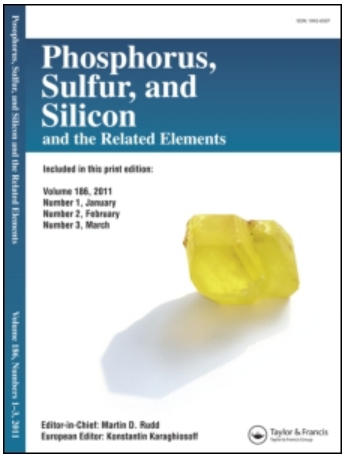

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MICROWAVE ASSISTED SYNTHESIS OF SOME FUSED THIAZOLOPYRIMIDINES

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MICROWAVE ASSISTED SYNTHESIS OF SOME FUSED THIAZOLOPYRIMIDINES

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*A simple and fast synthesis of some fused thiazolopyrimidine compounds **2**(**a–g**) in high yield has been developed using microwave assisted cyclocondensation reaction of **1** with chloroacetic acid, anhydrous sodium acetate, and corresponding aldehyde. Yields of products following recrystallization from ethanol were of the order of 88–94%. IR and ^1H NMR spectrscopies and elemental analysis were used for identification of these compounds.*

Keywords: Carboxylate; microwave irradiation; pyrimidine; thiazolo

Pyrimidine derivatives have been reported to possess a broad spectrum of pharmacological properties[1–9] including antiviral, antiumor, antibacterial,[2] and antihypertensive[3] effects. Thus pyrimidine has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. In order to prepare some new fused thiazolopyrimidine derivatives using a fast and simple method we have investigated cyclocondensation reaction of ethyl-4-aryl-6-methyl-2-thioxo-1,-2,3-4-tetrahydro-pyrimidine-5-carboxylate with chloroacetic acid, anhydrous sodium acetate, and substituted aromatic aldehydes by applying microwave irradiation in solvent free conditions.

Microwave irradiation is a nonconventional energy source that has blossomed recently into a useful technique for different applications in organic synthesis.[10–15] Some of the interesting features of this method are the rapid reaction rates, simplicity, solvent-free and cleaner reaction condition.[1,11] Also microwave irradiation generates rapid intense heating of polar substances, which results in reduction of reaction time compared to conventional heating.

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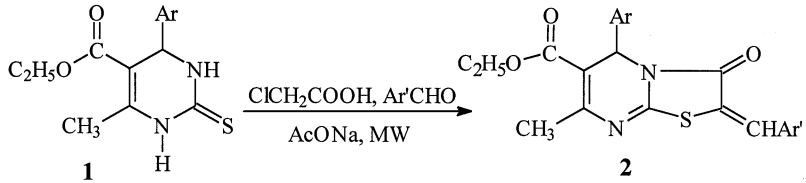
TABLE I Thiazolopyrimidine Derivatives **2**(**a–g**)

Entry	Time of Irradiation (s)	Yield (%)
2a	90	90
2b	60	94
2c	60	94
2d	30	88
2e	60	86
2f	40	92
2g	40	92

RESULTS AND DISCUSSION

Pyrimidine thiazole derivative **1**, chloroacetic acid, anhydrous sodium acetate, and the corresponding aldehyde were reacted under microwave irradiation to give the corresponding pyrimidine derivatives **2**(**a–g**) in high yields (Table I) according to Scheme 1.



a) Ar = C_6H_5, Ar′ = p-BrC_6H_4
b) Ar = C_6H_5, Ar′ = p-ClC_6H_4
c) Ar = C_6H_5, Ar′ = p-$NO_2C_6H_4$
d) Ar = C_6H_5, Ar′ = p-$(NCH_3)_2C_6H_4$
e) Ar = C_6H_5, Ar′ = C_4H_3S (Thienyl)
f) Ar = p-$CH_3C_6H_4$, Ar′ = p-ClC_6H_4
g) Ar = p-$CH_3C_6H_4$, Ar′ = p-$OCH_3C_6H_4$

SCHEME 1

Two isomeric cyclization products may be expected from an attack of the nucleophile on N-1 and N-3 of **1**. However it is well documented[17,18] that N-3 in pyrimidine compound **1** is more reactive toward electrophiles than the N-1, which is part of push-pull system with the ester group in the 5-position of the pyrimidine ring. Also the low field shift of pyrimididine proton in **2**, which is due to a deshielding effect of the neighboring carbonyl group, compared to that of **1** is in support of a nucleophilic attack on N-3.

The ^{1}H NMR spectra of compounds are very simple. The singlet signal at 2.20–2.55 ppm is due to the resonance of the CH_3 group of the pyrimidine ring. The CH_3 of ester group resonates at 1.01–1.15 ppm as a triplet signal. The singlet and multiplet signals at 6.00–6.10 and 7.20–7.7.50 ppm are assigned to H-5 and aryl protons respectively. The broad signal at 7.65–8.15 ppm is attributed to the resonance of the ylidene proton.

In the IR spectra of compounds **2**(**a–g**) absence of the absorption at 3300–3500 cm^{-1}, the characteristic absorption of NH group of starting material, **1**, is a good evidence of the expected reactions.

EXPERIMENTAL

Pyrimidine thiazole derivatives **1** were prepared using known method.[14,16] Melting points were measured on an electrothermal digital melting point apparatus. H^1 NMR spectra were recorded on a Brucker 500 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS (tetramethylsylan) as an internal standard. Spectra acquired in $CDCl_3$. IR spectra were performed on a Galaxy FT-IR 500 spectrophotometer. Reaction progress was routinely monitored by thin layer chromatography (TLC) on silica gel plates. 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

For preparation of compounds **2**(**a–g**) a mixture of the appropriate pyrimidine thiazole derivative **1** (0.0025 mmol), chloroacetic acid (0.0025 mmol) corresponding aldehyde (0.0025 mmol), and anhydrous sodium acetate (0.5 g) were ground with a pestle in a mortar for 3–4 min. The mixture was then placed in a 25 ml beaker. The beaker was put in a watch glass and then inserted into the microwave oven. The mixture was subjected to microwave irradiation at 100% power level for 30–90 s. The resulting liquid solidified at room temperature after 1–2 h. The crude product was dissolved in hot ethanol and filtered. The resulting solution was crystallized after 12 h and the crystals were collected by filtration.

Ethyl-5-phenyl-7-methyl-2-(4-bromophenyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2a)

Yield 90%, m.p. 177–178°C.

IR (KBr): $\nu = 3050, 2900, 1711, 1622, 1561, 1240, 1165$ cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.01 (t, J = 7.2 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.99, (q, J = 7.2 Hz, 2H, —OCH_2), 6.00 (s, 1H, H-5), 7.39 (m, 10H, H_{arom}), 7.95 (brs, 1H, ylidene).

Anal. Calcd for $C_{23}H_{19}N_2O_3SBr$: C, 57.14; H, 3.93; N, 5.80%. Found: C, 57.10; H, 4.10; N, 5.60.

Ethyl-5-phenyl-7-methyl-2-(4-chlorophenyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2b)

Yield 94%, m.p. 154–155°C.

IR (KBr): ν = 3050, 2900, 1711, 1609, 1549, 1227, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.05 (t, J = 7.2 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.10, (q, J = 7.2 Hz, 2H, —OCH_2), 6.10 (s, IH, H-5), 7.35 (m, 10H, H_{arom}), 7.75 (brs, 1H, ylidene).

Anal. Calcd for $C_{23}H_{19}N_2O_3SCI$: C, 62.93; H, 4.36; N, 6.39%. Found: C, 62.88; H, 4.42; N, 6.37%.

Ethyl-5-phenyl-7-methyl-2-(4-nitrophenyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2c)

Yield 94%, m.p. 188–189°C.

IR (KBr): ν = 3000, 2980, 1711, 1609, 1560, 1339, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.10, (q, J = 7.2 Hz, 2H, —OCH_2), 6.10 (s, 1H, H-5), 7.50 (m, 9H, H_{arom}), 8.15 (brs, 1H, ylidene).

Anal. Calcd for $C_{23}H_{19}N_3O_5S$: C, 61.46; H, 4.26; N, 9.34%. Found: C, 61.39; H, 4.30; N, 9.31%.

Ethyl-5-phenyl-7-methyl-2-(4-N,N-dimethylaminophenyl)-methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2d)

Yield 88%, m.p. 225–226°C.

IR (KBr): ν = 3050, 2920, 1707, 1580, 1155 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.00 (s, 6H, NMe_2), 4.05, (q, J = 7.2 Hz, 2H, —OCH_2), 6.10 (s, 1H, H-5), 7.20 (m, 9H, H_{arom}), 7.70 (brs, 1H, ylidene).

Anal. Calcd for $C_{25}H_{25}N_3O_3S$: C, 67.09; H, 5.63; N, 9.38%. Found: C, 67.02; H, 5.63; N, 9.37%.

Ethyl-5-Phenyl-7-methyl-2-(thienyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2e)

Yield 86%, m.p. 210–212°C.

IR (KBr): $\nu = 3080, 2990, 1703, 1595, 1547, 1236\ cm^{-1}$.

^1H NMR ($CDCl_3$): δ (ppm) = 1.10 (t, J = 7.2 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.05, (q, J = 7.2 Hz, 2H, $-OCH_2$), 6.10 (s, 1H, H-5), 7.30 (m, 8H, H_{arom}), 7.83 (brs, 1H, ylidene).

Anal. Calcd for $C_{21}H_{18}N_2O_3S_2$: C, 61.41; H, 4.41; N, 6.87%. Found: C, 61.45; H, 4.51; N, 6.89%.

Ethyl-5-methylphenyl-7-methyl-2-(4-chlorophenyl)-methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2f)

Yield 92%, m.p. 180–181°C.

IR (KBr): $\nu = 3050, 2900, 1709, 1618, 1549, 1225\ cm^{-1}$.

^1H NMR ($CDCl_3$): δ (ppm) = 1.11 (t, J = 7.2 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.00, (q, J = 7.2 Hz, 2H, $-OCH_2$), 6.00 (s, 1H, H-5), 7.35 (m, 8H, H_{arom}), 7.65 (brs, 1H, ylidene).

Anal. Calcd for $C_{24}H_{20}N_2O_3S_2$: C, 64.28; H, 4.45; N, 6.25%. Found: C, 64.10; H, 4.55; N, 6.40%.

Ethyl-5-methylphenyl-7-methyl-2-(4-methoxyphenyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo [a-2,3] Pyrimidine-6-carboxylate (2g)

Yield 92%, m.p. 180–182°C.

IR (KBr): $\nu = 3050, 2900, 1711, 1595, 1547, 1300\ cm^{-1}$.

^1H NMR ($CDCl_3$): δ (ppm) = 1.15 (t, J = 7.2 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.00, (q, J = 7.2 Hz, 2H, $-OCH_2$), 6.00 (s, 1H, H-5), 7.25 (m, 8H, H_{arom}), 7.65 (brs, 1H, ylidene).

Anal. Calcd for $C_{25}H_{23}N_2O_4S$: C, 67.09; H, 5.18; N, 6.25%. Found: C, 66.95; H, 5.46; N, 6.20%.

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