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Addition of Diazo Compounds *ipso*-C–H bond to Carbon Disulfide: Synthesis of 1,2,3-Thiadiazoles Under Mild Conditions

Lei Zhang, Beiqi Sun, Qianyi Liu and Fanyang Mo*

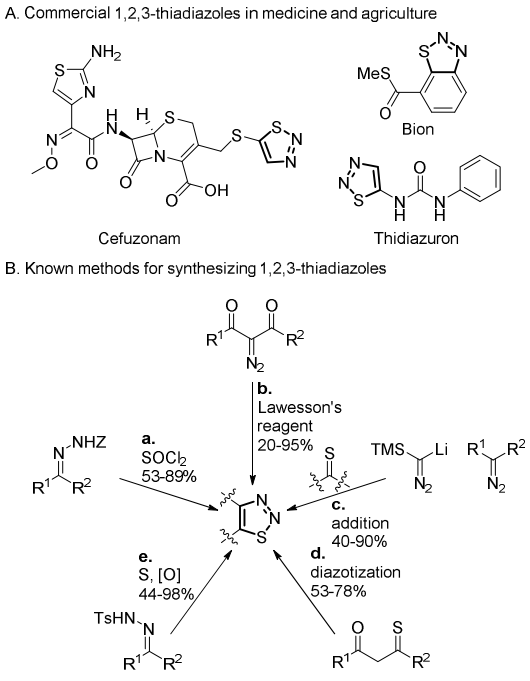
[†]Department of Energy and Resources Engineering, College of Engineering, Peking University, Beijing 100871, China.

Supporting Information Placeholder

ABSTRACT: We describe here an operationally simple and straightforward synthesis method for a series of diverse 4,5-disubstituted 1,2,3-thiadiazoles via the nucleophilic addition of α-diazo carbonyl compounds to carbon disulfide. This method features using abundant and inexpensive carbon disulfide with mild reaction conditions.

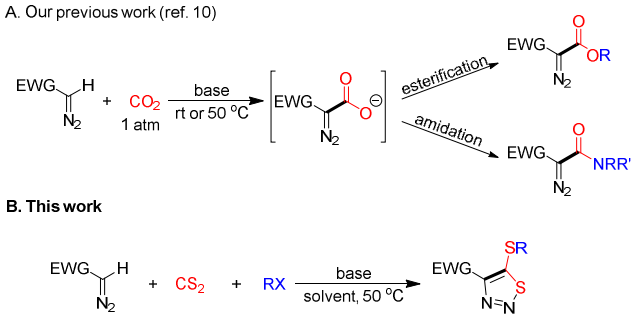
1,2,3-thiadiazoles[1] are versatile heterocycles present in various pharmaceutical molecules.[2] Due to their biological activities, many derivatives of 1,2,3-thiadiazole are important in industry, medicine and agriculture (Scheme 1A).[3] To date, the known methods for synthesizing 1,2,3-thiadiazoles can be summarized as shown in Scheme 1B: a) cyclization of hydrazones with thionyl chloride (Hurd-Mori synthesis);[4] b) treatment of α-diazo carbonyl compounds with Lawesson's reagent (Wolff synthesis);[5] c) addition of diazomethane (Pechmann synthesis)[6] or lithium (trimethylsilyl)diazomethane[7] to thiocarbonyl compounds; d) diazotization of α-enolicdithioesters;[8] and e) oxidative cyclization of *N*-tosylhydrazones and sulfur.[9] Although these techniques are frequently used, the synthesis of 1,2,3-thiadiazoles remains an active research area.

Scheme 1. Introduction of 1,2,3-Thiadiazoles



Recently, we have reported transition-metal-free diazo compounds *ipso*-C–H bond addition to carbon dioxide (CO_2) under very mild reaction conditions with the diazo group retained.[10] The resulting α-diazo carboxylate intermediate is readily converted to esters and amides in a one-pot manner (Scheme 2A). CO_2 is a greenhouse gas that has been attracting much attention as an inexpensive, nontoxic, nonflammable, renewable and abundant C1 building block for organic synthesis.[11] Meanwhile, carbon disulfide (CS_2), an analogue of CO_2, has long been used as a sulfur source for a variety of useful chemicals for agricultural, medicinal, and pharmaceutical applications.[12] As an extension of our previous work, here we report on diazo compound *ipso*-C–H bond addition to CS_2 for the synthesis of 1,2,3-thiadiazoles under mild conditions (Scheme 2B).

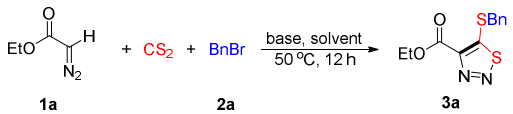
Scheme 2. Diazo Compound *ipso*-C–H Bond Addition to CO_2 and CS_2



To probe the feasibility of the nucleophilic addition of the diazo group to CS_2, we initiated our studies with ethyl diazoacetate (EDA) **1a** and benzyl bromide (BnBr) **2a** as the standard substrates. Various organic and inorganic bases were examined in the initial studies. As shown in Table 1, with Cs_2CO_3 as the base, the desired product ethyl 5-(benzylthio)-1,2,3-thiadiazole-4-carboxylate **3a** was obtained with 38% NMR yield (entry 1). CsF and KO^{t}Bu turned out to be less effective in this transformation (entries 2 and 3) and organic bases, such as DBU and Et_3N, were inactive (entries 4 and 5).

This suggested that bases with proper basicity might be a key issue for the desired transformation. Indeed, the yield was slightly improved with the use of KOH as the base (entry 6). **3a** was then obtained with 73% yield by switching the solvent from MeCN to DMF (entry 7). Other solvents, such as DMSO, THF and 1,4-dioxane, were less efficient (entries 8-10). Finally, an improved yield (81%) was obtained by using 2.0 equivalent of CS_2 (entry 11). The yield was not further improved by increasing the equivalency of CS_2 to 5.0 (entry 12). However, the product **3a** was not very stable during handling and the isolated yield diminished to about 10% compared with the NMR yield.

Table 1. Selected Optimization of Reaction Conditions[a]



1a 2a 3a

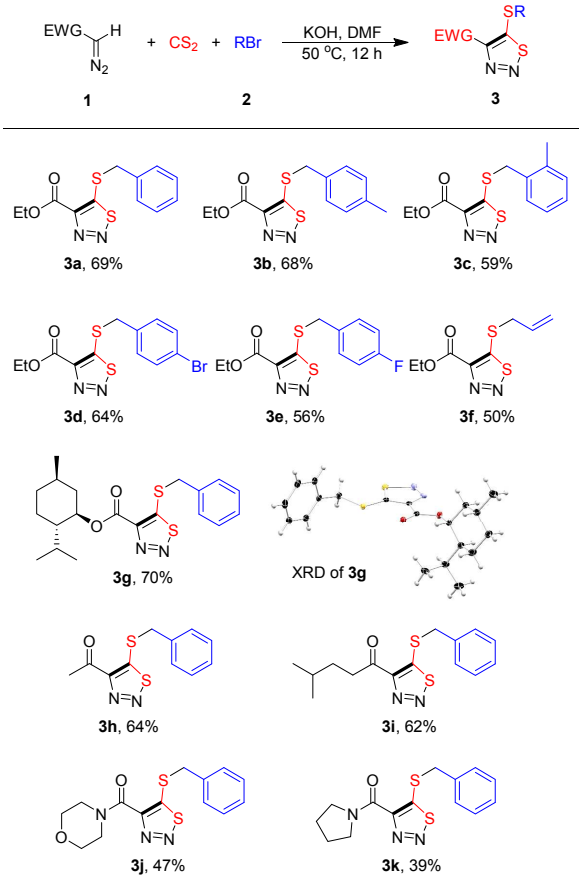
entry	base	solvent	equivalency of CS_2	yield (%)[b]
1	Cs_2CO_3	MeCN	1.5	38
2	CsF	MeCN	1.5	17
3	KO^{t}Bu	MeCN	1.5	20
4	DBU	MeCN	1.5	trace
5	Et_3N	MeCN	1.5	n. d.
6	KOH	MeCN	1.5	41
7	KOH	DMF	1.5	73
8	KOH	DMSO	1.5	36
9	KOH	THF	1.5	12
10	KOH	1,4-Dioxane	1.5	8
11	KOH	DMF	2.0	81 (69[c])
12	KOH	DMF	5.0	78

[a] Reaction conditions: EDA (0.5 mmol), BnBr (1.5 equiv), base (1.2 equiv), solvent (2 mL), reaction time 12 h, temperature 50 °C, sealed. n. d., not detected. [b] Yields were determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane used as internal standard. [c] Isolated yield.

After obtaining the optimal yield for **3a**, we next conducted substrate scope studies with the results shown in Table 2. Various benzyl bromides were evaluated with various substituent groups for this reaction. Both *para*- and *ortho*- substituents (**3b**-**3e**) on benzyl bromides were tolerated, giving good yields. Additionally, allyl bromide (**3f**) was also a good reagent to facilitate the construction of 1,2,3-thiadiazoles. To further demonstrate the expansibility of this methodology, various α-diazo carbonyl compounds were synthesized and tested using this transformation. In general, all these types of diazo substrates were suitable for the reaction with the products obtained with moderate to good yields. Menthyl diazoacetate was converted to 1,2,3-thiadiazole (**3g**) with 70% yield. XRD data was obtained for **3g**. Furthermore, α-diazo alkyl ketones (**3h** and **3i**) also worked well, while α-diazo amides (**3j** and **3k**) gave relatively low yields.

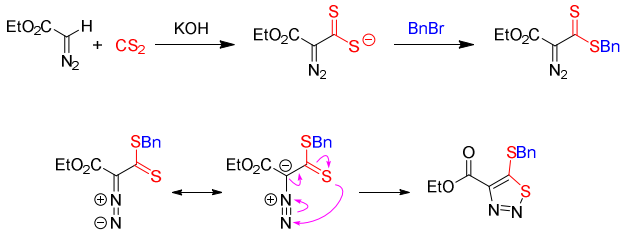
Compared with the known methods shown in Scheme 1B, our synthetic strategy is more close to the catalog c: addition of diazo compounds to C=S double bond. In reference 7, Aoyama suggested a nucleophilic addition/cyclization mechanism for the conversion of lithium (trimethylsilyl)diazomethane and carbon disulfide to the 1,2,3-thiadiazole product. Meanwhile, as a good electrophile, carbon disulfide has ready reactivity with a variety of nucleophiles, ranging from carbon-centered nucleophiles (e. g. Grignard reagents) to oxygen-centered nucleophiles (e. g. alkoxy) and amines.[12c] Based on the above, we proposed that our reaction mechanism is also a normal deprotonation-nucleophilic addition/cyclization process (Scheme 3).

Table 2. Substrates Scope[a]



[a] Reaction conditions: diazo compound (0.5 mmol), RBr (1.5 equiv), KOH (1.2 equiv), solvent (2 mL), reaction time 12 h, temperature 50 °C, sealed.

Scheme 3. Proposed Reaction Pathway



In summary, we have developed an operationally simple method for the synthesis of 4,5-disubstituted 1,2,3-thiadiazoles via the nucleophilic addition of α-diazo carbonyl compounds to carbon disulfide. This method can be applied as an alternative to traditional synthesis methods of 1,2,3-thiadiazoles with carbon disulfide as the C1 building block with mild reaction conditions.

EXPERIMENTAL SECTION

General Information. All the solvents were purchased from ENERGY CHEMICAL and kept dry by molecular sieves. The products were purified by column chromatography on silica gel (300-400 mesh, from Qingdao, China). NMR spectra were measured on a Bruker ARX400 (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 377 MHz) magnetic resonance spectrometer. The chemical shifts (δ) are reported as ppm using tetramethylsilane as the internal standard (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet) while the coupling constants (*J*) were reported in Hertz (Hz). Infrared spectra were recorded on a Thermal Fisher Nicolet iS50 Fourier transform spectrometer (FT-IR) and were reported as wave numbers (cm^{-1}). The HRMS data was obtained on a VG ZAB-HS mass spectrometer and a Brucker Apex IV FTMS spectrometer. The diazo starting materials were synthesized in the lab. For details, see Supporting Information.

General procedure for the synthesis of 1,2,3-thiadiazoles. In a glove box, charge a 4 mL vial equipped with a stir bar with potassium hydroxide (0.6 mmol, 1.2 equiv), dimethyl formamide (2 mL), the diazo compound (0.5 mmol), carbon disulfide (1.0 mmol, 2.0 equiv), bromide (0.75 mmol, 1.5 equiv) in succession. Then, seal the vial and stir the mixture at 50 °C for 12 h. Then, wash the reaction mixture with 20 mL ethyl acetate and water (3×20 mL). Separate the organic layer and dry over Na_2SO_4. After removal of the solvent, purify the residue by column chromatography (silica gel) to afford the desired product.

*Ethyl 5-(benzylthio)-1,2,3-thiadiazole-4-carboxylate(**3a**)*.[13] Yellowish-green solid, yield 78% (110 mg); mp = 83-84 °C; R_f = 0.25 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.30 (m, 5H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.26 (s, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 160.8, 146.4, 133.6, 129.14, 129.08, 128.6, 62.1, 42.3, 14.4.

*Ethyl 5-((4-methylbenzyl)thio)-1,2,3-thiadiazole-4-carboxylate (**3b**)*. White solid, yield 68% (100 mg); mp = 93-94 °C; R_f = 0.25 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.23 (s, 2H), 2.35 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.8, 146.4, 138.6, 130.5, 129.8, 129.0, 62.1, 42.1, 21.2, 14.4. IR (film) 2984, 2921, 1732, 1701, 1439, 1309, 1271, 1209, 1065, 1021, 842. HRMS (ESI): calcd for $C_{13}H_{15}N_2O_2S_2^+$ $[M+H]^+$: 295.0569; found: 295.0563.

*Ethyl 5-((2-methylbenzyl)thio)-1,2,3-thiadiazole-4-carboxylate (**3c**)*. White solid, yield 59% (87 mg); mp = 90-91 °C; R_f = 0.25 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 4H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.25 (s, 2H), 2.43 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 160.8, 146.2, 137.2, 131.6, 131.0, 130.0, 129.0, 126.6, 62.1, 41.0, 19.3, 14.4. IR (film) 2980, 2932, 1730, 1701, 1439, 1310, 1272, 1209, 1065, 1020, 842, 780. HRMS (ESI): calcd for $C_{13}H_{15}N_2O_2S_2^+$ $[M+H]^+$: 295.0569; found: 295.0562.

*Ethyl 5-((4-bromobenzyl)thio)-1,2,3-thiadiazole-4-carboxylate (**3d**)*. White solid, yield 64% (115 mg); mp = 93-94 °C; R_f = 0.20 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.21 (s, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.7, 146.5, 132.7, 132.3, 130.7, 122.8, 62.2, 41.6, 14.3. IR (film) 2984, 1730, 1700, 1487, 1440, 1310, 1271, 1210, 1066, 1012, 842, 780. HRMS (ESI): calcd for $C_{12}H_{12}BrN_2O_2S_2^+$ $[M+H]^+$: 358.9518; found: 358.9512.

*Ethyl 5-((4-fluorobenzyl)thio)-1,2,3-thiadiazole-4-carboxylate (**3e**)*. White solid, yield 56% (84 mg); mp = 63-64 °C; R_f = 0.20 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.06 (t, *J* = 8.5 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.24 (s, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (d, *J* = 2.1 Hz), 161.5, 160.8, 146.4, 130.9 (d, *J* = 8.4 Hz), 129.4 (d, *J* = 3.3 Hz), 116.2, 116.0, 62.2, 41.6, 14.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.5 – -112.6 (m). IR (film) 2984, 1730, 1700, 1508, 1439, 1310, 1271, 1210, 1159, 1064, 1017, 842, 780. HRMS (ESI): calcd for $C_{12}H_{12}FN_2O_2S_2^+$ $[M+H]^+$: 299.0319; found: 299.0311.

*Ethyl 5-(allylthio)-1,2,3-thiadiazole-4-carboxylate (**3f**)*. Yellow oil, yield 50% (58 mg); R_f = 0.25 (petroleum ether: EtOAc = 10:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.50 (dd, *J* = 17.0, 0.7 Hz, 1H), 5.38 (d, *J* = 10.1 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 3.71 (d, *J* = 6.7 H z, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.8, 146.7, 129.9, 121.7, 62.1, 40.6, 14.4. IR (film) 2984, 1730, 1701, 1438, 1307, 1271, 1207, 1063, 1020, 930, 842. HRMS (ESI): calcd for $C_8H_{11}N_2O_2S_2^+$ $[M+H]^+$: 231.0256; found: 231.0254.

*(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 5-(benzylthio)-1,2,3-thiadiazole-4-carboxylate (**3g**)*. White solid, yield 70% (136 mg); mp = 102-103 °C; R_f = 0.30 (petroleum ether: EtOAc = 20:1); petroleum ether: EtOAc = 100:1 ~ 50:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 5H), 5.08 – 5.01 (m, 1H), 4.25 (s, 2H), 2.23 – 2.11 (m, 1H), 2.07-2.00 (m, 1H), 1.80 – 1.48 (m, 4H), 1.23 (dd, *J* = 23.2, 12.0 Hz, 1H), 1.18-1.07 (m, 1H), 0.92 (dd, *J* = 10.8, 6.8 Hz, 6H), 0.80 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 160.4, 146.7, 133.7, 129.1, 129.1, 128.6, 76.5, 46.8, 42.4, 40.8, 34.1, 31.6, 26.2, 23.4, 22.0, 20.8, 16.3. IR (film) 2954, 2926, 2869, 1729, 1698, 1436, 1311, 1272, 1214, 1064, 980, 837, 704. HRMS (ESI): calcd for $C_{20}H_{27}N_2O_2S_2^+$ $[M+H]^+$: 391.1508; found: 391.1502.

*1-(5-(Benzylthio)-1,2,3-thiadiazol-4-yl)ethan-1-one (**3h**)*. Yellow solid, yield 64% (80 mg); mp = 100-101 °C; R_f = 0.20 (petroleum ether: EtOAc = 20:1); petroleum ether: EtOAc = 100:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 m, 5H), 4.23 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 164.1, 154.0, 133.6, 129.2, 129.1, 128.6, 42.8, 28.8. IR (film) 3063, 3032, 2915, 1672, 1413, 1273, 1175, 1066, 910, 790, 705, 604. HRMS (ESI): calcd for $C_{11}H_{11}N_2OS_2^+$ $[M+H]^+$: 251.0307; found: 251.0308.

*1-(5-(Benzylthio)-1,2,3-thiadiazol-4-yl)-4-methylpentan-1-one (**3i**)*. Yellow oil, yield 62% (95 mg); R_f = 0.20 (petroleum ether: EtOAc = 40:1); petroleum ether: EtOAc = 100:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 5H), 4.23 (s, 2H), 3.28 (t, *J* = 7.2 Hz 2H), 1.68 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 164.0, 153.7, 133.7, 129.2, 129.0, 128.6, 42.7, 39.3, 32.9, 27.8, 22.4. IR

(film) 2954, 2927, 2867, 1669, 1495, 1414, 1271, 1139, 1112, 1044, 1026, 908, 703. HRMS (ESI): calcd. $C_{15}H_{18}N_2NaOS_2^+$ $[M+Na]^+$: 329.0753. Found: 329.0753.

*(5-(Benzylthio)-1,2,3-thiadiazol-4-yl)(morpholino)methanone (**3j**)*. White solid, yield 47% (75 mg); mp = 96-97 °C; R_f = 0.50 (petroleum ether: EtOAc = 1:1); petroleum ether: EtOAc = 10:1 ~ 5:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 4.23 (s, 2H), 4.08 (s, 2H), 3.79 (m, *J* = 25.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.2, 150.1, 134.2, 129.2, 129.0, 128.5, 67.2, 66.9, 48.0, 43.3, 42.2. IR (film) 2964, 2913, 2859, 1616, 1472, 1443, 1302, 1269, 1218, 1114, 1076, 1030, 968, 705. HRMS (ESI): calcd for $C_{14}H_{16}N_3O_2S_2^+$ $[M+H]^+$: 322.0678; found: 322.0671.

*(5-(Benzylthio)-1,2,3-thiadiazol-4-yl)(pyrrolidin-1-yl)methanone (**3k**)*. White solid, yield 39% (60 mg); mp = 124-125 °C; R_f = 0.60 (petroleum ether: EtOAc = 1:1); petroleum ether: EtOAc = 10:1 ~ 5:1 as eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.38 – 7.28 (m, 3H), 4.21 (s, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.72 (t, *J* = 6.7 Hz, 2H), 2.08 – 1.85 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 159.8, 150.6, 134.3, 129.2, 128.9, 128.3, 49.4, 47.2, 42.3, 26.6, 23.9. IR (film) 2970, 2875, 1610, 1468, 1454, 1374, 1256, 1079, 843, 710. HRMS (ESI): calcd for $C_{14}H_{16}N_3OS_2^+$ $[M+H]^+$: 306.0729; found: 306.0729.

ASSOCIATED CONTENT

Supporting Information

Preparation of substrates, NMR spectra, and X-ray single crystal structure of compound **3g**.

AUTHOR INFORMATION

Corresponding Author

*Email: fmo@pku.edu.cn

Notes

The authors declare no competing financial interest.

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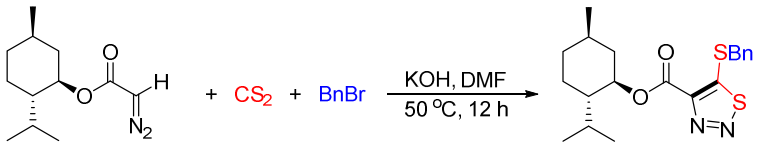

- ✔ A new strategy to construct 1,2,3-thiadiazole motifs
- ✔ Carbon disulphide as sulfur source
- ✔ Simple operation
- ✔ Mild temperature