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Short Note

8,18-Dithia-1,4,11,14-tetraazapentacyclo[11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione

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Abstract: 4*H*-3λ^2-Thieno[3,2-*d*]pyrimidin-4-one derivatives are of interest as biologically active compounds. In this communication, 2-(chloromethyl)-4*H*-3λ^2-thieno[3,2-*d*] pyrimidin-4-one (**1**) was investigated in the reaction with ammonia, potassium phthalimide, and other basic agents. The dimerization product—8,18-dithia-1,4,11,14-tetrazapentacyclo[11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione was formed in the reaction with potassium phthalimide in DMF, by heating at 110 °C for 5 h. The structure of the newly synthesized compound was established by means of elemental analysis, high resolution mass-spectrometry, ^{1}H, ^{13}C NMR, and IR spectroscopy, and mass-spectrometry.

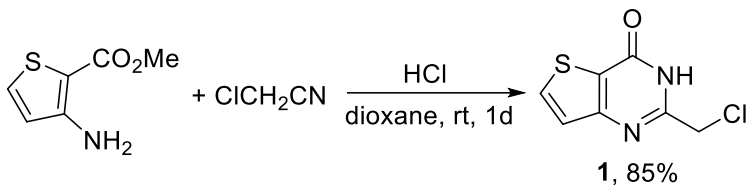
Keywords: 2-(chloromethyl)-4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one; sodium phthalimide; condensation

1. Introduction

O-, *S*-, and *N*-Methyl derivatives of 4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one were intensively studied as novel HIV-1 replication inhibitors [1], Aurora kinase A inhibitors [2], inhibitors of the Salicylate Synthase (MbtI) from Mycobacterium tuberculosis [3], tankyrase inhibitors [4], and Cdc7 inhibitors for cancer therapy [5]. The convenient precursor for these compounds is 2-(chloromethyl)-4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one (**1**), since the chlorine can be replaced by oxygen, sulfur, or nitrogen nucleophiles. Meanwhile, 2-(aminomethyl)-4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one (**2**), which could be a starting material for other *N*-substituted derivatives, is still unknown. In order to develop the chemistry of various biologically active thieno[3,2-*d*]pyrimidin-4-ones, the synthesis of this amine from chloromethyl derivative was attempted. Herein, we report the unexpected formation of 8,18-dithia-1,4,11,14-tetrazapentacyclo[11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione from compound **1**.

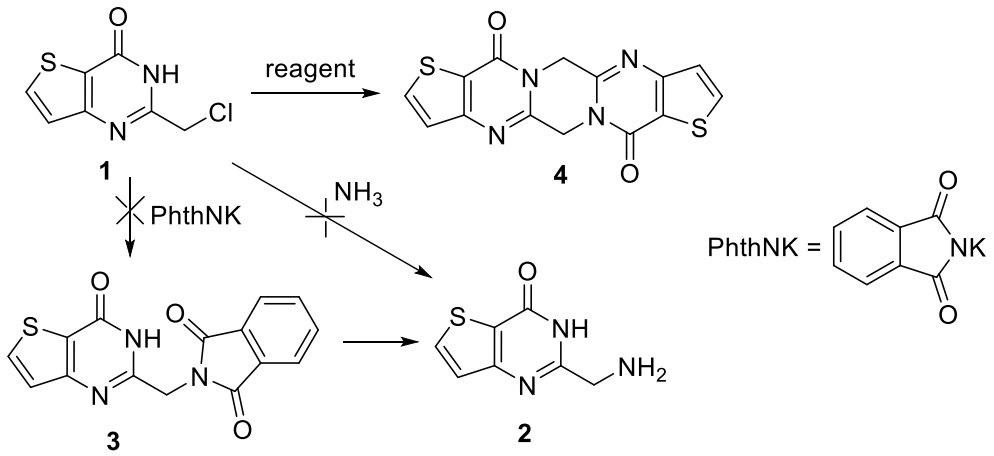
2. Results and Discussion

Compound **1** can be easily prepared from the commercial methyl 3-aminothiophene-2-carboxylate and chloroacetonitrile (Scheme 1) [6].



Scheme 1. Synthesis of 2-(chloromethyl)-4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one (**1**).

Its transformation into compound **2** was examined (Scheme 2). We found that the treatment of chloromethyl derivative **1** with ammonia in H_2O or EtOH gave no reaction. We attempted to synthesize amine **2** through its phthalimide derivative **3**, which can be obtained by nucleophilic substitution of the chloromethyl derivative **1** with potassium phthalimide. Unexpectedly, it was found that this reaction led to the formation of pentacycle **4** and no traces of phthalimide derivative **3** were detected (Table 1). It means that potassium phthalimide acts as a base, but not as a nucleophilic reagent to bind two thieno[3,2-*d*]pyrimidin-4-one moieties with the piperazino cycle. To rationalize the synthetic approach to compound **4**, we investigated this reaction with other bases. We found that with neither NaH (Entries 7,8) nor KOH (Entry 9), almost no reaction occurred at all. The best yield was achieved in the reaction with potassium phthalimide by heating in DMF at 110 °C for 5 h (Entry 6). The results are summarized in Table 1.



Scheme 2. Synthesis of 8,18-dithia-1,4,11,14-tetraazapentacyclo[11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione (**4**).

Table 1. Reaction of 2-(chloromethyl)-4*H*-3λ^2-thieno[3,2-*d*]pyrimidin-4-one (**1**) with basic agents.

Entry	Solvent	Reagent	Temperature (°C)	Time (h)	Yield (%)	
					4	**1**
1	THF	PhthNK	66	5	0	95
2	acetone	PhthNK	56	5	15	83
3	acetone	PhthNK	56	10	15	79
4	EtOH	PhthNK	78	5	24	0
5	DMSO	PhthNK	110	5	39	0
6	DMF	PhthNK	110	5	80	0
7	DMF	NaH	rt	10	0	0
8	THF	NaH	66	5	0	0
9	EtOH	KOH	78	10	4	0

The structure of pentacycle **4** was confirmed by means of elemental analysis, high resolution mass-spectrometry, ^{1}H, ^{13}C NMR, and IR spectroscopy, and mass-spectrometry.

In conclusion, unexpected dimerization of compound **1** into 8,18-dithia-1,4,11,14-tetrazapentacyclo [11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione **4** by the action of potassium phthalimide was discovered. Surprisingly, the common basic reagents (sodium hydride, potassium hydroxide) mostly caused decomposition of the starting material.

3. Experimental Section

3.1. General Information

The solvents and reagents were purchased from commercial sources and used as received. Compound **1** was prepared according to the published method [6]. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and was unaltered. ^{1}H and ^{13}C NMR spectra were taken with a Bruker DRX-500 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 500.1 and 125.8 MHz, respectively) in DMSO-d_6 solution, with TMS as the standard. *J* values are given in Hz. An MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). An IR spectrum was measured with a Bruker "Alpha-T" instrument in a KBr pellet. A high-resolution MS spectrum was measured on a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI). The measurement was performed in a positive ion mode (interface capillary voltage −4500 V) and in a negative ion mode (3200 V); mass range was from *m*/*z* 50 to *m*/*z* 3000 Da; external and internal calibration were done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solutions in acetonitrile, methanol, and water (flow rate 3 L/min). Nitrogen was applied as a dry gas and the interface temperature was set at 180 °C.

3.2. Synthesis of 8,18-Dithia-1,4,11,14-tetraazapentacyclo[11.7.0.0^{3,11}.0^{5,9}.0^{15,19}]icosa-3,5(9),6,13,15(19),16-hexaene-10,20-dione (**4**)

A suspension of 2-(chloromethyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**1**) (2.0 g, 10 mmol) and potassium phtalimide (1.85 g, 10 mmol) in DMF (20 mL) was heated at 110 °C and stirred for 5 h. The reaction mixture was cooled to room temperature and H_2O (30 mL) was added. The precipitate was filtrated and washed with ethanol and water, and dried. Yield 1.32 g (80.5%), light yellow crystals, mp > 300 °C, Rf = 0.14 (CH_2Cl_2: acetone 5:1). IR (KBr), ν, cm^{-1}: 3511, 3077, 3056 (C-H), 1675 (C=O), 1571 (C=N), 1504, 1444, 1332, 1189, 1126, 1047, 913, 800, 710, 631. ^{1}H NMR (ppm, *J*/Hz): δ 5.36 (s, 4H, 2 CH_2), 7.46 (d, 2H, thiophene, *J* = 5.2), 8.27 (d, 2H, thiophene, *J* = 5.2). ^{13}C NMR (ppm): δ 44.3 (2C, $\underline{C}H_2$), 120.8 (2C, C-thiophene), 125.0 (2C, CH-thiophene), 136.2 (2C, CH-thiophene), 151.1 (2C, C=O), 155.8 (2C, C-thiophene), 156.2 (2C, N-$\underline{C}$=N). HRMS (ESI-TOF): calcd for $C_{14}H_8N_4O_2S_2$ [M + H]$^+$ 329.0161; found *m*/*z* 329.0160; calcd for $C_{14}H_8N_4O_2S_2$ [M + Na]$^+$ 350.9981, found *m*/*z* 350.9978; MS (EI, 70 Ev), *m*/*z* (I, %): 328 (M$^+$, 75), 299 (10), 273 (7), 150 (22), 136 (20), 122 (16), 110 (12), 96 (15), 82 (12), 70 (12), 45 (10). Anal. Calcd. for $C_{14}H_8N_4O_2S_2$: C, 51.21; H, 2.46; N, 17.06; found: C, 51.42; H, 2.61; N, 16.95%.

Supplementary Materials: The following are available online, ^{1}H, ^{13}C NMR, IR, and mass-spectra for compound **4** are available online.

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Conflicts of Interest: The authors declare no conflict of interest.

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