Available online at www.sciencedirect.com

SciVerse ScienceDirect

Chinese Chemical Letters 23 (2012) 549–552

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

Facile synthesis of novel fluorinated thieno[2,3-*d*]pyrimidine derivatives containing 1,3,4-thiadiazole

Xin Jian Song [a,*], Zheng Chao Duan [a], Yu Shao [a], Xing Gao Dong [b]

[a] *Key Laboratory of Biological Resources Protection and Utilization of Hubei Province, Hubei University for Nationalities, Enshi 445000, China*
[b] *Medical School, Hubei University for Nationalities, Enshi 445000, China*

Received 8 December 2011
Available online 29 March 2012

Abstract

A series of novel fluorinated thieno[2,3-*d*]pyrimidine derivatives incorporating 1,3,4-thiadiazole were synthesized by a facile microwave-assisted procedure, including the cyclization of 2-aminothiophene-3-carbonitrile with trifluoroacetic acid, chlorination and nucleophilic substitution reaction. This protocol offered such advantages as mild reaction conditions, short reaction time, simple purification and good yields. The structures of the products were characterized by ^{1}H NMR, MS, elemental analysis and X-ray diffraction.

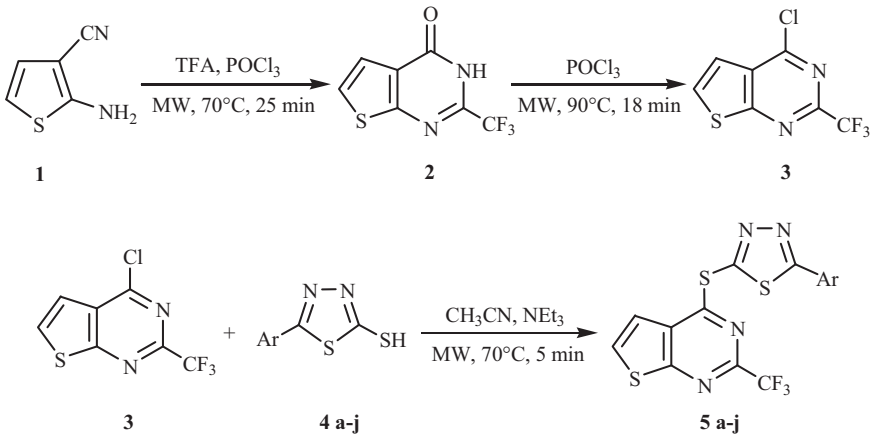
Keywords: Thieno[2,3-*d*]pyrimidine; 1,3,4-Thiadiazole; Trifluoromethyl; Microwave-assisted synthesis

Thieno[2,3-*d*]pyrimidines have attracted great attention from both synthetic and medicinal chemists due to a multitude of interesting pharmacological properties [1–4] such as antibacterial, antitumor and anti-inflammatory activities. 1,3,4-Thiadiazoles and their derivatives represent an important class of compounds possessing broad biological activities [5–7], especially anticancer properties [8–10]. In general, strategically positioned fluorine substituents, the trifluoromethyl group in particular, in heterocyclic compounds play a fundamental role in medicine and agrochemicals because of their enhanced activities and decreased toxicities [11,12]. In addition, microwave (MW) irradiation technique is well known to present the advantages of being efficient, rapid and eco-friendly compared with the traditional heating methods [13]. These observations prompted us to pursue the synthesis of some novel trifluoromethylthieno[2,3-*d*]pyrimidine derivatives incorporating 1,3,4-thiadiazole moiety under MW irradiation for evaluating their antitumor activity. The title compounds **5a–j** were prepared using the synthetic strategy outlined in Scheme 1.

The synthesis began by reacting accessible 2,5-dihydroxy-1,4-dithiane with malonitrile to deliver 2-aminothio-phene-3-carbonitrile **1** according to the modified Gewald procedures [14]. The aminothiophene **1** was then refluxed with trifluoroacetic acid (TFA) in the presence of phosphorus oxychloride to provide the key intermediate **2** under microwave heating. It is worth mentioning that 2-trifluoromethyl-3*H*-thieno[2,3-*d*]-pyrimidin-4-one **2** was obtained efficiently by a facile microwave-assisted one-pot procedure. However, the traditional conversion to 2-substituted-3*H*-thieno

* Corresponding author.
E-mail address: whxjsong@yahoo.com.cn (X.J. Song).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2012.02.007



Scheme 1. Synthetic route of the title compounds **5a–j**.

[2,3-*d*]pyrimidin-4-ones usually utilize multi-step procedures [15–17] which suffer from such disadvantages as rigorous conditions, long reaction time, complex handling and poor total yields. Compound **2** was transformed by the action of phosphorus oxychloride into 4-chlorothieno[2,3-*d*]pyrimidine **3** that was readily reacted with 1,3,4-thiadiazole-2-thiols **4a–j** [18] under MW irradiation to afford the desired products **5a–j** in good isolated yields (82–91%), as shown in Table 1. The overall three-step synthesis including cyclization, chlorination and nucleophilic substitution reaction involved MW irradiation which made the procedure rapid and efficient.

The structures of the newly synthesized compounds **5a–j** [19] were confirmed by ^{1}H NMR, mass spectroscopy and elemental analysis. The ^{1}H NMR spectra of **5** showed the thienyl protons emerged normally as a pair of doublets, each appearing near δ 8.42 and 7.90 with J = 6.0 Hz. However, their signals from one of the two protons in some products were indecipherable because they overlapped with aryl hydrogens. The EI mass spectra gave the anticipated molecular ion peaks and main fragmentation peaks, which were in accordance with the title structures. The structure of product **5g** was further proved by the X-ray diffraction.

A colorless single crystal of compound **5g** with dimensions of 0.34 mm × 0.28 mm × 0.23 mm was put on a BRUKER SMART APEX-CCD diffractometer equipped with a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation at 293(2) K. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were added according to theoretical models. The structure was refined by full-matrix least-squares method on F^2 with SHELXL-97. The molecular structure of compound **5g** is depicted in Fig. 1. The X-ray analysis revealed that the molecule of the title compound **5g** essentially assumes a planar conformation except for the F atoms and methyl H atoms. The pharmacological evaluation and structure–activity relationships of the title compounds are underway.

Table 1
Physical and MS data for the title compounds **5a–j**.

Entry	Compd.	Ar	Formula	m.p./°C	Yield/%	Appearance	EI-MS (*m/z*, M^+)
1	**5a**	C_6H_5	$C_{15}H_7F_3N_4S_3$	196–197	87	White crystal	396
2	**5b**	2-FC_6H_4	$C_{15}H_6F_4N_4S_3$	206–207	84	White crystal	414
3	**5c**	3-FC_6H_4	$C_{15}H_6F_4N_4S_3$	198–199	86	White crystal	414
4	**5d**	4-FC_6H_4	$C_{15}H_6F_4N_4S_3$	209–210	91	White crystal	414
5	**5e**	2-$CH_3C_6H_4$	$C_{16}H_9F_3N_4S_3$	161–162	83	White crystal	410
6	**5f**	3-$CH_3C_6H_4$	$C_{16}H_9F_3N_4S_3$	204–205	84	White crystal	410
7	**5g**	4-$CH_3C_6H_4$	$C_{16}H_9F_3N_4S_3$	218–219	88	White crystal	410
8	**5h**	2-$NO_2C_6H_4$	$C_{15}H_6F_3N_5O_2S_3$	183–184	82	Yellowish crystal	441
9	**5i**	3-$NO_2C_6H_4$	$C_{15}H_6F_3N_5O_2S_3$	224–225	83	Yellowish crystal	441
10	**5j**	4-$NO_2C_6H_4$	$C_{15}H_6F_3N_5O_2S_3$	219–220	85	Yellowish crystal	441

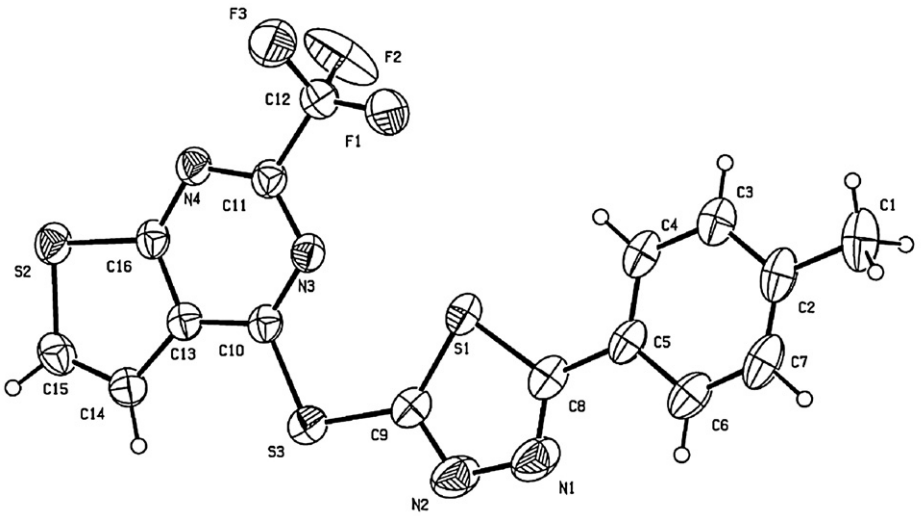


Fig. 1. Molecular structure of **5g** with the atomic labeling.

Acknowledgments

We are grateful for the Natural Science Foundation of Hubei Province (No. 2011CDB087), Scientific Research Fund of Hubei Provincial Education Department (No. D20111904) and Open Fund of Key Laboratory of Biological Resources Protection and Utilization of Hubei Province (No. PKLHB1102) for generous financial support.

References

[1] C.H. Wu, M.S. Coumar, C.Y. Chu, et al. J. Med. Chem. 53 (2010) 7316.
[2] A.G. Golub, V.G. Bdzhola, N.V. Briukhovetska, et al. Eur. J. Med. Chem. 46 (2011) 870.
[3] H.N. Hafez, A.B.A. EI-Gazzar, Bioorg. Med. Chem. Lett. 18 (2008) 5222.
[4] V. Alagarsamy, S. Meena, K.V. Ramseshu, et al. Eur. J. Med. Chem. 41 (2006) 1293.
[5] A.A. Kadi, E.S. Al-Abdullah, I.A. Shehata, et al. Eur. J. Med. Chem. 45 (2010) 5006.
[6] X.J. Song, F.S. Wang, S.R. Li, et al. Chin. J. Org. Chem. 31 (2011) 572.
[7] H. Rajak, C.K. Behera, R.S. Pawar, et al. Chin. Chem. Lett. 21 (2010) 1149.
[8] W. Rzeski, J. Matysiak, M. Kandefer-Szerszen, Bioorg. Med. Chem. 15 (2007) 3201.
[9] X.J. Song, Y. Shao, X.G. Dong, Chin. Chem. Lett. 22 (2011) 1036.
[10] X.J. Zou, Y. Liu, Z.M. Liu, et al. Chin. J. Org. Chem. 31 (2011) 1923.
[11] Y. Sugimoto, K. Konoki, M. Murata, et al. J. Med. Chem. 52 (2009) 798.
[12] D.J. Wang, L. Fan, C.Y. Zheng, et al. J. Fluorine Chem. 131 (2010) 584.
[13] C.O. Keppe, Angew. Chem. Int. Ed. 43 (2004) 6250.
[14] S. Hesse, E. Perspicace, G. Kirsch, Tetrahedron Lett. 48 (2007) 5261.
[15] T. Horiuchi, J. Chiba, K. Uoto, et al. Bioorg. Med. Chem. Lett. 19 (2009) 305.
[16] R.J. Gillespie, D.R. Adams, D. Bebbington, et al. Bioorg. Med. Chem. Lett. 18 (2008) 2916.
[17] R.M. Mohareb, S.M. Sherif, H.M. Gaber, et al. Heteroat. Chem. 14 (2003) 459.
[18] A. Saha, R. Kumar, R. Kumar, et al. J. Heterocycl. Chem. 47 (2010) 838.
[19] General procedure for the synthesis of the title compounds (**5a–j**): a mixture of 2-aminothiophene-3-carbonitrile **1** (10 mmol), trifluoroacetic acid (28 mL) and phosphorus oxychloride (2 mL) was irradiated at 70 °C for 25 min by microwave. The reaction mixture was allowed to cool to room temperature, and then poured into ice water. The resulting precipitate was filtered, washed with cold water, and dried to give 2-trifluoromethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one **2** in 81% yield. A mixture of **2** (10 mmol) and phosphorus oxychloride (8 mL) was irradiated with microwave at 90 °C for 18 min. Thereafter, $POCl_3$ was removed under vacuum and the residue obtained was poured onto ice-cold water and neutralized with sodium bicarbonate. The solid was filtrated and recrystallized from *n*-hexane to afford 4-chloro-2-trifluoromethylthieno[2,3-*d*]-pyrimidine **3** in 73% yield as yellowish solid. m.p. 77–78 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.41 (d, 1H, J = 6.0 Hz, Thienyl H), 7.77 (d, 1H, J = 6.0 Hz, Thienyl H); EI-MS (%): m/z 238 (M^+, 100), 203 (68.3), 134 (25.0), 69 (66.8). A solution of **3** (5 mmol) and the appropriate 1,3,4-thiadiazole-2-thiol **4** (5 mmol), triethylamine (0.5 mL) in dried acetonitrile (15 mL) was submitted to microwave irradiation for 5 min at 70 °C. The reaction mixture was concentrated under reduced pressure and the solid was filtered off, washed

with water and recrystallized from ethanol-DMF to give compounds **5a–j**. Analytical data of the representative compounds: **5a**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.42 (d, 1H, J = 6.0 Hz, Thienyl H), 7.90 (d, 1H, J = 6.0 Hz, Thienyl H), 8.02–7.62 (m, 5H, Ar-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.64, 166.96, 159.13, 155.98, 149.05, 148.77, 134.47, 132.35, 130.16, 129.43, 129.03, 128.06, 119.49; Anal. Calcd. for $C_{15}H_7F_3N_4S_3$: C 45.45, H 1.78, N 14.13; found: C 45.23, H 1.90, N 14.29. **5b**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.42 (d, 1H, J = 6.0 Hz, Thienyl H), 7.92 (d, 1H, J = 6.0 Hz, Thienyl H), 8.36–7.47 (m, 4H, Ar-H); Anal. Calcd. for $C_{15}H_6F_4N_4S_3$: C 43.47, H 1.46, N 13.52; found: C 43.58, H 1.32, N 13.37. **5f**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.42 (d, 1H, J = 6.0 Hz, Thienyl H), 7.91 (d, 1H, J = 6.0 Hz, Thienyl H), 7.86–7.45 (m, 4H, Ar-H), 2.44 (s, 3H, CH_3); Anal. Calcd. for $C_{16}H_9F_3N_4S_3$: C 46.82, H 2.21, N 13.65; found: C 47.03, H 2.09, N 13.53. **5g**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.42 (d, 1H, J = 6.0 Hz, Thienyl H), 7.93–7.43 (m, 5H, Ar-H and Thienyl H), 2.41 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.88, 167.01, 159.56, 155.47, 149.15, 148.80, 142.61, 134.49, 130.71, 129.08, 128.04, 126.73, 119.53, 21.54; Anal. Calcd. for $C_{16}H_9F_3N_4S_3$: C 46.82, H 2.21, N 13.65; found: C 46.94, H 2.07, N 13.82.