Reactivity of 3-benzylidene- and 3-ethylidene-2,3-dihydro-2-methyl-1,2-benzothiazin-4-one 1,1-dioxide towards alkylidenephosphoranes

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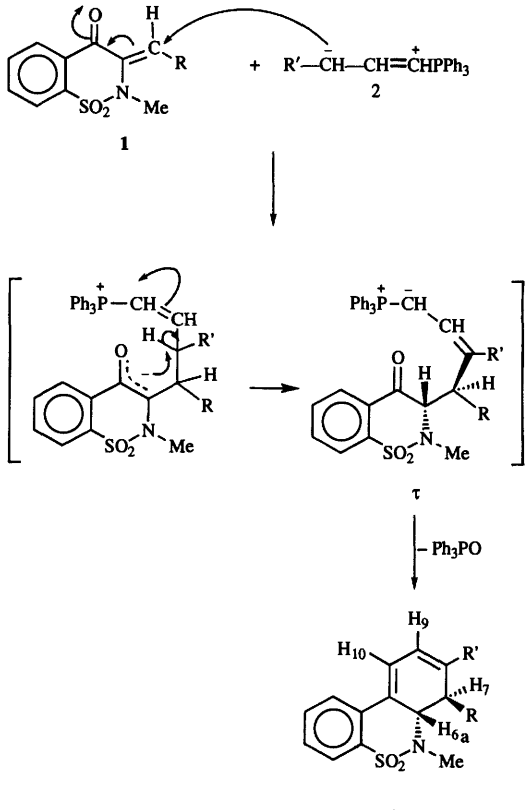
The reactivity of 3-benzylidene- and 3-ethylidene-2,3-dihydro-2-methyl-1,2-benzothiazin-4-one 1,1-dioxide 1a,b towards alkylidenephosphoranes 2 has been investigated. The reaction leads to the formation of 6a,7-dihydrodibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide derivatives 3, new heteropolycyclic systems containing the 1,2-benzothiazine 1,1-dioxide skeleton. A Michael addition of the alkylidenephosphoranes γ-carbon to the β-carbon of the α,β-unsaturated carbonyl system of (*Z*)-1a,b followed by a prototropy and an intramolecular Wittig condensation, explain the formation of products 3. Oxidation of compounds 3 gave the dibenzo[*c*,*e*][1,2]thiazine derivatives 4 whereas their reaction with PTSA·H_2O gave the (1,1'-biphenyl)-2-sulfonamides 5.

In a previous paper we described the synthesis[1] and the reactivity towards nucleophiles[1] of 3-benzylidene- and 3-ethylidene-2-methyl-2,3-dihydro-1,2-benzothiazin-4-one 1,1-dioxide **1a,b**. More recently we reported a new and simpler preparation of compounds **1a,b**[2] and their reaction with morpholino enamines[3] and vinyl ethers[4] to give polycyclic systems containing the skeleton of 1,2-benzothiazine 5,5-dioxide. Continuing in this field we now report the reaction between **1a,b** and alkylidene(triphenyl)phosphoranes **2** (Scheme 1) leading to the new heteropolycyclic 6a,7-dihydrodibenzo-[*c*,*e*][1,2]thiazine 5,5-dioxide derivatives **3**. This annelation, followed by oxidation of products **3**, represents a new and efficient synthesis of the dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide system **4**.[5]

The experiments were performed in tetrahydrofuran solution at room temperature for 12 h.† After chromatography on silica gel of the reaction mixture, products **3** were isolated in good yield (Table 1) together with an equimolar quantity of Ph_3PO. The structure of 6a,7-dihydrodibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide was assigned to products **3** on the basis of analytical and spectroscopic data. The IR spectra showed no carbonyl band. In the ^1H NMR spectra all the protons showed chemical shift values and multiplicities consistent with the indicated structures **3** (Table 2). In fact, protons 9-H and 10-H appeared as a doublet of doublets with a $^3J_{9,10}$ coupling constant (5.9–6.6 Hz) in agreement with two adjacent hydrogens in a cyclohexadiene ring, and a ^4J coupling constant with 7-H and 6a-H respectively. Also, 6a-H and 7-H showed a doublet of doublets with $^3J_{6a,7}$ and ^4J coupling constants.

Allylic ylides can react at both the α and γ carbons, depending on the substrates and the reaction conditions. In the case of α,β-unsaturated carbonyl compounds, the accepted mode of reaction[6] involves bond formation between the less hindered γ-carbon of the ylide and the β-position of the conjugated ketone followed by a proton shift and an intramolecular Wittig reaction to give cyclohexadiene derivatives. Following this scheme, the reaction of (*Z*)-**1a,b** with the allylic ylides **2** leads to phosphonium betaine τ (Scheme 1) as a result of [1,4] conjugate addition and accompanying proton transfer. The final Wittig cyclization allows the fused cyclohexadieno-1,2-benzothiazine ring system to be formed.



1a R = Ph
1b R = Me

2a R' = CO_2Me
2b R' = CN
2c R' = Ph
2d R' = Me

3aa R = Ph, R' = CO_2Me
3ab R = Ph, R' = CN
3ac R = Ph, R' = Ph
3ad R = Ph, R' = Me
3ba R = Me, R' = CO_2Me
3bb R = Me. R' = CN
3bc R = Me, R' = C_6H_5
3bd R = Me, R' = Me

Scheme 1

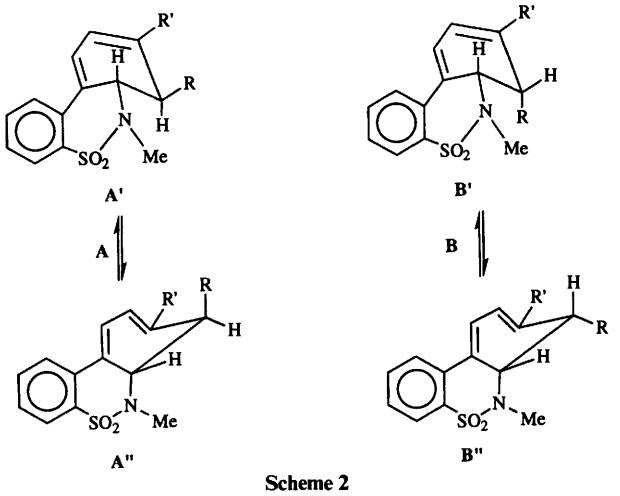
† The non-stabilized ylides **2c,d** were generated *in situ* from the corresponding phosphonium salts by the action of sodium hydride whereas **2a,b** were isolated as inner salts.

The other possible products deriving from the attack of the α-form of **2** were ruled out on the basis of the observed ^1H NMR spectra. The reactions were also completely diastereoselective

Table 1 Analytical data for products **3**

Comp. (formula)	Yield (%)	Crystallization solvent	Mp (°C)	Found (%) (required) C	H	N
3aa ($C_{21}H_{19}NO_4S$)	50	Pr^{i}OH	160–161	65.99 (66.14)	5.21 (4.99)	3.52 (3.67)
3ab ($C_{20}H_{16}N_2O_2S$)	45	EtOH	209–211	68.82 (68.96)	4.52 (4.60)	7.88 (8.05)
3ac ($C_{25}H_{21}NO_2S$)	52	EtOH	193–195	74.92 (75.18)	5.12 (5.26)	3.39 (3.51)
3ad ($C_{20}H_{19}NO_2S$)	87	Pr^{i}OH	192–194	71.07 (71.22)	5.59 (5.64)	4.08 (4.15)
3ba ($C_{16}H_{17}NO_4S$)	31	Pr^{i}OH	135–137	60.10 (60.19)	5.31 (5.33)	4.36 (4.39)
3bb ($C_{15}H_{14}N_2O_2S$)	76	Pr^{i}OH	159–161	63.10 (62.94)	4.76 (4.89)	9.89 (9.79)
3bc ($C_{20}H_{19}NO_2S$)	40	EtOH	168–170	71.01 (71.22)	5.58 (5.64)	3.98 (4.15)
3bd ($C_{15}H_{17}NO_2S$)	43	Pr^{i}OH	126–128	65.25 (65.45)	6.22 (6.18)	4.93 (5.09)

since only one of the two possible diastereoisomers **A** and **B** (as a pair of enantiomers) was ever obtained. They can exist as equilibria between the two conformers **A′**/**A″** and **B′**/**B″**, respectively (Scheme 2).

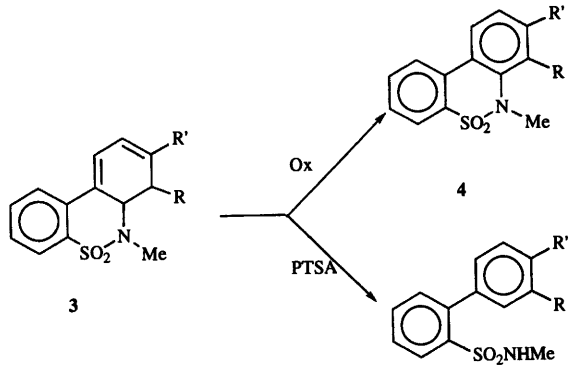


Scheme 2

In order to ascribe the correct diastereoisomeric structure **A** or **B** to products **3**, we considered the $^3J_{6a,7}$ values experimentally measured. When R′ = CO_2Me or Ph these values agree with an *eq,eq* relationship between 6a-H and 7-H (5.1–7.3 Hz) whereas when R′ = CN or Me they show an *ax,ax* relationship between these two hydrogens (14.5–17.6 Hz). This is independent of the nature of R (Ph or Me) (Table 2). The diastereoisomer **A** allows a rationalization of these results. In fact only conformer **A′** accounts for the typical *ax,ax* coupling of 6a-H/7-H observed in **3ab**, **3ad**, **3bb** and **3bd**; in the other diastereoisomer **B** there is either an *ax,eq* (**B′**) or an *eq,ax* (**B″**) relationship between these two hydrogens. Dreiding molecular models of **A** show that when R′ is a small group (CN, Me) the more stable conformation is that with R in the favoured equatorial position (**A′**) (consequently, 6a-H and 7-H resulted in an *ax,ax* relationship); in contrast when R′ is a bulky group (CO_2Me, Ph) the steric hindrance between R′ and R favours the **A″** conformer with R in an axial position (6a-H and 7-H in an *eq,eq* relationship). The $^3J_{6a,7}$ coupling constant values account for a conformational equilibrium in which **A′** prevails for products **3ab**, **3ad**, **3bb**, **3bd** and **A″** for **3aa**, **3ac**, **3ba**, **3bc**.

The complete preference observed for diastereoisomer **A** is a consequence of the depicted mechanism: the intramolecular proton shift concerted with C–C bond formation fixes the relative configuration of the 6a-C and 7-C centres.

The chemical behaviour of compounds **3** was successively studied. The aromatization of the cyclohexadiene ring to dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxides **4** was effected by several oxidizing agents because (see Experimental section) there was not found to be a general method which worked well for all the substrates (Scheme 3).



Scheme 3

The reaction of products **3aa**, **3ac**, **3ad** and **3bc** with toluene-*p*-sulfonic acid (PTSA·H_2O) in toluene at 80 °C gave unexpected and interesting results (Scheme 3).

The expected isomerization products[7] were not formed; a ring opening of the heterocyclic system followed by aromatization gave the 1,1′-biphenyl derivatives **5**. The initial protonation of the 6-N could be responsible for elimination of the 7-H proton by the water of crystallization of PTSA; with breaking of the C–N bond the system gains aromaticity. The use of anhydrous PTSA prevents this reaction course and starting materials are recovered unchanged probably because in the absence of water the toluenesulfonate anion is not sufficiently basic to cause elimination.

Experimental

Mps were determined with a Buchi apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with a Bruker WP-80-SY spectrometer. Chemical shifts are expressed as δ values from tetramethylsilane.

(*Z*)-3-Benzylidene- and -3-ethylidene-2,3-dihydro-2-methyl-1,2-benzothiazin-4-one 1,1-dioxide **1a** and **1b**,[1,2] methyl 4-(triphenylphosphoranylidene)but-2-enoate **2a**,[8] 4-(triphenylphosphoranylidene)but-2-enenitrile **2b**,[9] 3-phenylprop-2-enylidene(triphenyl)phosphorane **2c**[10] and but-2-enylidene-

Table 2 ^{1}H NMR data for products **3** [($CDCl_3$), δ_H (ppm from TMS), J/Hz]

Comp.	H-6a	H-7	H-9	H-10	N-Me	7-Me	8-Me	CO_2Me	Arom.	$^3J_{6a,7}$	$^3J_{9,10}$	$^4J_{6a,10}$	$^4J_{7,9}$
3aa	5.07 dd	4.29 dd	> 7.20	6.78 dd	2.60 s	—	—	3.65 s	7.2–7.8 m	6.30	6.59	1.46	1.22
3ab	5.00 dd	4.35 dd	6.90 dd	6.63 dd	2.35 s	—	—	—	7.2–7.9 m	17.60	5.98	2.80	2.68
3ac	5.07 dd	4.48 dd	6.64 dd	6.81 dd	2.60 s	—	—	—	7.1–7.8 m	7.30	6.47	1.47	1.22
3ad	5.06 dd	3.85 m	6.03 dt	6.64 dd	2.45 s	—	1.65 s	—	7.2–7.8 m	14.52	6.16	2.40	2.05
3ba	4.85 dd	3.20 m	7.05 dd	6.72 dd	2.60 s	1.35 d	—	3.80 s	7.4–7.9 m	5.13	6.47	1.22	0.98
3bb	4.55 dd	3.00 m	6.85 dd	6.67 dd	2.7 s	1.50 d	—	—	7.5–8.0 m	17.21	6.11	2.32	2.68
3bc	4.88 dd	3.27 m	6.32 dd	6.77 dd	2.65 s	1.25 d	—	—	7.3–7.9 m	7.20	6.53	1.46	0.78
3bd	4.60 dd	2.80 m	5.85 dt	6.65 dd	2.55 s	1.27 d	1.95 s	—	7.3–7.9 m	14.70	6.16	2.74	—

(triphenyl)phosphorane **2d**[11] were prepared according to reported methods.

Synthesis of products 3

Method A. A solution of **1** (10 mmol) and **2a** or **2b** (11 mmol) in THF was stirred at room temperature for 12 h. After evaporation of the solvent, the residue was treated with 5% aqueous HCl and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness. Compounds **3** were purified on a silica gel column using toluene–EtOAc (9:1) as eluent.

Method B. To a suspension of the phosphonium salt of **2c** or **2d** (11 mmol) in THF was added sodium hydride (22 mmol). After 15 min a solution of **1** (10 mmol) in THF was added dropwise to the mixture which was then stirred at room temperature for 12 h. After this it was worked up as indicated in method A. Analytical and spectroscopic data for products **3** are given in Tables 1 and 2.

Oxidation of products 3 to 4

Method A. To a solution of **3ab** or **3bb** (0.3 mmol) in dioxane (10 ml) were added aqueous NaOH (1.5 mmol) and aqueous potassium ferricyanide (2 mmol). After the mixture had been stirred at 70 °C for 7 h it was evaporated and the residue was treated with 5% aqueous acetic acid and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness. Compounds **4ab** and **4bb** were purified on a silica gel column using toluene–EtOAc (9:1) as eluent.

8-*Cyano*-6-*methyl*-7-*phenyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4ab**.—Mp 282–283 °C (Pr^{i}OH); yield 40%; δ_H 2.5 (3 H, s, NMe) and 7.5–8.1 (11 H, m, ArH) (Found: C, 68.9; H, 3.94; N, 7.89. $C_{20}H_{14}N_2O_2S$ requires C, 69.36; H, 4.05; N, 8.09%).

8-*Cyano*-6,7-*dimethyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4bb**.—Mp 220–221 °C (Pr^{i}OH); yield 38%; δ_H 2.7 (3 H, s, NMe), 2.9 (3 H, s, CMe) and 7.6–8.1 (6 H, m, ArH) (Found: C, 63.08; H, 4.15; N, 9.64. $C_{15}H_{12}N_2O_2S$ requires C, 63.38; H, 4.23; N, 9.86%).

Method B. To a solution of **3ac** (0.5 mmol) in acetic acid was added dropwise a solution of lead tetraacetate (0.6 mmol) in the same solvent. The mixture was stirred, under nitrogen atmosphere, at 70 °C for 2 h and then evaporated. The residue was treated with 5% aqueous HNO_3 and extracted with CH_2Cl_2. The extract was washed with 5% aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to dryness. Compound **4ac** was purified on a silica gel column using toluene as eluent.

7,8-*Diphenyl*-6-*methyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4ac**.—Mp 230–231 °C (EtOH); yield 40%; δ_H 2.3 (3 H, s, NMe) and 7.0–8.0 (16 H, m, ArH) (Found: C, 75.41; H, 4.87; N, 3.62. $C_{25}H_{19}NO_2S$ requires C, 75.57; H, 4.78; N, 3.53%).

Method C. A mixture of **3aa** or **3ad** or **3bd** (0.2 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.4 mmol) in toluene was stirred at 110 °C for 48 h and then evaporated. The residue was purified on a silica gel column using toluene–EtOAc (9:1) as eluent.

8-*Methoxycarbonyl*-6-*methyl*-7-*phenyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4aa**.—Mp 176–178 °C (Pr^{i}OH); yield 60%; δ_H 2.5 (3 H, s, NMe), 3.6 (3 H, s, OMe) and 7.2–8.1 (11 H, m, ArH) (Found: C, 72.48; H, 4.75; N, 3.87. $C_{21}H_{17}NO_2S$ requires C, 72.62; H, 4.90; N, 4.03%).

6,8-*Dimethyl*-7-*phenyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4ad**.—Mp 183–185 °C (Pr^{i}OH); yield 84%; δ_H 2.2 (3 H, s, CMe), 2.5 (3 H, s, NMe) and 7.3–8.0 (11 H, m, ArH) (Found: C, 71.39; H, 4.94; N, 4.03. $C_{20}H_{17}NO_2S$ requires C, 71.64; H, 5.07; N, 4.18%).

6,7,8-*Trimethyldibenzo*[c,e][1,2]*thiazine* 5,5-*dioxide* **4bd**.—Mp 186–188 °C (Pr^{i}OH); yield 83%; δ_H 2.4 (3 H, s, CMe), 2.5 (3 H, s, CMe), 2.9 (3 H, s, NMe) and 7.2–8.0 (6 H, m, ArH) (Found: C, 65.71; H, 5.32; N, 5.05. $C_{15}H_{15}NO_2S$ requires C, 65.93; H, 5.49; N, 5.13%).

Reaction of products 3 with PTSA·H_2O

General procedure. A mixture of **3aa** or **3ac** or **3ad** or **3bc** (0.3 mmol) and PTSA·H_2O (0.3 mmol) in toluene was stirred at 80 °C for 4 h and then washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated to dryness. Products were purified by recrystallization from the indicated solvent.

4′-*Methoxycarbonyl*-3′-*phenyl*-N-*methyl*-1,1′-*biphenyl*-2-*sulfonamide* **5aa**.—Mp 128–129 °C (cyclohexane); yield 78%; δ_H 2.4 (3 H, d, NMe), 3.5 (1 H, q, NH), 3.6 (3 H, s, OMe) and 7.1–8.2 (12 H, m, ArH) (Found: C, 65.89; H, 4.85; N, 3.50. $C_{21}H_{19}NO_4S$ requires C, 66.14; H, 4.99; N, 3.67%).

3′,4′-*Diphenyl*-N-*methyl*-1,1′-*biphenyl*-2-*sulfonamide* **5ac**.—Mp 151–153 °C (Pr^{i}OH); yield 70%; δ_H 2.4 (3 H, d, NMe), 3.7 (1 H, q, NH) and 7.2–8.2 (17 H, m, ArH) (Found: C, 74.98; H, 5.45; N, 3.61. $C_{25}H_{21}NO_2S$ requires C, 75.19; H, 5.26; N, 3.51%).

4′-*Methyl*-3′-*phenyl*-N-*methyl*-1,1′-*biphenyl*-2-*sulfonamide* **5ad**.—Mp 154–155 °C (Pr^{i}OH); yield 70%; δ_H 2.3 (3 H, s, CMe), 2.4 (3 H, d, NMe), 3.5 (1 H, q, NH) and 7.3–8.2 (12 H, m, ArH) (Found: C, 71.21; H, 5.82; N, 4.24. $C_{20}H_{19}NO_2S$ requires C, 71.22; H, 5.64; N, 4.15%).

3′-*Methyl*-4′-*phenyl*-N-*methyl*-1,1′-*biphenyl*-2-*sulfonamide* **5bc**.—Mp 135–136 °C (Pr^{i}OH); yield 80%; δ_H 2.3 (3 H, s, CMe), 2.4 (3 H, d, NMe), 3.6 (1 H, q, NH) and 7.3–8.2 (12 H, m, ArH) (Found: C, 70.73; H, 5.32; N, 4.05. $C_{20}H_{19}NO_2S$ requires C, 71.22; H, 5.64; N, 4.15%).

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References

1 P. Dalla Croce, D. Del Monaco and C. La Rosa, *J. Chem. Soc., Perkin Trans. 1*, 1986, 299.
2 P. Dalla Croce, R. Ferraccioli and C. La Rosa, *Synth. Commun.*, 1992, **22**, 2621.
3 P. Dalla Croce, C. La Rosa and H. Molinari, *Gazz. Chim. Ital.*, 1990, **120**, 443.
4 P. Dalla Croce, R. Ferraccioli and C. La Rosa, *Gazz. Chim. Ital.*, 1993, **123**, 35.
5 For the methods of synthesis of **4** see for example: (*a*) J. L. Huppatz and W. H. F. Sasse, *Aust. J. Chem.*, 1963, **16**, 417; (*b*) G. Ege and E. Beisiegel, *Liebigs Ann. Chem.*, 1972, **763**, 46; (*c*) H. Shimizu, K. Matsuo, T. Kataoka and M. Hori, *Chem. Pharm. Bull.*, 1984, **32**, 4360; (*d*) D. E. Ames and A. Opalko, *Tetrahedron*, 1984, 1919; (*e*) S. A. Glover, A. Goosen, C. W. McCleland and J. L. Schoonraad, *J. Chem. Soc., Perkin Trans. 2*, 1986, 645; (*f*) D. P. Curran and H. Liu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1377.
6 E. Vedejs and J. P. Bershas, *Tetrahedron Lett.*, 1975, **16**, 1359 and references therein.
7 G. Buchi and H. Wuest, *Helv. Chim. Acta*, 1971, **54**, 1767.
8 E. Buchta and F. Andree, *Chem. Ber.*, 1959, **92**, 3111.
9 P. Dalla Croce and D. Pocar, *J. Chem. Soc., Perkin Trans. 1*, 1976, 619.
10 R. N. McDonald and T. W. Campbell, *J. Org. Chem.*, 1959, 1969.
11 F. Bohlmann and H. J. Mannhardt, *Chem. Ber.*, 1956, **89**, 1307.

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