The reaction of amidoximes with carboxylic acids or their esters under high-pressure conditions*

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3,5-Disubstituted 1,2,4-oxadiazoles were synthesized by the reaction of amidoximes with carboxylic acids or their esters under high-pressure conditions (10 kbar). The reaction proceeds without the use of other reagents or catalysts. Both aliphatic and aromatic carboxylic acids undergo this reaction. The obtained 1,2,4-oxadiazoles possess high fungicidal activity.

Key words: amidoximes, carboxylic acids, esters, 1,2,4-oxadiazoles, high pressure, fungicidal activity.

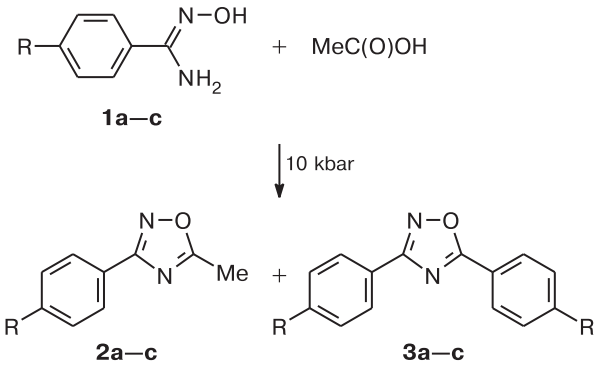
1,2,4-Oxadiazole moiety is a part of the Libexin,[1] Oxolamine,[2] and Ataluren[3] drug molecules, as well as of other substances being at different phases of clinical and pre-clinical trials.[4—6] In addition, their find application in the development of liquid-crystalline and high-energy materials.[7,8] Of specific interest are 1,2,4-oxatriazoles possessing fungicidal activity,[9—12] in particular, those of quinoline series.[13]

Among main methods for their synthesis is the reaction of amidoximes with carboxylic acid derivatives.[14] In the case of reactive acylating agents such as anhydrides and acid halides, the reaction proceeds in two steps: *O*-acylation of amidoxime and cyclization of the resulting ester; the rate of the second (rate-limiting) step strongly depends on the properties of the medium.[15]

The use of carboxylic acids requires special activation. Carbonyldiimidazole (CDI),[16,17] carbodiimides (DCC, EDC, DIC),[18—20] or alkyl chloroformates[21] are applied for this purpose. Carboxylic esters are also low-reactive; therefore, they would react in the presence of strong bases such as sodium hydride or alkoxides.[22,23] Only a few examples of the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles without the use of activating agents are known, when the reaction was carried out under extremely severe conditions.[24,25]

Earlier,[26] we have reported on the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and nitriles under ultrahigh-pressure conditions. In this work, we extended this approach to low-reactive carboxylic acids and their esters. First, we studied the reaction of a model benzamidoxime (**1a**) and acetic acid (Scheme 1, Table 1).

Scheme 1



R = H (**a**), NO_2 (**b**), OMe (**c**)

When the reaction was carried using the excess of acetic acid as a solvent, the reaction mass underwent crystallization due to a high pressure within the system (see Table 1, Run *1*). Crystallization was prevented by heating to 140 °C (see Table 1, Run *2*), which caused partial resinification and, as a consequence, a decrease in the yield of the target product. Besides the expected compound **2a**, 3,5-diphenyl-1,2,4-oxadiazole (**3a**) was isolated, the formation of which can be explained by dimerization of benzamidoxime **1a**.[27]

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Table 1. Reaction of amidoximes with carboxylic acids (10 kbar, amidoxime : acid = 1 : 3)

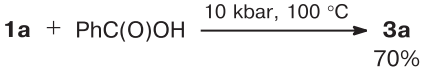
Run	Starting amidoxime	Acid	Solvent	*T*/°C	*t*/h	Products (yield (%))
1	**1a**	AcOH	AcOH	110	6	—
2	**1a**	AcOH	AcOH	140	6	**2a** (39), **3a** (11)
3	**1a**	AcOH	CH_2Cl_2	70	6	**2a** (5)
4	**1a**	AcOH	CH_2Cl_2	70	9	**2a** (10)
5	**1a**	AcOH	CH_2Cl_2	80	6	**2a** (35), **3a** (9)
6	**1a**	AcOH	CH_2Cl_2	90	6	**2a** (44), **3a** (15)
7	**1a**	AcOH	CH_2Cl_2	100	6	**2a** (52), **3a** (18)
8	**1a**	AcOH	THF	100	6	**2a** (51), **3a** (18)
9	**1b**	AcOH	THF	100	6	**2b** (54), **3b** (20)
10	**1c**	AcOH	THF	100	6	**2c** (61), **3c** (17)
11	**1a**	PhC(O)OH	THF	100	6	**3a** (70)
12	**4**	PhC(O)OH	CH_2Cl_2	100	6	**5a** (58)
13	**4**	$4\text{-}O_2NC_6H_4C(O)OH$	CH_2Cl_2	100	6	**5b** (56)
14	**4**	$3\text{-}F_3CC_6H_4C(O)OH$	CH_2Cl_2	100	6	**5c** (52)

The replacement of a portion of acetic acid with dichloromethane as a solvent allowed us to decrease the temperature to 70—100 °C (see Table 1, Runs *3—7*). At 70 °C, the yield of the target product **2a** did not exceed 10% even within 9 h; however, no dimer **3a** was observed. The most complete transformation of amidoxime **1a** into the target product **2a** was achieved at 100 °C, but dimer **3a** was produced in slight amounts along with compound **2a**. It should be noted that these compounds are easily separated by crystallization from ethanol.

Next, we performed the reaction of substituted benzamidoximes **1b,c** (see Scheme 1 and Table 1, Runs *9* and *10*). Due to their poor solubilities in dichloromethane, the reaction was carried out in THF. Higher yields of compounds **2b,c** are thought to be due to the fact that amidoximes containing electron-withdrawing substituents are less prone to condensation to form dimers **3b**,**c**.

Besides acetic acid, the reaction of benzamidoxime **1a** with benzoic acid was studied (Scheme 2), which gave compound **3a** as a single product.

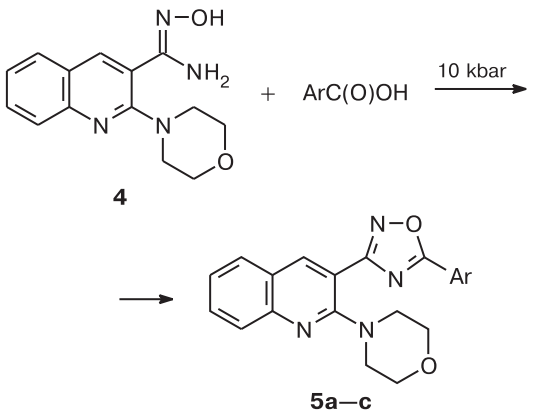
Scheme 2



Similarly, the reaction of amidoxime **4** with carboxylic acids affords smoothly 1,2,4-oxadiazoles **5a—c** possessing high fungicidal activity[13] (Scheme 3; see Table 1, Runs *12—14*).

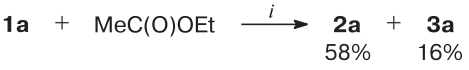
Benzamidoxime **1a** was also studied for the reaction with ethyl acetate acting as both a reagent and a solvent (Scheme 4). The reaction was carried out at 100 °C. The outcome was analogous to that in the case of acetic acid.

Scheme 3



Ar = Ph (**a**), $4\text{-}O_2NC_6H_4$ (**b**), $3\text{-}F_3CC_6H_4$ (**c**)

Scheme 4



i. 10 kbar, 100 °C, 6 h.

To finalize, we showed that 1,2,4-oxadiazoles could be synthesized from amidoximes and carboxylic acids or their esters under high-pressure conditions (10 kbar) without the use of additional reagents and catalysts.

Experimental

All experiments were carried out under high pressure on a Barostat machine[28] allowing one to perform reactions under pressures up to 18 kbar (1800 MPa) and at temperatures up to

350 °C. The ^{1}H and ^{13}C NMR spectra for solutions of analyzed compounds in DMSO-d_6 were recorded on a Bruker DRX-500 instrument. Electron impact mass spectra were recorded on a GC/MS Perkin—Elmer Clarus 500 instrument. High-resolution mass spectra (ESI) were obtained on a Bruker micrOTOF II instrument. The measurements were performed in a positive-ion mode (the capillary voltage was 4500 V), the m/z range was from 50 to 300 Da, external and internal calibration (Electrospray Calibrant Solution, Fluka). Solutions of samples were injected *via* a syringe, the flow rate was 3 μL min^{-1}, the nebulizer gas was nitrogen (4 L min^{-1}), and the interface temperature was 180 °C. The starting amidoximes **1a—c** were synthesized from commercially available nitriles (Sigma—Aldrich Co.) according to known procedures.[29] Amidoxime **4** was prepared as described in Ref. 13.

Reaction of amidoximes with carboxylic acids (general procedure). A solution of amidoxime (2.2 mmol) and carboxylic acid (6.6 mmol) in the corresponding solvent (see Table 1) was prepared in a 1.5-mL Teflon tube and the tube was placed in a high-pressure unit. The unit with plungers and sealings inserted thereto and a furnace place thereon was mounted in the Barostat machine. The reaction mixture was kept under specified conditions. The unit was cooled and the reaction mixture was removed from the unit and diluted with dichloromethane until a volume of 15 mL. The resulting solution was washed with an aqueous solution of sodium bicarbonate (10 mL) and water (10 mL), dried with sodium sulfate, and the solvent was removed under reduced pressure. Further purification was performed by column chromatography (SiO_2, ethyl acetate—hexane, 1 : 4) or recrystallization from ethanol.

Reaction of benzamidoxime (1a) with ethyl acetate. A solution of benzamidoxime (**1a**) (0.3 g, 2.2 mmol) in ethyl acetate was prepared in a 1.5-mL Teflon tube and the tube was placed in a high-pressure unit. The unit with plungers and sealings inserted thereto and a furnace placed thereon was mounted in the Barostat machine. The reaction mixture was kept for 6 h at 10 kbar and 100 °C. After the experiment has been completed, the unit was cooled, the reaction mixture was removed from the unit, and the excess of ethyl acetate was evaporated under reduced pressure. Further purification was performed by column chromatography (SiO_2, ethyl acetate—hexane, 1 : 4) or recrystallization from ethanol.

5-Methyl-3-phenyl-1,2,4-oxadiazole (2a). M.p. 43—44 °C (*cf.* Ref. 26: m.p. 43—44 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 2.65 (s, 3 H, CH_3); 7.55—7.61 (m, 3 H, H arom.); 8.01 (d, 2 H, H arom., J = 7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 12.0, 126.4, 126.9, 129.2, 131.4, 167.6, 177.4. MS (EI, 70 eV), m/z (I_{rel} (%)): 160 [M$^+$] (89), 119 (100), 103 (11), 91 (86), 89 (12), 77 (23), 76 (18), 64 (43), 63 (29), 51 (25).

5-Methyl-3-(4-nitrophenyl)-1,2,4-oxadiazole (2b). M.p. 142—143 °C (*cf.* Ref. 26: m.p. 142—143 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 2.72 (s, 3 H, CH_3); 8.23, 8.38 (both d, 2 H each, H arom., J = 8.7 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 12.1, 124.4, 128.3, 132.1, 149.1, 166.4, 178.3. MS (EI, 70 eV), m/z (I_{rel} (%)): 205 [M$^+$] (100), 175 (36), 164 (79), 159 (8), 147 (10), 134 (48), 117 (15), 106 (39), 90 (19), 88 (48), 87 (8), 76 (19), 75 (17), 62 (21), 51 (16).

3-(4-Methoxyphenyl)-5-methyl-1,2,4-oxadiazole (2c). M.p. 58—59 °C (*cf.* Ref. 26: m.p. 58—59 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 2.64, 3.84 (both s, 3 H each, CH_3); 7.10, 7.94 (both d, 2 H each, H arom., J = 8.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 12.0, 55.4, 114.6, 118.7, 128.6, 161.6, 167.3, 177.1. MS (EI, 70 eV), m/z (I_{rel} (%)): 190 [M$^+$] (100), 149 (87), 134 (24), 133 (23), 119 (8), 106 (56), 103 (7), 91 (14), 90 (9), 78 (18), 76 (18), 63 (14), 50 (12).

3,5-Diphenyl-1,2,4-oxadiazole (3a). M.p. 109—110 °C (*cf.* Ref. 26: m.p. 109—110 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.63, 7.68, 7.75 (all t, 2 H each, H arom., J = 7.5 Hz); 8.11 (d, 2 H, H arom., J = 8.0 Hz); 8.20 (d, 2 H, H arom., J = 8.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 123.4, 126.2, 127.1, 127.9, 129.3, 129.6, 131.6, 133.4, 168.3, 175.5. MS (EI, 70 eV), m/z (I_{rel} (%)): 222 [M$^+$] (56), 119 (100), 111 (5), 105 (6), 96 (7), 91 (23), 77 (23), 64 (18), 51 (18).

3,5-Bis(4-nitrophenyl)-1,2,4-oxadiazole (3b). M.p. 235—236 °C (*cf.* Ref. 30: m.p. 233—235 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 8.29 (d, 2 H, H arom., J = 8.8 Hz); 8.38—8.51 (m, 4 H, H arom.); 8.43 (d, 2 H, H arom., J = 9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 124.5, 124.6, 128.3, 128.5, 129.5, 131.4, 149.3, 150.1, 167.2, 174.4. MS (EI, 70 eV), m/z (I_{rel} (%)): 312 [M$^+$] (24), 282 (4), 164 (20), 150 (7), 134 (15), 116 (9), 105 (12), 104 (13), 102 (11), 90 (7), 88 (14), 76 (38), 62 (14), 50 (20) 30 (100).

3,5-Bis(4-methoxyphenyl)-1,2,4-oxadiazole (3c). M.p. 126—127 °C (*cf.* Ref. 31: m.p. 126—127 °C). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 3.86, 3.88 (both s, 3 H each, CH_3); 7.12, 8.01 (both d, 2 H each, H arom., J = 8.6 Hz); 7.18, 8.10 (both d, 2 H each, H arom., J = 8.7 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ: 55.4, 55.6, 114.6, 114.9, 115.9, 118.6, 128.8, 129.9, 161.7, 163.0, 167.8, 175.0. MS (EI, 70 eV), m/z (I_{rel} (%)): 282 [M$^+$] (100), 149 (6), 134 (6), 133 (7), 119 (6), 106 (6), 92 (5), 76 (8), 63 (8), 50 (6).

3-(2-Morpholinoquinolin-3-yl)-5-phenyl-1,2,4-oxadiazole (5a). M.p. 210—212 °C (*cf.* Ref. 13: m.p. 210—212 °C). ^{1}H NMR ($CDCl_3$), δ: 3.51—3.54 (m, 4 H, CH_2NCH_2); 3.87—3.91 (m, 4 H, CH_2OCH_2); 7.36—7.51 (m, 4 H, H arom.); 7.68—7.93 (m, 3 H, H arom.); 8.01—8.11 (m, 3 H, H arom.). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 50.3, 66.1, 113.8, 123.7, 124.0, 124.8, 127.0, 128.3, 129.0, 130.1, 131.8, 134.0, 142.2, 147.6, 157.5, 168.7, 175.3. HRMS, found: m/z 359.1527 [M + H]$^+$. Calculated for $C_{21}H_{18}N_4O_2$: M + H = 359.1502.

3-(2-Morpholinoquinolin-3-yl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (5b). M.p. 285—287 °C (*cf.* Ref. 13: m.p. 285—287 °C). ^{1}H NMR ($CDCl_3$), δ: 3.50—3.55 (m, 4 H, CH_2NCH_2); 3.88—3.93 (m, 4 H, CH_2OCH_2); 7.39—7.52 (m, 4 H, H arom.); 7.67—8.13 (m, 5 H, H arom.). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 50.0, 66.2, 113.3, 123.9, 125.1, 125.3, 127.2, 129.0, 130.1, 132.0, 142.4, 147.5, 150.4, 151.0, 157.2, 168.8, 174.0. HRMS, found: m/z 404.1375 [M + H]$^+$. Calculated for $C_{21}H_{17}N_5O_4$: M + H = 404.1353.

3-(2-Morpholinoquinolin-3-yl)-5-(3-trifluoromethylphenyl)-1,2,4-oxadiazole (5c). M.p. 245—247 °C (*cf.* Ref. 13: m.p. 245—247 °C). ^{1}H NMR ($CDCl_3$), δ: 3.45—3.54 (m, 4 H, CH_2NCH_2); 3.86—3.91 (m, 4 H, CH_2OCH_2); 7.41—7.53 (m, 4 H, H arom.); 7.69—8.22 (m, 5 H, H arom.). HRMS, found: m/z 427.1307 [M + H]$^+$. Calculated for $C_{22}H_{17}F_3N_4O_2$: M + H = = 427.1382.

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