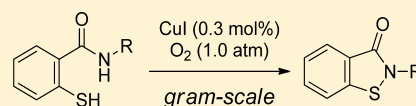


Copper-Catalyzed Intramolecular N–S Bond Formation by Oxidative Dehydrogenative Cyclization

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Supporting Information

ABSTRACT: Copper-catalyzed synthesis of benzo[*d*]isothiazol-3(2*H*)-ones and *N*-acyl-benzothiazetidine by intramolecular dehydrogenative cyclization is described. In this reaction, a new nitrogen–sulfur (N–S) bond is formed by N–H/S–H coupling. The present reaction has high functional group tolerance and gives products in gram scale. This method promotes double cyclization, allowing for synthesis of a drug intermediate.



Organic compounds bearing heteroatom–heteroatom bond(s) are important as reagents, bioactive molecules,¹ and functional materials.² Among them, there are many natural products and drugs that contain heteroatom–heteroatom bond(s) between two different heteroatoms such as N–O,³ N–S,⁴ and S–O⁵ bonds. One bioactive compound with an N–S bond is benzoisothiazolone which has effective antifungal, antibacterial, and antipsychotic properties (Figure 1).⁶ As

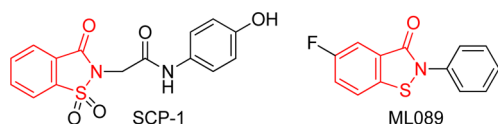
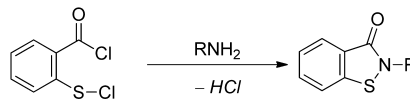


Figure 1. Bioactive molecules that contain benzo[*d*]isothiazol-3(2*H*)-one skeletons.

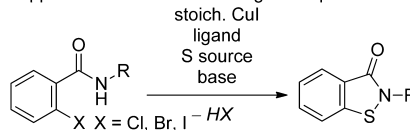
illustrated in Figure 2, several methods to construct benzoisothiazolone skeletons have been reported: (a) condensation of 2-(chlorocarbamoyl)phenyl hypochlorothioites with amines;⁷ (b) a CuI/1,10-phenanthroline-mediated reaction using 2-halo-arylamides, sulfur powder, and potassium carbonate as a substrate, S source, and base, respectively;⁸ and (c) a dehydrogenative N–H/S–H coupling reaction via the formation of an *N*-acylnitrenium ion using a hypervalent iodine reagent as an oxidant.⁹ These synthetic methods require multistep synthesis of the starting materials and/or highly reactive reagents, however, and produce some waste from the starting materials and reagents.¹⁰ We hypothesized that catalytic dehydrogenative cross-coupling reactions between N–H/S–H bonds might be the direct and efficient methods to produce benzoisothiazolones (Figure 2d). Our findings indicate that a small amount of a copper salt can promote an intramolecular dehydrogenative coupling reaction between N–H and S–H bonds to give N–S bonds using oxygen as an oxidant.

Treatment of 2-mercapto-*N*-phenylbenzamide (**1a**) with a catalytic amount of copper(I) iodide CuI in *N,N*-dimethylfor-

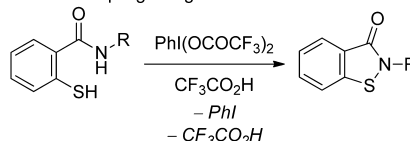
(a) Condensation of CO–Cl and S–Cl bonds with amines



(b) Copper-mediated reaction using sulfur powder



(c) N–H/S–H coupling using stoichiometric amount of a strong oxidant



(d) This work: catalytic N–H/S–H coupling

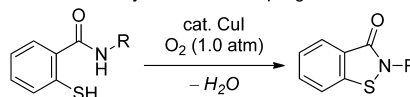


Figure 2. Previous and present methods for the synthesis of benzo[*d*]isothiazol-3(2*H*)-ones.

amide (DMF) at 70 °C for 5 h under O₂ conditions gave 2-phenylbenzo[*d*]isothiazol-3(2*H*)-one (**2a**) in quantitative yield (eq 1).^{11–18} This reaction did not proceed in the absence of O₂.



Received: May 15, 2013

The structure of **2a** was determined by single-crystal X-ray structure analysis (see the Supporting Information, Figure S1) that revealed the formation of an N–S bond and construction of a five-membered heterocyclic skeleton.

Next, the substrate scope was investigated (Table 1). *N*-aryl 2-mercaptobenzamides **1b–1l** provided the corresponding 2-

Table 1. Synthesis of Heterocyclic Compounds **2 via N–H and S–H Bond Activation of **1****

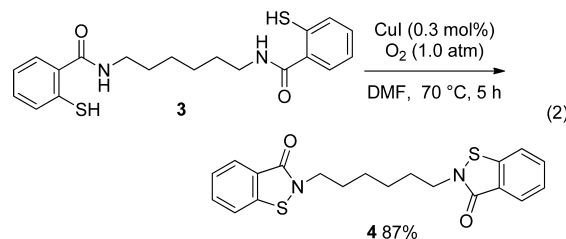
entry	1	yield / %
1		
1		2b 95
2		2c 95
3		2d 95
4		2e 99
5		2f 98
6 ^a		2g 83
7		2h 97
8		2i 98
9		2j 95
10		2k 95
11 ^a		2l 90
12		2m >99
13		2n 92
14		2o 95
15 ^a		2p 84

^aSolvent: dimethylsulfoxide (DMSO).

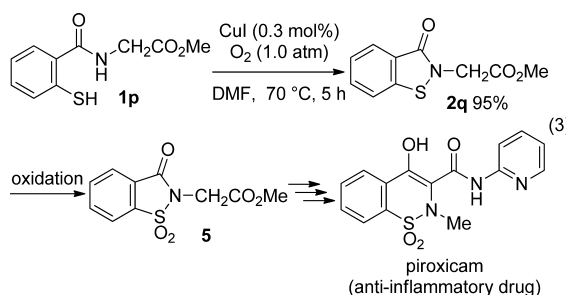
arylbenzo[d]isothiazol-3(2H)-ones **2b–2l** in excellent yields (entries 1–11). The reaction was not affected by electron-donating or -withdrawing groups (entries 1–4). In entries 5–7, the reaction proceeded without loss of the halogen atoms. The cyclization reaction was not inhibited by steric hindrance (entry 8). Pyridyl and quinolyl groups could be used as an aromatic ring on a nitrogen atom of the substrates **1k** and **1l** (entries 10 and 11). Alkyl-substituted 2-mercaptobenzamides **1m–1o**

afforded the corresponding benzoisothiazolones **2m–2o** in excellent yields (entries 12–14). The four-membered heterocyclic product **2p** was also obtained in 84% yield (entry 15). In the case of 2-(((4-fluorophenyl)amino)methyl)benzenethiol (2-(aminomethyl)benzenethiol instead of 2-(aminocarbonyl)benzenethiol), N–S bond formation proceeded; however, the reaction did not stop at this step, and further oxidation of the benzylic position also occurred to give **2d** in 29% yield.

A double-cyclization reaction also proceeded, and product **4** was obtained in 87% yield (eq 2). In this reaction, the yield of product **4** was comparable to that of single-cyclization products.



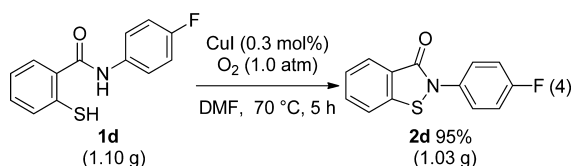
The present reaction was applied to the synthesis of a drug precursor (eq 3). Piroxicam is a nonsteroidal anti-inflammatory

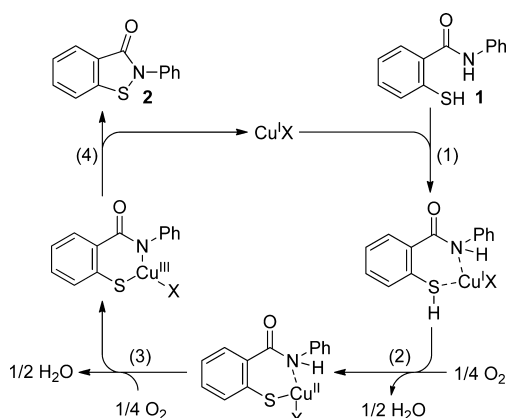


drug used to relieve the symptoms of rheumatoid and osteoarthritis, primary dysmenorrhea, and postoperative pain.^{19,20} Benzoisothiazolone **2q** could be synthesized using the present method. Oxidation of **2q**²¹ would give a precursor of piroxicam, **5**, and several successive transformations would lead to piroxicam following the reported method.^{18a}

Benzoisothiazolone **2a** was not obtained from the corresponding disulfide, which may be formed by dehydrogenative homocoupling of **1a**. This result indicated that cyclization did not proceed via formation of the disulfide. The proposed mechanism for the formation of benzoisothiazolone **2** is as follows (Scheme 1): (1) coordination of 2-mercaptobenzamide **1** to a copper atom; (2) oxidative formation of a Cu–S bond via the elimination of H₂O, (3) oxidative formation of a Cu–N bond via the elimination of H₂O²² (or the order of steps 2 and 3 is reversed), and (4) reductive elimination²³ to give benzoisothiazolone **2** and regenerate the copper catalyst.

The reaction can be performed in gram scale. Treatment of 1.10 g of **1d** with a catalytic amount of CuI produced 1.03 g of **2d** in 95% yield (eq 4), which is comparable to the yield in eq 1 (46 mg scale).



Scheme 1. Proposed Mechanism for the Formation of Benzoisothiazolone 2

In summary, we successfully achieved a copper-catalyzed synthesis of benzo[*d*]isothiazol-3(2*H*)-ones and *N*-acyl-benzothiazetidine by intramolecular dehydrogenative cyclization. This reaction proceeded using a small amount of the catalyst (0.3 mol %) and oxygen as an oxidant to form a new N–S bond by N–H/S–H coupling. Many natural products and drugs contain heteroatom–heteroatom bond(s) such as N–S bond(s), and it is therefore important to develop novel and efficient methods to construct N–S bonds. There have been several reports on the construction of N–S bonds, but there is room for improvement of the efficiency. On the other hand, the present reaction is more efficient because N–S bond-containing heterocyclic skeletons can be constructed catalytically by the direct formation of N–S bonds from NH and SH bonds. The present reaction affords products in gram scale. This method promotes double cyclization, allowing for the synthesis of a drug precursor. We believe that this reaction will be a useful method for the synthesis of heterocyclic compounds with an N–S bond.

EXPERIMENTAL SECTION

General. All reactions were carried out in dry solvents under argon atmosphere unless otherwise noted. Methyl thiosalicylate was purchased and was used without further purification. CuI (99.999% purity) was purchased from a chemical supplier and used as received. *N,N*-Dimethylformamide, methanol, dichloromethane, and dimethyl sulfoxide were purchased and were dried and degassed before use. **1c**^{24,25} was synthesized following the reported method. NMR spectra were recorded on 500 MHz (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR) and 400 MHz (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR) spectrometers. Proton chemical shifts are reported relative to residual solvent peak (CDCl₃ at 7.26 ppm, CD₃OD at 3.31 ppm, and DMSO-*d*₆ at 2.50 ppm). Carbon chemical shifts are reported relative to solvent peaks (CDCl₃ at 77.3 ppm, CD₃OD at 49.1 ppm, and DMSO-*d*₆ at 39.5 ppm). IR spectra were recorded on Fourier transform infrared spectrophotometer. High-resolution mass spectra (HRMS) were measured on a TOF spectrometer (for HRMS). The known starting materials, **1b**, **1f**, **1g**, **1j**, and **1o**, were identified by comparing their spectroscopic data with those of reported data.⁹

Typical Procedure for the Synthesis of 2-Mercapto-*N*-phenylbenzamide (1a). To a cooled (0 °C) solution of aniline (6.64 g, 71.3 mmol) in CH₂Cl₂ (150 mL) was added a solution of AlMe₃ in hexane (2.0 M, 35.7 mL, 71.3 mmol). The reaction mixture was warmed to room temperature and continued to stir for 30 min until the gas evolution ceased. Then, methyl thiosalicylate (5.00 g, 29.7 mmol) was added and the solution was refluxed for 12 h. The reaction mixture was cooled in an ice bath, and aq HCl (10%, 60 mL) was

added carefully. The solution was extracted with CH₂Cl₂ (3 × 150 mL), and the combined organic extracts were washed with a saturated aq solution of NaHCO₃ (150 mL) and brine (150 mL) consequently. Then, the organic layer was dried over sodium sulfate. After filtration and removal of the solvent under vacuum, the residue was purified by crystallization from Et₂O to afford 2-mercapto-*N*-phenylbenzamide (**1a**) as a white solid (6.52 g, 95% yield). TLC (hexane/AcOEt = 3:1): *R*_f = 0.14, ¹H NMR (400 MHz, CDCl₃) δ 7.83 (br s, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.36 (dd, *J* = 11.0, 4.2 Hz, 3H), 7.33–7.24 (m, 1H), 7.23–7.12 (m, 2H), 4.55 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 137.8, 133.7, 133.2, 131.6, 131.2, 129.3, 128.3, 125.7, 125.1, 120.5; IR (KBr, ν/cm^{−1}) 3448, 1646, 1639, 1599, 1540, 1508, 1438, 1322, 1253, 1176, 1003, 889, 753, 690; HRMS (ESI⁺) Calcd for C₁₃H₁₁NOS (M + Na⁺) 252.0454, Found 252.0454.

2-Mercapto-*N*-(4-methylphenyl)benzamide (1c). *p*-Toluidine (3.82 g, 35.7 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (1:1). 3.47 g, 96%, white solid. TLC (hexane/AcOEt = 3:1): *R*_f = 0.15, ¹H NMR (500 MHz, CDCl₃) δ 7.81 (br s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.17 (m, 3H), 4.65 (br s, 1H), 2.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.8, 135.2, 134.8, 133.7, 133.2, 131.5, 131.1, 129.8, 128.2, 125.6, 120.6, 21.2; IR (KBr, ν/cm^{−1}) 3435, 1644, 1514, 1403, 1321, 1300, 1253, 1113, 1060, 1038, 941, 894, 814, 785, 741, 652; HRMS (ESI⁺) Calcd for C₁₇H₁₁NOS (M + Na⁺) 264.0454, Found 264.0456. HRMS (ESI⁺) Calcd for C₁₄H₁₃NOS (M + Na⁺) 266.0610, Found 266.0610.

***N*-(4-Fluorophenyl)-2-mercaptobenzamide (1d).** 4-Fluoroaniline (6.51 mL, 71.3 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (3:1). 6.01 g, 82%, white solid, TLC (hexane/AcOEt = 3:1): *R*_f = 0.39, ¹H NMR (500 MHz, DMSO) δ 10.44 (br s, 1H), 7.75 (dd, *J* = 8.9, 8.9 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.36 (td, *J* = 7.7, 1.2 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.24–7.14 (m, 2H), 5.28 (br s, 1H); ¹³C NMR (100 MHz, DMSO) δ 166.4, 158.3 (*J* = 238 Hz), 135.4 (*J* = 2.4 Hz), 133.9, 133.2, 130.6, 128.6, 124.7, 121.7 (*J* = 8.4 Hz), 115.3 (*J* = 22.7 Hz); IR (KBr, ν/cm^{−1}) 3333, 2955, 2928, 2856, 1634, 1540, 1457, 1433, 1314, 1038, 742; HRMS (ESI⁺) Calcd for C₁₃H₁₀FNOS (M + Na⁺) 270.0359, Found 270.0357.

***N*-(4-Cyanophenyl)-2-mercaptobenzamide (1e).** 4-aminobenzonitrile (3.37 g, 11.9 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (3:1). 1.84 g, 61%, light-yellow solid, TLC (hexane/AcOEt = 2:1): *R*_f = 0.31, ¹H NMR (400 MHz, CDCl₃) δ 7.81–7.74 (m, 2H), 7.67–7.56 (m, 3H), 7.34 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 4.35 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 142.0, 133.54, 133.49, 132.8, 132.0, 131.8, 128.4, 125.9, 120.2, 119.0, 107.8; IR (KBr/cm^{−1}) 3446, 2887, 2778, 2359, 2342, 1637, 1541, 1275, 1104, 749, 668, 648; HRMS (ESI⁺) Calcd for C₁₄H₁₀N₂OS (M + Na⁺) 277.0406, Found 277.0415.

***N*-(2-Bromo-4-methylphenyl)-2-mercaptobenzamide (1h).** 2-Bromo-4-methylaniline (3.98 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (2:1). 2.57 g, 90%, white solid, TLC (hexane/AcOEt = 3:1): *R*_f = 0.25, ¹H NMR (500 MHz, CDCl₃) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.36–7.32 (m, 1H), 7.27–7.22 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 0.8 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.5, 139.0, 135.4, 134.6, 132.9, 132.1, 131.9, 131.5, 128.0, 126.8, 125.8, 122.8, 110.8, 21.6; IR (KBr, ν/cm^{−1}) 3257, 1643, 1526, 1474, 1303, 1029, 797, 740; HRMS (ESI⁺) Calcd for C₁₄H₁₂BrNOS (M + Na⁺) 343.9715, Found 343.9711.

***N*-(2,6-Dimethylphenyl)-2-mercaptobenzamide (1i).** 2,6-Dimethylaniline (2.59 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (1:1). 2.08 g, 90%, yellow white solid, TLC (hexane/AcOEt = 3:1): *R*_f = 0.11, ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.23–7.04 (m, 4H), 4.84 (s, 1H), 2.30 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 167.5, 135.8, 133.6, 133.5, 131.4, 131.1, 128.5, 128.2, 128.1,

127.9, 125.5, 18.8; IR (KBr, ν/cm^{-1}) 3433, 2956, 2928, 2856, 1634, 1540, 1457, 1433, 1313, 1263, 1038, 1009, 742, 649; HRMS (ESI⁺) Calcd for C₁₅H₁₅NOS (M + Na⁺) 280.0767, Found 280.0770.

2-Mercapto-*N*-(3-pyridinyl)benzamide (1k). Pyridin-3-amine (2.01 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O. 1.78 g, 87%, white solid, TLC (hexane/AcOEt = 1:1): R_f = 0.42, ¹H NMR (500 MHz, CD₃OD) δ 8.86 (d, J = 2.3 Hz, 1H), 8.31 (dd, J = 4.5, 1.2 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 7.9, 1.2 Hz, 1H), 7.46 (t, J = 4.5 Hz, 1H), 7.45 (s, 1H), 7.35 (td, J = 7.9, 1.2 Hz, 1H), 7.25 (td, J = 7.9, 1.2 Hz, 1H); ¹³C NMR (125 MHz, CD₃OD) δ 169.9, 145.5, 142.4, 137.7, 135.0, 134.8, 132.4, 132.2, 129.9, 129.7, 126.2, 125.5; IR (KBr, ν/cm^{-1}) 3442, 2721, 1637, 1558, 1540, 1456, 1419, 1330, 1302, 1129, 1005, 742, 630; HRMS (ESI⁺) Calcd for C₁₂H₁₀N₂OS (M + Na⁺) 253.0406, Found 253.0407.

2-Mercapto-*N*-(3-quinolinyl)benzamide (1l). Quinolin-3-amine (3.08 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O. 2.11 g, 84%, brown white solid, TLC (hexane/AcOEt = 1:1): R_f = 0.45, ¹H NMR (400 MHz, CDCl₃) δ 8.95 (d, J = 2.3 Hz, 1H), 8.85 (d, J = 2.3 Hz, 1H), 8.26 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.90–7.81 (m, 1H), 7.72–7.68 (m, 1H), 7.67–7.64 (m, 1H), 7.57 (ddd, J = 7.8, 7.8, 1.3 Hz, 1H), 7.41 (dd, J = 7.8, 1.3 Hz, 1H), 7.35 (td, J = 7.8, 1.3 Hz, 1H), 7.25 (td, J = 7.8, 1.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 167.3, 145.5, 144.1, 133.6, 132.9, 131.9, 131.7, 131.6, 129.1, 128.9, 128.43, 128.39, 128.1, 127.7, 125.9, 124.8; IR (KBr, ν/cm^{-1}) 3438, 1637, 1542, 1508, 1489, 1466, 1420, 1366, 1300, 1144, 990, 782, 741; HRMS (ESI⁺) Calcd for C₁₆H₁₂N₂OS (M + Na⁺) 303.0563, Found 303.0562.

***N*-Hexyl-2-mercaptobenzamide (1m).** Hexan-1-amine (3.64 g, 35.7 mmol), instead of aniline, was used following the general procedure. Purification: flash column chromatography with hexane/EtOAc (5:1). 3.26 g, 92%, blue–white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.23, ¹H NMR (500 MHz, CDCl₃) δ 7.40 (dd, J = 7.6, 1.2 Hz, 1H), 7.30 (dd, J = 7.6, 1.2 Hz, 1H), 7.23 (td, J = 7.6, 1.2 Hz, 1H), 7.11 (dd, J = 7.6, 7.6 Hz, 1H), 6.14 (s, 1H), 4.75 (s, 1H), 3.41 (m, 6.9 Hz, 2H), 1.64–1.53 (m, 2H), 1.42–1.24 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.8, 133.7, 133.0, 131.1, 130.7, 128.0, 125.3, 40.3, 31.7, 29.7, 26.9, 22.8, 14.2; IR (KBr, ν/cm^{-1}) 3433, 2955, 2928, 2855, 1634, 1620, 1540, 1457, 1433, 1313, 1263, 1162, 1038, 742; HRMS (ESI⁺) Calcd for C₁₃H₁₉NOS (M + Na⁺) 260.1080, Found 260.1080.

***N*-(*tert*-Butyl)-2-mercaptobenzamide (1n).** 2-Methylpropan-2-amine (2.27 mL, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et₂O/hexane (3:1). 1.76 g, 95%, brown–white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.27, ¹H NMR (500 MHz, CDCl₃) δ 7.39 (dd, J = 7.7, 1.3 Hz, 1H), 7.32–7.28 (m, 1H), 7.26–7.22 (m, 1H), 7.13 (m, 1H), 5.80 (s, 1H), 4.62 (s, 1H), 1.48 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 168.4, 135.0, 132.3, 131.0, 130.4, 127.9, 125.4, 52.2, 29.0; IR (KBr, ν/cm^{-1}) 3298, 2977, 2890, 1632, 1587, 1536, 1470, 1446, 1361, 1319, 1272, 1221, 1044, 878, 742, 676; HRMS (ESI⁺) Calcd for C₁₁H₁₅NOS (M + Na⁺) 232.0767, Found 232.0764.

***N*-(2-Mercaptophenyl)benzamide (1p).** 0.75 g, 75%, white solid, TLC (hexane/AcOEt = 1:2): R_f = 0.15, ¹H NMR (500 MHz, CDCl₃) δ 8.94 (s, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.73–7.66 (m, 2H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 7.50–7.41 (m, 3H), 7.31 (dd, J = 7.8, 7.8 Hz, 1H), 6.95 (td, J = 7.8, 1.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.2, 140.2, 136.9, 134.6, 132.6, 132.3, 129.1, 127.3, 124.6, 123.7, 120.8; IR (KBr, ν/cm^{-1}) 3445, 3120, 2980, 2960, 1681, 1577, 1509, 1478, 1433, 1313, 1225, 963, 766, 729, 688, 623; HRMS (ESI⁺) Calcd for C₁₃H₁₁NOS (M + Na⁺) 252.0454, Found 252.0451.

Methyl 2-(2-mercaptobenzamido)acetate (1q). 1.02 g, 76%, yellow oil, TLC (hexane/AcOEt = 1:2): R_f = 0.35, ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.45–7.35 (m, 1H), 7.29–7.19 (m, 1H), 6.64 (s, 1H), 4.23 (d, J = 5.1 Hz, 2H), 3.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 167.9, 137.7, 133.4, 131.9, 128.2, 127.9, 126.6, 52.8, 42.0; IR (KBr, ν/cm^{-1}) 3420, 2924, 2851, 1748, 1734, 1646, 1636, 1541, 1212, 1173, 1092, 801, 745, 635; HRMS (ESI⁺) Calcd for C₁₀H₁₁NO₃S (M + Na⁺) 248.0352, Found 248.0350.

Typical procedure for copper-catalyzed intramolecular N–S bond formation: Synthesis of 2-phenylbenzo[d]isothiazol-3(2*H*)-one (2a). A mixture of 2-mercapto-*N*-phenylbenzamide (1a, 45.9 mg, 0.20 mmol), CuI (0.11 mg, 0.60 μ mol), and DMF (2.0 mL) was stirred at 70 °C for 5 h under oxygen. Then, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. After filtration and removal of the solvent in vacuo, the residue was subjected to the flash column chromatography on silica gel with hexane/AcOEt (3:1) as eluent to give 2-phenylbenzo[d]isothiazol-3(2*H*)-one (2a, white solid, 45.6 mg, >99% yield). TLC (hexane/AcOEt = 2:1): R_f = 0.43, ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 2H), 7.63 (dd, J = 7.7, 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.50–7.39 (m, 3H), 7.30 (t, J = 7.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 164.2, 140.0, 137.4, 132.5, 129.5, 127.3, 127.2, 125.9, 125.0, 124.7, 120.3; IR (KBr, ν/cm^{-1}) 3447, 1653, 1592, 1487, 1448, 1323, 1301, 1267, 1114, 1017, 753, 737, 688, 670, 609; HRMS (ESI⁺) Calcd for C₁₃H₉NOS (M + Na⁺) 250.0297, Found 250.0299.

2-(4-Methoxyphenyl)benzo[d]isothiazol-3(2*H*)-one (2b): 48.6 mg, 95%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.29, ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 7.6, 7.6 Hz, 1H), 7.57–7.53 (m, 3H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.02–6.90 (m, 2H), 3.83 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.5, 158.9, 140.2, 132.3, 129.9, 127.3, 127.0, 125.9, 124.8, 120.3, 114.8, 55.8; IR (KBr, ν/cm^{-1}) 3465, 2835, 1651, 1508, 1447, 1329, 1297, 1248, 1179, 1128, 1030, 972, 860, 826, 783, 738, 671; HRMS (ESI⁺) Calcd for C₁₄H₁₁NO₃S (M + Na⁺) 280.0403, Found 280.0402.

2-(*p*-Tolyl)benzo[d]isothiazol-3(2*H*)-one (2c): 45.8 mg, 95%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.54, ¹H NMR (500 MHz, CDCl₃) δ 7.81 (dd, J = 8.0, 8.0 Hz, 1H), 7.40–7.32 (m, 1H), 7.27 (m, 3H), 7.18–7.10 (m, 1H), 6.98 (d, J = 8.0 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.4, 140.2, 137.4, 134.8, 132.4, 130.1, 127.3, 125.9, 125.1, 124.9, 120.3, 21.3; IR (KBr, ν/cm^{-1}) 3458, 1644, 1505, 1447, 1330, 1313, 1269, 1127, 928, 883, 814, 786, 749, 676, 636; HRMS (ESI⁺) Calcd for C₁₄H₁₁NOS (M + Na⁺) 264.0454, Found 264.0456.

2-(4-Fluorophenyl)benzo[d]isothiazol-3(2*H*)-one (2d): 46.5 mg, 95%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.32, ¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 7.9 Hz, 1H), 7.69–7.59 (m, 3H), 7.55 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 7.9, 7.9 Hz, 1H), 7.13 (dd, J = 7.9, 7.9 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 164.3, 161.3 (J = 246 Hz), 139.9, 133.2, 132.6, 127.3, 126.9 (J = 8.4 Hz), 126.0, 124.6, 120.3, 116.4 (J = 22.7 Hz); IR (KBr, ν/cm^{-1}) 3450, 1657, 1599, 1505, 1460, 1447, 1417, 1333, 1310, 1298, 1233, 1159, 1127, 824, 802, 732, 669; HRMS (ESI⁺) Calcd for C₁₃H₈FNOS (M + Na⁺) 268.0203, Found 268.0204.

4-(3-Oxobenzo[d]isothiazol-2(3*H*)-yl)benzonitrile (2e): 50.2 mg, 99%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.30, ¹H NMR (500 MHz, CDCl₃) δ 8.10 (d, J = 7.8 Hz, 1H), 7.99–7.92 (m, 2H), 7.78–7.68 (m, 3H), 7.60 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 11.3, 4.3 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 164.4, 141.8, 139.4, 133.5, 133.4, 127.7, 126.5, 124.8, 123.5, 120.4, 118.5, 109.7; IR (KBr, ν/cm^{-1}) 3446, 2887, 2778, 2359, 2342, 1637, 1541, 1275, 1104, 749, 668, 648; HRMS (ESI⁺) Calcd for C₁₄H₈N₂OS (M + Na⁺) 275.0255, Found 275.0261.

2-(2-Bromophenyl)benzo[d]isothiazol-3(2*H*)-one (2f): 59.8 mg, 98%, brown solid, TLC (hexane/AcOEt = 3:1): R_f = 0.36, ¹H NMR (400 MHz, CDCl₃) δ 8.16–8.12 (m, 1H), 7.74 (dd, J = 7.8, 1.6 Hz, 1H), 7.71–7.66 (m, 1H), 7.62–7.58 (m, 1H), 7.46 (m, 3H), 7.34 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 164.9, 141.5, 135.5, 134.1, 132.7, 131.5, 131.2, 128.7, 127.6, 126.0, 124.3, 123.6, 120.5; IR (KBr, ν/cm^{-1}) 3446, 3063, 1667, 1595, 1471, 1445, 1328, 1309, 1250, 1131, 1047, 782, 755, 739, 671, 656, 613; HRMS (ESI⁺) Calcd for C₁₃H₈BrNOS (M + Na⁺) 327.9402, Found 327.9398.

2-(2-Iodophenyl)benzo[d]isothiazol-3(2*H*)-one (2g): reaction conditions: DMSO (2 mL), 100 °C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 1:1) 58.6 mg, 83%, brown solid, TLC (hexane/AcOEt = 3:1): R_f = 0.28, ¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.71–7.66 (m,

1H), 7.62–7.58 (m, 1H), 7.50–7.41 (m, 3H), 7.19–7.15 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 164.7, 141.4, 140.4, 139.1, 132.7, 131.3, 130.9, 129.7, 127.7, 126.0, 123.9, 120.6, 99.7; IR (KBr, ν/cm⁻¹) 3447, 2921, 1660, 1596, 1464, 1447, 1328, 1308, 1250, 1131, 1019, 908, 781, 755, 738, 670, 613; HRMS (ESI⁺) Calcd for C₁₃H₈INOS (M + Na⁺) 375.9263, Found 375.9258.

2-(2-Bromo-4-methylphenyl)benzo[d]isothiazol-3(2H)-one (2h): 62.0 mg, 97%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.33, ¹H NMR (500 MHz, CDCl₃) δ 8.12 (d, J = 8.0 Hz, 1H), 7.67 (td, J = 8.0, 1.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 8.0, 8.0 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H), 7.14 (dd, J = 8.0, 1.5 Hz, 1H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.0, 141.5, 139.1, 135.1, 133.6, 132.6, 132.1, 132.0, 127.6, 125.9, 123.7, 120.7, 120.5, 21.0; IR (KBr, ν/cm⁻¹) 3446, 1645, 1474, 1444, 1400, 1324, 1308, 1249, 1113, 1038, 1017, 810, 785, 737, 670, 623; HRMS (ESI⁺) Calcd for C₁₄H₁₀BrNOS (M + Na⁺) 341.9559, Found 341.9557.

2-(2,6-Dimethylphenyl)benzo[d]isothiazol-3(2H)-one (2i): 50.1 mg, 98%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.38, ¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, J = 7.8 Hz, 1H), 7.72–7.64 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.45 (m, 1H), 7.29–7.24 (m, 1H), 7.17 (d, J = 7.8 Hz, 2H), 2.20 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 164.6, 141.6, 138.4, 133.6, 132.3, 129.9, 128.8, 127.6, 125.7, 124.4, 120.7, 18.2; IR (KBr, ν/cm⁻¹) 3444, 2951, 2919, 2854, 1653, 1598, 1471, 1445, 1325, 1307, 1245, 1129, 775, 740; HRMS (ESI⁺) Calcd for C₁₅H₁₃NOS (M + Na⁺) 278.0610, Found 278.0607.

2-(1-Naphthalenyl)benzo[d]isothiazol-3(2H)-one (2j): 52.8 mg, 95%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.30, ¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, J = 7.8 Hz, 1H), 7.99–7.92 (m, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.59–7.47 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 141.7, 134.7, 132.8, 132.6, 130.9, 130.3, 128.7, 127.9, 127.6, 127.5, 127.0, 126.0, 125.6, 123.9, 123.2, 120.5; IR (KBr, ν/cm⁻¹) 3444, 1659, 1596, 1507, 1446, 1394, 1305, 1272, 1139, 908, 798, 770, 739, 672, 645, 613; HRMS (ESI⁺) Calcd for C₁₇H₁₁NOS (M + Na⁺) 300.0454, Found 300.0449.

2-(3-Pyridinyl)benzo[d]isothiazol-3(2H)-one (2k): 43.8 mg, 95%, brown solid, TLC (hexane/AcOEt = 2:1): R_f = 0.43, ¹H NMR (500 MHz, CDCl₃) δ 8.93 (d, J = 2.2 Hz, 1H), 8.53 (d, J = 3.9 Hz, 1H), 8.16 (m, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 8.0 Hz, 1H), 7.40 (dd, J = 8.0, 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 164.6, 147.7, 145.1, 139.9, 134.7, 133.1, 131.7, 127.5, 126.3, 124.3, 124.0, 120.5; IR (KBr, ν/cm⁻¹) 3688, 3647, 3472, 3098, 1670, 1652, 1574, 1481, 1446, 1424, 1322, 1301, 1133, 801, 781, 734, 699, 670, 633; HRMS (ESI⁺) Calcd for C₁₂H₈N₂OS (M + Na⁺) 251.0250, Found 251.0240.

2-(3-Quinoliny)benzo[d]isothiazol-3(2H)-one (2l): reaction conditions: DMSO (2.0 mL), 100 °C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 1:1) 50.2 mg, 90%, brown solid, TLC (hexane/AcOEt = 3:1): R_f = 0.25, ¹H NMR (500 MHz, CDCl₃) δ 9.28 (d, J = 2.6 Hz, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 7.8 Hz, 2H), 7.88 (d, J = 7.8 Hz, 1H), 7.77–7.69 (m, 2H), 7.66–7.59 (m, 2H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 164.8, 146.8, 146.6, 140.1, 133.1, 131.4, 130.3, 130.1, 129.6, 128.1, 127.93, 127.87, 127.6, 126.4, 124.4, 120.6; IR (KBr, ν/cm⁻¹) 3442, 1664, 1630, 1597, 1426, 1344, 1320, 1296, 1423, 1107, 974, 781, 733, 670; HRMS (ESI⁺) Calcd for C₁₆H₁₀N₂OS (M + Na⁺) 301.0406, Found 301.0409.

2-Hexylbenzo[d]isothiazol-3(2H)-one (2m): 46.8 mg, >99%, pale-yellow solid, TLC (hexane/AcOEt = 3:1): R_f = 0.52, ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 7.5 Hz, 1H), 7.62–7.57 (m, 1H), 7.57–7.52 (m, 1H), 7.39 (ddd, J = 7.5, 7.5, 1.3 Hz, 1H), 3.89 (td, J = 7.4, 2.6 Hz, 2H), 1.82–1.68 (m, 2H), 1.42–1.24 (m, 6H), 0.88 (t, J = 5.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.5, 140.3, 131.8, 126.8, 125.6, 125.1, 120.5, 44.2, 31.6, 29.7, 26.5, 22.7, 14.2; IR (KBr, ν/cm⁻¹) 3457, 2955, 2928, 2857, 1649, 1598, 1447, 1339, 1303, 1248, 1189, 740, 673; HRMS (ESI⁺) Calcd for C₁₃H₁₇NOS (M + Na⁺) 258.0923, Found 258.0918.

2-(tert-Butyl)benzo[d]isothiazol-3(2H)-one (2n): 38.2 mg, 92%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.55, ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.7, 7.7 Hz,

1H), 7.48 (d, J = 7.7 Hz, 1H), 7.34 (dd, J = 7.7, 7.7 Hz, 1H), 1.69 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 165.8, 139.6, 131.5, 127.1, 126.3, 125.3, 119.9, 58.9, 28.6; IR (KBr, ν/cm⁻¹) 3479, 3065, 2970, 2929, 1644, 1594, 1540, 1394, 1365, 1324, 1303, 1204, 1155, 786, 741, 675; HRMS (ESI⁺) Calcd for C₁₁H₁₃NOS (M + Na⁺) 230.0616, Found 230.0608.

2-Allylbenzo[d]isothiazol-3(2H)-one (2o): 36.2 mg, 95%, yellow–white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.35, ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 8.2 Hz, 1H), 7.59 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 7.6, 7.6 Hz, 1H), 5.93 (ddt, J = 17.8, 12.0, 7.4 Hz, 1H), 5.33 (ddt, J = 17.8, 1.1, 1.0 Hz, 1H), 5.30 (ddt, J = 12.0, 1.3, 1.1 Hz, 1H), 4.56 (ddd, J = 7.4, 1.3, 1.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 165.3, 140.6, 132.6, 126.9, 125.7, 124.9, 120.6, 119.5, 46.4; IR (KBr, ν/cm⁻¹) 3447, 2918, 1644, 1447, 1334, 1314, 1284, 1240, 1192, 990, 932, 785, 740, 673; HRMS (ESI⁺) Calcd for C₁₀H₉NOS (M + Na⁺) 214.0297, Found 214.0293.

7-Thia-8-azabicyclo[4.2.0]octa-1,3,5-trien-8-yl(phenyl)-methanone (2p): reaction conditions: DMSO (2.0 mL), 100 °C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 3:1): 38.0 mg, 84%, white solid, TLC (hexane/AcOEt = 3:1): R_f = 0.63, ¹H NMR (500 MHz, CDCl₃) δ 8.09 (m, 3H), 7.91 (d, J = 7.6 Hz, 1H), 7.50 (m, 4H), 7.39 (dd, J = 7.6, 7.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 168.3, 154.4, 135.3, 133.9, 131.2, 129.3, 127.8, 126.6, 125.4, 123.5, 121.9; IR (KBr, ν/cm⁻¹) 3065, 3019, 1509, 1478, 1455, 1314, 1225, 1159, 1071, 963, 908, 764, 730, 688, 666, 622; HRMS (ESI⁺) Calcd for C₁₃H₉NOS (M + Na⁺) 250.0297, Found 250.0298.

Methyl 2-(3-oxobenzo[d]isothiazol-2(3H)-yl)acetate (2q): 43.0 mg, 96%, yellow oil, TLC (hexane/AcOEt = 1:2): R_f = 0.34, ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.42 (dd, J = 7.8, 7.8 Hz, 1H), 4.62 (s, 2H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.3, 166.1, 141.0, 132.6, 127.1, 125.9, 123.5, 120.6, 52.9, 44.8; IR (KBr, ν/cm⁻¹) 3446, 1749, 1647, 1636, 1339, 1316, 1213, 1088, 742; HRMS (ESI⁺) Calcd for C₁₀H₉NO₃S (M + Na⁺) 246.0195, Found 246.0186.

N,N'-(Hexane-1,6-diyl)bis(2-mercaptobenzamide) (3): 3.43 g, 93%, light green solid, TLC (hexane/AcOEt = 1:2): R_f = 0.18; ¹H NMR (400 MHz, DMSO) δ 8.51 (s, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 7.27 (dd, J = 7.5, 7.5 Hz, 2H), 7.15 (dd, J = 7.5, 7.5 Hz, 2H), 5.36 (s, 2H), 3.29–3.11 (m, 4H), 1.52 (m, 4H), 1.36 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 133.7, 133.1, 131.2, 130.8, 128.1, 125.5, 39.8, 29.7, 26.4; IR (KBr, ν/cm⁻¹) 3455, 3010, 2920, 1702, 1637, 1540, 1424, 1368, 1317, 1236, 1093, 744; HRMS (ESI⁺) Calcd for C₂₀H₂₄N₂O₂S₂ (M + Na⁺) 411.1171, Found 411.1156.

2,2'-(Hexane-1,6-diyl)bis(benzo[d]isothiazol-3(2H)-one) (4): 66.0 mg, 87%, white solid, TLC (hexane/AcOEt = 1:2): R_f = 0.34; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, J = 7.5 Hz, 2H), 7.59 (dd, J = 7.5, 7.5 Hz, 2H), 7.54 (d, J = 7.5 Hz, 2H), 7.40 (dd, J = 7.5, 7.5 Hz, 2H), 3.89 (t, J = 7.1 Hz, 4H), 1.81–1.73 (m, 4H), 1.50–1.41 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 140.3, 131.9, 126.9, 125.7, 125.0, 120.6, 44.0, 30.0, 26.4; IR (KBr, ν/cm⁻¹) 3453.9, 2929.3, 2856.1, 2799.2, 1638.2, 1459.9, 1446.4, 1187.9, 1160.0, 1100.2, 786.8, 741.5, 674.0; HRMS (ESI⁺) Calcd for C₂₀H₂₀N₂O₂S₂ (M + Na⁺) 407.0858, Found 407.0840.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all compounds; crystallographic information file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported in part by ERATO from JST.

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- (12) Investigation of the amount of catalyst loading (CuI, O₂, 1.0 atm; DMF; 70 °C; 6 h): 0.10 mol %, 87%; 0.30 mol %, 99%; 0.50 mol %, 99%.
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