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


Keywords: nucleophilic substitution at nitrogen; N-acyloxy-N-alkoxyureas; N,N-dialkoxyureas; methanolysis.

The methanolysis of N-acyloxy-N-n-propoxy-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-propoxy-N',N'-dimethylurea take place.

INTRODUCTION

Amides,1−9 carbamates,10,11 and ureas12−15 having at nitrogen atom two electronegative substituents, one of them is alkoxy group and other substituent may be alkoxy group, acyloxy group, chloride atom, 1-pyrindinium group, are called “anomeric amides” due to δD(AkR)=σ*N,X (X= OC(O)R, Cl, OAlk, N=C6H5) anomeric effect domination. In X=N−O(R) group amide nitrogen is sp2 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 Sn2 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-dialkoxyurases7 (Scheme 1). If the methanolysis of N-acyloxy-N-n-propoxy-N',N'-dimethylurea 1 arises during 55 hours, the final isopropanolation of compound 1 occurs during 1224 hours.10 The tert-butanalysis of compound 1 no take place at room temperature because steric hindrances to the nucleophilic substitution at nitrogen,10 realized, probably, via Sn2 mechanism.2,4,6,8,10

By alcoholysis at room temperatures N-acyloxy-N-n-propoxy-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 – Me2Si), 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-reactent isobutane. MeOH was dried by boiling and distillation over Ca.

N-Acetoxy-N-n-propoxy-N',N'-dimethylurea (1).18

Yellowish oil, nD20 1.4561. 1H NMR (300 MHz, CDCl3): 0.95 (t, 3H, OCH3-CH3Me, 3J = 7.2 Hz), 1.68 (sex, 2H, OCH2-CH2Me, 2J = 7.2 Hz), 2.15 (s, 3H, NOCMe), 3.04 (s, 6H, NMe2), 4.04 (t, 2H, OCH2-CH2Me, 3J = 7.2 Hz), IR (ν, cm−1): 1784 (C=O), 1732 (C=O), MS (Cl, m/z (I%)): 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 C14H18N2O4 (%): C 47.05, H 7.90, N 13.72.
Methanolysis of N-acetoxy-N-n-propyloxy-N',N'-dimethyleurea (1) in boiling MeOH.

The solution of N-acetoxy-N-n-propyloxy-N',N'-dimethyleurea 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'-dimethyleurea 4, colorless liquid, bp. 98 – 99.5 °C (7 Torr), ν<sub>30</sub> 1.4470, identified with the reference sample of 2,10 by 1H NMR. 1H NMR (300 MHz, CDCl<sub>3</sub>): 3.00 (s, 6H, NMe<sub>2</sub>), 3.75 (s, 6H, N(OMe)<sub>2</sub>).

N,N-Dimethoxy-N',N'-dimethyleurea (4)

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

N-Methoxy-N-n-propyloxy-N',N'-dimethyleurea (2).

Colorless oil, bp. 95-95.5 °C (1 Torr); ν<sub>30</sub> 1.4449, obtained by the methanolysis of N-acetoxy-N-n-propyloxy-N',N'-dimethyleurea 1 at 20 °C for 55 h with yield 80 %10 and n-propanolysis of N-acetoxy-N-methoxy-N',N'-dimethylurea,10 at 30 °C for 264 h with yield 82 %. 1H NMR (300 MHz, CDCl<sub>3</sub>): 0.96 (t, 3H, CH<sub>3</sub>CH<sub>2</sub>Me, δ = 7.1 Hz), 1.67 (sex, 2H, CH<sub>2</sub>CH<sub>2</sub>Me, δ = 7.1 Hz), 3.00 (s, 6H, NMe<sub>2</sub>), 3.73 (s, 3H, NOME<sub>2</sub>), δ = 7.1 Hz). MS (Cl, m/z (Irel(%)): 177 [M+H]<sup>+</sup> (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 CH<sub>11</sub>N<sub>2</sub>O<sub>3</sub> (%): C 47.71, H 9.15, N 15.90.

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

The solution of N-methoxy-N-n-propyloxy-N',N'-dimethyleurea 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 °C for 23 °C, yielding 0.052 g (72 %) N,N-dimethoxy-N',N'-dimethyleurea 4, identified by 1H NMR.

Methanolysis of N-acetoxy-N-n-propyloxy-N',N'-dimethyleurea (1) in the presence of CF<sub>3</sub>CO<sub>2</sub>H.

N-Acetoxy-N-n-propyloxy-N',N'-dimethyleurea 1 (1.474 mmol, 0.301 g) was added to solution of CF<sub>3</sub>CO<sub>2</sub>H (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 Et<sub>2</sub>O (6 ml). EtO-Extract was evaporated in vacuo, the residue was kept at 2 °C for 20 °C, yielding 0.214 g yellowish oil, which was identified by 1H NMR as mixture of N-methoxy-N-n-propyloxy-N',N'-dimethyleurea 2,10 and N,N-dimethoxy-N',N'-dimethyleurea 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'-dimethyleurea (1) in the presence of oxalic acid.

N-Acetoxy-N-n-propyloxy-N',N'-dimethyleurea 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 Et<sub>2</sub>O (10 ml). EtO-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'-dimethyleurea 4, identified by 1H NMR.

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

The mixture of N-methoxy-N-n-propyloxy-N',N'-dimethyleurea 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 Et<sub>2</sub>O (3 ml). EtO-Extract was evaporated in vacuo, the residue was extracted mixture of Et<sub>2</sub>O (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'-dimethyleurea 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 CH<sub>2</sub>Cl<sub>2</sub> (3 ml), the CH<sub>2</sub>Cl<sub>2</sub>-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, ν<sub>30</sub> 1.4493, identified by 1H NMR and MS. 1H NMR (300 MHz, CDCl<sub>3</sub>): 1.33 (t, 3H, CH<sub>2</sub>CH<sub>2</sub>Me, δ = 6.9 Hz), 3.84 (s, 3H, NOME<sub>2</sub>), 4.13 (q, 2H, NOCH<sub>2</sub>Me, δ = 6.9 Hz), 5.64 (br. s, 1H, NH), 5.96 (br. s, 1H, NH). MS (FAB, Na<sup>+</sup>, m/z (Irel(%))): 157 [M+Na]<sup>+</sup> (22), 89 H<sub>2</sub>NCO(O)N'Ome (25), 72 (77), 58 (100). Found (%): C 35.93, H 7.80, N 20.69. Calc. for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub> (%): 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 CH<sub>2</sub>Cl<sub>2</sub> (6 ml), the CH<sub>2</sub>Cl<sub>2</sub>-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-acetoxy-N-alkoxyureas on the nature of formed products. As we found the main product of methanolysis N-acetoxy-N-n-propyloxy-N',N'-dimethyleurea 1 in boiling methanol (4 h) was N,N-dimethoxy-N',N'-dimethyleurea 4 (Scheme 2).
Methanalysis of N-acetoxy-\(n\)-propoxy-\(N',N'\)-dimethylurea

Scheme 2

Probably, at the first stage \(N\)-methoxy-\(n\)-propoxy-\(N',N'\)-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 \(^1\)H NMR of reaction mixture. Then, at second stage, the transesterification of \(N,N\)-dialkoxyamino group of \(N,N\)-dialkoxycurea 2 by methanol arises yielding \(N,N\)-dimethoxy-\(N',N'\)-dimethylurea 4. Presumably the other product of propanolysis \(N\)-acetoxy-\(n\)-propoxy-\(N',N'\)-dimethylurea 1, acetic acid, catalyses this transesterification but only at boiling temperature (64 °C), not at room temperature.\(^{\text{10}}\) As found earlier,\(^{\text{17,18}}\) transesterification of \(N,N\)-dialkoxycurea group of \(N,N\)-dialkoxo-\(N',N'\)-dimethylureas,\(^{\text{17}}\) and \(N,N\)-dialkoxo-\(N\)-tert-alkylamines,\(^{\text{18}}\) took place by catalysis of more strong acids, such as TsOH.

This presumption is supposed by the independent transesterification of \(N\)-methoxy-\(n\)-propoxy-\(N',N'\)-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 aced, the secondary transesterification will be occur at methanalysis of \(N\)-acetoxy-\(n\)-propoxy-\(N',N'\)-dimethylurea 1 at room temperature. Actually, it methanalysis in presence of trifluoroacetic acid at 15 °C for 5 hours yields the mixture of \(N,N\)-dialkoxycurea 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-\(n\)-propoxy-\(N',N'\)-dimethylurea 1 converted by the methanalysis at 20 °C for 100 hour selectively in \(N,N\)-dimethoxy-\(N',N'\)-dimethylurea 4 (Scheme 5). The traces of \(N,N\)-dialkoxycurea 2 are absent in the reaction mixture.

Scheme 5

Indeed, \(N\)-methoxy-\(n\)-propoxy-\(N',N'\)-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-\(n\)-alkoxycureas \(5,7\) transesterication of \(N,N\)-dialkoxycurea 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-\(n\)-propoxy-\(N',N'\)-dimethylurea 1 and \(N\)-acetoxy-\(n\)-alkoxyurea 5,7 can be understood on the assumption of \(S_{\text{N}}\) mechanism of transesterification \(N,N\)-dialkoxycurea group (Scheme 8). Earlier Glover has found that \(N\)-acetoxy-\(n\)-alkoxybenzamides underwent acid-catalyzed solvolysis by the \(A_{\text{Al}}\) (\(S_{\text{N}}\)1) mechanism.\(^{\text{2,4,19}}\)

Scheme 8

At the first stage the nucleophilic substitution of acetoxy group by \(S_{\text{N}}\)2 mechanism,\(^{\text{2,4,6}}\) take place. Then reversible OH-protonation \(N,N\)-dialkoxycurea 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 it carbamoyl moiety has substantial electron-withdrawing effect.

Thus methanolation of N-acetoxy-N-η-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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References


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