A Facile Synthesis of Thieno[2,3-*d*]pyrimidine Derivatives

Using Inorganic Base Catalysis

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I. General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR and ^{13}C NMR spectra were recorded at 25°C at 500 MHz and 125 MHz, respectively, with TMS as internal standard. Elemental analyses were carried out on a Perkin-Elmer PE-2400 analyzer. Melting points were determined on a TECH X-4 micro-melting point apparatus.

II. Synthesis and analytical data of compound 1

The procedure for the preparation of **1**: To a solution of 1-benzylpiperidin-4-one (9.27 mL, 50 mmol), ethyl acetoacetate (5.87 mL, 55 mmol) and sulfur (1.76 g, 55 mmol) in DMF (20 mL) was added triethylamine (6 mL) in one portion. The reaction mixture was stirred at room temperature for 5.0 h. After the substrate was consumed as indicated by TLC, the resulting mixture was then poured into ice-water (200 mL) under stirring. The precipitated solid was collected by filtration, washed with water (3×100 mL), and dried in vacuo to afford the product **1** (14.71 g, yield: 93%) as a pale yellow solid.

ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (**1**)

pale yellow solid, mp 103-107°C: ^1H NMR (500 MHz, CDCl_3) δ = 1.310 (s, 3H), 2.746 (d, J = 5.5, 2H), 2.818 (s, 2H), 3.402 (s, 2H), 3.670 (s, 2H), 4.235-4.249 (d, J = 7.0, 2H), 5.976 (s, 2H), 7.310-7.375 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ = 14.46, 27.34, 50.29, 51.37, 59.46, 62.07, 105.40, 114.88, 127.21, 128.35, 129.16, 131.12, 138.28, 162.13, 166.00; Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 64.53; H, 6.37; N, 8.85. Found: C, 64.66; H, 6.45; N, 8.73.

III. Synthesis and analytical data of compound 2

The procedure for the preparation of **2**: To a solution of **1** (5.35 g, 17 mmol), PPh_3 (8.91 g, 34 mmol), and C_2Cl_6 (8.05 g, 34 mmol) was added triethylamine (8 mL) in one portion. The reaction mixture was stirred at 0-5°C for 5-6 h. After the substrate was consumed as indicated by TLC, the resulting mixture was concentrated, and the residue was crystallized from EtOH afforded **2** in 92% yield.

ethyl 6-benzyl-2-((triphenylphosphoranylidene)amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (2)

Orange crystals ; mp 95-98°C ; ^1H NMR (500 MHz, CDCl_3) δ = 1.317-1.346 (t, J = 7.0, 3H), 2.733 (d, J = 5.5, 2H), 2.885 (d, J = 5.0, 2H), 3.273 (s, 2H), 3.621 (s, 2H), 4.257-4.300 (m, 2H), 7.282-7.332 (m, 5H), 7.450-7.456 (m, 6H), 7.538-7.542 (m, 3H), 7.786-7.827 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ = 14.68, 27.43, 50.71, 51.74, 58.81, 62.09, 113.27, 113.42, 127.08, 128.21, 128.61, 128.71, 129.24, 129.43, 131.67, 132.17, 132.20, 132.98, 133.06, 162.18, 162.22, 165.10, 165.11; Anal. Calcd for $\text{C}_{35}\text{H}_{33}\text{N}_2\text{O}_2\text{PS}$: C, 72.89; H, 5.77; N, 4.86. Found: C, 72.99; H, 5.89; N, 4.62.

IV. Synthesis and analytical data of compounds 4a-f

1. Preparation of compounds 4a-f.

Typical procedure for the preparation of **4** (with **4a** as an example): To a solution of **2** (1.16 g, 2 mmol) in dry CH_2Cl_2 (10 mL), isocyanatobenzene (0.24 mL, 2.1 mmol) was added under N_2 at room temperature. The mixture was left standing for 6-12 hours. Then, the solvent was removed in vacuum, and Et_2O /petroleum ether (1:2) was added to precipitate triphenylphosphine oxide. Filtration and removal of the solvent gave the crude carbodiimides **3**, which were used directly without further purification. To a solution of **4** in CH_2Cl_2 (10 mL), diethylamine (2 mmol) was added at room temperature. After the reaction mixture was stirred for 0.5-1 h at room temperature, the solvent was removed and dry ethanol (10 mL) with catalytic solid K_2CO_3 (0.024 g, 0.2 mmol) was added. The mixture was stirred for 6 h at 60°C. The resulting mixture was slowly poured into saturated aqueous NaCl (100 mL), which was extracted with dichloromethane (10 mL $\times$ 3). The combined organic phase was washed with water, dried over anhydrous MgSO_4 , filtered and evaporated in vacuo. The crude product was purified by column chromatography (silica gel. Petroleum ether:ethyl acetate 4:1) to give **4a** in 79% yield.

entry	NR ¹ R ²	4	yield (%)
1	-NEt ₂	4a	79
2	-N	4b	81
3	-N	4c	89
4	-N	4d	78
5	-NCH ₂	4e	85
6	-N(n-Pr) ₂	4f	75

2. Analytical data of compounds 4a-f

7-benzyl-2-(diethylamino)-3-phenyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**4a**)

light yellow solid; 79 % yield; mp 151-154°C; ¹H NMR (500 MHz, CDCl₃) δ = 0.792-0.820 (t, *J* = 7.0, 6H), 2.820-2.842 (t, *J* = 5.5, 2H), 3.020-3.074 (m, 6H), 3.630 (s, 2H), 3.731 (s, 2H), 6.996-7.026 (m, 3H), 7.256-7.393 (m, 5H), 7.453-7.484 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 12.50, 25.51, 45.19, 49.89, 51.53, 61.82, 116.57, 119.73, 122.75, 127.27, 128.05, 128.37, 128.97, 129.06, 129.14, 129.88, 137.77, 154.82, 159.88, 164.14; Anal. Calcd for C₂₆H₂₈N₄OS: C, 70.24; H, 6.35; N, 12.60. Found: C, 70.65; H, 6.44; N, 12.20.

7-benzyl-3-phenyl-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**4b**)

yellow crystals; 81 % yield; mp 177-182°C; ¹H NMR (500 MHz, CDCl₃) δ = 1.686 (s, 4H), 1.937 (s, 2H), 2.800-2.822 (t, *J* = 5.5, 2H), 3.013 (s, 6H), 3.432 (s, 2H), 3.597 (s, 2H), 3.716 (s, 2H), 6.994-7.345 (m, 4H), 7.370-7.463 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ = 25.43, 25.63, 45.79, 49.96, 50.19, 51.60, 61.99, 114.22, 119.46, 122.64, 124.54, 127.26, 128.29, 128.83, 129.06, 129.21,

129.53, 129.63, 137.57, 138.13, 139.34, 152.42, 153.96, 159.67, 165.80; Anal. Calcd for C₂₆H₂₆N₄OS: C, 70.56; H, 5.92; N, 12.66. Found: C, 70.78; H, 5.56; N, 12.37

7-benzyl-3-phenyl-2-(piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4c)

white crystals; 89 % yield; mp 121-126°C; ¹H NMR (500 MHz, CDCl₃) δ = 1.215-1.253 (m, 2H), 1.611-1.630 (m, 4H), 2.851 (s, 2H), 3.055-3.076 (t, *J* = 5.0, 4H), 3.436-3.456 (t, *J* = 5.0, 2H), 3.652 (s, 4H), 7.261-7.389 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ = 24.04, 24.41, 24.89, 25.72, 29.72, 45.27, 50.25, 116.99, 119.75, 122.82, 128.01, 128.45, 128.83, 128.86, 128.88, 129.28, 137.53, 139.31, 155.62, 159.62, 164.04; Anal. Calcd for C₂₇H₂₈N₄OS: C, 71.02; H, 6.18; N, 12.27. Found: C, 71.38; H, 6.25; N, 12.33.

7-benzyl-2-morpholino-3-phenyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4d)

light yellow crystals; 78 % yield; mp 200-203°C; ¹H NMR (500 MHz, CDCl₃) δ = 2.824-2.846 (t, *J* = 5.5, 2H), 3.027-3.099 (m, 6H), 3.393-3.411 (t, *J* = 4.5, 4H), 3.639 (s, 2H), 3.733 (s, 2H), 7.259-7.417 (m, 8H), 7.476-7.507 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 25.55, 49.29, 49.85, 51.53, 61.90, 65.96, 117.47, 127.31, 128.39, 128.74, 129.01, 129.16, 130.02, 136.88, 154.38, 159.25, 163.43; Anal. Calcd for C₂₆H₂₆N₄O₂S: C, 68.10; H, 5.71; N, 12.22. Found: C, 68.32; H, 5.48; N, 12.53.

7-benzyl-2-(dicyclohexylamino)-3-phenyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4e)

light yellow solid; 85 % yield; mp 113-116°C; ^1H NMR (500 MHz, CDCl_3) δ = 0.843-0.870 (m, 4H), 1.038-1.054 (m, 4H), 1.324-1.348 (m, 4H), 1.654-1.722 (m, 8H), 2.803-2.825 (t, J = 5.5, 2H), 2.992-3.020 (m, 4H), 3.619 (s, 2H), 3.715 (s, 2H), 7.242-7.257 (m, 2H), 7.326-7.366 (m, 6H), 7.380-7.423 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ = 25.67, 26.74, 32.22, 49.94, 51.60, 60.15, 61.80, 116.73, 126.61, 127.26, 127.93, 128.39, 128.83, 129.13, 129.50, 129.80, 138.21, 138.82, 154.01, 160.62, 163.88; Anal. Calcd for $\text{C}_{34}\text{H}_{40}\text{N}_4\text{OS}$: C, 73.88; H, 7.29; N, 10.14. Found: C, 73.56; H, 7.42; N, 10.29.

7-benzyl-2-(dipropylamino)-3-phenyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4f)

white solid; 75 % yield; mp 92-96°C; ^1H NMR (500 MHz, CDCl_3) δ = 0.805-0.835 (t, J = 7.5, 6H), 1.290-1.318 (t, J = 7.0, 4H), 2.738-2.760 (t, J = 5.5, 2H), 2.841-2.864 (m, 2H), 3.053-3.082 (t, J = 7.0, 4H), 3.445 (s, 2H), 3.663 (s, 2H), 6.981-7.002 (m, 3H), 7.196-7.233 (m, 5H), 7.325-7.384 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ = 11.30, 14.35, 21.22, 26.76, 50.28, 51.09, 51.23, 59.92, 61.84, 116.31, 119.21, 121.28, 127.68, 128.15, 128.88, 129.01, 129.11, 129.23, 129.75, 136.28, 153.28, 153.62, 158.77, 163.19; Anal. Calcd for $\text{C}_{36}\text{H}_{48}\text{N}_4\text{OS}$: C, 73.93; H, 8.27; N, 9.58; Found: C, 73.79; H, 8.53; N, 9.31.

V. Synthesis and analytical data of compounds 5a-d

1. Preparation of compounds 5a-d.

The compounds **5a-d** were prepared according to the above procedure of **3** except for replacing K_2CO_3 by organic base.

2. Analytical data of compounds 5a-d

(E)-ethyl 6-benzyl-2-((diethylamino)(phenylamino)methyleneamino)-4,5,6,7-tetrahydrothieno[2,3-d]pyrimidin-4-carboxylate

3-c]pyridine-3-carboxylate (5a)

white solid; 81 % yield; mp 84-87°C; ^1H NMR (500 MHz, CDCl_3) δ = 1.088-1.115 (t, J = 7.0, 6H), 1.282-1.311 (t, J = 7.0, 3H), 2.271-2.744 (t, J = 6.0, 2H), 2.850 (s, 2H), 3.147 (s, 4H), 3.429 (s, 2H), 3.645 (s, 2H), 4.242 (d, J = 6.5, 2H); 6.857-6.917 (m, 3H), 7.222-7.337 (m, 7H), 10.276 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ = 12.92, 14.22, 26.76, 43.13, 50.22, 51.19, 59.84, 61.91, 107.80, 120.52, 121.34, 121.50, 121.72, 127.06, 128.17, 128.80, 129.06, 138.04, 147.27, 148.31, 153.59, 166.58; Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_2\text{S}$: C, 68.54; H, 6.98; N, 11.42. Found: C, 68.78; H, 7.25; N, 11.20.

(E)-ethyl 6-benzyl-2-(((phenylamino)(pyrrolidin-1-yl)methylene)amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (5b)

white solid; 88% yield; mp 123-126°C; ^1H NMR (500 MHz, CDCl_3) δ = 1.328-1.356 (t, J = 7.0, 3H), 1.089 (s, 4H), 2.747 (d, J = 5.5, 2H), 2.866 (s, 2H), 3.245 (s, 4H), 3.454 (s, 2H), 3.655 (s, 2H), 4.289 (d, J = 7.0, 2H); 6.841 (d, J = 8.0, 3H), 7.196-7.356 (m, 7H), 10.766 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ = 14.39, 25.42, 26.83, 48.66, 50.34, 51.35, 59.98, 62.00, 107.65, 120.44, 122.32, 122.53, 127.14, 128.27, 128.32, 128.38, 129.12, 129.18, 138.26, 144.27, 148.25, 153.40, 167.34; Anal. Calcd for $\text{C}_{28}\text{H}_{32}\text{N}_4\text{O}_2\text{S}$: C, 68.82; H, 6.60; N, 11.47. Found: C, 68.98; H, 6.68; N, 11.31.

(E)-ethyl**6-benzyl-2-(((phenylamino)(piperidin-1-yl)methylene)amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (5c)**

white solid; 76% yield; mp 92-95°C; ^1H NMR (500 MHz, CDCl_3) δ = 1.272-1.301 (t, J = 7.0, 3H), 1.555 (s, 6H), 2.748 (d, J = 5.5, 2H), 2.853 (s, 2H), 3.176 (s, 4H), 3.454 (s, 2H), 3.661 (s, 2H), 4.230 (d, J = 7.0, 2H); 6.906 (t, J = 7.0, 3H), 7.231-7.346 (m, 7H), 10.161 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ = 14.33, 24.39, 25.30, 26.90, 48.49, 50.34, 51.34, 59.95, 62.05, 108.10, 119.76, 121.61, 121.81, 127.18, 128.30, 128.93, 129.17, 138.19, 148.42, 148.58, 153.45, 166.57; Anal. Calcd for $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2\text{S}$: C, 69.29; H, 6.82; N, 11.15. Found: C, 69.38; H, 6.71; N, 11.21.

(*E*)-ethyl

6-benzyl-2-((morpholino(phenylamino)methylene)amino)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (5d)

white solid; 77 % yield; mp 107-110°C; ¹H NMR (500 MHz, CDCl₃) δ = 1.260-1.288 (t, *J* = 7.0, 3H), 2.744 (s, 2H), 2.850 (s, 2H), 3.240 (s, 4H), 3.463 (s, 4H), 3.679 (d, *J* = 6.5, 6H), 4.190-4.232 (t, *J* = 7.0, 2H); 6.910-6.973 (m, 3H), 7.235-7.351 (m, 7H), 10.104 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ = 14.30, 26.97, 47.72, 50.32, 51.36, 60.10, 62.14, 66.20, 108.50, 121.77, 122.23, 127.22, 128.33, 129.11, 129.16, 138.13, 147.89, 152.93, 166.43; Anal. Calcd for C₂₈H₃₂N₄O₃S: C, 66.64; H, 6.39; N, 11.10. Found: C, 66.81; H, 6.48; N, 11.01.

V. Copies of NMR spectra of compounds 1, 2, 4a-f and 5a-d.

1

4a

4b

4d

4e

4f

5a

5b

5c

5d