# 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.

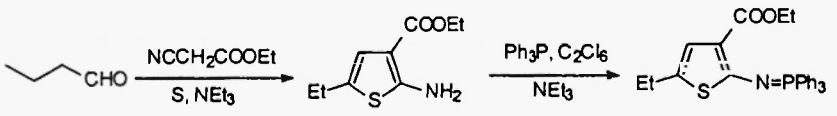
## Introduction

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).

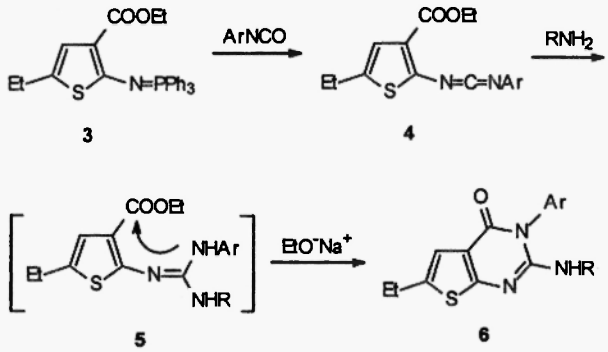



1 2 3

**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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