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One-pot synthesis of 1,2,4-oxadiazoles from carboxylic acid esters and amidoximes using potassium carbonate

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Abstract—A convenient one-pot synthesis of 1,2,4-oxadiazoles is described. The condensation of carboxylic acid esters and amidoximes in the presence of potassium carbonate was employed to synthesize a variety of mono-, bis- and tris-oxadiazoles in moderate to excellent yields.

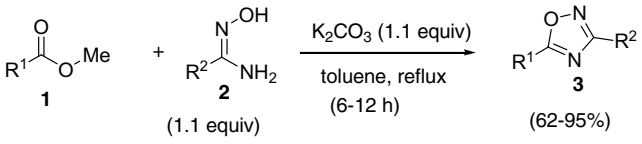
1,2,4-Oxadiazoles are a class of important heterocycles which have been well documented throughout the literature due to their biological importance. 1,2,4-Oxadiazoles have often been used as bioisosteres of esters and amides[1] and as dipeptide mimetics[2] in a number of pharmacologically important molecules. They can also be found in a number of biologically important molecules, such as muscarinic agonists,[3] serotoninergic (5-HT_3) antagonists,[4] benzodiazepine receptor agonists,[5] and dopamine ligands.[6]

Generally, 1,2,4-oxadiazoles are synthesized by cyclodehydration of O-acylamidoximes, promoted by either heat or by bases, such as NaH, NaOEt or pyridine.[7] A recent report has described the use of tetrabutylammonium fluoride (TBAF) as an activator to promote the cyclization of O-acylamidoximes.[8] Historically, the preferred method of obtaining O-acylamidoximes is the reaction of amidoximes with activated carboxylic acid derivatives or with carboxylic acids in the presence of a coupling reagent, such as EDC, DCC or DIC.

We were interested in a mild one-pot conversion of carboxylic acid esters and amidoximes to the corresponding 1,2,4-oxadiazoles with high yields. Such a transformation would be particularly useful for medicinal chemists since it would give them direct access to a useful bioisostere of the ester in a single chemical transformation. Existing methods of synthesizing 1,2,4-oxadiazoles from carboxylic acid esters require the presence of strong bases, such as NaH or NaOEt, in refluxing THF or EtOH, and generally give low yields.[7]

Herein we report a high-yielding one-pot synthesis of 1,3-disubstituted 1,2,4-oxadiazoles **3** by condensing carboxylic acid esters and amidoximes in refluxing toluene in the presence of potassium carbonate (Scheme 1). Both aliphatic and aromatic amidoximes were combined with a small set of simple methyl esters to give 1,2,4-oxadiazoles in good to excellent yields (Table 1).[9,10] When the reaction was carried out in the absence of K_2CO_3, no appreciable amounts of 1,2,4-oxadiazoles were detected. The use of Ce_2CO_3 as the base also gave 1,2,4-oxadiazoles in comparable yields. It is also important to note that only the methyl ester of *tert*-butyl methyl succinate reacted with acetamide oxime to give **3g**, leaving the *tert*-butyl ester intact.

This method was further employed to synthesize a variety of bis-1,2,4-oxadiazoles **5** (Scheme 2). Both dimethyl malonate and diethyl malonate reacted with acetamide



Scheme 1. Synthesis of 1,2,4-oxadiazoles.

Keywords: Oxadiazoles; Amidoximes; Potassium carbonate; Cyclodehydration.
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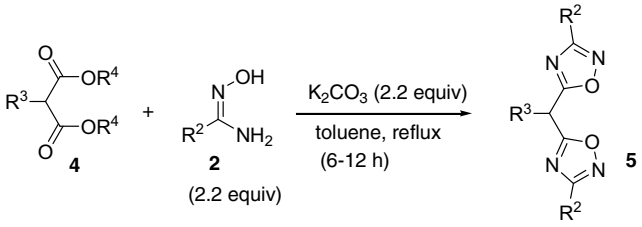
Table 1. Representative examples of the synthesis of 1,2,4-oxadiazoles **3**[8]

Compound #	R^1	R^2	Yield (%)[a]
3a	Benzyl	Methyl	91
3b	Benzyl	4-Methylphenyl	77
3c	4-Methylbenzyl	Methyl	95
3d	4-Methylbenzyl	4-Methylphenyl	65
3e	4-Methoxyphenyl	Methyl	86
3f	4-Methoxyphenyl	4-Methylphenyl	90
3g	*tert*-Butylpropionate	Methyl	62

[a] Purified products.



Scheme 2. Synthesis of bis-1,2,4-oxadiazoles.

Table 2. Representative examples of the synthesis of bis-1,2,4-oxadiazoles **5**

Entry	Compound	R^2	R^3	R^4	Yield (%)[a]
1	**5a**	Methyl	H	Methyl	75
2	**5a**	Methyl	H	Ethyl	64
3	**5b**	Ethyl	H	Ethyl	64
4	**5c**	Methyl	Benzyl	Ethyl	69
5	**5d**	Benzyl	Benzyl	Ethyl	68
6	**5e**	4-Fluorobenzyl	Benzyl	Ethyl	67
7	**5f**	3-(Thiophene)methyl	Benzyl	Ethyl	40
8	**5g**	Methoxyethyl	Benzyl	Ethyl	73
9	**5h**	Cyclopropylmethyl	Benzyl	Ethyl	40
10	**5i**	4-methoxyphenyl	Benzyl	Ethyl	83

[a] Purified products.

oxime to give bis-1,2,4-oxadiazole **5a** in comparable yields (Table 2, entries 1 and 2). A variety of functionalized amidoximes, including aliphatic, aromatic, heterocyclic and protected alcohols, participated in this reaction to give bis-1,2,4-oxadiazoles in moderate to good yields. Moreover, this method was amenable to the use of microwave irradiation. For example, microwave irradiation of a mixture of dimethyl malonate, acetamide oxime and K_2CO_3 in toluene at 180 °C for 10 min yielded 72% of **5a**.[11] Additionally, we used this method to synthesize tris-1,2,4-oxadiazole **6** in 42% yield and the reaction tolerated the presence of a nitro group in the phenyl ring (Fig. 1).[10] Reaction of L-Boc-Phe-OMe with acetamide oxime in the presence of K_2CO_3 in refluxing toluene for 6 h yielded oxadiazole **7** in 72% yield with complete racemization of the chiral center, as determined by ^{19}F analysis of its Mosher's amide (Fig. 1).

In summary, a general, practical method of synthesizing 1,2,4-oxadiazoles from carboxylic acid esters and amidoximes has been developed. This method tolerates a variety of functional groups on both reaction partners and gives 3,5 disubstituted 1,2,4-oxadiazoles in moderate to excellent yields.

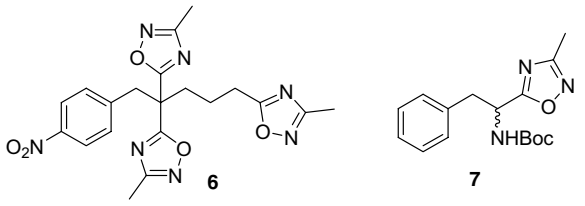


Figure 1. Additional examples of 1,2,4-oxadiazoles.

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9. General procedure: To a solution of methyl phenylacetate (100 mg, 0.67 mmol) in toluene (3 mL) was added acetamide oxime (104 mg, 1.4 mmol) followed by K_2CO_3 (193 mg, 1.4 mmol). The reaction mixture was stirred at reflux for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (25 mL) and washed successively with water (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on SiO_2 (0–20% EtOAc in hexane) to give 106 mg of **3a** as a colorless oil (91%).
10. All new compounds were fully characterized by ^1H and ^{13}C NMR, and mass spectrometry. Characterization data for a few selected compounds (**3a**): ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.22 (s, 2H), 7.29–7.39 (m, 5H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 11.86, 33.20, 127.90, 129.20, 133.75, 133.80, 167.6, 178.08; MS = 175 (MH^+). (**3g**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.26 (s, 3H), 2.67 (t, $J = 7.2$ Hz, 2H), 3.13 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.61, 22.18, 28.09, 31.73, 81.29, 164.12, 170.45, 138.51. (**5a**): ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 6H), 4.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.81, 25.32, 168.10, 171.86. (**6**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.79–1.88 (m, 4H), 2.35 (s, 3H), 2.85 (t, $J = 6.9$ Hz, 2H), 3.32 (s, 2H), 3.70 (s, 6H), 7.25 (d, $J = 8.7$ Hz, 2H), 8.07 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.75, 21.68, 26.56, 32.05, 38.53, 52.94, 58.86, 123.68, 129.92, 131.01, 143.87, 147.35, 167.31, 170.93, 178.76 (**7**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.37 (s, 3H), 3.21–3.27 (m, 2H), 5.26–5.31 (m, 1H), 7.08 (d, $J = 6.3$ Hz, 2H), 7.24–7.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.77, 28.74, 40.07, 49.51, 81.00, 127.54, 128.94, 129.49, 135.35, 156.00, 166.75, 178.80.

11. Microwave reactions were performed on a Biotage Initiator™ at a concentration of 1 M.