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Microwave-Assisted Synthesis of Some Pyrimidine Derivatives

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Microwave-Assisted Synthesis of Some Pyrimidine Derivatives

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Oxo- and thioxopyrimidines **4a-i** were synthesized using the Biginelli threecomponent cyclocondensation reaction of an appropriate β -diketone, arylaldehyde, and (thio)urea under microwave irradiation. Yields of products following recrystallization from ethanol were of the order of 65–90%. ¹H and ¹³C NMR spectroscopy and elemental analysis were used for structural assignment.

Keywords Carboxylate; microwave; pyrimidine; thiazolo

INTRODUCTION

Pyrimidine derivatives have attracted considerable attention because of their pharmacological properties,¹⁻¹⁰ including antiviral, antitumor, antibacterial,² and antihypertensive³ effects. Thus pyrimidine has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties.

In the last few years there has been an increased interest in the use of microwave heating in organic synthesis, and it forms now the basis of a number of commercial systems. Some interesting features of this method are the rapid reaction rates, simplicity, solvent-free conditions, the ease of work-up after the reaction, and better selectivity.^{1,11-13} Also, microwave irradiation generates rapid intense heating of polar substances, which result in the reduction of reaction time compared to conventional heating.

Continuing with our studies on the synthesis of pyrimidines using microwave irradiation,^{9,14–16} we have extended the Biginelli reactions in order to synthesize some new oxo- and thioxopyrimidine derivatives. The reported method offers a simple and efficient route for the preparation of pyrimidines.

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RESULTS AND DISCUSSION

1,3-diketone **1**, aryl aldehyde **2**, (thio)urea **3**, a few drops of ethanol, and HCl (37%) were reacted under microwave irradiation to give the corresponding oxo- and thioxopyrimidines **4** (Scheme 1). ¹H and ¹³C NMR spectra of the isolated compounds **4a–i** confirm the expected structures. In ¹H NMR spectra, the singlet at 2.00–2.38 ppm is due to the resonance of the CH₃ group of the pyrimidine ring. The CH₃ group of the ester moiety in **4a–g** resonates at 0.85–1.20 ppm as a triplet, whereas CH₃ of the acyl group in **4h–i** appears as a singlet at 2.35 ppm. The singlet and multiplets at 5.00–5.90 and 7.10–7.60 ppm are assigned to H-4 and to the aryl protons, respectively. The two NH protons give two broad signals at 9.05–9.78 and 10.00–10.50 ppm, in accord with the expected reaction products.



Potsherd allows the rapid synthesis of these compounds without using polyphosphate ester as a reaction mediator, which has been suggested by Kappe and coworkers.¹⁷ Rapid heating induced by microwave irradiation using potsherd as a heat sink avoids the forcing classical conditions and the decomposition of materials. This leads to the formation of products under mild conditions with increased yields (Table I).

In conclusion, we have described a highly efficient microwaveinduced procedure for the preparation of pyrimidine derivatives under mild conditions using a microwave oven as the irradiation source.

EXPERIMENTAL

¹H and ¹³C NMR spectra were recorded on a Brucker 500 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS (tetramethylsilane) as an internal standard. Spectra were acquired in DMSO. Reaction progress was routinely monitored by TLC on silica gel plates.

	Z	Х	R	Time (\mathbf{s})	Yield (%)
4a	\mathbf{S}	$2-NO_2$	OEt	40	86
4b	\mathbf{S}	$3-NO_2$	OEt	40	85
4c	\mathbf{S}	$4-NO_2$	OEt	40	90
4d	\mathbf{S}	3-Cl	OEt	50	70
4e	\mathbf{S}	4-Cl	OEt	50	66
4f	\mathbf{S}	3-Br	OEt	50	68
4g	0	4-acetamido	OEt	25	73
4h	\mathbf{S}	$4-NMe_2$	Me	30	65
4i	0	4-acetamido	Me	30	75

TABLE I Pyrimidine Derivatives 4a-i

Reactions were performed in a Samsung microwave oven with a 230 V– 50 Hz power source, 900 W output, and 2450 MHz operating frequency.

General Procedure

The corresponding 1,3-diketone (2.2 mmol), aryl aldehyde (3.0 mmol), and (thio)urea (3.0 mmol), along with a few drops of ethanol (or without solvent) and HCl (37%), were placed in a 25-mL glass beaker and stirred at r.t. for 3 min with a magnetic stirrer. The beaker was placed inside a larger container filled with potsherd and then was inserted into the microwave oven. The mixture was then subjected to microwave irradiation at 50% power level for the desired time. After cooling the reaction mixture, water (5 mL) was added, and the mixture was stirred at r.t. for 2 h. The crude products were filtered and recrystallized from ethanol to give the pure compounds.

Ethyl-4-(2-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

Yellow crystals, m.p. 115°C. ¹H NMR (DMSO-d₆): $\delta = 0.91$ (t, J = 7.2 Hz, 3H, CH₃), 2.30 (s, 3H, CH₃), 3.90 (q, J = 7.2 Hz, 2H, CH₂), 5.90 (bs, 1H, H-4), 7.25 (m, 4H, H_{arom}), 9.05 (bs, 1H, NH), 10.30 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): $\delta = 174.3$, 164.6, 147.4, 145.9, 138.1, 134.3, 129.6, 129.2, 124.3, 99.9, 59.6, 49.3, 17.2, 13.8. Anal. calcd. for C₁₄H₁₅N₃O₄S: C, 52.33; H, 4.70; N, 13.08%. Found: C, 52.27; H, 4.53; N, 13.47%.

Ethyl-4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

Pale yellow crystals, m.p. 111°C. ¹H NMR (DMSO-d₆): $\delta = 1.11$ (t, J = 7.3 Hz, 3H, CH₃), 2.38 (s, 3H, CH₃), 4.00 (q, J = 7.2 Hz, 2H, CH₂),

5.30 (bs, 1H, H-4), 7.85 (m, 4H, H_{arom}), 9.75 (bs, 1H, NH), 10.50 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 174.5, 164.7, 147.7, 145.7, 145.4, 132.8, 130.2, 122.5, 121.0, 99.8, 59.6, 53.4, 17.1, 13.8. Anal. calcd. for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08%. Found: C, 52.31; H, 4.41; N, 13.40%.

Ethyl-4-(4-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

Yellow crystals, m.p. 135°C. ¹H NMR (DMSO-d₆): $\delta = 0.85$ (t, J = 7.2 Hz, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.75 (q, J = 7.2 Hz, 2H, CH₂), 5.45 (bs, 1H, H = 4), 7.13 (m, 4H, H_{arom}), 9.50 (bs, 1H, NH), 10.25 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): $\delta = 183.9$, 173.8, 164.7, 145.5, 140.5, 131.7, 129.4, 129.3, 127.7, 99.7, 59.4, 51.6, 16.9, 13.8. Anal. calcd. for C₁₄H₁₅N₃O₄S: C, 52.33; H, 4.70; N, 13.08%. Found: C, 52.12; H, 4.51; N, 13.42%.

Ethyl-4-(3-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

White crystals, m.p. 161°C. ¹H NMR (DMSO-d₆): $\delta = 0.85$ (t, J = 7.2 Hz, 3H, CH₃), 2.20 (s, 3H, CH₃), 3.85 (q, J = 7.2 Hz, 2H, CH₂), 5.04 (bs, 1H, H-4), 7.20 (m, 4H, H_{arom}), 9.50 (bs, 1H, NH), 10.00 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): $\delta = 174.4$, 164.8, 145.7, 145.3, 139.5, 132.9, 130.0, 128.6, 127.4, 100.1, 61.1, 59.5, 17.0, 13.8. Anal. calcd. for C₁₄H₁₅N₂O₂SCl: C, 54.10; H, 4.86; N, 9.01%. Found: C, 54.31; H, 4.55; N, 9.33%.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

White crystals, m.p. 188°C. ¹H NMR (DMSO-d₆): $\delta = 1.10$ (t, J = 7.2 Hz, 3H, CH₃), 2.31 (s, 3H, CH₃), 4.00 (q, J = 7.2 Hz, 2H, CH₂), 5.10 (bs, 1H, H-4), 7.35 (m, 4H, H_{arom}), 9.70 (bs, 1H, NH), 10.40 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): $\delta = 174.2$, 165.0, 145.3, 142.3, 132.2, 128.5, 128.2, 100.3, 59.6, 53.4, 17.1, 13.9. Anal. calcd. for C₁₄H₁₅N₂O₂SCl: C, 54.10; H, 4.86; N, 9.01%. Found: C, 53.78; H, 4.44; N, 9.20%.

Ethyl-4-(3-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

White crystals, m.p. 171°C. ¹H NMR (DMSO-d₆): $\delta = 0.91$ (t, J = 7.2 Hz, 3H, CH₃), 2.11 (s, 3H, CH₃), 4.01 (q, J = 7.2 Hz, 2H, CH),

5.90 (bs, 1H, H-4), 7.35 (m, 4H, H_{arom}), 9.45 (bs, 1H, NH), 10.10 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 174.3, 164.6, 145.6, 145.5, 132.0, 130.9, 129.0, 128.4, 127.5, 100.0, 60.8, 59.3, 17.0, 13.7. Anal. calcd. for $C_{14}H_{15}N_2O_2SBr$: C, 47.33; H, 4.26; N, 7.89%. Found: C, 47.46; H, 4.31; N, 7.53%.

Ethyl-4-(4-acetamidophenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

Yellow crystals, m.p. 285°C. ¹H NMR (DMSO-d₆): δ = 1.20 (t, J = 7.2 Hz, 3H, CH₃), 2.00 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 3.80 (q, J = 7.2 Hz, 2H, CH₂), 5.00 (bs, 1H, H-4), 7.25 (m, 4H, H_{arom}), 7.60 (bs, 1H, NH), 9.10 (bs, 1H, NH), 9.85 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): δ = 201.9, 167.3, 164.4, 151.3, 147.1, 138.9, 137.5, 125.7, 118.2, 98.6, 58.2, 52.7, 22.9, 16.9, 13.2. Anal. calcd. for C₁₆H₁₉N₃O₄: C, 60.56; H, 6.03; N, 13.24%. Found: C, 60.84; H, 6.19; N, 13.49%.

4-(4-Dimethylaminophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-methylketo-ne (4h)

Green crystals, m.p. 239°C. ¹H NMR (DMSO-d₆): δ = 2.20 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.40 (s, 6H, 2 × CH₃), 5.40 (bs, 1H, H-4), 7.10 (m, 4H, H_{arom}), 9.30 (bs, 1H, NH), 10.30 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): δ = 193.3, 185.9, 181.6, 172.7, 155.8, 147.6, 93.2, 91.1, 67.5, 55.5, 31.6, 15.9. Anal. calcd. for C₁₅H₁₉N₃OS: C, 62.25; H, 6.62; N, 14.52%. Found: C, 61.87; H, 6.49; N, 14.70%.

4-(4-Acetamidophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-methylketone (4i)

Green crystals, m.p. 119°C. ¹H NMR (DMSO-d₆): δ = 2.00 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 5.20 (bs, 1H, H-4), 7.35 (m, 4H, H_{arom}), 9.10 (bs, 1H, NH), 9.75 (bs, 1H, NH). ¹³C NMR (DMSO-d₆): δ = 201.9, 194.1, 167.9, 151.8, 147.6, 138.7, 138.3, 129.6, 126.6, 119.1, 109.4, 53.4, 29.9, 23.7, 18.6. Anal. calcd. for C₁₅H₁₇N₃O₃: C, 62.71; H, 5.96; N, 14.63%. Found: C, 62.36; H, 6.31; N, 14.29%.

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