Tetrahedron Letters 49 (2008) 6709–6711

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient one-pot synthesis of substituted 2-amino-1,3,4-oxadiazoles

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ARTICLE INFO

Article history:
Received 29 August 2008
Revised 9 September 2008
Accepted 10 September 2008
Available online 15 September 2008

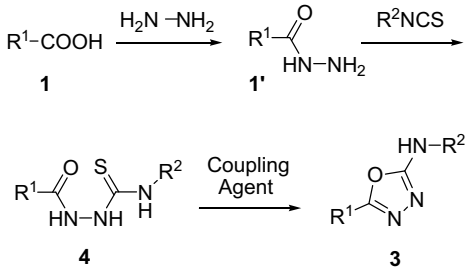
Keywords:
Oxadiazole
Kinase inhibitor
One-pot cyclization

ABSTRACT

A convenient one-pot method for the preparation of substituted 2-amino-1,3,4-oxadiazoles has been developed. The method is a significant improvement over previously reported syntheses. Reaction of carboxylic acids with thiosemicarbazides afforded the corresponding oxadiazoles in moderate to good yields. In general, the products precipitated from the reaction mixture, and were collected by filtration. In most of the cases, no chromatographic separations were required. To explore the scope and limitations of this reaction, various aliphatic, aromatic, and heteroaromatic carboxylic acids were reacted with different substituted thiosemicarbazides. The influence of R^1 and R^2 substituents on the reaction yield and additional results demonstrating the versatility of this method are presented.

2-Amino-1,3,4-oxadiazoles belong to a chemical class that displays diverse biological activity depending on the specific substitution within the molecule.[1] An aminooxadiazole analog is currently undergoing phase II clinical evaluation for the treatment of diabetes.[1e] The amino group and the adjacent azole nitrogen may be engaged in hydrogen bond donor-acceptor interactions similar to ones observed for ATP molecule as well as for various kinase inhibitors.[2] As a result of these potential interactions, 2-amino-1,3,4-oxadiazole motif became a kinase targeting scaffold.[2b,c] Our goal was to develop a convenient synthetic protocol for a quick assembly of 2-amino-1,3,4-oxadiazole core.

A variety of synthetic methods for the preparation of 2-amino-1,3,4-oxadiazoles have been reported. One of the most common procedures involves the cyclization of 2-acyl-hydrazinecarbothioamide **4** in the presence of a coupling agent to result in oxadiazole **3** (Scheme 1).[3] The preparation of the intermediate **4** requires a multi-step synthesis starting from the corresponding carboxylic acid or ester that contains the R^1 groups and an isothiocyanate or an isocyanate that incorporates the R^2 groups.[4] The cyclization of 2-acyl-hydrazinecarbothioamide **4** is complicated by 2-amino-1,3,4-thiodiazole formation. Thiodiazole can be inseparable from the desirable oxadiazole, and may become a major side product depending on the reaction conditions.[5] The cyclization step usually requires elevated temperatures and extensive purification of the product. In addition, mercury salts are often used as coupling agents to improve the yield of the key cyclization step. The use of toxic materials is highly undesirable particularly when the procedure has to be repeated in parallel fashion to generate a library of



Scheme 1. Literature method to prepare 2-amino-1,3,4-oxadiazoles.

targets. The overall sequence reported in literature (Scheme 1) often results in low yield of the desired 2-aminooxadiazoles.

In contrast, we report a highly efficient one-pot protocol to prepare the substituted 2-amino-1,3,4-oxadiazoles that often does not require any chromatographic purification. The procedure does not require an anhydrous solvent, inert gas atmosphere, or use of mercury salts, and it is amendable for high-throughput parallel synthesis. We established our methodology by synthesizing literature known 2-amino-1,3,4-oxadiazoles utilizing commercially available carboxylic acids and thiosemicarbazides. An initial attempt to discover a robust method to synthesize aminooxadiazoles was disclosed as a single example in our early work.[3a] Here, we describe a general protocol where R^1 and R^2 groups represent a broad spectrum of aliphatic, aromatic, and heteroaromatic substituents (Table 1). A carboxylic acid **1** and a thiosemicarbazide **2** are mixed in dichloromethane at room temperature with several equivalents of EDCI (Scheme 2). A typical procedure for the preparation of oxadiazole **3** involves filtering of the product precipitate that crystallizes from the reaction mixture in analytically pure form

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✠ In memory of our deceased colleague, Hassan M. Elokdah.

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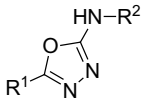
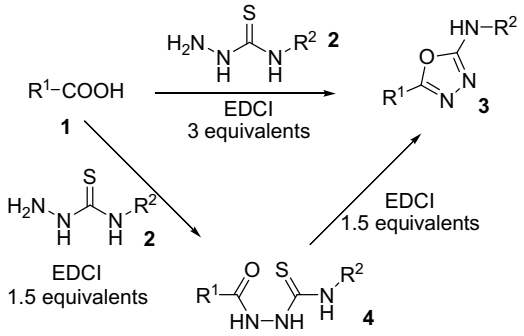
doi:10.1016/j.tetlet.2008.09.057

Table 1
Oxadiazoles prepared using a novel process



Compd	R^1	R^2	Yield[a] (%)	Ref.
5	Benzyl	Phenyl	70	6
6	4-Pyridyl	Phenyl	61	7
7	3-Pyridyl	Phenyl	56	7
8	Phenyl	Phenyl	67	8
9	2-Pyridyl	Phenyl	51	8
10	2-Thiophenyl	Phenyl	53	9
11	2-Benzthiazolyl	Phenyl	49	10
12	2-Indolyl	Phenyl	48	11
13	3-Indolyl	Phenyl	57	12
14	Phenyl	Benzyl	60	13
15	Phenyl	Allyl	42	14
16	Phenyl	Methyl	32	15
17	Phenyl	4-Methylphenyl	69	16
18	Phenyl	3-Chlorophenyl	73	17
19	Phenyl	4-Nitrophenyl	75	17
20	Phenyl	4-Bromophenyl	74	18
21	Phenyl	2,4-Difluorophenyl	66	19
22	Phenyl	4-Ethoxycarbonylphenyl	67	19
23	Phenyl	2-Nitrophenyl	72	20

[a] Yields calculated based on the amount of initially precipitated material using soluble EDCI reagent. Additional amount of material remained in the solution.



Scheme 2. One-pot and stepwise processes towards 2-amino-1,3,4-oxadiazoles.

that often passes elemental analysis criteria (see Supplementary data). Only oxadiazole **16** required an additional purification using column chromatography. The key element of this procedure is the use of EDCI (or EDAC) as a coupling reagent. The isolated yields of compounds **5**–**15** and **17**–**23** varied depending on the compound solubility in the reaction solvent, dichloromethane, or DMF. The reported yields (Table 1) reflect only the amounts of products that crystallized from the reaction mixture without further purification. Thus, highly crystalline products with both R^1 and R^2 as aromatic groups tend to render the higher yields compared to oxadiazoles with an aliphatic R^2 component.

Over the years, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) has emerged as a reagent of choice for amide coupling reactions. The use of this coupling reagent in this efficient procedure leads to a convenient process that does not require an elaborate purification. However, the best results in this one-pot multi-step condensation were achieved when the product had limited solubility in the organic solvent. This may potentially limit the application of the described method to highly crystalline or less soluble compounds. It became our goal to develop an alternative procedure to prepare oxadiazoles with potentially greater solubility in organic solvents. We found that the resin-bound EDCI reagent provides a useful alternative in these transformations. An attempt to develop a robust procedure to synthesize the oxadiazoles in efficient manner using solid phase reagents was reported.[15,19,21] However, reported unfavorable reaction conditions and the limited commercial availability of starting material make our method more attractive and more amendable to parallel synthesis. The corresponding oxadiazole derivative remains in solution while the resin can be easily removed upon completion of the reaction. 2-Aminooxadiazoles **15** and **16** that are relatively more soluble in dichloromethane than other oxadiazoles with aromatic R^2 groups were subjected to the new conditions using resin-based EDCI reagent in DMF as a solvent. The isolation of oxadiazoles **15** and **16** from the solid phase reaction mixture required chromatographic purification with the isolated yields higher than in the corresponding solution phase processes (53% and 61%, respectively).

We hypothesized that mechanistically the reaction proceeds through the formation of intermediate **4**, which undergoes cyclization to furnish target **3** (Scheme 1). To confirm that, we prepared and isolated intermediate **4**, where R^1 and R^2 = phenyl, and then subjected it to the same reaction conditions with 1.5 equiv of EDCI (Scheme 2). Re-subjecting intermediate **4** to the reaction conditions resulted in the formation of the same product in slightly better yields than in the one-pot protocol. Similar transformations have been reported in the literature using harsher reaction conditions.[15,19] These studies suggest that the title reaction is a combination of two processes, where the initial EDCI-promoted amide coupling to form intermediate **4** is followed by a cyclization to yield 2-aminooxadiazole **3**.

An additional simplification of the reaction protocol comes from a one-pot sequential formation of thiosemicarbazide **2** followed by addition of carboxylic acid **1** and coupling agent. The limited number of commercially available thiosemicarbazides **2** may narrow down the scope of the described methodology while the precursor isothiocyanates are more readily available. Thus, the thiosemicarbazide is formed by a standard protocol of reacting isothiocyanate with hydrazine at reflux in DCM. Once the reaction is completed, the reaction mixture is cooled down, and required reagents are added to render the desired 2-aminooxadiazole derivatives using the above-described protocol. Two title compounds **8** and **14** were produced using this three-step one-pot protocol in 60% and 61% yields, respectively.

In summary, we have described a protocol for a rapid assembly of 2-amino-1,3,4-oxadiazoles from thiosemicarbazides (or isothiocyanates) and carboxylic acids. The proposed reaction mechanism for this process involves the formation of acylthiosemicarbazide as an intermediate. The selected oxadiazole class representatives exhibited activity against kinase and non-kinase targets.

Acknowledgments

We thank Dr. Avdhoot Velankar and Mr. X. Ouyang formerly of ImClone Systems for helpful discussions at early stages of this work. We acknowledge Dr. B. Blass for helpful suggestions. We thank Wyeth Discovery Analytical Chemistry Department for characterizing our compounds.

Supplementary data

Experimental details, proton and carbon NMR spectra, mass spectrometry data, HPLC chromatograms for all compounds, and elemental analysis data for selected compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.057.

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