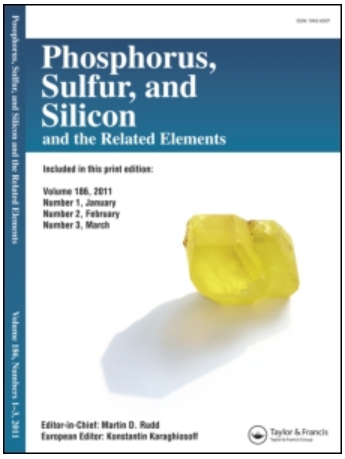

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A Synthetic and Stereochemical Study of 2,6-Diaroyl-3,5-Diaryl-4-Ethyltetrahydro-1,4-Thiazine-1,1-Dioxides

M. Gnanadeepam[a]; S. Selvaraj[b]; S. Perumal[b]; S. Renuga[a]; S. Selvaraj[c]
[a] Department of Chemistry, Fatima College, Madurai [b] School of Chemistry, Madurai Kamaraj University, Madurai [c] Drug Development, Isotechnika Inc., Alberta, Canada

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

M. Gnanadeepam,[a] *S. Selvaraj,*[b] *S. Perumal,*[b] *S. Renuga,*[a] *and S. Selvaraj*[c]
Department of Chemistry, Fatima College, Madurai-625018[a]*; School of Chemistry, Madurai Kamaraj University, Madurai-625021*[b]*; and Drug Development, Isotechnika Inc., Alberta, Canada T5S1E8*[c]

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Double aza-Michael addition of ethylamine over 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) gave the previously unknown title compounds in moderate yields. The decreased yields of the title compounds compared to 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxides or the corresponding 4-methyl derivatives is explained on the basis of steric size of the nucleophile. The structure and stereochemistry of the thianes have been deduced from elemental analyses and spectroscopic data.

Keywords: 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones); 2,6-diaroyl-3,5-diaryl-4-ethyltetrahydro-1,4-thiazine-1,1-dioxides; bis(aroylmethyl) sulfones; NMR spectroscopic data; stereochemistry; tandem Michael-retroKnoevenagal reaction

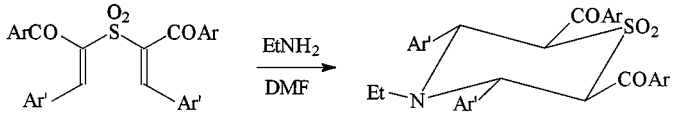
INTRODUCTION

The Michael addition of ammonia[1] or methylamine[2] over 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) yielded the tetrahydrothiazines in very good yields. In contrast, the reaction of bulky nucleophiles such as aniline and 2,4-dinitrophenylhydrazine afforded bis(aroylmethyl) sulfones as a result of cleavage of the sulfonylbis compounds instead of thiazines.[3] In addition, thiazines are known to be biologically active.[4–8] Hence the reaction of 2,2′-sulfonylbis (1,3-diarylprop-2-en-1-ones) with ethylamine, which is intermediate in size compared to methylamine and aniline, was investigated. The results are presented here.

Address correspondence to S. Selvaraj, School of Chemistry, Fatima College, Madurai-625018.

RESULTS AND DISCUSSION

Double aza-Michael addition of ethylamine over 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) **1** in DMF afforded 2,6-diaroyl-3,5-diaryl-4-ethyltetrahydro-1,4-thiazine-1,1-dioxides **2** in moderate yields (Scheme 1). The yield, m.p. and elemental analyses are presented in Table I.



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 ^{1}H NMR signals of all the compounds (**2a–2e**) have been completely assigned and are explained with 2,6-di(*p*-chlorobenzoyl)-3,5-di(*p*-methylphenyl)-4-ethyltetrahydrothiazine-1,1-dioxide (**2d**) as an example. The most downfield signal at 7.92 ppm integrating for four protons with an *ortho* coupling ($J = 8.9$ Hz) is assigned to the *ortho* protons of aroyl groups as they are deshielded by the carbonyl group. The other doublet at 7.60 ppm ($J = 8.9$ Hz) is assigned to the meta protons of the aroyl groups as it is a coupling partner of the doublet at 7.92 ppm. Of

TABLE I Physical Data of Compounds (**2a–2e**)

			Found (%)		Calcd (%)	
Compd	Yield (%)	m.p. (°C)	C	H	C	H
2a	58	222–24	73.45	5.53	73.40	5.58
2b	52	242[a]	64.79	4.55	64.87	4.59
2c	48	216–18	58.18	3.79	58.11	3.81
2d	52	198–200	65.73	5.07	65.80	5.03
2e	66	212–14	74.11	6.07	74.02	6.03

[a]Decomposed.

the two remaining signals in the aromatic region, the upfield signal at 7.06 ppm ($J = 7.6$ Hz) can be reasonably assigned to the *meta* protons of the aryl groups as they are *ortho* to tolyl methyl group and hence appear upfield. Consequently, the other broad signal at 7.40 ppm due to four protons is assigned to the *ortho* protons of the aryl groups.

The singlet at 2.15 ppm is assignable to Ar—Me. The triplet at 0.67 ppm integrating for three protons is assigned to N—CH_2Me and the signal due to N—CH_2Me appears as a quartet at 2.09 ppm. The two doublets appearing at 6.47 ppm and 4.70 ppm ($J = 10.5$ Hz) are assigned to H-2,6 and H-3,5 of the thiazine ring respectively. This vicinal coupling constant (10.5 Hz) clearly indicates the diaxial nature of the protons and hence the aroyl and aryl groups are all equatorially oriented. The proton signals of the other thiazines are deduced in a similar manner. The ^{1}H NMR data of 2,6-diaroyl-3,5-diaryl-4-ethyltetrahydro-1,4-thiazine- 1,1-dioxides **2** are presented in Table II.

It is interesting to note that the *ortho* protons of aryl groups in all the thiazines appear as a broad signal instead of a doublet. Similar observation have been made in the case of closely related system 2,6-diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides[2] but not in 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxides[1] where the

TABLE II ^{1}H NMR Data[a] of 2,6-diaroyl-3,5-diaryl-4-ethyltetrahydro-1,4-thiazine-1,1-dioxides **2** in DMSO-d_6

Compd	δ (ppm)
2a	4.78 (d, 2H, $J = 10.7$ Hz, H-3,5); 6.52 (d, 2H, $J = 10.7$ Hz, H-2,6); 7.90 (d, 4H, $J = 7.9$ Hz, H-*o*); 7.62 (t, 2H, $J = 7.9$ Hz, H-*p*); 7.48 (t, 4H, $J = 7.9$ Hz, H-*m*); 7.54 (bs, 4H, H-*o*′); 7.24 (t, 4H, $J = 7.3$ Hz, H-*m*′); 7.13 (t, 2H, $J = 7.3$ Hz, H-p′); 2.14 (q, 2H, N$\underline{CH_2}$Me); 0.70 (t, 3H, NCH$_2\underline{Me}$)
2b	4.79 (d, 2H, $J = 10.4$ Hz, H-3,5); 6.51 (d, 2H, $J = 10.4$ Hz, H-2,6); 7.94 (d, 4H, $J = 8.7$ Hz, H-*o*); 7.66 (t, 2H, $J = 7.0$ Hz, H-*p*); 7.52 (t, 4H, $J = 7.0$ Hz H-*m*); 7.64 (bs, 4H, H-*o*′); 7.34 (d, 4H, $J = 7.9$ Hz, H-*m*′); 2.08 (q, 2H, N$\underline{CH_2}$Me); 0.70 (t, 3H, NCH$_2\underline{Me}$)
2c	4.78 (d, 2H, $J = 10.4$ Hz, H-3,5); 6.49 (d, 2H, $J = 10.4$ Hz, H-2,6); 7.91 (d, 4H, $J = 7.3$ Hz, H-*o*); 7.64 (d, 4H, $J = 7.3$ Hz, H-*m*);); 7.57 (bs, 4H, H-*o*′); 7.36 (d, 4H, $J = 7.9$ Hz, H-*m*′); 2.10 (q, 2H, N$\underline{CH_2}$Me); 0.70 (t, 3H, NCH$_2\underline{Me}$)
2d	4.70 (d, 2H, $J = 10.5$ Hz, H-3,5); 6.47 (d, 2H, $J = 10.5$ Hz, H-2,6); 7.92 (d, 4H, $J = 8.9$ Hz, H-*o*); 7.60 (d, 4H, $J = 8.9$ Hz, H-*m*); 7.40 (bs, 4H, H-*o*′); 7.06 (d, 4H, $J = 7.6$ Hz, H-*m*′); 2.09 (q, 2H, N$\underline{CH_2}$Me); 0.67 (t, 3H, NCH$_2\underline{Me}$); 2.15 (s, 6H, Ar—$\underline{Me}$)
2e	4.77 (d, 2H, $J = 10.7$ Hz, H-3,5); 6.47 (d, 2H, $J = 10.7$ Hz, H-2,6); 7.82 (d, 4H, $J = 8.3$ Hz, H-*o*); 7.28 (d, 4H, $J = 8.3$ Hz, H-*m*); 7.53 (bs, 4H, H-*o*′); 7.23 (t, 4H, $J = 7.3$ Hz, H-*m*′); 7.13 (t, 2H, $J = 7.3$ Hz, H-*p*′); 2.10 (q, 2H, N$\underline{CH_2}$Me); 0.70 (t, 3H, NCH$_2\underline{Me}$); 2.33 (s, 6H, Ar—$\underline{Me}$)

[a]Chemical shifts are expressed with reference to tetramethylsilane.

TABLE III ^{13}C NMR Data[a] of 2,6-diaroyl-3,5-diaryl-4-ethyltetrahydro-1,4-thiazine-1,1-dioxides **2** in DMSO-d_6

Compd	δ (ppm)
2a	65.2 (C-3,5); 68.8 (C-2,6); 137.2 (C-*i*); 134.3 (C-*i*′); 138.5 (C-*p*); 128.3–128.8 (C-*o*, *m*, *o*′, *m*′ and *p*′); 41.8 (N$\underline{CH_2}$Me); 6.4 (NCH$_2\underline{Me}$); 189.1 (CO)
2b	64.3 (C-3,5); 68.5 (C-2,6); 137.0 (C-*i*); 137.5 (C-*i*′); 132.8 (C-*p*′); 128.6–129.0 (C-*o*, *m*, *p*, *o*′ and *m*′); 41.5 (N$\underline{CH_2}$Me); 6.4 (NCH$_2\underline{Me}$); 188.8 (CO)
2c	64.0 (C-3,5); 68.3 (C-2,6); 136.9 (C-*i*); 139.6 (C-*i*′); 135.1 (C-*p*); 132.6 (C-*p*′); 128.9 (C-*o*); 128.5[b] (C-*m*); 129.2 (C-*o*′); 128.4[b] (C-*m*′); 41.6 (N$\underline{CH_2}$Me); 6.2 (NCH$_2\underline{Me}$); 187.5 (CO)
2d	64.3 (C-3,5); 68.5 (C-2,6); 135.0[b] (C-*i*); 139.3 (C-*i*′); 135.3[b] (C-*p*); 137.2 (C-*p*′); 130.3 (C-*o*); 128.7[b] (C-*m*); 128.1 (C-*o*′); 128.8[b] (C-*m*′); 41.2 (N$\underline{CH_2}$Me); 6.0 (NCH$_2\underline{Me}$); 20.5 (Ar$-\underline{Me}$); 187.6 (CO)
2e	64.6 (C-3,5); 68.2 (C-2,6); 134.4 (C-*i*); 144.8 (C-*i*′); 138.3 (C-*p*); 128.1[b] (C-*p*′); 128.6 (C-*o*); 129.0 (C-*m*); 128.4 (C-*o*′); 127.9[b] (C-*m*′); 41.5 (N$\underline{CH_2}$Me); 6.0 (NCH$_2\underline{Me}$); 21.0 (Ar$-\underline{Me}$); 187.9 (CO)

[a]Chemical shifts are expressed with reference to tetramethylsilane.
[b]These assignments may be reversed.

nitrogen possesses only hydrogen. Hence broadening of the signal occurs only when the thiazine nitrogen bears a methyl or ethyl group suggesting restricted rotation of the aryl group which may probably be ascribed to steric interaction between the alkyl and the aryl groups. Such loss of splitting of the signal due to restricted rotation has been reported in the case of some pyrazolines.[9] The fact that aniline and substituted anilines bring about the cleavage of **1** leading to bis(aroylmethyl) sulfones also supports the above conclusion.[3]

The ^{13}C signals of all the thiazines assigned on the basis of substituent induced chemical shift considerations, multiplicity and APT spectra are given in Table III.

It is pertinent to note that the yields are only moderate because of the formation of bis(aroylmethyl) sulfones as by-products. This is in contrast to excellent yields (85–97%) of thiazines obtained from the conjugate addition of ammonia[1] or methylamine[2] over **1**. This may be attributed to the increase in the bulkiness of the alkyl group. As the size of the nucleophile increases, **1** may undergo cleavage via a tandem Michael-retroKnoevenagel reaction to give bis(aroylmethyl) sulfone as depicted in Figure 1.

EXPERIMENTAL

The melting points are uncorrected. NMR spectra were recorded at 20°C on a Bruker AMX 300 instrument operating at 300 MHz for ^{1}H

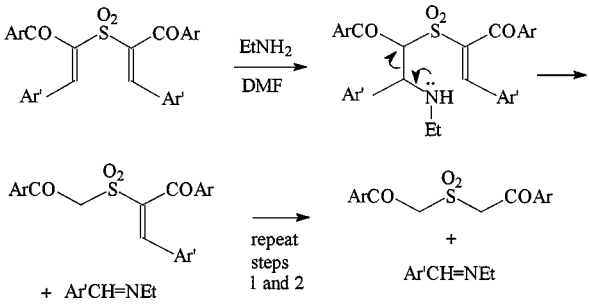


FIGURE 1 Mechanism of cleavage of 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones)

and at 75 MHz for ^{13}C. Solutions (in DMSO-d_6) were approximately 0.05 M and chemical shifts were referenced internally to TMS in all cases.

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

General Procedure for 2 by Conjugate Addition of Ethylamine

To a solution of 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-one)[10] (0.96 g, 2 mmol) in DMF (25 ml), an aqueous solution of ethylamine (40%, 0.3 ml) was added and kept at room temperature for 24 h. The reaction mixture was poured into ice water and the resulting solid was crystallized from chloroform-ethanol mixture.

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