New Efficient Synthesis of 2-Substituted Benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones via a Tandem Aza-Wittig Reaction

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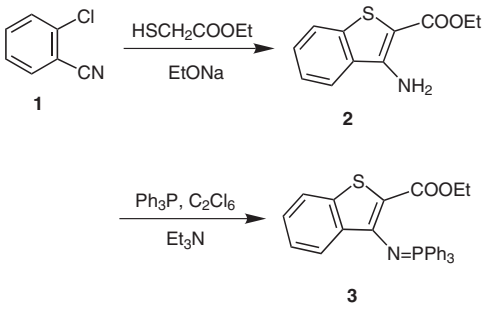
Abstract: 1-Aryl-3-[2-(ethoxycarbonyl)benzothien-3-yl]carbodiimides **4**, obtained from aza-Wittig reactions of iminophosphorane **3** with aryl isocyanates, reacted with secondary amines, phenols, or alkanols in the presence of a catalytic amount of potassium carbonate or sodium alkoxide to give 2-substituted benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6** in good yields. The reaction of carbodiimides **4** with primary amines RNH_2 ($R \neq H$, Me) in the presence of sodium ethoxide selectively produced one regioisomer **8** via a base-catalyzed cyclization mechanism. However, a different regioisomer **9** was obtained when primary amines RNH_2 (R = H, Me) were used in the absence of sodium ethoxide via a direct cyclization mechanism.

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

The derivatives of fused pyrimidinones have been the focus of great interest for many years. This is probably due to the fact that many compounds containing a fused pyrimidinone ring play an important part in the biochemistry of the living cell.[1] Thienopyrimidines are of great importance because of their significant antifungal and antibacterial activities, as well as their good anticonvulsant and angiotensin or H_1 receptor antagonistic activities.[2–6] Although some derivatives of benzothienopyrimidines have shown good antithrombotic, cardiotonic, and α adrenergic antagonistical activities,[7–10] there are few reports on the synthesis of benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones, which are of considerable interest as potential biologically active compounds or pharmaceuticals. The methods described for the preparation of some representative derivatives of this ring system involve the cyclization of ethyl 3-aminobenzothiophene-2-carboxylate with an orthoformate and an amine, or with formamide.[11–13] However, 2-substituted benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones are not easily accessible by current routes.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[14–17] Annulation of ring systems containing nitrogen heterocycles by means of an aza-Wittig reaction has been widely utilized because of the availability of functionalized iminophosphoranes. We are currently interested in the synthesis of quinazolinones, thienopyrimidinones, and imidazolinones via the aza-Wittig reaction of α- or β-ethoxycarbonyl-substituted iminophosphorane derivatives with aryl isocyanates and subsequent reaction with various nucleophiles under mild conditions.[18–21] Herein we wish to report a new efficient synthesis of benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones.

Ethyl 3-aminobenzothiophene-2-carboxylate (**2**), readily obtained by cyclization of 2-chlorobenzonitrile (**1**) with ethyl 2-sulfanylacetate under basic conditions (Scheme 1),[22] was converted into iminophosphorane **3** via reaction with triphenylphosphine, hexachloroethane, and triethylamine.



Scheme 1

Iminophosphorane **3** reacted with aryl isocyanates to give carbodiimides **4**, which were allowed to react with secondary amines to provide guanidine intermediates **5** (Scheme 2). Even in refluxing toluene, guanidines **5** did not cyclize, however, in the presence of a catalytic amount of sodium ethoxide guanidines **5** were readily converted into 3-aryl-2-(dialkylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6** in satisfactory yields at room temperature. The results are listed in Table 1.

The direct reaction of carbodiimides **4** with phenols also did not produce 3-aryl-2-(aryloxy)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6**. However, when carried our in the presence of a catalytic amount of potassium carbonate, the reaction took place to give **6** in good yields. The formation of **6** can be rationalized in terms of initial nucleophilic addition of phenoxide to the carbodiimide derivatives **4** to give the intermediates **5** that cyclize to give **6**. Regardless of whether the substituents on the phenols are electron-withdrawing (Table 1, entries 13, 14, and 17) or electron-donating (Table 1, entries 15 and 16), the cyclization can

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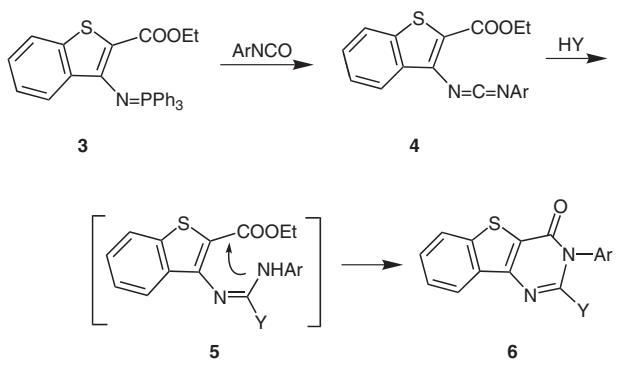


Scheme 2

be completed smoothly under mild conditions. The direct reaction of carbodiimides **4** with alkanols gave a complex mixture; however, when the reaction was carried out in the presence of a catalytic amount of sodium alkoxide the reaction took place smoothly and 2-alkoxybenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6** were obtained in satisfactory yields.

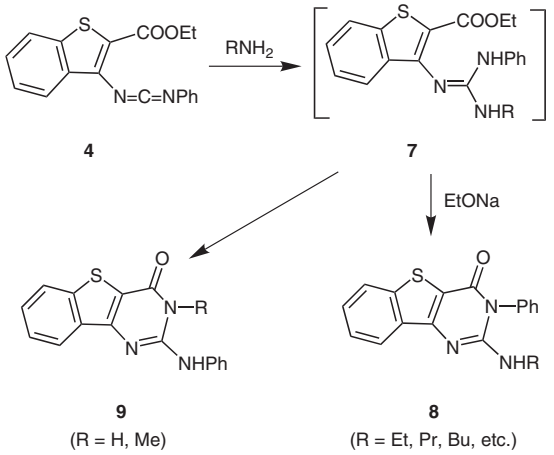
The reaction of carbodiimides **4** with primary amines RNH_2 (R ≠ H, Me) in the presence of sodium ethoxide provided only 2-(alkylamino)-3-arylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **8**, one of the possible regioisomers. We obtained only **8** from the reaction mixture after recrystallization; the other isomer was not found by ^{1}H NMR analysis of the reaction mixture. The structures of derivatives **8** were deduced from their ^{1}H NMR data. For example, the ^{1}H NMR spectrum of **8b** (R = Pr) shows the N–H signal at δ = 4.19 as a broad absorption and N–CH_2 at δ = 3.50–3.45 as multiple absorption, which strongly suggest the existence of $NHCH_2CH_2CH_3$ group in **8b**. Whenever the primary amine used was small (R = Pr) or bulky (R = *t*-Bu), the cyclizations were all achieved in good yields with similar selectivity. The results are also listed in Table 2 (entries 1–6). The sole formation of derivatives **8** can be rationalized in terms of a base-catalyzed cyclization of the guanidine intermediates **7** to give **8** across the arylamino group rather than the alkylamino group. This is probably due to the preferential generation of -N^-Ar from the more acidic -NHAr group. On the other hand, the reaction of phenylcarbodiimide **4** with ammonia

Table 1 Preparation of 2-Substituted 3-Arylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones

Entry	Product	Ar	Y	Conditions	Yield[a] (%)
1	**6a**	Ph	NEt_2	r.t., 5 h	84
2	**6b**	Ph	NPr_2	r.t., 6 h	75
3	**6c**	Ph	N(*i*-Bu)$_2$	r.t., 6 h	70
4	**6d**	Ph	N(*n*-C_5H_{11})$_2$	r.t., 6 h	66
5	**6e**	Ph	N(Me)Ph	r.t., 6 h	78
6	**6f**	Ph	morpholin-4-yl	r.t., 5 h	90
7	**6g**	Ph	piperidin-1-yl	r.t., 5 h	87
8	**6h**	4-MeC_6H_4	morpholin-4-yl	r.t., 5 h	92
9	**6i**	4-ClC_6H_4	piperidin-1-yl	r.t., 5 h	88
10	**6j**	4-MeC_6H_4	NEt_2	r.t., 6 h	81
11	**6k**	4-ClC_6H_4	NEt_2	r.t., 6 h	80
12	**6l**	Ph	OPh	60 °C, 5 h	75
13	**6m**	Ph	4-ClC_6H_4O	60 °C, 8 h	66
14	**6n**	Ph	4-BrC_6H_4O	60 °C, 8 h	73
15	**6o**	Ph	4-$MeOC_6H_4O$	60 °C, 5 h	87
16	**6p**	Ph	4-$MeSC_6H_4O$	60 °C, 6 h	86
17	**6q**	Ph	3-$O_2NC_6H_4O$	60 °C, 10 h	63
18	**6r**	Ph	OMe	r.t., 4 h	82
19	**6s**	Ph	OEt	r.t., 6 h	76
20	**6t**	4-ClC_6H_4	OMe	r.t., 5 h	87

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

or methylamine (R = H, Me) gave directly 2-(phenylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **9**, another of the possible regioisomers, as the sole product in the absence of sodium ethoxide (Table 2, entries 7 and 8). The reversed, selective formation of **9** can be rationalized in terms of direct cyclization of the guanidine intermediates **7** to give **9** across the sterically smaller amino or methylamino group rather than the arylamino group. The same selectivity has been observed in similar cases.[23]



Scheme 3

Table 2 Reaction of Carbodiimides with Amines

Entry	Product	R	Conditions	Yield[a] (%)
1	**8a**	Et	r.t., 4 h	79
2	**8b**	Pr	r.t., 4 h	88
3	**8c**	*i*-Pr	r.t., 6 h	81
4	**8d**	Bu	r.t., 4 h	84
5	**8e**	*t*-Bu	r.t., 8 h	85
6	**8f**	Bn	r.t., 5 h	80
7	**9a**	H	r.t., 1 h	87
8	**9b**	Me	r.t., 1 h	82

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

In conclusion, we have developed a new efficient and selective synthesis of 2-substituted benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones via reaction of functionalized carbodiimides with various amines, phenols, or alcohols. Due to the easily accessible and versatile starting material, this method can potentially be used for the synthesis of many biologically and pharmaceutically active benzothienopyrimidinone derivatives.

Melting points are uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 spectrophotometer as KBr pellets. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer with TMS as the internal reference. Elemental analyses were taken on a Vario EL III elementary analysis instrument.

Ethyl 3-[(Triphenylphosphoranylidene)amino]benzothieno[3,2-*d*]pyrimidine-2-carboxylate (3)

To a mixture of ethyl 3-aminobenzothieno[3,2-*d*]pyrimidine-2-carboxylate (**2**)[22] (1.77 g, 8 mmol), Ph_3P (3.14 g, 12 mmol), and C_2Cl_6 (2.84 g, 12 mmol) in anhyd MeCN (40 mL), was added dropwise Et_3N (2.42 g, 24 mmol) at r.t.; the mixture rapidly became yellow in color. The mixture was stirred for 4–6 h and then the solvent was removed under reduced pressure and the residue was recrystallized (EtOH) to give iminophosphorane **3** as white crystals; yield: 3.27 g (85%); mp 153–154 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.16 (m, 19 H, Ar-H), 3.82 (q, *J* = 7.2 Hz, 2 H, OCH_2), 0.99 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5 (C=O), 150.5, 140.0, 139.8, 138.7, 133.0, 132.4, 132.3, 132.0, 131.2, 128.2, 128.1, 126.9, 124.7, 123.0, 122.3, 108.5, 59.3, 14.3.

MS: *m*/*z* (%) = 481 (100) [M$^+$], 452 (17), 408 (61), 183 (57), 77 (55).

Anal. Calcd for $C_{29}H_{24}NO_2PS$: C, 72.33; H, 5.02; N, 2.91. Found: C, 72.58; H, 5.17; N, 2.84.

3-Aryl-2-(dialkylamino)- and 3-Aryl-2-(diarylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 6a–k; General Procedure

To a soln of iminophosphorane **3** (1.44g, 3 mmol) in anhyd CH_2Cl_2 (10 mL) was added the aryl isocyanate (3 mmol) under N_2 at 0–5 °C; the mixture was left to stand unstirred at 0–5 °C for 8–12 h. The solvent was then removed under reduced pressure and Et_2O–petroleum ether (1:2, 12 mL) was added to precipitate Ph_3PO. Removal of the solvent gave carbodiimides **4**, which were used directly without further purification.

To a soln of **4** in CH_2Cl_2 (10 mL) was added dialkylamine (3 mmol); the mixture was left to stand unstirred for 2–3 h. The solvent was then removed and anhyd EtOH (8 mL) and EtONa (0.3 mmol, 10% equiv) in EtOH were added. The mixture was stirred at r.t. for 4–6 h. The soln was condensed and the residue was recrystallized (EtOH) to give **6a–k**.

2-(Diethylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6a)

White crystals; mp 128–129 °C.

IR (KBr): 1670 (C=O), 1541, 1341, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.34 (m, 9 H, Ar-H), 3.15 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 0.90 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (C=O), 157.1, 152.4, 142.1, 137.8, 134.6, 129.0, 128.9, 128.6, 128.1, 124.5, 123.6, 123.3, 115.8, 45.3, 12.4.

MS: *m*/*z* (%) = 349 (100) [M$^+$], 277 (22), 200 (6), 146 (42), 77 (34).

Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.88; H, 5.54; N, 11.97.

2-(Dipropylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6b)

White crystals; mp 108–110 °C.

IR (KBr): 1688 (C=O), 1534, 1320, 656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.34 (m, 9 H, Ar-H), 3.05 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 1.34–1.28 (m, 4 H, 2 × CH_2), 0.74 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (C=O), 157.2, 152.5, 142.1, 137.8, 134.6, 129.0, 128.8, 128.6, 128.2, 124.5, 123.6, 123.3, 115.5, 53.1, 20.7, 11.4.

MS: *m*/*z* (%) = 377 (63) [M$^+$], 277 (72), 201 (20), 146 (100), 77 (58).

Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 70.18; H, 6.25; N, 11.08.

2-(Diisobutylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6c)
White crystals; mp 154–155 °C.

IR (KBr): 1687 (C=O), 1531, 1357, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–7.35 (m, 9 H, Ar-H), 2.92 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 1.95–1.81 (m, 2 H, 2 × CH), 0.80 (d, *J* = 7.0 Hz, 12 H, 4 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (C=O), 156.9, 152.8, 142.2, 137.7, 134.7, 129.0, 128.6, 128.3, 124.5, 123.7, 123.3, 114.8, 59.3, 27.4, 20.4.

MS: *m*/*z* (%) = 405 (54) [M$^+$], 277 (83), 200 (14), 146 (80), 77 (33).

Anal. Calcd for $C_{24}H_{27}N_3OS$: C, 71.08; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.79; N, 10.32.

2-(Dipentylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6d)
White crystals; mp 85–87 °C.

IR (KBr): 1680 (C=O), 1533, 1381, 654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–7.33 (m, 9 H, Ar-H), 3.10 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 1.32–1.09 (m, 12 H, 6 × CH_2), 0.84 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

MS: *m*/*z* (%) = 433 (67) [M$^+$], 277 (100), 200 (16), 146 (90), 77 (25).

Anal. Calcd for $C_{26}H_{31}N_3OS$: C, 72.02; H, 7.21; N, 9.69. Found: C, 72.26; H, 7.28; N, 9.67.

2-[Methyl(phenyl)amino]-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6e)
White crystals; mp 223–225 °C.

IR (KBr): 1677 (C=O), 1539, 1334, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36–6.60 (m, 14 H, Ar-H), 3.40 (s, 3 H, CH_3).

MS: *m*/*z* (%) = 383 (100) [M$^+$], 277 (97), 201 (25), 146 (98), 76 (96).

Anal. Calcd for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96. Found: C, 72.05; H, 4.54; N, 10.80.

2-(Morpholin-4-yl)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6f)
White crystals; mp 166–168 °C.

IR (KBr): 1674 (C=O), 1530, 1381, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–7.41 (m, 9 H, Ar-H), 3.48 (t, *J* = 4.8 Hz, 4 H, 2 × NCH_2), 3.21 (t, *J* = 4.8 Hz, 4 H, 2 × OCH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C=O), 156.7, 151.9, 142.0, 136.9, 134.4, 129.0, 128.7, 128.6, 128.5, 124.7, 123.6, 123.4, 117.4, 65.9, 49.4.

MS: *m*/*z* (%) = 363 (48) [M$^+$], 306 (31), 277 (49), 146 (100), 103 (38).

Anal. Calcd for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56. Found: C, 66.02; H, 4.94; N, 11.47.

3-Phenyl-2-(piperidin-1-yl)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6g)
White crystals; mp 177–178 °C.

IR (KBr): 1673 (C=O), 1540, 1374, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–7.39 (m, 9 H, Ar-H), 3.18 (q, *J* = 5.2 Hz, 4 H, 2 × NCH_2), 1.45–1.28 (m, 6 H, 3 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C=O), 157.8, 152.3, 142.0, 137.6, 134.5, 128.8, 128.7, 128.6, 128.0, 124.5, 123.6, 123.3, 116.6, 50.2, 24.9, 24.1.

MS: *m*/*z* (%) = 361 (19) [M$^+$], 277 (24), 146 (100), 77 (92).

Anal. Calcd for $C_{21}H_{19}N_3OS$: C, 69.78; H, 5.30; N, 11.62. Found: C, 69.92; H, 5.14; N, 11.78.

2-(Morpholin-4-yl)-3-(4-tolyl)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6h)
White crystals; mp 195–197 °C.

IR (KBr): 1678 (C=O), 1539, 1364, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–7.28 (m, 8 H, Ar-H), 3.48 (t, *J* = 4.8 Hz, 4 H, 2 × NCH_2), 3.21 (t, *J* = 4.8 Hz, 4 H, 2 × OCH_2), 2.42 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C=O), 156.8, 151.9, 142.0, 138.5, 134.5, 134.2, 129.7, 128.7, 128.2, 124.7, 123.6, 123.4, 117.3, 66.0, 49.3, 21.2.

MS: *m*/*z* (%) = 377 (100) [M$^+$], 291 (34), 146 (40), 91 (32).

Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13. Found: C, 67.07; H, 5.04; N, 10.98.

3-(4-Chlorophenyl)-2-(piperidin-1-yl)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6i)
White crystals; mp 202–204 °C.

IR (KBr): 1681 (C=O), 1533, 1369, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–7.34 (m, 8 H, Ar-H), 3.17 (q, *J* = 5.2 Hz, 4 H, 2 × NCH_2), 1.60–1.34 (m, 6 H, 3 × CH_2).

MS: *m*/*z* (%) = 395 (100) [M$^+$], 311 (10), 146 (39), 111 (15).

Anal. Calcd for $C_{21}H_{18}ClN_3OS$: C, 63.71; H, 4.58; N, 10.61. Found: C, 63.95; H, 4.74; N, 10.48.

2-(Diethylamino)-3-(4-tolyl)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6j)
White crystals; mp 143–145 °C.

IR (KBr): 1670 (C=O), 1542, 1340, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.21 (m, 8 H, Ar-H), 3.17 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 2.41 (s, 3 H, CH_3), 0.90 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

MS: *m*/*z* (%) = 363 (78) [M$^+$], 291 (49), 200 (13), 146 (64), 91 (24).

Anal. Calcd for $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.28; H, 6.04; N, 11.57.

3-(4-Chlorophenyl)-2-(diethylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6k)
White crystals; mp 176–178 °C.

IR (KBr): 1670 (C=O), 1542, 1341, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.30 (m, 8 H, Ar-H), 3.16 (q, *J* = 6.9 Hz, 4 H, 2 × NCH_2), 0.93 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

MS: *m*/*z* (%) = 383 (71) [M$^+$], 310 (41), 200 (26), 146 (100), 111 (9).

Anal. Calcd for $C_{20}H_{18}ClN_3OS$: C, 62.57; H, 4.73; N, 10.95. Found: C, 62.75; H, 4.64; N, 11.07.

2-(Aryloxy)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 6l–q; General Procedure
To the soln of carbodiimide **4** (ca. 3 mmol) in MeCN (15 mL) was added ArOH (3 mmol) and K_2CO_3 (0.3 mmol) in anhyd MeCN (10

mL). The mixture was stirred at 50–60 °C for 6–8 h. The soln was condensed and the residue was recrystallized (EtOH) to give **6l–q**.

2-Phenoxy-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6l)
White crystals; mp 220–222 °C.

IR (KBr): 1694 (C=O), 1551, 1356, 685 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.87 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.59–7.20 (m, 12 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 154.8, 151.9, 150.8, 141.8, 134.8, 133.9, 129.4, 129.3, 129.1, 128.8, 128.1, 125.9, 124.7, 123.7, 123.2, 121.4, 118.0.

MS: *m*/*z* (%) = 370 (100) [M^+], 277 (52), 146 (67), 77 (54).

Anal. Calcd for $C_{22}H_{14}N_2O_2S$: C, 71.33; H, 3. 81; N, 7.56. Found: C, 71.27; H, 3.94; N, 7.60.

2-(4-Chlorophenoxy)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6m)
White crystals; mp 215–216 °C.

IR (KBr): 1668 (C=O), 1488, 1348, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.88 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.60–7.15 (m, 11 H, Ar-H).

MS: *m*/*z* (%) = 404 (24) [M^+], 277 (29), 200 (6), 146 (58), 77 (59).

Anal. Calcd for $C_{22}H_{13}ClN_2O_2S$: C, 65.27; H, 3.24; N, 6.92. Found: C, 65.50; H, 3.19; N, 6.97.

2-(4-Bromophenoxy)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6n)
White crystals; mp 221–222 °C.

IR (KBr): 1688 (C=O), 1485, 1348, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.88 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.59–7.10 (m, 11 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C=O), 154.5, 150.9, 150.6, 141.8, 134.6, 133.9, 132.4, 129.5, 129.3, 128.9, 128.0, 124.8, 123.7, 123.3, 119.0, 118.3.

MS: *m*/*z* (%) = 448 (2) [M^+], 277 (36), 200 (8), 145 (96), 77 (100).

Anal. Calcd for $C_{22}H_{13}BrN_2O_2S$: C, 58.81; H, 2.92; N, 6.23. Found: C, 59.03; H, 2.84; N, 6.17.

2-(4-Methoxyphenoxy)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6o)
White crystals; mp 202–204 °C.

IR (KBr): 1688 (C=O), 1500, 1349, 693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–6.90 (m, 13 H, Ar-H), 3.83 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 157.2, 155.2, 150.9, 145.4, 141.7, 134.8, 134.0, 129.4, 129.0, 128.8, 128.1, 124.6, 123.7, 123.2, 122.2, 117.8, 114.2.

MS: *m*/*z* (%) = 400 (61) [M^+], 277 (86), 146 (100), 77 (52).

Anal. Calcd for $C_{23}H_{16}N_2O_3S$: C, 68.98; H, 4.03; N, 7.00. Found: C, 68.93; H, 4.14; N, 6.97.

2-[4-(Methylsulfanyl)phenoxy]-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6p)
White crystals; mp 211–212 °C.

IR (KBr): 1700 (C=O), 1556, 1346, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.12 (m, 13 H, Ar-H), 2.50 (s, 3 H, SCH_3).

MS: *m*/*z* (%) = 416 (71) [M^+], 277 (62), 200 (11), 146 (92), 139 (100), 77 (71).

Anal. Calcd for $C_{23}H_{16}N_2O_2S_2$: C, 66.32; H, 3.87; N, 6.73. Found: C, 66.60; H, 3.94; N, 6.67.

2-(3-Nitrophenoxy)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6q)
White crystals; mp 226–227 °C.

IR (KBr): 1684 (C=O), 1532, 1348, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–7.41 (m, 13 H, Ar-H).

MS: *m*/*z* (%) = 415 (5) [M^+], 277 (9), 200 (11), 146 (37), 77 (100).

Anal. Calcd for $C_{22}H_{13}N_3O_4S$: C, 63.61; H, 3.15; N, 10.11. Found: C, 63.65; H, 3.04; N, 10.07.

2-Alkoxy-3-arylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 6r–t; General Procedure
To the soln of **4** (ca. 3 mmol) in anhyd alkanol ROH (8 mL) was added EtONa (0.3 mmol, 10% equiv) in EtOH. The mixture was stirred for at r.t 4–6 h. The soln was condensed and the residue was recrystallized (ROH) to give **6r–t**.

2-Methoxy-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6r)
White crystals; mp 212–214 °C.

IR (KBr): 1676 (C=O), 1520, 1346, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28–7.28 (m, 9 H, Ar-H), 4.05 (s, 3 H, OCH_3).

MS: *m*/*z* (%) = 308 (100) [M^+], 277 (51), 200 (11), 146 (93), 77 (58).

Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08. Found: C, 66.48; H, 4.04; N, 9.01.

2-Ethoxy-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6s)
White crystals; mp 190–192 °C.

IR (KBr): 1673 (C=O), 1522, 1334, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26–7.28 (m, 9 H, Ar-H), 4.58 (q, *J* = 6.9 Hz, 2 H, OCH_2), 1.31 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C=O), 155.3, 151.3, 141.9, 134.9, 134.2, 129.2, 128.8, 128.7, 128.6, 128.1, 124.6, 123.5, 123.4, 117.0, 65.1, 14.0.

MS: *m*/*z* (%) = 322 (4) [M^+], 293 (6), 200 (9), 145 (100), 102 (32), 77 (50).

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.20; H, 4.29; N, 8.77.

3-(4-Chlorophenyl)-2-methoxybenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (6t)
White crystals; mp 240–242 °C.

IR (KBr): 1675 (C=O), 1538, 1346, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28–7.22 (m, 8 H, Ar-H), 4.06 (s, 3 H, CH_3).

MS: *m*/*z* (%) = 342 (100) [M^+], 311 (12), 200 (13), 145 (92), 102 (46), 102 (46), 76 (36).

Anal. Calcd for $C_{17}H_{11}ClN_2O_2S$: C, 59.56; H, 3.23; N, 8.17. Found: C, 59.67; H, 3.47; N, 8.02.

2-(Alkylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 8a–f; General Procedure
To the soln of **4** (ca. 3 mmol) in CH_2Cl_2 (10 mL) was added alkylamine (3 mmol) and the mixture was allowed to stand unstirred for

several minutes. The solvent was removed and anhyd EtOH (8 mL) with EtONa (0.3 mmol, 10% equiv) in EtOH was added. The mixture was stirred at r.t. for 4–6 h. The soln was condensed and the residue was recrystallized (EtOH) to give **8a–f**.

2-(Ethylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8a)
White crystals; mp 191–193 °C.

IR (KBr): 1673 (C=O), 1544, 1321, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.34 (m, 9 H, Ar-H), 4.17 (s, 1 H, NH), 3.56–3.51 (m, *J* = 7.0 Hz, 2 H, CH_2), 1.18 (t, *J* = 7.0 Hz, 3 H, CH_3).

MS: *m*/*z* (%) = 321 (55) [M^+], 277 (32), 200 (9), 146 (62), 77 (24).

Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.38; H, 4.54; N, 13.28.

3-Phenyl-2-(propylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8b)
White crystals; mp 147–149 °C.

IR (KBr): 1673 (C=O), 1544, 1319, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.34 (m, 9 H, Ar-H), 4.19 (s, 1 H, NH), 3.50–3.45 (m, 2 H, NCH_2), 1.62–1.56 (q, *J* = 7.0 Hz, 2 H, CH_2), 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3).

MS: *m*/*z* (%) = 335 (58) [M^+], 277 (22), 200 (8), 146 (56), 77 (26).

Anal. Calcd for $C_{19}H_{17}N_3OS$: C, 68.03; H, 5.11; N, 12.53. Found: C, 68.18; H, 5.04; N, 12.50.

2-(Isopropylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8c)
White crystals; mp 167–169 °C.

IR (KBr): 1675 (C=O), 1546, 1324, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.33 (m, 9 H, Ar-H), 4.37 (m, 1 H, NCH), 3.94 (d, *J* = 7.2 Hz, 1 H, NH), 1.19 (d, *J* = 6.4 Hz, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C=O), 153.8, 152.0, 142.0, 134.6, 134.5, 130.6, 129.9, 128.8, 128.5, 124.3, 123.6, 123.3, 112.4, 44.0, 22.5.

MS: *m*/*z* (%) = 335 (74) [M^+], 277 (25), 200 (6), 146 (93), 77 (68).

Anal. Calcd for $C_{19}H_{17}N_3OS$: C, 68.03; H, 5.11; N, 12.53. Found: C, 68.21; H, 5.14; N, 12.37.

2-(Butylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8d)
White crystals; mp 98–100 °C.

IR (KBr): 1675 (C=O), 1546, 1324, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27–7.34 (m, 9 H, Ar-H), 4.17 (s, 1 H, NH), 3.56–3.45 (m, 2 H, NCH_2), 1.34–1.28 (m, 4 H, 2 × CH_2), 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3).

MS: *m*/*z* (%) = 349 (46) [M^+], 277 (34), 200 (8), 146 (73), 77 (60).

Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.60; H, 5.34; N, 12.26.

2-(*tert*-Butylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8e)
White crystals; mp 237–239 °C.

IR (KBr): 1673 (C=O), 1551, 1323, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25–7.33 (m, 9 H, Ar-H), 4.07 (s, 1 H, NH), 1.45 (s, 9 H, 3 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C=O), 153.5, 151.5, 142.0, 134.9, 134.8, 130.6, 129.8, 128.8, 128.5, 124.3, 123.7, 123.3, 112.5, 52.8, 28.8.

MS: *m*/*z* (%) = 349 (44) [M^+], 277 (12), 200 (6), 146 (52), 77 (56).

Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.90; H, 5.64; N, 11.97.

2-(Benzylamino)-3-phenylbenzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8f)
White crystals; mp 205–207 °C.

IR (KBr): 1677 (C=O), 1549, 1328, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26–7.27 (m, 14 H, Ar-H), 4.74 (d, *J* = 5.6 Hz, 2 H, NCH_2), 4.59 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 153.5, 152.5, 141.9, 138.3, 134.5, 134.3, 130.6, 129.9, 128.7, 128.5, 127.4, 124.3, 123.6, 123.2, 112.9, 45.7.

MS: *m*/*z* (%) = 383 (100) [M^+], 277 (37), 200 (12), 146 (49), 77 (36).

Anal. Calcd for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96. Found: C, 72.19; H, 4.34; N, 10.77.

2-(Phenylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 9a,b; General Procedure
To the soln of **4** (ca. 3 mmol) in MeCN (10 mL) was added NH_3 or $MeNH_2$ (3 mmol) and the mixture was stirred for 0.5 h. The soln was condensed and the residue was recrystallized (EtOH) to give **9a**,**b**.

2-(Phenylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (9a)
White crystals; mp >300 °C.

IR (KBr): 1679 (C=O), 1545, 1346, 759 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 11.14 (s, 1 H, NHCO), 8.89 (s, 1 H, NHPh), 8.21–7.09 (m, 9 H, Ar-H).

MS: *m*/*z* (%) = 293 (100) [M^+], 201 (32), 146 (92), 77 (44).

Anal. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.38; H, 3.94; N, 14.07.

3-Methyl-2-(phenylamino)benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (9b)
White crystals; mp 297–299 °C.

IR (KBr): 1683 (C=O), 1544, 1343, 757 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 8.87 (s, 1 H, NHPh), 8.05–7.14 (m, 9 H, Ar-H), 3.64 (s, 3 H, NCH_3).

MS: *m*/*z* (%) = 307 (100) [M^+], 215 (25), 200 (21), 146 (90), 77 (36).

Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.58; H, 4.34; N, 13.35.

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