Conformational Effects on Photochemical Thiylation of 2′-Vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones

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Photochemical thiylation of 2′-vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones (1) to form allyl sulfides (3) was examined. Although the reactions proceeded with complete regioselectivity because of the high stabilizing ability of the capto-dative substituents, geometrical selectivity of the olefinic moiety was dependent on the substituents on the cyclopropane ring. The conformation of 1 probably plays an important role in the addition step of the thiyl radical to the double bond.

Key words vinylcyclopropane; benzothiazinone; conformational effect; photochemical thiylation

Some benzothiazinone derivatives such as semotiadil, a Ca^{2+} antagonist,[1] or SPR-210, an aldose reductase inhibitor,[2] possess pharmacological activity. Recently we reported the synthesis and transformation of 1-(electron-withdrawing group)-substituted 1-sulfenyl-2-vinylcyclopropanes, including 2′-vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones.[3] Vinylcyclopropanes have been extensively transformed and utilized for the synthesis of complex molecules.[4] Miura and co-workers have described highly regioselective photochemical thiylation of silyl-substituted vinylcyclopropanes.[5] 2′-Vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones consist of a capto-dative structure and should undergo regioselective thiylation due to the high stabilizing ability of the capto-dative substituents.[6] We aimed to synthesize new 2*H*-benzothiazine-3(4*H*)-one derivatives by regioselective photochemical thiylation and found that the stereoselectivity was dependent on the substituents of the cyclopropane ring, although the regioselectivity was independent of them. We will report here conformational effects on the stereoselective photochemical thiylation of 2′-vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones.

Results and Discussion

Vinylcyclopropanes **1** were treated with 1 eq of thiophenol in benzene under a nitrogen atmosphere at room temperature for 40 h with irradiation by a tungsten lamp (Chart 1). Allyl sulfide derivatives **3** were obtained in good to high yields by regioselective thiylation (Table 1). Regioselectivity would be achieved through the capto-dative substituent effect *via* a radical intermediate **2** which abstracts a hydrogen radical to form **3**. Stereoselectivity was dependent on the substituents R^1 and R^2. The reaction of the dimethyl derivative **1a** ($R^1=R^2=Me$) showed high (*Z*)-selectivity (entry 1), while high (*E*)-selectivity was observed in the reaction of **1b** ($R^1=R^2=H$) (entry 2). In the cases of phenyl derivatives **1c** and **1d**, the (*E*)-isomers were obtained as the major products (entries 3 and 4). The geometry of the allyl sulfides was determined either from a coupling constant between vic-olefinic protons in the ^{1}H-NMR spectrum of **3b** or from nuclear Overhauser effect (NOE) experiments on (*Z*)-**3a, d** and (*E*)-**3c**. Four percent NOE was observed between 1′- and 4′-H in the cases of (*Z*)-**3a** and (*Z*)-**3d** and 7% NOE was observed between 1′- and 3′-H in the case of (*E*)-**3c**.

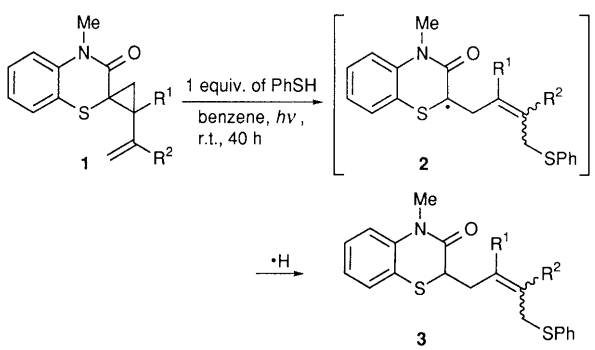

Chart 1

The dimethyl derivative **1a** exists in *anti*-conformation (**1a**-*anti*, Fig. 1) in which the olefinic site is in the opposite direction to the benzothiazinone skeleton.[7] Sulfides **1b** and **1c** should exist in similar conformation. On the other hand, the *syn*-conformer would be favored in the diphenyl derivative **1d** because of steric repulsion between a phenyl group and the benzothiazinone framework (see **1d**-*anti* and **1d**-*syn*, Fig. 1). The stereoselectivity can be explained as shown in Chart 2. In the case of the dimethyl derivative **1a** ($R^2=Me$), the phenylthiyl radical adds to the double bond from the opposite side to the cyclopropane ring in

Table 1. Photochemical Thiylation of Vinylcyclopropanes **1**

Entry	Sulfide	R^1	R^2	Product (% yield, *Z*:*E*)[a]
1	**1a**	Me	Me	**3a** (96, 9:1)
2	**1b**	H	H	**3b** (90, 1:9)
3	**1c**	Ph	H	**3c** (66, 1:4)
4	**1d**	Ph	Ph	**3d** (68, 1:2)

a) Isolated yield. The ratio was determined by ^{1}H-NMR.

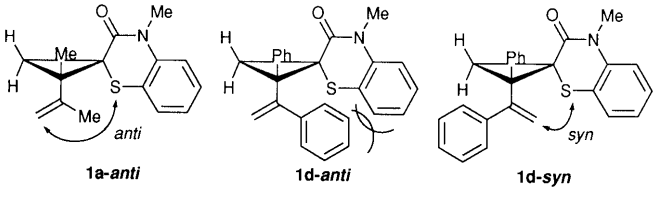

Fig. 1. Conformations of Some Vinylcyclopropanes **1**

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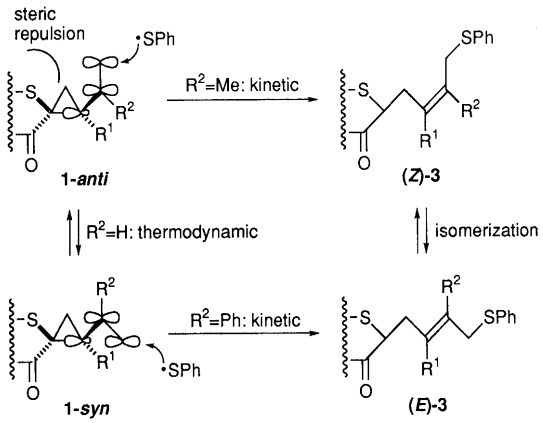

Chart 2

1a-*anti* under kinetic control to give the (*Z*)-isomer predominantly. The reaction of **1d** (R^2=Ph) proceeds *via* **1d**-*syn*, a more favored conformer than **1d**-*anti*, under kinetic control and the (*E*)-isomer is formed as a major product. In the cases of R^2=H (**1b** and **1c**), steric repulsion between the benzothiazinylmethyl and phenylthiomethyl groups becomes an important factor and predominant formation of (*E*)-isomers is achieved *via* **1**-*syn* under thermodynamic control. Because the steric effect is more significant in **1b** (R^1=R^2=H) than in **1c** (R^1=Ph, R^2=H), the ratio of the (*E*)-isomer in **1b** is greater than that in **1c**. Formation of (*Z*)-**3a** in preference to (*E*)-**3a** suggests that isomerization of (*Z*)-isomers to thermodynamically more stable (*E*)-isomers is not very significant. However, it could not be completely excluded that (*Z*)-allyl sulfides isomerize to (*E*)-allyl sulfides under photochemical conditions.

Experimental

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (NaCl) were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL GX-270 (270 MHz) or a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra and NOEs were obtained on a JEOL EX-400 spectrometer. The *J* values are given in hertz (Hz). Mass spectra were recorded on a JEOL JMS-D 300 spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed on a Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with Kieselgel 60 PF_{254} containing gypsum for preparative TLC.

Photochemical Thiylation of Vinylcyclopropanes 1 General Procedure: A mixture of a sulfide **1** (0.5 mmol) and thiophenol (55 mg, 0.5 mmol) in degassed dry benzene (1 ml) was stirred at room temperature under a nitrogen atmosphere for 40 h with concomitant irradiation by a tungsten lamp (60W). The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC on silica gel with ethyl acetate–hexane (1 : 5). The results are summarized in Table 1.

2-(2,3-Dimethyl-4-phenylthio-2-butenyl)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**3a**): Yield 96%. Colorless oil as a mixture of geometrical isomers. ^{1}H-NMR ($CDCl_3$) δ: (*Z*)-isomer$_{major}$: 1.68 and 1.85 (each 3H, s, Me×2), 2.13 (1H, dd, *J*=14, 9 Hz, 1′-H), 2.27 (1H, dd, *J*=14, 6 Hz, 1′-H), 3.24 and 3.35 (each 1H, d, *J*=12 Hz, 4′-H), 3.42 (3H, s, NMe), 3.51 (1H, dd, *J*=9, 6 Hz, 2-H), 7.00—7.43 (9H, m, ArH); (*E*)-isomer$_{minor}$: 1.56 and 1.61 (each 3H, s, Me×2), 2.35 (1H, dd, *J*=14, 10 Hz, 1′-H), 2.50 (1H, dd, *J*=14, 6 Hz, 1′-H), 3.43 (3H, s, NMe), 3.48—3.61 (2H, m, 4′-H), 3.51 (1H, dd, *J*=10, 6 Hz, 2-H), 7.00—7.43 (9H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: (*Z*)-isomer$_{major}$: 18.4 (q), 18.5 (q), 32.2 (q), 33.7 (t), 38.9 (t), 42.0 (d), 117.0 (d), 121.2 (s), 123.4 (d), 126.2 (d), 127.0 (d), 127.6 (s), 128.5 (d), 128.6 (d), 128.9 (d), 130.6 (d×2), 130.7 (s), 136.4 (s), 139.5 (s), 166.8 (s). FAB-MS *m/z*: 370 (M^++1, 25), 260 (100). IR (NaCl) cm^{-1}: 1660 (C=O). HRMS (FAB) Calcd for $C_{21}H_{23}NOS_2$+H: 370.1299. Found: 370.1287.

4-Methyl-2-(4-phenylthio-2-butenyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (**3b**): Yield 90%. Colorless oil as a mixture of geometrical isomers. ^{1}H-NMR ($CDCl_3$) δ: (*E*)-isomer$_{major}$: 2.21—2.28 and 2.52—2.57 (each 1H, m, 1′-H), 3.27 (1H, dd, *J*=9, 6 Hz, 2-H), 3.40 (3H, s, NMe), 3.48 (2H, d, *J*=6 Hz, 4′-H), 5.52 (1H, dt, *J*=15$_{(trans)}$, 6 Hz, 3′-H), 5.51—5.58 (1H, m, 2′-H), 6.98—7.03 (2H, m, ArH), 7.14 (1H, t, *J*=8 Hz, ArH), 7.20—7.32 (6H, m, ArH); (*Z*)-isomer$_{minor}$: 2.22 (1H, ddd, *J*=7.3, 8.8, 15 Hz, 1′-H), 2.51 (1H, ddd, *J*=6.3, 7.3, 15 Hz, 1′-H), 3.22 (1H, dd, *J*=6.3, 8.8 Hz, 2-H), 3.42 (2H, d, *J*=7.8 Hz, 4′-H), 3.43 (3H, s, NMe), 5.55 (1H, dt, *J*=11$_{(cis)}$, 7.3 Hz, 2′-H), 5.67 (1H , dt, *J*=11$_{(cis)}$, 7.8 Hz, 3′-H), 7.01—7.07 (2H, m, ArH), 7.13 (1H, t, *J*=7 Hz, ArH), 7.20—7.36 (6H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: (*E*)-isomer$_{major}$: 32.1 (t), 32.5 (q), 36.3 (t), 43.3 (d), 117.4 (d), 121.8 (s), 123.6 (d), 126.4 (d), 127.3 (d),128.9 (d), 129.1 (d), 129.2 (d), 130.2 (d), 135.9 (s), 139.9 (s), 167.1 (s). FAB-MS *m/z*: 342 (M^++1, 40), 232 (100). IR (NaCl) cm^{-1}: 1660 (C=O). HRMS (FAB) Calcd for $C_{19}H_{19}NOS_2$+H: 342.0987. Found: 342.0972.

4-Methyl-2-(2-phenyl-4-phenylthio-2-butenyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (**3c**): Yield 66%. Light yellow oil as a mixture of geometrical isomers. ^{1}H-NMR ($CDCl_3$) δ: (*E*)-isomer$_{major}$: 2.42 (1H, dd, *J*=14, 10 Hz, 1′-H), 2.97 (1H, dd, *J*=14, 5 Hz, 1′-H), 3.23 (1H, dd, *J*=10, 5 Hz, 2-H), 3.35 (3H, s, NMe), 3.45 (2H, d, *J*=7 Hz, 4′-H), 5.50 (1H, t, *J*=7 Hz, 3′-H), 6.98—7.34 (14H, m, ArH); (*Z*)-isomer$_{minor}$: 2.58 (1H, dd, *J*=15, 10 Hz, 1′-H), 2.86 (1H, dd, *J*=15, 6 Hz, 1′-H), 3.30—3.35 (1H, 2-H), 3.33 (3H, s, NMe), 3.46 (2H, d, *J*=8 Hz, 4′-H), 5.87 (1H, t, *J*=8 Hz, 3′-H), 6.94—7.34 (14H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: (*E*)-isomer$_{major}$: 32.2 (q), 32.8 (t), 38.6 (t), 41.2 (d), 117.0 (d), 121.2 (s), 123.4 (d), 126.1 (d), 126.7 (d), 127.1 (d), 127.5 (d), 128.3 (d), 128.5 (d), 128.7 (d), 128.9 (d), 129.9 (d), 135.8 (s), 137.8 (s), 139.5 (s), 139.7 (s), 166.9 (s). EI-MS *m/z*: 417 (M^+, 7), 308 (M^+−SPh, 72), 178 (100). IR (NaCl) cm^{-1}: 1665 (C=O). HRMS (EI) Calcd for $C_{25}H_{23}NOS_2$: 417.1221. Found: 417.1237.

2-(2,3-Diphenyl-4-phenylthio-2-butenyl)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**3d**): Yield 68%. Light yellow oil as a mixture of geometrical isomers. ^{1}H-NMR ($CDCl_3$) δ: (*E*)-isomer$_{major}$: 2.48 (1H, dd, *J*=14, 8 Hz, 1′-H), 2.82 (1H, dd, *J*=14, 7 Hz, 1′-H), 3.16 (1H, dd, *J*=7, 8 Hz, 2-H), 3.20 (3H, s, NMe), 3.72 and 3.79 (each 1H, d, *J*=12 Hz, 4′-H), 6.91—7.39 (19H, m, ArH); (*Z*)-isomer$_{minor}$: 2.55 (1H, dd, *J*=15, 9 Hz, 1′-H), 2.70 (1H, dd, *J*=14, 6 Hz, 1′-H), 3.25 (1H, dd, *J*=6, 9 Hz, 2-H), 3.34 (3H, s, NMe), 3.72 and 3.75 (each 1H, d, *J*=12 Hz, 4′-H), 6.65—7.39 (19H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 32.2 (q), 33.6 (t), 35.4 (t), 39.3 (t), 40.2 (t), 41.1 (d), 41.4 (d), 117.0 (d), 117.1 (d), 121.2 (s), 122.2 (s), 123.1 (d), 123.5 (d), 125.9 (d), 126.4 (d), 126.5 (d), 126.7 (d), 126.8 (d), 126.9 (d), 127.2 (d), 127.3 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.9 (d), 129.0 (d), 129.6 (d), 129.8 (d), 130.1 (d), 131.6 (d), 135.7 (s), 136.3 (s), 136.5 (s), 136.7 (s), 137.1 (s), 137.2 (s), 139.1 (s), 139.2 (s), 139.6 (s), 139.8 (s), 140.1 (s), 141.2 (s), 166.5 (s), 166.6 (s). EI-MS *m/z*: 493 (M^+, 2), 384 (M^+−SPh, 78), 178 (100). IR (NaCl) cm^{-1}: 1660 (C=O). HRMS (EI) Calcd for $C_{31}H_{27}NOS_2$: 493.1534. Found: 493.1523.

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7) X-Ray crystallographic analysis of **1a** shows this conformation in the solid state.[3b] Although an NOE experiment on **1a** failed to show any enhancement, 8% NOE was observed between a methylene proton of the cyclopropane ring and an olefinic proton in the ^{1}H-NMR of methyl 2-isopropenyl-2-methyl-1-(phenylthio)-cyclopropanecarboxylate.[3a] This result suggests that **1a** exists in *anti*-conformation in the solution state.