

## Synthesis of 2-Amino-1,3,4-Oxadiazoles Derivatives with Benzimidazole Skeleton

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### Abstract

The unsubstituted benzimidazole derivatives containing 2-amino-1,3,4-oxadiazoles were synthesized from the desulfurative cyclization reaction of mercury (II) acetate and substituted hydrazine-1-carbothioamides.

**Keywords:** 2-Amino-1,3,4-oxadiazole, benzimidazole, mercury (II) acetate, Pearson's soft acid.

### Introduction

Heterocyclic compounds have attracted considerable attention due to their important medicinal and biological applications, particularly those containing nitrogen in natural compounds have been of increasing interest [1-4]. Oxadiazole derivatives are important heterocyclic compounds containing nitrogen in a five-membered ring. They have applications in organic synthesis and pharmaceutical chemistry. These diazoles, particularly those with a 2-amino substituent, play a crucial role in drug design and serve as essential building blocks.

The synthesis methods and pharmacological properties of both benzimidazoles and 1,3,4-oxadiazoles are of great interest. The benzimidazole nucleus is widely recognized as a crucial bioactive heterocyclic unit for exploring new biologically active agents in medicinal chemistry [5-7]. The structure of benzimidazole derivatives is analogous to that of naturally occurring nucleotides, facilitating their interaction with proteins, enzymes, and receptors [8, 9]. Benzimidazoles bearing the 1,3,4-oxadiazole nucleus have shown significant enhancement in biological activities such as anticancer and antimicrobial activities [10-13].

Several methods for the synthesis of 1,3,4-oxadiazoles using different inorganic reagents have been reported in the literature [14]. The most commonly used synthesis routes for 1,3,4-oxadiazoles are: i) Cyclisation of diacyl hydrazines using anhydrous reagents such as P<sub>2</sub>O<sub>5</sub> [15], POCl<sub>3</sub> [16-18], H<sub>2</sub>SO<sub>4</sub> [19], and polyphosphoric acid [20]; ii) cyclization of acyl hydrazones, semicarbazones and thiosemicarbazides [21, 22]; iii) ring transformations [1,3].

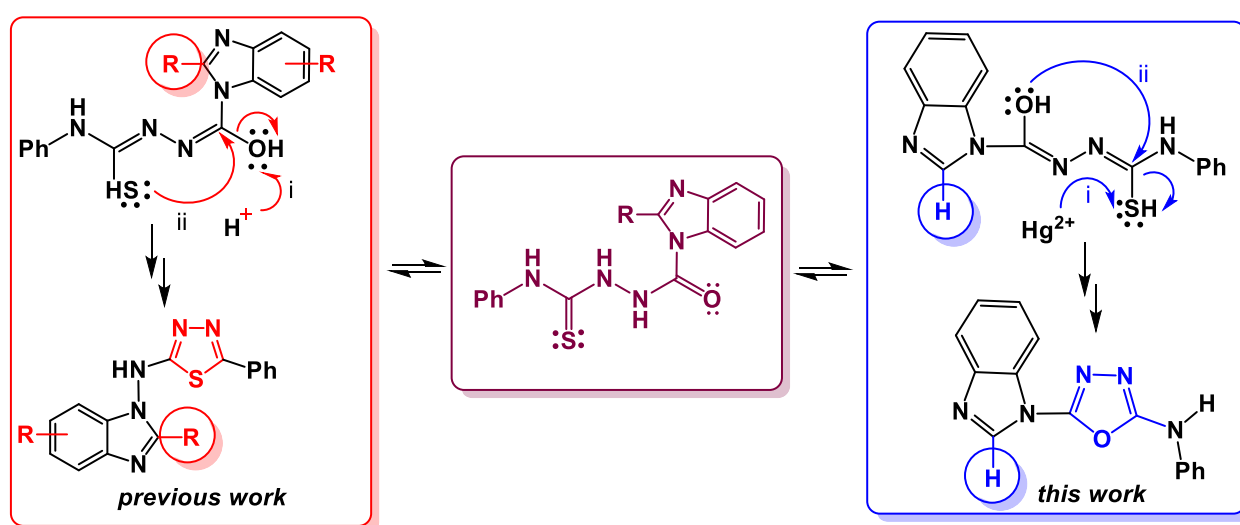
The above synthetic routes for the synthesis of 1,3,4-oxadiazoles often require harsh reaction conditions, but milder cyclization methods have been also mentioned in some publications [23]. According to the literature, bromine oxidation of a semicarbazide derivative and cyclo desulfurization of acyl thiosemicarbazide derivatives in solution with NaOH/I<sub>2</sub> or 1,3-dicyclohexylcarbodiimide and mercury (II) oxide [24-27] are common methods for the synthesis of 1,3,4-oxadiazoles. When thiosemicarbazides are

used as oxadiazole precursors, cyclization can be affected by H<sub>2</sub>S scavengers such as stoichiometric mercury salts or lead oxide [25, 28]. Furthermore, a report demonstrated the efficient and practical synthesis of 2-amino-1,3,4-oxadiazoles from *N*-acyl thiosemicarbazides using aerobic visible light photoredox catalysis [29].

The synthesis of some unsubstituted benzimidazole with 2-amino-1,3,4-oxadiazoles derivatives by a different method is reported in the literature [18]. These compounds were obtained by ring closure of both aliphatic and aromatic substituted carboxylic acids of 2-(2-substituted-1H-benzimidazol-1-yl)aceto hydrazides with POCl<sub>3</sub>. Both the method and the compounds obtained are different from our study. Furthermore, there are studies on the synthesis of the triazole [30] or aryl [31] substituted 1,3,4-oxadiazoles obtained from the reaction of thiosemicarbazides with mercuric acetate in glacial acetic acid in the literature.

## Results and Discussion

In this study, compounds **1-6** were synthesized by making appropriate modifications to the synthetic methods described in the literature [32]. Compound **1** was obtained by treatment of 1H-benzimidazole with ethyl bromoacetate in triethylamine. Compound **2** was synthesized by reacting hydrazine hydrate and ethyl-2- (1H-benzimidazol-1-yl) acetate for 3 hours in *n*-BuOH. The compounds **3-6** were synthesized from the reaction of compound **2** and the various isothiocyanates [32].



**Scheme 1.** 1,3,4-Oxadiazole and 1,3,4-thiazole ring formation mechanism based on Pearson hard/soft acid/base theory.

We have synthesized new hybrid compounds in which a 1,3,4-oxadiazole ring is attached to the *N*-1 position of the benzimidazole ring. According to Pearson's hard-soft acid-base theory, HCl and H<sub>2</sub>SO<sub>4</sub> are hard acids, but the Hg<sup>2+</sup> cation is a soft acid. There are both C=O and C=S functional groups in compounds **3-6**. The reaction of a strong acid with a strong base, such as the carbonyl oxygen of compounds **3-6**, leads to the protonation of the oxygen atom of the C=O group, followed by cyclization to form a 1,3,4-thiadiazole ring. On the other hand, the Hg<sup>2+</sup> cation interacts with the sulfur atom of the C=S bond, which has the soft base property. Thus, in the presence of a soft acid such as mercuric acetate, the 1,3,4-oxadiazole ring was formed from compounds **3-6** (**Scheme 1**).

The spectral and analytical data of all compounds obtained were found to agree with the suggested structures. The infrared spectra of compounds **7-10** display clear bands at about 3300-3105  $\text{cm}^{-1}$  and 1204-1200  $\text{cm}^{-1}$ . Moreover, a significant N-H absorption peak is visible within the range of 3461-3120  $\text{cm}^{-1}$  and a C=N absorption peak is evident around 1632-1568  $\text{cm}^{-1}$ . Additionally, the spectra show an absorption band at 1267 and 1055  $\text{cm}^{-1}$ , indicating C-O-C.

In the proton NMR spectra of compounds **7-10**, the proton signal of  $\text{NCH}_2$  was detected within the range of  $\delta$  5.69 to 5.83 ppm.

For compounds **3**, **4**, and **6**, the amide carbon signal was observed at 167 ppm (163 ppm for compound **5**) in the  $^{13}\text{C}$  NMR spectra. Additionally, the thioamide carbon signal was observed at 181 ppm (or 170 ppm for compound **5**) [32]. The  $^{13}\text{C}$ -NMR chemical shift of both C-2 and C-5 carbons in the unsubstituted 1,3,4-oxadiazole compounds was observed at 152.1 ppm [1]. The  $^{13}\text{C}$ -NMR spectra of compound **7-10** showed the signals corresponding to the C-2 and C-5 carbons of the oxadiazole ring appeared at  $\delta$  155.8 and about 160.8-167.1 ppm respectively. Substituted groups attached to C-2 of the oxadiazole ring induced a downfield shift of C-2 carbon by at least about 8–15 ppm in comparison with the unsubstituted 1,3,4-oxadiazole compound.

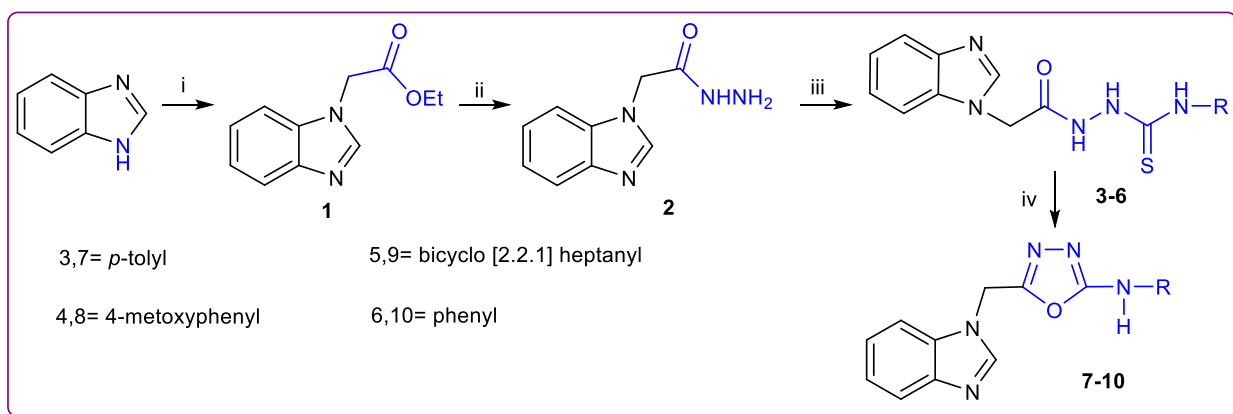
## Experimental

All reagents were of commercial quality and all solvents were used after purification. Melting points were determined using an Electrothermal IA 9100 instrument. Infrared (IR) spectra were determined using a Perkin-Elmer Spectrum One Fourier Transform Infrared (FT-IR) spectrometer. Chemical shifts are reported in parts per million relative to  $\text{DMSO-d}_6$  and tetramethylsilane as internal standard. Thin layer chromatography (TLC) was performed on aluminum plates precoated with silica gel 60 F254 (Merck).

Ethyl 2-(1H-benzimidazol-1-yl) acetate was synthesized from the reaction of benzimidazole and ethyl bromoacetate. 2-(1H-benzimidazol-1-yl) acetohydrazide was obtained from the reaction of this compound with hydrazine hydrate. The hydrazine-1-carbothioamide derivatives were synthesized from the reaction of 2-(1H-benzimidazol-1-yl) aceto hydrazide with various aryl isothiocyanates [32]. 2-Amino-1,3,4-oxadiazole derivatives were successfully synthesized from the reaction of  $\text{Hg}(\text{CH}_3\text{COO})_2$  and 2-{2-(1H-benzimidazol-1-yl)acetyl}-N-(substituted) hydrazine-1-carbothio amides. The synthetic routes for the preparation of the target compounds **1-7** have been outlined in **Scheme 2**. The preparation of these compounds is briefly described below.

### General method: Synthesis of the 2-Amino-1,3,4-Oxadiazoles Derivatives Bearing Benzimidazole (**7-10**):

A mixture of corresponding compounds **3-6** (2.4 mmol) and mercury (II) acetate (1.84 g, 2.4 mmol) was refluxed for 3 hours in 75 mL ethanol. The solvent was evaporated under a vacuum. The resulting residue was dissolved in chloroform and precipitated in water. The crude product was recrystallized from ethanol with active charcoal.



**Scheme 2.** General synthesis of the 2-unsubstituted benzimidazole derivatives having 2-amino-1,3,4-oxadiazoles. Reagents and conditions: (i)  $\text{BrCH}_2\text{COOEt}$ , TEA, THF, reflux, 12 hours; (ii)  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , *n*-BuOH, reflux, 3 hours; (iii) RNCS, EtOH; (iv)  $\text{Hg}(\text{CH}_3\text{COO})_2$ , EtOH, reflux, 3 hours.

**5-[(1*H*-Benzimidazol-1-yl) methyl]-*N*-(*p*-tolyl)-1,3,4-oxadiazol-2-amine (7):** Yields: 0.59 g (81%), white solid, m.p: 191-193 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3247, 3120 (NH), 3031 (aromatic C-H), 2851 (aliphatic C-H), 1632-1574 (C=N), 1515-1458 (C=C), 1267-1196 (C-O-C).  $^1\text{H}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm (*J*, Hz):  $\delta$ , ppm 2.51 (3H, s,  $\text{CH}_3$ ), 5.81 (2H, s,  $\text{NCH}_2$ ), 7.10-8.39 (9H, m, Ar-H), 10.38 (1H, broad, NH).  $^{13}\text{C}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 20.7, 39.3, 110.5, 111.1, 118.1, 119.3, 122.5, 123.4, 131.4, 133.0, 136.7, 145.3, 155.8, 161.0.

**5-[(1*H*-Benzimidazol-1-yl) methyl]-*N*-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (8):** Yields: 0.64 g (83%), white solid. m.p: 190-193 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3461-3197 (NH), 3083 (aromatic C-H), 2868 (aliphatic C-H), 1637 and 1568 (C=N), 1513 (C=C), 1200-1100 (C-O-C).  $^1\text{H}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm (*J*, Hz):  $\delta$ , ppm 3.34 (3H, s,  $\text{OCH}_3$ ); 5.80 (2H, s,  $\text{NCH}_2$ ), 7.10-8.38 (9H, m, Ar-H), 10.37 (1H, broad, NH).  $^{13}\text{C}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 44.3, 56.1, 110.9, 118.5, 119.9, 122.4, 123.6, 133.7, 134.2, 142.0, 144.6, 148.0, 155.8, 160.8.

**5-[(1*H*-Benzimidazol-1-yl)methyl]-*N*-(bicyclo[2.2.1]heptan-2-yl)-1,3,4-oxadiazol-2-amine (9):** Yields: 0.48 g (64%), white solid. m.p: 187-189 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3204 (NH), 3034 (aromatic C-H), 2869 (aliphatic C-H), 1635 (C=N), 1584 (C=C), 1197 (C-O-C).  $^1\text{H}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm (*J*, Hz):  $\delta$ , ppm 1.02-3.33 (11H, m, bicyclo [2.2.1] heptane aliphatic protons), 5.69 (2H, s,  $\text{NCH}_2$ ), 6.90-8.33 (5H, m, Ar-H), 10.49 (1H, s, NH).  $^{13}\text{C}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 26.2, 28.9, 35.3, 36.2, 38.6, 42.5, 56.4, 110.8, 119.2, 122.4, 123.7, 134.5, 144.5, 147.6, 155.4, 163.6.

**5-[(1*H*-Benzimidazol-1-yl)methyl]-*N*-phenyl-1,3,4-oxadiazol-2-amine (10):** Yields: 0.55 g (78%), white solid. m.p: 234-236 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3241-3080 (N-H), 3032 (aromatic C-H), 2851 (aliphatic C-H), 1630 and 1598 (C=N), 1572 (C=C), 1251-1055 (C-O-C).  $^1\text{H}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ , ppm (*J*, Hz):  $\delta$ , ppm 5.83 (2H, s,  $\text{NCH}_2$ ), 6.96-8.40 (10H, m, Ar-H), 10.50 (1H, s, NH).  $^{13}\text{C}$  NMR spectrum, (DMSO-*d*<sub>6</sub>),  $\delta$ : 46.1, 111.0, 117.1, 120.3, 122.4, 123.2, 129.1, 134.3, 139.8, 144.5, 145.5, 155.8, 167.1.

## Conclusions

While compounds **1-6** have been previously discussed in the literature [32], there are currently no 2-amino-1,3,4-oxadiazole compounds containing the unsubstituted benzimidazole. Continuing our research into the synthesis of biologically active heterocyclic compounds, 1,3,4-oxadiazole derivatives were successfully synthesized in high yields from the reaction of  $\text{Hg}(\text{CH}_3\text{COO})_2$  and 2-{2-(1H-benzimidazol-1-yl)acetyl}-N-(substituted) hydrazine-1-carbothioamides. This modified and transition metal protocol allows the efficient synthesis of a variety of aryl and alicyclic-substituted 2-amino-1,3,4-oxadiazoles.

## Author Contribution

Experimental studies and compound synthesis were conducted by Dilek Han, while the recording and interpretation of spectra were carried out by İrfan Çapan. Süleyman Servi planned the study, provided the research environment, and wrote the article.

## Conflict of Interests

The authors declare no conflict of interest.

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