

Efficient Synthesis of 2-Substituted Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via an Iminophosphorane

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ABSTRACT: The carbodiimides **4**, obtained from reactions of iminophosphorane **3** with aromatic isocyanates, were reacted with secondary amines to give 2-dialkylamino-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** in the presence of catalytic amount of EtONa. Reactions of **4** with phenols or ROH in the presence of the catalytic amount of K₂CO₃ or RONa gave 2-aryloxy- or 2-alkoxy-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** in satisfactory yields. The effects of the nucleophiles on cyclization have been investigated. © 2008 Wiley Periodicals, Inc. *Heteroatom Chem* 19:266–270, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20424

INTRODUCTION

The derivatives of heterocycles containing thienopyrimidine system are of great importance because of their remarkable biological activity for use as potential drugs. For example, some 2-alkoxy- or

2-alkyl-substituted thienopyrimidinones show significant antifungal and antibacterial activities [1–7], whereas others exhibited good anticonvulsant and angiotensin or H₁ receptor antagonistic activities [8–12]. The chemistry of thienopyrimidinones has also received attention because their starting materials, 2-amino-3-carboxythiophenes, can be conveniently synthesized by the Gewald reaction [13]. Synthetically useful approaches to thienopyrimidinones starting from easily accessible 2-amino-3-carboxythiophenes are, therefore, of great importance. Recently, we have become interested in the preparation of *N*-heteroaryliminophosphoranes because these species are promising building blocks for the synthesis of nitrogen heterocycles [14–18]. Herein, we report an efficient synthesis of various 2-substituted 5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via iminophosphorane **3**.

RESULTS AND DISCUSSION

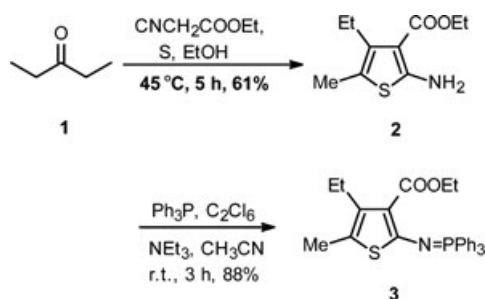
Ethyl-2-amino-5-ethyl-6-methyl-thiophene-3-carboxylate **2**, easily obtained by the Gewald method from 3-pentanone **1**, ethyl cyanoacetate, and sulfur in the presence of morpholine, was converted to iminophosphorane **3** by the treatment with triphenylphosphine, hexachloroethane, and

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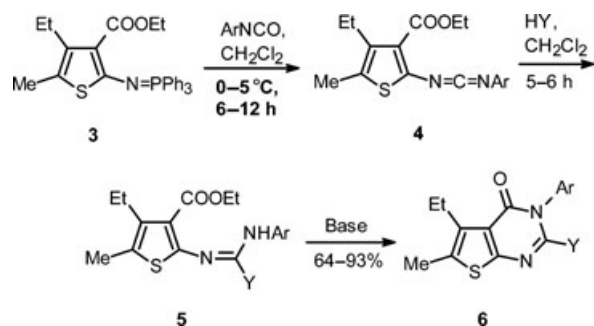
triethylamine in dry acetonitrile (Eq. (1)).



(1)

Iminophosphorane **3** reacted with an equimolecular quantity of the aromatic isocyanates to give the carbodiimides **4**, which were allowed to react with secondary amines to provide guanidine intermediates **5** ($Y = NR^1R^2$). Even in refluxing toluene, the intermediates **5** did not cyclize. However, by treatment with sodium ethoxide in ethanol at room temperature, the intermediates **5** underwent intramolecular heterocyclization to give the expected pyrimidinones **6** in satisfactory yields (Eq. (2)). The results are listed in Table 1. The yields of products **6** are related to the substituents R^1 and R^2 of the secondary amines. Better yields are obtained as R^1 and R^2 are small alkyl or cyclic alkyl group (**6a**, **6d**, **6f**, **6h**, **6j** in Table 1); however, lower yields are obtained when R^1 and R^2 are a long-chain alkyl group or one of them is a phenyl

group (**6e**, **6g** in Table 1).



(2)

The direct reaction of carbodiimide **4** with phenols did not produce 2-aryloxy-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**. However, when carried out in the presence of catalytic amount of potassium carbonate, the reaction gave **6** ($Y = OAr$) in good yields (Table 1). The formation of **6** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **4** to give the intermediates **5** that cyclize to give **6**. The yields of products **6** are also related to the substituents of phenols. Better yields are obtained as electron-donating substituents are present in the phenol ring (**6o**, **6p** in Table 1). The direct reaction of carbodiimide **4** with ROH gave a complex mixture; however, when the reaction was carried out in the presence of catalytic amount of RO^-Na^+ , the reaction took place smoothly and 2-alkoxy-thieno[2,

TABLE 1 Preparation of 2-Substituted Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**

No.	Ar	Y	Formula	Conditions	Yield (%) ^a	MP (°C)
6a	Ph	NEt ₂	C ₁₉ H ₂₃ N ₃ OS	r.t./6 h	93	144–145
6b	Ph	N(<i>i</i> -Bu) ₂	C ₂₃ H ₃₁ N ₃ OS	r.t./6 h	81	123–124
6c	Ph	N(<i>n</i> -C ₅ H ₁₁) ₂	C ₂₅ H ₃₅ N ₃ OS	r.t./6 h	85	73–74
6d	Ph		C ₂₀ H ₂₃ N ₃ OS	r.t./6 h	92	128–129
6e	Ph	NMePh	C ₂₂ H ₂₁ N ₃ OS	r.t./6 h	64	153–154
6f	4-MeC ₆ H ₄	NEt ₂	C ₂₀ H ₂₅ N ₃ OS	r.t./6 h	88	96–97
6g	4-MeC ₆ H ₄	N(<i>n</i> -C ₅ H ₁₁) ₂	C ₂₆ H ₃₇ N ₃ OS	r.t./6 h	64	70–71
6h	3-MeC ₆ H ₄	NEt ₂	C ₂₀ H ₂₅ N ₃ OS	r.t./6 h	86	103–104
6i	3-MeC ₆ H ₄	N(<i>n</i> -Bu) ₂	C ₂₄ H ₃₃ N ₃ OS	r.t./6 h	73	65–66
6j	3-MeC ₆ H ₄		C ₂₁ H ₂₅ N ₃ OS	r.t./6 h	87	157–158
6k	4-ClC ₆ H ₄		C ₁₉ H ₂₀ ClN ₃ O ₂ S	r.t./8 h	78	205–206
6l	4-MeC ₆ H ₄	MeO	C ₁₇ H ₁₈ N ₂ O ₂ S	r.t./6 h	82	153–154
6m	4-MeC ₆ H ₄	EtO	C ₁₈ H ₂₀ N ₂ O ₂ S	r.t./6 h	84	158–159
6n	4-ClC ₆ H ₄	MeO	C ₁₆ H ₁₅ ClN ₂ O ₂ S	r.t./8 h	77	184–185
6o	Ph	4-MeC ₆ H ₄ O	C ₂₂ H ₂₀ N ₂ O ₂ S	r.t./6 h	83	203–204
6p	Ph	4-MeOC ₆ H ₄ O	C ₂₂ H ₂₀ N ₂ O ₃ S	r.t./6 h	76	88–89
6q	Ph	4-ClC ₆ H ₄ O	C ₂₁ H ₁₇ ClN ₂ O ₂ S	r.t./6 h	74	138–139

r.t. = Room temperature.

^aIsolated yields are based on iminophosphorane **3**.

TABLE 2 The Elemental Analysis and IR Data of Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**

	Anal. (Calcd) (%)	IR (cm ⁻¹)
6a	C, 66.95 (66.83); H, 6.50 (6.79); N, 12.20 (12.31)	1681, 1592, 1540, 1497, 1469
6b	C, 69.52 (69.48); H, 8.06 (7.86); N, 10.54 (10.57)	1678, 1591, 1525, 1464, 1434
6c	C, 70.75 (70.55); H, 8.41 (8.29); N, 9.80 (9.87)	1692, 1589, 1541, 1497, 1469
6d	C, 67.96 (67.96); H, 6.54 (6.56); N, 11.74 (11.89)	1682, 1591, 1522, 1439, 1364
6e	C, 70.10 (70.37); H, 5.85 (5.64); N, 10.92 (11.19)	1682, 1594, 1529, 1488, 1439
6f	C, 67.43 (67.57); H, 7.00 (7.09); N, 11.64 (11.82)	1681, 1540, 1510, 1467, 1493
6g	C, 71.03 (71.03); H, 8.28 (8.48); N, 9.31 (9.56)	1686, 1587, 1537, 1498, 1469
6h	C, 67.28 (67.57); H, 7.23 (7.09); N, 11.79 (11.82)	1678, 1607, 1541, 1500, 1471
6i	C, 69.82 (70.03); H, 8.19 (8.08); N, 10.35 (10.21)	1686, 1606, 1540, 1493, 1452
6j	C, 68.60 (68.63); H, 7.03 (6.86); N, 11.24 (11.43)	1687, 1532, 1510, 1444, 1365
6k	C, 58.35 (58.53); H, 5.44 (5.17); N, 10.62 (10.78)	1681, 1593, 1584, 1540, 1491
6l	C, 64.87 (64.94); H, 5.67 (5.77); N, 8.98 (8.91)	1684, 1605, 1569, 1552, 1500
6m	C, 65.94 (65.83); H, 5.97 (6.14); N, 8.80 (8.53)	1693, 1551, 1500, 1474, 1439
6n	C, 57.44 (57.40); H, 4.78 (4.52); N, 8.58 (8.37)	1693, 1597, 1574, 1492, 1461
6o	C, 70.04 (70.19); H, 5.46 (5.35); N, 7.51 (7.44)	1693, 1599, 1570, 1549, 1506
6p	C, 67.44 (67.33); H, 5.31 (5.14); N, 6.92 (7.14)	1689, 1570, 1505, 1349, 1304
6q	C, 63.46 (63.55); H, 4.43 (4.32); N, 6.97 (7.06)	1693, 1602, 1572, 1545, 1485

3-*d*]pyrimidin-4(3*H*)-ones **6** (Y = OR) were obtained in satisfactory yields (Table 1).

The structure of the synthesized compound **6** was confirmed by their spectral data and elemental analyses (Tables 2 and 3). For example, the IR spectra of **6a** revealed C=O absorption bands at 1681 cm⁻¹. The ¹H NMR spectral data show the signals of -NCH₂ at 3.04 ppm as quartets and signals of CH₃ at 2.36, 1.13, and 0.80 ppm as singlets or triplets. The phenyl signals appeared at 7.26–7.50 (m, 5H, Ar-H). The MS spectrum of **6a** shows molecule ion peak (M⁺ + 1) at *m/z* 342.

In conclusion, we have developed an efficient method for the synthesis of 2-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via a base-catalyzed reaction of functionalized carbodiimides with various secondary amines, phenols, or alcohols. The synthetic approach shows that the aza-Wittig reaction of iminophosphorane affords a general route to the heterocyclic system, containing various substituents in the pyrimidine ring. Owing to the easily accessible and versatile starting material, this method has the potential in the synthesis of many biologically and pharmaceutically active thienopyrimidinone derivatives.

EXPERIMENTAL

Melting points were determined using a X-4 model apparatus (Beijing Taikang Company, Beijing, People's Republic of China) and were uncorrected. IR spectra were recorded on a Nicolet 7500 NXR infrared spectrometer (Thermo Nicolet Company, Waltham, Massachusetts) as KBr pellets with absorption given in cm⁻¹. MS were measured on a HP5988A spec-

trometer (Hewlett-Packard Company, Palo Alto, California). ¹H NMR spectra were recorded in CDCl₃ on a Varian Mercury Plus 400 (400 Hz) spectrometer (Varian Company, Palo Alto, California), and chemical shifts (δ) are given in ppm using (CH₃)₄Si as an internal reference (δ = 0). Elementary analyses were taken on a Perkin-Elmer CHN2400 elemental analysis instrument (PerkinElmer Company, Waltham, Massachusetts).

Preparation of Ethyl-3-ethyl-4-methyl-2-aminothiophene-3-carboxylate (**2**)

To a stirred mixture of 0.42 g (0.005 mol) of 3-pentanone (**1**), 0.16 g (0.005 mol) of sulfur, and 0.57 g (0.005 mol) of ethyl cyanoacetate in 10 mL of ethanol, 1.2 mL of morpholine was added. After the mixture was stirred at 45°C for 5 h, the solid was filtered and the filtrate was poured into water. The formed yellow solid was separated and recrystallized from methanol to give **2** as light yellow needles, 0.65 g (61%), mp 40–41°C. ¹H NMR (CDCl₃): δ 1.02 (t, 3H, *J* = 7.2 Hz, CH₃), 1.33 (t, 3H, *J* = 7.2 Hz, CH₃), 2.03 (s, 3H, CH₃), 2.66 (q, 2H, *J* = 7.2 Hz, CH₂), 4.32 (q, 2H, *J* = 7.2 Hz, OCH₂), 5.84 (s, 2H, NH₂); MS: *m/z* (%) 213 (M⁺, 53%), 183 (47), 107 (100). Anal. Calcd for C₁₀H₁₅NO₂S: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.22; H, 7.35; N, 6.71.

Preparation of Ethyl-3-ethyl-4-methyl-2-[(triphenylphosphanylidene)amino]thiophene-3-carboxylate (**3**)

To a mixture of ethyl-3-ethyl-4-methyl-2-aminothiophene-3-carboxylate (**2**; 0.64 g, 3 mmol),

TABLE 3 The MS and ^1H -NMR Data of Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones 6

	FAB-MS	^1H -NMR (CDCl_3 , δ)
6a	342 ($\text{M}^+ + 1$)	0.80 (t, 6H, $J = 7.0$ Hz, 2CH_3); 1.13 (t, 3H, $J = 6.8$ Hz, CH_3); 2.36 (s, 3H, CH_3); 2.85 (q, 2H, $J = 7.2$ Hz, CH_2); 3.04 (q, 4H, $J = 7.2$ Hz, 2NCH_2); 7.26–7.50 (m, 5H, Ar-H)
6b	398 ($\text{M}^+ + 1$)	0.77 (d, 12H, $J = 6.8$ Hz, 4CH_3); 1.13 (t, 3H, $J = 7.2$ Hz, CH_3); 1.75–1.81 (m, 2H, 2CH); 2.36 (s, 3H, CH_3); 2.79–2.86 (m, 6H, 3CH_2); 7.27–7.51 (m, 5H, Ar-H)
6c	425 (M^+)	0.84 (t, 6H, $J = 7.2$ Hz, 2CH_3); 1.13 (t, 3H, $J = 7.2$ Hz, CH_3); 1.17–1.24 (m, 6H, $2\text{CH}_2\text{CH}_2\text{CH}_2$); 2.36 (s, 3H, CH_3); 2.85 (q, 2H, $J = 7.2$ Hz, CH_2); 2.94 (t, 4H, $J = 7.2$ Hz, 2NCH_2); 7.26–7.47 (m, 5H, Ar-H)
6d	353 (M^+)	1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 1.22–1.40 (m, 6H, 3CH_2); 2.37 (s, 3H, CH_3); 2.86 (q, 2H, $J = 7.2$ Hz, CH_2); 3.06 (t, 4H, $J = 5.4$ Hz, 2CH_2); 7.27–7.49 (m, 5H, Ar-H)
6e	376 ($\text{M}^+ + 1$)	1.13 (t, 3H, $J = 7.2$ Hz, CH_3); 2.41 (s, 3H, CH_3); 2.86 (q, 2H, $J = 7.2$ Hz, CH_2); 3.25 (s, 3H, NCH_3); 6.58–7.26 (m, 10H, Ar-H)
6f	356 ($\text{M}^+ + 1$)	0.82 (t, 6H, $J = 7.2$ Hz, 2CH_3); 1.12 (t, 3H, $J = 6.4$ Hz, CH_3); 2.36 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 2.85 (q, 2H, $J = 6.8$ Hz, CH_2); 3.05 (t, 4H, $J = 7.2$ Hz, 2NCH_2); 7.15–7.28 (m, 4H, Ar-H)
6g	440 ($\text{M}^+ + 1$)	0.84 (t, 6H, $J = 7.2$ Hz, 2CH_3); 1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 1.16–1.24 (m, 12H, $2\text{CH}_2\text{CH}_2\text{CH}_2$); 2.36 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 2.84 (q, 2H, $J = 7.2$ Hz, CH_2); 2.95 (t, 4H, $J = 7.2$ Hz, 2CH_2); 7.28–7.13 (m, 4H, Ar-H)
6h	356 ($\text{M}^+ + 1$)	0.81 (t, 6H, $J = 7.2$ Hz, 2CH_3); 1.13 (t, 3H, $J = 7.2$ Hz, CH_3); 2.36 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 2.86 (q, 2H, $J = 7.2$ Hz, CH_2); 3.05 (q, 4H, $J = 7.2$ Hz, 2NCH_2); 7.07–7.38 (m, 4H, Ar-H)
6i	411 (M^+)	0.82 (t, 6H, $J = 6.8$ Hz, 2CH_3); 1.10–1.22 (m, 11H, $2\text{CH}_2\text{CH}_2$, and CH_3); 2.36 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 2.85 (q, 2H, $J = 7.2$ Hz, CH_2); 2.96 (t, 4H, $J = 7.2$ Hz, 2NCH_2); 7.06–7.38 (m, 4H, Ar-H)
6j	368 ($\text{M}^+ + 1$)	1.12 (t, 3H, $J = 6.8$ Hz, CH_3); 1.23–1.41 (m, 6H, 3CH_2); 2.36 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 2.85 (q, 2H, $J = 6.8$ Hz, CH_2); 3.07 (t, 4H, $J = 4.8$ Hz, 2NCH_2); 7.19–7.28 (m, 4H, Ar-H)
6k	390 ($\text{M}^+ + 1$)	1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 2.38 (s, 3H, CH_3); 2.84 (q, 2H, $J = 7.2$ Hz, CH_2); 3.08 (t, 4H, $J = 4.8$ Hz, 2NCH_2); 3.46 (t, 4H, $J = 4.8$ Hz, 2OCH_2); 7.27–7.49 (m, 4H, Ar-H)
6l	315 ($\text{M}^+ + 1$)	1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 2.37 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 2.86 (q, 2H, $J = 7.2$ Hz, CH_2); 3.91 (s, 3H, OCH_3); 7.10–7.31 (m, 4H, Ar-H)
6m	329 ($\text{M}^+ + 1$)	1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 1.24 (t, 3H, $J = 7.2$ Hz, CH_3); 2.37 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 2.86 (q, 2H, $J = 7.2$ Hz, CH_2); 4.41 (q, 2H, $J = 7.2$ Hz, OCH_2); 7.08–7.30 (m, 4H, Ar-H)
6n	334 (M^+)	1.12 (t, 3H, $J = 7.2$ Hz, CH_3); 2.38 (s, 3H, CH_3); 2.85 (q, 2H, $J = 7.2$ Hz, CH_2); 3.92 (s, 3H, OCH_3); 7.16–7.48 (m, 4H, Ar-H)
6o	377 ($\text{M}^+ + 1$)	1.14 (t, 3H, $J = 7.2$ Hz, CH_3); 2.35 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 2.88 (q, 2H, $J = 7.2$ Hz, CH_2); 6.98–7.56 (m, 9H, Ar-H)
6p	393 ($\text{M}^+ + 1$)	1.14 (t, 3H, $J = 7.2$ Hz, CH_3); 2.36 (s, 3H, CH_3); 2.88 (q, 2H, $J = 7.2$ Hz, CH_2); 3.80 (s, 3H, OCH_3); 6.87–7.56 (m, 9H, Ar-H)
6q	396 (M^+)	1.14 (t, 3H, $J = 7.2$ Hz, CH_3); 2.37 (s, 3H, CH_3); 2.88 (q, 2H, $J = 7.2$ Hz, CH_2); 7.05–7.57 (m, 9H, Ar-H)

triphenylphosphine (2.36 g, 9 mmol), and hexachloroethane (2.13 g, 9 mmol) in dry acetonitrile (10 mL), triethylamine (1.84 g, 18 mmol) was added dropwise in a nitrogen atmosphere. The mixture was stirred for 3 h at room temperature. After the reaction mixture was poured into cold water (200 mL), the precipitate obtained was recrystallized from ethanol to give the desired iminophosphorane **3** in 88% yield with mp 106–107°C. ^1H NMR (CDCl_3): δ 1.04 (t, 3H, $J = 7.2$ Hz, CH_3); 1.35 (t, 3H, $J = 7.2$ Hz, CH_3); 2.04 (s, 3H, CH_3); 2.66 (q, 2H, $J = 7.2$ Hz, CH_2); 4.29 (q, 2H, $J = 7.2$ Hz, OCH_2); 7.84–7.47 (m, 15H, Ar-H); MS: m/z (%) 473 (M^+ , 100%), 262 (78), 183 (74), 107 (63). IR (KBr, cm^{-1}): 1664, 1470, 1437,

1398, 1329. Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{NO}_2\text{PS}$: C, 71.02; H, 5.96; N, 2.96. Found: C, 70.24; H, 6.19; N, 2.93.

General Preparation of 2-Dialkylamino-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (6a–6k)

To a solution of iminophosphorane **3** (0.95 g, 2 mmol) in anhydrous CH_2Cl_2 (10 mL), aromatic isocyanate (2 mmol) was added under nitrogen atmosphere at room temperature. After the reaction mixture was left unstirred for 6–12 h at 0–5°C, the iminophosphorane **3** had disappeared (TLC monitored). The solvent was removed under reduced

pressure, and Et₂O/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** in dichloromethane (10 mL), dialkylamine (2 mmol) was added. After the reaction mixture was left unstirred for 5–6 h, the solvent was removed and anhydrous EtOH (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 6–12 h at room temperature. The solution was condensed, and the residue was recrystallized from EtOH to give the expected cyclic compounds **6a–6k** in good yields.

*General Preparation of 2-Alkoxy-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (6l–6n)*

To the solution of **4** prepared as mentioned above in ROH (10 mL), several drops of RONA in ROH were added. The mixture was stirred for 6 h at room temperature. The solution was condensed, and the residue was recrystallized from dichloromethane–petroleum ether to give 2-alkoxy-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6l–6n**.

*General Preparation of 2-Aryloxy-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (6o–6q)*

To the solution of **4** prepared as mentioned above in dry acetonitrile (10 mL), substituted phenol (2 mmol) and cat. solid K₂CO₃ (0.14 g, 10 mmol) were added. The mixture was stirred for 6 h at room temperature and filtered. The filtrate was condensed, and the residue was recrystallized from dichloromethane–petroleum ether to give 2-aryloxy-5-ethyl-6-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6o–6q**.

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