Synthesis of 5,6-Dihydrothieno(and furo)pyrimidines Bearing an Active Methine Group at the 4-Position

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The reactions of 2-benzamido-4,5-dihydro-3-thiophene(and -3-furan)carbonitriles (**1a-c** and **4a-c**) with ethyl acetoacetate in the presence of tin(IV) chloride and triethylamine provided the corresponding ethyl 2-(5,6-dihydro-2-phenylthieno(and furo)[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoates (**2a-c** and **9a-c**). Similarly, compounds **1a-c** and **4a-c** reacted with dialkyl malonates to give the corresponding dialkyl(5,6-dihydro-2-phenylthieno(and furo)[2,3-*d*]pyrimidin-4-yl)propanedioates (**5a-c, 6a-c, 10a-c** and **11a-c**).

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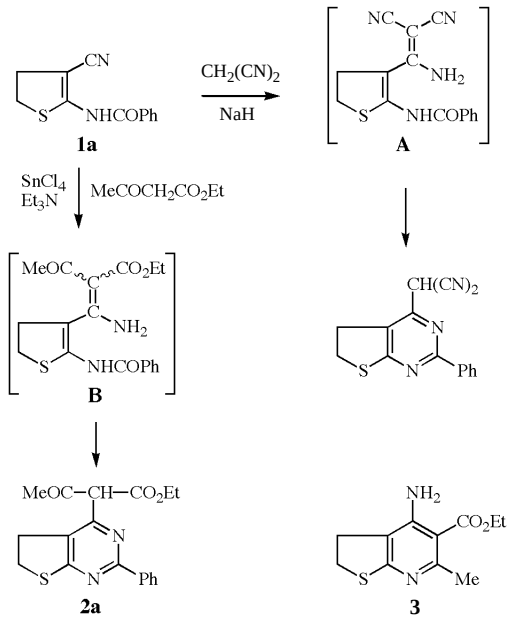
In search of new methods [1-4] for synthesizing 5,6-dihydrothieno[2,3-*d*]pyrimidines from 2-amino-4,5-dihydro-3-thiophenecarbonitriles, we showed that 2-benzamido-4,5-dihydro-3-thiophenecarbonitrile (**1a**) [5] reacts with malononitrile in the presence of sodium hydride to give the malononitrile derivative [3]. This reaction probably occurs *via* addition of the cyano group of **1a** to malononitrile to form the intermediate β-enaminonitrile **A**, which undergoes cyclization to give the malononitrile derivative. However, when **1a** was treated with active methylene compounds lacking cyano group such as ethyl acetoacetate and diethyl malonate under the same conditions, no reaction occurred, and **1a** was recovered unchanged. Hence, in order to overcome this limitation, we attempted to find the reaction conditions for the reaction of **1a** with ethyl acetoacetate.

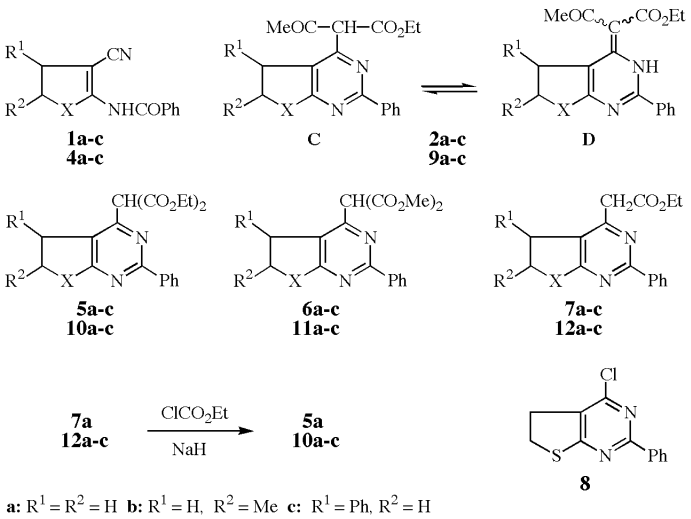
Scheme 1



Tin(IV) chloride has been shown to facilitate the carbon-carbon bond formation between the cyano group of nitriles and active methylene compounds [6-12]. This reaction suggests the possibility that when **1a** is treated with ethyl acetoacetate in the presence of tin(IV) chloride, the intermediate β-enaminoester **B** initially formed may undergo cyclization to furnish the expected **2a**. Although the reaction of **1a** with ethyl acetoacetate in the presence of tin(IV) chloride gave the 4-amino-2,3-dihydrothieno[2,3-*b*]-pyridine derivative **3** [13] in 44% yield, the desired **2a** could not be isolated. Iimori and co-workers [7] reported that this carbon-carbon bond formation is successfully effected by using a combination of Lewis acid and tertiary amine. Therefore, we examined the reaction of **1a** with ethyl acetoacetate in the presence of tin(IV) chloride and triethylamine, and found that the reaction proceeded smoothly to give **2a**. The present paper deals with the reaction of **1a-c** and 2-benzamido-4,5-dihydro-3-furancarbonitriles **4a-c** [14] with active methylene compounds.

When a mixture of **1a-c**, ethyl acetoacetate (1.5 equivalents), triethylamine (1.5 equivalents) and tin(IV) chloride (3 equivalents) in 1,2-dichloroethane was refluxed, **2a-c** were obtained in moderate yields. In a similar fashion, the reaction of **1a-c** with diethyl and dimethyl malonates resulted in the formation of the corresponding malonic ester derivatives **5a-c** and **6a-c** in good yields. The ^{1}H nmr spectra of **2a** and **2b** in deuteriochloroform show two singlets at near δ 2.00 and δ 2.40 for acetyl groups, a singlet at near δ 4.80 for a methine and a singlet at near δ 13.20 for a chelated amino group, whereas **2c** appears as a singlet δ 2.20 for an acetyl group and a singlet at δ 4.33 for a methine group, and the signal due to an amino group is not observed. These observations indicate that **2a** and **2b** exist as a tautomeric mixture of the 5,6-dihydrothieno[2,3-*d*]-pyrimidine forms **C** and the 3,4,5,6-tetrahydrothieno-[2,3-*d*]pyrimidine forms **D** in deuteriochloroform, while **2c** exists as the 5,6-dihydrothieno[2,3-*d*]pyrimidine form **C**. Compounds **2a-c** were easily hydrolyzed to the corresponding ethyl acetate derivatives **7a-c** when heated with aqueous triethylamine. These products **2a-c, 5a-c, 6a-c** and **7a-c** were characterized by elemental analyses and spectral data. The reaction of **7a** with ethyl chloroformate in the presence of sodium hydride afforded **5a** in 60% yield. Compound **5a** was also obtained by treatment of 4-chloro-5,6-dihydro-2-phenylthieno[2,3-*d*]pyrimidine (**8**) [1] with diethyl malonate and sodium hydride.

Scheme 2



a: $R^1 = R^2 = H$ **b:** $R^1 = H$, $R^2 = Me$ **c:** $R^1 = Ph$, $R^2 = H$
X = S: **1, 2, 5, 6, 7** X = O: **4, 9, 11, 12**

Subsequently, the reactions of **4a-c** with ethyl acetoacetate or diethyl and dimethyl malonates under the same conditions gave the corresponding ethyl acetoacetate derivatives **9a-c** or malonate derivatives **10a-c** and **11a-c**. On hydrolysis with aqueous triethylamine, **9a-c** provided the corresponding ethyl acetate derivatives **12a-c** in good yields. The ^{1}H nmr spectra of **9a-c** in deuteriochloroform indicate that **9a-c** consist of a tautomeric mixture of the dihydrofuro[2,3-*d*]-pyrimidine forms **C** and the tetrahydrofuro[2,3-*d*]pyrimidine forms **D**. Elemental analyses and the spectral data of **9-12** are consistent with the proposed structures. Compounds **12a-c** were converted into **10a-c** by treatment with ethyl chloroformate and sodium hydride.

Finally, we synthesized **11a** by an alternative route. Generally, *o*-acylaminonitriles undergo acid-catalyzed intramolecular cyclization on treatment with an acid to give condensed 4(3*H*)-pyrimidinones [1,15-17]. Compound **4a** was cyclized to 5,6-dihydro-2-phenylfuro[2,3-*d*]-pyrimidin-4(3*H*)-one (**13**) by heating it with benzoic acid in ethyl orthoformate. Chlorination of **13** with thionyl chloride and *N*,*N*-dimethylformamide [18, 19] provided 4-chloro-5,6-dihydro-2-phenylfuro[2,3-*d*]pyrimidine (**14**) in 50% yield. The reaction of **14** with dimethyl malonate led to the desired **11a**. This method has obviously proved to have several disadvantages such as a long reaction time and the low yield.

In conclusion, the reactions of **1** and **4** with active methylene compounds in the presence of tin(IV) chloride and triethylamine seem to provide an efficient method for the preparation of the 5,6-dihydrothieno(and furo)pyrimidines bearing an active methine group at the 4-position.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-302 spectrometer. The ^{1}H nmr spectra were recorded on a HITACHI R-90 H spectrometer (90 MHz) or a JEOL JNM-MH-100 spectrometer (100 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Elemental analyses were performed on a HERAUS CHNO-RAPID analyzer.

General Procedure for the Preparation of 5,6-Dihydro-2-phenylthieno(and furo)[2,3-*d*]pyrimidines **2, 5, 6, 9, 10** and **11**.

Tin(IV) chloride (7.82 g, 30 mmoles) was added dropwise to an ice-cooled and stirred solution of **1** or **4** (10 mmoles) and ethyl acetoacetate (1.95 g, 15 mmoles), diethyl malonate (2.40 g, 15 mmoles) or dimethyl malonate (1.98 g, 15 mmoles) and triethylamine (1.52 g, 15 mmoles) in 1,2-dichloroethane (10 ml). After the mixture had been refluxed for 5 hours, anhydrous sodium carbonate (10 g) and a saturated aqueous sodium carbonate solution (5 ml) were successively added to the reaction mixture with stirring and ice-cooling. The solid was removed by filtration and washed with hot chloroform. The combined filtrates were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with chloroform as the eluent to give **2, 5, 6, 9, 10** and **11**.

Ethyl 2-(5,6-Dihydro-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**2a**).

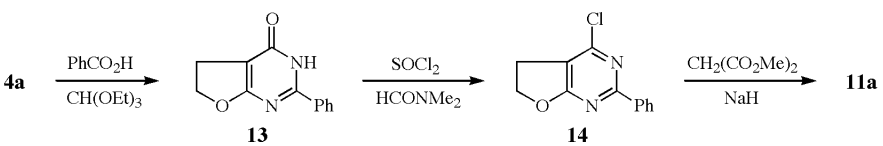
This compound was obtained as colorless needles (1.90 g, 56%), mp 133-134° (acetone-petroleum ether); ir (potassium bromide): ν 1725 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (t, J = 7 Hz, 1.5H, $CO_2CH_2CH_3$), 1.29 (t, J = 7 Hz, 1.5H, $CO_2CH_2CH_3$), 2.01 (s, 1.5H, $COCH_3$), 2.37 (s, 1.5H, $COCH_3$), 3.19-3.40 (m, 4H, 5-H, 6-H), 4.23 (q, J = 7 Hz, 1H, $CO_2CH_2CH_3$), 4.28 (q, J = 7 Hz, 1H, $CO_2CH_2CH_3$), 4.82 (s, 0.5H, methine H), 7.40-7.54 (m, 3H, aromatic H), 8.18-8.44 (m, 2H, aromatic H), 13.25 ppm (s, 0.5H, NH).

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.01; H, 5.41; N, 8.28.

Ethyl 2-(5,6-Dihydro-6-methyl-2-phenylthieno[2,3-*d*]-pyrimidin-4-yl)-3-oxobutanoate (**2b**).

This compound was obtained as colorless needles (1.99 g, 56%), mp 113-114° (acetone-petroleum ether); ir (potassium bromide): ν 1730 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (t, J = 7 Hz, 1.5H, $CO_2CH_2CH_3$), 1.29 (t, J = 7 Hz, 1.5H, $CO_2CH_2CH_3$), 1.50 (d, J = 7 Hz, 1.5H, 6-CH_3), 1.51 (d, J = 7 Hz, 1.5H, 6-CH_3), 1.99 (s, 1.5H, $COCH_3$), 2.37 (s, 1.5H, $COCH_3$), 2.70-3.06 (m, 1H, 5-H), 3.14-3.56 (m, 1H, 5-H), 3.87-4.41 (m, 1H, 6-H), 4.22 (q, J = 7Hz, 1H, $CO_2CH_2CH_3$), 4.28 (q, J = 7 Hz, 1H, $CO_2CH_2CH_3$), 4.84

Scheme 3



(s, 0.5H, methine H), 7.40-7.55 (m, 3H, aromatic H), 8.16-8.45 (m, 2H, aromatic H), 13.23 ppm (s, 0.5H, NH).

Anal. Calcd. for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: C, 64.02; H, 5.71; N, 7.99.

Ethyl 2-(5,6-Dihydro-2,5-diphenylthieno[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**2c**).

This compound was obtained as colorless needles (1.68 g, 40%), mp 139-141° (acetone-petroleum ether); ir (potassium bromide): ν 1729, 1720 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 2.20 (s, 3H, $COCH_3$), 3.29 (dd, J = 5.5, 11 Hz, 1H, 6-H), 3.87 (dd, J = 9, 11 Hz, 1H, 6-H), 4.00 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.33 (s, 1H, methine H), 4.74 (dd, J = 5.5, 9 Hz, 1H, 5-H), 7.16-7.52 (m, 8H, aromatic H), 8.35-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69. Found: C, 68.99; H, 5.39; N, 6.83.

Diethyl (5,6-Dihydro-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)-propanedioate (**5a**).

This compound was obtained as colorless needles (3.38 g, 91%), mp 93-94° (methylene chloride-petroleum ether); ir (potassium bromide): ν 1735 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7 Hz, 6H, $2xCO_2CH_2CH_3$), 3.03-3.60 (m, 4H, 5-H, 6-H), 4.29 (q, J = 7 Hz, 4H, $2xCO_2CH_2CH_3$), 4.86 (s, 1H, methine H), 7.31-7.47 (m, 3H, aromatic H), 8.34-8.46 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.31; H, 5.50; N, 7.57.

Diethyl (5,6-Dihydro-6-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)propanedioate (**5b**).

This compound was obtained as colorless prisms (3.48 g, 90%), mp 59-60° (diethyl ether-petroleum ether); ir (potassium bromide):ν 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7 Hz, 6H, $2xCO_2CH_2CH_3$), 1.51 (d, J = 7 Hz, 3H, 6-CH_3), 2.93 (dd, J = 6, 16 Hz, 1H, 5-H), 3.41 (dd, J = 7.5, 16 Hz, 1H, 5-H), 3.90-4.13 (m, 1H, 6-H), 4.29 (q, J = 7 Hz, 4H, $2xCO_2CH_2CH_3$), 4.87 (s, 1H, methine H), 7.34-7.51 (m, 3H, aromatic H), 8.29-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.34; H, 5.82; N, 7.38.

Diethyl (5,6-Dihydro-2,5-diphenylthieno[2,3-*d*]pyrimidin-4-yl)-propanedioate (**5c**).

This compound was obtained as colorless prisms (3.95 g, 88%), mp 132-133° (acetone-petroleum ether); ir (potassium bromide): ν 1755, 1740 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ l.13 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.21 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 3.29 (dd, J = 5.5, 11 Hz, 1H, 6-H), 3.76-4.26 (m, 5H, 6-H, $2xCO_2CH_2CH_3$), 4.35 (s, 1H, methine H), 4.76 (dd, J = 5.5, 9 Hz, 1H, 5-H), 7.13-7.51 (m, 8H, aromatic H), 8.35-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{25}H_{24}N_2O_4S$: C, 66.95; H, 5.39; N, 6.25. Found: C, 66.93; H, 5.43; N, 6.30.

Dimethyl (5,6-Dihydro-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)-propanedioate (**6a**).

This compound was obtained as colorless needles (2.77 g, 80%), mp 123-124° (acetone-petroleum ether); ir (potassium bromide): ν 1740 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.20-3.50 (m, 4H, 5-H, 6-H), 3.82 (s, 6H, $2xCO_2CH_3$), 4.90 (s, 1H, methine H), 7.38-7.47 (m, 3H, aromatic H), 8.32-8.43 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.34; H, 4.74; N, 8.24.

Dimethyl (5,6-Dihydro-6-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)propanedioate (**6b**).

This compound was obtained as colorless prisms (2.95 g, 82%), mp 103-104° (acetone-petroleum ether); ir (potassium bromide): 1760, 1725 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.51 (d, J= 6.5 Hz, 3H, 6-CH_3), 2.92 (dd, J = 6, 16 Hz, 1H, 5-H), 3.39 (dd, J = 7.5, 16 Hz, 1H, 5H), 3.82 (s, 6H, $2xCO_2CH_3$), 3.82-4.13 (m, 1H, 6-H), 4.91 (s, 1H, methine H), 7.36-7.50 (m, 3H, aromatic H), 8.33-8.44 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.35; H, 5.12; N, 7.93.

Dimethyl (5,6-Dihydro-2,5-diphenylthieno[2,3-*d*]pyrimidin-4-yl)propanedioate (**6c**).

This compound was obtained as colorless needles (3.49 g, 84%), mp 157-158° (acetone-petroleum ether); ir (potassium bromide): ν 1745 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.29 (dd, J = 5.5, 11 Hz, 1H, 6-H), 3.55 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 3.88 (dd, J = 9, 11 Hz, 1H, 6-H), 4.40 (s, 1H, methine H), 4.75 (dd, J = 5.5, 9 Hz, 1H, 5-H), 7.12-7.51 (m, 8H, aromatic H), 8.35-8.46 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66. Found: C, 65.78; H, 4.92; N, 6.74.

Ethyl 2-(5,6-Dihydro-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**9a**).

This compound was obtained as yellow columns (1.86 g, 57%), mp 98-100° (methylene chloride-petroleum ether); ir (potassium bromide): ν 1695 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (t, J = 7 Hz, 2.1 H, $CO_2CH_2CH_3$), 1.37 (t, J = 7 Hz, 0.9H, $CO_2CH_2CH_3$), 2.07 (s, 0.9H, $COCH_3$), 2.32 (s, 2.1H, $COCH_3$), 3.01-3.25 (m, 2H, 5-H), 4.13-4.42 (m, 2H, $CO_2CH_2CH_3$), 4.69 (t, J = 9 Hz, 2H, 6-H), 4.93 (s, 0.3H, methine H), 7.40-7.55 (m, 3H, aromatic H), 8.18-8.46 (m, 2H, aromatic H), 13.38 ppm (s, 0.7 H, NH).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.35; H, 5.59; N, 8.65.

Ethyl 2-(5,6-Dihydro-6-methyl-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**9b**).

This compound was obtained as colorless needles (1.44 g, 42%), mp 72-73° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1722 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.53 (d, J = 6.5 Hz, 3H, 6-CH_3), 2.07 (s, 0.6H, $COCH_3$), 2.33 (s, 2.4H, $COCH_3$), 2.69 (dd, J = 7, 16.5 Hz, 1H, 5-H), 3.24 (dd, J = 9, 16.5 Hz, 1H, 5-H), 4.13-4.60 (m, 2H, $CO_2CH_2CH_3$), 4.92 (s, 0.2H, methine H), 4.92-5.18 (m, 1H, 6-H), 7.40-7.66 (m, 3H, aromatic H), 8.18-8.52 (m, 2H, aromatic H), 13.37 ppm (s, 0.8H, NH).

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.81; H, 6.08; N, 8.44.

Ethyl 2-(5,6-Dihydro-2,5-diphenylfuro[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**9c**).

This compound was obtained as colorless needles (2.62 g, 65%), mp 152-153° (acetone-petroleum ether); ir (potassium bromide): ν 1740, 1722 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.04 (t, J =

7 Hz, 1.2H, $CO_2CH_2CH_3$), 1.15 (t, J = 7 Hz, 1.8H, $CO_2CH_2CH_3$), 1.58 (s, 1.2H, $COCH_3$), 2.20 (s, 1.8H, $COCH_3$), 4.09 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.34 (s, 0.4H, methine H), 4.37-4.79 (m, 2H, 6-H), 4.81-5.29 (m, 2H, 5-H), 6.95-7.59 (m, 8H, aromatic H), 8.24-8.48 (m, 2H, aromatic H), 12.93 ppm (s, 0.6H, NH).

Anal. Calcd. for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.41; H, 5.50; N, 6.90.

Diethyl (5,6-Dihydro-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)-propanedioate (**10a**).

This compound was obtained as colorless columns (2.85 g, 80%), mp 72-73° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1735 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7 Hz, 6H, 2x$CO_2CH_2CH_3$), 3.29 (t, J = 8.5 Hz, 2H, 5-H), 4.28 (q, J = 7 Hz, 4H, 2x$CO_2CH_2CH_3$), 4.70 (t, J = 8.5 Hz, 2H, 6-H), 4.92 (s, 1H, methine H), 7.36-7.48 (m, 3H, aromatic H), 8.35-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.12; H, 5.72; N, 7.99.

Diethyl (5,6-Dihydro-6-methyl-2-phenylfuro[2,3-*d*]pyrimidin-4-yl) propanedioate (**10b**).

This compound was obtained as colorless prisms (3.02 g, 82%), mp 89-90° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1750, 1740 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7 Hz, 6H, 2x$CO_2CH_2CH_3$), 1.54 (d, J = 6 Hz, 3H, 6-CH_3), 2.85 (dd, J = 7, 16.5 Hz, 1H, 5-H), 3.41 (dd, J = 9, 16.5 Hz, 1H, 5-H), 4.28 (q, J = 7 Hz, 4H, 2x$CO_2CH_2CH_3$), 4.94 (s, 1H, methine H), 4.94-5.19 (m, 1H, 6-H), 7.35-7.50 (m, 3H, aromatic H), 8.35-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.06; N, 7.59.

Diethyl (5,6-Dihydro-2,5-diphenylfuro[2,3-*d*]pyrimidin-4-yl)-propanedioate (**10c**).

This compound was obtained as colorless columns (3.83 g, 89%), mp 106-108° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1745, 1725 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.17 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.21 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 3.97-4.27 (m, 4H, 2x$CO_2CH_2CH_3$), 4.36 (s, 1H, methine H), 4.48 (dd, J = 7, 15 Hz, 1H, 6-H), 4.71 (dd, J = 8.5, 15 Hz, 1H, 6-H), 5.06 (dd, J = 7, 8.5 Hz, 1H, 5-H), 7.10-7.50 (m, 8H, aromatic H), 8.36-8.48 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.22; H, 5.64; N, 6.45.

Dimethyl (5,6-Dihydro-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)propanedioate (**11a**).

This compound was obtained as colorless scales (2.15 g, 66%), mp 124-125° (acetone-petroleum ether); ir (potassium bromide): ν 1755, 1742 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.26 (t, J = 8.5 Hz, 2H, 5-H), 3.81 (s, 6H, 2xCO_2CH_3), 4.70 (t, J = 8.5 Hz, 2H, 6-H), 4.95 (s, 1H, methine H), 7.35-7.49 (m, 3H, aromatic H), 8.33-8.44 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.16; H, 4.91; N, 8.63.

Dimethyl (5,6-Dihydro-6-methyl-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)propanedioate (**11b**).

This compound was obtained as colorless columns (2.28 g, 67%), mp 74-75° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1750, 1735 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.54 (d, J = 6.5 Hz, 3H, 6-CH_3), 2.83 (dd, J = 7, 16.5 Hz, 1H, 5-H), 3.39 (dd, J = 9, 16.5 Hz, 1H, 5-H), 3.81 (s, 6H, 2xCO_2CH_3), 4.94 (s, 1H, methine H), 4.94-5.19 (m, 1H, 6-H), 7.38-7.50 (m, 3H, aromatic H), 8.34-8.45 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.19; H, 5.35; N, 8.32.

Dimethyl (5,6-Dihydro-2,5-diphenylfuro[2,3-*d*]pyrimidin-4-yl)-propanedioate (**11c**).

This compound was obtained as colorless prisms (3.05 g, 75%), mp 108-109° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1745 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (s, 3H, CO_2CH_3), 3.66 (s, 3 H, CO_2CH_3), 4.41 (s, 1H, methine H), 4.44-4.81 (m, 2H, 6-H), 5.06 (dd, J = 7.5, 9 Hz, 1H, 5-H), 7.09-7.51 (m, 8H, aromatic H), 8.35-8.47 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.23; H, 5.01; N, 7.10.

The Reaction of **1a** with Ethyl Acetoacetate in the Presence of Tin(IV) Chloride.

To an ice-cooled and stirred solution of **1a** (2.30 g, 10 mmoles) and ethyl acetoacetate (2.60 g, 20 mmoles) in 1,2-dichloroethane (10 ml) was added tin(IV) chloride (7.82 g, 30 mmoles), and the resulting mixture allowed to reflux for 5 hours. After work-up as described for the preparation of 5,6-dihydro-2-phenylthieno(and furo)[2,3-*d*]pyrimidines, ethyl 4-amino-2,3-dihydro-6-methylthieno[2,3-*b*]pyridine-5-carboxylate (**3**) (1.05 g, 44%) was obtained. The melting point and ir spectrum of this compound coincided with those of an authentic sample [13].

General Procedure for the Preparation of Ethyl (5,6-Dihydro-2-phenylthieno(and furo)pyrimidin-4-yl)acetates **7** and **12**.

A solution of **2** or **9** (5 mmoles) and triethylamine (2 ml) in water (3 ml) was refluxed for 2 hours. The reaction mixture was acidified with 10% hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from an appropriate solvent to yield **7** and **12**.

Ethyl (5,6-Dihydro-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)acetate (**7a**).

This compound was obtained as colorless needles (1.45 g, 96%), mp 64-65° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1715 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 3.19-3.55 (m, 4H, 5-H, 6-H), 3.75 (s, 2H, $CH_2CO_2CH_2CH_3$), 4.20 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 7.38-7.48 (m, 3H, aromatic H), 8.33-8.45 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.19; H, 5.38; N, 9.34.

Ethyl (5,6-Dihydro-6-methyl-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)acetate (**7b**).

This compound was obtained as colorless prisms (1.18 g, 75%), mp 47-48° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.52 (d, J = 7 Hz, 3H, 6-CH_3), 2.96 (dd, J = 6.5, 16 Hz, 1H, 5-H), 3.46 (dd, J = 8, 16 Hz, 1H, 5-H), 3.75 (s, 2H, $CH_2CO_2CH_2CH_3$), 3.84-4.32 (m, 1H, 6-H), 4.20 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 7.39-7.50 (m, 3 H, aromatic H), 8.34-8.45 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.09; H, 5.81; N, 8.99.

Ethyl (5,6-Dihydro-2,5-diphenylthieno[2,3-*d*]pyrimidin-4-yl)-acetate (**7c**).

This compound was obtained as colorless needles (1.72 g, 91%), mp 120-121° (acetone-petroleum ether); ir (potassium bromide): ν 1727 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 3.29 (dd, J = 5.5, 11 Hz, 1H, 6-H), 3.37 (AB quartet, J = 16 Hz, 2H, $CH_2CO_2CH_2CH_3$), 3.89 (dd, J = 9, 11 Hz, 1H, 6-H), 4.08 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.84 (dd, J = 5.5, 9 Hz, 1H, 5-H), 7.14-7.52 (m, 8H, aromatic H), 8.37-8.48 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.36; N, 7.44. Found: C, 70.28; H, 5.41; N, 7.52.

Ethyl (5,6-Dihydro-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)acetate (**12a**).

This compound was obtained as colorless columns (1.31 g, 92%), mp 82-83° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1745 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 3.25 (t, J = 8.5 Hz, 2H, 5-H), 3.77 (s, 2H, $CH_2CO_2CH_2CH_3$), 4.21 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.70 (t, J = 8.5 Hz, 2H, 6-H), 7.36-7.48 (m, 3H, aromatic H), 8.35-8.46 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.58; H, 5.79; N, 9.93.

Ethyl (5,6-Dihydro-6-methyl-2-phenylfuro[2,3-*d*]pyrimidin-4-yl)acetate (**12b**).

This compound was obtained as pale yellow oil (1.39 g, 94%); ir (neat): ν 1733 (C=O) cm^{-1};^1H nmr (deuteriochloroform): δ 1.28 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.55 (d, J = 6 Hz, 3H, 6-CH_3), 2.83 (dd, J = 6.5, 16 Hz, 1H, 5-H), 3.40 (dd, J = 9, 16 Hz, 1H, 5-H), 3.76 (s, 2H, $CH_2CO_2CH_2CH_3$), 4.21 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.94-5.20 (m, 1H, 6-H), 7.34-7.51 (m, 3H, aromatic H), 8.32-8.49 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.15; H, 6.11; N, 9.27.

Ethyl (5,6-Dihydro-2,5-diphenylfuro[2,3-*d*]pyrimidin-4-yl)-acetate (**12c**).

This compound was obtained as colorless needles (1.41 g, 79%), mp 77-78° (diethyl ether-petroleum ether); ir (potassium bromide): ν 1723 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 3.42 (AB quartet, J = 16 Hz, 2H, $CH_2CO_2CH_2CH_3$), 4.09 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.46-4.88 (m, 2H, 6-H), 5.07 (dd, J = 7.5, 9 Hz, 1H, 5-H), 7.11-7.52 (m, 8H, aromatic H), 8.39-8.50 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.28; H, 5.65; N, 7.89.

General Procedure for the Preparation of **5a** and **10a-c** from **7a** and **12a-c**.

To an ice-cooled and stirred solution of **7a** or **12a-c** (5 mmoles) in tetrahydrofuran (10 ml) was added 60% sodium hydride (0.24 g, 6 mmoles). Stirring was continued at room temperature until the evolution of gas ceased, and then ethyl chloroformate (1.09 g, 10 mmloes) was added. The reaction mixture was stirred at 60° for 5 hours. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was acidified with 10% hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to give **5a** (1.11 g, 60%), **10a** (0.70 g, 39%), **10b** (0.54 g, 28%) and **10c** (1.09 g, 50%). These compounds were shown to be identical with samples prepared from diethyl malonate and **1a** or **4a-c** on the basis of a mixed melting point determination and a comparison of the ir spectra.

The Preparation of **5a** from Diethyl Malonate and 4-Chloro-5,6-dihydro-2-phenylthieno[2,3-*d*]pyrimidine (**8**).

To an ice-cooled and stirred solution of diethyl malonate (2.40 g, 15 mmoles) in dimethyl sulfoxide (10 ml) was added 60% sodium hydride (0.60 g, 15 mmoles). Stirring was continued at room temperature until the evolution of gas ceased, and then compound **8** (1.24 g, 5 mmoles) was added. The reaction mixture was stirred at 120° for 7 hours. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was acidified with 10% hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to give **5a** (0.62 g, 33%). The melting point and ir spectrum of this compound coincided with those of an authentic sample prepared from **1a** and diethyl malonate.

5,6-Dihydro-2-phenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**13**).

A solution of **4a** (2.14 g, 10 mmoles) and benzoic acid (1.22 g, 10 mmoles) in ethyl orthoformate (5 ml) was stirred at 145-150° for 6 hours. After removal of the solvent *in vacuo*, the residue was washed with diethyl ether and then recrystallized from methanol-chloroform (1:5) to give **13** (0.92 g, 43%) as colorless needles, mp 269-270°; ir (potassium bromide): ν 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.00 (t, J = 9 Hz, 2H, 5-H), 4.64 (t, J = 9 Hz, 2H, 6-H), 7.44-7.62 (m, 3H, aromatic H), 8.01-8.14 (m, 2H, aromatic H), 12.45 ppm (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.29; H, 4.68; N, 12.97.

4-Chloro-5,6-dihydro-2-phenylfuro[2,3-*d*]pyrimidine (**14**).

To a suspension of **13** (2.14 g, 10 mmoles) and *N,N*-dimethylformamide (4 ml) in 1,2-dichloroethane (30 ml) was added dropwise thionyl chloride (1.31 g, 11 mmoles) with stirring and ice-cooling. The mixture was refluxed for 3 hours. After removal of the solvent, cold water was added to the residue. The resulting mixture was basified with a saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on alumina with methylene chloride as the eluent to afford **14** (1.17 g, 50%) as colorless needles (acetone-petroleum ether), mp 163-165°;^1H nmr (deuteriochloroform): δ 3.30 (t, J = 8.5 Hz, 2H, 5-H), 4.74 (t, J = 8.5 Hz, 2H, 6-H), 7.25-7.61 (m, 3H, aromatic H), 8.34-8.45 ppm (m, 2H, aromatic H).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.99; H, 3.99; N, 12.01.

The Preparation of **11a** from Dimethyl Malonate and **14**.

A solution of dimethyl malonate (1.98 g, 15 mmoles), **14** (1.16 g, 5 mmoles) and 60% sodium hydride (0.60 g, 15 mmoles) in dimethyl sulfoxide (10 ml) was heated at 120° for 7 hours. After

work-up as described for the preparation of **5a** from diethyl malonate and **8**, compound **11a** (0.30 g, 18%) was obtained. The melting point and ir spectrum of this compound coincided with those of an authentic sample prepared from **4a** and dimethyl malonate.

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