A Novel, One-Pot, Three-Component Synthesis of 1,2,4-Oxadiazoles under Microwave Irradiation and Solvent-Free Conditions

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Abstract: A novel synthesis of 3,5-disubstituted 1,2,4-oxadiazoles is described from a one-pot, three-component reaction between nitriles, hydroxylamine, and Meldrum's acids under microwave irradiation and solvent-free conditions in good to excellent yields.

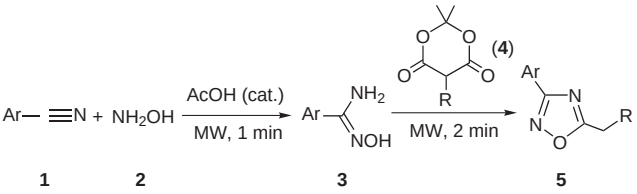
Key words: Meldrum's acids, nitriles, 1,2,4-oxadiazoles, three-component reaction, solvent-free synthesis

Five-membered heterocyclic systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) are of synthetic and pharmacological interest because of the occurrence of the saturated and partially saturated 1,2,4-oxadiazoles in biologically active compounds and natural products.[1] The rich chemistry of 1,2,4-oxadiazoles has been repeatedly reviewed.[1,2] 1,2,4-Oxadiazoles have been recently described as bioisosteres for amides or esters as a result of the increased hydrolytic and metabolic stability of the ring.[3] Furthermore, derivatives containing 1,2,4-oxadiazole ring systems have been employed as anti-inflammatory and antitumor agents,[4a] antirhinovirals,[4b] serotoninergic (5-HT_3) antagonists,[4c] muscarinic agonists,[4d] benzodiazepine receptor partial agonists,[4e] and growth hormone secretagogues.[4f] On the other hand some 1,2,4-oxadiazoles have been used as plant protection[5] and liquid crystalline mesophases.[6]

The most common methods recently reported for the synthesis of 1,2,4-oxadiazoles are cyclization of *O*-acylamidoximes obtained from acylation of amidoximes by carboxylic acids or acid chlorides. However, these methods have several drawbacks. Acid chlorides are very toxic and reactive chemicals and thus are hard to store and handle. Carboxylic acids need a coupling regent to react with amidoximes.[7] On the other hand, the reaction times are relatively long and in some cases the yields of the reactions are not very high.

The application of microwave irradiation in organic synthesis for conducting reactions at highly accelerated rates is an emerging technique. In fact, in recent years, the use of microwaves has become popular among synthetic organic chemists both to improve classical organic reactions (shortening reaction times and/or improving yields) as well as to promote new reactions.[8]

As part of our ongoing program to develop efficient methods for the preparation of biologically interesting compounds from readily available building blocks, in this Letter we would like to report a novel synthesis of 3,5-disubstituted 1,2,4-oxadiazoles via a one-pot three-component reaction between nitriles, hydroxylamine, and Meldrum's acids. Thus, arylnitriles **1** and hydroxylamine **2** are converted in situ to the corresponding amidoximes **3**. Next, the amidoximes react with the Meldrum's acids **4** under microwave irradiation[9] and solvent-free conditions to produce 1,2,4-oxadiazoles **5** in 81–98% yields (Scheme 1, Table 1).



Scheme 1

The reactions were carried out by first mixing the nitrile and hydroxylamine, proceeding in the presence of a catalytic amount of acetic acid under microwave irradiation. After a minute and nearly complete conversion to the corresponding amidoxime **3**, as indicated by TLC monitoring, the Meldrum's acid **4** was added to the reaction mixture which was irradiated for a further two minutes. TLC and ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of 1,2,4-oxadiazoles **5** in good to excellent yields. The structures of the isolated products, **5a**–**n**, were corroborated by the comparison of their physical and spectral data (high-field ^{1}H NMR and ^{13}C NMR spectra) with those of authentic samples.[11]

Mechanistically, it is reasonable to assume that first the in situ prepared amidoxime **3** attacks to the Meldrum's acid **4** to give the *O*-acylamidoxime intermediate **6** with removal of acetone. This intermediate is cyclized to the 1,2,4-oxadiazole intermediate **7** by removing H_2O. The isolated 1,2,4-oxadiazole **5** is finally formed by decarboxylation of **7** under the reaction conditions (Scheme 2).

In conclusion, we have developed a novel, microwave-assisted, one-pot, three-component reaction for the preparation of 1,2,4-oxadiazoles of potential synthetic and pharmacological interest. Good to excellent yields, short

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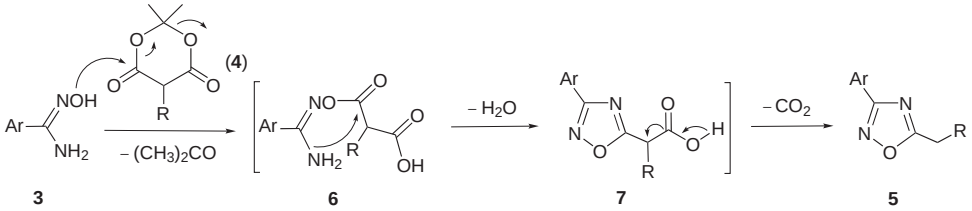

Scheme 2

Table 1 Synthesis of 1,2,4-Oxadiazoles **5a**–**n**

5	Ar	R	Mp (reported)	Yield (%)[a]
a	C_6H_5	H	37–39 (41)[10a]	98
b	2-$CH_3C_6H_4$	H	Colorless oil[10b]	94
c	3-$CH_3C_6H_4$	H	Colorless oil[10b]	97
d	4-$CH_3C_6H_4$	H	77–79 (80)[10a]	98
e	3-ClC_6H_4	H	70–72 (70–72)[10c]	98
f	4-ClC_6H_4	H	73–78	98
g	3-BrC_6H_4	H	58–61	95
h	4-BrC_6H_4	H	99–100 (103)[10a]	94
i	C_6H_5	CH_3	Colorless oil[10d]	84
j	4-$CH_3C_6H_4$	CH_3	Colorless oil	81
k	3-ClC_6H_4	CH_3	Colorless oil	85
l	4-ClC_6H_4	CH_3	30–32	85
m	3-BrC_6H_4	CH_3	Colorless oil	87
n	4-BrC_6H_4	CH_3	37–39	87

[a] Isolated yields.

reaction times, one-pot and solvent-free conditions and also using Meldrum's acids instead of carboxylic acid derivatives are the main advantages of this method. This method appears to have broad scope with respect to variation in the oxadiazole 3- and 5-positions and presents a straightforward procedure for the synthesis of 1,2,4-oxadiazoles.

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(11) **Preparation of 5-Methyl-3-phenyl-1,2,4-oxadiazole (5a); General Procedure.**
A mixture of benzonitrile (0.21 g, 2 mmol), NH_2OH 50% (0.13 g, 2 mmol), and a catalytic amount of AcOH was irradiated with microwaves at 100 °C for 1 min. After nearly complete conversion to the corresponding amidoxime as was indicated by TLC, Meldrum's acid (0.29 g, 2 mmol) was added to the reaction mixture and it was irradiated at 150 °C for a further 2 min. After cooling to r.t., the solid residue was sublimated and **5a** obtained as colorless crystals. In the case of the products **5d**–**h**, the obtained crude solid were purified by recrystallization from 95% EtOH, and the products **5b**,**c**,**i**–**n** were purified by column chromatography (4:1 *n*-hexane–EtOAc as eluent, Merck silica gel 60 mesh).

Selected Data.

Compound **5a**: colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.60 (3 H, s, CH_3), 7.45 (3 H, m, 3 × CH), 8.04 (2 H, dd, *J* = 7.8 Hz and *J* = 1.7 Hz, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 12.30 (CH_3), 124.01 (C), 127.32, 128.80, and 131.05 (3 × CH), 168.38 (NCN), 176.29 (NCO).

Compound **5d**: colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.36 (3 H, s, $PhCH_3$), 2.58 (3 H, s, CH_3), 7.23 (2 H, d, *J* = 7.8 Hz, 2 × CH), 7.92 (2 H, d, *J* = 7.8 Hz, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 12.25 (CH_3), 21.44 ($PhCH_3$), 124.00 (C), 127.21 and 129.48 (2 × CH), 141.31 (C), 168.32 (NCN), 176.27 (NCO).

Compound **5e**: colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.62 (3 H, s, CH_3), 7.37 (1 H, t, *J* = 7.9 Hz, CH), 7.43 (1 H, dd, *J* = 8.1 Hz and *J* = 1.1 Hz, CH), 7.91 (1 H, d, *J* = 7.7 Hz, CH), 8.03 (1 H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 12.30 (CH_3), 125.36 and 127.45 (2 × CH), 128.58 (C), 130.11 and 131.09 (2 × CH), 134.92 (C), 167.41 (NCN), 176.78 (NCO).

Compound **5j**: colorless oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.40 (3 H, t, *J* = 7.6 Hz, CH_2CH_3), 2.35 (3 H, s, CH_3), 2.91 (2 H, q, *J* = 7.6 Hz, CH_2), 7.22 (2 H, d, *J* = 8.0 Hz, 2 × CH), 7.92 (2 H, d, *J* = 8.0 Hz, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 10.78 (CH_2CH_3), 20.27 (CH_2), 21.45 ($PhCH_3$), 124.21 (C), 127.29 and 129.48 (2 × CH), 141.26 (C), 168.22 (NCN), 180.51 (NCO).

Compound **5l**: colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.42 (3 H, t, *J* = 7.6 Hz, CH_3), 2.94 (2 H, q, *J* = 7.6 Hz, CH_2), 7.42 (2 H, d, *J* = 8.5 Hz, 2 × CH), 7.98 (2 H, d, *J* = 8.5 Hz, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 10.78 (CH_3), 20.30 (CH_2), 125.51 (C), 128.69 and 129.11 (2 × CH), 137.15 (C), 167.46 (NCN), 180.91 (NCO).

Compound **5n**: colorless crystals. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.44 (3 H, t, *J* = 7.6 Hz, CH_3), 2.97 (2 H, q, *J* = 7.6 Hz, CH_2), 7.60 (2 H, d, *J* = 8.5 Hz, 2 × CH), 7.94 (2 H, d, *J* = 8.5 Hz, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 10.81 (CH_3), 20.33 (CH_2), 125.59 and 125.98 (2 × C), 128.91 and 132.11 (2 × CH), 167.59 (NCN), 180.98 (NCO).