New Efficient Synthesis of 2-Substituted 5,6,7,8-Tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones

Ming-Wu Ding,* Shang-Jun Yang, Jing Zhu

Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P. R. China
Fax +86(27)87876070; E-mail: ding5229@yahoo.com.cn

Received 19 September 2003; revised 17 October 2003

Abstract: The carbodiimides **4**, obtained from aza-Wittig reactions of iminophosphorane **3** with aromatic isocyanates, reacted with secondary amines to give 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** in presence of catalytic EtO^-Na^+. Reactions of **4** with phenols or ROH in presence of catalytic K_2CO_3 or RO^-Na^+ gave 2-aryl(alkyl)oxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** in satisfactory yields. The effects of the nucleophiles on cyclization have been investigated.

Key words: benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones, iminophosphorane, carbodiimide, aza-Wittig reaction, synthesis

The derivatives of heterocycles containing thienopyrimidine system, which are well known bioisosteres of quinazolines, are of great importances because of their remarkable biological properties. For example, some 2-alkoxy or 2-alkyl substituted thienopyrimidinones show significant antifungal and antibacterial activities,[1–4] whereas others exhibited good anticonvulsant and angiotensin or H_1 receptor antagonistic activities.[5–7] The chemistry of thienopyrimidinones have also received attention because their starting materials, 2-amino-3-carboxythiophenes, can be conveniently synthesized. Though there are many known methods for the synthesis of thienopyrimidinones,[8–10] 2-amino or 2-aryl(alkyl)oxy substituted thienopyrimidinones are not easily accessible by currently existing routes. Recently we became interested in the synthesis of imidazolinones and quinazolinones via aza-Wittig reaction, with the aim of evaluating their fungicidal activities.[11–15] Here we wish to report a new efficient synthesis of 2-substituted 5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** from easily accessible iminophosphorane **3**.

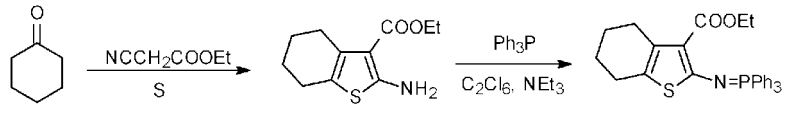
The tetrahydrobenzo[b]thiophene **2**, easily obtained by Gewald method from cyclohexanone **1**, ethyl cyanoactate and sulfur, was converted to iminophosphorane **3** via reaction with triphenylphosphine, hexachloroethane and Et_3N (Scheme 1).[16]

Iminophosphorane **3** reacted with aromatic isocyanates to give carbodiimides **4**, which were allowed to react with secondary amines to provide guanidine intermediates **5**. Even in refluxing toluene, **5** did not cyclize, however, in the presence of catalytic amount of NaOEt, **5** were converted easily to 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** in satisfactory yields at room temperature (Scheme 2). It is noteworthy that the isolated yields of **6** were good even when Y is the bulky di-*iso*-propylamino group. The results are listed in Table 1.

The direct reaction of carbodiimide **4** with phenols did not produce 2-aryloxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** either. However, when carried out in presence of catalytic K_2CO_3, the reaction took place to give **6** in good yields. The formation of **6** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **4** to give the intermediate **5** which cyclize to give **6**. Irrespective of the fact whether the substituents on the phenols were electron-withdrawing or electron-releasing groups, the cyclization was completed smoothly at room temperature.

The direct reaction of carbodiimide **4** with ROH gave a complex mixture, however, when the reaction was carried out in presence of catalytic RO^-Na^+, the reaction took place smoothly and 2-alkoxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** were obtained in satisfactory yields.

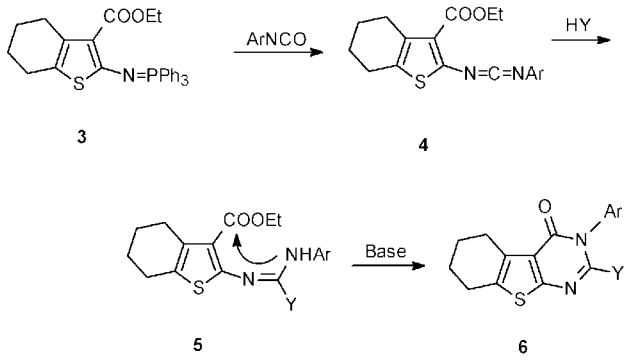
The structure of the synthesized compound **6** was confirmed by their spectral data. For example, the IR spectra of **6a** revealed C=O absorption bands at 1676 cm^{-1}. The



1 2 3

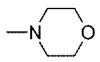
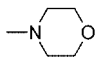
Scheme 1

SYNTHESIS 2004, No. 1, pp 0075–0079
Advanced online publication: 03.12.2003
DOI: 10.1055/s-2003-44358; Art ID: F08403SS



Scheme 2

Table 1 Preparation of 2-Substituted 5,6,7,8-Tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones

	Ar	Y	Conditions	Yield (%)[a]
6a	Ph	NEt_2	r.t./6 h	82
6b	Ph	N(*n*-Pr)$_2$	r.t./6 h	71
6c	Ph	N(*n*-Bu)$_2$	r.t./6 h	78
6d	Ph	N(*n*-Pentyl)$_2$	r.t./6 h	69
6e	Ph	N(*n*-Hexyl)$_2$	r.t./6 h	62
6f	Ph		r.t./6 h	88
6g	Ph		r.t./6 h	85
6h	Ph	N(*i*-Bu)$_2$	r.t./12 h	80
6i	Ph	N(*i*-Pr)$_2$	r.t./12 h	75
6j	4-ClC_6H_5	NEt_2	r.t./6 h	85
6k	4-ClC_6H_5		r.t./6 h	84
6l	4-ClC_6H_5		r.t./6 h	81
6m	Ph	3-$NO_2C_6H_5O$	r.t./10 h	62
6n	Ph	4-ClC_6H_5O	r.t./8 h	76
6o	Ph	4-BrC_6H_5O	r.t./8 h	66
6p	Ph	PhO	r.t./6 h	81
6q	Ph	4-MeSC_6H_5O	r.t./6 h	80
6r	Ph	4-MeOC_6H_5O	r.t./6 h	73
6s	4-ClC_6H_5	4-BrC_6H_5O	r.t./6 h	67
6t	4-MeC_6H_5	4-BrC_6H_5O	r.t./6 h	77
6u	4-MeC_6H_5	PhO	r.t./6 h	83
6v	Ph	MeO	r.t./6 h	71
6w	Ph	EtO	r.t./6 h	82

[a] Isolated yields based on iminophosphorane **3**.

^{1}H NMR spectral data of **6a** show the signals of –NCH_2 at 3.03 ppm as quartet and signals of cyclohexenyl CH_2 at 2.92–2.71 and 1.84–1.78 ppm as mutiplets. The other signals appeared at 7.46–7.23 (m, 5 H, Ar-H) and 0.80 (t, 6 H, J = 7.0 Hz, 2 CH_3). The MS spectrum of **6a** shows an obvious molecule ion peak at *m*/*z* 353 with 70% abundance.

In conclusion, we have developed an efficient synthesis of 2-substituted 5,6,7,8-tetrahydro- benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones via base-catalyzed reaction of functionalized carbodiimides with various amine, phenols or alcohols. Due to the easily accessible and versatile starting material, this method has the potential in the synthesis of many biologically and pharmaceutically active thienopyrimidinones derivatives.

Melting points were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption given in cm^{-1}. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument.

Preparation of 2-Dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones

To a solution of iminophosphorane **3**[16] (2.42g, 5 mmol) in anhyd CH_2Cl_2 (15 mL) was added aromatic isocyanate (5 mmol) under N_2 at r.t. After the reaction mixture was left unstirred for 6–12 h at 0–5 °C, the solvent was removed off under reduced pressure and Et_2O/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides **4**, which were used directly without further purification.

To the solution of **4** prepared above in CH_2Cl_2 (15 mL) was added dialkylamine (5 mmol). After the reaction mixture was left unstirred for 5–6 h, the solvent was removed and anhyd EtOH (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 6–12 h at r. t. The solution was condensed and the residue was recrystallized from EtOH to give 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**.

6a

White crystals; mp 144–145 °C.

IR (KBr): 1676 (C=O), 1532, 1383, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.23 (m, 5 H, Ar-H), 3.03 (q, J = 6.9 Hz, 4 H, 2 × NCH_2), 2.92–2.71 (m, 4 H, 2 × CH_2), 1.84–1.78 (m, 4 H, 2 × CH_2), 0.80 (t, J = 7.0 Hz, 6 H, 2 × CH_3).

MS: *m*/*z* (%) = 353 (70) [M^+], 324 (61), 281 (54), 248 (100), 179 (83), 152 (64).

Anal. Calcd for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.88; H, 6.74; N, 11.97.

6b

White crystals; mp 138–140 °C.

IR (KBr): 1675 (C=O), 1531, 1382, 705 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.24 (m, 5 H, Ar-H), 2.93 (t, J = 7.5 Hz, 4 H, 2 × NCH_2), 2.91–2.70 (m, 4 H, 2 × CH_2), 1.85–1.78 (m, 4 H, 2 × CH_2), 1.27–0.70 (m, 10 H, 2 × CH_2CH_3).

MS *m*/*z* (%) = 381 (100) [M^+], 352 (37), 338 (52), 281 (59), 262 (52), 179 (76), 119 (33).

Anal. Calcd for $C_{22}H_{27}N_3OS$: C, 69.26; H, 7.13; N, 11.01. Found: C, 69.52; H, 7.15; N, 10.91.

6c
White crystals; mp 120–122 °C.

IR (KBr): 1672 (C=O), 1534, 1383, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.21 (m, 5 H, Ar-H), 2.95 (t, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 2.90–2.69 (m, 4 H, 2 × CH_2), 1.85–1.78 (m, 4 H, 2 × CH_2), 1.23–0.79 (m, 14 H, 2 × $CH_2CH_2CH_3$).

MS: *m*/*z* (%) = 409 (100) [M^+], 380 (10), 352 (39), 281 (46), 179 (53), 91 (33).

Anal. Calcd for $C_{24}H_{31}N_3OS$: C, 70.38; H, 7.63; N, 10.26. Found: C, 70.42; H, 7.46; N, 10.17.

6d
White crystals; mp 50–51 °C.

IR (KBr): 1677 (C=O), 1531, 1379, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.22 (m, 5 H, Ar-H), 2.94 (t, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 2.90–2.70 (m, 4 H, 2 × CH_2), 1.86–1.78 (m, 4 H, 2 × CH_2), 1.24–0.81 [m, 18 H, 2 × $(CH_2)_3CH_3$].

MS: *m*/*z* (%) = 437 (100) [M^+], 380 (45), 366 (88), 291 (82), 179 (59), 91 (46).

Anal. Calcd for $C_{26}H_{35}N_3OS$: C, 71.36; H, 8.06; N, 9.60. Found: C, 71.12; H, 8.01; N, 9.75.

6e
White crystals; mp 54–55 °C.

IR (KBr): 1677 (C=O), 1531, 1383, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.22 (m, 5 H, Ar-H), 2.94 (t, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 2.90–2.70 (m, 4 H, 2 × CH_2), 1.85–1.77 (m, 4 H, 2 × CH_2), 1.25–0.83 [m, 22 H, 2 × $(CH_2)_4CH_3$].

MS: *m*/*z* (%) = 465 (100) [M^+], 394 (57), 380 (69), 281 (79), 179 (91), 91 (64).

Anal. Calcd for $C_{28}H_{39}N_3OS$: C, 72.22; H, 8.44; N, 9.02. Found: C, 72.31; H, 8.48; N, 8.86.

6f
White crystals; mp 188–190 °C.

IR (KBr): 1680 (C=O), 1529, 1442, 1242, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.23 (m, 5 H, Ar-H), 3.04 (t, *J* = 5.4 Hz, 4 H, 2 × NCH_2), 2.92–2.69 (m, 4 H, 2 × CH_2), 1.84–1.77 (m, 4 H, 2 × CH_2), 1.40–1.21 [m, 6 H, $(CH_2)_3$].

MS: *m*/*z* (%) = 365 (100) [M^+], 336 (15), 281 (24), 221 (27), 179 (85), 77 (65).

Anal. Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.17; H, 6.24; N, 11.38.

6g
White crystals; mp 198–200 °C.

IR (KBr): 1677 (C=O), 1529, 1442, 1241, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.29 (m, 5 H, Ar-H), 3.38 (t, *J* = 4.2 Hz, 4 H, 2 × OCH_2), 3.07 (t, *J* = 4.2 Hz, 4 H, 2 × NCH_2), 2.90–2.71 (m, 4 H, 2 × CH_2), 1.83–1.76 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 367 (100) [M^+], 310 (27), 281 (25), 246 (18), 179 (81), 77 (75).

Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.43. Found: C, 65.35; H, 5.45; N, 11.58.

6h
White crystals; mp 187–189 °C.

IR (KBr): 1683 (C=O), 1519, 1385, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.24 (m, 5 H, Ar-H), 2.80 (d, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 2.90–2.69 (m, 4 H, 2 × CH_2), 1.84–1.71 (m, 6 H, 2 × CH_2, 2 × CH), 0.77 (d, *J* = 6.6 Hz, 12 H, 4 × CH_3).

MS: *m*/*z* (%) = 409 (98) [M^+], 366 (99), 353 (82), 281 (100), 179 (62), 77 (84).

Anal. Calcd for $C_{24}H_{31}N_3OS$: C, 70.38; H, 7.63; N, 10.26. Found: C, 70.46; H, 7.75; N, 10.24.

6i
White crystals; mp 172–174 °C.

IR (KBr): 1670 (C=O), 1527, 1376, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 5 H, Ar-H), 3.51–3.41 (m, 2 H, 2 × NCH), 2.91–2.68 (m, 4 H, 2 × CH_2), 1.84–1.76 (m, 4 H, 2 × CH_2), 1.04 (d, *J* = 6.9 Hz, 12 H, 4 × CH_3).

MS *m*/*z* (%) = 381 (82) [M^+], 338 (100), 324 (34), 281 (78), 179 (38), 100 (76).

Anal. Calcd for $C_{22}H_{27}N_3OS$: C, 69.26; H, 7.13; N, 11.01. Found: C, 69.35; H, 7.37; N, 10.95.

6j
White crystals; mp 185–187 °C.

IR (KBr): 1678 (C=O), 1531, 1381, 800 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.43–7.18 (m, 4 H, Ar-H), 3.04 (q, *J* = 7.0 Hz, 4 H, 2 × NCH_2), 2.90–2.69 (m, 4 H, 2 × CH_2), 1.83–1.78 (m, 4 H, 2 × CH_2), 0.83 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

MS: *m*/*z* (%) = 389 (25), 387 (76) [M^+], 358 (50), 315 (51), 248 (65), 179 (100), 151 (70).

Anal. Calcd for $C_{20}H_{22}ClN_3OS$: C, 61.92; H, 5.72; N, 10.83. Found: C, 61.71; H, 5.65; N, 10.95.

6k
White crystals; mp 193–195 °C.

IR (KBr): 1691 (C=O), 1526, 1452, 1247, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 4 H, Ar-H), 3.03 (t, *J* = 4.8 Hz, 4 H, 2 & times; NCH_2), 2.88–2.70 (m, 4 H, 2 × CH_2), 1.85–1.75 (m, 4 H, 2 × CH_2), 1.42–1.25 [m, 6 H, $(CH_2)_3$].

MS: *m*/*z* (%) = 401 (34), 399 (100) [M^+], 370 (6), 315 (8), 221 (9), 179 (22).

Anal. Calcd for $C_{21}H_{22}ClN_3OS$: C, 63.07; H, 5.54; N, 10.51. Found: C, 63.16; H, 5.61; N, 10.39.

6l
White crystals; mp 191–193 °C.

IR (KBr): 1693 (C=O), 1530, 1437, 1247, 833 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.23 (m, 4 H, Ar-H), 3.44 (t, *J* = 4.2 Hz, 4 H, 2OCH_2), 3.07 (t, *J* = 4.2 Hz, 4 H, 2 × NCH_2), 2.90–2.70 (m, 4 H, 2 × CH_2), 1.86–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 403 (32), 401 (100) [M^+], 356 (30), 315 (38), 246 (35), 179 (90), 111 (36).

Anal. Calcd for $C_{20}H_{20}ClN_3O_2S$: C, 59.77; H, 5.02; N, 10.45. Found: C, 59.69; H, 5.25; N, 10.52.

Preparation of 2-Aryloxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones

To the solution of **4** prepared above in CH_3CN (15 mL) was added substituted phenol (5 mmol) and cat. solid K_2CO_3 (0.07 g, 0.5 mmol). The mixture was stirred for 6–10 h at r. t. and filtered, the filtrate was condensed and the residual was recrystallized from

CH_2Cl_2–petroleum ether to give 2-aryloxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**.

6m
White crystals; mp 189–191 °C.

IR (KBr): 1692 (C=O), 1529, 1350, 1219, 729 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11–7.22 (m, 9 H, Ar-H), 2.96–2.69 (m, 4 H, 2 × CH_2), 1.87–1.79 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 419 (100) [M^+], 391 (45), 281 (87), 253 (55), 122 (33).

Anal. Calcd for $C_{22}H_{17}N_3O_4S$: C, 63.00; H, 4.09; N, 10.02. Found: C, 62.88; H, 4.17; N, 9.84.

6n
White crystals; mp 179–180 °C.

IR (KBr): 1692 (C=O), 1552, 1485, 1215, 955 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): =7.53–7.01 (m, 9 H, Ar-H), 2.95–2.69 (m, 4 H, 2 × CH_2), 1.88–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 410 (30), 408 (92) [M^+], 281 (100), 254 (59), 77 (38).

Anal. Calcd for $C_{22}H_{17}ClN_2O_2S$: C, 64.62; H, 4.19; N, 6.85. Found: C, 64.76; H, 4.12; N, 6.87.

6o
White crystals; mp 204–206 °C.

IR (KBr): 1693 (C=O), 1549, 1484, 1215, 955 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–6.96 (m, 9 H, Ar-H), 2.93–2.70 (m, 4 H, 2 × CH_2), 1.87–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 454 (61), 452 (59) [M^+], 373 (9), 281 (39), 145 (76), 77 (100).

Anal. Calcd for $C_{22}H_{17}BrN_2O_2S$: C, 58.29; H, 3.78; N, 6.18. Found: C, 58.12; H, 3.05; N, 6.22.

6p
White crystals; mp 225–226 °C.

IR (KBr): 1692 (C=O), 1550, 1488, 1211, 956 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.07 (m, 10 H, Ar-H), 2.97–2.69 (m, 4 H, 2 × CH_2), 1.87–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 374 (81) [M^+], 346 (8), 281 (31), 227 (8), 77 (100).

Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.59; H, 4.75; N, 7.32.

6q
White crystals; mp 203–205 °C.

IR (KBr): 1692 (C=O), 1552, 1486, 1210, 958 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–6.99 (m, 9 H, Ar-H), 2.93–2.70 (m, 4 H, 2 × CH_2), 2.47 (s, 3 H, SCH_3), 1.88–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 420 (84) [M^+], 301 (56), 281 (54), 254 (100), 77 (49).

Anal. Calcd for $C_{23}H_{20}N_2O_2S_2$: C, 65.69; H, 4.79; N, 6.66. Found: C, 65.76; H, 4.87; N, 6.62.

6r
White crystals; mp 204–206 °C.

IR (KBr): 1691 (C=O), 1550, 1485, 1202, 956 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–6.83 (m, 9 H, Ar-H), 3.78 (s, 3 H, OCH_3), 2.95–2.68 (m, 4 H, 2 × CH_2), 1.88–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 404 (89) [M^+], 281 (100), 257 (79), 122 (60), 77 (86).

Anal. Calcd for $C_{23}H_{20}N_2O_3S$: C, 68.30; H, 4.98; N, 6.93. Found: C, 68.10; H, 4.76; N, 6.97.

6s
White crystals; mp 236–238 °C.

IR (KBr): 1692 (C=O), 1551, 1483, 1215, 957 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ = 7.48–6.95 (m, 8 H, Ar-H), 2.91–2.70 (m, 4 H, 2 × CH_2), 1.87–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 486 (70) [M^+], 460 (16), 408 (17), 315 (91), 253 (100), 122 (81).

Anal. Calcd for $C_{22}H_{16}BrClN_2O_2S$: C, 54.17; H, 3.31; N, 5.74. Found: C, 54.23; H, 3.25; N, 5.97.

6t
White crystals; mp 137–138 °C.

IR (KBr): 1693 (C=O), 1550, 1483, 1215, 956 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.06 (m, 8 H, Ar-H), 2.92–2.70 (m, 4 H, 2 × CH_2), 2.39 (s, 3 H, CH_3), 1.87–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 468 (85), 466 (83) [M^+], 440 (18), 349 (26), 295 (32), 253 (100), 122 (80).

Anal. Calcd for $C_{23}H_{19}BrN_2O_2S$: C, 59.11; H, 4.10; N, 5.99. Found: C, 59.34; H, 4.27; N, 5.85.

6u
White crystals; mp 191–193 °C.

IR (KBr): 1692 (C=O), 1549, 1488, 1206, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.06 (m, 9 H, Ar-H), 2.95–2.67 (m, 4 H, 2 × CH_2), 2.40 (s, 3 H, CH_3), 1.86–1.78 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 388 (87) [M^+], 360 (8), 295 (100), 255 (27), 77 (39).

Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.19; N, 7.21. Found: C, 71.27; H, 5.12; N, 7.43.

Preparation of 2-alkoxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones
To the solution of **4** prepared above in ROH (15 mL) was added several drops of RO^-Na^+ in ROH. The mixture was stirred for 6 h at r.t. The solution was condensed and the residual was recrystallized from CH_2Cl_2–petroleum ether to give 2-alkoxy-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**.

6v
White crystals; mp 146–148 °C.

IR (KBr): 1683 (C=O), 1555, 1356, 1262 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.17 (m, 5 H, Ar-H), 3.90 (s, 3 H, OCH_3), 2.93–2.70 (m, 4 H, 2 × CH_2), 1.86–1.76 (m, 4 H, 2 × CH_2).

MS: *m*/*z* (%) = 312 (100) (M^+), 298 (26), 284 (43), 226 (6), 119 (42).

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.41; H, 5.04; N, 9.05.

6w
White crystals, mp 154–156 °C.

IR (KBr): 1684 (C=O), 1554, 1322, 1008 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.16 (m, 5 H, Ar-H), 4.38 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.93–2.70 (m, 4 H, 2 × CH_2), 1.86–1.78 (m, 4 H, 2 × CH_2), 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3).

MS: *m*/*z* (%) = 326 (88) [M^+], 298 (26), 206 (30), 179 (100), 151 (47).

Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.15; H, 5.57; N, 8.74.

Acknowledgment

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (Project No.20102001).

References

(1) Walter, H. WO 9911631, **1999**; *Chem. Abstr.* **1999**, *130*, 237580e.
(2) Walter, H. WO 9914202, **1999**; *Chem. Abstr.* **1999**, *130*, 252368k.
(3) Aboulwafa, O. M.; Ismail, K. A.; Koreish, E. A. *Farmaco* **1992**, *47*, 631.
(4) Hozien, Z. A.; Atta, F. M.; Hassan, K. M.; Abdel-Wahab, A. A.; Ahmed, S. A. *Synth. Commun.* **1996**, *26*, 3733.
(5) Santagati, M.; Modica, M.; Santagati, A.; Russo, F.; Spampinato, S. *Pharmazie* **1996**, *51*, 7.
(6) Taguchi, M.; Ota, T.; Hatayama, K. WO 9303040, **1993**; *Chem. Abstr.* **1993**, *119*, 160309m.
(7) Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35*, 351.
(8) Shishoo, C. J.; Jain, K. S. *J. Heterocycl. Chem.* **1993**, *30*, 435.
(9) Santagati, A.; Santagati, M.; Modica, M. *Heterocycles* **1993**, *36*, 1315.
(10) Walter, H. WO 0034286, **2000**; *Chem. Abstr.* **2000**, *133*, 30738d.
(11) Ding, M. W.; Sun, Y.; Liu, Z. J. *Synth. Commun.* **2003**, *33*, 1267.
(12) Ding, M. W.; Sun, Y.; Yang, S. J.; Liu, X. P.; Liu, Z. J. *Synth. Commun.* **2003**, *33*, 1651.
(13) Ding, M. W.; Zeng, G. P.; Wu, T. J. *Synth. Commun.* **2000**, *30*, 1599.
(14) Ding, M. W.; Zeng, G. P.; Liu, Z. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1315.
(15) Ding, M. W.; Shu, Y. L.; Liu, X. P.; Liu, Z. J. *Acta Chim. Sin.* **2002**, *60*, 1893.
(16) Wamhoff, H.; Herrmann, S.; Stolbern, S.; Nieger, M. *Tetrahedron* **1993**, *49*, 581.