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Brief Communications

Hydrazoic acid in the Mannich reaction

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The possibility of the three-component condensation of hydrazoic acid and formaldehyde with primary or secondary amines, as well as with trialkylhydrazines, leading to the corresponding *N*-azidomethyl derivatives of amines and hydrazides was established.

Key words: hydrazoic acid, aminomethylation, the Mannich reaction, azidomethylamines.

Joint condensation of aldehydes with amines and C—H-acids (the Mannich reaction) is widely used in laboratory practice and in industry for the synthesis of diverse amines. On the basis of modern conceptions, a carbenium—immonium ion formed from aldehyde and amine in the Mannich reaction couples with the anion of a C—H-acid (X^-) and gives the final product, a Mannich base (Scheme 1).

Scheme 1

$$R_2NH + OCHR' \rightleftharpoons R_2NCH(R')OH \rightleftharpoons$$

$$\rightleftharpoons [R_2NCH(R')]^+ \rightleftharpoons R_2NCH(R')X$$

Aminomethylnitramines are formed by the analogous method in the three-component condensation of formaldehyde with nitramines and primary or secondary amines (Scheme 2).[1—5]

Scheme 2

$$RNHNO_2 + CH_2O + HNR'_2 \longrightarrow RN(NO_2)CH_2NR'_2$$

$$2\,RNHNO_2 + 2\,CH_2O + H_2NR' \longrightarrow [RN(NO_2)CH_2]_2NR'$$

It is considered that the given reaction is one of variants of the Mannich reaction in which N—H-acids, *viz.*, primary nitramines, act as the acid components. The use of the N—H-acids in the Mannich reaction considerably extends the synthetic potential of this reaction.

Hydrazoic acid (hydrogen azide) HN_3, which possesses diverse reactivity, is one of the most interesting objects among N—H-acids. The azide anion N_3^- is notable for high nucleophilicity and is widely used for the synthesis of organic azides. Specifically, a possibility of the synthesis of *N*,*N*-dialkyl-*N*-azidomethylamines by the reaction of *N*,*N*-dialkyl-*N*-halogenomethylamines with sodium azide in aqueous solution or silver azide in dichloromethane has been established (Scheme 3).[6]

N,*N*-Dialkyl-*N*-azidomethylamines undergo hydrolysis giving hydrogen azide and formaldehyde.[6] It can be

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Scheme 3

$$\mathrm{R_2NCH_2R' + MN_3 \longrightarrow R_2NCH_2N_3 + MR'}$$

R′ = Cl, Br; M = Na, Ag

assumed that hydrolysis of azidomethylamines is an equilibrium reverse process and the mixture of hydrogen azide, formadehyde, and dialkylamine should contain the product of the three-component condensation, *i.e.*, *N*,*N*-dialkyl-*N*-azidomethylamine (**1**) (Scheme 4).

Scheme 4

$$\mathrm{HN_3 + CH_2O + HN(R)R' \rightleftharpoons \underset{\mathbf{1}}{N_3CH_2N(R)R'} + H_2O}$$

Our investigations showed that the reaction of sodium azide with formadehyde and dimethylammonium chloride in aqueous medium gives the expected *N*-azidomethyl-*N*,*N*-dimethylamine (**1a**) in low yield (Table 1), which can be explained by the high rate of its hydrolysis. Analogous situation is observed for the reaction of diethylammonium chloride with formaldehyde and sodium azide. But the use of dialkylamines with more complex aliphatic radicals in the reaction increases the yield of the corresponding *N*,*N*-dialkyl-*N*-azidomethylamines. This is especially characteristic for dialkylamines containing cyanoethyl substituents (Table 1).

The reaction of hydrazoic acid with formaldehyde and monoalkylamines leads to *N*-alkyl-*N*,*N*-bis(azidomethyl)amines (**2**) irrespective of the reactant ratio (Scheme 5, Table 2).

Scheme 5

$$\mathrm{RNH_2 + 2\,CH_2O + 2\,HN_3 \rightleftharpoons \underset{\mathbf{2}}{RN(CH_2N_3)_2} + 2\,H_2O}$$

The reaction of sodium azide with formaldehyde and ammonium chloride gives *N*,*N*,*N*-tris(azidomethyl)amine $\mathrm{N(CH_2N_3)_3}$ (**2d**, Table 2).

N-Alkyl-*N*′,*N*′-dimethylhydrazine reacts with hydrazoic acid and formaldehyde to form the corresponding *N*-alkyl-*N*-azidomethyl-*N*′,*N*′-dimethylhydrazines (**3**) under the same conditions (Scheme 6, Table 3).

Scheme 6

$$\mathrm{Me_2NNHR + CH_2O + HN_3 \rightleftharpoons \underset{\mathbf{3}}{Me_2NN(R)CH_2N_3} + H_2O}$$

Methylhydrazine reacts with formaldehyde and hydrazoic acid to give formaldehyde *N*-azidomethyl-*N*-methylhydrazone in 10% yield (Scheme 7).

Scheme 7

$$\mathrm{MeNHNH_2 + 2\,CH_2O + HN_3 \rightleftharpoons CH_2{=}NN(Me)CH_2N_3 + 2\,H_2O}$$

The hydrazone is a liquid with b.p. 58—59 °C (14 Torr); d_4^{20} =1.0822; n_D^{20} =1.4859. IR spectrum (ν/cm^{-1}): 2120 ($\mathrm{N_3}$); 1589, 3067 ($\mathrm{N{=}CH_2}$).

The obtained azidomethyl derivatives of amines and hydrazines are chemically unstable. They hydrolyze to the

Table 1. Characteristics of *N*-azidomethyl-*N*,*N*-dialkinamines $\mathrm{R(R')NCH_3N_3}$ (**1**)

Compound	R	R′	Yield (%)	B.p./°C (*p*/Torr)	d_4^{20}	n_D^{20}	$\frac{\text{Found}}{\text{Calculated}}$ (%)					Molecular formula	IR spectrum, ν/cm^{-1}	
							MR$_D$	C	H	N	M		$\mathrm{N_3}$	CN
1a	Me	Me	10	48—50 (105)	0.9619	1.4380	27.11 27.98	36.46 36.00	8.16 8.00	55.10 56.00	— 100	$\mathrm{C_3H_8N_4}$	2110	—
1b	Et	Et	15	44—46 (12)	0.9349	1.4490	36.75 37.22	47.43 46.88	9.47 9.37	42.32 43.75	— 128	$\mathrm{C_5H_{12}N_4}$	2110	—
1c	Bu^n	Bu^n	46	55—55.5 (1)	0.8915	1.4519	55.67 55.67	59.37 58.69	11.43 10.87	29.41 30.44	169 184	$\mathrm{C_9H_{20}N_4}$	2115	—
1d	Me	$\mathrm{CH_2CH_2CN}$	63	84—84.5 (2)	1.0699	1.4770	36.71 37.04	43.68 43.16	6.80 6.47	49.66 50.37	130 139	$\mathrm{C_5H_9N_5}$	2115	2265
1e	Et	$\mathrm{CH_2CH_2CN}$	60	82—83 (2)	1.0417	1.4769	41.50 41.65	47.18 47.06	7.16 7.19	45.51 45.75	152 153	$\mathrm{C_6H_{11}N_5}$	2120	2265
1f	Pr	$\mathrm{CH_2CH_2CN}$	60	102—103 (2)	1.0131	1.4765	46.53 46.37	50.25 50.30	7.45 7.78	42.45 41.92	161 167	$\mathrm{C_7H_{13}N_5}$	2128	2270
1g	Bu^i	$\mathrm{CH_2CH_2CN}$	62	91—91.5 (1)	0.9967	1.4708	50.74 50.88	53.55 53.04	8.50 8.29	38.44 38.67	183 181	$\mathrm{C_8H_{15}N_5}$	2125	2265

Table 2. Characteristics of *N*,*N*-bis(azidomethyl)-*N*-alkylamines $RN(CH_2N_3)_2$ (**2**)

Compound	R	Yield (%)	B.p./°C (2 Torr)	d_4^{20}	n_D^{20}	Found/Calculated (%) MR$_D$	C	H	N	M	Molecular formula	IR spectrum, ν_{N_3}/cm^{-1}
2a	Me	64	42—43	1.1245	1.4920	36.38	25.45	5.11	68.90	140	$C_3H_7N_7$	2120
						35.97	25.53	4.97	69.50	141		
2b	Et	68	57.5—58	1.0950	1.4879	40.30	29.76	5.45	63.52	150	$C_4H_9N_7$	2120
						40.59	30.97	5.81	63.22	155		
2c	Pr	80	61.5—62	1.0704	1.4836	45.14	35.90	7.15	57.96	166	$C_5H_{11}N_7$	2120
						45.21	35.50	6.51	57.99	169		
2d	CH_2N_3	64	93—94	1.2734	1.5205	43.47	20.22	3.51	76.17	178	$C_3H_6N_{10}$	2120
						43.96	19.78	3.30	76.92	182		

starting compound in an aqueous medium. Azidomethylamines and azidomethylhydrazines intensively decompose at 120—130 °C. *N*-Alkyl-*N*,*N*-bis(azidomethyl)amines have explosive properties, they are sensitive to mechanical impact. *N*,*N*,*N*-Tris(azidomethyl)amine has especially high impact sensitivity.

The structures of the obtained azidomethylamines and azidomethylhydrazines were determined by elemental analysis, molecular weight determination and IR and NMR spectroscopy. *N*-Azidomethyl-*N*,*N*-dimethylamine was converted to earlier described[6] *N*-azidomethyl-*N*,*N*,*N*-trimethylammonium iodide (**4**) under the action of methyl iodide (Scheme 8).

Scheme 8

$$(CH_3)_2NCH_2N_3 + CH_3I \longrightarrow [(CH_3)_3NCH_2N_3]^+I^-$$

4

N,*N*-Bis(azidomethyl)-*N*-methylamine under the action of nitric acid — acetic anhydride mixture underwent nitrolysis to give 1-acetoxy-2-aza-2-nitropropane, which has earlier been described (Scheme 9).[7]

The obtained results are the evidence of the existence of the principal similarity between the aminomethylation reaction of hydrazoic acid and primary nitramines. The amino group nitrogen in azidomethylamines, as in aminomethylamines, retains nucleophlic properties and can react with electrophilic reagents.

Scheme 9

$$MeN(CH_2N_3)_2 + HNO_3 + (MeCO)_2O \longrightarrow$$

$$\longrightarrow MeN(NO_2)CH_2OCOMe$$

Aniline and its derivatives, as well as hydrazine and nonsymmetrical dimethylhydrazine react with formaldehyde and hydrazoic acid giving the products devoid of the azido group.

Experimental

N-Alkyl-*N*-(2-cyanoethyl)amines were obtained by addition of alkylamines to acrylonitrile.[8,9] Similarly, *N*,*N*-dimethyl-*N*´-(2-cyanoethyl)hydrazine was obtained from acrylonitrile and nonsymmetrical dimethylhydrazine.[10] *N*,*N*-Dimethyl-*N*´-propylhydrazine and *N*,*N*-dimethyl-*N*´-butylhydrazine were obtained by the known method[11] by the reaction of formaldehyde dimethylhydrazone with ethyl- and propylmagnesium iodides, respectively. Quaternization of *N*-azidomethyl-*N*,*N*-dimethylamine with methyl iodide was carried out by the known method.[6] IR spectra of the obtained compounds were obtained in a thin film on a UR-20 instrument, the layer thickness was 0.03 mm. NMR spectra were recorded on a Varian-T60 spec-

Table 3. Characteristics of *N*-azidomethyl-*N*-alkyl-*N*´,*N*´-dimethylhydrazines $(Me)_2NN(R)CH_2N_3$ (**3**)

Compound	R	Yield (%)	B.p./°C (2 Torr)	d_4^{20}	n_D^{20}	Found/Calculated (%) MR$_D$	C	H	N	M	Molecular formula	IR spectrum, ν_{N_3}/cm^{-1}
3a	Pr	60	30—35	0.9485	1.4569	45.07	46.13	10.95	44.76	155	$C_6H_{15}N_5$	2120
						45.81	45.86	9.55	44.59	157		
3b	Bu	62	41—44	0.9379	1.4578	49.71	49.32	10.09	40.13	174	$C_7H_{17}N_5$	2120
						50.16	49.12	9.94	40.94	171		
3c	CH_2CH_2CN	65	88	1.0612	1.4801	44.94	42.51	7.33	50.02	171	$C_6H_{12}N_6$	2120, 2265
						45.60	42.86	7.14	50.00	168		

trometer, the solvent was CCl_4, $SiMe_4$ was used as the internal standard. The signals for the $(CH_3)_2N$ (δ 2.14) and NCH_2N_3 (δ 4.06) groups were observed in the NMR spectrum for compound **1a**, the ratio of the peak intensities was 3 : 1. The analogous spectrum for compound **2a** contains signals for the CH_3N (δ 2.18) and NCH_2N_3 (δ 4.10) groups, the ratio of the peak intensities was 3 : 4. Molecular weight for compounds was determined by cryoscopy in benzene.

Synthesis of *N*,*N*-dialkyl-*N*-azidomethylamines 1, *N*-alkyl-*N*,*N*-bis(azidomethyl)amines 2 and *N*-alkyl-*N*-azidomethyl-*N*´,*N*´-dimethylhydrazines 3 (general procedure). Amines, trialkylhydrazines, formaldehyde, and hydrogen azide were introduced in the reaction in the equimolar amounts. Hydrazoic acid was obtained *in situ* as the result of the reaction of sodium azide with hydrogen chloride. Amines or hydrazines (bases) were preliminary mixed in the equimolar amounts with 35% HCl, then a solution of the amine or hydrazine salts was added to the mixture of sodium azide and 37% formaldehyde solution. The mixture was stirred for 30 min, the condensation products were dissolved in diethyl ether. Ethereal solution was separated, dried with anhydrous Na_2SO_4, concentrated *in vacuo*; the residue was distilled under reduced pressure. The characteristics of the obtained compounds are presented in Tables 1—3. Synthesis of compounds **1a,d** and **4** is described below.

***N*-Azidomethyl-*N*,*N*-dimethylamine (1a).** Dimethylammonium chloride (15.9 g, 0.2 mol) was added with stirring to a mixture of sodium azide (13 g, 0.2 mol) and 37% formadehyde solution (16 mL). The mixture was stirred for 30 min, saturated with sodium chloride and extracted with ether. The ethereal layer was dried with Na_2SO_4, and concentrated *in vacuo*; the residue was distilled under reduced pressure. Compound **1a** was obtained (2 g, 10%).

***N*-Azidomethyl-*N*-(2-cyanoethyl)-*N*-methylamine (1d).** Hydrochloric acid (35%, 9 mL) was added dropwise to *N*-(2-cyanoethyl)-*N*-methylamine (8.4 g, 0.1 mol) in water (5 mL) at 20—25 °C. The solution that obtained was added to a mixture of sodium azide (6.5 g, 0.1 mol) and 37% formadehyde solution (8 mL, 0.1 mol). The reaction mixture was intensively stirred for 30 min, then it was kept until oily condensation product sedimented as a separate layer. The condensation product was dissolved in ether. The ethereal solution was dried with Na_2SO_4, and concentrated *in vacuo*; the residue was distilled under reduced pressure. *N*-Azidomethyl-*N*-(2-cyanoethyl)-*N*-methylamine was obtained (8.8 g, 63%) .

***N*-Azidomethyl-*N*,*N*,*N*-trimethylammonium iodide (4).** *N*-Azidomethyl-*N,N*-dimethylamine (0.5 g, 0.005 mol) and methyl iodide (0.84 g, 0.006 mol) were mixed under ice-bath cooling. The crystal product that formed was recrystallized from ethanol. *N*-Azidomethyl-*N*,*N*,*N*-trimethylammonium iodide was obtained (0.9 g, 74%). M.p. 133—134 °C (decomp.) (lit. data[6]: m.p. 134 °C (decomp.)). IR spectrum: ν_{N3} 2110 cm^{-1}.

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