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PII: S0040-4039(17)31526-5
DOI: https://doi.org/10.1016/j.tetlet.2017.12.033
Reference: TETL 49535

To appear in: *Tetrahedron Letters*

Received Date: 21 November 2017
Revised Date: 7 December 2017
Accepted Date: 9 December 2017

Please cite this article as: Chauhan, S., Chaudhary, P., Singh, A.K., Verma, P., Srivastava, V., Kandasamy, J., *tert*-Butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.12.033

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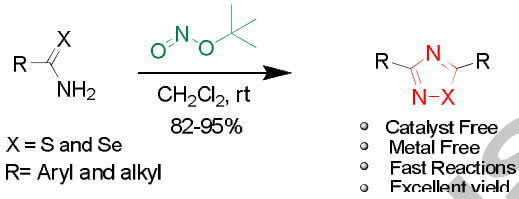

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Tetrahedron Letters
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
tert-Butyl nitrite
Thiobenzamides
Thiadiazoles
Dimerization
Green Chemistry

ABSTRACT

A simple and efficient method for the dimerization of primary thioamides into 1,2,4-thiadiazoles using *tert*-butyl nitrite is described. The optimized condition was also found to be suitable for the dimerization of benzoselenoamides into 1,2,4-selenadiazoles. All the reactions proceed smoothly at room temperature and gave the desired products in excellent yields in a short span of time.

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1,2,4-Thiadiazole is an important heterocyclic scaffold found in many drugs, bioactive molecules and natural products.[1] For example, cefozopran is a clinically used antibiotic possessing the 1,2,4-thiadiazole moiety (Figure 1). In addition, thiadiazole scaffold containing molecules act as G-protein coupled receptors, acetylcholinesterase inhibitors, angiotensin II receptor antagonists, pesticides and fungicides (e.g. Etridiazole, Figure 1) and thiol trapping agents.[2] Therefore, over the decades the interest has been maintained in the synthesis of organic compounds having thiadiazole moiety for different applications.[1-3]

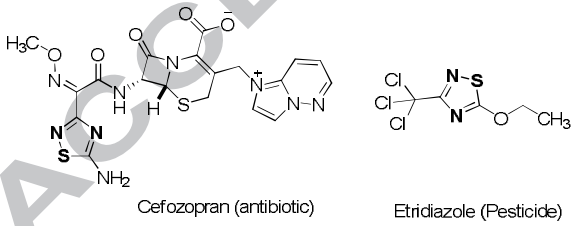
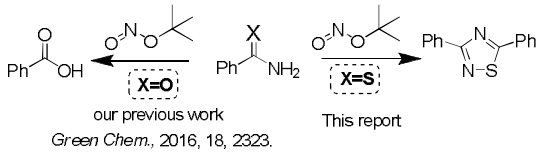


Figure 1. Examples of bioactive substituted thiadiazoles.

The simplest approach to the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerization of primary thioamides. This transformation has been achieved using various metal and metal free oxidizing reagents such as ceric ammonium nitrate (CAN),[4] 2-iodoxybenzoic acid (IBX),[5] bis-acetoxy iodobenzene (BAIB),[6] N-bromosuccinimide (NBS),[7] oxone,[8] nitrous acid,[9] phosphovanadomolybdic acids,[10] etc. However, many of these methods suffer from the use of excess reagents which produces large amounts of by-products, harsh reaction conditions, longer reaction times, tedious workup procedures, etc. Therefore, finding a simple and efficient reagent for the dimerization of primary thioamides is of great interest.



Scheme 1. Reaction of *tert*-butyl nitrite with benzamide and thiobenzamide.

tert-Butyl nitrite (TBN) is an important synthetic reagent widely used for nitration reactions.[11] For example, TBN has been explored for the nitration of phenols, azoarenes, arylboronic acids, acetanilides, sulfanilides, etc. under mild reaction conditions.[12] In addition, TBN has also been explored as a radical initiator for the aerobic cleavage of benzylic carbon-carbon double bonds and triple bonds.[13] TBN is a green, inexpensive and commercially available reagent which can be easily handled and stored. Our research group is mainly focused on developing simple, efficient and eco-friendly methods for organic transformations.[14] In pursuit of this, we have

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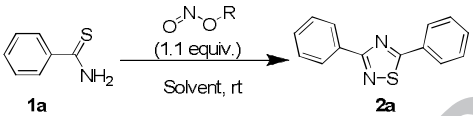
recently reported *N*-nitrosation of secondary amines using *tert*-butyl nitrite under solvent free conditions.[14d] In the same report, we have also disclosed that primary benzamides undergo hydrolysis to corresponding benzoic acids with *tert*-butyl nitrite in acetic acid (Scheme 1). In continuation of our previous work, here we would like to disclose an interesting outcome of the reaction between *tert*-butylnitrite and primary thioamides. In fact, while attempting hydrolysis of thiobenzamide with *tert*-butyl nitrite in acetic acid, a significant amount of dimerized product was observed (Scheme 1), instead of hydrolysis. This observation spurred us to optimize the reaction condition for obtaining the dimerized product exclusively (Table 1).

At the outset, the optimization of the dimerization reaction was investigated with thiobenzamide **1a** using 1.1 equiv. of TBN in various solvents at room temperature. In acetic acid, the dimerized product **2a** was obtained in 69% yield (Table 1, entry 1). Similarly, other polar protic solvents such as methanol, ethanol, *iso*-propanol, *tert*-butanol and water gave the desired product in 65-90% yield within the period of 30-60 mins (Table 1, entries 2-6). On the other hand, the dimerization was achieved efficiently in various aprotic solvents such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, benzene and toluene in short span of time at room temperature (Table 1, entries 7-12). Among them, dichloromethane gave the desired product, *i.e.* 3,5-diphenyl-1,2,4-thiadiazole (**2a**) in 95% yield within 5 mins (Table 1, entry 7). Further optimization was continued with other alkyl nitrites such as *iso*-amyl nitrite (IAN) and *n*-butyl nitrite (NBN) at room temperature. Both the reagents gave the desired product in a good yield, but they require slightly longer time (*i.e.* 15 mins) for completion of the reaction (Table 1, entries 13 and 14).

Table 1. Optimization of dimerization of thiobenzamide.[a]

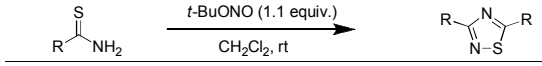


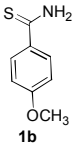
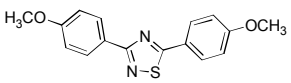
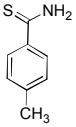
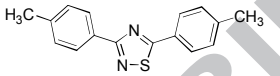
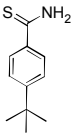
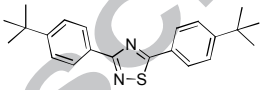
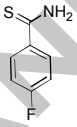
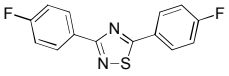
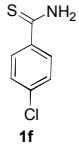
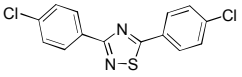
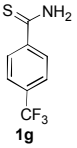
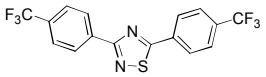
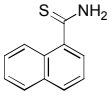
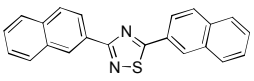
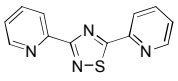
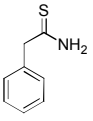
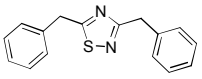
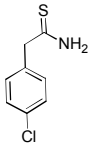
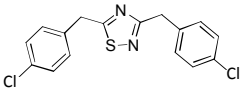
1a **2a**

S.No.	Solvent	Reagent	Time (min)	Yield (%)[b]
1	CH_3COOH	TBN	30	69
2	CH_3OH	TBN	30	90
3	C_2H_5OH	TBN	40	89
4	*iso*-Propanol	TBN	40	85
5	*tert*-butanol	TBN	60	79
6	H_2O	TBN	60	65
7	CH_2Cl_2	TBN	5	95
8	$CHCl_3$	TBN	10	90
9	CH_3CN	TBN	15	89
10	THF	TBN	15	88
11	Benzene	TBN	15	70
12	Toluene	TBN	15	70
13	CH_2Cl_2	IAN[c]	15	93
14	CH_2Cl_2	NBN[d]	15	92

[a]Reaction conditions: benzothioamide (1 mmol) and TBN were stirred in the respective solvents (2 mL) at room temperature. [b]Isolated yields. [c]IAN: *iso*-amyl nitrite. [d]NBN: *n*-butyl nitrite

Table 2. Dimerization of thioamides using *tert*-butyl nitrite.[a]



Entry	Substrate	Product	Time (min)	Yield (%)[b]
1	 **1b**	 **2b**	5	94
2	 **1c**	 **2c**	5	92
3	 **1d**	 **2d**	5	83
4	 **1e**	 **2e**	15	89
5	 **1f**	 **2f**	15	90
6	 **1g**	 **2g**	30	89
7	 **1h**	 **2h**	5	82
8	 **1i**	 **2i**	5	88
9	 **1j**	 **2j**	5	85
10	 **1k**	 **2k**	5	82

[a]Reaction conditions: Substrate (1 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b]Isolated yields.

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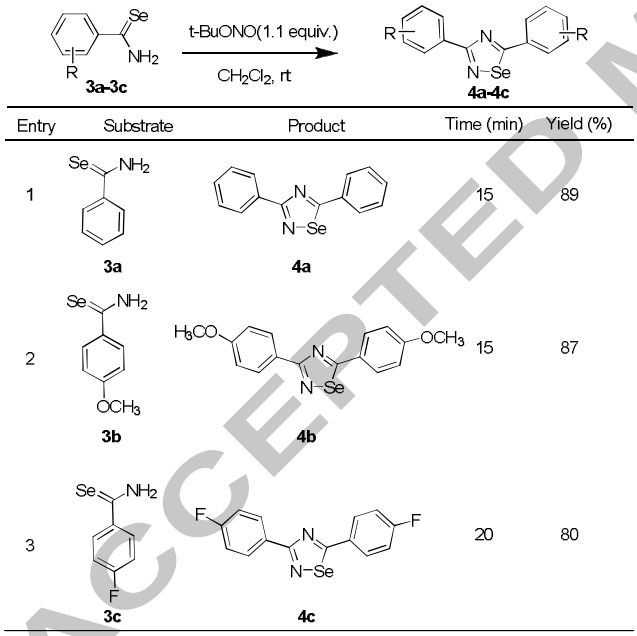
Having established the optimized condition, we examined the oxidative dimerization of various substituted thiobenzamides using *tert*-butyl nitrite in dichloromethane to explore the scope of substrates amenable to this method (Table 2). Electron donating groups such as methoxy, methyl and *tert*-butyl substituted thiobenzamides were successfully dimerized to **2b**-**2d**, respectively, in excellent yields within 5 mins (Table 2, entries 1-3). Similarly, dimerization of halogen substituted thiobenzamides such as 4-fluoro and chloro-thiobenzamides (**1e** and **1f**, respectively) was successfully accomplished to obtain the desired products **2e** and **2f** in >89% yield (Table 2, entries 4 and 5). Further, the analogue possessing the strongly electron withdrawing trifluoromethyl group was subjected to the dimerization under optimized condition. To our delight, the substrate **1g** underwent dimerization smoothly and gave the desired product **2g** in 89% yield; however it requires 30 mins (Table 2, entry 6). Likewise, 2-naphthyl thiobenzamide was successfully dimerized to 3,5-dinaphthyl 1,2,4-thiadiazoles **2h** in 82% yield (Table 2, entry 7). To our surprise, the optimized condition was also found to be suitable for the oxidative dimerization of heterocyclic thiobenzamide such as pyridine-2-carbothioamide (**1i**). The reaction proceeded smoothly to provide the 3,5-di(pyridin-2-yl)-1,2,4-thiadiazole (**2i**) in 88% yield within 5 minutes (Table 2, entry 8).

After the extensive study with thiobenzamides, oxidative dimerization of phenylthioacetamides (**1j** and **1k**) was investigated (Table 2, entries 9 and 10). The corresponding dimerized products, **2j** and **2k** were obtained in excellent yields, which demonstrate the broad scope of the current methodology.

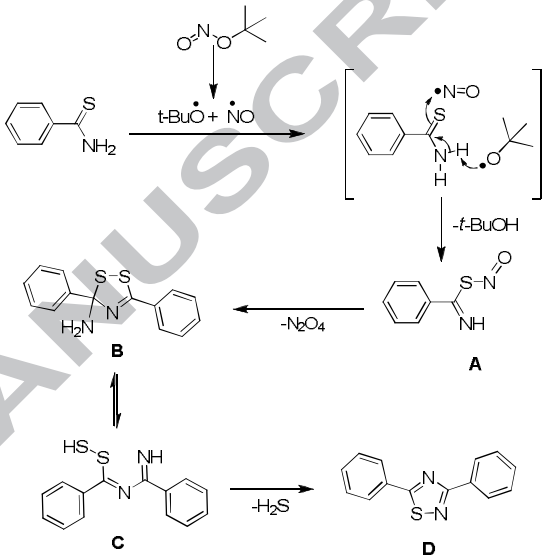
Table 3. Dimerization of benzoselenoamide using *tert*-butyl nitrite.[a,b]



[a]Reaction conditions: Substrate (1 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b]Isolated yields.

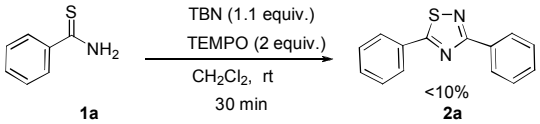
Similarly to thiadiazole, 1,2,4-selenadiazoles are also an important class of heterocyclic scaffold receiving considerable attention in different fields.[8,15] Encouraged by the results obtained from dimerization of thioamides, we have attempted the oxidative dimerization of benzoselenoamide to 1,2,4-selenadiazole using *tert*-butylnitrite (Table 3). For this study, differently substituted benzoselenoamides (**3a**-**3c**) were prepared and subjected to dimerization under the optimized condition. To our delight, corresponding 3,5-disubstituted 1,2,4-selenadiazoles **4a**-**4c** (Table 3, entries 1-3) were obtained in good yields within the period of 15-20 mins, which serves to extend the scope of the present methodology. Overall, this practical metal-free approach shows good functional group tolerance while the desired products were obtained in excellent yields.

A proposed mechanism for the TBN induced dimerization reaction is shown in Scheme 2. TBN undergoes radical dissociation to form *t*-butoxy and nitroso radicals which may react with thiobenzamide to form intermediate **A**.[13a] Further, this intermediate may undergo dimerization *via* elimination of dinitrogen tetroxide (N_2O_4) to form intermediate **B** which may be in equilibrium with intermediate **C**.[2b] Further, the intermediate **C** might release hydrogen sulfide (H_2S) to yield the desired product **D**.



Scheme 2. Proposed mechanism for the TBN induced dimerization reaction.

To support our mechanistic hypotheses, the dimerization reaction was carried out with a radical trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The experiment was performed with 2 equiv. of TEMPO under optimized conditions in dichloromethane at room temperature (Scheme 3). As expected, the dimerization process was inhibited by TEMPO with less than 10% of the desired product (i.e. 3,5-diphenyl-1,2,4-thiadiazole) observed.



Scheme 3. Control experiment with TEMPO.

In conclusion, an efficient and practical method for the oxidative dimerization of thioamides into 1,2,4-thiadiazoles was demonstrated using *tert*-butyl nitrite in dichloromethane. In addition, the current protocol was also found suitable for the efficient synthesis of 1,2,4-selenadiazoles from corresponding selenoamides. Broad substrate scope, excellent functional group tolerance, room temperature reactions, metal free conditions, quick conversion and excellent yields are important features of this methodology.

Acknowledgements

J. K. acknowledges IIT (BHU) for the institute research grant, 2016-17. J. K. also gratefully acknowledges, Max-Planck Society-Germany and DST-India (DST/INT/MPG/P-09/2016) for financial support through Indo-Max Planck partner group project. S. C and P.

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C. acknowledge IIT (BHU) for a research fellowship. A. K. S acknowledges the CSIR for senior research fellowship. J. K. and V.S thanks Central Instrumentation Facility Center (CIFC)-IIT BHU for the NMR facilities. J. K thanks to Mr. Albert Pape for a helpful discussion during the manuscript preparation.

Supplementary data

Supplementary data associated with this article can be found, in the online version.

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Highlights

1. Dimerization of thioamides and seleoamides was achieved with *tert*-butyl nitrite.
2. Reaction proceeds under catalyst and metal free conditions at room temperature
3. Reaction proceeds through radical mechanism
4. Easy operation, broad substrate scope and efficient conversion are the advantages

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