Diacetylketene N,S-acetals in synthesis of new functionalized 2(1H)-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(1H)-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. Among these, particular attention has been given to oxoketene N,S-acetals as functionalized enaminoes. Previously we reported a convenient procedure for the preparation of N-unsubstituted diacetylketene N,S-acetals from β-diketones and alkyl thiocyanates in the presence of Ni(acac)₂. These compounds were shown to be suitable starting materials for synthesizing 4-acetyl-5-aminopyrazoles, pyrazolo[3,4-d]pyrimidines, functionalized 2(1H)pyrimidinones, and 3-cyano-4-pyridones. 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, 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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-alkylthiouracil derivatives.\textsuperscript{7} It turned out that N,S-acetals 1\textsubscript{a,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\textsubscript{H})-pyrimidinethiones 2\textsubscript{a,b} and 3\textsubscript{a} (Scheme 1). The action of 1\textsubscript{a} 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 \textsuperscript{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 2\textsubscript{a,b} and 3\textsubscript{a} are easily soluble in DMF, CHCl\textsubscript{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 2\textsubscript{a,b}, 3\textsubscript{a}, and 5 were confirmed by spectral data (mass spectrometry, \textsuperscript{1}H and \textsuperscript{13}C NMR, IR spectroscopy).

The MeS group in pyrimidinethiones 2, 3 can be substituted by primary and secondary amines, and compound 2\textsubscript{a} was thus converted into the corresponding 4-amino-2(1\textsubscript{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 2\textsubscript{a} 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 2\textsubscript{a} reacted with benzyamine.

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.
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(1H),7(6H)-pyrimido[4,5-d]pyrimidinediones had been prepared from substituted 4-amino-5-acetyl-2(1H)-pyrimidonones 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).
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 ($\delta_A$ 4.36 and $\delta_B$ 4.37 for 11; $\delta_A$ 4.49 and $\delta_B$ 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 ($\delta$ 100.6 for 11 and $\delta$ 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(8H)-pyrido[2,3-d]pyrimidinone has earlier been prepared.\textsuperscript{13}
Recently we have suggested a method for the synthesis of alkyl 5-oxo-5,8-
dihydropyrido[2,3-d]pyrimidine-7-carboxylates\textsuperscript{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 \textsuperscript{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. \textsuperscript{1}H NMR (250 MHz) and \textsuperscript{13}C NMR (75 MHz) spectra were recorded on Bruker WM-250 and Bruker AM-300 spectrometers with CDCl\textsubscript{3} and DMSO-d\textsubscript{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\textsuperscript{5} were prepared according to published procedures.

5-Acetyl-6-methyl-4-acetylthio-1-phenyl-2(1\textsubscript{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 °C (from C\textsubscript{6}H\textsubscript{6} / n-hexane 8:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta\) 1.92 (3H, s, CH\textsubscript{3}CO), 2.60 (3H, s, CH\textsubscript{3}), 2.68 (3H, s, CH\textsubscript{3}), 7.15-7.21 (2H, m, 2H of Ph), 7.43-7.65 (3H, m, 3H of Ph). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta\) 13.34 (SCH\textsubscript{3}), 19.54 (CH\textsubscript{3}), 32.03 (CH\textsubscript{3}CO), 122.91 (C-5), 127.17, 129.32, 130.25, 140.84 (Ph), 151.56 (q, C-6, \(\text{J}=5.0\)), 167.45 (q, C-4, \(\text{J}=3.0\)), 181.88 (C-2), 199.48 (CO). MS m/z: 290 (M\textsuperscript{+}). IR (CHCl\textsubscript{3}) \(\nu/cm^{-1}\): 1705 (CO), 1580, 1500. Anal. Calcd for C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}OS\textsubscript{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-1-allyl-6-methyl-4-acetylthio-2(1\textsubscript{H})-pyrimidinethione (3a). A mixture of 1a (1.04 g, 5 milli-
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 C₆H₆ / n-hexane (1:1) to give yellow-brown solid 3a: 0.79 g (52%); mp 129-130 °C. ¹H NMR (CDCl₃): δ 2.34 (3H, s, CH₃), 2.54 (3H, s, CH₃), 2.61 (3H, s, CH₃), 5.12-5.37 (4H, m, CH₂=CHCH₂), 5.92-6.08 (1H, m, CH₂=CHCH₂). ¹³C NMR (CDCl₃): δ 13.17 (SCH₃), 17.81 (CH₃), 32.02 (CH₃CO), 54.04 (NCH₂), 118.35 (dd, CH₂=CH, ³J=154, ¹J=161), 123.64 (C-5), 129.82 (d, CH₂=CH, ¹J=159), 151.17 (q, C-6, ³J=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 (CHCl₃) ν/cm⁻¹: 1705 (CO), 1580, 1490. Anal. Calcd for C₁₁H₁₄N₂O₃: 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(1H)-pyrimidinethione (5). A mixture of 1a (1.04 g, 6 mmol) and benzoylisothiocyanate (0.97 mL, 7.2 mmol) in C₆H₆ (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 (¹H NMR (CDCl₃): δ 2.28 (6H, s, 2CH₃CO), 2.56 (3H, s, SCH₃), 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 H₂O (30 mL) and extracted with CHCl₃ (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. ¹H NMR (DMSO-d₆): δ 2.31 (3H, s, CH₃), 2.46 (3H, s, CH₃), 2.49 (3H, s, CH₃), 13.40 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 13.21 (SCH₃), 17.47 (CH₃), 31.71 (CH₃CO), 120.60 (C-5), 153.64 (q, C-6, ³J=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 C₈H₁₀N₂O₃S: 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 / C₆H₆ (1:1) and then C₂H₆ to afford the pure 6: 0.32 g (71%); mp 73-74 °C (from hexane). ¹H NMR (CDCl₃): δ 2.36 (3H, s, CH₃), 2.56 (3H, s, CH₃), 2.56 (3H, s, CH₃). ¹³C NMR (CDCl₃): δ 13.89 (2SCH₃), 22.23 (CH₃), 31.32 (CH₃CO), 127.50 (C-5), 160.72 (q, C-6, ³J=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 (CHCl₃) ν/cm⁻¹: 1698 (CO), 1530, 1518. Anal. Calcd for C₉H₁₂N₂O₂S: 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(1H)-pyrimidinethione (7). A mixture of 2a (2.03 g, 7.0 mmol) and benzyamine (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 C₆H₆). ¹H NMR (CDCl₃): δ 2.18 (3H, s, CH₃), 2.49 (3H, s, CH₃), 4.83 (2H, d, CH₂, 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$_3$): $\delta$ 22.65 (CH$_3$), 32.99 (CH$_3$CO), 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$_3$) $\nu$/cm$^{-1}$: 3340 (NH), 1690 (CO), 1588. Anal. Calcd for C$_{20}$H$_{10}$N$_3$OS: 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$_6$H$_6$ to afford pure N-benzyl-N'-phenylthiourea (0.57 g): mp 155-156 °C; lit.$^{15}$ mp 153-154 °C. $^1$H NMR (CDCl$_3$): $\delta$ 4.91 (2H, d, CH$_2$), 7.20-7.50 (10H, m, 10H of 2 Ph), 8.08 (1H, s, NH). MS m/z: 242 (M$^+$).

5-Acetyl-4-butyramino-6-methyl-1-phenyl-2(1H)-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. IR (CHCl$_3$) $\nu$/cm$^{-1}$: 3320 (NH), 1655 (CO). MS m/z: 315 (M$^+$). IR (CHCl$_3$) $\nu$/cm$^{-1}$: 3180 (NH), 1648 (CO). Anal. Calcd for C$_{17}$H$_{21}$N$_3$OS: 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(1H)-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$_6$H$_6$ to give colorless solid 9: 1.36 g (69%); mp 228-229 °C. $^1$H NMR (CDCl$_3$): $\delta$ 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$_3$): $\delta$ 18.85 (CH$_3$), 31.08 (CH$_3$CO), 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$_3$) $\nu$/cm$^{-1}$: 1690 (CO), 1575. Anal. Calcd for C$_{17}$H$_{19}$N$_3$OS: 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$_6$H$_6$ to afford colorless pyrimidine 10: 0.24 g (79%); mp 159-160 °C (from hexane). $^1$H NMR (CDCl$_3$): $\delta$ 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$_3$): $\delta$ 23.23 (CH$_3$), 30.10 (CH$_3$CO), 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$_3$) $\nu$/cm$^{-1}$: 1675 (CO), 1558, 1535, 1520. Anal. Calcd for C$_{15}$H$_{23}$N$_3$O$_3$: 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(1H)-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 C₆H₆ and then C₆H₆ / CHCl₃ (1:1) to afford the oil, which was dissolved in C₆H₆. 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. ¹H NMR (CDCl₃): δ 2.22 (3H, s, CH₃), 4.36 and 4.43 (both for 1H, both d, CH₂=J=2.5), 5.45 (2H, s, CH₂), 7.20-7.78 (15H, m, 15H of 3 Ph). ¹³C NMR (CDCl₃): δ 21.93 (CH₃), 45.19 (CH₂), 100.62 (t, CH₂=J=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,J=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 (CHCl₃) ν/cm⁻¹: 1708 (CO), 1624, 1605, 1590, 1520. Anal. Calcd for C₂₇H₂₂N₄O₆S: C, 71.97; H, 4.92; N, 12.44; S, 8.81. Found: C, 71.89; H, 5.00; N, 12.12; S, 8.69.

1-Benzyl-3,5-dimethyl-4-methylene-6-phenyl-7-thioxo-3,4,6,7-tetrahydro-2(1H)-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. ¹H NMR (CDCl₃): δ 2.25 (3H, s, CH₃), 3.29 (3H, s, NCH₃), 4.49 and 4.90 (both for 1H, both d, CH₂=J=2.5), 5.45 (2H, s, CH₂), 7.20-7.74 (5H, m, 5H of 2 Ph). ¹³C NMR (CDCl₃): δ 21.74 (CH₃), 32.54 (NCH₃), 45.04 (CH₂), 97.25 (CH₂=), 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 (CHCl₃) ν/cm⁻¹: 1698 (CO), 1624, 1605, 1590, 1522. Anal. Calcd for C₂₂H₂₀N₄OS: 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(8H)-pyrido[2,3-d]pyrimidinone (14). A mixture of 7 (0.35 g, 1 mmol) and DMF DMA (0.26 mL, 2 mmol) in C₆H₆ (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 CHCl₃ to give pyrimidine 13: 0.36 g (89%); mp 122-125 °C. ¹H NMR (CDCl₃): δ 2.03 (3H, s, CH₃), 2.22 (3H, s, CH₃), 2.88 and 3.15 (both for 3H, both d, 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 C₆H₆ (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. ¹H NMR (CDCl₃): δ 2.73 (3H, s, CH₃), 5.43 (2H, s, CH₂), 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). ¹³C NMR (CDCl₃): δ 21.61 (CH₃), 52.37 (CH₂), 109.64 (C-4a), 114.52 (d, C-6, J=171), 127.13, 128.50, 128.60, 129.05, 129.53, 130.42, 135.17, 141.18 (2 Ph), 142.01 (d, C-7, J=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 (CHCl₃) ν/cm⁻¹: 1652 (CO), 1567, 1560. Anal. Calcd for C₂₁H₁₇N₃OS: 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-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 °C, AcOH was added, and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (silica gel) and eluted with C₆H₆ and then C₆H₆ / 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 °C. ¹H NMR (CDCl₃): δ 2.77 (3H, s, CH₃), 3.71 (3H, s, CH₃O), 5.92 (2H, s, CH₂), 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). ¹³C NMR (CDCl₃): δ 21.71 (CH₃), 52.45 (CH₂), 53.65 (CH₃O), 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), 156.78 (C-4), 178.48 (C-5), 181.55 (C-2). MS m/z: 417 (M⁺). IR (CHCl₃) ν/cm⁻¹: 1740 (CO), 1644 (CO), 1560. Anal. Calcd for C₂₃H₁₉N₃O₃S: 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.

References