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Microwave Assisted Solid Support Synthesis of Novel 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazepines as Potent Antimicrobial Agents

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Abstract—An environmentally benign and economic synthesis of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines is described from readily accessible substituted 2-mercapto-1-amino triazoles and substituted chalcones on basic alumina that are accelerated by exposure to microwaves. The reaction time has been brought down from hours to seconds with improved yield as compared to conventional heating. The method reported herein is devoid of the hazards of solution phase reactions. All the synthesised compounds were tested for their in vitro antibacterial and antifungal activity. Some compounds showed significant antimicrobial properties. The best activity was observed with compounds **3a**, **3c**, **4a** and **4d**. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

During the past decades, the environment consciousness has compelled the chemist to make a new twist on an old theme.[1] In this endeavour, solid supported reagents[1,2] have made a landmark and made significant contributions to preserve the green environment by reducing the waste effluent. With the development of microwave ovens,[3,4] reactions in dry media became easier to do as the high heating efficiency of microwave gives remarkable rate enhancement, higher yields, greater selectivity and ease of manipulation. In addition, the limitations of the microwave assisted reactions in solvents, namely the development of high pressure and the need for specialized sealed vessels, are circumvented via this solid support strategy, which enables organic reactions to occur rapidly at atmospheric pressures[5] and upscale the reaction on a preparative scale.[6]

Tetrazole, thiadiazole, quinoline, indole and triazole derivatives are well known for their significant biological activities.[7–11] Thiadiazepines are not only known for their potent antimicrobial activities[12] but they are also excellent charge generating agents.[13] They also act as intermediates for preparation of substituted caprolactams useful for treatment of HIV disease.[14]

Keeping in view the biological importance of the above mentioned heterocyclic compounds and our ongoing endeavours[15–17] in the development of environmentally benign protocols, we now describe a microwave accelerated solid state approach for the rapid assembly of substituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines. The antibacterial activity against five bacterial strains and antifungal profile against *Aspergillus niger* and *Aspergillus flavus* are also described.

Results and Discussion

Chemistry

The reaction of 1-amino-2-mercapto-5-substituted triazoles **1a–e** and substituted chalcones **2a–b** on basic alumina under microwave irradiation (MWI) afforded the 5-substituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines **3a–e** and **4a–e** within 60–120 s (Scheme 1), while the same reaction was also carried out in solution phase MWI (7–10 min) and conventionally (10–18 h) using K_2CO_3 as a base (Table 1). The structures of all the synthesised compounds were established on the basis of their spectroscopic data. The IR spectra of condensed

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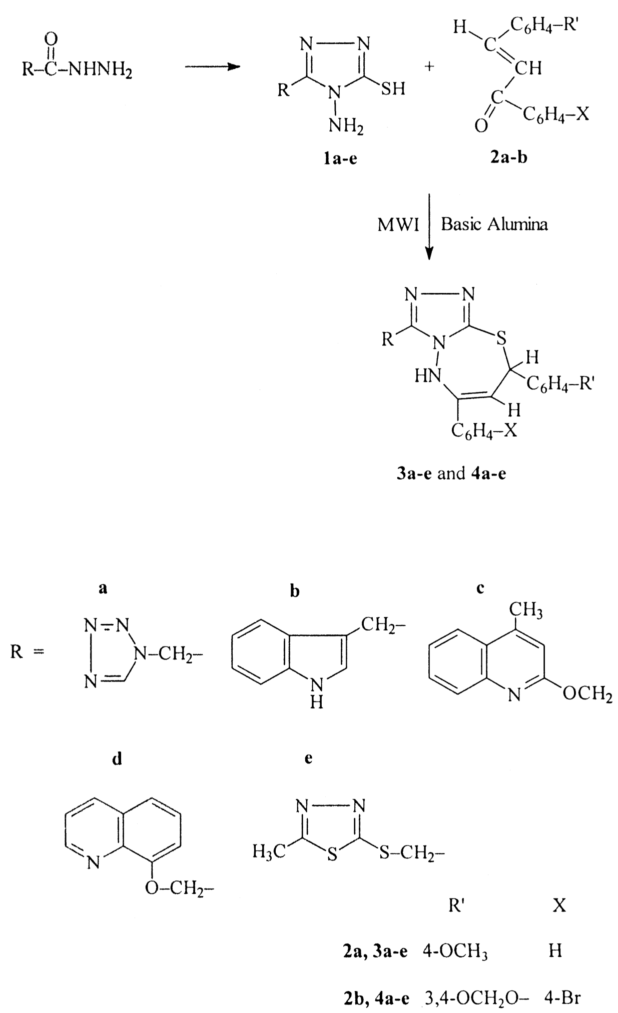

	R'	X
2a, 3a-e	4-OCH$_3$	H
2b, 4a-e	3,4-OCH$_2$O–	4-Br

Scheme 1.

Table 1. Physical data of compounds **3a–e** and **4a–e**

Compound no.	Reaction period (h[a])/(min[b])/(s[c])	Yield (%) a/b/c
3a	12/7/60	57/70/90
3b	14/9/90	70/73/95
3c	18/8/120	62/78/93
3d	11/10/60	73/79/96
3e	15/8/90	68/75/94
4a	13/9/90	65/73/92
4b	16/7/120	70/78/96
4c	12/10/90	72/80/97
4d	10/8/60	68/79/93
4e	16/7/120	60/78/91

[a] Conventional heating.
[b] Solution-phase MWI.
[c] Solid-phase MWI.

products displayed disappearance of band at 1650–1660 cm^{-1} due to C=O of chalcone and -SH of mercapto triazoles at 2570 cm^{-1} and appearance of a band at 1580–1640 cm^{-1} due to C=N, and at 3320–3400 due to -NH. The disappearance of the signal at δ 11–12 of -SH proton of mercapto triazoles and also the appearance of signal at δ 10.1–10.3 due to -NH of the thiadiazepine ring in the ^{1}H NMR spectrum confirmed product formation.

Pharmacological results

Antibacterial activity

All the synthesised compounds were screened for their in vitro antibacterial activity. *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aerogenosa*, *Klebsilla aerogenes* and *Brodettla bronchiseptica* were used to determine antibacterial activity as measured by the cup-plate agar diffusion method[18] (Table 2). Compounds were dissolved in phosphate buffer at concentration of 50 µg/mL. All compounds were active against *B. subtilis* and *P. aerogenosa*. Compounds **3a**, **3c**, **3e** and **4a** were most potent and comparable to activities of norfloxacin. **3b**, **4b** and **4e** also posses promising antibacterial activity. Only weak activity was observed with the other compounds **3d**, **4c** and **4d**.

Antifungal activity

All synthesised compounds were also screened for their in vitro antifungal activity at 25 and 50 µg/mL against *A. niger* and *A. flavus* by the paper disc diffusion method[19] (Table 3). The zone of inhibition was measured in millimetres. The antifungal activities of test compounds were compared to standard salicylic acid (13–18 mm).[20] DMF was used as solvent. All compounds

Table 2. Antibacterial activity[a] of thiadiazepine derivatives

Compound no.	EC	BS	PA	KA	BB
3a	+ +	+ + +	+ + +	+ +	+ + + +
3b	+ + +	+	+ +	+ +	+
3c	+ + + +	+ +	+ +	+ +	+ + +
3d	–	+	+	–	+ +
3e	+ +	+ + +	+	+ +	+ + +
4a	+ +	+	+ + + +	+ +	+
4b	+ +	+ +	+	+ +	+
4c	–	+	+ +	+	–
4d	+	+	+	–	+
4e	+ + +	+	+ +	+	+ +
Norfloxacin	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

[a] Data are zones of inhibition (mm). EC, *E. coli* K_{12}; BS, *B. subtilis*; PA, *P. aerogenosa*; KA, *K. aerogenes* 2281; BB, *B. bronchiseptica* 2267. – = No measurable activity; + = 3–9 mm; + + = 10–12 mm; + + + = 13–16 mm; + + + + = 17–21 mm; + + + + = >21 mm.

Table 3. Antifungal activity[a] of thiadiazepine derivatives

Compound no.	Inhibition of *A. niger*		Inhibition of *A. flavus*	
	25 μg/mL	50 μg/mL	25 μg/mL	50 μg/mL
3a	+ +	+ + + +	+ + +	+ +
3b	+	+ +	+ +	+ +
3c	+ +	+ + + +	+ + +	+ +
3d	+	+	+ + +	+ +
3e	+	+	+ +	+
4a	+ + +	+ +	+ +	+ +
4b	+ + +	+ + +	+ +	+ + +
4c	+	+ +	+	+ +
4d	+ + +	+ + + +	+ + +	+ + +
4e	+ +	+ +	+ +	+ +
Salicylic acid	+ + + +	+ + + +	+ + +	+ + +

[a] + = 3–9 mm; + + = 10–12 mm; + + + = 13–16 mm; + + + + = 17–21 mm; + + + + = >21 mm.

are active against *A. niger* and *A. flavus*. Compounds **3a**, **3c**, **4a**, **4b** and **4d** provided the best antifungal activity and compared well with the activity of salicylic acid. The compounds **3b**, **3d**, **3e**, **4c** and **4e** also possess promising antifungal activity.

In conclusion, this is the first report on the synthesis of triazolo thiadiazepines on a solid support using MWI, in the absence of any toxic and mineral acids, bases or organic solvents. In short, we have developed the facile rapid and economic methodology for various useful heterocyclic compounds keeping modernisation and simplication of classical procedure. The results shown in Table 1 demonstrate the versatility of the process as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to seconds with improved yield as compared to conventional heating.[21]

Experimental

Melting points were taken on Thomas Hoover apparatus and are uncorrected. Elemental analyses were performed on a Heraeus CHN-Rapid analyser. ^{1}H NMR spectra were recorded in $CDCl_3$ at 90 MHz on an FT NMR R-600 spectrophotometer using TMS as internal standard (chemical shift in δ, ppm). IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin–Elmer FTIR-1710 spectrophotometer. Microwave irradiations were carried out in a Padmini Essentia Domestic Microwave oven, model Brownie at 2450 MHz (5–7 W). The purity of compounds was checked on silica gel coated Aluminium plates (Merck).

General procedure for the synthesis of 1,2,4-triazoles (1a–e)

These were synthesised according to a previously published literature method.[22]

General procedure for the synthesis of chalcones (2a–b)

Prepared according to our laboratory method reported earlier.[23]

General procedure for the synthesis of 3-[1-(tetrazol-1′-yl/indol-3′-yl/4′-methyl quinoline-2′-yl/quinolin-8′-yl/5′-methyl-1′,3′,4′-thiadiazol-2′-ylthio)-methyl]-6-phenyl-8-(4″-methoxy phenyl/3″,4″-methylenedioxy phenyl)-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazepine (3a–e and 4a–e)

Method A: Solution-phase MWI. To a solution of substituted 1,2,4-triazoles **1a–e** (10 mmol) in acetone (10 mL) taken in an Erlenmeyer flask were added chalcones **2a–b** (10 mmol) and K_2CO_3. The reaction mixture was subjected to microwave irradiation for 7–10 min with an interval after every 20–30 s. The reaction mixture was cooled, inorganic salt was filtered off and solvent was evaporated. The solid obtained was recrystallised from a mixture of CH_2Cl_2/methanol.

Method B: Solid-phase MWI. Basic alumina (20 g)[24] was added to the solution of 1,2,4-triazoles **1a–e** (10 mmol) and chalcones **2a–b** (10 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was mixed and the adsorbed material was dried, placed in an alumina bath[25] inside the microwave oven then irradiated for 60–120 s. The mixture was cooled and product was extracted into CH_2Cl_2 (20 mL). The product was collected by evaporating the solvent and recrystallised from a mixture of CH_2Cl_2/methanol.

3a. Mp 125–127 °C. ^{1}H NMR ($CDCl_3$) δ 3.4 (s, 3H, 4″-OCH_3), 4.91 (s, 1H, H-8 of thiadiazepine) 5.25 (s, 1H, H-7 of thiadiazepine), 6.0 (s, 2H, 3-CH_2), 7.4–7.8 (m, 9H, Ar-H), 8.8 (s, 1H, H-5 of tetrazole), 10.1 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1580 (C=N), 3360 (NH). Anal. calcd for $C_{20}H_{17}N_8SO$: C, 57.55; H, 4.07; N, 26.85. Found: C, 57.57; H, 4.09; N, 26.83.

3b. Mp 132–134 °C. ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H, 4″-OCH_3), 3.53 (s, 2H, 3-CH_2), 4.95 (s, 1H, H-8 of thiadiazepine), 5.20 (s, 1H, H-7 of thiadiazepine), 7.2–8.1 (m, 13H, Ar-H), 8.8 (brs, 1H, NH), 10.2 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1595 (C=N), 3320 (NH). Anal. calcd for $C_{27}H_{22}N_5SO$: C, 69.82; H, 4.74; N, 15.08. Found: C, 69.84; H, 4.78; N, 15.05.

3c. Mp 178–181 °C. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H, 4′-CH_3), 3.42 (s, 3H, 4″-OCH_3), 4.98 (s, 1H, H-8 of thiadiazepine), 5.23 (s, 1H, H-7 of thiadiazepine), 5.45

(s, 2H, 3-OCH_2), 7.2–8.2 (m, 14H, Ar-H), 10.2 (brs, 1H, NH of thaidiazepine). IR (KBr cm^{-1}) 1585 (C=N), 3390 (NH). Anal. calcd for $C_{29}H_{24}N_5SO_2$: C, 68.77; H, 4.74; N, 13.03. Found: C, 68.79; H, 4.78; N, 13.85.

3d. Mp 162–164 °C. ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H, 4″-OCH_3), 5.01 (s, 1H, H-8 of thiadiazepine), 5.25 (s, 1H, H-7 of thiadiazepine), 5.45 (s, 2H, 3-OCH_2), 7.3–8.1 (m, 15H, Ar-H), 10.3 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1610 (C=N), 3400 (NH). Anal. calcd for $C_{28}H_{22}N_5SO_2$: C, 68.29; H, 4.47; N, 14.22. Found: C, 68.27; H, 4.49; N, 14.25.

3e. Mp 270–272 °C. ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H, 5′-CH3), 3.53 (s, 3H, 4″-OCH_3), 4.70 (s, 2H, 3-SCH_2), 5.10 (s, 1H, H-8 of thiadiazepine), 5.27 (s, 1H, H-7 of thiadiazepine), 7.4–8.4 (m, 9H, Ar-H), 10.4 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1605 (C=N), 3350 (NH). Anal. calcd for $C_{21}H_{19}N_6S_3O$: C, 53.96; H, 4.06; N, 17.98. Found: C, 53.94; H, 4.08; N, 17.96.

4a. Mp 152–154 °C. ^{1}H NMR ($CDCl_3$) δ 4.91 (s, 1H, H-8 of thiadiazepine), 5.2 (s, 1H, H-7 of thiadiazepine), 5.7 (s, 2H, 3-CH_2), 6.1 (s, 2H, 3″,4″-OCH_2O), 7.2–8.4 (m, 7H, Ar-H), 8.7 (s, 1H, H-5 of tetrazole), 10.3 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1595 (C=N), 3385 (NH). Anal. calcd for $C_{27}H_{19}N_5SO_2Br$: C, 47.05; H, 2.74; N, 21.96. Found: C, 47.04; H, 2.76; N, 21.98.

4b. Mp 160–162 °C. ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 2H, 3-CH_2), 4.99 (s, 1H, H-8 of thiadiazepine), 5.27 (s, 1H, H-7 of thiadiazepine), 6.2 (s, 2H, 3″,4″-OCH_2O), 7.1–8.3 (m, 11H, Ar-H), 8.7 (brs, 1H, NH of indole), 10.21 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1600 (C=N), 3370 (NH). Anal. calcd for $C_{20}H_{14}N_8SO_2Br$: C, 58.16; H, 3.41; N, 12.56. Found: C, 58.18; H, 3.44; N, 12.54.

4c. Mp 192–194 °C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 4′-CH_3), 5.13 (s, 1H, H-8 of thiadiazepine), 5.31 (s, 1H, H-7 of thiadiazepine), 5.5 (s, 2H, 3-OCH_2), 6.25 (s, 2H, 3″,4″-OCH_2O), 7.3–8.5 (m, 12H, Ar-H), 10.25 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1620 (C=N), 3400 (NH). Anal. calcd for $C_{29}H_{21}N_5SO_3Br$: C, 58.09; H, 3.50; N, 11.68. Found: C, 58.07; H, 3.53; N, 11.70.

4d. Mp 183–185 °C. ^{1}H NMR ($CDCl_3$) δ 4.95 (s, 1H, H-8 of thiadiazepine), 5.30 (s, 1H, H-7 of thiadiazepine), 5.45 (s, 2H, 3-OCH_2), 6.2 (s, 2H, 3″,4″-OCH_2O), 7.3–8.4 (m, 12H, Ar-H), 10.36 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1610 (C=N), 3395 (NH). Anal. calcd for $C_{28}H_{19}N_5SO_3Br$: C, 57.43; H, 3.24; N, 11.46. Found: C, 57.41; H, 3.23; N, 11.49.

4e. Mp 295–297 °C. ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3H, 5′-CH_3), 4.72 (s, 2H, 3-SCH_2), 5.15 (s, 1H, H-8 of thiadiazepine), 5.37 (s, 1H, H-7 of thiadiazepine), 6.43 (s, 2H, 3″,4″-OCH_2O), 7.25–8.34 (m, 7H, Ar-H), 10.20 (brs, 1H, NH of thiadiazepine). IR (KBr cm^{-1}) 1590 (C=N), 3380 (NH). Anal. calcd for $C_{22}H_{16}N_6S_3O_2Br$: C, 46.15; H, 2.79; N, 14.68. Found: C, 46.17; H, 2.77; N, 14.65.

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