“One-Pot” CuCl₂-Mediated Condensation/C–S Bond Coupling Reactions to Synthesize Dibenzothiazepines by Bi-Functional-Reagent N, N′-Dimethylethane-1,2-Diamine

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Abstract: The efficient “One-pot” CuCl₂-catalyzed C–S bond coupling reactions were developed for the synthesis of dibenzo[b,f][1,4]thiazepines and 11-methyldibenzo[b,f][1,4]thiazepines via 2-iodobenzaldehydes/2-iodoacetophenones with 2-aminobenzenethiols/2,2′-disulfanediyldianilines by using bifunctional-reagent N, N′-dimethylethane-1,2-diamine (DMEDA), which worked as ligand and reductant. The reactions were compatible with a range of substrates to give the corresponding products in moderate to excellent yields.

Keywords: “one-pot”; CuCl₂-catalyzed; C–S bond coupling; bi-functional-reagent; DMEDA; dibenzothiazepines

1. Introduction

Dibenzothiazepine derivatives are a class of molecules with important biological and pharmaceutical activities [1–4]. For example, Clotiapine (A) has good anti-hallucination, the delusion and the anti-excited restlessness function [5]. Quetiapine fumarate (B) is effective for both positive symptoms and negative symptoms of schizophrenia, it can also reduce the emotional symptoms associated with schizophrenia, such as depression, anxiety and cognitive deficits [6–8]. The 6-Sulfamoyl-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid (C) is a structural analogue of nitroxazepine with high activity, indicating its potential medicinal value (Figure 1) [9].
Compared to the previous reports of synthesizing dibenzothiazepines in entry 1, our research used DMEDA in small quantities as a bifunctional reagent, which worked as ligand and reductant; the substrate scope is wide (the reaction substrates 2-iodobenzaldehydes/2-iodoacetophenones and 2-aminobenzenethiols/2,2′-disulfanediyldianilines could cross-react with each other) and the reaction conditions were simplified, making the reaction conditions more suitable for large-scale production.

Figure 1. Some biological and pharmaceutical active dibenzothiazepines.
2. Results

First, 2-iodobenzaldehyde (1a) and 2,2'-Disulfanediyldianiline (1b) were selected to optimize the reaction conditions (Table 1). The reaction was conducted with CuCl₂ (15 mol%), 1a (0.3 mmol), 1b (0.15 mmol), Cs₂CO₃ (0.6 mmol) and 4 Å molecular sieve (25 mg) in DMEDA (0.50 mL) at 110 °C under N₂ atmosphere for 24 h, the product 1c was produced in 73% (Table 1, entry 1). When we decreased the amount of DMEDA, 0.25 mL showed the best results (Table 1, entries 1–3). There was a significant decrease without inorganic base Cs₂CO₃ (Table 1, entry 4). When K₃PO₄ (0.6 mmol) was used for the reaction, 1c was improved in 82% yield (Table 1, entries 5–6). Then, the reaction temperature was screened, it was found that higher reaction temperature did not change the reaction yield; 110 °C was the best choice (Table 1, entries 7–8). Finally, other copper salts, such as Cu(OAc)₂, CuSO₄·5H₂O, CuI, were surveyed under the conditions, the yields of 1c were not increased (Table 1, entries 9–11). Without the 4 Å molecular sieves, the reaction yield was also reduced (Table 1, entry 12). A gram-scale reaction was also conducted, the yield of 1c was the same as entry 5 (Table 1, entry 13). From the above results we could conclude that the bi-functional reagent DMEDA was necessary for the reaction.
were obtained in moderate-to-good yields (Table 2, entries 16–22).

Our initial studies were focused on the reaction of 2-iodobenzaldehydes with 2-aminobenzenethiols. 1b (0.15 mmol), base (0.6 mmol), 4 Å molecular sieve (25 mg) in DMEDA reacted at 110 °C. The yields were determined by 1H NMR analysis using 1,3,5-Trimethoxybenzene as the internal standard. The reaction temperature is 120 °C. No 4 Å molecular sieve was used. The reaction temperature is 100 °C. No 4 Å molecular sieve was used. Gram-scale (5 mmol scale) reaction.

With the optimized reaction conditions in hand, the reaction scope was investigated (Table 2). Our initial studies were focused on the reaction of 2-iodobenzaldehydes a, with 2,2′-disulfanediyldianilines b, and the products c could be isolated in moderate-to-good yields. The 2-Bromobenzaldehyde and 2-chlorobenzaldehyde were used to react with 1b, and the yields decreased. When 2,2′-disulfanediyldianilines bearing electron-donating and electron-withdrawing groups were used to react with 1a, the products were obtained in good yields (Table 2, entries 2–4). Substituted 2-iodobenzaldehydes were also used to react with 1b, and the reactions yields were basically kept in good yields (Table 2, entries 5–9). Some cross-reactions were tested, and moderate-to-excellent yields were obtained. (Table 2, entries 10–12). The above results indicated that the reaction yields of 2-iodobenzaldehydes a with 2,2′-disulfanediyldianilines b were not influenced significantly by the electronic effect and steric effect. Subsequently, we examined the reaction of 2-iodobenzaldehydes a with 2-aminobenzothiols b; the reactions proceeded smoothly, and the reaction yields were obtained in moderate-to-good yields (Table 2, entries 16–22).

| Entry | Catalyst | DMEDA (mL) | Base | Yield (%) |
|-------|----------|------------|------|-----------|
| 1     | CuCl2    | 0.50       | Cs2CO3 | 73        |
| 2     | CuCl2    | 0.25       | Cs2CO3 | 73        |
| 3     | CuCl2    | 0.15       | Cs2CO3 | 46        |
| 4     | CuCl2    | 0.25       | /     | 22        |
| 5     | CuCl2    | 0.25       | K3PO4 | 82        |
| 6     | CuCl2    | 0.25       | K2CO3 | 62        |
| 7     | CuCl2    | 0.25       | K3PO4 | 82        |
| 8     | CuCl2    | 0.25       | K3PO4 | 73        |
| 9     | Cu(OAc)2 | 0.25       | K3PO4 | 66        |
| 10    | CuSO4·5H2O | 0.25 | K3PO4 | 69        |
| 11    | CuI      | 0.25       | K3PO4 | 72        |
| 12    | CuCl2    | 0.25       | K3PO4 | 69        |
| 13    | CuCl2    | 1.25       | K3PO4 | 82        |

a Reaction conditions: copper catalyst (15 mol%), 2-iodobenzaldehyde 1a (0.3 mmol), 2,2′-disulfanediyldianiline 1b (0.15 mmol), base (0.6 mmol), 4 Å molecular sieve (25 mg) in DMEDA reacted at 110 °C under N2 atmosphere for 24 h. b The yields were determined by 1H NMR analysis using 1,3,5-Trimethoxybenzene as the internal standard. c The reaction temperature is 120 °C. d The reaction temperature is 100 °C. e No 4 Å molecular sieve was used. f Gram-scale (5 mmol scale) reaction.
Table 2. Scope of the CuCl₂-catalyzed condensation/C–S bond coupling reaction of 2-iodobenzaldehydes and 2,2'-disulfanediyldianilines/2-aminobenzenethiols in DMEDA a.

| Entry | a   | b/b′ | Product | Yield (%) b |
|-------|-----|------|---------|-------------|
| 1     | 2-CHO | 1a   | 1b | 1c | 82 (53 c, 35 d) |
| 2     | 1a | 2a | 1b | 2b | 80 |
| 3     | 1a | 3a | 1b | 3b | 86 |
| 4     | 1a | 4a | 1b | 4b | 89 |
| 5     | 2-CHO | 5a   | 1b | 5c | 84 |
| 6     | 3a | 6a | 1b | 6c | 73 |
| 7     | 4a | 4a | 1b | 7c | 86 |
| 8     | 5a | 5a | 1b | 8c | 78 |
| 9     | 6a | 6a | 1b | 9c | 83 |
| 10    | 2a | 2a | 3b | 10c | 74 |
| 11    | 6a | 6a | 2b | 11c | 84 |
| 12    | 6a | 6a | 3b | 12c | 75 |
| 13    | 1a | 1a | 1b′ | 1b′ | 81 |
Table 2. Cont.

| Entry | a | 2/b′ | Product | Yield (%) b |
|-------|---|------|---------|-------------|
| 14    | 1a |      | c       | 80          |
| 15    | 1a |      | 3c      | 86          |
| 16    | 2a | b/b′ | 5c      | 78          |
| 17    | 3a | b/b′ | 6c      | 83          |
| 18    | 4a | b/b′ | 7c      | 88          |
| 19    | 5a | b/b′ | 8c      | 89          |
| 20    | 6a | b/b′ | 9c      | 80          |
| 21    | 6a | b/b′ | 11c     | 78          |
| 22    | 6a | b/b′ | 12c     | 80          |

a Reaction conditions: CuCl\(_2\) (15 mol%), 2-iodobenzaldehydes a (0.3 mmol), 2,2′-disulfanediyldianilines b (0.15 mmol)/2-aminobenzenethiols b′ (0.3 mmol), K\(_3\)PO\(_4\) (0.6 mmol), 4 Å molecular sieve in DMEDA (0.25 mL) reacted at 110 °C under N\(_2\) atmosphere for 24 h. b Isolated yield after flash chromatography based on a. c 2-Bromobenzaldehyde was used; d 2-Chlorobenzaldehyde was used.

The scope of 2′-idoacetophenones d and 2,2′-disulfanediyldianilines b/2-aminobenzenethiol 1b′ was also investigated (Table 3). The 2′-idoacetophenone 1d and 2,2′-disulfanediyldianiline 1b were used under the optimal conditions, and 75% yield of 1e was isolated (Table 3, entry 1). We used 2′-idoacetophenones 1d and substituted 2,2′-disulfanediyldianilines 2b–5b to do the reaction, and the products e were isolated in moderate-to-good yields (Table 3, entries 2–5). Then, 2,2′-disulfanediyldianiline 1b was replaced by 2-aminobenzenethiols 1b′ and reacted with 2′-idoacetophenone 1d to obtain the desired product in 95% yield (Table 3, entry 6). Finally, (2-iodophenyl)(phenyl)methanone 3d was used, and it could not react with 1b to generate the product 6e (Table 3, entry 7).

Finally, a possible mechanism was proposed for the reaction based on the experimental results (Scheme 2). Firstly, CuCl\(_2\) coordinates with DMEDA and is reduced to generate the Cu(I) complex (A). At the same time, the starting material 1a could react with 1b to form the intermediate (B) through the intermolecular condensation. The intermediate (C) could be generated via the oxidative addition of (A) and (B). Then, (C) was converted to the intermediate (D), and DMEDA might act as the reductant. For the substrate 1a and 1b′, the intermediate (D) is also generated during the reaction process. After the transmetallation/reductive elimination reaction, the product 1c could be formed. From the possible mechanism, we found that the bifunctional reagent DMEDA worked as ligand and reductant.

Table 3. Scope of the CuCl\(_2\)-catalyzed condensation/C–S bond coupling reaction of 2′-idoacetophenones and 2,2′-disulfanediyldianilines/2-aminobenzenethiol in DMEDA a,b.

| Entry | d | 2/b′ | Product | Yield (%) b |
|-------|---|------|---------|-------------|
| 1     | 1d | b/b′ | 1b      | 75          |
Table 3. Cont.

| Entry | d   | b/b' | Product | Yield (%) b |
|-------|-----|------|---------|-------------|
| 2     | 1d  | 2b   |         | 74          |
| 3     | 1d  | 3b   |         | 69          |
| 4     | 1d  | 4b   |         | 61          |
| 5     | 2d  | 5b   |         | 77          |
| 6     | 1d  | 1b'  | 1e      | 95          |
| 7     | 3d  | 1b   | 6e      |             |

*a Reaction conditions: CuCl₂ (15 mol%), 2-iodoacetophenones d (0.3 mmol), 2,2'-disulfanediyldianilines b (0.15 mmol)/2-aminobenzenethiols 1b' (0.3 mmol) in DMEDA reacted at 110 °C for 24 h. b Isolated yield after flash chromatography based on d.*

Scheme 2. Possible mechanism.
3. Experimental Section

3.1. General

$^1$H NMR and $^{13}$C NMR spectra were recorded 500 MHz (Bruker, Kanton Zug, Switzerland) instrument; CDCl$_3$ ($\delta_{H} = 7.26$ ppm, $\delta_{C} = 77.16$ ppm) was used as the internal standard. Chemical shifts were reported in ppm. Multiplicity was recorded: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), m (multiplet). The direct used reagents and solvents were pure analytical grade and purchased from commercial sources, if not stated otherwise. The starting substrates were synthesized according to the known literature. Column chromatography was hand packed with silica gel (200–300 mesh). The melting points were uncorrected. High-resolution mass spectra (HRMS) were recorded on a Q-TOF Premier (ESI, Waters, Milford, CT, USA). The silica gel plates (GF254, 0.2 mm thick) were used for TLC testing.

3.2. General Procedure for the Synthesis of Dibenzo[b,f][1,4]thiazepines (1c–12c) Catalyzed by CuCl$_2$ in DMEDA

An oven-dried 25 mL flask equipped with a rubber stopper was charged with a magnetic stir bar, CuCl$_2$ (15 mol%, 0.045 mmol), 2-iodobenzaldehyde a (0.3 mmol), 2,2′-disulfanediyldianilines b (0.15 mmol)/2-aminobenzenethiols b′ (0.3 mmol), K$_3$PO$_4$ (0.6 mmol), 4 Å molecular sieve (25 mg) and DMEDA (0.5 mL). The reaction mixture was stirred at 110 $^\circ$C for 24 h. The reaction was monitored by TLC. When benzaldehydes a was consumed, the reaction was stopped and cooled to room temperature, the crude reaction mixture was diluted with 20 mL water, extracted with ethyl acetate (20 mL $\times$ 3), combined with organic phase, then washed organic phase with brine (20 mL), dried organic phase with anhydrous MgSO$_4$. The organic phase was concentrated and the residue was purified directly by column chromatography on silica gel using petrol/EtOAc as eluent to give the pure products c.

3.3. General Procedure for the Synthesis of 11-Methyldibenzo[b,f][1,4]thiazepines (1e–5e) Catalyzed by CuCl$_2$ in DMEDA

An oven-dried 25 mL flask equipped with a rubber stopper was charged with a magnetic stir bar, CuCl$_2$ (15 mol%, 0.045 mmol), 1-(2-iodophenyl)ethan-1-ones d (0.3 mmol), 2,2′-disulfanediyldianilines b (0.15 mmol)/2-aminobenzenethiols b′ (0.3 mmol), K$_3$PO$_4$ (0.6 mmol), 4 Å molecular sieve (25 mg) and DMEDA (0.5 mL). The reaction mixture was stirred at 110 $^\circ$C for 24 h. The reaction was monitored by TLC. When benzaldehydes d was consumed, the reaction was stopped and cooled to room temperature, the crude reaction mixture was diluted with 20 mL water, extracted with ethyl acetate (20 mL $\times$ 3), combined with organic phase, then washed organic phase with brine (20 mL), dried organic phase with anhydrous MgSO$_4$. The organic phase was concentrated and the residue was purified directly by column chromatography on silica gel using petrol/EtOAc as eluent to give the pure products e.

3.4. Characterization Data

The dibenzo[b,f][1,4]thiazepine 1c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 126–128 $^\circ$C (Lit: m.p. 124 $^\circ$C) [30]; 52.0 mg; 82% yield (1a and 1b were used); 51.3 mg; 81% yield (1a and 1b′ were used); $^1$H NMR (500 MHz, CDCl$_3$/TMS): $\delta$ 8.90 (s, 1H), 7.44–7.30 (m, 7H), 7.19–7.15 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$/TMS): $\delta$ 162.4, 148.7, 139.5, 137.4, 132.9, 131.8, 131.6, 129.5, 129.4, 129.0, 128.4, 127.3, 127.1.

The 7-methyldibenzo[b,f][1,4]thiazepine 2c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 115–117 $^\circ$C; 54.0 mg; 80% yield (1a and 2b were used); 54.0 mg; 80% yield (1a and 2b′ were used); $^1$H NMR (500 MHz, CDCl$_3$/TMS): $\delta$ 8.85 (s, 1H), 7.42 (d, $J = 7.5$ Hz, 1H), 7.39–7.33 (m, 3H), 7.24–7.20 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$/TMS): $\delta$ 161.8, 146.3, 139.3, 137.6, 137.5, 133.2, 131.7, 131.5, 130.2, 129.5, 128.5, 128.3, 127.0, 20.7.
The 7-methoxydibenzo[bf][1,4]thiazepine 3c (Flash column chromatography on silica gel using petrol/EtOAc (5:1, v/v) as eluent). Yellow solid; mp: 101–102 °C; 62.2 mg; 86% yield (1a and 3b were used); 62.2 mg; 86% yield (1a and 3b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.80 (s, 1H), 7.43–7.34 (m, 4H), 7.24 (s 1H), 6.95 (d, J = 3.0 Hz, 1H), 6.88 (dd, J1 = 9.0 Hz, J2 = 3.0 Hz, 1H), 3.79 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 160.8, 159.1, 142.4, 138.6, 137.5, 131.7, 131.5, 129.6, 129.4, 128.5, 117.0, 115.6, 55.7. HRMS (ESI): m/z calcd for C15H12NOS [M + H]+: 242.0634, found: 242.0641.

The 7-chlorodibenzo[bf][1,4]thiazepine 4c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 75–76 °C; 65.6 mg; 89% yield (1a and 4b were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.87 (s, 1H), 7.44–7.36 (m, 5H), 7.28 (dd, J1 = 8.5 Hz, J2 = 2.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H). 13C NMR (125 MHz, CDCl3/TMS): δ 162.7, 147.2, 138.6, 137.2, 132.8, 132.3, 131.90, 131.88, 130.3, 129.6, 129.5, 128.7, 128.0.

The 3-methyl(dibenzo[bf][1,4]thiazepine 5c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent) Yellow solid; mp: 93–94 °C; 56.7 mg; 84% yield (2a and 1b were used); 52.8 mg; 78% yield (2a and 1b' were used); 56.1 mg; 83% yield (3a and 1b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.86 (s, 1H), 7.42–7.40 (m, 1H), 7.33–7.28 (m, 3H), 7.20–7.14 (m, 3H), 2.33 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 162.5, 148.7, 138.5, 137.2, 136.2, 132.8, 132.4, 131.6, 130.1, 129.29, 129.28, 127.2, 127.0, 21.1.

The 2-methyl(dibenzo[bf][1,4]thiazepine 6c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 92–94 °C; 49.5 mg; 73% yield (3a and 1b were used); 56.1 mg; 83% yield (3a and 1b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.86 (s, 1H), 7.42–7.40 (m, 1H), 7.33–7.28 (m, 3H), 7.20–7.14 (m, 3H), 2.34 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 162.5, 148.8, 138.5, 137.2, 136.3, 132.8, 132.4, 131.6, 130.1, 129.53, 129.28, 127.2, 127.1, 21.1.

The 3-chlorodibenzo[bf][1,4]thiazepine 7c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent) White solid; mp: 107–109 °C; 63.3 mg; 86% yield (4a and 1b were used); 64.7 mg; 88% yield (4a and 1b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.84 (s, 1H), 7.45 (d, J = 1.0 Hz 1H), 7.41 (dd, J1 = 7.5 Hz, J2 = 1.0 Hz, 1H), 7.37–7.29 (m, 4H), 7.19 (td, J1 = 7.0 Hz, J2 = 1.5 Hz, 1H). 13C NMR (125 MHz, CDCl3/TMS): δ 161.2, 148.6, 141.1, 137.8, 135.7, 133.0, 131.6, 130.5, 129.7, 128.6, 128.2, 127.6, 127.2, 127.1.

The 3-fluorodibenzo[bf][1,4]thiazepine 8c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 54–56 °C; 53.5 mg; 78% yield (5a and 1b were used); 61.1 mg; 89% yield (5a and 1b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.84 (s, 1H), 7.42–7.30 (m, 4H), 7.22–7.15 (m, 2H), 7.05 (td, J1 = 8.5 Hz, J2 = 3.0 Hz, 1H). 13C NMR (125 MHz, CDCl3/TMS): δ 164.4 (d, J = 253.6 Hz), 161.2, 148.6, 141.8 (d, J = 8.3 Hz), 133.7 (d, J = 3.4 Hz), 133.0, 131.4 (d, J = 9.3 Hz), 129.7, 128.2, 127.5, 127.1, 118.8 (d, J = 22.3 Hz), 115.6 (d, J = 21.8 Hz).

The 2-chlorodibenzo[bf][1,4]thiazepine 9c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 111–112 °C; 61.2 mg; 83% yield (6a and 1b were used); 58.9 mg; 80% yield (6a and 1b' were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.82 (s, 1H), 7.41 (dd, J1 = 8.0 Hz, J2 = 1.5 Hz, 1H), 7.37–7.29 (m, 5H), 7.18 (td, J1 = 7.5 Hz, J2 = 1.5 Hz, 1H). 13C NMR (125 MHz, CDCl3/TMS): δ 160.7, 148.5, 138.5, 138.0, 134.7, 133.0, 132.9, 131.5, 129.7, 129.3, 128.5, 127.6, 127.1.

The 7-methoxy-3-methyl(dibenzo[bf][1,4]thiazepine 10c (Flash column chromatography on silica gel using petrol/EtOAc (5:1, v/v) as eluent). Yellow solid; mp: 128–129 °C; 56.8 mg; 74% yield (2a and 3b were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.76 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 7.0 Hz, 2H), 6.94 (d, J = 3.0 Hz, 1H), 6.87 (dd, J1 = 8.5 Hz, J2 = 2.5 Hz, 1H), 3.78 (s, 3H), 2.33 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 160.9, 159.0, 142.5, 138.6, 137.3, 135.2, 132.3, 131.6, 130.1, 129.7, 128.4, 116.9, 115.5, 55.7, 21.1. HRMS (ESI): m/z calcd for C15H14NOS [M + H]+: 256.0791, found: 256.0796.

The 2-chlorodibenzo[bf][1,4]thiazepine 11c (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Gray solid; mp: 110–111 °C; 65.4 mg; 84% yield
(6a and 2b were used); 60.8 mg; 78% yield (6a and 2b’ were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.77 (s, 1H), 7.36–7.32 (m, 3H), 7.24–7.19 (m, 2H), 7.16–7.13 (m, 1H), 2.30 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 160.1, 146.1, 138.5, 137.9, 137.8, 134.6, 133.2, 132.9, 131.4, 130.5, 129.3, 128.0, 127.0, 20.7. HRMS (ESI): m/z calcd for C14H11CINS [M + H]+: 260.0295, found: 260.0284.

The 2-chloro-7-methoxymidobenz[o,f][1,4]thiazepine 12c (Flash column chromatography on silica gel using petrol/EtOAc (5:1, v/v) as eluent). Yellow solid; mp: 111–112 °C; 62.0 mg; 75% yield (6a and 3b were used); 66.1 mg; 80% yield (6a and 3b’ were used); 1H NMR (500 MHz, CDCl3/TMS): δ 8.71 (s, 1H), 7.34 (s, 3H), 7.25 (d, J = 8.7 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.90 (dd, J1 = 1.3 Hz, J2 = 8.8 Hz, 1H), 3.79 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 159.3, 159.0, 142.2, 138.6, 137.0, 134.8, 133.0, 131.4, 129.3, 128.9, 128.6, 117.1, 115.8, 55.8. HRMS (ESI): m/z calcd for C14H11ClNO5[M + H]+: 276.0244, found: 276.0235.

The 11-methylidobenz[o,f][1,4]thiazepine 1e (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 75–76 °C (Lit: mp: 76 °C) [31]; 50.0 mg; 75% yield (1d and 1b were used); 64.2 mg; 95% yield (1d and 1b’ were used); 1H NMR (500 MHz, CDCl3/TMS): δ 7.46–7.45 (m, 1H), 7.42–7.40 (m, 2H), 7.34–7.30 (m, 2H), 7.28–7.24 (m, 1H), 7.18 (dd, J1 = 1.3 Hz, J2 = 8.0 Hz, 1H), 7.05 (td, J1 = 1.3 Hz, J2 = 7.5 Hz, 1H), 2.66 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 169.9, 148.8, 140.0, 139.5, 132.3, 132.0, 130.8, 129.2, 128.9, 128.5, 128.0, 125.6, 125.4, 29.6.

The 7,11-dimethylidobenz[o,f][1,4]thiazepine 2e (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent) Yellow solid; mp: 115–117 °C; 53.1 mg; 74% yield (1d and 2b were used); 1H NMR (500 MHz, CDCl3/TMS): δ 7.46–7.43 (m, 1H), 7.42–7.38 (m, 1H), 7.33–7.29 (m, 2H), 7.23 (s, 1H), 7.09–7.05 (m, 2H), 2.65 (s, 3H), 2.27 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 169.3, 146.4, 139.9, 139.5, 135.6, 132.8, 131.9, 130.7, 130.1, 128.40, 128.39, 128.0, 125.3, 125.0, 29.6.

The 7-methoxy-11-methylidobenz[o,f][1,4]thiazepine 3e (Flash column chromatography on silica gel using petrol/EtOAc (5:1, v/v) as eluent). Yellow solid; mp: 130–132 °C; 52.9 mg; 69% yield (1d and 2b’ were used); 1H NMR (500 MHz, CDCl3/TMS): δ 7.46–7.43 (m, 1H), 7.42–7.39 (m, 1H), 7.34–7.30 (m, 2H), 7.12 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 2.9 Hz, 1H), 6.83 (dd, J1 = 2.8 Hz, J2 = 8.8 Hz, 1H), 3.76 (s, 3H), 2.64 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 168.5, 157.6, 142.5, 139.6, 139.4, 132.0, 130.7, 129.2, 128.5, 128.0, 126.6, 116.6, 115.7, 55.7, 29.5. HRMS (ESI): m/z calcd for C15H13NOS [M + H]+: 256.0791, found: 256.0794.

The 7-chloro-11-methylidobenz[o,f][1,4]thiazepine 4e (Flash column chromatography on silica gel using petrol/EtOAc (6:1, v/v) as eluent). Yellow solid; mp: 115–117 °C; 47.5 mg; 61% yield (1d and 4b were used); 1H NMR (500 MHz, CDCl3/TMS): δ 7.47–7.44 (m, 1H), 7.43–7.39 (m, 2H), 7.36–7.33 (m, 2H), 7.21 (dd, J1 = 2.3 Hz, J2 = 8.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 2.65 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 170.4, 147.4, 143.9, 139.3, 139.2, 132.2, 131.9, 131.0, 130.8, 130.1, 129.3, 128.8, 128.0, 126.4, 29.6. HRMS (ESI): m/z calcd for C14H11ClNO5 [M + H]+: 260.0295, found: 260.0275.

The 2,3,9-trimethoxy-11-methylidobenz[o,f][1,4]thiazepine 5e (Flash column chromatography on silica gel using petrol/EtOAc (3:1, v/v) as eluent). Yellow solid; mp: 52–54 °C; 72.9 mg; 77% yield (2d and 5b were used); 1H NMR (500 MHz, CDCl3/TMS): δ 7.10 (d, J = 8.8 Hz, 1H), 6.95–6.90 (m, 2H), 6.86 (s, 1H), 6.83 (dd, J1 = 2.8 Hz, J2 = 8.8 Hz, 1H), 3.87 (d, J = 10.5 Hz, 6H), 3.76 (s, 3H), 2.62 (s, 3H). 13C NMR (125 MHz, CDCl3/TMS): δ 167.9, 157.5, 150.9, 149.3, 142.5, 132.0, 130.9, 129.7, 126.5, 116.4, 115.6, 114.3, 110.7, 56.3, 56.2, 55.7, 29.3. HRMS (ESI): m/z calcd for C14H17ClNO5 [M + H]+: 316.1002; found: 316.1012.

4. Conclusions

In summary, this paper reported a ‘one-pot’ CuCl2 catalyzed synthesis of dibenzo[b,f][1,4]thiazepines and 11-methylidobenz[o,f][1,4]thiazepines via the condensation/C–S bond coupling reactions of 2-ido benzaldehyde2/2-iodoacetophenones with 2-aminobenzethiols/2,2′-disulfanediyldianilines in moderate-to-good yields. The reaction is easy to operate, uses readily available and bi-functional-reagent MEDMA working as ligand and reductant, and exhibits functional group tolerance.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27217392/s1, Figure S1: $^1$H NMR (CDCl$_3$) spectrum of Compound (1c); Figure S2: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (1c); Figure S3: $^1$H NMR (CDCl$_3$) spectrum of Compound (2c); Figure S4: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (2c); Figure S5: $^1$H NMR (CDCl$_3$) spectrum of Compound (3c); Figure S6: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (3c); Figure S7: $^1$H NMR (CDCl$_3$) spectrum of Compound (4c); Figure S8: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (4c); Figure S9: $^1$H NMR (CDCl$_3$) spectrum of Compound (5c); Figure S10: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (5c); Figure S11: $^1$H NMR (CDCl$_3$) spectrum of Compound (6c); Figure S12: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (6c); Figure S13: $^1$H NMR (CDCl$_3$) spectrum of Compound (7c); Figure S14: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (7c); Figure S15: $^1$H NMR (CDCl$_3$) spectrum of Compound (8c); Figure S16: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (8c); Figure S17: $^1$H NMR (CDCl$_3$) spectrum of Compound (9c); Figure S18: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (9c); Figure S19: $^1$H NMR (CDCl$_3$) spectrum of Compound (10c); Figure S20: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (10c); Figure S21: $^1$H NMR (CDCl$_3$) spectrum of Compound (11c); Figure S22: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (11c); Figure S23: $^1$H NMR (CDCl$_3$) spectrum of Compound (12c); Figure S24: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (12c); Figure S25: $^1$H NMR (CDCl$_3$) spectrum of Compound (1c); Figure S26: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (1c); Figure S27: $^1$H NMR (CDCl$_3$) spectrum of Compound (2e); Figure S28: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (2e); Figure S29: $^1$H NMR (CDCl$_3$) spectrum of Compound (3e); Figure S30: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (3e); Figure S31: $^1$H NMR (CDCl$_3$) spectrum of Compound (4e); Figure S32: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (4e); Figure S33: $^1$H NMR (CDCl$_3$) spectrum of Compound (5e); Figure S34: $^{13}$C NMR (CDCl$_3$) spectrum of Compound (5e).

Author Contributions: Synthesis and investigation, D.W., Q.L., C.F. and R.L.; writing—original draft, G.S.; conceptualization and writing, G.S.; Project administration, B.Y. All authors have read and agreed to the published version of the manuscript.

Funding: We are grateful to by the Shandong Provincial Natural Science Foundation (ZR2019QB022) and Liaocheng University fund (318051403) for financial support of this research.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Not applicable.

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