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CONDITIONS FOR THE HETEROCYCLIZATION OF O-AROYL-β-MORPHOLINOPROPIOAMIDE OXIMES TO 5-ARYL-3-(β-MORPHOLINO)ETHYL-1,2,4-OXADIAZOLES

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A search has been made for the conditions of heterocyclization of O-aroyl-β-morpholinopropioamide oximes to 5-aryl-3-(β-morpholino)ethyl-1,2,4-oxadiazoles. We have investigated the heating of the starting compounds above their melting point, at their melting point, and holding in polar solvents (DMSO and DMF). Heating the O-aroylamide oxime hydrochlorides in DMF appeared optimal.

Keywords: β-aminopropioamide oximes, O-aroyl-β-morpholinopropioamide oximes, 5-aryl-3-(β-morpholino)ethyl-1,2,4-oxadiazoles, slow inversion, ^{1}H NMR spectroscopy.

It has previously been found that the heterocyclization of O-benzoyl-β-piperidinopropioamide oxime base to 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole occurs readily over many hours when standing in DMSO [1].

The general nature of the discovered method of heterocyclization was confirmed by us in the case of the O-aroyl-β-morpholinopropioamide oximes **1-6** as reported in the study [2] and for their hydrochlorides **7-12**. Thus when measuring the ^{1}H NMR spectra of the bases **1-6** in DMSO-d_6 we observed their conversion to the 1,2,4-oxadiazoles **13-18**. After the O-aroylamide oximes were dissolved, their ^{1}H NMR spectra began to show signals for the 1,2,4-oxadiazoles and with time the intensity of these obscured those of the starting materials.

In a search for a preparative method of obtaining 1,2,4-oxadiazoles we started with a known heterocyclization method which included heating the O-aroylamide oximes at 10°C above their melting point [3]. Heating the bases **1-6** under these conditions led to their decomposition. However, we have found that the bases **1**, **3**, and **5** can be converted to the 1,2,4-oxadiazoles **13**, **15**, and **17** in 65, 69, and 63% yields respectively by holding them at their melting point for 20 s. An increased yield of the 1,2,4-oxadiazoles **13-18** can be achieved by stirring the O-aroylamide oximes **1-6** in DMF for 1 h at room temperature (Table 1). More convenient is to heat the O-aroylamide oxime hydrochlorides **7-12** in DMF at 80°C over 2-4 h to give the 5-aryl-3-(β-morpholino)ethyl-1,2,4-oxadiazole hydrochlorides **19-24**. This route is to be preferred still more because it eliminates the stage of conversion of the starting O-aroylamide oximes hydrochlorides to their bases which were used in the conditions reported above. It should also be noted that, for such a dehydration method, the 1,2,4-oxadiazoles with electron-acceptor substituents in the phenyl ring separate in the free base forms **16-18**. A significant factor in this case is evidently the lowered basicity of the nitrogen atom of the β-morpholino ring as a result of the negative inductive effect of the phenyl ring substituent.

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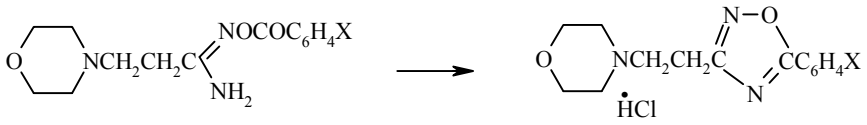

1–12 **13–24**

1, **7**, **13**, **19** X = *p*-MeO, **2**, **8**, **14**, **20** X = *p*-Me, **3**, **9**, **15**, **21** X = H, **4**, **10**, **16**, **22** X = *p*-Br, **5**, **11**, **17**, **23** X = *m*-Cl, **6**, **12**, **18**, **24** X = *p*-NO_2

TABLE 1. Physicochemical Data for Compounds **13-24**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	Cl (Br)	N		
13	$C_{15}H_{19}N_3O_3$	62.14 / 62.27	6.70 / 6.62		14.13 / 14.52	196	83
14	$C_{15}H_{19}N_3O_2$	66.44 / 65.91	6.83 / 7.01		14.86 / 15.37	194	85
15	$C_{14}H_{17}N_3O_2$	65.20 / 64.85	6.46 / 6.61		15.73 / 16.20	198	79
16	$C_{14}H_{16}BrN_3O_2$	49.28 / 49.72	5.02 / 4.77	(23.24) / (23.63)	12.23 / 12.42	193	81
17	$C_{14}H_{16}ClN_3O_2$	56.88 / 57.24	5.40 / 5.49	12.30 / 12.07	13.28 / 14.30	189	79
18	$C_{14}H_{16}N_4O_4$	55.33 / 55.26	5.30 / 5.30		18.86 / 18.41	197	91
19	$C_{15}H_{19}N_3O_3 \cdot HCl$	55.12 / 55.30	5.98 / 6.19	10.73 / 10.88	12.70 / 12.90	230	83
20	$C_{15}H_{19}N_3O_2 \cdot HCl$	58.52 / 58.16	6.24 / 6.51	11.38 / 11.44	14.00 / 13.56	246	87
21	$C_{14}H_{17}N_3O_2 \cdot HCl$	56.74 / 56.85	6.40 / 6.13	12.30 / 11.99	14.11 / 14.21	227	86
22	$C_{14}H_{16}BrN_3O_2 \cdot HCl$	44.34 / 44.88	5.02 / 4.57	9.18 / 9.46 (21.16) / (21.33)	10.90 / 11.22	244	78
23	$C_{14}H_{16}ClN_3O_2 \cdot HCl$	50.44 / 50.92	5.02 / 5.19	21.96 / 21.47	12.60 / 12.73	238	82
24	$C_{14}H_{16}N_4O_4 \cdot HCl$	49.34 / 49.34	5.09 / 5.03	9.94 / 10.40	16.30 / 16.44	255	86

TABLE 2. IR Spectra of Compounds **13-24**

Compound	ν (δ), cm^{-1}				
	$\nu_{C=N}$, δ_{N-H}, δ_{N^+-H}	$\nu_{C=C}$	ν_{C-O}, ν_{C-N}	ν_{N-O}	ν_{N^+-H}
13	1656	1600	1120	968	
14	1656	1610	1120	1078	
15	1660	1597	1120	970	
16	1670	1600	1130	1080	
17	1660	1600	1120	980	
18	1680	1610	1140	1080	
19	1660	1600	1310	1020	2400-2850
20	1660	1600	1120	1080	2400-2860
21	1665	1600	1125	1075	2400-2800
22	1660	1610	1250	950	2400-2850
23	1656	1590	1120	970	2400-2800
24	1670	1646	1120	1020	2400-2800

TABLE 3. ^{1}H NMR Spectra of Compounds **13-24** Recorded in DMSO-d_6

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)						
	$O(CH_2)_2$ (m, 4H)	$N(CH_2)_2$		α-CH_2 (t, 2H)	β-CH_2 (t, 2H)	N^+H	C_6H_4X
		ax. (δ 3.7, m, 2H)	eq. (δ 3.4, m, 2H)				
13	3.9	$^2J_{ae}$ = 12.6; $^3J_{aa}$ = 12.6; $^3J_{ae}$ = 3.3	$^2J_{ae}$ = 12.6; $^3J_{ae}$ = 3.3	3.2 (7.8)	3.9 (7.8)		3.7 (*p*-CH_3O); 6.8 (d, *J* = 8.7); 7.8 (d, *J* = 8.7)
14	3.9 m*	$^2J_{ae}$ = 14.1; $^3J_{aa}$ = 14.1; $^3J_{ae}$ = 4.2	$^2J_{ae}$ = 14.1; $^3J_{ae}$ = 4.2	3.2 (7.5)	3.9 m*		2.3 (*p*-CH_3); 7.0 (d, *J* = 7.8); 7.7 (d, *J* = 7.8)
15	3.9	$^2J_{ae}$ = 12.9; $^3J_{aa}$ = 12.9; $^3J_{ae}$ = 3.3	$^2J_{ae}$ = 12.9; $^3J_{ae}$ = 3.9	3.2 (8.1)	3.9 (8.1)		7.2-7.8 m
16	3.9	$^2J_{ae}$ = 12.6; $^3J_{aa}$ = 12.6; $^3J_{ae}$ = 4.3	$^2J_{ae}$ = 12.6; $^3J_{ae}$ = 4.3	3.2 (5.1)	4.0 (5.1)		7.7 (d, *J* = 8.7); 7.9 (d, *J* = 8.7)
17	3.9	$^2J_{ae}$ = 12.0; $^3J_{aa}$ = 9.3; $^3J_{ae}$ = 3.3	$^2J_{ae}$ = 12.0; $^3J_{ae}$ = 3.3	3.2 (7.8)	3.9 (7.8)		7.2-7.8 m
18	4.0	$^2J_{ae}$ = 12.4; $^3J_{aa}$ = 12.4; $^3J_{ae}$ = 4.3	$^2J_{ae}$ = 12.4; $^3J_{ae}$ = 4.3	3.2 (7.5)	4.0 (7.5)		8.3 (d, *J* = 8.1); 8.4 (d, *J* = 8.1)
19	3.9	$^2J_{ae}$ = 9.2; $^3J_{aa}$ = 9.2; $^3J_{ae}$ = 3.9	$^2J_{ae}$ = 9.2; $^3J_{ae}$ = 3.9	3.2 (7.8)	3.9 (7.8)	11.0	3.4 (*p*-CH_3O); 7.5 s
20	3.9	$^2J_{ae}$ = 12.9; $^3J_{aa}$ = 12.0; $^3J_{ae}$ = 3.3	$^2J_{ae}$ = 12.9; $^3J_{ae}$ = 3.3	3.2 (8.1)	4.0 (8.1)	10.6	3.5 (*p*-CH_3); 7.6 s
21	3.9	$^2J_{ae}$ = 8.7; $^3J_{aa}$ = 8.7; $^3J_{ae}$ = 4.2	$^2J_{ae}$ = 8.7; $^3J_{ae}$ = 4.2	3.2 (7.8)	4.0 (7.8)	10.2	7.6 s
22	3.9	$^2J_{ae}$ = 12.0; $^3J_{aa}$ = 12.0; $^3J_{ae}$ = 4.1	$^2J_{ae}$ = 12.0; $^3J_{ae}$ = 4.1	3.2 (6.0)	3.9 (6.0)	10.5	7.8 s
23	3.9	$^2J_{ae}$ = 12.3; $^3J_{aa}$ = 12.3; $^3J_{ae}$ = 3.0	$^2J_{ae}$ = 12.3; $^3J_{ae}$ = 3.0	3.2 (7.5)	4.0 (7.5)	10.0	7.6-8.0 m
24	4.0	$^2J_{ae}$ = 12.0; $^3J_{aa}$ = 8.7; $^3J_{ae}$ = 4.0	$^2J_{ae}$ = 12.0; $^3J_{ae}$ = 4.0	3.2 (7.0)	4.0 (7.0)	10.5	8.4 s

* Signals overlap.

In the IR spectra of the 1,2,4-oxadiazoles **13-24** a strong absorption band including the $\nu_{C=N}$ stretching vibration and δ_{N-H} (δ^{+}_{N-H}) bending vibration is found in the region 1595-1680 cm^{-1} for the base and in the region 1656-1670 cm^{-1} for their hydrochlorides. The absorption bands for the stretching vibrations of the N^{+}–H bond in the hydrochlorides **19-24** are observed in the range 2600-2800 cm^{-1} (Table 2).

The ^{1}H NMR spectra of compounds **13-24** (Table 3) show that, under the conditions for recording the spectra, there is observed a slow inversion of the morpholine ring. The signals for the protons of the methylene groups attached to a nitrogen atom appear as axial (δ 3.7 ppm) and equatorial (δ 3.4 ppm) signals with an intensity of two protons each. Assignment of the signals to the CH_2 group axial and equatorial protons was made on the basis that the signal of the former has a large half band width and is found to lower field than the proton signal for the equatorial CH_2 group. It should also be noted that, in the ^{1}H NMR spectra of the O-aroyl-β-morpholinopropioamide oximes, the signals for the methylene protons bonded to the nitrogen atom of the morpholine ring appear as triplets amounting to four protons at 2.40-2.52 for the bases **1-6** and at 3.4 ppm for the hydrochlorides **7-12** [2]. The slow inversion of the morpholine ring on changing from the O-aroylamide oximes **1-12** to the oxadiazoles **13-24** is possibly linked to a decrease in entropy and increase in rigidity of the system.

Hence the optimum conditions for the preparation of the potentially biologically active hydrochloride compounds **19-24** are heating the O-aroyl-β-morpholinopropioamide oximes **7-12** in DMF at 80°C for 2-4 h.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Mercury-300 (300 MHz) instrument with HMDS as internal standard. IR Spectra were taken on a UR-20 instrument for KBr tablets. Monitoring of the course of the reaction was carried out using TLC on Silufol UV-254 plates in the system methanol–benzene (1:3).

3-(β-Morpholino)ethyl-5-(*p*-nitrophenyl)-1,2,4-oxadiazole (18). K_2CO_3 (0.19 g, 2.8 mmol) was added to a solution of the O-*p*-nitrobenzoyl-β-morpholinopropioamide oxime (1.0 g, 2.8 mmol) dissolved in the minimum amount of water and extracted with benzene (3 × 20 ml). Drying the benzene solution with $MgSO_4$ and distillation of solvent gave the O-*p*-nitrobenzoyl-β-morpholinopropioamide oxime **6** (0.7 g, 77%) which was stirred in DMF (15 ml) for 1 h. The solvent was removed using an oil vacuum pump to give the base **18** (0.6 g, 91%); mp 197°C. Found, %: C 55.33; H 5.30; N 18.86. $C_{14}H_{16}N_4O_4$. Calculated, %: C 55.25; H 5.30; N 18.41.

1,2,4-Oxadiazoles 13-17 were synthesized similarly (Table 1).

5-(*p*-Methylphenyl)-3-(β-morpholino)ethyl-1,2,4-oxadiazole Hydrochloride (20). The O-*p*-methylbenzoyl-β-morpholinopropioamide oxime hydrochloride **8** (0.37 g, 1.1 mmol) was heated in DMF (10 ml) at 80°C for 2 h to give the 1,2,4-oxadiazole hydrochloride **20** (0.3 g, 87%); mp 246°C. Found, %: C 58.52; H 6.24; Cl 11.38; N 14.00. $C_{15}H_{19}N_3O_2 \cdot HCl$. Calculated, %: C 58.15; H 6.51; Cl 11.44; N 13.56.

1,2,4-Oxadiazole Hydrochlorides 19, 21 were prepared by the same method.

1,2,4-Oxadiazoles with electron acceptor substituents in the phenyl ring were separated by the same dehydration method (heating in DMF for 4 h) as the free bases and were converted to the hydrochlorides **22-24** by the action of an ethereal solution of HCl on their alcohol solutions (Table 1).

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