Oxidative Cyclization of Amidoximes and Thiohydroximic Acids: A Facile and Efficient Strategy for Accessing 3,5-Disubstituted 1,2,4-Oxadiazoles and 1,4,2-Oxathiazoles

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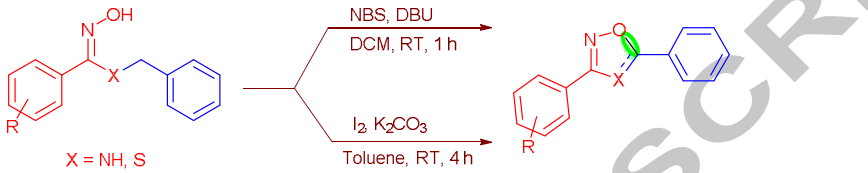

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ABSTRACT

A facile and practical protocol has been developed for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles and 1,4,2-oxathiazoles through oxidative cyclization of amidoximes and thiohydroximic acids, respectively at room temperature. Use of mild reaction conditions, inexpensive reagents, broad substrate scope and good to excellent yield of the products are the salient features of this protocol.

Introduction

1,2,4-Oxadiazole is an important heterocyclic scaffold, as it is prevalent in various bioactive molecules, pharmaceuticals and functional materials.[1-4] Particularly, 3,5-disubstituted 1,2,4-oxadiazoles have been utilized as anti-asthmatics,[5] anti-inflammatory agents,[6] anti-diabetics,[7] anti-microbial agents[8] and anti-cancer agents.[9]

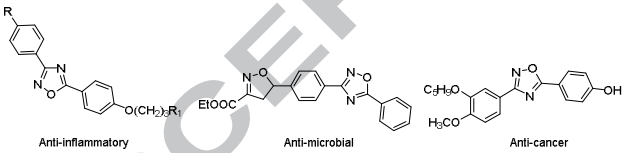

Figure 1. Examples of biologically active 1,2,4-oxadiazole scaffolds

Besides this, they have also been employed as ligands for the transition metal complexes and as G-quadruplex ligands for probing DNA superstructure in antitumor research.[10,11] Moreover, these five-membered heterocycles have also been applied as stable ester or amide bioisosteres in peptide mimetics.[12] On the other hand, 1,4,2-oxathiazoles are the five-membered heterocycles comprised of three different heteroatoms that are barely reported in the literature.[13] In addition, they are also known to serve as useful isothiocyanate (ITC) precursors upon their thermal decomposition.[14] In view of these aforementioned applications of 1,2,4-oxadiazoles, several methods have been developed for their synthesis.

Conventional methods for the synthesis of 1,2,4-oxadiazoles generally involve the use of amidoximes obtained by addition of hydroxylamine to nitriles as starting materials or as intermediates.[15] 1,2,4-oxadiazoles are prepared *via* a two-step protocol involving *O*-acylation of amidoximes by using carboxylic acids or their activated derivatives such as esters, anhydrides and acid chlorides followed by intramolecular cyclodehydration.[16] Besides this, microwave assisted methods and use of strong acids such as PTSA and $ZnCl_2$ have also been reported for the synthesis of these heterocycles.[17] The other common approach used for the synthesis of 1,2,4-oxadiazole includes intermolecular cyclodehydration of amidoximes with aldehyde to form 4,5-dihydro-1,2,4-oxadiazoles, followed by oxidative dehydrogenation.[18] Another widely used method for the synthesis of 1,2,4-oxadiazoles involves the 1,3-dipolar cycloaddition of nitrile oxides to nitriles or azetine derivatives.[19] *N*-acylamidines obtained by the condensation of amidines with carboxylic acids were used as the intermediates which on tandem reaction with hydroxylamine formed 1,2,4-oxadiazoles.[20] Moreover, Vidavalur *et al.* reported Brønsted acid-catalyzed synthesis of 1,2,4-oxadiazoles from 2,2,2-trichloroethyl imidates by using polyethylene glycol (PEG) as a solvent,[21] whereas Mirza described a one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and benzyl halides in the presence of a base.[22] Recently, Jiang *et al.* disclosed the synthesis of 1,2,4-oxadiazoles *via* copper-catalyzed cascade annulation of amidines with methylarenes by using *tert*-butyl hydroperoxide (TBHP) as an oxidant,[23] while Hong and co-workers demonstrated copper-catalyzed direct synthesis of 1,2,4-oxadiazoles from amides and nitriles through oxidative N-O bond formation by employing O_2 as the sole oxidant.[24]

The other scarcely used strategy for the synthesis of 1,2,4-oxadiazoles involves oxidative cyclization of *N*-benzyl amidoximes. In this context, Chiba *et al.*[25] reported an oxidative free radical transformation of *N*-benzyl amidoximes into 3,5-disubstituted 1,2,4-oxadiazoles in the presence of K_3PO_4 at 60 °C

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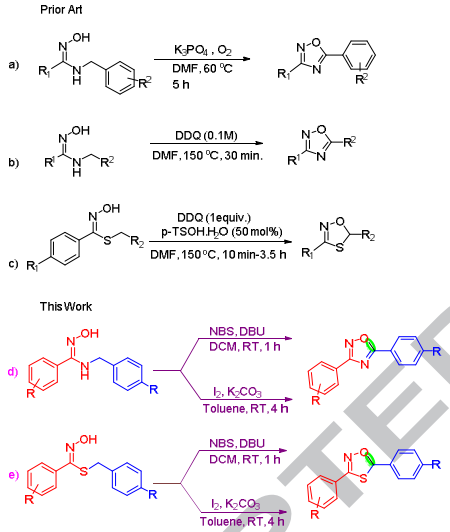
whereas, Pierce *et al.* employed 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant for oxidative cyclization of *N*-benzylamidoximes[26] and thiohydroximic acids[27] to form 1,2,4-oxadiazoles and 1,4,2-oxathiazoles, respectively at high reaction temperatures.

However, these methods suffer from drawbacks such as use of transition metal catalyst, harsh reaction conditions (microwave conditions and higher reaction temperatures), longer reaction times and low yield of the products. Therefore, development of a facile and practical method for the synthesis of 1,2,4-oxadiazoles and 1,4,2-oxathiazoles is highly desirable.

In continuation with our interest in the development of mild, operationally simple and environment-friendly protocols for the synthesis of heterocyclic compounds,[28] we envisaged to access pharmaceutically important 1,2,4-oxadiazole and 1,4,2-oxathiazole derivatives. In this context, herein we report the synthesis of 1,2,4-oxadiazoles and 1,4,2-oxathiazoles by using such oxidizers as *N*-bromosuccinimide (NBS)-1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and I_2-K_2CO_3 at room temperature (Scheme 1). To the best of our knowledge, this is the first report for oxidative cyclization of *N*-benzyl amidoximes and thiohydroximic acids at room temperature.

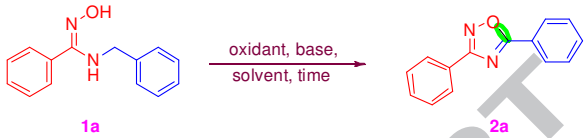


Scheme 1 Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles and 1,4,2-oxathiazoles

Results and Discussion

N-Benzyl amidoximes[15] **1a-1j** and thiohydroximic acids[27] **3a-3j** were prepared by using previously reported method in the literature staring from readily available aldehydes. An oxidative cyclization of *N*-benzyl-*N*'-hydroxybenzimidamide was used as a model for optimizing reaction conditions. The reaction carried out by using 1.0 equiv. *N*-bromosuccinimide (NBS) as an oxidant and 1.0 equiv. of K_2CO_3 as a base in DCM as a solvent at room temperature for 1 h afforded 3,5-diphenyl 1,2,4-oxadiazole (**2a**) in 50% yield (Table 1, entry 1). We next screened different bases to study their effect on the oxidative cyclization with an intention to increase the yield of the product. The reaction with 1.0 equiv. NBS and 1.0 equiv. NEt_3 gave 52% yield of the product **2a** in 1 h (Table 1, entry 2), while a higher yield (60%) was obtained by using 1.0 equiv. of pyridine as a base (Table 1, entry 3). To our delight, the use of 1.0 equiv. of NBS as an oxidant and 1.0 equiv. of DBU as a base was found to be the best reaction condition for this conversion resulting in 80% yield of the product in 1 h at room temperature (Table 1, entry 4). The reaction with 1.0 equiv. *N*-chlorosuccinimide (NCS) as an oxidant was also carried out to check the enhancement in the yield but it resulted in moderate yield (65%) of the product **2a** (Table 1, entry 5).

Table 1 Optimization of reaction conditions[a]



1a **2a**

Entry	Oxidant	Base	Time (h)	Solvent	Yield (%)[d]
1	NBS	K_2CO_3	1	DCM	50
2	NBS	NEt_3	1	DCM	52
3	NBS	Pyridine	1	DCM	60
4	NBS	DBU	1	DCM	80
5	NCS	DBU	1	DCM	65
6	NBS	DBU	1	DMF	35
7	NBS	DBU	1	CH_3CN	28
8	I_2	Na_2CO_3	4	Toluene	33
9	I_2	K_2CO_3	4	Toluene	72
10	I_2	Cs_2CO_3	4	Toluene	58
11	I_2	DBU	4	Toluene	53
12	I_2	Pyrrolidine	4	Toluene	42
13	I_2	Piperidine	4	Toluene	47
14	I_2	Pyridine	4	Toluene	35
15	I_2	NEt_3	4	Toluene	20
16[b]	-	K_2CO_3	4	Toluene	-
17[c]	I_2	-	4	Toluene	-
18	I_2	K_2CO_3	4	1,4-dioxane	Trace
19	I_2	K_2CO_3	4	CH_3CN	Trace
20	I_2	K_2CO_3	4	DMF	Trace

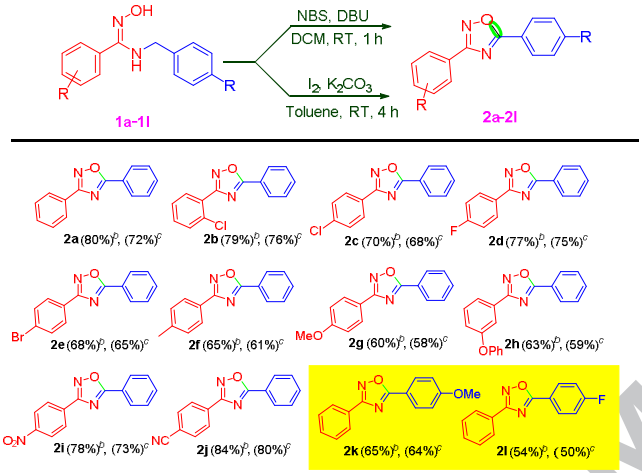
[a]Reaction conditions: **1a** (1.0 mmol), oxidant (1.0 mmol), base (1.0 mmol) and solvent (5 mL) for 1-4 h at room temperature. [b]Reaction in the absence of an oxidant. [c]Reaction in the absence of a base. [d]Isolated yields.

The reaction was also conducted in different solvents such as DMF and CH_3CN which afforded the product **2a** in low yields (Table 1, entries 6 and 7). Similarly, we also employed I_2 as an oxidant for this oxidative cyclization. Use of 1.0 equiv. of I_2 as an oxidant and 1.0 equiv. of Na_2CO_3 as a base in toluene at room temperature after 4 h furnished product **2a** in low yield (26%) (Table 1, entry 8), while the reaction by using K_2CO_3 (1.0 equiv.) as a base led to 72% yield of the product (Table1, entry 9). The reaction carried out by using Cs_2CO_3 and DBU as the bases offered product **2a** in 58% and 53% yield, respectively (Table 1, entries 10 and 11) whereas use of pyrrolidine, piperidine, pyridine and NEt_3 as the bases for this reaction offered product **2a** in low yields (20-47%) (Table 1, entries 12-15).The reaction in the absence of an oxidant failed to give product (Table 1, entry 16), thereby indicating significant role played by oxidant in this reaction. The reaction could not occur in the absence of a base too (Table 1, entry 17), thereby clearly highlighting the key role played by base in this reaction. Further, various solvents such as 1,4-dioxane, CH_3CN and DMF were tested to check if any of these could improve the yield of the product. The reactions in 1,4-dioxane, acetonitrile and DMF afforded product **2a** only in trace amounts (Table 1, entries 18-20). Similar results were obtained when oxidative cyclization of thiohydroximic acids to 3,5-diphenyl 1,4,2-oxathiazole was carried out under the same reaction conditions.

The scope and limitations of this oxidative cyclization was investigated by conducting the reaction of different *N*-benzyl amidoximes (**1**) under these optimized conditions (Table 2). The yields of products obtained by using NBS-DBU and I_2-K_2CO_3 were found to be comparable. The protocol is robust and can tolerate a variety of substituents. Amidoximes bearing halogen

substituents (-F, -Cl and -Br) at the *ortho* and *para* position of phenyl ring afforded products **2b**-**2e** in 65-79% yields. Oxidative cyclization of amidoximes bearing electron donating substituents such as -CH_3, -OMe and -OPh at the *ortho* and *para* position of phenyl ring occurred smoothly to offer products **2f**-**2h** in moderate yields (58-65%). Amidoximes bearing electron withdrawing substituents such as -NO_2 and -CN easily underwent oxidative cyclization to give product **2i** and **2j** in good to excellent yields (73-84%). Higher yields could be attributed to more stable imine double bond. We also carried out oxidative cyclization of amidoximes with substituents such as 4-OMe and 4-F on aromatic ring of the benzylic portion, which afforded product **2k** and **2l** in moderate yields (50-65%).

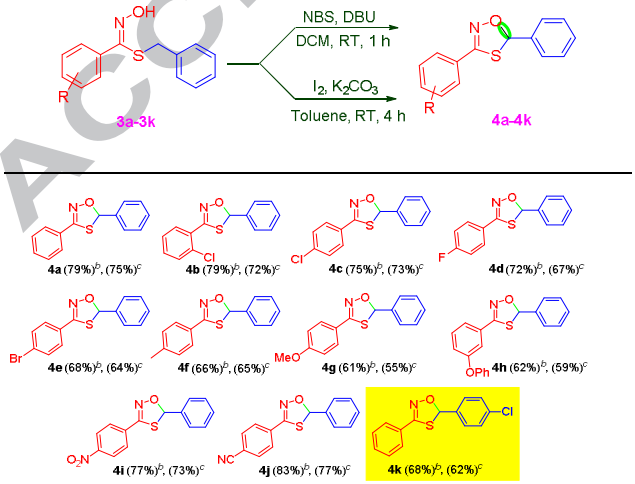
Table 2 Substrate scope study for oxidative cyclization of *N*-benzyl amidoximes[a]



[a]Reaction conditions: *N*-benzyl amidoxime **1** (1.0 mmol), oxidant (1.0 mmol), base (1.0 mmol) and solvent (5 mL) at room temperature. [b]Isolated yields by using NBS-DBU. [c]Isolated yields by using I_2-K_2CO_3.

Encouraged with these results, we turned our attention to oxidative cyclization of thiohydroximic acids under similar reaction conditions. We found that the above mentioned protocol can be successfully applied for oxidative cyclization of various thiohydroximic acids. Concomitant results were obtained in comparison with amidoximes.

Table 3 Substrate scope study for oxidative cyclization of thiohydroximic acids[a]



[a]Reaction conditions: Thiohydroximic acid **3** (1.0 mmol), oxidant (1.0 mmol), base (1.0 mmol) and solvent (5 mL) at room temperature. [b]Isolated yields by using NBS-DBU. [c]Isolated yields by using I_2-K_2CO_3.

The yields of products obtained by using both oxidants were found to be similar. Oxidative cyclization of thiohydroximic acid with no substituent on the phenyl ring formed product 3,5-diphenyl 1,4,2-oxathiazole **4a** in 75-79% yields. Thiohydroximic acids bearing halogen substituents (-F, -Cl and -Br) at the *ortho* and *para* position of phenyl ring resulted in formation of products **4b**-**4e** in 64-79% yields. Oxidative cyclization of thiohydroximic acids bearing electron donating substituents such as -CH_3, -OMe and -OPh at the *ortho* and *para* position of phenyl ring proceeded smoothly to afford products **4f**-**4h** in yields ranging from 55-66%. Thiohydroximic acids bearing electron withdrawing substituents such as -NO_2 and -CN at the *para* position of the phenyl ring furnished product **4i** and **4j** in good to excellent yields (73-83%). Higher yields could be attributed to more stable imine double bond. We also performed oxidative cyclization of thiohydroximic acid with 4-Cl substituent on aromatic ring of the benzylic portion, which afforded product **4k** in good yields (62-68%).

The possible mechanistic pathways for the formation of 3,5-diphenyl 1,4,2-oxadiazole in the presence of NBS-DBU and I_2-K_2CO_3 are depicted in Figure **2** and **3**, respectively. The reaction presumably occurs through *N*-halogenation of amidoxime (**1a**) to form halogenated derivative which in the presence of a base undergoes dehydrohalogenation to form intermediate **A**. Intermediate **A** *via* cyclization-aromatization sequence offers 3,5-diphenyl 1,2,4-oxadiazole (**2a**).

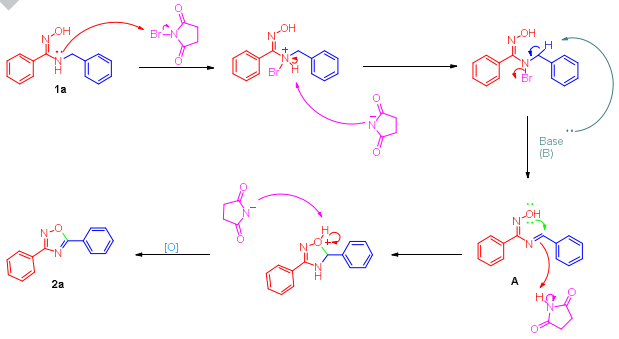


Figure 2 Proposed reaction mechanism for 3,5-diphenyl 1,2,4-oxadiazole in the presence of NBS-DBU.

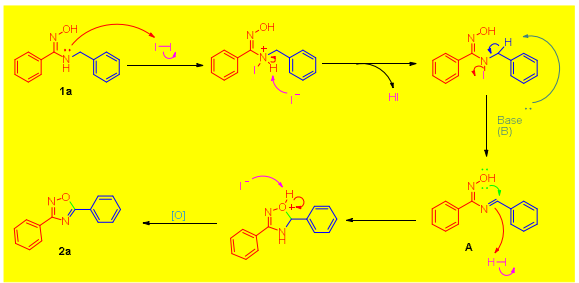


Figure 3 Proposed reaction mechanism for 3,5-diphenyl 1,2,4-oxadiazole in the presence of I_2-K_2CO_3

The possible mechanistic pathways for the formation of 3,5-diphenyl 1,4,2-oxathiazole in the presence of NBS-DBU and I_2-K_2CO_3 are depicted in Figure **4** and **5**, respectively. The reaction presumably occurs through halogenation of thiohydroximic acid

(**3a**) to form halogenated derivative which in the presence of a base undergoes dehydrohalogenation to form intermediate **B**. Intermediate **B** on cyclization offers 3,5-diphenyl 1,4,2-oxathiazole (**4a**).

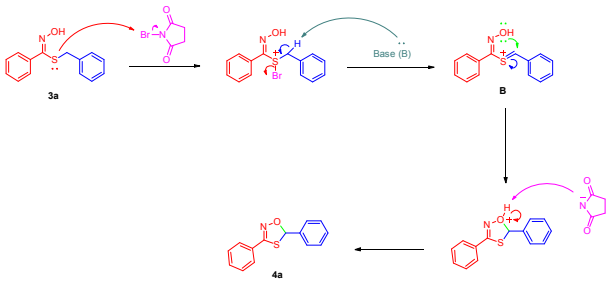


Figure 4 Proposed reaction mechanism for 3,5-diphenyl 1,4,2-oxathiazole in the presence of NBS-DBU.

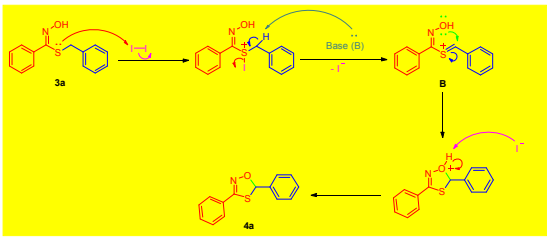


Figure 5 Proposed reaction mechanism for 3,5-diphenyl 1,4,2-oxathiazole in the presence of I_2-K_2CO_3.

In Conclusion, we have developed a mild, efficient and operationally simple method for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles and 1,4,2-oxathiazoles *via* oxidative cyclization of *N*-benzyl amidoximes and thiohydroximic acids, respectively at room temperature. We strongly believe that this protocol will be widely adopted and serve as practical and economical approach for straightforward synthesis of functionally diverse 1,2,4-oxadiazoles and 1,4,2-oxathiazoles having broad substrate scope and forming important motifs to drugs, natural products, pharmaceutical and agrochemical materials.

Acknowledgments

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Author Contributions

†These authors contributed equally to this work.

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29. General experimental procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazole and 3, 5-disubstituted-1,4,2-oxathiazole: To the solution of *N*-benzyl amidoxime **1**/ thiohydroximic acid **3** (1.0 mmol) in an appropriate solvent (5 mL) were added oxidant (1.0 mmol) and base (1.0 mmol) at room temperature. The resulting mixture was then stirred at room temperature for an appropriate time. After completion of reaction (monitored by TLC), 10 mL of saturated $Na_2S_2O_3$ solution and DCM (10 mL) were added to the reaction mixture. The organic layer after separation was washed with water (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on 60:120 mesh silica gel by using *n*-hexane:ethyl acetate (95:5) as the eluent to obtain the pure 3,5-disubstituted-1,2,4-oxadiazole (**2**)/ 3,5-disubstituted-1,4,2-oxathiazole (**4**).

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Highlights of the work

- Room temperature protocol to access 1,2,4-oxadiazoles and 1,4,2-oxathiazoles
- A metal-free protocol
- Use of inexpensive oxidants such as *N*-bromosuccinimide and iodine
- Operational Simplicity
- Good to excellent yields of the products