

Effect of Aliphatic Alcohols on the Reaction of Acetoacetic Ester with Formaldehyde and Primary Amines

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Abstract—Composition of hemiacetals formed by the reaction of paraformaldehyde with aliphatic alcohols in the presence of catalytic amounts of Et₃N was studied and the effect of the nature of hemiacetals on the yield and composition of the products of their condensation with acetoacetic ester and primary amines under the Mannich reaction conditions was examined.

Keywords: formaldehyde, acetoacetic ester, primary amines, Mannich reaction, aliphatic alcohols, 1,3-hexahydropyrimidines, piperidines

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Formaldehyde and primary amines are widely used in organic synthesis for preparation of tetrahydro-1,3-oxazines [1, 2], hexahydropyrimidines [1–6], 3-aza- and 3,7-diazabicyclo[3.3.1]nonanes [7–12], as well as 1,3,5-hexahydrotriazines [13]. Specimens of compounds of this series possess a wide spectrum of biological activity [14–17] (antimicrobial, antiviral, anti-tumor, etc.) and are used in oil chemistry as bactericides, neutralizing agents for hydrogen sulfide and inhibitors of salt deposition [18–20].

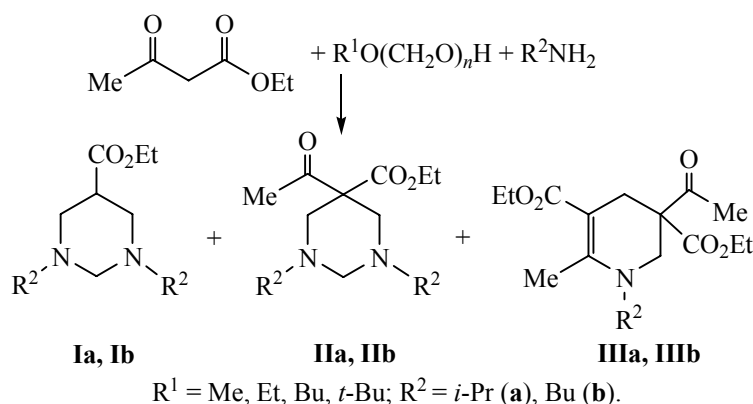
It is known that dissolving gaseous formaldehyde in protic polar solvents (water, methanol, ethanol) gives rise to an equilibrium mixture of methylene glycols and hemiacetals of general formula RO(CH₂O)_nH, where R = H, Me, Et (*n* = 1–4) [21–28]. The reactivity typical for formaldehyde is assumed to be retained also for its hemiacetal derivatives, since the reactions of these compounds are similar in many aspects. As a rule, the mechanisms of the reactions with participation of formaldehyde in aqueous and alcoholic media are described as transformations of formaldehyde. However, such an approach is not fully correct, since, firstly, in these solvents the content of formaldehyde does not exceed 1% and, secondly, the rate of

dissociation of hemiacetals is 2–3 times less than the rate of dissociation of methylene glycol [21, 22–29].

Earlier, we have shown that the reaction of acetoacetic ester with formaldehyde and primary amines in aqueous-alcoholic media leads to alkyl-5-acetyl-1,3-dimethylhexahydropyrimidine-5-carboxylates and alkyl-1,3-dimethylhexahydropyrimidine-5-carboxylates [4]. Hitherto, the effect of the nature of the hemiacetal derivatives of formaldehyde on the reaction of their condensation with acetoacetic ester and primary amines was not discussed. Note that this field of research is of interest from the viewpoint of development of new highly efficient neutralizing agents of hydrogen sulfide, whose application would exclude the deposition of polymethylene sulfides [30].

The present work comprises the investigation of the composition of hemiacetals formed in the reaction of paraformaldehyde with aliphatic alcohols in the presence of catalytic amounts of Et₃N and examination of the effect of the nature of hemiacetals on the yield and composition of the products of their condensation with acetoacetic ester and primary amines under the conditions of the Mannich reaction.

Scheme 1.



The Et_3N -catalyzed reaction of paraformaldehyde with aliphatic alcohols was carried out at 20°C for 24 h with the molar ratios $\text{CH}_2\text{O} : \text{alcohol} = 1 : 1, 3 : 4, 1 : 2, 1 : 4$. As the alcoholic component methanol, ethanol, 2-propanol, butanol and *tert*-butanol were employed. The quantitative composition and the structure of the formed products were established at 20°C by the methods of ^1H and ^{13}C NMR spectroscopy involving the literature data [23–28]. The signals in the ^1H and ^{13}C NMR spectra were assigned by the use of correlation spectroscopy (COSY and HECTOR).

The nature of the starting alcohols has a substantial effect on paraformaldehyde cleavage. Under the used conditions, methanol, ethanol, and butanol taken in the ratio $\text{CH}_2\text{O} : \text{alcohol} = 1 : 1$ vigorously reacted with paraformaldehyde giving a transparent homogeneous

equilibrium mixture of hemiacetals in which alkoxy-methanols predominated ($>50\%$) (Table 1). For 4-fold molar excess of these alcohols the fraction of alkoxy-methanols was no less than 88%. The quantitative composition of hemiacetals practically does not depend on the length of the alkyl radical of linear alcohols. 2-propanol gives a transparent mixture of hemiacetals only at the molar ratio $\text{CH}_2\text{O} : \text{alcohol} = 1 : 4$, whereas *tert*-butanol does not give hemiacetals under these conditions, apparently, because of a high sensitivity of the paraformaldehyde cleavage to steric effects. From the data of IR and ^1H , ^{13}C NMR spectroscopy, the examined mixtures of hemiacetals did not contain free formaldehyde.

The effect of the hemiacetal nature on the direction of their condensation with acetoacetic ester and primary amines under the Mannich reaction conditions was carried out at 65°C for 5 h with the molar ratio acetoacetic ester–formaldehyde–amine $1 : 17 : 4$. As primary amines, isopropylamine, butylamine, and aniline were used.

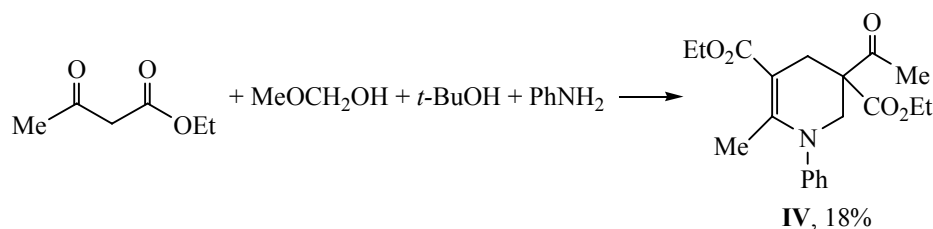
The reaction of acetoacetic ester with BuNH_2 and hemiacetals $\text{RO}(\text{CH}_2\text{O})_n\text{H}$ obtained from primary alcohols (molar ratio $\text{CH}_2\text{O} : \text{ROH} = 1 : 1$, $\text{R} = \text{Me, Et, Bu}$) after reflux for 5 h gave the mixture of ethyl 1,3-dibutylhexahydropyrimidine-5-carboxylate (**Ib**) and ethyl 5-acetyl-1,3-dibutylhexahydropyrimidine-5-carboxylate (**IIb**) in 69–82% yield (Table 2, Scheme 1).

In contrast, the condensation of the mixture of paraformaldehyde with *tert*-butanol (molar ratio $\text{CH}_2\text{O} : t\text{-BuOH} = 1 : 1$) with butylamine and acetoacetic ester in the presence of catalytic amounts of Et_3N results in the formation, along with 1,3-hexahydropyrimidines **Ib**, **IIb**, diethyl 3-acetyl-1-butyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (**IIIb**) in the yield of 34%.

Table 1. Effect of the alcohol and the ratio $\text{CH}_2\text{O} : \text{ROH}$ on the composition of hemiacetals (20°C , 3.8 mol % of Et_3N)

ROH	$\text{CH}_2\text{O} : \text{ROH}$	$\text{RO}(\text{CH}_2\text{O})_n\text{H}, \%$			
		$n = 1$	$n = 2$	$n = 3$	$n = 4$
Me	1 : 1	50	30	15	5
	3 : 4	73	19	6	2
	1 : 2	88	10	2	–
	1 : 4	90	9	1	–
Et	1 : 1	60	30	10	–
	3 : 4	65	25	10	–
	1 : 2	76	17	7	–
	1 : 4	88	10	2	–
<i>i</i> -Pr	1 : 4	73	21	6	–
Bu	1 : 1	59	19	10	12
	3 : 4	72	21	5	2
	1 : 2	85	13	2	–
	1 : 4	90	9	1	–

Scheme 2.



Note that in the reaction carried out in diluted methanol solutions (molar ratio $\text{CH}_2\text{O} : \text{ROH} : \text{MeOH} = 1 : 1 : 178$, the content of $\text{MeOCH}_2\text{OH} > 98\%$) the yield of diethyl 3-acetyl-1-butyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (**IIIb**) was increased to 59%.

The use of *iso*-propylamine gives rise to predominant formation of product **IIIa**. Thus, under these conditions, with molar ratio $\text{CH}_2\text{O} : t\text{-BuOH} : \text{MeOH} = 1 : 1 : 178$ hexahydropyrimidines **Ia**, **IIa** and diethyl 3-acetyl-1-*iso*-propyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate **IIIa** were formed in the yield of 9, 12, and 71% respectively.

Unlike reaction with butylamine, the reaction of acetoacetic ester with aniline and methoxymethanol under the same conditions ($\text{CH}_2\text{O} : \text{BuOH} : \text{MeOH} = 1 : 1 : 178$, 5 h) leads in 18% yield to diethyl 3-acetyl-1-phenyl-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (**IV**) formed with participation of two molecules of the starting acetoacetic ester. The observed selectivity as compared to butylamine is, apparently, due to a lower basicity of aniline [31] (Scheme 2).

The synthesized nitrogen heterocycles **I–IV** were isolated by preparative TLC and characterized by ^1H and ^{13}C spectra [4, 32].

Hence, the composition of hemiacetals formed by the reaction of paraformaldehyde with aliphatic alcohols (MeOH , EtOH , *i*- PrOH , BuOH , and *t*- BuOH) in the presence of 3.8 mol % of Et_3N was studied and the effect of the nature of hemiacetals on the yield and composition of the products of their condensation with acetoacetic ester and primary amines (*i*- PrNH_2 , BuNH_2 , and PhNH_2) under the conditions of the Mannich reaction was examined.

EXPERIMENTAL

NMR spectra were registered on a Bruker AM-300 spectrometer with working frequencies 300.13 (^1H), 75.47 MHz (^{13}C) and Bruker Avance-III 500 with working frequencies 500.13 (^1H), 125.47 (^{13}C) at 298 K.

Chemical shifts in the ^{13}C , ^1H NMR spectra are given with respect to internal reference TMS. Mass-spectra were obtained on a high resolution chromatomass spectrometer Thermo Finnigan MAT 95 XP (EI, 70 eV, temperature of the ionizing chamber 250°C, temperature of the direct insertion system 50–270°C, rate of heating 10 deg/min). IR spectra were taken on IR Prestige-21 Shimadzu spectrometer. Melting points were determined on a Boetius micro heating block. TLC analysis was performed on analytical plates Sorbfil PTSKh-AF-A from “Imid Ltd” (eluent – chloroform– MeOH , 9 : 1, eluent petroleum ether– AcOEt , 7 : 3). Preparative separation was performed by the use of column chromatography on silica gel Macherey-Nagel (70–230 mesh) (eluent chloroform with increasing content of MeOH from 0 to 10% or petroleum ether with increasing content of EtOAc from 0 to 2%).

Physicochemical constants of compounds **Ia**, **Ib** [4], **IIa**, **IIb** [4], **IIIa**, **IIIb** [32], and **IV** [32] coincided with the literature data.

Reaction of paraformaldehyde with aliphatic alcohols (general procedure). To 1 g (33.3 mmol) of paraformaldehyde and 0.1 g (0.97 mmol) of NEt_3 the required amount of aliphatic alcohol was added and the obtained mixture stirred for 24 h at 20°C till the formation of transparent homogeneous solution. The composition and structure of the formed hemiacetals was determined by ^1H and ^{13}C NMR spectroscopy [23–28].

Table 2. Reaction of hemiacetals with acetoacetic ester and butylamine (molar ratio $\text{CH}_2\text{O} : \text{ROH} = 1 : 1$, 65°C, 3.8 mol % of Et_3N)

ROH	Yield, % ^a		
	Ib	IIb	IIIb
Me	35 (14)	34 (9)	– (59)
Et	26 (21)	53 (18)	– (38)
Bu	40 (22)	42 (33)	– (25)
<i>t</i> -Bu	16 (5)	36 (5)	34 (55)

^a Molar ratio $\text{CH}_2\text{O} : \text{ROH} : \text{MeOH} = 1 : 1 : 178$.

Reaction of ethyl acetoacetate with primary amines and hemiacetals (general procedure). To 0.5 g (4 mmol) of ethyl acetoacetate 15 mmol of a primary amine and 68 mmol of formaldehyde in the form of hemiacetals was added at stirring and the mixture was heated for 5 h at 65°C. MeOH was distilled off at a reduced pressure, and 20 mL of CH₂Cl₂ was added. The reaction mixture was washed with water (3 × 10 mL), dried with anhydrous Na₂SO₄, the solvent removed at a reduced pressure. The residue was chromatographed on a column packed with silica gel (eluent chloroform with increasing content of MeOH from 0 to 10% or petroleum ether with increasing content of EtOAc from 0 to 2%). The yields of the products **Ia**, **Ib**, **Ila**, **Ilb**, **IIla**, **IIlb**, and **IV** are given in Table 2 and in the text.

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