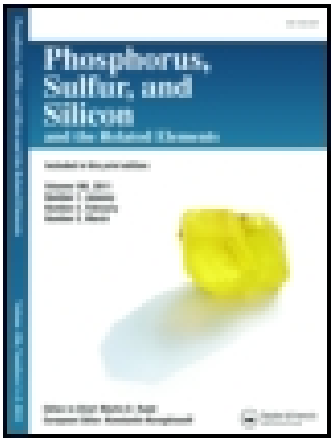


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Isolation of Intermediates in the Synthesis of Thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones Using Microwave Irradiation

A. Davoodnia [a] , A. Zare-Bidaki [a] & H. Eshghi [b]
[a] Department of Chemistry, School of Sciences , Islamic Azad University , Mashhad Branch, Mashhad, Iran
[b] Department of Chemistry, School of Sciences , Ferdowsi University of Mashhad , Mashhad, Iran
Published online: 03 Nov 2008.

To cite this article: A. Davoodnia , A. Zare-Bidaki & H. Eshghi (2008) Isolation of Intermediates in the Synthesis of Thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones Using Microwave Irradiation, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:12, 2968-2973, DOI: 10.1080/10426500802048573

To link to this article: http://dx.doi.org/10.1080/10426500802048573

Phosphorus, Sulfur, and Silicon, 183:2968–2973, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802048573

Taylor & Francis
Taylor & Francis Group

Isolation of Intermediates in the Synthesis of Thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones Using Microwave Irradiation

A. Davoodnia,[1] A. Zare-Bidaki,[1] and H. Eshghi[2]
[1]Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad Branch, Mashhad, Iran
[2]Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

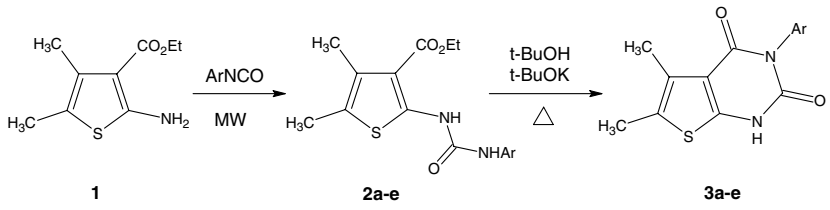
A simple and fast method for the isolation of intermediates in the synthesis of 3-arylthieno[2,3-d]pyrimidine-2,4(1H,3H)-diones has been developed by microwave-assisted condensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate with aryl isocyanates. The intermediates, subsequently, underwent cyclization in t-butanol in the presence of potassium t-butoxide on heating to reflux to give the desired bicyclic products, 3-arylthieno[2,3-d]pyrimidine-2,4(1H,3H)-diones.

Keywords Aryl isocyanates; condensation; ethyl 2-amino-4,5-dimethyl thiophene-3-carboxylate; microwave irradiation; thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones

INTRODUCTION

Our interest in thieno[2,3-d]pyrimidine synthesis emerges from the numerous reports on their diverse biological activities.[1–10] In connection with our interest in the synthesis of new heterocyclic compounds with potential biological activities,[11–18] we have recently reported a convenient one-pot synthesis of new 3-arylthieno[2,3-d]pyrimidine-2,4(1H,3H)-diones **3a–e** via cyclocondensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate **1** with aryl isocyanates in the presence of potassium t-butoxide in t-butanol under reflux.[19] Attempts to isolate the reaction intermediates **2a–e** failed when we monitored the reactions under careful observation. Due to our interest in the utilization of microwave irradiation for the synthesis of heterocyclic compounds,[20–24] we tried to extend this non-conventional synthetic

Received 23 January 2008; accepted 12 March 2008.
Address correspondence to A. Davoodnia, Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad Branch, Mashhad 91735-413, Iran. E-mail: adavoodnia@yahoo.com



SCHEME 1

method for the synthesis of 3-arylthieno[2,3-d]pyrimidine-2,4(1H,3H)-diones **3a–e**.

RESULTS AND DISCUSSION

Ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate **1**[25] was allowed to interact with aryl isocyanates under microwave irradiation in solvent-free conditions at 700 w. During monitoring of 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 **3a–e**, were forming. During work up and identification, it was established that a condensation and not a cyclocondensation reaction had occurred and the intermediates ethyl 2-[(arylcarbamoyl)amino]-4,5-dimethylthiophene-3-carboxylates **2a–e** were isolated. The reaction did not proceed to form cyclic products even after prolonged irradiation (Scheme 1).

The structure of new compounds **2a–e** were established from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **2a** showed the disappearance of a broad signal belonging to NH_2 moiety of the precursor **1** at δ 5.61 ppm and the appearance of two sharp signals for NH groups at δ 10.04 and 10.50 ppm, which was removed on deuteration, along with a multiplet at δ 6.90–7.50 ppm for phenyl protons. The IR spectrum showed the absorption bands at 3336, 3274, 1701, and 1654 cm^{-1} for two NH and two carbonyl groups respectively. The MS of **2a** showed a molecular ion peak at m/z 318 (M^+) corresponding to the molecular formula $C_{16}H_{18}N_2O_3S$. Also this compound gave satisfactory elemental analysis data (Experimental section).

When the intermediates **2a–e** were heated under reflux for 1 h in the presence of potassium t-butoxide in t-butanol, cyclization reaction

occurred, and the cyclic products **3a–e** were obtained (Scheme 1). The structure of these compounds were established by comparison with authentic samples.[19]

In conclusion, we have developed a facile method for isolation of intermediates in the synthesis of 3-arylthieno[2,3-d]pyrimidine-2,4(1H,3H)-diones using microwave assisted condensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate with aryl isocyanates.

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.

General Procedure for the Preparation of Ethyl 2-[(Arylcarbamoyl) amino]-4,5-dimethylthiophene-3-carboxylates 2a–e

A mixture of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate **1** (3 mmol) and the appropriate aryl isocyanate (4 mmol) was subjected to microwave irradiation at 700 w for 3 min. After this time, the crude product was collected, washed with n-hexane and recrystallized from ethanol to give compounds **2a–e** in 80–92% yields.

Ethyl 4,5-Dimethyl-2-[(phenylcarbamoyl)amino] thiophene-3-carboxylate (2a)

Yield 90%; M.p. 153–154°C; ^{1}H NMR (d_6-DMSO): δ 1.25 (t, 3H, J = 7Hz, CH_3), 2.10 (s, 6H, $2CH_3$), 4.22 (q, 2H, J = 7Hz, CH_2), 6.90–7.50 (m, 5H, Phenyl), 10.04 (s, 1H, NH), 10.50 (s, 1H, NH); FTIR (KBr disk): ν 3336, 3274 (two NH), 1701, 1654 cm^{-1} (two C=O); MS, *m/z*: 318 (M^+); anal. calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80; S, 10.07%. Found: C, 60.69; H, 5.47; N, 8.61; S, 10.25%.

Ethyl 4,5-Dimethyl-2-[(4-methylphenyl)carbamoyl]amino thiophene-3-carboxylate (2b)

Yield 87%; M.p. 178–180°Ñ; ^{1}H NMR (d_6-DMSO): δ 1.30 (t, 3H, J = 7Hz, CH_3), 2.15 (s, 6H, $2CH_3$), 2.23 (s, 3H, CH_3), 4.21 (q, 2H, J = 7Hz, CH_2), 7.00–7.50 (dd, 4H, arom-H), 10.08 (s, 1H, NH), 10.60 (s, 1H, NH);

FTIR (KBr disk): ν 3326, 3265 (two NH), 1695, 1656 cm^{-1} (two C=O); MS, *m/z*: 332 (M^+); anal. calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43; S, 9.65%. Found: C, 61.76; H, 6.19; N, 8.21; S, 9.46%.

Ethyl 4,5-dimethyl-2-[(3-methylphenyl)carbamoyl]amino thiophene-3- carboxylate (2c)

Yield 82%; M.p. 159–160°C; ^1H NMR (d_6-DMSO): δ 1.31 (t, 3H, J = 7Hz, CH_3), 2.18 (s, 6H, $2CH_3$), 2.27 (s, 3H, CH_3), 4.23 (q, 2H, J = 7Hz, CH_2), 6.75–7.40 (m, 4H, arom-H), 10.09 (s, 1H, NH), 10.59 (s, 1H, NH); FTIR (KBr disk): ν 3330, 3279 (two NH), 1700, 1656 cm^{-1} (two C=O); MS, *m/z*: 332 (M^+); anal. calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43; S, 9.65%. Found: C, 61.23; H, 6.14; N, 8.64; S, 9.51%.

Ethyl 2-[(3-Chlorophenyl)carbamoyl]amino-4,5-dimethylthiophene-3-carboxylate (2d)

Yield 92%; M.p. 172–174°C; ^1H NMR (d_6-DMSO): δ 1.35 (t, 3H, J = 7Hz, CH_3), 2.17 (s, 6H, $2CH_3$), 4.30 (q, 2H, J = 7Hz, CH_2), 7.00–7.80 (m, 4H, arom-H), 10.40 (s, 1H, NH), 10.65 (s, 1H, NH); FTIR (KBr disk): ν 3345, 3241 (two NH), 1698, 1657 cm^{-1} (two C=O); MS, *m/z*: 352 (M^+), 354 (M+2); anal. calcd. for $C_{16}H_{17}ClN_2O_3S$: C, 54.46; H, 4.86; N, 7.94; S, 9.09%. Found: C, 54.72; H, 4.97; N, 8.11; S, 8.89%.

Ethyl 2-[(3,4-Dichlorophenyl)carbamoyl]amino-4,5-dimethylthiophene-3-carboxylate (2e)

Yield 80%; M.p. 185–187°C; ^1H NMR (d_6-DMSO): δ 1.31 (t, 3H, J = 7Hz, CH_3), 2.18 (s, 6H, $2CH_3$), 4.23 (q, 2H, J = 7Hz, CH_2), 7.25–7.90 (m, 3H, arom-H), 10.50 (s, 1H, NH), 10.67 (s, 1H, NH); FTIR (KBr disk): ν 3340, 3255 (two NH), 1703, 1655 cm^{-1} (two C=O); MS, *m/z*: 386 (M^+), 388 (M+2), 390 (M+4); anal. calcd. for $C_{16}H_{16}Cl_2N_2O_3S$: C, 49.62; H, 4.16; N, 7.23; S, 8.28%. Found: C, 49.38; H, 4.03; N, 7.41; S, 8.46%.

General Procedure for the Preparation of 3-Aryl-5,6-dimethylthieno[2,3-d]pyrimidine-2,4 (1H,3H)-diones 3a–e

A mixture of ethyl 2-[(arylcarbamoyl)amino]-4,5-dimethylthiophene-3-carboxylates **2a–e** (1 mmol) and potassium *t*-butoxide (1 mmol) in *t*-butanol (10 mL) was heated under reflux for 1 h. After this time, the solvent was evaporated in vacuo, the residue was dissolved in water (10 mL) and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from ethanol to give compounds **3a–e** in 73, 82, 67, 71, and 66% yields respectively. Melting points, spectral

and microanalytical data of these compounds have been reported in our previous paper.[19]

REFERENCES

[1] (a) M. S. A. El-Gaby, *Phosphorus, Sulfur and Silicon.,* **156,** 157 (2000); (b) M. M. Ghorab, A. N. Osman, E. Noaman, H. I. Heiba, and N. H. Zaher,*ibid.,* **181,** 1983 (2006).

[2] (a) U. S. Pathak, S. Singh, and J. Padh, *Indian J. Chem., Sect B.*, **30** (B), 618 (1991); (b) U. S. Pathak, N. V. Gandhi, S. Singh, R. P. Warde, and K. S. Jain, *ibid.*, **31** (B), 223 (1992).

[3] I. S. Rathod, A. S. Pillai, and V. S. Shirsath, *Indian J. Heterocycl. Chem.,* **10,** 93 (2000).

[4] I. A. Kharizomenova, A. N. Grinev, N. V. Samsonova, E. K. Panisheva, N. V. Kaplina, I. S. Nikolaeva, T. V. Pushkina, and G. N. Pershin, *Khim. -Farm. Zh.,* **15,** 40 (1981).

[5] D. K. K. Showa, Jpn. Kokai. Tokkyo. Koho. 81,53,681 (1981); *Chem. Abstr.,* **95,** 115592y (1981).

[6] M. Perrissin, M. Favre, C. Luu-Duc, F. Bakri-Logeais, F. Huguet, and G. Narcisse, *Eur. J. Med. Chem - Chim. Ther.,* **19,** 420 (1984).

[7] A. K. El-Ansary and A. H. Omar, *Bull. Fac. Pharm.,* **39,** 17 (2001).

[8] T. Matsuda, K. Yamazaki, H. Ide, K. Noda, and K. Yamagata, Japan. Kokai. 74,11,895 (1974); *Chem. Abstr.,* **80,** 108567f (1974).

[9] T. Hiroyashi, H. Sato, S. Inaba, and H. Yamamoto, Ger. Offen. 2,323,149 (1973); *Chem. Abstr.,* **80,** 70825y (1974).

[10] M. Wiesenfeldt, K. H. Etzbach, P. Hofmeister, C. Kuenast, and K. O. Westphalen, Eur. Pat. Appl. EP. 447,891 (1991); *Chem. Abstr*., **115,** 256224y (1991).

[11] M. Bakavoli, A. Davoodnia, M. Rahimizadeh, and M. M. Heravi, *Phosphorus, Sulfur and Silicon.,* **177,** 2303 (2002).

[12] M. Bakavoli, A. Davoodnia, M. Rahimizadeh, M. M. Heravi, and M. Ghassemzadeh, *J. Chem. Res., Synop.,* **1,** 178 (2002).

[13] M. Roshani, A. Davoodnia, M. Sh. Hedayat, and M. Bakavoli, *Phosphorus, Sulfur and Silicon.,* **179,** 1153 (2004).

[14] A. Davoodnia, R. Zhiani, M. Roshani, M. Bakavoli, and M. Bashash, *Phosphorus, Sulfur and Silicon.,* **182,** 1219 (2007).

[15] A. Davoodnia, M. Momen-Heravi, E. Golshani, M. Bakavoli, and L. Dehabadi, *J. Chem. Res.,* **5,** 257 (2007).

[16] A. Davoodnia, M. Bakavoli, M. Bashash, M. Roshani, and R. Zhiani, *Turk. J. Chem,* **31,** 599 (2007).

[17] A. Davoodnia, M. Bakavoli, N. Pooryaghoobi, and M. Roshani, *Heterocycl. Commun.,* **13,** 323 (2007).

[18] A. Davoodnia, M. Bakavoli, Gh. Barakouhi, and N. Tavakoli-Hoseini, *Chin. Chem. Lett.,* **18,** 1483 (2007).

[19] A. Davoodnia, H. Behmadi, A. Zare-Bidaki, M. Bakavoli, and N. Tavakoli-Hoseini, *Chin. Chem. Lett.,* **18,** 1163 (2007).

[20] M. Rahimizadeh, A. Davoodnia, M. M. Heravi, and M. Bakavoli, *Phosphorus, Sulfur Silicon Relat. Elem.,* **177,** 2923 (2002).

[21] A. Davoodnia, M. Bakavoli, F. Khorramdelan, and M. Roshani, *Indian J. Heterocycl. Chem.,* **16,** 147 (2006).

[22] A. Davoodnia, M. Rahimizadeh, Sh. Rivadeh, M. Bakavoli, and M. Roshani, *Indian J. Heterocycl. Chem.,* **16,** 151 (2006).
[23] A. Davoodnia, M. Roshani, E. Saleh Nadim, M. Bakavoli, and N. Tavakoli-Hoseini.*Chin. Chem. Lett.,* **18,** 1327 (2007).
[24] A. Davoodnia, M. Roshani, S. H. Malaeke, and M. Bakavoli, *Chin. Chem. Lett.,* **19,** 525 (2008).
[25] K. Gewald, *Chem. Ber.,* **98,** 3571 (1965).