Heteroatom Chemistry
Volume 20, Number 6, 2009

# Investigation into the Reaction of 2-Amino-4,5-dimethylthiophene-3-carboxamide with Iso(and Isothio)cyanates under Microwave Irradiation

Abolghasem Davoodnia,[1] Mohammad Rahimizadeh,[2] Hoda Atapour-Mashhad,[1] and Niloofar Tavakoli-Hoseini[1]

[1]*Department of Chemistry, Faculty of Sciences, Islamic Azad University, Mashhad Branch, Mashhad, Iran*

[2]*Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran*

*Received 12 April 2009*

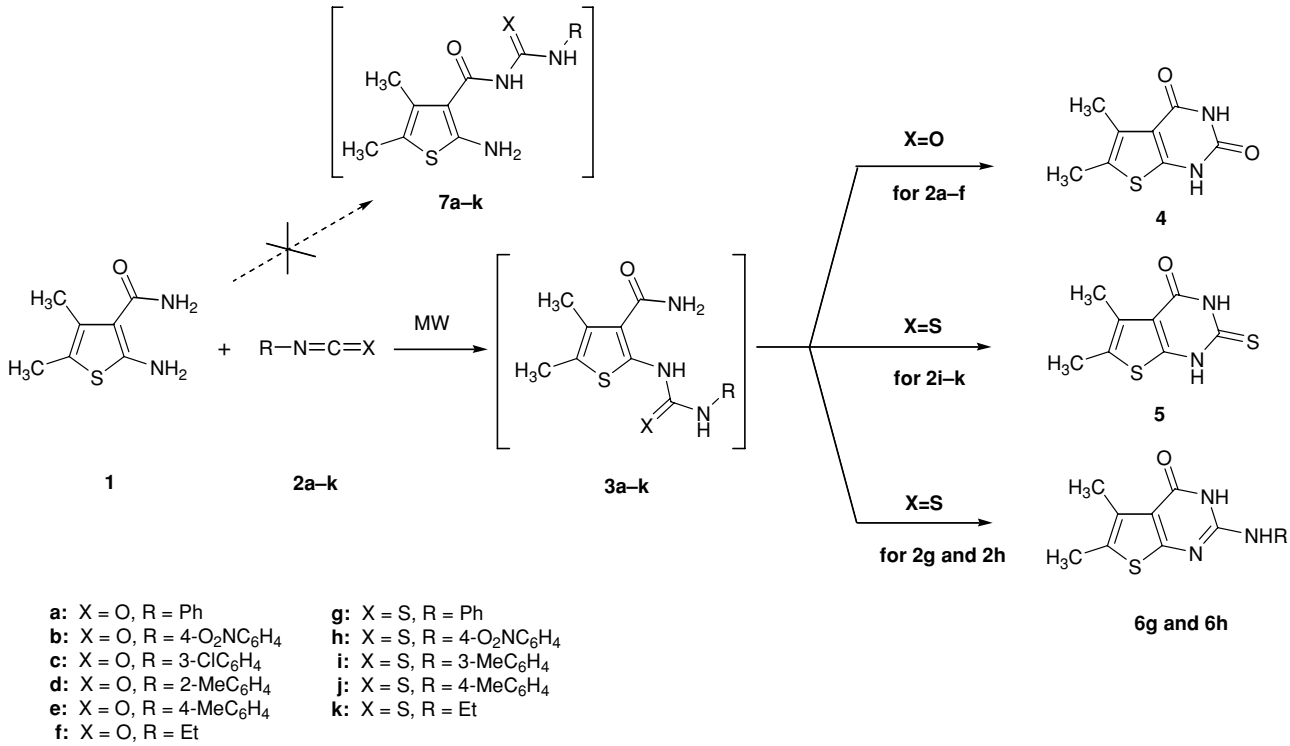
ABSTRACT: *The reaction of 2-amino-4,5-dimethylthiophene-3-carboxamide with iso(and isothio) cyanates for the synthesis of thieno[2,3-d]pyrimidines has been investigated. The reactions under microwave irradiation in the presence of N,N-dimethyl acetamide as solvent gave 5,6-dimethylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione, 5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one, and 2-arylamino-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one derivatives. These reactions probably proceed through intermediates 4,5-dimethyl-2-substitutedcarbamothioylaminothiophene-3-carboxamides. Two of these intermediates were isolated.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:346–349, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20557

## *INTRODUCTION*

Thieno[2,3-*d*]pyrimidines are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant analgesic [1,2], fungicidal [3], antibacterial [4], antiviral [5], and antiinflammatory [6] activities. Also, some thieno[2,3-*d*]pyrimidines show central nervous system depressing activity [7] and are useful as muscle relaxants [8], sedatives [8], diuretics [9], pesticides, and herbicides [10]. Various methods have already been proposed for the synthesis of these compounds, and the most general ones involve cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine [11], $\alpha$-substituted acetonitriles [12], formic acid [13], phosgene [14], ethyl chloroformate [14], and guanidine [15]. To the best of our knowledge, reaction of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** with isocyanates and isothiocyanates for the synthesis of thieno[2,3-*d*]pyrimidines under microwave irradiation has not been reported in the literature.

In pursuing these studies and in continuation of our work on the synthesis of thieno[2,3-*d*]pyrimidine derivatives [16–19] and due to our interest in the utilization of microwave irradiation for the synthesis of heterocyclic compounds [20–23], in this paper we tried to synthesize some thieno[2,3-*d*]pyrimidine derivatives with regard to the reaction of compound **1** with isocyanates and isothiocyanates under microwave irradiation conditions (Scheme 1).

*Correspondence to:* Abolghasem Davoodnia; e-mail: adavoodnia@yahoo.com, adavoodnia@mshdiau.ac.ir.




SCHEME 1

## *RESULTS AND DISCUSSION*

The starting material **1** was prepared according to the literature method [24]. First, treatment of this compound with isocyanates **2a–f** under microwave irradiation in the presence of *N*,*N*-dimethylacetamide (DMA) as solvent was explored. When the reactants were mixed together and irradiated at 700 W for the indicated time, using a domestic microwave oven model LG MS-543XD, we observed that the similar product was formed in all reactions and identified as 5,6-dimethylthieno-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **4** [25]. Therefore, the cyclization reactions occurred via leaving the amino groups instead of water (Scheme 1).

Next, reaction of compound **1** with isothiocyanates **2g–k** under same conditions was investigated. When this compound was allowed to interact with isothiocyanates **2g** and **2h** under microwave irradiation in the presence of DMA, the arylamino derivatives **6g** and **6h** were obtained, respectively, whereas irradiation of this compound with isothiocyanates **2i–k** produced compound **5** [26]. It is obvious that the formation of the products **6g, 6h**, and **5** has proceeded through leaving hydrogen sulfide and the amino groups, respectively.

The formation of the all above-mentioned products was assumed to proceed via the seemingly reactive intermediates **3a–k** with subsequent cyclization to furnish the cyclized products **4, 5, 6g**, and **6h**. Attempts to isolate these intermediates failed when we monitored the reactions under careful observation.

Finally, we were interested to study the role of DMA in these reactions. For this purpose, the reactions were carried out under microwave irradiation in the absence of DMA. Omission of DMA of the reaction mixture has no effect on the formation of the products except for **2h** and **2k**.

When compound **1** was allowed to interact with isothiocyanates **2h** and **2k** under microwave irradiation in solvent-free conditions and monitored the reaction mixture by TLC ($CHCl_3$:MeOH, 95:5), surprisingly we observed that unexpected products, with different $R_f$s of those expected for compounds **6h** and **5**, respectively, were formed. During workup and identification, it was established that a condensation and not a cyclocondensation reaction had occurred, and the intermediates **3h** and **3k** were isolated. The reaction did not proceed to form cyclic products even after prolonged irradiation, but when these intermediates were irradiated in the presence of DMA the cyclization reaction occurred and the cyclic products **6h** and **5** were obtained, respectively. The structure of new products **3h, 3k, 6g**, and **6h** was established from their spectral and microanalytical data and for known compounds **4** and **5** by comparison with authentic samples (see the Experimental section).

As it was shown in the previous paper [19], we believe that the formation of the intermediates **3h** and **3k** occurred via a nucleophilic attack of the amino group in 2-position of thiophene at the carbon site of isothiocyanates **2h** and **2k**, respectively. Therefore, the compounds **7h** and **7k** have not been formed (Scheme 1).

In conclusion, the reaction of compound **1** with iso(and isothio)cyanates **2a–k** under microwave irradiation in the presence of DMA as solvent gave the cyclized products thieno[2,3-*d*]pyrimidines. In the absence of DMA, two intermediates **3h** and **3k** were isolated.

## *EXPERIMENTAL*

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The $^1$H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

### *Synthesis of 4,5-Dimethyl-2-substitutedcarbamothioylaminothiophene-3-carboxamides (**3h**) and **3k**)*

*General Procedure.* A mixture of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (0.002 mol) and isothiocyanates **2h** or **2k** (0.003 mol) was subjected to microwave irradiation at 700 W for 6 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), the crude product was collected and recrystallized from ethanol/:ethyl acetate to give compounds **3h** and **3k** in good yields.

*4,5-Dimethyl-2-{[(4-nitrophenyl)carbamothioyl]-amino}thiophene-3-carboxamide (**3h**).* Yield, 65%; mp >350°C; $^1$H NMR: $\delta$ (DMSO-$d_6$) 2.20 (s, 6H, $2CH_3$), 7.35 (br, 2H, $NH_2$), 7.70 (d, 2H, Ar-H, $J = 9$ Hz), 8.20 (d, 2H, Ar-H, $J = 9$ Hz), 9.88 (br, 1H, NH), 10.65 (br, 1H, NH); IR (KBr, $\nu$/cm$^{-1}$): 3507, 3408, 3311, and 3237 ($NH_2$ and two NH), 1675 (C=O stretching and $NH_2$ bending), 1500, 1325 ($NO_2$); MS, *m/z*: 350 ($M^+$); Anal. Calcd for $C_{14}H_{14}N_4O_3S_2$: C, 47.99; H, 4.03; N, 15.99; S, 18.30; found C, 48.32; H, 4.38; N, 15.54; S, 18.08.

*2-[(Ethylcarbamothioyl)amino]-4,5-dimethylthiophene-3-carboxamide (**3k**).* Yield, 80%; mp >350°C; $^1$H NMR: $\delta$ (DMSO-$d_6$) 1.10 (t, 3H, $CH_3$, $J = 8$ Hz), 2.12 (s, 3H, $CH_3$), 2.17 (s, 3H, $CH_3$), 3.35 (q, 2H, $CH_2$, $J = 8$ Hz), 7.33 (s br, 2H, $NH_2$), 8.77 (s br, 1H, NH), 10.80 (br, 1H, NH); IR (KBr, $\nu$/cm$^{-1}$): 3471, 3308, 3264, and 3212 ($NH_2$ and two NH), 1647 (C=O stretching and $NH_2$ bending); MS, *m/z*: 257 ($M^+$); Anal. Calcd for $C_{10}H_{15}N_3OS_2$: C, 46.67; H, 5.87; N, 16.33; S, 24.92; found C, 46.94; H, 5.59; N, 15.98; S, 24.67.

### *Synthesis of 5,6-Dimethylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4**)*

A mixture of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (0.002 mol) and isocyanates **2a–f** (0.003 mol) in the presence of DMA (1 mL) as solvent was subjected to microwave irradiation at 700 W for 3–5 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), cyclohexane was added to the reaction mixture. The crude product was collected and recrystallized from ethanol to give compound **4** in 65–90% yields, mp. 335–337°C (lit. [25]. >310°C).

### *Synthesis of 5,6-Dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**5**)*

*Method A.* A mixture of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (0.0025 mol) and isothiocyanates **2i–k** (0.0040 mol) in the presence of DMA (1.2 mL) as solvent was subjected to microwave irradiation at 700 W for 3–4 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), cyclohexane was added to the reaction mixture. The crude product was collected and recrystallized from ethanol to give compound **5** in 60%–75% yields.

*Method B.* 2-[(Ethylcarbamothioyl)amino]-4,5-dimethylthiophene-3-carboxamide **3k** (0.0008 mol) in the presence of DMA (0.5 mL) as solvent was subjected to microwave irradiation at 700 W for 2 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), the crude product was recrystallized from ethanol to give compound **5** in 71% yield, mp. 268–270°C (lit. [26]. 260°C).

### *Synthesis of 5,6-Dimethyl-2-(phenylamino)-thieno[2,3-d]pyrimidin-4(3H)-one (**6g**)*

A mixture of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (0.002 mol) and phenyl isothiocyanate **2g** (0.003 mol) in the presence of DMA (1 mL) as solvent was subjected to microwave irradiation at 700 W for 3 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), cyclohexane was added to the reaction mixture. The crude product was collected and recrystallized from

ethanol to give compound **6g**. Yield, 80%; mp 315–318°C; $^1$H NMR: $\delta$ (DMSO-$d_6$) 2.17 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 7.1–7.7 (m, 5H, phenyl), 10.60 (s br, 1H, NH), 11.82 (br, 1H, NH); IR (KBr, $\nu$/cm$^{-1}$): 3310, 3171 (two NH), 1648 (C=O); MS, *m/z*: 271 ($M^+$); Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; S, 11.82; found C, 61.62; H, 4.59; N, 15.70; S, 12.07.

### *Synthesis of 5,6-Dimethyl-2-[(4-nitrophenyl) amino]thieno[2,3-d]pyrimidin-4(3H)-one (**6h**)*

*Method A.* A mixture of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (0.002 mol) and 4-nitrophenyl isothiocyanate **2h** (0.003 mol) in the presence of DMA (1 mL) as solvent was subjected to microwave irradiation at 700 W for 5 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), cyclohexane was added to the reaction mixture. The crude product was collected and recrystallized from ethanol to give compound **6h** in 72% yield.

*Method B.* 4,5-Dimethyl-2-{[(4-nitrophenyl)-carbamothioyl]amino}thiophene-3-carboxamide **3h** (0.0007 mol) in the presence of DMA (0.5 mL) as solvent was subjected to microwave irradiation at 700 W for 3 min. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), the crude product was recrystallized from ethanol to give compound **6h** in 75% yield.

mp 277–279°C; $^1$H NMR: $\delta$ (DMSO-$d_6$) 2.18 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 7.72 (d, 2H, Ar-H, $J = 9.5$ Hz), 8.13 (d, 2H, Ar-H, $J = 9.5$ Hz), 10.30 (br, 1H, NH), 10.64 (br, 1H, NH); IR (KBr, $\nu$/cm$^{-1}$): 3375, 3221 (two NH), 1674 (C=O), 1497, 1329 ($NO_2$); MS, *m/z*: 316 ($M^+$); Anal. Calcd for $C_{14}H_{12}N_4O_3S$: C, 53.16; H, 3.82; N, 17.71; S, 10.14; found C, 52.76; H, 4.18; N, 17.97; S, 9.92.

## *REFERENCES*


[1] Pathak, U. S.; Singh, S.; Padh, J. Indian J Chem Sec B 1991, 30, 618–619.
[2] Rathod, I. S.; Pillai, A. S.; Shirsath, V. S. Indian J Heterocycl Chem 2000, 10, 93–96.
[3] Showa Denko K. K. Jpn Kokai Tokkyo Koho 81, 53, 681; Chem Abs 1981, 95, 115592y.
[4] El-Gaby, M. S. A. Phosphorus Sulfur Silicon 2000, 156, 157–171.
[5] Kharizomenova, I. A.; Grinev, A. N.; Samsonova, N. V.; Panisheva, E. K.; Kaplina, N. V.; Nikolaeva, I. S.; Pushkina, T. V.; Pershin, G. N. Khim-Farm Zh 1981, 15, 40–44.
[6] El-Ansary, A. K.; Omar, A. H. Bull Faculty of Pharm; (Cairo University) 2001, 39, 17–25.
[7] Pathak, U. S.; Gandhi, N. V.; Singh, S.; Warde, R. P.; Jain, K. S. Indian J Chem Sec B 1992, 31, 223–229.
[8] Matsuda, T.; Yamazaki, K.; Ide, H.; Noda, K.; Yamagata, K. Japan Kokai 74, 11, 895; Chem Abs 1974, 80, 108567f.
[9] Hiroyashi, T.; Sato, H.; Inaba, S.; Yamamoto, H. Ger Offen 2, 323, 149; Chem Abs 1974, 80, 70825y.
[10] Wiesenfeldt, M.; Etzbach, K. H.; Hofmeister, P.; Kuenast, C.; Westphalen, K. O. Eur Pat Appl EP 447, 891; Chem Abs 1991, 115, 256224y.
[11] Donkor, I. O.; Li, H.; Queener, S. F. Eur J Med Chem 2003, 38, 605–611.
[12] Shishoo, C. J.; Devani, M. B.; Pathak, U. S.; Ananthan, S.; Bhadti, V. S.; Ullas, G. V.; Jain, K. S.; Rathod, I. S.; Talati, D. S.; Doshi, N. H. J Heterocycl Chem 1984, 21, 375–380.
[13] Csuros, Z.; Soos, R.; Palinkas, J.; Bitter, I. Acta Chim (Budapest) 1971, 68, 397–402.
[14] Sauter, F. Monatsh Chem 1970, 101, 535–543.
[15] Link, H. Helv Chim Acta 1990, 73, 797–803.
[16] Davoodnia, A.; Bakavoli, M.; Barakouhi, Gh.; Tavakoli-Hoseini, N. Chin Chem Lett 2007, 18, 1483–1486.
[17] Davoodnia, A.; Behmadi, H.; Zare-Bidaki, A.; Bakavoli, M.; Tavakoli-Hoseini, N. Chin Chem Lett 2007, 18, 1163–1165.
[18] Davoodnia, A.; Eshghi, H.; Salavaty, A.; Tavakoli-Hoseini, N. J Chem Res 2008, 1, 1–2.
[19] Davoodnia, A.; Bakavoli, M.; Soleimany, M.; Tavakoli-Hoseini, N. Monatsh Chem 2009, 140, 355–358.
[20] Davoodnia, A.; Bakavoli, M.; Khorramdelan, F.; Roshani, M. Indian J Heterocycl Chem 2006, 16, 147–150.
[21] Davoodnia, A.; Rahimizadeh, M.; Rivadeh, Sh.; Bakavoli, M.; Roshani, M. Indian J Heterocycl Chem 2006, 16, 151–154.
[22] Davoodnia, A.; Roshani, M.; Malaeke, S. H.; Bakavoli, M. Chin Chem Lett 2007, 19, 525–528.
[23] Davoodnia, A.; Roshani, M.; Saleh Nadim, E.; Bakavoli, M.; Tavakoli-Hoseini, N. Chin Chem Lett 2007, 18, 1327–1330.
[24] Sauter, F.; Deinhammer, W. Monatsh Chem 1973, 104, 1586–1592.
[25] Guetschow, M. Sulfur Lett 1993, 16, 71–76.
[26] Sauter, F.; Deinhammer, W. Monatsh Chem 1973, 104, 1593–1598.