Synthesis and Structure of 2-Substituted Thieno[3′,2′:5,6]pyrido-[4,3-*d*]pyrimidin-4(3*H*)-one Derivatives

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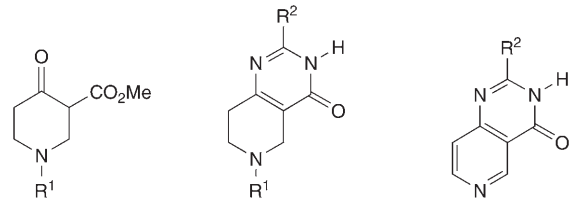
A series of new 2-substituted 3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **8** were synthesized *via* an aza-*Wittig* reaction. Phosphoranylideneamino derivatives **6a** or **6b** reacted with 4-chlorophenyl isocyanate to give carbodiimide derivatives **7a** or **7b**, respectively, which were further treated with amines or phenols to give compounds **8** in the presence of a catalytic amount of EtONa or K_2CO_3. The structure of 2-(4-chlorophenoxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**8j**) was comfirmed by X-ray analysis.

1. Introduction. – The derivatives of pyrido[4,3-*d*]pyrimidine have recently attracted the interest of pharmaceutical companies. Investigations of this family of compounds are stimulated by the fact that a number of publications have been concerned with the chemistry and the tumour-cell-growing activity of similar derivatives [1–5]. The 2-substituted 5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **2** were synthesized by *Bernath* and co-workers [6] from *N*-substituted 4-oxopiperidin-3-carboxylic acid methyl esters **1**. Compounds **2** underwent dehydrogenation in xylene or in nitrobenzene in the presence of a Pd/C catalyst, furnishing 2-substituted pyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **3**. However, this method required forcing conditions and long reaction time.



1 **2** **3**

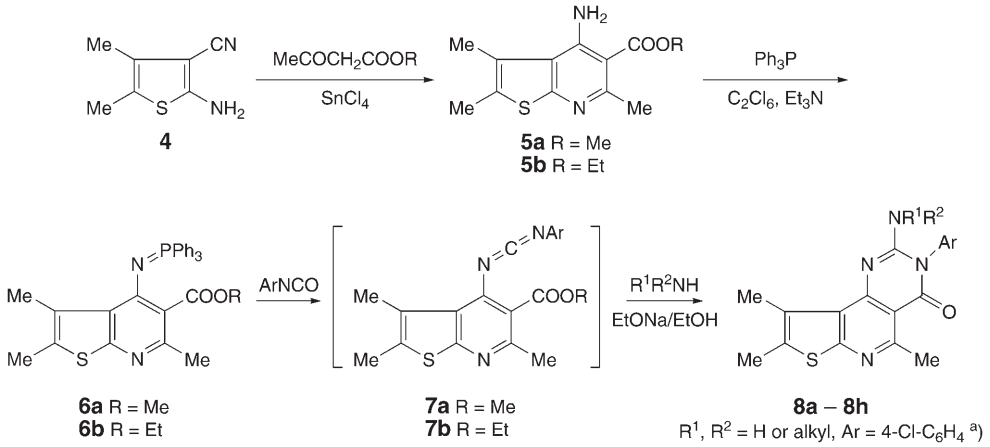
R^1 = $PhCH_2$, Me; R^2 = Ph, Me

Recently, we have been interested in the synthesis of quinazolinones, pyrazolopyrimidinones, and thienopyrimidinones *via* aza-*Wittig* reaction of (phosphoranylideneamino)carboxylic acid ethyl esters with aromatic isocyanates and subsequent reaction

with various nucleophiles [7][8], and 2-substituted 3-aryl-8,9,10,11-tetrahydro-5-methyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives were reported [9]. Here we wish to report a facile synthesis of 2-substituted thieno[3′,2′:5,6]-pyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **8** from easily accessible (phosphoranylideneamino)carboxylates **6**. The structures of **8** were confirmed by ^{1}H- and ^{13}C-NMR, EI-MS, IR spectroscopy, elemental analyses, and the single-crystal X-ray-analysis of **8j**.

2. Results and Discussions. – The 4-amino-2,3,6-trimethylthieno[2,3-*b*]pyridine-5-carboxylates **5**, easily obtained from 2-amino-4,5-dimethylthiophene-3-carbonitril (**4**) and methyl or ethyl 3-oxobutanoate in the presence of $SnCl_4$, were converted to 4-(phosphoranylideneamino) derivatives **6** *via* reaction with triphenylphosphine, hexachloroethane, and Et_3N (*Scheme 1*).

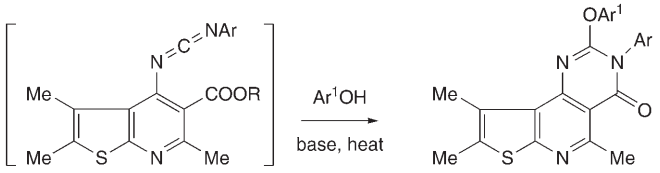
Scheme 1



[a]) See *Table* for R^1 and R^2.

Phosphoranylideneamino derivative **6b** reacted with 4-chlorophenyl isocyanate to give carbodiimide derivative **7b**, which was allowed to react with amines R^1R^2NH or phenols Ar^1OH to produce 2-substituted 3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **8**. Analogously, phosphoranylideneamino derivative **6a** reacted with 4-chlorophenyl isocyanate *via* **7a** to the target compounds **8**. The cyclizations of **7** with amines to **8a**–**h** proceeded smoothly in CH_2Cl_2 and in the presence of catalytic amounts of NaOEt at room temperature and gave satisfactory yields with both primary and secondary alkylamines (*Scheme 1* and *Table*). The cyclizations of **7** with phenols in MeCN in the presence of catalytic amounts of K_2CO_3 at room temperature did not lead to 2-(aryloxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones. However, the reaction took place smoothly to give **8i**–**r** in good yields at higher temperature (*Scheme 2* and *Table*), and this with both phenols substituted by electron-withdrawing groups and phenols substituted by electron-releasing groups. The yields of **8** from **6a** were a bit higher than those from **6b** (see *Table*). All the products **8** were purified by

Scheme 2



7a R = Me
7b R = Et

8i – **8r** Ar = 4-Cl-C_6H_4 [a])

[a]) For Ar^1, see *Table*.

Table. *Formation and Physical Constants of Compounds* **8**

	R^1R^2NH or Ar^1OH	Crystal color	M.p. [°]	Reaction time [h]	Reaction temp. [°]	Yield [%][a])	Yield [%][b])
8a	$MeCH_2CH_2NH_2$	colorless	251–252	10	25	94	90
8b	Me_2CHNH_2	colorless	298–299	9	25	89	88
8c	$Me(CH_2)_3NH_2$	colorless	248–249	11	25	90	86
8d	$MeCH_2CH(Me)NH_2$	colorless	258–259	11	25	89	82
8e	Me_3CNH_2	colorless	>300	10	25	85	84
8f	$(MeCH_2)_2NH$	colorless	220–223	10	20	92	89
8g	$(Me(CH_2)_3)_2NH$	colorless	199–201	9	20	87	76
8h	$(Me(CH_2)_2)_2NH$	colorless	190–194	11	25	93	80
8i	4-Me–C_6H_4–OH	yellow	284–286	12	70	91	89
8j	4-Cl–C_6H_4–OH	colorless	>300	12	70	95	91
8k	PhOH	colorless	276–277	13	70	94	86
8l	4-NO_2–C_6H_4–OH	colorless	254–258	13	70	77	70
8m	2,4-$Cl_2C_6H_3OH$	colorless	280–281	12	80	86	78
8n	2-Cl–C_6H_4–OH	colorless	270–273	13	80	80	80
8o	4-Br–C_6H_4–OH	colorless	298–299	12	80	67	57
8p	2,4-$F_2C_6H_3OH$	colorless	264–265	13	80	82	66
8q	3-F–C_6H_4–OH	colorless	265–266	12	80	69	50
8r	2-Cl(4-F)C_6H_3OH	colorless	265–267	12	80	92	79

[a]) Yields of **8** from **6a**. [b]) Yields of **8** from **6b**.

recrystallization from CH_2Cl_2 and EtOH and their structures elucidated by ^{1}H- and ^{13}C-NMR, IR, MS, and elementary analysis.

For example, the IR spectrum of **8a** reveals a C=O absorption band at 1672 cm^{-1}, and absorptions at 3361 and 3045 cm^{-1} are due to N–H and aromatic C–H groups. The ^{1}H-NMR spectra of **8a** show the signal of the Me group at the pyridine moiety at δ 2.96 as a *s* and those of the Me groups at the thiophene ring at δ 2.48 and 2.70. The signal of the NH group appears at δ 4.42, and the aromatic H-atoms absorb at δ 7.26–7.62 (*m*, 4 H). The ^{13}C-NMR shows nineteen signals. The MS of **8a** reveals the molecule ion peak at *m*/*z* 412 with 100% abundance. The structure of **8a** was also established on the basis of elemental-analysis data.

The structure of **8j** was determined by X-ray crystallography (*Fig.*).

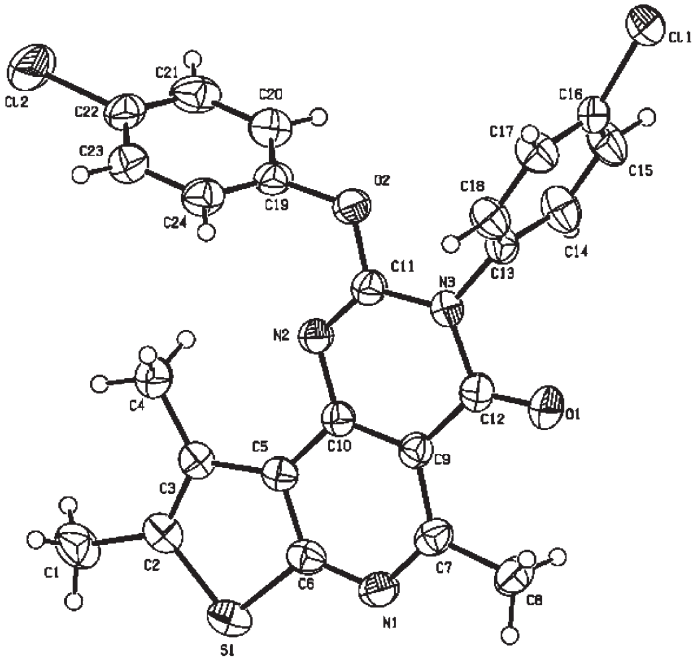


Figure. *X-Ray crystal structure of thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* **8j**

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Experimental Part

1. *General.* All of the solvents and materials were reagent grade and purified as required. Melting points: *WRS-1B* digital apparatus; uncorrected. IR Spectra: *PE-983 IR* spectrometer; KBr pellets; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian-Mercury-400* spectrometer; $CDCl_3$ solns.; δ in ppm rel. to $SiMe_4$, *J* in Hz. MS: *Finnigan-Trace-MS* spectrometer. Elemental analyses: *Vario-EL-III* instrument.

2. *4-Amino-2,3,6-trimethylthieno[2,3-*b*]pyridine-5-carboxylic Acid Methyl and Ethyl Ester* (**5a** and **5b**, resp.). The 2-amino-4,5-dimethylthiophene-3-carbonitrile (**4**; 1.52 g, 10 mmol) and $SnCl_4$ (2.3 ml, 20 mmol) were added to a stirred soln. of methyl 3-oxobutanoate (1.18 g, 10 mmol) in dry toluene (20 ml). The mixture was stirred at r.t. for 0.5 h and then heated under reflux for 4 h. Then the mixture was added to a sat. aq. Na_2CO_3 soln. (60 ml; pH 10–11), the suspension extracted with AcOEt (3 × 50 ml), and the combined extract dried (Na_2SO_4) and concentrated: 1.21 g (48%) of **5a**. Colorless crystals. M.p. 178–179°. ^1H-NMR ($CDCl_3$, 400 MHz): 2.40 (*s*, Me); 2.51 (*s*, Me); 2.69 (*s*, Me–C(6)); 3.91 (*s*, MeO); 6.68 (*s*, NH_2). Anal. calc. for $C_{12}H_{14}N_2O_2S$ (250.32): C 57.58, H 5.64, N 11.19; found: C 57.70, H 5.33, N 10.91.

Compound **5b** was prepared according to [10][11] in 69% yield. Colorless crystals. M.p. 131–132°.

3. *2,3,6-Trimethyl-4-[(triphenylphosphoranylidene)amino]thieno[2,3-*b*]pyridine-5-carboxylic Acid Methyl and Ethyl Ester* (**6a** and **6b**, resp.). To a soln. of **5a** (1.00 g, 4 mmol) in MeCN (15 ml) were added Ph_3P (1.30 g, 5 mmol) and C_2Cl_6 (1.20 g, 5 mmol). The mixture was treated with Et_3N (5.0 ml) and then stirred for 5–10 h at 0°. After evaporation, the residue was recrystallized from EtOH: 1.95 g (95%) of **5a**. M.p. 174–175. ^1H-NMR ($CDCl_3$, 400 MHz): 2.12 (*s*, Me); 2.35 (*s*, Me); 2.49 (*s*, Me–C(6)); 3.36 (*s*,

MeO); 7.42–7.62 (*m*, 18 arom. H). Anal. calc. for $C_{30}H_{27}N_2O_2PS$ (510.60): C 70.57, H 5.33, N 5.49; found: C 70.68, H 5.09, N 5.32.

Compound **6b** was prepared according to [10][11] in 93% yield. Colorless crystals. M.p. 174–175°.

4. *4-[[(4-Chlorophenyl)carbonimidoyl]amino}thieno[2,3-*b*]pyridine-5-carboxylic Acid Methyl and Ethyl Ester* (**7a** and **7b**, resp.). To a soln. of **6a** (0.51 g, 1 mmol) in dry CH_2Cl_2 (10 ml), 4-chlorophenyl isocyanate (1.1 mmol) was added under N_2 at r.t. The mixture was left unstirred for 30 min, then the solvent was evaporated, and Et_2O/petroleum ether was added to precipitate Ph_3PO. Removal of the solvent gave **7a**, which was used directly without further purification.

Following this procedure, **6b** (0.53 g, 1 mmol) gave **7b**.

5. *Compounds* **8a**–**h**: *General Procedure.* To the soln. of **7a** or **7b** (1 mmol) in CH_2Cl_2 (10 ml), the alkylamine (1.1 mmol) was added. The mixture was stirred for 30 min, the solvent was removed, and anh. EtOH (10 ml) with several drops of EtONa in EtOH were added. The mixture was stirred for 9–11 h at r.t., the soln. concentrated, and the residue recrystallized from EtOH: **8a**–**h**.

*3-(4-Chlorophenyl)-5,8,9-trimethyl-2-(propylamino)thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8a**): IR: 3361 (N–H), 3045 (arom. C–H), 2963, 2925, 2867 (C–H), 1672 (C=O), 1512, 1490, 1449, 1403, 1170, 1091, 808. ^{1}H-NMR: 0.90 (*t*, *J* = 7.2, Me); 1.61–1.64 (*m*, CH_2); 2.48 (*s*, Me); 2.70 (*s*, Me); 2.96 (*s*, Me); 3.45–3.47 (*m*, CH_2); 4.42 (*s*, NH); 7.26–7.62 (*m*, 4 arom. H). ^{13}C-NMR: 11.2; 13.6; 14.7; 22.5; 26.4; 43.8; 113.7; 119.5; 121.8; 125.1; 126.3; 128.1; 130.2; 132.8; 136.2; 151.2; 152.7; 157.7; 162.5. MS: 413 (31), 412 (100, M^+), 370 (13), 369 (18), 42 (28). Anal. calc. for $C_{21}H_{21}ClN_4OS$ (412.94): C 61.09, H 5.09, N 13.58; found: C 60.77, H 5.00, N 13.34.

*3-(4-Chlorophenyl)-2-(isopropylamino)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8b**): IR: 3438 (N–H), 3135 (arom. C–H), 1674 (C=O), 1560, 1511, 1490, 1401, 1085. ^{1}H-NMR: 1.21 (*d*, *J* = 6.8, Me); 1.25 (*d*, *J* = 6.8, Me); 2.48 (*s*, Me); 2.69 (*s*, Me); 2.95 (*s*, Me); 4.07 (*s*, Me); 4.36–4.39 (*m*, NH); 7.26–7.62 (*m*, 4 arom. H). MS: 413 (27), 412 (36, M^+), 411 (100), 373 (14), 368 (93), 352 (28), 260 (56), 258 (58), 189 (24), 80 (16). Anal. calc. for $C_{21}H_{21}ClN_4OS$ (412.94): C 61.09, H 5.09, N 13.58; found: C 60.78, H 4.93, N 13.42.

*2-(Butylamino)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8c**): IR: 3446 (N–H), 3187 (arom. C–H), 2959, 2924 (C–H), 1684 (C=O), 1552, 1509, 1490, 1450, 1161, 796. ^{1}H-NMR: 0.9 (*t*, *J* = 7.2, Me); 1.30–1.34 (*m*, CH_2); 1.56–1.59 (*m*, CH_2); 3.47–3.50 (*t*, CH_2); 2.48 (*s*, Me); 2.70 (*s*, Me); 2.96 (*s*, Me); 4.39 (*s*, NH); 7.26–7.61 (*m*, 4 arom. H). MS: 427 (26), 426 (100, M^+), 411 (17), 370 (9), 369 (16). Anal. calc. for $C_{22}H_{23}ClN_4OS$ (426.96): C 61.89, H 5.43, N 13.12; found: C 61.59, H 5.14, N 13.24.

*2-[(*sec*-Butyl)amino]-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8d**): IR: 3366 (N–H), 3035 (arom. C–H), 2958, 2924 (C–H), 1667 (C=O), 1557, 1511, 1491, 1449, 1402, 1091, 805. ^{1}H-NMR : 0.89 (*d*, *J* = 6.8, 2 Me); 1.95–1.99 (*m*, CH); 2.49 (*s*, Me); 2.71 (*s*, Me); 2.97 (*s*, Me); 3.32 (*t*, *J* = 6.8, CH_2); 4.42 (*s*, NH); 7.26–7.67 (*m*, 4 arom. H). MS: 427 (45), 426 (29, M^+), 368 (100), 352 (18), 189 (15), 172 (13). Anal. calc. for $C_{22}H_{23}ClN_4OS$ (426.96): C 61.89, H 5.43, N 13.12; found: C 61.60, H 5.24, N 12.97.

*2-[(*tert*-Butyl)amino]-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8e**): IR: 3434 (N–H), 3135 (arom. C–H), 2967, 2924 (C–H), 1673 (C=O), 1526, 1509, 1487, 1440, 1290, 1211, 1088, 809. ^{1}H-NMR: 1.44 (*s*, 3 Me); 2.49 (*s*, Me); 2.73 (*s*, Me); 2.96 (*s*, Me); 4.22 (*s*, NH); 7.26–7.62 (*m*, 4 arom. H). MS: 427 (14), 426 (64, M^+), 370 (100), 368 (86), 352 (16), 189 (10). Anal. calc. for $C_{22}H_{23}ClN_4OS$ (426.96): C 61.89, H 5.43, N 13.12; found: C 62.06, H 5.25, N 13.26.

*3-(4-Chlorophenyl)-2-(diethylamino)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8f**): IR: 3135 (arom. C–H), 2982, 2929 (C–H), 1675 (C=O), 1557, 1511, 1490, 1254, 1089, 795. ^{1}H-NMR: 0.95 (*t*, *J* = 6.8, 2 Me); 2.50 (*s*, Me); 2.69 (*s*, Me); 3.00 (*s*, Me); 3.27 (*q*, *J* = 6.8, CH_2); 7.26–7.51 (*m*, 4 arom. H). MS: 427 (19), 426 (82, M^+), 400 (22), 397 (100), 354 (24), 286 (22). Anal. calc. for $C_{22}H_{23}ClN_4OS$ (426.96): C 61.89, H 5.43, N 13.12; found: C 62.19, H 5.39, N 13.09.

*3-(4-Chlorophenyl)-2-(dibutylamino)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8g**): IR: 3135 (arom. C–H), 2928, 2866 (C–H), 1687 (C=O), 1558, 1510, 1490, 1459, 1402, 804. ^{1}H-NMR: 0.86 (*d*, *J* = 7.2, 2 Me); 1.16–1.19 (*m*, 2 CH_2); 1.30–1.36 (*m*, 2 CH_2); 2.49 (*s*, Me); 2.68 (*s*, Me); 2.98 (*s*, Me); 3.15 (*t*, *J* = 6.8, 2 CH_2); 7.26–7.49 (*m*, 4 arom. H). MS: 483 (34), 482 (100, M^+), 456 (14), 425

(87), 384 (15), 383 (62), 354 (40), 272 (26), 188 (19), 110 (11). Anal. calc. for $C_{26}H_{31}ClN_4OS$ (483.07): C 64.64, H 6.47, N 11.60; found: C 64.90, H 6.63, N 11.86.

*3-(4-Chlorophenyl)-2-(dipropylamino)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8h**): IR: 3125 (arom. C–H), 2962, 2929 (C–H), 1686 (C=O), 1520, 1490, 1485, 1402, 1090, 796. ^{1}H-NMR: 0.78 (*t*, *J* = 7.2, 2 Me); 1.33–1.39 (*m*, 2 CH_2); 2.49 (*s*, Me); 2.69 (*s*, Me); 2.97 (*s*, Me); 3.10–3.14 (*m*, $(CH_2)_2N$); 7.26–7.51 (*m*, 4 arom. H). MS: 455 (16), 454 (79, M^+), 425 (16), 413 (23), 411 (100), 353 (57), 300 (57), 258 (25), 212 (34), 76 (16). Anal. calc. for $C_{24}H_{27}ClN_4OS$ (455.02): C 63.35, H 5.98, N 12.31; found: C 63.08, H 5.73, N 12.07.

6. *Compounds* **8i**–**r**: *General Procedure.* To the soln. of **7a** or **7b** (1 mmol) in MeCN (10 ml), the corresponding phenol (1.1 mmol) and a catalytic amount of K_2CO_3 were added. The mixture was stirred for 12–13 h at 70–80°, the soln. concentrated, and the residue recrystallized from MeCN: **8i**–**r**.

*3-(4-Chlorophenyl)-5,8,9-trimethyl-2-(4-methylphenoxy)thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8i**): IR: 3140 (arom. C–H), 2924 (C–H), 1699 (C=O), 1504, 1490, 1405, 1316, 1198, 840. ^{1}H-NMR : 2.01 (*s*, Me); 2.38 (*s*, Me); 2.39 (*s*, Me); 3.03 (*s*, Me); 7.00–7.57 (*m*, 8 arom. H). MS: 464 (30), 463 (33), 462 (100, M^+), 356 (32), 354 (93), 308 (41), 188 (64), 172 (21), 154 (12), 106 (28), 76 (85). Anal. calc. for $C_{25}H_{20}ClN_3O_2S$ (461.96): C 65.00, H 4.36, N 9.10; found: C 65.25, H 4.16, N 8.96.

*2-(4-Chlorophenoxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8j**): IR: 3144 (arom. C–H), 1699 (C=O), 1561, 1511, 1488, 1404, 1317, 1089, 845. ^{1}H-NMR: 2.03 (*s*, Me); 2.40 (*s*, Me); 3.02 (*s*, Me); 7.09–7.58 (*m*, 8 arom. H). MS: 483 (37), 482 (52), 481 (100, M^+), 354 (9), 98 (8), 38 (17). Anal. calc. for $C_{24}H_{17}Cl_2N_3O_2S$ (482.38): C 59.76, H 3.55, N 8.71; found: C 60.01, H 3.66, N 8.52.

*3-(4-Chlorophenyl)-5,8,9-trimethyl-2-phenoxythieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8k**): IR: 3140 (atom. C–H), 2934 (C–H), 1693 (C=O), 1562, 1515, 1491, 1401, 1264, 1091, 806. ^{1}H-NMR: 1.97 (*s*, Me); 2.39 (*s*, Me); 3.06 (*s*, Me); 7.13–7.58 (*m*, 9 arom. H). MS: 449 (29), 448 (29), 447 (100, M^+), 356 (21), 355 (14), 354 (78), 76 (13), 64 (16). Anal. calc. for $C_{24}H_{18}ClN_3O_2S$ (447.94): C 64.35, H 4.05, N 9.38; found: C 64.30, H 3.75, N 9.63.

*3-(4-Chlorophenyl)-5,8,9-trimethyl-2-(4-nitrophenoxy)thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8l**): IR: 3114 (arom. C–H), 1700 (C=O), 1560, 1512, 1490, 1399, 1261, 1091, 862. ^{1}H-NMR: 1.99 (*s*, Me); 2.40 (*s*, Me); 3.03 (*s*, Me); 7.37–8.35 (*m*, 8 arom. H). MS: 493 (19), 492 (41, M^+), 445 (13), 372 (18), 370 (42), 369 (30), 292 (34), 214 (23), 76 (34), 62 (100). Anal. calc. for $C_{24}H_{17}ClN_4O_4S$ (492.93): C 58.48, H 3.48, N 11.37; found: C 58.72, H 3.67, N 11.60.

*3-(4-Chlorophenyl)-2-(2,4-dichlorophenoxy)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8m**): IR: 3120 (arom. C–H), 2919 (C–H), 1700 (C=O), 1562, 1489, 1402, 1251, 1089, 804. ^{1}H-NMR: 1.96 (*s*, Me); 2.41 (*s*, Me); 3.04 (*s*, Me); 7.17–7.59 (*m*, 7 arom. H). MS: 519 (47), 518 (27), 517 (100, M^+), 516 (24), 515 (98), 160 (46), 135 (21), 111 (17), 74 (18). Anal. calc. for $C_{24}H_{16}Cl_3N_3O_2S$ (516.83): C 55.77, H 3.12, N 8.13; found: C 55.71, H 2.98, N 7.97.

*2-(2-Chlorophenoxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8n**): IR: 3137 (arom. C–H), 2935 (C–H), 1689 (C=O), 1561, 1490, 1400, 1264, 1222, 1090, 804. ^{1}H-NMR: 1.89 (*s*, Me); 2.39 (*s*, Me); 3.06 (*s*, Me); 7.22–7.59 (*m*, 7 arom. H). MS: 483 (65), 482 (24), 481 (100, M^+), 354 (18), 126 (15), 110 (32), 98 (41). Anal. calc. for $C_{24}H_{17}Cl_2N_3O_2S$ (482.38): C 59.76, H 3.55, N 8.71; found: C 59.54, H 3.33, N 8.90.

*2-(4-Bromophenoxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8o**): IR: 3136 (arom. C–H), 2925 (C–H), 1699 (C=O), 1561, 1486, 1402, 1264, 1205, 1090, 843. ^{1}H-NMR: 2.04 (*s*, Me); 2.42 (*s*, Me); 3.04 (*s*, Me); 7.04–7.58 (*m*, 8 arom. H). ^{13}C-NMR: 13.6; 13.7; 26.3; 119.3; 122.4; 123.9; 125.7; 126.5; 128.0; 129.3; 129.7; 132.3; 132.4; 134.4; 137.7; 149.5; 150.6; 153.9; 157.6; 162.6. MS: 529 (30), 528 (24), 527 (100, M^+), 526 (23), 525 (83), 354 (11). Anal. calc. for $C_{24}H_{17}BrClN_3O_2S$ (526.83): C 54.72, H 3.25, N 7.98; found: C 54.53, H 3.37, N 8.23.

*3-(4-Chlorophenyl)-2-(2,4-difluorophenoxy)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8p**): IR: 3124 (arom. C–H), 2924 (C–H), 1704 (C=O), 1562, 1507, 1401, 1371, 1189, 962, 830. ^{1}H-NMR: 2.01 (*s*, Me); 2.42 (*s*, Me); 3.06 (*s*, Me); 6.93–7.59 (*m*, 7 arom. H). MS: 484 (18), 483 (81, M^+), 356 (26), 354 (100), 189 (28), 186 (12), 159 (18), 110 (16), 100 (19). Anal. calc. for $C_{24}H_{16}F_2ClN_3O_2S$ (483.92): C 59.57, H 3.33, N 8.68; found: C 59.52, H 3.57, N 8.59.

*3-(4-Chlorophenyl)-2-(3-fluorophenoxy)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8q**): IR: 3125 (arom. C−H), 2933 (C−H), 1698 (C=O), 1562, 1490, 1399, 1264, 1091, 866. ^{1}H-NMR: 2.04 (*s*, Me); 2.42 (*s*, Me); 3.07 (*s*, Me); 6.94–7.57 (*m*, 8 arom. H). MS: 467 (36), 466 (44), 465 (100, M^+), 354 (74), 189 (15), 110 (15), 94 (17), 82 (19). Anal. calc. for $C_{24}H_{17}FClN_3O_2S$ (465.93): C 61.87, H 3.68, N 9.02; found: C 62.10, H 3.61, N 9.20.

*2-(2-Chloro-4-fluorophenoxy)-3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**8r**): IR: 3128 (arom. C−H), 2927 (C−H), 1700 (C=O), 1559, 1490, 1399, 1371, 1267, 1188, 1090, 861. ^{1}H-NMR: 1.96 (*s*, Me); 2.41 (*s*, Me); 3.06 (*s*, Me); 7.07–7.59 (*m*, 7 arom. H). MS: 502 (13), 501 (48), 500 (26), 499 (100, M^+), 356 (29), 354 (100), 188 (37), 172 (12), 116 (21). Anal. calc. for $C_{24}H_{16}FCl_2N_3O_2S$ (500.37): C 57.61, H 3.22, N 8.40; found: C 57.57, H 3.26, N 8.52.

X-Ray Crystallographic Analysis of Compound **8j**. The structure of **8j**, which was recrystallized from EtOH, was determined by single-crystal X-ray diffraction analysis. The crystal is of monoclinic space group *P*2(1)/*n*, with $a = 11.186(2)$ Å, $b = 10.335(2)$ Å, $c = 19.517(3)$ Å, $\beta = 101.377(3)^\circ$, $V = 2212.0(6)$ Å^3, $Z = 4$, $D_c = 1.448$ g/cm^3, $S = 1.097$, $\mu = 0.295$ mm^{-1}, M_r 482.37, final $R = 0.0498$, and $wR = 0.1364$. The *Figure* shows the molecular structure of **8j**. CCDC-264861 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request.cif from the *Camdridge Crystallographic Data Center*.

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