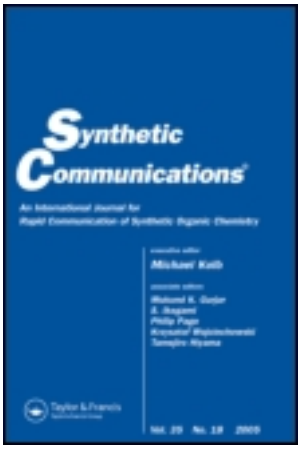

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Microwave-Assisted Three-Component Condensation on Montmorillonite K10: Solvent-Free Synthesis of Furopyrimidines, Furocoumarins, and Furopyranones

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Microwave-Assisted Three-Component Condensation on Montmorillonite K10: Solvent-Free Synthesis of Furopyrimidines, Furocoumarins, and Furopyranones

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Abstract: Rapid and efficient one-pot three-component condensation synthesis of furopyrimidines, furocoumarins, and furopyranones are described which occur in the presence of montmorillonite K10 using microwave irradiation under solvent-free conditions.

Keywords: Solvent-free, montmorillonite K10, furopyrimidines, furocoumarins, furopyranones, microwave

Furopyrimidines and furocoumarins are an important class of compounds, which exhibit a wide range of biological activities. For example, furo[2,3-*d*] pyrimidine derivatives[1] act as sedatives, antihistamines, diuretic, muscle relaxants, and antiulcer agent, and furocoumarins act presumably related to the natural defense of plants against fungal attack.[1–4]

The synthesis of furopyrimidines and furocoumarins has received little attention and only few procedures have been reported in the literature, most of which relied on multistep reactions with yields being low.[4–10]

Recently, Nair and his coworkers have devised a one-pot synthesis of furocoumarins and furopyranones.[11] Product yields are relatively good, but

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the reaction times necessary for these yields are very long. For example 14–16 h under reflux conditions in benzene as a toxic solvent, when furopyranones are the product and 16–24 h in the case of furocoumarins. Consequently, there is need to develop a simple, rapid, eco-friendly and easy experimental and products isolation procedure for the synthesis of these compounds.

In this article we have investigated the potential of microwaves irradiation to accelerate the reaction of *N*,*N*′-dimethylbarbituric acid **1** or 4-hydroxy coumarin or 4-hydroxy-6-methyl-2-pyrone **2**, with *para*-substituted benzaldehydes **3** and alkyl or aryl isocyanides **4** in the presence of montmorillonite K10 as an inexpensive inorganic solid support under solvent-free conditions.

Microwave-enhanced chemical reactions,[12–15] especially on inorganic solid supports[16,17] and that are conducted under solvent-free conditions, have attracted attention recently. They offer several advantages over the conventional reactions in view of the rapid reaction rates, higher yields, and the avoidance of large volumes of solvent.

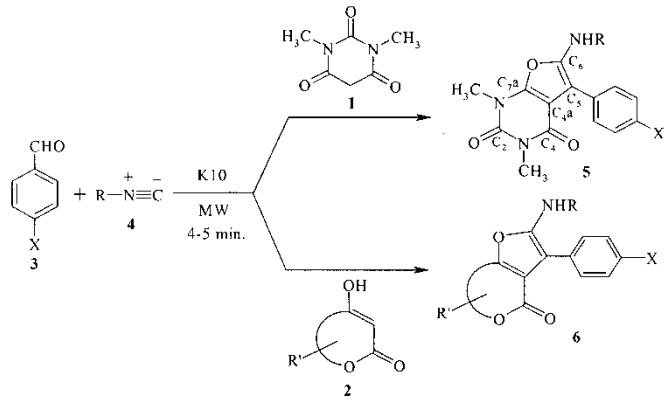
Our solvent-free one-pot method simply involves microwave irradiation of a mixture of *para*-substituted benzaldehyde **3** and corresponding *N*,*N*′-dimethylbarbituric acid **1** or 4-hydroxy coumarin or 4-hydroxy-6-methyl-2-pyrone **2** with isocyanide **4** in the presence of montmorillonite K10 to afford the corresponding products **5** or **6**. The reaction is completed in all cases within 4–5 mins. (see Scheme 1).

^{1}H and ^{13}C NMR spectra of crude product clearly indicated the formation furopyrimidines **5** or furocoumarines or furopyranones **6**. Any product other than **5** or **6** could not be detected by NMR spectroscopy. The structure of new compounds **5a**, **5b**, **6b**, **6f**, and **6g** were deduced from their elemental analysis and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks or M+1 peaks at the appropriate m/z values (see the Experimental section).

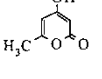
In order to select the best solid support, we carried out the reaction of 4-nitro benzaldehyde, *N*,*N*′-dimethylbarbituric acid, and cyclohexyl isocyanide on the surface of various supports such as montmorillonite K10, silica gel, alumina, amberlist resin, and zeolite under microwave irradiation. Under all conditions, product **5c** was produced with good yields (85, 60, 82, 73, and 78%, respectively). The higher yield was obtained with montmorillonite K10 as a solid support.

Yields of products under microwave irradiation under solvent-free conditions in the absence of solid supports and classical heating conditions were low and the reactants and products adhered to the reaction vessel and led to irreproducible results.

We have shown the combination of solvent-free supported reagents and microwave irradiation is a rapid and efficient method for the one-pot three-component condensation synthesis of furopyrimidines, furocoumarins, and furopyranones. In this approach the use of large volume of benzene[11] or



5	X	R	Yield (%)
a	OCH_3	Cyclohexyl	74
b	H	Cyclohexyl	77
c	NO_2	Cyclohexyl	85
d	NO_2	*tert*-Butyl	75
e	NO_2	2,6-Dimethylphenyl	72

6	Coumarin or Pyrone	X	R	Yield (%)
a		OCH_3	Cyclohexyl	74
b		H	Cyclohexyl	72
c		NO_2	Cyclohexyl	80
d		NO_2	*tert*-Butyl	72
e		NO_2	2,6-Dimethylphenyl	70
f		OCH_3	Cyclohexyl	73
g		H	Cyclohexyl	70
h		NO_2	Cyclohexyl	79
i		NO_2	*tert*-Butyl	81
j		NO_2	2,6-Dimethylphenyl	75

Scheme 1.

toluene[7] is avoided, work-up considerably simplified, and safety is increased by reducing the risk of overpressure and explosions.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus

CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka (Buchs, Switzerland) chemical companies. The microwave oven was a domestic (maximum 900 W) National model NN-6653 with five select power levels (one of which were used for this experiment; medium high 70% wattage).

Typical Procedure for Preparation of 5-*p*-Methoxyphenyl-6-cyclohexylamino-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5a)

In a 25 mL beaker, cyclohexyl isocyanide (0.121 g, 1.1 mmol), 4-methoxy benzaldehyde (0.150 g, 1.1 mmol), and *N*,*N*′-dimethylbarbituric acid (0.156 g, 1.0 mmol) were roughly mixed with montmorillonite K10 (0.5 g) and after 3 min of mechanical stirring, the mixture was irradiated at medium power for 4 min. Upon completion of the reaction, monitored on TLC (n-hexane:ethyl acetate, 3:1), the product was extracted in diethyl ether (2 × 15 mL), solvent removal of the solid residue was crystallized from $(C_2H_5)_2O$-EtOH (1:2) to yield **5a** as a cream powder (0.284 g, 74%). mp 122–124°C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3250 (N-H), 1697 and 1630 (C═O). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.13–1.94 (10 H, m, 5 CH_2), 3.11–3.14 (1 H, m, N-CH), 3.37 and 3.55 (6 H, 2 s, 2 NCH_3), 3.43 (1 H, d, $^{3}J_{HH} = 6.5$ Hz, NH), 3.83 (3 H, s, OCH_3), 6.95 and 7.49 (4 H, 2 d, $^{3}J_{HH} = 8.7$ Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.81, 25.62 and 33.92 (5 CH_2), 28.24 and 29.44 (2 NCH_3), 55.30 (N-CH), 55.85 (OCH_3), 96.20 (C_4a), 105.63 (C_5), 113.80 (C_{meta}-OCH_3), 122.75 (C_{para}-OCH_3), 130.51 (C_{ortho}-OCH_3), 142.44 (C-OCH_3), 149.94 (C_6), 150.10 (C_7a), 150.57 (C_2), 158.83 (C_4). MS (*m*/*z*, %) 383 (M^+, 83), 300 (100), 273 (51), 243 (27), 172 (30), 108 (10), 67 (75), 41 (73). Anal. Calcd. for $C_{21}H_{25}N_3O_4$ (383.44): C, 65.78; H, 6.57; N, 10.96%. Found: C, 65.72; H, 6.32; N, 11.06%.

5-Phenyl-6-cyclohexylamino-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5b)

Light pink crystals (0.273 g, 77%). mp 124–126°C. IR (KBr) (ν_{max}, cm^{-1}): 3260 (N-H), 1702 and 1660 (C═O). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.09–1.96 (10 H, m, 5 CH_2), 3.14–3.20 (1 H, m, N-CH), 3.38 and 3.56 (6 H, 2 s, 2 NCH_3), 3.57 (1 H, d, $^{3}J_{HH} = 6.6$ Hz, NH), 7.26–7.57 (5 H, m, arom.).

^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.81, 25.61 and 34.00 (5 CH_2), 28.33 and 29.45 (2 NCH_3), 55.60 (N-CH), 96.12 (C_4a), 104.61 (C_5), 127.00 (C_{para}), 128.33 (C_{meta}), 129.25 (C_{ortho}), 130.50 (C_{ipso}), 148.93 (C_6), 150.50 (C_7a), 150.84 (C_2), 158.22 (C_4). MS (m/z, %) 353 (M^+, 100), 271 (38), 243 (30), 214 (28), 186 (10), 142 (20), 83 (5), 67 (32). Anal. Calcd. for $C_{20}H_{23}N_3O_3$ (353.42): C, 67.97; H, 6.56; N, 11.89%. Found: C, 68.10; H, 6.41; N, 11.75%.

2-(Cyclohexylamino)-3-phenyl-4*H*-furo[3,2*c*]chromen-4-one (6b)

Yellow crystals (0.259 g, 72%). mp 130–131°C. IR (KBr) (ν_{max}, cm^{-1}): 3420 (N-H), 1721 (C═O), 1584 (C═C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.19–2.07 (10 H, m, 5 CH_2), 3.57 (1 H, m, N-CH), 4.28 (1 H, d, $^3J_{HH} = 8.2$ Hz, NH), 7.25–7.78 (8 H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.90, 25.53 and 34.13 (5 CH_2), 53.68 (N-CH), 97.49, 110.93, 112.86, 116.89, 119.47, 124.15, 126.78, 128.75, 128.64, 129.18, 130.72, 149.80, 151.32, 154.88 (arom. and 2 C═C), 157.92 (C═O). MS (m/z, %) 359 (M^+, 31), 277 (40), 248 (19), 220 (10), 129 (18), 83 (25), 55 (100). Anal. Calcd. for $C_{23}H_{21}NO_3$ (359.41): C, 76.86; H, 5.89; N, 3.90%. Found: C, 76.73; H, 5.95; N, 3.82%.

2-(Cyclohexylamino)-6-methyl-3-(4-methoxyphenyl)-4H-furo[3,2*c*]pyran-4-one (6f)

Yellow crystals (0.258 g, 73%). mp 91–93°C. IR (K Br) (ν_{max}, cm^{-1}): 3400 (N-H), 1714 (C═O), 1600 (C═C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.15–1.99 (10 H, m, 5 CH_2), 2.31 (3 H, s, CH_3), 3.37–3.41 (1 H, m, N-CH), 3.82 (1 H, br s, NH), 3.83 (3 H, s, OCH_3) 6.31 (1 H, s, C═CH), 6.96 and 7.41 (4 H, 2 d, $^3J_{HH} = 8.5$ Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 20.05 (CH_3), 24.89, 25.56 and 34.17 (5 CH_2), 53.86 (N-CH), 55.28 (OCH_3), 95.31, 97.02, 108.59, 114.13, 123.15, 130.23, 153.08, 155.10, 156.67, 158.34 (3 C═C and arom.), 159.94 (C═O). MS (m/z, %) 353 (M^+, 82), 271 (52), 226 (15), 186 (10), 159 (8), 77 (20), 55 (100). Anal. Calcd. for $C_{21}H_{23}NO_4$ (353.41): C, 71.37; H, 6.56; N, 3.96%. Found: C, 71.50; H, 6.49; N, 4.05%.

2-(Cyclohexylamino)-6-methyl-3-phenyl-4*H*-furo[3,2*c*] pyran-4-one (6g)

Light brown crystals (0.278 g, 70%). mp 126–128°C. 3400 (N-H), 1724 (C═O) 1606 (C═C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.18–2.08 (10 H, m, 5 CH_2), 2.36 (3 H, s, CH_3), 3.47 (1 H, m, N-CH), 4.16 (1 H, br s, NH), 6.37 (1 H, s, C═CH), 7.28–7.55 (5 H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C

20.45 (CH_3), 25.31, 25.95 and 34.57 (5 CH_2), 54.08 (N-CH), 95.68, 96.96, 108.89, 126.87, 128.98, 129.36, 131.45, 153.87, 155.54 and 157.13 (3 C=C and C_6H_5), 160.08 (C=O). MS (m/z, %) 323 (M^+, 98), 241 (98), 213 (40), 170 (48), 129 (27), 83 (17), 55 (97), 41 (97). Anal. Calcd. for $C_{20}H_{21}NO_3$ (323.38): C, 74.28; H, 6.55; N, 4.33%. Found: C, 74.30; H, 6.62; N, 4.21%.

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