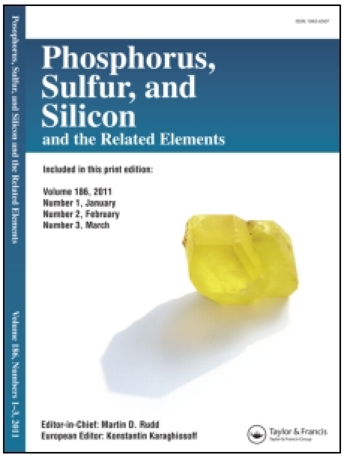

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2,6-DIAROYL-3,5-DIARYL-4-METHYLTETRAHYDRO-1,4-THIAZINE-1,1-DIOXIDES – A SYNTHETIC AND STEREOCHEMICAL STUDY

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Conjugate addition of methylamine over 2,2′-sulfonyl*bis*(1,3-diarylprop-2-en-1-ones) in dimethylformamide gave the hitherto unknown 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides in very good yields. The same thiazines were also obtained by condensation of *bis*(aroylmethyl)sulfones with aromatic aldehydes and methylamine. The structure and stereochemistry of the compounds were deduced from elemental analysis and spectral data.

Keywords: 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides; 2,2′-sulfonyl*bis*(1,3-diarylprop-2-en-1-ones); methylamine; *bis*(aroylmethyl)sulfones; NMR spectra; stereochemistry

INTRODUCTION

Tetrahydro-1,4-thiazine derivatives are known to be antiepileptics, tranquilizers, sedatives, antitumour, antitubercular, parasitical and bactericidal agents[1]. Hence we have recently investigated the synthesis of thiazine derivatives by condensation of *bis*(aroylmethyl)sulfides with aromatic aldehydes and methylamine[2] and also by Michael addition of methylamine over 2,2′-thio*bis*(1,3-diarylprop-2-en-1-ones)[3]. Herein we report

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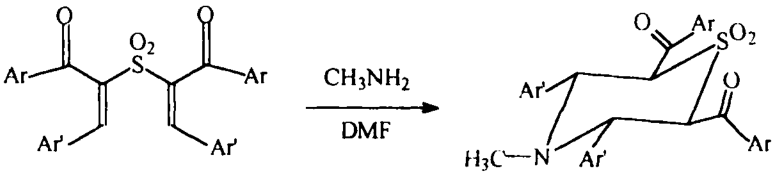
the synthesis and stereochemical investigations on the corresponding thiazine-1,1-dioxides.

RESULTS AND DISCUSSION

Michael addition of methylamine over 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) **1** in DMF afforded 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides **2** in very good yields (Scheme-1).



1 2

1& 2	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_5	*p*-Cl-C_6H_4-
c	*p*-Cl-C_6H_4-	*p*-Cl-C_6H_4-
d	*p*-Cl-C_6H_4-	*p*-MeC_6H_4-
e	*p*-MeC_6H_4-	C_6H_5

SCHEME 1

The yield, m.p. and elemental analysis are presented in Table-I. It is pertinent to note that very good yields of thiazines **2** were obtained.

The complete assignment of ^{1}H NMR signals of all the compounds (**2a-2e**) has been done and it is illustrated with 4-methyl-2,6-di(4-methylbenzoyl)-3,5-diphenyltetrahydro-1,4-thiazine-1,1-dioxide (**2e**) as an example.

TABLE I Physical data of compounds (**2a**-**2e**)

Compd.	*Yield (%)*	*m.p (°C)*	*Found (%)*		*Calcd (%)*	
			C	*H*	*C*	*H*
2a	88	216–18	73.18	5.37	73.06	5.34
2b	86	212–14	64.25	4.34	64.36	4.36
2c	92	206–08	57.66	3.60	57.51	3.58
2d	85	165–68	65.49	4.85	65.35	4.82
2e	90	214–16	73.60	5.79	73.72	5.81

The far downfield doublet at 7.84 ppm in the aromatic region with J=8.3 Hz is assigned to the *ortho* protons of 4-methylbenzoyl groups as they are deshielded by the carbonyl group. The H,H-COSY spectrum of **2e** shows that the doublet at 7.28 ppm is a coupling partner of the doublet at 7.84 ppm and hence the former is assigned to the *meta* protons of the aroyl groups. The triplet at 7.14 ppm integrating for two protons and the other triplet at 7.24 ppm due to four protons are coupling partners (evident from H,H-COSY spectrum) and they are assignable to the *para* and *meta* protons of the aryl groups respectively. The doublet at 7.51 ppm arises from the *ortho* protons of the aryl groups.

The singlet at 1.68 ppm integrating for three protons and that at 2.34 ppm integrating for six protons are assigned to N-methyl and C-methyl protons. The two doublets appearing at 6.53 and 4.43 ppm with a coupling constant of 10.6 Hz were assigned to H-2,6 and H-3,5 of the heterocyclic ring respectively. The vicinal coupling constant, 10.6 Hz, clearly indicates the diaxial nature of the protons and hence the aroyl and aryl groups are all equatorially oriented. The absence of correlation between H-2,6 and H-3,5 of **2e** (Figure 1) in the NOESY spectrum also supports the above conclusion that they are axially oriented. That there is a significant correlation between H-2,6 and the *ortho* protons of the aroyl ring (H-*o*) in the NOESY spectrum reveals that the rotamer **"a"** of **2e** (Figure 1) also contributes significantly.

The proton signals of the other thiazines **2a**-**2d** were deduced in a similar way. The ^{1}H NMR data of 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides **2** are presented in Table II.

TABLE II ^{1}H NMR data[a] of 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides **2** in CDCl$_3$

Compound	δ *(ppm)*
2a	4.65(d, 2H, J=10.6 Hz, H-3,5); 5.52(d, 2H, J=10.6 Hz, H-2,6); 7.73(d, 4H, J=7.7 Hz, H-*o*);7.48 (t, 2H, J=7.7 Hz H-*p*); 7.36 (t, 4H, J=7.7 Hz, H-*m*); 7.15(t, 2H, J=6.4 Hz, H-*p′*); 7.43(d, 4H, J=6.4 Hz, H-*o′*); 7.26 (t. 4H, J=6.4 Hz, H-*m′*); 1.83 (s, 3H, NMe);
2b	4.69(d, 2H, J=10.7 Hz, H-3,5); 5.46 (d, 2H,J=10.7 Hz, H-2,6); 7.75(d, 4H, J=7.3 Hz, H-*o*); 7.53(t, 2H, J=7.3 Hz, H-*p*); 7.40 [b](t, 4H, H-*m*); 7.21(d, 4H, J=8.5 Hz, H-*m′*); 7.40 [b](d, 4H, J=8.5 Hz, H-*o′*); 1.80 (s, 3H, NMe);
2c	4.62(d, 2H, J=10.7 Hz, H-3,5); 5.40 (d, 2H, J=10.7 Hz, H-2,6); 7.71(d. 4H, J=8.4 Hz, H-*o*); 7.36 [b](d, 4H, J=8.4 Hz, H-*m*); 7.22(d, 4H, J=8.2 Hz, H-*m′*); 7.36 [b](d, 4H, H-*o′*); 1.80 (s, 3H, NMe);
2d	4.56(d, 2H, J=10.8 Hz, H-3,5); 5.43 (d, 2H, J=10.8 Hz, H-2,6); 7.68(d, 4H, J=8.0 Hz, H-*o*); 7.33 (d, 4H, J=8.0 Hz, H-*m*);7.01(d, 4H, J=7.6 Hz, H-*m′*); 7.26 (d, 4H, J=7.6 Hz, H-*o′*); 2.21 (s, 6H, C-Me); 1.79 (s, 3H, NMe)
2e[c]	4.43(d, 2H, J=10.6 Hz, H-3,5); 6.53 (d, 2H, J=10.6 Hz, H-2,6); 7.84(d, 4H, J=8.3 Hz, H-*o*); 7.28 (d, 4H, J=8.3 Hz, H-*m*); 7 14 (t, 2H, J=7.0 Hz, H-*p′*); 7.24 (t, 4H, J=7.0 Hz H-*m′*); 7.51 (d, 4H, J=7.0 Hz, H-*o′*); 2.34 (s, 6H, C-Me); 1.68 (s, 3H, NMe);

[a] Chemical shifts are expressed with reference to tetramethylsilane.
[b] Overlapping signals in 1D-^{1}H NMR located from H,H-COSY spectra.
[c] Measured in DMSO-d$_6$.

The complete assignment of ^{13}C signals (Table III) has been done by multiplicity, substituent induced chemical shift considerations, DEPT and C,H-COSY spectra for a representative compound **2e**.

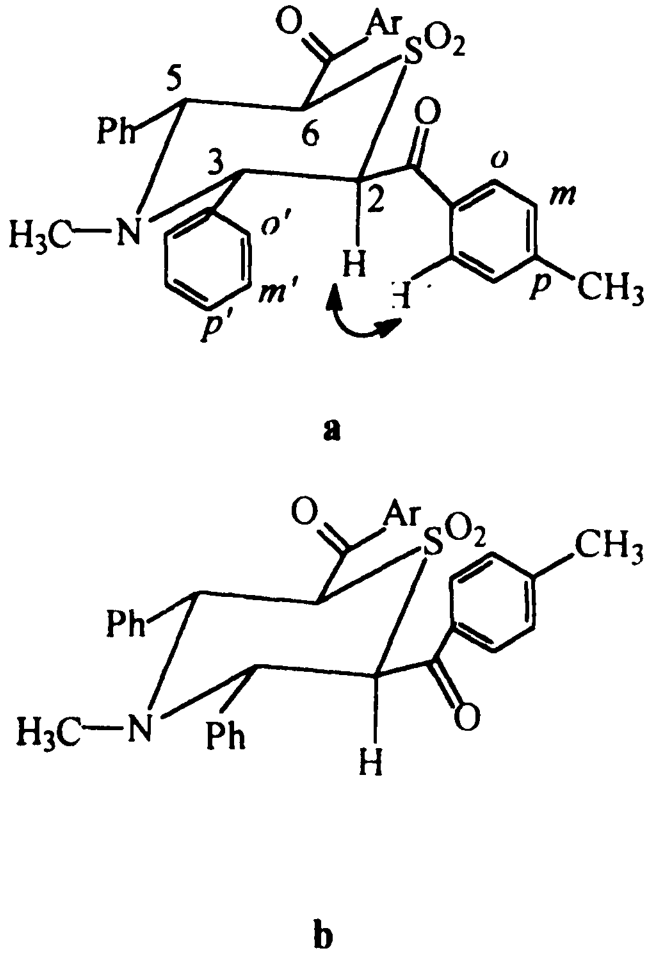


FIGURE 1

It is interesting to note that in all cases studied only double aza-Michael addition occurs affording thiazine derivatives. This is in contrast to exclusive retro Knoevenagel cleavage observed during the reaction of **1** with

2,4-dinitrophenylhydrazine leading to the corresponding bis(aroylmethyl) sulfone and 2,4-dinitrophenylhydrazone derivative of aromatic aldehydes[4].

TABLE III ^{13}C NMR data of 4-methyl-2,6-di(4-methylbenzoyl)-3,5-diphenyltetrahydro-1,4-thiazine-1,1-dioxide (**2e**) in DMSO-d_6

Compound	δ *(ppm)*
2e	68.1(C-3, C-5); 69.5(C-2, C-6); 134.6(C-*i*); 129.0(C-*o*); 129.3(C-*m*); 139.2(C-*p*); 145.1(C-*i*′); 128.7(C-*o*′); 128.4(C-*m*′); 128.1 (C-*p*′); 21.2(C-Me); 39.5(N-Me); 188.0 (CO)

The condensation of *bis*(aroylmethyl)sulfones with aromatic aldehydes and methylamine yielded the identical thiazines **2** obtained by the above method. The yields got in this method are also very good ranging from 75–90 %.

EXPERIMENTAL

The melting points are uncorrected. NMR spectra were recorded at 20° C on a Bruker AMX 360 instrument operating at 360 MHz for ^1H and at 90 MHz for ^{13}C. Solutions (in $CDCl_3$ or DMSO-d_6) were approximately 0.05M and chemical shifts were referenced internally to TMS in all cases. Standard Bruker software (UXNMR) was used throughout.

2,6-Diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides 2

General procedure for 2 by conjugate addition of methylamine

To a solution of 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-one)[3] (0.96g, 2 mmol) in DMF (25 ml), an aqueous solution of methylamine (40%, 0.3 ml) was added and kept at room temperature for 3 h. The reaction mixture was poured into ice water and the resulting solid was crystallized from chloroform-ethanol mixture.

General procedure for 2 by condensation reaction

A mixture of bis(aroylmethyl)sulfone (3.0 g, 10 mmol), an aldehyde (2.1 g, 20 mmol) and methylamine (40%, 1 ml) in ethanol (95%, 25 ml) was heated on a water-bath for 15 min and the resulting dark red mixture on cooling gave a white solid which was filtered, washed with ethanol, dried and crystallised from chloroform-ethanol mixture to afford 2,6-dibenzoyl-4-methyl-3,5-diphenyltetrahydro-1,4 thiazine-1,1-dioxide.

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References

[1] A.J. Boulton and A. McKillop, Eds., *Comprehensive Heterocyclic Chemistry*, 1st ed., (Pergamon Press, London) 1984, 1038.

[2] S. Selvaraj, A. Dhanabalan and N. Arumugam, *Indian J Chem*, **33B**, 67, 1994.

[3] S. Selvaraj, N.N. Vanitha and S. Perumal (unpublished results).

[4] M. Gnanadeepam, S. Selvaraj, S. Perumal and S. Sivakolunthu, Communicated.