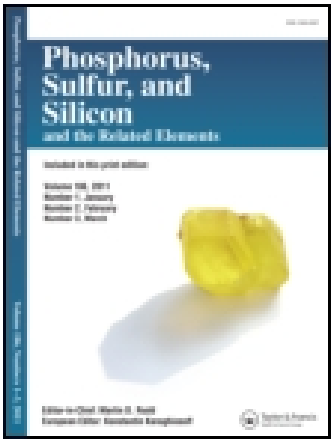

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Applying an Aza-Wittig Reaction for the Synthesis of Novel Thieno[3′,2′:5,6] Pyrido[4,3-*d*]pyrimidinone Derivatives

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A series of new 2-substituted tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6]pyrido[4,3-d] pyrimidin-4(3H)-ones ***5*** *has been designed and synthesized via an aza-Wittig reaction. Iminophosphorane* ***3a*** *or iminophosphorane* ***3b*** *reacted with 4-Cl-phenyl(or 4-F-phenyl) isocyanate to give carbodiimide* ***4a*** *or carbodiimide* ***4b****, which were further treated with phenols to cyclize to give compounds* ***5*** *in presence of a catalytic amount of* K_2CO_3*. The structures of compound* ***5*** *have been confirmed by* ^1H *NMR, EI-MS, IR spectroscopy, and elemental analyses.*

Keywords Aza-Wittig reaction; carbodiimide; iminophosphorane; pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones

INTRODUCTION

Thienopyridines are of chemical and pharmacological interest due to their structures being similar to quinolines and isoquinolines, two important heterocycles in many alkaloids.[1,2] The derivatives of pyridopyrimidine have also attracted the interest of pharmaceutical companies recently. This is due in part to the wide range of biological activities associated with this structure. For example, some related 4-(phenylamino)pyrido[*d*]pyrimidines have been reported as selective inhibitors of tyrosine phosphorylation by epidermal growth factor

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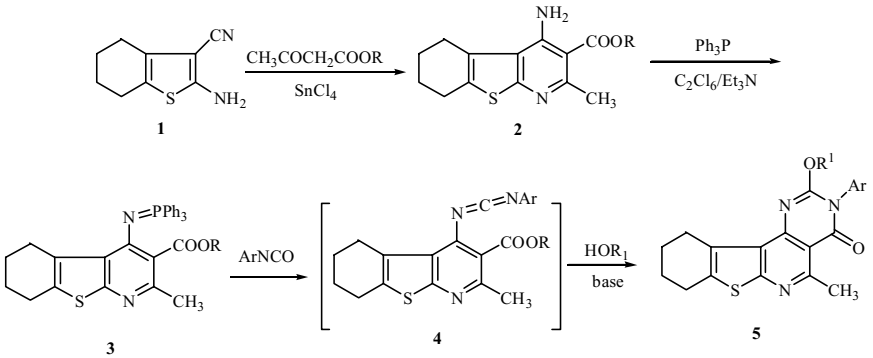
receptor (EGFR) and become an important class of potential anticancer drugs.[3,4] In this article, we are interested in the synthesis of new pyridine derivatives that contain the thienopyridine ring and the pyridopyrimidine ring.

The aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of nitrogen heterocyclic compounds.[5,6] Recently we have become interested in the synthesis of pyrazolopyrimidinones and thienopyrimidinones from various iminophosphoranes, with the aim of evaluating their biological activities.[7] Here we wish to report further a facile synthesis of tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **5,** in which are contained the thienopyridine ring and the pyridopyrimidine ring, from easily accessible iminophosphorane **3**.

RESULTS AND DISCUSSION

The tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine **2a** (or **2b**), easily obtained from tetrahydrobenzo[*b*]thiophene **1**, methyl acetoacetate (or ethyl acetoacetate), and stannic chloride, was converted to iminophosphorane **3a** (or **3b**) via reaction with triphenylphosphine, hexachloroethane, and Et_3N (see Scheme 1). The yield of **2a** (38%) is less than the yield of **2b** (64%), but the yield of **3a** (90%) is almost equal to that of **3b** (91%).

Iminophosphorane **3a** (or iminophosphorane **3b)** reacted with 4-Cl-phenyl(or 4-F-phenyl) isocyanate to give carbodiimide **4**. Even in refluxing toluene and by heating, **4** was not allowed to react



2,3: R=CH_3(a), C_2H_5(b); **5**: Ar=4-Cl-Ph, 4-F-Ph; R^1=Ph, 4-Cl-Ph, etc.

SCHEME 1

TABLE I Physical Constants of Compound 5

Compd.	R^1	Ar	Color	m.p./°C	[a]Yield /%	[b]Yield/%
5a	4-CH_3Ph	4-ClPh	White crystals	280~282	76	69
5b	4-ClPh	4-ClPh	White crystals	288~289	50	31
5c	Ph	4-ClPh	White crystals	272~275	64	63
5d	4-NO_2Ph	4-ClPh	Yellow crystals	220~221	62	71
5e	2,4-Cl_2Ph	4-ClPh	White crystals	290~292	85	74
5f	2-ClPh	4-ClPh	White crystals	283~285	43	30
5g	4-BrPh	4-ClPh	White crystals	300~301	68	57
5h	2,4-F_2Ph	4-ClPh	White crystals	261~262	68	66
5i	3-FPh	4-ClPh	White crystals	264~266	51	52
5j	2-Cl-4-FPh	4-ClPh	White crystals	252~254	78	69
5k	3-Cl-4-FPh	4-ClPh	White crystals	239~240	86	75
5l	2-Cl-5-CH_3Ph	4-ClPh	White crystals	276~279	63	49
5m	4-Cl-3-CH_3Ph	4-ClPh	White crystals	260~261	65	64
5n	3,5-F_2Ph	4-ClPh	White crystals	283~284	39	24
5o	3-MePh	4-ClPh	Yellow crystals	284~285	37	31
5p	4-NO_2Ph	4-FPh	White crystals	219~221	58	64
5q	2,4-Cl_2Ph	4-FPh	White crystals	248~249	70	58
5r	4-MePh	4-FPh	White crystals	300~301	62	44
5s	2-Cl-5-CH_3Ph	4-FPh	White crystals	265~266	57	34
5t	4-Cl-3-CH_3Ph	4-FPh	White crystals	221~223	59	52

[a]The yields of **5** from **3a**.
[b]The yields of **5** from **3b**.

with phenols to produce 2-aryloxy(ethoxy)-8,9,10,11-tetrahydrobenzo [4′,5′]thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one **5**. However, when carried out in the presence of catalytic K_2CO_3, the reaction took place to give **5** in good yields under the condition of heating (see Table I). Irrespective of whether the substitutes on the phenols were electron-withdrawing or electron-releasing groups, the cyclization was carried out smoothly. The yields of **5** from **3 a** are a bit more than those from **3b** (see Table I).

All the products **5** were purified by recrystallization from dichloromethane and petroleum ether. The results are listed in Table I. The structures of 8,9,10,11-tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6] pyrido[4,3-*d*]pyrimidin-4(3*H*)-one **5** was confirmed by ^{1}H NMR, IR, MS, and elementary analyses(see Tables II–IV). For example, the IR spectra of **5a** revealed C=O absorption band at 1701 cm^{-1} and 3124 cm^{-1} due to Ph-H group. The ^{1}H NMR spectral data of **5a** show the signal of CH_3 (CH_3 of pyridyl) at 3.02 ppm as singlet and signals of cyclohexenyl CH_2 at 1.59, 1.80, 2.44, and 2.79 ppm. 2.39 ppm is the signal of CH_3 of the benzene ring. The other signals appeared at 6.99~7.57 (m, 8H, Ar-H).

TABLE II Elemental Analyses and IR Spectral Data of Compound 5

Compd	Calcd. (Found)/%			IR (KBr, cm^{-1})
	C.	H.	N.	
5a	66.45(66.67)	4.54(4.41)	8.61(8.72)	3124(Ph-H), 2937(C—H), 2861(C—H), 1701(C=O), 1562, 1491, 1089, 804.
5b	61.42(61.15)	3.77(4.07)	8.26(8.17)	3123(Ph-H), 2936,2868(C—H), 1701(C=O), 1561, 1402, 1088, 846.
5c	65.89(65.63)	4.25(4.36)	8.87(8.63)	3120(Ph-H), 2942(C—H), 1698(C=O), 1563, 1418, 711.
5d	60.17(59.92)	3.69(3.78)	10.80(10.79)	3117(Ph-H), 2929,2858(C—H), 1699(C=O), 1562, 1400, 1162, 864.
5e	57.52(57.71)	3.34(3.51)	7.74(7.87)	3125(Ph-H), 2931,2863(C—H), 1705(C=O), 1562, 1490, 1092, 843, 805.
5f	61.42(61.54)	3.77(3.53)	8.26(8.45)	3104(Ph-H), 2933,2858(C—H), 1730(C=O), 1594, 1437, 1186, 1153, 755.
5g	56.48(56.30)	3.46(3.70)	6.41(6.33)	3094(Ph-H), 2936,2862(C—H), 1701(C=O), 1562, 1404, 1089, 844.
5h	61.24(61.52)	3.56(3.67)	8.24(8.45)	3103(Ph-H), 2940,2863(C—H), 1701(C=O), 1562, 1420, 1186, 832.
5i	63.48(63.29)	3.89(3.66)	8.54(8.40)	3136(Ph-H), 2935(C—H), 1702(C=O), 1562, 1261, 1090, 861.
5j	59.32(59.57)	3.45(3.49)	7.98(8.12)	3124(Ph-H), 2933,2863(C—H), 1706(C=O), 1563, 1401, 1261, 1089, 818.
5k	59.32(59.24)	3.45(3.67)	7.98(7.70)	3118(Ph-H), 2944,2860(C—H), 1701(C=O), 1562, 1261, 1091, 907, 784.
5l	62.07(61.88)	4.05(3.90)	8.04(8.32)	3123(Ph-H), 2936,2868(C—H), 1699(C=O), 1562, 1400, 1263, 1091, 816.
5m	62.07(61.93)	4.05(3.82)	8.04(8.30)	3124(Ph-H), 2936,2859(C—H), 1701(C=O), 1562, 1399, 1261, 1090, 824.
5n	61.24(60.95)	3.56(3.75)	8.24(8.49)	3076(Ph-H), 2933, 2858(C—H), 1730(C=O), 1562, 1277, 1091, 812.
5o	61.24(61.45)	3.56(3.49)	8.24(8.47)	3124(Ph-H), 2937(C—H), 2861(C—H), 1701(C=O), 1562, 1264, 1089, 804.
5p	62.14(62.38)	3.81(3.73)	11.15(11.16)	3117(Ph-H), 2926,2857(C—H), 1711(C=O), 1561, 1163, 833.
5q	59.32(59.52)	3.45(3.79)	7.98(8.17)	3087(Ph-H), 2935,2857(C—H), 1700(C=O), 1563, 1401, 1097, 864.
5r	68.77(68.59)	4.70(4.90)	8.91(9.11)	3124(Ph-H), 2937(C—H), 2861(C—H), 1701(C=O), 1562, 1264, 1016, 804.
5s	64.09(63.88)	4.18(4.15)	8.30(8.34)	3120(Ph-H), 2930,2861(C—H), 1703(C=O), 1563, 1264, 1166, 826.
5t	64.09(63.87)	4.18(3.93)	8.30(8.04)	3126(Ph-H), 2925,2859(C—H), 1700(C=O), 1563, 1265, 1158, 797.

TABLE III ^{1}H NMR Spectral Data of Compounds 5

Compd.	^{1}H NMR (ppm, $CDCl_3$, TMS, 400 MHz)
5a	1.60~1.80(m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3 of phenyl), 2.44~2.79 (m, 4H, $2CH_2$), 3.02 (s, 3H, CH_3 of pyridyl), 6.99~7.57 (m, 8H, Ar-H).
5b	1.59~1.81 (m, 4H, $2CH_2$), 2.45~ 2.81 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.08~7.58 (m, 8H, Ar-H).
5c	1.56~1.77 (m, 4H, $2CH_2$), 2.40~2.78 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.13~7.58 (m, 9H, Ar-H).
5d	1.56~1.78 (m, 4H, $2CH_2$), 2.41~2.80 (m, 4H, $2CH_2$), 3.04 (s, 3H, CH_3), 7.27~8.35 (m, 8H, Ar-H).
5e	1.61~1.81 (m, 4H, $2CH_2$), 2.34~2.80 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.15~7.58 (m, 7H, Ar-H).
5f	1.95~2.01 (m, 4H, $2CH_2$), 2.49~2.81 (m, 4H, $2CH_2$), 3.01 (s, 3H, CH_3), 7.09~7.57 (m, 8H, Ar-H).
5g	1.62~1.80 (m, 4H,$2CH_2$), 2.42~2.80 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.02~7.58 (m, 8H, Ar-H).
5h	1.60~1.79 (m, 4H, $2CH_2$), 2.41~2.80 (m, 4H, $2CH_2$), 3.04 (s, 3H, CH_3), 6.95~7.58 (m, 7H, Ar-H).
5i	1.63~1.81 (m, 4H, $2CH_2$), 2.50~2.82 (m, 4H, $2CH_2$), 3.05 (s, 3H, CH_3), 6.94~7.58 (m, 8H, Ar-H).
5j	1.59~1.79 (m, 4H, $2CH_2$), 2.36~2.82 (m, 4H, $2CH_2$), 3.04 (s, 3H, CH_3), 1.09~7.59 (m, 7H, Ar-H)
5k	1.69~1.82 (m, 4H, $2CH_2$), 2.54~2.83 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.01~7.58 (m, 7H, Ar-H).
5l	1.57~1.80 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3 of phenyl), 2.37~2.81 (m, 4H, $2CH_2$), 3.04 (s, 3H, CH_3 of pyridyl), 7.06~7.58 (m, 7H, Ar-H).
5m	1.65~1.83 (m, 4H, $2CH_2$), 2.47 (s, 3H, CH_3 of phenyl), 2.46~2.82 (m, 4H, $2CH_2$), 3.05 (s, 3H, CH_3 of pyridyl), 6.91~7.58 (m, 7H, Ar-H).
5n	1.95~2.02 (m, 4H, $2CH_2$), 2.91~3.08 (m, 4H, $2CH_2$), 3.00 (s, 3H, CH_3), 7.24~7.52 (m, 7H, Ar-H).
5o	1.59~1.80 (m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3 of phenyl), 2.74~2.97 (m, 4H, $2CH_2$), 3.00 (s, 3H, CH_3 of pyridyl), 7.09~7.54 (m, 8H, Ar-H).
5p	1.57~1.80 (m, 4H, $2CH_2$), 2.42~2.81 (m, 4H, $2CH_2$), 3.06 (s, 3H, CH_3), 7.27~8.35 (m, 8H, Ar-H).
5q	1.62~1.81 (m, 4H, $2CH_2$), 2.34~2.80 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3), 7.16~7.53 (m, 7H, Ar-H).
5r	1.59~1.80 (s, 4H, $2CH_2$), 2.39 (s, 3H, CH_3), 2.44~2.79 (m, 4H, $2CH_2$), 3.02 (s, 3H, CH_3), 6.99~7.57 (m, 8H, Ar-H).
5s	1.57~1.78 (m, 4H, $2CH_2$), 2.38 (s, 3H, CH_3 of phenyl), 2.38~2.79 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3 of pyridyl), 7.05~7.48 (m, 7H, Ar-H).
5t	1.65~1.81 (m, 4H, $2CH_2$), 2.47 (s, 3H, CH_3 of phenyl), 2.50~2.80 (m, 4H, $2CH_2$), 3.03 (s, 3H, CH_3 of pyridyl), 6.91~7.40 (m, 7H, Ar-H).

The MS spectrum of **5a** shows an obvious molecule ion peak at *m/z* 488 with 100% abundance. The structure of **5a** was also established on the basis of elemental analysis data: Anal. Calcd. (%) for $C_{27}H_{22}ClN_3O_2S$: C, 66.45; H, 4.54; N, 8.61. Found: C, 66.67; H, 4.41; N, 8.72.

TABLE IV The EI-Mass Spectra of Compound 5

Compd.	MS (EI, m/z, %)
5a	488(M^+ 100), 473(18), 396(8), 380(10).
5b	509(23), 508(M^+ 100), 495(11), 479(12), 396(10), 380(14).
5c	475(44), 474(M^+ 100), 458(22), 445(15).
5d	520(49), 519(M^+ 100), 518(80), 504(10), 491(16) , 396(29), 380(19).
5e	543(M^+ 100) , 543(90), 529(10), 396(16), 380(18), 354(15).
5f	508(M^+ 5), 400(36), 396(100), 368(11), 216(26).
5g	552(M^+ 100), 539(14), 526(11) .
5h	511(35), 510(M^+ 100) , 495(13), 481(18), 396(12), 380(26).
5i	493(39), 492(M^+ 100), 477(18), 463(20), 396(13), 380(18).
5j	528(64), 527(M^+ 35), 526(100), 510(12), 497(13), 396(12), 380(20).
5k	528(62), 527(M^+ 43), 526(100), 512(12), 510(19), 499(15), 497(30), 380(13).
5l	523(27), 522(M^+ 100), 506(11), 488(12), 396(14), 380(28).
5m	523(49), 522(M^+ 100), 508(12), 506(19), 493(14), 396(17), 380(28).
5n	510(M^+ 12), 398(100), 397(99), 393(11), 369(14), 272(35), 215(55).
5o	488(M^+ 100), 473(18), 397(58), 380(10).
5p	502(M^+ 100), 488(19), 475(26), 380(13), 364(13).
5q	527(21) , 526(M^+ 100), 510(11), 497(10), 380(9).
5r	473(33), 472(M^+ 100), 381(98), 353(38), 215(13).
5s	507(49), 506(M^+ 100), 505(86), 490(20), 470(15), 380(38), 360(10), 333(11).
5t	507(49), 506(M^+ 100), 505(99), 490(24), 382(30), 380(42), 364(54), 334(13).

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and were uncorrected. EI-MS spectra were measured on a Finnigan Trace Mass Spectrometer. IR spectra were recorded on a Shimadzu IR-408 Infrared Spectrometer. ^{1}H NMR spectra were taken on a Varian XL-300 Spectrometer. Elementary analyses were recorded on a Varian EL III elementary analysis instrument. All of the solvents and materials were reagent grade and purified as required.

Preparation of Thienopyridine Derivatives 2[8]

2-Amino-thienonitrile **1** (1.78 g, 10 mmol) and $SnCl_4$ (2.3 mL, 20 mmol) were added to a stirred solution of methyl acetoacetate (1.18 g, 10 mmol) in dry toluene (20 mL). The reaction mixture was stirred at room temperature for 1 h and then heated under reflux for 5 h. The mixture was added to a saturated aqueous solution of Na_2CO_3 (60 mL, pH = 10∼10.5). The suspension was extracted with ethyl acetate(3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the thienopyridine derivative **2a** in 38%.

White crystals, M.p.: 177∼179°C. Anal. Calcd. (%) for $C_{14}H_{16}N_2O_2S$: C 60.85, H 5.84, N 10.14; ound C 60.59, H 5.51, N 9.95. ^{1}H NMR ($CDCl_3$, 400 Hz): $\delta = 1.87\sim1.93$ (m, 4H, $-CH_2CH_2-$), 2.69 (s, 3H, CH_3 of pyridyl), 2.81∼3.02 (m, 4H, $2CH_2$), 3.92 (s, 3H, OCH_3), 6.63 (s, 2H, NH_2) ppm.

Following this procedure, with ethyl acetoacetate (1.30 g, 10 mmol) instead of methyl acetoacetate (1.18 g, 10 mmol), the compound **2b** was obtained in 64%.White crystals, M.p.: 137∼138°C. Anal. Calcd. (%) for $C_{15}H_{18}N_2O_2S$: C 62.04, H 6.25, N 9.65; Found C 62.53, H 6.31, N 9.95. ^{1}H NMR ($CDCl_3$, 400 Hz): $\delta = 1.42$(t, $J = 7.2$ Hz, 3H, CH_3), 1.87∼1.94 (m, 4H, $-CH_2CH_2-$), 2.73 (s, 3H, CH_3 of pyridyl), 2.80∼3.01 (m, 4H, $2CH_2$), 4.39 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.60 (s, 2H, NH_2) ppm.

Preparation of Iminophosphorane 3[9,10]

A solution of thienopyridine derivative **2a** (1.09 g, 4 mmol) in CH_3CN (15mL) was added to triphenylphosphine (1.31 g, 5 mmol) and C_2Cl_6 (1.19 g, 5 mmol). The mixture was treated with triethylamine (8.0 mL), then stirred for 18∼24 h at 0°C. The solution was condensed, and the residue was recrystallized from CH_3CH_2OH to give iminophosphorane **3a** in yield 91%. M.p.: 211∼212°C. Anal. Calcd. (%) for $C_{33}H_{31}N_2O_2PS$: C 71.98, H 5.67, N 5.09; Found C 71.69, H 5.90, N 5.28. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.63\sim1.66$ (m, 4H, $-CH_2CH_2-$), 2.39 (s, 3H, CH_3 of pyridyl), 2.53∼2.68 (m, 4H, $2CH_2$), 3.02 (s, 3H, OCH_3), 7.43∼7.62 (m, 15H, Ar-H) ppm.

Following this procedure with **2b** (1.16 g, 4 mmol) instead of **2a** (1.09 g, 4 mmol), the compound **3b** was obtained in yield 90%. M.p.:224∼225°C. Anal. Calcd. (%) for $C_{32}H_{29}N_2O_2PS$: C 71.62, H 5.45, N 5.22; Found C 71.90, H 5.28, N 5.49. ^{1}H NMR($CDCl_3$, 400 MHz): $\delta = 0.99$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.40∼1.64 (m, 4H, $-CH_2CH_2-$), 2.41 (s, 3H, CH_3 of pyridyl), 2.53∼2.67 (m, 4H, $2CH_2$), 3.38 (q, $J = 7.2$ Hz, 2H, OCH_2), 7.44∼7.62 (m, 15H, Ar-H) ppm.

General Procedure for the Preparation of Compound 5

Method A

To a solution of iminophosphorane **3a**(0.53 g, 1 mmol) in anhydro CH_2Cl_2 (10 mL), aromatic isocyanate (1.1 mmol) under N_2 at room temperature was added. After the reaction mixture was left unstirred for 30–40 min, the solvent was removed under reduced pressure, and Et_2O/petroleum ether 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_3CN (15 mL) was added phenol (1.1 mmol) and catalytic K_2CO_3. The mixture was stirred for 12 h at 80°C, the solution was condensed, and the residue was recrystallized from CH_3CN to give 2-alkoxyl(aryloxyl)-3-(4-Cl-phenyl or 4-F-phenyl)-5-methyl-8,9,10,11-tetrahydrobenzo[4′,5′]thieno [3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5**.

Method B

Following this general procedure with iminophosphorane **3b** (0.55 g, 1 mmol) instead of iminophosphorane **3a** (0.53 g, 1 mmol), the compounds 2-alkoxyl(aryloxyl)-3-(4-Cl-phenyl or 4-F-phenyl)-5-methyl-8,9,10,11-tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6]pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones **5 were** also obtained.

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