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SYNTHESIS OF PYRIDIN-2(1H)-ONES BY THE INTRAMOLECULAR CYCLIZATION OF AMIDES OF β-ENAMINO KETONES

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It has been shown that intramolecular cyclization of N-(1-methyl-3-oxobut-1-en-1-yl)phenyl- and -tosylacetamides in basic media lead to 3-phenyl- and 3-tosyl-substituted 4,6-dimethylpyridin-2(1H)-ones.

Keywords: amide, β-enamino ketone, pyridin-2(1H)-ones, intramolecular cyclization.

The sole example of intramolecular ring closing of β-amino ketone amides leading to pyridine-2(1H)-ones is the cyclization of pyridinium salts, formed from chloroacetamide **1a** and pyridine, to 1-(1,2-dihydro-2-oxo-3-pyridinyl)pyridinium chloride **2** [1].

With the aim of studying the possibility of a similar reaction for other representatives of β-enamino ketone amides we synthesized phenylacetamide **1b** and tosylacetamide **1c**. Compounds **1a,b** have been obtained by the acylation of enamino ketone **3** [2] with the acid chloride of the corresponding carboxylic acid, compound **1c** – by the reaction of chloroacetamide **1a** with sodium *p*-toluenesulfonamide in DMF.

It was established that cyclization does not occur under the action of an alcoholic solution of alkali on compound **1b**. According to TLC data enamino ketone **3**, the product of its hydrolysis was confirmed in the reaction medium. 4,6-Dimethyl-3-phenylpyridin-2(1H)-one (**4**) was successfully obtained in 53% yield on conducting the reaction in THF in the presence of potassium *tert*-butylate. However in this case also, according to chromato-mass spectrometry, enamino ketone **3** is the reaction by-product, obtained as a result of hydrolysis of compound **1b** by the water formed on cyclization.

Tosylacetamide **1c** is converted into pyridine-2(1H)-one **5** even by the action of potassium carbonate in DMF solution. Nucleophilic substitution of chlorine by a tosyl group in compound **1a** and cyclization of the resulting tosylacetamide **1c** may be carried out as a one-pot synthesis. On interacting chloroacetamide **1a** with sodium *p*-toluenesulfinate in the presence of potassium carbonate pyridin-2(1H)-one **5** is formed in 71% yield. The availability of the initial compounds, the simplicity of carrying out the experiment, and the good and satisfactory yields enable the conclusion to be made that such an approach to the synthesis of pyridin-2(1H)-ones is promising.

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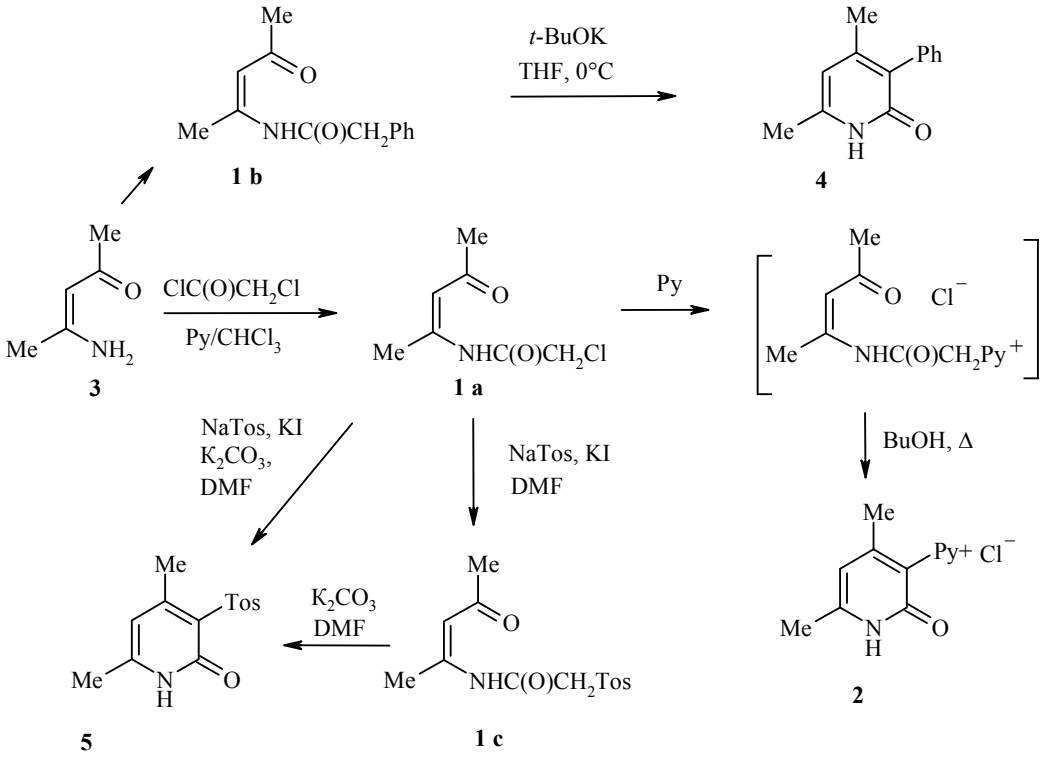

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of the investigated compounds were recorded on a Bruker ARX-300 spectrometer (300 and 75 MHz respectively) in $CDCl_3$ (compounds **1a-c**, **4**) and DMSO-d_6 (compound **5**), internal standard was TMS. The ^{13}C NMR spectra were obtained in *J*-modulation mode. The IR spectra were recorded on a INFRALUM FT-801 spectrometer in KBr disks. The mass spectra were recorded on an Agilent 5973N mass spectrometer (EI, energy of ionizing electrons 70 eV, evaporator temperature 230-250°C). A check on the progress of reactions and the purity of the compounds isolated was effected by TLC on Sorbfil AF-A-UV plates.

Preparation of Enamino Ketones 1a,b (General Method). The appropriate haloacid anhydride (10.5 mmol) was added dropwise to enamino ketone **3** (0.991 g, 10.0 mmol) and anhydrous pyridine (1 ml, 11.0 mmol) in absolute chloroform (15 ml) with stirring. The mixture was stirred for 1 h with cooling in ice and for 3 h at room temperature. Chloroform (10 ml) was then added and the solution was washed with 10% HCl solution (30 ml) and with water until the wash water gave a neutral reaction. The organic phase was dried with anhydrous sodium sulfate, and the chloroform distilled. The compound was recrystallized from an ethyl acetate–petroleum mixture, 40:70.

N-(1-Methyl-3-oxobut-1-en-1-yl)chloroacetamide (1a). Yield was 1.194 g (68%); mp 67-68°C (lit. mp 71°C [3]). IR spectrum, ν, cm^{-1}: 3150-3250 (NH), 1734 (C=O), 1593 (NC=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, $COCH_3$); 2.40 (3H, d, $^{4}J = 0.9$, =C–CH_3); 4.10 (2H, s, CH_2); 5.46 (1H, d, $^{4}J = 0.7$, =CH); 12.97 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.60 (=C–$\underline{C}H_3$); 30.47 (CO$\underline{C}H_3$); 43.17 (CH_2); 107.29 (=CH–); 153.51 (=C–N); 166.19 (NHCO); 199.77 ($\underline{C}$OMe).

N-(1-Methyl-3-oxobut-1-en-1-yl)phenylacetamide (1b). Yield was 1.138 g (56%); mp 42-43°C. IR spectrum, ν, cm^{-1}: 3300-3400 (NH), 1712 (C=O), 1598 (N–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, $COCH_3$); 2.35 (3H, d, $^{4}J = 0.9$, 1-CH_3); 3.66 (2H, s, CH_2); 5.30 (1H, s, =CH); 7.24-7.42 (5H, m, C_6H_5); 12.35 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.85 (=C–$\underline{C}H_3$); 30.43 (CO$\underline{C}H_3$); 45.65 (CH_2); 105.84 (=CH); 127.42

(C-4, C_6H_5); 128.88 (C-2, C-6, C_6H_5); 129.45 (C-3, C-5, C_6H_5); 133.73 (C-1, C_6H_5); 155.07 (=C–N); 170.69 (NHCO); 199.55 (COMe). Found, %: C 71.94; H 6.95; N 6.40. $C_{13}H_{15}NO_2$. Calculated, %: C 71.87; H 6.96; N 6.45.

N-(1-Methyl-3-oxobut-1-en-1-yl)-2-[(4-methylphenyl)sulfonyl]acetamide (1c). A mixture of chloroacetamide **1a** (0.176 g,1.0 mmol) sodium *p*-toluenesulfinate monohydrate (0.294 g, 1.5 mmol), and KI (0.017 g) in absolute DMF (3 ml) was stirred for 38 h, then poured into water (12 ml) and cooled. The precipitated solid was filtered off, and recrystallized from ethanol. Compound **1c** (0.265 g, 90%) was obtained with mp 160-161°C. IR spectrum, ν, cm^{-1}: 1601 (NC=O), 1704 (C=O), 3250-3400 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (3H, s, $COCH_3$); 2.30 (3H, d, ^4J = 0.7, =C–CH_3); 2.45 (3H, s, $C_6H_4CH_3$); 4.08 (2H, s, CH_2); 5.41 (1H, s, =CH); 7.36 (2H, d, ^3J = 8.1, Ar); 7.82 (2H, d, ^3J = 8.1, Ar); 12.60 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.64 ($C_6H_4CH_3$); 21.71 (=C–CH_3); 30.53 ($COCH_3$); 64.49 (CH_2); 107.23 (=CH-); 128.45, 129.98, 135.52, 145.54 (Ar); 153.42 (=C–N); 160.34 (NHCO); 199.82 (C=O). Found, %: C 55.55; H 5.42; N 4.94. $C_{13}H_{15}NO_4S$. Calculated, %: C 55.50; H 5.37; N 4.98.

4,6-Dimethyl-3-phenylpyridin-2(1H)-one (4). Potassium *tert*-butylate (0.084 g, 0.75 mmol) was added with ice-cooling and stirring to a solution of phenylacetamide **1b** (0.109 g, 0.5 mmol) in absolute THF (4 ml). After 2.5 h the solvent was evaporated, the residue triturated with water, the compound was filtered off, and recrystallized from ethanol. Compound **4** (0.053 g, 53%) was obtained with mp 212-213°C. IR spectrum, ν, cm^{-1}: 1628 (NC=O), 3300-3400 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, 4-CH_3); 2.22 (3H, s, 6-CH_3); 5.96 (1H, s, H-5); 7.19-7.50 (5H, m, C_6H_5); 12.87 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 18.74 (4-CH_3); 20.67 (6-CH_3); 109.10 (C-5); 126.95 (C-4, Ph); 127.16 (C-3); 128.03 (C-3, C-5, C_6H_5); 130.32 (C-2, C-6, C_6H_5); 135.97 (C-1, C_6H_5); 143.14 (C-4); 149.45 (C-6); 164.44 (C-2). Mass spectrum, *m/z*, 199 $[M]^{+\cdot}$. Found, %: C 78.40; H 6.53; N 6.98. $C_{13}H_{13}NO$. Calculated, %: C 78.36; H 6.58; N 7.03.

4,6-Dimethyl-3-[(4-methylphenyl)sulfonyl]pyridin-2-one (5). A mixture of compound **1a** (0.176 g, 1.0 mmol), K_2CO_3 (0.207 g, 1.5 mmol), sodium *p*-toluenesulfinate monohydrate (0.294 g, 1.5 mmol), 0.017g KI, and absolute DMF (3 ml) was stirred for 3 days, after which the mixture was poured into water (12 ml), and cooled. The solid was filtered off, and recrystallized from ethanol. Compound **5** (0.196 g, 71%) was obtained. Compound **5** (0.177 g, 64%) was also obtained having mp 268-270°C (decomp.) analogously, from compound **1c** (0.295 g, 1.0 mmol) and K_2CO_3 (0.207 g) in absolute DMF (3 ml) with stirring for 24 h. IR spectrum, ν, cm^{-1}: 1623 (NC=O), 3200-3400 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.16 (3H, s, 4-CH_3); 2.36 (3H, s, 6-CH_3); 2.62 (3H, s, $C_6H_4CH_3$); 6.07 (1H, s, H-5); 7.33 (2H, d, ^3J = 8.1, Ar); 7.80 (2H, d, ^3J = 8.1, Ar); 12.01 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.37 (6-CH_3); 20.91 (4-CH_3); 21.14 ($C_6H_4CH_3$); 109.15 (C-5); 122.70 (C-3); 127.55, 128.68, 139.46, 142.95 (Ar); 151.29 (C-6); 156.33 (C-4); 158.29 (NCO). Found, %: C 60.72; H 5.50; N 4.99. $C_{13}H_{13}NO_3S$. Calculated, %: C 60.63; H 5.45; N 5.05.

REFERENCES

1. K. Gewald, M. Rehwald, H. Müller, and P. Bellman, *Liebigs Ann. Chem.*, 787 (1995).
2. P. G. Baraldi, D. Simoni, and S. Manfredini, *Synthesis*, 902 (1983).
3. R. Shabana, J. B. Rasmussen, and S.-O. Lawesson, *Tetrahedron*, **37**, 1819 (1981).