Synthesis and Reactions of *N*-Methyl-4-(methylthio)thieno[2,3-*d*]-pyrimidinium Salts

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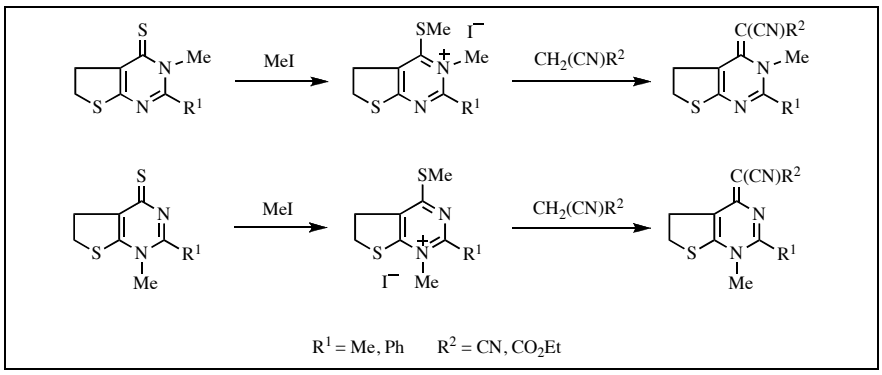

Two methods for the preparation of *N*-methyl-4-(methylthio)thieno[2,3-*d*]pyrimidinium salts **6a,b** and **13a,b** are described. Treatment of **6a,b** and/or **13a,b** with active methylene compounds such as malononitrile and ethyl cyanoacetate in the presence of sodium methoxide caused nucleophilic addition followed by elimination of methanethiol, giving the corresponding *N*-methyl-4-ylidenethieno[2,3-*d*]-pyrimidines **7a,b**, **8a,b**, **14a,b** and **15a,b**.

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INTRODUCTION

The fused pyrimidine ring system is a commonly encountered structural core in a number of natural and synthetic molecules with a wide range of biological activities [1–9]. In this context, the synthesis of compounds containing this ring system continues to attract attention and provides an interesting challenge [10–19]. For these reasons, we have been interested in the development of the methods for the synthesis of fused pyrimidine derivatives.

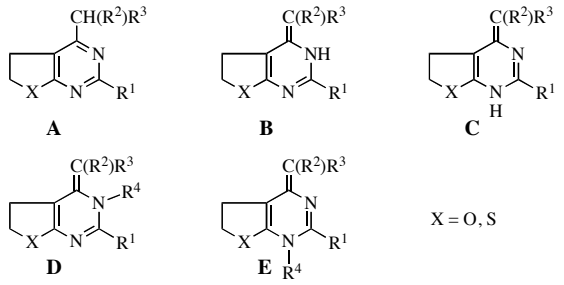
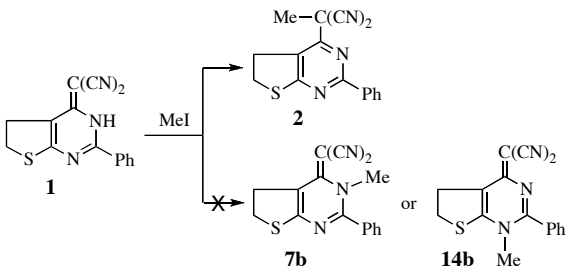


Figure 1 Five Different [*d*]Fused Pyrimidines

In our previous papers [20–22] we discussed the synthesis of 4-substituted furo(and thieno)[2,3-*d*]-pyrimidines through a nucleophilic addition of various nucleophiles to heterocyclic β-enaminonitriles (types **A** and **B** in Figure 1). More recently, we have also demonstrated the one-pot synthesis of 4-alkoxy-furo and -thienopyrimidines (type **A**) [23]. On the other hand, to the best of our knowledge, there are relatively few methods in the literature describing the preparation [24–27] of 4-ylidene-containing fused pyrimidines such as types **C**, **D** and **E**, even though they may have biological activity. Therefore we studied the reaction of malononitrile derivative **1** with a series of alkylating reagents. Although treatment of **1** with excess of methyl iodide and 1.1 equivalent of sodium hydride in *N*,*N*-dimethylformamide gave α-methylated malononitrile derivative **2** in 74% yield, the desired *N*-methyl-4-ylidenethieno[2,3-*d*]pyrimidine **7b** or **14b** was not obtained at all [21] (Scheme 1). This result indicates that the synthesis of *N*-alkylated 4-ylidenethieno[2,3-*d*]-pyrimidines is not easy. In continuation and in order to extend the scope of the method, we aimed to examine the possibility of synthesis a series of *N*-methyl-4-ylidene-

Scheme 1



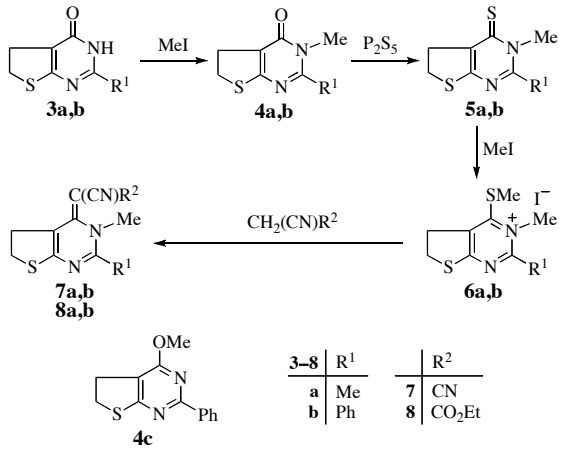
thieno[2,3-*d*]pyrimidines by the reaction of *N*-methyl-4-(methylthio)thieno[2,3-*d*]pyrimidinium salts with active methylene compounds.

RESULTS AND DISCUSSION

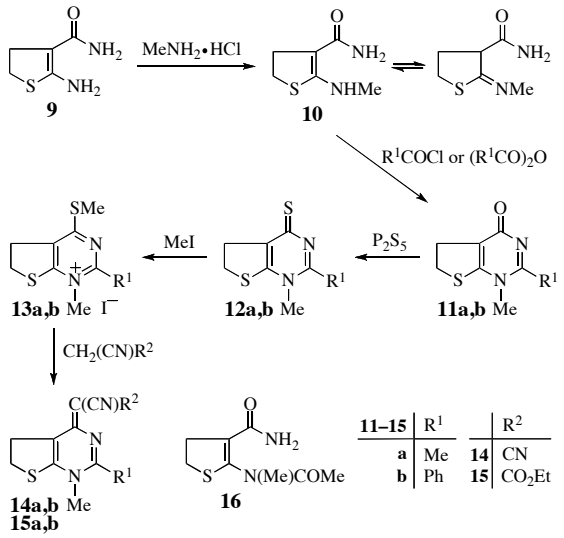
Initially, we examined the synthesis of 3-methyl-4-ylidenethieno[2,3-*d*]pyrimidines **7a,b** and **8a,b** starting from thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a,b**, which were prepared from 2-acylamino-4,5-dihydro-3-thiophenecarbonitrile [20,21]. Thus, the reaction of **3a,b** with methyl iodide in the presence of sodium methoxide in methanol gave the corresponding 3-methylthieno[2,3-*d*]-pyrimidin-4(3*H*)-ones **4a**,**b** (70,61%) together with 4-methoxylthieno[2,3-*d*]pyrimidine **4c** [23] (10%) as a minor product (Scheme 2). After treating **4a,b** with phosphorous pentasulfide in pyridine, 3-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-thiones **5a,b** were isolated in 73 and 79% yield, respectively. Subsequently, the alkylation reaction of **5a,b** with methyl iodide provided the corresponding 3-methyl-4-(methylthio)thieno[2,3-*d*]-pyrimidinium salts **6a**,**b** (97,75%). Treatment of **6a,b** with malononitrile or ethyl cyanoacetate in the presence of sodium hydride caused nucleophilic addition followed by elimination of methanethiol to afford 3-methyl-4-ylidene-thieno[2,3-*d*]pyrimidines **7a**,**b** (51,68%) or **8a**,**b** (69,84%), respectively. It makes us believe that since nucleophilic addition of activated methylene compounds to the 4-position of **6a,b** would easily occur, **7a,b** and **8a,b** could be obtained.

We next tried the synthesis of 1-methyl-4-ylidene-thieno[2,3-*d*]pyrimidines **14a,b** and **15a,b** (Scheme 3). First the construction of 1-methylated thieno[2,3-*d*]-pyrimidin-4(1*H*)-ones was investigated and second the preparation of 1-methylated 4-(methylthio)thieno[2,3-*d*]-pyrimidinium salts was examined. The reaction of 2-amino-4,5-dihydro-3-thiophenecarboxamide (**9**), prepared commonly from 2-amino-4,5-dihydro-3-thiophenecarbo-nitrile according to our earlier work [28], with methyl-amine hydrochloride gave 4,5-dihydro-2-(methylamino)-3-thiophenecarboxamide (**10**) in 75% yield. Treatment of **10** with acetic anhydride or benzoyl chloride in pyridine caused *N*-acylation of methylamino group and subsequent cyclocondensation with dehydration to yield 1-methyl-thieno[2,3-*d*]pyrimidin-4(1*H*)-ones **11a**,**b** (68, 77%). The reaction of compounds **11a,b** with phosphorous pentasulfide by the procedure described above provided 1-methylthieno[2,3-*d*]pyrimidin-4(1*H*)-thiones **12a**,**b** (66,84%), which were treated with methyl iodide to form 1-methyl-4-(methylthio)thieno[2,3-*d*]pyrimidinium salts **13a**,**b** (94,91%). Compounds **13a,b** reacted with malononitrile or ethyl cyanoacetate to afford 1-methyl-4-ylidenethieno[2,3-*d*]pyrimidines **14a**,**b** (44,43%) or **15a**,**b** (73,88%), respectively.

Scheme 2



Scheme 3



These products **4–8** and **10–15** gave satisfactory elemental analyses and spectroscopic data (^{1}H nmr, ^{13}C nmr and mass) consistent with their assigned structures. For example, the ir spectrum of **4a** displays a carbonyl band at 1650 cm^{-1}, whereas that of **11a** shows at 1615 cm^{-1}; the ^{1}H nmr spectrum of **4a** exhibits a three-proton singlet at δ 2.50 attributable to the 2-methyl protons and a three-proton singlet at δ 3.49 due to the *N*-methyl protons, whereas that of **11a** shows a three-proton singlet at δ 2.47 attributable to the 2-methyl protons and a three-proton singlet at δ 3.57 due to the *N*-methyl protons; the ^{13}C nmr spectrum of **4a** shows a signal at δ 30.7 due to the *N*-methyl carbon and a signal at δ 158.4 due to the carbonyl carbon, whereas that of **11a** exhibits a signal at δ 38.9 due to the *N*-methyl carbon and a signal at δ 166.2 due to the carbonyl carbon. Mass spectra and elemental analyses of **4a** and **11a** point to the same molecular ion and elemental composition $C_8H_{10}N_2OS$ (see experimental section). In

order to understand better the formation of **11a**, compound **10** was allowed to react with acetyl chloride under the milder conditions to furnish *N*-acetylated carboxamide derivative **16** in 64% yield. Upon heating, compound **16** was cyclized to 1-methylthieno[2,3-*d*]-pyrimidin-4(1*H*)-one **11a** in 97% yield. The melting point and ir spectrum of this compound coincided with those of an authentic sample prepared from **10** and acetyl chloride. Interestingly, in deuteriochloroform or dimethyl sulfoxide-d_6, the nmr spectra indicated that compounds **8a,b** and **15a,b** existed as a geometrical single isomer of *E*- or *Z*-configuration but their configuration was not confirmed by nmr spectroscopy.

In conclusion, we have developed a convenient method for the construction of *N*-methyl-4-ylidenethieno[2,3-*d*]-pyrimidines **7, 8, 14** and **15** by the reaction of *N*-methyl-4-(methylthio)thieno[2,3-*d*]pyrimidinium salts **6** and **13** with active methylene compounds. It is worth noting that very little study [29] has thus far been devoted to fused pyrimidinium salts such as compounds **6** and **13**. This methodology offers significant advantages with regard to the supply of ylidene-containing fused pyrimidines, which according to the literature may exhibit biological activities such as anti-inflammatory, anthelmintic, analgesic and anticonvulsive activities.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-302 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. The mass (70 eV, electron impact ionization) spectra were obtained on a JEOL JMS-D300 spectrometer. The elemental analyses were performed on a YANACO MT-6 CHN analyzer.

The Preparation of Compounds 4a,b from 3a,b and Methyl Iodide. A solution of **3a** [20] (1.68 g, 10 mmoles) or **3b** [21] (2.30 g, 10 mmoles), methyl iodide (5.68 g, 40 mmoles) and sodium (0.25 g, 11 mmoles) in anhydrous methanol (30 mL) was stirred at 50 °C overnight. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was isolated by filtration, washed with water, dried and purified by column chromatography on silica gel with chloroform–acetone (4:1) as the eluent to afford **4a,b**. In the case of the preparation of **4b**, the first elution with chloroform gave **4c** [23] (0.25 g, 10%).

5,6-Dihydro-2,3-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (4a). This compound was obtained as colorless columns (1.27 g, 70%), mp 149–151 °C (acetone–petroleum ether); ir (potassium bromide): ν 1650 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.50 (s, 3H, 2-Me), 3.23 (t, J = 8.4 Hz, 2H, 5-H), 3.38 (t, J = 8.4 Hz, 2H, 6-H), 3.49 ppm (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 23.3 (2-Me), 30.7 (3-Me), 30.8 (C-5), 30.9 (C-6), 116.2 (C-4a), 158.4 (C-4), 159.1 (C-2), 169.7 ppm (C-7a); ms: m/z 182 [M$^+$]. *Anal*. Calcd. for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.62; H, 5.55; N, 15.37.

5,6-Dihydro-3-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (4b). This compound was obtained as colorless needles (1.48 g, 60%), mp 156–158 °C (acetone–petroleum ether); ir (potassium bromide): ν 1650 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.29–3.33 (m, 2H, 5-H), 3.41–3.45 (m, 2H, 6-H), 3.42 (s, 3H, 3-Me), 7.47–7.49 ppm (m, 5H, aryl H); ^{13}C nmr (deuteriochloroform): δ 30.85 (C-5), 30.87 (C-6), 34.1 (3-Me), 117.1 (C-4a), 128.0, 128.8, 130.4, 134.6 (C aryl), 158.7 (C-4), 160.4 (C-2), 170.0 ppm (C-7a); ms: m/z 244 [M$^+$]. *Anal*. Calcd. for $C_{13}H_{12}N_2OS$+0.2H_2O: C, 62.98; H, 5.04; N, 11.30. Found: C, 62.95; H, 5.09; N, 11.29.

The Preparation of Compound 10 from 9 and Methylamine Hydrochloride. A mixture of **9** [28] (0.72 g, 5 mmoles) and methylamine hydrochloride (0.68 g, 10 mmoles) in pyridine (5 mL) was stirred at 130 °C for 3 hours in a sealed tube. After removal of pyridine *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from acetone–petroleum ether to afford 4,5-dihydro-2-(methylamino)-3-thiophenecarboxamide (**10**). This compound was obtained as colorless scales (0.59 g, 75%), mp 125–126 °C; ir (potassium bromide): ν 3400, 3200 (NH), 1665 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.44–2.57 (m, 2H, 4-H), 2.91 (t, J = 7.8 Hz, 0.4H, 3-H), 2.97 (d, J = 4.9 Hz, 0.4H, 5-H), 3.12–3.30 (m, 1.6H, 5-H), 3.17 (s, 1.2H, NMe), 3.18 (s, 1.8H, NH*Me*), 3.47–3.51 (m, 0.6H, N*H*Me), 4.83 (br. s, 0.4H, $CONH_2$), 5.72 (br. s, 0.6H, $CONH_2$), 7.76 (br. s, 0.6H, $CONH_2$), 8.56 ppm (br. s, 0.4H, $CONH_2$); ^{13}C nmr (deuteriochloroform): δ 30.02, 30.04 (C-4), 31.1, 33.1 (C-5), 33.3 (C-3), 43.9 (NMe), 53.8 (NHMe), 88.1 (C-3), 168.7, 170.6 (C-2), 173.0 ppm (C=O); ms: m/z 158 [M$^+$]. *Anal*. Calcd. for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.71. Found: C, 45.38; H, 6.31; N, 17.86.

The Preparation of Compounds 11a,b from 10. A mixture of **10** (1.58 g, 10 mmoles) and acetic anhydride (10 mL) or benzoyl chloride (1.55 g, 11 mmoles) in pyridine (20 mL) was stirred at 80 °C (in the case of the preparation of **11a**) or 60 °C (in the case of the preparation of **11b**) for 2 hours. Further processing of the resulting mixture is described in the following paragraphs.

(A) After removal of the solvent *in vacuo*, the residue was recrystallized from acetone to give **11a**.

(B) To a reaction mixture was added cold water with stirring. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from acetone to give **11b**.

5,6-Dihydro-1,2-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-one (11a). This compound was obtained as colorless prisms (1.24 g, 68%), mp 196–200 °C; ir (potassium bromide): ν 1615 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.47 (s, 3H, 2-Me), 3.28 (t, J = 8.5 Hz, 2H, 5-H), 3.46 (t, J = 8.5 Hz, 2H, 6-H), 3.57 ppm (s, 3H, 1-Me); ^{13}C nmr (deuteriochloroform): δ 22.0 (2-Me), 32.4 (C-5), 32.5 (C-6), 38.9 (1-Me), 117.4 (C-4a), 157.1 (C-7a), 158.5 (C-2), 166.2 ppm (C-4); ms: m/z 182 [M$^+$]. *Anal*. Calcd. for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.73; H, 5.56; N, 15.37.

5,6-Dihydro-1-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(1*H*)-one (11b). This compound was obtained as colorless needles (1.87 g, 77%), mp 178–179 °C; ir (potassium bromide): ν 1615 cm^{-1} (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.13 (t, J = 8.4 Hz, 2H, 5-H), 3.41 (s, 3H, 1-Me), 3.52 (t, J = 8.4 Hz, 2H, 6-H),

7.49–7.60 ppm (m, 5H, aryl H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 31.75 (C-5), 31.8 (C-6), 40.6 (1-Me), 117.0 (C-4a), 128.27, 128.29, 130.0, 133.6 (C aryl), 157.4 (C-7a), 159.4 (C-2), 164.7 ppm (C-4); ms: m/z 244 [M$^+$]. *Anal*. Calcd. for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 64.11; H, 5.11; N, 11.85.

The Preparation of Compounds 5a,b and 12a,b from 4a,b and/or 11a,b and Phosphorous Pentasulfide. A solution of **4a** (1.82 g, 10 mmoles), **4b** (2.44 g, 10 mmoles), **11a** (1.82 g, 10 mmoles) or **11b** (2.44 g, 10 mmoles) and phosphorous pentasulfide (2.66 g, 12 mmoles) in pyridine (20 mL) was refluxed for 6 hours (in the case of the preparation of **5a**,**b**) or stirred at 70 °C for 4 hours (in the case of the preparation of **12a,b**). After removal of pyridine *in vacuo*, cold water was added to the residue. The precipitate was isolated by filtration, washed with water, dried and purified by column chromatography on silica gel with chloroform (in the case of **5a,b**) or chloroform–acetone (4:1) (in the case of **12a,b**) as the eluent to afford **5a,b** and **12a,b**.

5,6-Dihydro-2,3-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-thione (5a). This compound was obtained as pale yellow needles (1.45 g, 73%), mp 186–187 °C (acetone); ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, 2-Me), 3.36–3.45 (m, 4H, 5- and 6-H), 3.96 ppm (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 24.7 (2-Me), 29.6 (C-5), 35.6 (C-6), 38.2 (3-Me), 132.9 (C-4a), 159.2 (C-2), 166.4 (C-7a), 177.4 ppm (C-4); ms: m/z 198 [M$^+$]. *Anal*. Calcd. for $C_8H_{10}N_2S_2$: C, 48.45; H, 5.08; N, 14.13. Found: C, 48.24; H, 5.06; N, 14.17.

5,6-Dihydro-3-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-thione (5b). This compound was obtained as pale yellow needles (2.04 g, 79%), mp 200–201 °C (acetone); ^{1}H nmr (deuteriochloroform): δ 3.41–3.46 (m, 2H, 5-H), 3.49–3.53 (m, 2H, 6-H), 3.83 (s, 3H, 3-Me), 7.26–7.53 ppm (m, 5H, aryl H); ^{13}C nmr (deuteriochloroform): δ 29.7 (C-5), 35.5 (C-6), 41.8 (3-Me), 127.9, 128.9, 130.6 (C aryl), 133.6 (C-4a), 135.0 (C aryl), 160.7 (C-2), 166.4 (C-7a), 177.7 ppm (C-4); ms: m/z 259 [M$^+$]. *Anal*. Calcd. for $C_{13}H_{12}N_2S_2$: C, 59.97; H, 4.65; N, 10.76. Found: C, 59.90; H, 4.76; N, 10.63.

5,6-Dihydro-1,2-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-thione (12a). This compound was obtained as yellow columns (1.31 g, 66%), mp 199–203 °C (acetone–methylene chloride); ^{1}H nmr (deuteriochloroform): δ 2.56 (s, 3H, 2-Me), 3.47 (s, 4H, 5-H), 3.61 ppm (s, 3H, 1-Me); ^{13}C nmr (deuteriochloroform): δ 21.9 (2-Me), 31.3 (C-5), 36.3 (C-6), 39.9 (1-Me), 132.4 (C-4a), 153.4 (C-2), 154.3 (C-7a), 190.1 ppm (C-4); ms: m/z 198 [M$^+$]. *Anal*. Calcd. for $C_8H_{10}N_2S_2$: C, 48.45; H, 5.08; N, 14.13. Found: C, 48.24; H, 5.05; N, 14.11.

5,6-Dihydro-1-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(1*H*)-thione (12b). This compound was obtained as yellow prisms (2.22 g, 84%), mp 171–172 °C (acetone); ^{1}H nmr (deuteriochloroform): δ 3.50–3.57 (m, 4H, 5- and 6-H), 3.53 (s, 3H, 1-Me), 7.44–7.52 (m, 3H, aryl H), 7.55–7.57 ppm (m, 2H, aryl H); ^{13}C nmr (deuteriochloroform): δ 31.3 (C-5), 36.3 (C-6), 41.5 (1-Me), 128.7, 128.8, 130.7, 132.6 (C-aryl), 132.9 (C-4a), 154.5 (C-2), 154.6 (C-7a), 189.9 ppm (C-4); ms: m/z 260 [M$^+$]. *Anal*. Calcd. for $C_{13}H_{12}N_2S_2$+0.25H_2O: C, 58.95; H, 4.76; N, 10.58. Found: C, 59.02; H, 4.71; N, 10.52.

The Preparation of Compounds 6a,b and 13a,b from 5a,b and/or 12a,b and Methyl Iodide. A solution of **5a** (1.98 g, 10 mmoles), **12a** (1.98 g, 10 mmoles) and **12b** (2.60 g, 10 mmoles) in methyl iodide (60 mL) (in the case of the preparation of **6a**, **13a** and **13b**) or **5b** (2.60 g, 10 mmoles) and methyl iodide (60 mL) in tetrahydrofuran (60 mL) (in the case of the preparation of **6b**) was stirred at room temperature overnight. The precipitate was isolated by filtration, washed with acetone and dried. The crude products **6a,b** and **13a,b** was sufficiently pure to be used without further purification.

5,6-Dihydro-2,3-dimethyl-4-(methylthio)thieno[2,3-*d*]-pyrimidinium Iodide (6a). This compound was obtained as yellow needles (3.29 g, 97%), mp 167–169 °C dec.; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.69 (s, 3H, SMe), 2.83 (s, 3H, 2-Me), 3.64–3.68 (m, 2H, 5-H), 3.71–3.75 (m, 2H, 6-H), 4.06 ppm (s, 3H, 3-Me); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.4 (SMe), 24.4 (2-Me), 31.4 (C-5), 32.4 (C-6), 40.9 (3-Me), 136.9 (C-4a), 154.1 (C-4), 164.0 (C-2), 183.1 ppm (C-7a); ms: m/z 213 [M-I]$^+$. *Anal*. Calcd. for $C_9H_{13}N_2IS_2$: C, 31.77; H, 3.85; N, 8.23. Found: C, 31.72; H, 3.86; N, 8.01.

5,6-Dihydro-3-methyl-4-(methylthio)-2-phenylthieno[2,3-*d*]-pyrimidinium Iodide (6b). This compound was obtained as yellow needles (3.01 g, 75%), mp 177–178 °C dec.; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.83 (s, 3H, SMe), 3.72–3.82 (m, 4H, 5- and 6-H), 3.95 (s, 3H, 3-Me), 7.62–7.72 (m, 3H, aryl H), 7.77–7.80 ppm (m, 2H, aryl H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.4 (SMe), 31.7 (C-5), 32.3 (C-6), 44.3 (3-Me), 128.8, 129.1, 131.8, 132.5 (C aryl), 136.8 (C-4a), 155.6 (C-4), 162.4 (C-2), 182.9 ppm (C-7a); ms: m/z 275 [M-I]$^+$. *Anal*. Calcd. for $C_{14}H_{15}N_2IS_2$: C, 41.80; H, 3.76; N, 6.96. Found: C, 41.78; H, 3.90; N, 6.85.

5,6-Dihydro-1,2-dimethyl-4-(methylthio)thieno[2,3-*d*]-pyrimidinium Iodide (13a). This compound was obtained as colorless prisms (3.28 g, 94%), mp 195–196 °C dec.; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.70 (s, 3H, 2-Me), 2.80 (s, 3H, SMe), 3.41 (t, J = 8.3 Hz, 2H, 5-H), 3.85 (t, J = 8.3 Hz, 2H, 6-H), 3.88 ppm (s, 3H, 1-Me); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.5 (2-Me), 22.3 (SMe), 31.2 (C-5), 34.0 (C-6), 42.4 (1-Me), 128.8 (C-4a), 160.4 (C-2), 165.7 (C-4), 168.3 ppm (C-7a); ms: m/z 213 [M-I]$^+$. *Anal*. Calcd. for $C_9H_{13}N_2IS_2$: C, 31.77; H, 3.85; N, 8.23. Found: C, 31.67; H, 3.75; N, 8.21.

5,6-Dihydro-1-methyl-4-(methylthio)-2-phenylthieno[2,3-*d*]-pyrimidinium Iodide (13b). This compound was obtained as yellow prisms (3.64 g, 91%), mp 191–192 °C dec.; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.69 (s, 3H, SMe), 3.49 (t, J = 8.4 Hz, 2H, 5-H), 3.81 (s, 3H, 1-Me), 3.92 (t, J = 8.4 Hz, 2H, 6-H), 7.63–7.70 (m, 3H, aryl H), 7.82–7.84 ppm (m, 2H, aryl H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.7 (SMe), 31.1 (C-5), 34.2 (C-6), 44.3 (1-Me), 128.7, 129.4 (C aryl), 129.6 (C-4a), 131.2, 131.8 (C aryl), 158.8 (C-2), 165.6 (C-4), 169.2 ppm (C-7a); ms: m/z 275 [M-I]$^+$. *Anal*. Calcd. for $C_{14}H_{15}N_2IS_2$: C, 41.80; H, 3.76; N, 6.96. Found: C, 41.75; H, 3.73; N, 6.91.

The Preparation of Compounds 7a,b, 8a,b and/or 14a,b, 15a,b from 6a,b and/or 13a,b and Active Methylene Compounds. To an ice-cooled and stirred solution of malononitrile (0.66 g, 10 mmoles) or ethyl cyanoacetate (1.13 g, 10 mmoles) in tetrahydrofuran (30 mL) was added 60% sodium hydride (0.40 g, 10 mmoles). Stirring was continued at room temperature until the evolution of gas ceased. To the obtained solution was added **6a** (1.70 g, 5 mmoles), **6b** (2.01 g, 5 mmoles), **13a** (1.70 g, 5 mmoles) or **13b** (2.01 g, 5 mmoles) with stirring and ice-cooling, and then the mixture was stirred at room temperature for 3 hours. After removal of the solvent *in vacuo*, cold water was added to the residue. Further processing of the resulting mixture is described in the following paragraphs.

(A) The resulting mixture was extracted with ethyl acetate (60 mL). The extract was dried over anhydrous sodium sulfate and

concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform–acetone (4:1) as the eluent to afford **7a** and **8a**.

(B) The precipitate was isolated by filtration, washed with water, dried and recrystallized from an appropriate solvent to yield **7b**, **8b**, **14a,b** and **15a,b**.

(5,6-Dihydro-2,3-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)propanedinitrile (7a). This compound was obtained as pale yellow plates (0.59 g, 51%), mp 219–220 °C dec. (acetone); ir (potassium bromide): ν 2200, 2190 cm^{-1} (CN); ^1H nmr (deuteriochloroform): δ 2.26 (s, 3H, 2-Me), 3.46 (t, J = 8.4 Hz, 2H, 5-H), 3.68 (t, J = 8.4 Hz, 2H, 6-H), 3.83 ppm (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 24.1 (2-Me), 30.4 (C-5), 33.3 (C-6), 42.0 (3-Me), 42.2 [=*C*$(CN)_2$], 118.4 (CN), 120.9 (C-4a), 155.3 (C-4), 160.2 (C-2), 173.4 ppm (C-7a); ms: m/z 230 [M^+]. *Anal*. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.38; H, 4.42; N, 24.39.

(5,6-Dihydro-3-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)propanedinitrile (7b). This compound was obtained as yellow plates (0.99 g, 68%), mp 261–262 °C dec. (chloroform–methanol); ir (potassium bromide): ν 2200, 2190 cm^{-1} (CN); ^1H nmr (deuteriochloroform): δ 3.51 (t, J = 8.5 Hz, 2H, 5-H), 3.76 (t, J = 8.5 Hz, 2H, 6-H), 3.78 (s, 3H, 3-Me), 7.52–7.56 (m, 2H, aryl H), 7.57–7.63 ppm (m, 3H, aryl H); ^{13}C nmr (deuteriochloroform): δ 30.6 (C-5), 33.2 (C-6), 44.3 [=*C*$(CN)_2$], 46.9 (3-Me), 118.1 (CN), 120.6 (C-4a), 128.9, 129.3, 132.2, 133.2 (C aryl), 156.3 (C-4), 161.7 (C-2), 173.3 ppm (C-7a); ms: m/z 291 [M^+]. *Anal*. Calcd. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.84; H, 4.22; N, 19.13.

(5,6-Dihydro-1,2-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-ylidene)propanedinitrile (14a). This compound was obtained as pale yellow needles (0.51 g, 44%), mp 293–294 °C dec. (chloroform); ir (potassium bromide): ν 2195, 2180 cm^{-1} (CN); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.48 (s, 3H, 2-Me), 3.49–3.52 (m, 2H, 5-H), 3.57–3.61 (m, 2H, 6-H), 3.62 ppm (s, 3H, 1-Me); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 21.2 (2-Me), 31.8 (C-5), 32.4 (C-6), 40.0 (1-Me), 48.1 [=*C*$(CN)_2$], 115.2 (C-4a), 118.0, 119.2 (CN), 157.2 (C-2), 159.7 (C-4), 160.8 ppm (C-7a); ms: m/z 230 [M^+]. *Anal*. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.43; H, 4.38; N, 24.37.

(5,6-Dihydro-1-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(1*H*)-ylidene)propanedinitrile (14b). This compound was obtained as pale yellow plates (0.63 g, 43%), mp 316–317 °C dec. (chloroform); ir (potassium bromide): ν 2200, 2180 cm^{-1} (CN); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.51 (s, 3H, 1-Me), 3.57–3.61 (m, 2H, 5-H), 3.64–3.68 (m, 2H, 6-H), 7.53–7.59 (m, 3H, aryl H), 7.63–7.65 ppm (m, 2H, aryl H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 31.8 (C-5), 32.3 (C-6), 41.6 (1-Me), 48.9 [=*C*$(CN)_2$], 115.8 (C-4a), 117.8, 118.9 (CN), 128.2, 128.5, 130.5, 132.1 (C aryl), 156.9 (C-2), 159.4 (C-4), 161.4 ppm (C-7a); ms: m/z 291 [M^+]. *Anal*. Calcd. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.79; H, 4.18; N, 19.12.

Ethyl cyano(5,6-dihydro-2,3-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)acetate (8a). This compound was obtained as yellow columns (0.96 g, 69%), mp 163–164 °C (acetone); ir (potassium bromide): ν 2190 (CN), 1645 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.31 (t, J = 7.2 Hz, 3H, OCH_2*Me*), 2.68 (s, 3H, 2-Me), 3.47–3.51 (m, 2H, 5-H), 3.55–3.59 (m, 2H, 6-H), 3.72 (s, 3H, 3-Me), 4.19 ppm (q, J = 7.2 Hz, 2H, O*C*H_2Me); ^{13}C nmr (deuteriochloroform): δ 14.7 (OCH_2*Me*), 24.2 (2-Me), 30.7 (C-5), 33.4 (C-6), 42.3 (3-Me), 60.0 (O*C*H_2Me), 60.4 [=*C*(CN)CO_2CH_2Me], 121.0 (CN), 126.3 (C-4a), 155.0 (C-4), 160.4 (C-2), 166.5 (C=O), 175.7 ppm (C-7a); ms: m/z 277 [M^+]. *Anal*. Calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.33; H, 5.54; N, 15.11.

Ethyl cyano(5,6-dihydro-3-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)acetate (8b). This compound was obtained as yellow needles (1.42 g, 84%), mp 204–206 °C (acetone); ir (potassium bromide): ν 2190 (CN), 1660 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.34 (t, J = 7.0 Hz, 3H, OCH_2*Me*), 3.53 (t, J = 8.3 Hz, 2H, 5-H), 3.68 (t, J = 8.3 Hz, 2H, 6-H), 3.69 (s, 3H, 3-Me), 4.24 (q, J = 7.0 Hz, 2H, O*C*H_2Me), 7.35–7.59 (m, 3H, aryl H), 7.67–7.69 ppm (m, 2H, aryl H); ^{13}C nmr (deuteriochloroform): δ 14.7 (OCH_2*Me*), 30.9 (C-5), 33.4 (C-6), 47.1 (3-Me), 60.2 (O*C*H_2Me), 63.3 [=*C*(CN)CO_2CH_2Me], 120.8 (CN), 125.6 (C-4a), 129.0, 129.1, 131.8, 133.7 (C aryl), 155.7 (C-4), 161.9 (C-2), 166.5 (C=O), 175.4 ppm (C-7a); ms: m/z 339 [M^+]. *Anal*. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.73; H, 5.22; N, 12.10.

Ethyl cyano(5,6-dihydro-1,2-dimethylthieno[2,3-*d*]pyrimidin-4(1*H*)-ylidene)acetate (15a). This compound was obtained as yellow needles (1.01 g, 73%), mp 231–232 °C (acetone–methylene chloride); ir (potassium bromide): ν 2190 (CN), 1690 cm^{-1} (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.18 (t, J = 7.2 Hz, 3H, OCH_2*Me*), 2.49 (s, 3H, 2-Me), 3.26–3.30 (m, 2H, 5-H), 3.50 (t, J = 8.2 Hz, 2H, 6-H), 3.64 (s, 3H, 1-Me), 4.30 ppm (q, J = 7.2 Hz, 2H, O*C*H_2Me); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.4 (OCH_2*Me*), 21.5 (2-Me), 32.3 (C-5), 34.8 (C-6), 40.1 (1-Me), 58.5 (O*C*H_2Me), 71.7 [=*C*(CN)CO_2CH_2Me], 117.5 (C-4a), 121.2 (CN), 155.6 (C-2), 159.1 (C-4), 161.4 (C-7a), 164.9 ppm (C=O); ms: m/z 277 [M^+]. *Anal*. Calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.33; H, 5.36; N, 15.01.

Ethyl cyano(5,6-dihydro-1-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4(1*H*)-ylidene)acetate (15b). This compound was obtained as yellow needles (1.49 g, 88%), mp 187–188 °C (acetone); ir (potassium bromide): ν 2190 (CN), 1670 cm^{-1} (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.19 (t, J = 7.0 Hz, 3H, OCH_2*Me*), 3.28–3.52 (m, 2H, 5-H), 3.54 (s, 3H, 1-Me), 3.55–3.59 (m, 2H, 6-H), 4.05 (q, J = 7.0 Hz, 2H, O*C*H_2Me), 7.54–7.61 (m, 3H, aryl H), 7.67–7.69 ppm (m, 2H, aryl H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.4 (OCH_2*Me*), 32.4 (C-5), 34.6 (C-6), 41.7 (1-Me), 58.7 (O*C*H_2Me), 72.7 [=*C*(CN)CO_2CH_2Me], 118.0 (C-4a), 121.0 (CN), 128.4, 129.0, 130.6, 132.6 (C aryl), 155.5 (C-2), 158.8 (C-4), 162.1 (C-7a), 164.9 ppm (C=O); ms: m/z 339 [M^+]. *Anal*. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.53; H, 5.11; N, 12.15.

The Preparation of Compound 16 from 10 and Acetyl Chloride. A mixture of **10** (1.58 g, 10 mmoles) and acetyl chloride (0.87 g, 11 mmoles) in pyridine (10 mL) was stirred at 40 °C for 3 hours, and then cold water was added to the reaction mixture. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from acetone to afford 4,5-dihydro-2-(*N*-methylacetamido)-3-thiophenecarboxamide **(16).** This compound was obtained as colorless prisms (1.28 g, 64%), mp 143–144 °C; ir (potassium bromide): ν 3320, 3300, 3140 (NH), 1680, 1650 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.14 (s, 3H, COMe), 3.13 (s, 3H, NMe), 3.17–3.22 (m, 2H, 4-H), 3.25–3.29 (m, 2H, 5-H), 5.81 ppm (br. s, 2H, NH_2); ^{13}C nmr (deuteriochloroform): δ 21.2 (CO*Me*), 29.5 (C-4), 34.7 (NMe), 35.4 (C-5), 124.5 (C-3), 151.4 (C-2), 136.6, 170.5 ppm (C=O); ms: m/z 158 [M^+]. *Anal*. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.99; H, 6.08; N, 14.16.

The Preparation of Compound 11a from 16. Compound **16** (2.00 g, 10 mmole) was heated at 160 ˚C for 1 hour. The crude product was recrystallized from acetone to afford **11a** (1.76 g, 97%). The melting point and ir spectrum of this compound coincided with an authentic sample prepared from **10** and acetic anhydride.

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