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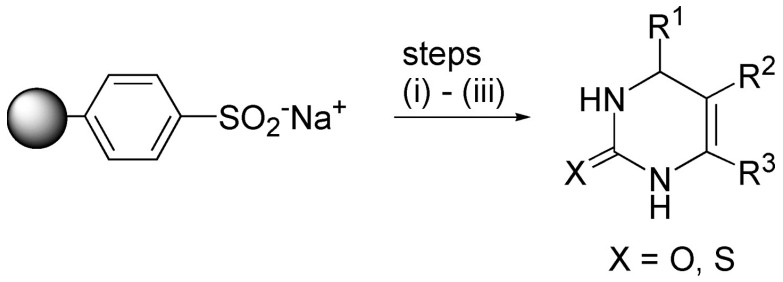

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Solid-Phase Synthesis of 3,4-Dihydro-1*H*-pyrimidine-2-ones Using Sodium Benzenesulfinate as a Traceless Linker

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The facile preparation of 3,4-dihydropyrimidine-2-one derivatives with traceless solid-phase sulfone linker strategy is described. Key steps involved in the solid-phase synthetic procedure include (i) sulfinate acidification, (ii) condensation of urea or thiourea with aldehydes and sulfinic acid, and (iii) traceless product release via a one-pot cyclization−dehydration process. A library of 18 compounds was synthesized.

Introduction

Heterocyclic moieties are important constituents that commonly exist in biologically active natural products and synthetic compounds of medicinal interest. Thus, it is not surprising that the generation of combinatorial libraries of heterocyclic compounds by solid-phase synthesis is of great interest for lead discovery and lead optimization in pharmaceutical research.[1] However, one of the challenges of solid-phase technologies for drug discovery is developing synthetic routes for the traceless tethering of compounds to the polymer supports. This is because complications may arise if these appendages are redundant and affect the activities of the compounds. In this regard, one of our interests is to develop the sulfone linker via polystyrene/1% divinylbenzene sodium sulfinate (**1**) as a traceless linker and explore new applications for it in solid-phase organic synthesis (SPOS). Earlier reports from other laboratories[2] and ours[3] have demonstrated the use of **1** as a solid support for SPOS and shown the resulting sulfone linker to be a versatile and robust tether that offers various on-resin functionalization and cleavage with additional changes.

3,4-Dihydropyrimidine-2-one derivatives are useful targets in chemical synthesis as they have been associated with a diverse range of therapeutic and medicinal properties.[4] Several marine alkaloids containing the dihydropyrimidinone scaffold have also been shown to possess antiviral, antitumor, antibacterial, and anti-inflammatory activities,[5] and in particular, the batzelladine alkaloids are known to be potent HIV gp-120-CD4 inhibitors.[6] This multifaceted profile bodes well for the interaction of such heterocycles with a variety of biological targets which has consequently led to the development of a number of lead compounds based on this structural core.[4] In recent years, various synthetic methods for the preparation of 3,4-dihydropyrimidine-2-ones on solid phase have been examined.[7] Among them, only one reports on the traceless synthesis of these compounds.[7d] In this paper, polymer-bound thiourea was reacted with Knoevenagel condensation products (prepared separately by solution-phase synthesis), using the Atwal modification of the Biginelli reaction, to give pyrimidines which were, in turn, converted to 3,4-dihydropyrimidine-2-ones during cleavage from the resin.

For the preparation of large libraries without massive parallel synthetic effort, it would be desirable if all steps of the reaction could be carried out on a solid-phase resin. To our knowledge, such a process resulting in the traceless solid-phase synthesis of 3,4-dihydropyrimidine-2-ones has not been previously demonstrated. We herein describe the application of **1** for a convenient traceless solid-phase approach to 3,4-dihydropyrimidine-2-ones. Key steps in the synthesis are (i) sulfinate acidification, (ii) condensation of urea or thiourea with aldehydes and sulfinic acid, and (iii) traceless product release by a one-pot cyclization−dehydration process (Scheme 1). Since a variety of reagents can be used in steps ii and iii, the overall strategy appears to be applicable to library generation.

Results and Discussion

Solution-Phase Synthesis of 3,4-Dihydropyrimidine-2-ones. Prior to the solid-phase synthesis, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications for the solid-phase synthesis. Benzenesulfinic acid **7** was prepared in 93% yield by treating sodium benzenesulfinate with HCl in water at room temperature (Scheme 2). For the synthesis of (benzenesulfonylphenylmethyl)-thiourea and -urea **8**, a three-component condensation of thiourea or urea with aldehyde and benzenesulfinic acid was used. Treatment of thiourea with equimolar ratios of benzenesulfinic acid and benzaldehyde in dimethyl formamide (DMF) for 16 h afforded **8a** in 85% yield. However, attempts to prepare (benzenesulfonylphenylmethyl)urea **8b** using the same reaction conditions gave significantly more N,N′-bi(benzenesulfonylphenylmethyl)urea (21%). To optimize the formation of **8b**, the proportion of urea used was increased, and at 5 equimolar, **8b** was obtained in 89% yield. Subsequent treatment of **8** with the sodium enolate of ethyl acetoacetate (which was generated in situ by the treatment of ethyl acetoacetate with NaH/CH_3CN) at room temperature for 8 h followed by TsOH gave **9** in ∼86% yield. We found that t-BuOK/DMSO and KOH/EtOH were equally effective in generating the enolate

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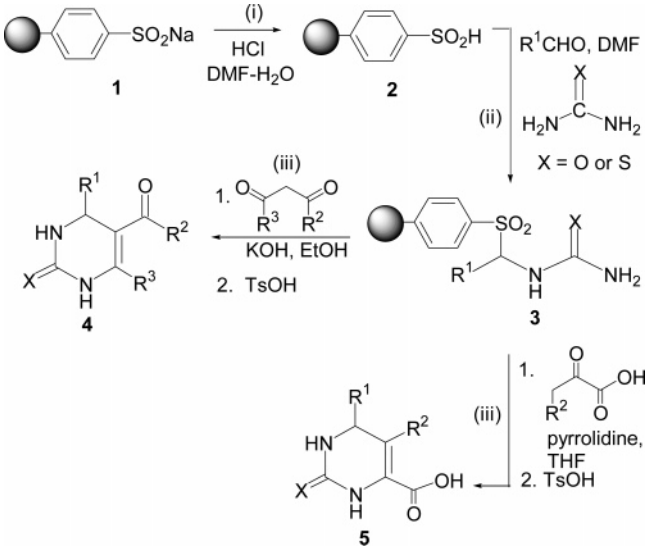
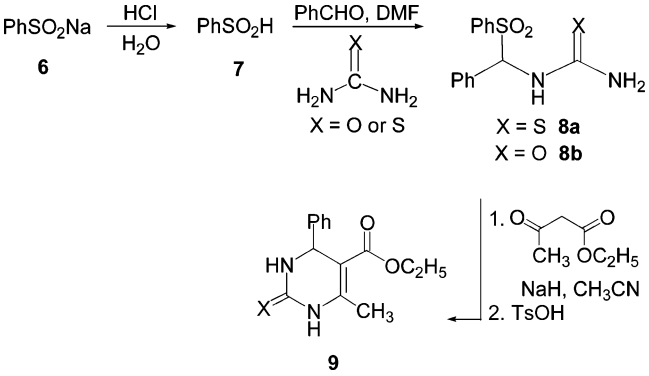
Scheme 1. SPOS of 3,4-Dihydropyrimidine-2-ones



Scheme 2. Solution-Phase Study



salt, and upon cyclization−dehydration, **9** was obtained in similar yield.

Solid-Phase Synthesis of 3,4-Dihydropyrimidine-2-ones. With the solution-phase pathway to 3,4-dihydropyrimidone established, we proceeded to develop the solid-phase route to these compounds. Because of the poor swelling ability of polystyrene/1% divinylbenzene (**1**, 100−200 mesh) in water, a DMF−H_2O (v/v 3:1) mixture was used as the solvent for the preparation of **2**. The formation of **2** was amenable to KBr Fourier transform infrared (FTIR) monitoring for the appearance of the sulfone stretch (ν_{asym} = 1443 and ν_{sym} = 1287 cm^{-1}). Condensation of **2** with an aldehyde and thiourea or urea gave resin **3**, which was easily monitored by IR spectroscopy for the appearance of the carbonyl stretch (ν_{max} 1610 cm^{-1}). Subsequent treatment of resin **3** with the potassium enolates of 1,3-dicarbonyl compounds or β-ketoesters (generated in situ by treating the latter reagents with KOH/EtOH) for 10 h at ambient temperature followed by the addition of TsOH·H_2O and 3 h of reflux gave **4** through a one-pot cyclization−dehydration process. Compound **4** precipitated readily from ice−water with overall yields of 20−40% (purities of >95% by NMR).

As illustrated in Figure 1, the versatility of this chemistry was demonstrated through the preparation of a library of 14 compounds (**4a**−**4n**). We have also examined the application of this methodology to the synthesis of dihydropyrimidine-carboxylic acids **5**. Cyclization of resin **3** with a mixture of pyrrolidine and β-ketoacid in ethanol followed by the addition of TsOH·H_2O gave the ester form of **5** (**5a**−**5b**) in 35−39% overall yield. However when THF was used as the solvent, the free carboxylic acid form of **5** was obtained (**5c**−**5d**) in comparable yields (Figure 1).

In summary, we have demonstrated a general protocol for the traceless solid-phase synthesis of 3,4-dihydropyrimidine-2-ones. Products **4** and **5** precipitated readily from cold water and could be expediently purified without the need for column chromatography. Since a variety of aldehydes, 1,3-dicarbonyl compounds, β-ketoesters, β-ketoacids, and 4-hydroxycoumarins could be used in steps ii and iii, the overall strategy is applicable not only for the 3,4-dihydropyrimidine-2-one library generation but can be expanded for the preparations of quinazoline-2,5-diones and 9-oxa-2,4-diaza-phenanthrene-3,10-diones.

Experimental Section

General Procedure. Polystyrene/1% divinylbenzene sodium sulfinate was purchased from Tianjin Nankai Hecheng Science and Technology Co. (100−200 mesh, Catalog No. HC8201-1). All chemicals were obtained from commercial suppliers and used without purification. Analytical thin-layer chromatography was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 Fourier Transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of tetramethylsilane (TMS). All IR spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under electron impact (EI).

Phenylsulfinic Acid (7). Sodium benzenesulfinate (2.46 g, 15 mmol) was dissolved in 150 mL of water, and the mixture was stirred for 20−30 min until a clear solution was obtained. Diethyl ether (60 mL) was added followed by the slow addition of 1.6 mL of concentrated aqueous hydrochloric acid (HCl) (15 mmol) over 2 min. The mixture was stirred for an additional 20−30 min, transferred to a separatory funnel, and the aqueous layer was removed. The organic layer was concentrated on a rotary evaporator, and the white solid obtained was dried under vacuum to give **7** (1.98 g, 13.95 mmol).

(Benzenesulfonylphenylmethyl)thiourea (8a). To a mixture of benzaldehyde (0.53 g, 5 mmol) in DMF (20 mL) was added thiourea (0.38 g, 5 mmol) followed by the phenylsulfinic acid (0.78 g, 5 mmol). The resulting suspension was stirred at room temperature for 16 h. The solvent was removed under high vacuum, and 20 mL of water was added to the residual mixture. The mixture was cooled to 0 °C, and the solid, which precipitated, was collected by filtration, washed carefully with ice water and diethyl ether, and dried to give **8a** as a white solid (1.30 g, 4.25 mmol). The obtained product was used in the pyrimidine synthesis without further purification. ^{1}H NMR (DMSO-d_6): δ 6.87 (1H, d, J = 10.5 Hz, CH), 7.43 (2H, m, ArH), 7.73 (3H, m, ArH), 6.95−8.00 (5H, m, ArH), 7.08 (1H, br, NH_2), 7.87 (1H, br, NH_2), 9.14 (1H, d, J = 10.5 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 175.5, 140.1, 137.5, 133.5,128.9, 128.3,

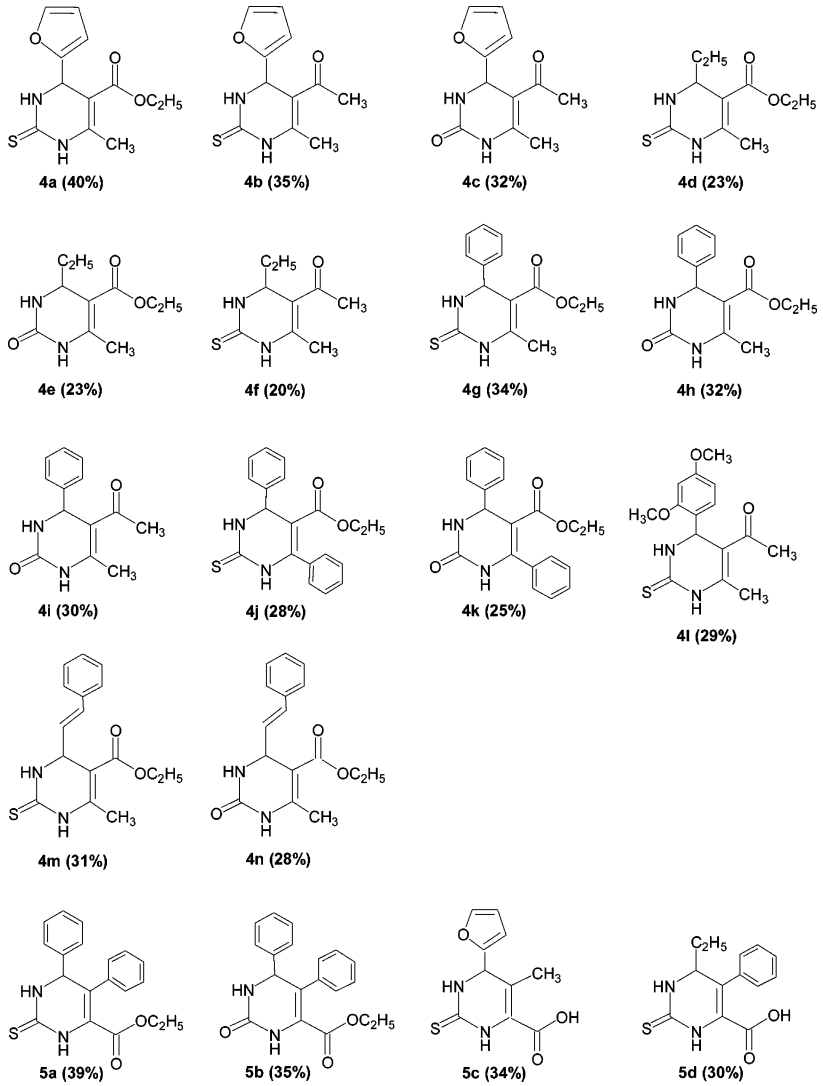


Figure 1. Library of 3,4-dihydropyrimidine-2-ones.

127.6,126.5, 126.1, 88.7. HRMS (EI) calcd for $C_{14}H_{14}N_2O_2S_2$ 306.0497. Found 306.0491.

(Benzenesulfonylphenylmethyl)urea (8b). The same procedure as for **8a** was used except for the amount of urea (1.50 g, 25 mmol). Compound **8b** was obtained as white solid (1.30 g, 4.48 mmol).

5-Ethoxymethyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (9a). To a stirred solution of NaH (0.168 g, 7 mmol) in CH_3CN (10 mL) was slowly added a solution of ethyl acetoacetate (0.9 g, 7 mmol) in CH_3CN (15 mL), and the resulting mixture was stirred for 30 min. After which, **8a** (1.53 g, 5 mmol) was added and the reaction mixture was stirred for 4.5 h at room temperature. The mixture was acidified by addition of $TsOH\cdot H_2O$ (0.94 g, 5 mmol) and refluxed for 2 h. The solvent was removed under reduced pressure and the solid residue was treated with water (20 mL). The mixture was cooled to 0°C and the precipitate that formed was filtered, washed carefully with ice water and diethyl ether, and dried to give **9a** (1.13 g, 4.31 mmol).

5-Ethoxymethyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidine-2-one (9b). The same procedure as for **9a** was used. Compound **9b** (1.20 g, 4.34 mmol) was obtained as a white solid.

Polymer-Supported Phenylsulfinic Acid (2). Polystyrene/1% divinylbenzene sodium sulfinate **1** (1 g, 2.1 mmol) was swollen in 20 mL of DMF−H_2O mixture (v/v 3:1) for 0.5 h. The resin was then treated with concentrated HCl (6 equiv, 12.6 mmol), and the reaction mixture was stirred at room temperature for 4 h, after which the resin was filtered, washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2), and dried in a vacuum oven at 35 °C to afford resin **2**.

General Procedure for the Preparation of Polymer-Supported (Benzenesulfonyl substituted)-thiourea and -urea (3). Resin **2** (1 g, 2.1 mmol) was swollen in 25 mL of anhydrous DMF at the room temperature for 0.5 h. The resin was sequentially treated with aldehyde (6 equiv) and thiourea or urea (12 equiv), and the reaction mixture was stirred at room temperature for 24 h, after which the resin was filtered, washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2), and dried overnight in a vacuum oven at 45 °C to afford resin **3**.

General Procedure for the Preparation of Substituted 3,4-Dihydro-1*H*-pyrimidine-2-ones (4). To a stirred solution of KOH (0.94 g, 16.8 mmol) in ethanol (15 mL) was added

a solution of 1,3-dione or acetoacetate (8 equiv) in ethanol (15 mL) at room temperature, and the resulting mixture was stirred for 30 min. Resin **3** (1 g, 2.1 mmol) was added, and the mixture was allowed to continue stirring overnight at room temperature, after which $TsOH \cdot H_2O$ (8 equiv) was added and the mixture was refluxed for an additional 3 h. When the mixture was still hot, it was suction filtered and washed with copious hot ethanol. The combined mixture was concentrated under reduced pressure, and the residue obtained was dissolved in water (20 mL). The aqueous solution was cooled to 0 °C, and the precipitate formed was filtered, washed carefully with ice water and diethyl ether, and dried in the vacuum oven at 45 °C overnight to give **4**.

General Procedure for the Preparation of 5,6-Disubstituted-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid and 5,6-Disubstituted-2-oxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (5). Resin **3** (1 g, 2.1 mmol) was swollen in THF (25 mL) at room temperature for 0.5 h. Pyrrolidine (9 equiv), and phenylpyruvic acid or 2-oxobutyric acid (8 equiv) were added, and the solution was stirred at room temperature for 2 h, after which, TsOH (12 equiv) was added, and the mixture was refluxed for a further 24 h. When the mixture was still hot, it was suction filtered and washed with copious hot THF. The combined mixture was concentrated under reduced pressure, and the residue obtained was dissolved in water (20 mL). The mixture was cooled to 0 °C, and the precipitates obtained was filtered, washed carefully with ice water and diethyl ether, and dried in the vacuum oven at 45 °C overnight to give **5**.

4-Furan-2-yl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4a). White solid, 40%. ^{1}H NMR (DMSO-d_6): δ 10.39 (s, 1H, NH), 9.63 (s, 1H, NH), 7.58 (m, 1H, ArH), 6.38 (m, 1H, ArH), 6.14 (m, 1H, ArH), 5.22 (m, 1H, CH), 4.04 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.13 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 174.9, 164.7, 154.5, 145.8, 142.5, 110.4, 106.1, 98.2, 59.5, 47.6, 17.0, 14.0. HRMS (EI) calcd for $C_{12}H_{14}N_2O_3S$ 266.0725. Found 266.0728.

1-(4-Furan-2-yl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-ethanone (4b). White solid, 35%. ^{1}H NMR (DMSO-d_6): δ 10.35 (s, 1H, NH), 9.74 (s, 1H, NH), 7.59 (m, 1H, ArH), 6.38 (m, 1H, ArH), 6.17 (m, 1H, ArH), 5.35 (m, 1H, CH), 2.29 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.3, 174.9, 154.6, 145.1, 142.8, 110.5, 108.2, 106.5, 47.8, 30.0, 18.2. HRMS (EI) calcd for $C_{11}H_{12}N_2O_2S$ 236.0619. Found 236.0622.

5-Acetyl-4-furan-2-yl-6-methyl-3,4-dihydro-1*H*-pyrimidin-2-one (4c). White solid, 32%. ^{1}H NMR (DMSO-d_6): δ 9.22 (s, 1H, NH), 7.84 (s, 1H, NH), 7.56 (m, 1H, ArH), 6.35 (m, 1H, ArH), 6.12 (m, 1H, ArH), 5.31 (m, 1H, CH), 2.24 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 193.7, 155.8, 152.3, 148.6, 142.2, 110.2, 107.2, 105.5, 47.8, 29.8, 18.8. HRMS (EI) calcd for $C_{11}H_{12}N_2O_3$ 220.0848. Found 220.0843.

4-Ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4d). White solid, 23%. ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H, NH), 9.21 (s, 1H, NH), 4.08 (m, 3H, CH and OCH_2), 2.20 (s, 3H, CH_3), 1.43 (m, 2H, CH_2), 1.19 (t, J = 6.9 Hz, 3H, CH_3), 0.78 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 174.8, 164.9, 144.9, 99.8, 59.1, 51.3, 28.9, 16.7, 13.8, 7.8. HRMS (EI) calcd for $C_{10}H_{16}N_2O_2S$ 228.0932. Found 228.0936.

4-Ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4e). White solid, 23%. ^{1}H NMR (DMSO-d_6): δ 8.90 (s, 1H, NH), 7.26 (s, 1H, NH), 4.05 (m, 3H, CH and OCH_2), 2.16 (s, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.18 (t, J = 6.9 Hz, 3H, CH_3), 0.79 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 165.4, 152.7, 148.3, 98.7, 58.9, 51.3, 29.5, 17.6, 14.1, 8.4. HRMS (EI) calcd for $C_{10}H_{16}N_2O_3$ 212.1161. Found 212.1163.

1-(4-Ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-ethanone (4f). White solid, 20%. ^{1}H NMR (DMSO-d_6): δ 10.03 (s, 1H, NH), 9.30 (s, 1H, NH), 4.14 (m, 1H, CH), 2.22 (m, 6H, CH_3), 1.37 (m, 2H, CH_2), 0.78 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.7, 174.8, 143.9, 110.7, 51.7, 30.1, 28.9, 17.9, 8.2. HRMS (EI) calcd for $C_9H_{14}N_2OS$ 198.0827. Found 198.0823.

6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4 g). White solid, 34%. ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 1H, NH), 9.63 (s, 1H, NH), 7.29 (m, 5H, ArH), 5.18 (m, 1H, CH), 4.02 (q, J = 6.9 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.10 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 174.2, 165.0, 144.9, 143.4, 128.4, 127.5, 126.3, 100.7, 59.4, 53.9, 17.0, 13.9. HRMS (EI) calcd for $C_{14}H_{16}N_2O_2S$ 276.0932. Found 276.0940.

6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4h). White solid, 32%. ^{1}H NMR (DMSO-d_6): δ 9.17 (s, 1H, NH), 7.73 (s, 1H, NH), 7.25 (m, 5H, ArH), 5.14 (m, 1H, CH), 3.98 (q, J = 6.9 Hz, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 165.2, 152.0, 148.2, 144.8, 128.3, 127.1, 126.1, 99.2, 59.0, 53.9, 17.7, 14.0. HRMS (EI) calcd for $C_{14}H_{16}N_2O_3$ 260.1161. Found 260.1153.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (4i). White solid, 30%. ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H, NH), 7.80 (s, 1H, NH), 7.25 (m, 5H, ArH), 5.25 (m, 1H, CH), 2.28 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.1, 152.0, 147.9, 144.1, 128.4, 127.2, 126.3, 109.5, 53.7, 30.1, 18.7. HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$ 230.1055. Found 230.1045.

4,6-Diphenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4j). White solid, 28%. ^{1}H NMR (DMSO-d_6): δ 8.68 (s, 1H, NH), 8.58 (s, 1H, NH), 7.95 (m, 2H, ArH), 7.67−7.32 (m, 8H, ArH), 5.01 (m, 1H, CH), 4.13 (q, J = 6.9 Hz, 2H, OCH_2), 1.17 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 176.8, 167.4, 141.7, 138.8, 133.7, 128.7, 128.3, 128.1, 127.9, 127.6, 126.1, 81.2, 60.5, 59.4, 13.9. HRMS (EI) calcd for $C_{19}H_{18}N_2O_2S$ 338.1089. Found 338.1093.

2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4k). White solid, 25%. ^{1}H NMR (DMSO-d_6): δ 9.73 (s, 1H, NH), 9.28 (s, 1H, NH), 8.04 (m, 3H, ArH), 7.71−7.37 (m, 7H, ArH), 4.88 (m, 1H, CH), 3.79 (q, J = 6.9 Hz, 2H, OCH_2), 0.78 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 165.3, 153.2, 147.5, 143.4, 135.0, 129.5, 128.8, 128.2, 128.0, 126.6, 102.4, 60.0, 55.8, 13.6. HRMS (EI) calcd for $C_{19}H_{18}N_2O_3$ 322.1317. Found 322.1315.

1-[4-(2,4-Dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-ethanone (4l). White solid, 29%. ^{1}H NMR (DMSO-d_6): δ 10.15 (s, 1H, NH), 9.27 (s, 1H, NH), 6.91 (m, 1H, ArH), 6.57 (m, 1H, ArH), 6.46 (m, 1H, ArH), 5.50 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.05 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 195.1, 173.9, 160.3, 157.2, 143.5, 129.7, 128.1, 122.6, 104.9, 98.6, 55.5, 55.2, 48.7, 29.3, 17.7. HRMS (EI) calcd for $C_{15}H_{18}N_2O_3S$ 306.1038. Found 306.1031.

6-Methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4m). White solid, 31%. ^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H, NH), 9.46 (s, 1H, NH), 7.34 (m, 5H, ArH), 6.38 (d, J = 15.7 Hz, 1H, CH), 6.18 (dd, J = 15.7, 5.9 Hz, 1H, CH), 4.76 (m, 1H, CH), 4.12 (q, J = 6.9 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.20 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 175.0, 164.9, 145.1, 135.9, 129.3, 128.6, 128.5, 127.7, 126.4, 99.4, 59.5, 52.1, 17.0, 14.1. HRMS (EI) calcd for $C_{16}H_{18}N_2O_2S$ 302.1089. Found 302.1081.

6-Methyl-2-oxo-4-styryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4n). White solid, 28%. ^{1}H NMR (DMSO-d_6): δ 9.12 (s, 1H, NH), 7.53 (s, 1H, NH), 7.31 (m, 5H, ArH), 6.38 (d, J = 15.7 Hz, 1H, CH), 6.20 (dd, J = 15.7, 5.9 Hz, 1H, CH), 4.73 (m, 1H, CH), 4.08 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.19 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 165.1, 152.4, 148.4, 136.2, 130.0, 128.5, 128.0, 127.5, 126.2, 97.7, 59.1, 51.8, 17.6, 14.1. HRMS (EI) calcd for $C_{16}H_{18}N_2O_3$ 286.1317. Found 286.1312.

5,6-Diphenyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (5a). White solid, 39%. ^{1}H NMR (DMSO-d_6): δ 9.64 (s, 1H, NH), 9.43 (s, 1H, NH), 7.38−7.18 (m, 8H, ArH), 7.01 (m, 2H, ArH), 5.15 (m, 1H, CH), 4.00 (q, J = 6.9 Hz, 2H, OCH_2), 0.94 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 173.1, 162.2, 141.3, 135.7, 128.7, 128.2, 128.1, 127.9, 127.6, 127.0, 124.7, 119.0, 61.3, 59.3, 13.2. HRMS (EI) calcd for $C_{19}H_{18}N_2O_2S$ 338.1089. Found 338.1084.

2-Oxo-5,6-diphenyl-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (5b). White solid, 35%. ^{1}H NMR (DMSO-d_6): δ 8.42 (s, 1H, NH), 7.58 (s, 1H, NH), 7.31−7.19 (m, 8H, ArH), 6.98 (m, 2H, ArH), 5.13 (m, 1H, CH), 3.94 (q, J = 6.9 Hz, 2H, CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 162.8, 152.4, 142.5, 136.8, 128.6, 128.5, 127.9, 127.5, 127.0, 126.0, 118.6, 61.0, 60.0, 13.2. HRMS (EI) calcd for $C_{19}H_{18}N_2O_3$ 322.1317. Found 322.1311.

6-Furan-2-yl-5-methyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (5c). White solid, 34%. ^{1}H NMR (DMSO-d_6): δ 13.90 (s, 1H, COOH), 9.19 (s, 1H, NH), 8.38 (s, 1H, NH), 7.66 (m, 1H, ArH), 6.44 (m, 1H, ArH), 6.32 (m, 1H, ArH), 4.97 (m, 1H, CH), 1.95 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 173.7, 163.2, 152.7, 143.4, 122.6, 118.8, 110.7, 107.8, 53.6, 16.0. HRMS (EI) calcd for $C_{10}H_{10}N_2O_3S$ 238.0412. Found 238.0410.

6-Ethyl-5-phenyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (5d). White solid, 30%. ^{1}H NMR (DMSO-d_6): δ 13.34 (s, 1H, COOH), 8.94 (s, 1H, NH), 8.75 (s, 1H, NH), 7.33−7.23 (m, 5H, ArH), 4.14 (m, 1H, CH), 1.46−1.32 (m, 2H, CH_2), 0.84 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 174.5, 163.1, 136.3, 128.1, 128.0, 127.4, 124.5, 120.4, 57.3, 26.8, 7.7. HRMS (EI) calcd for $C_{13}H_{14}N_2O_2S$ 262.0776. Found 262.0771.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra for **4a**, **4b**, **4c**, **4f**, **4g**, **4h**, **4i**, **5a**, **5c**, and **5d**. Crystallographic file in CIF format of **4m.** This material is available free of charge via the Internet at http://pubs.acs.org.

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