Chinese Chemical Letters Vol. 16, No. 9, pp 1177-1180, 2005
http://www.imm.ac.cn/journal/ccl.html

A Facile Synthesis of 2, 7-Diaminothieno[2, 3-d:5,4-d]-dipyrimidine-4, 5(3H, 6H)diones

Sheng Zhen XU, Min Hui CAO, Ming Wu DING*, Hong Wu HE

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079

Abstract: 2, 7-Diaminothieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)diones **4** were synthesized by a facile synthetic method, which includes bis-aza-Wittig reaction of bis-iminophosphorane **1** with aromatic isocyanate to give bis-carbodiimide **2** and subsequent reaction of **2** with various dialkylamine in the presence of solid K_2CO_3 or EtONa.

Keywords: Thieno[2,3-d:5,4-d]dipyrimidine-4,5(3H,6H)dione, bis-aza-Wittig reaction, bisimino-phosphorane, bis-carbodiimide, synthesis.

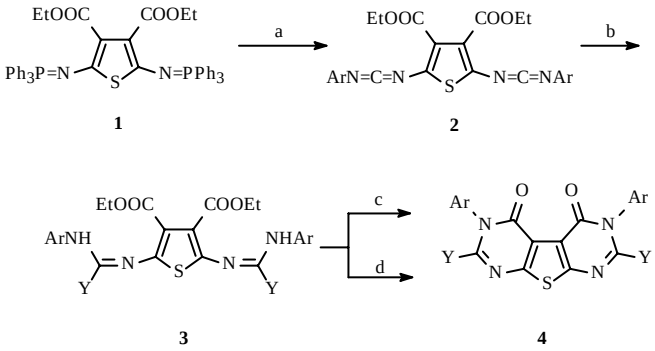
Thienopyrimidine derivatives are known to have various biological activities, such as antimicrobial[1], antifungal[2], antiinflammatory[3] and antihypertensive[4] activities. Some substituted thienopyrimidine system are reported as drugs[5-6]. Thienopyrimidinones are usually prepared from 2-amino-3-ethoxycarbonylthiophene with formamide, isocyanates or imidocarbonates[7-9], or from 2-isothiocyano-3-ethoxycarbonylthiophene with amine[10-11]. Recently we have been interested in the synthesis of imidazolinones, quinazolinones and thienodipyrimidinones *via* aza-Wittig reaction, with the aim of evaluating their fungicidal activities[12-16]. Our interest in this field[15] led us to prepare some unreported derivatives of thieno[2, 3-d:5,4-d]dipyrimidine-4, 5(3H, 6H)diones from bis-iminophosphorane **1** in the presence of potassium carbonate or sodium ethoxide.

Bis-iminophosphorane **1** reacted with two equivalents of aromatic isocyanate to give bis-carbodiimide **2**, which was allowed to react with secondary amines to provide guanidine intermediates **3**. In the presence of catalytic amount of sodium ethoxide[15], **3** were converted easily to 2, 7-diaminothieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)-diones **4** in satisfactory yields at room temperature. It is noteworthy that when solid potassium carbonate was used as base in place of sodium ethoxide, **4** were also obtained in comparable yields at 80 °C. The results are listed in **Table 1**.

The structure of **4** has been confirmed by spectral data ^{1}H NMR, IR and MS. For example, the ^{1}H NMR spectrum data of **4a** showed the signals of NCH_2 at 3.10 ppm as quaternary absorption. The other signals appeared at δ 7.21-7.13 (m, 8H, Ar-H), 2.36 (s, 6H, $2CH_3Ph$), 0.84 (t, J=7.2 Hz, 12H, $4CH_3$). The ^{13}C NMR spectrum data in **4a**

* E-mail: ding5229@yahoo.com.cn

Scheme 1



(a) ArNCO, CH_2Cl_2, 0-5 °C, 8-12 h; (b) HY, CH_2Cl_2, r.t., 0.5-6 h; (c) EtOH, EtONa, r.t., 1-6 h, 71-89%; (d) CH_3CN, K_2CO_3 (s), 80 °C, 12-14 h, 68-91%.

Table 1 Preparation of thieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)diones **4**

	Ar	Y	Condition	Yield (%)[a]	Mp (°C)
4a	4-MeC_6H_4	-NEt_2	EtONa/EtOH, r.t./6 hr	80	>300
			K_2CO_3(s)/CH_3CN, 80 °C, 13 h	78	
4b	Ph		EtONa/EtOH, r.t./4 hr	87	>300
			K_2CO_3(s)/CH_3CN, 80 °C, 12 h	88	
4c	4-MeC_6H_4		EtONa/EtOH, r.t./4 hr	85	>300
			K_2CO_3(s)/CH_3CN, 80 °C, 12 h	82	
4d	Ph		EtONa/EtOH, r.t./3 hr	89	>300
			K_2CO_3(s)/CH_3CN, 80 °C, 12 h	91	
4e	Ph	-N(*i*-Bu)$_2$	EtONa/EtOH, r.t./6 hr	72	256-257
			K_2CO_3(s)/CH_3CN, 80 °C, 14 h	75	
4f	4-Me-C_6H_4	-N(*i*-Pr)$_2$	EtONa/EtOH, r.t./6 hr	71	>300
			K_2CO_3(s)/CH_3CN, 80 °C, 14 h	68	

[a] Isolated yields based on iminophosphorane **1**

Table 2 Elementary analysis, IR and MS of **4**

	Elementary analysis (%, Calcd.)			IR (KBr, cm^{-1})	MS (*m/z*, %)
	C	H	N		
4a	66.21(66.40)	6.17(6.31)	15.74(15.49)	1717, 1531, 1505	542 (M^+, 63), 410 (22), 354 (44), 189 (77), 91 (100)
4b	66.81(66.89)	5.37(5.61)	15.70(15.60)	1718, 1531, 1504, 1452	538 (M^+, 88), 454 (14), 352 (77), 213 (14), 187 (100), 77 (98)
4c	67.94(67.82)	6.23(6.05)	14.78(14.83)	1716, 1536, 1503	566 (M^+, 100), 448 (16), 366 (46), 201 (48), 91 (39)
4d	61.75(61.98)	4.97(4.83)	15.63(15.49)	1714, 1534, 1502, 1452	542 (M^+, 79), 456 (26), 354 (42), 189 (64), 77 (100)
4e	69.15(68.98)	7.36(7.40)	13.58(13.41)	1719, 1523, 1506, 1458	626 (M^+, 47), 583 (14), 498 (10), 396 (12), 91 (23), 57 (100)
4f	68.27(68.20)	7.24(7.07)	13.77(14.03)	1719, 1528, 1498	598 (M^+, 54), 555 (30), 456 (12), 382 (28), 173 (34), 43 (100)

Table 3 ^{1}H NMR and ^{13}C NMR of **4**

	^{1}H NMR ($CDCl_3$, 400MHz, δ ppm)	^{13}C NMR ($CDCl_3$, 100MHz, δ ppm)
4a	7.21-7.13 (m, 8H, Ar-H), 3.09 (q, J=7.2 Hz, 8H, $4NCH_2$), 2.36 (s, 6H, $2CH_3$), 0.84 (t, J=7.2 Hz, 12H, $4CH_3$)	160.9 (2), 157.1 (2), 156.0 (2), 137.5 (2), 135.3 (2), 129.2 (4), 128.7 (4), 112.3 (2), 44.9 (4), 21.1 (2), 12.5 (4)
4b	7.43-7.30 (m, 10H, Ar-H), 3.12 (t, J=5.2 Hz, 8H, $4NCH_2$), 1.44-1.21 (m, 12H, $6CH_2$)	161.0 (2), 156.7 (2), 156.6 (2), 137.8 (2), 128.9 (4), 128.4 (4), 127.7 (2), 113.0 (2), 49.8 (4), 24.8 (4), 24.0 (2)
4c	7.19-7.10 (m, 8H, Ar-H), 3.11 (t, J=5.2 Hz, 8H, $4NH_2$), 2.36 (s, 6H, $2CH_3$), 1.42-1.23 (m, 12H, $6CH_2$)	160.9 (2), 156.8 (2), 156.7 (2), 137.4 (2), 135.1 (2), 129.0 (4), 128.5 (4), 113.0 (2), 49.8 (4), 24.8 (4), 24.0 (2), 21.1 (2)
4d	7.43-7.34 (m, 10H, Ar-H), 3.42 (t, J=4.8 Hz, 8H, $4OCH_2$), 3.13 (t, J=4.8 Hz, 8H, $4NCH_2$)	160.5 (2), 156.1 (2), 155.8 (2), 137.0 (2), 129.0 (4), 128.5 (4), 128.0 (2), 113.4 (2), 65.9 (4), 48.8 (4)
4e	7.42-7.27 (m, 10H, Ar-H), 2.84 (d, J=6.8 Hz, 8H, $4NCH_2$), 1.85-1.78 (m, 4H, 4CH), 0.78 (d, J=6.8Hz, 24H, $8CH_3$)	161.3 (2), 156.9 (2), 155.8 (2), 137.7 (2), 128.6 (4), 128.5 (4), 127.8 (2), 111.6 (2), 58.2 (4), 27.2 (4), 20.2 (8)
4f	7.18-7.09 (m, 8H, Ar-H), 3.57-3.50 (m, 4H, 4NCH), 2.34 (s, 6H, $2CH_3$), 1.06 (d, J=6.8Hz, 24H, $8CH_3$)	160.9 (2), 157.8 (2), 155.1 (2), 137.3 (2), 136.3 (2), 129.1 (4), 129.0 (4), 112.4 (2), 50.0 (4), 21.4 (8), 21.1 (2)

showed the signals of C=O and NCH_2 at 160.9 and 44.9 ppm. The IR of **4a** showed the strong stretching resonance peak of pyrimidinone C=O at 1717 cm^{-1}. The MS of **4a** showed M^+ at *m/z* 542 with 63% abundance.

The above synthetic method provides an efficient synthesis of 2, 7-dialkylamino-thieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)diones from bis-iminophosphorane in the presence of solid potassium carbonate or sodium ethoxide. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active thienodipyrimidinones derivatives.

General procedure for the synthesis of thieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)diones: To a solution of bis-iminophosphorane **1** (2.33 g, 3 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (6 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 8-12 hours 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. Filtered, the solvent of the filtrate was removed to give bis-carbodiimide **2**, which was used directly without further purification. To the solution of 2 prepared above in methylene dichloride (15 mL) was added dialkylamine (6 mmol). After the reaction mixture was allowed to stand for 0.5-6 hours, the solvent was removed and the residue was treated with following two methods. Method 1: to 3 prepared above in anhydrous ethanol (10 mL) was added several drops of EtONa in EtOH. The mixture was stirred for 1-6 hr at room temperature. The solution was concentrated under reduced pressure and the residual was recrystallized from ethanol to give 2, 7-diaminothieno[2, 3-d:5, 4-d]dipyrimidine-4, 5(3H, 6H)diones **4**. Method 2: to **3** prepared above in CH_3CN (10 mL) was added catalytic amount of solid K_2CO_3 (0.1 g). The mixture was stirred for 12-14 hr at 80 °C. The solution was concentrated under reduced pressure and the residue was recrystallized from ethanol to give **4**.

Acknowledgment

We gratefully acknowledge financial support of this work by the National Key Project for Basic Research (2003CB114400, 2003CB114406) and the National Natural Science Foundation of China (Project No. 20372023 and 20102001).

References

1. R. V. Chambhare, B. G. Khadse, A. S. Bobde, *et al.*, *Eur. J. Med. Chem.*, **2003**, *38*, 89.
2. R. M. Geddens, M. C. Klapproth, WO 2003103393.
3. A. K. EI-Ansary, A. H. Omar, *Bull. Faculty Pharm.*, **2001**, *39*, 17.
4. R. K. Russel, J. B. Press, R. A. Rampulla, *et al*., *J. Med. Chem*., **1988**, *31*, 1786.
5. M. E. Fraley, G. D. Hartman, W. F. Hoffman, WO 2003050064.
6. T. R. Caferro,S, D. Chamberlain, K. H. Donaldson, WO 2003053446.
7. J. Clark, G. Hitiris, *J. Chem. Soc., Perkin Trans 1*, **1984**, 2005.
8. K. Gewald, A. Martin, *J. Prakt. Chem*., **1981**, *323*, 843.
9. H. Walter, WO 0034286.
10. M. M. Ghorab, H. I. Heiba, M. A. El-Gawish, *Phosphorus, Sulfur Silicon Relat. Elem.*, **1995**, *106*, 85.
11. A. Santagati, M. Santagati, M. Modica, *Heterocycles*, **1993**, *36*, 1315.
12. M. W. Ding, Y. Liu, G. F. Zhang, *et al.*, *Chin. Chem. Lett*., **2004**, *15*, 280.
13. M. W. Ding, J. Zhu, S. F. Shi, *et al.*, *Chin. Chem. Lett*., **2002**, *13*, 942.
14. M. W. Ding, S. J. Yang, J. Zhu, *Synthesis*, **2004**, 75.
15. M. W. Ding, S. Z. Xu,J. F. Zhao, *J. Org. Chem.*, **2004**, *69*, 8366.
16. M. W. Ding, S. J. Yang, Y. F. Chen, *Chin. J. Org. Chem.*, **2004**, *24*, 923.
17. H. Wamhoff, S. Herrmann, S. Stolben, *et al.*, *Tetrahedron*, **1993**, *49*, 581.

Received 5 November, 2004