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Copper-Catalyzed Tandem Reaction of 2-Haloanilines with Thiocarbamoyl Chloride: Synthesis of 2-Aminobenzothiazoles

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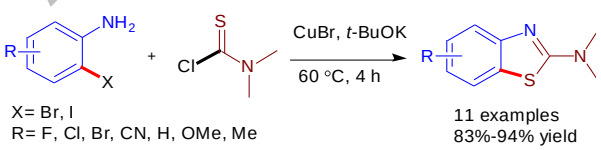
Abstract

A simple and efficient protocol for the synthesis of 2-aminobenzothiazoles by a ligand free copper-catalyzed tandem reaction has been developed. In the presence of CuBr and *t*-BuOK, a variety of 2-haloanilines (halogen=Br, I) underwent the reaction with thiocarbamoyl chloride efficiently to afford the corresponding 2-aminobenzothiazoles in good yields (83-94%). The features of this method includes good yield, cheap catalyst, mild reaction conditions and broad substrate scope, which make the protocol practical and attractive in the preparation of some potential pharmaceutically active compounds.

Graphical Abstract:



KEYWORDS: copper, tandem reaction, 2-haloanilines, thiocarbamoyl chloride, 2-aminobenzothiazoles

INTRODUCTION

The development of the formation of C-S bonds has drawn great attention since sulfur atom is ubiquitous in bioactive molecules.[1-2] To speak of these sulfur-containing compounds, the scaffold of 2-aminobenzothiazoles bearing C-S bonds has emerged in various pharmaceutical and agrochemical compounds.[3-4] All sorts of pharmacophores possessing this unit have shown great potential in the development of novel therapeutics. For instance, the treatment of amyotrophic lateral sclerosis (1),[5-6] the antiparasitic tioxidazole (2),[7] the immunosuppressive drug frentizole (3)[8] and anti-inflammatory drug (4)[9] (Figure 1). Due to the potential of the 2-aminobenzothiazoles, it has led to them being encountered through the development of various synthetic protocols. Despite great achievements in this area, the development of novel approaches towards 2-aminobenzothiazoles is still of importance.

In the last decades, classical synthesis of 2-aminobenzothiazoles involves: (a) intramolecular aromatic electrophilic substitution of thiobenzanilides using various oxidants, including Jacobson's and Hugerschoff's methods;[10-13] (b) transition metal-catalyzed intramolecular cyclisation of 2-halobenzothioureas;[14-16] (c) base promoted substitution reaction of 2-halobenzothiozoles or transition-metal-catalyzed

oxidative coupling of 2-unsubstituted benzothiazoles with amines;[17-18] (d) tandem condensation and cyclization of 2-haloanilines with isothiocyanates under transition-metal catalysis.[19-20] Rencently, it is reported that *n*-Bu_4NI was applied to form 2-aminobenzothiazoles[21-22] and 2-aminobenzothiazoles via a water mediated tandem reaction of 2-haloarylisothiocyanates with various amines.[23] These methods are commonly efficient, however, they also have many limitations such as highly toxic reagents, expensive catalysts or restricted substrates. Herein, we describe a new procedure for the formation of 2-aminobenzothiazoles by reacting 2-haloanilines (halogen=Br, I) with thiocarbamoyl chloride catalyzed by copper.

RESULTS AND DISCUSSIONS

We began our investigations by using 2-iodoaniline (**1a**) and *N*,*N*-dimethylthiocarbamoyl chloride (**2a**) as model substrates (Table 1). Among the different catalysts examined, CuO afforded the expected products in low yield (Table 1, entry 1). Whereas other catalysts, such as CuCl, $Cu(OTf)_2$, $Cu(OAc)_2$, $CuSO_4$, CuI and $CuCl_2$ resulted in good yields (Table 1, entries 2-7). Gratifyingly, the product was obtained in maximum yield when CuBr was served as catalyst (Table 1, entry 8). Subsequently, the effect of bases was evaluated (Table 1, entries 8-15), and the results indicated that NaOH, KOH, Cs_2CO_3, Na_2CO_3, K_2CO_3, NEt_3 and NaH were inferior to *t*-BuOK. A study of the solvent effect revealed that THF is the most suitable solvent (Table 1, entries 8 and 16-20). The control experiments revealed that the reaction did not proceed at room temperature (Table 1, entry 22) and the reaction was

sluggish at 40^{o}C (Table 1, entry 21). Decreasing the amount of *t*-BuOK from 3.0 to 2.0 equiv led to a further decrease of the yield to 41% (Table 1, entry 23) and no reaction was observed when the loading of *t*-BuOK was 1.0 equiv (Table 1, entry 24).

Under the optimized experimental conditions (Table 1, entry 8), we started to explore the generality and scope of the substrates (Scheme 1). The reaction of 2-haloaniline derivatives with thiocarbamoyl chloride produced the desired products in good yields. The results demonstrated that the standard conditions were consistent with a number of functional groups, such as cyano, fluoro, chloro, bromo, methoxyl and methyl group on the aryl moiety of 2-haloaniline derivatives (**3b-i**). For example, 2-iodoaniline derivatives with the electron-withdrawing fluoro group or an electron-donating methoxyl group underwent the tandem reaction with thiocarbamoyl chloride smoothly in 87% and 92% yields (**3d** and **3f**), respectively. Meanwhile, it was delightful to observe that the optimized condition could be equally applicable to the substituted 2-bromoaniline. The electron-withdrawing bromo or cholo groups and electron-donating methyl substituent could be readily incorporated, and excellent yields of the desired products were obtained (**3c** and **3g-i**). It was found that the electronic nature of the 2-haloanilines play either little or no effect on the reaction, which revealed the versatility of this protocol.

Though 2-iodoanilines and 2-bromoanilines could react with thiocarbamoyl chloride with a tandem manner to afford the product with nice yield, the protocol could not be applied to 2-chloroanilines successfully. The target molecular (benzothiazole) could be detected in

trace, and the intermediate *N*-(2-chloro)arylthiourea was obtained with an isolation yield of 88% (Scheme 2).

CONCLUSION

In conclusion, we demonstrated a novel protocol for the synthesis of 2-aminobenzothiazoles via a ligand free copper-catalyzed tandem reaction. The plausible mechanism for the reaction was proposed. The first step is the formation of aryl thioureas promoted by base, then subsequently transformed to aryl-isothioureas. The second step is the copper catalyzed intra-molecular cross-coupling reaction which let aryl-isothioureas afford 2-aminobenzothiazoles smoothly. This method enables the use of a wide range of 2-haloanilines (halogen=Br, I) and thiocarbamoyl chloride to assemble various products in good yields (83-94%). In this regard, this approach would be practical and attractive for library synthesis in drug discovery efforts.

EXPERIMENTAL

All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. DMSO was dried with molecular sieves. NMR spectra were recorded on a Bruker AM400 NMR instrument in $CDCl_3$. All melting points were determined on a RY-1G melting point instrument without correction. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan 90 mass instrument (ESI). TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and

visualized with UV light at 254 nm. Column chromatography was performed on silica gel with PE–EtOAc as the eluent.

General Procedure For Synthesis Of 2-Aminobenzothiazoles Derivatives (3a-I)

A mixture of 2-iodoanilines (1.0 mmol), THF (3 mL), and *t*-BuOK (3 mmol) was stirred in a 10 mL sealed Schlenk tube for 5 minutes, and then dimethylthiocarbamoyl chloride (1.2 mmol) and CuBr (10 mol%) were added. The reaction mixture was heated at 60^{o}C until completion as indicated by TLC. Then the mixture was cooled down to room temperature and quenched with sat. NH_4Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The obtained crude product was purified by flash column chromatography.

***N*,*N*-Dimethybenzo[*D*]Thiazol-2-Amine (3a)[24]**

Brown solid; m.p.: 83-85 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.57 (d, *J* = 8 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 3.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 168.3, 152.7, 130.4, 125.7, 120.7, 120.4, 118.5, 39.8; HRMS (ESI): calcd for $C_9H_{10}N_2S$: 178.0565; found: 178.0557.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION

The supporting material contains the spectral characterization data and copy of ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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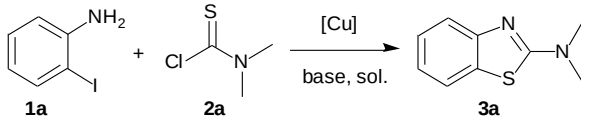
Table 1 Optimization of the Reaction Conditions[a]



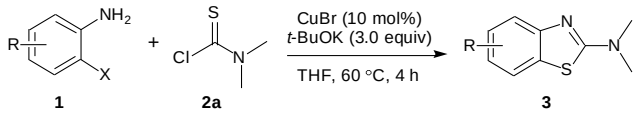
1a **2a** **3a**

Entry	Catalyst	Base(equiv)	Solvent	Temp (^{o}C)	Yield[b] (%)
1	CuO	*t*-BuOK	THF	60	21
2	CuCl	*t*-BuOK	THF	60	75
3	$Cu(OTf)_2$	*t*-BuOK	THF	60	74
4	$Cu(OAc)_2$	*t*-BuOK	THF	60	76
5	$CuSO_4$	*t*-BuOK	THF	60	79
6	CuI	*t*-BuOK	THF	60	80
7	$CuCl_2$	*t*-BuOK	THF	60	78
8	**CuBr**	***t*-BuOK**	**THF**	**60**	**83**
9	CuBr	NaOH	THF	60	46
10	CuBr	KOH	THF	60	57
11	CuBr	Cs_2CO_3	THF	60	67
12	CuBr	Na_2CO_3	THF	60	15
13	CuBr	K_2CO_3	THF	60	43
14	CuBr	NEt_3	THF	60	28
15	CuBr	NaH	THF	60	70

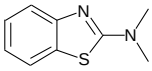
16	CuBr	*t*-BuOK	toluene	60	46
17	CuBr	*t*-BuOK	MeCN	60	trace
18	CuBr	*t*-BuOK	DMSO	60	61
19	CuBr	*t*-BuOK	DMF	60	21
20	CuBr	*t*-BuOK	DMAC	60	16
21	CuBr	*t*-BuOK	THF	40	63
22	CuBr	*t*-BuOK	THF	r.t	0
23[c]	CuBr	*t*-BuOK	THF	60	41
24[d]	CuBr	*t*-BuOK	THF	60	0

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (10 mol%), base (3 equiv), solvent (3 mL), 4 h; [b] Isolated yield based on **1a**; [c] base (2 equiv); [d] base (1 equiv).

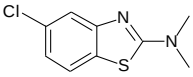
Scheme 1 Scope of the reaction



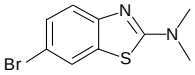
1 **2a** **3**



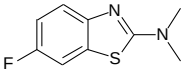
3a
X=I: 83%
X=Br: 84%



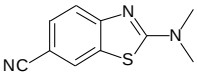
3b
X=I: 84%



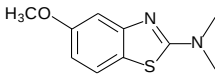
3c
X=I: 86%
X=Br: 84%



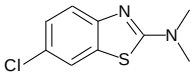
3d
X=I: 87%



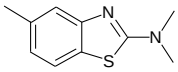
3e
X=I: 82%



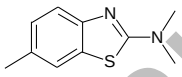
3f
X=I: 92%



3g
X=Br: 91%

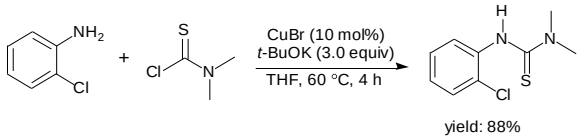


3h
X=Br: 94%



3i
X=Br: 87%

Scheme 2 The reaction limitation for 2-chloroaniline



yield: 88%

Figure 1 Structures of bioactive 2-*N*-substituted benzothiazoles