

Supplementary material

Continuous flow synthesis of some 6- and 1,6-substituted 4-methyl-3-cyano-2-pyridones

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The preparation of the reactant solutions for synthesis in continuous flow microreactor system

In the first set of the experiments the following solutions were made: acetylacetone (0.06 mol, 6.008 g) and ethylacetoacetate (0.06 mol, 7.808 g) were added to volumetric flasks, sequentially, then methanol was added up to a volume of 100 mL. The solution of N-substituted cyanoacetamide was made in the same way. The corresponding N-substituted cyanoacetamide (0.06 mol) was placed in a volumetric flask and deionized water was added up to a volume of 100 mL. Sodium hydroxide pellets (0.07 mol, 2.8 g) were dissolved in deionized water up to a volume of 100 mL.

In the second set of experiments compounds **1** and **2** were synthesized from the solutions prepared using the following procedure: acetylacetone (0.10 mol, 10.013 g) and ethyl acetoacetate (0.10 mol, 13.014 g) were placed in the volumetric flasks, sequentially, and methanol was added up to a volume of 100 mL. Cyanoacetamide (0.15 mol, 12.612 g) and NaOH pellets (0.2 mol, 8 g) were dissolved in the volumetric flasks, up to a volume of 100 mL in deionized water.

The characterization data of the products obtained in the continuous flow microreactor system

4,6-dimethyl-3-cyano-2-pyridone (1)

White powder, Mp 285-286 °C (Lit. 290-291 °C¹); FT-IR (KBr, ν/cm^{-1}): 3292 (N-H), 2219 (CN), 1659 (C=O); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 2.23 (3H, s, 6-CH₃), 2.30 (3H, s, 4-CH₃), 6.17 (1H, s, C5), 12.32 (1H, s, O-H); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 330.

6-hydroxy-4-methyl-3-cyano-2-pyridone (2)

White powder, Mp 315-317 °C (Lit. 315-320 °C²). FT-IR (KBr, ν/cm^{-1}): 3294 (OH), 2223 (CN), 1593 (C=O); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 2.51 (3H, s, CH₃), 5.61 (1H, s, C5); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 325.

4,6-dimethyl-1-(2-hydroxyethyl)-3-cyano-2-pyridone (3)

White powder, Mp 140-142 °C (Lit. 139-141 °C³), FT-IR (KBr, ν/cm^{-1}): 2222 (CN), 1663 (C=O), 3268 (OH); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 2.39 (3H, s, CH₃), 2.57 (3H, s, CH₃), 3.71 (2H, m, CH₂), 4.11 (2H, t, J = 5.4 Hz, CH₂), 5.04 (1H, m, OH), 6.37 (1H, s, C5-H); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 334.

6-hydroxy-4-methyl-1-(2-hydroxyethyl)-3-cyano-pyridone (4)

White powder, Mp 172-174 °C (Lit. 171-172 °C⁴); FT-IR (KBr, ν/cm^{-1}): 3367, 3268 (OH), 2223 (CN), 1663 (C=O); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 2.20 (3H, s, CH₃), 3.51 (2H, t, J = 6.4 Hz, CH₂CH₂OH), 3.99 (2H, t, J = 6.6 Hz, CH₂CH₂OH), 5.58 (1H, s, C5); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 325.

4,6-dimethyl-1-N-propyl-3-cyano-2-pyridone (5)

White powder, Mp 110-112 °C (Lit. 114 °C¹); FT-IR (KBr, ν/cm^{-1}): 2216 (CN), 1646 (C=O); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 0.98 (3H, t, J=7.4 Hz, CH₃CH₂), 1.67 (2H, m, CH₃CH₂), 2.38 (3H, s, 4-CH₃), 2.59 (3H, s, 6-CH₃), 3.98 (2H, t, J=7.8 Hz, CH₂-N), 6.38 (1H, s, 5-H); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 324.

6-hydroxy-4-methyl-1-propyl-3-cyano-2-pyridone (6)

White powder, Mp 238-240 °C (Lit. 239-240 °C⁵), FT-IR (KBr, ν/cm^{-1}): 1660 (C=O), 2210 (CN); ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 0.98 (3H, t, J=7.4 Hz, CH₃CH₂), 1.58 (2H, m, CH₃CH₂), 2.20 (3H, s, CH₃), 3.98 (2H, t, J=7.2 Hz, CH₂-N), 5.58 (1H, s, 5-H); UV-Vis (EtOH, $\lambda_{\text{max}}/\text{nm}$): 325.

Synthesis under conventional conditions

6- and 1,6-substituted-4-methyl-3-cyano-2-pyridones were prepared from corresponding 1,3-dicarbonyl reagent and N-substituted cyanoacetamides using a modified literature procedure.¹

The procedure for the preparation of N-substituted-4,6-dimethyl-3-cyano-2-pyridone in the batch system

Equimolar amounts of acetylacetone and the corresponding N-substituted cyanoacetamide (0.06 mol) were heated under reflux in a water/methanol mixture (120 mL) in the presence of NaOH (0.07 mol) as catalyst for 4 h, except for 4,6-dimethyl-3-cyano-2-pyridone where the reaction time was 1 h. The products were isolated by filtration and purified by crystallization from ethanol.

The procedure for the preparation of N-substituted-6-hydroxy-4-methyl-3-cyano-2-pyridone in the batch system

Equimolar amounts of ethyl acetoacetate and the corresponding N-substituted cyanoacetamide (0.06 mol) were heated under reflux in a water/methanol mixture (120 mL) in the presence of NaOH (0.07 mol) as a catalyst for 8 h. The products were isolated by filtration and dissolved in 100 mL of hot water. After cooling, the solution was acidified with

concentrated HCl to precipitate 2-pyridone. The final product was isolated by filtration, washed with deionized water and air dried.

References:

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