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Microwave-assisted efficient, one-pot, three-component synthesis of 3,5-disubstituted 1,2,4-oxadiazoles under solvent-free conditions

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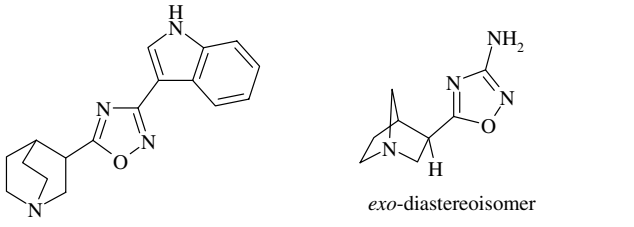
Abstract—A novel synthesis of 1,2,4-oxadiazoles is described from a one-pot, three-component reaction between nitriles, hydroxylamine, and aldehydes under microwave irradiation and solvent-free conditions in excellent yields.

Nitrogen–oxygen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities.[1] The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) stems from the occurrence of saturated and partially saturated 1,2,4-oxadiazoles in biologically active compounds and natural products.[2] 1,2,4-Oxadiazoles have recently received considerable attention as heterocyclic amide and ester bioisosteres. Bioisosteric replacement of the amide moiety represents an area that is currently a center of focus because of its implications in peptide chemistry and the development of peptidomimetics.[3] Furthermore, derivatives containing 1,2,4-oxadiazole ring systems have been employed as antirhinovirals, tyrosin kinase inhibitors, serotoninergic (5-HT_3) antagonists (Fig. 1, **1**), dopamine receptor (D_4) ligands, anti-inflammatory agents, antitumor agents, monoamine oxidase inhibitors, coronary artery dilators, anesthetic agents, muscle relaxants, antischistosomal agents, and aldose reductase inhibitors.[2,4] Moreover the oxadiazole nucleus, a well studied traditional pharmacophoric scaffold, is the core structural unit of various muscarinic agonists (Fig. 1, **2**), benzodiazepine receptor partial agonists and growth hormone secretagogues.[4,5]



1, potent 5-HT_3 antagonist **2**, highly efficacious muscarinic agonist

Figure 1. Examples of biologically active 1,2,4-oxadiazoles.

So far, five general synthetic methods have been reported for the preparation of 1,2,4-oxadiazole ring systems: (i) condensation of amidoximes with derivatives of carboxylic acids to give *O*-acylamidoximes, which are cyclized to 1,2,4-oxadiazoles; (ii) cyclization of *N*-acylamidoximes; (iii) 1,3-dipolar cycloaddition of nitrile oxides to nitriles; (iv) electrocyclic ring closure of nitrenoids; and (v) oxidation of 4,5-dihydro-1,2,4-oxadiazoles.[2]

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.[6] However, these methods have several drawbacks. Acid chlorides are very toxic and reactive chemicals and thus are hard to store and handle, and only a few acid chlorides are

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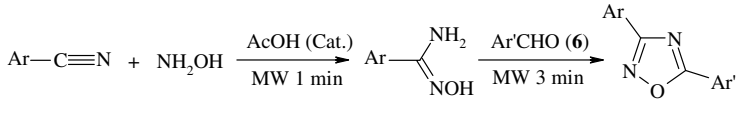
readily available. On the other hand, carboxylic acids need a coupling reagent such as DCC, EDC, CDI, TBTU, HOBt, or HBTU[7] to react with amidoximes[6,8] and also the reaction time is relatively long.

The application of microwave irradiation in organic synthesis for conducting reactions at highly accelerated rates is an emerging technique.[9] In fact, in recent years, the use of microwaves have 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.

Knowing the pharmacological importance of the 1,2,4-oxadiazole ring systems, we have recently focused on improving the synthesis of this nucleus bearing in mind new synthetic methodologies. To date, we know of no published report concerning the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using aldehydes as the third reactant coupled with nitriles and hydroxylamine (or as the second coupled with amidoximes). In this letter we report a facile synthesis of 3,5-disubstituted 1,2,4-oxadiazoles via a one-pot, three-component reaction between nitriles, hydroxylamine, and aldehydes. Thus, arylnitriles **3** and hydroxylamine **4** are converted in situ to amidoximes **5**. Next, the amidoximes are condensed with aldehydes **6** under microwave irradiation[10] and solvent-free conditions to produce 1,2,4-oxadiazoles **7** in 92–97% yields (Scheme 1).

The reactions were carried out by first mixing the nitrile and hydroxylamine. Reaction proceeded in the presence of a catalytic amount of acetic acid under microwave irradiation. After a minute and nearly complete conversion to the corresponding amidoxime intermediate, as indicated by TLC monitoring, the aldehyde was added to the reaction mixture, which was irradiated for a further three minutes. TLC and ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of 1,2,4-oxadiazoles **7** in excellent yields.[11] Mechanistically, it is reasonable to assume that first, the in situ prepared amidoxime is condensed with the aldehyde to form the imine derivative **8**. Then, this intermediate is cyclized to the 4,5-dihydro-1,2,4-oxadiazole derivative **9**, which is finally oxidized under the reaction conditions to produce 1,2,4-oxadiazole **7** (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. Excellent yields, a simplified purification process, short reaction times, one-pot, and solvent-free conditions and finally using aldehydes 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 efficient synthesis of 3,5-disubstituted 1,2,4-oxadiazoles.

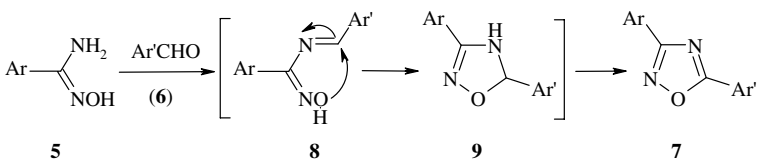


3 **4** **5** **7**

7	Ar	Ar	% Yield[a]
a	C_6H_5	C_6H_5	95
b	C_6H_5	4-$CH_3C_6H_4$	92
c	C_6H_5	4-$CH_3OC_6H_4$	94
d	C_6H_5	4-ClC_6H_4	97
e	4-$CH_3C_6H_4$	C_6H_5	94
f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	92
g	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	93
h	3-ClC_6H_4	C_6H_5	96
i	3-ClC_6H_4	3-ClC_6H_4	93
j	3-ClC_6H_4	4-$CH_3C_6H_4$	94
k	3-ClC_6H_4	4-$CH_3OC_6H_4$	92
l	3-ClC_6H_4	4-ClC_6H_4	96

[a]Isolated yields

Scheme 1.



5 **8** **9** **7**

Scheme 2.

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7. DCC, dicyclohexyl carbodiimide; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; CDI, 1,1-carbonyldiimidazole; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; HOBt, 1,2,3-benzotriazole-1-hydroxide; HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.
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10. The experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis.
11. The procedure for the preparation of 3,5-diphenyl-1,2,4-oxadiazole **7a** is described as an example: A mixture of benzonitrile (0.21 g, 2 mmol), hydroxylamine 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, benzaldehyde (0.21 g, 2 mmol) was added to the reaction mixture and it was irradiated at 150 °C for a further three minutes. After cooling to room temperature, the solid residue was recrystallized from 95% ethanol. The product **7a** was obtained as colorless crystals, mp 106–108 °C (lit.: 109–110 °C);[12] ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.49–7.55 (5H, m, 5CH), 7.59 (1H, t, $J = 7.1$ Hz, CH), 8.17 (2H, dd, $J = 7.5$ and $J = 1.5$ Hz, 2CH), 8.21 (2H, d, $J = 7.8$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 124.29 and 126.95 (2C), 127.50, 128.13, 128.82, 129.06, 131.15, and 132.69 (6CH), 168.94 (NCN), 175.68 (NCO). Compound **7b**: Colorless crystals, mp 113–115 °C (lit.: 117–118 °C);[13] ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 7.28 (2H, d, $J = 8.0$ Hz, 2CH), 7.47–7.49 (3H, m, 3CH), 8.06 (2H, d, $J = 8.0$ Hz, 2CH), 8.17 (2H, dd, $J = 7.3$ and $J = 1.9$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.65 (CH_3), 121.55 and 127.10 (2C), 127.44, 128.05, 128.76, 129.72, and 131.03 (5CH), 143.35 (C), 168.80 (NCN), 175.76 (NCO). Compound **7c**: Colorless crystals, mp 94–96 °C (lit.: 98 °C);[13] ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.83 (3H, s, OCH_3), 6.99 (2H, d, $J = 8.7$ Hz, 2CH), 7.45–7.55 (3H, m, 3CH), 8.12 (2H, d, $J = 8.8$ Hz, 2CH), 8.15 (2H, dd, $J = 8.4$ and $J = 1.7$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 55.41 (OCH_3), 114.43 (CH), 116.82 and 127.14 (2C), 127.45, 128.74, 129.98, and 130.99 (4CH), 163.10 (O–C), 168.74 (NCN), 175.52 (NCO). Compound **7d**: Colorless crystals, mp 118–119 °C (lit.: 121–122 °C);[13] ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.45–7.55 [3H: m; and 2H: d ($J = 8.7$ Hz), 5CH], 8.12 (2H, d, $J = 8.7$ Hz, 2CH), 8.14 (2H, dd, $J = 7.4$ and $J = 1.4$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 122.72 and 126.74 (2C), 127.47, 128.81, 129.38, 129.44, and 131.22 (5CH), 139.11 (C), 168.98 (NCN), 174.72 (NCO). Compound **7f**: Colorless crystals, mp 135–136 °C (lit.: 134–135 °C);[14] ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.39 and 2.40 (6H, 2s, $2CH_3$), 7.27 (2H, d, $J = 7.6$ Hz, 2CH), 7.28 (2H, d, $J = 7.8$ Hz, 2CH), 8.05 (2H, d, $J = 7.8$ Hz, 2CH), 8.06 (2H, d, $J = 7.6$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.51 and 21.64 ($2CH_3$), 124.28 (C), 127.39 and 128.03 (2CH), 128.87 (C), 129.46 and 129.68 (2CH), 141.28 and 143.25 (2C), 168.79 (NCN), 175.57 (NCO).
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