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Synthesis of *N*-benzothiazol-2-yl-amides by a copper-catalyzed intramolecular cyclization process

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Abstract

Employing *N*-(4,5-dihydrooxazol-2-yl)benzamide as novel and efficient ligand, the copper-catalyzed intramolecular cyclization of various substituted 1-acyl-3-(2-bromophenyl)thioureas could be successfully carried out under mild conditions. A variety of *N*-benzothiazol-2-yl-amides were synthesized in good to excellent yields.

Keywords: Benzothiazol-2-yl-amide; Intramolecular cyclization; Thiourea; Copper

Substituted *N*-benzothiazol-2-yl-amides are an important class of heterocyclic compounds that exhibit a wide range of biological properties[1] such as ubiquitin ligase inhibitors,[1a] antitumor,[1b] antirotavirus infections,[1c] the adenosine receptor,[1d,e] and the nuclear hormone receptor[1e]. In particular, some benzothiazoles substituted at the 2-position with a benzoylamino moiety showed antibacterial, antifungal, and antitubercular activities.[1f] Although *N*-benzothiazol-2-yl-amides play an important role in pharmaceutical science, the available synthetic strategies that lead to these compounds are limited.[2] The classical method for the preparation of these molecules include acylation processes from 2-aminobenzothiazole.[2a,b] The drawback of this procedure is the limited diversity of the commercially available starting materials. Furthermore, the preparation of 2-aminobenzothiazole required the use of the toxic bromine.

Recent years have witnessed great progress in the development of mild Cu-catalyzed Ullmann-type reactions.[3] The recent trend shows that the inexpensive copper catalysts are beginning to supplant the palladium catalyst.[4] These coupling reactions have been developed to include a wide range of substrates under mild conditions by the appropriate combination of ligand, copper source, base, and solvent.[5] Particularly, the choice of ligands is very important since proper ligands could notably accelerate the reaction rates and significantly lower the reaction temperatures. The synthesis of 2-aminobenzothiazoles has been reported.[6] However, the reaction via transition metal-catalyzed intermolecular cross-coupling is rare. Furthermore, these methods suffered from some disadvantages such as long time and higher temperature, and these procedures were limited to the synthesis of *N*-alkylbenzothiazol-2-amine. Recently, Batey's group[6a] reported copper-catalyzed intramolecular C–S bond formation to synthesize 2-aminobenzothiazoles. Therefore, we envisioned that Cu-catalyzed cyclization of 1-acyl-3-(2-halophenyl)thiourea **1** would represent a viable method for the formation of substituted *N*-benzothiazol-2-yl-amides **2** (Fig. 1).

While not being commercially available, *ortho*-halobenzothioureas **1** are stable and easily synthesized[7] from least expensive starting materials in high yields and on a

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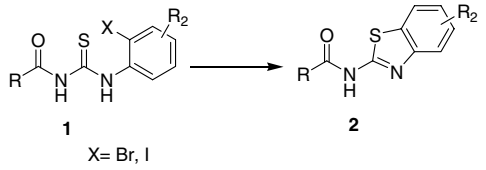
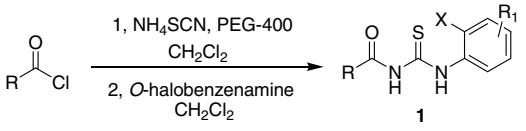


Fig. 1.

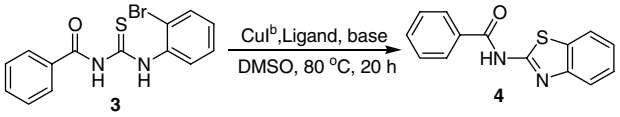
multigram scale. Following Scheme 1, the synthesis of **1** is a straightforward process starting from aryl acid chloride and *ortho*-haloarylamines, which are inexpensive. Aryl acid chloride was treated with ammonium sulfocyanide in the presence of PEG-400 in CH_2Cl_2, followed by the addition of *ortho*-haloarylamines, to obtain 1-arylacyl-3-phenylthiourea **1** in good to excellent yields. This intermediate can be employed directly without further purification.

In the preliminary experimental, we investigated the intramolecular cyclization of 1-benzoyl-3-(2-bromophenyl)thiourea **1** by utilizing CuI (5 mol %) and BINOL (10 mol %), in the presence of a mild base (Cs_2CO_3, 2 equiv), in DMSO for 20 h. at 80 °C. However, the reaction almost did not take place. Subsequently, we screened several ligands including 1,10-phenanthroline, β-keto ester, β-diketone, and L-proline. However, the desired yield was not obtained. Surprisingly, when Batey's condition was used, the yield was still very low (33%) (Table 1, entry 6). As shown in Table 1, the choice of the ligands is important for the intramolecular cyclization (Table 1, entries 1–5 and 15), which promoted us to explore the synthesis of a new class of bidentate ligands and to evaluate their scope as ligands in the CuI-catalyzed intramolecular cyclization of *ortho*-halobenzothioureas. In our previous study,[8] *N*-(4,5-dihydrooxazol-2-yl)benzamide as *N*,*O*-bidentate ligand could coordinate well with metal. Therefore, we focused on synthesis of several *N*-(4,5-dihydrooxazol-2-yl)arylamides[9] (Fig. 2, **F**, **G**, **H**, **I**). To further confirm the structure of these ligands, the crystal of ligand **F** was obtained (Fig. 3). Then, we carried out the reaction of 1-benzoyl-3-(2-bromophenyl)thiourea catalyzed by CuI as copper source in DMSO by screening these novel ligands (Table 1, entries 7–10), and we were pleased to find that the use of these ligands can notably improve the yield of the product under the same condition, and that the substituted groups on the oxazoline and phenyl rings in the ligands have no obvious influence on the catalytic activity. Thus, we chose **F** as ligand for this reaction. Furthermore, we also investigated the other solvents (DMF, DME, and toluene) and the bases (K_2CO_3 and K_3PO_4), and found that the best condition in this reaction is the combination of



Scheme 1.

Table 1
Copper-catalyzed intramolecular cyclization of 1-benzoyl-3-(2-bromophenyl)thiourea: optimization of the catalytic conditions[a]



Entry	Ligands	Base	Solvent	Yield (%)[c]
1	A	K_2CO_3	DMSO	Trace
2	B	K_2CO_3	DMSO	36
3	C	K_2CO_3	DMSO	24
4	D	K_2CO_3	DMSO	68
5	E	K_2CO_3	DMSO	64
6	E	Cs_2CO_3	DME	33
7	F	K_2CO_3	DMSO	81
8	G	K_2CO_3	DMSO	80
9	H	K_2CO_3	DMSO	76
10	I	K_2CO_3	DMSO	81
11	F	K_2CO_3	Toluene	No reaction
12	F	K_2CO_3	DMF	70
13	F	K_2CO_3	DME	25
14	F	Cs_2CO_3	DMSO	94(93[d])
15	F	K_3PO_4	DMSO	36
16	D	Cs_2CO_3	DMSO	72

[a] Reaction conditions: 1-benzoyl-3-(2-bromophenyl)thiourea (1 mmol), ligand (0.1 mmol), base (2 mmol), solvent (1 mL) for 20 h. at 80 °C under N_2 unless specified.
[b] Amount of catalyst based on 1-benzoyl-3-(2-bromophenyl)-thiourea.
[c] Isolated yield.
[d] The reaction was carried out at 70 °C.

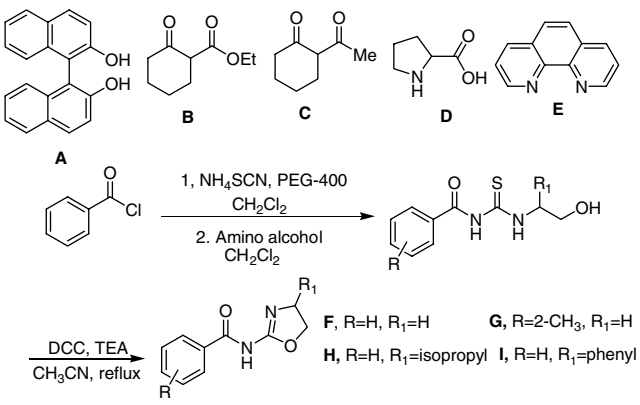


Fig. 2.

Cs_2CO_3 as base and DMSO as solvent. We then tried to transform **3** into **4** at lower temperature, and found that compound **4** was still formed in high yield when the reaction was carried out by using CuI/ligand **F** as catalyst and $CsCO_3$ as base in DMSO at 70 °C within 10 h. Since the product is also bidentate ligand, it was used as ligand instead of ligand **E** to test the reaction. However, the reaction was poorly promoted under the same conditions. The difference in the catalytic activity results from their structure. Since the oxazoline N is a much stronger base than a benzothiazole N due to the resonance effect of the neighboring O, which favors the coordination with Cu.

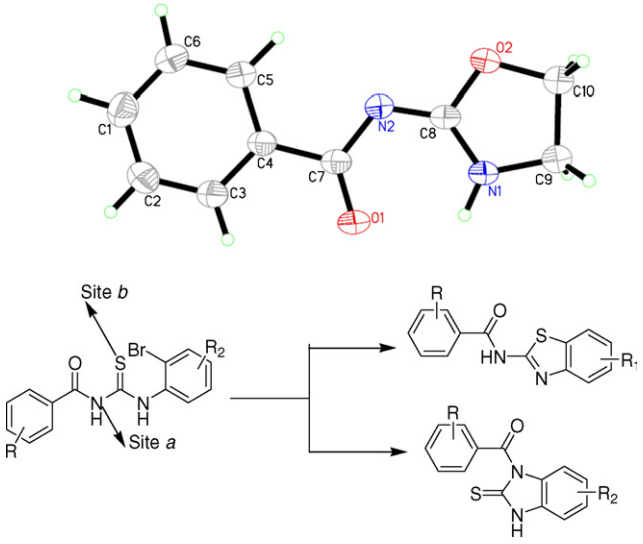


Fig. 3.

Although the polarity of the product is similar to that of the catalyst, it is easy to separate the corresponding product by TLC.

When we immerse ourselves in gratification, the structure of the product puzzled us, since *N* is also potential reactive site (site *a*).[10] (Fig. 3). When site *a* participated in the coupling reaction, the obtained compound should be benzoimidazole-thione, while site *b* participated in the coupling reaction, the obtained compound should be benzothiazole. Only by using all the spectral analytical, it is difficult to confirm the construct of the compound. Therefore, we have cultivated the single crystal of **4** (Fig. 4). X-ray crystallographic analysis of the product revealed that the product was not a benzoimidazole-thione derivative rather it is benzothiazole. It seems that under these conditions, site *b* is more active than site *a*.

In response to this encouraging result, we used a range of substituted 1-acyl-3-(2-bromophenyl)thioureas to investigate the scope and limits of this reaction.[11] As shown in Table 2, both electron-rich and electron-deficient material can provide the corresponding benzothiazole in good yield. Little affect of the substituted groups on the phenyl ring was observed for the coupling reactions. This result is consistent with the literature.[6] We also investigated *ortho*-iodoaryl precursors **1**, it was found that the corresponding products have been obtained in somewhat higher yields (Table 2, entry 13). However, in comparison with the aryl

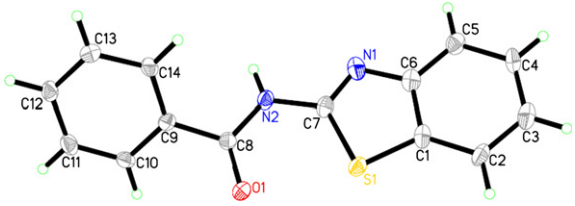
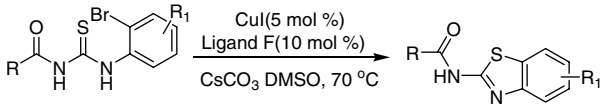
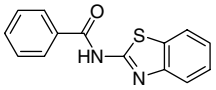
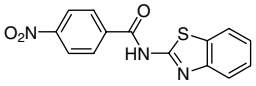
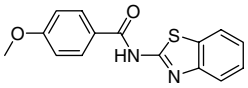
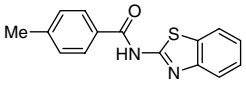
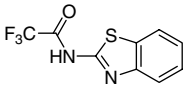
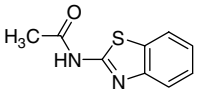
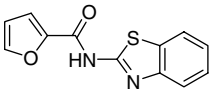
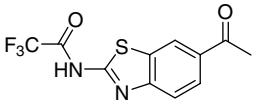
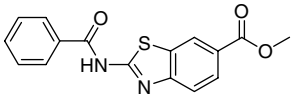
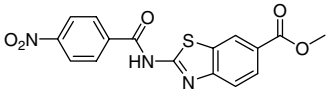
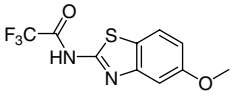
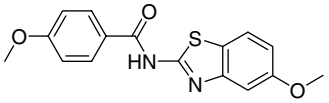
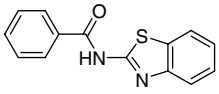


Fig. 4.

Table 2
Synthesis of *N*-benzothiazol-2-yl-amides from 1-benzoyl-3-(2-bromophenyl)thiourea[a]



Entry	Product	Time	Yields[b]
1		10	94
2		12	82
3		10	90
4		10	92
5		8	93
6		10	90
7		8	85
8		10	98
9		10	98
10		15	78
11		10	86
12		9	78
13[c]		8	95

[a] Reaction conditions:1-benzoyl-3-(2-bromophenyl)thiourea (1 mmol), ligand (0.1 mmol), base (2 mmol), solvent (1 mL) at 70 °C under N_2 unless specified.
[b] Isolated yield.
[c] *ortho*-iodoaryl precursor was used.

bromide, slightly shorter time was required to complete the intramolecular cyclization.

In conclusion, we found that the novel *N*-(4,5-dihydrooxazol-2-yl)benzamide as *N*,*O*-bidentate ligands were efficient ligands, and demonstrated an efficient intramolecular cyclization of substituted 1-arylacyl-3-(2-bromophenyl)thiourea using CuI/*N*-(4,5-dihydrooxazol-2-yl)benzamide. Generally, good to excellent yields of the desired products could be successfully obtained. This method can provide more diversiform *N*-benzothiazol-2-yl-amides under relative mild condition avoiding the use of the toxic bromine. Furthermore, the procedure extends the scope of the carbon–heteroatom forming by using the more cost effective Cu-catalyzed process.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.100.

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9. *The preparation of the ligands*: To a mixture of thiourea (5.0 mmol), TEA (0.5 mmol), and DCC (5 mmol) was added reagent grade CH_3CN (10 mL). The reaction mixture was refluxed for 5–8 h, and subsequently diluted with EtOAc (20 mL) and washed with H_2O (2×20 mL) and brine (1×10 mL). The organic layer was dried over $MgSO_4$, the solvent removed in vacuo, and the crude product purified using silica gel column chromatography. As for ligand **F**:[12] Mp: 98–100 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.56 (s, 1H), 7.42–7.26 (m, 5H), 4.57 (t, 2H), 3.94 (t, 2H); Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.41; H, 5.38; N, 14.57.
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11. *General procedure:* A Schlenk tube was charged with 1-acyl-3-(2-bromophenyl)thiourea (1 mmol), Cs_2CO_3 (2.0 mmol), CuI (0.05 mmol, 5 mol %) and ligand (0.1 mmol, 10 mol %), evacuated and backfilled with N_2. DMSO was added. The reaction mixture was heated at 60 °C for 8–10 h. until the 1-arylacyl-3-(2-bromophenyl)thiourea disappeared monitored by TLC. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (2×30 mL) and brine (2×20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to provide the desired product. *Entry 1*: ^{1}H NMR (300 MHz, DMSO-d_6): 12.89 (s, 1H); 8.20 (d, $J = 8.4$ Hz, 2H); 8.09 (s, 1H); 7.80 (m, 2H); 7.72–7.54 (m, 3H); 7.36 (m, 1H); ^{13}C NMR: (75 MHz, DMSO-d_6) 170.1, 162.3, 150.6, 135.4, 133.8, 132.6, 130.7, 129.3, 128.6, 125.4, 123.5, 122.7. Anal. Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.37; H, 4.10; N, 10.82. *Entry 8*: ^{1}H NMR (300 MHz, DMSO-d_6): 8.60 (s, 1H); 8.38 (d, $J = 8.6$ Hz, 1H); 8.29 (d, $J = 8.6$ Hz, 1H); 2.71 (s, 3H). ^{13}C NMR: (75 MHz, DMSO-d_6) 201.2, 176.0, 155.8 154.5, 135.8. 126.0, 125.4 121.9, 116.3, 30.1. Anal. Calcd for $C_{11}H_7F_3N_2O_2S$: C, 45.84; H, 2.45; N, 9.72. Found: C, 46.04; H, 2.49; N, 9.43.
12. Burkhardt, J.; Hamann, K.; Forschungsins, L.; Pigmente, S. *Chem. Ber.* **1967**, *100*, 2569–2576.