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Efficient synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones by a sequential aza-Wittig reaction/base catalyzed cyclization

Zhong-Xu Dai[1], Hong Chen[1,*], Ming-Guo Liu[1] and Ming-Wu Ding[2]

[1] Hubei Key Laboratory of Natural Products Research and Development, China Three Gorges University, Yichang 443002, PR China

[2] Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, PR China

*Corresponding author
e-mail: chenhong3736@sina.com

Abstract

7-Benzyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones were synthesized by base catalyzed reactions of nucleophilic reagents (aliphatic amines, alcohols or phenols) with carbodiimides **4**, which in turn were obtained by the aza-Wittig reaction of iminophosphoranes **3** with aromatic isocyanates.

Keywords: aza-Wittig reaction; carbodiimide; iminophosphorane; thieno[2,3-*d*]pyrimidin-4(3*H*)-one.

Introduction

Thienopyrimidinones show significant biological activities (Modica et al., 2000, 2001; Jennings et al., 2005; Wang et al., 2005; Warshakoon et al., 2006; Witty et al., 2006; Zhang et al., 2007; Amr et al., 2010; Mavrova et al., 2010). Over the past 20 years, the aza-Wittig reactions of iminophosphoranes have been the focus of increasing attention in view of their utility in the synthesis of *N*-heterocyclic compounds (Brase et al., 2005; Lertpibulpanya et al., 2006; Palacios et al., 2007). 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. Consequently, the discovery of novel functionalized iminophosphoranes is important in this respect. Recently, we have become interested in the synthesis of thienopyrimidinones, quinazolinones, and imidazolinones by aza-Wittig reaction, with the aim of evaluating their fungicidal activities (Ding et al., 2004; Yuan et al., 2006; Li et al., 2007; He et al., 2009; Huang et al., 2009). Here, we report an efficient synthesis of new derivatives of 7-benzyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones under mild conditions. This work is a continuation of our previous synthetic efforts.

Results and discussion

2-Amino-6-benzyl-3-ethoxycarbonyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine **2** was synthesized by the Gewald reaction in good yield (85%). Compound **2** was easily converted to iminophosphorane **3** by treatment with triphenylphosphine, hexachloroethane, and triethylamine in dry acetonitrile in good yield (Scheme 1). The conversion of compound **2** to iminophosphorane **3** involves initial formation of Ph_3PCl_2 from the reaction of Ph_3P with C_2Cl_6, and further reaction with compound **2** to give iminophosphorane **3** in the presence of Et_3N (Ding, 1997).

Iminophosphorane **3** was treated with an equimolar amount of aromatic isocyanate to give the corresponding carbodiimide **4**, which was allowed to react with an aliphatic amine to provide guanidine intermediate **5** (Scheme 2). Even in refluxing toluene, the intermediate products **5** did not cyclize. However, by treatment with EtONa in EtOH at room temperature, compounds **5** underwent intramolecular heterocyclization to give the expected 2-alkylamino-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6a–g** in 82–90% yields. The reaction of carbodiimides **4** with alcohols in the presence of a catalytic amount of sodium alkoxide produced 2-alkyloxy-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6h–j** in 87–93% yields. The reaction of carbodiimides **4** with phenols in the presence of a catalytic amount of solid potassium carbonate produced 2-aryloxy-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6k–m** in 89–93% yields (Scheme 2).

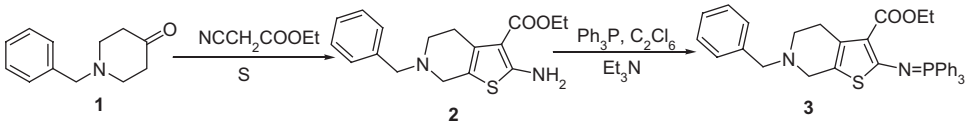
Carbodiimides **4** were allowed to react with hydrazine hydrate to give the 3-amino-2-arylamino-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **7** in 85–87% yields (Scheme 3). It is worth noting that the formation of **7** is rather surprising. The formation of **7** rather than **8** can be rationalized in terms of an initial nucleophilic addition of hydrazine to give the guanidine intermediate **5**, which then undergoes cyclization to give **7** (Liang et al., 2003).

Owing to the high reactivity of carbodiimide **4**, its preparation must be carried out at low temperature (0–5°C) under anhydrous conditions. Otherwise, hydrolysis and polymerization of carbodiimide **4** take place, which results in low yields of **6** and **7** (Ding et al., 2003, 2005; Blanco et al., 2006).

Experimental section

General

Melting points were determined on a Bibby SMP3 apparatus and were uncorrected. IR spectra were recorded on a PE-983 infrared spectrometer in KBr pellets. The ^{1}H NMR (600 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on Varian Mercury 600 and Bruker Vector 22FT-IR 400 spectrometers, respectively.



Scheme 1 Synthesis route of iminophosphorane **3**.

Electron-impact mass spectra (EI-MS) were measured on a Finnigan Trace MS spectrometer (70 eV). The electrospray ionization spectra (ESI-MS) were measured on a Bruker amaZon X&ETD MS spectrometer. Elemental analyses were obtained on a Vario EL III instrument. Compound **2** was synthesized as previously reported (Nakanishi and Tahara, 1971; Sabnis et al., 1999).

Iminophosphorane 3

A mixture of 2-amino-6-benzyl-3-ethoxycarbonyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**2**, 2.53 g, 8 mmol), triphenylphosphine (3.14 g, 12 mmol), and hexachloroethane (2.84 g, 12 mmol) in anhydrous acetonitrile (40 mL) was treated dropwise with triethylamine (2.42 g, 24 mmol) at room temperature. The color of the mixture quickly turned yellow. After stirring for 4–6 h, the solvent was removed under reduced pressure and the residue was crystallized from ethanol to give iminophosphorane **3** as light yellow needles: yield 3.83 g (83%); mp 115–116°C; IR: 1684, 1462, 1174, 684, 524 cm^{-1}; ^1H NMR: δ 7.81–7.21 (m, 20H), 4.28 (q, *J*=7.2 Hz, 2H), 3.61 (s, 2H), 3.26 (s, 2H), 2.88 (t, *J*=5.6 Hz, 2H), 2.71 (t, *J*=5.6 Hz, 2H), 1.33 (t, *J*=7.2 Hz, 3H); EI-MS: m/z 576 (M^+, 65), 262 (63), 183 (100), 108 (41), 91 (63). Anal. Calcd for $C_{35}H_{33}N_2O_2PS$: C, 72.89; H, 5.77; N, 4.86. Found: C, 73.02; H, 5.51; N, 4.98.

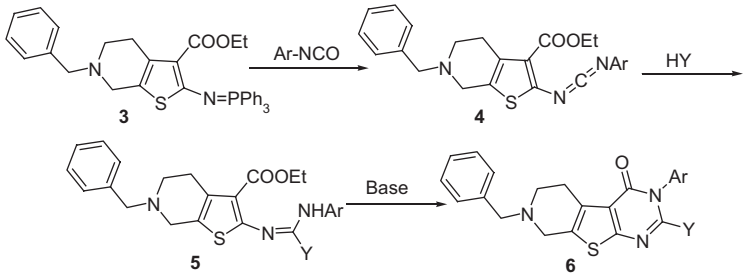
General preparation of 2-(alkylamino)-thieno[2,3-*d*] pyrimidin-4(3*H*)-ones (6a–f)

Aromatic isocyanate (2 mmol) under nitrogen atmosphere was added to a solution of iminophosphorane **3** (1.15 g, 2 mmol) in anhydrous dichloromethane (10 mL) at room temperature. Iminophosphorane **3** was consumed after 12 h at 0–5°C, as monitored by thin layer chromatography (volume ratio, ether:petroleum ether=1:2). The solvent was removed under reduced pressure and the residue was treated with ether/petroleum ether (volume ratio 1:2, 20 mL), which caused precipitation of triphenylphosphine oxide. Concentration of the solution gave carbodiimide **4**, which was used directly without further purification. Aliphatic amine (2 mmol) was added to the solution of carbodiimide **4** in anhydrous dichloromethane (10 mL). After 5–6 h at room temperature the solvent was removed and the residue was treated with anhydrous ethanol (10 mL) containing EtONa (1 mmol). The mixture was stirred for another 6–8 h at room temperature and then concentrated. The residue was crystallized from ethanol.

7-Benzyl-3-(4-chlorophenyl)-2-propylamino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6a) White crystals; yield 87%; mp 215–216°C; IR: 3373,1673, 1540, 696 cm^{-1}; ^1H NMR: δ 7.54–7.21 (m, 9H, Ar-H), 4.03 (br, 1H), 3.72 (s, 2H), 3.59 (s, 2H), 3.30 (q, *J*=7.2 Hz, 2H), 2.97 (t, *J*=5.8 Hz, 2H), 2.81 (t, *J*=5.8 Hz, 2H), 1.49 (q, *J*=7.2 Hz, 2H), 0.84 (s, *J*=7.2 Hz, 3H); EI-MS: m/z 464 (M^+, 34), 345 (57), 177 (19), 152 (24), 91 (100). Anal. Calcd for $C_{25}H_{25}ClN_4OS$: C, 64.57; H, 5.42; N, 12.05. Found: C, 64.78; H, 5.15; N, 12.27.

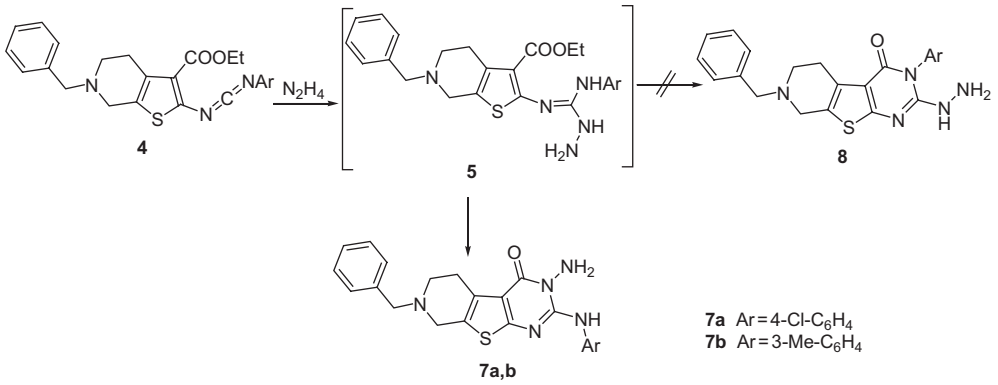
7-Benzyl-3-phenyl-2-(isobutylamino)-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6b) White crystals; yield 82%; mp 158–159°C; IR: 3457,1675, 1537, 671 cm^{-1}; ^1H NMR: δ 7.58–7.28 (m, 10H), 4.11 (br, 1H), 3.73 (s, 2H), 3.61 (s, 2H), 3.18 (t, 2H), 3.01 (t, *J*=4.8 Hz, 2H), 2.83 (t, *J*=4.8 Hz, 2H), 1.77 (m, 1H), 0.80 (s, 6H); ^{13}C NMR: δ 165.9, 158.7, 150.5, 138.1, 134.5, 130.5, 129.8, 129.5, 129.1, 128.8, 128.3, 127.1, 124.1, 114.2, 61.9, 51.4, 49.8, 49.0, 27.8, 25.5, 19.9; EI-MS: m/z 444 (M^+, 66), 353 (21), 325 (78), 269 (72), 91 (100). Anal. Calcd for $C_{26}H_{28}N_4OS$: C, 70.24; H, 6.35; N, 12.60. Found: C, 70.37; H, 6.55; N, 12.92.

7-Benzyl-3-(3-methylphenyl)-2-cyclohexylamino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6c) White crystals; yield 89%; mp 183–184°C; IR: 3395, 1679,



6a: Ar = 4-Cl-C_6H_4, Y = $NHCH_2CH_2CH_3$; **6b:** Ar = Ph, Y = $NHCH_2CH(CH_3)_2$;
6c: Ar = 3-Me-C_6H_4, Y = NH(Cyclohexyl); **6d:** Ar = 4-F-C_6H_4, Y = $N(CH_2CH_3)_2$;
6e: Ar = Ph, Y = Morpholino; **6f:** Ar = 4-Cl-C_6H_4, Y = Pyrrolidino;
6g: Ar = 4-F-C_6H_4, Y = MeO; **6h:** Ar = 4-Cl-C_6H_4, Y = EtO;
6i: Ar = Ph, Y = *n*-PrO; **6j:** Ar = Ph, Y = 1-Naphthyloxy;
6k: Ar = 4-Cl-C_6H_4, Y = 4-MeO-C_6H_4O; **6l:** Ar = Ph, Y = 4-Me-C_6H_4O

Scheme 2 **6a**: Ar=4-Cl-C_6H_4, Y=$NHCH_2CH_2CH_3$; **6b**: Ar=Ph, Y=$NHCH_2CH(CH_3)_2$; **6c**: Ar=3-Me-C_6H_4, Y=NH(Cyclohexyl); **6d**: Ar=4-F-C_6H_4, Y=$N(CH_2CH_3)$; **6e**: Ar=Ph, Y=Morpholino; **6f**: Ar=4-Cl-C_6H_4, Y=Pyrrolidino; **6g**: Ar=4-F-C_6H_4, Y=MeO; **6h**: Ar=4-Cl-C_6H_4, Y=ETO; **6i**: Ar=Ph, Y=n-PrO; **6j**: Ar=Ph, Y=1-Naphthyloxy; **6k**: Ar=4-Cl-C_6H_4, Y=4-MeO-C_6H_4O; **6l**: Ar=Ph, Y=4-Me-C_6H_4O.



Scheme 3 Synthesis route of compound **7**.

1535, 689 cm^{-1}; ^1H NMR: δ 7.47–7.05 (m, 9H), 3.95 (d, 1H), 3.91–3.86 (m, 1H), 3.72 (s, 2H), 3.61 (s, 2H), 2.99 (t, *J*=5.1 Hz, 2H), 2.82 (t, *J*=5.1 Hz, 2H), 2.42 (s, 3H), 1.99–0.99 (m, 10H); ^{13}C NMR: δ 165.9, 158.7, 149.7, 140.6, 138.0, 134.3, 130.4, 130.2, 129.4, 129.1, 129.0, 128.2, 127.0, 125.4, 123.7, 114.0, 61.8, 51.4, 49.7, 32.6, 32.5, 25.4, 25.3, 24.4, 21.2; EI-MS: m/z 484 (M^+, 28), 365 (33), 283 (24), 177 (14), 91 (100). Anal. Calcd for $C_{29}H_{32}N_4OS$: C, 71.87; H, 6.66; N, 11.56. Found: C, 71.98; H, 6.51; N, 11.78.

7-Benzyl-3-(4-fluorophenyl)-2-diethylamino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6d) White crystals; yield 83%; mp 149–150°C; IR: 1673, 1540, 1335, 696 cm^{-1}; ^1H NMR: δ 7.37–7.14 (m, 9H), 3.71 (s, 2H), 3.60 (s, 2H), 3.06–3.02 (m, 6H), 2.81 (t, *J*=5.4 Hz, 2H), 0.83 (t, *J*=6.9 Hz, 6H); ^{13}C NMR: δ 164.0, 160.6, 159.7, 154.6, 138.0, 130.7, 130.6, 129.8, 129.0, 128.3, 127.2, 126.9, 116.0, 115.8, 61.8, 51.5, 49.8, 45.1, 25.5, 12.5; EI-MS: m/z 462 (M^+, 60), 343 (56), 193 (32), 137 (29), 91 (100). Anal. Calcd for $C_{26}H_{27}FN_4OS$: C, 67.51; H, 5.88; N, 12.11. Found: C, 67.64; H, 5.61; N, 12.44.

7-Benzyl-3-phenyl-2-morpholino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6e) White crystals; yield 89%; mp 189–190°C; IR: 1675, 1541, 1223, 691 cm^{-1}; ^1H NMR: δ 7.50–7.26 (m, 10H), 3.73 (s, 2H), 3.63 (s, 2H), 3.40 (t, *J*=4.2 Hz, 4H), 3.09 (t, *J*=4.2 Hz, 4H), 3.03 (t, *J*=5.4 Hz, 2H), 2.83 (t, *J*=5.4 Hz, 2H); EI-MS: m/z 458 (M^+, 69), 367 (20), 339 (82), 253 (27), 91 (100). Anal. Calcd for $C_{26}H_{26}N_4O_2S$: C, 68.10; H, 5.71; N, 12.22. Found: C, 68.41; H, 5.98; N, 12.51.

7-Benzyl-3-(4-chlorophenyl)-2-pyrrolidino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6f) White crystals; yield 90%; mp 193–194°C; IR: 1677, 1533, 1135, 683 cm^{-1}; ^1H NMR: δ 7.44–7.25 (m, 9H), 3.72 (s, 2H), 3.59 (s, 2H), 3.04–2.99 (m, 6H), 2.82 (t, *J*=5.4 Hz, 2H), 1.72 (t, *J*=5.1 Hz, 4H); EI-MS: m/z 477 (M^+, 28), 357 (62), 207 (27), 165 (31), 91 (100). Anal. Calcd for $C_{26}H_{25}ClN_4OS$: C, 65.46; H, 5.28; N, 11.75. Found: C, 65.71; H, 5.06; N, 11.51.

General preparation of 2-alkyloxythieno[2,3-*d*]pyrimidin-4(3*H*)-ones (6g–i)

A solution of sodium alkoxide RONa (5% in ROH) was added to the solution of carbodiimide **4** in anhydrous dichloromethane (10 mL). The mixture was stirred for 4–7 h at room temperature, then concentrated, and the residue was crystallized from ethanol.

7-Benzyl-3-(4-fluorophenyl)-2-methoxy-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6g) White crystals; yield 93%; mp 203–204°C; IR: 1678, 1562, 1274, 686 cm^{-1}; ^1H NMR: δ 7.39–7.17 (m, 9H), 3.92 (s, 3H), 3.73 (s, 2H), 3.64 (s, 2H), 3.04 (t, *J*=5.1 Hz, 2H), 2.84 (t, *J*=5.1 Hz, 2H); ^{13}C NMR: δ 163.6, 162.4, 161.1, 158.5, 153.3, 129.9, 129.8, 129.7, 129.0, 128.2, 127.4, 127.1, 117.2, 116.3, 61.8, 55.9, 51.3, 49.6, 25.4; EI-MS: m/z 421 (M^+, 39), 330 (14), 302 (100), 137 (41), 91 (100). Anal. Calcd for $C_{23}H_{20}FN_3O_2S$: C, 65.54; H, 4.78; N, 9.97. Found: C, 65.78; H, 4.62; N, 9.71.

7-Benzyl-3-(4-chlorophenyl)-2-ethoxy-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6h) White crystals; yield 91%; mp 160–161°C; IR: 1673, 1570, 1179, 776 cm^{-1}; ^1H NMR: δ 7.46–7.14 (m, 9H), 4.39 (q, *J*=7.2 Hz, 2H), 3.73 (s, 2H), 3.63 (s, 2H), 3.03 (t, *J*=5.7 Hz, 2H), 2.84 (t, *J*=5.7 Hz, 2H), 1.24 (t, *J*=6.9 Hz, 3H); EI-MS: m/z 451 (M^+, 27), 332 (64), 304 (16), 151 (52), 91 (100). Anal. Calcd for $C_{24}H_{22}ClN_3O_2S$: C, 63.78; H, 4.91; N, 9.30. Found: C, 63.94; H, 5.14; N, 9.61.

7-Benzyl-3-phenyl-2-propoxy-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6i) White crystals (yield 87%); mp 145–146°C; IR: 1679 (C=O), 1556, 1335, 739 cm^{-1}; ^1H NMR: δ 7.50–7.20 (m, 10H), 4.28 (q, *J*=6.3 Hz, 2H), 3.73 (s, 2H), 3.63 (s, 2H), 3.05 (t, *J*=5.7 Hz, 2H), 2.84 (t, *J*=5.7 Hz, 2H), 1.59 (m, *J*=7.2 Hz, 2H), 0.78 (t, *J*=7.2 Hz, 3H); EI-MS: m/z 431 (M^+, 10), 312 (21), 270 (21), 151 (28), 91 (100). Anal. Calcd for $C_{25}H_{25}N_3O_2S$: C, 69.58; H, 5.84; N, 9.74. Found: C, 69.81; H, 5.65; N, 9.91.

General preparation of 2-aryloxy-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (6j–l)

A phenol was added to the solution of carbodiimide **4** in anhydrous acetonitrile (10 mL). The mixture was stirred for 0.5–1 h at room temperature, treated with solid potassium carbonate, stirred for an additional 6–8 h at 40–50°C, and filtered. The filtrate was concentrated and the residue was crystallized from dichloromethane/petroleum ether.

7-Benzyl-3-phenyl-2-(1-naphthyloxy)-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6j) White crystals; yield 93%; mp 187–188°C; IR: 1687, 1553, 1357, 876 cm^{-1}; ^1H NMR: δ 7.85–7.25 (m, 17H), 3.71 (s, 2H), 3.59 (s, 2H), 3.08 (t, *J*=5.7 Hz, 2H), 2.84 (t, *J*=5.7 Hz, 2H); ^{13}C NMR:

δ 162.0, 158.7, 152.5, 147.4, 137.9, 134.9, 134.6, 129.8, 129.6, 129.1, 129.0, 128.5, 128.3, 128.1, 127.9, 127.2, 126.5, 126.47, 126.42, 126.1, 125.3, 120.9, 118.2, 117.8, 61.8, 51.4, 49.7, 25.4; EI-MS: m/z 515 (M^+, 48), 396 (56), 277 (32), 253 (42), 91 (100). Anal. Calcd for $C_{32}H_{25}N_3O_2S$: C, 74.54; H, 4.89; N, 8.15. Found: C, 74.20; H, 4.61; N, 8.31.

7-Benzyl-3-(4-chlorophenyl)-2-(4-methoxyphenoxy)-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6k) White crystals; yield 90%; mp 203–204°C; IR: 1693, 1531, 1277, 903 cm^{-1}; ^1H NMR: δ 7.51–6.87 (m, 13H), 3.80 (s, 3H), 3.72 (s, 2H), 3.61(s, 2H), 3.05(t, *J*=5.7 Hz, 2H), 2.84 (t, *J*=5.7 Hz, 2H); EI-MS: m/z 529 (M^+, 23), 410 (34), 287 (49), 257 (18), 91 (100). Anal. Calcd for $C_{29}H_{24}ClN_3O_3S$: C, 65.71; H, 4.56; N, 7.93. Found: C, 65.94; H, 4.79; N, 8.12.

7-Benzyl-3-phenyl-2-(4-methylphenoxy)-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6l) White crystals; yield 89%; mp 155–156°C; IR: 1696, 1563, 933, 696 cm^{-1}; ^1H NMR: δ 7.51–6.97 (m, 14H), 3.70 (s, 2H), 3.59 (s, 2H), 3.06 (t, *J*=5.1 Hz, 2H), 2.82 (t, *J*=5.1 Hz, 2H), 2.32 (s, 3H); EI-MS: m/z 479 (M^+, 61), 388 (15), 360 (83), 253 (78), 91 (100). Anal. Calcd for $C_{29}H_{25}N_3O_2S$: C, 72.63; H, 5.25; N, 8.76. Found: C, 72.91; H, 5.48; N, 8.92.

General preparation of 3-amino-2-arylamino-thieno-[2,3-*d*]pyrimidin-4(3*H*)-ones (7a–b)

A solution of hydrazine hydrate (0.35 g, 6 mmol, 85%) in anhydrous acetonitrile (5 mL) was added to the solution of carbodiimide **4** in anhydrous acetonitrile (15 mL). The mixture was stirred for 0.5–1 h at room temperature and the resultant solid was filtered and crystallized from dichloromethane/petroleum ether.

3-Amino-2-[(4-chlorophenyl)amino]-7-benzyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (7a) White crystals; yield 87%; mp 166–167°C; IR: 3475, 3319, 3276, 1661, 1529, 1357 cm^{-1}; ^1H NMR: δ 8.43 (s, 1H), 7.52–7.26 (m, 9H), 4.85 (s, 2H), 3.70 (s, 2H), 3.47 (s, 2H), 3.02 (t, *J*=5.6 Hz, 2H), 2.81 (t, *J*=5.6 Hz, 2H); ^{13}C NMR: δ 163.0, 157.5, 146.9, 137.4, 136.1, 129.5, 128.7, 128.6, 128.4, 128.1, 127.5, 125.3, 120.8, 114.5, 62.6, 51.3, 50.3, 25.6; ESI-MS: $[M+H]^+$ peak at m/z 438.8, M^+ peak at m/z 437.8. Anal. Calcd for $C_{22}H_{20}ClN_5OS$: C, 60.34; H, 4.60; N, 15.99. Found: C, 60.12; H, 4.88; N, 15.67.

3-Amino-2-[(3-methylphenyl)amino]-7-benzyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (7b) White crystals; yield 85%; mp 145–146°C; IR: 3463, 3342 (N-H), 3307, 1680, 1536, 1357 cm^{-1}; ^1H NMR: δ 8.39 (s, 1H), 7.49–6.89 (m, 9H), 4.80 (s, 2H), 3.69 (s, 2H), 3.49 (s, 2H), 3.02 (t, *J*=5.4 Hz, 2H), 2.80 (t, *J*=5.4 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR: δ 163.6, 157.9, 147.4, 138.7, 137.7, 137.4, 129.3, 128.8, 128.7, 128.4, 127.4, 125.3, 124.4, 120.5, 117.1, 114.5, 62.4, 51.5, 50.1, 25.6, 21.5; ESI-MS: M^+ peak at m/z 417.9. Anal. Calcd for $C_{23}H_{23}N_5OS$: C, 66.16; H, 5.55; N, 16.77. Found: C, 66.49; H, 5.21; N, 16.61.

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