Diacetylketene N,S-acetals in synthesis of new functionalized 2(1*H*)-pyrimidinethiones

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Dedicated to Professor Branko Stanovnik on the occasion of his 65th birthday

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Abstract

New 5-acetyl-4-alkylthio-6-methyl-2(1H)-pyrimidinethiones were prepared from diacetylketene N,S-acetals and isothiocyanates. They were converted into 4-amino derivatives, which can be applied for the construction of functionalized pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines.

Keywords: Diacetylketene N,S-acetals, isothiocyanates, heterocyclization, 2(1*H*)-pyrimidinethiones, pyrimido[4,5-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines

Introduction

Ketene N,S-acetals are known to be useful reagents in heterocyclic synthesis.[1,2] Among these, particular attention has been given to oxoketene N,S-acetals as functionalized enaminones.[3,4] Previously we reported a convenient procedure for the preparation of N-unsubstituted diacylketene N,S-acetals from β-diketones and alkyl thiocyanates in the presence of $Ni(acac)_2$.[5] These compounds were shown to be suitable starting materials for synthesizing 4-acetyl-5-aminopyrazoles,[6] pyrazolo[3,4-*d*]pyrimidines,[6] functionalized 2(1*H*)pyrimidinones,[7] and 3-cyano-4-pyridones.[8] In continuation of our work on the synthetic utility of dioxoketene N,S-acetals, we describe the synthesis of functionalized 2-pyrimidinethiones from diacetylketene N,S-acetals and isothiocyanates. Although 2-pyrimidinethiones have been extensively investigated and different approaches to their preparation have been developed,[9] new methods for the synthesis of 2-pyrimidinethiones carrying functional groups in the 5- and 6-positions are desirable, since compounds of this type may be used for constructing fused pyrimidines.

Monoaroylketene N,S-acetals are reported to react with benzoyl isothiocyanate as C-nucleophiles to give the corresponding adducts which undergo cyclization into 4-pyrimidine-

thiones.[10] It is quite general that the C-C bond is formed by the attack of the enaminone nucleophilic C atom to the electrophilic C atom of isothiocyanate,[11] although enaminones as N-nucleophiles were found to react with phenylisothiocyanate in the presence of NaH affording 1-phenyl-4,6-disubstituted 2-pyrimidinethiones.[12]

Results and Discussion

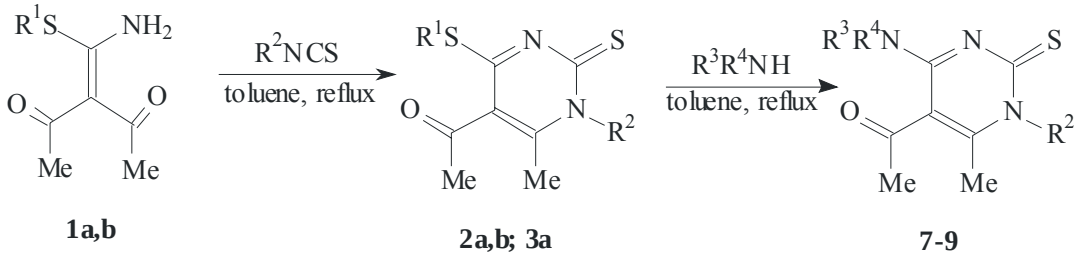
We have previously shown that the condensation of diacetylketene N,S-acetals with isocyanates occurs in the absence of basic catalysts and gives 4-alkylthiouracyl derivatives.[7] It turned out that N,S-acetals **1a,b** react in similar manner with phenylisothiocyanate and allylisothiocyanate in boiling toluene providing the corresponding N-substituted 5-acetyl-4-alkylthio-6-methyl-2(1*H*)-pyrimidinethiones **2a,b** and **3a** (Scheme 1). The action of **1a** on the benzoylisothiocyanate in toluene at room temperature results in thiourea **4,** which is isolated as crude material. The structure of **4** is confirmed by ^{1}H NMR spectra (see the Experimental Section). When **4** is boiled with MeONa in MeOH, the closure of the pyrimidine ring is accompanied by debenzoylation, and the subsequent treatment with AcOH or MeI leads to pyrimidinethione **5** or its S-methyl derivative **6**. Evidently, the formation of pyrimidinethiones **2, 3** is also supposed to involve the attack by isothiocyanate at the N-nucleophilic center of acetals **1** but the intermediate thioureas formed easily undergo cyclization in the absence of MeONa.

Crystalline pyrimidinethiones **2a,b** and **3a** are easily soluble in DMF, $CHCl_3$, EtOH, and acetone, moderately soluble in benzene and toluene, and insoluble in petroleum ether and water. Compound **5** is soluble only in DMF and DMSO. The structures of **2a,b, 3a,** and **5** were confirmed by spectral data (mass spectrometry, ^{1}H and ^{13}C NMR, IR spectroscopy).

The MeS group in pyrimidinethiones **2, 3** can be substituted by primary and secondary amines, and compound **2a** was thus converted into the corresponding 4-amino-2(1*H*)-pyrimidinethione derivatives **7-9**. It should be noted that the yields of **7, 8** (42-43%) appear to be lower than the yield of **9** (69%), because the reaction of **2a** with primary amines is accompanied by the partial cleavage of the pyrimidine ring. Indeed, the N-benzyl-N`-phenylthiourea was isolated as by-product when **2a** reacted with benzylamine.

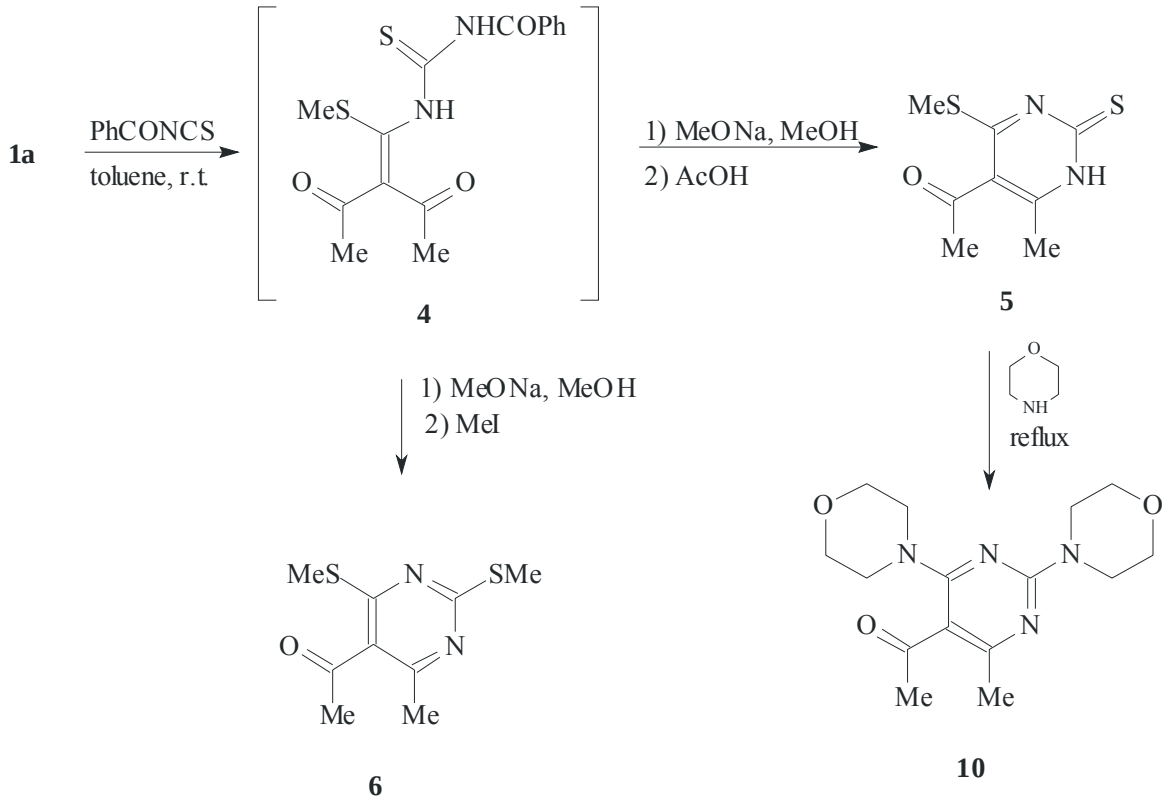
In the case of **5,** the double substitution by morpholine can be achieved, and dimorpholino-pyrimidine **10** was obtained in 79% yield.

The presence of vicinal MeCO and NH groups in the molecules of compounds **7, 8** is favorable for the annelation of the second nitrogen-containing ring to the pyrimidine cycle.



1a,b **2a,b; 3a** **7-9**

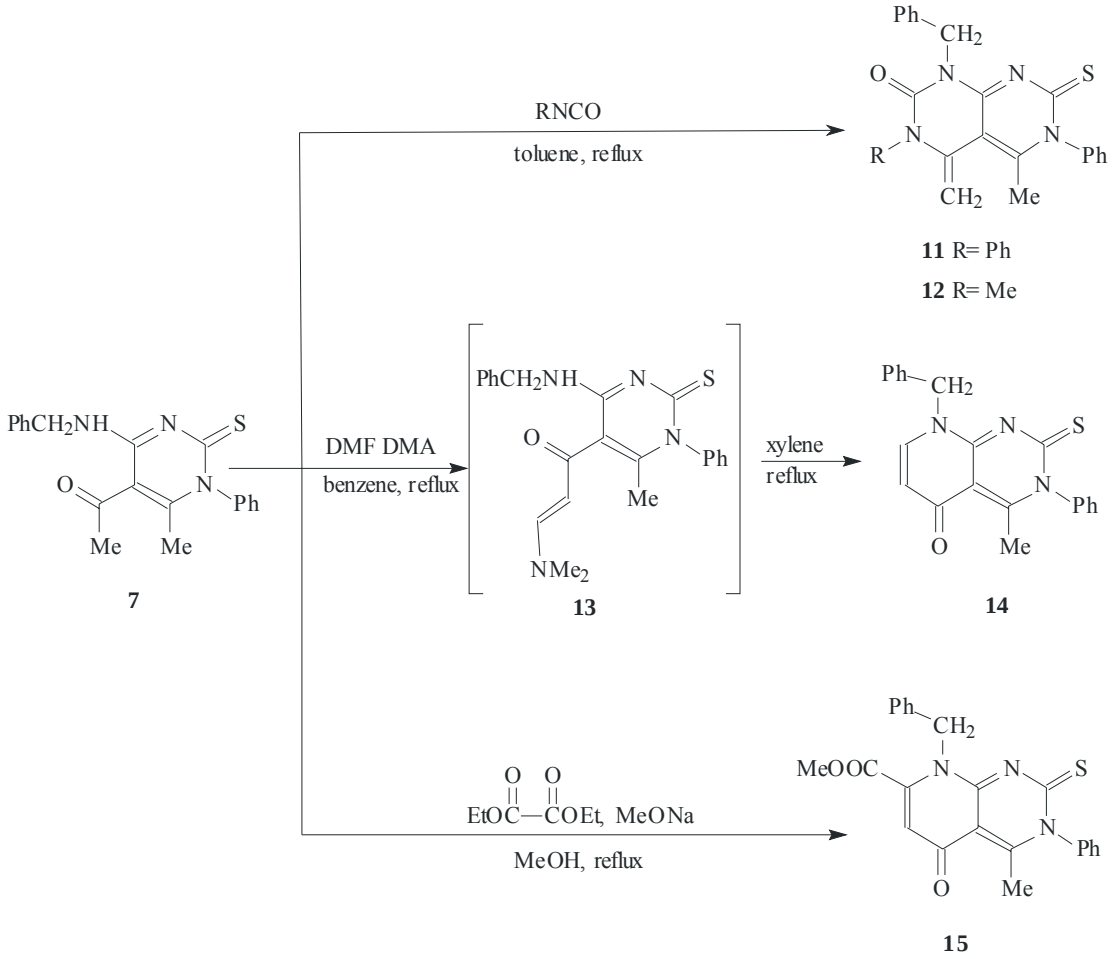
R^1=Me(**a**); Et(**b**); R^2=Ph(**2, 7-9**); All(**3**); R^3=$PhCH_2$, R^4=H(**7**); R^3=Bu, R^4=H(**8**);
R^3,R^4= -$(CH_2)_2O(CH_2)_2$-(**9**)



4 **5** **6** **10**

Scheme 1

We have chosen pyrimidinethione **7** to demonstrate the selected examples for fused pyrimidines construction. Earlier the series of 4-methylene-3,4-dihydro-2(1*H*),7(6*H*)-pyrimido[4,5-*d*]pyrimidinediones[7] had been prepared from substituted 4-amino-5-acetyl-2(1*H*)-pyrimidinones and isocyanates. Now we synthesized new representatives of pyrimido[4,5-*d*]pyrimidine system **11, 12** containing oxo-, thio-, and *exo*-methylene groups in 75-82% yields by the reaction of **7** with isocyanates (Scheme 2).



Scheme 2

The process probably involves the addition of **7** to isocyanate with the formation of intermediate ureas, intramolecular cyclization of which gives **11** and **12**. However, compound **7** failed to react with less electrophilic isothiocyanates.

Yellow crystalline compounds **11, 12** are soluble in most organic solvents. The presence of the *exo*-methylene group in their molecules is confirmed by NMR spectroscopy. Thus, in ^{1}H NMR spectra, methylene protons display the signals of the AB system (δ_A 4.36 and δ_B 4.37 for **11**; δ_A 4.49 and δ_B 4.90 for **12**, J=2.5 Hz), while the C atom of the CH_2 group in ^{13}C NMR spectra gives a triplet (δ 100.6 for **11** and δ 97.2 for **12**).

Different approaches to the construction of pyrido[2,3-*d*]pyrimidine system were applied. In accordance with Scheme 2, refluxing of **7** with dimethylformamide dimethylacetal (DMF DMA) in benzene results in the condensation product **13**, which in the boiling xylene undergoes cyclization to give the corresponding functionalized pyrido[2,3-*d*]pyrimidine **14**. In a similar manner, 8-benzyl-4-methylthio-2-phenyl-5(8*H*)-pyrido[2,3-*d*]pyrimidinone has earlier been prepared.[13]

Recently we have suggested a method for the synthesis of alkyl 5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-7-carboxylates[14] based on the condensation of 2,6-disubstituted 5-acetyl-4-aminopyrimidines with ethyl oxalate in the presence of MeONa or EtONa. Accordingly, the compound **7** was transformed into methyl ester **15** isolated in moderate yield. Evidently, the process is accompanied by transesterification. No traces of ethyl ester were detected by ^{1}H NMR spectroscopy.

The structures of pyrido[2,3-*d*]pyrimidine derivatives **14, 15** were confirmed by spectroscopic methods and microanalysis data (see below in Experimental Section).

Experimental Section

General Procedures. Melting points were determined using a Koffler apparatus and were uncorrected. ^{1}H NMR (250 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker WM-250 and Bruker AM-300 spectrometers with $CDCl_3$ and DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were obtained on a Varian MAT-311A instrument (EI, 70eV). IR spectra were recorded on a Specord M-80 spectrometer. Column chromatography was conducted with silica gel, grade 100-160 mesh. Phenyl-, allyl- and benzoylisothiocyanates, DMF DMA, phenyl- and methylisocyanates, and also diethyl oxalate were purchased from Lancaster. Diacetylketene N,S-acetals[5] were prepared according to published procedures.

5-Acetyl-6-methyl-4-methylthio-1-phenyl-2(1*H*)-pyrimidinethione (2a). A mixture of **1a** (2.60 g, 15 mmol) and phenylisothiocyanate (3.60 mL, 30 mmol) in toluene (25 mL) was heated under reflux for 3 h. After cooling, the precipitate was collected by filtration to give light yellow **2a**: 2.22 g (51%); mp 226-227 ^{o}C (from C_6H_6 / *n*-hexane 8:1). ^{1}H NMR ($CDCl_3$): δ 1.92 (3H, s, CH_3CO), 2.60 (3H, s, CH_3), 2.68 (3H, s, CH_3), 7.15-7.21 (2H, m, 2H of Ph), 7.43-7.65 (3H, m, 3H of Ph). ^{13}C NMR ($CDCl_3$): δ 13.34 (SCH_3), 19.54 (CH_3), 32.03 (CH_3CO), 122.91 (C-5), 127.17, 129.32, 130.25, 140.84 (Ph), 151.56 (q, C-6, ^2J=5.0), 167.45 (q, C-4, ^3J=3.0), 181.88 (C-2), 199.48 (CO). MS m/z: 290 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1705 (CO), 1580, 1500. Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 58.28; H, 4.99; N, 9.29; S, 22.06.

5-Acetyl-4-ethylthio-6-methyl-1-phenyl-2(1*H*)-pyrimidinethione (2b). A mixture of **1b** (1.50 g, 8 mmol) and phenylisothiocyanate (1.92 mL, 16 mmol) in toluene (15 mL) was heated under reflux for 4 h. After cooling to 20 ^{o}C, hexane (30 mL) was added to the reaction mixture.The precipitate was collected by filtration, subjected to column chromatography, and eluted with C_6H_6 to give yellow solid **2b**: 1.24 g (51%); mp 155-156 ^{o}C (from C_6H_6 / *n*-hexane 1:1). ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, CH_3CH_2), 1.91 (3H, s, CH_3CO), 2.59 (3H, s, CH_3), 3.35 (2H, q, CH_2), 7.16-7.21 (2H, m, 2H of Ph), 7.45-7.62 (3H, m, 3H of Ph). MS m/z: 304 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1702 (CO), 1580, 1470. Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.20; H, 5.50; N, 9.39; S, 20.74.

5-Acetyl-1-allyl-6-methyl-4-methylthio-2(1*H*)-pyrimidinethione (3a). A mixture of **1a** (1.04 g,

6 mmol) and allylisothiocyanate (1.17 mL, 12 mmol) in toluene (12 mL) was heated under reflux for 3 h. After cooling to 20 °C, hexane (20 mL) was added to the reaction mixture. The precipitate obtained was filtered off and recrystallized from C_6H_6 / *n*-hexane (1:1) to give yellow-brown solid **3a**: 0.79 g (52%); mp 129-130 °C. ^{1}H NMR ($CDCl_3$): δ 2.34 (3H, s, CH_3), 2.54 (3H, s, CH_3), 2.61 (3H, s, CH_3), 5.12-5.37 (4H, m, CH_2=$CHCH_2$), 5.92-6.08 (1H, m, CH_2=$CHCH_2$). ^{13}C NMR ($CDCl_3$): δ 13.17 (SCH_3), 17.81 (CH_3), 32.02 (CH_3CO), 54.04 (NCH_2), 118.35 (dd, CH_2=CH, ^1J=154, ^1J=161), 123.64 (C-5), 129,82 (d, CH_2=CH, ^1J=159), 151.17 (q, C-6, ^2J=5.6), 166.02 (q, C-4, ^3J=4.3), 181.23 (t, C-2, ^3J=4.4), 199.76 (CO). MS m/z: 254 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1705 (CO), 1580, 1490. Anal. Calcd for $C_{11}H_{14}N_2OS_2$: C, 51.94; H, 5.55; N, 11.01; S, 25.21. Found: C, 51.84; H, 5.63; N, 10.90; S, 24.82.

5-Acetyl-6-methyl-4-methylthio-2(1*H*)-pyrimidinethione (5). A mixture of **1a** (1.04 g, 6 mmol) and benzoylisothiocyanate (0.97 mL, 7.2 mmol) in C_6H_6 (30 mL) was stirred for 3 h at 20 °C. Hexane (60 mL) was added to the reaction mixture. The precipitate obtained was filtered off to give 1.49 g (74%) of crude urea **4** (^{1}H NMR ($CDCl_3$): δ 2.28 (6H, s, $2CH_3CO$), 2.56 (3H, s, SCH_3), 7.50-7.57 (2H, m, 2H of Ph), 7.62-7.68 (1H, m, 1H of Ph), 7.85-7.92 (2H, m, 2H of Ph), 9.45 (1H, s, NH), 16.64 (1H, s, NH).). A mixture of **4** (0.67 g, 2 mmol) and 2.4 mmol MeONa in MeOH (20 mL) was heated under reflux for 1.5 h. The solvent was evaporated *in vacuo*, the residue was triturated with H_2O (30 mL) and extracted with $CHCl_3$ (2 x 30 mL). The aqueous solution was separated and treated with AcOH. The precipitate obtained was filtered off and washed with ether (2 x 30 mL) to give colorless solid **5**: 0.274 g (64%); mp 210-211 °C. ^{1}H NMR (DMSO-d_6): δ 2.31 (3H, s, CH_3), 2.46 (3H, s, CH_3), 2.49 (3H, s, CH_3), 13.40 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 13.21 (SCH_3), 17.47 (CH_3), 31.71 (CH_3CO), 120.60 (C-5), 153.64 (q, C-6, ^2J=6.3), 170.02 (q, C-4, ^3J=4.3), 178.73 (C-2), 198.85 (CO). MS m/z: 214 (M^+). IR (KBr) ν/cm^{-1}: 3425, 3150 (NH), 1660 (CO), 1585, 1540. Anal. Calcd for $C_8H_{10}N_2OS_2$: C, 44.83; H, 4.70; N, 13.07; S, 29.92. Found: C, 44.68; H, 4.96; N, 12.75; S, 29.75.

5-Acetyl-6-methyl-2,4-dimethylthiopyrimidine (6). A mixture of crude **4** (0.67 g, 2 mmol) and MeONa (2.4 mmol) in MeOH (20 mL) was heated under reflux for 1.5 h. After cooling to 20 °C, MeI (0.25 mL, 4 mmol) was added and the mixture was stirred for 30 min. The solvent was evaporated *in vacuo.* The residue was subjected to column chromatography (silica gel) and eluted with hexane / C_6H_6 (1:1) and then C_6H_6 to afford the pure **6**: 0.32 g (71%); mp 73-74 °C (from hexane). ^{1}H NMR ($CDCl_3$): δ 2.36 (3H, s, CH_3), 2.56 (3H, s, CH_3), 2.58 (6H, s, 2 SCH_3). ^{13}C NMR ($CDCl_3$): δ 13.89 (2 SCH_3), 22.23 (CH_3), 31.32 (CH_3CO), 127.50 (C-5), 160.72 (q, C-6, ^2J=6.3), 166.06 (q, C-4, ^3J=4.5), 170.97 (q, C-2, ^3J=4.3), 201.78 (CO). MS m/z: 228 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1698 (CO), 1530, 1518. Anal. Calcd for $C_9H_{12}N_2OS_2$: C, 47.34; H, 5.30; N, 12.27; S, 28.09. Found: C, 47.33; H, 5.56; N, 11.94; S, 28.04.

5-Acetyl-4-benzylamino-6-methyl-1-phenyl-2(1*H*)-pyrimidinethione (7). A mixture of **2a** (2.03 g, 7.0 mmol) and benzylamine (1.14 mL, 10.5 mmol) in toluene (20 mL) was heated under reflux for 3 h. The precipitate obtained after cooling to 20 °C was filtered off to give colorless solid **7**: 1.03 g (42%); mp 217-218 °C (from C_6H_6). ^{1}H NMR ($CDCl_3$): δ 2.18 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.83 (2H, d, CH_2, *J*=5.5), 7.19-7.60 (10H, m, 10H of 2 Ph), 8.47 (1H, t, NH,

J=5.5). ^{13}C NMR ($CDCl_3$): δ 22.65 (CH_3), 32.99 (CH_3CO), 45.22 (CH_2), 109.48 (C-5), 127.66, 128.03, 128.12, 128.78,129.09, 129.95, 137.22, 141.45 (2 Ph), 154.22 (C-4), 157.46 (q, C-6, ^2J=5.4), 182.89 (C-2), 200.08 (CO). MS m/z: 349 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 3340 (NH), 1655 (CO), 1588. Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.03; S, 9.18. Found: C, 69.05; H, 5.63; N, 12.39; S, 9.02.

The filtrate was subjected to column chromatography (silica gel) and eluted with C_6H_6 to afford pure N-benzyl-N'-phenylthiourea (0.57 g): mp 155-156 °C; lit.[15] mp 153-154 °C. ^{1}H NMR ($CDCl_3$): δ 4.91 (2H, d, CH_2, *J*=5.0), 6.32 (1H, t, NH, *J*=5.0), 7.20-7.50 (10H, m, 10H of 2 Ph), 8.08 (1H, s, NH). MS m/z: 242 (M^+).

5-Acetyl-4-butylamino-6-methyl-1-phenyl-2(1*H*)-pyrimidinethione (8). A mixture of **2a** (0.44 g, 1.5 mmol) and $BuNH_2$ (0.23 mL, 2.3 mmol) in toluene (10 mL) was heated under reflux for 3 h. After cooling to 20 °C, hexane (10 mL) was added to the reaction mixture. The precipitate obtained was filtered off to give solid **8**: 0.19 g (41%); mp 219-220 °C. (from C_6H_6 / *n*-hexane 1:1). ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, t, CH_3CH_2), 1.38-1.48 (2H, m, CH_2), 1.57-1.67 (2H, m, CH_2), 2.16 (3H, s, CH_3CO), 2.50 (3H, s, CH_3), 3.62-3.68 (2H, m, CH_2N), 7.18-7.24 (2H, m, 2H of Ph), 7.42-7.60 (3H, m, 3H of Ph), 8.10 (1H, t, NH, *J*=5.5). MS m/z: 315 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 3320 (NH), 1648 (CO), 1580. Anal. Calcd for $C_{17}H_{21}N_3OS$: C, 64.73; H, 6.71; N, 13.32; S, 10.17. Found: C, 64.70; H, 6.76; N, 13.03; S, 10.38.

5-Acetyl-6-methyl-4-morpholino-1-phenyl-2(1*H*)-pyrimidinethione (9). A mixture of **2a** (1.74 g, 6.0 mmol) and morpholine (1.04 mL, 12 mmol) in toluene (20 mL) was heated under reflux for 6 h. The solvent and excess morpholine were evaporated *in vacuo*. The residue obtained was recrystallized from C_6H_6 to give colorless solid **9**: 1.36 g (69%); mp 228-229 °C. ^{1}H NMR ($CDCl_3$): δ 1.99 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.75 (8H, s, 4 CH_2), 7.19-7.23 (2H, m, 2H of Ph), 7.40-7.62 (3H, m, 3H of Ph). ^{13}C NMR ($CDCl_3$): δ 18.85 (CH_3), 31.08 (CH_3CO), 41.81 (CH_2), 66.52 (CH_2), 111.67 (C-5), 127.95, 129.06, 129.80, 141.31 (Ph), 155.51 (q, C-6, ^2J=6.0), 156.89 (C-4), 181.58 (C-2), 200.08 (CO). MS m/z: 329 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1690 (CO), 1575. Anal. Calcd for $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76; S, 9.73. Found: C, 62.22; H, 5.96; N, 12.51; S, 9.36.

5-Acetyl-6-methyl-2,4-dimorpholinopyrimidine (10). A mixture of **5** (0.21 g, 1 mmol) and morpholine (9 mL, 102 mmol) was heated under reflux for 6 h. A morpholine excess was evaporated *in vacuo*. The residue obtained was subjected to column chromatography (silica gel) and eluted with C_6H_6 to afford colorless pyrimidine **10**: 0.24 g (79%); mp 159-160 °C (from hexane). ^{1}H NMR ($CDCl_3$): δ 2.30 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.40 (4H, t, 2 CH_2), 3.72 (8H, t, 4 CH_2), 3.79 (4H, t, 2 CH_2). ^{13}C NMR ($CDCl_3$): δ 23.23 (CH_3), 30.10 (CH_3CO), 44.14 (CH_2), 49.22 (CH_2), 66.49 (CH_2), 66.85 (CH_2), 111.01 (C-5), 159.55 and 164.36 (C-2 and C-4), 166.19 (q, C-6, ^2J=6.0), 202.45 (CO). MS m/z: 306 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1675 (CO), 1558, 1535, 1520. Anal. Calcd for $C_{15}H_{22}N_4O_3$: C, 58.80; H, 7.24; N, 18.29. Found: C, 59.07; H, 7.43; N, 18.04.

1-Benzyl-5-methyl-4-methylene-3,6-diphenyl-7-thioxo-3,4,6,7-tetrahydro-2(1*H*)-pyrimido[4,5-*d*]pyrimidinone (11). A mixture of **7** (0.17 g, 0.5 mmol) and PhNCO (0.11 mL, 1

mmol) in toluene (6 mL) was heated under reflux for 3 h. The solvent was evaporated *in vacuo*. The residue obtained was subjected to column chromatography (silica gel) and eluted with C_6H_6 and then C_6H_6 / $CHCl_3$ (1:1) to afford the oil, which was dissolved in C_6H_6. Hexane (6 mL) was added to the solution, and the precipitate obtained was filtered off to give yellow solid **11**: 0.18 g (82%); mp 137-138 °C. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, CH_3), 4.36 and 4.43 (both for 1H, both d, CH_2=, *J*=2.5), 5.45 (2H, s, CH_2), 7.20-7.78 (15H, m, 15H of 3 Ph). ^{13}C NMR ($CDCl_3$): δ 21.93 (CH_3), 45.19 (CH_2), 100.62 (t, CH_2=, ^1J=164.0), 104.40 (C-4a), 127.57, 127.66, 128.34, 128,66, 128.80, 129.37, 129.95, 130.16, 130.35, 136.76, 137.69, 137.89 (3 Ph), 141.89 (t, C-4, ^2J=8.0), 149.94, 152.31 (C-2 and C-8a), 154.01 (q, C-5, ^2J=6.0), 182.73 (C-7). MS m/z: 450 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1708 (CO), 1625, 1605, 1590, 1520. Anal. Calcd for $C_{27}H_{22}N_4OS$: C, 71.97; H, 4.92; N, 12.44; S, 7.12. Found: C, 71.89; H, 5.00; N, 12.12; S, 6.92.

1-Benzyl-3,5-dimethyl-4-methylene-6-phenyl-7-thioxo-3,4,6,7-tetrahydro-2(1*H*)-pyrimido[4,5-*d*]pyrimidinone (12). A mixture of **7** (0.17 g, 0.5 mmol) and MeNCO (0.06 mL, 1 mmol) in toluene (6 mL) was heated in a sealed tube in an oil bath (110-115 °C) for 6 h. The further procedure was analogous to the above experiment and afforded solid **12**: 0.146 g (75%); mp 216-217 °C. ^{1}H NMR ($CDCl_3$): δ 2.25 (3H, s, CH_3), 3.29 (3H, s, NCH_3), 4.49 and 4.90 (both for 1H, both d, CH_2=, *J*=2.5), 5.45 (2H, s, CH_2), 7.20-7.40 (5H, m, 5H of 2 Ph), 7.48-7.68 (5H, m, 5H of 2 Ph). ^{13}C NMR ($CDCl_3$): δ 21.74 (CH_3), 32.54 (NCH_3), 45.04 (CH_2), 97.25 (CH_2=), 104.29 (C-4a), 127.60, 128.32, 129.28, 129.55, 130.28, 136.74, 136.95 (2 Ph), 141.96 (C-4), 150.39 and 152.16 (C-2 and C-8a), 153.79 (C-5), 182.76 (C-7). MS m/z: 388 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1698 (CO), 1624, 1605, 1590, 1522. Anal. Calcd for $C_{22}H_{20}N_4OS$: C, 68.02; H, 5.19; N, 14.42; S, 8.25. Found: C, 67.88; H, 5.02; N, 14.48; S, 8.01.

8-Benzyl-4-methyl-3-phenyl-2-thioxo-2,3-dihydro-5(8*H*)-pyrido[2,3-*d*]pyrimidinone (14). A mixture of **7** (0.35 g, 1 mmol) and DMF DMA (0.26 mL, 2 mmol) in C_6H_6 (6 mL) was heated under reflux for 1 h. The solvent was evaporated *in vacuo*. The residue obtained was subjected to column chromatography (silica gel) and eluted with $CHCl_3$ to give pyrimidine **13**: 0.36 g (89%); mp 122-125 °C. ^{1}H NMR ($CDCl_3$): δ 2.03 (3H, s, CH_3), 2.88 and 3.15 (both for 3H, both s, $N(CH_3)_2$), 4.82 (2H, d, CH_2, *J*=5.5), 5.17 and 7.67 (both for 1H, both d, CH=CH, *J*=12.8), 7.18-7.60 (11H, m, 10H of 2 Ph and NH). A solution of **13** (0.36 g) in *m*-xylene (20 mL) was heated under reflux for 6 h. The solvent was evaporated *in vacuo*. The residue obtained was dissolved in C_6H_6 (5 mL). Hexane (8 mL) was added to the solution, and the precipitate obtained was filtered off to give yellow solid **14**: 0.23 g, (73%); mp 170-171 °C. ^{1}H NMR ($CDCl_3$): δ 2.73 (3H, s, CH_3), 5.43 (2H, s, CH_2), 6.07 and 7.40 (both for 1H, both d, H-6 and H-7, *J*=6.5), 7.28-7.65 (10H, m, 10H of 2 Ph). ^{13}C NMR ($CDCl_3$): δ 21.61 (CH_3), 52.37 (CH_2), 109.64 (C-4a), 114.52 (d, C-6, ^1J=171), 127.13, 128.50, 128.60, 129.05, 129.53, 130.42, 135.17, 141.18 (2 Ph), 142.01 (d, C-7, ^1J=178), 152.90 (C-8a), 166.90 (q, C-4, ^2J=6.5), 179.06 (C-5), 181.59 (C-2). MS m/z: 359 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1652 (CO), 1567, 1560. Anal. Calcd for $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69; S, 8.92. Found: C, 69.85; H, 4.89; N, 11.37; S, 8.69.

Methyl 8-benzyl-4-methyl-5-oxo-3-phenyl-2-thioxo-2,3,5,8-tetrahydropyrido[2,3-*d*]-pyrimidine-7-carboxylate (15). A mixture of **7** (0.14 g, 0.4 mmol), diethyl oxalate (0.16 mL, 1.2 mmol), and MeONa (1.2 mmol) in MeOH (8 mL) was heated under reflux for 2 h. After cooling to 20 ^{o}C, AcOH was added, and the solvent was evaporated *in vacuo.* The residue was subjected to column chromatography (silica gel) and eluted with C_6H_6 and then C_6H_6 / MeOH (50:0.2). The solvents were removed and diethyl ether (3 mL) was added. The precipitate obtained was filtered off to afford yellow solid **15**: 0.07 g (42%); mp 155-156 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 2.77 (3H, s, CH_3), 3.71 (3H, s, CH_3O), 5.92 (2H, s, CH_2), 6.41 (1H, s, H-6), 7.15-7.25 (4H, m, 4H of 2 Ph), 7.25-7.38 (3H, m, 3H of Ph), 7.50-7.68 (3H, m, 3H of Ph). ^{13}C NMR ($CDCl_3$): δ 21.71 (CH_3), 52.45 (CH_2), 53.65 (CH_3O), 109.77 (C-4a), 116.04 (C-6), 126.94, 128.53, 128.64, 129.10, 129.57, 130.42, 135.28, 140.97 (2 Ph), 143.96 (C-7), 153.30 (C-8a), 162.89 (COO), 166.78 (C-4), 178.48 (C-5), 181.55 (C-2). MS m/z: 417 (M^+). IR ($CHCl_3$) ν/cm^{-1}: 1740 (CO), 1644 (CO), 1560. Anal. Calcd for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.07; S, 7.68. Found: C, 66.12; H, 4.61; N, 9.86; S, 7.80.

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