Microwave-assisted synthesis of 1,3,4-thiadiazole Schiff base derivatives

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A rapid and efficient microwave-assisted synthesis method for the preparation of 1,3,4-thiadiazole Schiff base derivatives is described. These 1,3,4-thiadiazole Schiff bases (**5a-h**) were identified by IR, ^{1}H NMR, elemental analyses. The target compounds were performed in a shorter reaction time compared with conventional heating methods.

Keywords: 1,3,4-thiadiazole, Schiff base, microwave-assisted synthesis

In recent years, there has been intense investigation of different 1,3,4-thiadiazole compounds. Derivatives of 1,3,4-thiadiazole compounds have diverse pharmacological activities such as fungicidal, insecticidal, bactericidal, herbicidal, anti-tumor, antituberculosis, anti-inflammatory properties.[1–7] The 1,3,4-thiadiazole nucleus with N–C–S linkage exhibits a large number of biological activities.[8]

Organic compounds containing Schiff base are of increasing interest because of their diverse biological properties such as antifungal, antibacterial, antiparasitic, anti-inflammatory, analgesic, and antitumoural activities.[9–13]

Conventional synthesis reactions suffered from drawbacks such as the use of high boiling solvents, long reaction time and lower yields.[14] Microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug discovery applications because it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds.[15–17]

In connection with our research interest directed toward the synthesis of novel *N*-(substitutedd benzylidene)-5-(substitutedd phenyl)-1,3,4-thiadiazol-2-amine derivatives, we have designed and synthesised a series of new compounds containing the 1,3,4-thiadiazole and Schiff base under microwave irradiation.

Results and discussion

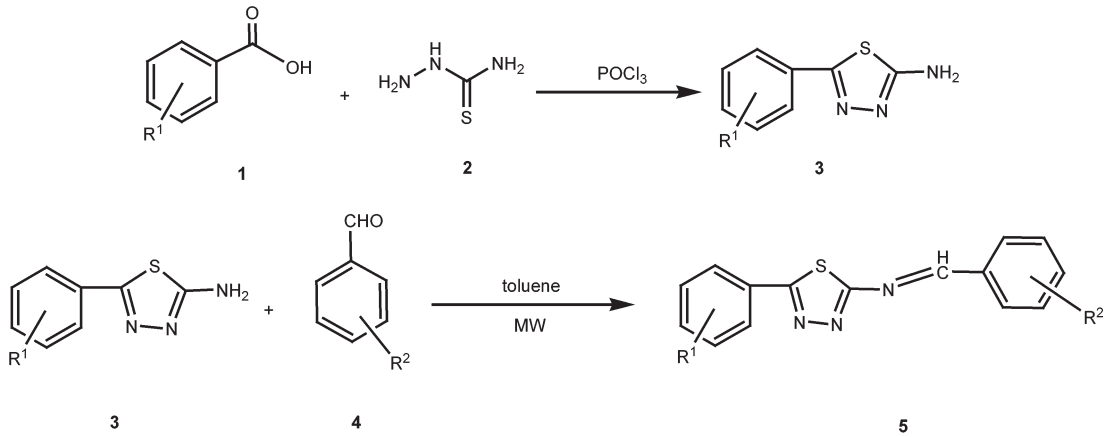
Previously the imines were synthesised by substitutedd aryl amine and substituted benzaldehyde with yields of 80–90%. In this paper, the *N*-(substituted benzylidene)-5-(substituted phenyl)-1,3,4-thiadiazol-2-amine (**5a–h**) was designed and prepared by the reaction of 2-amino-5-aryl-1,3,4-thiadiazole and substituted benzaldehyde under microwave irradiation as shown in Scheme1. The results are reported in Table 1.

In conclusion, we have developed a fast, convenient, and efficient draft for the preparation of *N*-(substituted benzylidene)-5-(substituted phenyl)-1,3,4-thiadiazol-2-amine under MW irradiation. The ease of the reaction procedure and workup, high yields, and very short reaction time make this procedure useful and attractive compared with the currently available methods.[18]

The compound (*E*)-*N*-[4-(methylsulfanyl)benzylidene]-5-(3,5-dimethylphenyl)-1,3,4-thiadiazol-2-amine (**5a**) was subjected to single crystal X-ray diffraction.[19]

Experimental

Melting points were recorded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. IR spectra in KBr were recorded by



5a R^1=3,5-dimethyl	R^2=4- methylsulfanyl	5b R^1= H	R^2=4- methylsulfanyl
5c R^1=4-fluoro	R^2=4- methylsulfanyl	5d R^1=4-methoxy	R^2=4- methylsulfanyl
5e R^1=2,4-dichloro	R^2=4-nitro	5f R^1=4-methyl	R^2=4-nitro
5g R^1=4-methyl	R^2=4-chloro	5h R^1=4-bromine	R^2=4-chloro

Scheme 1 The synthetic route for compounds **5a–h**.

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Table 1 Synthesis of compounds **5a–h**

Entry	R^1	R^2	Mode of activation	Time	Power/temp.	Yield / %
5a	3,5-Dimethyl	4-Methylsulfanyl	MW	7 min	300 W	83
5b	H	4-Methylsulfanyl	MW	7 min	300 W	79
5c	4-Fluoro	4-Methylsulfanyl	MW	7 min	300 W	82
5d	4-Methoxy	4-Methylsulfanyl	MW	7 min	300 W	89
5e	2,4-Dichloro	4-Nitro	MW	7 min	300 W	88
5f	4-Methyl	4-Nitro	MW	7 min	300 W	85
5g	4-Methyl	4-Chloro	MW	7 min	300 W	82
5h	4-Bromine	4-Chloro	MW	7 min	300 W	80
5b	H	4-Methylsulfanyl	CH	8 h	110 °C	48

MW, microwave irradiation; CH conventional heating.

a Perkin-Elmer PE-683 IR spectrometer. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. MW experiments were carried out on a WF-4000M microwave fast reaction system (Shanghai Qiyao Analysis Instrument Co., Shanghai, China).

Synthesis of **3***; general procedure*

To a mixture of substitutedd benzoic acid **1** (0.1 mol) and thiosemicarbazide (0.1 mol) was added $POCl_3$ (0.3 mol) dropwise at 0–5 °C and maintained for 30 minutes. The reaction mixture was heated to reflux and stirred for 4 h. After cooling, water (50 mL) was added to the reaction mixture. The pH of the reaction solution was adjusted to the range of 8–9 with 50% NaOH solution. The crude product was precipitated, filtered, washed with water, dried, and recrystallised from ethanol to afford compounds **3**.

Synthesis of **5***; general procedure*

A mixture of compounds **3** (0.01 mol), **4** (0.014 mol) and a few drops of acetic acid in toluene was stirred and irradiated in a WF-4000M microwave fast reaction system under 300W for a few minutes at 110 °C. After cooling and filtering, crude compound **5** was obtained. The pure compound was obtained by recrystallisation from ethanol.

(E)-N-[4-(Methylsulfanyl)benzylidene]-5-(3,5-dimethylphenyl)-1,3,4-thiadiazol-2-amine (**5a**): (89%): M.p. 184–185 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.37 (s, 6H, CH_3), 2.57 (s, 3H, S–CH_3), 7.22–7.99 (m, 7H, ArH), 8.99 (s, 1H, H–C=N); IR(KBr)υ: 683 (C–S), 1558 (C=N, ring), 1654 (C=N, imine), 2856, 2920 (CH_3–H), 3128 (ArH)cm^{-1}; Anal. Calcd for $C_{18}H_{17}N_3S_2$: C, 63.68; H, 5.05; N, 12.38; S, 18.89. Found: C, 63.56; H, 5.11; N, 12.30; S, 19.01%.

(E)-N-[4-(Methylsulfanyl)benzylidene]-5-phenyl-1,3,4-thiadiazol-2-amine (**5b**): (83%): M.p. 180–183 °C; ^{1}H NMR(DMSO-d_6, 300 MHz) δ: 2.58 (s, 3H, S–CH_3), 7.44–7.99 (m, 9H, ArH), 9.00 (s, 1H, H–C=N); IR (KBr)υ: 658 (C–S), 1552 (C=N, ring), 1683 (C=N, imine), 2910 (CH_3–H), 3004 (ArH) cm^{-1}; Anal. Calcd for $C_{16}H_{13}N_3S_2$: C, 61.71; H, 4.21; N, 13.49; S, 20.59. Found: C, 61.78; H, 4.25; N, 13.41; S, 20.62%.

(E)-5-(4-Fluorophenyl)-N-[4-(methylsulfanyl)benzylidene]-1,3,4-thiadiazol-2-amine (**5c**): (82%): M.p. 190–192 °C; ^{1}H NMR (DMSO-d_6, 300MHz) δ: 2.58(s, 3H, S–CH_3), 7.40–8.05(m, 8H, ArH), 8.99(s, 1H, H–C=N); IR (KBr)υ: 667 (C–S), 1558 (C=N, ring), 1683 (C=N, imine), 2905 (CH_3-H), 3062 (ArH)cm^{-1}; Anal. Calcd for $C_{16}H_{12}FN_3S_2$: C, 58.34; H, 3.67; N, 12.76; S, 19.47. Found: C, 58.30; H, 3.72; N, 12.82; S, 19.52%.

(E)-5-(4-Methoxyphenyl)-N-[4-(methylsulfanyl)benzylidene]-1,3,4-thiadiazol-2-amine (**5d**): (79%): M.p. 194–195 °C; ^{1}H NMR (DMSO-d_6, 300MHz) δ: 2.57 (s, 3H, S–CH_3), 3.85 (s, 3H, OCH_3), 7.12–7.97 (m, 8H, ArH), 8.97 (s, 1H, H–C=N); IR (KBr)υ: 653 (C–S), 1584 (C=N, ring), 1609 (C=N, imine), 2912 (CH_3–H), 3064 (ArH)cm^{-1}; Anal. Calcd for $C_{17}H_{15}N_3OS_2$: C, 59.80; H, 4.43; N, 12.31, S, 18.78. Found: C, 59.67; H, 4.52; N, 12.29; S, 18.81%.

(E)-5-(2,4-Dichlorophenyl)-N-(4-nitrobenzylidene)-1,3,4-thiadiazol-2-amine (**5e**): (85%): M.p. 172–174 °C; ^{1}H NMR(DMSO-d_6, 300MHz) δ: 7.31–8.42 (m, 8H, ArH), 9.20 (s, 1H, H–C=N); IR (KBr)υ: 1172 (C–Cl), 1344 (N–O), 1413 (C–N), 1574 (C=N, ring), 1609 (C=N, imine), 3056 (ArH) cm^{-1}; Anal. Calcd for $C_{15}H_8Cl_2N_4O_2S$: C, 47.51; H, 2.13; N, 14.77; S, 8.46. Found: C, 47.55; H, 2.18; N, 14.82; S, 8.50%.

(E)-5-p-Tolyl-N-(4-nitrobenzylidene)-1,3,4-thiadiazol-2-amine (**5f**): (85%): M.p. 206–207 °C; ^{1}H NMR (DMSO-d_6, 300MHz) δ: 2.34(s, 3H, CH_3), 7.39–8.43 (m, 8H, ArH), 9.23 (s, 1H, H–C=N); IR (KBr)υ: 1350 (*N*-O), 1425 (C–N), 1582 (C=N, ring), 1675 (C=N, imine), 2935 (CH_3–H), 3031 (ArH) cm^{-1}; Anal. Calcd for $C_{16}H_{12}N_4O_2S$: C, 59.25; H, 3.73; N, 17.27; S, 9.89. Found: C, 59.32; H, 3.88; N, 17.21; S, 9.92%.

(E)-N-(4-Chlorobenzylidene)-5-p-tolyl-1,3,4-thiadiazol-2-amine (**5g**): (85%): M.p. 176–179 °C; ^{1}H NMR (DMSO-d_6, 300MHz) δ: 2.34 (s, 3H, CH_3), 7.39–8.43 (m, 8H, ArH), 9.23 (s, 1H, H–C=N); IR (KBr)υ: 1185 (C–Cl), 1592 (C=N, ring), 1685 (C=N, imine), 2942 (CH_3–H), 3059 (ArH) cm^{-1}; Anal. Calcd for $C_{16}H_{12}ClN_3S$: C, 61.24; H, 3.85; N, 13.39; S, 10.22. Found: C, 61.32; H, 3.88; N, 13.51; S, 10.17%.

(E)-5-(4-Bromophenyl)-N-(4-chlorobenzylidene)-1,3,4-thiadiazol-2-amine (**5h**): (85%): M.p. 168–170 °C; ^{1}H NMR (DMSO-d_6, 300MHz) δ: 7.67–8.11 (m, 8H, ArH), 9.10 (s, 1H, H–C=N); IR (KBr)υ: 515 (C-Br), 1203 (C–Cl), 1616 (C=N, ring), 1692 (C=N, imine), 3093 (ArH) cm^{-1}; Anal. Calcd for $C_{15}H_9BrClN_3S$: C, 47.58; H, 2.40; N, 11.10; S, 8.47. Found: C47.62; H, 2.38; N, 11.01; S, 8.52%.

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