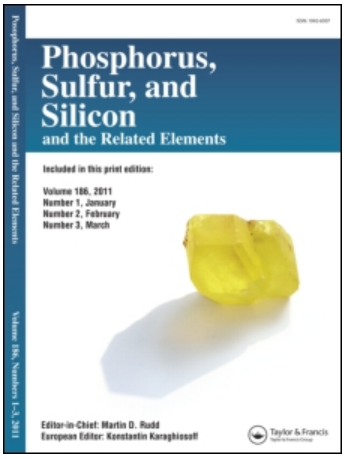

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Studies on Reactions of Pyrimidine Compounds. 2[1]. Microwave-Assisted Synthesis of 1,2,3,4-Tetrahydro-2-Thioxopyrimidine Derivatives

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*The 5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (**1a**) and 5-benzoyl-4-(2-chlorophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (**1b**) were synthesized using the Biginelli three-component cyclocondensation reaction of a β-diketone, arylaldehyde, and thiourea under microwave irradiation. Thiazolopyrimidine (**2**), (**3**) and pyrimido[2,3-b]thiazine (**4**) derivatives were obtained by a simple one-pot condensation reaction of starting compound **1b** and 2-bromopropionic acid, bromoacetic acid and 3-bromopropionic acid, respectively. These reactions performed under microwave irradiation and conventional conditions.*

That study is suggested a simple and efficient route for the preparation of 1,2,3,4-tetrahydro-2-thioxopyrimidine and derivatives.

Keywords Microwave-Assisted; Biginelli reaction; thioxopyrimidine; synthesis; cyclocondensation; multicomponent reaction

INTRODUCTION

Recently, there has been focused interest in the three-component cyclocondensation reaction of β-diketone, arylaldehyde, and (thio)urea under Brönsted acid catalysis that was firstly reported by Pietro Biginelli in 1893.[2] The reaction products are dihydropyrimidine derivatives, which display various types of biological and agricultural activities[3] such as analgesic,[3a] antipyretic,[3b] antihypertensive,[3c] anti-inflammatory,[3d]

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pesticides,[3e] herbicides,[3f] plant growth regulators,[3g] and as modulators for the transport of calcium ions across the cell membrane.[4]

In the last few years there has been an increased interest in the use of microwave heating in organic synthesis,[5] 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, and the case of work-up after the reaction, and better selectivity. Also, microwave irradiation generates rapid intense heating of polar substances, which result in the reduction of reaction time compared to conventional heating.[6]

At present continuing with our studies on the synthesis of 1,2,3,4-tetrahydropyrimidine derivatives using conventional heating and microwave irradiation. The purpose of that works is to extend the Biginelli reactions in order to synthesize some 1,2,3,4-tetrahydro-2-thioxopyrimidine derivatives. The reported method is suggested that a simple and efficient route for the preparation of 1,2,3,4-tetrahydro-2-thioxopyrimidine derivatives.

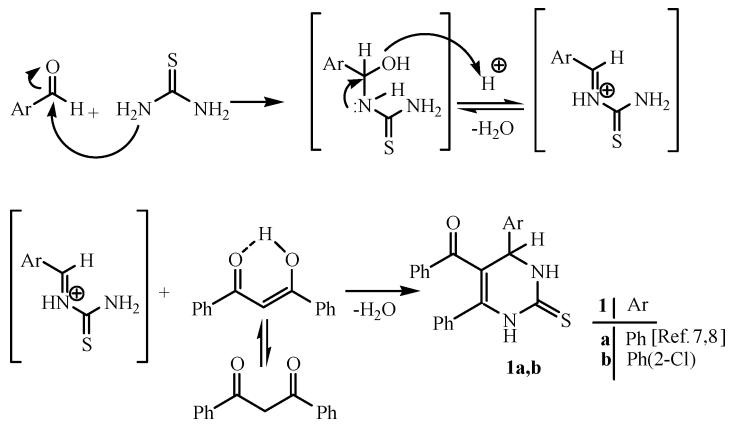
RESULTS AND DISCUSSION

In the present study, we achieved the synthesis of the pyrimidine derivatives via conventional heating as well as microwave irradiation experiments. The synthesis of derivative **1a** via conventional heating method was published in our previous work.[7] The derivative is also available in the product list of Aurora Fine Chemicals.[8] The reaction was performed 1,3-diphenyl-1,3-propanedione, benzaldehyde, and thiourea in glacial acetic acid containing a few drops of concentrated hydrochloric acid. The mixture was heated under reflux condition for 8 h. The reaction was finalized in good yield (93%). In a similar way, the compound **1b** was synthesized use 2-chlorobenzaldehyde instead of benzaldehyde (Scheme 1). Yield of product following recrystallization from 1-butanol was of the order of 90%.

When 1,3-diketone, aryl aldehyde, thiourea, and a few drops of concentrated HCl were reacted in glacial acetic acid under microwave irradiation for 5 min obtained the same final products (**1a,b**).

^{1}H and ^{13}C NMR spectra of the isolated compounds **1a**[7,8] and**1b** confirm the expected structures. In ^{1}H NMR spectra of compound **1b**, the singlets at 10.6 and 9.7 ppm are due to the resonance of the two NH groups of the pyrimidine ring. The doublet and multiplet at 5.8 ($J =$ 2.6) and 7.0–7.6 ppm are assigned to C_4H and to the aryl protons, respectively.

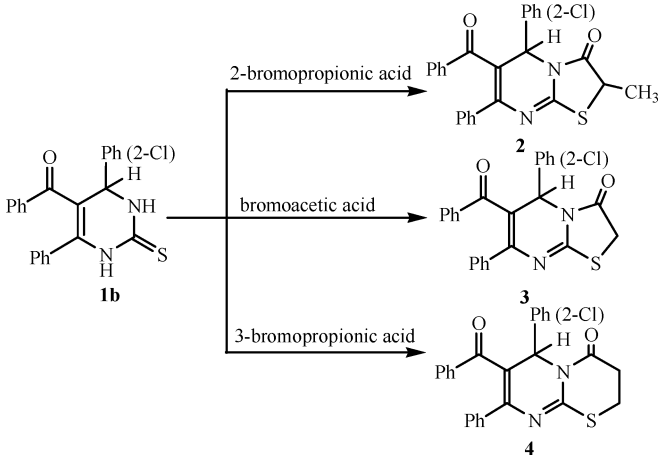
On the other hand, the reactions of thioxopyrimidine derivatives having the NH and C=S group in the suitable position with various bromo



SCHEME 1

compounds were convenient methods to build the thiazolopyrimidine and pyrimido[2,3-b]thiazine derivatives.[9,10] Thus, the compounds **1a** and **1b** were cyclized with various bromo compounds to the thiazolopyrimidine (**2,3**) and pyrimido[2,3-b]thiazine (**4**) derivatives (Scheme 2), in approximately 35–48% yields. (The reactions of **1a** were described Aslanoğlu et al.[7]).

The reactions of **1b** and 2-bromopropionic acid as a cyclocondensation reagent in dioxane[10] under reflux gave compound **2**. The IR spectrum of **2** showed absorption band at 1730, 1646 m^{-1} because of two carbonyl absorption bands. In ^1H NMR spectra, the singlet at 6.6 ppm is due to



SCHEME 2

TABLE I Comparative Study of the Synthesis of 1a, 1b, 2, 3, 4

Compound	Medium	Yield (%)		Reaction time/min	
		MW	CONV.	MW	CONV.
1a	Glacial acetic acid	75	93	5	480
1b	Glacial acetic acid	80	90	5	480
2	Dioxane	48	35	5	120
3	Glacial acetic acid Acetic anhydride CH_3COONa	44	41	5	60
4	Glacial acetic acid Acetic anhydride CH_3COONa	30	48	5	120

the resonance of the C_5H proton. The quintet and doublet at 4.1 and 1.5 ppm ($J = 7.2$ Hz) are assigned to C_2H and to the methyl protons, respectively.

The reaction of **1b** with bromoacetic acid lead to 6-benzoyl-5-(2-chlorophenyl)-7-phenyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidine (**3**), whereas reaction with 3-bromopropionic acid afforded 7-benzoyl-6-(2-chlorophenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-b]thiazine (**4**). In the IR spectra of compounds **3** and **4** absence of the absorption at IR 3389 and 3146 cm^{-1}, the characteristic absorption of NH group of starting material, is a good evidence of the expected reactions. The IR spectrum data of **3** and **4** are in agreement with similar published data.[9,10] The ^1H NMR data of the compounds **3** and **4** are in accord with the expected reaction product (See Experimental Section for details).

The compounds **2–4** were also prepared under microwave irradiation. In that way, we isolated the corresponding thioxopyrimidine derivatives, in good yields within a few minutes. The reaction times are shortened from 480 min to 5 min (Table I).

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agents and distilled before use. Melting points were determined on a Barnstead Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on LECO CHNS 932 Elemental Analyzer. The IR spectra were obtained in as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-200 spectrometers, using TMS as an internal standard. All experiments were followed by TLC using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm). The

microwave induced reactions for the synthesis of **1a,b** were carried out in a Sinbo SMO 3606 domestic oven with a 230 V–50 Hz power source, 700W output, and 2450 MHz operating frequency.

Conventional Synthesis— Preparation of the Starting Compounds 1,2,3,4-Tetrahydro-2-thioxopyrimidines (1a,b)

A mixture of 1,3-diphenyl-1,3-propanedione (0.3584 g, 1.6 mmol), aryl aldehyde (1.1 mmol), thiourea (0.084 g, 1.1 mmol) and 20 ml of glacial acetic acid containing a few drops concentrated hydrochloric acid was heated under reflux for 8 h. The solution was allowed several hours to yield 0.36 g (90%) of product **1b**, mp 198–199°C (1-butanol). IR (KBr): 3389 and 3146 cm^{-1} (2NH), 2961 cm^{-1} (C_4H), 1625 (C=O) and 1270 cm^{-1} (C=S)[11]. ^{1}H-NMR (DMSO-d_6): δ 10.6 (s, 1H, NH), 9.7 (s, 1H, NH), 7.0–7.6 (m, 14H, Harom.), 5.8 (d, $J = 2.6$, 1H, C_4H). ^{13}C NMR (DMSO-d_6): δ = 196.1 (C=O), 176.5 (C=S),[12] 145.3, 141.4, 140.2, 134.1, 133.6, 133.1, 131.6, 131.5, 131.4, 131.3, 131.1, 130.2, 129.5, 129.3, 129.2, 111.1, 55.6 ppm. Anal. Calcd. for $C_{23}H_{17}ClN_2OS$ (404): C, 68.22; H, 4.23; N, 6.92. Found: C, 68.13; H, 4.16; N, 6.79.

The Compound **1a** was yield 93% which have been described in Aslanoğlu et al.[7]

6-Benzoyl-5-(2-chlorophenyl)-2-methyl-7-phenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine (2)

A mixture of **1b** (0.404 g, 1 mmol) and 2-bromopropionic acid (0.1 ml, 1 mmol) in dioxane (5 ml) were refluxed for 2 h. The reaction mixture was cooled and the precipitate filtered off and then washed with water. The crude product was recrystallizsed from ethanol. Yield 0.16 g (35%). M.p. 199–200°C, IR(KBr): 3059 cm^{-1} (C_5H), 1730, 1646 cm^{-1} (C=O), ^{1}H-NMR (DMSO-d_6): δ 6.9–7.5 (m, 14H, Harom.), 6.6 (s,1H, $-C_5H$), 4.1 (q, 1H, $-C_2H$, J = 7.2 Hz), 1.5 (d, 3H, $-CH_3$, J = 7.2 Hz). Anal. Calcd. for $C_{26}H_{19}ClN_2O_2S$ (458). C, 68.04; H, 4.17; N, 6.10. Found: C, 68.10; H, 4.19; N, 6.06.

6-Benzoyl-5-(2-chlorophenyl)-7-phenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine(3)

A mixture of **1b** (0.404 g, 1mmol), bromoacetic acid (0.153 g, 1.1 mmol), anhydrous sodium acetate (2 mmol), acetic anhydride (1.2 ml) in acetic acid (20 ml) was heated under reflux for 1 h. The residue was treated with water (100 ml) and the precipitate filtered off and the formed crude product was recrystallized from ethanol. Compound **3** was obtained in yield 0.18 g (41%). M.p. 200–201°C, IR(KBr): 3058 cm^{-1} (C_5H), 1734, 1638 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 6.9–7.6 (m, 14H, Harom.), 6.4

(s, 1H, $-C_5H$), 3.8–4.0 (q, 2H, CH_2, J = 8.7 Hz, AB system). Anal. Calcd. for $C_{25}H_{17}ClN_2O_2S$ (444). C, 67.49; H, 3.85; N, 6.30. Found: C, 67.52; H, 3.81; N, 6.36.

7-Benzoyl-6-(2-chlorophenyl)-8-phenyl-4-oxo-2,3-dihydro-6H-pyrimido[2,3-b]thiazine (4)

A mixture of **1b** (0.404 g, 1 mmol), 3-bromopropionic acid (0.168 g, 1.1 mmol), anhydrous sodium acetate (2 mmol), acetic anhydride (2 ml) in acetic acid (20 ml) was heated under reflux for 2 h. The residue was treated with water (100 ml) and the precipitate filtered off; the formed crude product was recrystallized from 2-propanol. The compound **4** was obtained in yield 0.22 g (48%). M.p. 257–258°C, IR(KBr): 3059 cm^{-1} (C_6H), 1707, 1638 cm^{-1} (C=O), ^{13}C-NMR ($CDCl_3$-DMSO-d_6): $\delta = 195.4$ (C=O, benzoyl), 167.5 (C=O), 154.4, 145.4, 137.1, 136.9, 136.0, 132.0, 131.6, 130.5, 129.8, 129.3, 128.7, 128.5, 128.3, 127.3, 127.2, 126.9, 117.7, 52.7, 35.4, 21.4 ppm. Anal. Calcd. for $C_{26}H_{19}ClN_2O_2S$ (458). C, 68.04; H, 4.17; N, 6.10. Found: C, 68.49; H, 4.76; N, 6.45.

Microwave Mediated Synthesis—Preparation of the Starting Compounds 1,2,3,4-Tetrahydro-2-thioxopyrimidines (1a,b)

A mixture of 1,3-diphenyl-1,3-propanedione (1.6 mmol), aryl aldehyde (1.1 mmol), thiourea (1.1 mmol), and concentrated hydrochloric acid (0.2 ml) with glacial acetic acid (10 ml) were placed in a 25-ml glass beaker and stirred at room temperature for 5 min with a magnetic stirrer. The beaker was placed inside a larger container filled with boiling chips and then was inserted into the microwave oven. The mixture was then subjected to microwave irradiation, 5 min for the compound **1a** and **1b**.

5-Benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (1a)

The reaction mixture was cooled and the crude products were filtered and recrystallized from acetic acid to give the pure compound **1a**, yield 75%.

5-Benzoyl-4-(2-chlorophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (1b)

The crude products were filtered and recrystallized from 1-butanol to give **1b**, yield 80%.

6-Benzoyl-5-(2-chlorophenyl)-2-methyl-7-phenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine (2)

A mixture of **1b** (0.404 g, 1mmol) and 2-bromopropionic acid (0.1 ml, 1 mmol) in dioxane (2 ml) were stirred at room temperature for 5 min

with a magnetic stirrer. The mixture was irradiated for 5 min in microwave oven. The reaction mixture was cooled and then washed with ethanol and the crude products were filtered. The crude product was recrystallized from ethanol. Yield 0.22 g (48%).

6-Benzoyl-5-(2-chlorophenyl)-7-phenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine(3)

A mixture of **1b** (0.404 g, 1 mmol), bromoacetic acid (0.153 g, 1.1 mmol), anhydrous sodium acetate (2 mmol), acetic anhydride (1.2 ml) in acetic acid (15 ml) were stirred at room temperature for 5 min with a magnetic stirrer. The mixture was irradiated for 5 min in a microwave oven. The reaction mixture was cooled and the residue was treated with water (100 ml); the precipitate filtered off and the formed crude product was recrystallized from ethanol. Yield 0.196 g (44%).

7-Benzoyl-6-(2-chlorophenyl)-8-phenyl-4-oxo-2,3-dihydro-6H-pyrimido[2,3-b]thiazine (4)

A mixture of **1b** (0.404 g, 1mmol), 3-bromopropionic acid (0.168 g, 1.1 mmol), anhydrous sodium acetate (2 mmol), acetic anhydride (2 ml) in acetic acid (15 ml) were stirred at room temperature for 5 min with a magnetic stirrer. The mixture was irradiated for 5 min in microwave oven. The reaction mixture was cooled and the crude products were filtered and washed with water and the formed crude product was recrystallized from 2-propanol. Yield 0.134 g (30%).

CONCLUSION

In conclusion, we have described a simple and good yielding preparation for thioxopyrimidines by conventional heating and microwave irradiation via Biginelli three-component cyclocondensation reaction. Our investigations will continue on this subject, and the results will be published when our studies are complete.

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