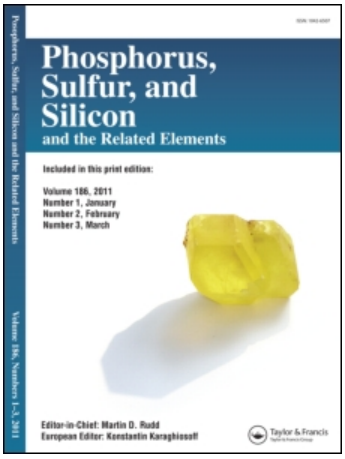

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Biological Active Chromene Benzothiadiazole Derivatives

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To cite this Article Rao, G. V. Panakala , Rajitha, B. , Reddy, Y. Thirupathi , Reddy, P. Narsimha and Kumar, V. Naveen(2005) 'Synthesis of Biological Active Chromene Benzothiadiazole Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 9, 2119 — 2126
To link to this Article: DOI: 10.1080/104265090917556
URL: http://dx.doi.org/10.1080/104265090917556

Phosphorus, Sulfur, and Silicon, 180:2119–2126, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090917556

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Synthesis of Biological Active Chromene Benzothiadiazole Derivatives

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In this article, we describe the synthesis of various substituted Chromene-[1,3]thiazolo [2,1,3] benzothiadiazoles ***4a-l*** *by conventional (****Method A****) and microwave-assisted (****Method B****) which achieved reductions in reaction times, higher yields, and a cleaner reaction than the conventional method. A comparative study of these two methods has been discussed.*

Keywords Benzothiadiazole; mercapto acetic acid; microwave irradiation

INTRODUCTION

Heterocyclic compounds of thiazolo [2,1,3] benzothiadiazoles were reported as anticancer agents.[1] There is a considerable interest in the chemotherapeutic activity of heterocyclic compounds such as thiadiazole, thiazole, thiadiazolidinone, and [2,1,3] benzothiadiazoles.[2–4] It is already reported that thiazolidinones and benzothiadiazoles are potent anti-HIV agents.[5,6] Chromene nucleus is common to many natural and synthetic products associated with anticancer and other biological activities.[7] In view of these biological activities, it is interesting to synthesize unreported chromene [1,3] thiazole [2,1,3] benzothiadiazoles and the evaluation of biological activity exhibited by them.

Received July 29, 2004; accepted November 3, 2004.
The authors are thankful to the University Grants Commission for financial assistance and the director IICT for analytical support.
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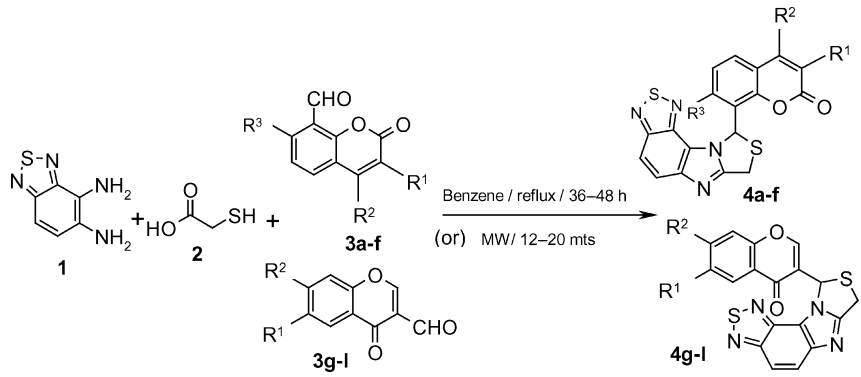


FIGURE 1

Drug discovery in chemistry is critical, especially at the lead optimization phase, since lead optimization time is usually very long with a very high manpower requirement. New ways to improve the efficiency output and quality in this phase always is needed. One feasible solution is microwave-assisted synthesis, which is in many ways superior to traditional heating reactions and is completed in minutes. Yields are generally higher than conventional, methods work up is simple, heating is immediate and quantitative, and the temperature accurately is controlled so that reactions can be more easily repeated.[8]

RESULTS AND DISCUSSION

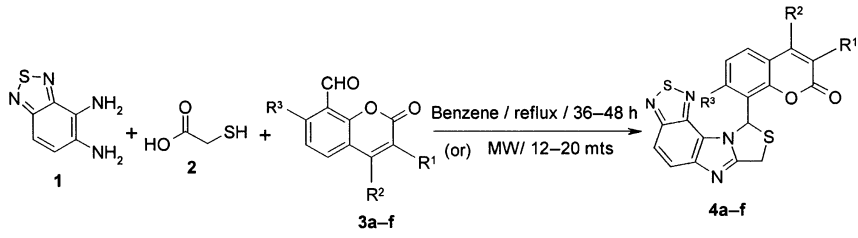
2,1,3-benzothiadiazole-4,5-diamine[9] **1** was condensed with various substituted chromene-2 one 8-aldehyde **3a–f** in the presence of mercapto acetic acid and benzene at reflux for 36–48 h to give rise to the corresponding chromene benzothiadiazoles **4a–f** and condense with chromene-4-one-3-aldehyde[10] **3g–l** and mercapto acetic acid in benzene at reflux for 36–48 hours to give rise to the corresponding chromen benzothiadiazoles **4g–l**. These compounds alternatively also were prepared by microwave irradiation at a 300-watt power level in an open vessel for 12–20 mts in good yields. The yields of these two methods and physical data of the compounds **4a–l** are tabulated in Table I. In microwave-irradiation technique, the yields are better than the conventional method and time drastically is reduced.

The IR spectra of compounds **3a–l** showed an absorption 1650–1700 (C=O), 3450–3350 (OH), 1600–1650 (C=N), 1567–1540 (C=C), and 600–700 (C–S) stretching, respectively. The ^{1}H NMR spectra of **3a** showed two singlets at δ 7.80 and 7.60 for two aromatic protons of

TABLE I Yields and Physical Data of the Compounds 4a–l

Compound	Mol. F (Mol. Wt)	Reaction time A (h)	Reaction time B (mts)	Yield (%) A	Yield (%) B	M.P (°C) A	M.P (°C) B	Calcd (found) C	Calcd (found) H	Calcd (found) N
4a	$C_{19}H_{12}N_4O_3S_2$ (408)	40	15	52	65	170–175	171–174	55.90 (55.88)	2.92 (2.94)	13.72 (13.71)
4b	$C_{24}H_{14}N_4O_3S_2$ (470)	48	20	45	60	195–200	198–200	61.27 (61.29)	2.98 (2.96)	11.91 (11.91)
4c	$C_{19}H_{11}BrN_4O_3S_2$ (487)	42	16	55	60	205–210	205–208	46.81 (46.82)	2.25 (2.24)	11.50 (11.49)
4d	$C_{19}H_{11}ClN_4O_3S_2$ (442.5)	36	13	60	70	172–176	174–176	51.52 (51.51)	2.47 (2.48)	12.68 (12.65)
4e	$C_{18}H_8N_4O_3S_2$ (463)	38	15	55	65	182–185	179–183	46.65 (46.66)	1.72 (1.71)	12.09 (12.10)
4f	$C_{18}H_8BrN_4O_3S_2$ (552)	42	16	50	62	182–186	182–184	39.12 (39.13)	1.45 (1.44)	10.14 (10.13)
4g	$C_{18}H_{10}N_4O_3S_2$ (394)	48	15	50	65	169–175	170–172	54.82 (54.84)	2.53 (2.52)	14.20 (14.10)
4h	$C_{18}H_9ClN_4O_3S_2$ (428.5)	42	12	53	62	175–180	178–182	50.40 (50.39)	2.10 (2.11)	13.06 (13.07)
4i	$C_{18}H_9BrN_4O_3S_2$ (473)	48	16	50	65	180–185	183–185	45.65 (45.66)	19.03 (19.02)	11.83 (11.84)
4j	$C_{18}H_{10}N_4O_2S_2$ (378)	40	15	55	70	185–190	188–190	57.14 (57.15)	2.64 (2.63)	14.81 (14.80)
4k	$C_{18}H_9ClN_4O_2S_2$ (412.5)	42	18	50	65	182–187	181–187	52.36 (52.34)	2.18 (2.20)	13.57 (13.56)
4l	$C_{18}H_9BrN_4O_2S_2$ (457)	48	16	55	70	190–195	192–195	47.26 (47.24)	19.69 (19.70)	12.25 (12.26)

A, Conventional Heating; B, Microwave Irradiation.



Compound	R^1	R^2	R^3
4a	H	CH_3	OH
4b	H	C_6H_5	OH
4c	Br	CH_3	OH
4d	Cl	CH_3	OH
4e	Cl	Cl	OH
4f	Br	Br	OH

SCHEME 1

benzothiadiazole, two doublets at δ 7.40 and 7.20 due to aromatic protons of coumarin, one singlet is observed at δ 6.25 for C-3H coumarin, and one singlet is observed at δ 5.00 for chiral proton. One singlet is observed at δ 4.20 due to two protons of S-CH_2, one singlet is observed at δ 10.12 due to an OH proton, and one singlet observed at δ 2.20 for three CH_3 protons. The mass spectra of **3a** at m/z 408 (30%) of is consistent with its molecular formula. The ^{1}H NMR and mass data of all the compounds were tabulated in Table II.

TABLE II NMR and Mass Spectral Data of Compounds 4a–l

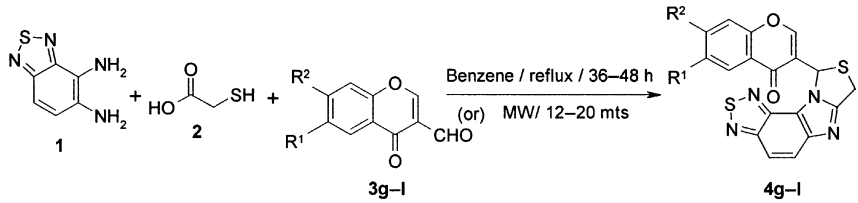
Compound	^{1}H NMR data
4a	δ7.80 (s, 1H, ArH), δ7.60 (s, 1H, ArH), δ7.40 (d, 1H, ArH, J = 7.25 Hz), δ7.20 (d, 1H, ArH, J = 7.25 Hz), δ6.25 (s, 1H, C-3, Coumarin H), δ5.00 (s, 1H, Chiral H), δ4.20 (s, 2H, S-CH_2), δ10.12 (s, 1H, OH), δ 2.20 (s, 3H, CH_3), m/z: 408 (M+).
4b	δ7.78–7.00 (m, 9H, ArH), δ6.10 (s, 1H, C-3 Coumarin H), δ5.00 (s, 1H, Chiral H), δ4.00 (s, 2H, S-CH_2), δ10.10 (s, 1H, OH), m/z: 471 (M+1).
4c	δ7.60–7.10 (m, 4H, ArH), δ4.98 (s, 1H, Chiral H), δ3.90 (s, 2H, S-CH_2), δ9.87 (s, 1H, OH), δ2.00 (s, 3H, CH_3), m/z: 489 (M+1).
4d	δ7.60 (s, 1H, ArH), δ7.50 (s, 1H, ArH), δ7.30 (d, 1H, C-6 Coumarin H, J = 7.10 Hz), δ7.10 (d, 1H, Coumarin C-5H, J = 7.10 Hz), δ4.90 (s, 1H, Chiral CH), δ4.30 (s, 2H, S-CH_2) δ 10.10 (s, 1H, OH), δ2.10 (s, 3H-CH_3), m/z: 443.5 (M+1).
4e	δ7.50–7.10 (m, 4H, ArH), δ5.10 (s, 1H, Chiral H), δ4.30 (s, 2H, S-CH_2), δ10.17 (s, 1H, OH), m/z: 464 (M+1).
4f	δ7.60–7.10 (m, 4H, ArH), δ4.99 (s, 1H, Chiral H), δ4.20 (s, 2H, S-CH_2), δ10.20 (s, 1H, OH), m/z: 554 (M+1).
4g	δ7.60 (s, 1H, ArH), δ7.40 (s, 1H, ArH), δ7.41 (s, 1H, ArH), δ7.30 (d, 1H, ArH, J = 7.25 Hz), δ7.20 (d, 1H, ArH, J = 7.27 Hz), δ6.10 (s, 1H, Coumarin C-2H), δ5.10 (s, 1H, Chiral H), δ4.10 (s, 2H, S-CH_2), δ10.19 (s, 1H, OH), m/z: 396 (M+1).
4h	δ7.50 (s, 1H, ArH), δ7.40 (s, 1H, ArH), δ7.30 (s, 1H, ArH), δ7.29 (s, 1H ArH), δ6.00 (s, 1H, Chromene C-2H), δ4.80 (s, 1H, Chiral H), δ4.20 (s, 2H, S-CH_2), δ10.20 (s, 1H, OH), m/z: 429.5 (M+1).
4i	δ7.60 (s, 1H, ArH), δ7.41 (s, 1H, ArH), δ7.50 (s, 1H, ArH), δ7.20 (s, 1H, ArH), δ5.98 (s, 1H, C-2 Chromene H), δ5.10 (s, 1H, Chiral H), δ4.28 (s, 2H, S-CH_2), m/z: 474 (M+1).
4j	δ7.60 (s, 1H, ArH), δ7.50 (s, 1H, ArH), δ7.50–7.10 (m, 4H, ArH), δ5.98 (s, 1H, Chromene C-2H), δ4.90 (s, 1H, Chiral H), δ4.50 (s, 2H, S-CH_2), m/z: 378 (M+1).
4k	δ7.61 (s, 1H, ArH), δ7.40 (s, 1H, ArH), δ7.40 (d, 1H, ArH J = 7.10 Hz), δ7.30 (d, 1H ArH J = 7.10 Hz), δ6.10 (s, 1H, Chromene C-2H), δ4.99 (s, 1H, Chiral H), δ4.20 (2H, S, S-CH_2), m/z: 413.5 (M+1).
4l	δ7.50 (s, 1H, ArH), δ7.40 (s, 1H, ArH), δ7.45 (d, 1H, ArH, J = 7.25 Hz), δ7.30 (d, 1H, ArH, J = 7.25 Hz) δ7.20 (s, 1H, ArH), δ6.10 (s, 1H, Chromene C-2H), δ5.10 (Chiral, 1H), δ4.20 (s, 2H), m/z: 459 (M+2).

TABLE III Results of Antibacterial and Antifungal Activity of Compounds 4a–l

	Zone of inhibition in mm			
	Antibacterial		Antifungal	
Compound	*S. aureous*	*E. Coli*	*A. Niger*	*C-albicans*
4a	4	5	3	4
4b	6	3	5	6
4c	8	5	4	6
4d	10	14	13	15
4e	11	15	14	15
4f	4	3	5	7
4g	3	7	6	10
4h	11	15	12	13
4i	4	6	4	6
4j	3	3	8	7
4k	10	12	14	17
4l	6	7	7	8
Ciproflxacin	20	21	—	—
Griseofulvin	—	—	26	25

ANTIBACTERIAL ACTIVITY

All the compounds were evaluated for antibacterial activity by the cup-plate diffusion method against *Staphylococcus aureous* and *Escherichia coli*. The concentration of the test compound was 1 mg/mL and Ciprofloxacin was used a standard drug. The compounds **4d, 4h,** and **4k** are moderate active and other compounds are weekly active



Compound	R^1	R^2
4g	H	OH
4h	H	OH
4i	Br	OH
4j	H	H
4k	Cl	H
4l	Br	H

SCHEME 2

against both bacterial. It was observed that chloro substitution increased activity while Bromo substitution diminished activity.

ANTIFUNGAL ACTIVITY

The synthesized compounds were screened for their antifungal activity against *A-Niger* and *C-albicans* at a concentration of 1 mg/mL using griseofulvin as a standard drug by the cup-plate diffusion method. The compound **4d, 4e, 4h,** and **4k** were moderately active and the others were weekly active against *A. Niger* and *C. albicans*. All the results were reported in Table III.

EXPERIMENTAL

All melting points were determined on the cintex melting point apparatus and were uncorrected. The purity of the compounds was monitored by TLC performed on silica gel plates (Merck) using ethylactate and hexane. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX series FT-IR Spectrophotometer. The ^1H NMR spectra were recorded on a Varian Gemini 200 MHZ Spectrometer using TMS as an internal standard and mass spectra were scanned on a Jeol JMC D-300 spectrometer. Microwave irradiation reactions were carried out in a BPL-800-G domestic microwave oven. The elementary analysis was carried out by Carlo Erba stumentazone, Itali Model 1108.

Synthesis of 2-(7-Hydroxy-4-methyl-2H-chromene-2-one)-8H-imidazo-[4,5-e]-[1,3]thiazole-[2,1,3]-benzothiadiazole 4a

Method A: Conventional Heating

A mix of 2,1,3-benzothiadiazole-4,5-diamine (1.66 g, 0.01 mole), 2-mercapto acetic acid (1.84 g, 0.02 mole), and 7-hydroxy-4-methyl-coumarin-8-aldehyde (2.04 g, 0.01 mole) were mixed in benzene (10 mL) and refluxed for 40 h. Then reaction mass was cooled to an ambient temperature and neutralized with 10% aq $NaHCO_3$ solution (10 mL). The organic layer was dried over Na_2SO_4. The solvent was removed in a vacuum and residue was purified by column chromatography (ethylacetate/hexane, 1:1) to give **4a** (2.12 g, 52%). The compounds similarly **4b–f** were prepared.

Method B: Microwave Irradiation

A mixture of 2,1,3-benzothiadiazole-4,5-diamine (1.66 g, 0.01 mole), 2-mercapto acetic acid (1.84 g, 0.02 mole), and 7-hydroxy-4-methyl-coumarin-8-aldehyde (2.04 g, 0.01 mole) were finely grounded in watch

glass and irradiated in a microwave oven at 300 watts for 15 mts. Then this crude product was dissolved in methylenechloride and washed with a 10% aq $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4. The solvent was removed in vacuum and residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to give **4a** (2.65 g, 65%). All the compounds **4b–f** similarly were prepared.

Synthesis of 2-(7-hydroxy-2H-chromene-4-one)-8H-imidazo-[4,5,e]-[1,3] Thiazole-(2,1,3)-benzothiadiazole 4g

Method A: Conventional Heating

A mixture of 2,1,3 benzothiadiazole-4, 5-diamine (1.66 g, 0.01 mole), 2-mercapto acetic (1.84 g, 0.02 moles), and 7-hydroxy chromene-4-one –3-aldehyde (1.90 g, 0.01 mole) were mixed in benzene (10 mL) and refluxed for 48 h. Then reaction mass was cooled to an ambient temperature and neutralized with 10% aq. $NaHCO_3$ solution (10 mL). The organic layer was dried over Na_2SO_4. The solvent was removed in a vacuum and residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to give **4g** (1.97 g, 50%). The compounds **4h–l** similarly were prepared.

Method B: Microwave Irradiation

A mixture of 2,1,3-benzothiadiazole-4, 5-diamine (1.66 g, 0.01 mole), 2-mercapto acetic acid (1.84 g, 0.02 mole), and 7-hydroxy chromene-4-one-3-aldehyde (1.90 g, 0.01 mole) were finely grounded in watch glass and irradiated in a microwave oven at 300-watt power level for 15 mts. Then this crude product was dissolved in methylenechloride and washed with 10% aq. sodium bicarbonate solution. The organic layer was dried over Na_2SO_4. The solvent was removed in vacuum and residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to give **4g** (2.56 g, 65%). All the compounds **4h–l** similarly were prepared.

CONCLUSION

In conclusion, we have designed and synthesized a new series of pharmacologically valuable chromene-substituted benzothiadiazoles **4a–l**. In this study, we observed that chlorosubstituted compounds are more active than bromo substituted compounds.

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