Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 84 (6) S130–S137 (2019)
Supplementary material

SUPPLEMENTARY MATERIAL TO

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

JULIJANA TADIĆ[1], MARINA MIHAJLOVIĆ[1], MIĆA JOVANOVIĆ[2] and DUŠAN MIJIN[2]*

[1]*Innovation Center, Faculty of Technology and Metallurgy, Karnegijeva 4, 11120 Belgrade, Serbia and* [2]*Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, 11020 Belgrade, Serbia*

J. Serb. Chem. Soc. 84 (6) (2019) 531–538

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]

* Corresponding author. E-mail: kavur@tmf.bg.ac.rs

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[1]); FT-IR (KBr, cm^{-1}): 3292 (N–H), 2219 (C–N), 1659 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.23 (3H, *s*, 6-CH_3), 2.30 (3H, *s*, 4-CH_3), 6.17 (1H, *s*, C5-H), 12.32 (1H, *s*, OH); UV–Vis (EtOH, λ_{max} / nm): 330.

*3-Cyano-6-hydroxy-4-methyl-2-pyridone (**2**)*. White powder; m.p.: 315–317 °C (Lit. 315–320 °C[2]); FT-IR (KBr, cm^{-1}): 3294 (OH), 2223 (CN), 1593 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.23 (3H, s, CH_3), 5.61 (1H, s, C5-H); UV–Vis (EtOH, λ_{max} / nm): 325.

*3-Cyano-1-(2-hydroxyethyl)-4,6-dimethyl-2-pyridone (**3**)*. White powder; m.p.: 140–142 °C (Lit. 139–141 °C[3]); FT-IR (KBr, cm^{-1}): 2222 (CN), 1663 (C=O), 3268 (OH); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.39 (3H, *s*, CH_3), 2.57 (3H, *s*, CH_3), 3.71 (2H, *m*, CH_2), 4.11 (2H, *t*, J = 5.4 Hz, CH_2), 5.04 (1H, *m*, OH), 6.37 (1H, *s*, C5-H); UV–Vis (EtOH, λ_{max} / 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[4]); FT-IR (KBr, cm^{-1}): 3367, 3268 (OH), 2223 (CN), 1663 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.20 (3H, *s*, CH_3), 3.51 (2H, *t*, J = 6.4 Hz, C$\mathbf{H}_2$$CH_2$OH), 3.99 (2H, *t*, J = 6,6 Hz, CH_2C$\mathbf{H}_2$OH), 5.58 (1H, *s*, C5-H); UV–Vis (EtOH, λ_{max} / nm): 325.

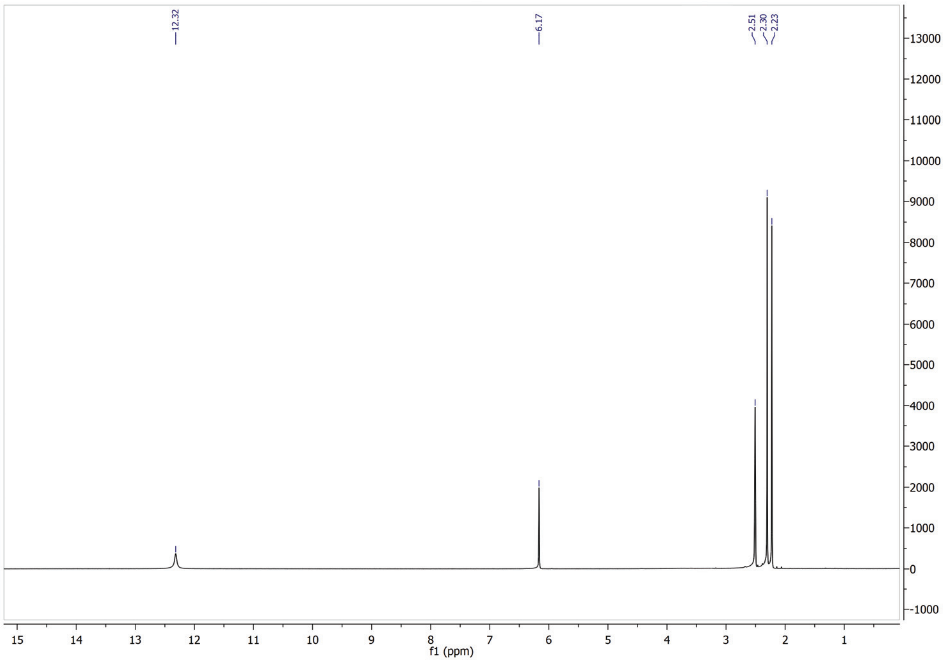
*3-Cyano-4,6-dimethyl-1-propyl-2-pyridone (**5**)*. White powder; m.p.: 110–112 °C (Lit. 114 °C[1]); FT-IR (KBr, cm^{-1}): 2216 (CN), 1646 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 0.98 (3H, *t*, J = 7.4 Hz, C$\mathbf{H}_3$$CH_2$), 1.67 (2H, *m*, $CH_3$$\mathbf{CH}_2$), 2.38 (3H, *s*, 4-$CH_3$), 2.53 (3H, *s*, 6-$CH_3$), 3.98 (2H, *t*, J = 7.8 Hz, CH_2–N), 6.38 (1H, *s*, 5-H); UV-Vis (EtOH, λ_{max} / nm): 324.

*3-Cyano-6-hydroxy-4-methyl-1-propyl-2-pyridone (**6**)*. White powder; m.p.: 238–240 °C (Lit. 239–240 °C[5]); FT-IR (KBr, cm^{-1}): 1660 (C=O), 2210 (CN);

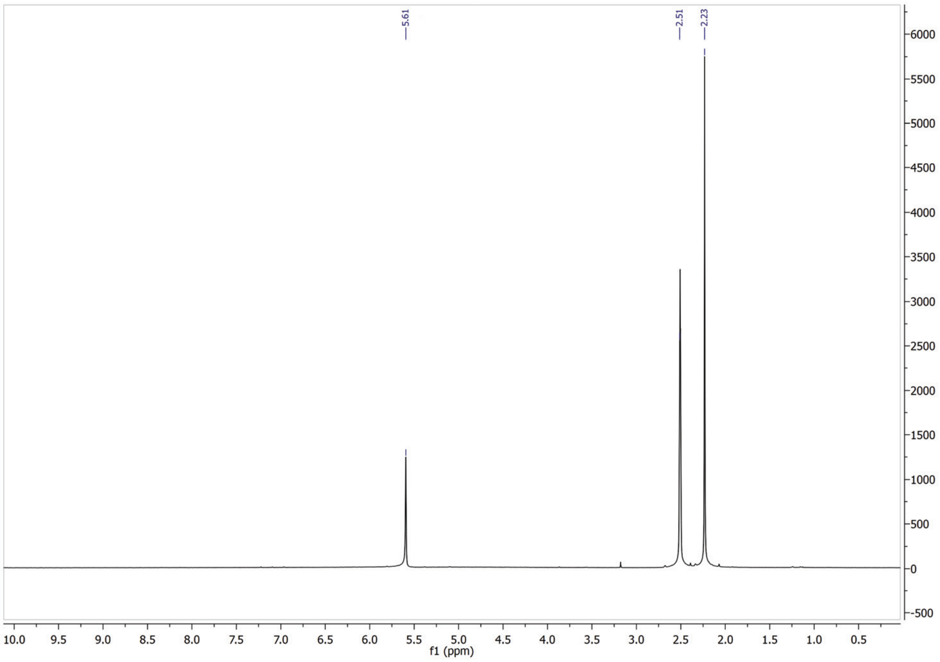
^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 0.98 (3H, *t*, *J* = 7.4 Hz, C**H**$_3$CH$_2$), 1.58 (2H, *m*, CH$_3$C**H**$_2$), 2.20 (3H, *s*, CH$_3$), 3.98 (2H, *t*, *J* = 7.2 Hz, CH$_2$–N), 5.58 (1H, *s*, 5-H); UV-vis (EtOH, λ_{max} / nm): 325.

^{1}H-NMR SPECTRA OF THE OBTAINED 2-PYRIDONES

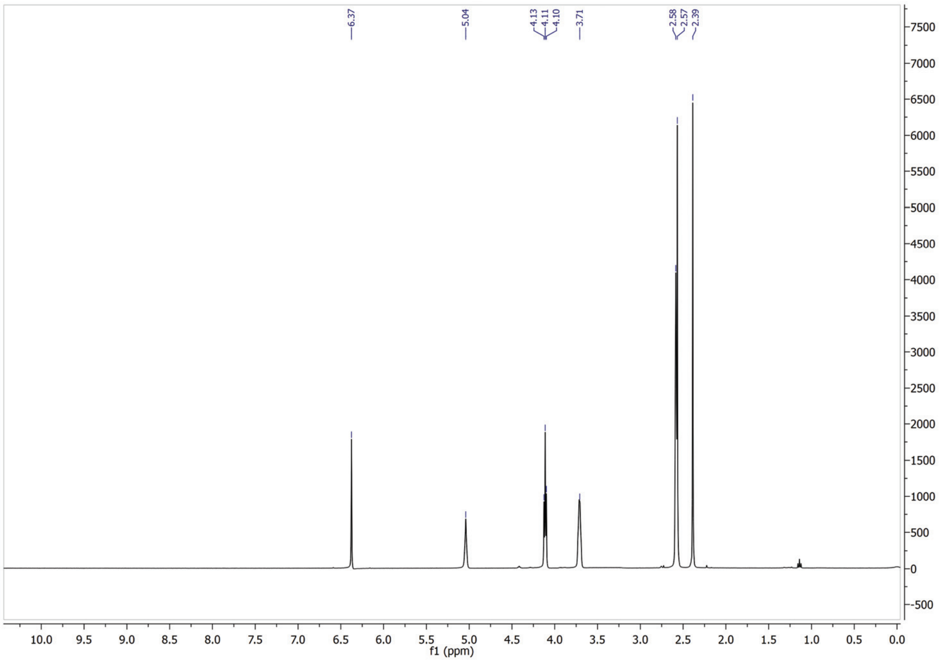
3-Cyano-4,6-dimethyl-2-pyridone (1)



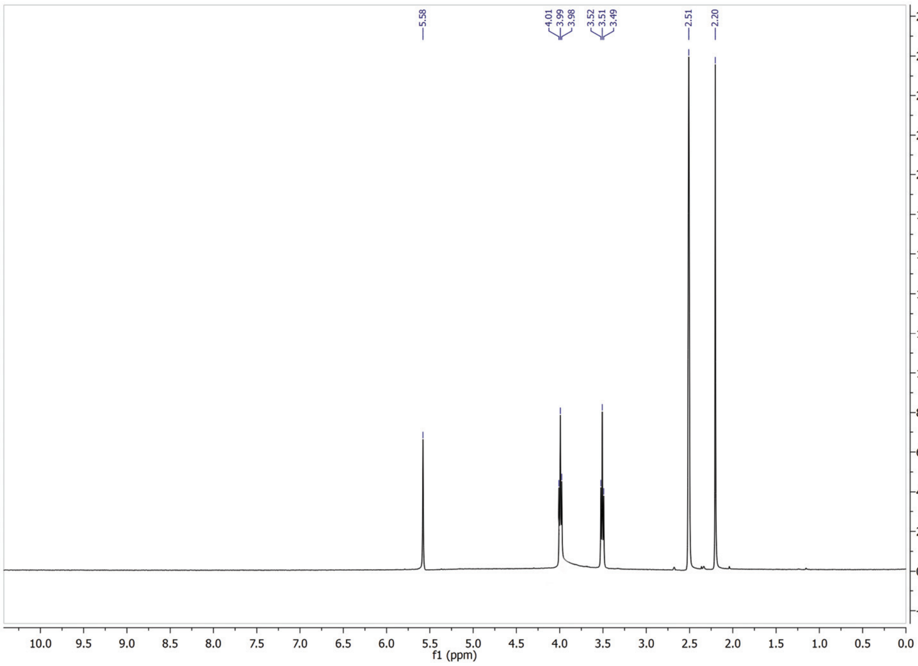
*3-Cyano-6-hydroxy-4-methyl-2-pyridone (**2**)*



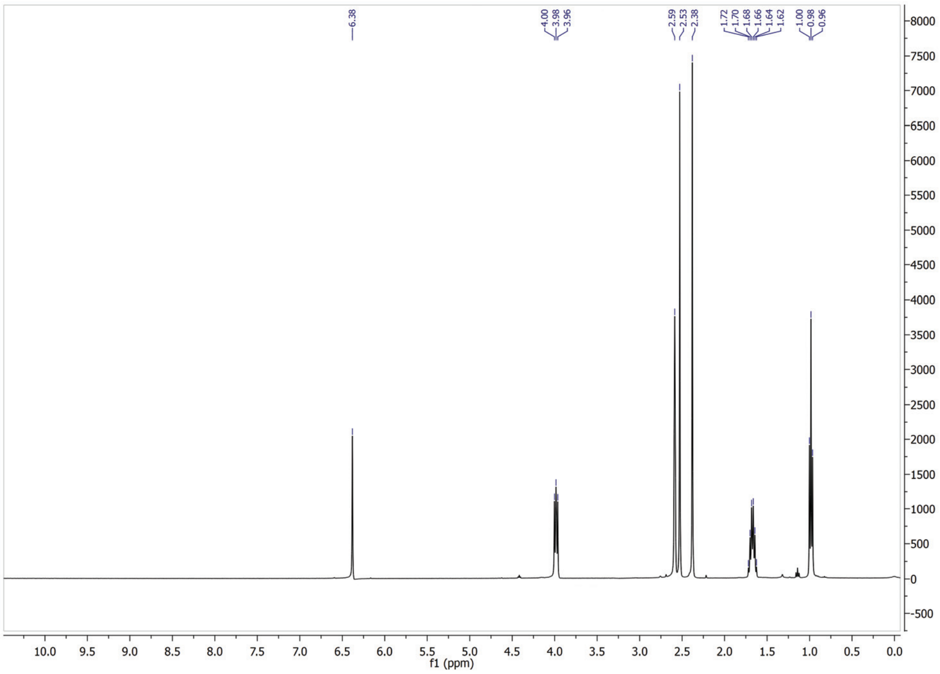
*3-Cyano-1-(2-hydroxyethyl)-4,6-dimethyl-2-pyridone (**3**)*



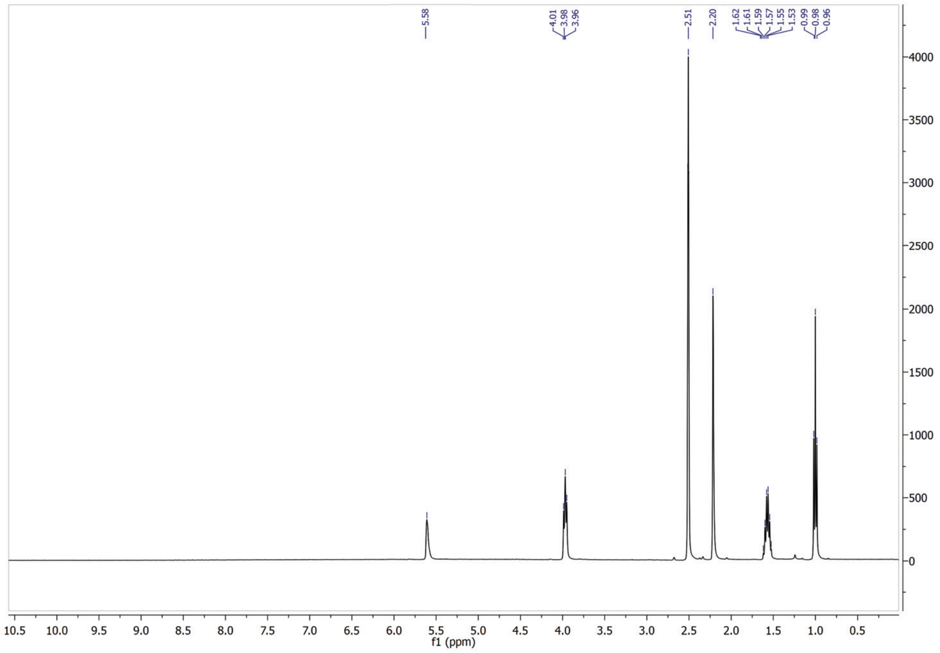
*3-Cyano-6-hydroxy-1-(2-hydroxyethyl)-4-methyl-2-pyridone (**4**)*



*3-Cyano-4,6-dimethyl-1-propyl-2-pyridone (**5**)*



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



REFERENCES

1. D. Mijin, A. Marinković, *Synth. Commun.* **36** (2006) 193 (https://dx.doi.org/10.1080/00397910500334421)
2. D. Ž. Mijin, M. M. Mišić-Vuković, *J. Serb. Chem. Soc.* **59** (1994) 959
3. A. F. El-Essawy, A. F. Khattab, *J. Heterocycl. Chem.* **41** (2004) 311 (https://dx.doi.org/10.1002/jhet.5570410302)
4. B. D.Tilak, N. R. Ayyangar, U. S. Rao, *Indian J. Chem., Sect. B* **23** (1984) 18
5. S. Balalaie, E. Kowsari, M. S. Hashtroudi, *Monatsh. Chem.* **134** (2003) 453 (https://dx.doi.org/10.1007/s00706-002-0551-2).