



METHANOLYSIS OF *N*-ACETOXY-*N*-*n*-PROPYLOXY-*N*',*N*'-DIMETHYLUREA IN DIFFERENT CONDITIONS

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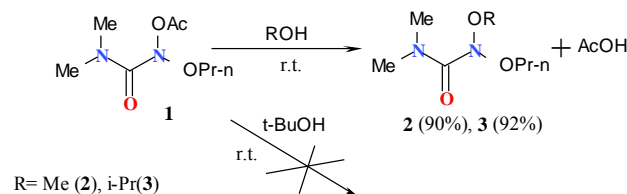
The methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea in the presence of strong acids at room temperatures or in the boiling methanol yields *N,N*-dimethoxy-*N*',*N*'-dimethylurea as final product. Primarily the nucleophilic substitution acetoxy group at nitrogen on methoxy group arises. At second stage the transesterification of *N,N*-dialkoxyamino group of formed *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea take place.

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Scheme 1

INTRODUCTION

Amides,²⁻⁹ carbamates,^{10,11} and ureas,¹⁰⁻¹⁵ having at nitrogen atom two electronegative substituents, one of them is alkoxy group and other substituent may be alkoxy group, acyloxy group, chlorine atom, 1-pyridinium group, are called “anomeric amides” due to $n_{O(Alk)} \rightarrow \sigma^*_{N-X}$ ($X = OC(O)R, Cl, OAlk, N^+C_5H_5$) anomeric effect domination. In $X-N-O(R)$ group amide nitrogen is sp^3 hybridized and has pyramidal configuration, $(Alk)O-N$ bond is shortened and $N-X$ bond is elongated and destabilized. Due to this $N-X$ bond destabilization the S_N2 nucleophilic substitution at amide nitrogen atom becomes possible.^{2,4,6}

Earlier we had found that alcoholysis of *N*-acyloxy-*N*-alkoxyureas by primary and secondary alcohols at room temperatures (18-25 °C) yields the proper *N,N*-dialkoxyureas⁷ (Scheme 1). If the methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** arises during 55 hours, the final isopropanolysis of compound **1** occurs during 1224 hours.¹⁰ The *tert*-butanolysis of compound **1** no take place at room temperature because steric hindrances to the nucleophilic substitution at nitrogen,¹⁰ realized, probably, via S_N2 mechanism.^{2,4,6-8,10}

By alcoholysis at room temperatures *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** selectively converts in *N,N*-dialkoxyureas **2,3** and acetic acid. In these conditions acetic acid is indifferent to *N,N*-dialkoxyureas **2,3**.

But the influence of alcoholysis temperature and the presence of strong acids on the alcoholysis process remained practically unstudied.

EXPERIMENTAL

¹H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz, internal standard – Me₄Si), chemical shifts in σ -scale (ppm), coupling constants in Hz). Mass spectra were recorded on a VG-70EQ 770 mass spectrometer in FAB mode (FAB) and on Kratos MS 890 mass spectrometer electron impact mode (EI) and chemical ionization mode (CI), gas-reagent isobutane. MeOH was dried by boiling and distillation over Ca.

N-Acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (**1**).¹⁰

Yellowish oil, n_D^{20} 1.4561. ¹H NMR (300 MHz, CDCl₃): 0.95 (t, 3H, OCH₂CH₂Me, ³J = 7.2 Hz), 1.68 (sex, 2H, OCH₂CH₂Me, ³J = 7.2 Hz), 2.15 (s, 3H, NO₂CMe), 3.04 (s, 6H, NMe₂), 4.04 (t, 2H, OCH₂CH₂Me, ³J = 7.2 Hz), IR (ν , cm⁻¹): 1784 (C=O), 1732 (C=O). MS (CI, m/z (I_{rel}(%))): 206 [M+2H]⁺ (17.3); 205 [M+H]⁺ (100), 204 M⁺ (9.4), 203 (11.9), 174 (15.3), 160 (16.0), 148 (10.8), 132 (25.8). Found (%): C 47.12, H 8.02, N 13.65. Calc. for C₈H₁₆N₂O₄ (%): C 47.05, H 7.90, N 13.72.

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (1) in boiling MeOH.

The solution of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1**,¹⁰ (3.95 mmol, 0.81 g) in MeOH (6 ml) was boiled for 4 h, then reaction mixture was evaporated *in vacuo*, the residue was distilled at 1 Torr, yielding 0.45 g (76 %) of *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4**, colorless liquid, bp. 98 – 99.5 °C (7 Torr), n_D^{20} 1.4470, identified with the reference sample of **2**,¹⁰ by ¹H NMR. ¹H NMR (300 MHz, CDCl₃): 3.00 (s, 6H, NMe₂), 3.75 (s, 6H, N(OMe)₂).

***N,N*-Dimethoxy-*N*',*N*'-dimethylurea (4)**

N,N-dimethoxy-*N*',*N*'-dimethylurea (the reference sample) was obtained by methanolysis of *N*-acetoxy-*N*-methoxy-*N*',*N*'-dimethylurea,¹⁰ at 20 °C for 34 h with yield 67 %.

***N*-Methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (2).**

Colorless oil, bp. 95-95.5 °C (1 Torr); n_D^{26} 1.4449, obtained by the methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** at 20 °C for 55 h with yield 80 %¹⁰ and *n*-propanolysis of *N*-acetoxy-*N*-methoxy-*N*',*N*'-dimethyl-urea,¹⁰ at 30 °C for 264 h with yield 82 %. ¹H NMR (300 MHz, CDCl₃): 0.96 (t, 3H, CH₂CH₂Me, ³J = 7.1 Hz), 1.67 (sex, 2H, CH₂CH₂Me, ³J = 7.1 Hz), 3.00 (s, 6H, NMe₂), 3.73 (s, 3H, NOME), 3.91 (t, 2H, NOCH₂, ³J = 7.1 Hz). MS (CI, m/z (*I*_{rel}(%)): 177 [M+H]⁺ (7.7), 175 (6.4), 174 (9.9), 161 (32.8), 160 (11.0), 146 (14.0), 145 (19.0), 133 (11.2), 118 (13.9), 117 (46.5), 116 (29.3), 105 (12.9), 104 (24.3), 103 (40.2), 90 (14.3), 89 (100);, 73 (20.7), 72 (23.5). Found (%): C 47.82, H 9.17, N 15.63. Calc. for C₇H₁₆N₂O₃ (%): C 47.71, H 9.15, N 15.90.

Transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (2) by MeOH in the presence of AcOH.

The solution of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2** (0.500 mmol, 0.085 g) and AcOH (0.500 mmol, 0.030 g) in MeOH (1 ml) was boiled for 1 h, then MeOH was evaporated *in vacuo*, the residue was kept at 5 Torr and 23 °C, yielding 0.052 g (72 %) *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4**, identified by ¹H NMR.

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (1) in the presence of CF₃CO₂H.

N-Acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** (1.474 mmol, 0.301 g) was added to solution of CF₃CO₂H (0.79 mmol, 0.09 g) in MeOH (4 ml). The reaction mixture was kept at 15 °C for 5 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et₂O (6 ml). Et₂O-Extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.214 g yellowish oil, which was identified by ¹H NMR as mixture of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2**,¹⁰ and *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4** in molar ratio 69.8 %:30.2 % (molar). It means 60.5 % yield of urea **2** and 26.1 % yield of urea **4**.

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (1) in the presence of oxalic acid.

N-Acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** (2.34 mmol, 0.60 g) was added to solution of oxalic acid (0.29 mmol, 0.03 g) in MeOH (4 ml). The reaction mixture was kept at 18-20 °C for 100 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et₂O (10 ml). Et₂O-Extract was evaporated *in vacuo*, the residue was kept at 1 Torr and 20 °C, yielding 0.31 g (71 %) *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4**, identified by ¹H NMR.

Transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea (2) by MeOH in the presence of oxalic acid.

The mixture of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2**,¹⁰ (0.466 mmol, 0.081 g), oxalic acid (0.052 mmol, 0.005 g) and MeOH (1 ml) was kept at 20 °C for 73 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et₂O (3 ml). Et₂O-Extract was evaporated *in vacuo*, the residue was extracted mixture of Et₂O (4 ml) and hexane (1 ml), the extract was evaporated *in vacuo*, the residue was kept at 5 Torr and 20 °C, yielding 0.045 g (66 %) of *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4**, identified by NMR ¹H.

Ethanolysis of *N*-acetoxy-*N*-methoxyurea (5) in boiling EtOH.

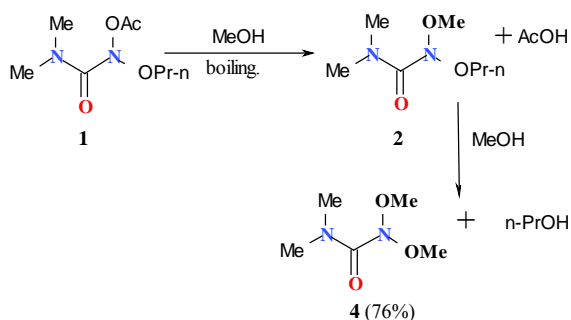
The solution of *N*-acetoxy-*N*-methoxyurea **5**,^{11,16} (0.1601 mmol, 0.0237 g) in EtOH (4 ml) was boiled for 1 h, then EtOH was evaporated *in vacuo*, the residue was extracted by CH₂Cl₂ (3 ml), the CH₂Cl₂-extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.0172 g (80 %) of *N*-ethoxy-*N*-methoxyurea **6**, colourless oil, n_D^{20} 1.4493, identified by ¹H NMR and MS. ¹H NMR (300 MHz, CDCl₃): 1.33 (t, 3H, NOCH₂Me, ³J = 6.9 Hz), 3.84 (s, 3H, NOME), 4.13 (q, 2H, NOCH₂Me, ³J = 6.9 Hz), 5.64 (br. s, 1H, NH), 5.96 (br. s, 1H, NH). MS (FAB, NaI, m/z (*I*_{rel} %)): 157 [M+Na]⁺ (22), 89 H₂NC(O)N⁺OMe (25), 72 (77), 58 (100). Found (%): C 35.93, H 7.80, N 20.69. Calc. for C₄H₁₀N₂O₃ (%): C 35.82, H 7.51, N 20.88. Also, *N*-ethoxy-*N*-methoxyurea **6** was obtained by ethanolysis of *N*-acetoxy-*N*-methoxyurea **5** at 15 °C for 69 h with yield 88 %.

Methanolysis of *N*-acetoxy-*N*-ethoxyurea (7) in boiling MeOH.

The solution of *N*-acetoxy-*N*-ethoxyurea **7**,^{10,11} (0.925 mmol, 0.150 g) in MeOH (3.5 ml) was boiled for 4 h, then MeOH was evaporated *in vacuo*, the residue was extracted by CH₂Cl₂ (6 ml), the CH₂Cl₂-extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.089 g (72 %) of *N*-ethoxy-*N*-methoxyurea **6**, identified by ¹H NMR.

RESULTS AND DISCUSSION

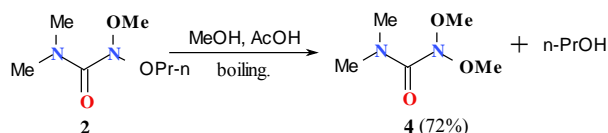
This work is devoted to study of the influence of conditions of alcoholysis of *N*-acyloxy-*N*-alkoxyureas on the nature of formed products. As we found the main product of methanolysis *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** in boiling methanol (4 h) was *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4** (Scheme 2).



Scheme 2

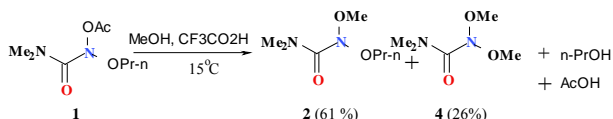
Probably, at the first stage *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2** forms by nucleophilic substitution of acetoxy group at nitrogen in compound **1**. The weak signals of protons of urea **2** can be observed in ^1H NMR of reaction mixture. Then, at second stage, the transesterification of *N,N*-dialkoxyamino group of *N,N*-dialkoxyurea **2** by methanol arises yielding *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4**. Presumably the other product of propanolysis *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1**, acetic acid, catalyses this transesterification but only at boiling temperature (64°C), not at room temperatures.¹⁰ As was found earlier,^{17,18} transesterification of *N,N*-dialkoxyamino group of *N,N*-dialkoxy-*N*',*N*'-dimethylureas,¹⁷ and *N,N*-dialkoxy-*N*-*tert*-alkylamines,¹⁸ took place by catalysis of more strong acids, such as TsOH.

This presumption is supposed by the independent transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2** to *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4** by the boiling of methanolic solution of compound **2** in the presence of acetic acid during 4 hours (Scheme 3)



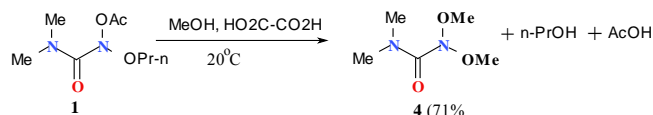
Scheme 3

We suggested that in the presence of acid, which is more strong than acetic acid, the secondary transesterification will be occur at methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** at room temperature. Actually, it methanolysis in presence of trifluoroacetic acid at 15°C for 5 hour yields the mixture of *N,N*-dialkoxyureas **2** and **4** in molar ratio 69.8 %:30.2 %. Respectively, yield of **2** is 61 %, yield of **4** is 26 %.



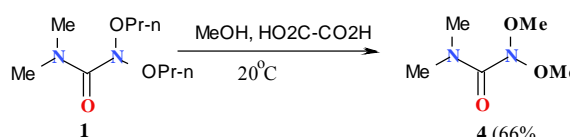
Scheme 4

In the presence of oxalic acid *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** converted by the methanolysis at 20°C for 100 hour selectively in *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4** (Scheme 5). The traces of *N,N*-dialkoxyurea **2** are absent in the reaction mixture.



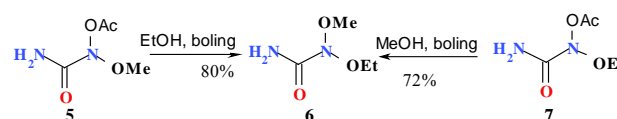
Scheme 5

Indeed, *N*-methoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **2** easily react with MeOH on the presence of oxalic acid (20°C , 73 h), yielding *N,N*-dimethoxy-*N*',*N*'-dimethylurea **4** (Scheme 6)



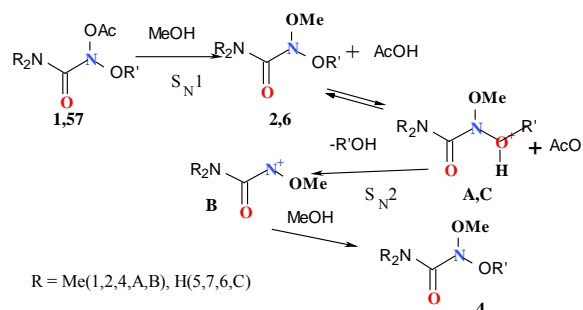
Scheme 6

Interestingly that for “unsubstituted” *N*-acetoxy-*N*-alkoxyureas **5,7** transesterification of *N,N*-dialkoxyamino group in boiling alcohols in the presence of acetic acid don't take place (Scheme 7).



Scheme 7

This difference in the reactivity of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea **1** and *N*-acetoxy-*N*-alkoxyureas **5,7** can be understood on the assumption of $\text{S}_{\text{N}}1$ mechanism of transesterification *N,N*-dialkoxyamino group (Scheme 8). Earlier Glover has found that *N*-acetoxy-*N*-alkoxybenzamides underwent acid-catalyzed solvolysis by the $\text{A}_{\text{Al}}1$ ($\text{S}_{\text{N}}1$) mechanism.^{2,4,19}



Scheme 8

At the first stage the nucleophilic substitution of acetoxy group by $\text{S}_{\text{N}}2$ mechanism,^{2,4,6} take place. Then reversible O-protonation *N,N*-dialkoxyureas **2,6** arises. At the methanol boiling temperature protonated intermediate **A** (R=Me)

dissociates to nitrenium cation **B**, which reacts with methanol yielding *N,N*-dimethoxyurea **4**. The dimethylcarbamoyl moiety is only weakest electron-withdrawing substituent than methoxynitrenium cation **B** destabilization arises.

In the case of protonated intermediate **C** (R = H) it further dissociation to unstable methoxynitrenium cation becomes impossible because its carbamoyl moiety has substantial electron-withdrawing effect.

Thus methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N*',*N*'-dimethylurea in the presence of strong acids at room temperatures or in the boiling methanol proceeds as two stage process yielding *N,N*-dimethoxy-*N*',*N*'-dimethylurea as final product.

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