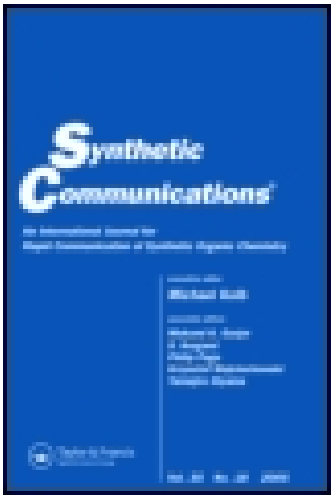

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Tribromo Phloroglucinol as a Novel and Highly Efficient Reagent for the Conversion of Benzothioamides to the Corresponding 1,2,4-Thiadiazoles

Hassan Zali-Boeini[a] & Seyed Gholamhossein Mansouri[a]

[a] Department of Chemistry, University of Isfahan, Isfahan, Iran

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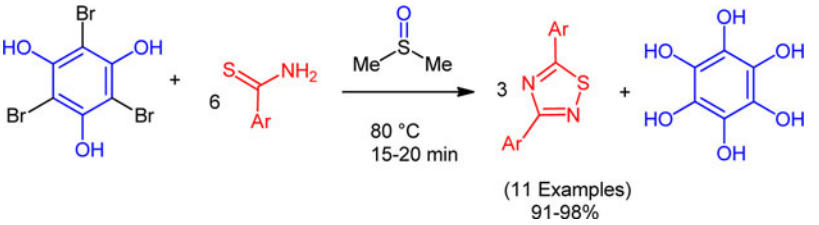
TRIBROMO PHLOROGLUCINOL AS A NOVEL AND HIGHLY EFFICIENT REAGENT FOR THE CONVERSION OF BENZOTHIOAMIDES TO THE CORRESPONDING 1,2,4-THIADIAZOLES

Hassan Zali-Boeini and Seyed Gholamhossein Mansouri
Department of Chemistry, University of Isfahan, Isfahan, Iran

GRAPHICAL ABSTRACT



Abstract *2,4,6-Tribromo-1,3,5-trihydroxybenzene (TBTHB) as a reagent was efficiently reacted with 6 molar equivalents of benzothioamides in dimethyl sulfoxide (DMSO), and the corresponding 3,5-diaryl-1,2,4-thiadiazoles were obtained in almost quantitative yields (91–98%) and in short times (15–20 min) with the formation of hexahydroxybenzene as a rather valuable by-product.*

Keywords Heterocycles; thiadiazole; thioamide

INTRODUCTION

Undoubtedly, thioamides are very important building blocks in organic synthesis and especially in construction of heterocyclic compounds.[1] They have been used as multipurpose synthons in the synthesis of five- and six-membered heterocycles.[2] Among them, benzothioamides are good substrates for the synthesis of the wide varieties of thiazole[3] and thiadiazole derivatives. Various types of oxidants have been employed for the C-S coupling of benzothioamide derivatives to the corresponding thiadiazoles such as halogens[4] [12], nitrous acid,[5] hydrogen peroxide,[6] thionyl chloride,[7] a mixture of HCl–dimethylsulfoxide (DMSO),[8]

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Address correspondence to Hassan Zali-Boeini, Department of Chemistry, University of Isfahan, 81746-73441 Isfahan, Iran. E-mail: h.zali@chem.ui.ac.ir
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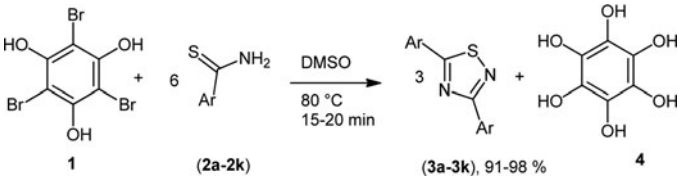


Scheme 1.

and pyridinium salt–DMSO.[9] Meanwhile, the reaction of 1-monosubstituted thioureas with bis(acyloxyiodo)arene derivatives has been utilized as a synthetic procedure to obtain 3,5-bis-(phenylamino)-1,2,4-thiadiazoles.[10] Thiadiazoles are interesting building blocks in medicinal chemistry[11–13] and industrial chemical[14] that are easy to access.

In continuation of our attempts to develop novel synthetic routes for the preparation of sulfur heterocycles and sulfur-containing organic compounds using thioamides,[15] an unexpected result in the reaction of benzothioamides with 2,4,6-tribromo-1,3,5-trihydroxy benzene (TBTHB) in DMSO is reported. When a mixture of TBTHB and 6 molar equivalents of a benzothioamide derivative in DMSO was heated to 80 °C, complete conversion of starting materials was observed and the corresponding 3,5-diaryl-1,2,4-thiadiazole was obtained in excellent yields (91–98%) and very short times (15–20 min, Scheme 1).

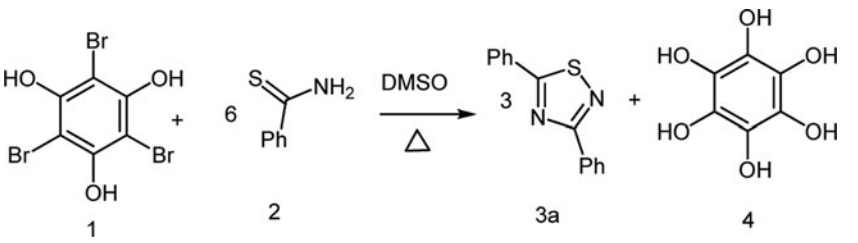
RESULTS AND DISCUSSION

The initial study examined the reaction of benzothioamide as a test substrate with tribromophloroglucinol in DMSO. Fortunately, the course of the reaction could even be pursued visually. At the outset of the reaction, a light yellow color is visible in the reaction mixture due to presence of the benzothioamide in the solution. After 10 min of heating at 80 °C, the reaction mixture turned orange in color and then changed to red after a further 5 min of heating at the same temperature. Finally, a rapid and exothermic reaction occurred during the final minutes alongside the evolution of Me_2S and H_2S gases, leading to the corresponding 3,5-diphenyl-1,2,4-thiadiazole **3a** in almost quantitative yield (98%). The reaction temperature was found to be very effective on the reaction time and the product yields of the reaction. The full results of the temperature and time optimization for this reaction is outlined in Table 1.

Although oxidative cyclization reactions of benzothioamides to the corresponding 1,2,4-thiadiazoles using various oxidative agents are known and there is a reasonable mechanism to explain the course of those reactions,[9] in Scheme 2 we offer a mechanism to explain the unusual stoichiometric ratio of the reactants, one to six, in our novel method.

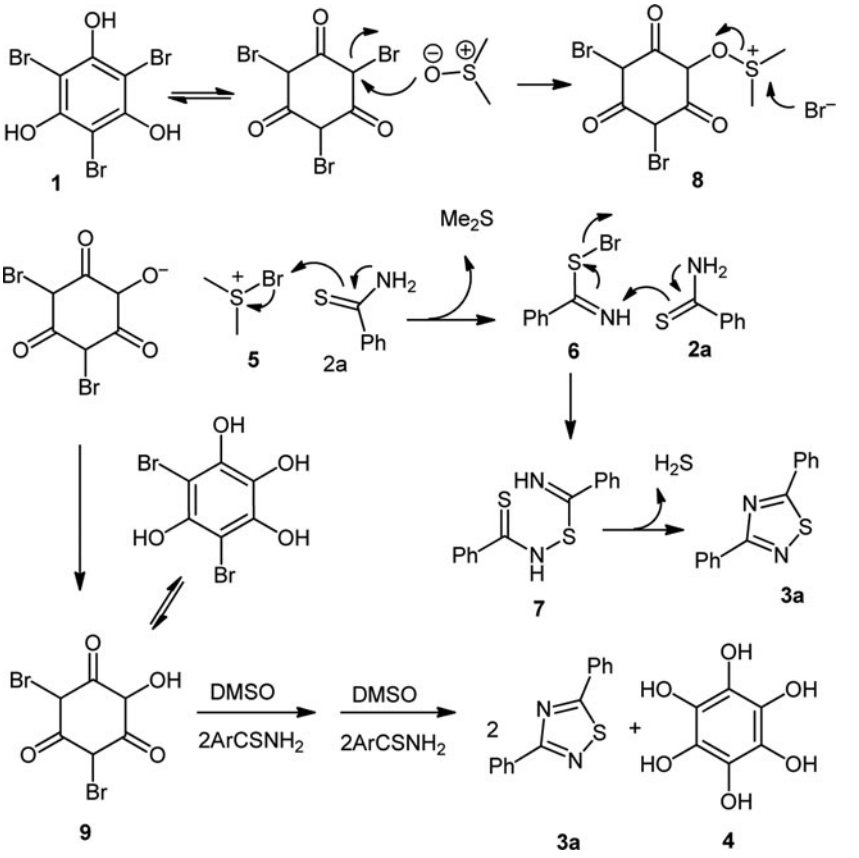
It seems that bromodimethylsulfonium ion **5** formed via the reaction of dimethyl sulfoxide and TBTHB **1** is the active intermediate in the reaction. Meanwhile, benzothioamide **2a** undergoes an *S*-bromination with this reactive intermediate to produce species **6,** which after subsequent reaction with another benzothioamide molecule transforms to *N*-(imino(phenyl)methylthio) benzothioamide **7**. Eventually, this intermediate cyclizes to the corresponding 3,5-diphenyl-1,2,4-thiadiazole **3a** alongside with the elimination of H_2S.

Table 1. Temperature screening in the synthesis of thiadiazoles



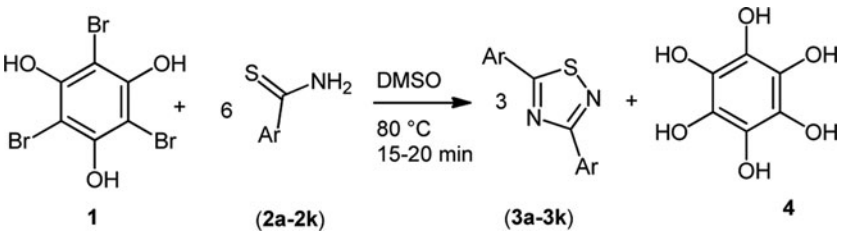
Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	rt	120	40
2	40	60	58
3	60	40	81
4	80	15	98
5	100	10	98[b]
6	120	6	96[b]

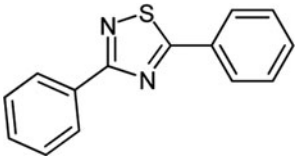
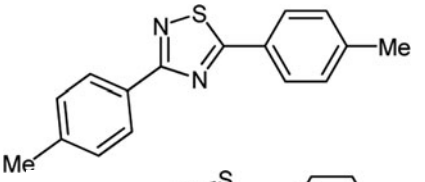
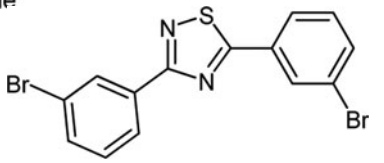
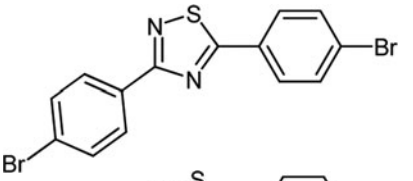
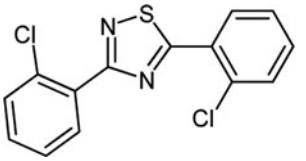
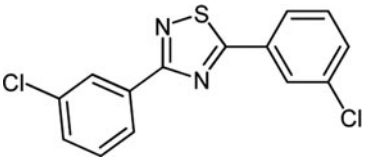
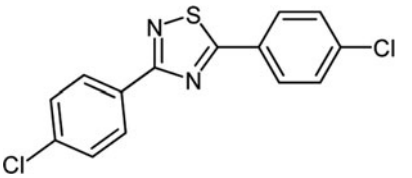
[a]Pure isolated yields.
[b]Formation of some dark-colored impurities were observed.



Scheme 2.

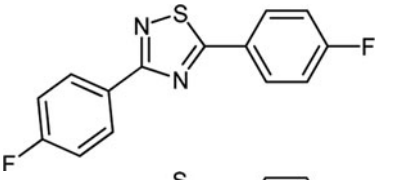
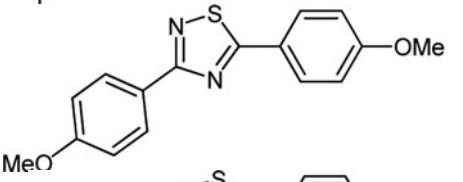
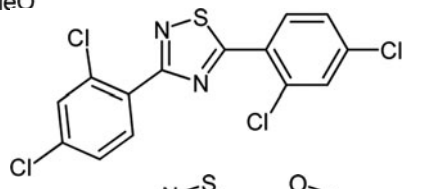
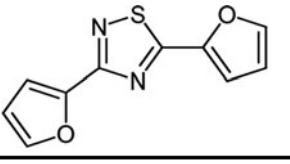
Table 2. TBTHB as a novel reagent for the preparation of 1,2,4-thiadiazoles[a]



Entry	Ar	Time	Product	Yield (%)[b]
1	C_6H_5	15		98
2	4-MeC_6H_4	15		98
3	3-BrC_6H_4	18		92
4	4-BrC_6H_4	15		94
5	2-ClC_6H_4	18		93
6	3-ClC_6H_4	17		94
7	4-ClC_6H_4	15		96

(*Continued*)

Table 2. Continued

Entry	Ar	Time	Product	Yield (%)[b]
8	4-FC_6H_4	17		91
9	4-$MeOC_6H_4$	15		97
10	2,4-$Cl_2C_6H_4$	20		91
11	2-furyl	15		94

[a]Reaction conditions: Benzothioamide derivative (3 mmol), TBTHB (0.5 mmol), and DMSO (1 mL).
[b]Isolated yields.

As is clear from the proposed mechanism, DMSO has a dual function in the course of the reaction because it plays both the role of the reagent as well as the solvent. Formation of hexahydroxybenzene by-product **4** was proven by comparison of its thin-layer chromatographic (TLC), physical, and spectral data with the authentic sample prepared by the known method.[16] Ten different benzothioamide derivatives were probed in the course of reaction to evaluate the generality of this new reagent and the results are summarized in Table 2. Unfortunately, only aromatic and heteroaromatic thioamides (except pyridyl thioamides) work well in this method and our attempts to obtain 3,5-dialkyl-1,2,4-thiadiazoles by the presented method were not successful.

Significant values of the presented reagent and the method lie in very high reaction yield, short reaction times, and simplicity involved in the isolation of the products. After completion of the reaction and cooling, the thiadiazole product was precipitated as fine crystals. Also, hexahydroxybenzene as a rather valuable by-product was produced during the reaction and found to be freely soluble in the reaction media as well as in water. Therefore, the reaction mixture was poured in a mixture of MeOH–water (50:50) to achieve complete isolation of the pure thiadiazole product.

The hexahydroxybenzene is a very simple to remove and rather valuable by-product. The presented method could also find application in other reaction classes such as the Pfitzner–Moffatt oxidation.[17]

CONCLUSIONS

In summary, a novel reagent for the rapid and extremely efficient conversion of benzothioamide derivatives to the corresponding thiadiazoles has been developed. To our knowledge, the method also seems to be one of the simplest and fastest routes for the preparation of 3,5-diaryl-1,2,4-thiadiazoles so far developed.

EXPERIMENTAL

General Procedure for the Preparation of 3,5-Diaryl-1,2,4-thiadiazoles

Benzothioamide derivatives (3 mmol) and 2,4,6-tribromo-1,3,5-trihydroxy benzene (TBTHB, 0.5 mmol, 182 mg) was dissolved in DMSO (1 mL) and heated at 80 °C for 15–20 min. After completion of the reaction (TLC) and cooling to ambient temperature, MeOH–water (1:1, 5 mL) was added to the reaction mixture and the resulting crystals of the product were filtered, washed with MeOH–water (1:1, 2 × 5 mL), and dried to obtain the pure compound as white crystals.

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SUPPLEMENTAL MATERIAL

Full experimental details and ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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