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MICROWAVE-ASSISTED SYNTHESIS OF SOME BI- AND TRICYCLIC PYRIMIDINE DERIVATIVES

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Pyrimidine derivatives 4a–4c was prepared by a Biginelli cyclocondensation of β -ketoesters, aryl aldehydes, and thiourea derivatives under microwave irradiation. A simple and fast synthesis of bicyclic pyrimidine derivatives 6a–6c was performed by microwave-assisted reaction of 4a–4c with bromomalononitrile (5). Reaction of bicyclic pyrimidines 6a–6c with HCO_2H and HONH_3Cl under microwave irradiation gave tricyclic pyrimidines 7a–7c and 8a–8c respectively.

Keywords: Bromomalononitrile; microwave; neutral alumina; pyrimidine

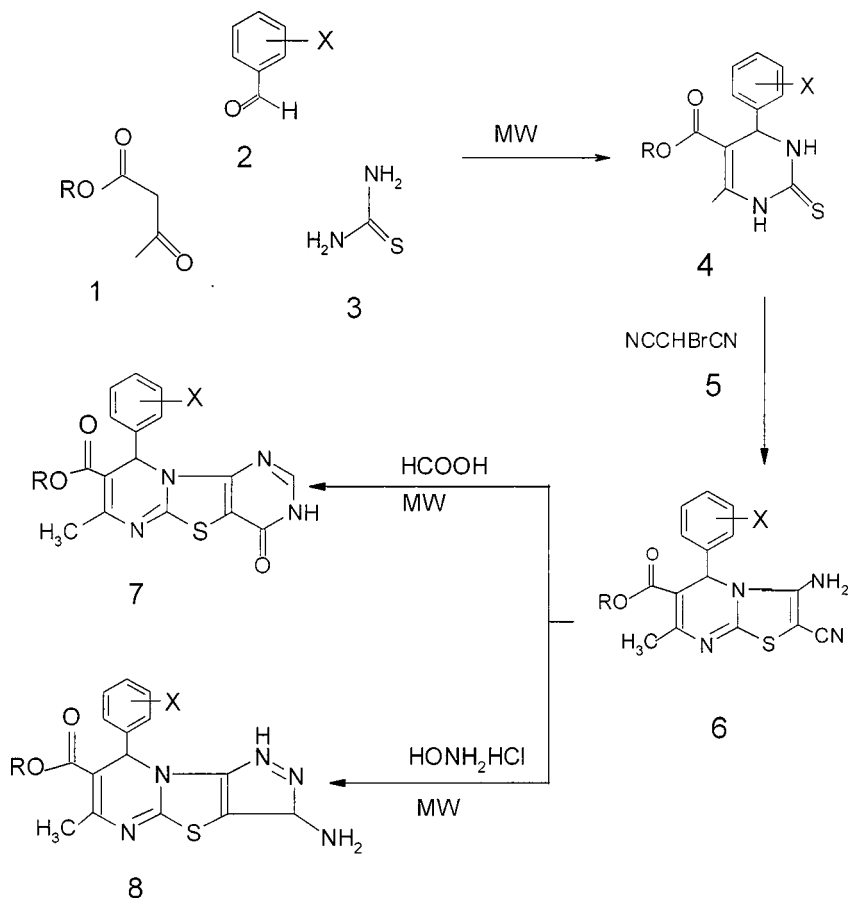
Pyrimidine is known as a versatile heterocyclic compound, which has been subjected to a various structural modifications in order to prepare some derivatives with different biological effects. Some of pyrimidines possess remarkable pharmacological efficiency.^{1–15} Microwave irradiation is a nonconventional energy source whose application in organic synthesis has been increased recently^{16–19} and technologically is becoming more popular. Some of the more salient features of this method are the rapid reaction rates and simple and cleaner reaction conditions.^{6,16,19}

Therefore, due to the versatile biological properties of pyrimidine derivatives, we have extended the microwave-assisted cyclocondensation reactions in order to synthesize some novel bicyclic and tricyclic pyrimidine derivatives in high yield.

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RESULTS AND DISCUSSION

Starting materials **4(a-c)** were synthesized on the basis of already reported procedure. β -ketoester **1**, aryl aldehyde **2**, (thio)urea **3**, and polyphosphate ester (PPE) were reacted under microwave irradiation to give the corresponding pyrimidine derivatives **4a-4c** in high yields (Table I) according to Scheme 1.



SCHEME 1

Reactions of **4(a-c)** with bromomalononitrile (**5**) under microwave irradiation lead to the formation of corresponding bicyclic pyrimidine compounds **6(a-c)** in high yields (Table II).

TABLE I Pyrimidine Derivatives **4a–4c**

Entry	R	X	Yield
4a	Et	H	85
4b	Et	<i>p</i> -CH ₃	71
4c	Et	<i>p</i> -N(CH ₃) ₂	81

¹H NMR, IR, and mass spectroscopies were used to identification of these compounds. In the IR spectra of compounds **6(a–c)** the sharp absorption at 2180–2202 cm^{−1} indicate the existence of the nitrile group. Also the absorption at 3203–3379 cm^{−1} in IR spectra were assigned to the −NH₂ group which is supported by the ¹H NMR data. The ¹H NMR spectra **6(a–c)** show a singlet signal at 7.6–7.7 ppm due to −NH₂ group. The multiplet signal at 6.5–7.3 ppm and the singlet signal at 6.2–6.3 ppm are due to resonance of aryl and pyrimidine ring protons respectively.

Reactions of bicyclic pyrimidines **6(a–c)** with HCO₂H under microwave irradiation afforded tricyclic pyrimidines **7a–7c** (Table III). ¹H NMR of compounds **7a–7c** could not be obtained due to their insolubility in DMSO. However the IR and mass spectroscopies data suggested these compounds should be pure. The IR spectra of these compounds have an absorption in the region 3327–3340 cm^{−1} which is the characteristic of secondary amines.

Compounds **8a–8c** (Table IV) were synthesized by reaction of bicyclic pyrimidines **6(a–c)** with HONH₃Cl under microwave irradiation. ¹H NMR measurements of compounds **8a–8c** confirmed their purity to be more than 95%. In ¹H NMR spectra the sharp singlet signal at 2.2–2.5 ppm is assigned to resonance of −CH₃ group on the pirimidine ring. Resonance at 6.50–7.69 ppm is attributed to aromatic protons of the phenyl and pyrimidine rings. The two different singlet signals in the regions 7.90–8.50 and 9.00–9.20 ppm, respectively, are due to resonance of −NH and −NH₂ groups of five-member heterocyclic ring containing two nitrogens. This was supported by IR spectra, which included signals in the region 3160–3526 cm^{−1}.

TABLE II Pyrimidine Bicyclic Derivatives **6a–6c**

Entry	R	X	Yield
6a	Et	H	83
6b	Et	<i>p</i> -CH ₃	75
6c	Et	<i>p</i> -N(CH ₃) ₂	86

TABLE III Pyrimidine Tricyclic Derivatives **7a–7c**

Entry	R	X	Yield (%)
7a	Et	H	75
7b	Et	<i>p</i> -CH ₃	70
7c	Et	<i>p</i> -N(CH ₃) ₂	82

We also have made a comparison of time scales and yields on the formation of pyrimidines **6–8** using microwave irradiation and conventional heating method. It can be concluded that synthesis of bi-cyclic and tricyclic pyrimidine derivatives under microwave irradiation is quite faster (20–1080 times) and the yields are higher than conventional heating methods (Table V).

In conclusion the rapid heating induced by microwave irradiation not only avoids the force conditions and the decomposition of the reagents but also results in formation of clean product under mild conditions, thus increasing the yield.

EXPERIMENTAL

An Electrothermal digital melting point apparatus was used to determination of melting points. IR spectra were recorded on a Galaxy series FT-IR 5000 spectrophotometer by using KBr pellets. ¹H NMR spectra were recorded on Bruker 400 and 500 MHz spectrometers with using Me₄Si (TMS) as an internal standard. Mass spectra were obtained from an EI (70 eV)+Q1MSLMR up LP spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography.

General Procedure for Preparation (**4a–4c**)

The mixture of aryl aldehyde (2 mmol), ethylacetoacetate (2.2 mmol), thiourea (6.0 mmol), and polyphosphate ester (PPE, 0.30 g) were placed in 25-ml glass beaker and stirred for 3–4 min with a magnetic stirrer. The reaction container was inserted into a 200-ml pyrex beaker filled with neutral alumina (100–290 mesh) and irradiated in the microwave oven at 50% power level for 90 s. After cooling and addition of H₂O (5 mL) the mixture was stirred at room temperature for 2 h. The

TABLE IV Pyrimidine Tricyclic Derivatives **8a–8c**

Entry	R	X	Yield (%)
8a	Et	H	65
8b	Et	<i>p</i> -CH ₃	60
8c	Et	<i>p</i> -N(CH ₃) ₂	70

TABLE V Comparison of Time and Yields on the Formation of Some Pyrimidine Derivatives Using Microwave Irradiation and Conventional Heating

Entry	Microwave Irradiation			Conventional Heating		
	Power/W%	t/min	Yield (%)	t/min	Yield (%)	t _c /t _{mw}
6a	50	1.5	83	30	65	20
6b	50	1.5	75	30	63	20
6c	50	1.5	86	30	65	20
7a	100	2/3	75	600	65	900
7b	100	2/3	70	720	60	1080
7c	100	2/3	82	720	65	1080
8a	100	1	65	300	67	300
8b	100	1	60	300	65	300
8c	100	1	70	360	65	360

solid products were filtered, washed with H₂O and subsequently dried (Table I).

Preparation of Bromomalononitrile (5)

A mixture of malononitrile (0.825 g, 0.025 mmol) and water (8 ml) were placed in a 50-ml narrow-neck flask. The mixture was put on an ice-bath and stirred for 2–3 min with a magnetic stirrer. Then Br₂ (1.275 ml, 0.025 mmol) was added as small portions. After the completion of the reaction, 0.025 mmol of malononitrile was added and the mixture shaken for 10 min at room temperature. The mixture was kept at –4°C for overnight and the white crystals precipitated, filtered, washed with H₂O, and subsequently dried.

General Procedure for Preparation of Thiazole Pyrimidine (6a–6c)

A mixture of pyrimidine derivative (**4a–4c**) (0.01 mmol), bromomalononitrile (0.011 mmol) and PPE (0.3 g) were placed in a 25-ml beaker. The reaction container was inserted into a 200-ml pyrex beaker filled with neutral alumina (100–290 mesh). This set-up was irradiated in the microwave oven 50% power level for 90s (one-step). The result was then cooled at room temperature for 2 h and filtered. The precipitate was crystallized from dilute DMF.

General Procedure for Preparation of (7a–7c)

A mixture of formic acid (1.2 mmol) and appropriate pyrimidine thiazole derivatives, **6a–6c**, (1 mmol) into a 25-ml glass beaker were stirred for

2 min. The reaction container was inserted into a 200-ml pyrex beaker filled with neutral alumina (alumina bath). This set-up was subjected to microwave irradiation (100% power level) for 40 s. Then the result was cooled for 4 h and recrystallized from ethanol.

General Procedure for Preparation (8a–8c)

A mixture of appropriate thiazole pyrimidine derivative, **6a–6c**, (0.01 mmol), hydroxylamin chloride (0.012 mmol) and PPE (0.6 g) were stirred in a 50-ml glass beaker for 2 min. The reaction container was inserted into a 200-ml pyrex beaker filled with neutral alumina and subjected to microwave irradiation (100% power level) for 60 s. Then result mixture was cooled at room temperature for 4 h. The result solid was stirred in H₂O, filtered, and recrystallized from ethanol.

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

Yield 85%, m.p. 206–207°C.

IR (KBr): ν = 3340, 3180, 3100, 2990, 1676 cm⁻¹.

¹H NMR (DMSO-d₆), δ = 1.1 (t, j = 7.2 Hz, 3H, CH₃), 2.3 (s, 3H, CH₃), 4.0 (q, j = 7.2 Hz, 2H, CH₂), 5.3 (d, 1H, H-4), 7.3 (m, 5H, H_{aromat}), 9.6, 10.3 (s, 1H, NH).

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

Yield 71%, m.p. 186–187°C.

IR (KBr): ν = 3325, 3177, 3109–2924, 1674 cm⁻¹.

¹H NMR (DMSO-d₆): δ = 1.0 (t, j = 7.2 Hz, 3H, CH₃), 2.3 (s, 6H, 2CH₃), 4.0 (q, j = 7.2 Hz, 2H, CH₂), 5.2 (d, 1H, H-4), 7.2 (s, 4H, H_{aromat}), 9.5 (bs, 1H, NH), 10.2 (s, 1H, NH).

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

Yield 81%, m.p. 197–198°C.

IR (KBr): ν = 3320, 3160, 3100, 2920, 1720 cm⁻¹.

¹H NMR (DMSO-d₆): δ = 1.2 (t, j = 7.2 Hz, 3H, CH₃), 2.3 (s, 3H, CH₃), 2.9 (s, 6H, CH₃), 4.1 (q, j = 7.2 Hz, 2H, CH₂), 5.2 (d, 1H, H-4), 6.6–7.2 (m, 4H, H_{aromat}), 7.2, 7.9 (bs, 1H, NH).

Ethyl-3-amino-5-phenyl-2-cyano-7-methyl-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (6a)

Yield 83%, m.p. 231–232°C.

IR (KBr): ν = 3369–3271, 3115, 2980, 2191, 1705, 1680 cm⁻¹.

¹H NMR (DMSO-d₆): δ = 1.2 (t, 3H, CH₃), 2.3 (s, 3H, CH₃), 4.09 (q, 2H, CH₂), 6.2 (s, 1H, H-4), 7.3 (s, 5H, H_{aromat}), 7.7 (s, 2H, NH₂).

MS: m/z (%) = 340 (M⁺, 100), 292 (83), 267(56), 263 (33).

Ethyl-3-amino-5-(4-methyl phenyl)-2-cyano-7-methyl-5H-thiazolo[a-2,3] pyrimidine-6-carboxylate (6b)

Yield 75%, m.p. 216–218°C.

IR (KBr): $\nu = 3379\text{--}3291, 3146, 2985, 2202, 1709, 1651\text{ cm}^{-1}$. $^1\text{H NMR}$ (DMSO- d_6): $\delta = 1.2$ (t, $j = 7.2$ Hz, 3H, CH_3), 2.3 (s, 6H, 2CH_3), 4.0 (q, 2H, CH_2), 6.3 (s, 1H, H-4), 7.2 (m, 4H, H_{aromat}), 7.8 (s, 2H, NH_2).MS: m/z (%) = 354 (M^+ , 100), 324 (22), 306 (63), 281 (60), 263 (23).**Ethyl-3-amino-5-(4-dimethyl aminophenyl)-2-cyano-7-methyl-5H-thiazolo[a-2,3]pyrimidine-5-carboxylate (6c)**

Yield 86%, m.p. 209–210°C.

IR (KBr): $\nu = 3303\text{--}3215, 3070, 2980, 2180, 1655\text{ cm}^{-1}$. $^1\text{H NMR}$ (DMSO- d_6): $\delta = 1.2$ (t, 3H, CH_3), 2.3 (s, 6H, CH_3), 4.0 (q, 2H, CH_2), 6.2 (s, 1H, H-4), 6.5–7.2 (m, 4H, H_{aromat}), 7.6 (s, 2H, NH_2).MS: m/z (%) = 383 (M^+ , 100), 336 (46), 310 (97), 263 (25).**Ethyl-9-phenyl-4-oxo-7-methyl-9H-3,4 dihydrothiazolo[a-2,3; b-4,5] dipyrimidine-8-carboxylate (7a)**

Yield 75%, m.p. 206–207°C.

IR (KBr): $\nu = 3340, 3140, 2980, 1680, 1630\text{ cm}^{-1}$.MS: m/z (%) = 368 (M^+ , 80), 339 (32), 323 (10), 295 (17), 291 (100).**Ethyl-9-(4-methyl phenyl)-4-oxo-7-methyl-9H-3,4-dihydrothiazolo [a-2,3; b-5,4] dipyrimidine-8-carboxylate (7b)**

Yield 70%, m.p. 202–204°C.

IR (KBr): $\nu = 3327, 3140, 2980, 1678, 1625\text{ cm}^{-1}$.MS: m/z (%) = 382 (78), 353 (32), 309 (82), 291 (100).**Ethyl-9-(4-dimethyl amino phenyl)-4-oxo-7-methyl-9H-3,4-dihydropyrimidine-8-carboxylate (7c)**

Yield 82%, m.p. 181–182°C.

IR (KBr): $\nu = 3337, 3136, 2980, 1668, 1630\text{ cm}^{-1}$.MS: m/z (%) = 411 (29), 389 (25), 338 (100), 291 (85).**Ethyl-3-amino-8-phenyl-6-methyl-1H,8H-pyrazole [d-3,4] thiazole [a-2,3]pyrimidine-7-carboxylate (8a)**

Yield 65%, m.p. 202–204°C.

IR (KBr): $\nu = 3526\text{--}3160, 3120, 2972, 1710, 1525\text{ cm}^{-1}$. $^1\text{H NMR}$ (DMSO- d_6): $\delta = 1.2$ (t, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.5 (q, 2H, CH_2), 6.7 (s, 1H, H-4), 7.2–7.6 (m, 5H, H_{aromat}), 7.9 (s, 1H, NH), 9.0 (s, 2H, NH_2).MS: m/z (%) = 355 (M^+ , 21), 310 (38), 280 (100), 278 (42).**Ethyl-3-amino-8-(4-methylphenyl)-6-methyl-1H,8H-pyrazole [d-3,4] thiazole[a-2,3]pyrimidine-7-carboxylate (8b)**

Yield 60%, m.p. 182–183°C.

IR (KBr): $\nu = 3480, 3180, 3125, 2980, 1699, 1525\text{ cm}^{-1}$. $^1\text{H NMR}$ (DMSO- d_6): $\delta = 1.2$ (t, 3H, CH_3), 2.3 (s, 6H, 2CH_3), 4.0 (q,

2H, CH₂), 5.2 (s, 1H, H-4), 6.7–7.4 (m, 4H, H_{aromat}), 8.5 (s, 1H, NH), 9.2 (s, 2H, NH₂).

Ethyl-3-amino-8-(4-dimethylaminophenyl)-6-methyl-1H, 8H-pyrazole[d-3,4] thiazole [a-2,3] pyrimidine-7-carboxylate (8c)
Yield 70%, m.p. 176–178°C.

IR (KBr): ν = 3380, 3212, 3060, 2958, 1650 cm⁻¹.

¹H NMR (DMSO-d₆): δ = 1.2 (t, 3H, CH₃), 2.2 (s, 3H, CH₃), 2.8 (s, 6H, CH₃), 4.0 (q, 2H, CH₂), 6.2 (s, 1H, H-4), 6.5–7.2 (m, 4H, H_{aromat}), 8.0 (s, 1H, NH), 9.0 (s, 2H, NH₂).

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