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Some Regularities of the Synthesis of Ethyl 3-Aryl-1,2,4-oxadiazole-5-carboxylates

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Abstract—Features of amidoximes reactions with ethyl chlorooxalate in a wide range of solvents at the use of a number of bases were investigated. An efficient preparation method for ethyl 3-aryl-1,2,4-oxadiazole-5-carboxylates in acetonitrile in the presence of triethylamine was developed.

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Among the numerous specimens of 3,5-disubstituted 1,2,4-oxadiazoles are the 1,2,4-oxadiazoles containing functional groups as substituents [1]. Thus alkyl 1,2,4-oxadiazole-5-carboxylates are precursors in the synthesis of many practically important structures, for instance, exhibiting pesticidal [2, 3], antithrombotic [4] properties. They underlie the synthesis of efficient inhibitors of kinase-3 glycogensynthese (GSK-3) [5], sirtuins of types I and II (SIRT1, SIRT2) [6], and hydrolase of fatty acids amides [7], and also of a series of reverse agonists of benzodiazepine receptors [8].

Commonly ethyl 3-aryl-1,2,4-oxadiazole-5-carboxylates **III** are obtained from amidoximes **I** and ethyl chlorooxalate (**II**) in weakly polar solvents [1, 9]. This method is characterized by a long reaction time, and the yields of the target products vary in a wide range. On the other hand, we formerly have demonstrated that the polarity and pH of the environment essentially affect the formation of the 1,2,4-oxadiazole ring [10].

Aiming at the modification of the existing method we investigated the reactions of amidoximes and ethyl chlorooxalate in a wide set of solvents either possessing strong polarity or capable of specific solvation. The results obtained in reaction carried out in pyridine are comprehensively described in [11]. In this paper the data are presented on the features of the reaction

Scheme.

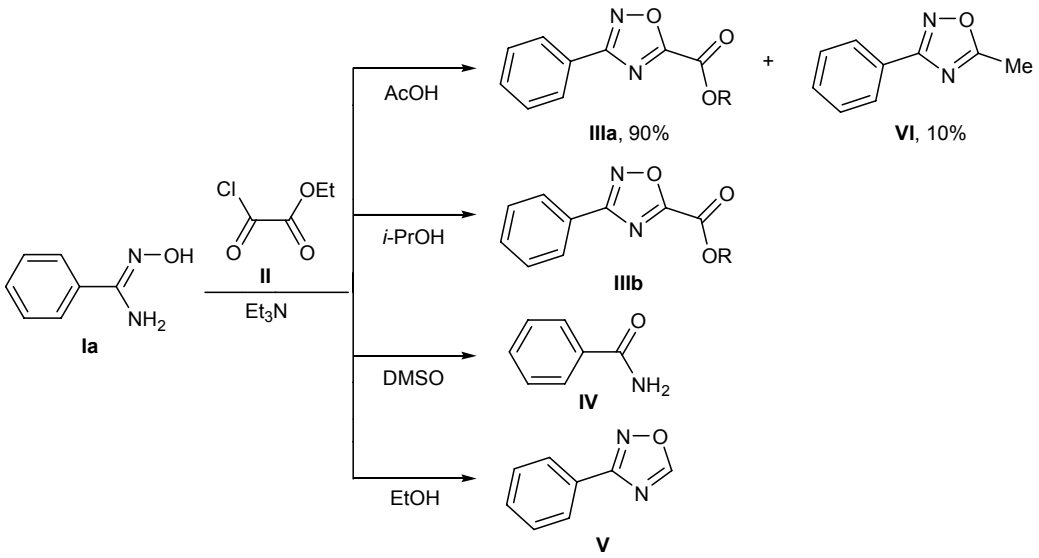


Table 1. Synthesis conditions and the yield of ester **IIIa** (molar ratio (**Ia**)–(**II**)–base 1 : 1.3 : 1.5, 3 h)

Solvent	Base	Temperature, °C	Yield, %
DMF	Et_3N	100	42
t-BuOH	Et_3N	80	38
t-BuOH	Py	80	39
t-BuOH	$NaHCO_3$	80	88
MeCN	Et_3N	80	78
MeCN	Py	80	75
MeCN	$NaHCO_3$	80	63
1,4-dioxane	Et_3N	100	63
1,4-dioxane	Py	100	50
1,4-dioxane	$NaHCO_3$	100	75
Me_2CO	Et_3N	56	63
Me_2CO	Py	56	81
Me_2CO	$NaHCO_3$	56	50

occurring in acetic acid, acetone, acetonitrile, 1,4-dioxane, ethanol, 2-propanol, and *tert*-butanol, DMF, DMSO.

As the model reaction we have chosen that with benzamidoxime (**Ia**) with ethyl chlorooxalate in the presence of Et_3N (see the scheme).

The main reaction product in DMSO in the presence of Et_3N was benzamide (**IV**). The target ester **IIIa** was detected in trace quantity. The heating of ester **IIIa** in DMSO in the presence of Et_3N led to the formation of unsubstituted 5-phenyl-1,2,4-oxadiazole (**V**). Compound **V** is unstable in basic media (pK_a of Et_3N^+H in DMSO is 9.0 [12]) and decomposes liberating benzonitrile [13] that further suffers hydrolysis into the amide of benzoic acid (**IV**). In the absence of a base the heating of ester **IIIa** in DMSO did not result in decomposition.

Table 2. Yields of oxadiazoles **IIIc–IIIj** (acetonitrile, 80°C, amidoxime–ethyl chlorooxalate–Et_3N 1 : 1.3 : 1.5, 3 h)

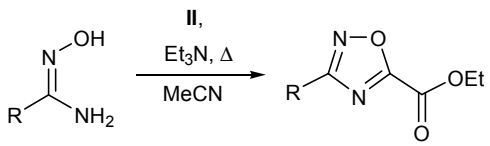
Compound no.	R	Yield, %
IIIc	4-Py	74
IIId	4-MeC_6H_4	91
IIIe	4-$NO_2C_6H_4$	86
IIIf	4-$MeOC_6H_4$	90
IIIg	4-ClC_6H_4	91
IIIh	4-BrC_6H_4	94
IIIi	4-$MeOC_6H_4CH_2$	73
IIIj	3,4-$(MeO)_2C_6H_3$	85

In ethanol the main reaction product was compound **V**, in 2-propanol it was isopropyl ester **IIIb** (see the scheme). Its formation evidently results from transesterification catalyzed with Et_3N.

In acetic acid at 100°C alongside the target ester **IIIa** formed 5-methyl-3-phenyl-1,2,4-oxadiazole (**VI**). The products ratio according to ^1H NMR data was 9 : 1. The decrease in the temperature to 80°C did not affect the products ratio. At the use of sodium acetate instead of Et_3N the reaction products were obtained in the same ratio. The formation of 1,2,4-oxadiazole (**VI**) may be ascribed to the reaction between the amidoxime and a mixed anhydride obtained by the reaction of ethyl chlorooxalate with acetic acid or its salt.

The reaction in acetone, acetonitrile, DMF, and 1,4-dioxane afforded a single product: the target ester **IIIa**. Besides Et_3N pyridine and sodium hydrogen carbonate were also used as bases (Table 1).

It is evident from the above findings that quite a number of polar solvents and various bases are suitable for the synthesis of ethyl 1,2,4-oxadiazole-5-carboxylate. Since the most practically important compounds are amides and hydrazides of 1,2,4-oxadiazole-5-carboxylic acids, we have taken into account in the choice of the best system its suitability for performing a one-pot synthesis of these compounds. Therefore in the preparation of esters **IIIc–IIIj** we used acetonitrile and Et_3N (Table 2).



IIIc-IIIj

Thus as a result of the study of conditions of the reaction between amidoximes and ethyl chlorooxalate a method was developed of synthesis in a high yield of various ethyl 3-aryl-1,2,4-oxadiazole-5-carboxylates.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Perkin Elmer Spektrum RX-1 from mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker MSL (300 MHz) in DMSO-d_6, internal reference TMS. Mass spectra were measured

on an instrument GC/MS Perkin Elmer Clarus 500, quadrupole mass detector, EI, 70 eV. Elemental analysis was carried out on a Perkin Elmer 2400, Series II analyzer.

The solvents and auxiliary substances were prepared by procedures [14, 15].

Condensation of benzamidoxime (I) with ethyl chlorooxalate (II) in diverse solvents. In 5 mL of solvent was charged at stirring 0.2 g (1.6 mmol) of amidoxime, 2.4 mmol of a base was added. The mixture was cooled to 0–10°C and at maintaining this temperature 0.2 mL (2 mmol) of ethyl chlorooxalate was added. Then the reaction mixture was stirred at room temperature for 30 min, further the mixture was heated to the desired temperature and maintained at it for 3 h. Afterwards it was cooled, diluted with cold water, and extracted with chloroform (3 × 4 mL), the extract was evaporated at a reduced pressure.

Ethyl 3-aryl-1,2,4-oxadiazole-5-carboxylates (III). In 5 mL of acetonitrile was dissolved at stirring 2 mmol of amidoxime and 3 mmol of triethylamine was added. The mixture was cooled to 0–10°C and at maintaining this temperature 2.2 mmol ethyl chlorooxalate was added. Then the reaction mixture was stirred at room temperature for 30 min, boiled for 3 h, cooled, poured into cold water, and worked up according to the general procedure.

Ethyl 3-phenyl-1,2,4-oxadiazole-5-carboxylate (IIIa). White powder, mp 51–52°C (54–55°C [16]). IR spectrum, ν, cm^{-1}: 1742 (C=O), 1561 (C–C_{Ar}), 1189 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, *J* 7.1 Hz), 4.48 d.d (2H, CH_2, *J* 7.1 Hz), 7.63 m (3H, 3CH), 8.07 m (2H, 2CH). ^{13}C NMR spectrum, δ, ppm: 14.2, 63.7, 125.7, 127.5, 129.8, 132.5, 154.1, 167.3, 168.9. Mass spectrum, *m/z* (I_{rel}, %): 218 (70) $[M]^+$, 190 (10), 173 (3), 145 (5), 119 (100), 103 (33), 91 (30), 89 (6), 77 (27), 76 (13), 64 (14), 51 (19). $C_{11}H_{10}N_2O_3$. M_{calc} 218.21.

Isopropyl 3-phenyl-1,2,4-oxadiazole-5-carboxylate (IIIb). White powder, mp 51–52°C. ^{1}H NMR spectrum, δ, ppm: 1.42 t (6H, $2CH_3$, *J* 6.3 Hz), 5.26–5.31 m (1H, CH), 7.55–7.59 m (3H, 3CH), 8.07 d (2H, 2CH, *J* 6.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 232 (98) $[M]^+$, 190 (99), 173 (5), 145 (52), 130 (4), 119 (100), 103 (47), 91 (20), 77 (55), 76 (18), 64 (10), 51 (30). Found, %: C 62.29; H 5.02; N 11.42. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.06; H 5.21; N 12.06. *M* 232.24

Ethyl 3-(4-pyridyl)-1,2,4-oxadiazole-5-carboxylate (IIIc). Yield 74%, light yellow powder, mp 93–94°C (92–94°C [5]). IR spectrum, ν, cm^{-1}: 1749 (C=O), 1567 (C–C_{Ar}), 1193 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_3, *J* 7.0 Hz), 4.48 m (2H, CH_2), 7.99 d (2H, 2CH, *J* 5.9 Hz), 8.84 d (2H, 2CH, *J* 5.9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 219 (65) $[M]^+$, 191 (15), 174 (5), 146 (7), 120 (100), 104 (31), 92 (39), 90 (23), 78 (25). $C_{10}H_{19}N_3O_3$. M_{calc} 219.20.

Ethyl 3-(4-methylphenyl)-1,2,4-oxadiazole-5-carboxylate (IIId). Yield 91%, white powder, mp 61–62°C. IR spectrum, ν, cm^{-1}: 1751 (C=O), 1559 (C–C_{Ar}), 1183 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3, *J* 7.1 Hz), 2.41 s (3H, CH_3), 4.47 m (2H, CH_2), 7.37 d (2H, 2CH, *J* 8.1 Hz), 7.94 d (2H, 2CH, *J* 8.1 Hz). Mass spectrum, *m/z* (I_{rel}, %): 232 (100) $[M]^+$, 204 (10), 159 (10), 133 (100), 117 (20), 91 (30). Found, %: C 62.15; H 5.11; N 11.37. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.06; H 5.21; N 12.06. *M* 232.24.

Ethyl 3-(4-nitrophenyl)-1,2,4-oxadiazole-5-carboxylate (IIIe). Yield 86%, light yellow powder, mp 113–114°C (118–120°C [17]). IR spectrum, ν, cm^{-1}: 1745 (C=O), 1579 (C–C_{Ar}), 1528 (NO_2), 1295 (C–O). ^{1}H NMR spectrum, δ, ppm: 1.43 t (3H, CH_3, *J* 7.2 Hz), 4.50 m (2H, CH_2), 8.33 d (2H, 2CH, *J* 8.9 Hz), 8.42 d (2H, 2CH, *J* 8.6 Hz). Mass spectrum, *m/z* (I_{rel}, %): 263 (100) $[M]^+$, 235 (20), 164 (45), 134 (40). $C_{11}H_9N_3O_5$. M_{calc} 263.21.

Ethyl 3-(4-methoxyphenyl)-1,2,4-oxadiazole-5-carboxylate (IIIf). Yield 90%, white powder, mp 63–64°C. IR spectrum, ν, cm^{-1}: 1752 (C=O), 1564 (C–C_{Ar}), 1179 (C–O), 1029 (OCH_3). ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, *J* 7.1 Hz), 3.86 s (3H, CH_3), 4.47 m (2H, CH_2), 7.14 d (2H, 2CH, *J* 8.9 Hz), 8.00 d (2H, 2CH, *J* 8.6 Hz). Mass spectrum, *m/z* (I_{rel}, %): 248 (100) $[M]^+$, 220 (20), 203 (2), 175 (5), 149 (40), 133 (50), 106 (22). Found, %: C 58.34; H 4.67; N 11.09. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.87; N 11.28. *M* 248.24.

Ethyl 3-(4-chlorophenyl)-1,2,4-oxadiazole-5-carboxylate (IIIg). Yield 91%, white powder, mp 69–70°C. IR spectrum, ν, cm^{-1}: 1747 (C=O), 1555 (C–C_{Ar}), 1181 (C–O), 745 (Cl). ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3, *J* 7.0 Hz), 4.48 m (2H, CH_2), 7.61 d (2H, 2CH, *J* 8.4 Hz), 8.05 d (2H, 2CH, *J* 8.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 252 (100) $[M]^+$, 224 (9), 207 (7), 179 (12), 153 (100), 137 (20). Found, %: C 52.49; H 3.44; N 10.71. $C_{11}H_9ClN_2O_3$. Calculated, %: C 52.29; H 3.59; N 11.09. *M* 252.66.

Ethyl 3-(4-bromophenyl)-1,2,4-oxadiazole-5-carboxylate (IIIh). Yield 94%, white powder, mp 84–85°C. IR spectrum, ν, cm^{-1}: 1753 (C=O), 1569 (C–C_{Ar}), 1188 (C–O), 667 (Br). ^{1}H NMR spectrum, δ, ppm: 1.35 t

(3H, CH_3, *J* 7.2 Hz), 4.44 m (2H, CH_2), 7.77 d (2H, 2CH, *J* 8.6 Hz), 7.96 d (2H, 2CH, *J* 8.5 Hz). Mass spectrum, *m/z* (I_{rel}, %): 296 (100) $[M]^+$, 269 (13), 250 (2), 196 (85), 182 (23), 168 (10), 154 (13). Found, %: C 44.75; H 2.97; N 9.53. $C_{11}H_9BrN_2O_3$. Calculated, %: C 44.47; H 3.05; N 9.73. *M* 297.11.

Ethyl 3-(4-methoxybenzyl)-1,2,4-oxadiazole-5-carboxylate (IIIi). Yield 73%, white powder, mp 55–56°C. IR spectrum, ν, cm^{-1}: 1757 (C=O), 1551 (C–C_{Ar}), 1185 (C–O), 1034 (OCH_3). ^1H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, *J* 7.1 Hz), 3.86 s (2H, CH_2), 4.47 m (2H, CH_2), 7.14 d (2H, 2CH, *J* 8.9 Hz), 8.00 d (2H, 2CH, *J* 8.6 Hz). Mass spectrum, *m/z* (I_{rel}, %): 262 (100) $[M]^+$, 234 (3), 217 (2), 189 (20), 174 (12), 162 (41), 161 (100), 147 (43), 134 (28), 121 (81), 107 (9), 91 (18), 78 (25), 77 (37), 63 (9). Found, %: C 59.83; H 5.31; N 10.48. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68. *M* 262.27.

Ethyl 3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole-5-carboxylate (IIIj). Yield 85%, white powder, mp 94–95°C. IR spectrum, ν, cm^{-1}: 1755 (C=O), 1608 (C–C_{Ar}), 1183 (C–O), 1023 (OCH_3). ^1H NMR spectrum, δ, ppm: 1.42 t (3H, CH_3, *J* 7.1 Hz), 3.86 s (3H, CH_3), 3.87 s (3H, CH_3), 4.48 m (2H, CH_2), 7.10 d (2H, 2CH, *J* 8.2 Hz), 7.64 d (2H, 2CH, *J* 8.2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 278 (100) $[M]^+$, 250 (8), 233 (10), 205 (16), 179 (34), 163 (21). Found, %: C 56.34; H 4.97; N 9.86. $C_{13}H_{14}N_2O_5$. Calculated, %: C 56.11; H 5.07; N 10.07. *M* 278.27.

Benzamide (IV), mp 127–129°C (125–128°C [18]). Mass spectrum, *m/z* (I_{rel}, %): 121 (71) $[M]^+$, 114 (3), 106 (7), 105 (100), 103 (4), 83 (3), 78 (10), 77 (90), 74 (11), 52 (8), 51 (45), 50 (23). C_7H_7NO. M_{calc} 121.14.

3-Phenyl-1,2,4-oxadiazole (V), mp 15–16°C (15°C [19]). ^1H NMR spectrum, δ, ppm: 7.63 m (3H, 3CH), 8.31 m (2H, 2CH), 9.10 s (1H, CH). Mass spectrum, *m/z* (I_{rel}, %): 146 (100) $[M]^+$, 119 (88), 103 (25), 91 (39), 89 (15), 77 (12), 63 (25), 51 (18). $C_8H_6N_2O$. M_{calc} 146.15.

5-Methyl-3-phenyl-1,2,4-oxadiazole (VI). White powder, mp 43–44°C (41–42°C [20]). IR spectrum, ν, cm^{-1}: 1573 (C–C_{Ar}). ^1H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 7.55–7.61 m (3H, 3CH), 8.01 d (2H, 2CH, *J* 7.9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 160 (89) $[M]^+$, 119 (100), 103 (11), 91 (86), 89 (12), 77 (23), 76 (18), 64 (43), 63 (29), 51 (25). $C_9H_8N_2O$. M_{calc} 160.18.

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