A Simple One-Pot Synthesis of 1,2,3,4-Tetrahydro-2-thioxopyrimidine Derivatives

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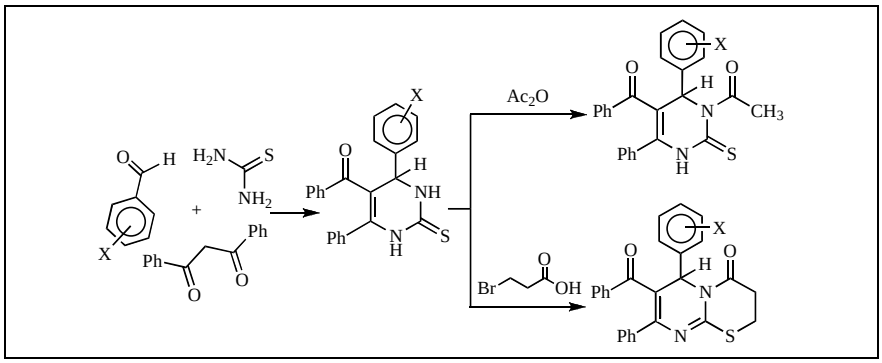

5-Benzoyl-4-(substituted phenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidines (**4a-d**) were synthesized using the Biginelli three component cyclocondensation reaction of an appropriate β-diketone, arylaldehyde, and thiourea in acetic acid under reflux condition in approximately 52-65% yields. The acetylation of compounds **4a-d** gave 3-acetyl thioxopyrimidine derivatives **5a-d**. Also, pyrimidothiazine compounds **6a-d** were prepared by a simple one-pot condensation reaction of starting pyrimidine derivatives **4a-d** and 3-bromopropionic acid. The structures of compounds were characterized on the basis of elemental analyses, IR, ^{1}H and ^{13}C-NMR spectra.

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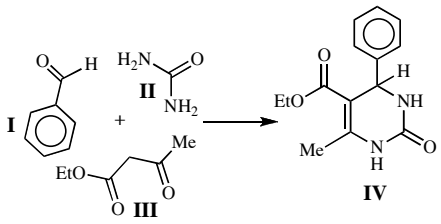
INTRODUCTION

The pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Many substituted pyrimidine rings play an important role as analgesic, antipyretic, antihypertensive and anti-inflammatory drugs also as pesticides, herbicides, plant growth regulators and organic calcium channel modulators [1-7].

Various synthesis methods have been reported in the literature for pyrimidine derivatives [1-17]. Most of them are based on the simple Biginelli three component cyclocondensation reaction. This is very simple one-pot, acid catalyzed cyclocondensation reaction of benzaldehyde (**I**), urea (**II**) and ethyl acetoacetate (**III**). The reaction was carried out in ethanol with a few drops of concentrated hydrochloric acid and finalized 3,4-dihydropyrimidine-2(1*H*)-one (**IV**) (Scheme 1)[18,19].

At present, our studies are continuing on the synthesis of 1,2,3,4-tetrahydro-2-(oxo)thioxopyrimidines [20]. Herein, we have reported the synthesis of 1,2,3,4-tetrahydro-2-thioxopyrimidines (**4a-d**), *via* the general method of Biginelli cyclocondensation reaction in acetic acid. Also their various derivatives such as 3-acetyl thioxopyrimidines (**5a-d**) and pyrimidothiazine compounds (**6a-d**) were obtained.

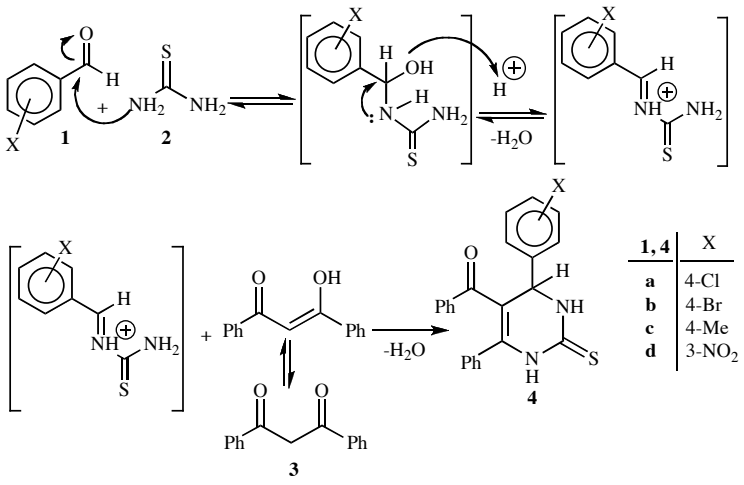
Scheme 1



RESULTS AND DISCUSSION

5-Benzoyl-4-(substituted phenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidines (**4a-d**) were prepared according to the Biginelli reaction which involves one-pot condensation of 1,3-diphenyl-1,3-propandione, thiourea and arylaldehydes (Scheme 2) under strongly acidic condition in approximately 52-65% yields. All compounds were characterized on the basis of their spectral data and elementary analyses. The IR spectra of the thioxopyrimidine compounds displayed absorption bands characteristic for the NH (3426-3139 cm^{-1}), C=O (1635-1595 cm^{-1}) and C=S (1280-1274 cm^{-1}) functions.

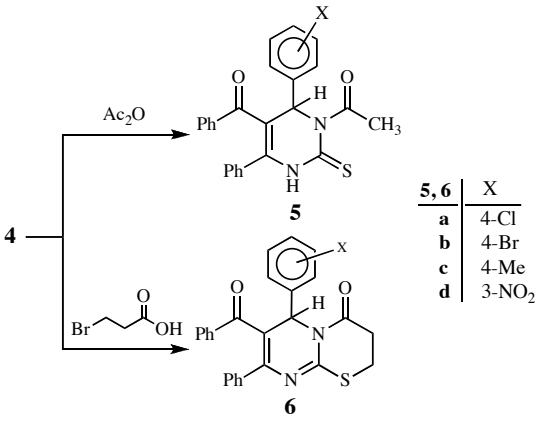
Scheme 2



In ^{1}H NMR spectra, the formation of the thioxopyrimidine ring in this reaction was clearly demonstrated by the fact that the C_4 methine proton of compounds **4a-d** appeared at 5.48-5.32 ppm as doublet. The signals of the N_3H and N_1H protons of compounds **4a-d** appeared one proton singlets at 10.12-9.86 and 10.85-10.55 ppm, respectively. The signals of the other proton resonances are observed at the expected chemical shifts and integral values.

The 3-acetyl thioxopyrimidine derivatives **5a-d** were prepared *via* reaction of compounds **4a-d** with acetic anhydride (Scheme 3).

Scheme 3



^{1}H NMR spectra of the compounds **5a-d** revealed the absence of N_3H signals instead they exhibited three proton singlets at 2.95-2.31 ppm assigned for the N_3COCH_3 protons of the acetyl groups. The ^{13}C NMR spectrum of **5a** revealed signals at δ 194.6 (C=O, benzoyl), 177.9 (C=S), 173.5 (C=O, acetyl) and 27.3 ppm CH_3.

The compounds 7-benzoyl-6-(substituted phenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazines (**6a-d**) were synthesized *via* the reactions of the starting pyrimidine derivatives **4a-d** and 3-bromopropionic acid (Scheme 3).

In the IR spectra of compounds **6a-d**, the absence of the absorption at 3426-3139 cm^{-1} and the characteristic absorption of NH group of starting materials are a good evidence of the expected reactions.

The signals of two NH function groups of starting materials **4a-d** disappeared in the ^{1}H NMR spectra of compounds **6a-d** which are the characteristic absorption of NH groups of starting materials **4a-d**. The ^{1}H NMR spectrum of compounds **6a-d** revealed multiplet signals at δ 3.74-2.79 due to thiazine methylene protons.

The purpose of the present work is to extend the Biginelli reactions in order to synthesize some 1,2,3,4-tetrahydro-2-thioxopyrimidine derivatives. The method reported here suggests a simple and efficient route for the preparation of 1,2,3,4-tetrahydro-2-thioxopyrimidine derivatives.

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agents and distilled before use. Melting points were determined on an Electrothermal Barnstead 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 ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 or Bruker 300 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).

General procedure for the synthesis of 5-benzoyl-4-(substituted phenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxo-pyrimidines (4a-d). A mixture of 1,3-diphenyl-1,3-propanedione (3.58 g, 16 mmol), aryl aldehyde (11 mmol), thiourea (0.84 g, 11 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 to stand approximately 3-4 hours to yield 52-65% of product **4a-d**.

5-Benzoyl-4-(4-chlorophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (4a). The compound **4a** was prepared according to the general procedure. The precipitate was collected by filtration to give crude product that was recrystallized from 2-propanol. Compound **4a** was obtained in yield 2.489 g (56%). Mp 200-201°C, IR (KBr): 3401 and 3147 cm^{-1} (2NH), 2967 cm^{-1} (C_4H), 1622 (C=O) and 1276 cm^{-1} (C=S) [15]. ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.66 (s, 1H, NH), 9.92 (d, 1H, NH, J=2), 7.40-7.29 (dx2, 4H, 4-chlorophenyl, J= 10.8 Hz), 7.26-6.96 (m, 10H, two phenyl groups), 5.32 (d, 1H, C_4H J= 3.6 Hz). ^{13}C NMR (DMSO-d6): δ 195.39, 175.88, 145.99, 142.41, 139.54, 132.99, 131.69, 131. 78, 130. 97, 130.65, 129.27, 129.17, 129.13, 128.39, 128.21, 110.35, 55.40. *Anal*. Calcd. for $C_{23}H_{17}ClN_2OS$ (404). C, 68.22; H, 4.23; N, 6.92. Found: C, 68.32; H, 4.20; N, 6.90.

5-Benzoyl-4-(4-bromophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (4b) [21]. Compound **4b** was obtained in yield 2.562 g (52%). Mp 239-240°C (2-propanol), IR (KBr): 3426 and 3171 cm^{-1} (2NH), 1635 (C=O) and 1274 cm^{-1} (C=S). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.68 (s, 1H, NH), 9.95 (d, 1H, NH, J=2.4), 7.60-7.58 (dx2, 4H, 4-bromophenyl, J= 6.6 Hz), 7.41-6.98 (m, 10H, two phenyl groups), 5.34 (d, 1H, C_4H, J= 3.6 Hz). ^{13}C NMR (DMSO-d6): δ 195.39, 175.88, 146.07, 142.84, 139.53, 132.99, 132.21, 131.71, 130.68, 130.97, 129.52, 129.21, 128.40, 128.22, 121.59, 110.29, 55.52. *Anal*. Calcd. for $C_{23}H_{17}BrN_2OS$ (448). C, 61.48; H, 3.81; N, 6.23. Found: C, 61.38; H, 3.82; N, 6.25.

5-Benzoyl-4-tolyl-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (4c). The compound **4c** was obtained in yield 2.378 g (55%). Mp 200-201°C (xylene), IR (KBr): 3425-3139 cm^{-1} (2NH), 1595 (C=O) and 1275 cm^{-1} (C=S). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.55 (s, 1H, NH), 9.86 (d, 1H, NH, J=2), 7.33-6.96 (m, 14H, ArH), 5.32 (d, 1H, C_4H, J= 3.6 Hz), 2.30 (s, 3H, CH_3). ^{13}C NMR (DMSO-d6): δ 195.48, 175.64, 145.52, 140.59, 139.61, 137.59, 133.15, 131.68, 130.59, 130.33, 129.47, 128.96, 128.39, 128.21, 127.18, 110.88, 55.89, 21.39. *Anal*. Calcd. for $C_{24}H_{20}N_2OS$ (384). C, 74.97; H, 5.24; N, 7.29. Found: C, 75.00; H, 5.22; N, 7.30.

5-Benzoyl-4-(3-nitrophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (4d). The compound **4d** was obtained in yield 2.960 g (65%). Mp 213-214°C (2-propanol), IR (KBr): 3291 and 3152 cm^{-1} (2NH), 2989 cm^{-1} (C_4H), 1601 (C=O) and 1280 cm^{-1} (C=S). ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.85 (s, 1H, NH), 10.12 (d, 1H, NH, J=2.8 Hz), 8.33-7.00 (m, 14H, ArH), 5.48 (d, 1H, C_4H, J= 4 Hz). ^{13}C NMR (DMSO-d6): δ 195.35, 176.07, 148.62, 147.26, 145.51, 139.42, 133.97, 132.78, 131.76, 131.08, 130.95, 130.82, 129.31, 128.47, 128.23, 123.42, 122.02, 109.38, 55.07. *Anal*. Calcd. for $C_{23}H_{17}N_3O_3S$ (415). C, 66.49; H, 4.12; N, 10.11. Found: C, 66.51; H, 4.14; N, 10.14.

Preparation of 3-acetyl-5-benzoyl-4-(substituted phenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidines (5a-d).

General Procedure. A mixture of **4 (a-d)** (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 several min. The separated solid was collected by filtration, washed with water and recrystallized from suitable solvents to give **5a-d.**

3-Acetyl-5-benzoyl-4-(4-chlorophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (5a). Compound **5a** was obtained in yield 0.232 g (52%). Mp 197-198ºC, IR(KBr): 3213 cm^{-1} (NH), 2964 cm^{-1} (C_4H), 1715 and 1610 cm^{-1} (two C=O), 1268 cm^{-1} (C=S), ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.96 (s, 1H, NH), 7.52-7.06 (m, 14H, ArH), 6.46 (s, 1H, C_4H), 2.83 (s, 3H, CH_3). ^{13}C NMR (DMSO-d6): δ 194.6, 177.9 [22], 173.5, 146.2, 137.9, 137.8, 132.5, 131.5, 131.2, 130.6, 130.4, 129.0, 128.5, 128.3, 127.8, 127.5, 114.3, 54.1, 27.3 ppm. *Anal*. Calcd. for $C_{25}H_{19}ClN_2O_2S$ (446). C, 67.18; H, 4.28; N, 6.27. Found: C, 67.22; H, 4.29; N, 6.25.

3-Acetyl-5-benzoyl-4-(4-bromophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (5b). Compound **5b** was obtained in yield 0.299 g (61%). Mp 200-201ºC, IR(KBr): 3218 cm^{-1} (NH), 2965 cm^{-1} (C_4H), 1716 and 1609 cm^{-1} (two C=O), 1268 cm^{-1} (C=S), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H, NH), 7.48-7.02 (m, 14H, ArH), 6.69 (s, 1H, C_4H), 2.88 (s, 3H, CH_3). *Anal*. Calcd. for $C_{25}H_{19}BrN_2O_2S$ (490). C, 61.10; H, 3.90; N, 5.70. Found: C, 61.08; H, 3.91; N, 5.72.

3-Acetyl-5-benzoyl-4-tolyl-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (5c). Compound **5c** was obtained in yield 0.235 g (54%). Mp 213-214ºC, IR(KBr): 3223 cm^{-1} (NH), 2963 cm^{-1} (C_4H), 1707 and 1598 cm^{-1} (two C=O), 1270 cm^{-1} (C=S), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H, NH), 7.38-7.00 (m, 14H, ArH), 5.96 (s, 1H, C_4H), 2.85 (s, 3H, CH_3), 2.31 (s, 3H, CH_3, tolyl). *Anal*. Calcd. for $C_{26}H_{22}N_2O_2S$ (426). C, 73.21; H, 5.20; N, 6.57. Found: C, 73.18; H, 5.19; N, 6.59.

3-Acetyl-5-benzoyl-4-(3-nitrophenyl)-6-phenyl-1,2,3,4-tetrahydro-2-thioxopyrimidine (5d). Compound **5d** was obtained in yield 0.255 g (54%). Mp 205-206ºC, IR(KBr): 3258 cm^{-1} (NH), 3085 cm^{-1} (C_4H), 1712 and 1601 cm^{-1} (two C=O), 1267 cm^{-1} (C=S), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H, NH), 7.41-7.14 (m, 14H, ArH), 5.82 (s, 1H, C_4H), 2.95 (s, 3H, CH_3). *Anal*. Calcd. for $C_{25}H_{19}N_3O_4S$ (457). C, 65.63; H, 4.19; N, 9.18. Found: C, 65.65; H, 4.17; N, 9.21.

Synthesis of 7-benzoyl-6-(substituted phenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine (6a-d).

General Procedure. A mixture of **4(a-d)** (1 mmol), 3-bromopropionic acid (0.17 g, 1.1 mmol), anhydrous sodium acetate (0.16 g, 2 mmol), acetic anhydride (2.0 g, 21 mmol) in acetic acid (20 mL) was heated under reflux for 2 h. The residue was treated with water (100 mL) and the precipitate collected by filtration to give crude product was recrystallized from suitable solvents to give **6 a-d**.

7-Benzoyl-6-(4-chlorophenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine (6a). Compound **6a** was obtained in yield 0.225 g (46%). Mp 221-222ºC, IR(KBr): 1696, 1622 cm^{-1} (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65-7.07 (m, 14H, ArH.), 5.87 (s,1H, -CH), 2.86-3.74 (m, 4H, thiazine -CH_2). *Anal*. Calcd. for $C_{26}H_{19}ClN_2O_2S$ (458). C, 68.04; H, 4.17; N, 6.10. Found: C, 68.01; H, 4.18; N, 6.08.

7-Benzoyl-6-(4-bromophenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine (6b). Compound **6b** was obtained in yield 0.294 g (55%). Mp 179-180ºC, IR(KBr): 1704, 1626 cm^{-1} (C=O), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-6.97 (m, 14H, ArH.), 5.63 (s,1H, -CH), 2.84-3.72 (m, 4H, thiazine -CH_2). ^{13}C NMR (DMSO-d6): δ 196.19, 169.42, 156.67, 148.71, 139.72, 138.16, 136.98, 132.76, 132.69, 129.96, 129.75, 129.57, 129.41, 128.58, 128.30, 122.29, 118.47, 52.27, 35.85, 21.85. *Anal*. Calcd. for $C_{26}H_{19}BrN_2O_2S$ (503). C, 62.03; H, 3.80; N, 5.56. Found: C, 62.07; H, 3.78; N, 5.58.

7-Benzoyl-6-tolyl-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine (6c). Compound **6c** was obtained in yield 0.216 g (45%). Mp 236-237ºC, IR(KBr): 1697, 1626 cm^{-1} (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84-6.98 (m, 14H, ArH.), 5.56 (s,1H, -CH), 2.91-3.62 (m, 4H, thiazine -CH_2), 2.36 (s, 3H, CH_3, tolyl). *Anal*. Calcd. for $C_{27}H_{22}N_2O_2S$ (438). C, 73.95; H, 5.06; N, 6.39. Found: C, 73.92; H, 5.08; N, 6.41.

7-Benzoyl-6-(3-nitrophenyl)-8-phenyl-4-oxo-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine (6d). Compound **6d** was obtained in yield 0.275 g (55%). Mp 220-221ºC, IR(KBr): 1707, 1630 cm^{-1} (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.10 (m, 14H, ArH.), 5.53 (s,1H, -CH), 2.79-3.64 (m, 4H, thiazine -CH_2). *Anal*. Calcd. for $C_{26}H_{19}N_3O_4S$ (469). C, 66.51; H, 4.08; N, 8.95. Found: C, 66.54; H, 4.09; N, 8.93.

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