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Ultrasound-Assisted Synthesis of 2-Amino-1,3,4-Oxadiazoles *via* NBS-Mediated Oxidative Cyclization of Semicarbazones

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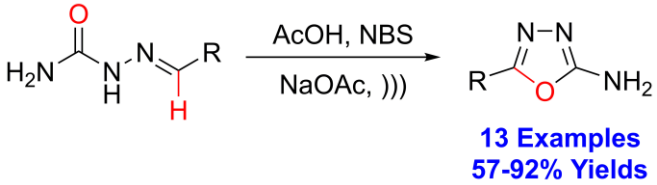
Abstract

A ultrasound-assisted oxidative cyclization of semicarbazones using NBS in the presence of sodium acetate was established providing efficient and rapid access to a variety of 2-amino-1,3,4-oxadiazoles. Moreover, the new synthetic protocol provides a simple procedure utilizing a safer oxidizing system that affords the target products in high regioselectivity, satisfactory yields, and elevated purities.

Graphical Abstract



KEYWORDS: 1,3,4-oxadiazole, sonochemical conditions, NBS, cyclization, semicarbazones

INTRODUCTION

Heterocycles are described as the largest of the divisions of organic chemistry.[1] Their utilization in areas such as medicinal chemistry, materials science, and organic synthesis has increased over the years.[1,2] In particular, 1,3,4-oxadiazole-containing molecules have attracted significant interest among the medicinal and synthetic organic chemistry communities.[3,4] These compounds have shown a wide range of pharmaceutical and biological activities including antitubercular,[5] antimicrobial,[6] antitrypanosomal,[7] anti-inflammatory,[8] antihypertensive,[9] sedative-hypnotic,[10] antidiabetic[11] and anticancer[12] properties. The widespread use of 1,3,4-oxadiazoles as scaffolds in drug discovery campaigns has been justified by their singular electronic properties, favorable metabolic profiles, and their use in bioisosteric replacement with amide, ester or carboxylic acid groups.[13,14] In addition, the 1,3,4-oxadiazole system comprises part of the structure of marketed drugs such as the antiretroviral drug raltegravir; a first in class HIV integrase inhibitor.[15] Considering synthetic organic chemistry applications, 1,3,4-oxadiazoles have been used as azadienes in tandem [4 + 2]/[3 + 2] cycloaddition reactions[16] and as substrates for heterocyclic rearrangements produced by ANRORC processes.[17] Specifically, the presence of an amino group at the 2-position of 1,3,4-oxadiazoles improves the synthetic possibilities of this system, facilitating the synthesis of more complex molecules.

As an alternative to classical methods, cavitation phenomenon generated using ultrasound has been used to enhance the rates of a large variety of chemical reactions and processes.[1,18,19] The singular conditions attained during ultrasound-assisted methods have leaded to products in more environmentally benign and sustainable protocols by avoiding the extensive use of hazardous reactants or solvents, harsh reaction conditions, and toxic catalysts.[1,18,19] Moreover, the use of ultrasound has been associated with increased selectivity, lower energy consumption for desired transformations, and significant reduction in the reaction times.

Several methods have been reported in the literature for the synthesis of 2-amino-1,3,4-oxadiazoles.[3,4] However, to the best of our knowledge, there is no method describing the synthesis of these compounds by cyclization of semicarbazones under ultrasound conditions. Existing sonochemical-based methods have described the treatment of trichloroacetamidoxime with acyl chlorides[20] and the reaction between benzoic acid derivatives and (*N*-isocyanimino)triphenylphosphorane in the presence[21] or absence[22] of acenaphthoquinone for the synthesis of the desired compounds. The few procedures devoted to the synthesis of 2-amino-1,3,4-oxadiazoles by direct cyclization of semicarbazones have used hazardous oxidizing agents with limited scalability and laborious workup protocols.[10,23–27] Recently, the synthesis of these compounds from semicarbazones was revisited using molecular iodine in the presence of potassium carbonate[28] and, in another method, using tetrabromomethane under photoredox conditions, with eosin Y acting as a catalyst[29] for the *O*-heterocyclizations.

As part of our ongoing research we were interested in the development of more efficient methods for organic synthesis using economical materials that are safe and easy to handle, aiming to use them in further drug discovery projects. Therefore, because a wide range of applications for the use of 1,3,4-oxadiazole-based compounds, in an attempt to improve synthesis, a new ultrasound-assisted oxidative method for the cyclization of semicarbazones is described. Herein, the synthetic protocol employed *N*-bromosuccinimide (NBS) as a bromine source in the presence of sodium acetate. The evaluation of other *N*-halo-succinimides as oxidizing agents and the proposed chemical mechanism are also described.

RESULTS AND DISCUSSION

The approach for obtaining the 2-amino-1,3,4-oxadiazoles was accomplished in two synthetic steps. First, semicarbazones **1** were synthesized from the condensation reaction of semicarbazide hydrochloride with benzaldehydes or naphthaldehydes in the presence of sodium acetate (NaOAc). The products were obtained in reflux of ethanol for 2 h, with yields of 72–98% (Supplementary information). The subsequent synthetic step involved intramolecular C-O bond formation from sonochemical-assisted oxidative cyclization of semicarbazones, obtaining the desired 2-amino-1,3,4-oxadiazoles. Initially, the oxidative system was investigated using the semicarbazone **1a**, which was previously prepared in a condensation reaction of benzaldehyde with semicarbazide hydrochloride.

First, the time and molar ratio required to obtain the 2-amino-1,3,4-oxadiazole **2a** were investigated (Scheme 1). Considering the reaction times, better results were obtained when the reaction mixtures containing acetic acid (AcOH) as solvent in the presence of NBS and NaOAc were sonicated for 15 min. In addition, the 1: 1.1: 1.1 molar ratios between semicarbazone **1a**, NBS, and NaOAc, respectively, provided higher yields when compared to the equimolar concentrations (Scheme 1, Entry 5 – 8). Increasing the molar ratio of the reagents, the product **2a** was isolated with more impurities which were difficult to separate in the subsequent purification step. It is noteworthy that the absence of sodium acetate or changing the solvent (acetic acid) significantly reduced the conversion to the compound **2a** (Scheme 1, Entry 9 and 10). The presence of base in the reaction medium has been reported as being preponderant in obtaining the sole 2-amino-1,3,4-oxadiazole products *via* semicarbazone-based ring closure.[30] In this system, the amino group can compete with an oxygen atom during the cyclization step, leading to the formation of triazolone derivative compounds.[30] According to spectroscopic and spectrometric experiments, exclusive *O*-heterocyclization was observed in our proposed methodology. With the aim of verifying the catalytic effect of the ultrasonic waves on the synthetic process under study, the synthesis of compound **2a** was performed under conventional thermal heating using the same experimental conditions used in the ultrasound-assisted protocol. After 15 min at 110 ° C the reaction provided a mixture of **1a**:**2a** in a ratio of 22:78 based on HPLC determination (Scheme 1, Entry 11).

Furthermore, semicarbazone **1a** was subjected to the above optimal oxidative cyclization conditions (AcOH, NBS, NaOAc,))), 25 – 110 °C, 15 min) using *N*-Chlorosuccinimide

(NCS) or *N*-Iodosuccinimide (NIS) as oxidant agents instead of NBS. Both reagents furnished a mixture of the start material (**1a**) and the cyclized product (**2a**). Based on HPLC determinations, NCS furnished a mixture of **1a**:**2a** in a close ratio of 48:52 whereas NIS afforded the semicarbazone **1a** and 1,3,4-oxadiazole **2a** in a proportion of 34:66 (Scheme 1, Entry 12 and 13). Moreover, other unidentified products were also isolated in these protocols. Despite these unsatisfactory results with NCS and NIS their use, after optimization, should not be discounted. NCS, for example, has been described in cyclization reactions of structurally diverse acyl hydrazones in the presence of DBU as base.[31]

To further explore the scalability and robustness of this new procedure, the synthesis of compound **2a** was performed on a scale up to five and ten times larger (5 and 10 mmol). The reactions were successfully accomplished leading to 1,3,4-oxadiazole **2a** with yield in both scales of 65% and elevated purity (95%).

Using the template procedure developed for **2a**, a range of semicarbazone (**1b**–**m**) synthesized from benzaldehydes bearing both electron-donating and electron-withdrawing groups afforded the 2-amino-1,3,4-oxadiazoles (**2b**−**m**) with 57–92% yields (Scheme 2). Moreover, other aromatic aldehydes, such as 1- and 2-naphthaldehyde as well as aliphatic aldehydes were able to form the target heterocyclic compounds in satisfactory yields without further adaptation in reaction times or conditions. All synthesized compounds showed physical, spectroscopic, and spectrometric data consistent with their proposed chemical structures (Supplementary information).

Finally, we examined the NBS-NaOAc oxidizing system under conventional conditions in order to compare with the previously developed ultrasound procedure. Using conventional stirring, better results were obtained when NBS was added to a solution containing semicarbazone **1a** in AcOH at 0 °C. The resulting mixture was stirred for 30 min while the temperature was allowed to warm up to 25 °C. Afterwards, sodium acetate was added to the reaction and the mixture was stirred for an additional 60 min leading to 2-amino-1,3,4-oxadiazoles **2a-h** and **2j-m** with 53–87% yields (Scheme 2). It is important to mention that semicarbazone **1i** did not lead to the cyclization product under conventional stirring conditions. This result indicated a possible competition between the deprotection and heterocyclization reactions in the tested conditions. Conventional stirring provided the compounds in similar yields to those obtained in the ultrasound-assisted method. However, whereas the 2-amino-1,3,4-oxadiazoles were synthesized under conventional conditions in 90 min, the sonochemical protocol furnished the products in 15 min.

Interestingly, when the semicarbazone obtained from 4-(dimethylamino)benzaldehyde was submitted to the above-described *O*-cyclization conditions the electrophilic aromatic substitution product was obtained in a mixture of 74:26 with the starting semicarbazone. NBS has been used also in regioselective electrophilic substitution of electron rich aromatic rings.[32] It is important to mention that under our tested conditions, ring bromination of the semicarbazones **1a**–**m** was not observed according to spectroscopy, or in high-resolution mass spectrometry assays.

The proposed mechanism for obtaining the 2-amino-1,3,4-oxadiazoles **2** starts with the formation of the intermediate hydrazonyl bromide **3** after treatment of semicarbazones **1** with NBS in the presence of AcOH.[30] Supporting the formation of this intermediate, a hydrazonyl chloride derivative has been isolated and characterized before cyclization to form the five-membered ring **2**.[33] Subsequent 1,3-dipolar elimination yields nitrilimines **4** which are prone to 1,5-electrocyclization to furnish the heterocyclic compounds **2** (Scheme 3).[34]

EXPERIMENTAL

General Procedure For The Preparation Of 2-Amino-1,3,4-Oxadiazoles Under Ultrasound Conditions

Semicarbazone **1** (1 mmol), NBS (0.196 g, 1.1 mmol), and sodium acetate (0.090 g, 1.1 mmol) were mixed in acetic acid (20 mL) in a 50-mL beaker. The reaction mixture was sonicated for 15 min using an ultrasonic probe. Afterward, the resulting solution was poured into cool water and the solid obtained was filtered and washed with water. Finally the product was dried under reduced pressure. Compounds **2e** and **2m** did not precipitate and were extracted from water with chloroform (3 x 15 mL). The products were isolated in satisfactory purity.

5-Phenyl-1,3,4-oxadiazol-2-amine (**2a**): Yield 62%; m.p.: 238-239 °C (m.p.: 242-243 °C)[27]; HPLC 97% (t_R = 14.50 min); ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 7.28 (br, 2H, NH_2), 7.53-7.55 (m, 3H, Ph), 7.82-7.84 (m, 2H, Ph); ^{13}C NMR (100 MHz, DMSO-

d6) δ ppm 124.4, 125.0, 129.1, 130.3, 157.3, 163.9; (^{13}C NMR (100 MHz, DMSO-*d6*) δ 124.8, 125.4, 129.6, 130.8, 157.7, 164.3)[27]; FTMS (ESI) m/z 162.0654 $[M + H]^+$; calcd for $C_8H_7N_3O$: 162.0662.

CONCLUSION

In summary, 2-amino-1,3,4-oxadiazoles have been successfully prepared *via* cyclization of semicarbazones using NBS and NaOAc under ultrasound conditions. The simplicity of execution coupled with the low cost of reagents and reactants, short reaction times (15 min), satisfactory yields (56-92%), and purity of the isolated products make this process attractive. Additionally, the methodology enabled the creation of the products under metal-free and mild conditions making the scale-up of the synthetic protocol easier. Finally, the use of a safer oxidant system compared to those already reported permitted the generation of compounds with important pharmaceutical applications through a method that has lower environmental and operational costs.

SUPPLEMENTARY MATERIAL

Supporting Information: Experimental synthetic details, spectroscopic and spectrometric data, ^{1}H and ^{13}C NMR spectra for new compounds, HPLC traces. This material can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.’’

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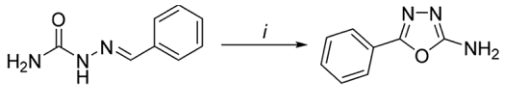
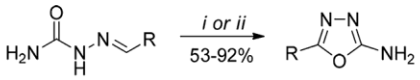
Scheme 1. Reagents and conditions: *i*) = Solvent, NXS, presence or absence of NaOAc, ultrasound or conventional, 25 – 110 °C, 5 – 20 min. [a]Isolated yields. [b]Reaction performed without NaOAc; mixture **1a**:**2a** ratio 38:62. [c]Mixture **1a**:**2a** ratio 36:64. [d]Reaction performed under conventional thermal heating (110 °C); mixture **1a**:**2a** ratio 22:78.[e]Mixture **1a**:**2a** ratio 48:52. [f]Mixture **1a**:**2a** ratio 34:66.



1a **2a**

Entry	Time (min)	Molar ratio (1a: NBS: NaOAc)	Solvent	Oxidant	Yield (%)[a] (1a:2a yield)[a]
1	5	1: 1: 1	AcOH	NBS	41
2	10	1: 1: 1	AcOH	NBS	37
3	15	1: 1: 1	AcOH	NBS	43
4	20	1: 1: 1	AcOH	NBS	44
5	5	1: 1.1: 1.1	AcOH	NBS	48
6	10	1: 1.1: 1.1	AcOH	NBS	44
7	15	1: 1.1: 1.1	AcOH	NBS	57
8	20	1: 1.1: 1.1	AcOH	NBS	53
9	15	1: 1.1: 0	AcOH	NBS	(19%:31%)[b]
10	15	1: 1.1: 1.1	EtOH	NBS	(27%:48%)[c]
11	15	1: 1.1: 1.1	AcOH	NBS	(13%:49%)[d]
12	15	1: 1.1: 1.1	AcOH	NCS	(30%:33%)[e]
13	15	1: 1.1: 1.1	AcOH	NIS	(22%:44%)[f]

Scheme 2. Reagents and conditions: *i*) = AcOH, NBS, NaOAc,))), 25 – 110 °C, 15 min. *ii*) = (1) AcOH, NBS, 0 – 25 °C, 30 min; (2) NaOAc, 25 °C, 60 min. [a]Isolated yields. [b]Ultrasound-assited method. [c]Conventional stirring method. [d]This compound was not obtained in the conventional stirring method.



1a-m **2a-m**

Compound 1,2	R	Yield (%)[a,b]	Yield (%)[a,c]
a	Ph	57	53
b	4-Me-C_6H_4	80	76
c	4-MeO-C_6H_4	75	73
d	4-F-C_6H_4	67	76
e	2-Cl-C_6H_4	56	70
f	4-Cl-C_6H_4	69	75
g	3,4-$(Cl)_2$-C_6H_3	88	86
h	4-Br-C_6H_4	74	75
i	4-(Benzyloxy)phenyl	92	[d]
j	1-Naphthyl	82	79
k	4-MeO-1-Naphthyl	75	72
l	2-Naphthyl	84	87
m	Bn	70	80

Scheme 3. Proposed mechanism for NBS-mediated synthesis of 2-amino-1,3,4-oxadiazoles from semicarbazones.