A Facile Synthesis of 2-substituted Thieno[3',2'-5,6]-pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones

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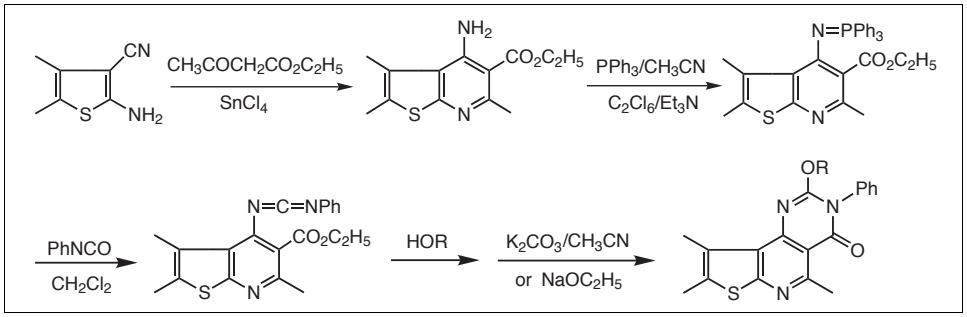

The thienopyridine derivative **2**, obtained from reaction of acetoacetic ester with **1** in the presence of tin tetrachloride, was treated with triphenylphosphine in hexachloroethane and Et_3N to give iminophosphorane **3**. Iminophosphorane **3** reacted with phenyl isocyanate to give carbodiimide **4**, which was further treated with phenols or ethenol to produce 2-substituted 5,8,9-trimethyl-3-phenyl-thieno[3',2'-5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5** in presence of catalytic amount of K_2CO_3 or EtONa. The structures of compounds **5** were confirmed by ^{1}H NMR, IR, MS, and elemental analysis.

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Introduction.

The derivatives of heterocycles containing pyrido-pyrimidine system are of great importances because of their remarkable biological properties [1]. For example, some pyridopyrimidine derivatives were used as a novel class of adenosine kinase inhibitors [2,3]. Thus, a large number of general methods for the preparation of fused pyridines have been reported [4-7].

Recently we have been interested in the synthesis of fused pyrimidinones *via* aza-Wittig reaction of β-ethoxy-carbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophiles under mild conditions [8]. As a continuation of our research for new bioactive heterocycles [9], here we wish to report an efficient synthesis of 2-substituted thieno[3',2'-5,6]pyrido-[4,3-*d*]pyrimidin-4(3*H*)-ones, a series of compounds which have not been reported before.

Results and Discussion.

The 2,3-dimethyl-4-cyano-5-aminothiophene **1** [10] was converted to thienopyridine derivative **2** *via* reaction with acetoacetic ester and tin tetrachloride under heating (Scheme 1). The iminophosphorane **3** was subsequently obtained in a satisfactory yield when **2** was treated with triphenylphosphine, hexachloroethane and Et_3N. Iminophosphorane **3** reacted with phenyl isocyanate to give carbodiimide **4**. The direct reaction of carbodiimide **4** with phenols did not cyclize to produce 2-aryloxyl-thieno-[3',2'-5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5**. However, the reaction took place to give compound **5** in good yields under the condition of heating in presence of catalytic amount of K_2CO_3. Irrespective of the fact whether the substitutes on the phenols were electron-withdrawing or electron-releasing groups, the cyclization was carried out smoothly. Thin layer chromatography was employed to follow the progress of every above reaction. Most of the compounds **5** were readily soluble in polar organic solvents and melt within 223-300 °C. The results are listed in Table 1.

It is noteworthy that the direct reaction of carbodiimide **4** with EtOH gave a complex mixture. However, when the reaction was achieved in presence of catalytic amount of EtONa, the reaction took place completely and 2-ethoxy-thieno[3',2'-5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one **5r** was obtained in satisfactory yields.

The structure of compounds **5** was confirmed by their elemental analysis and spectral data. IR spectral data of compound **5** are presented in Table 2. The elemental analysis and ^{1}H NMR spectra are given in Table 3. The EI-mass spectra are presented in Table 4. For example, the IR spectra of compound **5a** revealed C=O absorption bands at 1699 cm^{-1} and 1688 cm^{-1} and absorption bands at 3136 cm^{-1} due to Ar-H group. The ^{1}H NMR spectral data of **5a** show the signals of three

CH_3 at 1.98 ppm, 2.39 ppm, 3.06 ppm as singlet with the other signals appeared at 7.14~7.60 (m, 10H, Ar-H). The MS spectrum of **5a** shows an obvious molecule ion peak at *m/z* 413 with 100% abundance. The structure of **5a** was also established on the basis of elemental analysis data. The difference between found value and calculated value of elemental analysis of all compounds was under 0.5%.

Scheme 1

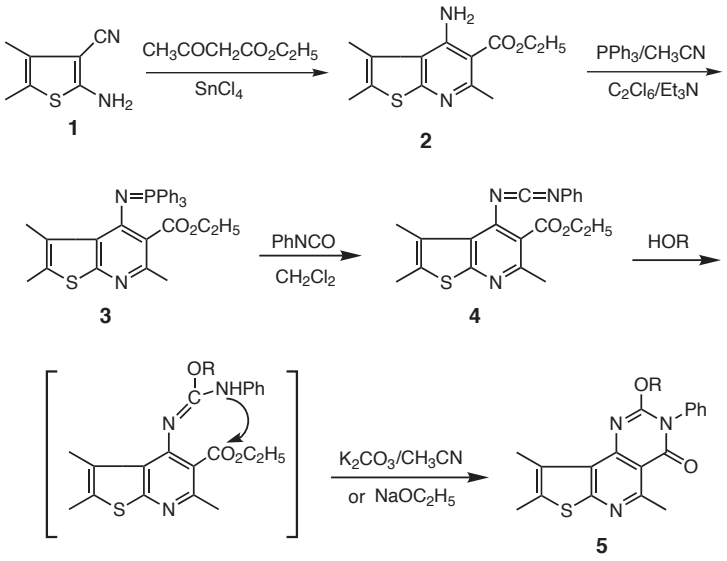

Table 1

Physical Constants of Compounds **5**

Compd.	R	Formula	Color	m. p .(°C)	r. t. (h)	Yield (%)
5a	Ph-	$C_{24}H_{19}N_3O_2S$	colorless crystals	268~269	14	87
5b	2-MePh-	$C_{25}H_{21}N_3O_2S$	colorless crystals	258~260	13	60
5c	4-CH_3Ph-	$C_{25}H_{21}N_3O_2S$	colorless crystals	243~244	13	84
5d	4-ClPh-	$C_{24}H_{18}ClN_3O_2S$	colorless crystals	267~268	12	68
5e	2,4-diClPh-	$C_{24}H_{17}Cl_2N_3O_2S$	colorless crystals	240~241	14	69
5f	2-ClPh-	$C_{24}H_{18}ClN_3O_2S$	colorless crystals	260~261	13	70
5g	4-BrPh-	$C_{24}H_{18}BrN_3O_2S$	colorless crystals	276~277	12	67
5h	2,4-diFPh-	$C_{24}H_{17}F_2N_3O_2S$	colorless crystals	250~252	13	76
5i	3-FPh-	$C_{24}H_{18}FN_3O_2S$	colorless crystals	290~292	11	82
5j	2-Cl-4-FPh-	$C_{24}H_{17}FClN_3O_2S$	colorless crystals	254~255	12	67
5k	3-Cl-4-FPh-	$C_{24}H_{17}FClN_3O_2S$	colorless crystals	266~267	13	75
5l	2-Cl-5-CH_3Ph-	$C_{25}H_{20}ClN_3O_2S$	colorless crystals	271~273	12	40
5m	4-Cl-3-CH_3Ph-	$C_{25}H_{20}ClN_3O_2S$	colorless crystals	257~259	12	74
5n	3,5-diFPh-	$C_{24}H_{17}F_2N_3O_2S$	colorless crystals	>300	13	59
5o	4-NO_2Ph-	$C_{24}H_{18}N_4O_4S$	colorless crystals	235~237	13	60
5p	2-NO_2Ph-	$C_{24}H_{18}N_4O_4S$	colorless crystals	299~300	13	44
5q	PentaClPh-	$C_{24}H_{14}Cl_5N_3O_2S$	colorless crystals	>300	11	43
5r	CH_3CH_2-	$C_{20}H_{19}N_3O_2S$	colorless crystals	223~225	14	55

Table 2

IR Spectral Data of Compounds **5**

Compd.	IR (KBr, ν/ cm^{-1})
5a	3136(Ph-H), 2910(C-H), 1699,1688(C=O), 1617, 1561, 1511, 1490, 1401, 1373, 1266, 1205, 807, 731, 690
5b	3136(Ph-H), 2925(C-H), 1733,1697(C=O), 1617, 1593, 1562, 1514, 1491, 1400, 1372, 1319, 1266, 1240, 1157, 750, 688
5c	3125(Ph-H), 2917(C-H), 1699(C=O),1618,1561,1504,1402,1370,1266,1201,835,807,700
5d	3135(Ph-H), 2924(C-H), 1700,1687(C=O), 1616, 1560, 1510, 1488, 1402, 1263, 1208, 1012, 844, 740, 690
5e	3137(Ph-H), 2926(C-H), 1699(C=O), 1622, 1563, 1516, 1403, 1371, 1251, 1225, 1096, 1049, 834, 757, 690
5f	3137(Ph-H), 2935(C-H), 1696(C=O), 1618, 1562, 1514, 1477, 1401, 1371, 1263, 1221, 1051, 806, 745

Table 2 (continued)

Compd.	IR (KBr, ν/ cm^{-1})
5g	3098(Ph-H), 2927(C-H), 1701(C=O), 1614, 1560, 1512, 1485, 1402, 1371, 1322, 1263, 1207, 1066, 1009, 842, 740, 630
5h	3124(Ph-H), 2921(C-H), 1700(C=O), 1621, 1561, 1506, 1402, 1372, 1265, 1195, 1143, 965, 830, 746, 703
5i	3136(Ph-H), 2936(C-H), 1696(C=O), 1621, 1592, 1562, 1516, 1489, 1400, 1373, 1264, 1141, 944, 810, 706
5j	3124(Ph-H), 2927(C-H), 1732, 1701(C=O), 1623, 1594, 1561, 1490, 1420, 1371, 1265, 1182, 1047, 830, 702
5k	3117(Ph-H), 2924(C-H), 1699(C=O), 1620, 1560, 1493, 1400, 1319, 1247, 1194, 1054, 873, 773, 693
5l	3136(Ph-H), 2926(C-H), 1699(C=O), 1621, 1562, 1518, 1399, 1367, 1268, 1236, 1171, 1050, 806, 703, 687
5m	3136(Ph-H), 2926(C-H), 1700(C=O), 1622, 1562, 1519, 1476, 1401, 1371, 1323, 1265, 1243, 1163, 1047, 877, 752
5n	3134(Ph-H), 2932(C-H), 1701,1686(C=O), 1618, 1560, 1510, 1491, 1466, 1400, 1375, 1264, 1156, 1120, 1091, 992
5o	3116(Ph-H), 2928(C-H), 1700(C=O), 1621, 1562, 1520, 1490, 1419, 1403, 1342, 1322, 1261, 1214, 1160, 863, 734
5p	3147(Ph-H), 2935(C-H), 1695(C=O), 1620, 1562, 1525, 1492, 1401, 1349, 1263, 1220, 1047, 806, 733, 692
5q	3094(Ph-H), 2915(C-H), 1737,1721(C=O), 1656, 1592, 1573, 1495, 1423, 1396, 1376, 1270, 1200, 1009, 806, 705, 662
5r	3152(Ph-H), 2927(C-H), 1689(C=O), 1604, 1589, 1560, 1515, 1493, 1419, 1340, 1310, 1263, 1174, 764, 694

Table 3

Elemental Analysis and ^{1}H NMR Spectral Data of Compounds **5**

Compd.	Calcd. (Found)/%			^{1}H NMR (δ / ppm, $CDCl_3$, TMS, 400 MHz)
	C.	H.	N.	
5a	69.73(69.47)	4.60(4.63)	10.17(10.33)	1.98 (s, 3H, CH_3), 2.39(s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.14~7.60 (m, 10H, Ar-H)
5b	70.24(69.95)	4.95(4.83)	9.83(10.02)	2.06 (s, 3H, CH_3), 2.39(s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.04 (s, 3H, CH_3), 6.96~7.62 (m, 9H, Ar-H)
5c	70.24(70.50)	4.95(5.02)	9.83(9.86)	2.02(s, 3H, CH_3), 2.38(s,3H, CH_3), 2.40(s,3H,CH_3), 3.05(s, 3H, CH_3), 7.07~7.60 (m, 9H, Ar-H)
5d	64.36(64.09)	4.02(4.03)	9.39(9.50)	2.04 (s, 3H, CH_3), 2.40(s, 3H, CH_3), 3.03 (s, 3H, CH_3), 7.10~7.62 (m, 9H, Ar-H)
5e	59.75(59.90)	3.53(3.67)	8.71(8.53)	1.96 (s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.05 (s, 3H, CH_3), 7.19~7.61 (m, 8H, Ar-H)
5f	64.36(64.69)	4.02(4.18)	9.39(9.41)	1.89 (s, 3H, CH_3), 2.39(s, 3H, CH_3), 3.07 (s, 3H, CH_3), 7.23~7.61 (m, 9H, Ar-H)
5g	58.54(58.35)	3.66(3.79)	8.54(8.49)	2.04 (s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.03 (s, 3H, CH_3), 7.04~7.60 (m, 9H, Ar-H)
5h	64.14(63.86)	3.79(3.84)	9.35(9.48)	2.01 (s, 3H, CH_3), 2.65(s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.26~7.61 (m, 8H, Ar-H)
5i	66.82(66.64)	4.18(4.25)	9.74(9.90)	2.05 (s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.05 (s, 3H, CH_3), 6.96~7.60 (m, 9H, Ar-H)
5j	61.87(61.85)	3.65(3.72)	9.02(9.11)	1.98 (s, 3H, CH_3), 2.52(s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.26~7.56 (m, 8H, Ar-H)
5k	61.87(62.16)	3.65(3.82)	9.02(9.09)	2.10 (s, 3H, CH_3), 2.43(s, 3H, CH_3), 3.04 (s, 3H, CH_3), 7.26~7.60 (m, 8H, Ar-H)
5l	65.00(64.79)	4.36(4.45)	9.10(9.04)	1.94 (s, 3H, CH_3), 2.35(s, 3H, CH_3), 2.40(s, 3H, CH_3), 3.07 (s, 3H, CH_3), 7.06~ 7.60 (m, 8H, Ar-H)
5m	65.00(64.86)	4.36(4.27)	9.10(9.29)	2.06 (s, 3H, CH_3), 2.39(s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.03 (s, 3H, CH_3), 6.94~7.62 (m, 8H, Ar-H)
5n	64.13(64.22)	3.81(3.92)	9.35(9.32)	2.14 (s, 3H, CH_3), 2.44(s, 3H, CH_3), 3.07 (s, 3H, CH_3), 6.78~7.61 (m, 8H, Ar-H)
5o	62.87(62.65)	3.96(3.91)	12.22(12.37)	2.00 (s, 3H, CH_3), 2.41(s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.26~8.34 (m, 9H, Ar-H)
5p	62.87(63.03)	3.96(3.99)	12.22(12.03)	1.86 (s, 3H, CH_3), 2.38(s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.26~8.24 (m, 9H, Ar-H)
5q	49.21(48.97)	2.41(2.56)	7.17(7.30)	2.53 (s, 3H, CH_3), 2.67(s, 3H, CH_3), 3.01 (s, 3H, CH_3), 7.26~7.59 (m, 5H, Ar-H)
5r	65.75(66.01)	5.21(5.28)	11.51(11.40)	1.33(d, 3H, J=7.2Hz, CH_3), 2.51(s, 3H, CH_3), 2.71 (s,3H,CH_3), 3.03(s, 3H, CH_3), 4.55(m,2H, J=7.2Hz ,CH_2), 7.25~7.54(m, 5H, Ar-H)

Table 4

The EI-mass Spectra of Compounds **5**

Compd.	MS (EI, m/z, %)
5a	415 (M^++2, 6), 414 (M^++1, 21), 413 (M^+, 100), 321 (11), 320 (66), 189 (12), 76 (24), 64 (10), 49 (9)
5b	429 (M^++2, 8), 428 (M^++1, 27), 427 (M^+, 100), 320 (10), 90 (19), 76 (31), 64 (12), 50 (7)
5c	428 (M^++1, 11), 427 (M^+, 28), 320 (11), 252 (12), 169 (10), 166 (48), 98 (27), 95 (15), 82 (64), 67 (38), 66 (34), 55 (100), 40 (48), 38 (38)
5d	449 (M^++1, 20), 448 (M^+, 32), 447 (100), 336 (25), 126 (17), 110 (19), 98 (48), 76 (58), 74 (19), 72 (10), 58 (13), 49 (13)
5e	485 (M^++3, 15), 484 (M^++2, 20), 483 (M^++1, 64), 482 (M^+, 33), 481 (100), 160 (8), 134 (17), 132 (31), 76 (96), 50 (15), 44 (14), 41 (22)
5f	449 (M^++1, 38), 448 (M^+, 29), 447 (100), 127 (6), 110 (20), 98 (31), 76 (69), 74 (18), 50 (14)
5g	494 (M^++2, 26), 493 (M^++1, 90), 492 (M^+, 31), 491 (100), 320 (9), 144 (9), 142 (10), 76 (35), 62 (10), 49 (7)
5h	451 (M^++2, 9), 450 (M^++1, 25), 449 (M^+, 100), 128 (10), 118 (12), 100 (19), 76 (73), 62 (13), 50 (16), 49 (9)
5i	433 (M^++2, 8), 432 (M^++1, 27), 431 (M^+, 100), 320 (8), 111 (13), 94 (53), 82 (43), 76 (85), 74 (25), 56 (12), 50 (25)
5j	467 (M^++2, 27), 466 (M^++1, 23), 465 (M^+, 74), 144 (10), 128 (12), 118 (32), 116 (30), 90 (28), 76 (100), 62 (11), 50 (30)
5k	467 (M^++2, 19), 465 (M^+, 88), 337 (14), 319 (100), 190 (13), 188 (51), 127 (6), 76 (29), 50 (5)
5l	464 (M^++2, 11), 463 (M^++1, 36), 462 (M^+, 30), 461 (100), 426 (20), 124 (12), 112 (9), 76 (72), 62 (7), 50 (15)
5m	464 (M^++3, 24), 463 (M^++2, 16), 461 (M^+, 85), 432 (13), 319 (100), 307 (24), 305 (22), 189 (18), 172 (11), 112 (10), 76 (38)
5n	451 (M^++2, 6), 450 (M^++1, 19), 449 (M^+, 65), 320 (10), 112 (28), 100 (21), 76 (100), 50 (24)
5o	460 (M^++2, 8), 459 (M^++1, 26), 458 (M^+, 100), 427 (6), 320 (37), 76 (17), 56 (9), 54 (9), 38 (8)
5p	458 (M^+, 100), 441 (53), 412 (35), 411 (64), 337 (20), 336 (31), 333 (15), 319 (61), 92 (19), 76 (28), 66 (21)
5q	585 (M^+, 1), 340 (8), 339 (21), 337 (100), 292 (27), 245 (31), 218 (11), 190 (26), 189 (12), 171 (24), 119 (10)
5r	365 (M^+, 100), 337 (13), 336 (14), 76 (5), 63 (3)

EXPERIMENTAL

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

Thienopyridine derivative **2** was prepared according to the literature procedures [10] in 69%, Colorless crystals, mp 131~132 °C. ^{1}H NMR ($CDCl_3$, δ): 6.65~6.73 (s, 2H, NH_2), 4.40 (m, 2H, J=7.2Hz, CH_2CO), 2.77 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 1.20 (s, 3H, J=7.2Hz, CH_3).

Preparation of iminophosphorane **3**.

A solution of thienopyridine derivative **2** (1.06 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 **3** in yield 93%, Colorless crystals, mp 174~175 °C. ^{1}H NMR ($CDCl_3$, δ): 7.42~7.63 (m, 18H, 3Ph-H), 3.16 (m, 2H, J = 7.2 Hz, CH_2CO), 2.46 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.02 (s, 3H, J = 7.2 Hz, CH_3).

Preparation of carbodiimides **4.**

To a solution of iminophosphorane **3** (0.525 g, 1 mmol) in anhyd CH_2Cl_2 (10 mL) was added aromatic isocyanate (1.1 mmol) under N_2 at r.t. After the reaction mixture was left unstirred for 5-12 h, 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.

General Procedure for the Preparation of Compounds **5a~5q.**

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 11~14 h at 80 °C, the solution was concentrate and the residue was recrystallized from CH_3CN to give 2-aryloxyl-5,8,9-trimethyl-3-phenylthieno[3',2'-5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5a~5q**.

Preparation of compound **5r.**

To the solution of **4** prepared above in CH_3CH_2OH (15 mL) were added several drops of CH_3CH_2ONa in CH_3CH_2OH. After the mixture was stirred for 14 h at room temperature, the solution was condensed and the residue was recrystallized from CH_3CH_2OH to give 2-ethyloxyl-5,8,9-trimethyl-3-phenyl thieno-[3',2'-5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5r**.

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