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SYNTHESIS OF 3-(ARYLHYDRAZONO)-5,5-DI(HYDROXYMETHYL)-2-OXOMORPHOLINES

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Esters of (arylhydrazono)chloroacetic acid reacted with tris(hydroxymethyl)aminomethane in the presence of trimethylamine under mild conditions to give 3-(arylhydrazonoyl)-5,5-di(hydroxymethyl)-2-oxomorpholines.

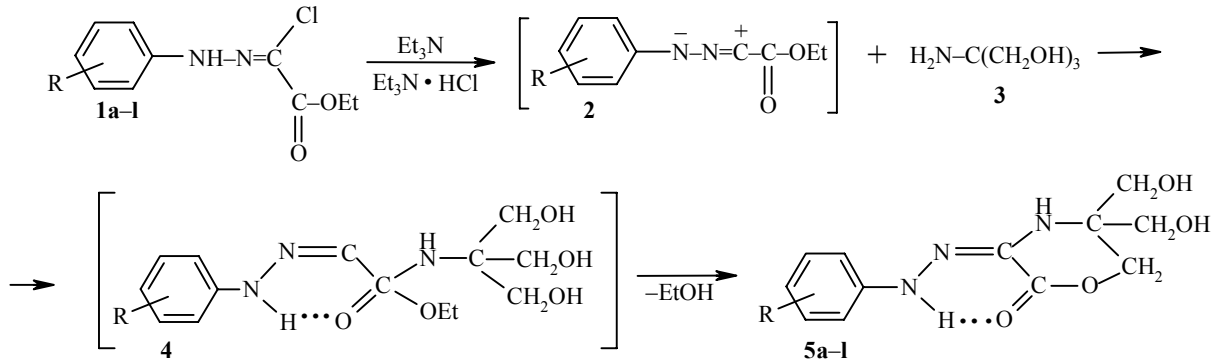
Keywords: morpholine, esters of (arylhydrazono)chloroacetic acids, heterocyclization.

Esters of (arylhydrazono)chloroacetic acids are very reactive compounds which may be used as the starting materials for the synthesis of a variety of nitrogen-containing heterocyclic systems [1-6].

Previously we observed that ethyl (arylhydrazono)chloroacetates were converted to 1,4-diaryl-3,6-dicarbethoxy-1,4-dihydro-1,2,4,5-tetrazines on treatment with sodium ethoxide. In a continuation of this study we have established that ethyl (arylhydrazono)chloroacetates **1a-l** reacted with tris(hydroxymethyl)-aminomethane (**3**) in aqueous ethanol in the presence of triethylamine at 30-40°C by cyclization to give 3-(arylhydrazono)-5,5-bis(hydroxymethyl)-2-oxomorpholines (**5a-l**) (see Tables 1 and 2).

The characteristic ^{1}H NMR signals of the compounds synthesized are those of the morpholine ring (the CH_2 groups which appear as a singlet in the 4.31-4.42 ppm region, and the NH group which appears as a broad singlet in the 6.21-7.22 ppm region).

In agreement with other results [1,2] it may be concluded that the first stage is the formation of the nitrilimine **2**, which then reacts with tris(hydroxymethyl)aminomethane to give the intermediate **4** (similar (arylhydrazono)aminoacetates were isolated and characterized previously [6]). Evidently intramolecular condensation then occurs with the elimination of ethanol to form the 5,5-di-(hydroxymethyl)-2-oxomorpholines **5a-l**.



1, 5 a R = H, **b** R = 4-Me, **c** R = 4-Br, **d** R = 4-Cl, **e** R = 4-NO_2, **f** R = 2-NO_2, **g** R = 3,4-di-Cl, **h** R = 2-Br-4-NO_2, **i** R = 2-NO_2-5-Cl, **j** R = 3-Cl-4-Me, **k** R = 5-CF_3-2-Cl, **l** R = 4-OEt-2-NO_2

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TABLE 1. Characteristics of Compounds **5a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	M^+	Yield, %
		C	H	N			
5a	$C_{12}H_{15}N_3O_4$	54.09 / 54.33	5.44 / 5.69	15.61 / 15.84	190-191	65	38
5b	$C_{13}H_{17}N_3O_4$	55.71 / 55.90	6.01 / 6.13	14.80 / 15.04	192-194	279	27
5c	$C_{12}H_{14}BrN_3O_4$	41.50 / 41.87	3.92 / 4.10	11.90 / 12.20	197-199	344	36
5d	$C_{12}H_{14}ClN_3O_4$	47.77 / 48.08	4.57 / 4.70	13.84 / 14.02	179-181	300	52
5e	$C_{12}H_{14}N_4O_6$	46.27 / 46.45	4.34 / 4.54	17.72 / 18.05	259-261	310	57
5f	$C_{12}H_{14}N_4O_6$	46.39 / 46.45	4.25 / 4.54	18.19 / 18.05	185-187	310	52
5g	$C_{12}H_{13}Cl_2N_3O_4$	42.70 / 43.11	3.97 / 3.89	12.39 / 12.57	213-215	334	46
5h	$C_{12}H_{13}BrN_4O_6$	37.50 / 37.03	3.51 / 3.36	14.21 / 14.39	198-200	389	40
5i	$C_{12}H_{13}ClN_4O_6$	41.70 / 41.81	3.63 / 3.80	16.11 / 16.25	187-189	345	31
5j	$C_{13}H_{16}ClN_3O_4$	49.57 / 49.77	4.93 / 5.14	13.01 / 13.39	215-218	314	32
5k	$C_{13}H_{13}ClF_3N_3O_4$	42.50 / 42.46	3.41 / 3.56	11.30 / 11.42	183-185	368	38
5l	$C_{14}H_{18}N_4O_7$	47.60 / 47.46	5.31 / 5.12	15.63 / 15.82	182-183	354	24

It is known that hydrazones can exist in *syn* and *anti* forms in consequence of the sp^2-hybridization of the imino nitrogen atom, while in the case of hydrazones of α-carbonyl compounds *s-cis* and *s-trans* conformations are possible in consequence of hindered rotation around the =C–C= bond which, as a result of conjugation has a partial double bond character. However it can be concluded from the ^{1}H NMR spectroscopic data that the 3-(arylhydrazono)-5,5-di(hydroxymethyl)-2-oxomorpholines **5a-l** exist in only one conformation. Hence it can be proposed that in this case compounds **5a-l** are formed in the *syn-s-cis* form which is stabilized by an intramolecular hydrogen bond N–H···O=C analogous to the arylhydrazone, the structure of which we investigated previously [9].

TABLE 2. ^{1}H NMR Spectra of Compounds **5a-l**

Compound	Chemical shifts, δ, ppm (*J*Hz)*					
	CH_2OH (4H, s)	CH_2O (2H, s)	OH (2H, s)	NH_{Het} (1H, s)	Ar	Ar–NH=N (1H, s)
1	2	3	4	5	6	7
5a	3.43	4.31	5.32	6.33	7.03-7.22 (5H, m, C_6H_5)	9.05
5b	3.42	4.31	5.14	6.21	6.92 (2H, d, *J* = 10.2, *p*-C_6H_4); 7.05 (2H, d, *J* = 10.2, *p*-C_6H_4)	8.93
5c	3.41	4.32	5.24	6.34	6.98 (2H, d, *J* = 8.7, *p*-C_6H_4); 7.33 (2H, d, *J* = 8.7, *p*-C_6H_4)	9.16
5d	3.38	4.32	5.10	6.34	7.01 (2H. d, *J* = 10.8, *p*-C_6H_4); 7.25 (2H, d, *J* = 10.8, *p*-C_6H_4)	9.19
5e	3.49	4.37	5.30	6.84	7.13 (2H, d, *J* = 8.6, *p*-C_6H_4); 8.15 (2H, d, *J* = 8.6, *p*-C_6H_4)	10.03

TABLE 2 (continued)

1	2	3	4	5	6	7
5f	3.52	4.42	5.11	7.22	6.93 (1H, t, *J* = 10.5, *o*-C_6H_4); 7.62-7.83 (2H, m, *o*-C_6H_4); 8.07 (1H, d, *J* = 10.5, *o*-C_6H_4)	10.14
5g	3.46	4.33	5.16	6.41	6.92 (1H, d, *J* = 8.8, 3,4-C_6H_3); 7.19 (1H,s, 3,4-C_6H_3); 7.41 (1H, d, *J* = 8.8, 3,4-C_6H_3)	9.39
5h	3.49	4.38	5.21	6.83	7.27 (1H, d, *J* = 9.6, 2,4-C_6H_3); 7.41 (1H, s, 2,4-C_6H_3); 8.15 (1H, d, *J* = 9.6, 2,4-C_6H_3)	10.27
5i	3.50	4.42	5.15	6.19	7.72 (1H, d, *J* = 9.5, 2,5-C_6H_3); 7.87 (1H, d, *J* = 9.5, 2,5-C_6H_3); 8.09 (1H, s, 2,5-C_6H_3)	10.15
5j	3.45	4.31	5.13	6.29	6.87 (1H, d, *J* = 7.8, 3,4-C_6H_3); 7.08 (1H, s, 3,4-C_6H_3); 7.15 (1H, d, *J* = 7.8, 3,4-C_6H_3)	9.14
5k	3.47	4.38	5.15	7.18	7.01 (1H, d, *J* = 10.1, 2,5-C_6H_3); 7.59 (1H, d, *J* = 10.1, 2,5-C_6H_3)	8.84
5l	3.51	4.41	5.11	7.12	7.41 (1H, d, *J* = 12.1, 2,4-C_6H_3); 7.53 (1H, s, 2,4-C_6H_3); 7.78 (1H, d, *J* = 12.1, 2,4-C_6H_3)	10.05

* Protons of other groups: **5b** 2.20 (3H, s, CH_3); **5j** 2.23 (3H, s, CH_3); **5l** 1.33 (3H, t, *J* = 10.1, $OCH_2\underline{CH_3}$); 4.07 (2H, d, $O\underline{CH_2}CH_3$).

It should be noted that the yields of the 5,5-di(hydroxymethyl)-2-oxomorpholines **5a-l** depend to a considerable extent on the nature of the substituent in the aromatic ring. Thus the greatest yields (31-57%) were observed for compounds with electron-acceptor substituents in the aromatic ring (nitro and trifluoromethyl groups, halogens), while the minimal yields (27-38%) occur in the case of electron-donor substituents (hydrogen, methyl), while in the case of the methoxy group heterocyclization does not occur at all, most probably because of low activity of the corresponding nitrilimine **2**.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutons with TMS as internal standard were recorded with a Varian-300 machine (300 MHz). Mass spectra were recorded with a MX-1303 machine.

Ethyl (phenylhydrazono)chloroacetates **1a-l** were synthesized by a known method [10].

3-(Arylhydrazono)-5,5-di(hydroxymethyl)-2-oxomorpholines (5a-l). A mixture of tris(hydroxymethyl)aminomethane (0.01 mol) and triethylamine (0.01 mol) in 60% aqueous ethanol (30 ml) was added dropwise at 30-40°C over 30 min to a stirred solution of an ethyl (phenylhydrazono)chloroacetate (0.01 mol) in ethanol (100 ml). The reaction mixture was stirred at this temperature for 3-5 h and the solvent was then removed to dryness. The residue was washed with water (2 × 30 ml), dried, washed with benzene (2 × 30 ml), dried, and recrystallized from ethanol.

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