Microwave-assisted solvent-free synthesis of 3-alkyl-6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

Xin-Ping Hui*, Ren-Lin Wang and Zi-Yi Zhang

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730 000, P.R. China

An efficient microwave-assisted solvent-free synthesis of 3-alkyl-6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives is reported. Twelve derivatives have been synthesised in excellent yields in short reaction times.

Keywords: microwave heating, solvent-free synthesis, fused 1,2,4-triazoles, fused 1,3,4-thiadiazines

[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazine derivatives have received extensive attention in recent years because of their diverse biological activities, including analgesic, anti-inflammatory, antibacterial and antiviral activities.[1-8] Although the condensation of 4-amino-5-substituted-1,2,4-triazol-3(2*H*)-thiones with 2-halogencarbonyl compounds has been carried out in solution, this cyclisation affords different products under various reaction conditions. There are also some problems associated with above synthesis, such as severe conditions, long time and low to moderate yields for the reaction, difficulty in separating the products from the system, and serious environmental pollution.

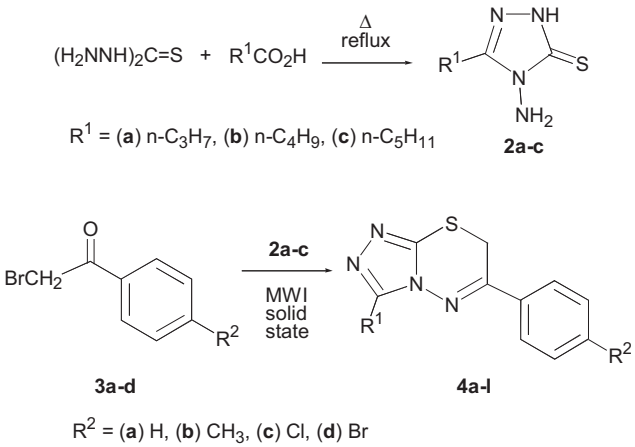
In recent years, microwave-induced rate acceleration technology has become a powerful tool in organic synthesis[9-12] in view of the mild, clean, and convenient methodology and the enhanced selectivity of the reaction processes in comparison to conventional solution reactions, and the associated ease of manipulation. Solvent-free synthesis has many advantages including high efficiency and selectivity, easy separation and purification and environmental acceptability.[13] One particularly attractive field is the coupling of microwave irradiation with solvent-free synthesis, since it reduces the risks of hazards by pressure build-up in the reaction vessel, and scale-up is made easier. This method has been widely used in organic synthesis.[14] However, the microwave-assisted synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine derivatives under solvent-free conditions has not so far been reported. We now report the efficient condensation reaction of 5-alkyl-4-amino-1,2,4-triazole-3(2*H*)-thiones with 2-bromo-4′-substituted acetophenones.

The target compounds **4a–l** were prepared by irradiating a mixture of 5-alkyl-4-amino-1,2,4-triazole-3(2*H*)-thiones (**2a–c**) and 2-bromo-4′-substituted acetophenones (**3a–d**) in a microwave oven under solvent-free conditions. The results are presented in the Experimental section. From this it is evident that the reactions proceed well; reaction times are short and yields are high.

The products were characterised by their elemental analysis and spectral data. The IR spectra showed three characteristic absorption bands at 1583–1609 cm^{-1} (C=N), 1224–1266 cm^{-1} (N–N=C) and 658–691 cm^{-1} (C–S–C), respectively. In the ^1H NMR spectra, SCH_2 protons exhibited signals at around δ 4 ppm. The signal of SCH_2 accorded with those of the compounds synthesised by Eweiss.[15] Their mass spectra exhibited the expected molecular peaks.

In conclusion, we have developed an efficient microwave-assisted solvent-free synthesis of 3-alkyl-6-aryl[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine derivatives. The advantages of the reaction are high yields (82–91%), short working time (1 min) and easy purification. This procedure also avoids the usage of organic solvent.

* Correspondent. E-mail address: huixp@lzu.edu.cn



Scheme 1

Experimental

The melting points were determined on an X-4 microscopic melting point apparatus. Elemental analyses were carried out using an Elementar Vario EL analyser. IR spectra were obtained in KBr discs on a 5-DX spectrometer. ^1H NMR spectra were recorded in DMSO-d_6 on a Mercury-Plus 300 instrument with TMS as an internal standard. MS were measured on a VG-7070E spectrometer (EI at 70 eV). The microwave oven was a domestic model (LG WD700).

Thiocarbohydrazide[16] (**1**) and 5-alkyl-4-amino-1,2,4-triazol-3(2*H*)-thiones[17] (**2a–c**) were prepared according to the literature methods. Thiocarbohydrazide (**1**), m.p. 169–171°C (lit.[16] m.p. 171°C). 4-Amino-5-propyl-1,2,4-triazol-3(2*H*)-thione (**2a**), yield 50%, m.p. 104–105°C (lit.[17] m.p. 103–104°C). 4-Amino-5-butyl-1,2,4-triazol-3(2*H*)-thione (**2b**), yield 62%, m.p. 96–97°C (lit.[17] m.p. 95–97°C). 4-Amino-5-pentyl-1,2,4-triazol-3(2*H*)-thione (**2c**), yield 64%, m.p. 108–109°C (lit.[17] m.p. 106–108°C).

3-Alkyl-6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (**4a–l**): *general procedure*

The requisite 5-alkyl-4-amino-1,2,4-triazol-3(2*H*)-thione (**2**) (5 mmol) and 2-bromo-4′-substituted acetophenone (**3**) (5 mmol) were mixed and heated under microwave irradiation at 750W for 1 minute. The reaction mixture was cooled and ground with water (50 ml). The solid product was filtered off, washed with water, and recrystallised from ethanol.

6-Phenyl-3-propyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4a**), Yellow powder (yield 87%), m.p. 152–153°C (lit.[18] m.p. 155°C).

6-(4-Methylphenyl)-3-propyl[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine (**4b**): Yellow powder (yield 84%), m.p. 174–176°C (lit.[15] m.p. 170°C). IR: 3036 (w, ArH), 2960, 2931 (w, CH_3, CH_2), 1610 (m, C=N), 1533 cm^{-1} (m, C–N). ^1H NMR: δ 1.06 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2$), 1.61–2.08 (m, 2H, $CH_3CH_2CH_2$), 2.46 (s, 3H, CH_3), 2.93 (t, J = 7.2 Hz, 2H, $CH_3CH_2CH_2$), 3.96 (s, 2H, SCH_2), 7.46 (d, J = 8.8 Hz, 2H, ArH), 7.78 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 272 (M^+, 20), 244 (100), 204 (11), 155 (12), 140 (17), 127 (87), 117 (17), 91 (33).

6-(4-Chlorophenyl)-3-propyl[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine (**4c**): Yellow needles (yield 91%), m.p. 186–187°C (lit.[18] m.p. 183°C). IR: 3063 (w, ArH), 2958, 2922 (w, CH_3, CH_2), 1588 (m, C=N), 1526 cm^{-1} (m, C–N). ^1H NMR: δ 1.06 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2$), 1.66–2.12 (m, 2H, $CH_3CH_2CH_2$), 2.97 (t, J = 7.2 Hz,

2H, $CH_3CH_2CH_2$), 3.99 (s, 2H, SCH_2), 7.52 (d, J = 8.8 Hz, 2H, ArH), 7.87 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 294 (2), 292 (5.4) (M^+), 264 (54), 137 (23), 127 (100), 111 (25), 101 (45), 84 (46).

6-(4-Bromophenyl)-3-propyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4d**): Yellow powder (yield 88%), m.p. 191–192°C (lit.[18] m.p. 185°C). IR: 3059 (w, ArH), 2957, 2922 (w, CH_3, CH_2), 1583 (m, C=N), 1526 cm^{-1} (m, C–N); ^1H NMR: δ 1.06 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2$), 1.68–2.10 (m, 2H, $CH_3CH_2CH_2$), 2.95 (t, J = 7.2 Hz, 2H, $CH_3CH_2CH_2$), 4.00 (s, 2H, SCH_2), 7.48 (d, J = 8.8 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 338 (11), 336 (11) (M^+), 308 (96), 257 (10), 155 (23), 127 (94), 102 (51), 84 (29).

3-Butyl-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4e**): Yellow powder (Yield 85%), m.p. 112–113°C. IR: 3045 (w, ArH), 2965, 2933 (w, CH_3, CH_2), 1599 (m, C=N), 1527 cm^{-1} (m, C–N). ^1H NMR: δ 1.00 (t, J = 7.2 Hz, 3H, $CH_3(CH_2)_2CH_2$), 1.12–2.10 (m, 4H, $CH_3(CH_2)_2CH_2$), 2.98 (t, J = 7.2 Hz, 2H, $CH_3(CH_2)_2CH_2$), 4.06 (s, 2H, SCH_2), 7.67 (s, 5H, ArH). EI-MS: *m/z* 272 (M^+, 7), 243 (21), 230 (100), 169 (8), 140 (13), 127 (28), 103 (6), 77 (8). Anal. calcd. for $C_{14}H_{16}N_4S$: C, 61.74; H, 5.92; N, 20.57. Found C, 61.77; H, 5.88; N, 20.51%.

3-Butyl-6-(4-methylphenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4f**): Yellowish pellets (yield 84%), m.p. 143–145°C. IR: 3038 (w, ArH), 2955, 2930 (w, CH_3, CH_2), 1594 (m, C=N), 1530 cm^{-1} (m, C–N). ^1H NMR: δ 1.00 (t, J = 7.2 Hz, 3H, $CH_3(CH_2)_2CH_2$), 1.12–2.12 (m, 4H, $CH_3(CH_2)_2CH_2$), 2.37 (s, 3H, CH_3), 2.97 (t, J = 7.2 Hz, 2H, $CH_3(CH_2)_2CH_2$), 4.03 (s, 2H, SCH_2), 7.67 (d, J = 8.8 Hz, 2H, ArH), 7.82 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 286 (M^+, 14), 257 (21), 244 (100), 204 (9), 140 (30), 127 (81), 117 (14), 91 (33). Anal. calcd. for $C_{15}H_{18}N_4S$: C, 62.91; H, 6.33; N, 19.56. Found C, 62.81; H, 6.23; N, 19.50%.

3-Butyl-6-(4-chlorophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4g**): Yellow powder (yield 90%), m.p. 147–148°C. IR: 3041 (w, ArH), 2956, 2929 (w, CH_3, CH_2), 1590 (m, C=N), 1525 cm^{-1} (m, C–N). ^1H NMR: δ 1.00 (t, J = 7.2 Hz, 3H, $CH_3(CH_2)_2CH_2$), 1.10–2.12 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.00 (t, J = 7.2 Hz, 2H, $CH_3(CH_2)_2CH_2$), 4.00 (s, 2H, SCH_2), 7.45 (d, J = 8.8 Hz, 2H, ArH), 7.72 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 308 (2), 306 (5.4) (M^+), 278 (25), 264 (57), 127 (100), 111 (25), 101 (52), 75 (50). Anal. calcd. for $C_{14}H_{15}ClN_4S$: C, 54.81; H, 4.93; N, 18.26. Found C, 54.62; H, 4.81; N, 18.12%.

6-(4-Bromophenyl)-3-butyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4h**): Yellow powder (yield 87%), m.p. 165–166°C. IR: 3060 (w, ArH), 2959, 2932 (w, CH_3, CH_2), 1584 (m, C=N), 1522 cm^{-1} (m, C–N). ^1H NMR: δ 1.00 (t, J = 7.2 Hz, 3H, $CH_3(CH_2)_2CH_2$), 1.12–2.14 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.01 (t, J = 7.2 Hz, 2H, $CH_3(CH_2)_2CH_2$), 4.02 (s, 2H, SCH_2), 7.60 (d, J = 8.8 Hz, 2H, ArH), 7.76 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 352 (2), 350 (1.4) (M^+), 308 (15), 183 (11), 155 (13), 140 (30), 127 (91), 102 (65). Anal. calcd. for $C_{14}H_{15}BrN_4S$: C, 47.87; H, 4.30; N, 15.95. Found C, 47.80; H, 4.41; N, 15.79%.

3-Pentyl-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4i**): Yellow powder (yield 86%), m.p. 115–116°C (lit.[19] m.p. 115°C). IR: 3065 (w, ArH), 2954, 2930 (w, CH_3, CH_2), 1593 (m, C=N), 1533 cm^{-1} (m, C–N). ^1H NMR: δ 0.92 (t, J = 6.3 Hz, 3H, CH_3), 1.19–1.56 (m, 4H, $CH_3(CH_2)_2CH_2CH_2$), 1.70–1.96 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$), 3.04 (t, J = 7.5 Hz, 2H, $CH_3(CH_2)_3CH_2$), 4.00 (s, 2H, SCH_2), 7.58 (s, 5H, ArH). EI-MS: *m/z* 286 (M^+, 6), 257 (27), 230 (86), 169 (8), 140 (16), 127 (100), 103 (16), 77 (87).

6-(4-Methylphenyl)-3-pentyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4j**): Yellow powder (yield 82%), m.p. 106–107°C. IR: 3050 (w, ArH), 2961, 2924 (w, CH_3, CH_2), 1588 (m, C=N), 1523 cm^{-1} (m, C–N). ^1H NMR: δ 0.92 (t, J = 6.3 Hz, 3H, CH_3), 1.19–1.56 (m, 4H, $CH_3(CH_2)_2CH_2CH_2$), 1.70–1.96 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$), 2.47 (s, 3H, $ArCH_3$), 2.99 (t, J = 7.5 Hz, 2H, $CH_3(CH_2)_3CH_2$), 3.97 (s, 2H, SCH_2), 7.34 (d, J = 8.8 Hz, 2H, ArH), 7.81 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 300 (M^+, 21), 272 (28), 257 (70), 244 (100), 140 (58), 127 (67), 117 (16), 91 (41). Anal. calcd. for $C_{16}H_{20}N_4S$: C, 63.97; H, 6.71; N, 18.65. Found C, 64.06; H, 6.60; N, 18.52%.

6-(4-Chlorophenyl)-3-pentyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4k**): Yellow powder (yield 90%). m.p. 171–172°C (lit.[19] m.p. 175°C). IR: 3098 (w, ArH), 2957, 2925 (w, CH_3, CH_2), 1589 (m, C=N), 1532 cm^{-1} (m, C–N). ^1H NMR: δ 0.92 (t, J = 6.3 Hz, 3H, CH_3), 1.18–1.54 (m, 4H, $CH_3(CH_2)_2CH_2CH_2$), 1.74–1.97 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$), 3.03 (t, J = 7.5 Hz, 2H, $CH_3(CH_2)_3CH_2$), 4.02 (s, 2H, SCH_2), 7.42 (d, J = 8.8 Hz, 2H, ArH), 7.84 (d, J = 8.8 Hz, 2H, ArH). EI-MS: *m/z* 322 (2), 320 (5.3) (M^+), 264 (61), 154 (24), 140 (100), 127 (74), 101 (50), 84 (75).

6-(4-Bromophenyl)-3-pentyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**4l**): Yellow powder (yield 86%), m.p. 177–178°C (lit.[19] m.p. 182°C).

We are grateful for financial support from the National Natural Science Foundation of China (No. 20 021 001) and the Natural Science Foundation of Gansu Province (3ZS051-A25-005).

Received 30 August 2006; accepted 20 December 2006
Paper 06/4162 doi:10.3184/030823407X198203

References

1 A.R. Prasad, T. Ramalingam, A.B. Rao, P.V. Diwan and P.B. Sattur, *Eur. J. Med. Chem.*, 1989, **24**, 199.
2 G. Turan-Zitouni, Z.A. Kaplancikli, K. Erol and F.S. Kilic, *Il Farmaco*, 1999, **54**, 218.
3 B.S. Holla, B. Kalluraya, K.R. Sridhar, E. Drake, L.M. Thomas, K.K. Bhandary and M.J. Levine, *Eur. J. Med. Chem.*, 1994, **29**, 301.
4 B.S. Holla, P.M. Akberali and M.K. Shivananda, *Il Farmaco*, 2001, **56**, 919.
5 B.S. Holla, B.S. Rao, B.K. Sarojini, P.M. Akberali and N.S. Kumari, *Eur. J. Med. Chem.*, 2006, **41**, 657.
6 S.A. Khanum, S. Shashikanth, S. Umesha and R. Kavitha, *Eur. J. Med. Chem.*, 2005, **40**, 1156.
7 M.R. Shaaban and T. Fuchigami, *Tetrahedron Lett.*, 2002, **43**, 273.
8 P. Vainilavicius, R. Smicius, V. Jakubkiene and S. Tumkevicius, *Monatsh. Chem.*, 2001, **132**, 825.
9 S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
10 M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, 2002**,** **35**, 717.
11 C.O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250.
12 B.L. Hayes, *Aldrichimica Acta*, 2004, **37**, 66.
13 G.R. Desiraju, *Organic Solid State Chemistry*, Elsevier, Amsterdam, 1987, 179.
14 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathé, *Synthesis*, 1998, 1213.
15 N.F. Eweiss and A.A. Bahajaj, *J. Heterocyclic Chem.*, 1987, **24**, 1173.
16 F. Audrieth, E.S. Scott and P.S. Kippur, *J. Org. Chem.*, 1954, **19**, 533.
17 Z.-Y. Zhang, L. Zhao, M. Li, Z.-M. Li and R.-A. Liao, *Chin. J. Org. Chem.*, 1994, **14**, 74.
18 K.S. Dhaka, J. Mohan, V.K. Chadha and H.K. Pujari, *Indian J. Chem.*, 1974, **12**, 287.
19 J. Mohan, *Indian J. Chem.*, 1983, **22B**, 270.