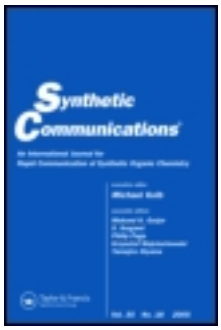

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Stereoselective Synthesis of Polyfunctionalised Nitrothianes: Enhancement of Stereoselectivity by Microwaves

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Abstract

The Michael addition of nitromethane to (*Z,Z*)-2,2'-thiobis(1,3-diarylprop-2-en-1-ones) in the presence of NaOEt in DMF/alcohol under thermal conditions affords a diastereomeric mixture of 2a,6e-diaroyl-3a,5e-diaryl-4e-nitrothianes and 2e,6e-diaroyl-3e,5e-diaryl-4e-nitrothianes with a *dr* of ~ 3:1 / 4:1 respectively. This reaction under microwave irradiation in DMF/alcohol afforded solely 2a,6e-diaroyl-3a,5e-diaryl-4e-nitrothianes disclosing enhancement of stereoselectivity by microwaves.

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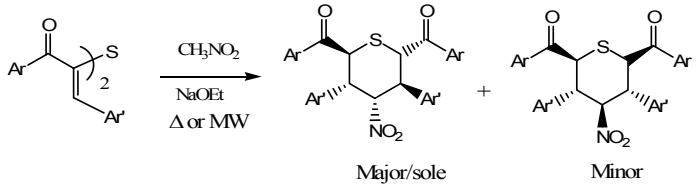

KEYWORDS: 2,2'-thiobis(1,3-diarylprop-2-en-1-ones); Michael addition; stereoselectivity; nitrothianes; microwave irradiation.

INTRODUCTION

Studies on the synthesis of thianes continue to attract keen interest[1] due to their importance as building blocks for molecules of biological or medicinal interest.[2,3] They exhibit important pharmacological properties such as antiulcer,[4] antimicrobial,[5] antibacterial,[6] anti-inflammatory,[7] antihypertensive,[8] and analgesic,[9] besides their use in industry as antiwear[10] and bleaching[11] agents and stabilizing agents in color photography.[12] Thiane nucleus also plays a key role in the biological activities of drugs such as cephalosporins[13] and dithiathromboxane.[14] Their scant natural occurrence[15] further adds to the importance of thiane synthesis. The above importance of thianes and our continued interest in the synthesis of novel heterocycles[16] from 2,2'-thiobis/2,2'sulfonylbis(1,3-diarylprop-2-en-1-ones) as synthons prompted us now to report the stereoselective synthesis of multi-substituted nitrothianes bearing significant synthetic potential for elaboration into polycyclic ring systems.

RESULTS AND DISCUSSION

In the present investigation, the reaction of (*Z,Z*)-2,2'-thiobis(1,3-diarylprop-2-en-1-ones) **1** with nitromethane in the presence of sodium ethoxide in DMF at room temperature afforded a diastereomeric mixture of novel 2,6-diaroyl-3,5-diaryl-4-nitrothianes comprising **2** and **3** in good yields (Scheme 1), which were separated by column chromatography. It is interesting to note that the diastereomer **2** with two groups, *viz.* an aryl and an aroyl, axially oriented is the major product, while the diastereomer **3** having all the five groups in equatorial orientations is the minor one, as evident from the

diastereomeric ratio ~ 3:1 obtained from the ^{1}H NMR spectra of the diastereomeric mixture in all cases. The above reaction when performed in ethyl alcohol instead of DMF under reflux for 20–25 min. led to an improvement in overall yields with enhanced selectivity towards **2** with *dr* of ~ 4:1 (Table 1), ascribable to the fact that the Michael addition proceeding through ionic intermediates could be facilitated by the protic solvent, alcohol.

The above reaction was also investigated under microwave irradiation with a view to finding whether (i) the reaction could be expedited and (ii) an improvement in the yield/selectivity occurs, as it is common to witness rate and yield enhancements under microwave irradiation relative to thermal reactions, besides realizing different selectivities in reactions under microwave irradiation and thermal conditions.[17–22]

In a typical reaction, nitromethane was added into a solution of sodium ethoxide, prepared by dissolving sodium in absolute ethanol, in a 10mL quartz vial, followed by the addition of 2,2'-thiobis(1,3-diarylprop-2-en-1-ones) and the vial was sealed and subjected to microwave irradiation at 110°C, 15 W at 0 bar level pressure in a focused microwave synthesiser. Within 1-2 min, the temperature reached 110°C and remained constant thereafter. Completion of the reaction (TLC) required 8 min. of microwave irradiation. The reaction mixture was then poured into water and the separated solid on purification by column chromatography afforded good yields of exclusively one diastereomer, 2a,6e-diaroyl-3a,5e-diaryl-4-nitrothianes as the only isolable product. Thus, besides significant reduction in the reaction time, increased stereoselectivity was realized under microwave

irradiation compared to the thermal method. The above reaction under microwave irradiation in DMF also led to the diastereomer **2** in comparable yields (Table 1).

The thianes were characterized by elemental analysis and IR, ^{1}H and ^{13}C NMR, and H,H-COSY spectroscopic data. The ^{1}H NMR spectrum of **2a** showed five signals for the heterocyclic ring hydrogens indicating that all these are nonequivalent. The most downfield among them at 6.30 ppm is assignable to H-4, being attached to carbon bearing nitro group. It appears as a doublet of doublets (*J*=11.7, 6.3 Hz) indicating one vicinal hydrogen in axial and the other in equatorial orientation. The doublet of doublets at 4.35 ppm (*J*=6.3 and 2.4 Hz) corresponds to H-3, having a common *J* value of 6.3 Hz with H-4. The small *J* value of 2.4 Hz indicates an e,e coupling between H-3 and H-2 implying axial orientation of the aryl ring at C-3 and aroyl ring at C-2. Hence the signal at 4.89 ppm (*J* = 2.4 Hz) is assigned to H-2. The triplet at 4.56 ppm (*J*=11.7 Hz) is assigned to H-5, oriented axially, from its coupling with H-4. The remaining signal, a doublet at 5.12 ppm (*J*=11.7 Hz) is due to H-6 in axial orientation. These hydrogen assignments are supported by H,H-COSY correlations as well. The stereochemistry of thianes is also corroborated by the fact that **2a** exhibits twenty one carbon signals pointing to its unsymmetrical nature. Thus the stereochemistry of **2** is assigned as 2a,6e-diaroyl-3a,5e-diaryl-4e-nitrothianes (Figure 1).

The structure determined by an X-ray crystallographic study[23] of a single crystal of **2c** (Figure 2) confirms the stereochemistry deduced from NMR spectroscopic data. It is pertinent to note that the *J* value of 6.3 Hz between H-3 and H-4 is large for vicinal

hydrogens, one in axial and another in equatorial orientations. This presumably suggests deformation of the chair due to the axial orientation of benzoyl and phenyl rings at C-2 and C-3 respectively. This conclusion is also supported by the dihedral angle between H-3 and H-4 (φ= 45.27°) determined by the X-ray structure, significantly smaller than 60° expected for vicinal axial-equatorial protons. The X-ray crystallographic structure of **2c** (Figure 2) further discloses (i) a C-H…O hydrogen bonding involving the axial aroyl group at C-2 and the H-4 and (ii) orientation of the aroyl ring away from the cyclohexane ring plane. Such an arrangement presumably diminishes the steric interaction of the aroyl ring with the syn axial hydrogens and enhances the stability of the conformation by the intramolecular hydrogen bonding. Further, the other axially oriented phenyl ring at C-3 placed perpendicular to the cyclohexane ring facing one syn axial hydrogen might not result in significant steric interaction. On the above basis, it can be inferred that the diastereomer **2** may not be rendered significantly unstable.

The ^{1}H NMR spectrum of **3c** shows a triplet at 5.28 ppm corresponding to H-4. The two-proton doublet at 5.19 ppm (*J*=10.5 Hz) and the two-proton triplet at 4.37 ppm (*J*=10.5 Hz) are respectively assignable to H-2,6 and H-3,5. The large *J* values of 10.5 Hz for all the ^{1}H signals of the ring indicate axial orientation of all ring hydrogens, which in turn implies equatorial orientation for all the groups attached to the ring, *viz.* aryl, aroyl and nitro of **3c** (Figure 1). The other thianes **3** also displayed similar spectroscopic features. The thianes **2** and **3** are formed presumably by two successive Michael additions of the carbanions sequentially generated from nitromethane to **1**.

It is also pertinent to note that the major diastereomer in the present study is the one with two bulky groups, *viz.* aryl and aroyl in axial orientations. With a view to assessing the relative thermodynamic stabilities of **2** and **3**, equilibration of one representative case of each diastereomer, *viz.* **2g** and **3e** with sodium ethoxide was investigated. It was found that either heating or microwave irradiation of **2g** or **3e** in the presence of equimolar amount of sodium ethoxide failed to facilitate equilibration. While **2g** failed to react and remained unreacted, **3e** underwent decomposition both under thermal condition in ethanol medium and under microwave irradiation. These results reveal that the predominance of the diastereomers **2** is likely to arise from kinetic control.

The mechanism for the predominance of the diastereomer **2** is given in Scheme 2, which involves one inter- and one intramolecular Michael additions. The latter preferentially occurs from the anion **5** to afford **2**. The formation of the diastereomer **3** presumably arises from an initial NaOEt mediated isomerization of the (*Z,Z*)-**1** into (*Z,E*)-**1** via addition-elimination mechanism, which is followed by intramolecular Michael addition. The fact that the (*E*)-form is likely to be less stable than the (*Z*)-form explains the smaller amount of the diastereomer in this reaction. Similar isomerisation of (*Z*)-C=C bond of **1** into (*E*)-C=C form has been found in the oxidation of (*Z,Z*)-**1** into their (*E,E*)-sulfonyl analogs via addition-elimination mechanism.[24]

The formation of disatereomer **2** solely in the reaction performed under microwave irradiation is explicable by the fact that since microwave reactions raise the energy of the

reacting species rapidly, presumably before the isomerisation of the (*E*)-C=C bond into its (*Z*)-form occurs, the intramolecular Michael addition may be completed.

CONCLUSION

The present work describes the synthesis of multifunctional thianes by conventional reaction and microwave irradiation. In the conventional method, better yields and selectivity were realized in alcohol compared to DMF. Microwave irradiation in the presence of DMF/alcohol led to enhanced stereoselectivity affording solely one diastereomer with aroyl and aryl groups at C-2 and C-3 respectively in axial orientation apart from diminished reaction time compared to the thermal solution method.

EXPERIMENTAL

General

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (□-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80^{o}C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Microwave reactions are carried out in a Biotage Microwave synthesizer.

SYNTHESIS OF 2,6-DIAROYL-4-NITRO-3,5-DIARYLTHIANES - GENERAL PROCEDURE

Method 1A: By Conventional Thermal Method In DMF

Nitromethane (0.3 g, 5 mmol) was added dropwise with stirring into a solution of sodium ethoxide prepared by dissolving sodium metal (0.12 g, 5mmol) in absolute ethyl alcohol (4 mL). To this mixture, a solution of 2,2'-thiobis(1,3-diphenylprop-2-en-1-one) (2.2 g, 5 mmol) in dimethyl formamide (40 mL) was added with stirring and kept at room temperature for 1 h. The reaction mixture was then poured into water and separated solid was filtered. The solid on separation by column chromatography with petroleum ether and ethyl acetate mixture [19:1 (v/v)] as eluent gave a mixture of 2a,6e-dibenzoyl-4e-nitro-3a,5e-diphenylthiane and 2e,6e-dibenzoyl-4e-nitro-3e,5e-diphenylthiane in the ratio of ~3:1.

Method 1B: By Conventional Thermal Method In Ethanol

Nitromethane (0.3 g, 5 mmol) was added dropwise with stirring into a solution of sodium ethoxide prepared by dissolving sodium metal (0.12 g, 5mmol) in absolute ethanol (4 mL). To this mixture, a solution of 2,2'-thiobis(1,3-diphenylprop-2-en-1-one) (2.2 g, 5 mmol) in ethyl alcohol (40 mL) was added with stirring and refluxed for 20 min. The reaction mixture was then poured into water and the separated solid was filtered. The solid on separation by column chromatography with petroleum ether and ethyl acetate mixture [19:1(v/v)] as eluent gave 2a,6e-dibenzoyl-4e-nitro-3a,5e-diphenylthiane and 2e,6e-dibenzoyl-4e-nitro-3e,5e-diphenylthiane in the ratio 4:1. Yields of thianes thus obtained in methods 1A and 1B are given in Table 1.

Method 2A: By Microwave Irradiation In DMF

Nitromethane (0.3 g, 5 mmol) was added dropwise with stirring into a solution of sodium ethoxide, (0.34 g, 5mmol) in DMF (4 mL) taken in a 10mL quartz vial. After the addition of 2,2'-thiobis(1,3-diarylprop-2-en-1-ones) (2.2 g, 5 mmol) into the above solution, the vial was sealed and subjected to microwave irradiation at 110°C, 15 W at 0 bar level pressure in a Biotage microwave synthesiser. After 1-2 min, the temperature reached a plateau of 110°C and remained constant thereafter. After 8 min., the vial was cooled to room temperature which took about 5 min., the reaction mixture was then poured into water and the separated solid was filtered off. The solid on purification by column chromatography with petroleum ether and ethyl acetate mixture [19:1(v/v)] as eluent gave 2a,6e-dibenzoyl-4e-nitro-3a,5e-diphenylthiane as a colorless solid.

Method 2B: By Microwave Irradiation In Ethanol

This experiment was repeated using ethanol as the solvent after preparing sodium ethoxide by dissolving sodium (0.12g, 5mmol) in absolute ethanol (4 mL) and adding mixture of the reactants as described above in method 2A. Yields of thianes thus obtained in methods 2A and 2B are given in Table 1.

Data

2a,6e-Dibenzoyl-4e-Nitro-3a,5e-Diphenylthiane (2a)

Obtained as a colorless solid [1.5 g, (60%) in method 1A and 2.1 g, (84%) in method 2A], mp=150-152°C; IR (KBr) ν cm^{-1} 1368, 1552, 1669, 1685; ^{1}H NMR (300 MHz,

$CDCl_3$) δ_H: 4.35 (dd, *J*=2.4, 6.3 Hz, 1H), 4.56 (t, *J*=11.7 Hz, 1H), 4.89 (d, *J*=2.4 Hz, 1H), 5.12 (d, *J*=11.7 Hz, 1H), 6.30 (dd, *J*=6.3, 11.7 Hz, 1H), 7.04-7.84 (m, 18H), 7.98 (d, *J*=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 42.9, 43.6, 46.9, 47.2, 89.6, 127.8, 128.3, 128.6, 128.6 (7), 128.7(1), 128.8, 129.0, 129.4, 133.8, 134.0, 134.2, 135.3, 136.9, 138.0, 194.1, 195.0. Anal. Calcd for $C_{31}H_{25}NO_4S$: C, 73.35; H, 4.96; N, 2.76%. Found: C, 73.55; H, 4.85; N, 2.70%.

2e,6e-Dibenzoyl-4e-Nitro-3e,5e-Diphenylthiane (3a)

Obtained as a colorless solid [0.5 g, (20%) in method 1A], mp=238-240°C; IR (KBr) ν cm^{-1} 1368, 1558, 1668; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.40 (t, *J*=10.8 Hz, 2H), 5.3 (m, 3H), 7.14-7.55 (m, 16H), 7.83 (d, *J*=8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 50.1, 50.2, 96.1, 128.0, 128.4, 128.6, 128.9, 133.8, 135.4, 135.9, 193.0. Anal. Calcd for $C_{31}H_{25}NO_4S$: C, 73.35; H, 4.96; N, 2.76%. Found: C, 73.46; H, 5.01; N, 2.83%.

2e,6e-Di(*P*-Chlorobenzoyl)-4e-Nitro-3e,5e-Diphenylthiane (3c)

Obtained as a colorless solid [0.7 g, (24%) in method 1A], mp=194-196°C; IR (KBr) ν cm^{-1} 1366, 1546, 1687; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.37 (t, *J*=10.5 Hz, 2H), 5.19 (d, *J*=10.5 Hz, 2H), 5.28 s (t, *J*=10.5 Hz, 1H), 7.13-7.25 (m, 10H), 7.34 (d, *J*=8.4 Hz, 4H), 7.74 (d, *J*=8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 49.9, 50.2, 95.8, 128.0, 128.6, 129.1, 129.9, 133.6, 135.8, 140.5, 191.9. Anal. Calcd for $C_{31}H_{23}Cl_2NO_4S$: C, 64.59; H, 4.02; N, 2.43%. Found: C, 64.48; H, 4.10; N, 2.52%.

Complete experimental details are available online in the Supporting Information.

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23. Crystallographic data (excluding structure factors) for **2c** in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 765249. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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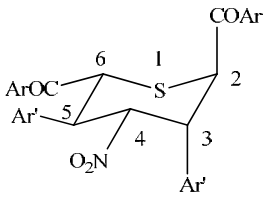
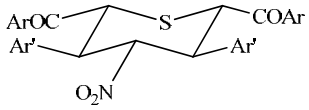
Table 1. Yield and mp of diastereomeric nitrothianes

Compd. **1**	Thermal Yield (%)				MW irradiation Yield (%)		Mp (ºC)	
	2		3		2		2	3
	DMF	EtOH	DMF	EtOH	DMF	EtOH		
a	60	70	20	17	84	85	150–152	238–240
b	66	72	21	18	83	83	160–162	288–290
c	59	75	24	18	79	85	166–168	194–196
d	66	71	19	18	81	84	190–192	218–220
e	50	66	17	16	77	80	74–76	146–148
f	59	69	19	17	78	82	180–182	224–226
g	57	65	23	16	73	78	156–158	282–284

Figure 1. Stereochemistry of the diastereomeric nitrothianes **2** and **3**

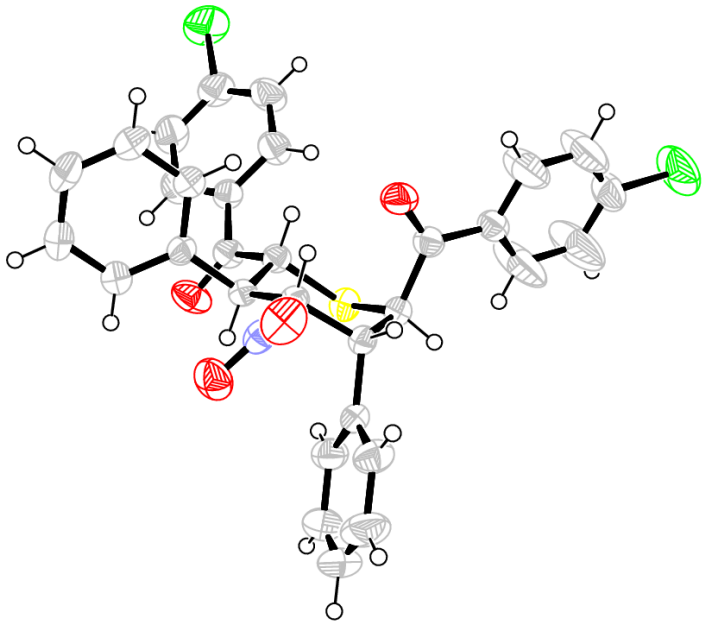


2

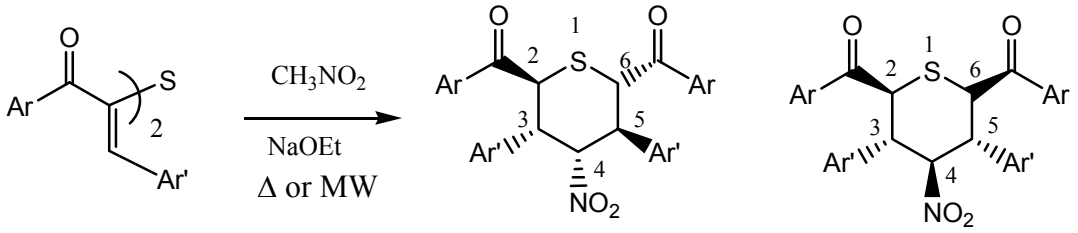


3

Figure 2. X-ray structure of **2c**



Scheme1. Synthesis of multisubstituted 4-nitrothianes



1-3	Ar	Ar’
a	C_6H_5	C_6H_5
b	C_6H_5	*p*-Cl-C_6H_4
c	*p*-Cl-C_6H_4	C_6H_5
d	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4
e	*p*-Cl-C_6H_4	*p*-Me-C_6H_4
f	*p*-Me-C_6H_4	C_6H_5
g	*p*-Me-C_6H_4	*p*-Cl-C_6H_4

Scheme 2. Plausible mechanism for the stereoselective formation of multisubstituted 4-nitrothianes