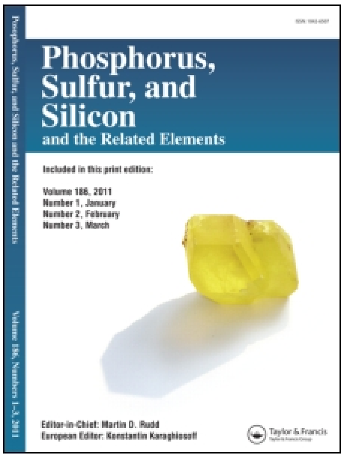


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS, NMR AND MOLECULAR MODELING STUDY OF 4,9a-DIARYL-9,9a-DIHYDRO 1*H*-[1,4]THIAZINO[4,3-a][1,3]BENZIMIDAZOLES

E. Karthikeyan[a]; S. Perumal[a]; S. Selvaraj[a]
[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai, India

To cite this Article Karthikeyan, E. , Perumal, S. and Selvaraj, S.(2004) 'SYNTHESIS, NMR AND MOLECULAR MODELING STUDY OF 4,9a-DIARYL-9,9a-DIHYDRO 1*H*-[1,4]THIAZINO[4,3-a][1,3]BENZIMIDAZOLES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 12, 2561 — 2567

To link to this Article: DOI: 10.1080/10426500490494525

URL: http://dx.doi.org/10.1080/10426500490494525

Phosphorus, Sulfur, and Silicon, 179:2561–2567, 2004
Copyright © Taylor & Francis Inc.
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490494525

SYNTHESIS, NMR AND MOLECULAR MODELING STUDY OF 4,9a-DIARYL-9,9a-DIHYDRO-1*H*-[1,4]THIAZINO[4,3-a][1,3]BENZIMIDAZOLES

E. Karthikeyan, S. Perumal, and S. Selvaraj
Department of Organic Chemistry, School of Chemistry,
Madurai Kamaraj University, Madurai, India

(Received March 16, 2004; accepted May 21, 2004)

A series of substituted 4,9a-diaryl-9,9a-dihydro-1H-[1,4]thiazino[4,3-a][1,3]benzimidazoles was prepared in good yields from the reaction of bis(aroylmethyl) sulfides with ortho-phenylenediamine in glacial acetic acid under reflux and under microwave irradiation. Microwave irradiation is found to accelerate the reaction, besides giving better yield in the case of the thiazinobenzimidazoles with electron-withdrawing groups in the aryl rings than the thermal reaction.

Keywords: ^{1}H NMR; ^{13}C NMR; benzimidazole; microwave irradiation; thiazine

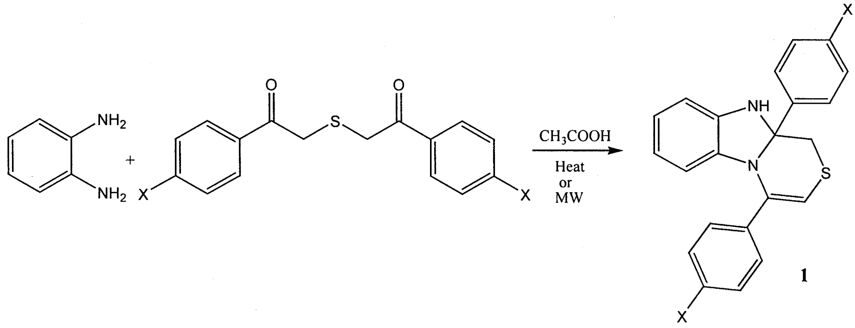
INTRODUCTION

Thiazines display diverse biological activities and act as tranquilizers, sedatives, antiepileptics, and antitubercular, antitumour, bactericidal, and parasiticidal agents.[1] They have also found use as cardiovascular agents,[2] herbicide antidote,[3] antihypertensives, and antithrombic agents.[4,5] Thiazine derivatives are also used in the preparation of peptide resin inhibitors and good color photographic materials,[6,7]

The authors (S. Perumal and S. Selvaraj) thank the DST and CSIR, New Delhi for major research projects, and for DST for funds under the IRHPA programme for the purchase of a high-resolution 300 MHz NMR spectrometer. Funding by DST under the FIST programme and the UGC for a major research project and for funds under the ASIST and the DRS programmes are also gratefully acknowledged. S. Perumal thanks Professor Jose Carlos Menendez, Departamento de Quimica Organica y Farmaceutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain for molecular modeling.

Address correspondence to S. Perumal, Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India. E-mail: subbu_perum@rediffmail.com

where they act as image stabilizers.[8] Benzimidazoles and their derivatives display a number of important biological activities such as analgesic,[9] HIV-1 reverse transcriptase inhibitors,[10]and antimicrobial agents,[11] and thus they possess great chemotherapeutic potential. In view of the above bioapplications of these two classes of heterocycles, we embarked on the synthesis of 4,9a-diaryl-9,9a-dihydro-1*H*-[1,4]thiazino[4,3-a][1,3]benzimidazoles (**1**) (Scheme 1), which comprise both thiazine and benzimidazole rings, and we report our results in this article.



1

Compound	**X**
1a	H
1b	Br
1c	Cl
1d	Me
1e	NO_2

SCHEME 1

RESULTS AND DISCUSSION

In the present investigation, the synthesis of 4,9a-diaryl-9,9a-dihydro-1*H*-[1,4]thiazino[4,3-a][1,3]benzimidazoles (**1**) was performed both under thermal conditions and microwave irradiation. The thermal reaction was performed by refluxing a mixture of bis(aroylmethyl) sulphides and *ortho*-phenylenediamine in an equimolar ratio in glacial acetic acid (Table I). The microwave-assisted reaction was performed by irradiating a mixture of the reagents along with two drops of acetic acid in a domestic microwave oven at power level 3 (Table I). In both the thermal

TABLE I Synthesis of 4,9a-Diaryl-9,9a-dihydro-1*H*-[1,4]thiazino[4,3-a][1,3]-benzimidazoles (**1**) Under Thermal and Microwave Conditions

	Time (min.)			Yield (%)			Calcd./(found) (%)		
1	Thermal[a]	MW (Temp.°C)[b]	m.p. (°C)	Thermal	MW	Mol. formula	C	H	N
a	30	4 (63)	152	80	81	$C_{22}H_{18}N_2S$	77.16	5.30	8.18
							(77.11	5.27	8.12)
b	30	2 (50)	140	78	83	$C_{22}H_{16}Br_2N_2S$	52.82	3.22	5.60
							(52.76	3.18	5.58)
c	60	8 (75)	164	80	98	$C_{22}H_{16}Cl_2N_2S$	64.24	3.92	6.81
							(64.21	3.91	6.78)
d	30	6 (67)	119	76	79	$C_{24}H_{22}N_2S$	77.80	5.98	7.56
							(77.76	5.96	7.54)
e	[c]	4 (63)	148	[c]	88	$C_{22}H_{16}N_4O_4S$	61.10	3.73	12.96
							(61.06	3.75	12.94)

[a] Under reflux in acetic acid.

[b] Temperature of the silica bath found immediately after the irradiation.

[c] Decomposition and NMR fails to show any characterizable product.

TABLE II ^{1}H and ^{13}C NMR Data of 4,9a-Diaryl-9,9a-dihydro-1*H*-[1,4]-thiazino[4,3-a][1,3]-benzimidazoles (**1**)

Compound	^{1}H NMR ($CDCl_3$/TMS, δ (ppm))	^{13}C NMR ($CDCl_3$/TMS, δ (ppm))
1a	3.29 (s, 2H); 4.75 (b, 1H, N—H); 5.72 (s, 1H); 5.87 (d, *J* = 8 Hz, 1H); 6.50–6.70 (m, 3H); 7.21–8.21 (m, 10H)	31.2, 79.9, 103.7, 111.5, 112.3, 120.3, 121.4, 125.6, 125.8, 127.5, 127.9, 128.5, 128.7, 128.8, 134.2, 136.9, 137.1, 140.4.
1b	3.16 (s, 2H); 4.38 (b, 1H, N—H); 5.66 (s, 1H); 5.81 (d, *J* = 8 Hz, 1H); 6.40–6.61 (m, 3H); 7.19–8.08 (m, 8H)	30.7, 79.6, 104.6, 111.5, 112.1, 120.7, 121.4, 121.8, 122.6, 127.1, 127.5, 131.9, 132.0, 132.9, 135.7, 136.6, 139.2, 139.6.
1c	2.97 (b, 1H, N—H); 3.20 (d, *J* = 12 Hz, 1H); 3.32 (d, *J* = 12 Hz, 1H); 5.74 (s, 1H); 5.84 (d, *J* = 8 Hz, 1H); 6.43–6.68 (m, 3H); 7.32–7.59 (m, 8H)	29.7, 79.6, 104.0, 110.6, 111.0, 119.4, 120.2, 126.3, 126.9, 128.2, 128.5, 132.4, 132.9, 133.4, 135.0, 137.1, 138.4, 139.0.
1d	2.28 (s, 3H); 2.34 (s, 3H); 2.51 (b, 1H, N—H); 3.37 (s, 2H); 5.66 (d, *J* = 8 Hz, 1H); 5.87 (s, 1H); 6.24–6.55 (m, 3H); 7.15–7.85 (m, 8H)	21.0, 21.1, 29.4, 80.8, 103.3, 108.6, 110.3, 118.1, 120.4, 125.5, 126.0, 129.0, 129.8, 133.7, 134.6, 137.1, 137.4, 138.6, 138.9.
1e	3.36 (s, 2H); 3.57 (b, 1H, N—H); 5.87 (d, *J* = 8 Hz, 1H); 6.07 (s, 1H); 6.60–6.77 (m, 3H); 7.29–8.43 (m, 8H)	20.1, 79.5, 108.6, 108.9, 110.1, 118.2, 120.4, 122.2, 122.7, 123.0, 123.4, 124.8, 126.1, 126.5, 135.4, 147.0, 148.3, 172.0.

and microwave conditions, the reactions were conducted for sufficient time durations to ensure completion of the reaction, as indicated by the thin layer chromatography (TLC) analysis of the reaction mixture. When the irradiation was carried out for periods either shorter or longer time durations, either incomplete reaction or decomposition was found. The data given in Table I show that the reaction proceeds faster under microwave irradiation. The yields of the products are almost the same under thermal and microwave conditions when the substituent in the aryl ring is H or Me or Br. In the case of chlorine substituent, the yield under microwave irradiation is significantly enhanced over the thermal reaction. In the case of nitro substituent, the thermal reaction did not lead to the product at all. Instead, it led to a heavy decomposition wherein no characterizable product could be inferred from the NMR spectrum. In contrast, the microwave reaction of the nitro-substituted sulfide resulted in the formation of an excellent yield of the product. Presumably, the lower maximum temperature reached under microwave irradiation is insufficient to cause the decomposition of the product, which is in line with the often-cited advantage of microwave-assisted reactions. That the reaction is completed more rapidly and at low temperature under microwave irradiation means that some special effects of microwaves, other than the simple heating associated with them, are involved in this reaction. In general, microwave irradiation is known to significantly increase the rate of the reactions that occur through polar transition states and in polar solvents.[12] Similar effects probably play a role in the reaction of diphenacyl sufides bearing electron-withdrawing groups, Cl and NO_2 in this reaction. All the thiazinobenzimidazoles obtained in the present work are hitherto unreported. The analytical data and the ^1H and ^{13}C NMR data are in accordance with the structure proposed (**1**).

The ^1H NMR spectrum of a representative example **1c** is discussed below. That the broad singlet at 2.97 ppm can be described to the N—H proton is evident from the fact that this signal vanishes upon addition of D_2O. The diastereotopic methylenic protons of the thiazine ring give an AB-type signal centering at 3.26 ppm. Apart from the NH proton, another singlet integrating for one proton at 5.74 ppm is readily assigned to the alkenic proton on the basis of its singlet multiplicity as this is the only proton that does not have a coupling partner. The doublet at 5.84 ppm integrating for one proton with the *J* value of 8 Hz is due to one of the protons of the benzene ring of the benzimidazole substructure, which is evident from the H,H-COSY correlation. It is surprising that an aromatic proton occurs at such a high field strength at 5.84 ppm. This suggests that this proton is probably highly shielded by a neighbouring group present in this molecule. This prompted us to perform optimization of the structure of the molecule (**1a**) employing AM1 calculations, which shows that the proton (H-5) lies in the shielding zone of the aryl ring at C-4, as the benzimidazole ring and the aryl ring at C-4 are almost in mutually orthogonal orientations. Presumably, such an orientation for the aryl ring at C-4 is favored in a bid to minimize the steric interactions between H-5 of the benzimidazole ring and the *ortho* protons of the aryl ring at C-4 (Figure 1). The other aromatic protons occur in the region of 6.43–6.68 and 7.32–7.59 ppm. The ^{13}C NMR spectrum is also in agreement with the structure, showing the expected number of signals. All the other thiazinobenzimidazoles also give similar spectroscopic features.

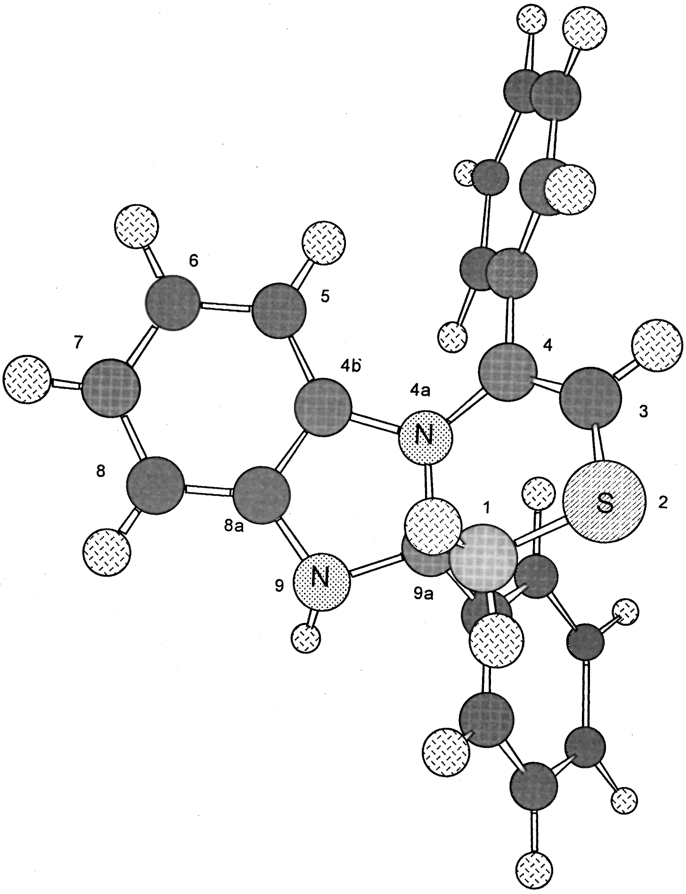


FIGURE 1 AM1 Molecular modeling of 4,9a-diaryl-9,9a-dihydro-1*H*-[1,4]thiazino[4,3-a][1,3]benzimidazoles **1**.

EXPERIMENTAL

The melting points reported in this work are uncorrected. The bis(aroylmethyl) sulfides required for this study were prepared by the usual literature procedures.[13] The ^{1}H and ^{13}C NMR spectra of the compounds in $CDCl_3$ were measured in a Bruker (Avance) instrument operating at 300 and 75 MHz, and their chemical shifts referenced to tetramethylsilane (TMS). All the one- and two-dimensional NMR measurements were made employing standard Bruker software.

The microwave irradiation was done in a domestic IFB microwave oven (model–Electron) of 1000 W capacity and microwave frequency of 2450 MHz at a power level of 3 in a total scale of 5. Molecular modeling of **1a** was performed on a Silicon Graphics Octane workstation running under the IRIX 6.5.14 operating system (Silicon Graphics Inc., Mountain View, CA, USA). Using Spartan's implementation of MMFF, energy minimization of the molecule was performed and the structure was further subjected to geometry optimization using the semiempirical AM1 method.[14]

Synthesis of 4,9a-Diaryl-9,9a-dihydro-1*H*-[1,4]thiazino-[4,3-a][1,3]benzimidazoles (1a–e) Under Thermal Condition: General Procedure

A mixture of finely powdered bis(benzoylmethyl) sulfide (1 g, 0.0037 mol) and an equimolar amount of *ortho*-phenylenediamine (0.4 g, 0.0037 mol) in glacial acetic acid (25 ml) was refluxed for 30 min to ensure completion of the reaction as evident from TLC analysis of the reaction mixture. Then the reaction mixture was neutralized with sodium bicarbonate and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over anhydrous calcium chloride, and the solvent removed. The compound was purified on column chromatography over silica gel with pet. ether: ethyl acetate (98:2 (v/v)) as eluent.

Synthesis of 4,9a-Diaryl-9,9a-dihydro-1*H*-[1,4]thiazino-[4,3-a][1,3]benzimidazoles (1a–e) Under Microwave Irradiation: General Procedure

A mixture of finely powdered bis(benzoylmethyl) sulfide (0.11 g, 0.0004 mol) and an equimolar amount of *ortho*-phenylenediamine (0.043 g, 0.0004 mol) was ground well in a glass tube into which two drops of acetic acid were added, the tube placed over a silica bath in a domestic microwave oven and subjected to microwave irradiation at power level 3 for 4 min. The course of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was worked up as given for the thermal procedure.

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