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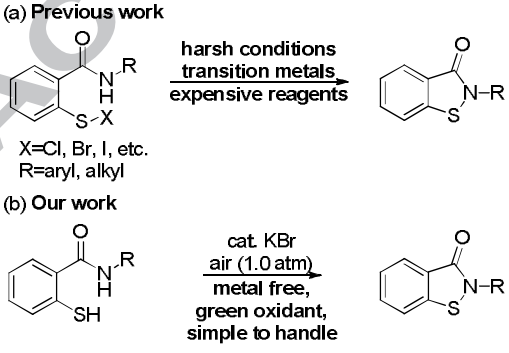
ABSTRACT

N-substituted benzo[*d*]isothiazol-3(2*H*)-ones are a family of compounds with extremely important application. Recently, we have developed a new green pathway to synthesize these compounds via potassium bromide-catalyzed intramolecular oxidative dehydrogenative cyclization. This reaction has high functional group tolerance and affords excellent yield even in gram scale.

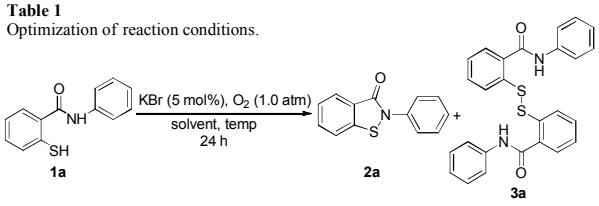
Introduction

N-Substituted benzo[*d*]isothiazol-3(2*H*)-ones play a very important role in many fields of everyday life. On one hand, the compounds are used as bioactive substances like pharmaceuticals,[1] such as antimicrobial,[2] antifungal,[3] antithrombotic agents[4] and antitumor pills.[5] On the other hand, in the fields of agriculture, they were also used as bactericidal preservatives,[6] herbicide and plant growth regulator and so on.[7] However, to our best knowledge, the traditional methods of synthesizing benzo[*d*]isothiazol-3(2*H*)-ones are much too inconvenient as tedious process,[8] expensive reagents[9] and transition metals[10] are all required (Scheme 1a).



Scheme 1. Examples of N-S bond formation reactions.

Table 1
Optimization of reaction conditions.



Entry	Solvent	Temp (°C)	Yield (%)	
			2a	3a
1[a]	DMSO	80	0	0
2[b]	DMSO	80	5	0
3[c]	DMSO	80	0	0
4	DMSO	80	21	0
5	DMF	80	80	0
6	DMA	80	52	0
7	CH_3CN	80	0	0
8	THF	80	0	0
9	Dioxane	80	55	23
10	Toluene	80	0	0
11	DMF	90	82	0
12	DMF	100	86	0
13	DMF	110	>95	0
14	DMF	120	88	0
15[d]	DMF	110	73	0
16[e]	DMF	110	>95	0
17[f]	DMF	110	83	0

Unless otherwise noted, the reactions were performed in a sealed tube with **1a** (0.1 mmol), KBr (5.0 mol%), and O_2 (1.0 atm) in 1 mL solvent for 24 h. All yields listed are isolated yield. [a] Without O_2 .[b] Without KBr. [c] Without O_2 or KBr. [d] 12h. [e] Under air condition. [f] KBr (2.5 mol%).

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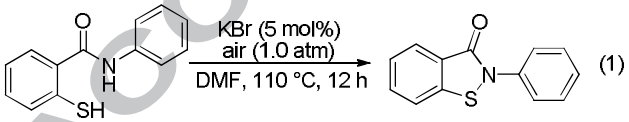
What's more, toxic matters and heavy metal salts waste produced during these processes can't be ignored. Considering the widely application of these compounds and their values in pharmaceutical industry,[1] developing a novel and green pathway to construct N-S bond(s) is significant. Herein, we report a potassium bromide(KBr)-catalyzed oxidative dehydrogenation reaction for synthesizing this kind of compounds (Scheme 1b).

According to the previous reports, bromide ion (Br^-) can be oxidized to bromine(Br_2) in oxygen atmosphere to further oxidize S-H bond to S-Br bond,[11] so KBr is selected as the catalyst. We initiated the experiment by using *o*-mercapto-N-phenylbenzamide **1a** as the starting material in the presence of KBr in DMSO at 80 °C with O_2, only 21% yield was achieved in this trial (Table 1, entry 4). The following control reactions showed that KBr and oxygen are necessary (Table 1, entries 1-3).

We then screened a series of solvents and found that the reaction proceeded well in high polar solvents (Table 1, entries 4-10), and DMF (Table 1, entries 5) afforded the highest yield of **2a**. Surprisingly, when the solvent was changed to dioxane, 2,2'-disulfanediylbis(N-phenylbenzamide) **3a** was obtained as well (Table 1, entry 9). The effect of temperature was checked (Table 1, entries 11-14) and 110 °C was found to be the best. When the reaction time was shortened to 12 h, the yield decreased slightly (Table 1, entry 15). O_2 was also changed to air to further screen the reaction conditions, and the target compound was found to have a high yield as well (Table 1, entry 16). When the amount of KBr was decreased to 2.5 mol%, a slightly decrease occurred in the yield of the target compound (Table 1, entry 17). We also evaluated a series of inorganic salts including NaBr, CuBr, $CuBr_2$, NaI and KI, and all of them exhibited slightly lower yields than KBr.

With the optimal reaction condition in hand, substrate scope was investigated. In substrates **1b**-**1g**, the reaction was proved to be unaffected by electron-donating or -withdrawing groups, and the functional groups remained unreacted. Sterically hindered aryl with two bromide substituents in the ortho position **1h** also served as a substrate without any by-product. Excellent yields were obtained as well for the substrates containing other aryl substituents including thiazolyl group. Then the alkyl substituents were checked and we found that they all have an excellent yield, even when a more crowded *tert*-butyl group was used. Besides, cyclopropanyl group didn't change in this reaction, either.

The reaction can also be performed well in gram scale. Treatment of 1.02 g of **1a** with 5 mol% amount of KBr produced 0.75 g of **2a** in 74% yield [eq. (1)].

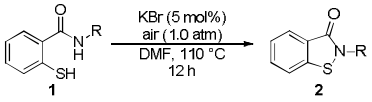


1a (1.02 g) **2a** (0.75 g)

A sulfoxide **4** was quantitively obtained when **2a** was treated in CH_3COOH with H_2O_2 at room temperature 5 h, and the structure of the compound was confirmed by X-ray crystallography (Figure 1).

In an attempt to check the synthetic utility of the resulting products, the reaction of **2a** with a terminal alkyne was carried out under standard conditions,[12] and it afforded a mercaptoacetylene **6** in 67% isolated yield [eq.(2)], which can be further transformed into an acetylene **7** via Sonogashira coupling reaction [eq. (3)].[12]

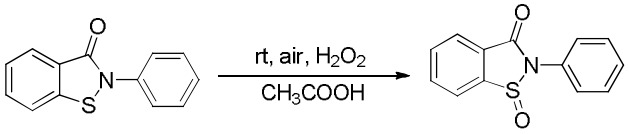
Table 2
Synthesis of N-substituted benzo[*d*]isothiazol-3(2*H*)-ones.



1 **2**

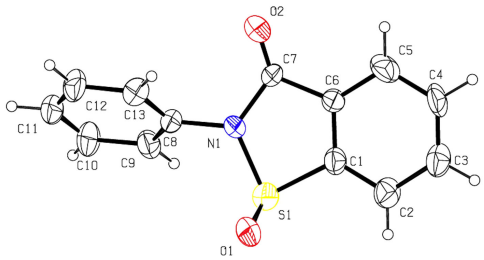
entry	1			yield / %
1	R_1= F	**1b**	**2b**	83
2	Cl	**1c**	**2c**	75
3	Br	**1d**	**2d**	87
4	I	**1e**	**2e**	>95
5	CH_3	**1f**	**2f**	72
6	OCH_3	**1g**	**2g**	89
7		**1h**	**2h**	65
8		**1i**	**2i**	>95
9		**1j**	**2j**	83
10		**1k**	**2k**	>95
11		**1l**	**2l**	>95
12		**1m**	**2m**	>95
13		**1n**	**2n**	>95
14		**1o**	**2o**	>95

Fig. 1. Insight of the unexpected compound.



2a **4**

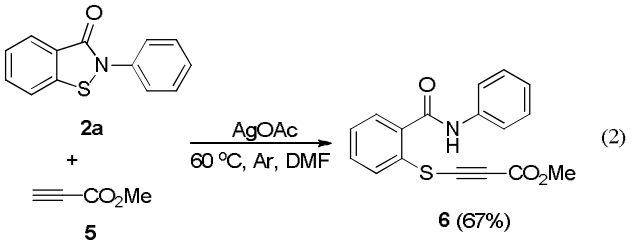
a. **2a** oxidized to sulfoxide **4**.

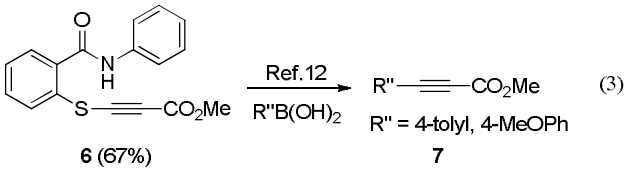


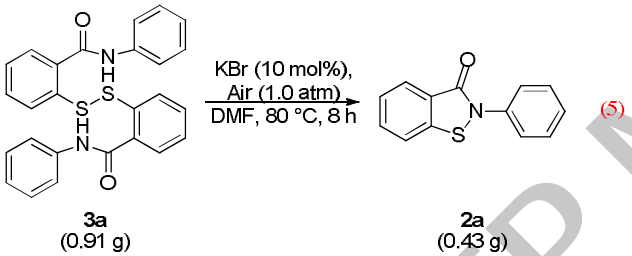
b. X-ray structure of **4**.

A primary mechanism research was conducted at last. According to previous reports[11], Br^- can be oxidized to Br_2, so Br_2 was trialed in the optimal reaction conditions [eq.(4)]. However, only a moderate yield was got, which proved the Br_2 is essential for this reaction. Besides, considering the result of entry 9 from Table 1, disulfide **3a** was formed during our reaction as well. Therefore, we used **3a** as a starting material in the optimal

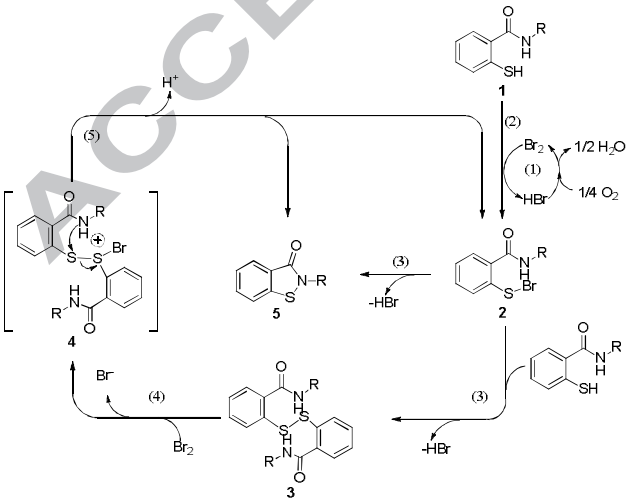
conditions, the desired product was also acquired in a 95% yield [eq. (5)], indicating the validation of the mechanism.







The proposed mechanism for the formation of benzoisothiazolone **2a** is shown as follows (Scheme 2), just like the one proposed by DeLion.[13](1) Br^- is oxidized to Br_2;[11] (2) S-H bond is oxidized to S-Br bond via the elimination of HBr;[14] (3) desired compound or disulfide is formed via the elimination of HBr; (4) disulfide is oxidized by Br_2 to an activated intermediate **4**; (5) **4** is then converted into the desired product and **2**.



Scheme 2. Proposed mechanism for the formation of benzoisothiazolone.

Conclusions

In summary, we have successfully realized the KBr-catalyzed synthesis of benzo[*d*]isothiazol-3(2*H*)-ones via intramolecular oxidative-dehydrogenative cyclization. In this reaction, a small amount of green catalyst (5 mol% KBr) was used under air condition at 110 °C to construct a new N-S bond, making this pathway efficient and environmentally friendly. The simple and easy handling method also makes our reaction an attractive pathway for the synthesis of heterocyclic compounds with N-S bond(s). Further research is still going on in our laboratory.

Acknowledgments

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References and notes

1. (a) Dahl R, Bravo Y, Sharma V, Ichikawa M, Dhanya RP, Hedrick M, Brown B, Rascon J, Vicchiarelli M, Mangravita-Novo A, Yang, L, Stonich D, Su Y, Smith LH, Sergienko E, Freeze HH, Cosford ND. *J Med Chem.* 2011;54:3661-3668. (b) Gorsuch S, Bavetsias V, Rowlands MG, Aherne GW, Workman P, Jarman M, McDonald E. *Bioorgan Med Chem.* 2009;17:467-474. (c) Sivaramakrishnan S, Keerthi K, Gates KS. *J Am Chem Soc.* 2005;127:10830-10831. (d) Shimizu M, Sugano Y, Konakahara T, Gama Y, Shibuya I. *Tetrahedron*. 2002;58:3779-3783. (e) Binev YI, Petkov CT, Pejov L. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2000;56:1949-1956. (f) Naumov P, Jovanovski G. *Struct Chem.* 2000;11:19-33. (g) Bao M, Shimizu M. *Tetrahedron*. 2003;59:9655-9659. (h) Henke A, Srogl J. *J Org Chem.* 2008;73:7783-7784. (i) Shimizu M, Kikumoto H, Konakahara T. *Heterocycles*. 1999;51:3005-3012. (j) Wright SW, Petraitis JJ, Batt DG, Corbett RL, Di Meo SV, Freimark B, Giannaras JV, Orwat MJ, Pinto DJ, Pratta MA, Sherk SR, Stampfli HF, Williams JM, Magolda RL, Arner EC. *Bioorgan Med Chem.* 1995;3:227-234. (k) Anand D, Patel O P S, Maurya R K, Kant R, Yadav PP. *J Org Chem.* 2015;80:12410-12419.
2. (a) Stumpf B, Abraham W R, Kieslich K. *Appl Microbiol Biot.* 1986;23:215-217. (b) Borgna P, Carmellino ML, Natangelo M, Pagani G, Pastoni F, Pregnolato M, Terreni M. *Eur J Med Chem.* 1996;31:919-925. (c) Remko M. *J Phys Chem A*. 2003;107: 720-725. (d) Dakova B, Müller R, Lamberts L, Evers M. *Electrochim Acta*. 1994;39:661-666. (e) Pagani G, Borgna P, Piersimoni C, Nista D, Terreni M, Pregnolato M. *Arch. Pharm.* 1996;329:421-425.
3. (a) Wright SW, Abelman MM, Bostrom LL, Corbett RL, *Tetrahedron Lett.* 1992;33:153-156. (b) Kharul RK, Prajapati PN, Thorave AA, Shah HA, Dhar A, Joshi DA, Jain MR, Patel PR, Pancholi SS. *Synth Commun*. 2011;41:3269-3279. (c) Kharul RK, Prajapati PN, Thorave AA, Shah HA, Dhar A, Joshi DA, Jain MR, Patel PR, Pancholi SS. *Synthetic Commun*. 2011;41:3265-3279. (d) Zani F, Vicini P, Incerti M. *Eur J Med Chem.* 2004;39:135-140. (e) Morley JO, Oliver AJ, Charlton MH. *J Mol Struc-Theoch.* 1998;42:103-110.
4. Baggaley KH, English PD, Jennings LJA, Morgan B, Nunn B, Tyrrell AWR. *J Med Chem.* 1985;28:1661-1667.
5. (a) Gopinath P, Ramalingam K, Muraleedharan KM, Karunagaran D. *Med Chem Commun*. 2013;4:749-752. (b) Kim W, Dannaldson J, Gates KS. *Tetrahedron Lett.* 1996;37:5337-5340.
6. Zhang PY, Yu X, Chen ZY, Wang YL, Chen SH, Yang ZR, Hou RT. *Chinese J Org Chem.* 2005;25:1142-1146.
7. Wang X, Yin X, Feng W, Yang J, Lin Q. *Chinese Journal of Pesticide Science*. 2012;14:225-228.
8. Volonterio A, Bravo P, Zanda M. *Tetrahedron Lett.* 2002;43:6537-6540.
9. Correa A, Tellitu I, Domínguez E, SanMartin R. *Org Lett.* 2006;8: 4811-4813.
10. (a) Bhakuni BS, Balkrishna SJ, Kumar A, Kumar S. *Tetrahedron Lett.* 2012;53:1354-1357. (b) Paul R, Punniyamurthy T. *RSC Advances*. 2012;2:7057-7060.

11. Fuchs B, Mayer WJW, Abramson S. *J Chem Soc, Chem Commun.* 1985;23:1711-1713.
12. Henke A, Srogl J. *Chem Comm.* 2010;46:6819-6821.
13. Kersting B, DeLion M. *Zeitschrift für Naturforschung B.* 1999;54:1042-1047.
14. Grivas JC. *J Org Chem.* 1975;40:2029-2032.

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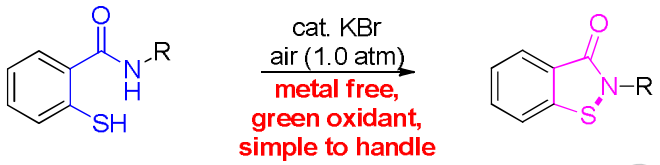

1. We realized potassium bromide, a green and highly efficient catalyst, to catalyze the formation of the desired N-S bond.
2. The reaction proceeded in an excellent yield.
3. High functional group tolerance is exhibited in this reaction as well.
4. The products are obtained in excellent yields even in gram scale,
5. The products exhibit promising applications in industry.