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An efficient route for synthesis of 2-alkylamino benzo[b]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

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Abstract

The carbodiimide **2**, obtained from the aza-Wittig reactions of iminophosphorane **1** with alkyl isocyanates, reacted with primary amino to give 2-alkylamino benzo[b]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** and **5**. The formation mechanism of the title compounds has been investigated.

Keywords: Carbodiimides; Aza-Wittig reaction; Iminophosphorane; Isocyanates; Synthesis

Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring [1,2], thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Some thienopyrimidine shows significant antifungal and antibacterial as well as their good anticonvulsant and angiotensin or A_{2A}-receptor antagonistic activities [3–7].

The aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their useful utilities in the synthesis of nitrogen heterocyclic compounds under mild conditions [8–10]. The very reactive carbodiimides can be used as synthetic intermediates of a wide variety of polyheterocycles by domino processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW–NA–IC). A series of thienopyrimidine have been prepared, but 2-amino substituted thienopyrimidinones are not easily accessible by currently existing routes. Recently we have been interested in the synthesis of triazoloquinazolinones, thienopyrimidinones and imidazolinones *via* aza-Wittig reaction, with the aim of evaluating their fungicidal activities [11–15]. Reported herein is a new efficient synthesis of 2-alkylamino benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** and **5** from easily accessible iminophosphorane **1** [16].

Iminophosphorane **1** reacted with aromatic isocyanates to give carbodiimide **2**, which were allowed to react with primary amines to provide guanidine intermediate **3**. Even in refluxing toluene, **3** did not cyclize, however, in the presence of catalytic amount of sodium ethoxide, **3** was converted easily to 2-alkylamino benzo[b]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** and **5** in satisfactory yields at room temperature. The results are listed in Table 1.

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Table 1
Preparation of compds. **4** and **5**.

Entry	Compd.	R	R′	Condition	Yield[a] (%)	Mp (°C)
1	**4a**	*i*-Pr	*t*-Bu	EtOH/CH_2Cl_2/EtONa, 10 h, r.t.	79	175–176
2	**4b**	*n*-Bu	*i*-Pr	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	78	219–220
3	**4c**	*n*-Bu	*n*-C_6H_{11}	EtOH/CH_2Cl_2/EtONa, 6 h, r.t.	63	159–160
4	**4d**	*n*-Bu	Bn	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	74	156–157
5	**5a**	*i*-Pr	Et	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	85	230–232
6	**5b**	*i*-Pr	*n*-Pr	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	82	249–250
7	**5c**	*i*-Pr	*i*-Pr	EtOH/CH_2Cl_2/EtONa, 10 h, r.t.	79	194–196
8	**5d**	*i*-Pr	*n*-Bu	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	76	219–221
9	**5e**	*i*-Pr	*n*-C_6H_{13}	EtOH/CH_2Cl_2/EtONa, 8 h, r.t.	61	154–155
10	**5f**	*i*-Pr	Bn	EtOH/CH_2Cl_2/EtONa, 6 h, r.t.	78	237–239
11	**5g**	*i*-Pr	H	EtOH/CH_2Cl_2, 0.5 h, r.t.	89	281–283
12	**5h**	*i*-Pr	Me	EtOH/CH_2Cl_2, 0.5 h, r.t.	87	259–260
13	**5i**	*n*-Bu	H	EtOH/CH_2Cl_2, 0.5 h, r.t.	85	>300
14	**5j**	*n*-Bu	Me	EtOH/CH_2Cl_2, 0.5 h, r.t.	83	251–253

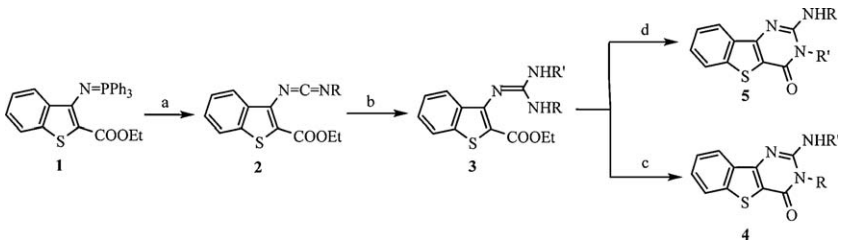
[a] Isolated yield based on the iminophosphorane **1**.

It is interesting to note that a differentiation between the carbodiimide **2** reacted with variable primary amine to obtain guanidine intermediate **3**. When R < R′, such as R = *i*-Pr, R′ = *t*-Bu or R = *n*-Bu, R′ = *i*-Pr, cyclohexyl or Bn, the cyclization can be completed smoothly at room temperature through the RNH in the presence of catalytic amount of RO^-Na^+ (Scheme 1 and Table 1, entries 1–4), provided only 2-alkylaminobenzo[b]thieno[3,2-d]pyrimidin-4(3*H*)-one **4**, one of the possible regioisomers. When R ≥ R′(R′ ≠ H, Me), the guanidine intermediate **3** was treated with ROH in the presence of catalytic RO^-Na^+, one of the possible regioisomers **5** (entries 5–10) was obtained in satisfactory yields. When R′ = H or Me, no matter how R = *n*-Bu or *i*-Pr, we obtained only **5** (entries 11–14) from the reaction mixture in the absence of sodium ethoxide after recrystallization, the other isomer **4** was not found by ^1H NMR analysis of the reaction mixture. The structure of **4** and **5** is deduced from its ^1H NMR data (Table 2). For example, the ^1H NMR spectrum in **5j** (R = Me) shows the signals of N–CH_3 (s, 3H, NCH_3) at 3.54 as a simple absorption which strongly suggests the existence of NCH_3 group but not $NHCH_3$ in **5j**. The results are listed in Table 3.

Reagents and chemicals were obtained from Acros, Aldrich, Shanghai or Beijing chemicals and were used without further purification. All solvents were freshly distilled. Melting points are uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR is recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR is recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 spectrometer and resonances are given in ppm relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

General procedure for the synthesis of compounds **4** and **5**: to a solution of iminophosphorane **1** (2 mmol) in dry methylene chloride (15 mL) was added alkyl isocyanate (2 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 10 h at 0–5 °C, the solvent was removed off under reduced pressure and ether–petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration, the solvent was removed to give carbodiimide **2**, which was used directly without further purification.

To the solution of **2** prepared above in CH_2Cl_2 (15 mL) was added primary amine (2 mmol). After the reaction mixture was allowed to stand for 0.5 h, the solution was condensed and anhyd. EtOH–CH_2Cl_2 (4:1, 10 mL) with



Scheme 1. (a) RNCO, CH_2Cl_2, 0–5 °C, 8–12 h; (b) R′NH_2, CH_2Cl_2, 0.5–1 h; (c) EtOH/CH_2Cl_2/EtONa, 6–10 h; and (d) EtOH/CH_2Cl_2/EtONa, 6–10 h or EtOH/CH_2Cl_2, 0.5 h.

Table 2
Elementary analysis, MS of compds. **4** and **5**.

	Elementary analysis (%, calcd.)			MS (*m*/*z*,%)
	C	H	N	
4a	64.73 (64.87)	6.71 (6.89)	13.32 (13.20)	315 (44) [M+], 243 (65), 146 (90), 77 (62)
4b	64.73 (64.84)	6.71 (6.85)	13.32 (13.23)	315 (38) [M+], 257 (67), 146 (100), 77 (61)
4c	67.57 (67.67)	7.09 (7.17)	11.82 (11.69)	355 (32) [M+], 257 (66), 146 (87), 77 (59)
4d	69.39 (69.57)	5.82 (5.94)	11.56 (11.46)	363 (36) [M+], 257 (71), 146 (89), 77 (68)
5a	62.69 (62.77)	5.96 (6.14)	14.62 (14.49)	287 (89) [M+], 229 (59), 146 (100), 77 (79)
5b	63.76 (63.81)	6.35 (6.45)	13.94 (13.76)	301 (37) [M+], 243 (55), 146 (95), 77 (63)
5c	63.76 (63.82)	6.35 (6.47)	13.94 (13.72)	301 (49) [M+], 243 (53), 146 (89), 77 (75)
5d	64.73 (64.87)	6.71 (6.89)	13.32 (13.20)	315 (46) [M+], 257 (66), 146 (80), 77 (62)
5e	66.81 (66.94)	8.13 (8.25)	11.69 (11.54)	359 (29) [M+], 285 (31), 146 (93), 77 (59)
5f	68.74 (68.88)	5.48 (5.64)	12.02 (11.86)	349 (75) [M+], 291 (78), 146 (100), 77 (55)
5g	60.21 (60.17)	5.05 (4.94)	16.20 (16.37)	259 (100) [M+], 201 (86), 146 (100), 77 (64)
5h	61.51 (61.47)	5.53 (5.47)	15.37 (15.48)	273 (93) [M+], 215 (85), 146 (88), 77 (71)
5i	61.51 (61.47)	5.53 (5.47)	15.37 (15.48)	273 (76) [M+], 215 (74), 146 (88), 77 (71)
5j	62.69 (62.55)	5.96 (5.86)	14.62 (14.78)	287 (88) [M+], 215 (82), 146 (87), 77 (69)

Table 3
^{1}H NMR of compounds **4a–d**, and **5a–j**.

	^{1}H NMR ($CDCl_3$, 400 MHz), δ
4a	8.16 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.81 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.50–7.40 (m, 2H, Ar-H), 5.78 (s, 1H, NH), 4.65 (m, 1H, NCH), 1.62–1.50 (m, 15H, $5CH_3$)
4b	8.19 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.82 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.52–7.40 (m, 2H, Ar-H), 4.51–4.43 (m, 1H, NCH), 4.40 (d, 1H, *J* = 6.8 Hz, NH), 4.06 (t, 2H, *J* = 7.6 Hz, NCH_2), 1.76–1.65 (m, 2H, CH_2), 1.51–1.41 (m, 2H, CH_2), 1.40–1.31 (m, 6H, $2CH_3$), 1.40–0.97 (m, 3H, CH_3)
4c	8.18 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.81 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51–7.39 (m, 2H, Ar-H), 4.57 (d, 1H, *J* = 7.2 Hz, NH), 4.20–4.13 (m, 1H, NCH), 4.06 (t, 2H, *J* = 7.6 Hz, NCH_2), 2.19–2.15 (m, 2H, CH_2), 1.81–1.66 (m, 4H, $2CH_2$), 1.56–1.26 (m, 8H, $4CH_2$), 0.98 (t, 3H, *J* = 7.2 Hz, CH_3)
4d	8.19 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.82 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.52–7.40 (m, 2H, Ar-H), 7.36–7.24 (m, 5H, Ar-H), 5.31 (s, 2H, NCH_2), 4.66 (s, 1H, NH), 3.47–3.40 (m, 2H, NCH_2), 1.47–1.40 (m, 2H, CH_2), 1.17–1.09 (m, 2H, CH_2), 0.83 (t, 3H, *J* = 7.4 Hz, CH_3)
5a	8.20 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.83 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51–7.40 (m, 2H, Ar-H), 4.48 (t, 1H, *J* = 6.4 Hz, NH), 4.47–4.35 (m, 1H, NCH), 4.15 (q, 2H, *J* = 6.4 Hz, NCH_2), 1.62–1.30 (m, 9H, $3CH_3$)
5b	8.19 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.82 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.53–7.40 (m, 2H, Ar-H), 4.50 (t, 1H, *J* = 6.8 Hz, NH), 4.48–4.43 (m, 1H, NCH), 4.04 (t, 2H, *J* = 7.6 Hz, NCH_2), 1.84–1.72 (m, 2H, CH_2), 1.36 (d, 6H, *J* = 6.4 Hz, $2CH_3$), 1.04 (t, 3H, *J* = 7.6 Hz, CH_3)
5c	8.17 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.81 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51–7.40 (m, 2H, Ar-H), 5.60 (s, 1H, NH), 4.53–4.49 (m, 1H, NCH), 4.48–4.40 (m, 1H, NCH), 1.58 (d, 6H, *J* = 6.8 Hz, $2CH_3$), 1.37 (d, 6H, *J* = 6.0 Hz, $2CH_3$)
5d	8.19 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.80 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.50–7.40 (m, 2H, Ar-H), 4.64 (t, 1H, *J* = 6.8 Hz, NH), 4.50–4.46 (m, 1H, NCH), 4.08 (t, 2H, *J* = 7.6 Hz, NCH_2), 1.74–1.60 (m, 2H, CH_2), 1.48–1.39 (m, 2H, CH_2), 1.35 (d, 6H, *J* = 6.4 Hz, $2CH_3$), 0.97 (t, 3H, *J* = 7.2 Hz, CH_3)
5e	8.20 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.89 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.48–7.38 (m, 2H, Ar-H), 4.75 (t, 1H, *J* = 6.4 Hz, NH), 4.54–4.44 (m, 1H, NCH), 4.07 (t, 2H, *J* = 7.6 Hz, NCH_2), 1.76–1.66 (m, 2H, CH_2), 1.40–1.18 (m, 8H, $4CH_2$), 1.31 (d, 6H, *J* = 8.0 Hz, $2CH_3$), 0.85 (t, 6H, *J* = 7.0 Hz, $2CH_3$)
5f	8.20 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.85 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.55–7.28 (m, 7H, Ar-H), 5.38–5.34 (m, 2H, NCH_2), 4.36 (t, 1H, *J* = 6.4 Hz, NH), 4.31–4.24 (m, 1H, NCH), 1.11 (d, 6H, *J* = 6.4 Hz, $2CH_3$)
5g	11.52 (s, 1H, NHCO), 8.27 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.85 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58–7.40 (m, 2H, Ar-H), 6.39 (d, 1H, *J* = 7.6 Hz, NH), 4.46 (q, 1H, *J* = 6.8 Hz, NCH), 1.44 (d, 6H, *J* = 6.4 Hz, $2CH_3$)
5h	8.25 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57–7.40 (m, 2H, Ar-H), 4.59 (s, 1H, NH), 3.56 (q, 1H, *J* = 6.8 Hz, NCH), 3.54 (s, 3H, NCH_3), 1.44 (d, 6H, *J* = 6.4 Hz, $2CH_3$)
5i	11.54 (s, 1H, NH), 8.26 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.85 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58–7.40 (m, 2H, Ar-H), 6.34 (s, 1H, NH), 3.67–3.60 (m, 2H, NCH_2), 1.83–1.72 (m, 2H, CH_2), 1.58–1.48 (m, 2H, CH_2), 1.02 (t, 3H, *J* = 7.4 Hz, CH_3)
5j	8.21 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.83 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.54–7.40 (m, 2H, Ar-H), 4.65 (s, 1H, NH), 3.63 (t, 2H, *J* = 6.4 Hz, NCH_2), 3.54 (s, 3H, NCH_3), 1.76–1.67 (m, 2H, CH_2), 1.53–1.43 (m, 2H, CH_2), 1.01 (t, 3H, *J* = 6.4 Hz, CH_3)

several drops of EtONa in EtOH was added. The mixture was stirred for 6–10 h at r.t. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give the 2-alkylamino benzo[b]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** (entries 1–4) and **5** (entries 5–10).

To the solution of **2** prepared above in EtOH (15 mL) was added ammonia or methylamino (2 mmol). After the reaction mixture was allowed to stand for 0.5 h, the solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give the 2-alkylaminobenzo[b]thieno[3,2-*d*]pyrimidin-4(3*H*)-one **5** (entries 11–14).

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