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Metal-free synthesis of 2-mercaptobenzothiazoles and 6-(4-substituted-1H-1,2,3-triazol-1-yl)-2-mercaptobenzothiazoles *via* microwave-assisted synthesis pathway

Truong Thanh Tung[a,b] and Luong Xuan Huy[a,b]

[a]Faculty of Pharmacy, PHENIKAA University, Hanoi, Vietnam; [b]PHENIKAA Institute for Advanced Study (PIAS), PHENIKAA University, Hanoi, Vietnam

ABSTRACT

A simple, efficient, and metal-free methodology for the preparation of 2-mercaptobenzothiazole and derivatives in excellent yields *via* microwave-assisted pathway is reported. Our condition provides a convenient protocol for the synthesis of a diverse collection of 2-mercaptobenzothiazoles and 6-(4-substituted-1*H*-1,2,3-triazol-1-yl)-2-mercaptobenzothiazoles with a very simple purification process. This report provides an alternative protocol for fast access to the wide range of compounds for sequence synthesis and biological studies.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
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KEYWORDS
microwave-assisted synthesis; metal-free; 2-mercaptobenzothiazole

Introduction

Small molecule libraries are important sources for drug discovery and development. A good collection of compounds could provide a higher chance of finding biologically active agents.[1] Generally, the construction and designing of the library compounds started from a privileged substructure, the structure in which they appeared or confirmed a pivotal role in targeting many biological systems.[1,2] Due to the high demand of constructing hundreds to thousands of compounds, a fast, convenient method for preparation of the key skeleton is needed.

2-Mercaptobenzothiazole is an active agent and also a privileged structure that can be found in many biologically active agents.[3–5] The compound itself was used as a dermatological drug for veterinary (US drug name *Sulfodene*) or even human use in some countries. In addition, it showed good inhibitory activity in viruses, fungi, and many other pathogens.[6–11] Therefore, 2-mercaptobenzothiazole is an important intermediate for the synthesis of bioactive library compounds (Figure 1).

There are several methods for the synthesis of 2-mercaptobenzothiazole derivatives. Chaudhuri was the first to report the conversion of the 2-bromo-4-substituted-anilines

CONTACT Tung Truong Thanh tung.truongthanh@phenikaa-uni.edu.vn Faculty of Pharmacy, PHENIKAA University, Hanoi 12116, Vietnam.

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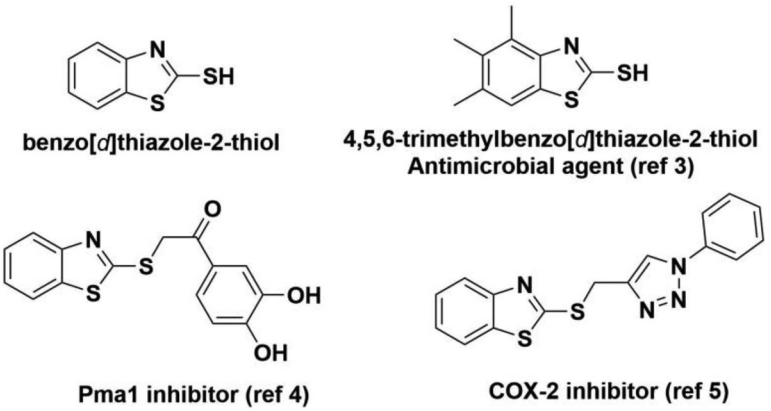


Figure 1. 2-Mercaptobenzothiazole moiety in bioactive compounds.

to 2-mercaptobenzothiazole derivatives *via* reaction with potassium ethyl xanthogenate under reflux condition (5 examples).[12] The reaction afforded good yields and a required reaction time of 4 hours. Due to very limited information and only 4-substituted-anilines tested, the selectivity of the reaction has not been reported. Intrigued by Chaudhuri reports, Zhu *et. al* investigated the ortho-selectivity of this reaction which provides essential information to the scope of Chaudhuri's initial report.[13] The expanded version of this research was published from the same group in the same year.[14] Instead of the normal heating process, Huang et al. have used microwave-assisted synthesis for improvement of Chaudhuri's reaction yields and time.[15]

Another route to the preparation of 2-mercaptobenzothiazole derivatives is *via* carbon disulfide (CS_2). Mighri reacts *o*-haloanilines with CS_2 under basic condition (TEA) followed by dehydrosulfurization to afford the products in medium to good yields.[16] Instead of TEA, in other research, Xi et al. have used DBU to promote the reaction.[17] (Figure 2)

Overall, all of the reports focused on the simple substitution of the *o*-haloanilines which may be limited in understanding the full scope of the reaction.

O-isopropylxanthic acid potassium salt (PIX) is a stable solid and easier to handle and storage than CS_2. In this work, we report the first synthesis of 2-mercaptobenzothiazole derivatives using PIX in Dimethylacetamide (DMAC) under microwave irradiation .In addition, the complex system of 6-(4-substituted-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiols was constructed for the first time using our reported condition.

Results and discussion

2,6-dichloroaniline was chosen as a model substrate. The optimization of the reaction condition was reported in Table 1. For comparison, normal heating condition was performed along with microwave irradiation.

Microwave irradiation at 150 °C was found to be the best condition with quantitative yields (entries 3, 4). We were able to reduce the reaction time to only 5 min without

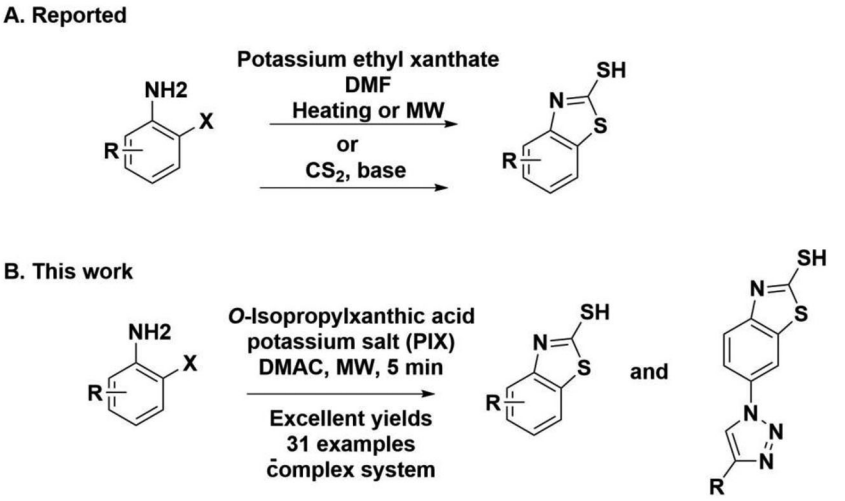
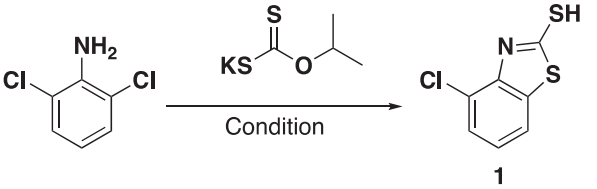


Figure 2. Current methods for preparation of 2-mercaptobenzothiazole derivatives.

Table 1. Optimization of the reaction condition[a].



1

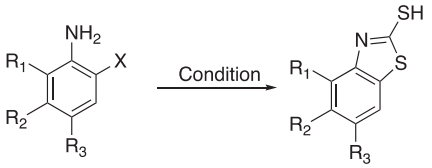
500 mg (3 mmol)

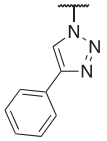
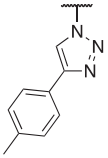
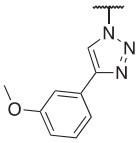
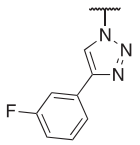
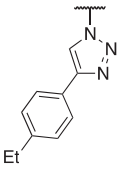
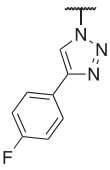
Entry	Method	Solvent	Temp.	Time (min)[b]	Yield (%)[c]
1	MW	DMAC	90	120	70
2	MW	DMAC	110	100	90
3	MW	DMAC	150	15	99
4	MW	DMAC	150	5	99
5	MW	DMSO	150	30	60
6	MW	ACN	60	200	51
7	MW	Toluene	100	30	63
8	MW	Chlorobenzene	100	30	33
9	MW	DMF	150	240	87
10	Heat	DMAC	110	300	30
11	Heat	DMSO	110	1440	62
12	Heat	ACN	60	1440	42
13	Heat	Toluene	110	1440	18
14	Heat	Chlorobenzene	110	1440	30
15	Heat	DMF	110	240	89

[a]Experiments were performed in triplicate, 500 mg (3 mmol scale).
[b]required to get the highest yield(s).
[c]Isolated yields.

decreasing reaction yield (entry 4). However, lowering the temperature leads to prolonged reaction times (to obtain the best conversion) and decreases the total yield of the reaction (entries 1, 2). DMAC was found to be the optimal solvent since any replacements lead to lower yields (entries 5–9).

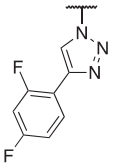
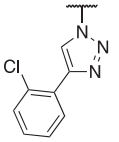
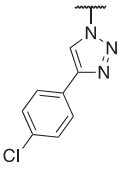
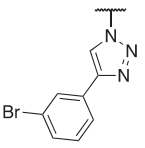
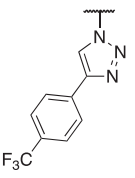
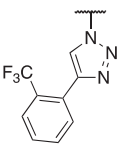
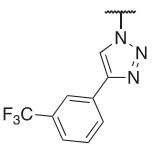
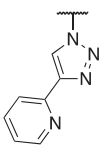
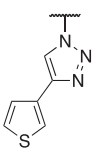
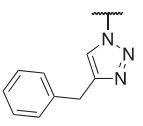
Table 2. Scope of the reaction.



Entry	Cpds	R_1	R_2	R_3	X	Yield (%)[a]
1	**1**	Cl	H	H	Cl	99
2	**2**	H	F	H	Cl	89
3	**3**	H	H	Cl	Cl	90
4	**4**	H	Br	H	Cl	81
5	**5**	H	H	CF_3	Cl	76
6	**6**	Me	H	H	Cl	85
7	**7**	H	H	MeO	Cl	85
8	**8**	H	H	EtO	Cl	94
9	**9**	H	H	F	Br	92
10	**10**	H	H	Cl	Br	91
11	**11**	H	H	*i*Pr	Br	88
12	**12**	Me	H	Me	Br	97
13	**13**	H	H	CF_3O	Br	68
14	**14**	H	H	NO_2	F	63
15	**15**	H	H	NH_2	F	70
16	**16**	H	H		F	93
17	**17**	H	H		F	90
18	**18**	H	H		F	87
19	**19**	H	H		F	82
20	**20**	H	H		Cl	90
21	**21**	H	H		Cl	81

(*continued*)

Table 2. Continued.

22	**22**	H	H		Cl	88
23	**23**	H	H		Cl	74
24	**24**	H	H		Cl	92
25	**25**	H	H		Cl	81
26	**26**	H	H		Cl	65
27	**27**	H	H		Cl	70
28	**28**	H	H		Cl	79
29	**29**	H	H		Cl	61
30	**30**	H	H		Cl	77
31	**31**	H	H		Cl	82

[a]Isolated yields.

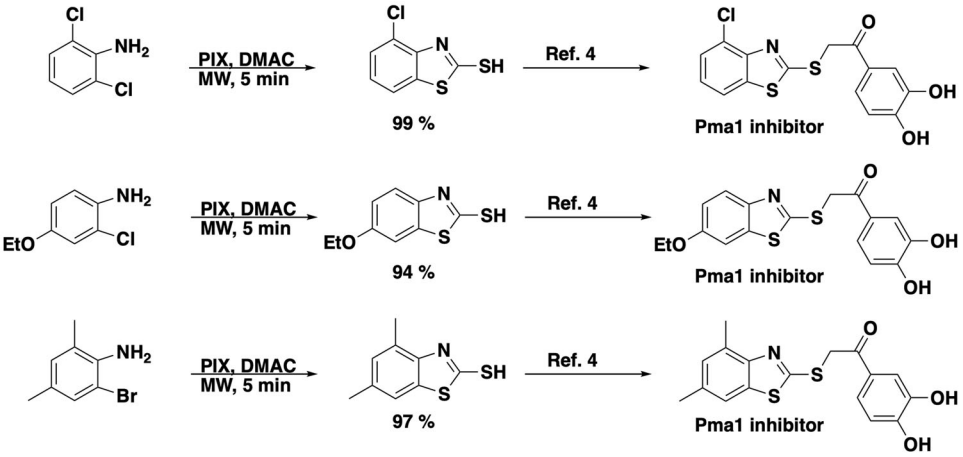


Figure 3. Application of our reaction condition on synthesis of pma1 inhibitors.

Microwave irradiation gave higher yields within a short period of time as compared to normal heating conditions (entries 10–15). For example, the yield of the optimized condition (entry 4, 99%) is greatly decreased under traditional heating (entry 10, 30%).

With optimized reaction conditions in hand, we have successfully prepared 30 diverse 2-mercaptobenzothiazole derivatives as shown in Table 2.

The reaction ran smoothly with different substitutions of the *o*-haloanilines (500 mg, 3 mmol scale) to afford products in excellent yields. The presence of the halo-substituted groups in phenyl ring was well tolerated to our condition (entry 1–15). Under our optimized reaction conditions, a similar reactivity of F, Cl, and Br at position 2 of aniline (X group) was observed. Additionally, the reaction of 2-Iodoanilines gave very low yields (data not shown). Overall, PIX was found to be a more powerful reagent than of potassium O-ethyl dithiocarbonate[15] in terms of reactivity.

To explore more the scope of the reaction, various 4-substituted-1,2,3-triazoles of the *o*-haloanilines were tested. Interestingly, the products were formed in good to excellent yields without forming by-products (entries 16–31). The presence of heterocycles on the triazole ring was also well tolerated in these reactions (entries 29, 30). Overall, the reaction condition is compatible with the modification of the substitutions on the phenyl ring as well on the 1,2,3-triazole moiety.

To demonstrate the practicality of our method, the possible route to the synthesis of bioactive compounds in reference[4] was depicted in Figure 3.

Conclusion

In conclusion, we have reported a fast and efficient method for the preparation of a diverse collection of 2-mercaptobenzothiazole derivatives from the reaction between *o*-haloanilines, *O*-isopropylxanthic acid potassium salt in DMAC under microwave irradiation. The broad scope of the reaction has been demonstrated by applying to the more complex system of triazole-containing *o*-haloanilines as a starting material. This report will provide an alternative protocol for the preparation of 2-mercaptobenzothiazole

derivatives and 6-(4-substituted-1H-1,2,3-triazol-1-yl)-2-mercaptobenzothiazoles for organic and medicinal chemistry research.

Experimental

In a 20 mL microwave reaction vial (Biotage), a mixture of substituted 2-halogeno-aniline (1 equiv, 500 mg), *O*-isopropylxanthic acid potassium salt (PIX) (2 equiv), and DMAC (8 mL) was added. The vial was irradiated at 150 °C for 5 min in a Biotage microwave reactor. The mixture was cooled to room temperature. Then it was poured into cold H_2O and adjusted to pH 3 by HCl 1 N. The precipitate was filtered and washed (5 times) with H_2O to afford products without additional purification.

*6-(4-phenyl-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (**16**)*. Yield 93%; mp 267.1-268.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.01 (s, 1H), 9.26 (s, 1H), 8.34 (d, $J = 2.2$ Hz, 1H), 8.00–7.90 (m, 3H), 7.55–7.46 (m, 3H), 7.39 (t, $J = 7.4$ Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 191.0, 147.8, 141.7, 133.6, 131.2, 130.6, 129.5, 128.8, 125.8, 120.3, 120.2, 114.3, 113.6. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_4S_2^+$ 311.0425, found 311.0425.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Supporting Information

Full experimental detail, characterization data of new compounds, ^{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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ORCID

Truong Thanh Tung http://orcid.org/0000-0002-5263-203X

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