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Facile One-Pot Synthesis of 2,3,5-Substituted 1,2,4-Oxadiazolines from Nitriles in Aqueous Solution

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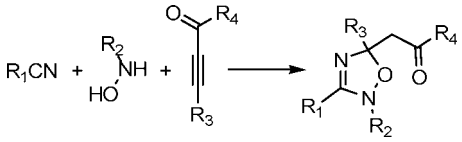
ABSTRACT



Alkyl/aryl amidoximes, prepared from the corresponding nitriles and *N*-alkylhydroxylamines, have readily undergone consecutive Michael additions to electron-deficient alkynes and provided highly substituted 1,2,4-oxadiazolines in good yields in homogeneous aqueous solution.

Oxadiazolines represent a class of heterocycle that, although known for over a century, is rather limited in number. These are partially reduced forms of well-known oxadiazoles. Recently, these heterocycles have been receiving increased attention due to their promising biological activity[1] and usefulness as synthetic intermediates.[2] For example, oxadiazolines are reported to possess antitumor,[1a] anti-HIV,[1b] antifungal,[1c] antiinflammatory,[1d] and anticonvulsant[1e] properties.

In 1889, Tiemann reported the first synthesis of a 1,2,4-oxadiazoline derivative via cyclocondensation of benzamidoxime with acetaldehyde.[3] This route is one of the most robust and direct approaches to the synthesis of 1,2,4-oxadiazolines. Many groups have used this or a slightly modified route for the synthesis of these compounds.[4] Furthermore, 1,2,4-oxadiazolines have also been prepared by cycloaddition reactions. For example, Ibata and co-workers employed a formal [2 + 3]-cycloaddition of oxazoles and nitrosobenzenes to prepare 1,2,4-oxadiazolines.[5a,b] Recently, Wagner et al. disclosed platinum(IV)-assisted [2 + 3]-cycloaddition of nitrones to organonitriles to provide 1,2,4-oxadiazolines and then extended this methodology to the first asymmetric synthesis of oxadiazolines using a chiral sulfoxide ligand.[5c,d] Eguchi and co-workers synthesized 1,2,4-oxadiazolines by the 1,3-dipolar cycloaddition of alkyl or arylnitriles with nitrones under high-pressure conditions.[6a,b] More recently, Wang and colleagues described an efficient route suitable for the rapid synthesis of 1,2,4-oxadiazolines via the 1,3-dipolar cycloaddition of in situ-generated nitrile

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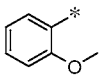
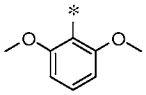
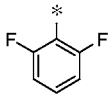
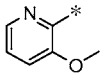
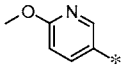
Table 1. Synthesis of Highly Substituted 1,2,4-Oxadiazolines from Nitriles[a]

Entry	Amidoxime **3**/Product **6**	R_1	R_2	Reaction Time (h) Step 1	Step 2	Yield (%)[b]
1	**a**	$PhCH_2$	Me	2	0.5	78
2	**b**	$PhCH_2$	i-Pr	5	0.5	64
3	**c**	$PhCH_2$		2	0.5	36
4	**d**	Me	$PhCH_2$	2	0.5	81[c]
5	**e**	i-Pr	Me	2	0.5	65
6	**f**		Me	2	0.5	58
7	**g**	Ph	Me	2	0.5	78
8	**g**	Ph	Me	-[d]	0.5	100
9	**h**		Me	2	0.5	79
10	**i**		Me	3	0.5	83
11	**j**		Me	2	0.5	76
12	**k**		Me	2	0.5	65
13	**l**		Me	2	0.5	82
14	**m**		Me	2	0.5	69
15	**n**		Me	2	0.5	72
16	**o**		Me	2	0.5	85
18	**p**		Me	3	0.5	63

[a] Unless otherwise mentioned, reactions were conducted in 1:1 EtOH/H_2O as the solvent. [b] Isolated yields. [c] This reaction was conducted in 1:1 CH_3CN/H_2O as solvent. [d] This reaction was carried out using purified benzamidoxime **3g**.

oxides with imines.[6c−e] Furthermore, 1,2,4-oxadiazolines have been prepared by the addition of alkyllithiums to 1,2,4-oxadiazoles[2c] and diborane reduction of 1,2,4-oxadiazoles.[7] However, the methods described above suffer from several limitations, including expensive starting materials, harsh reaction conditions, and multiple steps. Herein, we disclose a simple and efficient one-pot synthetic protocol for the synthesis of highly substituted 1,2,4-oxadiazolines from the corresponding nitriles.

During the course of our drug discovery efforts, we discovered that the treatment of alkyl or arylamidoximes **3**, which were prepared by reacting nitriles **1** and *N*-alkylhydroxylamines **2** in 1:1 ethanol/water, with diethyl acetylenedicarboxylate (DEAD) provided exclusively 1,2,4-oxadiazolines **6** (Scheme 1).[8] The addition of amidoximes to DEAD is exothermic, extremely fast, and complete within a few minutes.[9] The formation of oxadiazolines in this process involves a sequential double Michael addition of amidoximes to the electron-deficient alkyne. In the first step, Michael addition of the amidoxime hydroxyl group to DEAD generates the transient intermediate **5**. Subsequently, the

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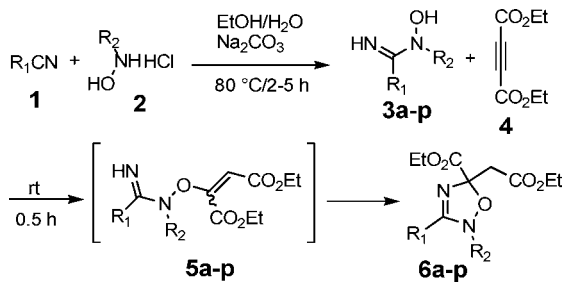
Scheme 1. Oxadiazolines from Diethyl Acetylenedicarboxylate

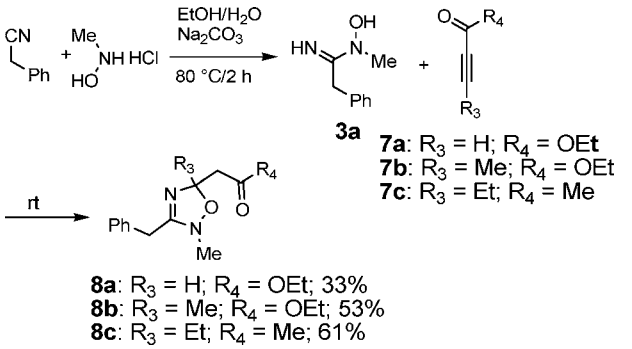


amidoxime NH in **5** regioselectively undergoes an intramolecular Michael addition at the most electron-deficient carbon, producing the five-membered 1,2,4-oxadiazoline heterocycle **6**.[10]

As shown in Table 1, the amidoximes derived from a variety of nitriles, including alkyl, cycloalkyl, aryl, and heteroaryl and *N*-methyl, *N*-isopropyl, *N*-cyclohexyl, or *N*-benzylhydroxylamine, reacted with DEAD very smoothly to provide 1,2,4-oxadiazolines **6a**−**p** in good isolated yields. From entries 1−6, it is clear that the yields of some products are significantly reduced as the steric bulkiness of the amidoxime substituents increases. For example, amidoximes **3b**,**c**, derived from sterically hindered *N*-isopropyl and *N*-cyclohexyl hydroxylamines and benzylnitrile, provided products in reduced yields. Similarly, amidoximes **3e**,**f**, derived from isobutyronitrile and cyclopentanecarbonitrile and *N*-methylhydroxylamine, also furnished products in low yields. Amidoximes **3g**−**p**, derived from aryl- or heteroarylnitriles and *N*-methylhydroxylamine, reacted with DEAD uneventfully and provided the corresponding oxadiazolines **6g**−**p** in very good yields. When pure benzamidoxime **3g** was used, quantitative formation of **6g** (cf. entries 7 and 8) indicates that the addition of amidoximes to DEAD is a very efficient and high-yielding process. Consequently, reduced yields in some cases are presumably due to the poor formation of amidoximes in the first step.

As exemplified in Scheme 2, 1,2,4-oxadiazolines can also be prepared by conjugative addition of amidoximes to other electron-deficient alkynes. As expected, addition of amidoxime **3a** to alkynes **7a**−**c** was slower compared with the more electron-deficient DEAD. Reaction of amidoxime **3a** with ethyl propiolate **7a** was complete in 2 h and furnished **8a** in 33% yield. The addition of **3a** to **7b** was significantly slower, furnishing oxadiazoline **8b** in 53% yield after 58 h. Coupling of **3a** and ketone **7c** was complete in 6 h and provided oxadiazoline **8c** in 61% isolated yield.

Scheme 2. Oxadiazolines from Monoactivated Alkynes



In summary, we have described an easy and practical one-pot approach to the synthesis of 1,2,4-oxadiazolines from nitriles. This method works well with a variety of amidoximes derived from the combination of different alkyl or aryl nitriles and *N*-alkylhydroxylamines and provided highly substituted 1,2,4-oxadiazolines in good yield. One of the most important advantages with this methodology is that there is no need to isolate the amidoxime intermediates. This process therefore constitutes a short and practical protocol for the formation of such heterocycles. In addition, these reactions are carried out in an environmentally benign solvent system.

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Supporting Information Available: General experimental conditions, representative procedure, and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) **Typical Procedure for the Synthesis 1,2,4-Oxadiazolines.** A mixture of benzylnitrile (2.343 g, 20 mmol), *N*-methylhydroxylamine hydrochloride (0.835 g, 10 mmol), and Na_2CO_3 (0.64 g, 6 mmol) in 1:1 EtOH/H_2O (20 mL) was heated at 80 °C for 2 h. Then, the reaction mixture was cooled to ambient temperature, and diethyl acetylenedicarboxylate (1.76 mL, 11 mmol) was added via syringe over 5 min. After 30 min, the reaction mixture was taken up into EtOAc (100 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated, and the resulting yellow residue was purified by flash chromatography on silica gel column using a 3:7 EtOAc/hexanes mixture to afford the desired product **6a** as a yellow oil (2.61 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32−7.23 (5H, m), 4.33−4.20 (2H, m), 4.13 (2H, q, J = 7.0 Hz), 3.67 (2H, s), 3.31 (1H, d, J_{AB} = 16.2 Hz), 3.00 (3H, s), 2.96 (1H, d, J_{AB} = 16.2 Hz), 1.29 (3H, t, J = 7.0 Hz), 1.23 (3H, t, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 168.4, 165.6, 134.0, 128.9, 128.7, 127.4, 103.7, 62.1, 60.8, 42.3, 40.1, 32.8, 14.2, 14.1. HRMS (M + H): calcd for $C_{17}H_{23}N_2O_5$, 335.1607; found, 335.1607. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.37. Found: C, 60.80; H, 6.66; N, 8.30.

(9) *Caution*: We highly recommend cooling the reaction flask in an ice−water bath before adding DEAD when carrying out these reactions on a larger scale (>10 mmol of amidoxime).

(10) In cases where R_2 = H, **5** is stable and isolated as a mixture of cis/trans isomers. See: Culbertson, T. P. *J. Heterocycl. Chem.* **1979**, *16*, 1423−1424 and references therein.