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Application of Bis(iminophosphorane) in Heterocyclic Synthesis: New Entries to Symmetrically or Unsymmetrically Substituted Thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3H,6H)-diones

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The bis(carbodiimides) **4**, obtained from bis-aza-Wittig reactions of bis(iminophosphorane) **3** with 2 equiv of aromatic isocyanates, were reacted with secondary amine to give symmetrically substituted 2,7-diaminothieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione **6** in the presence of a catalytic amount of EtO^-Na^+. Reactions of **4** with phenols or ROH in the presence of a catalytic amount of potassium carbonate or RO^-Na^+ gave symmetrically substituted 2,7-diaryl(alkyl)-oxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **6** in satisfactory yields. However, iminophosphoranes **9** were obtained via reaction of bis(iminophosphorane) **3** with 1 equiv of aromatic isocyanate and subsequent reaction with an amine in the presence of a catalytic amount of EtO^-Na^+. Further reaction of iminophosphoranes **9** with aromatic isocyanates and various nucleophile generated unsymmetrically substituted thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **12** in good yields.

Introduction

The derivatives of fused pyrimidinones have been the focus of great interest over many years. This is probably due to the fact that many compounds containing a fused pyrimidinone ring play a very important part in the biochemistry of the living cell. Recent development of physiologically highly potent purine analogues with interesting antiviral, antiallergic, and specially anticancer activities has promoted a great current interst in facile and general routes to these molecules in synthetically useful yields.[1] The thienopyrimidine systems are also of great importance because of their remarkable biological properties.[2] For example, some 2-alkoxy- or 2-alkyl-substituted thienopyrimidinones show significant antifungal and antibacterial activities,[2a−d] whereas others exhibited good anticonvulsant and angiotensin II or H_1 receptor antagonistic activities.[2e−h] Although some derivatives of thienodipyrimidines have been synthesized and some of them show good antitumor activity,[3] there is no report of a generally useful synthesis of thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones, compounds which are of considerable interest as potential biologically active compounds or pharmaceuticals.

Over the past 20 years, the aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[4] 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. However, the chemistry of bis(iminophosphoranes) has been studied less extensively. Bis(iminophosphoranes) have been shown to have synthetic potential as a result of their ability to react with reagents bearing two functional groups or with two separate reagents with the same or different functionality. Various heterocycles have been synthesized via bis(iminophosphoranes).[5] Some of these heterocycles include 11*H*-quinazolino[2,3-*b*]quinazolines,[5a] indazolo-[2′,3′:1,5]-1,2,4-triazolo[4,3-*a*]-1,3,5-benzotriazepines,[5b] diquino[4,3-*b*:3′,4′-*d*]pyrroles,[5c] benzimidazo[1,2-*a*]benzimidazoles,[5d] pyrido[2,3,4-*de*]quinazolines,[5e] 1,3-diazeto-[1′,2′-*a*]pyrazolo[3,4-*d*]-1,3-diazopines,[5f] and pyrido[5″,6″:4,5;3″2″:4′,5′]dithieno[3,2-*d*:3′,2′-*d*′]dipyrimidine- 4,8-

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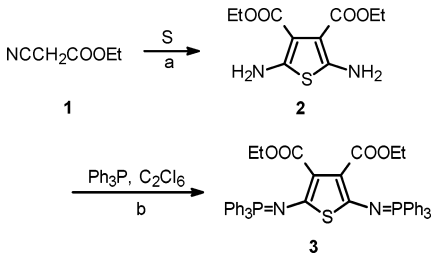
SCHEME 1. Preparation of Bis(iminophosphorane) 3[a]



[a] Reagents and conditions: (a) DMF, NEt_3, rt, 4 h, 35%; (b) CH_3CN, NEt_3, rt, 4 h, 70%.

(3*H*,9*H*)-dione.[5g] Recently we have been interested in the synthesis of quinazolinones, thienopyrimidinones, and imidazolinones via aza-Wittig reaction of α or *β* ethoxycarbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophiles under mild conditions.[6] Here we wish to report a fundamentally new approach to the synthesis of symmetrically and unsymmetrically substituted thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones from bis(iminophosphorane) **3**.

Results and Discussion

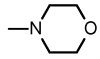
The 2,5-diamino-3,4-(diethoxycarbonyl)thiophene **2**, easily obtained by cyclization of ethyl 2-cyanoacetate **1** with sulfur under basic condition,[3c] was converted to bis(iminophosphorane) **3** via reaction with triphenylphosphine, hexachloroethane, and triethylamine.[7]

Iminophosphorane **3** reacted with 2 equiv of aromatic isocyanate to give bis(carbodiimide) **4**, which was allowed to react with secondary amines to provide guanidine intermediates **5**. Even in refluxing toluene, **5** did not cyclize; however, in the presence of a catalytic amount of sodium ethoxide, **5** were converted easily to symmetrically substituted 2,7-diaminothieno[2,3-*d*:5,4-*d*′]-dipyrimidine-4,5(3*H*,6*H*)-diones **6** in satisfactory yields at room temperature. It is noteworthy that the isolated yield of **6** was good even when Y was a bulky diisopropylamino group. The results are listed in Table 1.

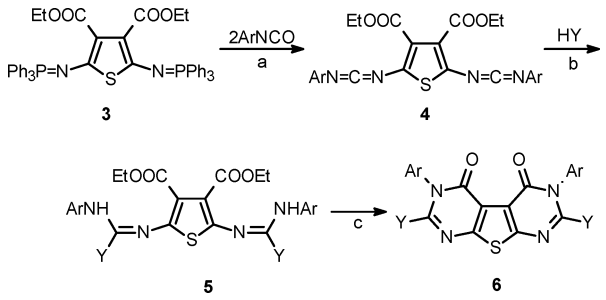
The direct reaction of bis(carbodiimide) **4** with phenols did not produce symmetrically substituted 2,7-diaryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **6** either. However, when carried our in the presence of catalytic potassium carbonate, the reaction took place to give **6** in good yields. The formation of **6** can be rationalized in terms of an initial nucleophilic addition of phenoxide to the bis(carbodiimide) **4** to give the intermediate **5**, which cyclizes to give **6**. The reaction is relatively insensitive to the presence or absence of substituents on the phenols and the cyclization can be completed smoothly at 40−50 °C.

The direct reaction of bis(carbodiimide) **4** with ROH gave a complex mixture; however, when carried out in the presence of catalytic RO^-Na^+, the reaction took place smoothly and symmetrically substituted 2,7-dialkoxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **6** were obtained in satisfactory yields.

TABLE 1. Yields of Compounds 6a−o

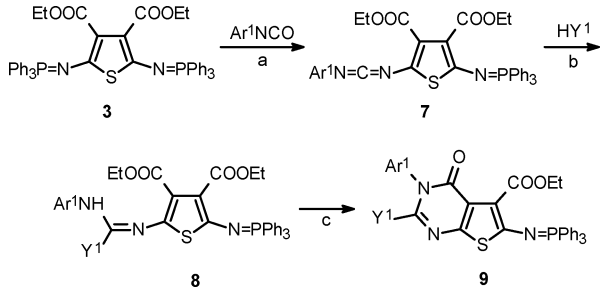
compd	Ar	Y	yield (%)
6a	Ph	NEt_2	85
6b	Ph	N(*n*-Pr)$_2$	76
6c	Ph	N(*n*-Bu)$_2$	82
6d	Ph	N(*n*-C_5H_{11})$_2$	71
6e	Ph	N(*n*-C_6H_{13})$_2$	67
6f	Ph	N(*i*-Pr)$_2$	72
6g	4-Me-C_6H_4		87
6h	4-Cl-C_6H_4		81
6i	Ph	4-Cl-C_6H_4O	82
6j	Ph	4-Br-C_6H_4O	73
6k	Ph	4-MeS-C_6H_4O	84
6l	4-Me-C_6H_4	4-Br-C_6H_4O	70
6m	3-Me-C_6H_4	4-Me-C_6H_4O	77
6n	Ph	MeO	73
6o	Ph	EtO	75

SCHEME 2. Synthesis of Compounds 6[a]



[a] Reagents and conditions: (a) CH_2Cl_2, 0−5 °C, 8−12 h; (b) CH_2Cl_2, rt, 0.5−6 h; (c) EtOH, EtO^-Na^+, rt, 1−6 h; or CH_3CN, K_2CO_3 (s), 40−50 °C, 6−8 h.

SCHEME 3. Synthesis of Iminophosphoranes 9[a]



[a] Reagents and conditions: (a) CH_2Cl_2, 0−5 °C, 12 h; (b) CH_2Cl_2, rt, 0.5−1 h; (c) EtOH, EtO^-Na^+, rt, 1−2 h.

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TABLE 2. Yields of Compounds 9a,b and 12a–*l*

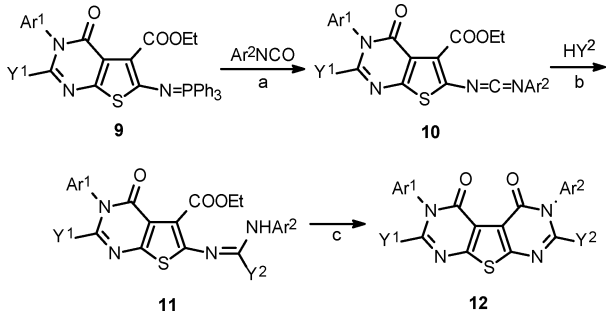
compd	Ar^1	Y^1	Ar^2	Y^2	yield (%)
9a	Ph				81
9b	Ph				77
12a	Ph		4-Cl-C_6H_4	NEt_2	82
12b	Ph		4-Me-C_6H_4	NEt_2	86
12c	Ph		4-Cl-C_6H_4		81
12d	Ph		4-Cl-C_6H_4	$N(n\text{-}Pr)_2$	74
12e	Ph		4-Cl-C_6H_4	$N(n\text{-}Bu)_2$	72
12f	Ph		4-Me-C_6H_4	NEt_2	83
12g	Ph		4-Me-C_6H_4	$N(n\text{-}Bu)_2$	74
12h	Ph		Ph	NEt_2	73
12i	Ph		Ph	4-MeO-C_6H_4O	78
12j	Ph		Ph	4-MeO-C_6H_4O	73
12k	Ph		Ph	EtO	78
12l	Ph		Ph	MeO	75

It is interesting to note that a differentiation between the two iminophosphorane functions appears when an equimolar amount of aromatic isocyanate is used. In this case, only the carbodiimide **7** is generated and monopyrimidinone **9** is obtained when carbodiimide **7** is further treated with amine under basic condition. This may be due to the lower reactivity of the second triphenylphosphoranylidenamino group of **7** compared with bis(iminophosphorane) **3**.

Iminophosphorane **9** reacted further with other aromatic isocyanates to give carbodiimides **10**, which were allowed to react with secondary amines and subsequently with sodium ethoxide to provide unsymmetrically substituted 2,7-diaminothieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5-(3*H*,6*H*)-diones **12** in satisfactory yields at room temperature. The results are listed in Table 2.

The direct reaction of carbodiimide **10** with phenols in the presence of catalytic potassium carbonate gave unsymmetrically substituted 2,7-diaryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **12** in good yields. The formation of **12** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **10** to give the intermediate **11**, which cyclizes to give **12**. No matter if the substituents on the phenols are electron-withdrawing or electron-releasing groups, the cyclization can be completed smoothly at room temperature. When carbodiimide **10** was treated with ROH in the presence of catalytic RO^-Na^+, unsymmetrically substituted 2,7-dialkoxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3H,6H)-diones **12** were obtained in satisfactory yields.

SCHEME 4. Synthesis of Compounds 12[a]



[a] Reagents and conditions: (a) CH_2Cl_2, 0–5 °C, 8–12 h; (b) CH_2Cl_2, rt, 0.5–6 h; (c) EtOH, EtO^-Na^+, rt, 1–6 h; or CH_3CN, K_2CO_3 (s), 40–50 °C, 6–8 h.

In conclusion, we have developed an efficient synthesis of symmetrically or unsymmetrically 2,3,6,7-tetrasubstituted thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones from bis(iminophosphorane). Due to the mild reaction condition, good yields, easily accessible starting material, and straightforward product isolation, we think that this new synthetic approach discussed here has potential in

the synthesis of many biologically and pharmaceutically active thienodipyrimidinone derivatives.

Experimental Section

Diethyl 2,5-Bis(triphenylphosphoranylideneamino)-thiophen-3,4-dicarboxylate (3). 3 was prepared from diethyl 2,5-diaminothiophene-3,4-carboxylate[3c] according to a literature report.[7] Deep yellow crystals (yield 70%); mp 200−202 °C (lit.[7] mp 201−203 °C).

2,7-Diaminothieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones (6). To a solution of bis(iminophosphorane) **3** (2.33 g, 3 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (6 mmol) under nitrogen at room temperature. After the reaction mixture was left to stand for 8−12 h at 0−5 °C, the solvent was removed reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration the solvent was removed to give bis(carbodiimide) **4**, which was used directly without further purification. To the solution of **4** prepared above in methylene dichloride (15 mL) was added dialkylamine (6 mmol). After the reaction mixture was allowed to stand for 0.5−6 h, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 1−6 h at room temperature. The solution was then concentrated under reduced pressure and the residual was recrystallized from ethanol to give 2,7-diaminothieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **6**.

2,7-Di(diethylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]-dipyrimidine-4,5(3*H*,6*H*)-dione (6a). White crystals (yield 85%); mp >300 °C. IR (KBr) 1715 (C=O), 1536, 1508, 1286, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, J = 7.2 Hz, 12H), 3.11 (q, J = 7.2 Hz, 8H), 7.26−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5 (4), 45.0 (4), 112.4 (2), 127.7 (2), 128.6 (4), 129.1 (4), 138.1 (2), 156.0 (2), 157.0 (2), 161.1 (2). MS *m/z* 514 (M$^+$, 100), 486 (11), 396 (22), 340 (35), 175 (26), 119 (38). Anal. Calcd for $C_{28}H_{30}N_6O_2S$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.27; H, 5.94; N, 16.57.

2,7-Di(di-*n*-propylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6b). White crystals (yield 76%); mp 288−289 °C. IR (KBr) 1718 (C=O), 1533, 1507, 1244, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.73 (t, J = 7.2 Hz, 12H), 1.24−1.30 (m, 8H), 2.98 (t, J = 7.6 Hz, 8H), 7.26−7.42 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.2 (4), 20.6 (4), 52.5 (4), 112.1 (2), 127.6 (2), 128.4 (4), 128.9 (4), 137.9 (2), 155.9 (2), 156.8 (2), 160.9 (2). MS *m/z* 570 (M$^+$, 72), 541 (16), 470 (25), 368 (50), 203 (46), 119 (100). Anal. Calcd for $C_{32}H_{38}N_6O_2S$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.56; H, 6.88; N, 14.64.

2,7-Di(di-*n*-butylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6c). White crystals (yield 82%); mp 224−226 °C. IR (KBr) 1719 (C=O), 1532, 1507, 1229, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, J = 7.2 Hz, 12H), 1.10−1.24 (m, 16H), 3.01 (t, J = 7.2 Hz, 8H), 7.26−7.41 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (4), 19.9 (4), 29.4 (4), 50.5 (4), 112.1 (2), 127.5 (2), 128.3 (4), 128.9 (4), 137.9 (2), 155.9 (2), 156.8 (2), 160.9 (2). MS *m/z* 626 (M$^+$, 74), 570 (8), 498 (11), 396 (41), 231 (27), 119 (79), 57 (100). Anal. Calcd for $C_{36}H_{46}N_6O_2S$: C, 68.98; H, 7.40; N, 13.41. Found: C, 68.85; H, 7.16; N, 13.63.

2,7-Di(di-*n*-pentylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6d). White crystals (yield 71%); mp 189−190 °C. IR (KBr) 1718 (C=O), 1532, 1508, 1458, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.2 Hz, 12H), 1.04−1.28 (m, 24H), 3.00 (t, J = 7.6 Hz, 8H), 7.26−7.42 (m, 10H). MS *m/z* 682 (M$^+$, 64), 625 (6), 424 (28), 354 (8), 259 (14), 119 (56), 43 (100). Anal. Calcd for $C_{40}H_{54}N_6O_2S$: C, 70.35; H, 7.97; N, 12.30. Found: C, 70.18; H, 7.91; N, 12.47.

2,7-Di(di-*n*-hexylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6e). White crystals (yield 67%); mp 169−170 °C. IR (KBr) 1718 (C=O), 1534, 1508, 1466, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.2 Hz, 12H), 1.08−1.26 (m, 32H), 3.00 (t, J = 7.2 Hz, 8H), 7.26−7.42 (m, 10H). MS *m/z* 738 (M$^+$, 100), 667 (20), 554 (12), 452 (38), 287 (13), 119 (49). Anal. Calcd for $C_{44}H_{62}N_6O_2S$: C, 71.51; H, 8.46; N, 11.37. Found: C, 71.62; H, 8.35; N, 11.39.

2,7-Di(diisopropylamino)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6f). White crystals (yield 72%); mp >300 °C. IR (KBr) 1717 (C=O), 1526, 1498, 1127, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (d, J = 6.8 Hz, 24H), 3.51−3.57 (m, 4H), 7.23−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2 (8), 49.8 (4), 112.3 (2), 127.2 (2), 128.1 (4), 129.3 (4), 138.8 (2), 154.8 (2), 157.2 (2), 160.4 (2). MS *m/z* 570 (M$^+$, 56), 527 (41), 470 (18), 368 (27), 250 (12), 119 (58), 43 (100). Anal. Calcd for $C_{32}H_{38}N_6O_2S$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.25; H, 6.83; N, 14.75.

2,7-Di(4-morpholinyl)-3,6-di(4-methylphenyl)thieno-[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6g). White crystals (yield 87%); mp >300 °C. IR (KBr) 1717 (C=O), 1535, 1505, 1113, 952 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 6H), 3.13 (t, J = 4.4 Hz, 8H), 3.43 (t, J = 4.4 Hz, 8H), 7.21 (s, 8H). MS *m/z* 570 (M$^+$, 82), 539 (10), 484 (21), 368 (34), 203 (71), 91 (100). Anal. Calcd for $C_{30}H_{30}N_6O_4S$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.21; H, 5.36; N, 14.86.

3,6-Di(4-chlorophenyl)-2,7-di(1-piperidinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6h). White crystals (yield 81%); mp >300 °C. IR (KBr) 1712 (C=O), 1535, 1489, 1251, 944 cm^{-1}. ^{1}H NMR ($CDCl_3$ + TFA, 400 MHz) δ 1.40−1.56 (m, 12H), 3.31 (t, J = 5.6 Hz, 8H), 7.32−7.57 (m, 8H). MS *m/z* 608/606 (M$^+$, 60/100), 522 (7), 467 (11), 386 (17), 221 (13), 165 (8). Anal. Calcd for $C_{30}H_{28}Cl_2N_6O_2S$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.25; H, 4.46; N, 13.91.

2,7-Diaryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5-(3*H*,6*H*)-diones (6). To the solution of **4** prepared above in CH_3CN (15 mL) was added substituted phenol (6 mmol) and solid K_2CO_3 (0.14 g, 1.0 mmol). The mixture was stirred for 6−8 h at 40−50 °C and filtered, the filtrate was condensed, and the residual was recrystallized from methylene dichloride/petroleum ether to give 2,7-diaryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **6**.

2,7-Di(4-chlorophenoxy)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6i). White crystals (yield 82%); mp >300 °C. IR (KBr) 1729 (C=O), 1561, 1484, 1211, 941 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04−7.44 (m, 18H). MS *m/z* 626/624 (M$^+$, 76/100), 497 (88), 378 (5), 119 (29), 77 (56). Anal. Calcd for $C_{32}H_{18}Cl_2N_4O_4S$: C, 61.45; H, 2.90; N, 8.96. Found: C, 61.49; H, 2.78; N, 8.80.

2,7-Di(4-bromophenoxy)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6j). White crystals (yield 73%); mp >300 °C. IR (KBr) 1730 (C=O), 1560, 1484, 1209, 939 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00−7.45 (m, 18H). MS *m/z* 716/714/712 (M$^+$, 66/100/56), 543 (96), 514 (10), 119 (30), 77 (56). Anal. Calcd for $C_{32}H_{18}Br_2N_4O_4S$: C, 53.80; H, 2.54; N, 7.84. Found: C, 53.93; H, 2.36; N, 7.54.

2,7-Di(4-methylthiophenoxy)-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6k). White crystals (yield 84%); mp >300 °C. IR (KBr) 1731 (C=O), 1560, 1484, 1209, 939 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 6H), 7.04−7.46 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (2), 114.7 (2), 119.2 (2), 123.3 (4), 128.0 (4), 129.9 (4), 131.9 (2), 132.6 (4), 138.8 (2), 150.6 (2), 154.1 (2), 155.7 (2), 159.7 (2). MS *m/z* 648 (M$^+$, 41), 529 (14), 509 (68), 139 (45), 77 (100). Anal. Calcd for $C_{34}H_{24}N_4O_4S_3$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.72; H, 3.87; N, 8.84.

2,7-Di(4-bromophenoxy)-3,6-di(4-methylphenyl)thieno-[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6l). White crystals (yield 70%); mp >300 °C. IR (KBr) 1729 (C=O), 1562, 1481, 1212, 945 cm^{-1}. ^{1}H NMR ($CDCl_3$ + TFA, 400 MHz) δ 2.46 (s, 6H), 7.03−7.58 (m, 16H). MS *m/z* 744/742/740 (M$^+$, 13/23/11), 571 (9), 133 (50), 39 (100). Anal. Calcd for $C_{34}H_{22}Br_2N_4O_4S$: C, 55.00; H, 2.99; N, 7.55. Found: C, 55.14; H, 2.92; N, 7.48.

2,7-Di(4-methylphenoxy)-3,6-di(3-methylphenyl)thieno-[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6m). White

crystals (yield 77%); mp >300 °C. IR (KBr) 1726 (C=O), 1560, 1495, 1203, 940 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 6H), 2.37 (s, 6H), 7.00−7.38 (m, 16H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (2), 21.2 (2), 114.4 (2), 121.0 (4), 125.1 (2), 128.8 (4), 129.5 (2), 129.9 (4), 134.6 (2), 135.6 (2), 139.0 (2), 149.3 (2), 154.3 (2), 155.8 (2), 159.9 (2). MS *m/z* 612 (M^+, 35), 505 (49), 372 (96), 133 (23), 91 (100). Anal. Calcd for $C_{36}H_{28}N_4O_4S$: C, 70.57; H, 4.61; N, 9.14. Found: C, 70.35; H, 4.78; N, 9.25.

2,7-Dialkoxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones (6). 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 room temperature. The solution was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give 2,7-dialkoxythieno[2,3-*d*:5,4-*d*′] dipyrimidine-4,5(3*H*,6*H*)-diones **6**.

2,7-Dimethoxy-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6n). White crystals (yield 73%); mp >300 °C. IR (KBr) 1724 (C=O), 1562, 1509, 1257, 967 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.96 (s, 6H), 7.20−7.48 (m, 10H). MS *m/z* 432 (M^+, 84), 313 (8), 134 (15), 119 (100). Anal. Calcd for $C_{22}H_{16}N_4O_4S$: C, 61.10; H, 3.73; N, 12.96. Found: C, 61.43; H, 3.58; N, 12.81.

2,7-Diethoxy-3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (6o). White crystals (yield 75%); mp >300 °C. IR (KBr) 1716 (C=O), 1561, 1508, 1257, 944 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J = 7.2 Hz, 6H), 4.42 (q, J = 7.2 Hz, 4H), 7.19−7.45 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (2), 65.2 (2), 113.6 (2), 128.3 (2), 128.4 (4), 128.7 (4), 134.7 (2), 154.4 (2), 155.9 (2), 159.9 (2). MS *m/z* 460 (M^+, 10), 432 (4), 119 (71), 77 (100). Anal. Calcd for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.47; H, 4.46; N, 12.36.

5-Ethoxycarbonyl-6-triphenylphosphoranylideneaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (9). To a solution of bis(iminophosphorane) **3** (2.33 g, 3 mmol) in dry methylene dichloride (15 mL) was added phenyl isocyanate (0.36 g, 3 mmol) under nitrogen at room temperature. After the reaction mixture had stood for 12 h at 0−5 °C, dialkylamine (3 mmol) was added. After this reaction mixture had stood for 0.5−1 h at room temperature, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 1−2 h at room temperature. The solution was condensed and the residual was recrystallized from ethanol to give 5-ethoxycarbonyl-6- triphenylphosphoranylideneaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **9**.

2-(1-Piperidinyl)-3-phenyl-5-ethoxycarbonyl-6-triphenylphosphoranylideneaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (9a). White crystals (yield 81%); mp 195−196 °C. IR (KBr) 1705 and 1674 (C=O), 1525, 1491, 1342, 695 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14−1.34 (m, 9H), 2.91 (t, J = 5.2 Hz, 4H), 4.35 (q, J = 7.2 Hz, 2H), 7.29−7.81 (m, 20H). MS *m/z* 658 (M^+, 51), 277 (100), 262 (73), 183 (74), 77 (44). Anal. Calcd for $C_{38}H_{35}N_4O_3PS$: C, 69.28; H, 5.36; N, 8.50. Found: C, 69.52; H, 5.42; N, 8.73.

2-(4-Morpholinyl)-3-phenyl-5-ethoxycarbonyl-6-triphenylphosphoranylideneaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (9b). White crystals (yield 77%); mp 254−255 °C. IR (KBr) 1704 and 1684 (C=O), 1524, 1496, 1204, 695 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, J = 7.2 Hz, 3H), 2.95 (t, J = 4.4 Hz, 4H), 3.33 (t, J = 4.4 Hz, 4H), 4.35 (q, J = 7.2 Hz, 2H), 7.30−7.82 (m, 20H). MS *m/z* 660 (M^+, 94), 615 (17), 588 (20), 277 (55), 262 (100), 183 (85), 108 (72). Anal. Calcd for $C_{37}H_{33}N_4O_4PS$: C, 67.26; H, 5.03; N, 8.48. Found: C, 67.18; H, 5.25; N, 8.23.

2-Aminothieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones (12). To a solution of iminophosphorane **9** (3 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (3 mmol) under nitrogen at room temperature. After the reaction mixture had stood for 6−12 h at 0−5 °C, dialkylamine (3 mmol) was added. After this reaction mixture had stood for 3−6 h at room temperature, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 6 h at room temperature. The solution was condensed and the residual was recrystallized from ethanol to 2-aminothieno[2,3-*d*:5,4-*d*′]dipyrimidine- 4,5(3*H*,6*H*)-diones **12**.

2-Diethylamino-3-(4-chlorophenyl)-6-phenyl-7-(1-piperidinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12a). White crystals (yield 82%); mp >300 °C. IR (KBr) 1716 (C=O), 1536, 1450, 1249, 946 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.2 Hz, 6H), 1.24−1.42 (m, 6H), 3.06−3.12 (m, 8H), 7.23−7.43 (m, 9H). MS *m/z* 560 (M^+, 100), 532 (8), 408 (14), 352 (25), 209 (18), 187 (16). Anal. Calcd for $C_{29}H_{29}ClN_6O_2S$: C, 62.08; H, 5.21; N, 14.98. Found: C, 62.24; H, 5.10; N, 14.74.

2-Diethylamino-3-(4-methylphenyl)-6-phenyl-7-(1-piperidinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12b). White crystals (yield 86%); mp >300 °C. IR (KBr) 1717 (C=O), 1533, 1457, 1250, 944 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.2 Hz, 6H), 1.23−1.41 (m, 6H), 2.36 (s, 3H), 3.07−3.12 (m, 8H), 7.14−7.40 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.4 (2), 21.0, 23.8, 24.6 (2), 44.8 (2), 49.6 (2), 112.1, 112.9, 127.3, 128.1 (2), 128.7 (2), 128.9 (4), 135.2, 137.2, 137.7, 156.0, 156.3, 156.4, 156.7, 160.4, 160.9. MS *m/z* 540 (M^+, 98), 510 (18), 407 (37), 352 (57), 189 (67), 132 (100). Anal. Calcd for $C_{30}H_{32}N_6O_2S$: C, 66.64; H, 5.97; N, 15.54. Found: C, 66.31; H, 5.85; N, 15.79.

2-(4-Morpholinyl)-3-(4-chlorophenyl)-6-phenyl-7-(1-piperidinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12c). White crystals (yield 81%); mp >300 °C. IR (KBr) 1718 (C=O), 1534, 1505, 1115, 950 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.43 (m, 6H), 3.05−3.13 (m, 8H), 3.42 (m, 4H), 7.26−7.44 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 24.8 (2), 48.8 (2), 49.9 (2), 65.8 (2), 112.6, 113.4, 127.6, 128.3 (2), 128.5 (2), 129.2 (2), 130.6 (2), 133.6, 135.5, 137.7, 155.5, 155.7, 156.2, 156.9, 160.1, 161.0. MS *m/z* 576/574 (M^+, 36/100), 540 (5), 490 (10), 388 (25), 223 (11), 77 (20). Anal. Calcd for $C_{29}H_{27}ClN_6O_3S$: C, 60.57; H, 4.73; N, 14.61. Found: C, 60.33; H, 4.93; N, 14.48.

2-(Di-*n*-propylamino)-3-(4-chlorophenyl)-6-phenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5-(3*H*,6*H*)-dione (12d). White crystals (yield 74%); mp >300 °C. IR (KBr) 1717 (C=O), 1536, 1506, 1245, 955 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (t, J = 7.2 Hz, 6H), 1.23−1.36 (m, 4H), 2.98 (t, J = 7.2 Hz, 4H), 3.08−3.10 (m, 4H), 3.40 (t, J = 4.0 Hz, 4H), 7.24−7.41 (m, 9H). MS *m/z* 592/590 (M^+, 34/85), 561 (5), 490 (8), 77 (24), 43 (100). Anal. Calcd for $C_{30}H_{31}ClN_6O_3S$: C, 60.96; H, 5.29; N, 14.22. Found: C, 60.68; H, 5.34; N, 14.15.

2-(Di-*n*-butylamino)-3-(4-chlorophenyl)-6-phenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12e). White crystals (yield 72%); mp >300 °C. IR (KBr) 1717 (C=O), 1534, 1450, 1259, 955 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.2 Hz, 6H), 1.14−1.27 (m, 8H), 3.01 (t, J = 7.2 Hz, 4H), 3.09−3.11 (m, 4H), 3.39−3.41 (m, 4H), 7.24−7.41 (m, 9H). MS *m/z* 620/618 (M^+, 42/100), 562 (9), 490 (14), 354 (27), 77 (21). Anal. Calcd for $C_{32}H_{35}ClN_6O_3S$: C, 62.07; H, 5.70; N, 13.57. Found: C, 62.14; H, 5.56; N, 13.59.

2-(Diethylamino)-3-(4-methylphenyl)-6-phenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12f). White crystals (yield 83%); mp >300 °C. IR (KBr) 1716 (C=O), 1532, 1459, 1114, 956 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.2 Hz, 6H), 2.37 (s, 3H), 3.09−3.14 (m, 8H), 3.40−3.42 (m, 4H), 7.17−7.42 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5 (2), 21.1, 45.0 (2), 48.8 (2), 65.9 (2), 112.1, 113.6, 127.9, 128.4 (2), 128.8 (2), 129.0 (2), 129.1 (2), 135.3, 137.1, 137.5, 155.5, 156.1, 156.2, 156.8, 160.0, 161.3. MS *m/z* 542 (M^+, 100), 513 (7), 470 (7), 410 (10), 354 (20), 91 (25). Anal. Calcd for $C_{29}H_{30}N_6O_3S$: C, 64.19; H, 5.57; N, 15.49. Found: C, 64.34; H, 5.31; N, 15.42.

2-(Di-*n*-butylamino)-3-(4-methylphenyl)-6-phenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12g). White crystals (yield 74%); mp 299−300 °C. IR (KBr) 1715 (C=O), 1536, 1454, 1114, 955 cm^{-1}. ^1H NMR

($CDCl_3$, 400 MHz) δ 0.84 (t, J = 7.2 Hz, 6H), 1.11−1.27 (m, 8H), 2.37 (s, 3H), 3.00−3.06 (m, 8H), 3.37−3.38 (m, 4H), 7.16−7.39 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (2), 20.0 (2), 20.9, 29.6 (2), 48.6 (2), 50.8 (2), 65.7 (2), 111.8, 113.4, 127.5, 128.1 (2), 128.9 (4), 129.1 (2), 135.2, 137.0, 137.2, 155.5, 155.9, 156.2, 156.3, 159.7, 160.9. MS *m/z* 598 (M^+, 100), 555 (23), 470 (26), 354 (54), 189 (53), 77 (69). Anal. Calcd for $C_{33}H_{38}N_6O_3S$: C, 66.20; H, 6.40; N, 14.04. Found: C, 66.37; H, 6.28; N, 14.21.

2-(Diethylamino)-3,6-diphenyl-7-(4-morpholinyl)thieno-[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12h). White crystals (yield 73%); mp >300 °C. IR (KBr) 1716 (C=O), 1532, 1456, 1115, 955 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.2 Hz, 6H), 3.11−3.15 (m, 8H), 3.41−3.43 (m, 4H), 7.26−7.43 (m, 10H). MS *m/z* 528 (M^+, 100), 499 (7), 456 (5), 119 (18), 77 (72). Anal. Calcd for $C_{28}H_{28}N_6O_3S$: C, 63.62; H, 5.34; N, 15.90. Found: C, 63.47; H, 5.16; N, 15.98.

2-Aryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones (12). To the solution of **10** prepared above in CH_3CN (15 mL) was added substituted phenol (3 mmol) and solid K_2CO_3 (0.07 g, 0.5 mmol). The mixture was stirred for 6−10 h at 40−50 °C and filtered, the filtrate was condensed, and the residual was recrystallized from methylene dichloride/petroleum ether to give 2,7-diaryloxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones **12**.

2-(4-Methoxyphenoxy)-3,6-diphenyl-7-(1-piperidinyl)-thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12i). White crystals (yield 78%); mp >300 °C. IR (KBr) 1725 (C=O), 1542, 1506, 1203, 942 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24−1.42 (m, 6H), 3.13 (t, J = 5.0 Hz, 4H), 3.81 (s, 3H), 6.88−7.48 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 24.8 (2), 49.8 (2), 55.5, 112.5, 114.4 (2), 114.7, 122.3 (2), 127.7, 128.3 (2), 128.4 (2), 128.7, 129.0 (4), 134.9, 137.8, 145.0, 154.2, 155.7, 156.7, 156.8, 157.3, 159.1, 161.7. MS *m/z* 577 (M^+, 100), 454 (66), 391 (31), 288 (38), 187 (26), 77 (58). Anal. Calcd for $C_{32}H_{27}N_5O_4S$: C, 66.54; H, 4.71; N, 12.12. Found: C, 66.35; H, 4.47; N, 12.34.

2-(4-Methoxyphenoxy)-3,6-diphenyl-7-(4-morpholinyl)-thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12j). White crystals (yield 73%); mp >300 °C. IR (KBr) 1725 (C=O), 1541, 1500, 1200, 945 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.08 (t, J = 4.4 Hz, 4H), 3.38 (t, J = 4.4 Hz, 4H), 3.82 (s, 3H), 6.87−7.47 (m, 14H). MS *m/z* 579 (M^+, 67), 456 (48), 391 (12), 288 (7), 189 (17), 77 (100). Anal. Calcd for $C_{31}H_{25}N_5O_5S$: C, 64.24; H, 4.35; N, 12.08. Found: C, 64.37; H, 4.41; N, 11.93.

2-Alkoxythieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones (12). To the solution of **10** prepared above in ROH (15 mL) was added several drops of RO^-Na^+ in ROH. The mixture was stirred for 6 h at room temperature. The solution was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give 2-alkoxythieno[2,3-*d*:5,4-*d*′]-dipyrimidine-4,5(3*H*,6*H*)-diones **12**.

2-Ethoxy-3,6-diphenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12k). White crystals (yield 81%); mp 284−285 °C. IR (KBr) 1721 (C=O), 1537, 1507, 1260, 947 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J = 7.2 Hz, 3H), 3.14 (t, J = 4.4 Hz, 4H), 3.42 (t, J = 4.4 Hz, 4H), 4.42 (q, J = 7.2 Hz, 2H), 7.19−7.45 (m, 10H). MS *m/z* 501 (M^+, 100), 473 (8), 381 (26), 313 (15), 189 (18), 77 (26). Anal. Calcd for $C_{26}H_{23}N_5O_4S$: C, 62.26; H, 4.62; N, 13.96. Found: C, 62.41; H, 4.54; N, 13.71.

2-Methoxy-3,6-diphenyl-7-(4-morpholinyl)thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-dione (12l). White crystals (yield 85%); mp >300 °C. IR (KBr) 1720 (C=O), 1538, 1507, 1259, 955 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.13 (t, J = 4.4 Hz, 4H), 3.42 (t, J = 4.4 Hz, 4H), 3.95 (s, 3H), 7.20−7.45 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.9 (2), 56.1, 65.8 (2), 113.3, 113.9, 128.1, 128.4 (2), 128.6 (2), 128.8 (2), 128.9 (2), 134.7, 137.0, 155.0, 155.7, 155.9, 156.3, 159.8, 160.7. MS *m/z* 487 (M^+, 100), 401 (17), 377 (37), 248 (28), 117 (24), 43 (60). Anal. Calcd for $C_{25}H_{21}N_5O_4S$: C, 61.59; H, 4.34; N, 14.36. Found: C, 61.85; H, 4.57; N, 14.22.

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Supporting Information Available: General experimental procedures, copies of ^{1}H NMR spectra for all compounds and ^{13}C NMR spectra for typical compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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