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Conventional and microwave-assisted solvent-free synthesis of fused [1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxide derivatives

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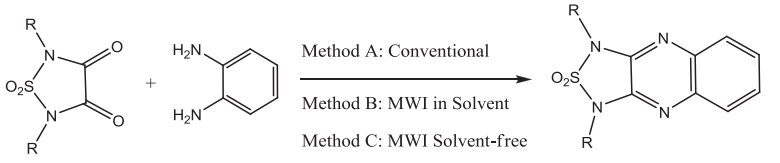
A simple, highly efficient and environmentally friendly procedure for the condensation of *o*-phenylenediamine with 2,5-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides via two microwave-assisted reactions is described. These compounds were also prepared via a conventional heating method to provide a comparison with the microwave-assisted irradiation reaction protocol. The structures of the synthesized compounds were confirmed using infrared, ^{1}H NMR and mass spectral analysis.



Keywords: microwave; cyclic sulfamides; sulfur heterocycles; thiadiazolidine; quinoxaline

1. Introduction

Nitrogen- and sulfur-containing heterocycles are an important class of compounds in organic and medicinal chemistry due to their biological relevance, which includes anti-HIV, anti-HCV and anti-cancer activities (*1–4*). Among five-membered heterocyclic structures, the 1,2,5-thiadiazolidine nucleus **1** exhibits a range of properties (*5–7*). These compounds are known to inhibit several families of enzymes, including serine proteases (*8*, *9*), γ-secretases (*10*) and constrained peptides (*11–13*). Consequently, fused heterocyclic derivatives with thiadiazole moieties are prospective targets in modern drug discovery.

The quinoxaline structure **2** (*14*) is one of the most fascinating classes of compounds that exhibit biological activity, as previously summarized (*15*). This motif is found in a number of important biological compounds, including riboflavin (also known as vitamin B2), folic

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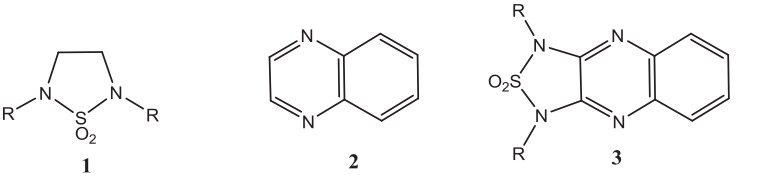


Figure 1. General structures of thiadiazolidines, quinoxalines and fused thiadiazolo-quinoxalines.

acid and pyocyanine. Other quinoxalines exhibit anti-fungal (*16*), anti-tuberculosis (*17*), anti-epilepsy (*18*), anti-bacterial (*19*) and anti-tumor activities (*20*). In addition, quinoxaline and its analogues have been investigated as ligands for metal centers in catalytic reactions (*21*). Their wide range of physiological activities makes the quinoxaline ring system an attractive synthetic target.

In recent years, the synthesis of quinoxalines fused to other heterocyclic systems has attracted considerable attention (*22*), and a variety of synthetic methods have been developed for preparing these quinoxaline derivatives (*23*). While traditional synthetic methodologies involve catalysts and solvents (*24–29*), newer synthetic methods have focused on techniques involving alternative modes of activation. Many contemporary techniques involve microwave-assisted synthesis, an efficient and versatile method for performing condensation reactions (*30–32*).

Considering the biological importance of condensed quinoxalines, we have continued our earlier synthetic studies of biologically active heterocyclic compounds (*33–35*), specifically the discovery of new fused sulfur-containing heterocycles with intriguing biological activity. Herein, we report the synthesis of a fused 1,2,5-thiadiazol[3,4-b]quinoxaline scaffold **3** (Figure 1) via conventional and microwave-assisted methods and their characterization using infrared (IR), ^{1}H NMR and mass spectroscopy.

2. Results and discussion

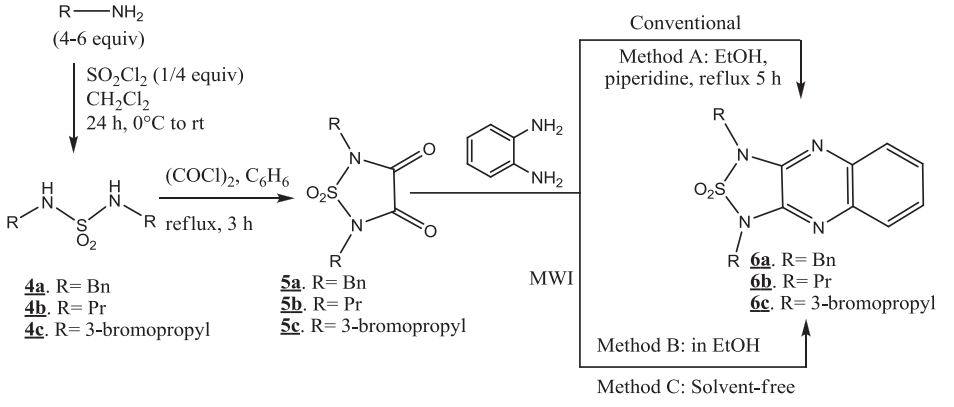
Following previous work in our laboratory on the synthesis of sulfur-containing heterocycles (*33–35*), we report here two different, useful synthetic approaches to the synthesis of [1,2,5]thiadiazol[3,4-b]quinoxaline **6a–6c**.

A number of methods have been developed for the synthesis of quinoxaline derivatives, but the most common approach is a Hinsberg-type condensation reaction, which involves the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound under reflux conditions (*36*).

The key starting intermediates, *N*, *N*′-disubstituted symmetric sulfamides **4a–4c**, were prepared by reacting sulfuryl chloride (SO_2Cl_2) with an excess of the corresponding primary amine in methylene chloride for 24 h (*37*, *38*). These sulfamides were then used as intermediates in the generation of 1,2,5-thiadiazolidine scaffolds **5a–5c** via condensation with oxalyl dichloride (1 equiv.) in benzene in the presence of triethylamine at reflux. The structural assignments of compounds **5a–5c** were supported by spectroscopic analysis (IR, ^{1}H-NMR and mass spectra).

Scheme 1 (Method A) illustrates the synthesis of the title compounds **6a–6c** using conventional thermal heating. The two carbonyl groups of the prepared *N*, *N*′-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides **5a–5c** condense with aryl-1,2-diamines in ethanol under reflux (piperidine, 5 h); two equivalents of water are lost to generate the fused [1,2,5]thiadiazol[3,4-b]quinoxalines **6a–6c** in moderate yields (42–48%).

To determine a suitable method for the synthesis of quinoxalines from aryl-1,2-diamines and α-dicarbonyls, the synthesis of compounds **6a–6c** was also attempted with microwave-assisted



Scheme 1. Synthetic routes to target compounds **6a**–**6c**.

irradiation (MWI) following two methodologies (Method B and Method C of Scheme 1). Detailed procedures for carrying out these reactions are included in the experimental section.

The first non-conventional approach to synthesize title compounds **6a**–**6c** (Method B of Scheme 1) involves the intermolecular cyclocondensation of the corresponding *N*, *N′*-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides and aryl-1,2-diamines in dry ethanol solvent for 20 min.

Using microwave-assisted solvent-free conditions (Method C of Scheme 1) (*39*), the condensation of the 1,2-diketone, that is, 1,5-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides, **5a**–**5c** and 1,2-phenylenediamine for 10 min, resulted in the formation of the products, 1,3-dialkyl[1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxides **6a**–**6c**, in yields typically greater than 75%. This protocol provides an opportunity to work with open vessels, thus avoiding the typical problems associated with the use of organic solvents under MWI, such as high pressure and flammability. Furthermore, this approach enhances the feasibility of scaling up the reactions (*40*). The results of the condensation reaction for several cyclic sulfamides under various conditions are shown in Table 1.

As Table 1 demonstrates, the efficiency and versatility of microwave-assisted synthesis for performing condensation reactions led to dramatic reductions in reaction times, that is, from days and hours to minutes and seconds. A comparison with the conventional method illustrates the advantages of microwave irradiation in synthetic heterocyclic chemistry (*41*). This technique can be denoted as "e-chemistry," because the reactions are easy, economical, efficient, eco-friendly and a step toward green chemistry (*42*). The formation of fused [1,2,5]thiadiazolo[3,4-b] quinoxaline-2,2-dioxides **6a**–**6c** was confirmed by the interpretation of their Fourier Transform Infrared Spectroscopy (FT-IR), ^{1}H-NMR and mass spectra. The FT-IR spectra of compounds

Table 1. Reaction times and yields for the synthesis of compounds **6a**–**6c**.

		MWI					
		Method B, MWI in EtOH, 245 W, 110°C		Method C, MWI solvent-free, 300 W, 110°C		Conventional, Method A	
Compound	R	Time (min)	Yield %	Time (min)	Yield %	Time (h)	Yield %
6a	Benzyl	20	68	10	76	5	46
6b	Propyl	20	70	10	81	5	48
6c	3-Bromopropyl	20	64	10	79	5	42

6a–**6c** each exhibited strong bands at $\nu = 1140$ and $1300\,cm^{-1}$ corresponding to a sulfonyl (SO_2) group and at $\nu = 1600\,cm^{-1}$ corresponding to C=N groups. The ^{1}H-NMR spectra exhibited two characteristic dd peaks at δ 7.65–7.70 and 7.85–7.90 ppm corresponding to the quinoxaline ring protons that are characteristic of *meta*-coupling on the quinoxaline ring.

3. Conclusion

In conclusion, we have successfully demonstrated the application of microwave activation in the synthesis of fused [1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxide derivatives. In comparison to conventional methods, microwave heating offers advantages that include reduced reaction times and temperatures and better yields, selectivity and reproducibility, particularly due to the advent of single-mode technology. Biological evaluation of the compounds synthesized in this work is currently being performed.

4. Experimental

4.1. *Instrumentation*

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 300 and 75 MHz, respectively. The chemical shifts, δ, are reported in parts per million (ppm) and were measured in $CDCl_3$ relative to TMS, which was employed as the internal standard. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. The mass spectrometry data were obtained using an HP 5989A instrument at 70 eV for the EI spectra and using methane as the reagent gas for the CI spectra. Electrospray Ionization Mass Spectrometry spectra were obtained on Mariner (ESI TOF) and API 365 (ESI 3Q) mass spectrometers using methanol as the spray solvent. Ultraviolet–Visible Spectroscopy spectra were recorded on a Perkin-Elmer Lambda 20 spectrometer. Melting points (Mp) were determined using a Reichert Thermovar or an Electrothermal 9200 apparatus and are uncorrected. The microwave-assisted reactions were carried out using a commercial Synthewave^{TM} 402 – Prolabo monomode reactor specifically designed for organic synthesis.

4.2. *General procedure for the synthesis of N,N′-disubstituted symmetric sulfamides 4a–4c*

Compounds **4a**–**4c** were prepared as described in previously published protocols (*26*)–*27*. The reaction was performed by the dropwise addition of a solution of sulfuryl chloride (1 equiv.) in 20 ml of CH_2Cl_2 to a solution of the corresponding amine (4–6 equiv.) in 50 ml of CH_2Cl_2 at 0°C in darkness. Gas evolution was observed during sulfuryl chloride addition. The reaction mixture was warmed to room temperature (r.t.), stirred for 24 h and monitored by TLC (SiO_2). The crude product was washed with HCl (2N, 2 × 20 ml) and water (2 × 30 ml) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to yield a yellow solid as the crude product. Column chromatography (CH_2Cl_2: MeOH = 95 : 5) afforded the *N*,*N*′-dialkylsulfamide in moderate yields.

4.2.1. *N,N′-dibenzylsulfamide (**4a**)*

This compound was prepared according to the above general procedure using a solution of benzylamine (6 equiv.) in CH_2Cl_2 and SO_2Cl_2 (1 equiv.) in CH_2Cl_2. Compound **4a** was obtained as a white solid in 59% yield. $R_f = 0.37$ (SiO_2, CH_2Cl_2); Mp: 182–184°C (reported 180–182°C);

IR (KBr, ν cm^{-1}): 3270 (NH), 3034 (CH–Ar), 1350 and 1143 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 4.17 (d, 4H, CH_2), 4.37 (t broad, 2H, NH), 7.28–7.34 (m, 10H, Ar–H); Low-Resolution Mass Spectroscopy (LRMS) (CI): 277 M$^+$, 199, 91.

4.2.2. *N,N′-dipropylsulfamide (**4b**)*

Compound **4b** was obtained as a white solid in 60% yield. $R_f = 0.45$ (SiO_2, CH_2Cl_2 : MeOH = 95 : 5); Mp: 64–65°C (reported: 62–63°C); IR (KBr, ν cm^{-1}): 3280 (NH), 1333 and 1150 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.95 (t, $J = 7.2$ Hz, 6H, CH_3), 1.57 (sext, $J = J' = 7.1$ Hz, 4H, β-CH_2), 2.99 (q, 4H, α-CH_2), 4.27 (t broad, 2H, NH); ^{13}C NMR ($CDCl_3$): 11.26 (γ-C), 22.89 (β-C), 44.95 (α-C); LRMS (CI): 181 M$^+$.

4.2.3. *N,N′-Di(3-bromopropyl)sulfamide (**4c**)*

Compound **4c** was obtained as a white solid in 73% yield. $R_f = 0.58$ (SiO_2, CH_2Cl_2:MeOH = 95:5); Mp: 72–74°C; IR (KBr, ν cm^{-1}): 3286 (NH), 1133 and 1351 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 2.13 (t, 4H, β-CH_2), 3.26 (q, 4H, α-CH_2), 3.51 (t, 4H, γ-CH_2), 4.39 (t, 2H, NH); LRMS (CI): 339 [M+H]$^+$, 257, 231, 138.

4.3. *General procedure for the synthesis of 2,5-Dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides (5a–5c)*

A solution of oxalyl dichloride (1 equiv., 1 mmol) in dry $C_6H_6$was added dropwise to a mixture of *N,N′*-disubstituted symmetric sulfamides (1 equiv., 1 mmol), triethylamine (2.5 equiv, 2.5 mmol) and dry C_6H_6 (100 ml) in a round-bottomed flask. After the addition was complete, the reaction mixture was stirred under reflux for 3 h and then cooled to r.t. Filtration of the white solid, $Et_3N^+H{\bullet}Cl^-$, followed by solvent removal under reduced pressure yielded an oily crude product. Recrystallization of the crude material from a mixture of CH_2Cl_2/*n*-hexane at low temperature or flash chromatography on silica gel using CH_2Cl_2 as the eluent afforded 1,2,5-thiadiazolidine-1,1-dioxides in 70–85% yield.

4.3.1. *2,5-Dibenzyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxide (**5a**)*

Compound **5a** was obtained as a white solid in 82% yield. $R_f = 0.45$ (SiO_2, CH_2Cl_2); Mp: 115–116°C; IR (KBr, ν cm^{-1}): 1761 and 1772 (C=O), 1187 and 1356 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 4.90 (s, 4H, CH_3), 7.35–7.44 (m, 10H, Ar–H); LRMS (CI): 331 M$^+$, 91 (100%)$^+$.

4.3.2. *2,5-Dipropyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxide (**5b**)*

Compound **5b** was obtained as a white solid in 63% yield. $R_f = 0.42$ (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1765 (C=O); 1191 and 1336 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.01 (t, 6H, $2CH_3$), 1.86 (m, 4H, $2CH_2$), 3.77 (t, 4H, $2CH_2$–N); LRMS (CI): 235 M$^+$, 193, 151.

4.3.3. *2,5-Di(3-bromopropyl)-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxides (**5c**)*

Compound **5c** was obtained as a white solid in 75% yield. $R_f = 0.44$ (SiO_2, CH_2Cl_2); Mp: 95–97°C; IR (KBr, ν cm^{-1}): 1770 (C=O); 1166 and 1348 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm):

2.38 (m, 4H, $2CH_2$), 3.47 (t, 4H, $2CH_2$–Br), 4.01 (t, 4H, $2CH_2$–N); LRMS (CI): 393 M^+, 313, 270, 151.

4.4. *Conventional heating procedure for the synthesis of fused [1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxides (6a–6c, Method A)*

A mixture of the 2,5-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxide (1 equiv., 1 mmol), *o*-phenylenediamine (1 equiv., 1 mmol) and piperidine (5 equiv., 5 mmol) in 20 ml of anhydrous ethanol was heated under reflux for 5 h. During this time, precipitation of the product was observed. The precipitate was filtered and washed with water. The solid product was dissolved in CH_2Cl_2, washed with HCl (0.1 N) (2 × 20 ml) and water (2 × 30 ml) and dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using CH_2Cl_2, or by recrystallization from EtOH/*n*-hexane to yield pure fused thiadiazolo[3,4-b]quinoxalines **6a**–**6c**.

4.5. *Microwave-assisted procedure for the synthesis of fused 6a–6c (Method B)*

Compounds **6a**–**6c** were prepared according to previously published protocols (*27*). Equimolar quantities of 2,5-dialkyl-1,2,5-thiadiazolidine-3,4-dione-1,1-dioxide (1 equiv., 1 mmol) and *o*-phenylenediamine (1 equiv., 1 mmol) were dissolved in absolute ethanol and subjected to microwave irradiation at 245 W for 20 min. After completion of the reaction as judged by TLC, the reaction mixture was cooled and poured onto crushed ice. The solid product was separated and recrystallized from a mixture of EtOH/*n*-hexane.

4.6. *Microwave-assisted solvent-free synthesis of fused 6a–6c (Method C)*

Compounds **6a**–**6c** were prepared according to previously published protocols (*27*). A mixture of the appropriate α-dicarbonyl **5a**–**5c** (1.1 mmol) and *o*-phenylenediamine (1.0 mmol) were mixed in a glass microwave reaction tube. The mixture was placed inside the microwave oven and irradiated at 300 W for 10 min (Table 1). The reaction was monitored by TLC using 7:3 *n*-hexane–ethyl acetate as an eluent and developed with UV light to determine when the reaction was complete. The final reaction time was recorded when only trace amounts of *o*-phenylenediamine were observed by TLC. No solvents or catalysts were used in the synthesis, and the water formed in the reaction was rapidly eliminated by evaporation due to the high microwave temperature, eliminating the need for dehydrating agents. 1,2,5-thiadiazolo[3,4-b]quinoxalines **6a**–**6c** were obtained as yellowish-white solids after recrystallization from 7:3 *n*-hexane–ethyl acetate in yields ranging from 75–81%. The structures for all of the compounds were confirmed by their spectral and analytical data.

4.6.1. *1,3-Dibenzyl[1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxide (**6a**)*

Compound **6a** was prepared using **5a** (1 equiv., 1 mmol, 0.402 g) and was obtained as a yellowish-white solid in 46% yield by conventional heating, 68% yield by MWI in ethanol and 76% yield in the MWI solvent-free reaction. $R_f = 0.36$ (SiO_2, CH_2Cl_2); Mp: >350°C; IR (KBr, ν cm^{-1}): 1388 and 1140 (SO_2), 1595 (C=N *str*); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 4.81 (s, 4H, CH_2Ph), 7.34 (s *broad*, 10H, 2Ph), 7.67–7.70 (dd, 2H, H–Ar, quinoxaline ring protons), 7.86–7.90 (dd, 2H, H–Ar, quinoxaline ring protons); LRMS (CI): 403 $[M+H]^+$; HRMS ESI^+: *m/z*: 425 $[M + Na]^+$, 827. Elemental analysis: Calcd for $C_{22}H_{18}N_4O_2S$: C = 65.65; H = 4.51; N = 13.92. Found: C = 65.59; H = 4.46; N = 13.96.

4.6.2. *1,3-Dipropyl[1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxide (**6b**)*

Compound **6b** was prepared using **5b** (1 equiv., 1 mmol, 0.306 g) and was obtained as a yellowish-white solid in 48% yield by conventional heating, 70% yield by MWI in ethanol and 81% yield by solvent-free MWI. $R_f = 0.30$ (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1332 and 1139 (SO_2), 1595 (C=N *str*); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.99 (t, 6H, $2CH_3$), 1.78 (m, 4H, $2CH_2$), 3.92 (s, 4H, $2CH_2$), 7.66–7.69 (dd, 2H, H–Ar, quinoxaline ring protons), 7.85–7.88 (dd, 2H, H–Ar, quinoxaline ring protons); LRMS (CI): 307 $[M + H]^+$, 265. Elemental analysis: Calcd for $C_{14}H_{18}N_4O_2S$: C = 54.88; H = 5.92; N = 18.29. Found: C = 54.82; H = 5.95; N = 18.24.

4.6.3. *1,3-Di-(3-bromopropyl)[1,2,5]thiadiazolo[3,4-b]quinoxaline-2,2-dioxide (**6c**)*

Compound **6c** was prepared using **5c** (1 equiv., 1 mmol, 0.460 g) and was obtained as a yellowish-white solid in 42% yield by conventional heating, 64% yield by MWI in ethanol and 79% yield by solvent-free MWI. $R_f = 0.25$ (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1334 and 1149 (SO_2), 1594 (C=N *str*); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 2.23 (m, 4H, $2CH_2$), 3.63 (t, 2H, CH_2), 4.10–4.26 (t, 4H, CH_2), 7.69–7.72 (dd, 2H, H–Ar, quinoxaline ring protons), 7.88–7.91(dd, 2H, H–Ar, quinoxaline ring protons); LRMS (CI): 465 $[M+H]^+$, 386. Elemental analysis: Calcd for $C_{14}H_{16}Br_2N_4O_2S$: C = 36.23; H = 3.47; N = 12.07. Found: C = 36.18; H = 3.51; N = 12.09.

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