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Copper catalyzed synthesis of benzoxazoles and benzothiazoles *via* tandem manner

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Dedicated to Prof. Herbert Mayr at Ludwig-Maximilians-Universität on the occasion of his 70th birthday.

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ABSTRACT

A useful protocol for the preparation of substituted 2-aminobenzoxazoles and 2-aminobenzothiazoles was presented. Under the catalysis of copper, 2-aminophenols or 2-aminothiophenols reacted with thiocarbamoyl chlorides *via* a tandem manner, furnishing a series of 17 benzoheterocycles smoothly with good to excellent yields (70–91%). The broad substrate scope, short reaction time, mild react conditions, easy performance and nice yields make this approach attractive, showing its practical synthetic value for the preparation of some biologically or pharmaceutically active compounds.

Introduction

N-containing heterocyclic compounds are generally biocompatible, which could be widely used as pharmaceutical and agrochemical agents.[1] The scaffolds of benzazoles, such as benzoxazoles and benzothiazoles are typical *N*-containing heterocyclics that represent core structure of many trade drugs. Benzothiazoles have been found to possess interesting biological activities like anti-inflammatory,[2] antibacterial.[3–6] They are also popular construction units in fatty acid amide hydrolase inhibitors[7] and antitumor agents (Fig. 1). Moreover, benzothiazole-based compounds have been applied in other fields, for example as ratiometric fluorescent pH indicators.[8] The benzoxazole derivatives are significant targets in drug discovery,[9] and also find applications in material chemistry as photochromic agents.[10]

Instead, the benzoxazole scaffold is found in a varied spectrum of biologically active compounds.[11–14] Further important significant physiological activities related with benzoxazoles are HIV-1 protease inhibitors,[15,16] butyrylcholinesterase inhibitors,[17,18] topoisomerase II inhibitors[19] (Fig. 2).

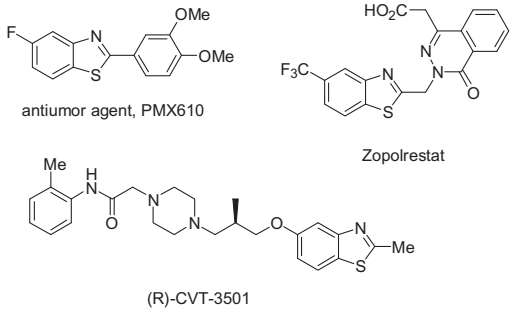

Fig. 1. Examples of bioactive benzothiazoles.

A variety of synthetic routes for these compounds have been developed due to their great importance. Generally, the traditional approaches for the preparation of these compounds mostly based on the condensation of *o*-aminophenol (or *o*-aminothiophenol) with aldehydes, derivatives of carboxylic acids, and ester[20–22] or the oxidative intramolecular cyclization of thiobenzanilides.[23] Other protocols such as transition metal catalyzed cross coupling reaction of *o*-haloanilides or their analogues through intramolecular or intermolecular cyclization, were also studied.[24] Among these,

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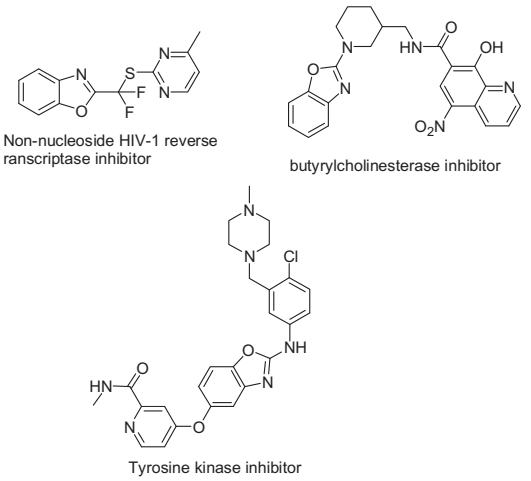
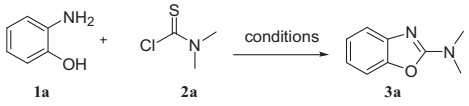


Fig. 2. Benzoxazole derivatives with biological activities.

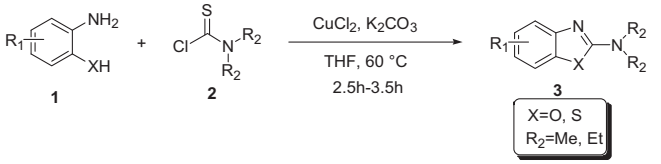
Table 1
Screening reaction conditions for 2-aminophenol (**1a**) with thiocarbamoyl chloride (**2a**).[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	Yield[b] (%)
1	–	NaH	THF	60	31
2	–	*t*-BuOK	THF	60	19
3	–	CH_3ONa	THF	60	25
4	–	KOH	THF	60	27
5	–	NEt_3	THF	60	36
6	–	K_2CO_3	THF	60	46
7	–	Na_2CO_3	THF	60	21
8	CuBr	K_2CO_3	THF	60	80
9	CuI	K_2CO_3	THF	60	81
10	CuO	K_2CO_3	THF	60	72
11	**$CuCl_2$**	**K_2CO_3**	**THF**	**60**	**86**
12	$Cu(OTf)_2$	K_2CO_3	THF	60	74
13	$Cu(OAc)_2$	K_2CO_3	THF	60	70
14	$NiCl_2$	K_2CO_3	THF	60	77
15	$NiBr_2$	K_2CO_3	THF	60	73
16	$CuCl_2$	K_2CO_3	DMSO	60	27
17	$CuCl_2$	K_2CO_3	DMF	60	39
18	$CuCl_2$	K_2CO_3	DMAC	60	68
19	$CuCl_2$	K_2CO_3	CH_3CN	60	46
20	$CuCl_2$	K_2CO_3	CH_2Cl_2	60	53
21	$CuCl_2$	K_2CO_3	THF	40	63
22	$CuCl_2$	K_2CO_3	THF	r.t	30
23[c]	$CuCl_2$	K_2CO_3	THF	60	85
24[d]	$CuCl_2$	K_2CO_3	THF	60	73
25	$CuCl_2$	–	THF	60	71
26[e]	$CuCl_2$	K_2CO_3	THF	60	47
27[f]	$CuCl_2$	K_2CO_3	THF	60	63

The entry with bold means the optimal reaction conditions.
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), [Cat.] (5 mol%), base loading (1 equiv), solvent (2.5 mL) for 2.5 h.
[b] Isolation yields.
[c] Base loading (2 equiv).
[d] Base loading (0.5 equiv).
[e] **1a** (1.0 mmol), **2a** (1.5 mmol).
[f] **1a**(1.0 mmol), **2a** (2.0 mmol).

Table 2
$CuCl_2$-catalyzed synthesis of benzoxazoles and benzothiazoles.[a]



Entry	Aminophenol/ aminothiophenol	Thiocarbamoyl chloride	Product	Yield[b] (%)
1	**1a**	**2a**	**3a**	86
2	**1b**	**2a**	**3b**	83
3	**1c**	**2a**	**3c**	82
4	**1d**	**2a**	**3d**	82
5	**1e**	**2a**	**3e**	77
6	**1f**	**2a**	**3f**	74
7	**1g**	**2a**	**3g**	84
8	**1h**	**2a**	**3h**	85
9	**1i**	**2a**	**3i**	87
10	**1j**	**2a**	**3j**	89
11	**1k**	**2a**	**3k**	91