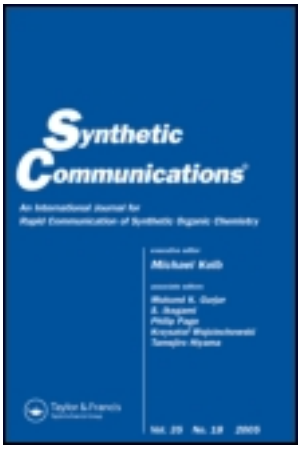

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Synthesis of N-Substituted 4,6-Dimethyl-3-cyano-2-pyridones Under Microwave Irradiation

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Synthesis of N-Substituted 4,6-Dimethyl-3-cyano-2-pyridones Under Microwave Irradiation

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Abstract: N-substituted 4,6-dimethyl-3-cyano-2-pyridones have been prepared from acetylacetone, N-substituted cyanoacetamide, and pyperidine as catalyst under microwave irradiation without solvent. The rapid and simple method produced pure products in high yields.

Keywords: Synthesis, microwave, pyridone, cyanoacetamide, acetylacetone

Microwave irradiation has become an important method in organic synthesis that can be applied to a wide range of reactions within short reaction times and with high yields. Reactions in the absence of solvent (solvent-free synthesis) under microwave irradiation also offer several advantages. The absence of solvent reduces risk of explosion and simplifies the workup.[1]

Some studies have been published on synthesis of a wide variety of heterocycles using microwave irradiation.[1,2] A few studies can be found about organic synthesis under microwave irradiation of some 3-cyano-2-pyridones such as synthesis of some derivatives of 6-hydroxy-3-cyano-2-pyridones[3] and lately 4,6-disubstituted 3-cyano-2-pyridones from chalkones and cyanoacetamide.[4]

Substituted 3-cyano-2-pyridones are important intermediates in the pharmaceutical, dye, and photo industries. Their syntheses have been

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widely studied using conventional heating in the presence of various catalysts and usually in polar solvents.[5,6]

In the study of condensation of various 1,3-diketones with cyanoacetamide in our department, different reaction conditions, including phase-transfer catalysis and enzymes, have been used.[6] Now, we report the synthesis of N-substituted 4,6-dimethyl-3-cyano-2-pyridones using microwave irradiation.

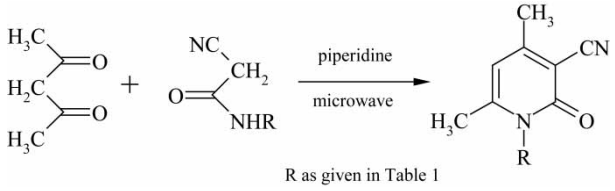
A series of N-alkyl- and N-(4-substituted phenyl)-4,6-dimethyl-3-cyano-2-pyridones were synthesized starting from acetylacetone (2,4-pentanedione) and corresponding N-substituted cyanoacetamide using microwave irradiation as well as conventional synthesis (Scheme 1). Starting N-substituted cyanoacetamides were obtained by known methods.[5,7] In both syntheses of pyridones, piperidine was used as the catalyst. In conventional synthesis, a water/ethanol mixture was used as the solvent and heating was performed at reflux temperature. Microwave synthesis was performed in a domestic commercial microwave oven. Unsubstituted pyridone was also obtained. Some of these compounds have not been found in literature and to our knowledge were synthesized for the first time. The obtained results are given in Table 1.

Except the 4,6-dimethyl-3-cyano-2-pyridone, which was obtained at 100 W and after 30 s (conventional synthesis 30 min, reflux), all other N-substituted 4,6-dimethyl-3-cyano-2-pyridones were obtained at 200 W after 7 min of irradiation. In comparison to the conventional, microwave synthesis gives products in higher yields in almost all cases and in very short reaction time (conventional synthesis 4 h, reflux). The obtained products were characterized by melting point, IR, and ^{1}H NMR data.

This simple and rapid microwave procedure, which gives the product in high yield with high purity, can be used for the preparation of similar heterocyclic substances that contain a 2-pyridone unit.

EXPERIMENTAL

IR spectra were obtained using FTIR BOMEM MB 100 in the form of KBr pellets. ^{1}H NMR spectra were recorded on a Varian-Gemini 200-MHz spectrometer using DMSO-d_6 or CF_3COOD as solvent and TMS as internal standard.



Scheme 1.

Table 1. N-substituted 4,6-dimethyl-3-cyano-2-pyridones obtained by microwave and conventional synthesis

		Microwave synthesis		Conventional synthesis	
No.	R	Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
1	H	85	285–7	80	285–6
2	Me	81	198–200	60	197–9
3	Et	71	168–70	55	170–1
4	Pr	72	101–3	46	104–6
5	Bu	66	94–6	30	99–100
6	Ph	96	250–2	75	252–3
7	4-$MeOC_6H_4$	95	240–2	72	247–9
8	4-ClC_6H_4	95	307–8	73	314–6
9	4-MeC_6H_4	97	268–70	75	274–6
10	4-FC_6H_4	99	266–8	72	266–8
11	4-EtC_6H_4[a]	84	226–8	73	222–4
12	4-$NMe_2C_6H_4$[a]	90	303–6	73	300–3
13	4-BrC_6H_4	86	306–8	76	307–9
14	4-IC_6H_4	86	300–2	73	300–2
15	4-AcC_6H_4	91	259–61	80	259–61
16	4-$NO_2C_6H_4$	84	280–2	64	278–81
17	4-$COOHC_6H_4$[a]	78	325 (dec.)	13	323 (dec.)
18	4-OHC_6H_4[a]	34	246–7	91	245–7

[a]New compounds.

General Procedure for the Preparation of Pyridones

Method A (Microwave)

A mixture of equimolar amounts of acetylacetone and corresponding N-substituted cyanoacetamide (5 mmol) and piperidine (0.5 cm^3) was placed in a flask and irradiated at 200 W for 7 min in a domestic microwave oven. Obtained product was purified by crystallization from ethanol.

Method B (Conventional)

Equimolar amounts of acetylacetone and corresponding N-substituted cyanoacetamide (10 mmol) were heated under reflux in a water/ethanol mixture (20 cm^3) in the presence of a few drops of piperidine as catalyst for 4 h. Product was purified by crystallization from ethanol.

4,6-Dimethyl-3-cyano-2-pyridone (1): mp 290–1°C,[8] IR ν_{max} (cm^{-1}) (KBr): 2200, 1640, ^{1}H NMR (δ/ppm) (CF_3COOD): 2.62 (3H, s, CH_3); 2.68 (3H, s, CH_3), 6.80 (1H, s, 5H).

N-Methyl-4,6-dimethyl-3-cyano-2-pyridone (2): 203–4°C,[9] IR ν_{max} (cm^{-1}) (KBr): 2213, 1650, ^{1}H NMR (δ/ppm) (DMSO-d_6): 2.30 (3H, s, 4-CH_3), 2.42 (3H, s, 6-CH_3), 3.44 (3H, s, 1-CH_3), 6.32 (1H, s, 5H).

N-Ethyl-4,6-dimethyl-3-cyano-2-pyridone (3): 174–5°C,[9]IR ν_{max}(cm^{-1}) (KBr): 2213, 1644, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.20 (3H, t, $C\underline{H}_3-CH_2$), 2.30 (3H, s, 4-CH_3), 2.45 (3H, s, 6-CH_3), 4.00 (2H, q, CH_2), 6.30 (1H, s, 5H).

N-n-Propyl-4,6-dimethyl-3-cyano-2-pyridone (4): 114°C,[9] IR ν_{max} (cm^{-1}) (KBr): 2216, 1646, ^{1}H NMR (δ/ppm) (DMSO-d_6): 0.90 (3H, t, $C\underline{H}_3-CH_2$), 1.60 (2H, m, $CH_3-C\underline{H}_2$), 2.30 (3H, s, 4-CH_3), 2.44 (3H, s, 6-CH_3), 3.90 (2H, q, CH_2-N), 6.28 (1H, s, 5H).

N-n-Butyl-4,6-dimethyl-3-cyano-2-pyridone (5): 99–100°C,[9] IR ν_{max} (cm^{-1}) (KBr): 2214, 1653, ^{1}H NMR (δ/ppm) (DMSO-d_6): 0.95 (3H, t, $C\underline{H}_3-CH_2$), 1.45 [4H, m, $CH_3-(C\underline{H}_2)_2$], 2.31 (3H, s, 4-$CH_3$), 2.45 (3H, s, 6-$CH_3$), 3.95 (2H, t, CH_2-N), 6.30 (1H, s, 5H).

N-Phenyl-4,6-dimethyl-3-cyano-2-pyridone (6): 255°C,[10] IR ν_{max} (cm^{-1}) (KBr): 2219, 1670, 1656, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.960 (3H, s, 4-CH_3); 2.388 (3H, s, 6-CH_3) 6.459 (1H, s, 5H); 7.290–7.607 (5H, m, Ph).

N-(4-Methoxy phenyl)-4,6-dimethyl-3-cyano-2-pyridone (7): 247–9°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2217, 1658, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.976 (3H, s, 4-CH_3); 2.379 (3H, s, 6-CH_3); 3.817 (3H, s, CH_3O); 6.441 (1H, s, 5H); 7.053–7.252 (4H, dd, Ph).

N-(4-Chloro phenyl)-4,6-dimethyl-3-cyano-2-pyridone (8): 314–6°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2219, 1661, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.975 (3H, s, 4-CH_3); 2.389 (3H, s, 6-CH_3); 6.467 (1H, s, 5H); 7.366–7.649 (4H, dd, Ph).

N-(4-Methyl phenyl)-4,6-dimethyl-3-cyano-2-pyridone (9): 274–6°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2218, 1661, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.962 (3H, s, 4-CH_3); 2.381 (6H, s, 6-CH_3, and CH_3Ph); 6.448 (1H, s, 5H); 7.157–7.372 (4H, dd, Ph).

N-(4-Fluoro phenyl)-4,6-dimethyl-3-cyano-2-pyridone (10): 272–4°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2221, 1663, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.975 (3H, s, 4-CH_3); 2.388 (3H, s, 6-CH_3); 6.462 (1H, s, 5H); 7.383–7.418 (4H, d, Ph).

N-(4-Ethyl phenyl)-4,6-dimethyl-3-cyano-2-pyridone (11): IR ν_{max} (cm^{-1}) (KBr): 2218, 1659, ^{1}H NMR (δ/ppm) (DMSO-d_6) 1.231 (3H, t, $C\underline{H}_3-CH_2$); 1.961 (3H, s, 4-CH_3); 2.382 (3H, s, 6-CH_3); 2.680 (2H, q, $CH_3-C\underline{H}_2$); 6.448 (1H, s, 5H); 7.181–7.406 (4H, dd, Ph).

N-(4-N,N-Dimethyl phenyl)-4,6-dimethyl-3-cyano-2-pyridone (12): IR ν_{max} (cm^{-1}) (KBr): 2215, 1658, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.983 (3H, s, 4-CH_3); 2.366 (3H, s, 6-CH_3); 2.957 [6H, s, $N(CH_3)_2$]; 6.408 (1H, s, 5H); 6.769–7.065 (4H, dd, Ph).

N-(4-Bromo phenyl)-4,6-dimethyl-3-cyano-2-pyridone (13): >300°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2219, 1661, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.974 (3H, s, 4-CH_3); 2.387 (3H, s, 6-CH_3); 6.465 (1H, s, 5H); 7.299–7.780 (4H, dd, Ph).

N-(4-Iodo phenyl)-4,6-dimethyl-3-cyano-2-pyridone (14): 300–2°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2218, 1659, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.970 (3H, s, 4-CH_3); 2.383 (3H, s, 6-CH_3); 6.461 (1H, s, 5H); 7.133–7.938 (4H, dd, Ph).

N-(4-Acetyl phenyl)-4,6-dimethyl-3-cyano-2-pyridone (15): IR ν_{max} (cm^{-1}) (KBr): 2218, 1685, 1650, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.975 (3H, s, 4-CH_3); 2.404 (3H, s, 6-CH_3); 2.649 (3H, s, CH_3–CO); 6.501 (1H, s, 5H); 7.497–8.143 (4H, dd, Ph).

N-(4-Nitro phenyl)-4,6-dimethyl-3-cyano-2-pyridone (16): 278–281°C,[5] IR ν_{max} (cm^{-1}) (KBr): 2220, 1660, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.989 (3H, s, 4-CH_3); 2.412 (3H, s, 6-CH_3); 6.517 (1H, s, 5H); 7.685–8.430 (4H, dd, Ph).

N-(4-Carboxy phenyl)-4,6-dimethyl-3-cyano-2-pyridone (17): IR ν_{max} (cm^{-1}) (KBr): 2222, 1730, 1718, 1643, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.976 (3H, s, 4-CH_3); 2.401 (3H, s, 6-CH_3); 6.481 (1H, s, 5H); 7.461–8.124 (4H, dd, Ph); 13.238 (1H, s, COOH).

N-(4-Hydroxy phenyl)-4,6-dimethyl-3-cyano-2-pyridone (18): IR ν_{max} (cm^{-1}) (KBr): 2223, 1647, ^{1}H NMR (δ/ppm) (DMSO-d_6): 1.972 (3H, s, 4-CH_3); 2.366 (3H, s, 6-CH_3); 6.409 (1H, s, 5H); 6.854–7.089 (4H, dd, Ph); 9.843 (1H, s, OH).

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REFERENCES

1. (a) Majetich, G.; Hicks, R. Applications of microwave-accelerated organic synthesis. *Radiat. Phys. Chem.* **1995**, *45* (4), 567–579; (b) Tanaka, K.; Toda, F. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100* (3), 1025–1074; (c) Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic

considerations. *Tetrahedron* **2001**, *57* (45), 9199–9223; (d) Lindstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave-assisted organic synthesis: A review. *Tetrahedron* **2001**, *57* (45), 9225–9283.
2. Hamelin, J.; Bazureau, J. P.; Texier-Boullet, F. Microwaves in heterocyclic chemistry. In *Microwaves in Organic Synthesis*; Loupy, A., ed., Wiley-VCH: Weinheim, 2002; pp. 253–293.
3. Schmidt, H. Process for the preparation of pyridine compounds. DE 4,314,430, November 10, 1994.
4. Dave, C. G.; Shah, D. A.; Agrawal, Y. K. A simple and convenient synthesis of 4,6-disubstituted 3-cyanopyridin-2(1H)-ones under solvent-free microwave conditions. *Ind. J. Chem.* **2004**, *43B* (4), 885–887.
5. Siedel, M. C.; Viste, K. L.; Yih, R. Y. Plant growth inhibition with N-aryl-pyrid-2-ones. U.S. 3,761,240, September 25, 1973.
6. Mišić-Vuković, M.; Mijin, D.; Radojković-Veličković, M.; Valentić, N.; Krstić, V. Condensation of 1,3-diketones with cyanoacetamide: 4,6-disubstituted-3-cyano-2-pyridones. *J. Serb. Chem. Soc.* **1998**, *63* (8), 585–599.
7. (a) Sues, O.; Schaefer, H. Diazotype materials and processes. GB 1,284,608, August 9, 1972; (b) Piccinini, G.; Delpiano, A. Über die cyanoacetylmonochloroaniline und die entsprechenden Oxamsäuren. *Chem. Zentr.* **1907**, *78* (1), 335–336.
8. Alberola, A.; Andres, C.; Gonzalez Ortega, A.; Pedrosa, R.; Vincente, M. The reaction of β-aminoenamines with substituted acetonitriles. Regiospecific synthesis of 2(1H)-pyridones. *J. Heterocycl. Chem.* **1987**, *24* (3), 709–713.
9. Gaureschi, J. Oxypiridines aus β-Diketonen. *Chem. Zentr.* **1899**, *70* (4), 289–290.
10. Wilhelm, E. Condensation of N-substituted acetoacetamides yielding α-pyridones: derivatives of these compounds. *Ann. Chem.* **1977**, *10*, 1642–1660.