Chemistry of Heterocyclic Compounds, Vol. 42, No. 6, 2006

INTERMEDIATES IN THE TRANSFORMATION OF 1,2-DIALKYLPYRIMIDINIUM IODIDES IN THE KOST-SAGITULLIN REARRANGEMENT

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Intermediate recyclization products were obtained in a study of the Kost–Sagitullin rearrangement of a series of 1,2-dialkylpyrimidinium iodides. The initial attack of the nucleophile leads to the formation of products of the addition of the hydroxyl group, namely, the corresponding pseudo bases. Heating one of these intermediates in ethanol or in the presence of primary amines leads to rearrangement to give a pyridone derivative. Upon heating in chloroform, the pseudo bases readily lose a water molecule and are converted to anhydro bases, namely, derivatives of 1-alkyl-1,2-dihydro-2-methylidenepyrimidine.

Keywords: alkylamines, 1-alkyl-1,2-dihydro-2-methylidenepyrimidines, anhydro bases, 1,2-dialkylpyrimidinium iodides, pyridone, pyrimidone, Kost–Sagitullin rearrangement, pseudo bases.

Pseudo base **2a** is formed upon the action of KOH on 2-(ethoxycarbonyl)methyl-1,4,6-trimethylpyrimidinium iodide (**1a**) at 0°C, which indicates initial attack of the hydroxide ion at $C_{(2)}$ in the pyrimidine ring [1]. The structure of **2a** was indicated by ^{1}H NMR and IR spectroscopy, while the mass spectrum corresponded to the product of the elimination of water, namely, anhydro base **3a.**

We have shown in subsequent studies that brief heating of pseudo base **2a** in chloroform leads to anhydro base **3a** in quantitative yield, while the complete accord of the mass spectrum of **3a** with the mass spectrum previously recorded in a study of **2a** (discrepancies only in the peak intensities) supports our previous proposal [1] of the loss of water upon electron impact during the recording of the mass spectrum of **2a**.

The similar attack of the hydroxide ion at $C_{(2)}$ in the pyrimidine ring was also noted in the reaction of 2-(ethoxycarbonyl)methyl-1-ethyl-4,6-dimethylpyrimidinium iodide (**1b**) with KOH, leading to pseudo base **2b**, which also loses a water molecule upon heating in chloroform.

We note that the elimination of water from pseudo base **2b** upon heating in chloroform proceeds very rapidly. Thus, only anhydro base **3b** is recorded in the mass spectrum and also in the ^{1}H NMR spectrum in $CDCl_3$. Products **2b** and **3b** differ in their physicochemical characteristics and IR spectral data, which served to establish the structure of pseudo base **2b** (Table 1).

Heating 2-(carbamoyl)methyl-1,4,6-trimethylpyrimidinium iodide (**1c**) with an equivalent of KOH in absolute ethanol for 1 min leads to anhydro base **3c**, probably also through the intermediate formation of pseudo base **2c**. Anhydro base **3c** was isolated by chloroform extraction. By analogy with the previous examples, this transformation also involves water elimination. The chloroform extraction was carried out to avoid side reactions occurring when using polar solvents since the intermediates of the transformation of iodide **1c** do not dissolve in nonpolar solvents.

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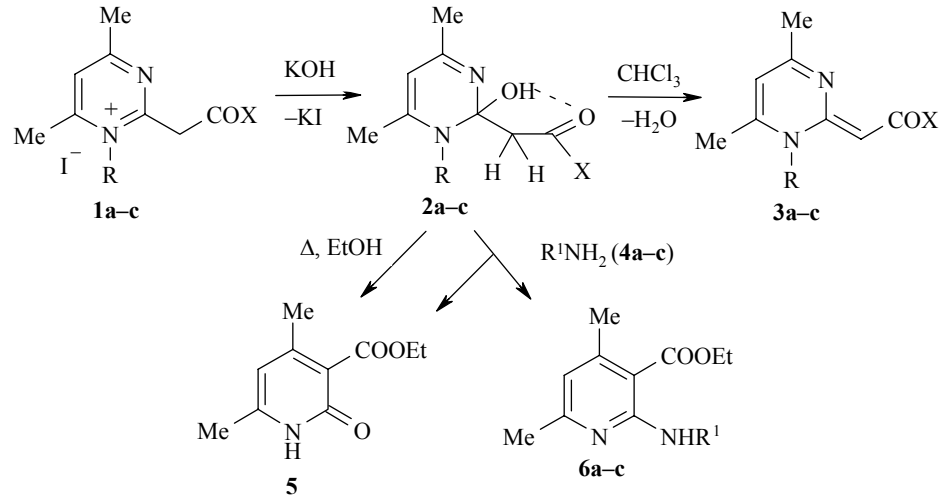
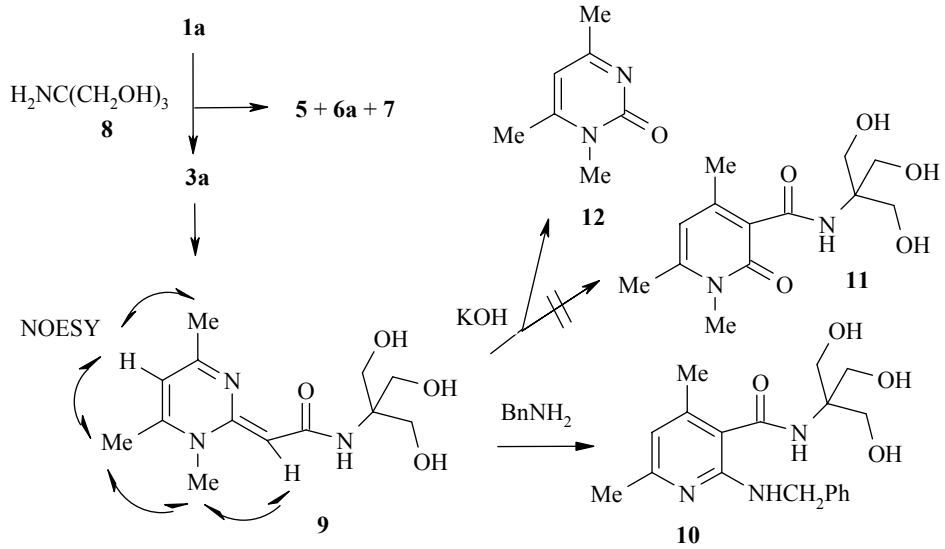


1-3 a R = Me, X = OEt; **b** R = Et, X = OEt; **c** R = Me, X = NH_2;
4,6 a R^1 = Me, **b** R^1 = Bn, **c** R^1 = CH_2CH_2OH

Pseudo base **2a** rearranges upon heating in absolute ethanol and also in the presence of primary amines **4a-c** to give mostly pyridone **5**, which is also formed in the rearrangement of **1a** by the action of primary amines in an aqueous medium [2]. The product of the normal rearrangement, 2-methylamino derivative **6a**, and in the reaction with amines **4b** and **4c** the "product of the rearrangement with transamination" **6b** and **6c**, are formed in small amounts. Partial demethylation also occurs, leading to pyrimidines **7**.

The reaction of salt **1a** in absolute ethanol with tris(hydroxymethyl)aminomethane (**8**) gave anhydro base **9** in 32% yield. When this reaction is carried out in 96% aq. ethanol, the yield drops to 12% due to a proportional increase in the yield of pyridone **5** (from 26 to 48%). Anhydro base **3a** is probably formed initially. The reaction of **3a** with the amine possessing bulky substituents proceeds not on the pyrimidine ring but rather at the ethoxycarbonyl group. Pseudo base **2a** also forms when water, attributed to the hygroscopicity of amine **8**, is present in the reaction medium and either recyclizes to give **5** and **6a** or converts to anhydro base **3a**.



We should stress that anhydro base **9** recyclizes upon the action of benzylamine to give the corresponding product of rearrangement with transamination **10**, which further indicates the steric reason for the impossibility of recyclization by the action of amine **8**.

TABLE 1. Physicochemical Characteristics of Compounds **2b, 3a-c, 9, 10** and **12**

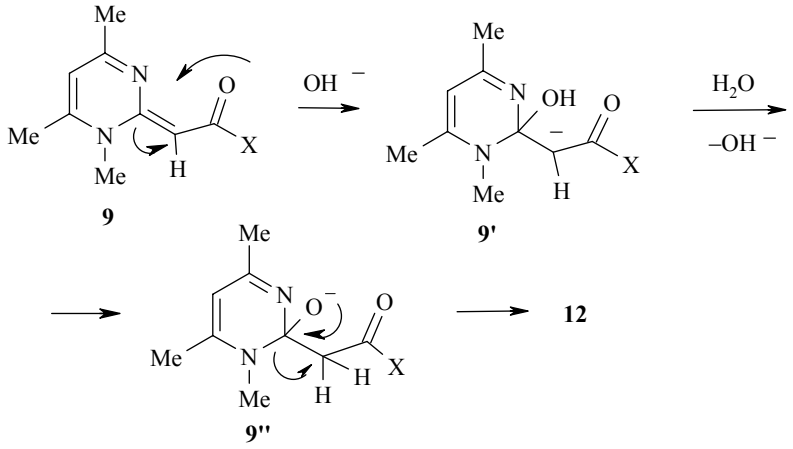
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (2-propanol–ammonia)	IR spectrum, characteristic bands, ν, cm^{-1}			Yield, %
		C	H	N			C=O*	C=C and C=N	other	
2b	$C_{12}H_{20}N_2O_3$	60.22 / 59.98	8.74 / 8.39	11.97 / 11.66	162-164, bright-yellow crystals	0.64 (1:1)	1640	1530, 1550, 1600	3350-3460 (OH)	89
3a	$C_{11}H_{16}N_2O_2$	63.19 / 63.44	8.12 / 7.74	13.59 / 13.45	dark-yellow liquid	0.63 (1:1)	1680 (1730)	1540, 1590, 1600, 3060, 3140, 3235	3450-3560 (H_2O)	98
3b	$C_{12}H_{18}N_2O_2$	64.58 / 64.84	8.32 / 8.16	12.89 / 12.60	dark-yellow liquid	0.66 (1:1)	1675 (1735)	1540, 1600, 1610, 3070, 3140, 3240	3370-3530 (H_2O)	99
3c	$C_9H_{13}N_3O$	60.24 / 60.32	7.44 / 7.31	23.63 / 23.45	200-201, bright-yellow crystals	0.62 (1:1)	1625 (1650)	1540, 1580, 1600	3300, 3450 (NH_2)	73
9	$C_{13}H_{21}N_3O_4$	55.26 / 55.11	7.36 / 7.47	14.69 / 14.83	230-231, bright-yellow crystals	0.41 (2:1)	1620	1530, 1560, 1590	3200-3350 (OH)	32, 12*[2]
10	$C_{19}H_{25}N_3O_4$	63.62 / 63.49	7.16 / 7.01	11.56 / 11.69	brown liquid	0.51 (2:3)*[3]	1625	1510, 1580, 1595	3300-3420 (NH, OH)	25
12	$C_7H_{10}N_2O$	60.69 / 60.85	7.38 / 7.29	20.22 / 20.27	60-61 (63 [9]), white crystals (rapidly turn red in the air)	0.53 (2:1)	—	—	—	82

* Data for **1a-c** given correspondingly in parentheses.

*[2] When reaction is carried out in 96% aq. ethanol.

*[3] Toluene–acetone as eluent.

We could not isolate the product of the rearrangement of pyridone **11** upon the action of a solution of KOH in aqueous ethanol on anhydro base **9**. This reaction gave pyrimidone **12**, which probably forms through the attack of the hydroxide ion at $C_{(2)}$ of the corresponding anhydro base to give carbanion **9'**, whose subsequent transformation through intermediate **9"** leads to cleavage of the $C_{(2)}$–$C_{(2')}$ bond and formation of pyrimidone **12**.



Carbonyl group stretching bands are found in the IR spectra of starting salts **1a** and **1b** at 1730-1735 cm^{-1} (Table 1). In previous work [1], we have shown that the carbonyl group band for pseudo base **2a** is shifted by 90 cm^{-1} due to intramolecular hydrogen bonding and is found at 1640 cm^{-1}. As expected, a similar shift is observed for anhydro base **3a.** In comparison with starting salts **1a** and **1b**, the C=O group bands for **3a** and **3b** are shifted by 50 cm^{-1} due to double bond conjugation. The carbonyl band for iodide **1c** is found at 1650 cm^{-1}, while this band for anhydro base **3c** is shifted by 25 cm^{-1} and found at 1625 cm^{-1}. The band for the carbonyl group of the amide fragment of anhydro base **9** is also found in this region at 1620 cm^{-1}.

The ^1H NMR spectra of anhydro bases **3a-c** and **9** show characteristic signals for the methine group protons at 4.16-4.49 ppm, while the ^{13}C NMR spectra of **3c** and **9** show characteristic signals at 83.00-84.39 ppm. The ^1H NMR spectra of anhydro bases **3a-c** and **9** show a strong shift for the pyrimidine ring H-5 protons (5.62-5.76 ppm) relative to the signals for these protons in starting iodides **1a-c** (7.98-8.17 ppm) and their nonquaternized analogs (6.93-7.0 ppm) [3], which is attributed to rearomatization of the pyrimidine ring. The ^1H and ^{13}C NMR spectral data for pyrimidone **12** are virtually the same as the literature data [4]. Cross peaks between the protons of a series of groups indicated in the scheme shown above are found in the ^1H NMR spectrum of anhydro base **9** taken using NOESY two-dimensional spectroscopy, which is in accord with the structure assigned for **9**.

Thus, the Kost–Sagitullin rearrangement in a series of 1,2-dialkylpyrimidinium iodides by the action of hydroxide ion proceeds through initial attack on $C_{(2)}$ of the pyrimidine ring. The resultant pseudo bases **2a-c** readily lose a water molecule in chloroform and convert to the corresponding anhydro base form **3a-c.** The major product of the transformation of pseudo base **2a** upon heating in ethanol and also in the presence of amines is pyridone **5**.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ (**3a-c**) and DMSO-d_6 (**9, 10, 12**) using TMS as the internal standard. The mass spectra were taken on an MK-1321 mass spectrometer with direct sample inlet into the ion source and 70 eV ionizing

energy. The IR spectra were taken on a UR-20 spectrometer for KBr pellets, chloroform solution, or vaseline mull. The thin-layer chromatography was carried out on Silufol UV-254 plates with detection by iodine vapor and Ehrlich reagent. Preparative separation was carried out on a silica gel column (L5/40): **5** [R_f 0.52 (1:2 toluene–acetone)], **6a** [R_f 0.62 (4:1 toluene–acetone)], **6b** [R_f 0.75 (10:1 toluene–acetone)], **6c** [R_f 0.52 (2:1 toluene–acetone)], **7** (R_f 0.67 (1:1 toluene–acetone)]. The chromatographic mobility, melting point, and NMR spectral data of these compounds are identical to those found for authentic samples [2, 5-8].

2-(Ethoxycarbonyl)methyl-1-ethyl-2-hydroxy-4,6-dimethyl-1,2-dihydropyrimidine (2b). A solution of salt **1b** (2.1 g, 6 mmol) in absolute ethanol (7 ml) was cooled to 0°C and KOH (0.4 g, 6 mmol) pellets (containing 85% KOH) in absolute ethanol (5 ml) was gradually added with stirring. The precipitate formed was filtered off and washed with cold absolute ethanol (5 ml) to give 1.28 g (89%) pseudo base **2b**. Mass spectrum, *m/z* (I_{rel}, %): 222 (67), 194 (15), 176 (69), 149 (100), 123 (68), 109 (10), 81 (18), 69 (28), 42 (36), 29 (21).

2-(Ethoxycarbonyl)methylidene-1,4,6-trimethyl-1,2-dihydropyrimidine (3a). A sample of pseudo base **2a** (1.13 g, 5 mmol) in $CHCl_3$ (5 ml) was heated for 1 min. The solvent was distilled off and dried in vacuum to give 1.02 g (98%) of anhydro base **3a**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, $\underline{CH_3}CH_2O$); 2.22 (3H, s, 4-CH_3); 2.30 (3H, s, 6-CH_3); 3.19 (3H, s, 1-CH_3); 4.16 (2H, q, *J* = 7.1, O$\underline{CH_2}CH_3$); 4.46 (1H, s, H-2'); 5.76 (1H, s, H-5). Mass spectrum, *m/z* (I_{rel}, %): 208 (76), 179 (8), 162 (100), 136 (64), 134 (64), 108 (65), 93 (20), 80 (25), 65 (28), 55 (30), 43 (31), 28 (60).

2-(Ethoxycarbonyl)methylidene-1-ethyl-4,6-dimethyl-1,2-dihydropyrimidine (3b). By analogy to the procedure for anhydro base **3a**, pseudo base **2b** (1.2 g, 5 mmol) gave 1.1 g (99%) of anhydro base **3b.** ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, $\underline{CH_3}CH_2O$); 1.35 (3H, t, *J* = 7.1, $\underline{CH_3}CH_2N$); 2.24 (3H, s, 4-CH_3); 2.27 (3H, s, 6-CH_3); 3.73 (2H, q, *J* = 7.1, N–CH_2); 4.16 (2H, q, *J* = 7.1, O$\underline{CH_2}$); 4.54 (1H, s, H-2'); 5.71 (1H, s, H-5).

2-(Carbamoyl)methylidene-1,4,6-trimethyl-1,2-dihydropyrimidine (3c). A sample of KOH pellets (containing 85% KOH) (0.33 g, 5 mmol) was dissolved in absolute ethanol (5 ml) and then added to a solution of salt **1c** (1.5 g, 4.9 mmol) in absolute ethanol (20 ml). The mixture was then heated for 1 min until the salt completely dissolved. The solvent was distilled off in vacuum. The residue was washed with chloroform (8 × 10 ml). Removal of the solvent gave 0.64 g (73%) anhydro base **3c**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, 4-CH_3); 2.20 (3H, s, 6-CH_3); 3.14 (3H, s, 1-CH_3); 4.49 (1H, s, H-2'); 5.23 (1H, br. s, NH); 5.62 (1H, s, H-5); 8.87 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.11 (4-CH_3), 24.76 (6-CH_3), 34.62 (1-CH_3), 84.39 (2-CH), 103.14 ($C_{(5)}$), 154.22 ($C_{(4)}$), 154.74 ($C_{(6)}$), 166.08 ($C_{(2)}$), 171.39 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 179 (89), 162 (100), 149 (45), 135 (43), 108 (49), 94 (33), 67 (26), 55 (46), 42 (60), 28 (61).

Recyclization of Pseudo Base 2a upon Heating in Ethanol. A mixture of **2a** (1.13 g, 5 mmol) in absolute ethanol (10 ml) was heated for 10 h. The solvent was distilled off and the residue was washed with chloroform. The chloroform extract was subjected to preparative separation by column chromatography using 2:1 toluene–acetone as the eluent to give 0.6 g (61%) pyridone **5**, 0.07 g (7%) **6a**, and 0.05 g (5%) 2-(ethoxycarbonyl)methyl-4,6-dimethylpyrimidine (**7**).

Recyclization of Pseudo Base 2a upon Reaction with Amines 4a-c in Ethanol (General Procedure). A mixture of **2a** (1.13 g, 5 mmol) and amine **4a-c** (5 mmol) in absolute ethanol (10 ml) was heated at reflux for 12-16 h. The solvent and, in the case of methylamine, excess amine were distilled off. The residue was dissolved in water and extracted with toluene (5 × 10 ml). Column chromatography of the toluene solution using 4:1 toluene–acetone as the eluent gave a) in the case of methylamine **4a**, 0.48 g (49%) pyridone **5**, 0.8 g (8%) **6a**, and 0.04 g (4%) **7**, b) in the case of benzylamine **4b**, 0.54 (55%) pyridone **5**, 0.05 g (5%) **6a**, 0.07 g (7%) **7**, and 0.013 g (9%) **6b**, and c) in the case of ethanolamine **4c**, 0.58 g (60%) pyridone **5**, 0.07 g (7%) **7**, and 0.06 g (5%) pyridine **6c**.

Reaction of Salt 1a with Tris(hydroxymethyl)aminomethane (8) in Absolute Ethanol. A mixture of salt **1a** (4 g, 12 mmol) and amine **8** (4.35 g, 24 mmol) in absolute ethanol (15 ml) was heated at reflux for 30 h. The precipitate formed was filtered off and recrystallized from absolute ethanol to give 0.78 g (32%)

1,4,6-trimethyl-2-[tris(hydroxymethyl)methylcarbamoyl]methylidene-1,2-dihydropyrimidine (**9**). The solvent was distilled off the filtrate and the residue was separated on a column using 1:1 toluene–acetone as the eluent to give 0.6 g (26%) **5**, 0.15 g (6%) pyridine **6a**, and 0.2 g (9%) pyrimidine **7**. ^{1}H NMR spectrum of **9**, δ, ppm (*J*, Hz): 2.18 (3H, s, 4-CH_3); 2.26 (3H, s, 6-CH_3); 3.12 (3H, s, 1-CH_3); 3.43 (6H, s, CH_2); 4.24 (1H, s, H-2'); 5.17 (3H, br. s, OH); 5.74 (1H, s, H-5); 9.79 (1H, br. s, CONH). ^{13}C NMR spectrum of **9**, δ, ppm: 20.29 (4-CH_3), 23.63 (6-CH_3), 34.31 (1-CH_3), 61.39 (CH_2), 61.66 (NHC), 83.00 (2-CH), 102.60 ($C_{(5)}$), 153.47 ($C_{(4)}$), 155.85 ($C_{(6)}$), 165.69 ($C_{(2)}$), 169.22 (C=O).

Reaction of Salt 1a with Tris(hydroxymethyl)aminomethane (8) in 96% Aqueous Ethanol. A mixture of salt **1a** (2 g, 6 mmol) and amine **8** (1.45 g, 8 mmol) in 96% aq. ethanol (15 ml) was heated at reflux for 20 h. The solvent was distilled off and the residue was dissolved in absolute ethanol (15 ml). After cooling, the reaction solution was treated analogously to the procedure for the reaction of **1a** and **8** in absolute ethanol to give 0.2 g (12%) **9**, 0.56 g (48%) **5**, 0.05 g (4%) **6a**, and 0.1 g (9%) **7**.

2-Benzylamino-4,6-trimethyl-3-[N-tris(hydroxymethyl)methyl]carbamoylpyrimidine (10). A mixture of anhydro base **9** (0.9 g, 3.2 mmol) and amine **4b** (2 ml, 18 mmol) was heated at reflux for 2 h. Preparative separation by column chromatography using 3:1 toluene–acetone gave 0.29 g (25%) **10**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.20 (3H, s, 4-CH_3); 2.25 (3H, s, 6-CH_3); 3.68 (6H, d, *J* = 5.6, $\underline{CH_2}$OH); 4.56 (3H, t, *J* = 5.6, OH); 4.59 (2H, d, *J* = 6.0, NH$\underline{CH_2}$); 6.20 (1H, s, H-5); 6.61 (1H, t, *J* = 6.0, 2-NH); 7.17 (1H, br. s, CONH); 7.14, 7.24, and 7.34 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 18.63 (4-CH_3), 23.76 (6-CH_3), 43.82 ($NHCH_2$), 62.34 (CH_2OH), 112.32 ($C_{(5)}$), 114.67 ($C_{(3)}$), 125.66 ($C_{(4')}$), 127.14 ($C_{(2')}$), $C_{(6')}$), 127.14 ($C_{(3')}$, $C_{(5')}$), 140.69 ($C_{(1')}$), 143.88 ($C_{(4)}$), 154.21 ($C_{(6)}$), 155.25 ($C_{(2)}$).

Reaction of Anhydro Base 9 with KOH in Aqueous Ethanol. Anhydro base **10** (0.425 g, 1.5 mmol) was dissolved in 50% aq. ethanol (10 ml). Then, 85% KOH (0.396 g, 6 mmol) was added and the mixture was heated at reflux for 5 h. The solvent was distilled off in vacuum. The residue was washed with chloroform (3 × 5 ml), collecting the chloroform extracts. Removal of the solvent gave 0.17 g (82%) 1,4,6-trimethyl-2-oxo-1,2-dihydropyrimidine (**12**). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, 4-CH_3); 2.34 (3H, s, 6-CH_3); 3.42 (3H, s, 1-CH_3); 6.09 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 19.75 (4-CH_3), 24.11 (6-CH_3), 31.31 (1-CH_3), 104.19 ($C_{(5)}$), 155.85 ($C_{(4)}$), 156.70 ($C_{(6)}$), 172.38 ($C_{(2)}$). Mass spectrum, *m/z* (I_{rel}, %): 138 (100), 123 (75), 110 (13), 96 (13), 80 (12), 56 (18), 54 (17), 42 (17), 28 (43), 18 (15).

This work was carried out with the financial support of the National Fund for Science and Advanced Technology of Armenia and the Civilian Research and Development of the United States (NFSAT RA-US CRDF, Grant No. CH 090-02/12040) and as part of Science Subject 0543 of the Ministry of Science and Education of the Republic of Armenia.

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