purified by column chromatography to get the intended product **2** or **4**.

Data of the products

***N,N*-dimethylbenzo[*d*]thiazol-2-amine (2a)**[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2a** as a yellow crystal (73 mg, yield = 82%). mp: 83-85 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.56 (t, 2H, *J* = 8.0 Hz), 7.27 (t, 1H, *J* = 8.0 Hz), 7.03 (t, 1H, *J* = 8.0 Hz), 3.17 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 168.1, 152.4,130.4, 125.4, 120.3, 120.0, 118.1, 39.6. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{11}N_2S$ (179.0638), found: 179.0640.

6-fluoro-*N,N*-dimethylbenzo[*d*]thiazol-2-amine (2b)[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2b** as a white solid (84 mg, yield = 86%). mp: 116-118 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.54-7.51 (m, 1H), 7.33 (d, 1H, *J*=8.0 Hz), 7.05 (t, 1H, *J* = 8.0 Hz), 3.16 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.4, 157.0 (d, *J* = 238.0 Hz), 148.4, 130.6 (d, *J* = 11.0 Hz), 118.1 (d, *J* = 9.0 Hz), 112.7 (d, *J* = 23.0 Hz), 106.5 (d, *J* = 27.0 Hz), 39.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}FN_2S$ (197.0543), found: 197.0541.

6-chloro-*N,N*-dimethylbenzo[*d*]thiazol-2-amine (2c)[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2c** as a brown crystals (90 mg, yield = 86%). mp: 102-103 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.50 (s, 1H), 7.42 (d, 1H, *J* = 12.0 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 3.15 (s, 6H).

^{13}C NMR (100 MHz, in CDCl3 with TMS as inner standard): δ (ppm) 167.7, 150.5, 131.0, 125.2, 124.8, 119.1, 118.2, 39.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}ClN_2S$ (213.0248), found: 213.0248.

6-bromo-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2d)[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2d** as a yellow solid (106 mg, yield = 83%). mp: 109-111 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.68 (d, 1H, *J* = 1.0 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 7.38-7.36 (m, 1H), 3.20 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.6, 150.6, 131.3, 128.0, 121.9, 118.6, 112.1, 39.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}BrN_2S$ (256.9743), found: 256.9739.

***N*,*N*-dimethyl-6-nitrobenzo[*d*]thiazol-2-amine (2e)**[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 1:1) to afford **2e** as a bright yellow solid (80 mg, yield = 72%). mp: 196-199 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 8.44 (s, 1H), 8.14 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 12.0 Hz), 3.23 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 171.8, 158.1, 141.1, 131.0, 122.4, 117.5, 117.0, 40.2. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}N_3O_2S$ (224.0488), found: 224.0491.

2-(dimethylamino)benzo[*d*]thiazole-6-carbonitrile (2f)[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 2:1) to afford **2f** as a grey solid (69 mg, yield = 68%). mp: 158-160 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.78 (s, 1H), 7.47 (s, 2H), 3.19 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 170.9, 156.5, 131.6, 130.0, 124.7, 119.7, 118.7, 103.1, 40.3.

HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{10}N_3S$ (204.0590), found: 204.0595.

6-methyl-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2g)[17b]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2g** as a red-brown solid (88 mg, yield = 92%). mp: 100-101 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.43 (d, 1H, *J* = 8.0 Hz), 7.10 (d, 1H, *J* = 4.0 Hz), 6.86-6.84 (m, 1H), 3.76 (s, 3H), 3.10 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.0, 148.7, 128.8, 128.4, 124.9, 118.5, 116.1, 37.9, 19.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{13}N_2S$ (193.0794), found: 193.0791.

6-methoxy-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2h)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2h** as a light yellow solid (93 mg, yield = 90%). mp: 89-91 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.43 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.0 Hz), 6.86-6.83 (m, 1H), 3.75 (s, 3H), 3.10 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.4, 154.6, 147.2, 131.8, 119.0, 113.4, 105.2, 55.8, 40.2. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{13}N_2OS$ (209.0743), found: 209.0742.

4-methyl-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2i)[19]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2i** as a white solid (91 mg, yield = 94%). mp: 50-52 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.35 (d, 1H, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 8.0 Hz), 3.09 (s, 6H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.7, 151.1, 129.7, 127.4, 125.4, 119.5, 116.8, 38.8, 17.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{13}N_2S$ (193.0794), found: 193.0795.

4-chloro-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2j)

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2j** as a white solid (78 mg, yield = 74%). mp: 95-97 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.27 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 8.0 Hz), 6.76 (t, 1H, *J* = 8.0 Hz), 2.98 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 165.6, 147.0, 129.1, 122.9, 119.7, 115.9, 36.9. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}ClN_2S$ (213.0248), found: 213.0244.

4,6-dichloro-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2k)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 3:1) to afford **2k** as a white solid (72 mg, yield = 59%). mp: 116-118 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.43 (d, 1H, *J* = 4.0 Hz), 7.30 (d, 1H, *J* = 4.0 Hz), 3.20 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.7, 147.0, 130.9, 124.2, 123.5, 121.2, 116.8, 38.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_9Cl_2N_2S$ (246.9858), found: 246.9853.

4-fluoro-*N*,*N*-dimethylbenzo[*d*]thiazol-2-amine (2l)

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **2l** as a white crystals (76 mg, yield = 81%). mp: 86-88 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.25 (d, 1H, *J* = 8.0 Hz), 6.95-6.85 (m, 2H), 3.11 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.7, 152.1 (d, *J* = 248.0 Hz), 140.6 (d, *J* = 13.0 Hz), 132.7 (d, *J* = 5.0 Hz), 120.0 (d, *J* = 7.0 Hz), 115.3 (d, *J* = 4.0 Hz), 110.0 (d, *J* = 9.0 Hz), 39.2. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}FN_2S$ (197.0543), found: 197.0546.

***N*,*N*-dimethyl-4-nitrobenzo[*d*]thiazol-2-amine (2m)**

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 3:1) to afford **2m** as a dark yellow solid (69 mg, yield = 62%). mp: 189-191 ^{o}C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.98 (d, 1H, *J* = 8.0 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.02 (t, *J* = 8.0 Hz), 3.24 (s, 6H). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 169.6, 145.7, 137.1, 133.6, 124.3, 121.0, 117.9, 38.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_9H_{10}N_3O_2S$ (224.0488), found: 224.0482.

***N*,*N*-diethylbenzo[*d*]thiazol-2-amine (4a)**[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to afford **4a** as a light yellow oil (79 mg, yield = 77%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.42 (t, 2H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 8.0 Hz), 6.89 (t, 1H, *J* = 8.0 Hz), 3.45-3.39 (m, 4H), 1.13 (t, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 173.0, 159.0, 136.4, 131.5, 126.4, 126.2, 124.2, 51.1, 18.6. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{15}N_2S$ (207.0951), found: 207.0956.

6-fluoro-*N*,*N*-diethylbenzo[*d*]thiazol-2-amine (4b)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to afford **4b** as a yellow oil (88 mg, yield = 79%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.36-7.33 (m, 1H), 7.18 (d, 1H, *J* = 8.0 Hz), 6.89 (t, 1H, *J* = 8.0 Hz), 3.47-3.41 (m, 4H), 1.17 (t, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 165.9, 156.7 (d, *J* = 257.0 Hz), 148.8, 130.3 (d, *J* = 10.0 Hz), 117.8 (d, *J* = 9.0 Hz), 112.3 (d, *J* = 23 Hz), 106.3 (d, *J* = 27 Hz), 44.4, 11.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}FN_2S$ (225.0856), found: 225.0850.

6-chloro-*N*,*N*-diethylbenzo[*d*]thiazol-2-amine (4c)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to give **4c** as a yellow oil (100 mg, yield = 84%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.40 (s, 1H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.0 Hz), 3.46-3.40 (m, 4H), 1.16 (t, 6H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 165.8, 150.2, 130.1, 124.6, 124.0, 118.5, 117.4, 43.9, 11.2. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}ClN_2S$ (241.0561), found: 241.0558.

6-bromo-*N*,*N*-diethylbenzo[*d*]thiazol-2-amine (4d)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to afford **4d** as a yellow oil (107 mg, yield = 76%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.63 (s, 1H), 7.36-7.30 (m, 2H), 3.54-3.49 (m, 4H), 1.24 (t, 6H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 165.4, 150.1, 130.2, 127.0, 120.9, 117.5, 110.9, 43.5, 10.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}BrN_2S$ (285.0056), found: 285.0054.

***N*,*N*-diethyl-6-methylbenzo[*d*]thiazol-2-amine (4e)**[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to afford **4e** as a colorless oil (93 mg, yield = 85%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.31 (d, 1H, *J* = 8.0 Hz), 7.24 (s, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 3.44-3.39 (m, 4H), 2.25 (s, 3H), 1.13 (t, 6H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.8, 150.9, 130.5, 130.4, 126.9, 120.6, 118.1, 45.3, 21.2, 12.9. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{12}H_{17}N_2S$ (221.1107), found: 221.1103.

***N*,*N*-diethyl-6-methoxybenzo[*d*]thiazol-2-amine (4f)**[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 7:1) to afford **4f** as a yellow oil (103 mg, yield = 88%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.43 (d, 1H, *J* = 8.0 Hz), 7.12 (s, 1H), 6.88-6.85 (m, 1H), 3.79 (s, 3H), 3.55-3.50 (m, 4H), 1.26 (t, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 165.9, 154.5, 147.5, 131.4, 118.8, 113.2, 105.2, 55.9, 45.2, 12.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{12}H_{17}N_2OS$ (237.1056), found: 237.1057.

2-(diethylamino)benzo[*d*]thiazole-6-carbonitrile (4g)[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4g** as a bright yellow oil (67 mg, yield = 58%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.81 (s, 1H), 7.49 (s, 2H), 3.61-3.56 (m, 4H), 1.30 (t, 6H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 168.9, 156.0, 130.5, 129.2, 123.8, 119.0, 117.8, 102.2, 45.1, 12.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{12}H_{14}N_3S$ (232.0903), found: 232.0900.

***N*,*N*-diethyl-6-nitrobenzo[*d*]thiazol-2-amine (4h)**[18]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4h** as a pale-yellow oil (67 mg, yield = 62%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 8.41 (d, 1H, *J* = 4.0 Hz), 8.12-8.09 (m, 1H), 7.41 (d, 1H, *J* = 12.0 Hz), 3.55 (d, 4H, *J* = 8.0 Hz), 1.25 (t, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 169.7, 157.6, 140.2, 129.9, 121.4, 116.5, 116.0, 45.0, 11.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O_2S$ (252.0801), found: 252.0799.

4-(benzo[*d*]thiazol-2-yl)morpholine (4i)[20]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was

isolated by column (PE/EA = 5:1) to afford **4i** as a white crystals (99 mg, yield = 90%). mp: 118-120 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.62-7.57 (m, 2H), 7.31 (t, 1H, *J* = 8.0 Hz), 7.10 (t, 1H, *J* = 8.0 Hz), 3.83 (t, 4H, *J* = 12.0 Hz), 3.62 (t, 4H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.8, 151.2, 129.3, 124.9, 120.5, 119.5, 118.0, 65.0, 47.2. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{13}N_2OS$ (221.0743), found: 221.0743.

4-(6-methoxybenzo[d]thiazol-2-yl)morpholine (4j)[20]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4j** as a white crystals (118 mg, yield = 95%). mp: 108-110 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.40 (d, 1H, *J* = 8.0 Hz), 7.08 (d, 1H, *J* = 4.0 Hz), 6.85-6.82 (m, 1H), 3.74 (t, 7H, *J* = 8.0 Hz), 3.49 (t, 4H, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.6, 154.2, 145.6, 130.6, 118.8, 112.8, 104.2, 65.2, 54.8, 47.5. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_2S$ (251.0849), found: 251.0850.

4-(6-chlorobenzo[*d*]thiazol-2-yl)morpholine (4k)[20]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4k** as a white crystals (111 mg, yield = 88%). mp: 121-123 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.48 (d, 1H, *J* = 1.0 Hz), 7.37 (d, 1H, *J* = 8.0 Hz), 7.18-7.16 (m, 1H), 3.74 (t, 4H, *J* = 12.0 Hz), 3.51 (t, 4H, *J* = 12.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.8, 149.9, 130.5, 125.5, 125.3, 119.2, 118.7, 64.9, 47.2. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{12}ClN_2OS$ (255.0354), found: 255.0352.

4-(6-nitrobenzo[*d*]thiazol-2-yl)morpholine (4l)[20]

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 1:1) to afford **4l** as a bright yellow solid (106 mg, yield

= 80%). mp: 185-187 °C. ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 8.52 (d, 1H, *J* = 4.0 Hz), 8.22-8.19 (m, 1H), 7.52 (d, 1H, *J* = 8.0 Hz), 3.85 (t, 4H, *J* = 4.0 Hz), 3.71 (t, 4H, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 171.0, 156.8, 140.9, 129.7, 121.6, 117.4, 116.3, 65.1, 47.6. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{12}N_3O_3S$ (266.0594), found: 266.0590.

2-(2-methylpiperidin-1-yl)benzo[*d*]thiazole (4m)

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4m** as a colorless oil (97 mg, yield = 84%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.49-7.43 (m, 2H), 7.18 (t, 1H, *J* = 8.0 Hz), 6.94 (t, 1H, *J* = 8.0 Hz), 4.30 (t, 1H, *J* = 8.0 Hz), 3.92-3.88 (m, 1H), 3.16-3.09 (m, 1H), 1.75-1.51 (m, 6H), 1.19 (d, 3H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 167.6, 151.9, 129.4, 124.8, 119.9, 119.5, 117.7, 51.0, 42.8, 29.1, 24.4, 17.7, 13.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_{17}N_2S$ (233.1107), found: 233.1110.

6-methoxy-2-(2-methylpiperidin-1-yl)benzo[d]thiazole (4n)

Based on **THE ABOVE MENTIONED PROCEDURE**, the crude material was isolated by column (PE/EA = 5:1) to afford **4n** as a colorless oil (104 mg, yield = 80%). ^{1}H NMR (400 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 7.35 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 1H, *J* = 1.0 Hz), 6.81-6.78 (m, 1H), 4.28-4.22 (m, 1H), 3.88-3.84 (m, 1H), 3.72 (s, 3H), 3.15-3.08 (m, 1H), 1.76-1.52 (m, 6H), 1.19 (d, 3H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, in $CDCl_3$ with TMS as inner standard): δ (ppm) 166.1, 153.4, 145.9, 130.1, 117.8, 112.1, 104.0, 54.7, 50.7, 42.5, 28.8, 24.2, 17.5, 13.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{19}N_2OS$ (263.1213), found: 263.1214.

Supporting Information: list of ^{1}H and ^{13}C NMR of products.

ACKNOWLEDGMENT

The financial support from Hubei Key Laboratory of Radiation Chemistry and Functional Materials, Hubei University of Science & Technology (2019-20KZ01), Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University (KLSAOFM1810), Hubei Provincial Science and Technology (2019CFB596) are all greatly appreciated.

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