# A RAPID PARALLEL SYNTHESIS OF 2-DIALKYLAMINO-5,6,7,8- TETRAHYDRO-BENZOTHIENO[2,3-*d*]PYRIMIDIN-4(3*H*)-ONES

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**Abstract:** 2-Dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4** were rapidly synthesized by a solution-phase parallel synthetic method, which includes aza-Wittig reaction of iminophosphorane **1** with aromatic isocynate to give carbodiimide **2** and subsequent reaction of **2** with various aliphatic secondary amine in presence of catalytic amount of EtONa in a parallel fashion.

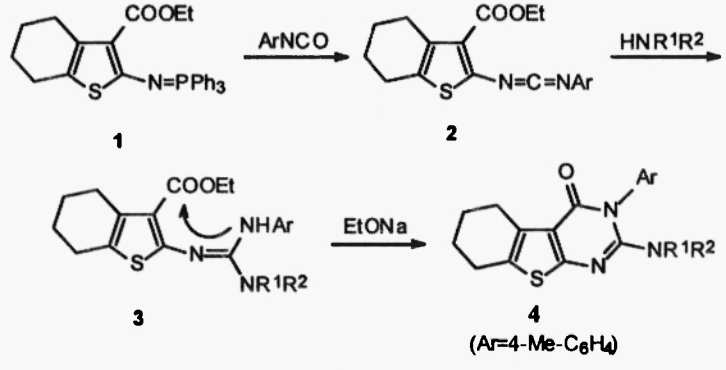
## Introduction

Many benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones have shown biological and pharmaceutical activities. Some of them showed significant antifungal and antibacterial activities(1,2), whereas others exhibited good anticonvulsant and angiotensin II or $H_1$ receptor antagonistic activities(3-5).

Recently, combinatorial synthesis of libraries containing small organic molecules by solid-phase or solution-phase synthetic techniques has become a rapid evolving area of research(6,7). However, there is no combinatorial solution phase synthesis of 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*] pyrimidin-4(3*H*)-ones. We have been interested in the synthesis of imidazolinones, quinazolinones and thienopyrimidinones via aza-Wittig reaction of α or β ethoxycarbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophile under mild condition(8-10). Here we wish to report further an efficient solution-phase parallel synthesis of some unreported derivatives of 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4**. By using this parallel synthetic method, **4** was rapidly obtained and the separation of **4** from the reaction mixture was easily carried out by simple recrystallization.

## Results and Discussions

Iminophosphorane **1** reacted with aromatic isocyanate to give carbodiimide **2**. After removing the by-product $Ph_3PO$ by recrystallization, the solution of **2** was divided equivalently into several parts to which were added various aliphatic secondary amines separately. The resulted solution was further treated with EtONa in EtOH at room temperature and then recrystallized to give 5,6,7,8-tetrahydro- benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4** in satisfactory yields. The formation of **4** can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate **3**, which cyclized to give **4** in presence of EtONa (Scheme-1). The results are listed in Table-1.




Scheme-1

**Table-1**: Preparation of 2-Dialkylaminothienopyrimidinones **4**

| Compound | Ar | $NR^1R^2$ | Condition | Yield* (%) |
|---|---|---|---|---|
| **4a** | 4-Me-$C_6H_4$ | $NEt_2$ | r.t./2 hr | 87 |
| **4b** | 4-Me-$C_6H_4$ | N(*n*-Pr)$_2$ | r.t./3 hr | 81 |
| **4c** | 4-Me-$C_6H_4$ | N(*n*-Bu)$_2$ | r.t./3 hr | 78 |
| **4d** | 4-Me-$C_6H_4$ | N(*n*-$C_5H_{11}$)$_2$ | r.t./4 hr | 75 |
| **4e** | 4-Me-$C_6H_4$ | N(*n*-$C_6H_{13}$)$_2$ | r.t./4 hr | 76 |
| **4f** | 4-Me-$C_6H_4$ | N(*i*-Pr)$_2$ | r.t./10 hr | 80 |
| **4g** | 4-Me-$C_6H_4$ | N(*i*-Bu)$_2$ | r.t./6 hr | 83 |
| **4h** | 4-Me-$C_6H_4$ |  | r.t./2 hr | 90 |
| **4i** | 4-Me-$C_6H_4$ |  | r.t./2 hr | 85 |

*Isolated yields based on iminophosphorane **1**.

The structure of the synthesized compounds **4** were confirmed by their spectral data. For example, the $^1H$ NMR spectral data in **4a** show the signals of $-NCH_2$ at 3.03 ppm as quartet and signals of cyclohexenyl $CH_2$ at 2.90-2.72 and 1.86-1.71 ppm as mutiple absorptions. The other signals appeared at 7.25-7.14 (m, 4H, Ar-H), 2.40 (s, 3H, $CH_3$) and 0.84 (t, 6H, $J$ = 7.2 Hz, $2CH_3$). The MS spectrum of **4a** shows strong molecule ion peak at m/z 367 with 95% abundance.

In summary, the above solution-phase parallel synthetic method provides a high-speed synthesis of 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[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.

**Exeperimental**

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 or 300 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

***General Preparation of 2-Dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-d]pyrimidin-4(3H)-ones 4-*** To a solution of iminophosphorane **1**(11) (4.36 g, 9 mmol) in dry methylene chloride (30 mL) was added 4-methylphenyl isocyanate (1.20 g, 9 mmol) at room temperature. After the reaction mixture was stood for 12 hours at 0~5 °C, the solvent was removed under reduced pressure and ether/petroleum ether (1:2, 60 mL) was added to precipitate triphenylphosphine oxide. Filtered, the filtrate was condensed and methylene chloride was added to make a solution of carbodiimide **2** (45 mL), which was divided into nine parts (5 mL every part). To each part of **2** prepared above (5 mL) was added separately diethylamine (0.10 mL, 1 mmol), or di-*n*-propylamine (0.14 mL, 1 mmol), or di-*n*-butylamine (0.17 mL, 1 mmol), or di-*n*-pentylamine (0.20 mL, 1 mmol), or di-*n*-hexylamine (0.24 mL, 1 mmol), or di-*iso*-propylamine (0.14 mL, 1 mmol), or di-*iso*-butylamine (0.17 mL, 1 mmol), or piperidine (0.10 mL, 1 mmol), or morpholine (0.09 mL, 1 mmol). After the reaction mixture was stood for 5-6 hours, the solvent was removed and anhydrous ethanol (10 ml) with several drops of EtONa in EtOH was added. The mixture was stirred for 2-10 hr at room temperature. The solution was condensed and the residual was recrystallized from ethanol to give 2-dialkylamino-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4a**~**4i** separately.

**4a**: white crystals, m. p. 179-181 °C, $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.25-7.14 (m, 4H, Ar-H), 3.03 (q, 4H, $J$ = 7.2 Hz, $2NCH_2$), 2.90-2.72 (m, 4H, $2CH_2$), 2.40 (s, 3H, $CH_3$), 1.86-1.71 (m, 4H, $2CH_2$), 0.84 (t, 6H, $J$ = 7.2 Hz, $2CH_3$); MS (m/z, %), 367 ($M^+$, 95), 338 (53), 281 (100), 254 (60), 178 (16); Anal. Calcd. for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.86; N, 11.43. Found: C, 68.50; H, 6.93; N, 11.67.

**4b**: white crystals, m. p. 138-139 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.13 (m, 4H, Ar-H), 2.94 (t, 4H, *J* = 7.6 Hz, $2NCH_2$), 2.90-2.70 (m, 4H, $2CH_2$), 2.40 (s, 3H, $CH_3$), 1.85-1.77 (m, 4H, $2CH_2$), 1.28-0.71 (m, 10H, $2CH_2CH_3$); MS (m/z, %), 394 ($M^+$-1, 100), 366 (76), 352 (93), 295 (69), 178 (45); Anal. Calcd. for $C_{23}H_{29}N_3OS$: C, 69.84; H, 7.39; N, 10.62. Found: C, 69.78; H, 7.33; N, 10.75.

**4c**: white crystals, m. p. 131-132 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.12 (m, 4H, Ar-H), 2.98 (t, 4H, *J* = 7.2 Hz, $2NCH_2$), 2.92-2.70 (m, 4H, $2CH_2$), 2.40 (s, 3H, $CH_3$), 1.86-1.78 (m, 4H, $2CH_2$), 1.22-0.80 (m, 14H, $2CH_2CH_2CH_3$); MS (m/z, %), 423 ($M^+$, 100), 379 (32), 366 (86), 294 (30), 178 (30); Anal. Calcd. for $C_{25}H_{33}N_3OS$: C, 70.88; H, 7.85; N, 9.92. Found: C, 70.94; H, 7.93; N, 9.81.

**4d**: white crystals, m. p. 93-94 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.12 (m, 4H, Ar-H), 2.96 (t, 4H, *J* = 7.2 Hz, $2NCH_2$), 2.92-2.70 (m, 4H, $2CH_2$), 2.39 (s, 3H, $CH_3$), 1.86-1.78 (m, 4H, $2CH_2$), 1.25-0.82 (m, 18H, $2(CH_2)_3CH_3$); MS (m/z, %), 450 ($M^+$-1, 99), 408 (30), 380 (98), 290 (100), 178 (75); Anal. Calcd. for $C_{27}H_{37}N_3OS$: C, 71.80; H, 8.26; N, 9.30. Found: C, 71.88; H, 8.12; N, 9.44.

**4e**: white crystals, m. p. 90-91 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.12 (m, 4H, Ar-H), 2.96 (t, 4H, *J* = 7.2 Hz, $2NCH_2$), 2.92-2.70 (m, 4H, $2CH_2$), 2.39 (s, 3H, $CH_3$), 1.86-1.78 (m, 4H, $2CH_2$), 1.27-0.85 (m, 22H, $2(CH_2)_4CH_3$); MS (m/z, %), 479 ($M^+$, 100), 408 (33), 395 (53), 295 (21), 178 (9); Anal. Calcd. for $C_{29}H_{41}N_3OS$: C, 72.61; H, 8.61; N, 8.76. Found: C, 72.36; H, 8.48; N, 8.84.

**4f**: white crystals, m. p. 159-161 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.10 (m, 4H, Ar-H), 3.52-3.45 (m, 2H, 2NCH), 2.92-2.71 (m, 4H, $2CH_2$), 2.38 (s, 3H, $CH_3$), 1.85-1.79 (m, 4H, $2CH_2$), 1.05 (d, *J* = 6.4 Hz, 12H, $4CH_3$); MS (m/z, %), 395 ($M^+$, 99), 380 (21), 351 (98), 294 (100), 178 (29); Anal. Calcd. for $C_{23}H_{29}N_3OS$: C, 69.84; H, 7.39; N, 10.62. Found: C, 69.65; H, 7.47; N, 10.48.

**4g**: white crystals, m. p. 111-113 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.14 (m, 4H, Ar-H), 2.83 (d, 4H, *J* = 7.2 Hz, $2NCH_2$), 2.90-2.70 (m, 4H, $2CH_2$), 2.40 (s, 3H, $CH_3$), 1.83-1.78 (m, 6H, $2CH_2$ and 2CH), 0.78 (d, *J* = 6.4 Hz, 12H, $CH_3$); MS (m/z, %), 423 ($M^+$, 98), 380 (100), 366 (96), 323 (96), 294 (89), 178 (18); Anal. Calcd. for $C_{25}H_{33}N_3OS$: C, 70.88; H, 7.85; N, 9.92. Found: C, 70.71; H, 7.87; N, 9.74.

**4h**: white crystals, m. p. 200-202 °C, $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.14 (m, 4H, Ar-H), 3.05 (t, 4H, *J* = 5.1 Hz, $2NCH_2$), 2.91-2.68 (m, 4H, $2CH_2$), 2.38 (s, 3H, $CH_3$), 1.84-1.76 (m, 4H, $2CH_2$), 1.40-1.22 (m, 6H, $3CH_2$); MS (m/z, %), 379 ($M^+$, 100), 350 (19), 295 (33), 274 (33), 221 (50), 179 (58); Anal. Calcd. for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07. Found: C, 69.78; H, 6.89; N, 10.83.

**4i**: white crystals, m. p. 214-216 °C, $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.16 (m, 4H, Ar-H), 3.41 (t, *J* = 4.2 Hz, 4H, $2OCH_2$), 3.08 (t, *J* = 4.2 Hz, 4H, $2NCH_2$), 2.90-2.72 (m, 4H, $2CH_2$), 2.39 (s, 3H, $CH_3$), 1.83-1.78 (m, 4H, $2CH_2$); MS (m/z, %), 381 ($M^+$, 100), 350 (15), 336 (38), 295 (46), 246 (34), 179 (60); Anal. Calcd. for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01. Found: C, 66.26; H, 6.26; N, 10.80.

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