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New iminophosphorane-mediated synthesis of thieno[3′,2′:4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-ones and 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes

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ABSTRACT

Mono(iminophosphorane) **4** was selectively prepared from the reaction of 3,4-diaminothieno[2,3-*b*]thiophene **3** with excess triphenylphosphine, C_2Cl_6, and Et_3N due to intramolecular double hydrogen bond formation. Mono(iminophosphorane) **4** reacted with aromatic isocyanates to give stable carbodiimides **8**, which were further treated with aliphatic secondary or primary amines to give 2-amino substituted thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **10** or **12** in the presence of a catalytic amounts of EtO^-Na^+. However, in the presence of a catalytic amounts of potassium carbonate, the carbodiimides **8** were transformed into previously unreported 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes **13** via direct cyclization in high yields. The reaction of carbodiimides **8** with phenols in the presence of a catalytic amounts of potassium carbonate gave a mixture of 2-aryloxy substituted thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **14** and **13**. X-ray structure analysis of **10m** supported the structure and the proposed reactivity of amino group.

1. Introduction

The derivatives of fused pyrimidines are valued not only for their rich and varied chemistry, but also for many important biological properties.[1] Among them, the thienopyrimidine ring system, because of a formal isoelectronic relationship with purine, is of special biological interest.[2–5] For example, some 2-alkoxy or 2-alkyl substituted thienopyrimidines show significant anticancer, antifungal, and antibacterial activities,[2] whereas others have been used as tyrosine kinase, tissue transglutaminase, and VEGFR-2 kinase inhibitors.[3–5] On the other hand, the derivatives of thienothiophenes have been developed for different purposes in the pharmaceutical field and have been tested as potential antitumor,[6] antiviral,[7] antibiotic,[8] and antiglaucoma[9] drugs, or as inhibitors of platelet aggregation.[10] Recently, some conjugated thienothiophenes, structurally related to several current applications, have been reported.[11–13] For example, thienothiophenes BDT and DTT have been shown to be effective p-type semiconductor or charge transport material for organic FETs with very high charge carrier mobility. However, little is known about the thienothienopyrimidines with different features and applications in the literature, and there is no report of a generally useful synthesis of thienothienopyrimidines, compounds which are of considerable interest as potential biological active compounds or pharmaceuticals.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[14,15] Annelation of ring systems with *N*-heterocycles by means of an aza-Wittig reaction has been widely utilized because of the availability of functionalized iminophosphoranes. Recently, we have been interested in the synthesis of quinazolinones, thienopyrimidinones, and imidazolinones via aza-Wittig reaction, with the aim of evaluating their fungicidal activities.[16,17] Here, we wish to report a fundamentally new approach to the synthesis of 2-substituted thieno[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-ones and 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes from mono(iminophosphorane) **4**.

2. Results and discussion

It was reported that diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate **3** was prepared from one pot reaction of malononitrile, CS_2, and ethyl bromoacetate in K_2CO_3/DMF through the ketene dithioacetals dipotassium salts **1** in 83% yield.[18] However, in our laboratory, this one pot reaction gave actually thiophene **2** in only 25% yield. The deep red color of the reaction mixture implies that side reactions may take place. Therefore, we carried out the reaction in MeOH/H_2O (4:1), which yielded **2** in 75% yield. Further reaction of **2** in a mixed solvent (CH_2Cl_2/EtOH) produced **3** in high yield in the presence of EtONa (Scheme 1).

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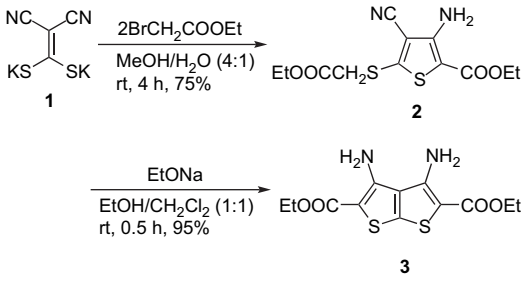
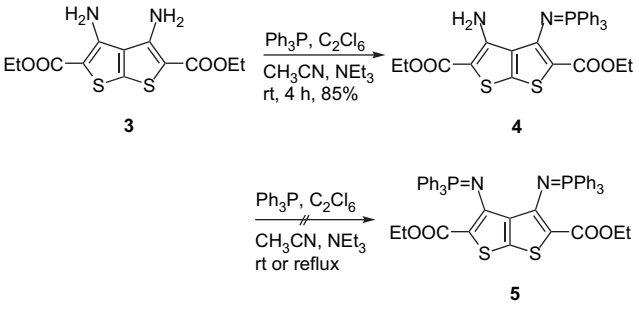
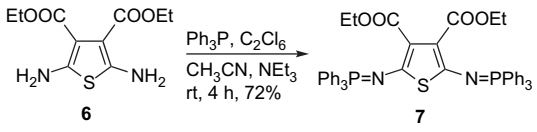


Scheme 1. Preparation of thieno[2,3-*b*]thiophene **3**.

With the diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate **3** in hand, we switched our attention to prepare bis(iminophosphorane) **5** from **3**. However, it was surprising to find that only mono(iminophosphorane) **4** was obtained in 83% yield when **3** was treated with excess triphenylphosphine, hexachloroethane, and triethylamine at room temperature or even in refluxing acetonitrile (Scheme 2). No matter how we changed the reactant ratio, solvent, reaction time, and temperature, only mono(iminophosphorane) **4** was obtained. Further reaction of the isolated mono(iminophosphorane) **4** with triphenylphosphine, hexachloroethane, and triethylamine did not yield bis(iminophosphorane) **5** with **4** recovered unchanged. Generally, bis(iminophosphorane) can be easily prepared from the reaction of aromatic diamine with excess triphenylphosphine, hexachloroethane, and triethylamine. For example, bis(iminophosphorane) **7** was obtained from corresponding diamino thiophene **6** in 72% yield (Scheme 3).[19] The difficult preparation of bis(iminophosphorane) **5** from mono(iminophosphorane) **4** may be due to intramolecular double hydrogen bond formation between amino hydrogen with both nitrogen of iminophosphorane and carboxylate oxygen, which results in low reactivity of the amino group. To our knowledge this is the first example of selective synthesis of a monoiminophosphorane from the reaction of aromatic diamine with triphenylphosphine, hexachloroethane, and triethylamine.

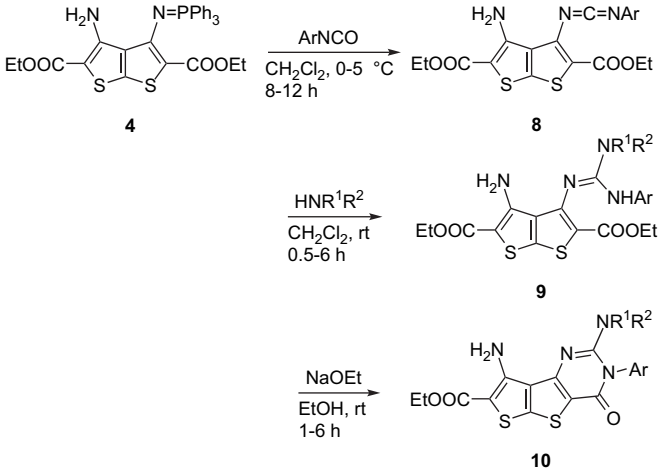


Scheme 2. Preparation of monoiminophosphorane **4**.



Scheme 3. Literature preparation of bis(iminophosphorane) **7**.

Iminophosphorane **4** reacted with aromatic isocyanate to give stable carbodiimide **8**, in which intramolecular double hydrogen bond may form and act to retard intramolecular nucleophilic attack of the amino group to the carbodiimide carbon. It is noteworthy that the carbodiimide with adjacent amino group generally tend to cyclize directly to form five or six membered heterocycles.[20] To our knowledge this is the first example of stable carbodiimide with adjacent amino group. Further reaction of **8** with secondary amines provided guanidine intermediates **9**. In the presence of catalytic amount of sodium ethoxide, **9** were converted easily to 2-dialkylamino-thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **10** in satisfactory yields at room temperature (Scheme 4). It is noteworthy that the isolated yield of **10** was good even when NR^1R^2 is bulky di-*iso*-propylamino group. The results are listed in Table 1.



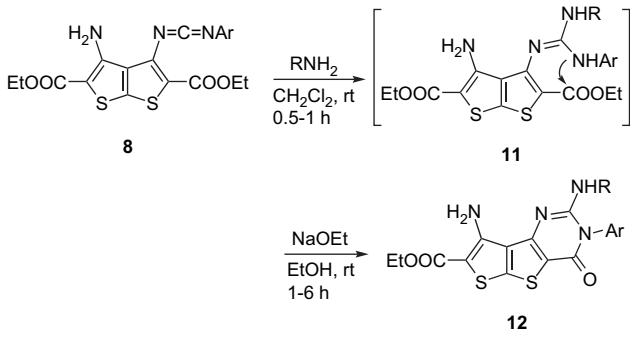
Scheme 4. Synthesis of compounds **10**.

The reaction of carbodiimides **8** with primary amine RNH_2 in the presence of EtONa provided only 2-alkylamino-thieno[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **12**, one of the possible regioisomers. We obtained only **12** from the reaction mixture after recrystallization; the other isomer was not found by ^1H NMR analysis of the reaction mixture. The structure of **12** is deduced from its ^1H NMR data. For example, the ^1H NMR spectrum in **12a** (R=*n*-Pr) shows the signals of NH at 4.26 ppm as a broad triple absorption and NCH_2 at 3.39–3.34 ppm as multiple absorption, which strongly suggest the existence of $NHCH_2CH_2CH_3$ group in **12a**. Whenever the primary amine used is small (R=*n*-Pr) or bulky (R=*t*-Bu), the cyclization was achieved all in good yields with similar selectivity. The results are also listed in Table 1. The solitary

Table 1
Preparation of compounds **10a–l** and **12a–g**

Compd	Ar	NR^1R^2(NHR)	Yield (%)
10a	Ph	NMe_2	86
10b	Ph	N(*n*-Pr)$_2$	91
10c	Ph	N(*i*-Pr)$_2$	78
10d	Ph	N(*n*-Bu)$_2$	81
10e	Ph	N(*i*-Bu)$_2$	84
10f	Ph	N(*n*-C_5H_{11})$_2$	74
10g	Ph	N(*n*-C_6H_{13})$_2$	71
10h	4-Cl-C_6H_4	NMe_2	83
10i	4-Cl-C_6H_4	N(*n*-Pr)$_2$	88
10j	4-Cl-C_6H_4	N(*n*-C_5H_{11})$_2$	78
10k	4-Cl-C_6H_4	N(*n*-C_6H_{13})$_2$	75
10l	4-F-C_6H_4	N(Me)Ph	87
10m	4-F-C_6H_4	Pyrrolidin-1-yl	90
12a	Ph	NH(*n*-Pr)	76
12b	Ph	NH(*i*-Pr)	78
12c	Ph	NH(*n*-Bu)	82
12d	Ph	NH(*i*-Bu)	74
12e	Ph	NH(*t*-Bu)	88
12f	4-Cl-C_6H_4	NH(*n*-Pr)	85
12g	4-F-C_6H_4	NH(*n*-Pr)	82

formation of **12** can be rationalized in terms of a base catalytic cyclization of the guanidine intermediate **11** to give **12** across the arylamino group rather than the alkylamino one. This may probably be due to the preferential generation of $-N^{-}Ar$ from more acidic –NHAr. The same selectivity is also observed in similar cases (Scheme 5).[21]



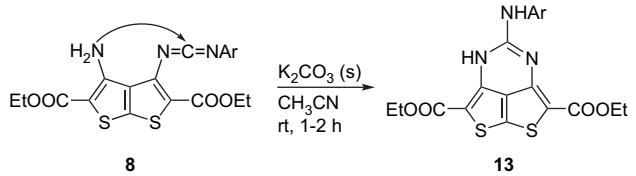
Scheme 5. Synthesis of compounds **12**.

It is interesting to note that when solid potassium carbonate was added to the solution of carbodiimides **8** in CH_3CN, a precipitate gradually formed, which was verified to be previously unreported 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes **13** (87–93% yields, Table 2). Presumably, the conversion of **8** into **13** involves an intramolecular nucleophilic attack of the amino group to the carbodiimide carbon in the catalysis of solid potassium carbonate (Scheme 6).

Table 2
Yields of compounds **13a–d** and **14a–h**

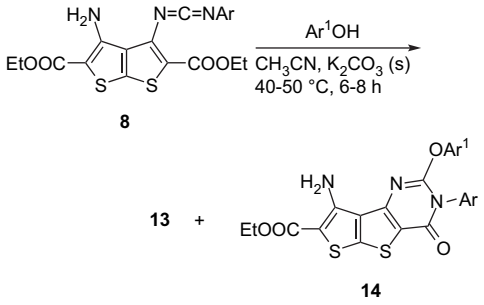
Compd	Ar	Ar^1	Yield (%)[a]
13a	Ph		87
13b	4-Cl-C_6H_4		93
13c	4-F-C_6H_4		90
13d	3-Me-C_6H_4		88
14a	Ph	4-MeO-C_6H_4	70 (11)
14b	Ph	2-MeO-C_6H_4	66 (13)
14c	Ph	3-Me-C_6H_4	63 (17)
14d	Ph	2-Me-C_6H_4	60 (15)
14e	Ph	2,4-Cl-6-Me-C_6H_2	55 (18)
14f	Ph	3,4-Me-C_6H_3	62 (15)
14g	3-Me-C_6H_4	3-Me-C_6H_4	67 (17)
14h	3-Me-C_6H_4	2,4-Cl-C_6H_3	61 (16)

[a] Yields in parenthesis are that of compounds **13**.



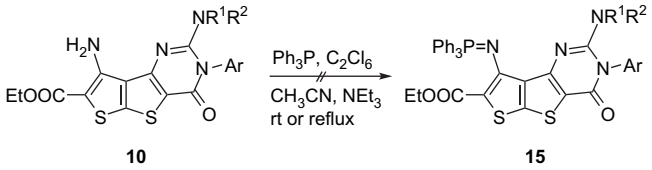
Scheme 6. Synthesis of compounds **13**.

The direct reaction of carbodiimide **8** with phenols produced both 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes **13** (yields 11–18%) and 2-aryloxy thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **14** (yields 55–70%, Table 2) in the presence of solid potassium carbonate. Both the formation of **13** and **14** can result from competition reaction between direct cyclization of carbodiimide **8** in the basic condition and the nucleophilic addition of phenoxide to the carbodiimide **8** with subsequent cyclization (Scheme 7).



Scheme 7. Synthesis of compounds **13** and **14**.

Attempt to prepare iminophosphorane **15** from **10**, **12**, or **14** via reaction with triphenylphosphine, hexachloroethane, and triethylamine at room temperature or even in refluxing acetonitrile failed. In every case the starting material **10**, **12**, or **14** was recovered unchanged (Scheme 8). This might be due to intramolecular double hydrogen bond formation between amino hydrogen with both nitrogen of pyrimidine ring and carboxylate oxygen, which result in low reactivity of the amino group.



Scheme 8. Attempted preparation of iminophosphorane **15**.

The structure of thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **10**, **12**, **13**, and **14** was confirmed by their spectral data. Furthermore, a single crystal of **10m** was obtained from a CH_2Cl_2/EtOH solution of **10m**. X-ray structure analysis verified again the proposed structure, and showed that intramolecular double hydrogen bond formation between amino hydrogen with both nitrogen of pyrimidine ring and carboxylate oxygen (Fig. 1), which support the above discussion about the amino reactivity.

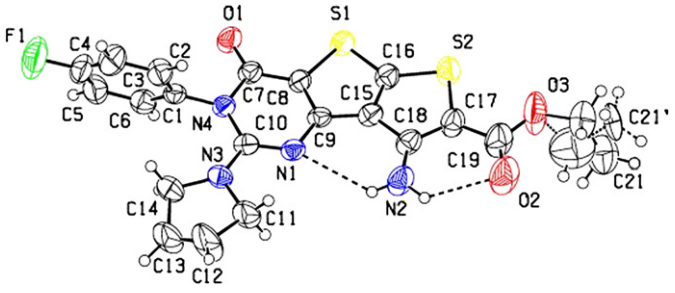


Figure 1. ORTEP diagram of the crystal structure of tricyclic compound **10m** (50% thermal ellipsoids). The intramolecular N–H···N/O hydrogen bonds are indicated by dashed lines.

3. Conclusion

We have developed an efficient synthesis of previously unreported thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones and 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes from iminophosphorane. The selective formation of different product was explained by intramolecular hydrogen bond formation. Due to the mild reaction condition, good yields and selectivity, easily

accessible starting material and straightforward product isolation, we think that this new synthetic approach discussed here has the potential in synthesis of many biologically and pharmaceutically active thienothienopyrimidine derivatives.

4. Experimental

4.1. General

Melting points were uncorrected. MS were recorded on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 or 600 spectrometer and resonances relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

4.2. Synthesis of diethyl 3-amino-4-[(triphenylphosphoranylidene)amino]thieno[2,3-*b*]thiophene-2,5-dicarboxylate (4)

To a mixture of diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate **3** (2.51 g, 8 mmol), PPh_3 (3.14 g, 12 mmol), and C_2Cl_6 (2.84 g, 12 mmol) in dry CH_3CN (40 mL), was added dropwise NEt_3 (2.42 g, 24 mmol) at room temperature. The color of the reaction mixture quickly turned yellow. After stirred for 4–6 h, the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give 3.90 g (85%) of iminophosphorane **4** as colorless crystals. Mp: 188–190 °C, IR (KBr): 3457, 1709, 1676, 1496, 1438, 1282, 1112 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66–7.42 (m, 15H), 6.70 (br, 2H), 4.26 (q, J=7.2 Hz, 2H), 3.63 (q, J=7.2 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H). MS *m/z*: 574 (M^+, 41), 545 (100), 499 (87), 262 (55), 201 (83), 183 (97), 108 (44). Anal. Calcd for $C_{30}H_{27}N_2O_4PS_2$: C, 62.70; H, 4.74; N, 4.87. Found: C, 62.53; H, 4.94; N, 4.96.

4.3. Synthesis of carbodiimide 8

*4.3.1. Diethyl 3-amino-4-{[(phenylimino)methylene]amino}-thieno[2,3-b]thiophene-2,5-dicarboxylate (**8a**)*

To a solution of iminophosphorane **4** (1.15 g, 2 mmol) in dry methylene dichloride (15 mL) was added phenyl isocyanate (0.24 g, 2 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 8–12 h at 0–5°C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration the solvent was removed to give carbodiimide **8a**, which was generally used directly without further purification. Carbodiimide **8a** was also isolated from the reaction mixture by column chromatography on silicon gel to give 0.60 g (72%) of carbodiimide **8a** as light yellow solid. Mp: 110–111 °C, IR (KBr): 3471, 3359, 2151, 1675, 1595, 1490, 1300, 1144 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.37–7.23 (m, 5H), 6.41 (br, 2H), 4.33–4.28 (m, 4H), 1.36 (t, J=7.2 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.2, 161.6, 147.6, 144.7, 136.0, 135.4, 132.4, 129.8, 129.4 (2), 126.1 (2), 124.8 (2), 120.4, 61.2, 60.2, 14.5, 14.3. MS *m/z*: 415 (M^+, 100), 369 (84), 323 (60), 295 (46), 194 (18), 77 (37). Anal. Calcd for $C_{19}H_{17}N_3O_4S_2$: C, 54.92; H, 4.12; N, 10.11. Found: C, 54.68; H, 4.27; N, 10.24.

*4.3.2. Diethyl 3-amino-4-{[(4-chlorophenyl)imino]methylene}-amino)thieno[2,3-b]thiophene-2,5-dicarboxylate (**8b**)*

Operation as above with 4-fluorophenyl isocyanate (0.31 g, 2 mmol), compound **8b** (0.55 g, 61%) was also isolated as light yellow solid. Mp: 102–104 °C, IR (KBr): 3482, 3361, 2138, 1675, 1593, 1490, 1283, 1091 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.33–7.26 (m, 4H), 6.38 (br, 2H), 4.33–4.28 (m, 4H), 1.36 (t, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H). MS *m/z*: 449 (M^+, 56), 403 (100), 361 (43), 324 (20), 291 (36), 134 (40). Anal. Calcd for $C_{19}H_{16}ClN_3O_4S_2$: C, 50.72; H, 3.58; N, 9.34. Found: C, 50.64; H, 3.79; N, 9.07.

*4.3.3. Diethyl 3-amino-4-({[(4-fluorophenyl)imino]-methylene}amino)thieno[2,3-b]thiophene-2,5-dicarboxylate (**8c**)*

Operation as above with 4-fluorophenyl isocyanate (0.27 g, 2 mmol), compound **8c** (0.55 g, 64%) was also isolated as light yellow solid. Mp: 132–134 °C, IR (KBr): 3491, 3362, 2150, 1668, 1591, 1498, 1292, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.33–7.03 (m, 4H), 6.39 (br, 2H), 4.33–4.28 (m, 4H), 1.36 (t, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.2, 161.7, 160.7, 147.6, 144.7, 135.5, 132.3, 132.0, 130.1, 126.3 (2), 126.2, 120.2, 116.3 (2), 116.1, 61.1, 60.2, 14.5, 14.2. MS *m/z*: 433 (M^+, 98), 387 (93), 341 (100), 315 (60), 285 (59), 121 (23). Anal. Calcd for $C_{19}H_{16}FN_3O_4S_2$: C, 52.64; H, 3.72; N, 9.69. Found: C, 52.47; H, 3.87; N, 9.83.

*4.3.4. Diethyl 3-amino-4-({[(3-methylphenyl)imino]-methylene}amino)thieno[2,3-b]thiophene-2,5-dicarboxylate (**8d**)*

Operation as above with 3-methylphenyl isocyanate (0.27 g, 2 mmol), compound **8d** (0.58 g, 68%) was also isolated as light yellow solid. Mp: 145–147 °C, IR (KBr): 3456, 3350, 2165, 1677, 1594, 1500, 1288, 1113 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.03 (m, 4H), 6.41 (br, 2H), 4.33–4.26 (m, 4H), 2.35 (s, 3H), 1.36 (t, J=7.2 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H). MS *m/z*: 429 (M^+, 99), 383 (100), 337 (93), 309 (53), 281 (46), 91 (18). Anal. Calcd for $C_{20}H_{19}N_3O_4S_2$: C, 55.93; H, 4.46; N, 9.78. Found: C, 55.71; H, 4.53; N, 9.62.

4.4. Synthesis of 2-dialkylamino-thieno[3′,2′:4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-ones (10)

*4.4.1. 8-Amino-2-dimethylamino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10a**)*

To the solution of **8** prepared above in methylene dichloride (15 mL) was added dimethylamine (0.25 g, 40%, 2 mmol). After the reaction mixture was allowed to stand for 0.5–6 h, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 1–6 h at room temperature. The solution was concentrated under reduced pressure and the residual was recrystallized from ethanol to give 0.71 g (86%) of 2-dimethylamino-thieno[3′,2′:4,5] thieno[3,2-*d*]-pyrimidin-4(3*H*)-ones **10a** as colorless crystals. Mp: 226–228 °C, IR (KBr): 3461, 3349, 1685, 1664, 1523, 1315, 1252 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.34 (m, 5H), 6.44 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 2.72 (s, 6H), 1.38 (t, J=7.2 Hz, 3H). MS *m/z*: 414 (M^+, 100), 353 (33), 297 (25), 132 (34), 77 (58). Anal. Calcd for $C_{19}H_{18}N_4O_3S_2$: C, 55.06; H, 4.38; N, 13.52. Found: C, 55.17; H, 4.42; N, 13.46.

*4.4.2. 8-Amino-2-di(n-propyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10b**)*

Operation as above with di(*n*-propyl)amine (0.20 g, 2 mmol), compound **10b** (0.86 g, 91%) was isolated as colorless crystals. Mp: 174–176 °C, IR (KBr): 3498, 3380, 1669, 1601, 1521, 1316, 1245 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.31 (m, 5H), 6.43 (br, 2H), 4.34 (q, J=7.2 Hz, 2H), 3.02 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.34–1.26 (m, 4H), 0.75 (t, J=7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 158.2, 157.5, 150.7, 148.7, 137.4, 130.7, 128.8, 128.7, 128.1, 116.6, 59.9, 53.0, 20.3, 14.3, 11.2. MS *m/z*: 470 (M^+, 100), 427 (20), 381 (26), 352 (23). Anal. Calcd for $C_{23}H_{26}N_4O_3S_2$: C, 58.70; H, 5.57; N, 11.90. Found: C, 58.66; H, 5.74; N, 11.83.

*4.4.3. 8-Amino-2-di(i-propyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10c**)*

Operation as above with di(*i*-propyl)amine (0.20 g, 2 mmol), compound **10c** (0.73 g, 78%) was isolated as colorless crystals. Mp: 235–237 °C, IR (KBr): 3477, 3350, 1674, 1514, 1308, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.29 (m, 5H), 6.44 (br, 2H), 4.34 (q, J=6.8 Hz, 2H), 3.64–3.57 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 1.17 (d, J=6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.0, 158.9, 156.7, 150.2, 148.7, 138.5, 130.9, 129.3, 128.8, 128.0, 117.5, 60.0, 50.1, 21.5, 14.4. MS *m/z*: 470 (M^+, 100), 427 (86), 381 (95), 367 (20). Anal. Calcd for $C_{23}H_{26}N_4O_3S_2$: C, 58.70; H, 5.57; N, 11.90. Found: C, 58.92; H, 5.78; N, 11.77.

*4.4.4. 8-Amino-2-di(n-butyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10d**)*

Operation as above with di(*n*-butyl)amine (0.26 g, 2 mmol), compound **10d** (0.81 g, 81%) was isolated as colorless crystals. Mp: 173–175 °C, IR (KBr): 3482, 3379, 1669, 1526, 1312, 1256 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.30 (m, 5H), 6.44 (br, 2H), 4.34 (q, J=7.2 Hz, 2H), 3.05 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.30–1.10 (m, 8H), 0.84 (t, J=7.2 Hz, 6H). MS *m/z*: 498 (M^+, 100), 454 (14), 395 (35), 252 (13), 105 (16). Anal. Calcd for $C_{25}H_{30}N_4O_3S_2$: C, 60.22; H, 6.06; N, 11.24. Found: C, 60.27; H, 6.23; N, 11.07.

*4.4.5. 8-Amino-2-di(i-butyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10e**)*

Operation as above with di(*i*-butyl)amine (0.26 g, 2 mmol), compound **10e** (0.84 g, 84%) was isolated as colorless crystals. Mp: 164–166 °C, IR (KBr): 3479, 3365, 1679, 1516, 1313, 1253 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53–7.32 (m, 5H), 6.44 (br, 2H), 4.34 (q, J=6.8 Hz, 2H), 2.87 (d, J=7.2 Hz, 4H), 1.92–1.85 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 0.81 (d, J=6.4 Hz, 12H). MS *m/z*: 498 (M^+, 22), 367 (90), 320 (86), 250 (99), 221 (98), 189 (67), 104 (100), 77 (99). Anal. Calcd for $C_{25}H_{30}N_4O_3S_2$: C, 60.21; H, 6.06; N, 11.24. Found: C, 60.14; H, 6.27; N, 11.15.

*4.4.6. 8-Amino-2-di(n-pentyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10f**)*

Operation as above with di(*n*-pentyl)amine (0.31 g, 2 mmol), compound **10f** (0.78 g, 74%) was isolated as colorless crystals. Mp: 156–158 °C, IR (KBr): 3480, 3367, 1665, 1521, 1313, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.30 (m, 5H), 6.44 (br, 2H), 4.34 (q, J=7.2 Hz, 2H), 3.04 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.31–1.06 (m, 12H), 0.85 (t, J=7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.0, 158.2, 157.5, 150.7, 148.8, 137.5, 130.7, 128.9, 128.8, 128.1, 116.7, 59.9, 51.4, 29.0, 26.7, 22.2, 14.3, 13.9. MS *m/z*: 526 (M^+, 31), 409 (18), 324 (19), 91 (14), 44 (100). Anal. Calcd for $C_{27}H_{34}N_4O_3S_2$: C, 61.57; H, 6.51; N, 10.64. Found: C, 61.42; H, 6.52; N, 10.81.

*4.4.7. 8-Amino-2-di(n-hexyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10g**)*

Operation as above with di(*n*-hexyl)amine (0.37 g, 2 mmol), compound **10g** (0.79 g, 71%) was isolated as colorless crystals. Mp: >300 °C, IR (KBr): 3497, 3381, 1667, 1519, 1312, 1233 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.30 (m, 5H), 6.43 (br, 2H), 4.34 (q, J=6.8 Hz, 2H), 3.04 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.30–1.10 (m, 16H), 0.87 (t, J=7.2 Hz, 6H). MS *m/z*: 554 (M^+, 89), 423 (41), 353 (37), 324 (53), 167 (21), 43 (100). Anal. Calcd for $C_{29}H_{38}N_4O_3S_2$: C, 62.78; H, 6.90; N, 10.10. Found: C, 62.95; H, 6.86; N, 10.34.

*4.4.8. 8-Amino-3-(4-chlorophenyl)-2-dimethylamino-7-ethoxycarbonyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10h**)*

Operation as above with 4-chlorophenyl isocyanate (0.31 g, 2 mmol) and dimethylamine (0.25 g, 40%, 0.2 mmol), compound **10h** (0.74 g, 83%) was isolated as colorless crystals. Mp: 262–264 °C, IR (KBr): 3487, 3380, 1684, 1520, 1311, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.30 (m, 4H), 6.43 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 2.73 (s, 6H), 1.38 (t, J=7.2 Hz, 3H). MS *m/z*: 448 (M^+, 100), 358 (36), 277 (22), 125 (30), 44 (47). Anal. Calcd for $C_{19}H_{17}ClN_4O_3S_2$: C, 50.83; H, 3.82; N, 12.48. Found: C, 50.97; H, 3.93; N, 12.24.

*4.4.9. 8-Amino-3-(4-chlorophenyl)-2-(di-n-propyl)amino-7-ethoxycarbonyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10i**)*

Operation as above with 4-chlorophenyl isocyanate (0.31 g, 2 mmol) and di(*n*-propyl)amine (0.20 g, 2 mmol), compound **10i** (0.89 g, 88%) was isolated as colorless crystals. Mp: 190–191 °C, IR (KBr): 3495, 3375, 1668, 1521, 1315, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.26 (m, 4H), 6.41 (br, 2H), 4.33 (q, J=6.8 Hz, 2H), 3.02 (t, J=7.2 Hz, 4H), 1.40–1.34 (m, 7H), 0.77 (t, J=7.2 Hz, 6H). MS *m/z*: 504 (M^+, 100), 415 (55), 277 (37), 153 (36), 100 (46), 43 (57). Anal. Calcd for $C_{23}H_{25}ClN_4O_3S_2$: C, 54.70; H, 4.99; N, 11.09. Found: C, 54.62; H, 4.83; N, 11.15.

*4.4.10. 8-Amino-3-(4-chlorophenyl)-2-(di-n-pentyl)amino-7-ethoxycarbonyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10j**)*

Operation as above with 4-chlorophenyl isocyanate (0.31 g, 2 mmol) and di(*n*-pentyl)amine (0.31 g, 2 mmol), compound **10j** (0.87 g, 78%) was isolated as colorless crystals. Mp: 163–164 °C, IR (KBr): 3480, 3367, 1677, 1521, 1314, 1251 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.26 (m, 4H), 6.42 (br, 2H), 4.34 (q, J=7.2 Hz, 2H), 3.04 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.31–1.10 (m, 12H), 0.87 (t, J=7.2 Hz, 6H). MS *m/z*: 560 (M^+, 100), 443 (52), 358 (47), 277 (52), 125 (59), 77 (27). Anal. Calcd for $C_{27}H_{33}ClN_4O_3S_2$: C, 57.79; H, 5.93; N, 9.98. Found: C, 57.71; H, 5.95; N, 9.80.

*4.4.11. 8-Amino-3-(4-chlorophenyl)-2-(di-n-hexyl)amino-7-ethoxycarbonyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10k**)*

Operation as above with 4-chlorophenyl isocyanate (0.31 g, 2 mmol) and di(*n*-hexyl)amine (0.37 g, 2 mmol), compound **10k** (0.88 g, 75%) was isolated as colorless crystals. Mp: 127–128 °C, IR (KBr): 3498, 3383, 1667, 1518, 1311, 1251 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.25 (m, 4H), 6.41 (br, 2H), 4.33 (q, J=6.8 Hz, 2H), 3.04 (t, J=7.6 Hz, 4H), 1.38 (t, J=7.2 Hz, 3H), 1.30–1.12 (m, 16H), 0.88 (t, J=6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.7, 157.8, 157.2, 150.4, 148.5, 135.9, 134.0, 130.5, 130.3, 128.9, 116.4, 59.8, 51.3, 31.3, 26.9, 26.5, 22.3, 14.2, 13.8. MS *m/z*: 588 (M^+, 100), 457 (42), 277 (35), 125 (31), 43 (66). Anal. Calcd for $C_{29}H_{37}ClN_4O_3S_2$: C, 59.12; H, 6.33; N, 9.51. Found: C, 59.37; H, 6.11; N, 9.38.

*4.4.12. 8-Amino-7-ethoxycarbonyl-3-(4-fluorophenyl)-2-methyl(phenyl)amino-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10l**)*

Operation as above with 4-fluorophenyl isocyanate (0.27 g, 2 mmol) and *N*-methyl-*N*-phenylamine (0.27 g, 2 mmol), compound **10l** (0.86 g, 87%) was isolated as colorless crystals. Mp: 276–278 °C, IR (KBr): 3481, 3362, 1671, 1509, 1320, 1221 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.12–6.63 (m, 9H), 6.50 (br, 2H), 4.35 (q, J=7.0 Hz, 2H), 3.34 (s, 3H), 1.39 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.2, 162.5, 160.8, 158.1, 156.6, 150.6, 149.2, 146.4, 132.2, 131.1, 130.5, 130.4, 129.4, 125.9, 125.3, 118.6, 115.4, 115.2, 60.2, 43.0, 14.5. MS *m/z*: 494 (M^+, 100), 447 (22), 342 (33), 224 (16), 109 (13). Anal. Calcd for $C_{24}H_{19}FN_4O_3S_2$: C, 58.29; H, 3.87; N, 11.33. Found: C, 58.41; H, 3.72; N, 11.39.

*4.4.13. 8-Amino-7-ethoxycarbonyl-3-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**10m**)*

Operation as above with 4-fluorophenyl isocyanate (0.27 g, 2 mmol) and pyrrolidine (0.14 g, 2 mmol), compound **10m** (0.82 g,

90%) was isolated as colorless crystals. Mp: 242–244 °C, IR (KBr): 3466, 3353, 1674, 1514, 1328, 1224 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.16 (m, 4H), 6.41 (br, 2H), 4.32 (q, J=7.2 Hz, 2H), 3.11 (t, J=6.6 Hz, 4H), 1.80–1.77 (m, 4H), 1.38 (t, J=7.2 Hz, 3H). MS *m/z*: 458 (M^+, 100), 342 (26), 206 (14), 164 (25), 70 (28). Anal. Calcd for $C_{21}H_{19}FN_4O_3S_2$: C, 55.01; H, 4.18; N, 12.22. Found: C, 55.14; H, 4.01; N, 12.16.

4.5. Synthesis of 2-alkylamino-thieno[3′,2′:4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-ones (12)

*4.5.1. 8-Amino-7-ethoxycarbonyl-3-phenyl-2-(n-propyl) amino-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12a**)*

To the solution of **8** prepared above in methylene dichloride (15 mL) was added *n*-propylamine (0.12 g, 2 mmol). After the reaction mixture was allowed to stand for 0.5 h, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 1–6 h at room temperature. The solution was concentrated under reduced pressure and the residual was recrystallized from ethanol to give 0.65 g (76%) of 2-(*n*-propyl)amino-thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **12a** as colorless crystals. Mp: 201–203 °C, IR (KBr): 3442, 1671, 1592, 1527, 1307, 1133 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.32 (m, 5H), 6.47 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.26 (t, J=5.2 Hz, 1H), 3.39–3.34 (m, 2H), 1.62–1.53 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H). MS *m/z*: 428 (M^+, 100), 339 (30), 177 (20), 77 (31). Anal. Calcd for $C_{20}H_{20}N_4O_3S_2$: C, 56.06; H, 4.70; N, 13.07. Found: C, 56.34; H, 4.84; N, 13.14.

*4.5.2. 8-Amino-7-ethoxycarbonyl-3-phenyl-2-(i-propyl) amino-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12b**)*

Operation as above with *i*-propylamine (0.12 g, 2 mmol), compound **12b** (0.67 g, 78%) was isolated as colorless crystals. Mp: 228–229 °C, IR (KBr): 3470, 3433, 3357, 1683, 1601, 1524, 1318, 770 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.31 (m, 5H), 6.46 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.21–4.16 (m, 1H), 4.01 (d, J=7.2 Hz, 1H), 1.38 (t, J=7.2 Hz, 3H), 1.17 (d, J=6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 157.1, 152.2, 152.0, 148.7, 137.9, 134.0, 130.7, 130.5, 129.8, 128.7, 114.1, 59.9, 44.1, 22.2, 14.4. MS *m/z*: 428 (M^+, 100), 338 (18), 119 (9), 58 (13). Anal. Calcd for $C_{20}H_{20}N_4O_3S_2$: C, 56.06; H, 4.70; N, 13.07. Found: C, 56.32; H, 4.51; N, 13.16.

*4.5.3. 8-Amino-2-(n-butyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12c**)*

Operation as above with *n*-butylamine (0.15 g, 2 mmol), compound **12c** (0.72 g, 82%) was isolated as colorless crystals. Mp: 174–176 °C, IR (KBr): 3478, 3368, 1674, 1592, 1525, 1317, 1252 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.32 (m, 5H), 6.47 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.25 (t, J=4.8 Hz, 1H), 3.42–3.37 (m, 2H), 1.55–1.49 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 1.33–1.24 (m, 2H), 0.91 (t, J=7.2 Hz, 3H). MS *m/z*: 442 (M^+, 3), 382 (100), 341 (42), 338 (38), 267 (48), 191 (43), 56 (41). Anal. Calcd for $C_{21}H_{22}N_4O_3S_2$: C, 56.99; H, 5.01; N, 12.66. Found: C, 57.32; H, 5.15; N, 12.71.

*4.5.4. 8-Amino-2-(i-butyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12d**)*

Operation as above with *i*-butylamine (0.15 g, 2 mmol), compound **12d** (0.65 g, 74%) was isolated as colorless crystals. Mp: 218–220 °C, IR (KBr): 3482, 3437, 3368, 1678, 1595, 1528, 1307, 1134 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.33 (m, 5H), 6.46 (br, 2H), 4.36–4.29 (m, 3H), 3.21 (t, J=6.0 Hz, 2H), 1.90–1.84 (m, 1H), 1.38 (t, J=7.2 Hz, 3H), 0.85 (d, J=6.4 Hz, 6H). MS *m/z*: 442 (M^+, 100), 386 (74), 295 (25), 175 (28), 77 (39). Anal. Calcd for $C_{21}H_{22}N_4O_3S_2$: C, 56.99; H, 5.01; N, 12.66. Found: C, 57.29; H, 5.06; N, 12.79.

*4.5.5. 8-Amino-2-(t-butyl)amino-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12e**)*

Operation as above with *t*-butylamine (0.15 g, 2 mmol), compound **12e** (0.65 g, 88%) was isolated as colorless crystals. Mp: 242–243 °C, IR (KBr): 3500, 3436, 3387, 1668, 1587, 1530, 1338, 1057 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.31 (m, 5H), 6.43 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.14 (s, 1H), 1.42–1.37 (m, 12H). MS *m/z*: 442 (M^+, 100), 386 (86), 339 (59), 167 (31), 77 (76). Anal. Calcd for $C_{21}H_{22}N_4O_3S_2$: C, 56.99; H, 5.01; N, 12.66. Found: C, 56.87; H, 5.09; N, 12.59.

*4.5.6. 8-Amino-3-(4-chlorophenyl)-7-ethoxycarbonyl-2-(n-propyl)amino-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12f**)*

Operation as above with 4-chlorophenyl isocyanate (0.31 g, 2 mmol), compound **12f** (0.79 g, 85%) was isolated as colorless crystals. Mp: 212–214 °C, IR (KBr): 3477, 3447, 3360, 1670, 1593, 1523, 1310, 1257 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.26 (m, 4H), 6.44 (br, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.23 (t, J=4.2 Hz, 1H), 3.39–3.34 (m, 2H), 1.63–1.56 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 157.0, 152.7, 152.1, 149.0, 136.1, 132.6, 130.8, 130.7, 130.3, 114.0, 60.0, 43.9, 22.0, 14.4, 11.3. MS *m/z*: 462 (M^+, 100), 373 (27), 248 (19), 167 (61), 111 (40). Anal. Calcd for $C_{20}H_{19}ClN_4O_3S_2$: C, 51.89; H, 4.14; N, 12.10. Found: C, 51.98; H, 4.08; N, 12.17.

*4.5.7. 8-Amino-7-ethoxycarbonyl-3-(4-fluorophenyl)-2-(n-propyl)amino-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**12g**)*

Operation as above with 4-fluorophenyl isocyanate (0.27 g, 2 mmol), compound **12g** (0.73 g, 82%) was isolated as colorless crystals. Mp: 200–202 °C, IR (KBr): 3453, 3357, 1674, 1593, 1522, 1303, 1214 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.27 (m, 4H), 6.42 (br, 2H), 4.32 (q, J=7.2 Hz, 2H), 4.25 (t, J=4.2 Hz, 1H), 3.39–3.34 (m, 2H), 1.61–1.56 (m, 2H), 1.38 (t, J=7.2 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H). MS *m/z*: 446 (M^+, 100), 387 (46), 285 (13), 166 (13), 94 (25). Anal. Calcd for $C_{20}H_{19}FN_4O_3S_2$: C, 53.80; H, 4.29; N, 12.55. Found: C, 53.85; H, 4.41; N, 12.62.

4.6. Synthesis of 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indenes (13)

*4.6.1. Diethyl 6-phenylamino-5H-2,3-dithia-5,7-diazacyclopenta[c,d]indene-1,4-dicarboxylate (**13a**)*

To the solution of **8a** (0.42 g, 1 mmol) prepared above in CH_3CN (10 mL) was added solid K_2CO_3 (0.03 g, 0.2 mmol). The mixture was stirred for 1–2 h at room temperature and filtered. The obtained solid was washed with water (20 mL) and ethanol (20 mL) to give 0.36 g (87%) of 5*H*-2,3-dithia-5,7-diaza-cyclopenta[*c*,*d*]indene **13a** as colorless crystals. Mp: 269–271 °C, IR (KBr): 3327, 3252, 1686, 1667, 1563, 1481, 1317, 1154 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.23 (s, 1H), 9.52 (s, 1H), 7.93–7.04 (m, 5H), 4.31 (q, J=7.2 Hz, 2H), 4.24 (q, J=7.2 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H), 1.31 (t, J=7.2 Hz, 3H). MS *m/z*: 415 (M^+, 71), 369 (100), 323 (47), 295 (84), 267 (62), 77 (16). Anal. Calcd for $C_{19}H_{17}N_3O_4S_2$: C, 54.93; H, 4.12; N, 10.11. Found: C, 54.85; H, 4.33; N, 10.03.

*4.6.2. Diethyl 6-(4-chlorophenyl)amino-5H-2,3-dithia-5,7-diaza-cyclopenta[c,d]indene-1,4-dicarboxylate (**13b**)*

Operation as above with **8b** (0.45 g, 1 mmol), compound **13b** (0.42 g, 93%) was isolated as colorless crystals. Mp: >300 °C, IR (KBr): 3332, 1687, 1651, 1555, 1474, 1326, 1177 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.23 (s, 1H), 9.62 (s, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.33 (d, J=9.2 Hz, 2H), 4.31–4.24 (m, J=7.2 Hz, 4H), 1.36 (t, J=7.2 Hz, 3H), 1.31 (t, J=7.2 Hz, 3H). MS *m/z*: 449 (M^+, 42), 403 (100), 357 (55), 329 (28), 301 (30), 266 (28). Anal. Calcd for

$C_{19}H_{16}ClN_3O_4S_2$: C, 50.72; H, 3.58; N, 9.34. Found: C, 50.57; H, 3.41; N, 9.39.

*4.6.3. Diethyl 6-(4-fluorophenyl)amino-5H-2,3-dithia-5,7-diaza-cyclopenta[c,d]indene-1,4-dicarboxylate (**13c**)*

Operation as above with **8c** (0.43 g, 1 mmol), compound **13c** (0.39 g, 90%) was isolated as colorless crystals. Mp: 279–281 °C, IR (KBr): 3340, 3265, 1686, 1650, 1564, 1473, 1326, 1176 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 9.22 (br, 1H), 8.09–7.03 (m, 4H), 4.21 (q, J=7.2 Hz, 4H), 1.31 (t, J=7.2 Hz, 6H). MS *m/z*: 433 (M^+, 46), 387 (100), 341 (64), 313 (40), 285 (62), 241 (26), 109 (56), 44 (70). Anal. Calcd for $C_{19}H_{16}FN_3O_4S_2$: C, 52.64; H, 3.72; N, 9.69. Found: C, 52.81; H, 3.51; N, 9.83.

*4.6.4. Diethyl 6-(3-methylphenyl)amino-5H-2,3-dithia-5,7-diaza-cyclopenta[c,d]indene-1,4-dicarboxylate (**13d**)*

Operation as above with **8d** (0.43 g, 1 mmol), compound **13d** (0.38 g, 88%) was isolated as colorless crystals. Mp: >300 °C, IR (KBr): 3340, 3274, 1680, 1651, 1561, 1469, 1327, 1179 cm^{-1}. ^1H NMR (DMSO-d_6, 600 MHz): δ 10.25 (br, 1H), 9.47 (br, 1H), 7.89–6.86 (m, 4H), 4.29–4.26 (m, 4H), 2.32 (s, 3H), 1.34–1.30 (m, 6H). MS *m/z*: 429 (M^+, 100), 383 (41), 337 (32), 309 (30), 281 (27). Anal. Calcd for $C_{20}H_{19}N_3O_4S_2$: C, 55.93; H, 4.46; N, 9.78. Found: C, 55.71; H, 4.54; N, 9.95.

4.7. Synthesis of 2-aryloxy-thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (14)

*4.7.1. 8-Amino-7-ethoxycarbonyl-2-(4-methoxyphenoxy)-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14a**)*

A mixture of substituted 4-methoxyphenol (0.25 g, 2 mmol) and solid K_2CO_3 (0.03 g, 0.2 mmol) in CH_3CN (10 mL) was stirred for 10 min. A solution of **8** prepared above in CH_3CN (10 mL) was added. The mixture was stirred for 6–8 h at 40–50 °C and filtered, the obtained solid was washed with water (20 mL) and ethanol (20 mL) to give **13**. The filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give 0.69 g (70%) of 8-amino-7-ethoxycarbonyl-2-(4-methoxy-phenoxy)-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one **14** as colorless crystals. Mp: 128–130 °C, IR (KBr): 3478, 3370, 1694, 1671, 1533, 1500, 1311, 1248 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59–6.89 (m, 9H), 5.99 (br, 2H), 4.30 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.35 (t, J=7.2 Hz, 3H). MS *m/z*: 493 (M^+, 8), 214 (47), 123 (100), 95 (84), 77 (57). Anal. Calcd for $C_{24}H_{19}N_3O_5S_2$: C, 58.41; H, 3.88; N, 8.51. Found: C, 58.38; H, 3.72; N, 8.74.

*4.7.2. 8-Amino-7-ethoxycarbonyl-2-(2-methoxyphenoxy)-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14b**)*

Operation as above with 2-methoxyphenol (0.25 g, 2 mmol), compound **14b** (0.65 g, 66%) was isolated as colorless crystals. Mp: 233–234 °C, IR (KBr): 3458, 3350, 1692, 1669, 1540, 1496, 1314, 1256 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58–6.95 (m, 9H), 5.90 (br, 2H), 4.29 (q, J=7.2 Hz, 2H), 3.79 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 157.3, 155.6, 150.8, 149.2, 148.8, 140.7, 134.4, 130.7, 129.3, 129.1, 128.2, 127.2, 122.6, 120.6, 119.2, 112.5, 60.1, 56.0, 14.4. MS *m/z*: 493 (M^+, 100), 448 (5), 324 (15), 167 (11), 77 (17). Anal. Calcd for $C_{24}H_{19}N_3O_5S_2$: C, 58.41; H, 3.88; N, 8.51. Found: C, 58.62; H, 3.68; N, 8.36.

*4.7.3. 8-Amino-7-ethoxycarbonyl-2-(3-methylphenoxy)-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14c**)*

Operation as above with 3-methylphenol (0.22 g, 2 mmol), compound **14c** (0.60 g, 63%) was isolated as colorless crystals. Mp: 244–246 °C, IR (KBr): 3510, 3385, 1693, 1662, 1541, 1486, 1358, 1239 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58–6.96 (m, 9H), 5.97 (br, 2H), 4.29 (q, J=7.2 Hz, 2H), 2.36 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). MS *m/z*: 477 (M^+, 100), 370 (9), 286 (21), 167 (17), 77 (29). Anal. Calcd for $C_{24}H_{19}N_3O_4S_2$: C, 60.36; H, 4.01; N, 8.80. Found: C, 60.21; H, 3.92; N, 8.97.

*4.7.4. 8-Amino-7-ethoxycarbonyl-2-(2-methylphenoxy)-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14d**)*

Operation as above with 2-methylphenol (0.22 g, 2 mmol), compound **14d** (0.57 g, 60%) was isolated as colorless crystals. Mp: 227–228 °C, IR (KBr): 3459, 3350, 1694, 1669, 1542, 1486, 1356, 1253 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.13 (m, 9H), 5.89 (br, 2H), 4.30 (m, J=7.2 Hz, 2H), 2.13 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). MS *m/z*: 477 (M^+, 100), 430 (11), 324 (13), 286 (17), 77 (14). Anal. Calcd for $C_{24}H_{19}N_3O_4S_2$: C, 60.36; H, 4.01; N, 8.80. Found: C, 60.27; H, 4.19; N, 8.84.

*4.7.5. 8-Amino-2-(2,4-dichloro-6-methylphenoxy)-7-ethoxy-carbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14e**)*

Operation as above with 2,4-dichloro-6-methylphenol (0.33 g, 2 mmol), compound **14e** (0.60 g, 55%) was isolated as colorless crystals. Mp: 223–225 °C, IR (KBr): 3486, 3389, 1696, 1670, 1543, 1354, 1171 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.18 (m, 7H), 5.87 (br, 2H), 4.30 (q, J=7.2 Hz, 2H), 2.18 (s, 3H), 1.35 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.7, 156.9, 153.6, 148.7, 148.6, 144.8, 134.0, 133.9, 131.6, 130.4, 129.6, 129.4, 129.2, 128.2, 127.8, 127.7, 127.3, 119.5, 60.2, 16.4, 14.3. MS *m/z*: 545 (M^+, 100), 464 (14), 391 (19), 324 (15), 117 (13), 77 (18), 44 (46). Anal. Calcd for $C_{24}H_{17}Cl_2N_3O_4S_2$: C, 52.75; H, 3.14; N, 7.69. Found: C, 52.93; H, 3.11; N, 7.91.

*4.7.6. 8-Amino-2-(3,4-dimethylphenoxy)-7-ethoxycarbonyl-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14f**)*

Operation as above with 3,4-dimethylphenol (0.24 g, 2 mmol), compound **14f** (0.61 g, 62%) was isolated as colorless crystals. Mp: 202–204 °C, IR (KBr): 3509, 3388, 1693, 1659, 1541, 1357, 1247 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59–6.87 (m, 8H), 6.02 (br, 2H), 4.30 (q, J=7.2 Hz, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 1.35 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 157.2, 155.7, 149.5, 149.0, 148.8, 137.8, 134.4, 134.3, 130.7, 130.0, 129.4, 129.1, 128.1, 122.0, 119.1, 118.3, 60.1, 19.7, 19.1, 14.4. MS *m/z*: 491 (M^+, 100), 446 (16), 324 (30), 300 (70), 167 (20), 77 (32). Anal. Calcd for $C_{25}H_{21}N_3O_4S_2$: C, 61.08; H, 4.31; N, 8.55. Found: C, 61.25; H, 4.44; N, 8.47.

*4.7.7. 8-Amino-7-ethoxycarbonyl-2-(3-methylphenoxy)-3-(3-methylphenyl)-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14g**)*

Operation as above with 3-methylphenol (0.22 g, 2 mmol), compound **14g** (0.66 g, 67%) was isolated as colorless crystals. Mp: 230–232 °C, IR (KBr): 3486, 3365, 1674, 1533, 1354, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46–6.96 (m, 8H), 5.98 (br, 2H), 4.29 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.35 (t, J=7.2 Hz). MS *m/z*: 491 (M^+, 100), 338 (31), 286 (42), 167 (15), 77 (39). Anal. Calcd for $C_{25}H_{21}N_3O_4S_2$: C, 61.08; H, 4.31; N, 8.55. Found: C, 60.94; H, 4.58; N, 8.54.

*4.7.8. 8-Amino-2-(2,4-dichlorophenoxy)-7-ethoxycarbonyl-3-(3-methylphenyl)-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**14h**)*

Operation as above with 2,4-dichlorophenol (0.33 g, 2 mmol), compound **14h** (0.66 g, 61%) was isolated as colorless crystals. Mp: 279–280 °C, IR (KBr): 3487, 3365, 1674, 1534, 1476, 1355, 1268 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.19 (m, 7H), 5.89 (br, 2H), 4.30 (q, J=7.2 Hz, 2H), 2.45 (s, 3H), 1.35 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 157.0, 154.5, 149.0, 148.5, 146.3, 139.7, 133.8, 132.3, 130.6, 130.4, 130.1, 129.3, 128.6, 127.9, 127.8, 125.0, 124.7, 119.8, 60.2, 16.3, 21.3, 14.4. MS *m/z*: 545 (M^+, 100), 464 (13), 338

(27), 266 (13), 132 (17), 44 (39). Anal. Calcd for $C_{24}H_{17}Cl_2N_3O_4S_2$: C, 52.75; H, 3.14; N, 7.69. Found: C, 52.66; H, 3.02; N, 7.84.

5. Crystallographic material

Crystallographic data for **10m** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 691893. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.036.

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