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Mendeleev Commun., 2016, **26**, 264–265
Mendeleev Communications

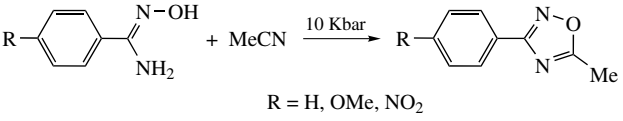
Reaction of amidoximes with acetonitrile at high pressure

Sergey V. Baykov,[a] Aleksey A. Zharov,[b] Galina A. Stashina,[b] Igor V. Zavarzin*[b] and Evgeniy R. Kofanov[c]

[a] *K. D. Ushinsky Yaroslavl State Pedagogical University, 150000 Yaroslavl, Russian Federation. E-mail: sergei.v.baikov@yandex.ru*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: zavi@ioc.ac.ru*
[c] *Yaroslavl State Technical University, 150023 Yaroslavl, Russian Federation*

DOI: 10.1016/j.mencom.2016.05.015

Reaction of amidoximes with acetonitrile giving 1,2,4-oxadiazoles occurs at 80–100 °C under a pressure of 10 Kbar without catalysts.

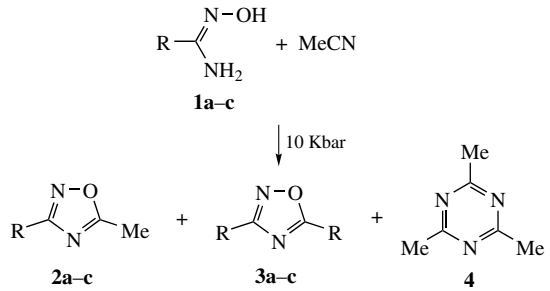


The reaction of nitriles with amidoximes affording 1,2,4-oxadiazoles under rigid conditions (at 180 °C) in low yields has first been described in 1986.[1] The yield can be increased and the temperature of the process can be decreased with the use of $ZnCl_2$/HCl system as the catalyst.[2–4] The TsOH/$ZnCl_2$ system in DMF allows one to carry out the reaction under mild conditions and achieve good yields.[5]

It is known that cycloaddition reactions are successfully intensified using high and superhigh pressures.[6] An advantage of this approach is a decrease in the reaction temperature, which is especially important for thermolabile compounds, including amidoximes.

We assumed that execution of the reaction between amidoximes and nitriles under fairly high pressure would allow one to diminish temperature and avoid the use of catalysts and additional reagents. Herein we studied the reaction of amidoximes **1a–c** with acetonitrile under a pressure of 10 Kbar (Scheme 1). Acetonitrile (excess) was used as a solvent and a reactant. The yield of the corresponding 1,2,4-oxadiazoles **2a–c** was found to be dependent on the temperature, being 36–68%.† The yield of side products **3a–c** resulting from dimerization of amidoximes **1a–c** was not higher than 20% (Table 1). These data show that the nature of substituents in the benzene ring slightly affects the formation of 1,2,4-oxadiazoles.

In addition to 1,2,4-oxadiazoles **2** and **3**, the formation of 1,3,5-trimethyltriazine **4** was detected in all cases, whose yields were about 26%.



Scheme 1

Table 1 Results of the reaction of amidoximes **1a–c** (concentration 1.47 mmol cm^{-3}) with acetonitrile under a pressure of 10 Kbar.

Entry	Starting amidoxime	*T*/°C	*t*/h	Yield (%)	
				2	**3**
1	**1a**	70	6	5	trace
2	**1a**	70	9	10	trace
3	**1a**	80	6	36	9
4	**1a**	90	6	43	11
5	**1a**	100	6	53	19
6	**1b**	100	6	61	20
7	**1c**	100	6	68	20

In conclusion, we showed for the first time that amidoximes can react with poorly reactive acetonitrile to afford the corresponding 1,2,4-oxadiazoles in moderate yields at relatively low temperatures and high pressures.

† *General procedure for the reaction at high pressure.* The Barostat type[7] setup suitable for studies at pressures below 15 Kbar was used in this work. A solution of amidoxime **1a** (300 mg, 2.2 mmol) in acetonitrile was prepared in a fluoroplastic 1.5 cm^3 tube. The tube was placed in a high-pressure block. The block with inserted plungers, compactions, and a heater was mounted in a barostat. The pressure in the system was raised to 10 Kbar. The reaction mixture was kept under specified conditions (see Table 1). After the end of the experiment, the block was cooled down, the pressure was decreased to atmospheric, and the reaction mixture was removed from the block. The volatiles were evaporated under reduced pressure, the residue was subjected to column chromatography (SiO_2, ethyl acetate–hexane, 1:4) or crystallization from ethanol or hexane.

5-Methyl-3-phenyl-1,2,4-oxadiazole **2a**. Yield 53%, mp 43–44 °C (lit.,[8] 40–41 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.65 (s, 3H, Me), 7.55–7.61 (m, 3H, Ar), 8.01 (d, 2H, Ar, *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), *m*/*z*: 160 (M$^+$, 89), 119 (100), 103 (11), 91 (86), 89 (12), 77 (23), 76 (18), 64 (43), 63 (29), 51 (25).

3-(4-Methoxyphenyl)-5-methyl-1,2,4-oxadiazole **2b**. Yield 61%, mp 58–59 °C (lit.,[9] 58–59 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.64 (s, 3H, Me), 3.84 (s, 3H, OMe), 7.10 (d, 2H, Ar, *J* 8.5 Hz), 7.94 (d, 2H, Ar, *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), *m*/*z*: 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).

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5-Methyl-3-(4-nitrophenyl)-1,2,4-oxadiazole **2c**. Yield 68%, mp 142–143 °C (lit.,[10] 143–145 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.72 (s, 3H, Me), 8.23 (d, 2H, Ar, *J* 8.7 Hz), 8.38 (d, 2H, Ar, *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), *m*/*z*: 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).

3,5-Diphenyl-1,2,4-oxadiazole **3a**. Yield 19%, mp 109–110 °C (lit.,[11] 103–105 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.63 (t, 2H, Ar, *J* 7.5 Hz), 7.68 (t, 2H, Ar, *J* 7.5 Hz), 7.75 (t, 2H, Ar, *J* 7.5 Hz), 8.11 (d, 2H, Ar, *J* 8.0 Hz), 8.20 (d, 2H, Ar, *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), *m*/*z*: 222 (M^+, 56), 119 (100), 111 (5), 105 (6), 96 (7), 91 (23), 77 (23), 64 (18), 51 (18).

3,5-Bis(4-methoxyphenyl)-1,2,4-oxadiazole **3b**. Yield 20%, mp 126–127 °C (lit.,[12] 126–128 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.12 (d, 2H, Ar, *J* 8.6 Hz), 7.18 (d, 2H, Ar, *J* 8.7 Hz), 8.01 (d, 2H, Ar, *J* 8.6 Hz), 8.10 (d, 2H, Ar, *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), *m*/*z*: 282 (M^+, 100), 149 (6), 134 (6), 133 (7), 119 (6), 106 (6), 92 (5), 76 (8), 63 (8), 50 (6).

3,5-Bis(4-nitrophenyl)-1,2,4-oxadiazole **3c**. Yield 20%, mp 235–236 °C (lit.,[13] 238–240 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.29 (d, 2H, Ar, *J* 8.8 Hz), 8.38–8.51 (m, 4H, Ar), 8.43 (d, 2H, Ar, *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), *m*/*z*: 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).

2,4,6-Trimethyl-1,3,5-triazine **4**. Yield 26%, mp 54–56 °C (lit.,[14] 54–56 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.43 (s, 9H, Me). MS (EI), *m*/*z*: 123 (M^+, 88), 103 (43), 96 (18), 85 (52), 83 (100), 76 (15), 67 (8), 66 (8), 47 (18).

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Received: 14th October 2015; Com. 15/4751