Tetrahedron Letters 51 (2010) 5009–5012

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient copper(II)-catalyzed synthesis of benzothiazoles through intramolecular coupling-cyclization of *N*-(2-chlorophenyl)benzothioamides

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ARTICLE INFO

Article history:
Received 1 June 2010
Revised 6 July 2010
Accepted 14 July 2010
Available online 18 July 2010

Keywords:
Copper catalyst
Coupling reaction
Benzothiazole
Diamine ligands
$C_{(aryl)}$-*S* bond formation

ABSTRACT

A wide range of 2-aryl or 2-alkyl-substituted benzothiazoles are synthesized through intramolecular $C_{(aryl)}$-*S* bond forming-cyclization using copper(II)–BINAM-catalyzed coupling of less reactive *N*-(2-chlorophenyl)benzo or alkylthioamide under mild reaction conditions (82 °C).

Benzothiazole moieties are found in a variety of biologically important natural products[1] and they are used as drugs for several diseases such as tumors, diabetes, Parkinson's disease, tuberculosis, inflammatory diseases, epilepsy, viral infections, insomnia, and atherosclerosis (Fig. 1).[2] Also, they are inhibitors of several enzymes[3] and function as antioxidants.[4] Due to the importance of benzothiazole-containing compounds, an efficient synthesis of benzothiazoles under very mild reaction conditions has become very important.

The conventional method for the construction of a benzothiazole moiety is condensation of 2-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides or esters.[5] But synthesis of different substituted benzothiazoles will be difficult because of the expensive and readily oxidizable nature of substituted 2-aminothiophenols.[6] Intramolecular cyclization of *N*-(2-halophenyl) benzothioamide is one of the attractive methods for the synthesis of benzothiazoles.[7] Though highly reactive *N*-(2-iodophenyl) benzothioamide yields benzothiazole without any catalyst[8] but *N*-(2-bromophenyl) benzothioamide needs Pd[9] or Cu[10] catalyst. Particularly, *N*-(2-chlorophenyl) benzothioamide is very less reactive toward intramolecular cyclization and is not much explored. There are only two reports in the literature for the cyclization of 2-chlorophenyl benzothioamide to the corresponding benzothiazoles where the reaction requires more than 140 °C with very limited substrate scope[8a,10a] or it requires a photochemical condition.[11]

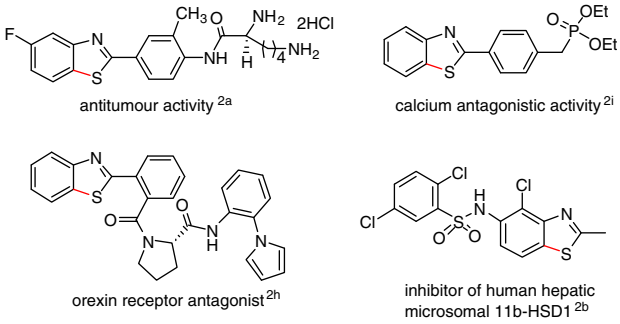
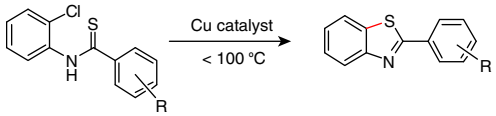


Figure 1. Biologically active compounds containing benzothiazole skeleton.

Herein for the first time we report BINAM–Cu(II) complex as an efficient catalyst for the synthesis of benzothiazole through intramolecular coupling cyclization from *N*-(2-chlorophenyl) benzothioamide under mild reaction conditions (Scheme 1).

As part of our ongoing research toward copper-catalyzed oxidation chemistry,[12] very recently we reported copper complex to be an efficient catalyst for the synthesis of ethers, sulfides, N-arylated indoles, arylated alkynes, benzoxazines, and benzothiazines



Scheme 1.

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doi:10.1016/j.tetlet.2010.07.079

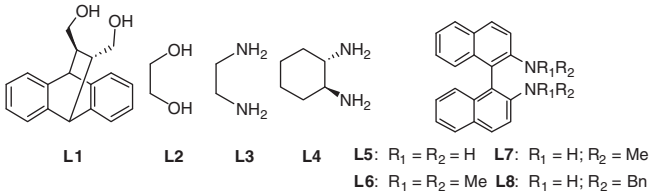


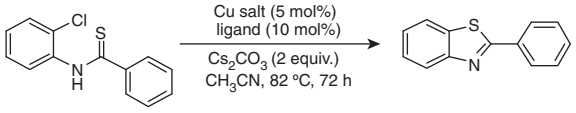
Figure 2. Ligands screened for copper catalyzed 2-phenylbenzothiazole synthesis.

through $C_{(aryl)}$–*O*, $C_{(aryl)}$–*S*, $C_{(aryl)}$–*N* and $C_{(aryl)}$–*C* bond forming-Ullmann type/Sonogashira coupling.[13] In this Letter, we report a simple procedure for the synthesis of benzothiazoles from very less reactive *N*-(2-chlorophenyl)benzo or alkylthioamide under mild reaction conditions (82 °C) using BINAM–Cu(II) catalyst.

In preliminary studies, we used 10 mol % of *trans*-(±)-diol **L1**[14] as a ligand (Fig. 2) with 5 mol % of $Cu(OTf)_2$ for the intramolecular cyclization of *N*-(2-chlorophenyl)benzothioamide using Cs_2CO_3 as a base in acetonitrile solvent at 82 °C. After 72 h the coupling reaction provided 19% isolated yield of 2-phenylbenzothiazole (Table 1, entry 1). When we replaced the **L1** with ethylene glycol **L2**, the yield was slightly increased to 30% (entry 2). When replacing the ligand **L2** by diamine ligands **L3** or **L4**, the yield decreased (entries 3 and 4). To our surprise, when we used 1,1'-binaphthyl-2,2'-diamine (BINAM) **L5** as a ligand the yield for the synthesis of 2-phenylbenzothiazole was increased to 71% at 82 °C (entry 5). Replacing BINAM by other N-substituted derivatives such as **L6**–**L8** reduced the yield drastically to 21–24% (entries 6–8). Then the reaction was screened with several other copper salts and $CuCl_2$ turned out to be the best choice with ligand **L5**, which provided 78% isolated yield for the coupling cyclization (entry 12). When the intramolecular cyclization was carried out without the ligand, in the presence of $CuCl_2$ it provided only 28% yield for benzothiazole formation, suggesting the mandatory presence of the ligand in this reaction (entry 15).

The reaction was then screened with several solvents, bases, and different ratios of the catalyst to increase the efficiency of

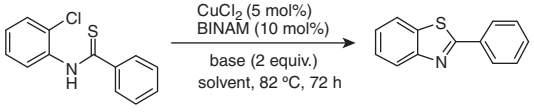
Table 1
Effect of different ligands and copper salts for the synthesis of 2-phenyl benzothiazoles



Entry	Ligand	Cu salt	Yield[a] (%)
1	L1	$Cu(OTf)_2$	19
2	L2	$Cu(OTf)_2$	30
3	L3	$Cu(OTf)_2$	23
4	L4	$Cu(OTf)_2$	27
5	L5	$Cu(OTf)_2$	71
6	L6	$Cu(OTf)_2$	21
7	L7	$Cu(OTf)_2$	21
8	L8	$Cu(OTf)_2$	24
9	L5	Cu_2O	30
10	L5	$CuSO_4$	25
11	L5	$Cu(OAC)_2$	42
12	L5	$CuCl_2$	78
13	L5	CuBr	42
14	L5	CuI	48
15	—	$CuCl_2$	28

[a] Isolated yield.

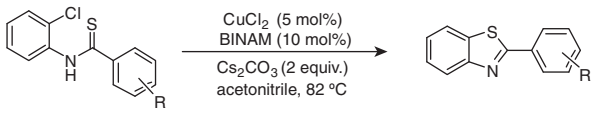
Table 2
Effect of various solvents and bases

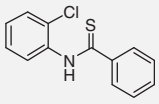
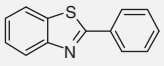
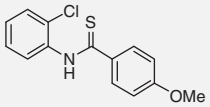
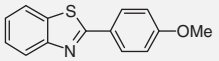
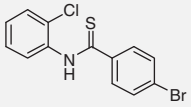
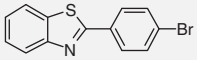
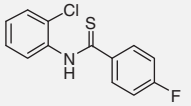
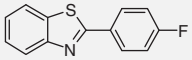
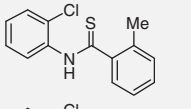
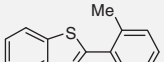
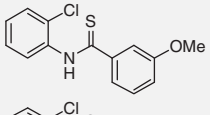
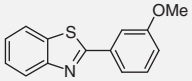
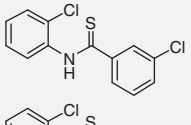
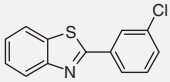
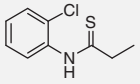
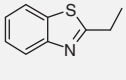
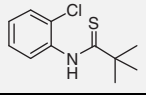
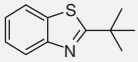


Entry	Solvent	Base	Yield[a] (%)
1	Toluene	Cs_2CO_3	Trace
2	DMF	Cs_2CO_3	25
3	DMSO	Cs_2CO_3	42
4	1,4-Dioxane	Cs_2CO_3	49
5	THF	Cs_2CO_3	12[b]
6	Acetonitrile	Cs_2CO_3	78
7	Acetonitrile	K_2CO_3	23
8	Acetonitrile	Na_2CO_3	17
9	Acetonitrile	K_3PO_4	21
10	Acetonitrile	Cs_2CO_3	79[c]
11	Acetonitrile	Cs_2CO_3	48[d]
12	Acetonitrile	Cs_2CO_3	62[e]

[a] Isolated yield.
[b] Reaction was carried out in pressure tube.
[c] 10 mol % $CuCl_2$ and 20 mol % BINAM.
[d] 5 mol % $CuCl_2$ and 5 mol % BINAM.
[e] 10 mol % $CuCl_2$ and 10 mol % BINAM.

Table 3
Synthesis of benzothiazoles via copper(II)-catalyzed coupling of various *N*-(2-chlorophenyl)benzothioamides[15]



Entry	Benzothioamide	Benzothiazole[16]	Time (h)	Yield[a] (%)
1			72	78
2			96	50
3			48	81[b]
4			96	50
5			72	52
6			46	60[b]
7			36	92[b]
8			45	70[b]
9			72	60

[a] Isolated yield.
[b] Reaction was carried out at 110 °C.[17]

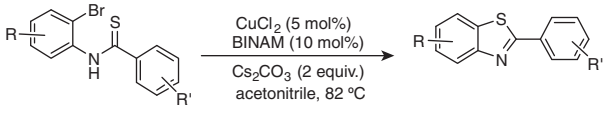
the cyclization (Table 2). Acetonitrile turned out to be the best solvent of choice in view of the isolated yield. Cs_2CO_3 as the base provided the best result in comparison with Na_2CO_3, K_2CO_3, and K_3PO_4. The 1:2 ratio of $CuCl_2$ and ligand **L5** (5:10 and 10:20; entries 6 and 10) provided better results than the 1:1 complex (5:5 and 10:10; entries 11 and 12). In the 1:2 complex, both 5:10 and 10:20 ratios of $CuCl_2$ and ligand **L5**, respectively, provided almost the same yield for the intramolecular cyclization.

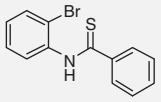
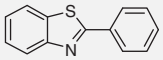
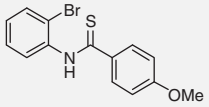
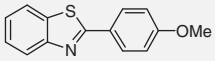
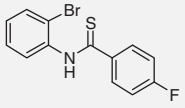
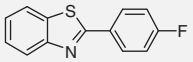
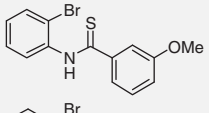
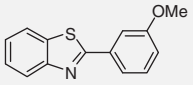
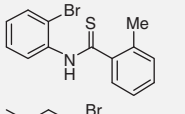
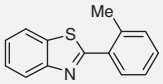
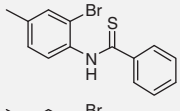
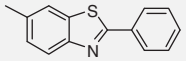
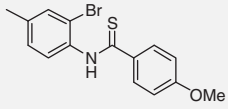
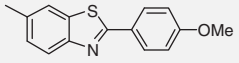
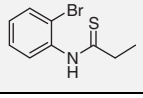
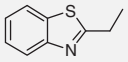
Using the above mentioned optimized reaction conditions,[15] we initiated our investigations into the scope of the $CuCl_2$–BINAM complex-catalyzed intramolecular cyclization of various substituted *N*-(2-chlorophenyl)benzothioamide and the results are summarized in Table 3. A wide range of *N*-(2-chlorophenyl)arylthioamide with both electron-releasing (entries 2 and 6) and electron-withdrawing groups (entries 3, 4, and 7) produced the corresponding benzothiazoles in good yields using the optimal reaction conditions. Interestingly, 2-alkyl-substituted benzothiazoles were also synthesized in good yields (entries 8 and 9). Similarly, sterically hindered *ortho*-substituted benzothioamide also cyclized to give the corresponding benzothiazole in good yield (entry 5).

The new catalytic system was also successfully utilized for the synthesis of 2-substituted benzothiazoles from the corresponding *N*-(2-bromophenyl)benzothioamide in excellent yields at 82 °C in acetonitrile (Table 4). In case of bromo substrates, electron-withdrawing group (entry 3), electron-releasing group (entries 2, 4, and 7), and sterically hindered-*ortho*-substituted benzothioamide (entry 5) are well tolerated and provided an excellent isolated yield at 82 °C. 2-Ethyl-substituted benzothiazole was also synthesized in good yield (entry 8). Importantly, substitution on the 2-bromo aniline moiety of *N*-(2-bromophenyl) benzothioamide also provided excellent yields (entries 6 and 7).

In summary, for the first time we have demonstrated that BINAM–$CuCl_2$ can be used as an efficient catalyst for the synthesis of 2-substituted benzothiazoles by intramolecular cyclization through $C_{(aryl)}$–*S* bond formation at 82 °C from very less reactive *N*-(2-chlorophenyl)benzothioamide or *N*-(2-bromophenyl)benzothioamide. The *N*-(2-halophenyl) benzothioamide containing electron-withdrawing, electron-releasing groups, and sterically hindered *ortho*-substituted benzothioamide is well tolerated. Similarly, 2-alkyl-substituted benzothiazoles are also synthesized in good yields. This synthetic method is expected to find valuable applications in various areas, as the reaction is carried out under mild reaction conditions. Further investigations using this methodology to construct biologically active benzothiazole-containing molecules are underway.

Table 4
Synthesis of benzothiazoles using copper(II)–BINAM coupling cyclization of *N*-(2-bromophenyl) benzothioamide[15]



Entry	Benzothioamide	Benzothiazole[16]	Time (h)	Yield[a] (%)
1			28	98
2			28	89
3			36	90
4			27	95
5			36	96
6			29	99
7			33	83
8			28	71

[a] Isolated yield.

Acknowledgments

We thank the DST (Project No.: SR/S1/OC-06/2008), New Delhi for the financial support. E.A.J. thanks the CSIR, New Delhi and D.J.C Prasad thanks the UGC, New Delhi for SRF. We thank the DST, New Delhi for funding toward the 400-MHz NMR machine to the department of Chemistry, IIT-Madras under the IRPHA Scheme and for funding the ESI-MS facility under the FIST Program

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14. Diol ligand **L1** (*trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol) with CuI was used as an efficient catalyst for the arylation of phenols and thiophenols under mild reaction conditions (82 °C).[13a,13h]
15. *Typical experimental procedure*: Anhydrous $CuCl_2$ (3.36 mg, 0.025 mmol), (±)-BINAM (14.2 mg, 0.05 mmol), Cs_2CO_3 (325.8 mg, 1 mmol), and *N*-(2-chlorophenyl)benzothioamide (123.9 mg, 0.5 mmol) were taken in a 10 ml reaction tube equipped with a septum. The reaction tube was evacuated and back-filled with nitrogen. Acetonitrile (2 mL) was added to the reaction mixture at room temperature. The reaction tube was sealed with a glass stopper and the reaction mixture was heated for 72 h at 82 °C. After the complete disappearance of starting material (the progress of the reaction was followed by TLC), the reaction mixture was allowed to cool to room temperature and the crude reaction mixture was directly purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluents to afford 2-phenylbenzothiazole 82.4 mg (78%) as a white solid (Table 3, entry 1). Mp 112 °C (lit. 110–111 °C)[10b], R_f 0.48 (5% ethyl acetate: hexanes); IR (neat): 3064, 1476, 1439, 1312, 1224, 962, 764, 690, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, J = 7.6 Hz, 1H), 7.47–7.54 (m, 4H), 7.91 (d, J = 7.6 Hz, 1H), 8.07–8.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8, 123.3, 125.3, 126.5, 127.7, 129.2, 131.1, 133.7, 135.1, 154.2, 168.2; HRMS (*m*/*z*): $[MH]^+$ calcd for $C_{13}H_{10}NS$: 212.0534; found: 212.0534.
16. All the products gave satisfactory spectral data.
17. Entries 3, 6, 7, and 8 of Table 4 gave good yield of the corresponding benzothiazoles at 110 °C (in pressure tube). At 82 °C, these reactions gave approximately 20% less yield.