Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 20 (2009) 1055–1058
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Efficient synthesis of 5,6-dihydrothieno[3′,2′:4,5] thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via an iminophosphorane

Yu Lu Chen [a,b], Yi Bo Nie [a], Ming Wu Ding [a,*]

[a] *Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, China*
[b] *Department of Biology, Xianning Vocational and Technical College, Xianning 437100, China*

Received 6 January 2009

Abstract

5,6-Dihydrothieno[3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** were synthesized in yields of 71–87% by a consecutive method, which includes aza-Wittig reaction of iminophosphorane **3** with aromatic isocynate to give carbodiimide **4** and subsequent reaction of **4** with various amines, phenols or alcohols in the presence of catalytic amount of sodium ethoxide or solid potassium carbonate.

Keywords: 5,6-Dihydrothieno[3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one; Iminophosphorane; Aza-Wittig reaction; Carbodiimide; Isocyanate

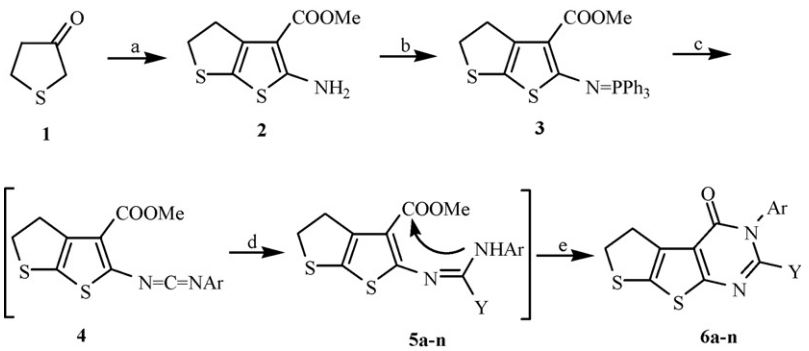
The derivatives of heterocycles containing thienopyrimidine system are of great importance because of their remarkable biological activity for use as potential drugs. They proved to show significant antifungal, antibacterial, antimicrobial, anticonvulsant and angiotensin antagonistic activities [1–5]. Also some of these compounds show good antimalarial [6] or potent multitargeted receptor tyrosine kinase inhibitive activities [7]. However, there are few reports about the related thienothienopyrimidinone system [8], which is considerable interest as potential biological active heterocycles or pharmaceuticals. Synthetically useful approaches to thienothienopyrimidinones starting from easily accessible 2-amino-3-carboxythiophenes are therefore of great importance. Recently we have become interested in the preparation of N-heteroaryliminophosphoranes because these species are promising building blocks for the synthesis of nitrogen heterocycles [8–12]. Herein we wish to report an efficient synthesis of various 2-substituted 5,6-dihydrothieno[3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)- ones via an iminophosphorane **3**.

The methyl 2-amino-4,5-dihydrothieno[2,3-*b*]thiophene-3-carboxylate **2** was obtained by Gewald reaction from dihydrothiophen-3(2*H*)-one **1**, methyl cyanoacetate and sulfur in the presence of diethylamine [13]. The three component reaction was easily carried out in one-pot at mild condition and the yield was moderate. Compound **2** was further converted to iminophosphorane **3** by treatment with triphenylphosphine, hexachloroethane and triethylamine in dry acetonitrile in good yield (Scheme 1).

Iminophosphorane **3** reacted with an equimolar quantity of the aromatic isocyanates to give the carbodiimides **4**, which were allowed to react with aliphatic secondary amines to provide guanidine intermediates **5** (Y = NR^1R^2). By

* Corresponding author.
E-mail address: ding5229@yahoo.com.cn (M. Wu Ding).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.04.004



Scheme 1. (a) $NCCH_2COOMe$, S, $HNEt_2$, CH_3OH, 40–50 °C, 3 h, 52%. (b) Ph_3P, C_2Cl_6, CH_3CN, r.t., 4 h, 81%. (c) ArNCO, CH_2Cl_2, 0–5 °C, 6–12 h. (d) HY, CH_2Cl_2, r.t., 2–6 h. (e) EtONa, CH_2Cl_2, r.t., 4–8 h, or K_2CO_3 (s), CH_3CN, 40–50 °C, 4–6 h, 71–87%.

treatment with sodium ethoxide in ethanol at room temperature, the intermediates **5** underwent intramolecular heterocyclization to give the expected 2-dialkylamino 5,6-dihydrothieno[3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6a–g** in satisfactory yields. It is noteworthy that the isolated yield of **6** was good even when NR^1R^2 is bulky di-*iso*-propylamino group. The results are listed in Table 1. The reaction of carbodiimide **4** with phenols produced 2-aryloxy-5,6-dihydrothieno[3′,2′:4,5] thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6h–k** (Y = OAr) in the presence of catalytic amount of potassium carbonate in good yields (Table 1). All of the reactions between carbodiimide **4** and phenols proceeded smoothly at 50–60 °C, though the reactivity of the carbodiimides **4** and phenols varied with the substituent on the benzene ring. This implied the high reactivity of the carbodiimide **5**. When carried out in the presence of catalytic amount of RONa, the reaction of carbodiimide **4** with ROH took place also smoothly and 2-alkoxy-5,6-dihydrothieno[3′,2′:4,5] thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6l–n** (Y = OR) were obtained in satisfactory yields (Table 1).

The structure of the synthesized compound **6** was confirmed by their spectral data and elemental analyses. For example, ^{1}H NMR spectral data of **6b** show the signals of $-NCH_2$ at 3.04 ppm as quartlets and signals of CH_3 at 0.86 ppm as triplets. The dihydrothiophene ring's signals appeared at 3.77 ppm (6-CH) and 3.32 ppm (5-CH) as two triplets. The phenyl signals appeared at 7.48–7.23 ppm. The MS spectrum of **6b** shows strong molecule ion peak (M^+) at *m/z* 391 with 100% abundance Table 2.

In conclusion, we have developed an efficient synthesis of various 2-substituted 5,6-dihydrothieno [3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via aza-Wittig reaction of an iminophosphorane with aromatic isocyanate and subsequent base catalytic reaction with various amines, phenols and alcohols. Due to the easily

Table 1
Synthesis of 5,6-dihydrothieno[3′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3H)-ones **6a–6n** by aza-Wittig reaction.

	Ar	Y	Condition	Yield (%)	Elementary analysis (%, calcd.)		
					C	H	N
6a	Ph	Pyrrolidin-1-yl	r.t., 4 h	87	60.67 (60.82)	4.94 (4.82)	11.94 (11.82)
6b	4-Cl-C_6H_4	NEt_2	r.t., 4 h	83	55.34 (55.16)	4.84 (4.63)	10.64 (10.72)
6c	4-Cl-C_6H_4	N(*i*-Pr)$_2$	r.t., 8 h	79	57.17 (57.20)	5.03 (5.28)	10.26 (10.00)
6d	4-Cl-C_6H_4	Pyrrolidin-1-yl	r.t., 6 h	79	55.68 (55.45)	4.11 (4.14)	10.67 (10.78)
6e	4-F-C_6H_4	NEt_2	r.t., 4 h	82	57.72 (57.58)	4.60 (4.83)	11.25 (11.19)
6f	4-F-C_6H_4	N(*i*-Pr)$_2$	r.t., 8 h	76	59.45 (59.53)	5.33 (5.50)	10.68 (10.41)
6g	4-F-C_6H_4	Pyrrolidin-1-yl	r.t., 8 h	81	57.74 (57.89)	4.52 (4.32)	11.13 (11.25)
6h	Ph	4-MeOC_6H_4O	40–50 °C, 4 h	81	61.79 (61.75)	3.77 (3.95)	6.63 (6.86)
6i	4-Cl-C_6H_4	4-MeC_6H_4O	40–50 °C, 6 h	73	59.34 (59.08)	3.69 (3.54)	6.48 (6.56)
6j	4-Cl-C_6H_4	4-MeOC_6H_4O	40–50 °C, 4 h	78	56.81 (56.94)	3.24 (3.41)	6.57 (6.32)
6k	4-F-C_6H_4	4-MeC_6H_4O	40–50 °C, 6 h	85	61.52 (61.45)	3.83 (3.68)	6.64 (6.82)
6l	Ph	EtO	r.t., 4 h	73	58.33 (58.16)	4.08 (4.27)	8.21 (8.48)
6m	4-Cl-C_6H_4	EtO	r.t., 6 h	71	52.84 (52.67)	4.34 (3.59)	7.64 (7.68)
6n	4-F-C_6H_4	EtO	r.t., 6 h	82	55.38 (55.16)	3.71 (3.76)	8.17 (8.04)