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A Selective Synthesis of 2-Alkylamino-5, 6, 7, 8-tetrahydro-benzothieno[2, 3-d]pyrimidin-4(3H)-ones

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Abstract: 2-Alkylamino-5, 6, 7, 8-tetrahydrobenzothieno [2, 3-d] pyrimidin-4(3H)-ones **7** were synthesized by a new selective synthetic method, which includes aza-Wittig reaction of imino-phosphorane **4** with aromatic isocynate to give carbodiimide **5** and subsequent reaction of **5** with various aliphatic primary amine in the presence of EtO^-Na^+.

Keywords: Benzothieno[2, 3-d]pyrimidin-4(3H)-ones, aza-Wittig reaction, iminophosphorane, carbodiimide, synthesis.

Thienopyrimidines are of great importances because of their remarkable biological properties. For example, some 2-substituted thienopyrimidinones show significant antifungal and antibacterial activities[1-3], whereas others exhibited good anticonvulsant and angiotensin Ⅱ or H_1 receptor antagonistic activities[4-6]. There are many known methods for the synthesis of thienopyrimidinones[7-9], however, 2-amino substituted thienopyrimidinones were not easily accessible by currently existing routes. Recently we have been interested in the synthesis of imidazolinones, quinazolinones and thieno-pyrimidinones *via* aza-Wittig reaction, with the aim of evaluating their fungicidal activities[10-13]. We have also reported a selective synthesis of 2-alkylaminoimidazolones and 2-alkylaminoquinazolinones by reaction of aliphatic primary amine with functiona-lized carbodiimides[13-15]. This method was further utilized in the synthesis of 2-alkyl-amino substituted 5, 6, 7, 8-tetrahydrobenzothieno[2, 3-d]pyrimidin-4(3H)-ones **7** from easily accessible iminophosphorane **4**.

The tetrahydrobenzo[b]thiophene **2**, easily obtained by Gewald method from cyclohexanone **1**, ethyl cyanoacetate and sulfur[16], was converted to iminophosphorane **4** *via* reaction with triphenylphosphine, hexachloroethane and triethylamine[17]. Imino-phosphorane **4** could also be prepared by Staudinger reaction of triphenylphosphine with azide **3** which was obtained by first diazotization of tetrahydrobenzo[b]thiophene **2** with $NaNO_2$/HCl and subsequent azidation with NaN_3 (**Scheme 1**).

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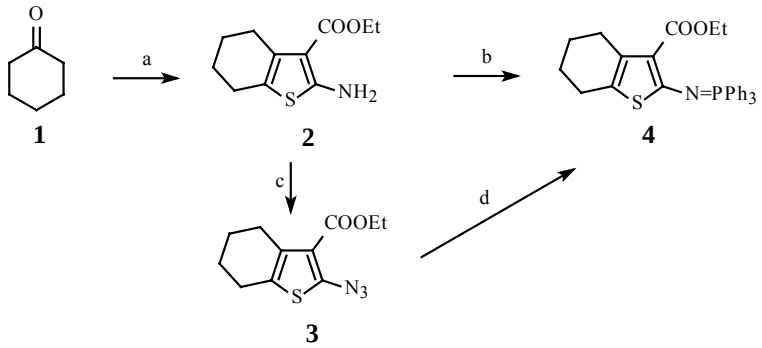
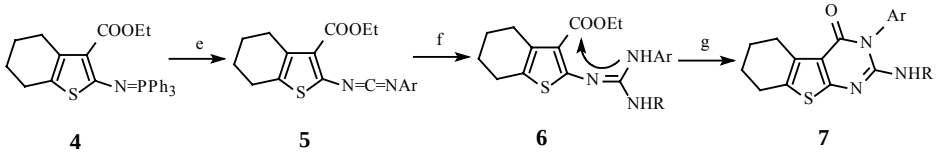
Scheme 1



(a) $EtOOCCH_2CN$, S, morpholine, C_2H_5OH, r.t., 12 h, 76%; (b) Ph_3P, C_2Cl_6, Et_3N, CH_2Cl_2, r.t., 5h, 78%. (c) $NaNO_2$, HCl, actone-H_2O, then NaN_3, NaAc, 25%; (d) Ph_3P, CH_2Cl_2, r.t., 6h, 85%.

Scheme 2



(e) ArNCO, CH_2Cl_2, 0-5℃, 12 h; (f) RNH_2, CH_2Cl_2, r.t., 10min; (g) EtONa, EtOH, r.t., 6-12 h, 51-83%.

Table 1 Preparation of 2-alkylaminothieno[2, 3-d]pyrimidin-4(3H)-ones **7**

	Ar	R	Condition	Yield (%)	Mp (℃)	Elementary analysis (%, Calcd.)		
						C	H	N
7a	Ph	*n*-C_3H_7	r.t./6 hr	55	132-134	67.38(67.23)	6.20(6.24)	12.59(12.38)
7b	Ph	*i*-C_3H_7	r.t./8 hr	67	155-157	67.25(67.23)	6.11(6.24)	12.24(12.38)
7c	Ph	cyclohexyl	r.t./8 hr	72	181-183	69.54(69.62)	6.47(6.64)	11.12(11.07)
7d	Ph	*t*-C_4H_9	r.t./12 hr	83	182-184	67.81(67.96)	6.62(6.56)	11.93(11.89)
7e	4-Cl-C_6H_4	*n*-C_3H_7	r.t./6 hr	51	185-187	61.20(61.03)	5.35(5.39)	11.31(11.24)
7f	4-Cl-C_6H_4	*n*-C_4H_9	r.t./6 hr	54	132-134	61.78(61.92)	5.74(5.72)	10.89(10.83)
7g	4-Cl-C_6H_4	*i*-C_3H_7	r.t./10 hr	60	190-191	61.12(61.03)	5.47(5.39)	11.12(11.24)
7h	4-Cl-C_6H_4	cyclohexyl	r.t./10 hr	68	186-187	63.75(63.83)	5.90(5.84)	11.34(10.15)
7i	4-Cl-C_6H_4	*t*-C_4H_9	r.t./12 hr	81	242-244	61.84(61.92)	5.65(5.72)	10.93(10.83)
7j	4-Me-C_6H_4	*i*-C_3H_7	r.t./8 hr	75	139-141	67.94(67.96)	6.68(6.56)	11.96(11.89)

Iminophosphorane **4** reacted with aromatic isocyanates to give carbodiimides **5**, which were allowed to react with aliphatic primary amines in the presence of EtO^-Na^+ to provide only 2-alkylamino-5, 6, 7, 8-tetrahydrobenzothieno[2, 3-d]pyrimidin-4(3H)-ones **7**, one of the possible regioisomers (**Scheme 2**). Different from the early result in similar cases[13-15], we obtained only **7** from the reaction mixture after recrystallization; the other isomer was not found by GC-MS detection or ^1H NMR analysis of the reaction

mixture. The structure of **7** is deduced from their ^{1}H NMR data. For example, the ^{1}H NMR spectrum in **7a** shows the signals of NH at 4.04 ppm as triple absorption and NCH_2 at 3.35-3.29 ppm as multiple absorption, which strongly suggest the existence of $NHCH_2CH_2CH_3$ group in **7a**. Moreover, when the sample was treated with deuterated water, the ^{1}H NMR spectrum in **7a** shows the absorption of NCH_2 at 3.32 ppm as triplets with the disappearance of signals of NH absorption. Whenever the primary amine used is small (R= *n*-Pr) or bulky (R= *t*-Bu), the cyclization was achieved all in moderate to good yields with the similar selectivity. The results are listed in **Table 1**. The solitary formation of **7** can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate **6**, which cyclized to give **7** across the arylamino group rather than the alkylamino one. This may probably due to the preferential generation of $-N^-Ar$ from more acidic-NHAr under the catalysis of EtO^-Na^+.

Table 2 IR, MS and ^{1}H NMR of **7**

	IR (KBr, cm^{-1})	MS (*m/z*, %)	^{1}H NMR ($CDCl_3$, 400MHz, δ ppm)
7a	3431, 1677, 1556, 1240	339 (M^+, 100), 311 (33), 297 (77), 269 (62), 220 (32), 77 (52)	7.60-7.26 (m, 5H, Ar-H), 4.04 (t, 1H, J=4.8 Hz, NH), 3.35-3.29 (m, 2H, NCH_2), 2.90-2.67 (m, 4H, $2CH_2$), 1.88-1.76 (m, 4H, $2CH_2$), 1.52-0.81 (m, 5H, CH_2CH_3)
7b	3328, 1672, 1544, 1172	339 (M^+, 100), 311 (38), 297 (34), 269 (65), 221 (33), 77 (56)	7.61-7.25 (m, 5H, Ar-H), 4.25-4.15 (m, 1H, NCH), 3.81 (d, 1H, J=7.6 Hz, NH), 2.90-2.67 (m, 4H, $2CH_2$), 1.86-1.76 (m, 4H, $2CH_2$), 1.10 (d, 6H, J=6.8 Hz, $2CH_3$)
7c	3427, 1683, 1545, 1236	379 (M^+, 24), 297 (58), 269 (71), 179 (18), 77 (100)	7.65-7.26 (m, 5H, Ar-H), 4.00-3.88 (m, 2H, NCH and NH), 2.90-2.67 (m, 4H, $2CH_2$), 1.93-0.97 (m, 14H, $7CH_2$)
7d	3433, 1685, 1543, 1209	353 (M^+, 98), 296 (96), 269 (96), 179 (17), 77 (58)	7.59-7.24 (m, 5H, Ar-H), 3.91 (s, 1H, NH), 2.90-2.68 (m, 4H, $2CH_2$), 1.86-1.77 (m, 4H, $2CH_2$), 1.34 (s, 9H, $3CH_3$)
7e	3441, 1681, 1551, 1252	375 (35), 373 (M^+, 100), 331 (64), 303 (67), 220 (61), 179 (69), 111 (57)	7.57-7.22 (m, 4H, Ar-H), 4.00 (s, 1H, NH), 3.38-3.30 (m, 2H, NCH_2), 2.88-2.67 (m, 4H, $2CH_2$), 1.87-1.77 (m, 4H, $2CH_2$), 1.54-0.83 (m, 5H, CH_2CH_3)
7f	3447, 1676, 1552, 1186	389 (33), 387 (M^+, 88), 331 (58), 303 (70), 220 (46), 111 (95), 41 (100)	7.57-7.21 (m, 4H, Ar-H), 3.94 (t, 1H, J=4.8 Hz, NH), 3.40-3.33 (m, 2H, NCH_2), 2.88-2.67 (m, 4H, $2CH_2$), 1.86-1.77 (m, 4H, $2CH_2$), 1.48-0.87 (m, 7H, $CH_2CH_2CH_3$)
7g	3436, 1683, 1544, 1176	375 (8), 373 (M^+, 23), 331 (8), 303 (20), 221 (11), 179 (25), 43 (100)	7.57-7.20 (m, 4H, Ar-H), 4.24-4.16 (m, 1H, NCH), 3.76 (d, 1H, J=7.2 Hz, NH), 2.88-2.67 (m, 4H, $2CH_2$), 1.87-1.76 (m, 4H, $2CH_2$), 1.12 (d, 6H, J=6.4 Hz, $2CH_3$)
7h	3424, 1685, 1541, 1298	415 (9), 413 (M^+, 25), 331 (54), 303 (64), 179 (27), 55 (100)	7.57-7.21 (m, 4H, Ar-H), 4.00-3.91 (m, 1H, NCH), 3.86 (d, 1H, J=7.2 Hz, NH), 2.88-2.67 (m, 4H, $2CH_2$), 1.95-0.98 (m, 14H, $7CH_2$)
7i	3445, 1680, 1553, 1211	389 (39), 387 (M^+, 100), 331 (94), 303 (59), 111 (13)	7.56-7.19 (m, 4H, Ar-H), 3.85 (s, 1H, NH), 2.88-2.67 (m, 4H, $2CH_2$), 1.85-1.77 (m, 4H, $2CH_2$), 1.35 (s, 9H, $3CH_3$)
7j	3431, 1683, 1531, 1172	353 (M^+, 35), 311 (14), 283 (26), 221 (12), 133 (36), 91 (100)	7.38-7.12 (m, 4H, Ar-H), 4.24-4.17 (m, 1H, NCH), 3.88 (d, 1H, J=7.2 Hz, NH), 2.89-2.68 (m, 4H, $2CH_2$), 2.44 (s, 1H, CH_3), 1.85-1.77 (m, 4H, $2CH_2$), 1.11 (d, 6H, J=6.4 Hz, $2CH_3$)

The above synthetic method provides a selective synthesis of 2-alkylamino substituted 5, 6, 7, 8-tetrahydrobenzothieno[2, 3-d]pyrimidin-4(3H)-ones *via* EtO^-Na^+ catalyzed reaction of functionalized carbodiimides with various aliphatic primary amines. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active thienopyrimidinones derivatives.

General Procedure for selective synthesis of 2-alkylamino-5, 6, 7, 8-tetrahydrobenzothieno[2, 3-d]pyrimidin-4(3H)-ones 7**:** To a solution of iminophosphorane **4** (2.42 g, 5 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (5 mmol) under nitrogen at 0-5℃. After the reaction mixture was stood for 12 hours at 0-5℃, 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 **5**, **5** can be used directly without further purification. To the solution of **5** in methylene dichloride (15 mL) was added alkylamine (5 mmol). After the reaction mixture was stood for 10 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 6-12 hr at room temperature. The solution was condensed and the residual was recrystallized from ethanol to give 2-alkylamino-5, 6, 7, 8-tetrahydrobenzothieno[2, 3-d]pyrimidin-4(3H)-ones **7**. The yields of **7** based on iminophosphorane **4** are listed in **Table 1**.

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