A SELECTIVE SYNTHESIS OF 2-ALKYLAMINO THIENO[2,3-*d*]PYRIMIDIN-4(3*H*)-ONES

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Abstract : 2-Alkylamino-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** were synthesized by a selective synthetic method, which includes aza-Wittig reaction of iminophosphorane **3** with aromatic isocynate to give carbodiimide **4** and subsequent reaction of **4** with various aliphatic primary amine in the presence of sodium ethoxide.

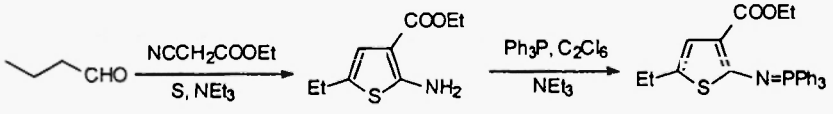
Introduction

Thienopyrimidines are of great importances because of their remarkable biological properties. For example, some 2-substituted thienopyrimidinones show significant antifungal and antibacterial activities(1,2), whereas others exhibited good anticonvulsant or H_1 receptor antagonistic activities(3,4). There are many known methods for the synthesis of thienopyrimidinones(5-7), however, 2-amino substituted thienopyrimidinones were not easily accessible by currently existing routes.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds(8-10). 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. Here we wish to report a selective synthesis of 2-alkylamino substituted thieno[2, 3-*d*]pyrimidin-4(3*H*)-ones **6** from easily accessible iminophosphorane **3**.

Results and Discussion

The 2-amino-3-(ethoxycarbonyl)thiophene **2**, easily obtained by Gewald method from butyraldehyde **1**, ethyl cyanoactate and sulfur(11), was converted to iminophosphorane **3** via reaction with triphenylphosphine, hexachloroethane and triethylamine (Scheme-1).

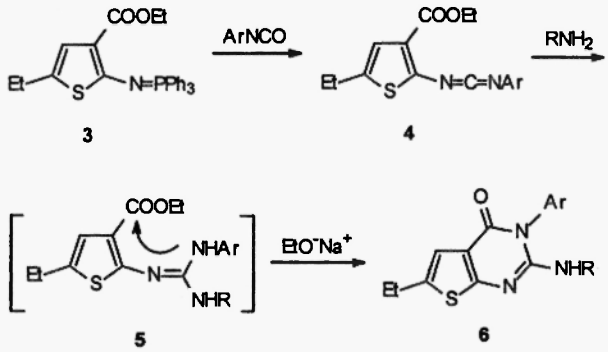


1 2 3

Scheme-1

Iminophosphorane **3** reacted with aromatic isocyanates to give carbodiimides **4**, which were allowed to react with aliphatic primary amines in the presence of EtO^-Na^+ to provide only 2-alkylamino-thieno[2, 3-*d*]pyrimidin-4(3*H*)- ones **6**, one of the possible regioisomers (Scheme 2). We obtained only **6** from the reaction mixture after recrystallization; the other isomer was not found by ^1H NMR analysis of the reaction mixture. The structure of **6** is deduced from its ^1H NMR data. For example, the ^1H NMR spectrum in **6a** (R = *n*-Pr) shows the signals of NH at 4.00 ppm as a broad absorption and NCH_2 at 3.41~3.30 ppm as multiple absorption, which strongly suggest the existence of $NHCH_2CH_2CH_3$ group in

6a(12). Whenever the primary amine used is small (R= *n*-Pr) or bulky (R= *t*-Bu), the cyclization was achieved all in good yields with similar selectivity. The results are listed in Table-1. The solitary formation of **6** can be rationalized in terms of a base catalytic cyclization of the guanidine intermediate **5** to give **6** across the arylamino group rather than the alkylamino one. This may probably be due to the preferential generation of $-N^{-}Ar$ from more acidic –NHAr under the catalysis of $EtO^{-}Na^{+}$.



Scheme-2

Table-1 : Preparation of 2-alkylaminothienopyrimidinones **6**

Compound	Ar	R	Condition	Yield* (%)
6a	Ph	*n*-C_3H_7	r.t./6 hr	87
6b	Ph	*n*-C_4H_9	r.t./6 hr	74
6c	Ph	*n*-C_5H_{11}	r.t./6 hr	69
6d	Ph	$PhCH_2$	r.t./6 hr	88
6e	Ph	*i*-C_3H_7	r.t./7 hr	85
6f	Ph	cyclohexyl	r.t./8 hr	79
6g	Ph	*t*-C_4H_9	r.t./8 hr	84
6h	Ph	Ph	r.t./6 hr	78
6i	4-Cl-C_6H_4	*n*-C_3H_7	r.t./7 hr	81
6j	4-Cl-C_6H_4	*n*-C_4H_9	r.t./6 hr	85

*Isolated yields based on iminophosphorane **3**.

In summary, the above synthetic method provides a selective synthesis of 2-alkylamino- thieno[2,3-*d*]pyrimidin-4(3*H*)-ones. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active thienopyrimidinones derivatives.

Experimental

Melting points were uncorrected. MS were measured on Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Preparation of 3-ethoxycarbonyl-5-ethyl-2-(triphenylphosphoranylidene)amino-thieno[2,3-d]pyrimidin-4(3H)-one 3- To a mixture of 2-amino-3-ethoxycarbonyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one(11) **2** (1.59 g, 8 mmol), PPh_3 (3.14 g, 12 mmol) and C_2Cl_6 (2.84 g, 12 mmol) in dry CH_3CN (40 mL), was added dropwise NEt_3 (2.42 g, 24 mmol) at 0-5 °C. The

colour of the reaction mixture quickly turned yellow. After stirred for 4 h, the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give iminophosphorane 3 (3.08 g, 84% yield). White crystals; mp 129-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86~7.46 (m, 15H, Ph-H), 6.78 (s, 1H, thiophene-4-H), 4.28 (q, *J*=7.2 Hz, 2H, OCH_2), 2.47 (q, *J*=7.2 Hz, 2H, CH_2), 1.35 (t, *J*=7.2 Hz, 3H, CH_3), 1.11 (t, *J*=7.2 Hz, 3H, CH_3); IR (*cm*$^{-1}$, KBr), 1695 (C=O), 1492, 1200, 1149, 696; MS (*m/z*, %), 459 (M^+, 30), 444 (23), 277 (100), 183 (91), 77 (42); Anal. Calcd. for $C_{27}H_{26}NO_2PS$: C, 70.57; H, 5.70; N, 3.05. Found: C, 70.41; H, 5.57; N, 3.25.

General Preparation of 2-alkylamino-thieno[2,3-d]pyrimidin-4(3H)-ones 6-To a solution of iminophosphorane 3 (1.38 g, 3 mmol) in dry methylene chloride (15 mL) was added aromatic isocyanate (3 mmol) under nitrogen at 0-5 °C. After the reaction mixture was stood for 12 hours at 0-5 °C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 30 mL) was added to precipitate triphenylphosphine oxide, which was filtered, the solvent was removed to give carbodiimide 4, 4 can be used directly without further purification. To the solution of 4 in methylene chloride (15 mL) was added alkylamine (3 mmol). After the reaction mixture was stood for 10-30 minutes, the solvent was removed and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added (pH=10). The mixture was stirred for 6-8 hr at room temperature. The solution was condensed and the residual was recrystallized from ethanol to give 2-alkylamino-thieno[2, 3-*d*]pyrimidin-4(3*H*)-ones 6a~6i separately.

6a: white crystals, m. p. 90-91 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61~7.25 (m, 5H, Ar-H), 6.98 (s, 1H, thiophene-4-H), 4.00 (s, 1H, NH), 3.41~3.30 (m, 2H, NCH_2), 2.80 (q, *J*=7.2 Hz, 2H, CH_2), 1.50~0.83 (m, 8H, CH_3 and CH_2CH_3); IR (cm^{-1}, KBr), 3432 (NH), 1682 (C=O), 1535, 1265; MS (m/z, %), 313 (M^+, 100), 299 (35), 285 (27), 255 (78), 153 (86); Anal. Calcd. for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 65.39; H, 6.05; N, 13.54.

6b: white crystals, m. p. 132-133 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60~7.26 (m, 5H, Ar-H), 6.96 (s, 1H, thiophene-4-H), 4.00 (s, 1H, NH), 3.40~3.30 (m, 2H, NCH_2), 2.79 (q, *J*=7.2 Hz, 2H, CH_2), 1.46~0.86 (m, 10H, CH_3 and $CH_2CH_2CH_3$); IR (cm^{-1}, KBr), 3425 (NH), 1680 (C=O), 1535, 1278; MS (m/z, %), 327 (M^+, 34), 313 (100), 299 (18), 256 (89), 153 (58); Anal. Calcd. for $C_{18}H_{21}N_3OS$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.08; H, 6.52; N, 12.61.

6c: white crystals, m. p. 133-134 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60~7.25 (m, 5H, Ar-H), 6.94 (s, 1H, thiophene-4-H), 4.03 (s, 1H, NH), 3.40~3.30 (m, 2H, NCH_2), 2.78 (q, *J*=7.2 Hz, 2H, CH_2), 1.48~0.81 (m, 12H, CH_3 and $(CH_2)_3CH_3$); IR (cm^{-1}, KBr), 3430 (NH), 1684 (C=O), 1534, 1274; MS (m/z, %), 341 (M^+, 42), 313 (31), 285 (65), 257 (57), 153 (84), 77 (100); Anal. Calcd. for $C_{19}H_{23}N_3OS$: C, 66.83; H, 6.79; N, 12.31. Found: C, 66.68; H, 6.63; N, 12.35.

6d: white crystals, m. p. 245-247 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60~7.18 (m, 10H, Ar-H), 6.94 (s, 1H, thiophene-4-H), 4.56 (d, *J*=5.4 Hz, 2H, NCH_2), 4.50 (s, 1H, NH), 2.80 (q, *J*=7.2 Hz, 2H, CH_2), 1.32 (t, *J*=7.2 Hz, 3H, CH_3); IR (cm^{-1}, KBr), 3385 (NH), 1678 (C=O), 1538, 1070; MS (m/z, %), 361 (M^+, 58), 347 (27), 333 (51), 257 (78), 153 (81), 91 (100); Anal. Calcd. for $C_{21}H_{19}N_3OS$: C, 69.78; H, 5.30; N, 11.62. Found: C, 69.71; H, 5.52; N, 12.71.

6e: white crystals, m. p. 100-102 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62~7.24 (m, 5H, Ar-H), 6.96 (s, 1H, thiophene-4-H), 4.26~4.16 (m, 1H, NCH), 3.78 (s, 1H, NH), 2.79 (q, *J*=7.2 Hz, 2H, CH_2), 1.33 (t, *J*=7.2 Hz, 3H, CH_3), 1.10 (d, *J*=7.2 Hz, 6H, $2CH_3$); IR (cm^{-1}, KBr), 3332 (NH), 1674 (C=O), 1540, 1184; MS (m/z, %), 313 (M^+, 47), 299 (17), 285 (34), 255 (56), 153 (94), 77 (100); Anal. Calcd. for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 65.07; H, 6.38; N, 13.64.

6f: white crystals, m. p. 122-123 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61~7.23 (m, 5H, Ar-H), 6.97 (s, 1H, thiophene-4-H), 4.02~3.86 (m, 2H, NCH and NH), 2.79 (q, *J*=7.2 Hz, 2H, CH_2), 1.98~0.97 (m, 13H, CH_3 and $5CH_2$); IR (cm^{-1}, KBr), 3378 (NH), 1677 (C=O), 1542, 1182; MS (m/z, %), 353 (M^+, 63), 339 (42), 255 (79), 153 (57), 77 (100); Anal. Calcd. for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.89; H, 6.78; N, 11.62.

6g: white crystals, m. p. 150-152 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59~7.25 (m, 5H, Ar-H), 6.95 (s, 1H,thiophene-4-H), 3.90 (s, 1H, NH), 2.80 (q, *J*=7.2 Hz, 2H, CH_2), 1.36~1.32 (m, 12H, CH_3 and $3CH_3$); IR (cm^{-1}, KBr), 3431 (NH), 1683 (C=O), 1543, 1238; MS (m/z, %), 327 (M^+, 79), 270 (100), 256 (73), 153 (72); Anal. Calcd. for $C_{18}H_{21}N_3OS$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.24; H, 6.41; N, 12.90.

6h: white crystals, m. p. 159-160 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60~7.20 (m, 10H, Ar-H), 6.98 (s, 1H, thiophene-4-H), 6.04 (s, 1H, NH), 2.81 (q, *J*=7.2 Hz, 2H, CH_2), 1.34 (t, *J*=7.2 Hz, 3H, CH_3); IR (cm^{-1}, KBr), 3386 (NH), 1676 (C=O), 1542, 1048; MS (m/z, %), 347 (M^+, 15), 333 (25), 319 (53), 153 (88), 77 (100); Anal. Calcd. for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.01; H, 4.71; N, 12.31.

6i: white crystals, m. p. 132-133 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57~7.22 (m, 4H, Ar-H), 6.96 (s, 1H, thiophene-4-H), 3.98 (s, 1H, NH), 3.41~3.30 (m, 2H, NCH_2), 2.79 (q, *J*=7.2 Hz, 2H, CH_2), 1.52~0.83 (m, 8H, CH_3 and CH_2CH_3); IR (cm^{-1}, KBr), 3436 (NH), 1680 (C=O), 1534, 1268; MS (m/z, %), 349 (M^+, 30), 347 (100), 333 (28), 319 (37), 255 (85), 153 (73); Anal. Calcd. for $C_{17}H_{18}ClN_3OS$: C, 58.70; H, 5.22; N, 12.08. Found: C, 58.52; H, 5.04; N, 12.10.

6j: white crystals, m. p. 147-148 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57~7.22 (m, 4H, Ar-H), 6.95 (s, 1H, thiophene-4-H), 3.99 (s, 1H, NH), 3.40~3.30 (m, 2H, NCH_2), 2.79 (q, *J*=7.2 Hz, 2H, CH_2), 1.47~0.85 (m, 10H, CH_3 and $CH_2CH_2CH_3$); IR (cm^{-1}, KBr), 3432 (NH), 1683 (C=O), 1535, 1276; MS (m/z, %), 363 (M^+, 26), 361 (85), 333 (27), 319 (44), 256 (75), 153 (78), 77 (100); Anal. Calcd. for $C_{18}H_{20}ClN_3OS$: C, 59.74; H, 5.57; N, 11.61. Found: C, 59.78; H, 5.35; N, 11.75.

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