Supporting Information

Multicomponent Coupling Reactions of Two *N*-Tosyl Hydrazones and Elemental Sulfur: Selective Denitrogenation Pathway toward Unsymmetric 2,5-Disubstituted 1,3,4-Thiadiazoles

Zhen Zhou, Yang Liu, Jiangfei Chen, En Yao, and Jiang Cheng*

School of Petrochemical Engineering, Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Jiangsu Province Key Laboratory of Fine Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China.

jiangcheng@cczu.edu.cn

Table of Contents

1. General Considerations

Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a 300 or 400 MHz NMR spectrometer (75 or 100 MHz for ^{13}C). NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants J are given in Hz. High-resolution mass spectra (HRMS) were obtained using a Bruker micro-TOF II focus spectrometer (ESI). IR spectra were recorded on a spectrometer using KBr discs. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

2. Synthesis and Reaction

2.1 General procedure for the preparation of *N*-tosylhydrazones

Substrates 2a-2j, 1b-1e and 1i, were synthesized according to Method A:[1]

Method A:

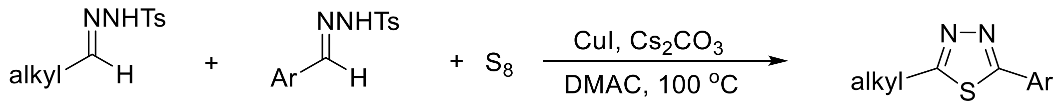
A solution of pure 4-methyl-benzenesulfonohydrazide (5 mmol) in methanol (5 mL) was stirred and heated to 60 ^{o}C until the 4-methyl-benzenesulfonohydrazide was completely dissolved. Then carbonyl compounds (5 mmol) were dropped to the mixture slowly. After approximately 5-30 min., the crude products were obtained as precipitates. The precipitates were washed by petroleum ether then were dried *in vacuo* to afford the pure product.

Substrates 1a, 1f, 1g and 1h were synthesized according to Method B:[2]

Method B:

A solution of pure 4-methyl-benzenesulfonohydrazide (25 mmol) in methanol (10 mL) was stirred and heated to 60 ^{o}C until the 4-methyl-benzenesulfonohydrazide was completely dissolved. Then the reaction mixture was cooled to 0 ^{o}C. Subsequently, carbonyl compounds (25 mmol) were dropped to the mixture slowly. After approximately 30 min, 10 mL of water was added. The crude products were obtained as precipitates. The precipitates were washed by petroleum ether then were dried *in vacuo* to afford the pure products.

2.2 General procedure for the preparation of thiadiazoles

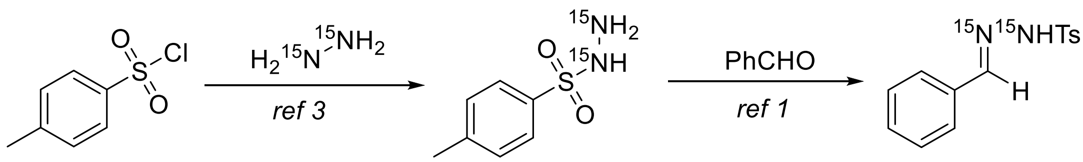


Scheme S1. Standard procedure of the synthesis of thiadiazoles

A 20 mL of Schlenk tube equipped with a stir bar was charged with alkyl aldehyde *N*-tosyl hydrazones (0.12 mmol), aryl aldehyde *N*-tosyl hydrazones (0.1 mmol), S_8 (0.0625 mmol), Cs_2CO_3 (0.2 mmol), CuI (3.8 mg, 20 mol %). The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 ℃ for 12 h in oil bath. Then the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc as the eluent to give the desired product.

3. Mechanism Study

3.1 General procedure for the preparation of ^{15}N-benzaldehyde *N*-tosyl hydrazone (Scheme S2)



Scheme S2. Synthesis of ^{15}N-benzaldehyde *N*-tosyl hydrazine

Preparation of ^{15}N-4-methyl-benzenesulfonohydrazide:[3]

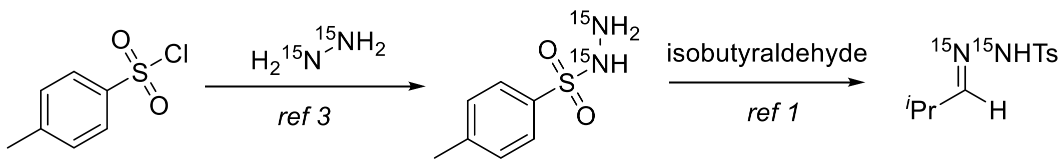
A water (0.9 mL) solution of ^{15}N-hydrazine hydrate (37.5 mg; 0.75 mmol) was cooled in ice-water bath to ~ 5 ^{o}C. The temperature was then maintained below 8 ^{o}C, while the tetrahydrofuran (0.75 mL) solution of 4-methyl-benzenesulfonyl chloride (71.25 mg, 0.375 mmol) was slowly added with stirring under nitrogen atmosphere.

After the addition was completed the reaction mixture was stirred at room temperature for thirty minutes and tetrahydrofuran was evaporated at reduced pressure. Then the reaction mixture was extracted with EtOAc (8 mL). The combined extract was dried over Na_2SO_4. Then the solvent was removed under reduced pressure to get the crude product.

Preparation of ^{15}N- benzaldehyde *N*-tosyl hydrazone[1]

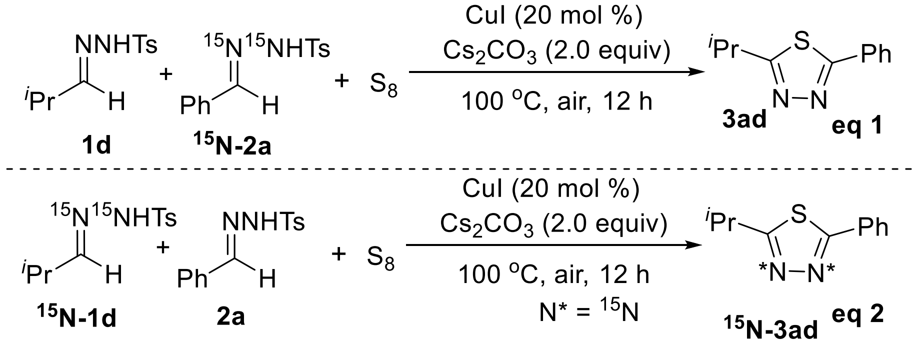
A solution of pure ^{15}N-4-methyl-benzenesulfonohydrazide (0.15 mmol) in methanol (0.15 mL) was stirred and heated to 60 ^{o}C until the ^{15}N-4-methyl-benzenesulfonohydrazide was completely dissolved. Then benzaldehyde (0.15 mmol) was dropped to the mixture slowly. After the addition was completed the reaction mixture was stirred for thirty min. Then the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc as the eluent to give the desired product.

3.2 General procedure for the preparation of ^{15}N-isobutyraldehyde *N*-tosylhydrazone (Scheme S3)



Scheme S3. Synthesis of ^{15}N-isobutyraldehyde *N*-tosylhydrazone

3.3 ^{15}N Labelling Experiments



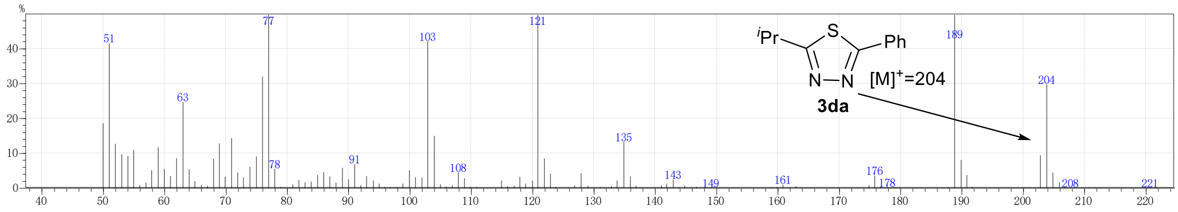


Fig S1. MS of 3da

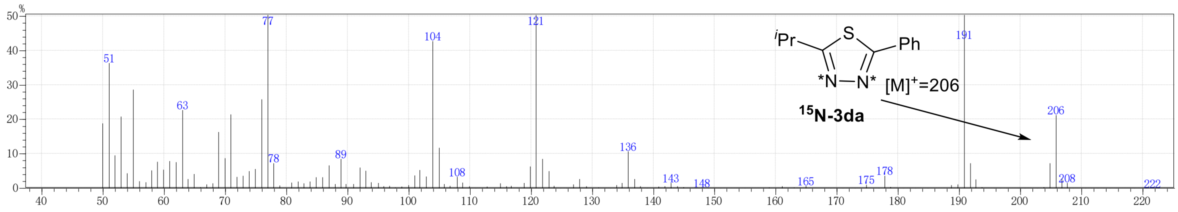
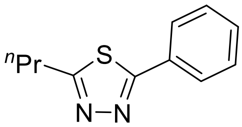


Fig S2. MS of ^{15}N-3da

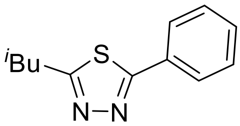
4. Characterization Data for the Products

2-(*n*-propyl)-5-phenyl-1,3,4-thiadiazole (3aa):[4]



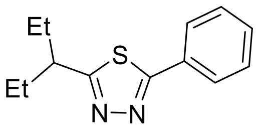
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3aa** (12.6 mg, 62% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.92 (m, 2H), 7.47-7.46 (m, 2H), 3.12 (t, J = 7.6 Hz, 2H), 1.92-1.83 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 168.4, 130.8, 130.3, 129.1, 127.8, 32.1, 23.4, 13.6.

2-isobutyl-5-phenyl-1,3,4-thiadiazole (3ba)[5]



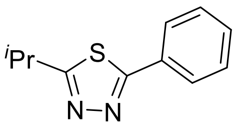
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ba** (11.1 mg, 51% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.93 (m, 2H), 7.49-7.43 (m, 3H), 3.01 (d, J = 7.2 Hz, 2H), 2.19-2.08 (m, 1H), 1.04 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 168.4, 130.8, 130.3, 129.1, 127.8, 127.8, 38.9, 29.8, 22.2.

2-(pentan-3-yl)-5-phenyl-1,3,4-thiadiazole (3ca)



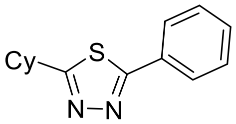
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ca** (12.1 mg, 52% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.93 (m, 2H), 7.49-7.45 (m, 3H), 3.15-3.08 (m, 1H), 1.90-1.83 (m, 2H), 1.78-1.70 (m, 2H), 0.93 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 168.0, 130.8, 130.4, 129.0, 127.8, 45.0, 29.2, 11.7; HRMS (ESI) m/z calcd for $C_{13}H_{17}N_2S(M+H)^+$ 233.1107, found 233.1103; IR (KBr) 3065, 2963, 2928, 2874, 2856, 1637, 1458, 1383, 1331 cm^{-1}.

2-isopropyl-5-phenyl-1,3,4-thiadiazole (3da)[6]



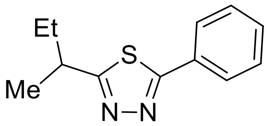
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3da** (12.2 mg, 60% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94-7.92 (m, 2H), 7.47-7.45 (m, 3H), 3.55-3.45 (m, 1H), 1.48 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 168.0, 130.8, 130.4, 129.0, 127.8, 30.9, 23.4.

2-cyclohexyl-5-phenyl-1,3,4-thiadiazole (3ea)



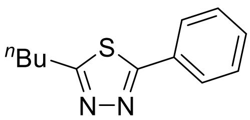
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ea** (12.7 mg, 52% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94-7.92 (m, 2H), 7.47-7.44 (m, 3H), 3.22-3.15 (m, 1H), 2.14-2.17 (m, 2H), 1.90-1.85 (m, 2H), 1.79-1.74 (m, 1H), 1.64-1.54 (m, 2H), 1.50-1.39 (m, 2H), 1.36-1.28 (m, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 167.7, 130.7, 130.4, 129.0, 127.8, 40.0, 33.9, 25.9, 25.6; HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2S(M+H)^+$ 245.1107, found 245.1103; IR (KBr) 3063, 2927, 2852, 1684, 1453, 1428, 1382, 1314 cm^{-1}.

2-(*sec*-butyl)-5-phenyl-1,3,4-thiadiazole (3fa)[5]



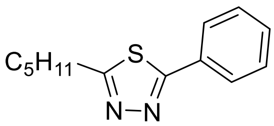
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3fa** (10.2 mg, 47% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.93 (m, 2H), 7.47-7.45 (m, 3H), 3.35-3.26 (m, 1H), 1.89-1.72 (m, 2H), 1.44 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.0, 168.0, 130.8, 130.4, 129.0, 127.8, 37.7, 31.0, 21.1, 11.6.

2-(*n*-butyl)-5-phenyl-1,3,4-thiadiazole (3ga)[4]



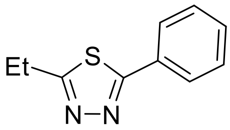
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ga** (11.8 mg, 54% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94-7.92 (m, 2H), 7.50-7.43 (m, 3H), 3.13 (t, J = 7.7 Hz, 2H), 1.86-1.78 (m, 2H), 1.51-1.42(m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 168.3, 130.8, 130.3, 129.0, 127.8, 32.1, 29.9, 22.1, 13.6.

2-pentyl-5-phenyl-1,3,4-thiadiazole (3ha)[7]



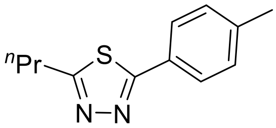
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ha** (9.5 mg, 41% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94-7.91 (m, 2H), 7.47-7.44 (m, 3H), 3.12 (t, J = 7.7 Hz, 2H), 1.88-1.78 (m, 2H), 1.44-1.34 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 168.3, 130.8, 130.3, 129.0, 127.8, 31.1, 30.0, 29.7, 22.2,13.9.

2-ethyl-5-phenyl-1,3,4-thiadiazole (3ia)[8]



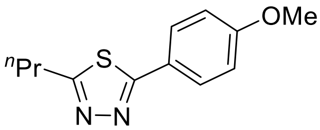
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ia** (10.8 mg, 57% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.92 (m, 2H), 7.48-7.45 (m, 3H), 3.20-3.14 (m, 2H), 1.46 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 168.4, 130.8, 130.3, 129.1, 127.8, 23.9, 14.4.

2-(*n*-propyl)-5-(*p*-tolyl)-1,3,4-thiadiazole (3ab)



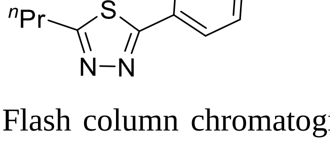
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ab** (11.1 mg, 51% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 4.0 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H), 1.91-1.82 (m, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 168.5, 141.2, 129.7, 127.7, 127.6（weak）, 32.1, 23.5, 21.5, 13.6; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S(M+H)^+$ 219.0950, found 219.0949; IR (KBr) 3021, 2962, 2926, 2872, 1612, 1463, 1382, 1312 cm^{-1}.

2-(*n*-propyl)-5-(*p*-methoxyphenyl)-1,3,4-thiadiazole (3ac)[4]



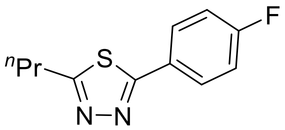
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ac** (12.4 mg, 53% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.08 (t, J = 7.6 Hz, 2H), 1.90-1.81 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 168.1, 161.7, 129.3, 123.0, 114.4, 55.4, 32.6, 23.4, 13.6;

2-(*n*-propyl)-5-(*p*-(trifluoromethyl)phenyl)-1,3,4-thiadiazole (3ad)



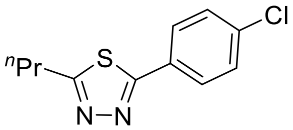
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ad** (12.2 mg, 45% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 8.17 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 3.14 (t, J = 7.6 Hz, 2H), 1.94-1.84 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 166.8, 133.6, 132.49 (q, $J_{C\text{-}F}$ = 35.0 Hz), 128.1, 126.1 (q, $J_{C\text{-}F}$ = 3.0 Hz), 123.7 (q, $J_{C\text{-}F}$ = 271.0 Hz), 32.1, 23.4, 13.6; HRMS (ESI) m/z calcd for $C_{12}H_{12}F_3N_2S(M+H)^+$ 273.0668, found 273.0664; IR (KBr) 3075, 2963, 2926, 2881, 2854, 1639, 1615, 1464, 1384, 1335 cm^{-1}.

2-(*n*-propyl)-5-(*p*-fluorophenyl)-1,3,4-thiadiazole (3ae)



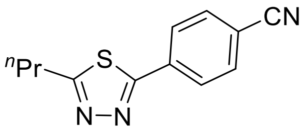
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ae** (10.0 mg, 45% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94-7.91 (m, 2H), 7.17-7.13 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H), 1.91-1.82 (m, 2H), 1.07-1.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 167.2, 164.2 (d, $J_{C\text{-}F}$ = 250.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.3 (d, $J_{C\text{-}F}$ = 4.0 Hz), 116.2 (d, $J_{C\text{-}F}$ = 22.0 Hz), 32.1, 23.4, 13.6; HRMS (ESI) m/z calcd for $C_{11}H_{12}FN_2S(M+H)^+$ 223.0700, found 223.0692; IR (KBr) 3076, 2960, 2929, 2901, 2872, 2855, 1637, 1463 1376 1301cm^{-1}.

2-(*n*-propyl)-5-(*p*-chlorophenyl)-1,3,4-thiadiazole (3af)



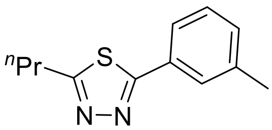
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3af** (11.4 mg, 48% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 1.91-1.82 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 167.1, 136.9, 129.3, 128.9, 128.8, 32.1, 23.4, 13.6; HRMS (ESI) m/z calcd for $C_{11}H_{12}ClN_2S(M+H)^+$ 239.0404, found 239.0399; IR (KBr) 3083, 3069, 2957, 2929, 2872, 1642, 1463, 1438, 1384, 1338 cm^{-1}.

4-(5-propyl-1,3,4-thiadiazol-2-yl)benzonitrile (3ag)



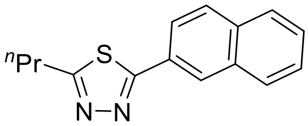
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ag** (9.8 mg, 43% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H), 1.92-1.83 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 166.3, 134.2, 132.8, 128.2, 118.0, 114.2, 32.1, 23.4, 13.5; HRMS (ESI) m/z calcd for $C_{12}H_{12}N_3S(M+H)^+$ 230.0746, found 230.0746; IR (KBr) 3073, 3054 2965, 2926, 2874, 1651, 1462, 1384, 1317 cm^{-1}.

2-(*n*-propyl)-5-(*m*-tolyl)-1,3,4-thiadiazole (3ah)



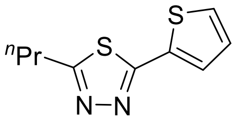
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ah** (10.9 mg, 50% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.28 (s, 1H), 3.10 (t, J = 7.6 Hz, 2H), 2.41 (s, 3H), 1.91-1.82 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 168.6, 138.9, 131.6, 130.2, 129.0, 128.3, 125.1, 32.1, 23.4, 21.3, 13.6; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2S(M+H)^+$ 219.0950, found 219.0948; IR (KBr) 3031, 2968, 2932, 2858, 1632, 1451, 1373, 1342 cm^{-1}.

2-(*n*-propyl)-5-(naphthalen-2-yl)-1,3,4-thiadiazole (3ai)



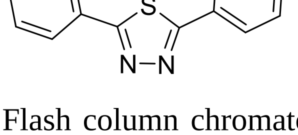
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3ai** (13.2 mg, 52% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (s, 1H), 8.10-8.07 (m, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.87 (t, J = 4.0 Hz, 1H), 7.57-7.52 (m, 2H), 3.14 (t, J = 6.0 Hz, 2H), 1.89 (t, J = 8.0 Hz, 2H), 1.08 (t, J = 6.0 Hz, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2S$ $(M+H)^+$ 255.0950, found 255.0947; IR (KBr) 3083, 2959, 2923, 2852, 1637, 1617, 1457, 1425, 1384, 1339 cm^{-1}.

2-(*n*-propyl)-5-(thiophen-2-yl)-1,3,4-thiadiazole (3aj)



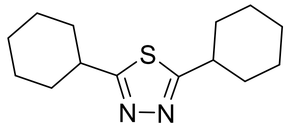
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **3aj** (11.6 mg, 55% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.49 (m, 1H), 7.46-7.44 (m, 1H), 7.11-7.09 (m, 1H), 3.08 (t, J = 7.6 Hz, 2H), 1.90-1.80 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 168.5, 134.4, 133.1, 128.9, 128.6, 127.9, 127.8, 127.7, 127.4, 126.9, 124.5, 32.1, 23.5, 21.5, 13.6; HRMS (ESI) m/z calcd for $C_9H_{11}N_2S_2$ $(M+H)^+$ 211.0358, found 211.0359; IR (KBr) 3104, 3083, 2959, 2926, 2870, 2859, 1639, 1452, 1411, 1384, 1338 cm^{-1}.

2,5-diphenyl-1,3,4-thiadiazole (4)[9]



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **4** (8.0 mg, 67% yield) as a white solid. m.p. 141-142 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05-7.99 (m, 4H), 7.54-7.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 131.1, 130.1, 129.2, 127.9.

2,5-dicyclohexyl-1,3,4-thiadiazole (5)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 15) give **5** (5.5 mg, 44% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14-3.07 (m, 1H), 2.45-2.26 (m, 1H), 2.22-1.95 (m, 3H), 1.86-1.56 (m, 7H), 1.54-1.28 (m, 9H), 0.89-0.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 39.9, 33.9, 25.9, 25.7; HRMS (ESI) m/z calcd for $C_{14}H_{23}N_2S$ $(M+H)^+$ 251.1576, found 251.1572.

5. Reference

1 Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc*. **2012**, *134*, 5742.

2 Pieper, M.; Teichert, W.; Meier, H. *Liebigs Ann. Chem*. **1986**, 1334.

3 Backes, G. L.; Neumann, D. M.; Jursic. B. S. *Bioorg. Med. Chem.* **2014**, *22*, 4629.

4 Demchuk, D. V.; Lutsenko, A. I.; Troyanskii, E. I.; Nikishin, G. I. *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya* **1989**, *8*, 1843.

5 Pakal'nis, V. V.; Zerova, I. V.; Alekseev, V. V.; Yakimovich, S. I. *Vestnik Sankt-Peterburgskogo Universiteta, Seriya 4: Fizika, Khimiya* **2013**, *4*, 125.

6 Knaus, G.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189.

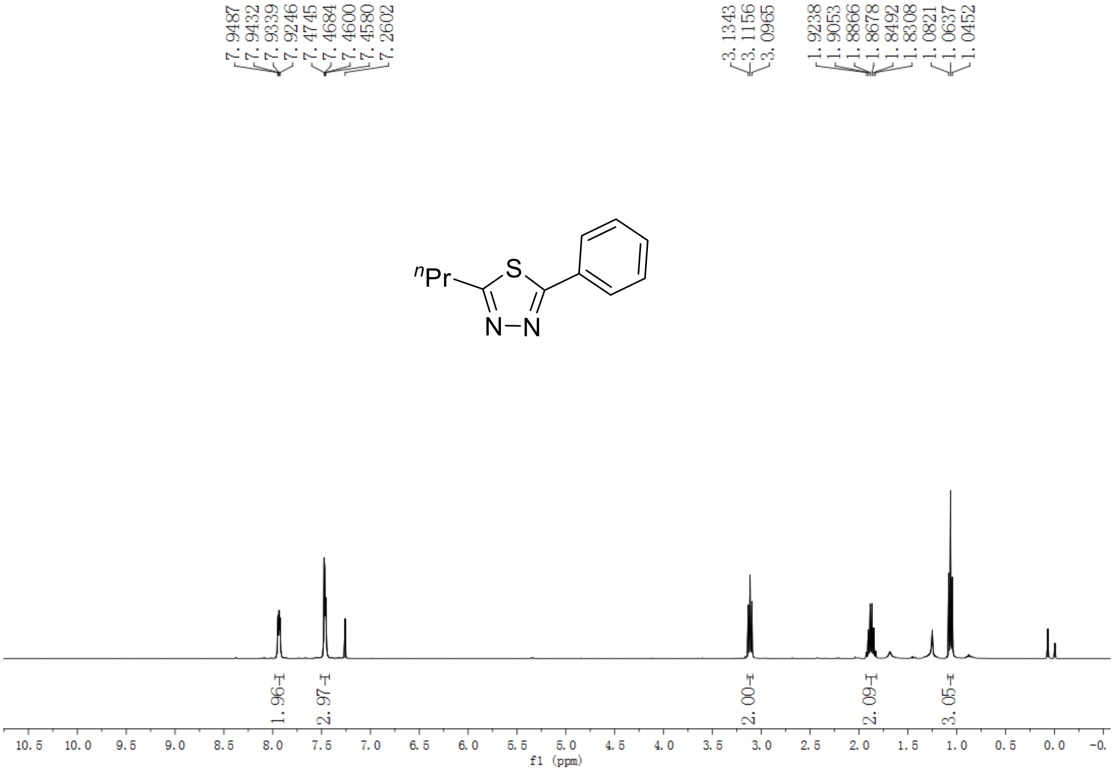
7 Gierczyk, B.; Zalas, M. *Org. Prep. Proced. Int.* **2005**, *37*, 213.

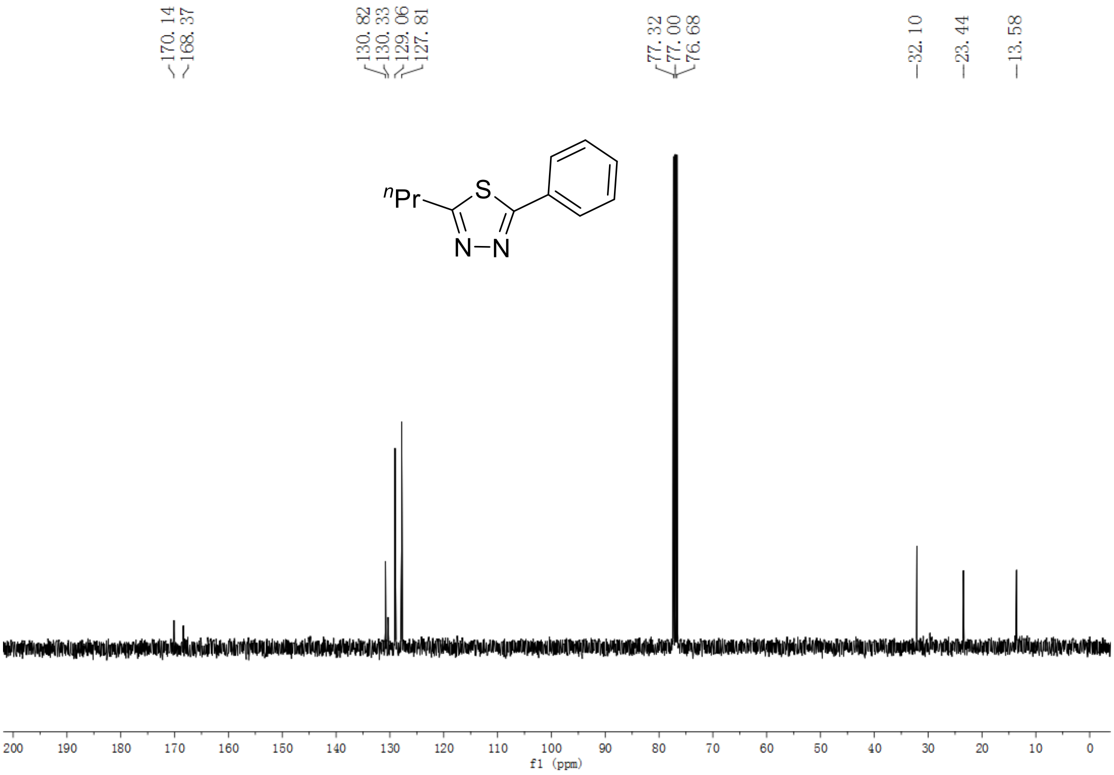
8 Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1973**, *95*, 3408.

9 Fan, X.; Jiang, X.; Zhang, Y.; Chen, Z.; Zhu, Y. *Org. Biomol. Chem.* **2015**, *13*, 10402.

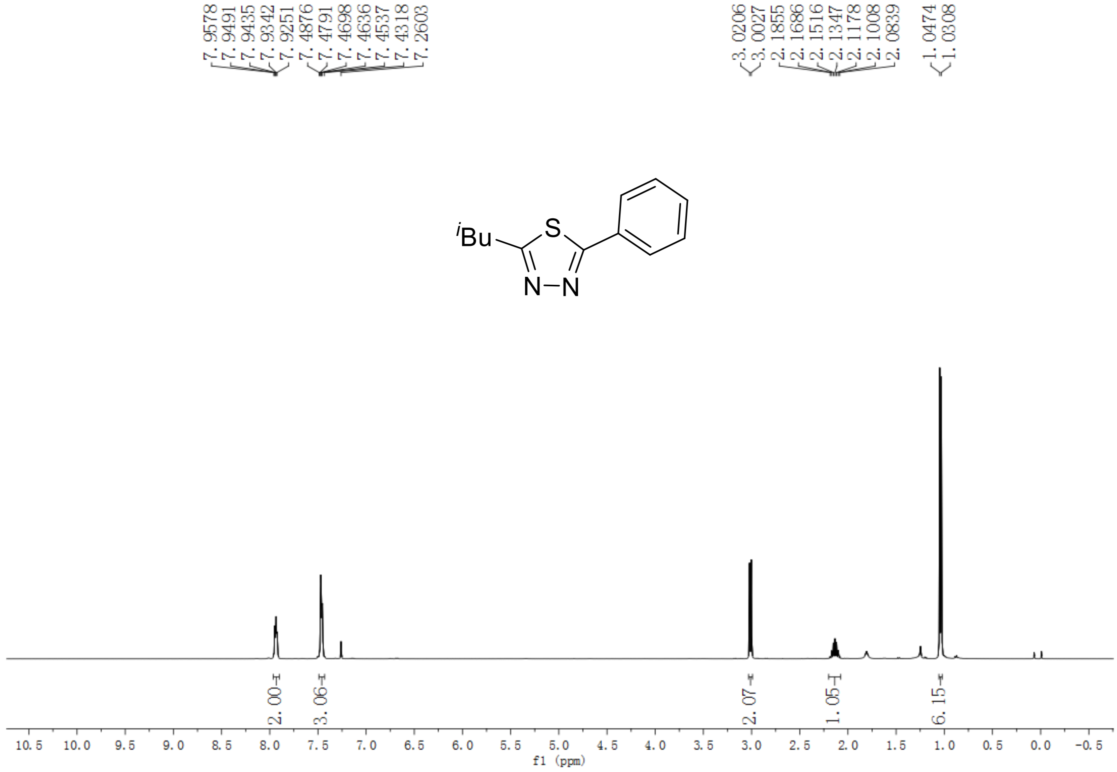
6. Copies of the ^{1}H NMR, ^{13}C NMR Spectra

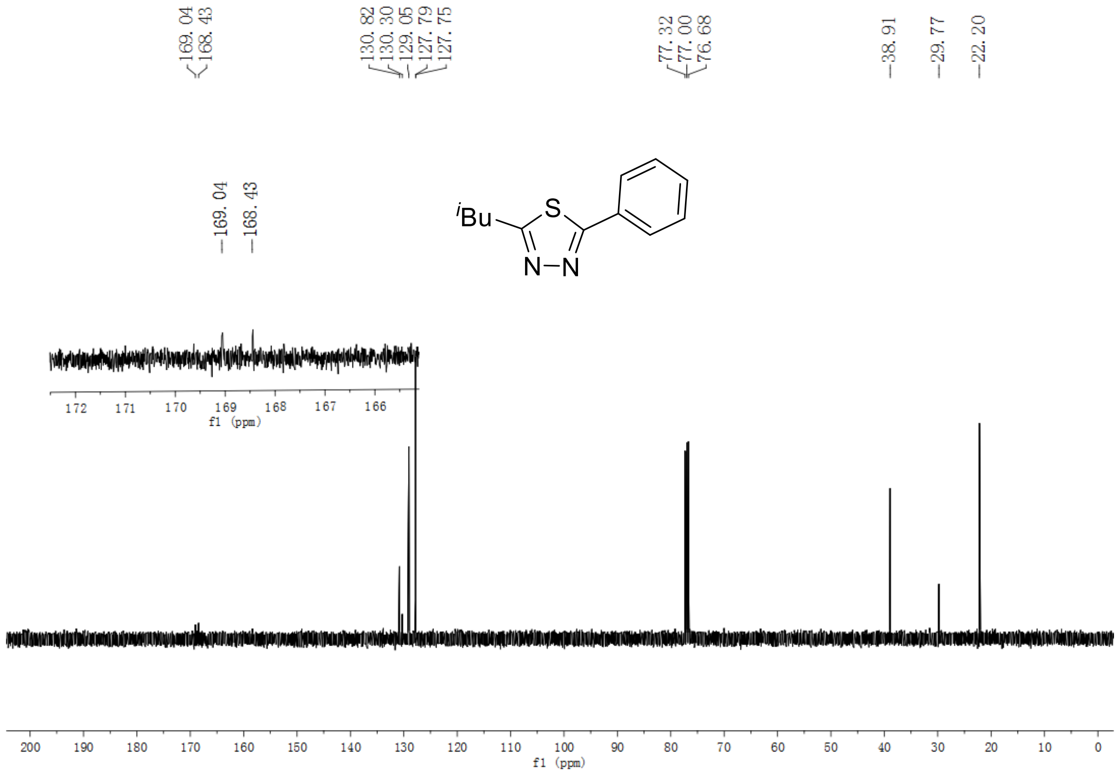
2-(*n*-propyl)-5-phenyl-1,3,4-thiadiazole (3aa)



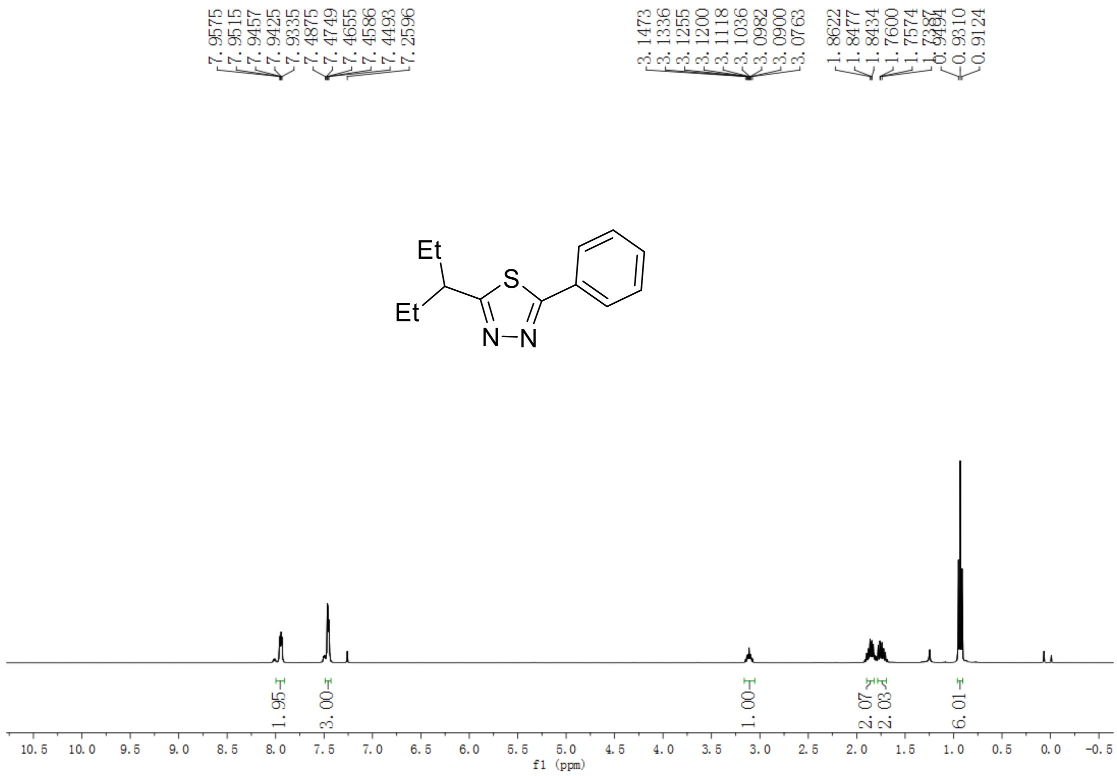


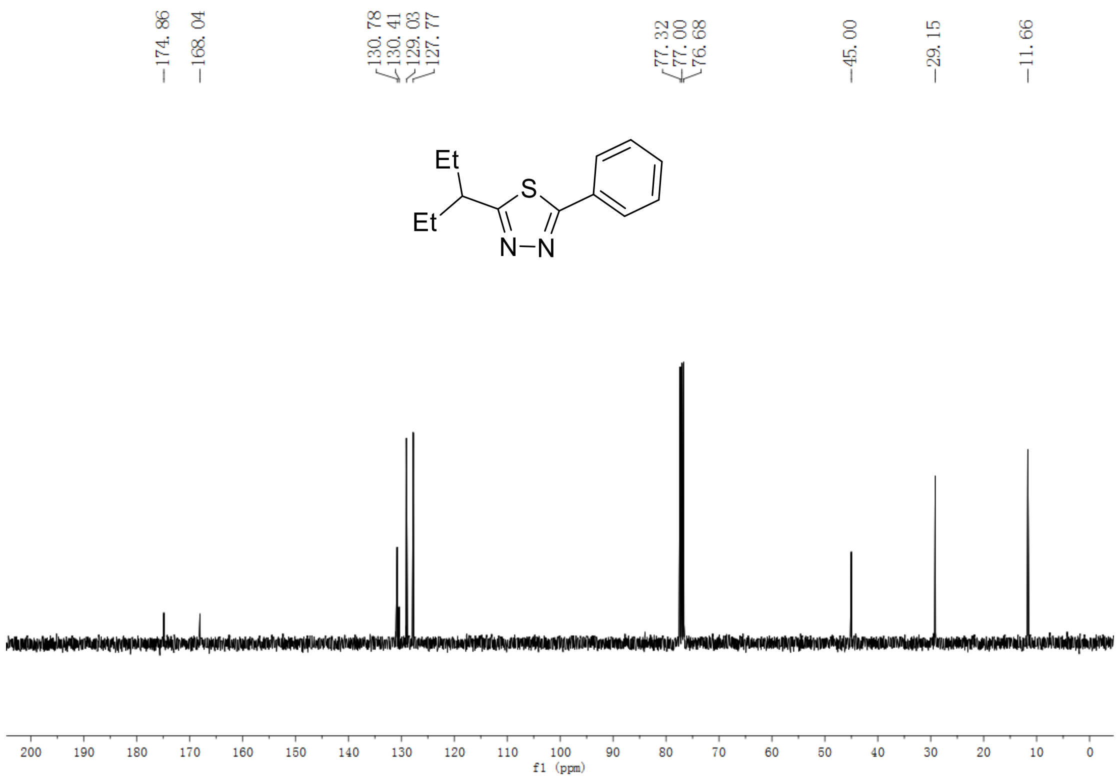
2-isobutyl-5-phenyl-1,3,4-thiadiazole (3ba)



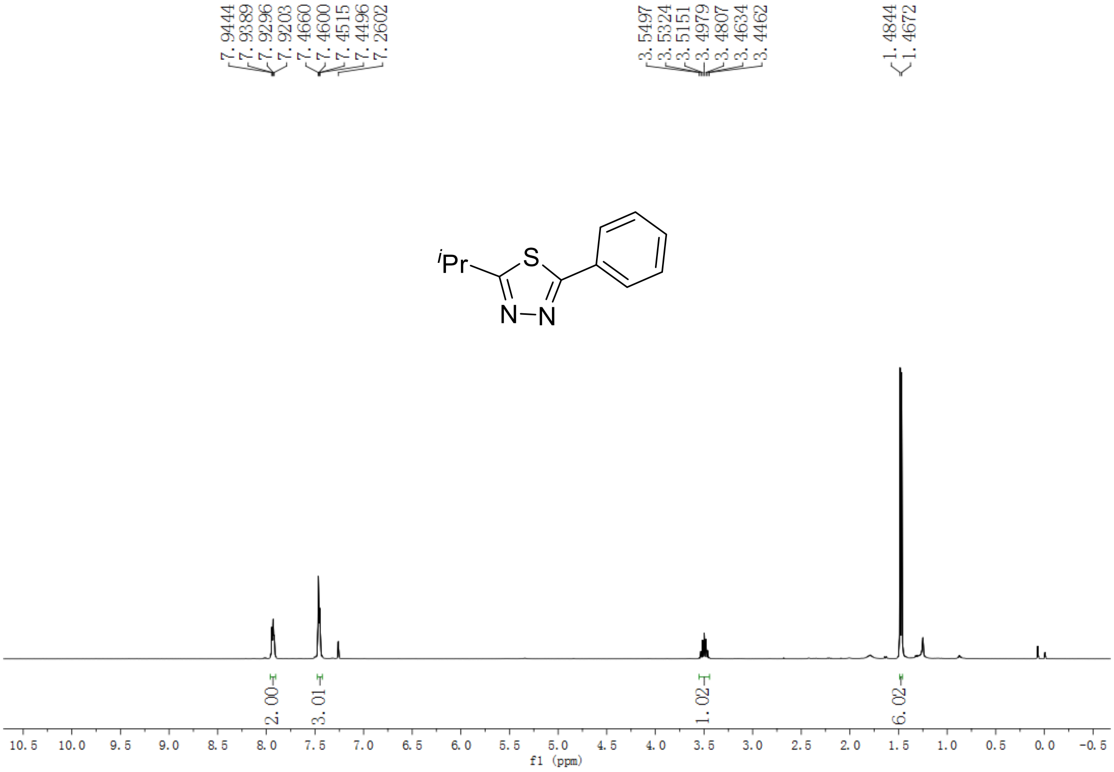


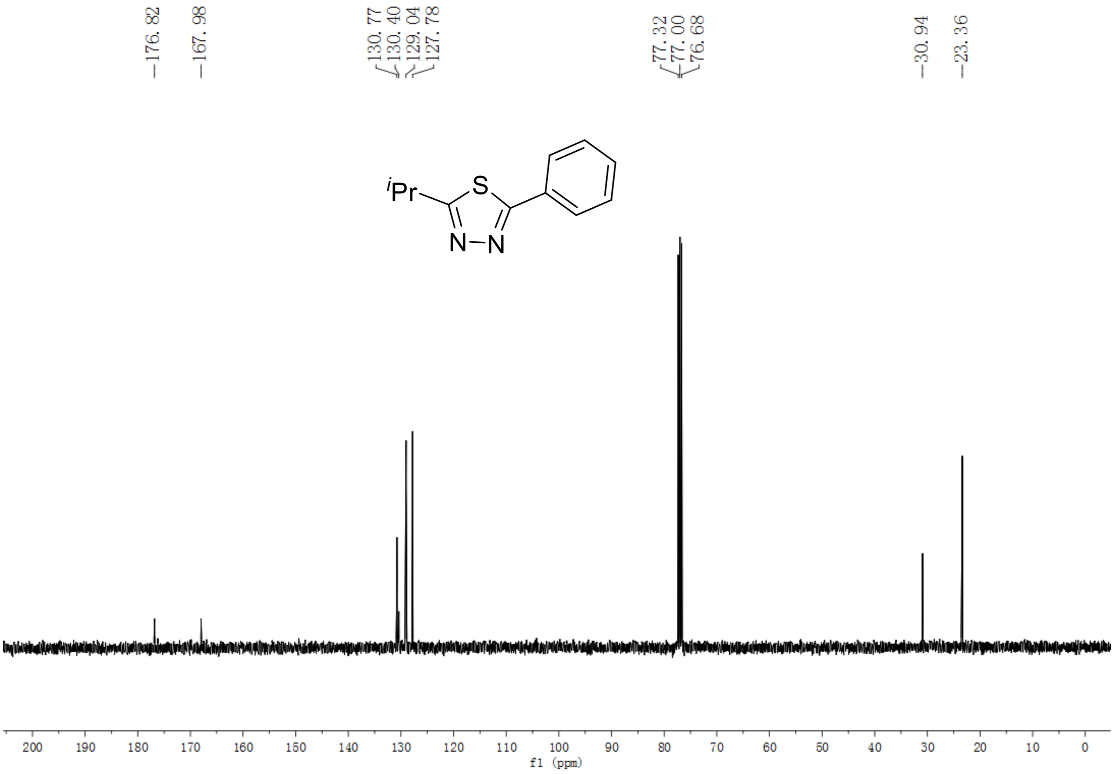
2-(pentan-3-yl)-5-phenyl-1,3,4-thiadiazole (3ca)



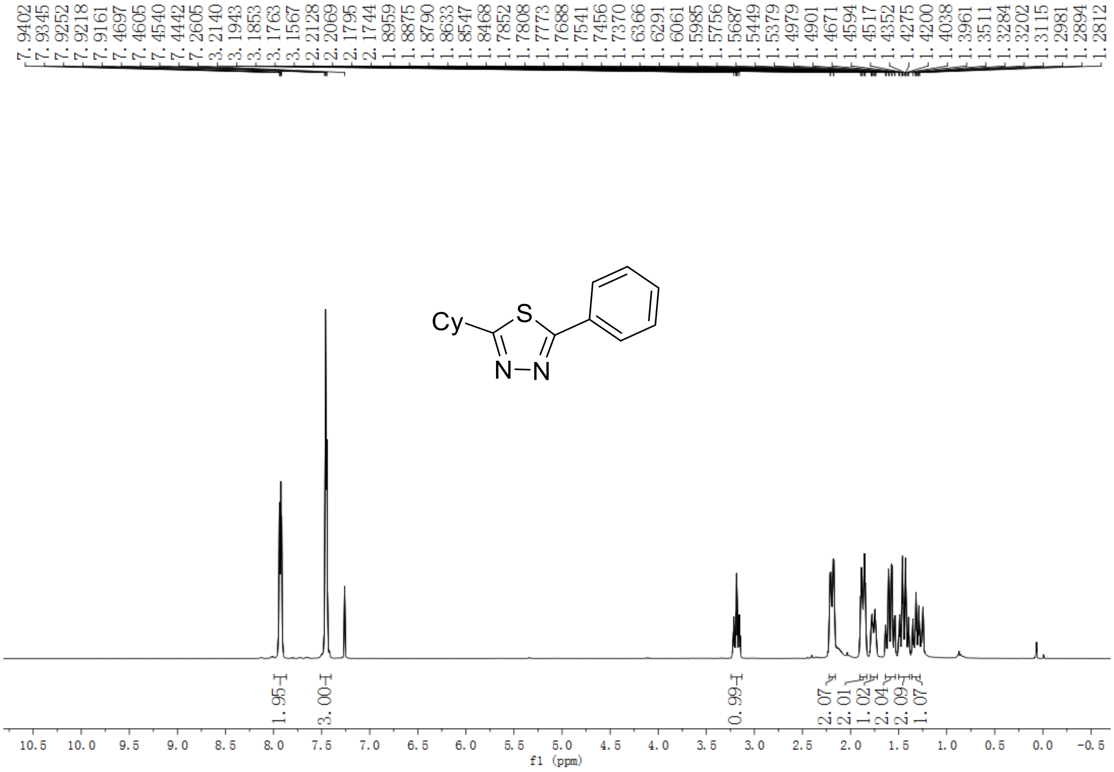


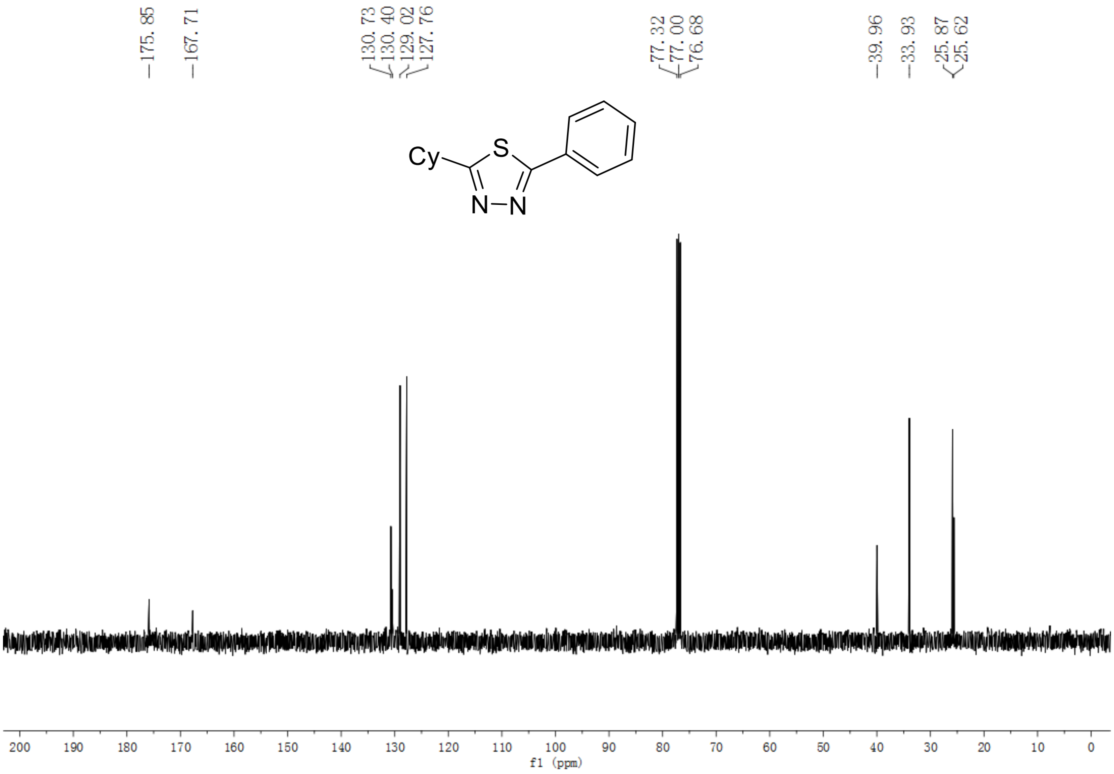
2-isopropyl-5-phenyl-1,3,4-thiadiazole (3da)



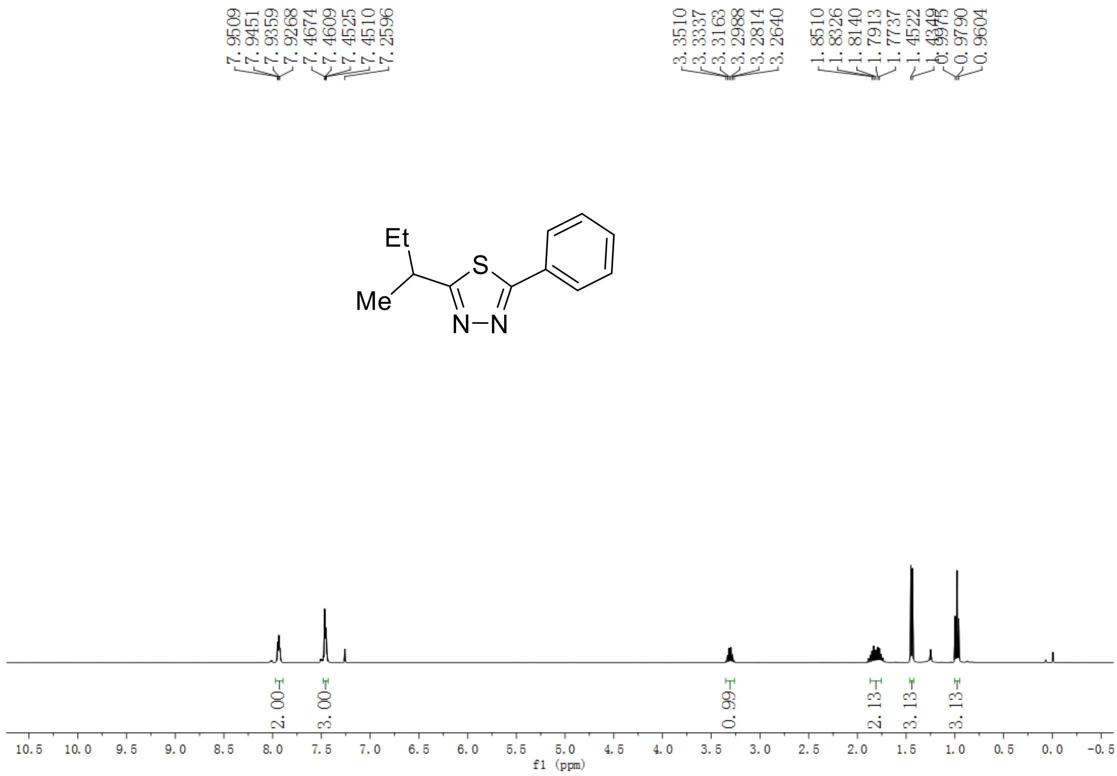


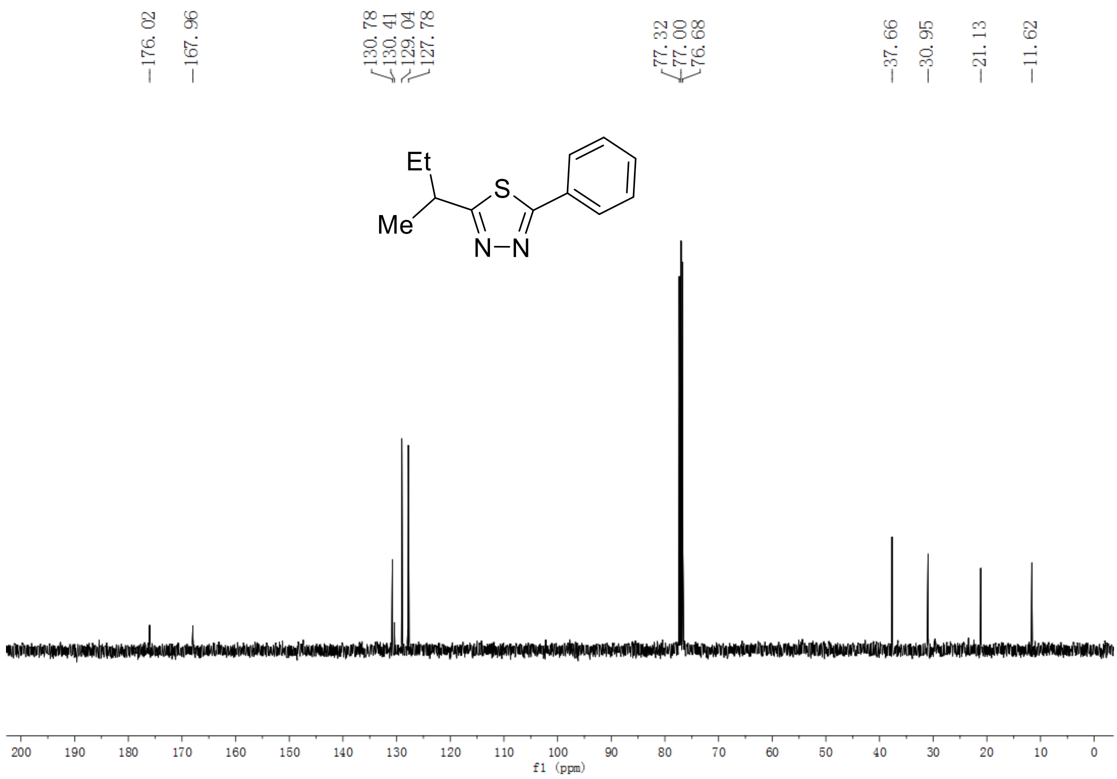
2-cyclohexyl-5-phenyl-1,3,4-thiadiazole(3ea)



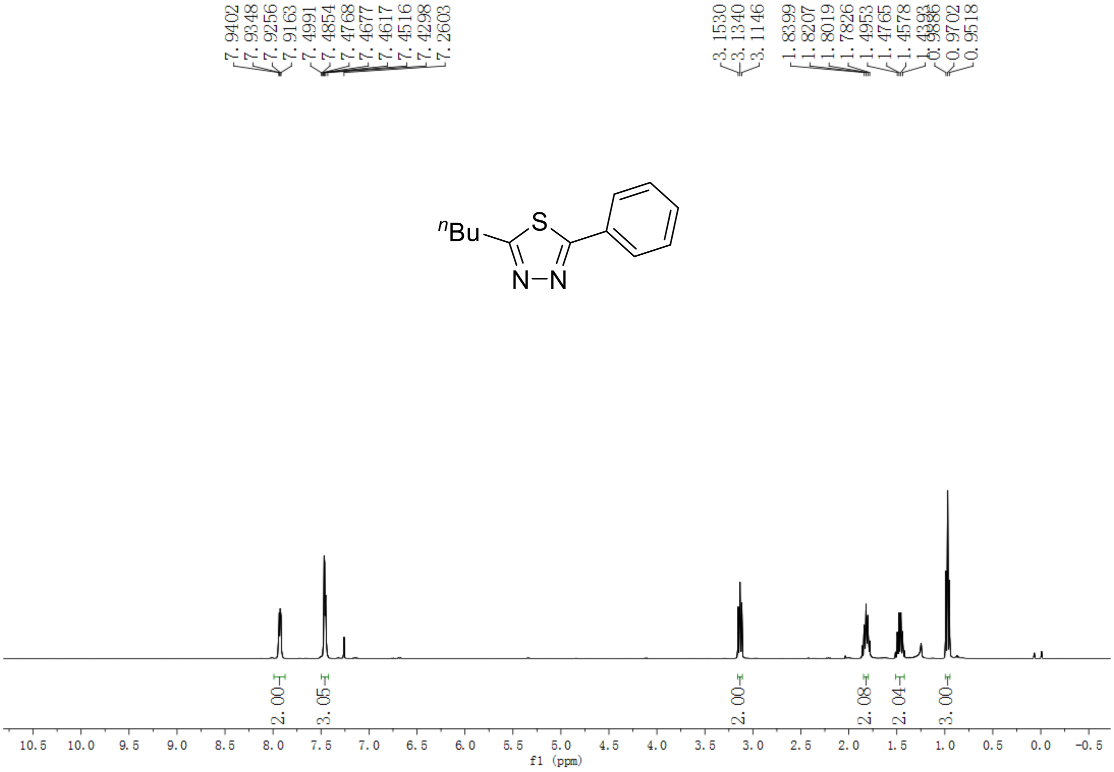


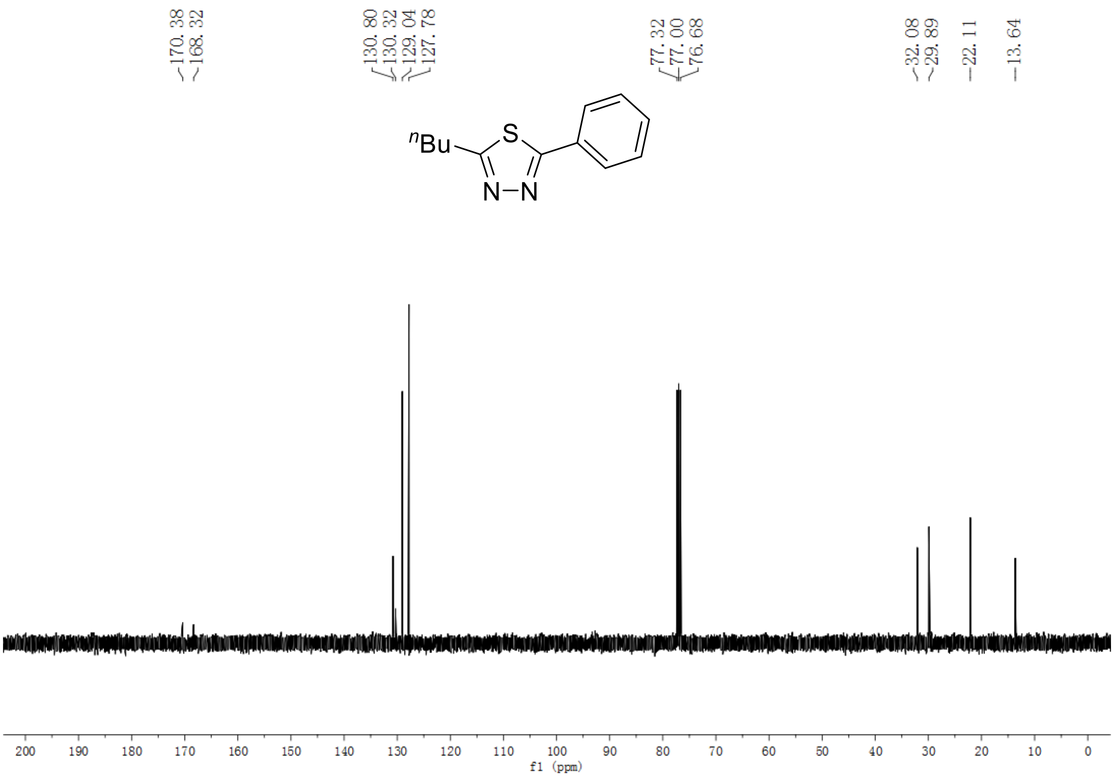
2-(*sec*-butyl)-5-phenyl-1,3,4-thiadiazole(3fa)



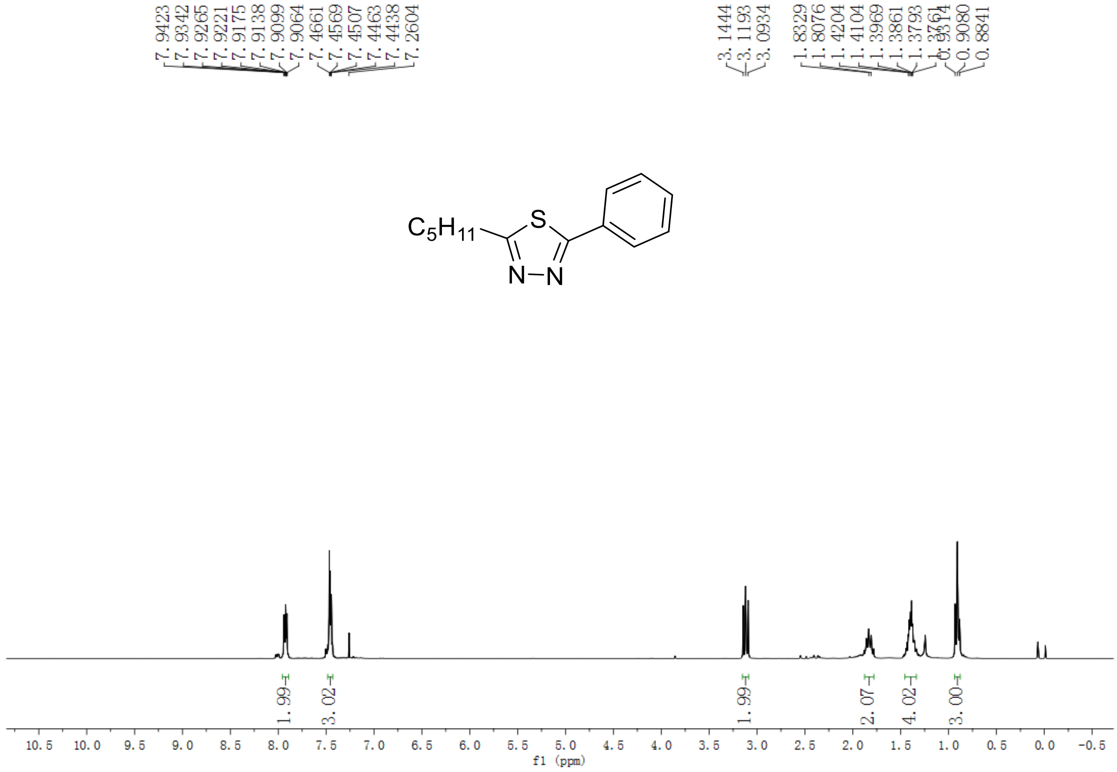


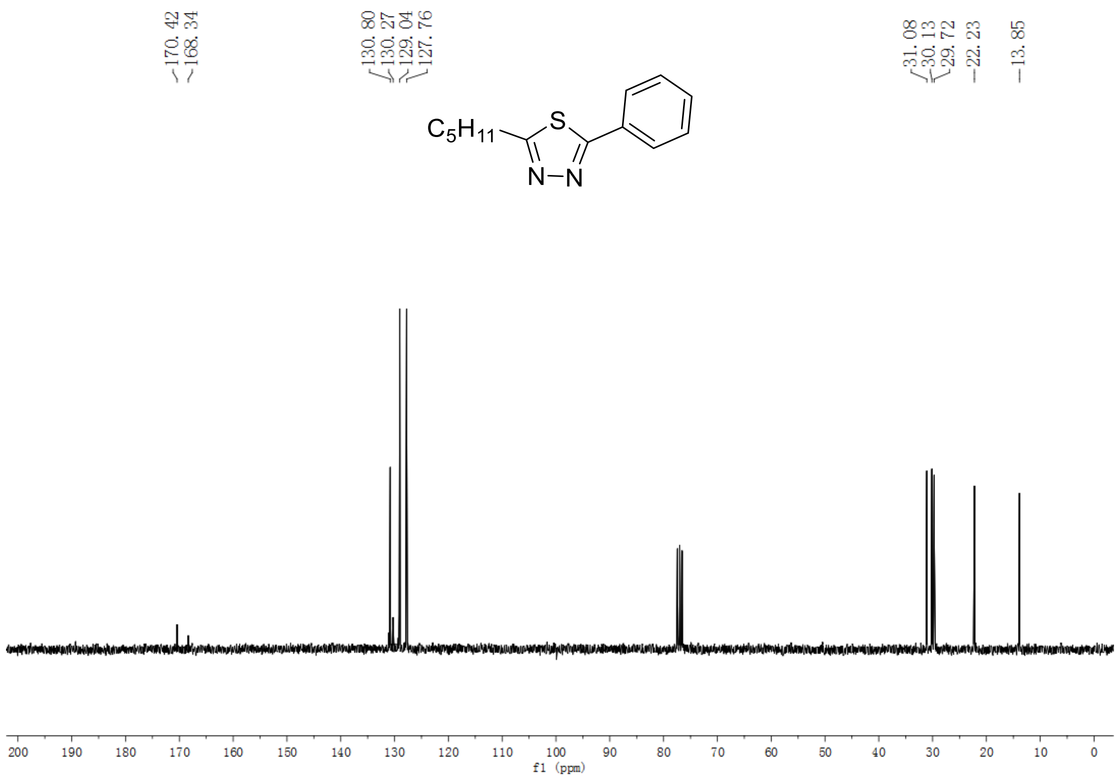
2-(*n*-butyl)-5-phenyl-1,3,4-thiadiazole(3ga)



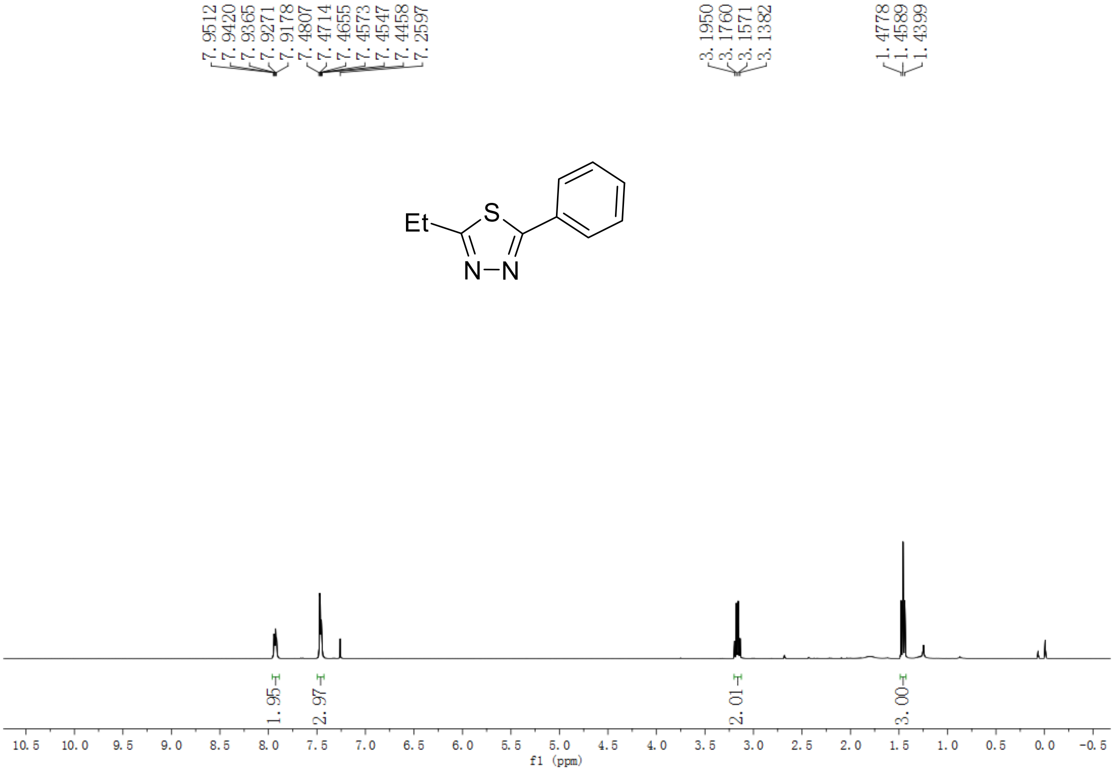


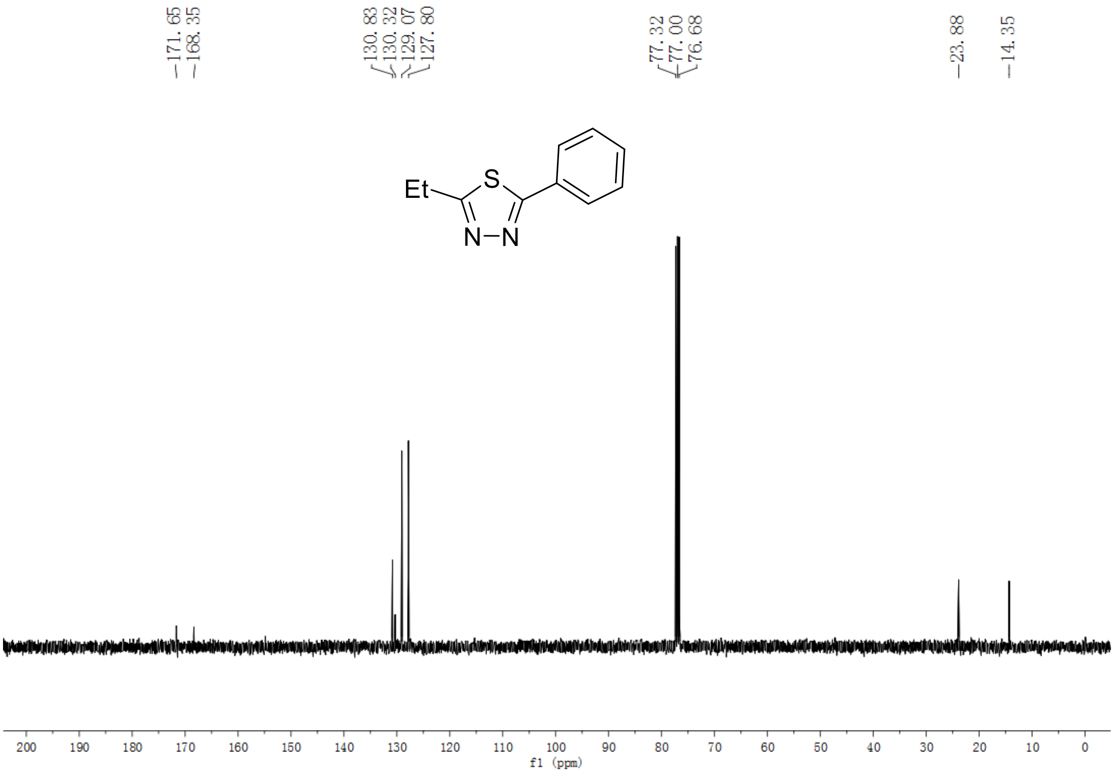
2-pentyl-5-phenyl-1,3,4-thiadiazole (3ha)



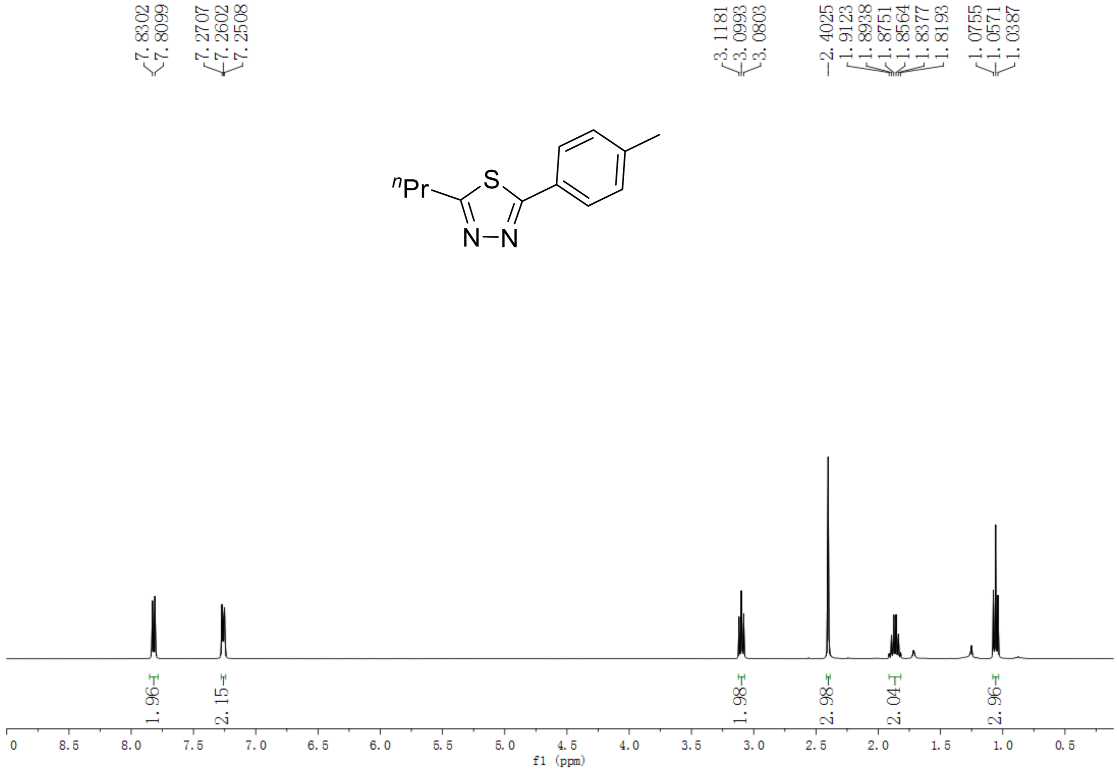


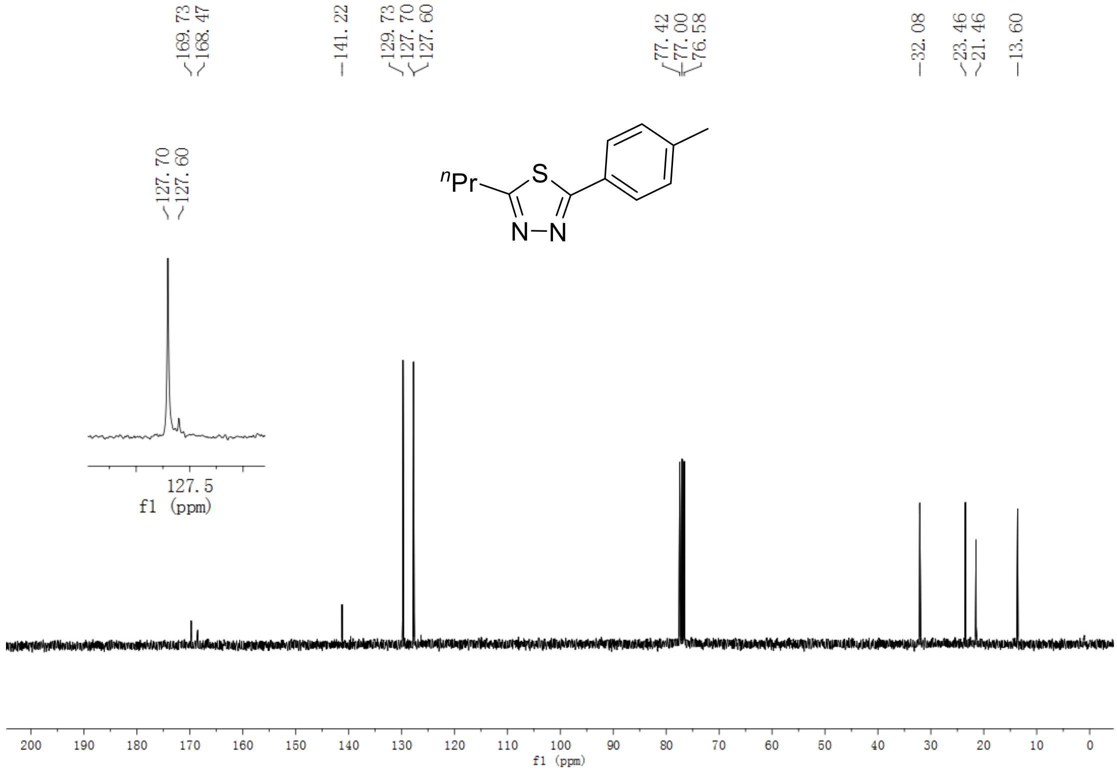
2-ethyl-5-phenyl-1,3,4-thiadiazole (3ia)



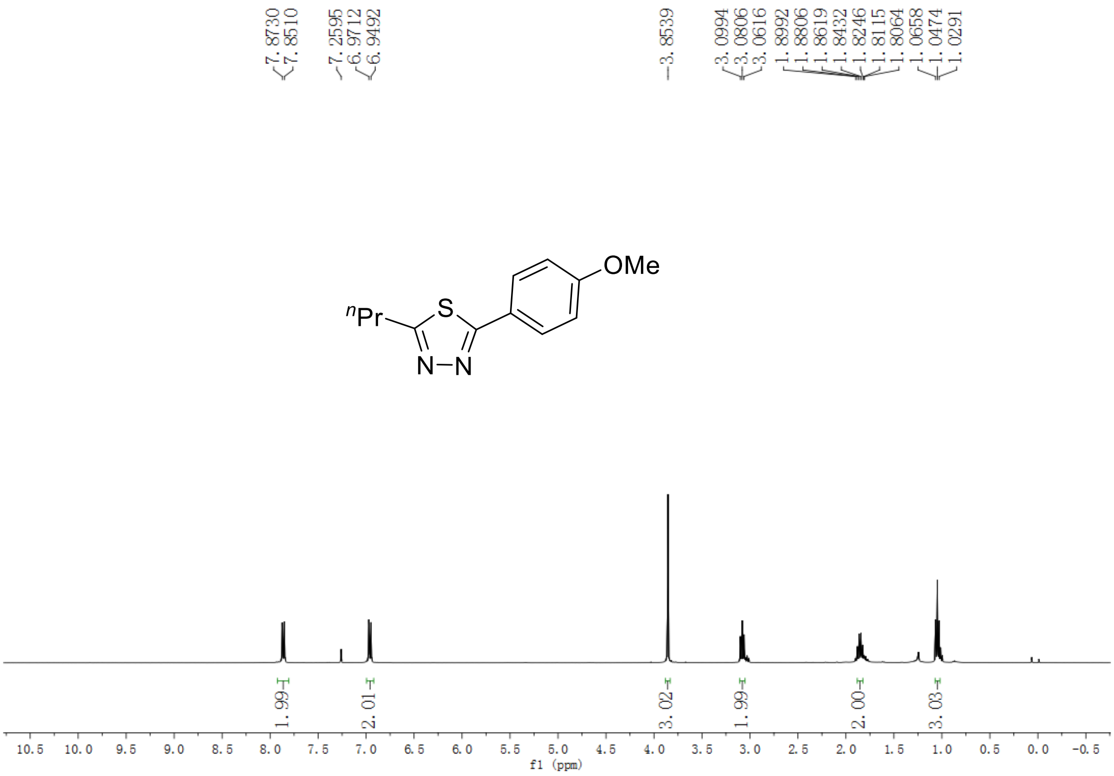


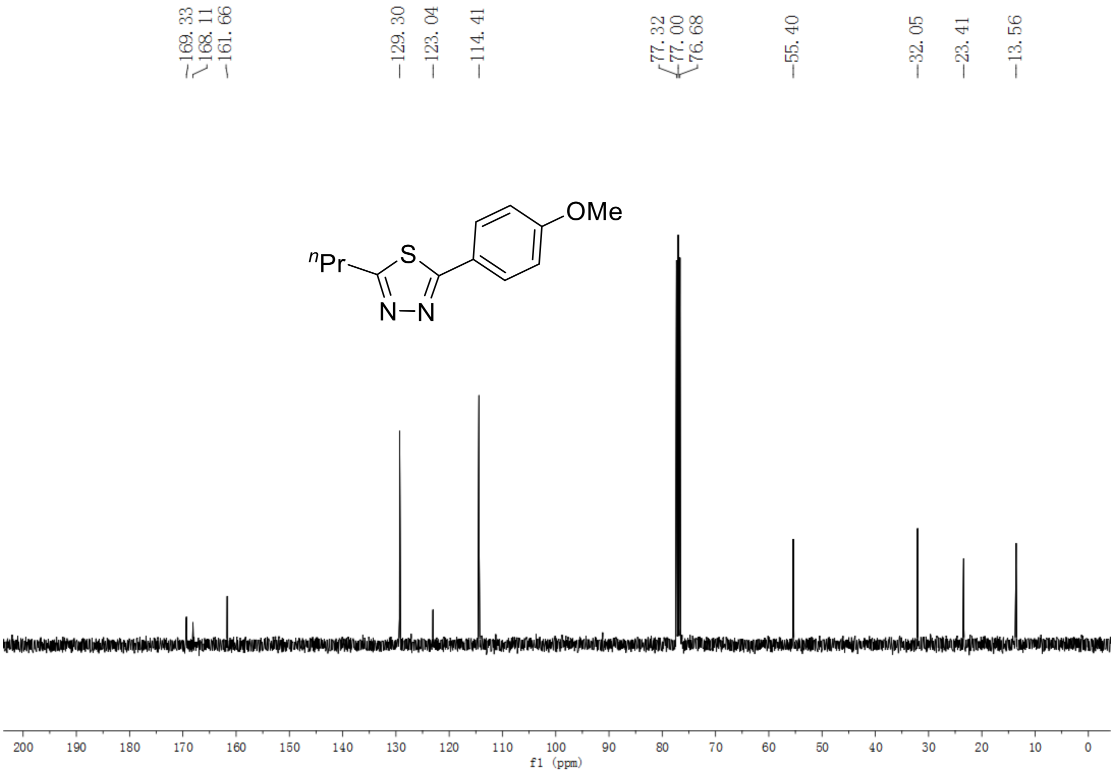
2-(*n*-propyl)-5-(*p*-tolyl)-1,3,4-thiadiazole（3ab）



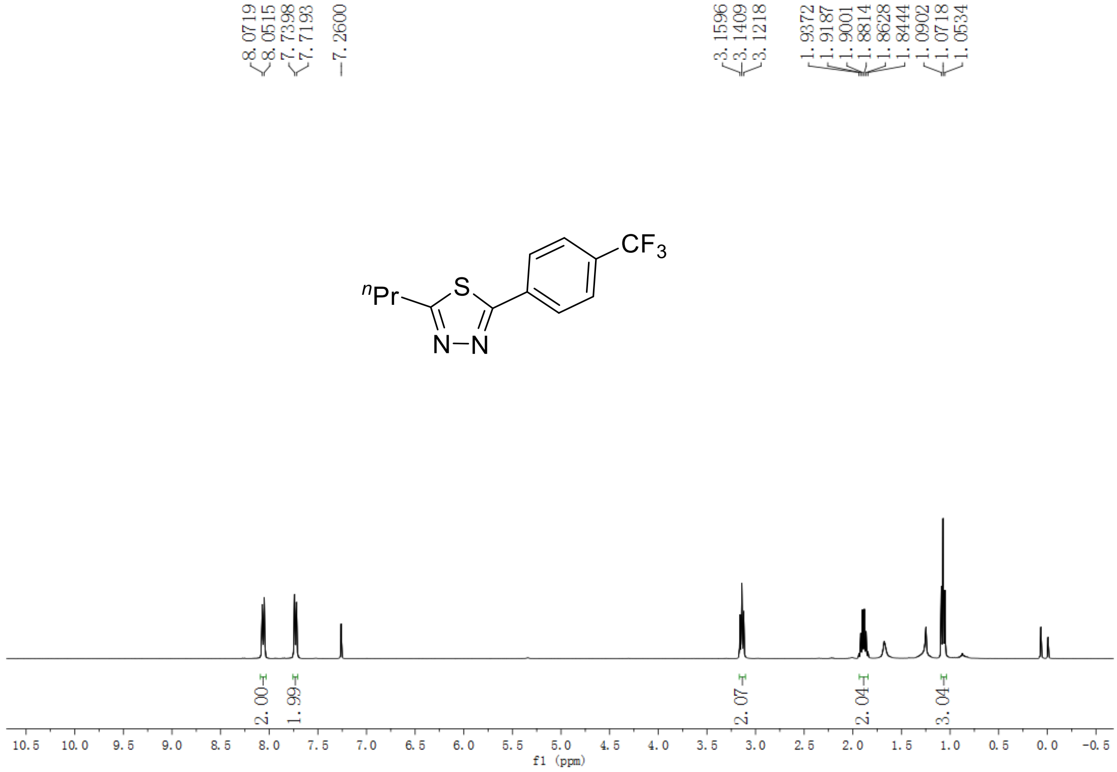


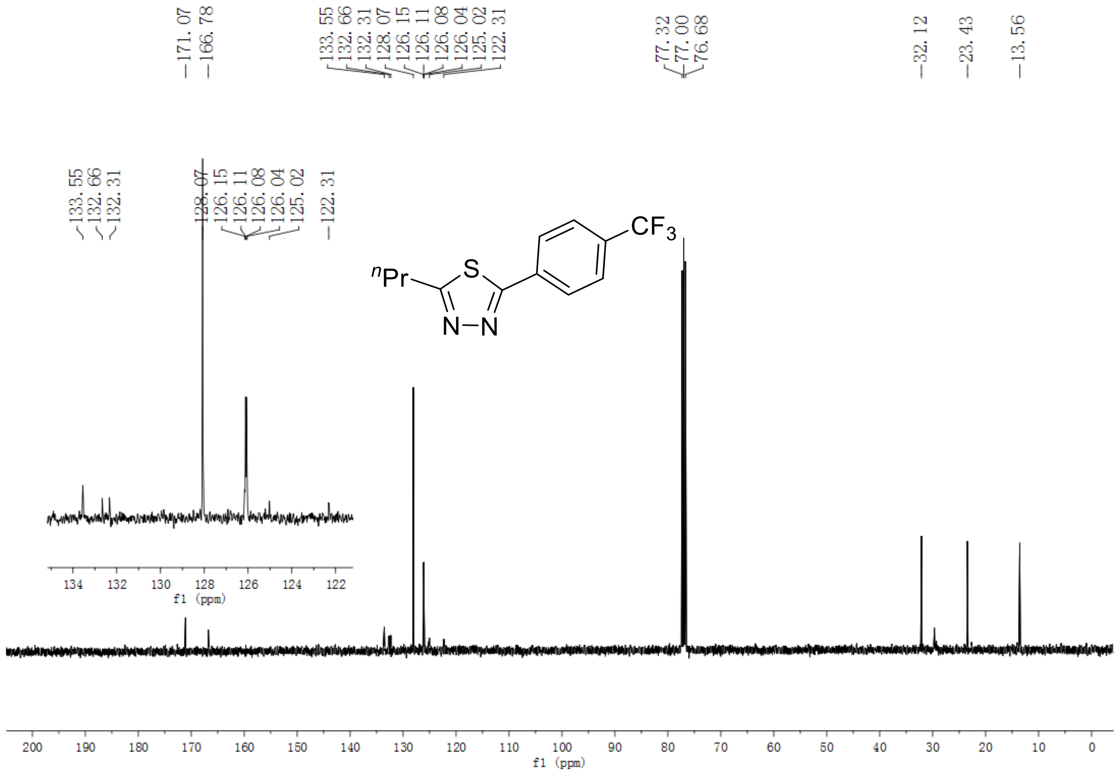
2-(*n*-propyl)-5-(*p*-methoxyphenyl)-1,3,4-thiadiazole (3ac)



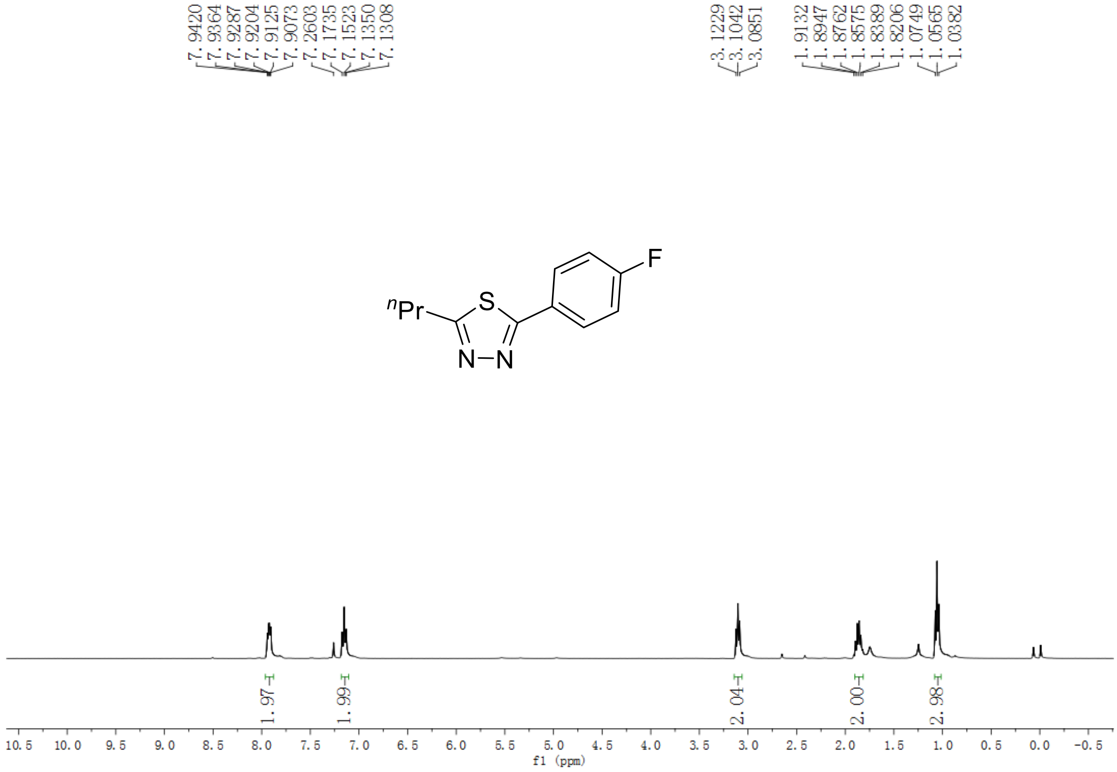


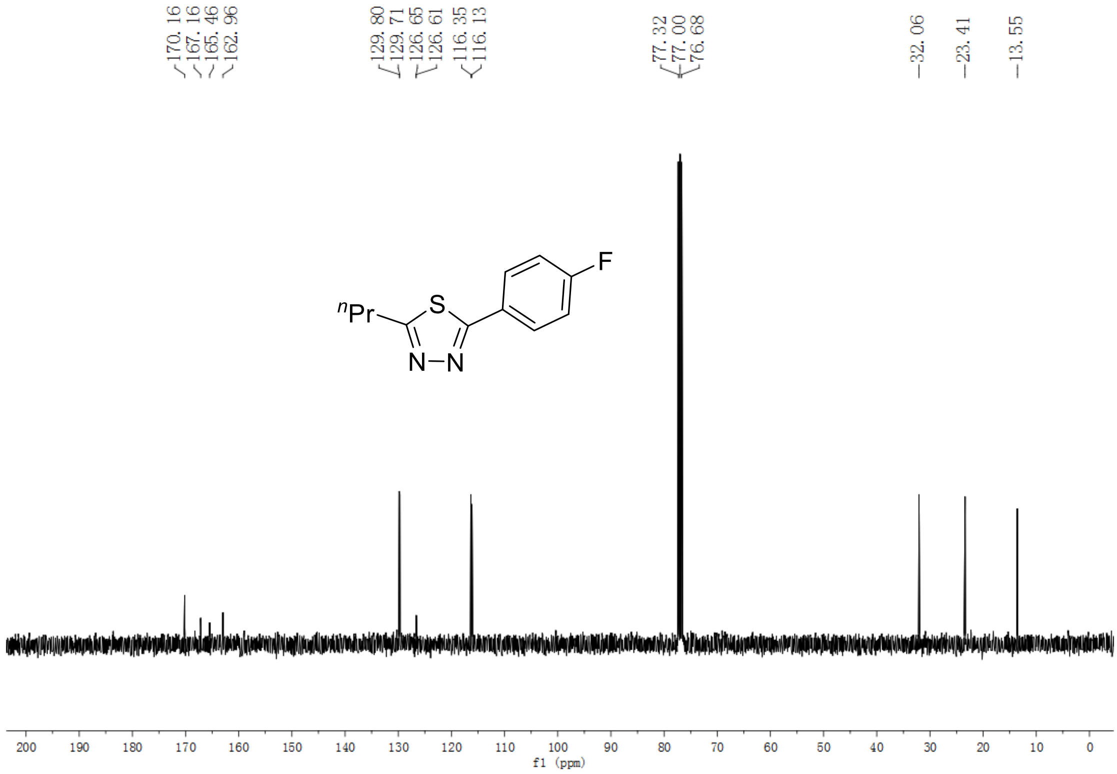
2-(*n*-propyl)-5-(*p*-(trifluoromethyl)phenyl)-1,3,4-thiadiazole(3ad)



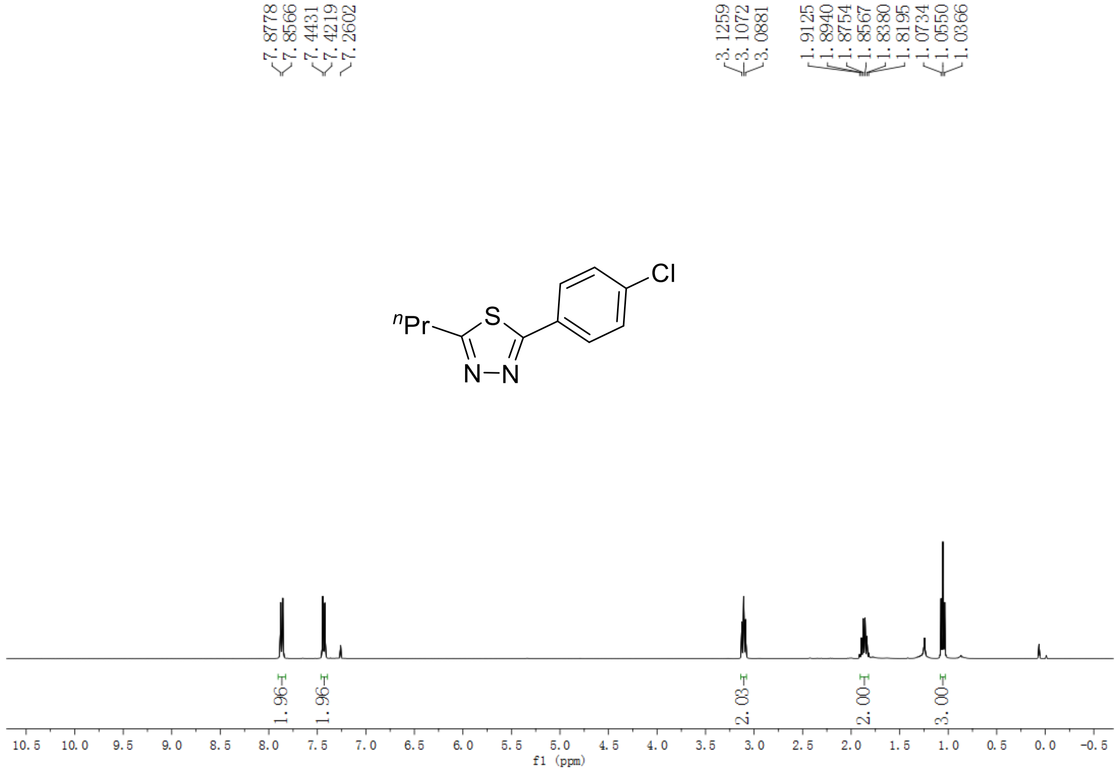


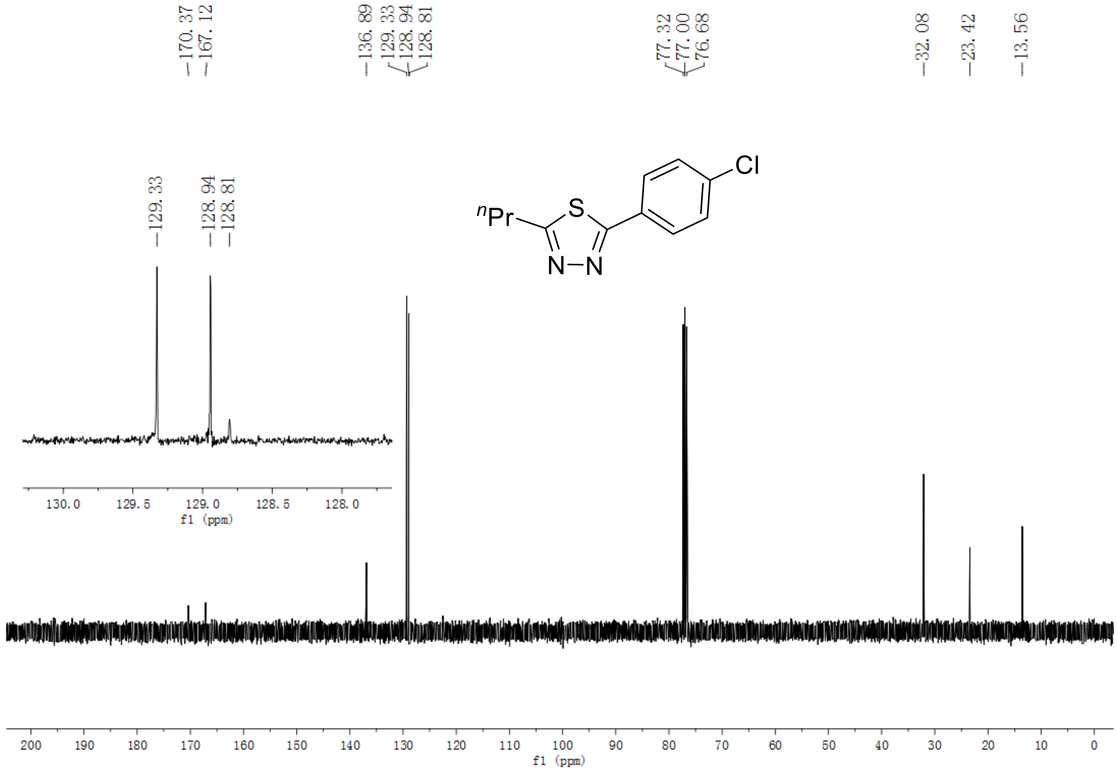
2-(*n*-propyl)-5-(*p*-fluorophenyl)-1,3,4-thiadiazole(3ae)



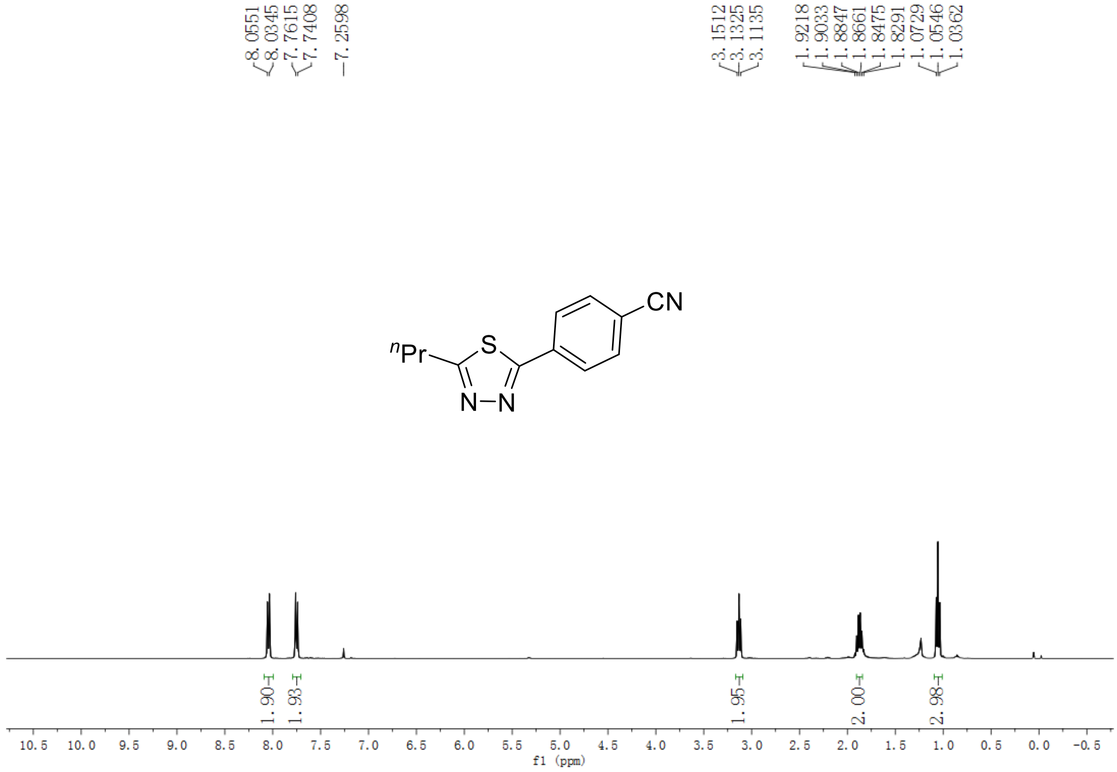


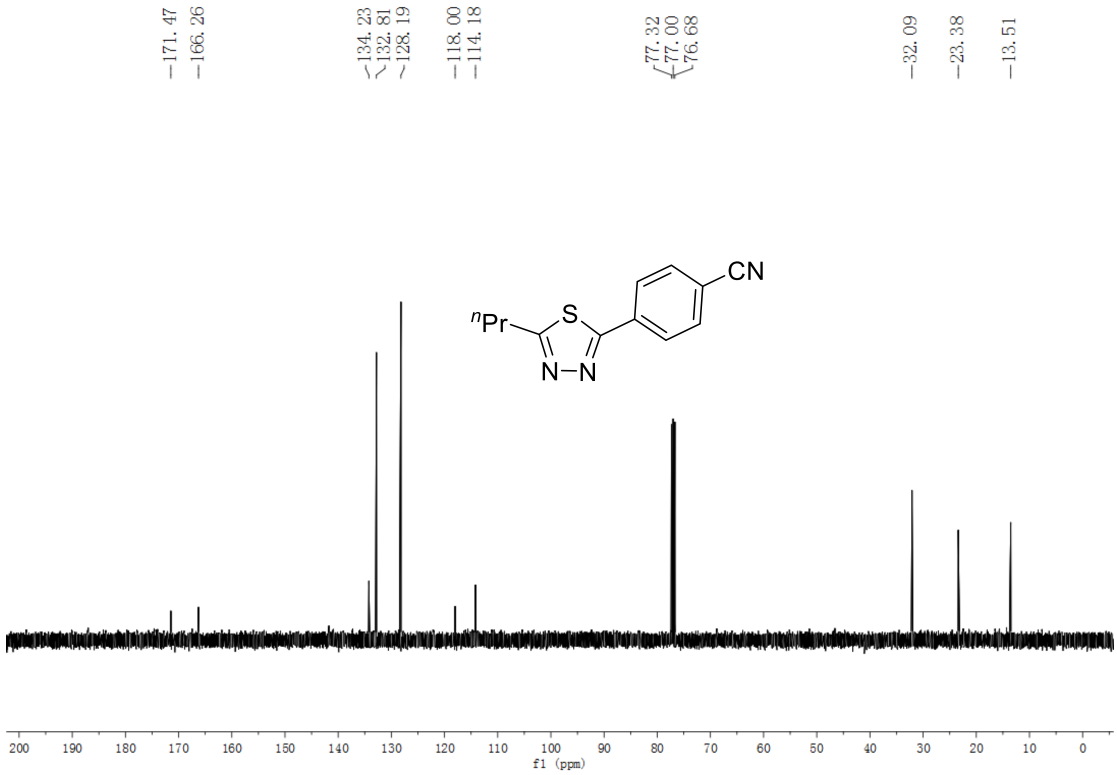
2-(*n*-propyl)-5-(*p*-chlorophenyl)-1,3,4-thiadiazole (3af)



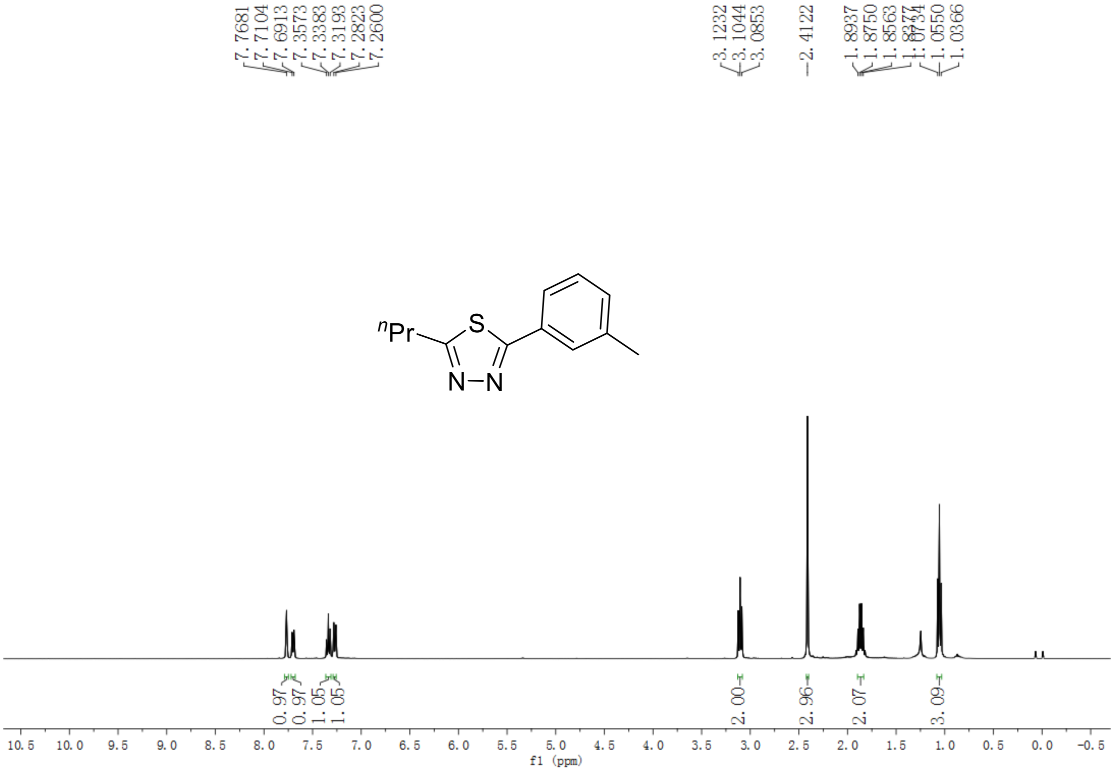


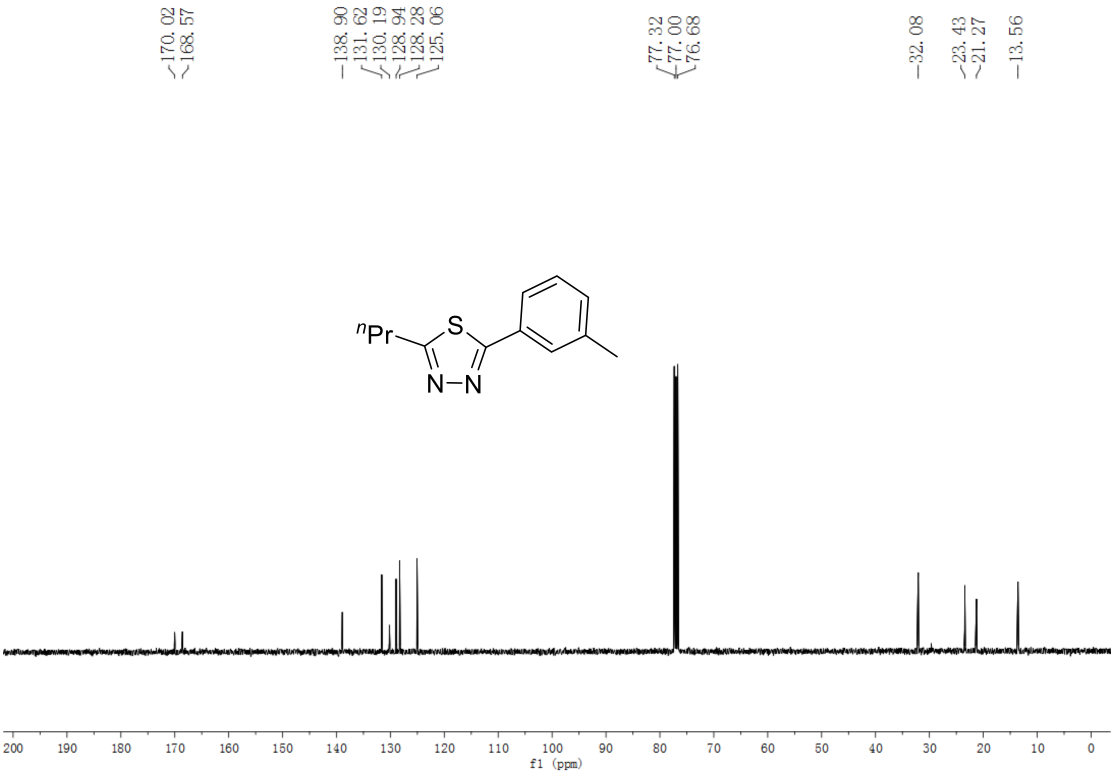
4-(5-propyl-1,3,4-thiadiazol-2-yl)benzonitrile (3ag)



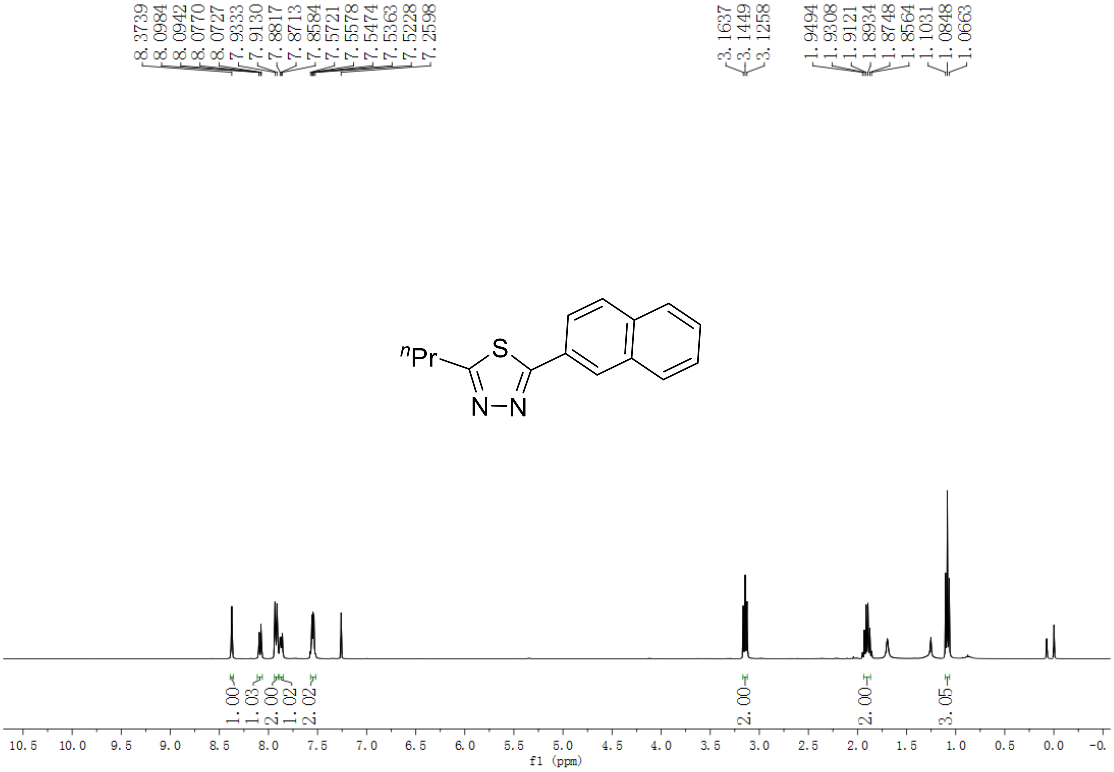


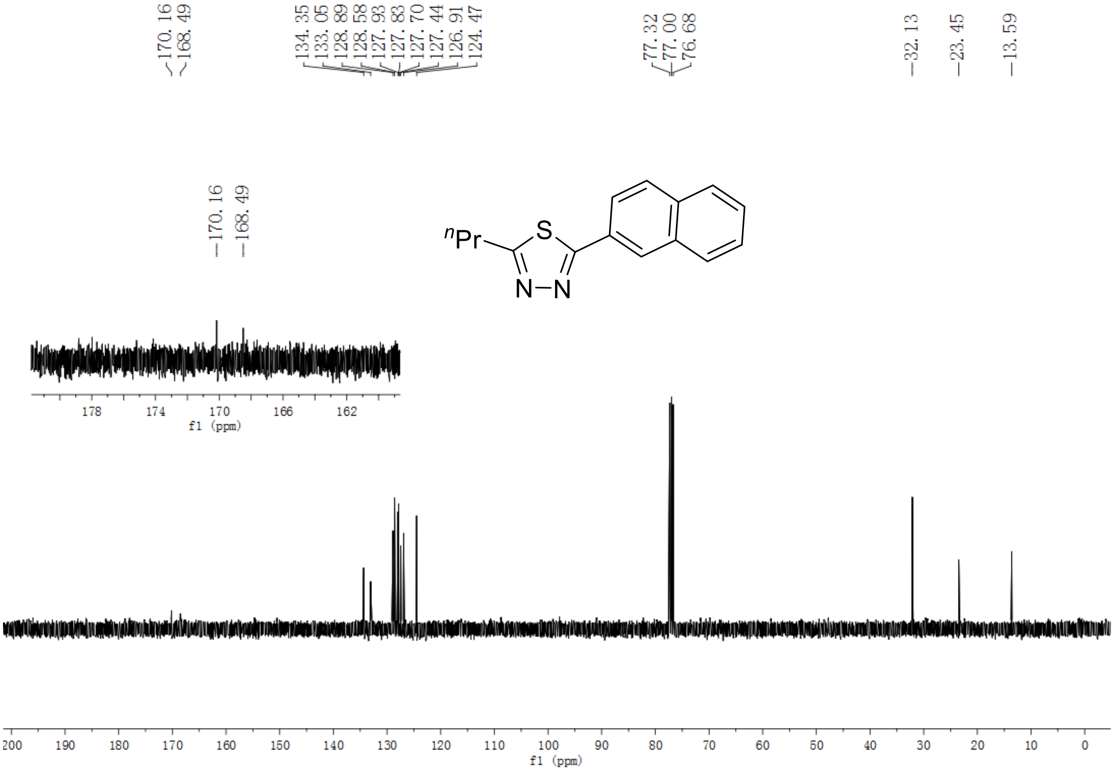
2-(*n*-propyl)-5-(*m*-tolyl)-1,3,4-thiadiazole (3ah)



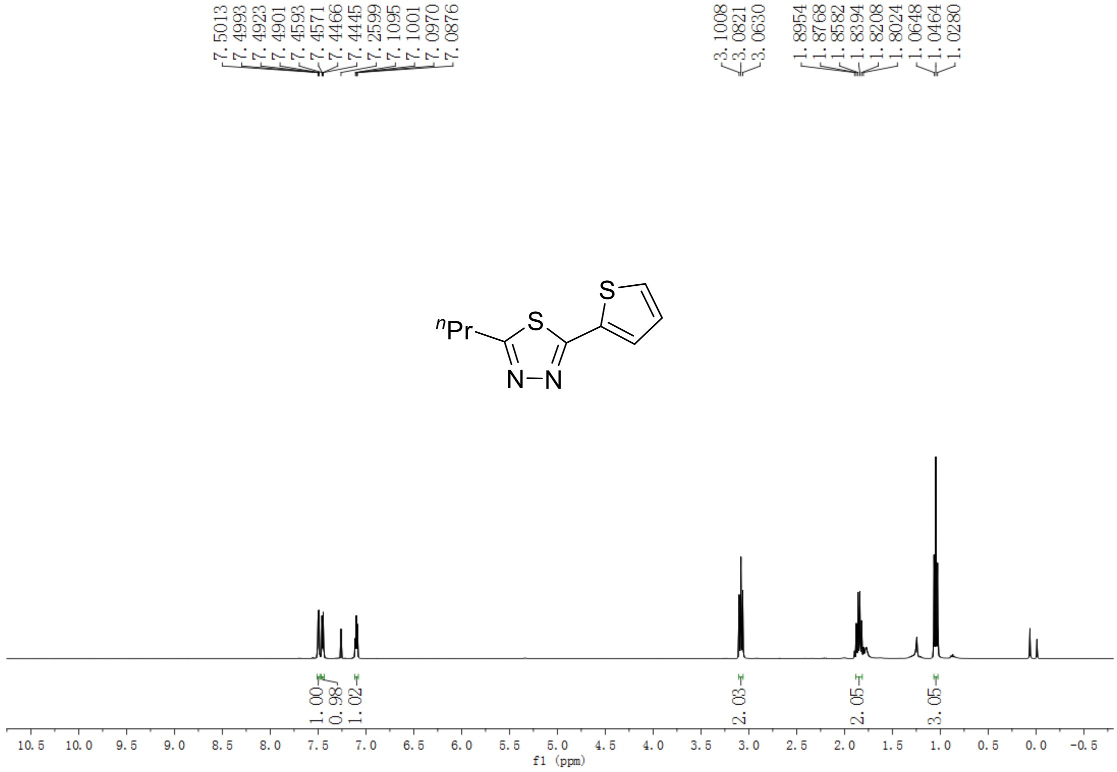


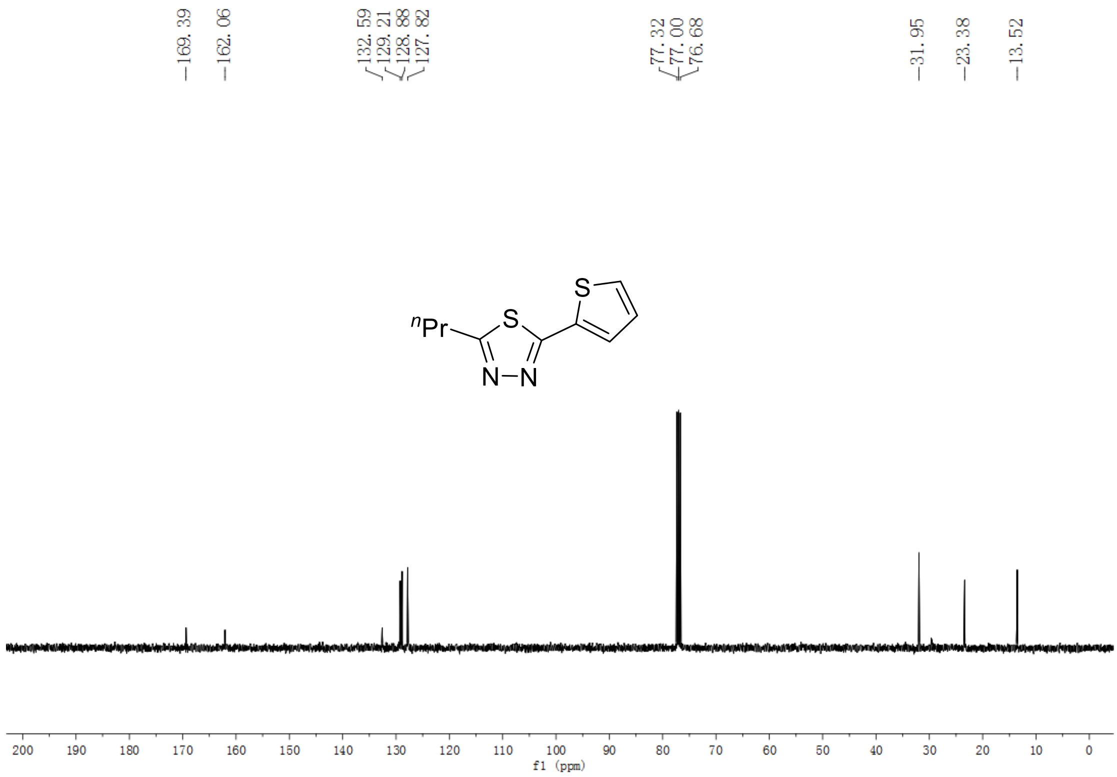
2-(*n*-propyl)-5-(naphthalen-2-yl)-1,3,4-thiadiazole (3ai)



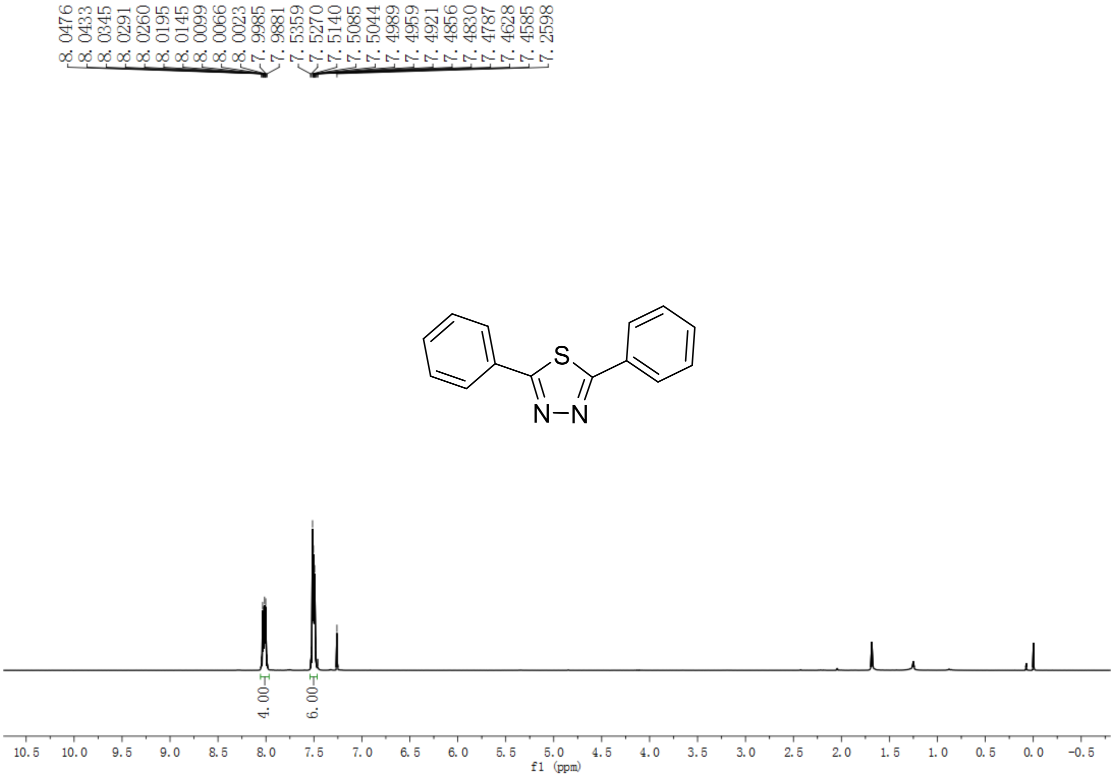


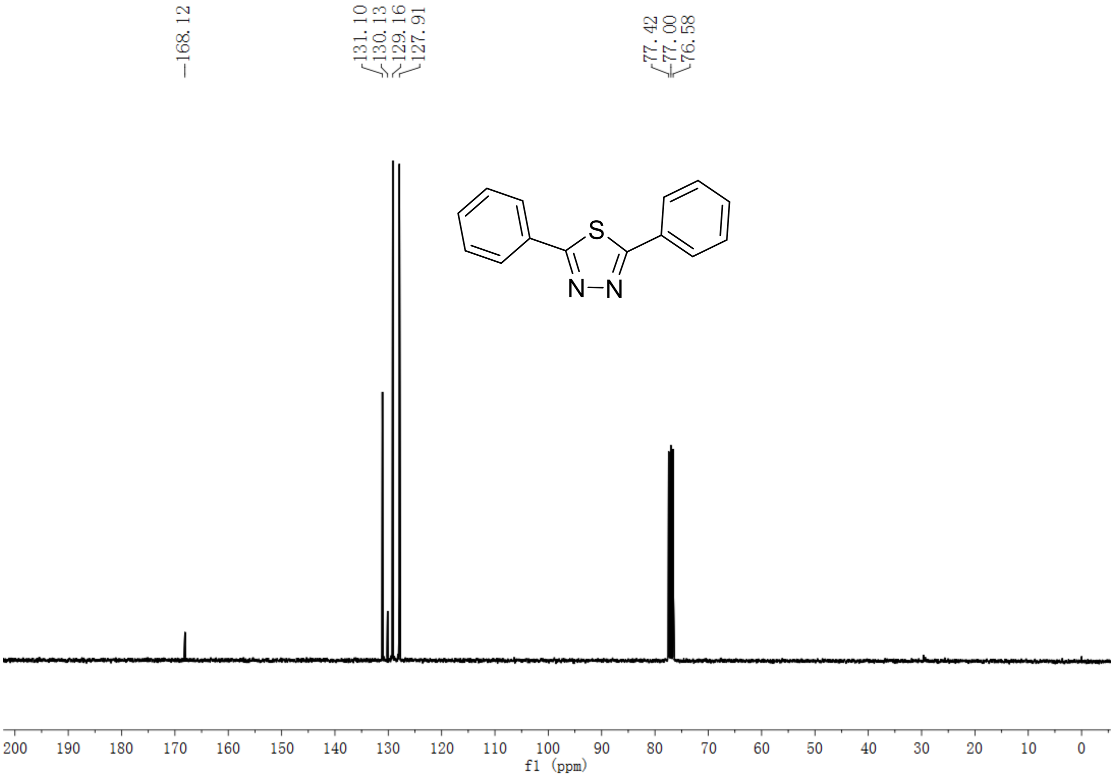
2-(*n*-propyl)-5-(thiophen-2-yl)-1,3,4-thiadiazole (3aj)





2,5-diphenyl-1,3,4-thiadiazole (4)





2,5-dicyclohexyl-1,3,4-thiadiazole (5)