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Selective synthesis of 2-aminobenzoxazoles and 2-mercaptobenzoxazoles by using *o*-aminophenols as starting material

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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

2-Aminobenzoxazoles and 2-mercaptobenzoxazoles were selectively synthesized by treating *o*-aminophenols with dithiocarbamates and tetramethylthiuram disulfide (TMTD), respectively. With the promotion of NaH/CuI, the reaction of *o*-aminophenols with dithiocarbamates gave 2-aminobenzoxazoles with good yield (70–92%) in one pot manner, and 2-mercaptobenzoxazoles were synthesized (yield: 55–80%) in the presence of K_2CO_3 by treating *o*-aminophenols with tetramethylthiuram disulfide (TMTD). The feature of this method includes good to excellent yield, easy performance and broad substrate scope, which makes the protocol practical and attractive in the preparation of some potential pharmaceutically active compounds.

Introduction

Benzoxazole derivatives have attracted medical scientists' interest due to their potential biological activities. Benzoxazole derivatives are used in various drugs and pesticides including various proteases inhibitors, such as chymase inhibitors,[1] HIV-1 protease inhibitors,[2,3] kinase inhibitors,[4,5] receptor agonist,[6,7] diacylglycerol acyltransferase I inhibitors,[8] butyrylcholinesterase inhibitors,[9,10] topoisomerase II inhibitors,[11] and cyanine tau aggregation inhibitors[12] (Fig. 1). In addition, they can be also used as potential positron emission tomography probes for imaging of plaques in Alzheimer's disease.[13] Except the medical science, benzoxazole derivatives could be also applied in the field of materials. They could be used as dopants in the fabrication of bright-blue organic light-emitting diodes to enhance the efficiency and stability due to their fluorescence properties.[14,15]

Mercaptobenzoxazoles with essential free thiol group exhibit the expression of potential inhibitory properties. What have been reported are inhibition of human liver iodothyronine 5′-deiodinase,[16] tyrosinase inhibition for melanoma targeting,[17] inhibitors of alkaline nuclease[18] and antifungal activity.[19] Mercaptobenzoxazoles not only themselves but also the modified nanoparticles and the metal complexes all show biological activities. Haick developed a device called "SNIFFPHONE" that use gold nanoparticles functioned with 2-mercaptobenzoxazole to diagnose lung cancer.[20,21] Co(II) and Ru(II) complexes with 2-mercaptobenzoxazoles show good antifungal and anticancer activities.[22,23]

Various procedures for the synthesis of 2-aminobenzoxazoles were reported, such as 2-substituted benzoxazoles reacting with amine,[24] cyclodesulfurization of 2-hydroxyarylthioureas[25] and direct amination of benzoxazoles.[26,27] More importantly, 2-aminobenzoxazoles can be expediently synthesized from 2-aminophenol with chloroformamidinium salts *via* cyclization of guanidine intermediate.[28–30] To the best of our knowledge, the most widely used method to prepare 2-mercaptobenzoxazoles is by treating 2-aminophenols with CS_2 in the presence of KOH,[31–34] and 2-mercaptobenzoxazoles could be subsequently transformed to 2-aminobenzoxazoles.[31–34] Both 2-aminobenzoxazoles and 2-mercaptobenzoxazoles can be synthesized starting from 2-aminophenols with aryl isothiocyanates under various conditions.[7,35–37] While these protocols have some disadvantages, such

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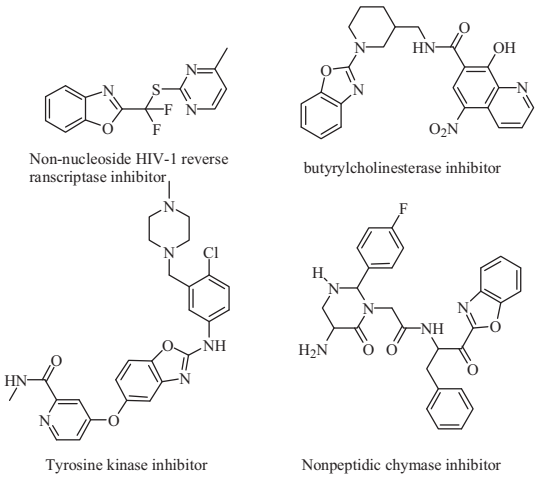
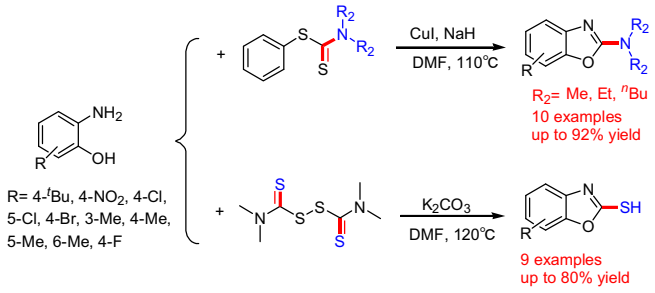


Fig. 1. Benzoxazole derivatives with biological activities.



Scheme 1. This work: selective synthesis of 2-aminobenzoxazoles and 2-mercaptobenzoxazoles by using *o*-aminophenols as starting material.

as toxicity of reactants and catalysts, isolation of intermediates which make them less attractive from a sustainable point of view.

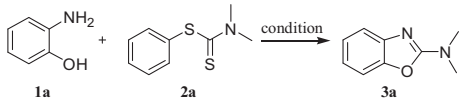
In this work (Scheme 1), 2-aminobenzoxazoles and 2-mercaptobenzoxazoles were selectively synthesized by 2-aminophenols reacting with dithiocarbamates and tetramethylthiuram disulfide (TMTD), respectively. With the mediation of CuI, *o*-aminophenols reacted with dithiocarbamates to give 2-aminobenzoxazoles up to 92% yield in one pot manner. 2-Mercaptobenzoxazoles were synthesized up to 80% yield in the presence of K_2CO_3 by treating *o*-aminophenols with tetramethylthiuram disulfide (TMTD).

Results and discussion

Initially, we used 2-aminophenol (**1a**) and dithiocarbamate (**2a**) as starting materials to furnish 2-aminobenzoxazole, and the reaction conditions were optimized. Among different solvents, DMF was found to be the most suitable solvent (Table 1. Entry 5). In order to observe the effect of base on the reaction, various organic and inorganic bases such as NaH, *t*-BuOK, Cs_2CO_3, NEt_3 and *t*-BuONa (Table 1. Entries 5, 7–10) were tested and the reaction could undergo better in the presence of NaH. Then catalysts were screened to improve the yield. It's disappointing that the yield was not improved when CuI was added as catalyst loading (0.1 equiv) (Table 1. Entry 15), other catalysts (Table 1. Entries 11–14) could not help the reaction. Gratifyingly, the reaction underwent well when the loading of CuI and the reaction temperature increased both (Table 1. Entries 17–26), the optimal copper loading is 1.5 equiv and the best reaction temperature is 110 °C. The optimized reaction conditions were summarized in Entry 25.

With the optimal reaction conditions in hand, we began to scope the substrate of 2-aminophenols and dithiocarbamates. Various 2-aminobenzoxazoles (**3a**–**j**) were synthesized in good yields

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



Entry	Catalyst (equiv)	Base (equiv)	Solvent	T (°C)	Yied[b] (%)
1	–	NaH(1.0)	DMSO	60	N.D.[c]
2	–	NaH(1.0)	MeCN	60	N.R.[d]
3	–	NaH(1.0)	DMAC	60	29
4	–	NaH (1.0)	DMF	60	30
5	–	NaH (2.0)	DMF	60	43
6	–	NaH (3.0)	DMF	60	39
7	–	*t*-BuOK (2.0)	DMF	60	33
8		Cs_2CO_3 (2.0)	DMF	60	28
9	–	NEt_3 (2.0)	DMF	60	N.R.[d]
10	–	*t*-BuONa (2.0)	DMF	60	17
11	CuO(0.1)	NaH (2.0)	DMF	60	32
12	$FeBr_3$(0.1)	NaH (2.0)	DMF	60	20
13	$PdCl_2$(0.1)	NaH (2.0)	DMF	60	N.D.[c]
14	$NiCl_2$(0.1)	NaH (2.0)	DMF	60	N.D.[c]
15	CuI(0.1)	NaH (2.0)	DMF	60	36
16	CuI(0.1)	NaH (2.0)	DMF	50	10
17	CuI(0.1)	NaH (2.0)	DMF	80	40
18	CuI(0.1)	NaH (2.0)	DMF	100	45
19	CuI(0.1)	NaH (2.0)	DMF	110	45
20	CuI(0.1)	NaH (2.0)	DMF	120	49
21	CuI(0.2)	NaH (2.0)	DMF	110	47
22	CuI(0.3)	NaH (2.0)	DMF	110	50
23	CuI(0.5)	NaH (2.0)	DMF	110	52
24	CuI(1.0)	NaH (2.0)	DMF	110	55
25	**CuI(1.5)**	**NaH (2.0)**	**DMF**	**110**	**72**
26	CuI(2.0)	NaH (2.0)	DMF	110	74

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), solvent (3.0 mL) for 10 h.
[b] Isolated yield.
[c] N.D.: not determined.
[d] N.R.: no reaction.