Synthesis of new Schiff bases derived from dimers of 4-amino-3-(1-naphthyl)-5-thiomethyl-1, 2, 4- triazole using microwave irradiation

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An efficient method for the synthesis of novel Schiff bases derived from dimers of 4-amino-3-(1-naphthyl)-5-thiomethyl-1, 2, 4-triazole using microwave irradiation has been developed. Its distinct advantages are short reaction times, good conversions and eco-friendly to methodology. The structures of these new Schiff bases were established by ^{1}H NMR, IR, MS spectra and elemental analysis.

Keywords: Schiff base, 1, 2, 4-triazole, microwave irradiation

Triazole derivatives and Schiff base compounds have attracted wide attentions in the light of their biological activity. Jantova *et al.*[1,2] reported that triazole derivatives can inhibit tumor proliferation, induce tumor cell differentiation and apoptosis; Qiang *et al*.[3–5] found that triazole derivatives could be used as fungicides with the efficient absorption and low toxicity. It was also reported that triazole derivatives exhibit many other activities such as plant growth regulation[6], anti-viral[7], anti-fungal[8] and anti-TB[9] effects. Schiff bases were also reported to possess antibacterial[10,11], anti-tumor[12] and antiviral[13] effects. Moreover, triazole sulfides have good antibacterial activity.[14] Based on these results and the principle of active superposition, we connected two sulfhydryl triazole Schiff bases by using 1,2 -dibromoethane and obtained a series of dimeric triazole Schiff bases. We anticipated that these new triazole Schiff bases might have a useful biological activity.

Green chemistry is an important part of modern organic chemistry. Microwave synthesis as an important technique in green chemistry has been widely applied in organic synthesis in recent years.[15–17] Recently, we reported our efforts in the pharmaceutical synthesis using microwave methods.[18,19] As a continuation of this work, we now report the synthesis of novel Schiff bases containing triazole units under microwave irradiation. The synthetic route is shown in Scheme 1.

Results and discussion

The structures of **7a**–**j** were established on the basis of their spectroscopic data and elemental analysis. The IR spectra of **6** showed absorption bands at 3328–3167 cm^{-1} due to the NH_2 group, which were absent in the IR spectra of **7a**–**j**. There were strong bands at 1626–1610 cm^{-1} assigned to the absorption of C=N. The ^{1}H NMR spectra of **6** showed a singlet at 6.00 ppm attributed to the NH_2 group which was not present in the spectra of compounds **7a**–**j**. The singlet at 8.75–8.36 ppm was assigned to the ArCHN. The protons of the ArH appeared at 8.37–6.64 ppm. The singlet at about 3.75 ppm was assigned to SCH_2CH_2S. Their ESI-MS spectra showed the expected molecular ions with high intensity.

The comparison of microwave irradiation and conventional heating

As shown in Table 1, Compared to conventional method, microwave method greatly decreased the reaction time from 1440 to 1800 min to 3–4 min and the yields were increased from 47–65% to 81–94%. The microwave-enhanced procedure is a rapid, efficient and green synthetic method for Schiff base compounds containing triazole. The details of biological activities of compounds **7a–j** are under investigation.

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Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were determined on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyzer. All reactions were performed in a commercial microwave reactor (XH-100A, 100-1000 W, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, P.R. China). All the solvents were purified before use. Intermediates **2**, **3**, **4, 5** were prepared following a reported procedure.[20]

Preparation of intermediate **6**

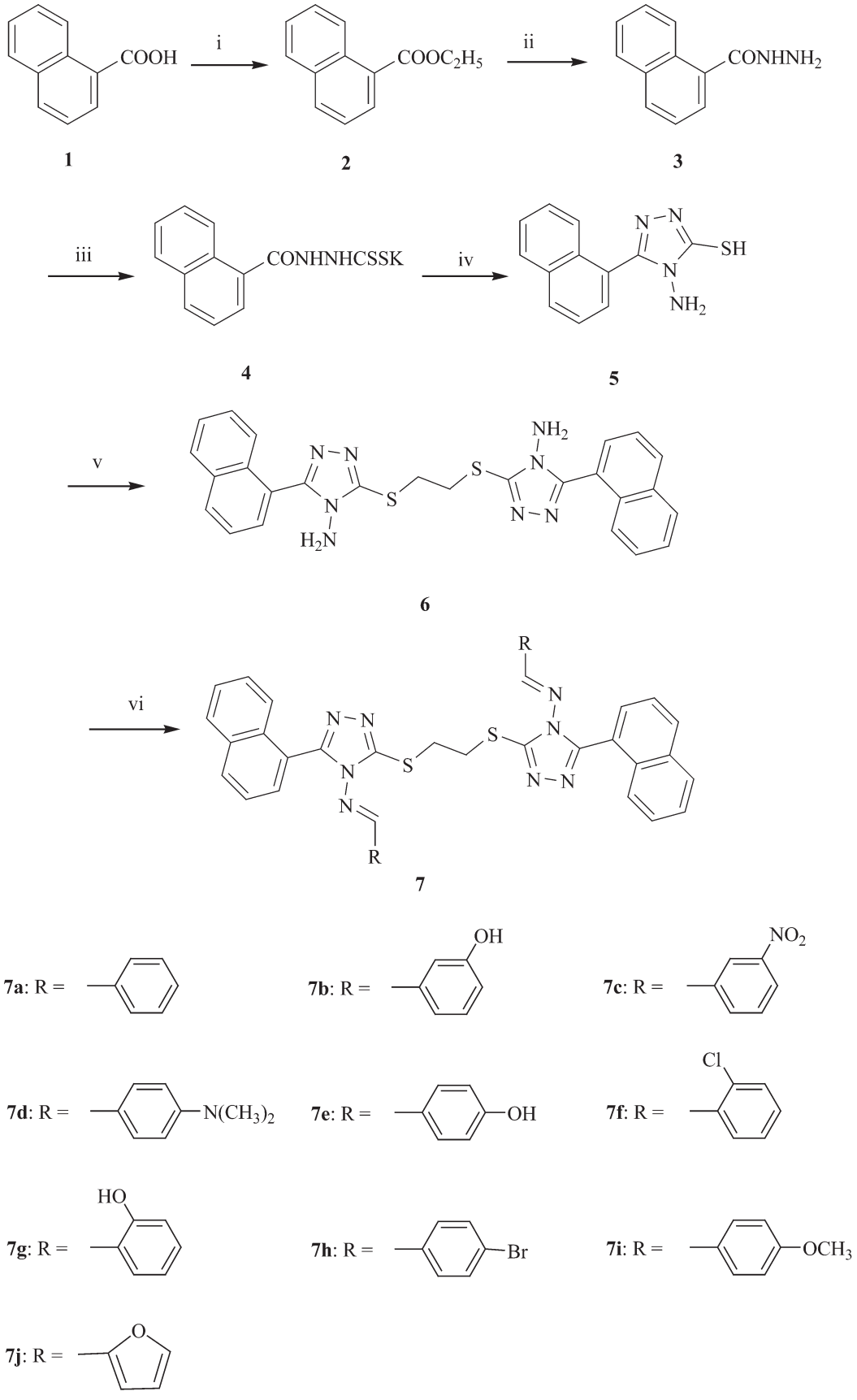
Compound **5** (1.9 mmol), KOH (1.6 mmol) and N, N-dimethylformamide (5 mL) were placed in a round-bottomed flask and 1, 2-dibromoethane (0.8 mmol) was added dropwise. Then the reaction mixture was irradiated at 350 W for 10 min. After cooling to room temperature, water (10 mL) was added to the mixture. The deposit was separated by filtration and recrystallised from N, N-dimethylformamide to give the pure compound **6** as a white solid, yield 88%, m.p. 240–242 °C; IR (KBr) (cm^{-1}): 3328, 3167, 3048, 2983, 2848, 1572, 1507, 1498, 1458, 778; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.12 (d, J = 8.0 Hz, 2H, ArH), 8.07–8.03(m, 4H, ArH), 7.87(t, J = 6.4 Hz, 2H, ArH), 7.68–7.57 (m, 6H, ArH); 6.00(s, 4H, NH), 3.70 (s, 4H, SCH_2CH_2S); ESI–MS *m/z* (%): 511 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{22}N_8S_2$: C, 61.15; H, 4.34, N, 21.94. Found: C, 61.08; H, 4.32; N, 21.97%.

Microwave method for the preparation of compounds **7a–j**

Compound **6** (0.11 mmol), two drops of acetic acid (catalyst), the aldehyde (RCHO, R = **a–j**) (0.27 mmol) and neutral solid alumina (2.0 g) were mixed thoroughly in a porcelain mortar. After grinding, the mixture was placed in a 25 ml beaker, and the beaker was placed in the microwave oven and irradiated at 300 W for 3–4 min. The reaction was monitored by TLC until it was complete. The mixture was extracted with DMF (5 mL × 3). Then ethanol (10 mL) was added to the DMF mixture. A solid was formed and collected by filtration, recrystallised with DMF to give the pure product **7a–j** as **a** white or yellow solid.

7a: White solid, yield 81%, m.p. 178–180 °C; IR (KBr) (cm^{-1}): 3036, 2973, 2863, 1626, 1546, 1468, 772; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.62 (s, 2H, ArCHN), 8.13 (d, J = 8.0 Hz, 2H, ArH), 8.03 (d, J = 7.2 Hz, 2H, ArH), 7.95 (d, J = 8.0 Hz, 2H, ArH), 7.77 (d, J = 7.2 Hz, 2H, ArH), 7.64 (d, J = 8.0 Hz, 2H, ArH), 7.60–7.52 (m, 10H, ArH), 7.41 (t, J = 7.6 Hz, 4H, ArH), 3.75 (s, 4H, SCH_2); ESI–MS *m/z* (%): 687 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{30}N_8S_2$: C, 59.95; H, 4.40, N, 16.31. Found: C, 59.85; H, 4.43; N, 16.26%.

7b: White solid, yield 91%, m.p. 259–261 °C; IR (KBr) (cm^{-1}): 3489, 3048, 2944, 2823, 1618, 1574, 1440, 1297, 800; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.81 (s, 2H, ArOH), 8.51 (s, 2H, ArCHN), 8.13 (d, J = 8.4 Hz, 2H, ArH), 8.03 (d, J = 6.4 Hz, 2H, ArH), 7.92 (d, J = 7.2 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH), 7.65–7.55 (m, 6H, ArH), 7.22 (t, J = 8.0 Hz, 2H, ArH), 7.01–6.92 (m, 6H, ArH), 3.76 (s, 4H, SCH_2); ESI–MS *m/z* (%): 719 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{30}N_8O_2S_2$: C, 66.83; H, 4.21; N, 15.59. Found: C, 66.79; H, 4.27; N, 15.54%.



Scheme 1 Reagents and conditions: (i) $SOCl_2$, C_2H_5OH, MWI; (ii) $NH_2NH_2{\cdot}H_2O$, MWI; (iii) CS_2, KOH, C_2H_5OH; (iv) $NH_2NH_2{\cdot}H_2O$, MWI; (v) $BrCH_2CH_2Br$, KOH, MWI; (vi) RCHO, Al_2O_3, MWI.

7c: Pale yellow solid, yield 84%, m.p. 222–224 °C; IR (KBr) (cm^{-1}): 3082, 2973, 2847, 1610, 1525, 1477, 731; ^1H NMR (400 MHz, DMSO-d_6,) δ: 8.75(s, 2H, ArCHN), 8.37 (s, 2H, ArH), 8.32 (t, J = 8.0 Hz, 2H, ArH), 8.11 (d, J = 8.0 Hz, 2H, ArH), 8.02 (t, J = 7.2 Hz, 2H, ArH), 7.98 (d, J = 8.0 Hz, 2H, ArH), 7.76 (d, J = 6.4 Hz, 2H, ArH), 7.67 (t, J = 8.0 Hz, 2H, ArH), 7.61 (t, J = 8.0 Hz, 2H, ArH),

Table 1 The synthetic comparison of triazole Schiff base compounds **7a–j** between the solvent-free condition under microwave irradiation and conventional heating

Compounds		Traditional method		Microwave method		t_c/t_w[a]
		Time/min	Yield/%	Time/min	Yield/%	
7a	R = C_6H_5	1680	57	3	81	560
7b	R = 3-HOC_6H_4	1560	47	4	91	390
7c	R = 3-$O_2NC_6H_4$	1680	65	4	84	560
7d	R = 4-$(CH_3)_2NC_6H_4$	1500	61	3	86	500
7e	R = 4-HOC_6H_4	1440	48	3	90	480
7f	R = 2-Cl C_6H_4	1560	60	3	86	520
7g	R = 2-HOC_6H_4	1620	56	4	92	405
7h	R = 4-BrC_6H_4	1560	51	3	84	520
7i	R = 4-$CH_3OC_6H_4$	1680	70	4	94	420
7j	R = 2-Furyl	1800	49	3	88	600

[a] t_c, Conventional method time; t_w, microwave method time.

7.59-7.51 (m, 6H, ArH), 3.78 (s, 4H, SCH_2); ESI–MS *m/z* (%): 777 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{28}N_{10}O_4S_2$: C, 61.84; H, 3.63; N, 18.03. Found: C, 61.81; H, 3.65; N, 18.09%.

7d: Yellow solid, yield 86%, m.p. 233–235 °C; IR (KBr) (cm^{-1}): 3052, 2912, 2844, 1616, 1586, 1536, 1466, 780; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.36 (s, 2H, ArCHN), 8.09 (d, J = 8.0 Hz, 2H, ArH), 8.01 (t, J = 6.0 Hz, 2H, ArH), 7.96 (d, J = 8.8 Hz, 2H, ArH), 7.73 (d, J = 6.8 Hz, 2H, ArH), 7.62–7.55 (m, 6H, ArH), 7.41 (d, J = 8.8 Hz, 4H, ArH), 6.64 (d, J = 8.8 Hz, 4H, ArH), 3.71 (s, 4H, SCH_2), 2.95 (s, 12H, NCH_3); ESI–MS *m/z* (%): 773 [(M+1)$^+$, 100]. Anal. Calcd for $C_{44}H_{40}N_{10}S_2$: C, 68.37; H, 5.22; N, 18.12. Found: C, 68.42; H, 5.26; N, 18.15%.

7e: White solid, yield 90%, m.p. 273–275 °C; IR (KBr) (cm^{-1}): 3433, 3062, 2954, 2842, 1623, 1594, 1431, 1291, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.24 (s, 2H, PhOH), 8.47 (s, 2H, ArCHN), 8.10 (d, J = 8.4 Hz, 2H, ArH), 8.02 (d, J = 8.4 Hz, 2H, ArH), 7.85 (d, J = 7.6 Hz, 2H, ArH), 7.73 (d, J = 7.2 Hz, 2H, ArH), 7.66–7.53 (m, 4H, ArH), 7.45 (d, J = 8.4 Hz, 4H, ArH), 6.77 (d, J = 8.0 Hz, 4H, ArH), 3.72 (s, 4H, SCH_2); ESI–MS *m/z* (%): 719 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{30}N_8O_2S_2$: C, 66.83; H, 4.21; N, 15.59. Found: C, 66.78; H, 4.24; N,15.64%.

7f: White solid, yield 86%, m.p. 247–249 °C; IR (KBr) (cm^{-1}): 3062, 2951, 2866, 1619, 1589, 1445, 773; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.65 (s, 2H, ArCHN), 8.15 (d, J = 8.0 Hz, 2H, ArH), 8.05 (d, J = 8.0 Hz, 2H, ArH), 7.79–7.76 (m, 6H, ArH), 7.59–7.48 (m, 6H, ArH), 7.42–7.33 (m, 6H, ArH), 3.82 (s, 4H, SCH_2); ESI–MS *m/z* (%): 755 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{28}Cl_2N_8S_2$: C, 63.57; H, 3.73; N,14.83. Found: C, 63.63; H,3.70; N, 14.78%.

7g: White solid, yield 92%, m.p. 124–126 °C; IR (KBr) (cm^{-1}): 3422, 3052, 2969, 2838, 1615, 1539, 1462, 1429, 1260, 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.24 (s, 2H, PhOH), 8.69 (s, 2H, ArCHN), 8.11 (d, J = 8.0 Hz, 2H, ArH), 8.02 (t, J = 8.0 Hz, 2H, ArH), 7.90 (d, J = 7.2 Hz, 2H, ArH), 7.76 (d, J = 6.8 Hz, 2H, ArH), 7.63-7.52 (m, 10H, ArH), 7.34–7.30 (m, 4H, ArH), 3.77 (s, 4H, SCH_2); ESI–MS *m/z* (%): 719 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{30}N_8O_2S_2$: C, 66.83; H, 4.21; N, 15.59. Found: C, 66.89; H, 4.18; N, 15.56%.

7h: White solid, yield 84%, m.p. 121–123 °C; IR (KBr) (cm^{-1}): 3052, 2981, 2870, 1624, 1587, 1428, 771; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.59 (s, 2H, ArCHN), 8.12 (d, J = 8.4 Hz, 2H, ArH), 8.03 (d, J = 7.6 Hz, 2H, ArH), 7.92 (d, J = 8.0 Hz, 2H, ArH), 7.74 (d, J = 6.8 Hz, 2H, ArH), 7.64-7.49 (m, 14H, ArH), 3.75 (s, 4H, SCH_2); ESI–MS *m/z* (%): 846 [(M+2)$^+$, 100]. Anal. Calcd for $C_{40}H_{28}Br_2N_8S_2$: C, 56.88; H, 3.34; N 13.27. Found: C 56.86, H 3.36, N 13.29%.

7i: White solid, yield 94%, m.p. 197–199 °C; IR (KBr) (cm^{-1}): 3057, 2928, 2832, 1615, 1566, 1510, 1425, 1166, 774; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.53 (s, 2H, ArCHN), 8.11 (d, J = 8.4 Hz, 2H, ArH), 8.02 (d, J = 6.8 Hz, 2H, ArH), 7.94 (d, J = 8.4 Hz, 2H, ArH), 7.74 (d, J = 7.2 Hz, 2H, ArH), 7.63-7.54 (m, 10H, ArH), 6.95 (d, J = 8.8 Hz, 4H, ArH), 3.77 (s, 6H, OCH_3), 3.73 (s, 4H, SCH_2); ESI–MS *m/z* (%): 747 [(M+1)$^+$, 100]. Anal. Calcd for $C_{42}H_{34}N_8O_2S_2$: C, 67.54; H, 4.59; N,15.00. Found: C, 67.49; H, 4.62; N; 15.05%.

7j: White solid, yield 88%, m.p. 171–173 °C; IR (KBr) (cm^{-1}): 3063, 2939, 2877, 1611, 1569, 1473, 1426, 1026, 753; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.45 (s, 2H, ArCHN), 8.12 (d, J = 8.0 Hz, 2H, ArH), 7.93 (t, J = 7.2 Hz, 2H, ArH,), 7.95 (s, 2H, 5-Furyl-H), 7.81 (d, J = 7.6 Hz, 2H, ArH), 7.72 (d, J = 7.2 Hz, 2H, ArH), 7.64 (d, J = 7.2 Hz, 2H, ArH), 7.61-7.53 (m, 4H, ArH), 7.13 (d, J = 3.6 Hz, 2H, 3-furyl-H), 6.66–6.63 (m, 2H, 4-furyl-H), 3.72 (s, 4H, SCH_2); ESI–MS *m/z* (%): 1356 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{36}H_{26}N_8O_2S_2$: C, 64.85; H, 3.93; N, 16.81. Found: C, 64.81; H, 3.90; N,16.79%.

Conventional method for the preparation of compounds **7a-j**

Compound **6** (0.11 mmol), the aldehyde (RCHO R = **a–j**)(0.27 mmol) and glacial acetic acid (5 mL) were placed in a round-bottomed flask. Then it was heated to reflux for 24–30 h. On completion of the reaction, the mixture was cooled to room temperature and evaporated to remove the glacial acetic acid. Then ethanol (5 mL) was added into the mixture. A solid formed immediately. This was collected by filtration and recrystallised from N, N-dimethylformamide to give the pure compounds **7a–j** as white or yellow solids.

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