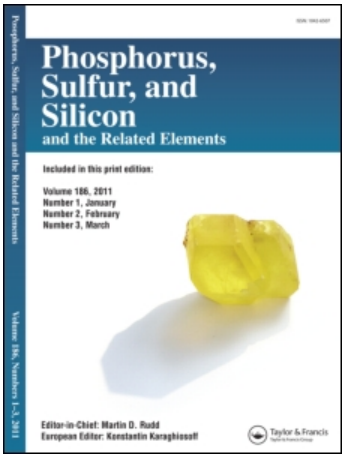

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Studies on Reactions of Pyrimidine Compounds: Synthesis and Reactions of 5-Benzoyl-4,6-Diphenyl-1,2,3,4-Tetrahydro-2-Thioxopyrimidine

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To cite this Article Aslanoğlu, Furgan , Akbaş, Esvet , Sönmez, Mehmet and Anıl, Barış(2007) 'Studies on Reactions of Pyrimidine Compounds: Synthesis and Reactions of 5-Benzoyl-4,6-Diphenyl-1,2,3,4-Tetrahydro-2-Thioxopyrimidine', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 7, 1589 — 1597
To link to this Article: DOI: 10.1080/10426500701263554
URL: http://dx.doi.org/10.1080/10426500701263554

Phosphorus, Sulfur, and Silicon, 182:1589–1597, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701263554

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Studies on Reactions of Pyrimidine Compounds: Synthesis and Reactions of 5-Benzoyl-4,6-Diphenyl-1,2,3,4-Tetrahydro-2-Thioxopyrimidine

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*The 5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidin (**1**) have been prepared via Biginelli cyclocondensation reaction in acetic acid under reflux condition in good yield (93%). Reactions of **1** and iodomethane to afford thiopyrimidine compounds **3** and **5**. Also, the acetylation of compounds **1** and **3** gave 3-acetyl thioxopyrimidine **2** and methylthiopyrimidine **4**, respectively. Thioxopyrimidine derivative **6** was synthesized from **1** and $POCl_3$/DMF. Furthermore, the starting compound **1** were cyclized with various bromo compounds to the thiazolopyrimidine **7**, **8**, **9** and pyrimido[2,3-b]thiazine **10** derivatives, in approximately 55–78% yields. The purpose of synthesizing the thioxopyrimidine derivatives is because of the high biological activities. All of these derivatives have been characterized by analytical and spectroscopic studies and the reaction mechanism is discussed.*

Keywords Biginelli reaction; cyclocondensation; multicomponent reaction; one-pot condensation reactions; synthesis; tetrahydropyrimidine

Received December 4, 2006; accepted January 5, 2007.

This work was supported by the Scientific and Technical Research Council of Turkey (TBAG 2392 103T136). The authors would like to thank Department of Chemistry, Faculty of Arts and Sciences, Ataturk University, for providing spectroanalytical facilities and Dr. Musa Turker from the Department of Biology, Faculty of Arts and Sciences, Yuzuncu Yil University for his helpful comments.

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INTRODUCTION

Many condensed heterocyclic systems, particularly when substituted to a pyrimidine ring, play an important role as analgesic (**1a**), antipyretic (**1b**), antihypertensive (**1c**), and antiinflammatory drugs (**1d**), also as pesticides (**1e**), herbicides (**1f**), plant growth regulators, and organic calcium channel modulators (**2**). Thus, pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties.

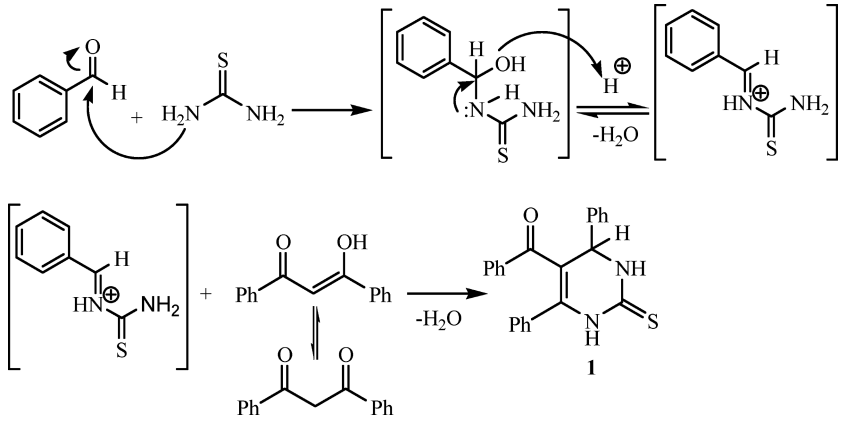
Various synthesis methods have been reported in the literature for the synthesis of pyrimidine derivatives.[1–9] Most of them are based on the simple Biginelli[2k] three-component cyclocondensation reaction. This very simple one-pot, acid-catalyzed cyclocondensation reaction of an β-diketone, arylaldehyde, and (thio)urea.

Herein, due to versatile biological properties of pyrimidine derivatives, we have reported synthesis of 5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine[10] (**1**), and its various derivatives via the general method of Biginelli cyclocondensation reaction in good yield.

RESULTS AND DISCUSSION

The synthetic pathway employed in the preparation of **1** is outlined in Scheme 1. The condensation of 1,3-diphenyl-1,3-propanedione, benzaldehyde, and thiourea in acetic acid, catalyzed by HCl, proceeded according to the Biginelli reaction.

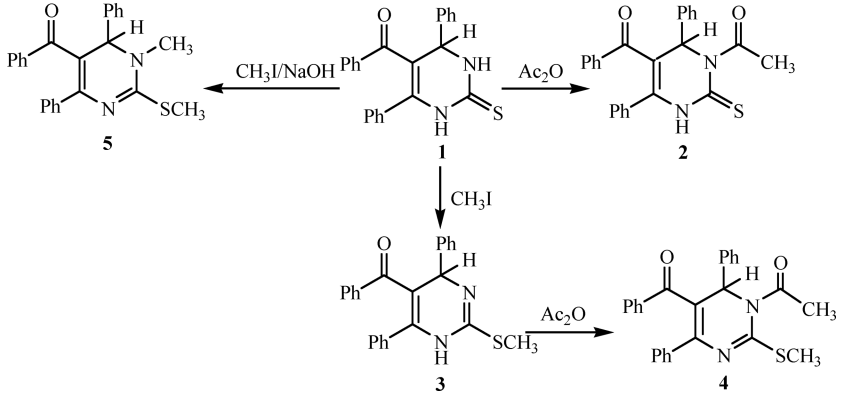
The 3-acetyl thioxopyrimidine derivative **2** was prepared via reaction of compound **1** with acetic anhydride. The ^{13}C NMR spectrum of **2**



SCHEME 1

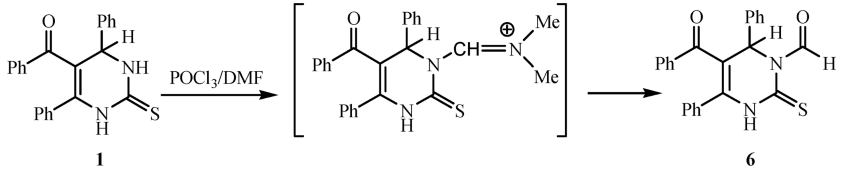
revealed signals at δ 196.2 (C=O, benzoyl), 180.2 (C=S),[11] 175.2 (C=O), and 29.8 CH_3. In ^{1}H NMR spectra, the singlet at 2.9 ppm is due to the resonance of the CH_3 group of the acetyl. The singlet and multiplets at 6.8 and 7.0–7.5 ppm are assigned to H-4 and to the aryl protons, respectively. The NH proton gives broad signal at 8.5 ppm, in accord with the expected reaction product.

When *S*-methylation of compound **1** in methanol[6] was formed 5-benzoyl-4,6-diphenyl-1,4-dihydro-2-methylthio pyrimidine (**3**), which upon acetylation gave 3-acetyl-5-benzoyl-4,6-diphenyl-4*H*-2-methylthio pyrimidine (**4**). The acetylation compound **4** was supported by ^{1}H NMR spectrum. The ^{1}H NMR spectrum showed that 2.6 and 2.5 singlet signals for methyl protons. The ^{13}C NMR spectrum of **4** revealed signals at δ 26.1 and 16.9 methyl groups (See Experimental section for details).



SCHEME 2

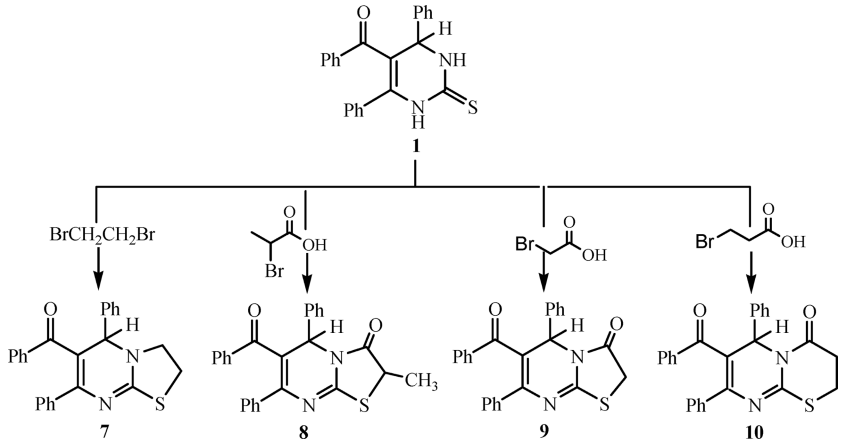
The methylation of compound **1** with methyl iodide in 1N sodium hydroxide[7] afforded the product 5-benzoyl-3-methyl-4,6-diphenyl-4*H*-2-methylthio pyrimidine (**5**) (Scheme 2). It was identified on the basis of its elemental analysis and spectra. Its IR spectrum showed absorption bands at 1624 cm^{-1} due to C=O. The ^{1}H NMR spectrum of **5** exhibited singlet signals at δ 5.8 H-4 and 2.8, 2.5 ppm due to CH_3 protons, respectively.



SCHEME 3

The compound **1** was treated with phosphoros oxychloride in dimethylformamide at room temperature,[6] intermediate product was readily formed, which upon hydrolysis gave the formyl derivative **6** (Scheme 3). In the ^{1}H NMR spectra of **6**, as a singled signal at δ 9.9 was exhibited due to formyl proton (See experimental for details).

The compound **7** was synthesized reaction of the starting pyrimidine derivative **1** and 1,2-dibromoethane in dimethylformamide under reflux. The signals of two NH function groups disappeared in the IR and ^{1}H NMR spectra of compound **7**. The ^{1}H NMR spectrum of compound **7** revealed multiplet signals at δ 3.8–4.5 due to thiazole methylen protons. Also reaction of **1** and 2-bromopropionic acid as a cyclocondensation reagent in dioxane[8] under reflux gave compound **8**. The IR spectrum of **8** showed absorption band at 1737, 1634 cm^{-1} because of two carbonyl absorption bands.



1 **7** **8** **9** **10**

SCHEME 4

On the other hand, the reaction of **1** with 2-bromoacetic acid lead to 6-benzoyl-5,7-diphenyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidine-2,3-dione (**9**), whereas reaction with 3-bromopropionic acid afforded 7-benzoyl-6,8-diphenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-b]thiazine (**10**) (Scheme 4). In the IR spectra of compounds **9** and **10** absence of the characteristic absorption signals of the of NH groups of starting material, is good evidence of the expected reactions.

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agents and distilled before use. Melting points were determined on an Electrothermal Gallenkamp 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 ^{1}H 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).

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

(The synthesis method of **1** was not to be able to reached, in spite of it is availablity from the product list of Aurora Fine Chemicals. Therefore, we think that the method applied in the present study is different). A mixture of 1,3-diphenyl-1,3-propanedione (0.3584 g, 1.6 mmol), benzaldehyde (0.11 ml, 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 0.38 g (93%) of product.

3-Acetyl-5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (2)

A mixture of **1** (0.370 g, 1 mmol) in acetic anhydride (3 ml) was heated under reflux for 1 h, then the reaction mixture was allowed to cool to room temperature, and poured over crushed ice and stirred for several minutes. The separated solid filtered off, washed with water, and recrystallized from ethanol to give 0.218 g (59%) of **2**, m.p. 190–191°C, IR(KBr): 3200 (NH), 2962 (CH), 1708, 1628 (C=O), 1608, 1576, 1271(C=S)[9] cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 8.5 (bs, 1H, NH), 7.0–7.5 (m, 15H, Harom.), 6.8 (s, 1H, CH), 2.9 (s, 3H, -CH_3), ^{13}C NMR ($CDCl_3$): δ = 196.2 (C=O, benzoyl) and 180.2 (C=S)[11], 175.2 (C=O), 145.8, 140.4, 139.8, 133.8, 133.6, 132.9, 132.5, 131.2, 131.1, 130.8, 130.0, 129.7, 128.5, 117.5, 57.8, and 29.8 ppm (CH_3). Anal. Calcd. for $C_{25}H_{20}N_2O_2S$ (412). C, 72.79; H, 4.89; N, 6.79. Found: C, 72.76; H, 4.56; N, 6.65.

5-Benzoyl-4,6-diphenyl-1,4-dihydro-2-methylthio Pyrimidine (3)

A solution of **1** (0.370 g, 1 mmol) in 20 ml methanol and methyl iodide (0.074 ml, 1.2 mmol) was added. The mixture was then refluxed for 2

h, and after addition of pyridine (0.5 ml), the solution was refluxed for another 10 min. The reaction mixture was cooled and poured into 100 ml of ice-water. The precipitate was filtered off and washed with water and cyclohexane. Compound **3** was obtained in yield 0.2 g (54%). m.p. 138–139°C, IR(KBr): 3382 (NH), 1624 (C=O) cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 8.3 (s, 1H, NH), 7.0–7.4 (m, 15H, Harom.), 5.7 (s, 1H, -CH), 2.5 (s, 3H, $-CH_3$). Anal. Calcd. for $C_{24}H_{20}N_2OS$ (384). C, 74.97; H, 5.24; N, 7.29. Found: C, 75.42; H, 5.31; N, 7.67.

3-Acetyl-5-benzoyl-4,6-diphenyl-4*H*-2-methylthio Pyrimidine (4)

A mixture of **3** (0.384 g, 1 mmol) in acetic anhydride (3 ml) was heated under reflux for 1 h. The solvent was evaporated, then the oily residue was treated with dry ether, and the formed crude product was recrystallized from ethanol. Compound **4** was obtained in yield 0.058 g (15%). m.p. 197–198°C, IR(KBr): 1708, 1664 (C=O) cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 7.1–7.5 (m, 15H, Harom.), 6.7 (s, 1H, -CH), 2.6 (s, 3H, $-CH_3$),and 2.5 (s, 3H, $-CH_3$), ^{13}C NMR ($CDCl_3$): δ = 197.0 and 171.9 (C=O), 158.2, 149.8, 140.2, 139.0, 137.5, 133.9, 131.2, 131.0, 130.8, 130.6, 130.2, 129.7, 129.5, 128.2, 123.4, 56.7, 26.1, and 16.9 ppm. Anal. Calcd. for $C_{26}H_{22}N_2O_2S$ (426). C, 73.21; H, 5.20; N, 6.57. Found: C, 73.23; H, 5.22; N, 6.56.

5-Benzoyl-3-methyl-4,6-diphenyl-4H-2-methylthio Pyrimidine (5)

To a suspension of **1** (0.370 g, 1 mmol) in 1N sodium hydroxide (4 ml), methyl iodide (0.24 ml, 3.85 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The solid was precipitated, collected, washed with water, and dried. Yield 0.35 g (95%), yellow crystals (2-propanol), m.p. 210–211°C, IR(KBr): 1624 cm^{-1} (C=O), ^{1}H-NMR (DMSO-d_6): δ 7.0–7.5 (m, 15H, Harom.), 5.8 (s, 1H, -CH), 2.8 (s, 3H, CH_3), 2.5 (s, 3H, CH_3). Anal. Calcd. for $C_{25}H_{22}N_2OS$ (398). C, 75.35; H, 5.56; N, 7.03. Found: C, 75.38; H, 5.54; N, 6.98.

5-Benzoyl-4,6-diphenyl-3-formyl-1,2,3,4-tetrahydro-2-thioxo-pyrimidine (6)

To a solution of **1** (0.370 g, 1 mmol) in dry DMF (6 ml); 0.168 ml $POCl_3$ was added under stirring in an ice-bath. Stirring was continued at room temperature for another 30 min, and then the solution was poured into ice-water, filtered, dried, and recrystallized from ethanol to give **6**. Yield

0.2 g (54%), m.p. 212–213°C, IR(KBr): 3200 cm^{-1} (NH), 1703, 1625 cm^{-1} (C=O), 1253 (C=S), ^{1}H-NMR ($CDCl_3$): δ 9.9 (s, 1H, -CHO), 8.6 (s, 1H, -NH), 7.0–7.5 (m, 15H, Harom.), 6.6 (s, 1H, -CH), ^{13}C-NMR ($CDCl_3$): δ 196.2 (C=O, benzoyl), 179.9 (C=S), 164.9 (C=O, formyl), 143.1, 140.6, 139.7, 134.0, 133.6, 132.8, 131.0, 130.9, 130.89, 130.80, 130.6, 129.8, 128.7, 116.9, and 56.1. Anal. Calc. for C_{24} $H_{18}N_2O_2S$(398). C, 72.34; H, 4.55; N, 7.03. Found: C, 72.32; H, 4.58; N, 7.07.

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

Compound **7** was prepared as a HBr salt. To a solution of **1** (0.370 g, 1mmol) in dry DMF (5 ml); 1.1 mmol dibromoethane was added under stirring and the reaction mixture was refluxed for 3 h. The solvent was evaporated, then the oily residue was treated with dry ether, and the formed crude product was recrystallized from ethanol. Yield 0.236 g (64%). m.p. 274–275°C, IR(KBr): 3055, 2763 (-CH), 1626 cm^{-1} (C=O), ^{1}H-NMR (DMSO-d_6): δ 7.3–7.8 (m, 15H, Harom.), 5.3 (s,1H, -CH), 3.8–4.5 (m, 4H, thiazole -CH_2),^{13}C-NMR (DMSO-d_6): δ 193.2, 173.2, 170.3, 160.8, 137.3, 136.7, 136.2, 134.5, 133.5, 131.4, 131.0, 130.9, 130.6, 130.2, 129.9, 129.7, 58.8, 46.9, and 30.1.

6-Benzoyl-2-methyl-5,7-diphenyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a] Pyrimidine (8)

A mixture of **1** (0.370 g, 1mmol) and 2-bromopropionic acid (1 mmol) in dioxane (5 ml) were refluxed for 1 to 2 h. The reaction mixture was cooled and the precipitate filtered off and then washed with water. The crude product was recrystallized from 2-propanol. Yield 0.064 g (15%). m.p. 247–248°C, IR(KBr): 1737, 1634 cm^{-1} (C=O), ^{1}H-NMR (DMSO-d_6): δ 7.1–7.9 (m, 15H, Harom.), 6.1 (s,1H, -CH), 4.6 (q,1H, -CH), 1.7 (d, 3H, -CH_3). Anal. Calc. for $C_{26}H_{20}N_2O_2S$ (424). C, 73.56; H, 4.75; N, 6.60. Found: C, 73.54; H, 4.76; N, 6.62.

6-Benzoyl-5,7-diphenyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a] Pyrimidine (9)

A mixture of **1** (0.370 g, 1mmol), bromoacetic acid (1.1 mmol), and anhydrous sodium acetate (2 mmol), acetic anhydride (1.2 ml) in acetic acid (20ml) was heated under reflux for 1 h. The residue was treated with water (100 ml), the precipitate filtered off, and the formed crude product was recrystallized from 2-propanol. Compound **9** was obtained

in yield 0.277 g (75%). mp 169–170°C, IR(KBr): 1737, 1635 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.3–7.9 (m, 15H, Harom.), 6.0 (s, 1H, -CH), 3.9 (2H, d, CH_2, J = 8.8 Hz, A part of AB system), 3.8 (2H, d, CH_2, J = 8.8 Hz, B part of AB system). Anal. Calc. for $C_{25}H_{18}N_2O_2S$ (410). C, 73.15; H, 4.42; N, 6.82. Found: C, 73.13; H, 4.41; N, 6.80.

7-Benzoyl-6,8-diphenyl-4-oxo-2,3-dihydro-6H-pyrimido[2,3-b] Thiazine (10)

A mixture of **1** (0.370 g, 1 mmol), 3-bromopropionic acid (1.1 mmol), anhydrous sodium acetate (2 mmol), and acetic anhydride (2 ml) in acetic acid (20 ml) was heated under reflux for 2 h. The residue was treated with water (100 ml), the precipitate filtered off, and the formed crude product was recrystallized from 2-propanol. Compound **10** was obtained in yield 0.288 g (78%). m.p. 202–203°C, IR(KBr): 1699, 1624 cm^{-1} (C=O), ^{1}H-NMR (DMSO-d_6): δ 7.0–7.8 (m, 15H, Harom.), 5.6 (s,1H, -CH), 2.8–3.2 (m, 4H, thiazine -CH_2). Anal. Calc. for $C_{26}H_{20}N_2O_2S$ (424). C, 73.56; H, 4.75; N, 6.60. Found: C, 73.58; H, 4.74; N, 6.58.

CONCLUSIONS

This article deals with the synthesis of the 5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine[10] by Biginelli cyclocondensation reaction under Brönsted acid catalysis in acetic acid. This protocol has got advantages of high yield (93%), and simple work-up procedure. Thereafter, various derivatives of 5-benzoyl-4,6-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine was prepared because of the high biological activity of the pyrimidine derivatives.[1]

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