3-N-ACYLATION OF 5-ETHOXYCARBONYL-6-METHYL-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2-ONE

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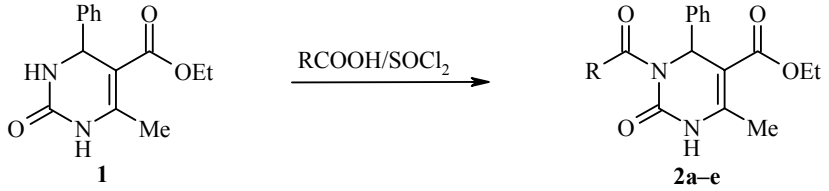
We know that acetylation of derivatives of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one (**1**) at the N(3) atom occurs in good yields when compound **1** is boiled in acetic anhydride [1, 2]. However, anhydrides of higher fatty acids are less accessible than the acids themselves, so it would be sensible to develop a general method for acylation that proposes using the carboxylic acids directly.

We have developed a convenient preparative method for synthesis of 3-acyl derivatives of compound **1** by boiling its solution in a mixture of the corresponding carboxylic acid and thionyl chloride in 10-fold excess relative to compound **1**. Under these conditions, we could obtain 3-acyl derivatives **2a-e** in 47-70% yields.



1 **2a–e**

a R = Me, **b** R = Et, **c** R = *n*-Pr, **d** R = *n*-Bu, **e** R = *n*-Am

Elemental analysis, IR and ^{1}H NMR spectra of the compounds obtained are completely consistent with the structure of 3-acyl derivatives of 5-carbethoxy-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one.

Compounds 2a-d (General Procedure). A mixture of $SOCl_2$ (4.8 g, 40 mmol) and 1 drop of DMF were added to a solution of compound **1** (4 mmol) in the corresponding carboxylic acid (40 mmol) that was cooled down to 20°C. Then the solution was boiled for 1-3 h (monitored by TLC). 4 ml water was added to the solution obtained; this was cooled and then EtOH was added dropwise until the solution was homogenized. Crystallization of the material was stimulated by rubbing with a rod. The material was filtered out and washed three times with 3 ml EtOH each.

3-Acetyl-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidinin-2-one (2a). Yield 47%; mp 176-177°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 10.15 (1H, s, NH); 7.13-7.37 (5H, m, Ph); 6.45 (1H, s, CH); 4.1 (2H, quartet, J = 8, OCH_2); 2.42 (3H, s, CH_3); 2.29 (3H, s, CH_3); 1.29 (3H, t, J = 8, $\underline{CH_3}CH_2$). IR spectrum (KBr), ν, cm^{-1}: 1649, 1702, 1715, 2970, 3196, 3236. Found, %: N 9.30. $C_{16}H_{18}N_2O_4$. Calculated, %: N 9.27.

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5-Ethoxycarbonyl-6-methyl-4-phenyl-3-propionyl-3,4-dihydropyrimidin-2-one (2b). Yield 70%; mp 185-186°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6, 200 MHz), δ, ppm (*J*, Hz): 10.14 (1H, s, NH); 7.14-7.37 (5H, m, Ph); 6.48 (1H, s, CH); 4.10 (2H, quartet, *J* = 7, OCH_2), 2.84-3.06 (1H, m, $COCH_2$); 2.62-2.84 (1H, m, $COCH_2$); 2.29 (3H, s, CH_3); 1.16 (3H, t, *J* = 7, $\underline{CH_3}CH_2O$); 1.02 (3H, t, *J* = 7.2, $\underline{CH_3}CH_2CO$). IR spectrum (KBr), ν, cm^{-1}: 1642, 1689, 1709, 2990, 3096, 3230, 3263. Found, %: N 9.09. $C_{17}H_{20}N_2O$. Calculated, %: N 8.86.

3-Butyroyl-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one (2c). Yield 54%; mp 138-140°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 10.13 (1H, s, NH); 7.12-7.37 (5H, m, Ph); 6.47 (1H, s, CH); 4.10 (2H, quartet, *J* = 7.4, OCH_2); 2.82-3.02 (1H, m, $COCH_2$); 2.60-2.80 (1H, m, $COCH_2$); 2.29 (3H, s, CH_3); 1.36-1.75 (2H, m, $COCH_2\underline{CH_2}$); 1.16 (3H, t, *J* = 7.4, $\underline{CH_3}CH_2O$); 0.86 (3H, t, *J* = 7.4, $\underline{CH_3}(CH_2)_2CO$). IR spectrum (KBr), ν, cm^{-1}: 1648, 1702, 2959, 3129, 3227. Found, %: N 8.59. $C_{18}H_{22}N_2O_4$. Calculated, %: N 8.48.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3-valeroyl-3,4-dihydropyrimidin-2-one (2d). Yield 67%; mp 167-168°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 10.15 (1H, s, NH); 7.12-7.37 (5H, m, Ph); 6.46 (1H, s, CH); 4.10 (2H, quartet, *J* = 7, OCH_2), 2.84-3.03 (1H, m, $COCH_2$); 2.62-2.82 (1H, m, $COCH_2$); 2.28 (3H, s, CH_3); 1.35-1.70 (2H, m, $COCH_2\underline{CH_2}Et$); 1.15-1.37 (2H, m, $CO(CH_2)_2\underline{CH_2}CH_3$); 1.16 (3H, t, *J* = 7, $\underline{CH_3}CH_2O$); 0.84 (3H, t, *J* = 7, $\underline{CH_3}(CH_2)_3CO$). IR spectrum, (KBr), ν, cm^{-1}: 1635, 1702, 2863, 2963, 3243, 3390. Found, %: N 8.20. $C_{19}H_{24}N_2O_4$. Calculated, %: N 8.14.

3-Caproyl-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one (2e). Yield 58%; mp 180-181°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 10.12 (1H, s, NH); 7.12-7.37 (5H, m, Ph); 6.45 (1H, s, CH); 4.10 (2H, quartet, *J* = 7, OCH_2); 2.82-3.02 (1H, m, $CO\underline{CH_2}Bu$); 2.62-2.82 (1H, m, $CO\underline{CH_2}Bu$); 2.28 (3H, s, CH_3); 1.42-1.68 (2H, m, $COCH_2\underline{CH_2}Pr$); 1.17-1.30 (4H, m, $CO(CH_2)_2\underline{CH_2}\underline{CH_2}CH_3$); 1.16 (3H, t, *J* = 7, $\underline{CH_3}CH_2O$); 0.83 (3H, t, *J* = 6.4, $\underline{CH_3}(CH_2)_4CO$). IR spectrum (KBr), ν, cm^{-1}: 1635, 1695, 1710, 2956, 2920, 3130, 3236, 3396. Found, %: N 7.93. $C_{20}H_{26}N_2O_4$. Calculated, %: N 7.82.

REFERENCES

1. K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, **56**, 1374 (1934).
2. D. Dallinger, N. Yu. Gorobets, and C. O. Kappe, *Mol. Diversity*, **7**, 229 (2003).