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Article

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C−H Imidation and Dual C−H Bond Aminobromination of Five-Membered Heterocycles

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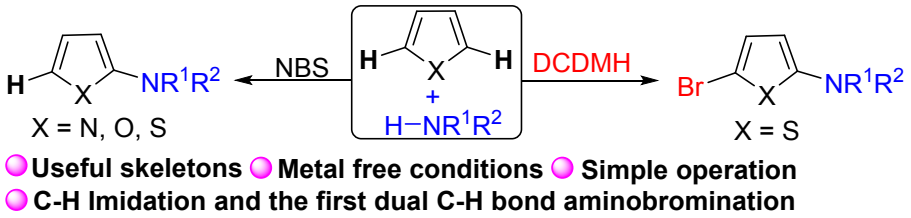


ABSTRACT: Here, we report a practical C−H imidation of five-membered heterocycles under metal free conditions. We also report the first dual C−H bond aminobromination of thiophenes, with benzotriazole, saccharin, 1,2,4-triazole, benzimidazole, pyrazole, 4-bromopyrazole, 5-methyltetrazole, and dibenzenesulfonimides as effective amine sources. Mechanistic studies support the radical pathway of the imidation and aminobromination reactions.

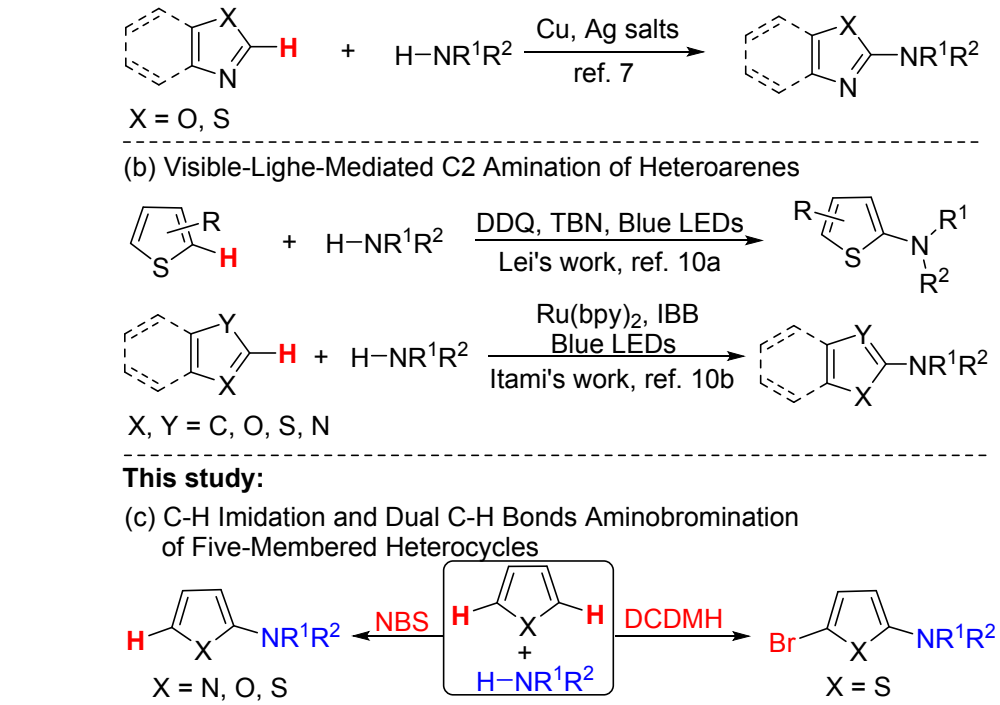
INTRODUCTION

Structures containing amino groups are prevalent in natural products, pharmaceutical agents, synthetic intermediates, and materials.[1] The development of convenient and direct strategies for the construction of C–N bonds has become a fascinating topic in synthetic chemistry. Transition metal-catalyzed direct C−H aminations have emerged as a step- and atom-economical synthetic route and have made impressive achievements during recent years.[2] Site-selectivity in C–H aminations is a crucial problem to be solved because of the similarity of C–H bonds in organic molecules. Besides, several disadvantages also still exist, such as (1) the installation and elimination of directing-groups, (2) limited substrate scope, especially for 5-membered heterocycles without acidic C–H bond,[3] (3) the need preactivated amino precursors,[4] and (4) the inevitable metal residue, which restricts use for pharmaceutical chemistry applications. Therefore, there is a great demand for the establishment of sustainable new strategies to functionalize specific C–H bonds, and the development of C−H aminations under metal-free conditions is one of complementary avenues to established methods.

Five-membered heterocycles bearing an amine group are commonly found in natural products, bioactive compounds, and pharmaceuticals.[5] For example, 2-aminothiophenes are widely used as inhibitors of APE 1 and tubulin polymerization.[6] Zyprexa (Olanzapine), which contains a 2-aminothiophene core, is ranked as one of the world's top 200 drugs in terms of sales. The dehydrogenative C–H amination of five-membered heterocycles is one of the most reliable and atom-economical approaches for nitrogen atom incorporation. In 2009, Mori et al.,

Schreiber et al., and Chang et al. successfully reported the metal-catalyzed C−H amination of azoles bearing a relatively active acidic C−H bond (Scheme 1a).[7] In 2015, Itami et al. described an elegant copper-catalyzed regioselective *α*-position C−H imidation of substituted thiophenes with *N*-fluorobenzenesulfonimide.[8] The substrate scope of these reactions was wide enough to cover a variety of 5-membered heteroarenes, including materials and biology-oriented aromatics. Subsequently, Pan et al. and our group described the copper-catalyzed imidation of heterocycles such as thiophene, furan, and pyrrole.[9] Recently, the Lei group, Itoh group, and Itami group expanded their C–H imidation chemistry with photoredox technology suitable for producing a thiophene radical cation or imidyl radical for the dehydrogenative imidation of five-membered heterocycles (Scheme 1b).[10] Our interest in metal-catalyzed[11] and organocatalyst enabled C−H aminations[12] inspired us to explore new amination strategies of five-membered heterocycles involed nitrogen radicals[13] with suitable amination reagents and halogenides under metal-free conditions. Dual C−H bond functionalization, such as both C−H halogenation and amination of five-membered heterocycles, may be achieved simultaneously (Scheme 1c).

Scheme 1. C2 Amination of five-membered heterocycles

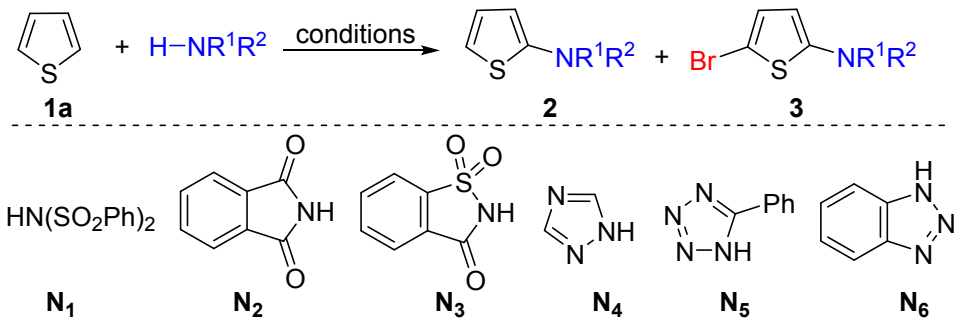


RESULTS AND DISCUSSION

To probe the feasibility of the proposed nitrogen radicals involed C−H functionalization strategy under metal-free conditions, we initially chose thiophene **1a** as a model substrate. A mixture of *N*-bromosuccinimide (NBS, 2.0 equiv) and dibenzenesulfonimide **N1** (1.0 equiv) in 1,2-dichloroethane (DCE, 2.0 mL) were added to the thiophene **1a**. When the reaction proceeded at 90 °C for 12 h, the desired C−H imidation product **2a** was obtained in 76% yield (Table 1, entry 1). Reducing the amount of NBS to 1.0 equivalent significantly decreased the yield of **2a** to 44% (Table 1, entry 2). Further amino source screenings revealed that phthalimide **N2**, saccharin **N3**, and 1,2,4-triazole **N4** were not suitable amino sources, and no C−H imidation occurred (Table 1, entries 3−5). Using 5-phenyltetrazole **N5** as an amino

source resulted in the desired product **2b** in 62% yield (Table 1, entry 6). Benzotriazole **N6** produced only trace amounts of the C−H imidation product, while simultaneous dual C−H bond functionalization formed the aminobromination product **3a** in 74% yield (Table 1, entry 7). *To our knowledge, this is the first example of a simultaneous dual C−H bond aminobromination of thiophene.* Inspired by this result, we studied the effect of different halogen reagents, such as *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), molecular bromine **B1**, 1,3-dibromo-5,5-dimethylhydantoin (DCDMH, **B2**), and tetrabutylammonium tribromide **B3**, with dibenzenesulfonimide **N1** on aminohalogenation. Screening results revealed that only C−H imidation occurred when using NCS, NIS, and **B1**. No reaction occurred at all with **B3** added (Table 1, entries 8−12). **B2** afforded a 79% yield of the desired aminobromination product **3b** (Table 1, entry 11). No significant improvement of product yield was found by increasing the reaction temperature to 120 °C. The yield of **3a** decreased to 39% when the reaction was carried out at 60 °C (Table 1, entries 13 and 14).

Table 1. Survey of the Reaction Conditions[a]



entry	halogen reagent	amino source	temp (°C)	yields of **2**/**3**(%) [b]

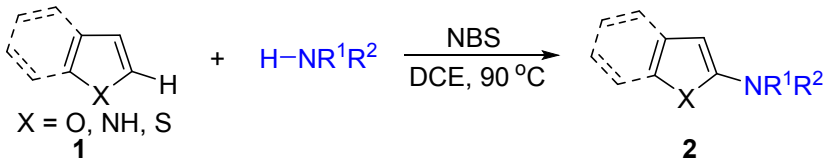
1	NBS	**N1**	90	76/0
2[c]	NBS	**N1**	90	44/0
3	NBS	**N2**	90	0/0
4	NBS	**N3**	90	0/0
5	NBS	**N4**	90	0/0
6	NBS	**N5**	90	62/0
7	NBS	**N6**	90	trace/74
8	NCS	**N1**	90	71/0
9	NIS	**N1**	90	55/0
10	**B1**	**N1**	90	41/0
11	**B2**	**N1**	90	trace/79
12	**B3**	**N1**	90	0/0
13[d]	**B2**	**N1**	120	Trace/77
14[e]	**B2**	**N1**	60	trace/39

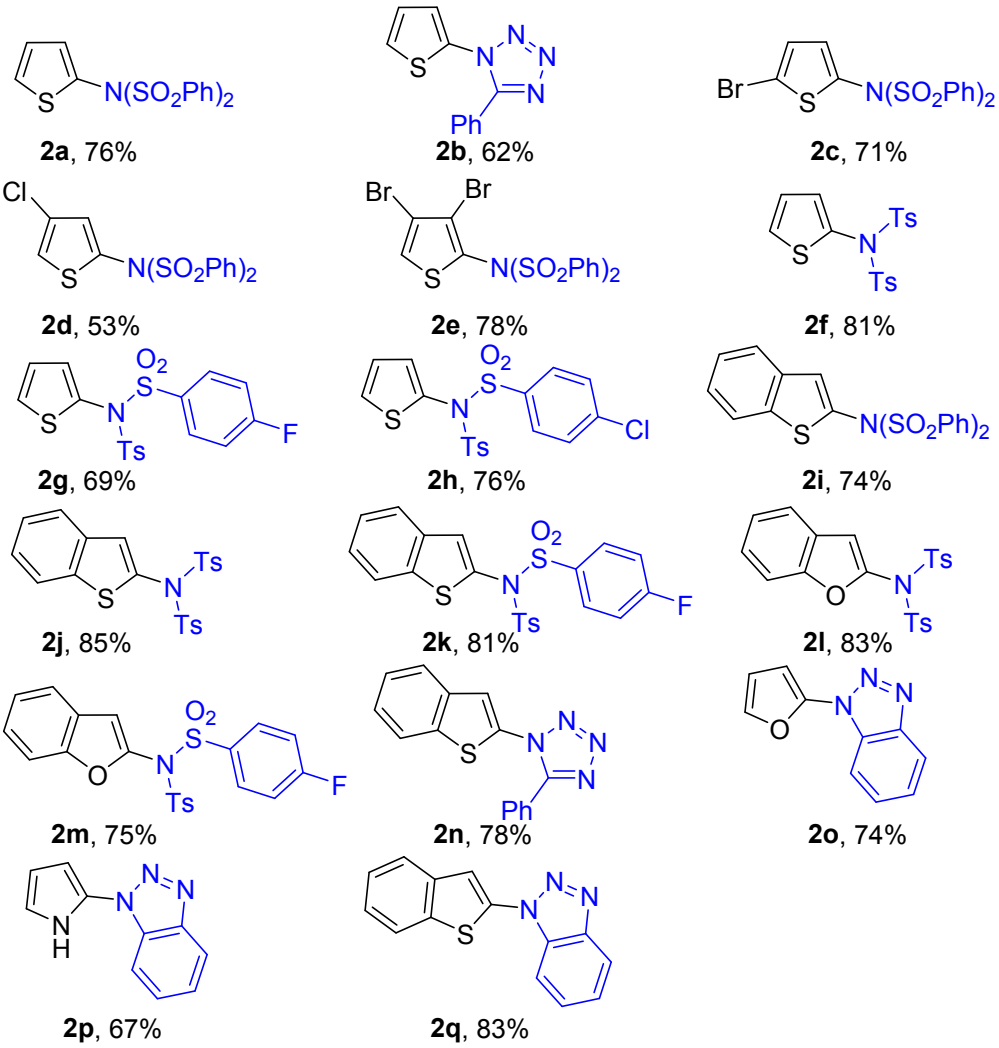
[a]Reactions were carried out with **1a** (0.3 mmol), halogen reagent (2.0 equiv) and amino source (1.0 equiv) in DCE (2.0 mL) under an air atmosphere at 90 °C for 12 h. [b]Yield of the isolated product. [c]1.0 equiv NBS was added. [d]Reactions were performed at 120 °C. [e]Reactions were performed at 60 °C.

With standard conditions established, we evaluated the scope of C−H imidation using different five-membered heterocycles and dibenzenesulfonimides as substrates. As shown in Scheme 2, thiophenes (**1a**) bearing the electron-withdrawing Cl or Br

were well tolerated under the current reaction conditions and delivered the desired **2c** and **2d** in good yields (71% and 53%). However, no desired products were obtained when thiophene bearing electron-donating substituents, such as 2-methylthiophene and 3-methoxythiophene, were employed as substrates. The regioselective C–H imidation of thiophene **1a** with **N1** type dibenzenesulfonimides bearing different electron-donating and electron-withdrawing substituents on the benzene ring occurred at the 2-position, affording **2f–2h** in high yields (69%−81%). Furthermore, benzothiophene, and benzofuran also reacted with dibenzenesulfonimide **N1** and 5-phenyltetrazole **N5** to successfully give the desired **2i–2n** in good yields (74%−85%). It should be noted that although dual C−H bond aminobromination occurred when benzotriazole **N6** was tested with thiophene **1a**, benzotriazole **N6** produced only C2 imidation products **2o** and **2p** (74% and 67%), with pyrrole and furan, respectively. As expected, benzothiophene was also suitable substrates with benzotriazole **N6** and gave the desired product **2q** in 83% yield.

Scheme 2. C–H imidation of five-membered heterocycles and derivatives[a,b]



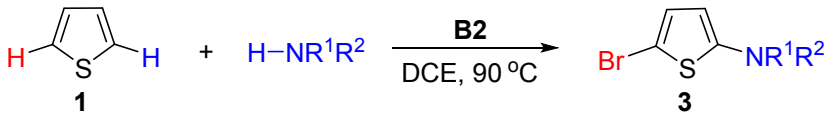


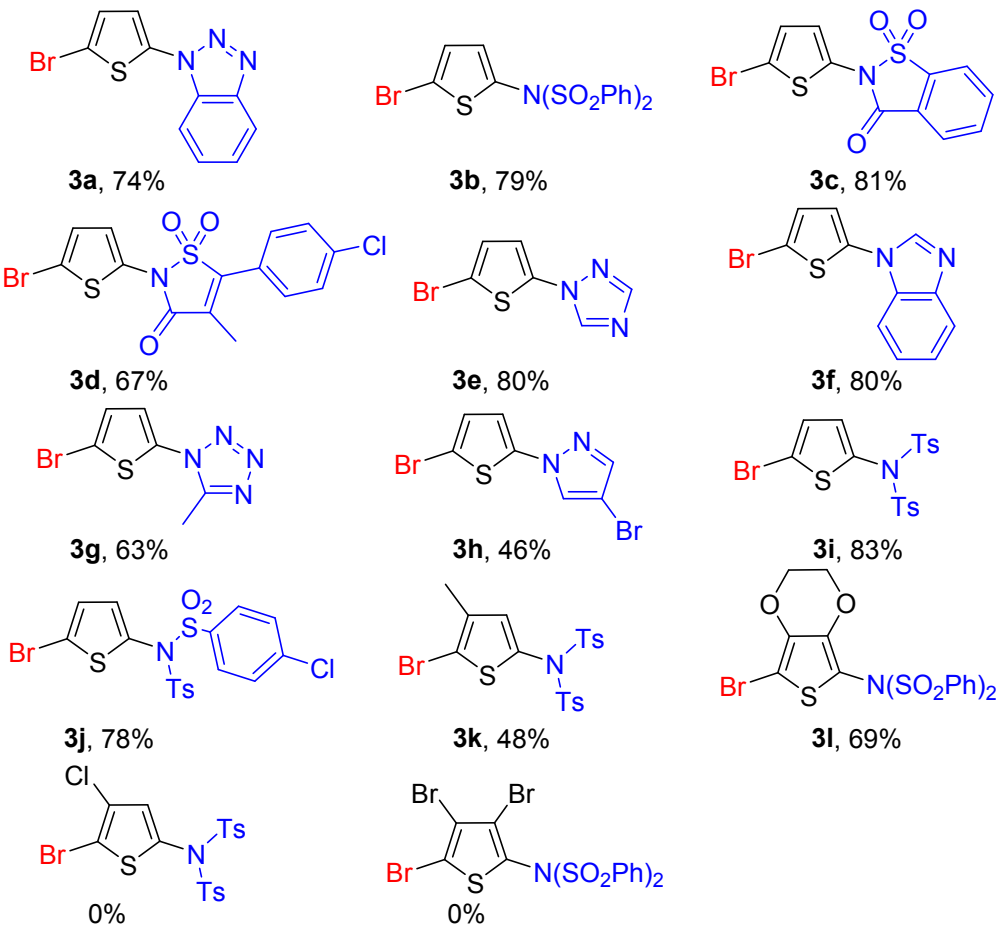
[a]Reaction conditions: **1** (0.3 mmol), NBS (2.0 equiv) and amino source (1.0 equiv) in DCE (2.0 mL) under an air atmosphere at 90 °C for 12 h. [b]The percentage yields represent the isolated yields.

To enrich the dual C−H bonds aminobromination strategy, we further examined and explored the scope of amino sources under the optimized reaction conditions. As shown in Scheme 3, saccharin **N3** and 1,2,4-triazole **N4**, which were not suitable for C−H imidation reactions, performed well during the dual C−H bond aminobromination process. The desired difunctionalized products **3c**−**3e** were

produced in good yields (67%−81%). Because azoles are structural motifs in many antibacterial, anticancer, antidepressant, antifungal, and antimalarial compounds,[14] benzimidazole, 5-methyltetrazole and 4-bromopyrazole were examined as potential nitrogen radical precursors. Benzimidazole, 5-methyltetrazole and 4- bromopyrazole were well tolerated and afforded the corresponding aminobromination products **3f**–**3h** in moderate to high yields (46%–80%). Imidazole and purine were not compatible with this catalytic system, and no difunctionalization occurred under the optimized conditions. The current methodology is also applicable for dibenzenesulfonimide derivatives, affording the corresponding **3i** and **3j** in good yields (83% and 78%). Finally, thiophene derivatives, such as 3-methylthiophene and thieno[3,4-*d*][1,3]dioxole, were tested and produced the desired products **3k** and **3l** in moderate yields (48% and 69%). No aminobromination occurred with 3-chlorothiophene and 3,4-dibromothiophene as the substrates.

Scheme 3. Dual C−H bonds aminobromination of thiophenes[a,b]



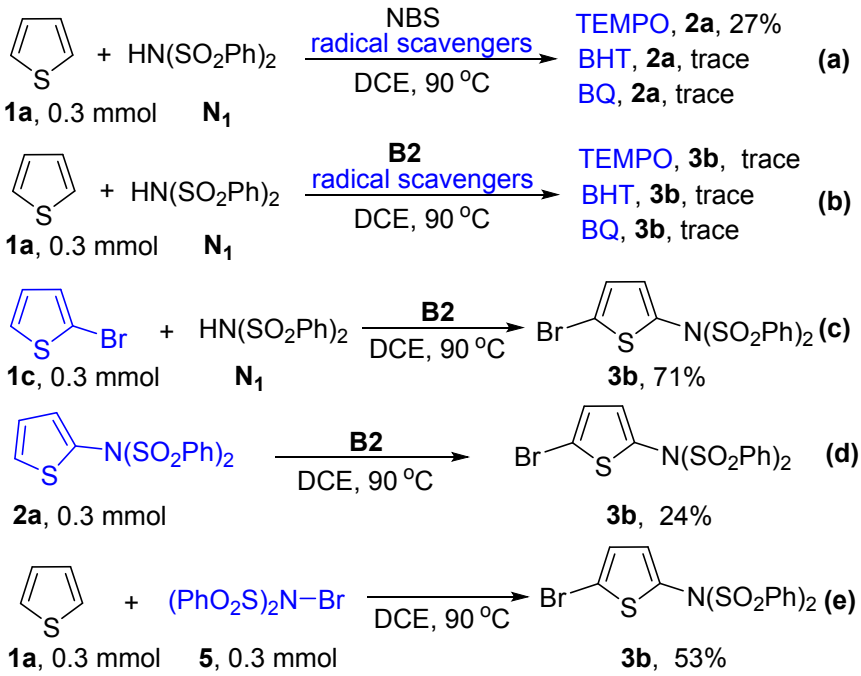


[a]Reaction conditions: **1** (1.8 mmol), benzimidazoles **2** (0.3 mmol), DBDMH (1.0 equiv) at 90 °C in DCE (2.0 mL). [b]Yield of isolated product.

Control experiments were carried out to acquire mechanistic insights into the reaction pathway (Scheme 4). When radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 2.0 equiv), 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.0 equiv), and *p*-benzoquinone (BQ, 2.0 equiv) were added to the optimized imidation reaction, the reaction was markedly inhibited, and the adduct **4** between benzotriazole and 2,6-di-*tert*-butyl-4-methylphenol (see SI) was detected via GC-MS analysis (Scheme 4a). Similar results were observed when TEMPO, BHT, and BQ were added

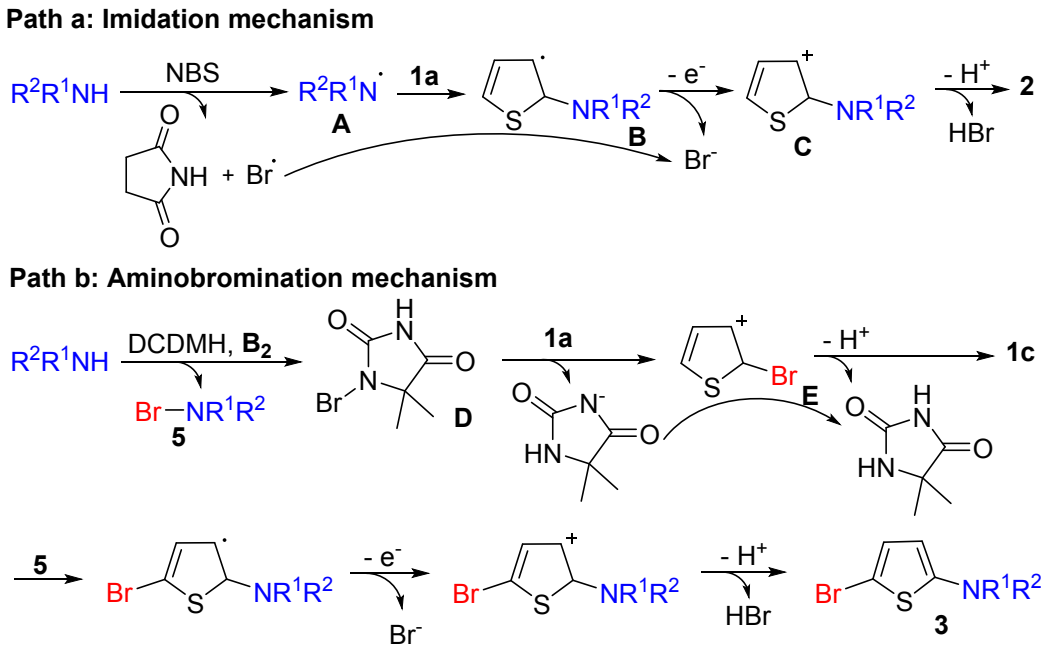
to the optimized aminobromination reaction, and only trace amounts of **3b** were detected (Scheme 4b). These observations imply that nitrogen radical species may involved in the reaction. To identify the possible intermediate in the aminobromination reaction, control experiments with 2-bromothiophene **1c** and **2a** were examined as the substrates, separately. As described, **3b** could be isolated with a 71% yield when 2-bromothiophene **1c** was tested, while a 24% yield of the desired **3b** was obtained with **2a** as the substrate (Scheme 4c and 4d). To provide further evidence regarding the possible intermediate, we prepared the N-Br reagent **5** according to a previous literature report.[15] When the reaction between **1a** and **5** was performed in DCE, **3b** could be isolated in 53% yield (Scheme 4e).

Scheme 4. Reactions determining the mechanism



Although further studies are still needed to fully uncover the precise mechanism of the C−H imidation and aminobromination, the possible mechanism was proposed based on the present findings and previous reports,[16] as shown in Scheme 5. For the imidation mechanism (path a), the initial interaction between the amino source and NBS would generate the corresponding nitrogen-centered radical **A**, which undergoes electrophilic addition with **1a** to deliver the radical intermediate **B**. Subsequently, single electron oxidation and hydrogen proton trap processes led to the final product **2**. For the aminobromination mechanism (path b), the interaction between the amino source and **B2** would generate the corresponding **5** and **D**. Compared with NBS, the electron-deficiency of **D** is prone to electrophilic addition with **1a** to generate the intermediate **E**. Then, a hydrogen proton trap process gave the 2-bromothiophene **1c**. Subsequently, similar single electron oxidation and hydrogen proton trap processes led to the final product **3**.

Scheme 5. Proposed reaction mechanism



CONCLUSIONS

In summary, we have presented a practical and economical regioselective C−H imidation of five-membered heterocycles. This synthetic technique does not require additional treatments process to remove metal residues. We also achieved the first dual C−H bond aminobromination of thiophenes, with benzotriazole, saccharins, 1,2,4-triazole, pyrazole, benzimidazole, tetrazole and dibenzenesulfonimides as effective amine sources and 1,3-dibromo-5,5-dimethylhydantoin as the bromination reagent. The possible radical mechanism was proposed to explain the imidation and aminobromination process based on control experiments. Further mechanistic studies and applications of this strategy to more complicated materials and drug candidates are underway in our laboratory.

Experimental Section

General Information. All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ascend™ 400 spectrometer in deuterated solvents containing TMS as an internal reference standard. High-resolution mass spectrometry (HRMS) analyses were conducted on a Waters LCT Premier/XE. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All the reactions were conducted in oil bath and monitored by thin-layer chromatography (TLC) using GF254 silica gel-coated TLC plates. Purification by flash column chromatography was performed over SiO_2 (silica gel 200−300 mesh).

General procedure:

Synthesis procedure for compounds 2:

To a reaction tube equipped with a stir bar was sequentially added **1** (0.3 mmol), NBS (0.6 mmol, 2.0 equiv) and amino source (0.3 mmol, 1.0 equiv) in DCE (2.0 mL) under an air atmosphere. Then the reaction mixture was stirred at 90 °C in an oil bath. Upon completion of the reaction (as monitored by TLC), the mixture was cooled to room temperature and quenched with water before being extracted with dichloromethane (5 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography to give the desired product **2**.

Synthesis procedure for compounds 3:

To a reaction tube equipped with a stir bar was sequentially added **1** (0.3 mmol), 1,3-dibromo-5,5-dimethylhydantoin (**B2**, 0.6 mmol, 2.0 equiv) and amino source (0.3 mmol, 1.0 equiv) in DCE (2.0 mL) under an air atmosphere. Then the reaction mixture was stirred at 90 °C in an oil bath. Upon completion of the reaction (as monitored by TLC), the mixture was cooled to room temperature and quenched with water before being extracted with dichloromethane (5 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography to give the desired product **3**.

***N*-(phenylsulfonyl)-*N*-(thiophen-2-yl)benzenesulfonamide (2a)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (76%, 86.4 mg), melting point: 130-131 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 6.75 (dd, J_1 = 1.2, J_2 = 4.0, 1H), 6.95 (q, J = 4.0, 1H), 7.38 (dd, J_1 = 1.2, J_2 = 4.0, 1H), 7.56-7.59 (m, 4H), 7.70 (t, J = 7.2, 2H), 8.00 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 125.6, 128.7, 128.8, 129.0, 131.3, 133.9, 134.2, 138.7. HRMS (ESI-TOF) Calcd for $C_{16}H_{14}NO_4S_3$, $[M+H]^+$ 380.0085; Found 380.0091.

5-phenyl-1-(thiophen-2-yl)-1*H*-tetrazole (2b). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 7:1), white solid (62%, 42.4 mg), melting point: 153-154 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.11 (q, J = 4.0, 1H), 7.31 (q J = 4.0, 1H), 7.52-5.54 (m, 3H), 7.71 (dd, J_1 = 1.6, J_2 = 4.0, 1H), 8.23 (t, J = 3.2, 2H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 119.0, 119.1, 123.6, 126.5, 126.7, 127.1, 128.9, 130.6, 165.1. HRMS (ESI-TOF) Calcd for $C_{11}H_9SN_4$, $[M+H]^+$ 229.0548;

Found 229.0552.

***N*-(5-bromothiophen-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (2c)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (71%, 97.6 mg), melting point: 93-94 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.51 (d, J = 4.0, 1H), 6.94 (d, J = 4.4, 1H), 7.59 (t, J = 8.0, 4H), 7.70-7.38 (m, 2H), 8.00 (d, J = 8.0, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 115.7, 128.7, 128.8, 129.1, 130.8, 132.1, 134.3, 134.4, 138.5, 139.1. HRMS (ESI-TOF) Calcd for $C_{16}H_{13}NBrO_4S_3$, $[M+H]^+$ 457.9192; Found 457.9195.

***N*-(4-chlorothiophen-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (2d)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (53%, 65.8 mg), melting point: 201-202 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.67 (d, J = 1.6, 1H), 7.17 (d, J = 1.6, 1H), 7.59 (t, J = 8.0, 4H), 7.72 (d, J = 7.6, 2H), 8.02 (d, J = 7.6, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 123.4, 124.0, 128.7, 129.2, 131.2, 134.2, 134.4, 138.4. HRMS (ESI-TOF) Calcd for $C_{16}H_{13}NClO_4S_3$, $[M+H]^+$ 413.9695; Found 413.9691.

***N*-(3,4-dibromothiophen-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (2e)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (78%, 125.1 mg), melting point: 182-183 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.49 (s, 1H), 7.58 (t, J = 8.0, 4H), 7.71 (d, J = 7.6, 2H), 8.03 (d, J = 7.6, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 113.4, 121.0, 126.0, 129.2, 130.4, 134.6, 138.7. HRMS (ESI-TOF) Calcd for $C_{16}H_{12}NBr_2O_4S_3$, $[M+H]^+$ 535.8297;

Found 535.8301.

4-methyl-*N*-(thiophen-2-yl)-*N*-tosylbenzenesulfonamide (2f). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (81%, 99.0 mg), melting point: 180-181 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.74 (dd, J_1 = 1.2, J_2 = 3.6, 1H), 6.94 (q, J = 4.0, 1H), 7.34-7.38 (m, 5H), 7.86 (d, J = 8.4, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 21.7, 125.6, 128.6, 128.7, 129.6, 131.1, 134.2, 135.8, 145.3. HRMS (ESI-TOF) Calcd for $C_{18}H_{18}NO_4S_3$, $[M+H]^+$ 408.0398; Found 408.0393.

4-fluoro-*N*-(thiophen-2-yl)-*N*-tosylbenzenesulfonamide (2g). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (69%, 85.2 mg), melting point: 142-143 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.75 (dd, J_1 = 1.2, J_2 = 3.6, 1H), 6.96 (d, J = 4.0, 1H), 7.24 (d, J = 7.6, 2H), 7.38 (q, J = 8.8, 3H), 7.86 (d, J = 8.4, 2H), 8.02 (q, J = 5.2, 2H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 166.16 (d, J = 257.4 Hz), 145.71, 135.82, 134.92 (d, J = 3.0 Hz), 134.07, 131.86 (d, J = 9.6 Hz), 131.38, 129.85, 129.00, 128.93, 125.86, 116.51 (d, J = 22.8 Hz), 21.88. HRMS (ESI-TOF) Calcd for $C_{17}H_{15}NFO_4S_3$, $[M+H]^+$ 412.0148; Found 412.0152.

4-chloro-*N*-(thiophen-2-yl)-*N*-tosylbenzenesulfonamide (2h). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (76%, 97.6 mg), melting point: 168-169 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.76 (dd, J_1 = 1.2, J_2 = 4.0, 1H), 6.95 (q, J = 3.6, 1H), 7.38 (d, J = 8.4, 3H), 7.53 (d,

J = 8.4, 2H), 7.86-7.95 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 21.7, 125.7, 128.8, 128.9, 129.3, 129.7, 130.1, 131.2, 133.8, 135.5, 137.2, 140.9, 145.6. HRMS (ESI-TOF) Calcd for $C_{17}H_{15}NClO_4S_3$, $[M+H]^+$ 427.9852; Found 427.9857.

***N*-(benzo[*b*]thiophen-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (2i)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (74%, 95.3 mg), melting point: 161-162 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.03 (s, 1H), 7.38-7.42 (m, 2H), 7.59 (d, J = 8.0, 4H), 7.71-7.74 (m, 4H), 8.05 (d, J = 7.6, 4H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 122.4, 124.7, 126.1, 128.7, 128.8, 129.1, 134.2, 134.3, 136.7, 138.7, 140.3. HRMS (ESI-TOF) Calcd for $C_{20}H_{16}NO_4S_3$, $[M+H]^+$ 430.0240; Found 430.0247.

***N*-(benzo[*b*]thiophen-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide (2j)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 7:1), white solid (85%, 116.7 mg), melting point: 206-207 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.50 (s, 6H), 7.04 (s, 1H), 7.36-7.41 (m, 6H), 7.75 (t, J = 8.0, 2H), 7.92 (d, J = 8.4, 4H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 21.7, 122.3, 124.6, 124.7, 125.9, 128.5, 128.8, 129.6, 134.5, 135.9, 136.8, 140.3, 145.4. HRMS (ESI-TOF) Calcd for $C_{22}H_{20}NO_4S_3$, $[M+H]^+$ 458.0554; Found 458.0561.

***N*-(benzo[*b*]thiophen-2-yl)-4-fluoro-*N*-tosylbenzenesulfonamide (2k)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (81%, 112.1 mg), melting point: 193-194 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.50 (s, 3H), 7.05 (s, 1H), 7.24 (t, J = 8.8, 2H), 7.40 (t, J = 8.8, 4H), 7.76

(t, J = 7.6, 2H), 7.94 (d, J = 8.4, 2H), 8.07-8.10 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 166.23 (d, J = 257.6 Hz), 145.84, 140.42, 136.90, 135.88, 134.96 (d, J = 2.9 Hz), 134.34, 131.95 (d, J = 9.8 Hz), 129.91, 129.01, 128.80, 126.27, 124.95, 124.91, 122.55, 116.57 (d, J = 22.8 Hz), 21.90. HRMS (ESI-TOF) Calcd for $C_{21}H_{17}NFO_4S_3$, $[M+H]^+$ 462.0304; Found 462.0308.

***N*-(benzofuran-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide (2l)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (83%, 109.9 mg), melting point: 167-168 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.47 (s, 6H), 7.06 (d, J = 7.6, 1H), 7.15 (d, J = 7.2, 1H), 7.32-7.34 (m, 4H), 7.38 (d, J = 8.0, 1H), 7.50 (t, J = 4.8, 2H), 7.86 (d, J = 8.0, 4H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 21.7, 116.3, 116.5, 122.4, 124.8, 126.1, 128.6, 128.8, 129.7, 131.7, 131.8, 134.2, 134.8, 135.7, 136.7, 140.2, 145.7, 164.8, 167.3. HRMS (ESI-TOF) Calcd for $C_{22}H_{20}NO_5S_2$, $[M+H]^+$ 442.0783; Found 442.0788.

***N*-(benzofuran-2-yl)-4-fluoro-*N*-tosylbenzenesulfonamide (2m)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (75%, 100.2 mg), melting point: 157-158 ^oC; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.48 (s, 3H), 6.62 (s, 1H), 7.04-7.23 (m, 6H), 7.33 (d, J = 8.0, 1H), 7.51 (d, J = 8.4, 1H), 7.88 (d, J = 8.4, 2H), 8.02 (d, J = 5.2, 2H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 166.15 (d, J = 257.5 Hz), 154.65, 146.17, 145.68, 136.21, 135.34 (d, J = 3.0 Hz), 131.69 (d, J = 9.9 Hz), 129.86, 128.76, 125.49, 125.18, 123.94, 119.62, 117.30, 116.51 (d, J = 22.8 Hz), 112.27, 21.84. HRMS (ESI-TOF) Calcd for $C_{21}H_{17}NFO_5S_2$,

$[M+H]^+$ 446.0533; Found 446.0539.

1-(benzo[*b*]thiophen-2-yl)-5-phenyl-1*H*-tetrazole (2n). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (78%, 65.1 mg), melting point: 132-133 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.45 (t, J = 4.0, 2H), 7.54 (dd, J_1 = 2.0, J_2 = 5.2, 3H), 7.86 (dd, J_1 = 2.0, J_2 = 5.2, 2H), 7.95 (s, 1H), 8.26 (dd, J_1 = 2.0, J_2 = 8.0, 2H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 114.9, 122.4, 124.7, 125.5, 126.0, 126.6, 127.2, 128.9, 130.8, 136.7, 137.0, 137.6, 165.4. HRMS (ESI-TOF) Calcd for $C_{15}H_{11}N_4S$, $[M+H]^+$ 279.0703; Found 279.0706.

1-(furan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (2o). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (74%, 41.1 mg), melting point: 117-119 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.65 (t, J = 3.2, 1H), 6.70 (d, J = 3.2, 1H), 7.46-7.61 (m, 3H), 7.79 (d, J = 8.0, 1H), 8.12 (d, J = 8.4, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 100.6, 110.7, 111.9, 120.2, 124.7, 128.8, 132.3, 140.4, 143.7, 145.5. HRMS (ESI-TOF) Calcd for $C_{10}H_8N_3O$, $[M+H]^+$ 186.0667; Found 186.0662.

1-(1*H*-pyrrol-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (2p). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (67%, 37.0 mg), melting point: 111-112 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.39 (d, J = 3.2, 1H), 6.48 (s, 1H), 6.90 (d, J = 1.2, 1H), 7.43 (t, J = 7.6, 1H), 7.57 (t, J = 7.2, 1H), 7.73 (d, J = 8.4, 1H), 8.09 (d, J = 8.4, 1H), 9.36 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 99.3, 109.0, 110.5, 116.7, 120.1, 124.6, 125.0, 128.4, 131.9,

145.7. HRMS (ESI-TOF) Calcd for $C_{10}H_9N_4$, $[M+H]^+$ 185.0827; Found 185.0825.

1-(benzo[*b*]thiophen-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (2q). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (83%, 62.6 mg), melting point: 146-147 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.47-7.64 (m, 6H), 7.88-7.96 (m, 2H), 7.98 (d, J = 7.2, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 106.6, 110.8, 120.4, 122.7, 124.3, 124.7, 125.3, 126.0, 127.1, 128.8, 133.8, 136.3, 136.6, 145.6. HRMS (ESI-TOF) Calcd for $C_{14}H_{10}N_3S$, $[M+H]^+$ 252.0595; Found 252.0599.

1-(5-bromothiophen-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (3a). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (74%, 62.2 mg), melting point: 104-105 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.12 (q, J = 4.0, 2H), 7.46 (d, J = 8.0, 1H), 7.58 (q, J = 7.2, 1H), 7.68 (d, J = 8.4, 1H), 8.10 (d, J = 8.4, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 109.9, 110.6, 119.9, 120.5, 124.9, 129.0, 132.4, 137.7, 146.0. HRMS (ESI-TOF) Calcd for $C_{10}H_7N_3SBr$, $[M+H]^+$ 279.9544; Found 279.9541.

***N*-(5-bromothiophen-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (3b)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (79%, 108.5 mg), melting point: 93-94 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.51 (d, J = 4.0, 1H), 6.94 (d, J = 4.4, 1H), 7.59 (t, J = 8.0, 4H), 7.70-7.38 (m, 2H), 8.00 (d, J = 8.0, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 115.7, 128.7, 128.8, 129.1, 130.8, 132.1, 134.3, 134.4, 138.5, 139.1. HRMS (ESI-TOF)

Calcd for $C_{16}H_{13}NBrO_4S_3$, $[M+H]^+$ 457.9192; Found 457.9195.

2-(5-bromothiophen-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3c). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (81%, 83.6 mg), melting point: 133-134 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.10 (q, J = 4.0, 2H), 7.91-8.02 (m, 3H), 8.16 (d, J = 7.2, 1H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 114.0, 121.5, 126.5, 127.2, 127.5, 128.9, 134.7, 135.5, 137.3, 157.6. HRMS (ESI-TOF) Calcd for $C_{11}H_7NBrO_3S_2$, $[M+H]^+$ 343.9051; Found 343.9055.

2-(5-bromothiophen-2-yl)-5-(4-chlorophenyl)-4-methylisothiazol-3(2*H*)-one 1,1-dioxide (3d). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (67%, 84.2 mg), melting point: 145-146 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.26 (s, 3H), 7.03 (d, J = 4.0, 1H), 7.09 (d, J = 4.0, 1H), 7.55 (d, J = 8.4, 2H), 7.64 (d, J = 8.4, 2H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 10.5, 113.7, 122.7, 126.8, 127.4, 128.9, 129.9, 130.4, 132.8, 138.3, 144.0, 159.4. HRMS (ESI-TOF) Calcd for $C_{14}H_{10}NBrClO_3S_2$, $[M+H]^+$ 417.8975; Found 417.8981.

1-(5-bromothiophen-2-yl)-1*H*-1,2,4-triazole (3e). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (80%, 55.2 mg), melting point: 88-89 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.96 (d, J = 4.0, 1H), 7.01 (d, J = 4.0, 1H), 8.08 (s, 1H), 8.43 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ = 110.2, 117.8, 124.5, 128.8, 141.6, 152.5. HRMS (ESI-TOF) Calcd

for $C_6H_5N_3BrS$, $[M+H]^+$ 229.9388; Found 229.9392.

1-(5-bromothiophen-2-yl)-1*H*-benzo[*d*]imidazole (3f). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1), white solid (80%, 66.9 mg), melting point: 144-146 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.94 (d, J = 4.0, 1H), 7.10 (d, J = 3.6, 1H), 7.37 (q, J = 4.0, 1H), 7.46 (dd, J_1 = 2.0, J_2 = 8.4, 2H), 7.51-7.65 (m, 1H), 7.70 (d, J = 8.4, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 110.2, 113.4, 120.6, 122.8, 123.4, 123.5, 124.4, 126.9, 129.1, 143.4. HRMS (ESI-TOF) Calcd for $C_{11}H_8N_2BrS$, $[M+H]^+$ 278.9592; Found 278.9597.

1-(5-bromothiophen-2-yl)-5-methyl-1*H*-tetrazole (3g). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (63%, 46.3 mg), melting point: 71-73 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.61 (s, 3H), 7.05 (d, J = 4.0, 1H), 7.35 (d, J = 4.0, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 10.8, 111.2, 118.6, 129.2, 163.3. HRMS (ESI-TOF) Calcd for $C_6H_6N_4BrS$, $[M+H]^+$ 244.9497; Found 244.9503.

4-bromo-1-(5-bromothiophen-2-yl)-1*H*-pyrazole (3h). The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (46%, 42.5 mg), melting point: 87-88 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.77 (d, J = 4.0, 1H), 6.93 (d, J = 4.0, 1H), 7.61 (s, 1H), 7.77 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 96.1, 108.1, 114.4, 127.7, 128.6, 141.8, 143.0. HRMS (ESI-TOF) Calcd for $C_7H_5N_2Br_2S$, $[M+H]^+$ 306.8540; Found 306.8543.

***N*-(5-bromothiophen-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide (3i)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (83%, 121.0 mg), melting point: 183-184 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.49 (d, J = 4.0, 1H), 6.93 (d, J = 4.0, 1H), 7.36 (d, J = 8.0, 4H), 7.86 (d, J = 8.4, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 21.7, 125.5, 128.6, 129.6, 131.1, 134.2, 135.8, 145.3. HRMS (ESI-TOF) Calcd for $C_{18}H_{17}NBrO_4S_3$, $[M+H]^+$ 485.9503; Found 485.9509.

***N*-(5-bromothiophen-2-yl)-4-chloro-N-tosylbenzenesulfonamide (3j)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (78%, 118.6 mg), melting point: 166-167 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.51 (d, J = 4.0, 1H), 6.95 (d, J = 4.0, 1H), 7.37 (d, J = 8.4, 2H), 7.55 (d, J = 8.8, 2H), 7.86 (d, J = 8.0, 2H), 7.93 (d, J = 8.8, 2H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 115.7, 128.7, 129.4, 129.8, 130.1, 132.1, 134.0, 135.3, 136.9, 141.1, 145.8. HRMS (ESI-TOF) Calcd for $C_{17}H_{14}NClBrO_4S_3$, $[M+H]^+$ 505.8957; Found 505.8954.

***N*-(5-bromo-4-methylthiophen-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide (3k)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1), white solid (48%, 72.1 mg), melting point: 162-164 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 1.84 (s, 3H), 2.48 (s, 6H), 6.61 (s, 1H), 7.35 (d, J = 8.4, 4H), 8.82 (d, J = 8.8, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 12.5, 21.7, 107.3, 127.3, 128.0, 128.5, 129.5, 129.6, 130.3, 136.4, 144.6, 145.3. HRMS (ESI-TOF)

Calcd for $C_{19}H_{19}NBrO_4S_3$, $[M+H]^+$ 499.9660; Found 499.9667.

***N*-(7-bromo-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)-*N*-(phenylsulfonyl)benzene sulfonamide (3l)**. The product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1), white solid (69%, 106.9 mg), melting point: 182-184 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 3.86-3.88 (m, 2H), 4.15-4.17 (m, 2H), 7.56 (t, J = 7.6, 4H), 7.69 (t, J = 7.2, 2H), 8.02 (d, J = 8.0, 4H). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ = 64.5, 64.6, 90.4, 108.0, 128.8, 134.1, 138.5, 139.1, 141.5. HRMS (ESI-TOF) Calcd for $C_{18}H_{15}NBrO_6S_3$, $[M+H]^+$ 515.9245; Found 515.9251.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx. Copies of ^{1}H and ^{13}C NMR spectra for Compounds **2**, **3** and **4** (PDF).

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