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

Preparation of the reactant solutions for synthesis in continuous flow microreactor system

In the first set of experiments, the following solutions were made: acetylacetone (0.06 mol, 6.008 g) and ethyl acetoacetate (0.06 mol, 7.808 g) and 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 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 deionized water in volumetric flasks up to a volume of 100 mL.

Work-up of the reaction mixture in the continuous flow microreactor system

The reaction mixture assembled in the microreactor was delivered to a test tube containing 1 mL of concentrated HCl. After 9 mL of the mixture was collected, resulting crystals were separated by filtration and washed with deionized water (2 times with 5 mL). Obtained crystals were air dried and analyzed without further purification.

Synthesis under conventional conditions

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

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**Procedure for the preparation of N-substituted 3-cyano-4,6-dimethyl-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 3-cyano-4,6-dimethyl-2-pyridone where the reaction time was 1 h. The products were isolated by filtration and purified by crystallization from ethanol.

**Procedure for the preparation of N-substituted 3-cyano-6-hydroxy-4-methyl-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 the 2-pyridone. The final product was isolated by filtration, washed with deionized water and air-dried.

**CHARACTERIZATION DATA OF THE PRODUCTS OBTAINED IN THE CONTINUOUS FLOW MICROREACTOR SYSTEM**

**3-Cyano-4,6-dimethyl-2-pyridone (1).** White powder; m.p.: 285–286 °C (Lit. 290–291 °C); FT-IR (KBr, cm–1): 3292 (N–H), 2219 (C–N), 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-H), 12.32 (1H, s, OH); UV–Vis (EtOH, λmax / nm): 330.

**3-Cyano-6-hydroxy-4-methyl-2-pyridone (2).** White powder; m.p.: 315–317 °C (Lit. 315–320 °C); FT-IR (KBr, cm–1): 3294 (OH), 2223 (CN), 1593 (C=O); 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 2.23 (3H, s, CH3), 5.61 (1H, s, C5-H); UV–Vis (EtOH, λmax / nm): 325.

**3-Cyano-1-(2-hydroxyethyl)-4,6-dimethyl-2-pyridone (3).** White powder; m.p.: 140–142 °C (Lit. 139–141 °C); FT-IR (KBr, cm–1): 3222 (CN), 1663 (C=O); 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 2.39 (3H, s, CH3), 2.57 (3H, s, CH3), 3.71 (2H, t, J = 5.4 Hz, CH2), 5.04 (1H, m, OH), 6.37 (1H, s, C5-H); UV–Vis (EtOH, λmax / nm): 334.

**3-Cyano-6-hydroxy-1-(2-hydroxyethyl)-4-methyl-2-pyridone (4).** White powder; m.p.: 172–174 °C (Lit. 171–172 °C); FT-IR (KBr, cm–1): 3367, 3268 (OH), 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 2.20 (3H, s, CH3), 3.51 (2H, t, J = 6.4 Hz, CH2–OCH2OH), 3.99 (2H, t, J = 6.6 Hz, CH2CH2OH), 5.58 (1H, s, C5-H); UV–Vis (EtOH, λmax / nm): 325.

**3-Cyano-4,6-dimethyl-1-propyl-2-pyridone (5).** White powder; m.p.: 110–112 °C (Lit. 114 °C); FT-IR (KBr, cm–1): 2216 (CN), 1646 (C=O); 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 0.98 (3H, t, J = 7.4 Hz, CH3), 1.67 (2H, m, CH3CH2), 2.38 (3H, s, 4-CH3), 2.53 (3H, s, 6-CH3), 3.98 (2H, t, J = 7.8 Hz, CH2–N), 6.38 (1H, s, 5-H); UV–Vis (EtOH, λmax / nm): 324.

**3-Cyano-6-hydroxy-1-propyl-2-pyridone (6).** White powder; m.p.: 238–240 °C (Lit. 239–240 °C); FT-IR (KBr, cm–1): 1660 (C=O), 2210 (CN);
$^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ / ppm): 0.98 (3H, $t$, $J = 7.4$ Hz, CH$_3$CH$_2$), 1.58 (2H, $m$, CH$_3$CH$_2$), 2.20 (3H, $s$, CH$_3$), 3.98 (2H, $t$, $J = 7.2$ Hz, CH$_2$–N), 5.58 (1H, $s$, 5-H); UV-vis (EtOH, $\lambda_{\text{max}}$ / nm): 325.

$^1$H-NMR SPECTRA OF THE OBTAINED 2-PYRIDONES

3-Cyano-4,6-dimethyl-2-pyridone (1)
3-Cyano-6-hydroxy-4-methyl-2-pyridone (2)
3-Cyano-1-(2-hydroxyethyl)-4,6-dimethyl-2-pyridone (3)
3-Cyano-6-hydroxy-1-(2-hydroxyethyl)-4-methyl-2-pyridone (4)
3-Cyano-4,6-dimethyl-1-propyl-2-pyridone (5)
3-Cyano-6-hydroxy-4-methyl-1-propyl-2-pyridone (6)

REFERENCES