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Synthesis of Sulfonamides from Azoles and Sodium Sulfinates at Ambient Temperature

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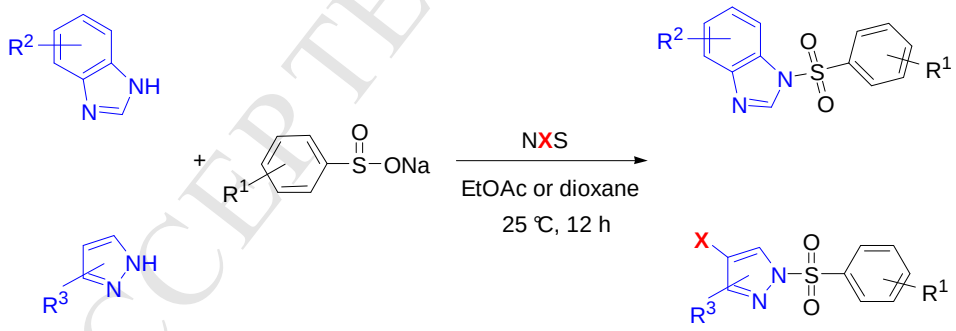
Graphical Abstract:



ABSTRACT. NBS or NIS mediated direct S-N bond formation between azoles and sodium sulfinates is described. The reaction shows good substrate scope and tolerates a wide range of functionalities in both azoles and sodium sulfinate substrates. Pyrazoles are also suitable for this method, various 4-halopyrazoles derivatives were obtained by using *N*-halosuccinimide (NXS) as the halogen source.

Key words: Synthetic methods; Sodium sulfinates; azoles; sulfonylation; halogenation

1. Introduction

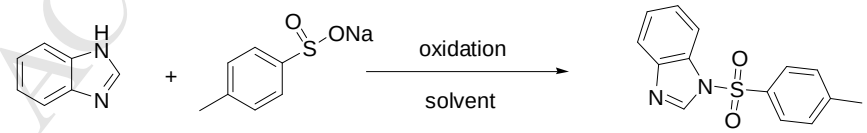
Sulfonamides are important building blocks for pharmaceuticals and bioactive compounds, owing to their well-known anticonvulsant, antibacterial, anticancer, antitumor, anti-inflammatory, and HIV protease inhibitory activities.[1] Sulfonamides are widely applicated in herbicides and dyes.[2] Therefore, the development of general methods for the synthesis of sulfonamides is consequently an important goal in organic chemistry. Traditionally, sulfonamides are produced from the reaction of an amine and a sulfonyl chloride in the presence of a base.[3] Recently, a few examples have been reported on direct synthesis of the sulfonamides from sulfinates and amines. Jiang and co-workers reported an elegant work for $CuBr_2$-catalyzed oxidative synthesis of sulfonamides from sodium sulfinatesand amines with DMSO or O_2.[4] It was found that sulfonamides could also be formed via oxidative amination of sodium sulfinate under metal-free conditions later.[5] Zeng and co-workers reported a protocol for the synthesis of sulfonamides via the electrochemical oxidative amination of sodium sulfinates.[6] These methods avoid the prefunctionalization of the sulfonate component, therefore they are step and atom economical methods. To extend the application scope of this methodology, we have developed a route for synthesis of sulfonamides by using NIS or NBS as the oxidant.

Azoles are ubiquitous motifs in nature and exhibit potential biological activities and medicinal significance.[7] Thus the development of new synthetic methods for the functionalization of azoles is of great interest.[8] The *N*-alkylation and *N*-arylation of azoles present the most straightforward method for the synthesis of azole derivatives. As a part of our continuous interest in the functionalization of azoles,[8e,8f] herein, we report a metal-free sulfonamides formation between sodium sulfinates and azoles mediated by NBS or NIS at room temperature.

2. Results and Discussion

Benzimidazole (**1a**) and sodium *p*-tolylsulfinate (**2a**) was selected as the model substrates to establish optimized reaction conditions, and selected results were summarized in Table 1. When the reaction of **1a** with **2a** was carried out in the presence of I_2 (1 equiv) under air in 1,2-dichloroethane (DCE) at room temperature for 12 h, the product **3a** could be obtained in 44% yield (Table 1, entry 1). Next, various oxidants were screened, and different oxidants had distinct effects on the yield of **3a** (entries 2-5). A significant enhancement of the reaction yield (87%) was accomplished when NBS was used (entry 3). When the amount of NBS was increased to 2 or 3 equiv, the yield of **3a** was slightly decreased (entries 6 and 7). Lower yields of product **3a** were obtained and some unidentified byproducts were observed when the temperature was increased to 50 and 90 °C (entries 8 and 9). The effect of solvents on the model reaction was also surveyed (entries 10−18), and a significant enhancement of the reaction yield (93%) was accomplished when 1,4-dioxane was used (entry 15). We also found that relatively lower yields were obtained when the reaction took place in polar solvents such as DMSO, DMF and ethanol (entries 16-18). We found that running reaction with 100 mg 4 Å MS did not enhance the reaction yield (entry 19). Other oxidants such as *N*-Bromophthalimide and *N*-Bromoacetamide were also tested, the products was obtained in 93% and 84% yields, respectively (entries 20 and 21).

Table 1. Optimization of Reaction Conditions [a]



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

Entry	Oxidant	Temp (°C)	Solvent	Yield (%)
1	I_2	25	DCE	44
2	NIS	25	DCE	78
3	NBS	25	DCE	87

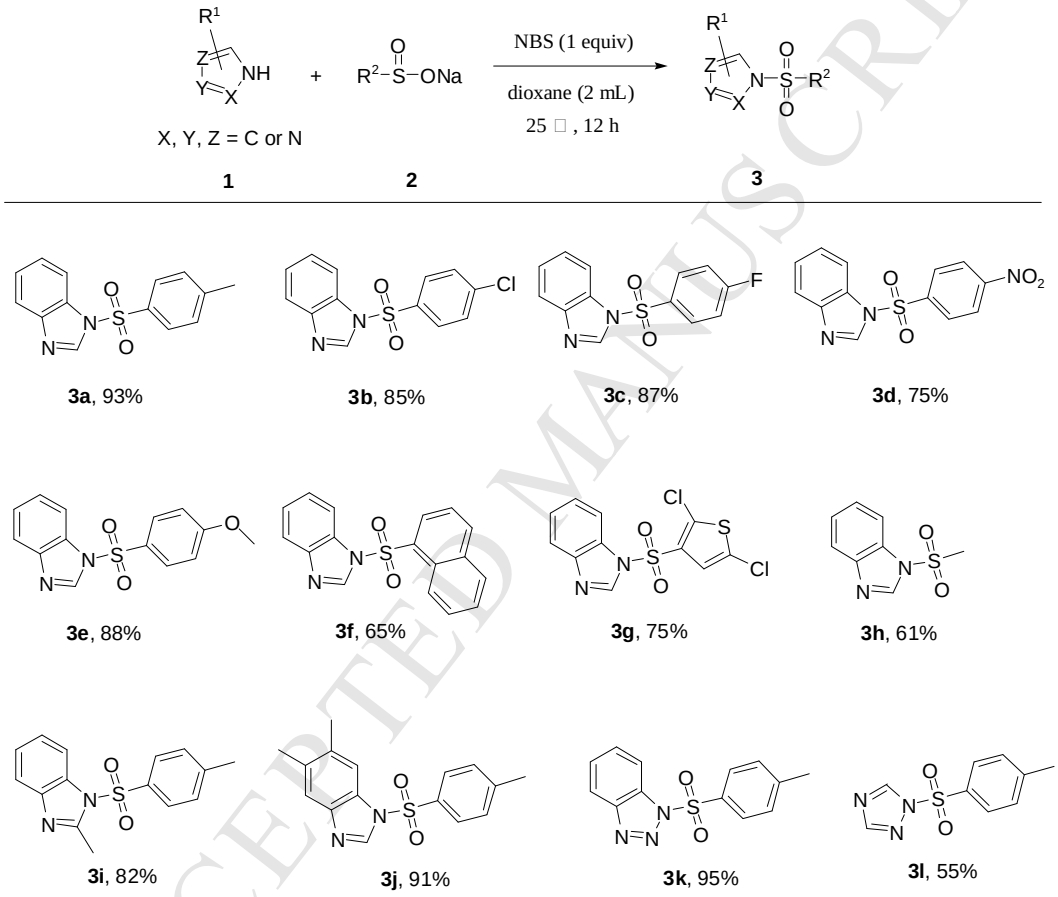
4	NCS	25	DCE	52
5	TBHP	25	DCE	20
6 [b]	NBS	25	DCE	85
7 [c]	NBS	25	DCE	83
8	NBS	50	DCE	79
9	NBS	90	DCE	60
10	NBS	25	EtOAc	86
11	NBS	25	CH_2Cl_2	62
12	NBS	25	CH_3CN	77
13	NBS	25	Tol	68
14	NBS	25	THF	69
15	**NBS**	**25**	**1,4-dioxane**	**93**
16	NBS	25	DMSO	22
17	NBS	25	DMF	15
18	NBS	25	C_2H_5OH	26
19 [d]	NBS	25	1,4-dioxane	92
20	*N*-Bromophthalimide	25	1,4-dioxane	93
21	*N*-Bromoacetamide	25	1,4-dioxane	84

[a] Reaction conditions: **1a** 0.5 mmol, **2a** 1.0 mmol, oxidant 0.5 mmol, solvent 2 mL, 12 h, under air. [b] 1.0 mmol NBS was used. [c] 1.5 mmol was used. [d] 4 Å MS (100 mg) was used.

Under the optimized reaction conditions, we next examined the scope of different azoles and sodium sulfinates (Scheme 1). The reactions of sodium sulfinates **2b**−**2e** bearing both electron-rich and electron-deficient functional groups at the para-position of the aryl ring afforded the corresponding products (**3b**−**3e**) in good yields. Moreover, sodium naphthalene-1-sulfinate **2f** was successfully employed as the substrate, and the desired product **3f** was obtained with a moderate yield (65%). Sodium 2,5-dichloro-thiophene-3-sulfinate **2g** was also a suitable substrate, and the expected product **3g** was obtained in 75% yield. To our delight, sodium methanesulfinate could also be used as substrates with

benzimidazole (**1a**) to afford the desired product **3h** in 61% yield. The scope of azoles was also examined in this reaction. 2-Methyl-1*H*-benzoimidazole **2i** and 5,6-dimethyl-1*H*-benzoimidazole **2j** reacted with sodium *p*-tolylsulfinate smoothly, and gave the corresponding products **3i** and **3j** in 82% and 91% yields, respectivelty. Additionally, triazoles such as benzotriazole **2k** and 1,2,4-triazole **2l** were also tolerated in this reaction leading to the products in moderate to good yields.

Scheme 1. Reactions of various azoles with sodium sulfinates [a]



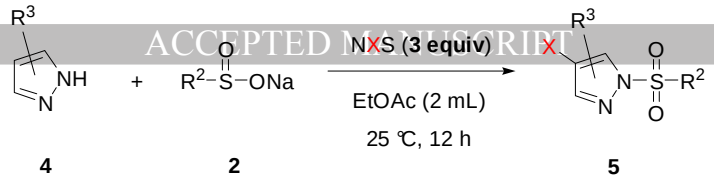
[a] Reaction conditions: **1** 0.5 mmol, **2** 1.0 mmol, oxidant 0.5 mmol, 1,4-dioxane 2 mL, 12 h, under air.

Pyrazoles are essential skeletons of many biologically active organic compounds that have found wide applications in pesticides, medicines, and functional materials.[9] To further explore the potential of this efficient reaction, various pyrazoles were examined as substrates to react with sodium sulfinates (Scheme 2). However, an unexpected compound 4-iodo-1-tosyl-1*H*-pyrazole **5a** was obtained instead of our desired product. Clearly, 4-iodination of pyrazoles was carried out during the N-S bond formation reaction. NIS was

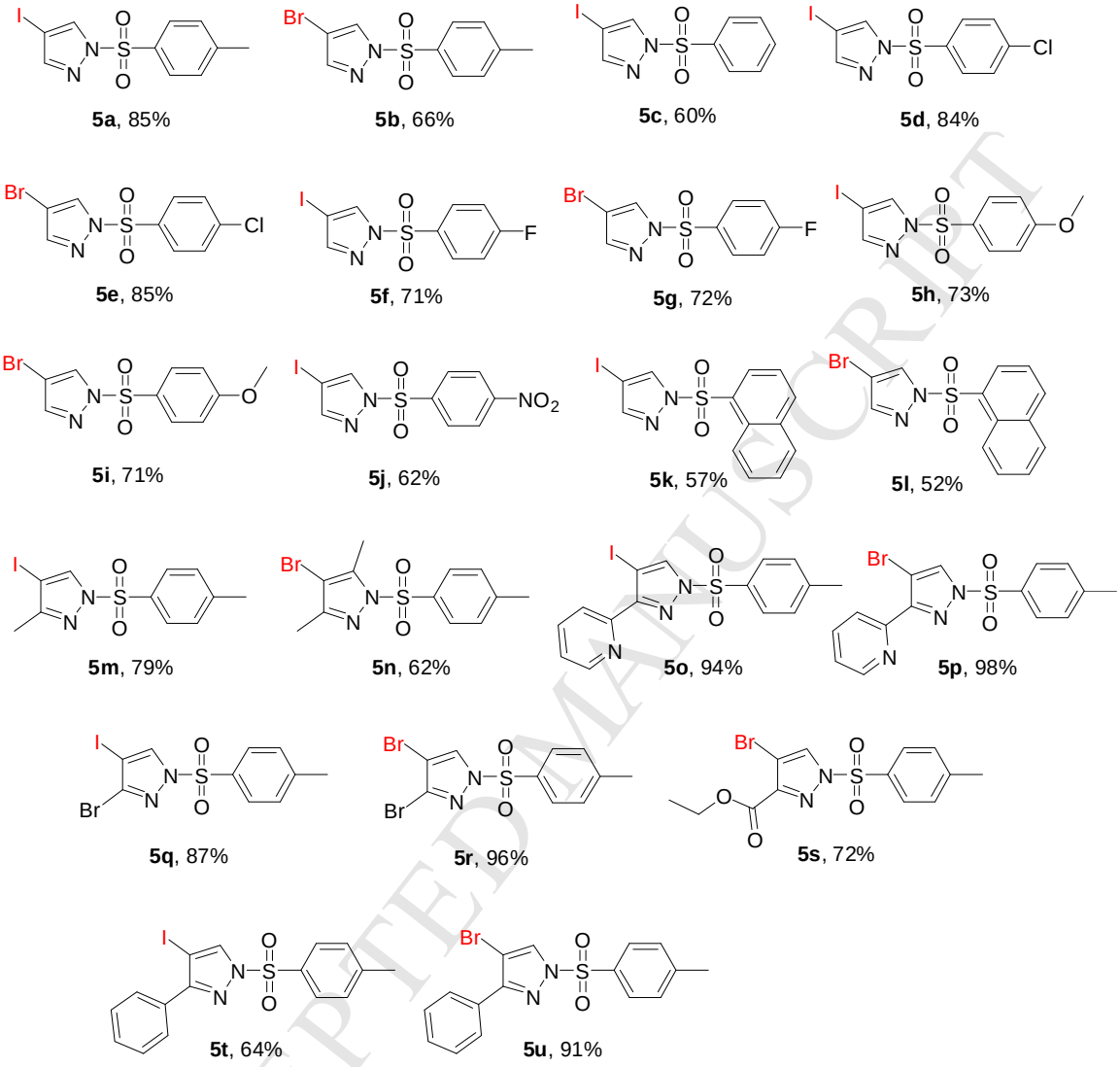
used as both oxidant and iodination reagent. 4-Halopyrazoles, which possess a useful functional handle at the 4-position, represent valuable intermediates toward the syntheses of these targets.[10] A 85% yield of **5a** was obtained when NIS was increased to 3 equiv. NBS was also suitable for this transformation, generating the corresponding bromination product **5b** in 66% yield. In addition to sodium *p*-tolylsulfinate **2a**, various substituted sodium arenesulfinates were all favorable substrates to generate the corresponding halogenation products in moderate to good yields (**5c**-**5j**). Additionally, sodium naphthalene-1-sulfinate was also tolerated in this reaction leading to the iodination and bromination products in moderate yields (**5k** and **5l**).

Subsequently, the scope of pyrazoles was investigated under the standard reaction conditions. 3-Substituted pyrazoles such as 3-Methyl-1*H*-pyrazole, 3-phenyl-1*H*-pyrazole, 3-bromo-1*H*-pyrazole and 2-(1*H*-Pyrazol-3-yl)-pyridine were effective substrates in this transformation furnishing the corresponding products in good yields (**5m**, **5o**, **5p**, **5q**, **5r**, **5t** and **5u**). Pyrazole bearing an electron-withdrawing group gave the corresponding product in 72% yield (**5s**). We further found that substitution was tolerated at both the 3- and 5-positions (**5n**).

Scheme 2. Reactions of pyrazoles with sodium sulfinates [a]



4 + **2** → **5**

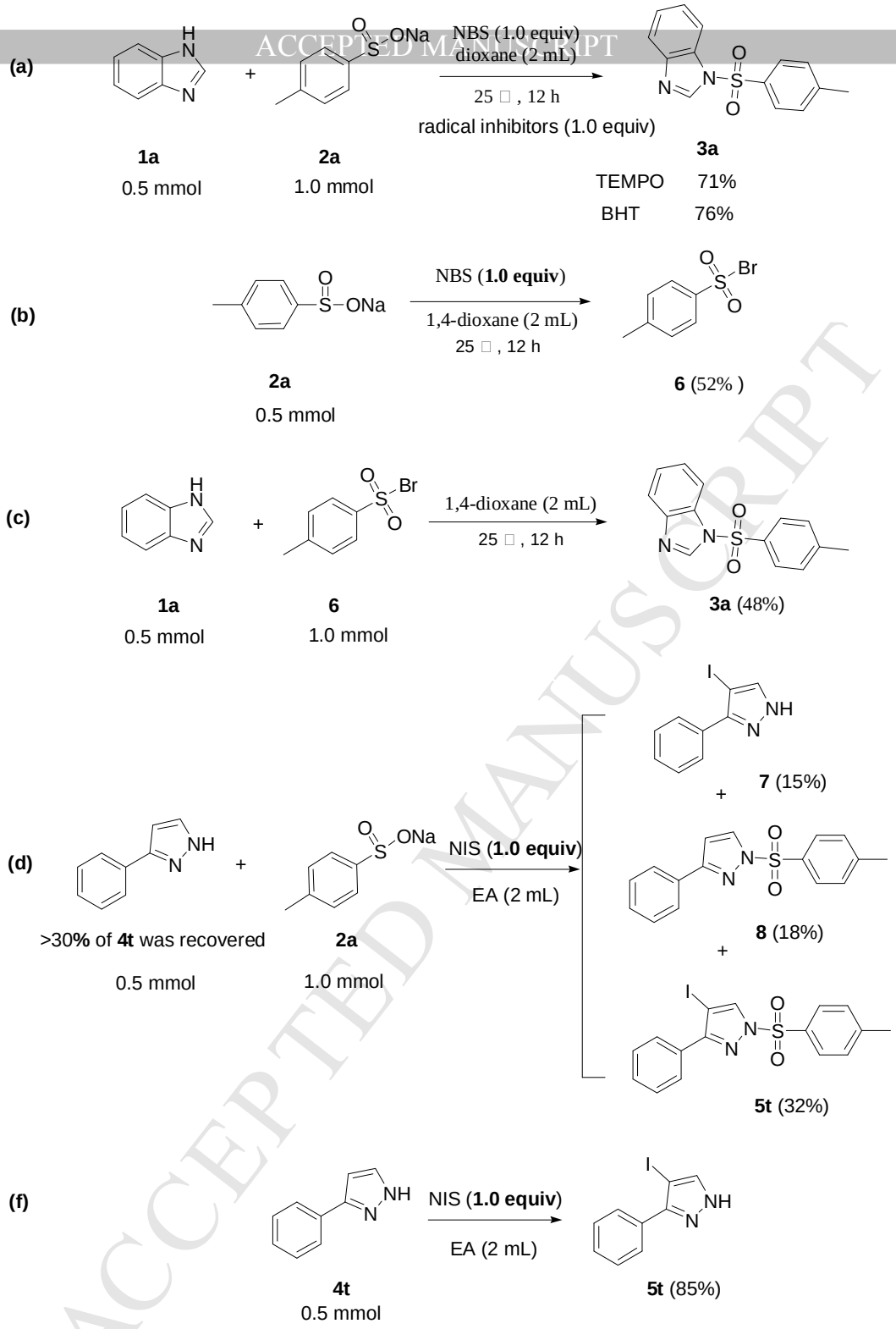


[a] Reaction conditions: **4** 0.5 mmol, **2** 1.0 mmol, oxidant 1.5 mmol, ethyl acetate 2 mL, 12 h, under air.

To investigate the reaction mechanism, several control experiments were conducted. A radical scavenger was added to the reaction system, 71% and 76% of desired product 3aa was obtained in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl) and BHT (2,6-di-tert-butyl-4-methylphenol), respectively (Scheme 3a). Therefore, we think that a radical-based reaction mechanism can be excluded. Treatment of sodium *p*-tolylsulfinate **2a** with 1 equiv of NBS at room temperature gave 4-methyl-benzenesulfonyl bromide **6** in 52% yield (scheme 3b). Further reaction of benzoimidazole **1a** with isolated **6** afforded **4c** in

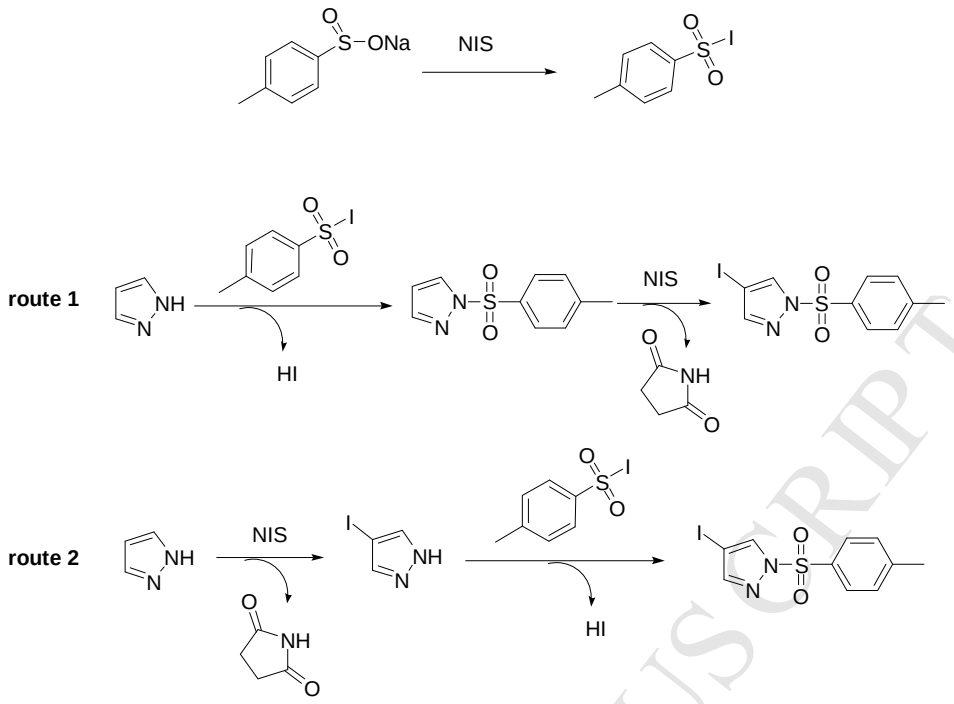
48% yield (scheme 3c). The result implies that sulfonyl bromide is a likely intermediate in the reaction. As we know, NIS or NBS was used both as the catalyst and halogen source. When the reaction of 4t with 2a was carried out in the presence of 1 equiv of NIS, 4-Iodo-3-phenyl-1H-pyrazole **7**, 3-Phenyl-1-(toluene-4-sulfonyl)-1H-pyrazole **8** and 4-Iodo-3-phenyl-1-(toluene-4-sulfonyl)-1H-pyrazole **5t** were obtained in 15%, 18% and 32% yields, respectively (Scheme 3d). Moreover, 3-Phenyl-1H-pyrazole 4t could be converted to the corresponding 4-Iodo-3-phenyl-1H-pyrazole 5t in 85% yield under 1 equiv of NIS (Scheme 3e). These results indicating that the halogenation and sulfonylation occurred simultaneously during the reaction.

Scheme 3. Control experiments



A possible reaction pathway is proposed based on the control experiments. Initially, sodium sulfinate interacted with NIS to generate sulfonyl iodide. Then, nucleophilic reaction of azoles with sulfonyl iodide would form the product. The halogenation could occur before or after the sulfonylation during the reaction (Scheme 4).

Scheme 4. Possible reaction pathway



3. Conclusions

In summary, we have developed a new method of NIS or NBS-mediated direct *N*-sulfonylation of azoles with sodium sulfinates. This protocol provides a simple and green approach for the preparation of sulfonamides derivatives. The optimized method works successfully with diverse ranges of azoles and sodium sulfinates. Moreover, the present method gives a diverse range of 4-Halopyrazoles that can be explored for pharmacological applications and as intermediates in organic synthesis.

4. Experimental Section

4.1. General Procedures.

All of the reagents and solvents were purchased from commercial suppliers and used without further purification. All experiments were carried out under air, and oven-dried glassware was used in all cases. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard or residual nondeuterated solvent peak as an internal standard. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer.

4.2. General procedure for the synthesis of products 3

Azoles **1** (0.5 mmol), sodium sulfinate **2** (1.0 mmol) and NBS (0.5 mmol) were dissolved in 2 mL of 1,4-dioxane solvent. the reaction mixture was stirred at room temperature under air for 12 h. After the reaction, the resulting mixture was extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent was then removed under vacuum. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford the corresponding product.

1-Tosyl-1H-benzo[d]imidazole (3a).[5d] Light yellow oil (126 mg, 93% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.04 (d, J = 7.0 Hz, 2H), 7.88 (d, J = 6.5 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.45~7.38 (m, 4H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 143.5, 142.4, 133.6, 130.6, 130.1, 127.3, 125.6, 124.9, 120.7, 112.4, 21.08.

1-((4-Chlorophenyl)sulfonyl)-1H-benzo[d]imidazole (3b).[11] White solid (124 mg, 85% yield); Mp 122-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 9 Hz, 2H), 7.43~7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 141.7, 141.1, 136.0, 130.6, 130.1, 128.6, 125.8, 125.0, 121.3, 112.4.

1-((4-Fluorophenyl)sulfonyl)-1H-benzo[d]imidazole (3c). White solid (117 mg, 85% yield); Mp 135-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 9.0 Hz, 2H), 7.43~7.38 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 144.1, 141.7, 141.1, 136.0, 130.6, 130.1, 128.6, 125.8, 125.0, 121.3, 112.4; HRMS (ESI): *m/z* calcd for $C_{13}H_9FN_2O_2S$ $[M + H]^+$: 277.0447. Found: 277.0443.

1-(4-Nitro-benzenesulfonyl)-1H-benzoimidazole (3d). Yellow solid (114 mg, 75% yield); Mp 155-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.37 (d, J = 9.0 Hz, 2H), 8.19 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.0 Hz, 2H), 7.46~7.39 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 151.2, 144.1, 142.9, 140.8, 130.5, 128.6, 126.2, 125.5, 125.0, 121.6, 112.2; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_4S$ $[M + H]^+$: 304.0392. Found: 304.0395.

1-(4-Methoxy-benzenesulfonyl)-1H-benzoimidazole (3e).[5d] Colorless oil (127 mg, 88% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.40~7.33 (m, 2H), 6.94 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 144.0, 141.3, 130.7, 129.6, 128.7, 125.5, 124.7, 121.0, 114.9, 112.5, 55.8.

1-(Naphthalene-1-sulfonyl)-1H-benzoimidazole (3f). White solid (100 mg, 65% yield); Mp 137-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 9.0 Hz, 1H), 8.63 (s, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.74~7.72 (m, 1H), 7.68~7.56 (m, 4H), 7.31~7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 141.4, 136.8, 134.3, 132.2, 130.9, 129.5, 127.9, 127.6, 125.5, 124.7, 124.1, 123.1, 121.1, 112.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_2O_2S$ $[M + H]^+$: 309.0698. Found: 309.0691.

1-((2,5-Dichlorothiophen-3-yl)sulfonyl)-1H-benzo[d]imidazole (3g). White solid (125 mg, 75% yield); Mp 122-125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 9.5 Hz, 1H), 7.43~7.41 (m, 2H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 141.3, 133.9, 132.9, 130.6, 128.9, 125.9, 125.8, 125.2, 121.4, 112.3; HRMS (ESI): *m/z* calcd for $C_{11}H_6Cl_2N_2O_2S_2$ $[M + H]^+$: 332.9326. Found: 332.9330.

1-Methanesulfonyl-1H-benzoimidazole (3h).[12] White solid (60 mg, 61% yield); Mp 121-124□; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.86~7.81 (m, 2H), 7.48~7.42 (m, 2H), 3.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 141.0, 130.9, 125.9, 125.1, 121.4, 112.1, 42.3.

2-Methyl-1-tosyl-1H-benzo[d]imidazole (3i).[13] White solid (117 mg, 82% yield); Mp 135-137□; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.0 Hz,1H), 7.36~7.28 (m, 4H), 2.81(s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.4, 146.0, 141.9, 135.5, 133.2, 130.3, 126.8, 124.7, 124.6, 119.7, 113.5, 21.6, 16.9.

5,6-Dimethyl-1-tosyl-1H-benzo[d]imidazole (3j). White solid (137 mg, 91% yiel); Mp 140-144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ8.26 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H) 7.50 (s, 1H), 7.29 (d, J = 8.0 Hz,2H), 2.37(s, 6H), 2.33(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 142.6, 140.5, 135.0, 134.9, 133.9, 130.3, 129.3, 127.1, 121.0, 112.7, 21.6, 20.6, 20.1; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}N_2O_2S$ $[M + H]^+$: 301.1011. Found:301.1023.

1-Tosyl-1H-benzo[d][1,2,3]triazole (3k).[14] White solid (130 mg, 95% yield); Mp 128-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12~8.07 (m, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 145.5, 134.2, 131.7, 130.3, 128.0, 125.8, 120.6, 112.1, 21.7.

1-Tosyl-1H-1,2,4-triazole (3l).[15] White solid (61 mg, 55% yield); Mp 99-102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.02 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 147.2, 144.5, 132.7, 130.4, 128.7, 21.8.

*4.3. General procedure for the synthesis of products **5***

Pyrazoles **4** (0.5 mmol), sodium sulfinate **2** (1.0 mmol) and NBS or NIS (1.5 mmol) were dissolved in 2 mL of EtOAc solvent. the reaction mixture was stirred at room temperature under air for 12 h. After the reaction, the resulting mixture was extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent was then removed under vacuum. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford the corresponding product.

4-Iodo-1-(toluene-4-sulfonyl)-1H-pyrazole (5a).[16] White solid (148 mg, 85% yield); Mp 85-87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.89 (d, J = 7.0 Hz, 2H), 7.68 (s, 1H), 7.34 (d, J = 7Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 146.5, 134.9, 133.6, 130.3, 128.5, 61.3, 21.9; HRMS (ESI): *m/z* calcd for $C_{10}H_9IN_2O_2S$ $[M + Na]^+$: 370.9327. Found: 370.9316.

4-Bromo-1-(toluene-4-sulfonyl)-1H-pyrazole (5b).[17] White solid (99 mg, 66% yield); Mp 109-111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.65 (s, 1H), 7.35 (d, J = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.4, 145.6, 133.5, 130.4, 130.2, 128.4, 97.4, 21.7; HRMS (ESI): *m/z* calcd for $C_{10}H_9BrN_2O_2S$ $[M + Na]^+$: 322.9466. Found: 322.9462.

4-Iodo-1-(phenylsulfonyl)-1H-pyrazole (5c). White solid (100 mg, 60% yield); Mp 125-128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.70~7.66 (m, 2H), 7.563 (t, J = 8Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 136.6, 134.9, 134.8, 129.5, 128.3, 61.3; HRMS (ESI): *m/z* calcd for $C_9H_7IN_2O_2S$ $[M + H]^+$: 334.9351. Found: 334.9343.

1-((4-Chlorophenyl)sulfonyl)-4-iodo-1H-pyrazole (5d). White solid (155 mg, 84% yield); Mp 120-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.71 (s, 1H), 7.53 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 141.9, 134.9, 134.8, 129.9, 129.7, 61.6; HRMS (ESI): *m/z* calcd for $C_9H_6ClIN_2O_2S$ $[M + H]^+$: 368.8961. Found: 368.8960.

4-Bromo-1-((4-chlorophenyl)sulfonyl)-1H-pyrazole (5e). White solid (136 mg, 85% yield); Mp 117-119°C; ^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.11 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.68 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 142.0, 134.9, 130.5, 129.7, 129.7, 97.9; HRMS (ESI): *m/z* calcd for $C_9H_6BrClN_2O_2S$ $[M + H]^+$: 320.9100. Found: 320.9091.

1-((4-Fluorophenyl)sulfonyl)-4-iodo-1H-pyrazole (5f). White solid (125 mg, 71% yield); Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.07~8.04 (m, 2H), 7.71 (s, 1H), 7.26~7.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5 (d, $J_{C\text{-}F}$ = 258.6 Hz), 150.0, 134.8, 132.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 131.4 (d, $J_{C\text{-}F}$

= 9.9 Hz), 117.0 (d, J_{C-F} = 23.4 Hz), 61.4; HRMS (ESI): *m/z* calcd for $C_9H_6FIN_2O_2S$ $[M + H]^+$: 352.9257. Found: 352.9258.

4-Bromo-1-((4-fluorophenyl)sulfonyl)-1H-pyrazole (5g). White solid (109 mg, 72% yield); Mp 106-107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.07~8.04 (m, 2H), 7.68 (s, 1H), 7.26~7.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5 (d, J_{C-F} = 257.9 Hz), 146.0, 132.4 (d, J_{C-F} = 3.6 Hz), 131.4 (d, J_{C-F} = 9.9 Hz), 130.5, 117.0 (d, J_{C-F} = 23.3 Hz), 97.8; HRMS (ESI): *m/z* calcd for $C_9H_6BrFN_2O_2S$ $[M + H]^+$: 304.9396. Found: 304.9408.

4-Iodo-1-(4-methoxy-benzenesulfonyl)-1H-pyrazole (5h). Yellow oil (133 mg, 73% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.68 (s, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 149.5, 134.6, 130.8, 127.5, 114.8, 60.9, 55.9; HRMS (ESI): *m/z* calcd for $C_{10}H_9IN_2O_3S$ $[M + H]^+$: 364.9457. Found: 364.9458.

4-Bromo-1-(4-methoxy-benzenesulfonyl)-1H-pyrazole (5i). Colorless oil (112 mg, 71% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.65 (s, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 145.4, 130.8, 130.3, 127.4, 114.8, 97.2, 55.9; HRMS (ESI): *m/z* calcd for $C_{10}H_9BrN_2O_3S$ $[M + H]^+$: 316.9595. Found: 316.9587.

4-Iodo-1-(4-nitro-benzenesulfonyl)-1H-pyrazole (5j). Yellow solid (117 mg, 62% yield); Mp 125-128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 9.0 Hz, 2H), 8.18 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 150.8, 141.9, 135.1, 129.8, 124.7, 62.5; HRMS (ESI): *m/z* calcd for $C_9H_6IN_3O_4S$ $[M + H]^+$: 379.9202. Found: 379.9208.

4-Iodo-1-(naphthalene-1-sulfonyl)-1H-pyrazole (5k). White solid (109 mg, 57% yield); Mp 165-168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (d, J = 8.5 Hz, 1H), 8.52 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.5 Hz, 1H), 7.62-7.59 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3, 137.0, 134.7, 134.2, 131.5, 129.3, 129.2, 128.3, 127.5, 124.3, 124.1, 61.1; HRMS (ESI): *m/z* calcd for $C_{13}H_9IN_2O_2S$ $[M + H]^+$: 384.9508. Found: 384.9513.

4-Bromo-1-(naphthalene-1-sulfonyl)-1H-pyrazole (5l). Yellow oil (87 mg, 52% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 8.5 Hz, 2H), 8.26 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.5 Hz, 1H), 7.64-7.60 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 137.0, 134.2, 132.0, 131.5, 130.4, 129.3, 129.3, 128.3, 127.5, 124.3, 124.1, 97.4; HRMS (ESI): *m/z* calcd for $C_{13}H_9BrN_2O_2S$ $[M + H]^+$: 336.9646. Found: 336.9635.

4-Iodo-3-methyl-1-tosyl-1H-pyrazole (5m). White solid (143 mg, 79% yield); Mp 97-100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.0, 146.0, 135.6, 130.1, 128.2, 65.8, 21.7, 14.0; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}IN_2O_2S$ $[M + H]^+$: 362.9664. Found: 362.9660.

4-Bromo-3,5-dimethyl-1-tosyl-1H-pyrazole (5n).[18] White solid (102 mg, 62% yield); Mp 127-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.42 (s, 3H) , 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 145.6, 141.1, 134.9, 130.0, 127.8, 100.9, 21.7, 12.8, 12.2; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}BrN_2O_2S$ $[M + H]^+$: 328.9959. Found: 328.9960.

2-(4-Iodo-1-tosyl-1H-pyrazol-3-yl)pyridine (5o). White solid (200 mg, 94% yield); Mp 120-124°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, J = 4.5 Hz, 1H), 8.25 (s, 1H) , 7.94~7.91 (m, 3H) , 7.75 (t, J = 7.5 Hz ,1H) , 7.34~7.30 (m,3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 150.2, 148.9, 146.3, 137.6, 136.6, 133.6, 130.2, 128.4, 123.8, 122.9, 60.9, 21.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}IN_3O_2S$ $[M + H]^+$: 425.9773. Found: 425.9771.

2-(4-Bromo-1-tosyl-1H-pyrazol-3-yl)pyridine (5p). White solid (185 mg, 98% yield); Mp 104-107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72~8.71 (m, 1H), 8.22 (s, 1H) , 7.94~7.91 (m, 3H) , 7.78~7.74 (m, 1H), 7.33~7.30 (m,3H), 2.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 149.6, 149.2, 146.5, 136.8, 133.3, 132.3, 130.2, 128.4, 123.9, 123.2, 96.9, 21,7; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}BrN_3O_2S$ $[M + H]^+$: 377.9912. Found: 377.9920.

3-Bromo-4-iodo-1-tosyl-1H-pyrazole (5q). White solid (185 mg, 87% yield); Mp 134-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 139.4, 136.6, 132.9, 130.3, 128.6, 68.7, 21.8; HRMS (ESI): *m/z* calcd for $C_{10}H_8BrIN_2O_2S$ $[M + H]^+$: 426.8613. Found: 426.8617.

3,4-Dibromo-1-tosyl-1H-pyrazole (5r).[19] White solid (181 mg, 96% yield); Mp 116-119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 135.2, 132.9, 131.8, 130.3, 128.6, 101.4, 21.8; HRMS (ESI): *m/z* calcd for $C_{10}H_8Br_2N_2O_2S$ $[M + Na]^+$: 400.8571. Found: 400.8562.

Ethyl 4-bromo-1-tosyl-1H-pyrazole-3-carboxylate (5s). White solid (134 mg, 72% yield); Mp 108-111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz ,2H), 4.39 (q, J = 7.0 Hz, 2H), 2.44 (s, 3H), 1.38 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 147.0, 145.4,

132.7, 132.5, 130.4, 128.7, 98.6, 61.9, 21.8, 14.2; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}BrN_2O_4S$ $[M + H]^+$: 372.9858. Found: 372.9875.

4-Iodo-3-phenyl-1-tosyl-1H-pyrazole (5t). White solid (136 mg, 64% yield); Mp 139-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.42~7.41 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 146.2, 137.0, 133.7, 131.0, 130.1, 129.3, 128.5, 128.4, 128.3, 62.0, 21.7; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}IN_2O_2S$ $[M + Na]^+$: 446.9640. Found: 446.9645.

4-Bromo-3-phenyl-1-tosyl-1H-pyrazole (5u).[18] White solid (184 mg, 98% yield); Mp 97-100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.85~7.84 (m, 2H), 7.42~7.40 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 146.3, 133.6, 132.3, 130.2, 130.1, 129.4, 128.7, 128.4, 128.3, 128.2, 96.7, 21.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}BrN_2O_2S$ $[M + H]^+$: 376.9959. Found: 376.9961.

4-Methyl-benzenesulfonyl bromide (6).[20] White solid (115 mg, 98% yield); Mp 94-97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 144.7, 130.1, 126.5, 21.8;

4-Iodo-3-phenyl-1H-pyrazole (7). White solid (20 mg, 15% yield); Mp 135-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (br, 1H), 7.71 (dd, J_1= 8.0 Hz, J_2= 1.5 Hz, 2H), 7.58 (s, 1H), 7.47~7.42 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5, 141.6, 130.3, 130.0, 128.7, 128.0, 57.2; HRMS (ESI): *m/z* calcd for $C_9H_7IN_2$ $[M + H]^+$: 270.9654. Found: 270.9652.

3-Phenyl-1-(toluene-4-sulfonyl)-1H-pyrazole (8).[21] White solid (27 mg, 18% yield); Mp 130-133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 2.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.39~7.31 (m, 5H), 6.69 (d, J = 2.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 145.7, 134.3, 132.5, 131.5, 130.0, 129.2, 128.6, 128.2, 126.4, 106.4, 21.7;

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