

SYNTHESIS OF SOME NEW THIENO[2,3-d]PYRIMIDIN-4-AMINE DERIVATIVES

Abolghasem Davoodnia*, Mehdi Bakavoli, Mohammad-Reza Asadi and Niloofar Tavakoli-Hoseini

Department of Chemistry, Faculty of Sciences, Islamic Azad University, Mashhad Branch, Mashhad 91735-413, Iran.

Fax: +98 511 8424020; e-mail: adavoodnia@yahoo.com, adavoodnia@mshdiau.ac.ir

Abstract: Some new thieno[2,3-d]pyrimidin-4-amines have been prepared through base-catalyzed cyclocondensation reaction of 2-amino-4,5-dimethylthiophene-3-carbonitrile with aryl nitriles.

Keywords: 2-Amino-4,5-dimethylthiophene-3-carbonitrile; Aryl nitriles; Cyclocondensation; Thieno[2,3-d]pyrimidin-4-amines.

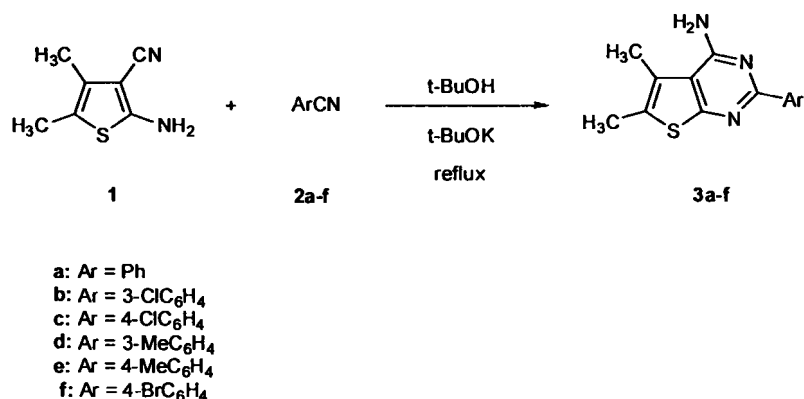
Introduction

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 antiviral⁵ and antiinflammatory⁶ activities. Also, some thieno[2,3-d] pyrimidines show CNS depressing activity⁷ and are useful as muscle relaxants,⁸ sedatives⁸ diuretics,⁹ pesticides and herbicides.¹⁰ Various methods have already been proposed for the synthesis of these compounds and the most general ones involves cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine,¹¹ α -substituted acetonitriles,¹² formic acid,¹³ phosgen,¹⁴ ethyl chloroformate¹⁴ and guanidine.¹⁵ To the best of our knowledge, cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** with aryl nitriles for the synthesis of 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** has not been reported in the literature.

Prompted by these findings and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities¹⁶⁻²⁶ and in continuation of our work on the synthesis of new thieno[2,3-d]pyrimidine derivatives,²⁷⁻²⁹ we report herein a convenient synthesis of some new 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** that might be of pharmacological importance.

Results and Discussion

Cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** with aryl nitriles **2a-f** in the presence of potassium t-butoxide in t-butanol under reflux gave products identified as 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** (Scheme 1). The structural assignments of new compounds **3a-f** were based upon the spectral and microanalytical data. For example, the IR spectrum of **3a** was devoid of the stretching vibration band at 2191 cm^{-1} for CN absorption of the precursor.³⁰ Further proof came from the ¹H NMR spectrum which showed two singlet (δ 2.45 and 2.49 ppm) for methyl groups as well as a single broad band (δ 6.08 ppm) for NH₂ protons and the appearance of characteristic signals at δ 7.4-8.5 ppm for phenyl group. The MS of **3a** showed a molecular ion peak at m/z 255 (M^+) corresponding to the molecular formula C₁₄H₁₃N₃S. Also this compound gave satisfactory elemental analysis data.



Scheme 1

In conclusion, we have developed a facile method for the synthesis of new 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amines through base catalyzed cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile with aryl nitriles.

Experimental Section

Melting points were recorded on an Stuart Model SMP3 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ¹H 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 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amines 3a-f

To a solution of the 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** (5 mmol) and potassium *t*-butoxide (5 mmol) in *t*-butanol (25 mL), aryl nitriles **2a-f** (6 mmol) was added. The reaction mixture was heated under reflux for 6.0 hours. After the completion of the reaction (monitored by TLC, CHCl₃:MeOH, 95:5), the solvent was evaporated in vacuo, the residue was dissolved in water (15 mL) and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from ethanol/water to give compounds **3a-f** in 58-70% yields.

5,6-Dimethyl-2-phenylthieno[2,3-*d*]pyrimidin-4-amine (3a)

Yield 70%; mp 188-190 °C; ¹H NMR (CDCl₃) δ (ppm) 2.45 (s, 3H, CH₃), 2.49 (s, 3H, CH₃), 6.08 (s br, 2H, NH₂), 7.4-8.5 (m, 5H, phenyl); IR (KBr disc) ν 3300, 3170 (NH₂) cm⁻¹; MS, *m/z*, M⁺ 255; Anal. Calcd for C₁₄H₁₃N₃S: C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.64; H, 5.29; N, 16.64; S, 12.42.

2-(3-Chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine (3b)

Yield 58%; mp 233-235 °C; ¹H NMR (CDCl₃) δ (ppm) 2.47 (s, 3H, CH₃), 2.49 (s, 3H, CH₃), 5.45 (s br, 2H, NH₂), 7.3-8.5 (m, 4H, arom-H); IR (KBr disc) ν 3286, 3162 (NH₂) cm⁻¹; MS, *m/z*, M⁺ 289, (M+2) 291; Anal. Calcd for C₁₄H₁₂ClN₃S: C, 58.03; H, 4.17; N, 14.50; S, 11.07. Found: C, 57.85; H, 4.03; N, 14.72; S, 10.91.

2-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine (3c)

Yield 63%; mp 219-222°C; ¹H NMR (CDCl₃) δ (ppm) 2.47 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 5.37 (s br, 2H, NH₂), 7.4-8.5 (dd, 4H, arom-H); IR (KBr disc) ν 3277, 3149 (NH₂) cm⁻¹; MS, m/z, M⁺ 289, (M+2) 291; Anal. Calcd for C₁₄H₁₂ClN₃S: C, 58.03; H, 4.17; N, 14.50; S, 11.07. Found: C, 58.17; H, 4.08; N, 14.33; S, 11.19.

5,6-Dimethyl-2-(3-methylphenyl)thieno[2,3-d]pyrimidin-4-amine (3d)

Yield 60%; mp 201-203°C; ¹H NMR (CDCl₃) δ (ppm) 2.43 (s, 6H, 2CH₃), 2.45 (s, 3H, CH₃), 5.45 (s br, 2H, NH₂), 7.3-8.3 (m, 4H, arom-H); IR (KBr disc) ν 3285, 3158 (NH₂) cm⁻¹; MS, m/z, M⁺ 269; Anal. Calcd for C₁₅H₁₅N₃S: C, 66.88; H, 5.61; N, 15.60; S, 11.90. Found: C, 66.69; H, 5.77; N, 15.86; S, 11.74.

5,6-Dimethyl-2-(4-methylphenyl)thieno[2,3-d]pyrimidin-4-amine (3e)

Yield 64%; mp 220-222°C; ¹H NMR (CDCl₃) δ (ppm) 2.38 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 5.40 (s br, 2H, NH₂), 7.3-8.4 (dd, 4H, arom-H); IR (KBr disc) ν 3282, 3157 (NH₂) cm⁻¹; MS, m/z, M⁺ 269; Anal. Calcd for C₁₅H₁₅N₃S: C, 66.88; H, 5.61; N, 15.60; S, 11.90. Found: C, 67.11; H, 5.73; N, 15.35; S, 12.01.

2-(4-Bromophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine (3f)

Yield 62%; mp 231-233°C; ¹H NMR (CDCl₃) δ (ppm) 2.43 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 5.43 (s br, 2H, NH₂), 7.5-8.4 (dd, 4H, arom-H); IR (KBr disc) ν 3280, 3149 (NH₂) cm⁻¹; MS, m/z, M⁺ 333, (M+2) 335; Anal. Calcd for C₁₄H₁₂BrN₃S: C, 50.31; H, 3.62; N, 12.57; S, 9.59. Found: C, 50.12; H, 3.77; N, 12.70; S, 9.48.

References

1. Pathak, U.S.; Singh, S.; Padh, J. *Indian. J. Chem. Sec B.*, **30B**, 618 (1991)
2. Rathod, I.S.; Pillai, A.S.; Shirsath, V.S. *Indian. J. Heterocycl. Chem.*, **10**, 93 (2000)
3. Showa Denko K.K. *Jpn. Kokai. Tokkyo. Koho.* **81 53,681**; *Chem. Abstr.*, **95**, 115592y (1981)
4. El-Gaby, M.S.A. *Phosphorus, Sulfur and Silicon.*, **156**, 157 (2000)
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.*, **15**, 40 (1981)
6. El-Ansary, A.K.; Omar, A.H. *Bulletin of the Faculty of Pharmacy (Cairo University)*, **39**, 17 (2001)
7. Pathak, U.S.; Gandhi, N.V.; Singh, S.; Warde, R.P.; Jain, K.S. *Indian. J. Chem. Sec B.*, **31B**, 223 (1992)
8. Matsuda, T.; Yamazaki, K.; Ide, H.; Noda, K.; Yamagata, K. *Japan. Kokai.* **74,11,895**; *Chem. Abstr.*, **80**, 108567f (1974)
9. Hiroyashi, T.; Sato, H.; Inaba, S.; Yamamoto, H. *Ger. Offen.* **2,323,149**; *Chem. Abstr.*, **80**, 70825y (1974)
10. Wiesenfeldt, M.; Etzbach, K. H.; Hofmeister, P.; Kuenast, C.; Westphalen, K.O. *Eur. Pat. Appl. EP.* **447,891**; *Chem. Abstr.*, **115**, 256224y (1991)
11. Donkor, I.O.; Li, H.; Queener, S.F. *Eur. J. Med. Chem.*, **38**, 605 (2003)
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.*, **21**, 375 (1984)
13. Csuros, Z.; Soos, R.; Palinkas, J.; Bitter, I. *Acta. Chim. (Budapest)*, **68**, 397 (1971)
14. Sauter, F. *Monatsh. Chem.*, **101**, 535 (1970)
15. Link, H. *Helv. Chim. Acta.*, **73**, 797 (1990)
16. Bakavoli, M.; Davoodnia, A.; Rahimizadeh, M.; Heravi M.M.; Ghassemzadeh, M. *J. Chem. Res. (S)*, **1**, 178 (2002)
17. Bakavoli, M.; Davoodnia, A.; Rahimizadeh, M.; Heravi, M.M. *Phosphorus, Sulfur, and Silicon.*, **177**, 2303 (2002)
18. Roshani, M.; Davoodnia, A.; Hedayat, M.Sh.; Bakavoli, M. *Phosphorus, Sulfur and Silicon.*, **179**, 1153 (2004)
19. Davoodnia, A.; Bakavoli, M.; Vahedinia, A.; Rahimizadeh, M.; Roshani, M. *Heterocycles.*, **68**, 801 (2006)

20. Davoodnia, A.; Zhiani, R.; Roshani, M.; Bakavoli, M.; Bashash, M. *Phosphorus, Sulfur and Silicon*, **182**, 1219 (2007)
21. Davoodnia, A.; Momen-Heravi, M.; Golshani, E.; Bakavoli, M.; Dehabadi, L. *J. Chem. Res.*, **5**, 257 (2007)
22. Davoodnia, A.; Bakavoli, M.; Bashash, M.; Roshani, M.; Zhiani, R. *Turk. J. Chem.*, **31**, 599 (2007)
23. Davoodnia, A.; Bakavoli, M.; Pooryaghoobi, N.; Roshani, M. *Heterocycl. Commun.*, **13**, 323 (2007)
24. Davoodnia, A.; Bakavoli, M.; Mohseni, Sh.; Tavakoli-Hoseini, N. *Monatsh.Chem.*, **139**, 963 (2008)
25. Davoodnia, A.; Zhiani, R.; Tavakoli-Hoseini, N. *Monatsh.Chem.*, **139**, 1405 (2008)
26. Davoodnia, A.; Roshani, M.; Saleh Nadim, E.; Bakavoli, M.; Tavakoli-Hoseini, N. *Chin. Chem. Lett.*, **18**, 1327 (2007)
27. Davoodnia, A.; Bakavoli, M.; Barakouhi, Gh.; Tavakoli-Hoseini, N. *Chin. Chem. Lett.*, **18**, 1483 (2007)
28. Davoodnia, A.; Behmadi, H.; Zare-Bidaki, A.; Bakavoli, M.; Tavakoli-Hoseini, N. *Chin. Chem. Lett.*, **18**, 1163 (2007)
29. Davoodnia, A.; Eshghi, H.; Salavaty, A.; Tavakoli-Hoseini, N. *J. Chem. Res.* **1**, 1 (2008)
30. Gewald, K.; Schinke, E.; Bottcher, H. *Chem. Ber.*, **99**, 94 (1966)

Received on January 20,2009.