Chemical Behavior of 2′-Vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones in Acidic Media

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Received August 11, 1997; accepted September 9, 1997

Reactions of 2′-vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones (1) with several proton acids were examined. Reactions of 1 with HCl and HBr predominantly gave (*Z*)-allyl halide derivatives (2). In the cases of $HClO_4$ and HBF_4 4,4a,5,6-tetrahydro-5-oxo-1*H*-thiopyrano[1,2-*a*]-1,4-benzothiazinium salts (3) were isolated. Allyl halides (2) were also obtained by treatment of the salts (3) with HCl and HBr.

Key words vinylcyclopropane; benzothiazinone; inorganic acid; 4,4a,5,6-tetrahydro-5-oxo-1*H*-thiopyrano[1,2-*a*]-1,4-benzothiazinium salt

Several benzothiazinone derivatives have pharmacological activities, such as semotiadil, a Ca^{2+} antagonist[1] or SPR-210, an aldose reductase inhibitor.[2] In our previous paper, we described the synthesis and transformation of tricyclic benzothiazinium salts bearing a bridgehead sulfur atom as part of a program to synthesize benzothiazinone derivatives possessing unusual skeletons.[3] In this study, we have obtained benzothiazinones bonded with spirovinylcyclopropane. The vinylcyclopropane unit has been subjected to a variety of chemical transformations,[4] and we have explored a novel transformation of 1-(electron-withdrawing group)-substituted 1-sulfenyl-substituted 2-vinylcyclopropanes under acidic conditions.[5] The reaction involves C^1–C^2 bond fission and subsequent 1,5-sulfenyl shift, and a 2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-one derivative also underwent C^1–C^2 bond fission on treatment with 1 eq of *p*-toluenesulfonic acid under refluxing in benzene to give isomerized products. In contrast, treatment of the benzothiazinone derivatives with other proton acids such as HCl, HBr, $HClO_4$ and HBF_4 gave different results. This paper describes the chemical behavior of 2′-vinyl-2*H*-benzothiazine-2-spirocyclopropan-3(4*H*)-ones in acidic media.

Results and Discussion

First, we examined the reactions of vinylcyclopropyl sulfides (**1**) with concentrated HCl, concentrated HBr and acetic acid (Table 1). Treatment of **1a** with 1 eq of concentrated HCl in ether at room temperature for 72 h gave stereoselectively a small amount of (*Z*)-allyl chloride [(*Z*)-**2aA**] (8%), along with the recovered **1a** (70%). The use of an excess amount of concentrated HCl shortened the reaction time (12 h) and improved the yield of (*Z*)-**2aA** to 76% (entry 2). A (*Z*)-allyl bromide [(*Z*)-**2aB**] including a trace amount of (*E*)-isomer [(*E*)-**2aB**] was obtained in 46% yield from the reaction of **1a** with 1 eq of concentrated HBr for 72 h (entry 3). The amount of (*E*)-**2aB** increased when an excess amount of concentrated HBr was used (entry 4). Reactions of **1b** with an excess amount of concentrated HCl provided (*Z*)-**2bA** in high yields (entries 6 and 7). No reaction occurred on treatment of the sulfides **1a** and **1b** with acetic acid (entries 5 and 8). The reaction rate is probably dependent on the acidity of the acid used. The geometry of allyl halides **2a** (R=H) was determined from the coupling constants between vic-olefinic protons in the ^{1}H-NMR spectra and that of allyl chloride **2bA** (R=Me) was confirmed by nuclear Overhauser effect (NOE) measurement (Fig. 1).

Table 1. Reactions of Vinylcyclopropanes with Acids

Entry	1	Acid	Solvent	Time (h)	Products (% yield)
1	**1a**	Concentrated HCl (1 eq)	Ether	72	(*Z*)-**2aA** (8), **1a** (70)
2	**1a**	Concentrated HCl (excess)	Ether	12	(*Z*)-**2aA** (76), **1a** (20)
3	**1a**	Concentrated HBr (1 eq)	Ether	72	(*Z*)-**2aB** (46),[a] **1a** (31)
4	**1a**	Concentrated HBr (excess)	Ether	12	**2aB** (84, *Z*:*E*=5:1)[b]
5	**1a**	AcOH (excess)	Ether	72	No reaction
6	**1b**	Concentrated HCl (excess)	THF	12	(*Z*)-**2bA** (100)
7	**1b**	Concentrated HCl (excess)	Ether	12	(*Z*)-**2bA** (88)
8	**1b**	AcOH (excess)	Ether	12	No reaction
9	**1a**	42% HBF_4 (excess)	Ether	12	**3aC** (94)
10	**1a**	70% $HClO_4$ (excess)	Ether	12	**3aD** (85)
11	**1b**	70% $HClO_4$ (excess)	Ether	12	**3bD** (87)
12	**1a**	Me_3OBF_4 (1.1 eq)	CH_2Cl_2	ON[c]	**3aC** (74)

a) A small amount of (*E*)-**2aB** was apparent in the ^{1}H-NMR spectrum of (*Z*)-**2aB**. *b*) An inseparable mixture of (*Z*)- and (*E*)-**2aB**. The ratio was determined from the ^{1}H-NMR spectrum. *c*) Overnight. THF=tetrahydrofuran.

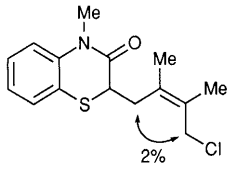

Fig. 1. NOE in the Allyl Chloride (*Z*)-**2bA**

Table 2. Reactions of Benzothiazinium Salts with Acids

Entry	3	Acid	Solvent	Time (h)	Products (% yield)
1	**3aC**	Concentrated HCl	Ether	72	(*Z*)-**2aA** (67)
2	**3aC**	Concentrated HBr	CH_3CN	12	**2aB** (89, *Z*:*E*=2:1)[a]
3	**3aD**	Concentrated HCl	THF	72	(*Z*)-**2aA** (74)
4	**3bD**	Concentrated HCl	THF	72	(*Z*)-**2bA** (88)

a) An inseparable mixture of (*Z*)- and (*E*)-**2aB**. The ratio was determined from the ^{1}H-NMR spectrum. THF=tetrahydrofuran.

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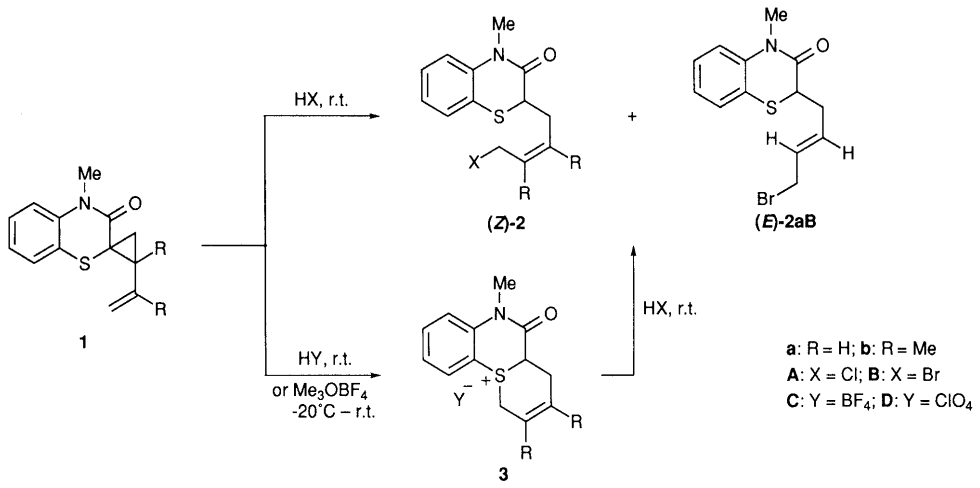

Next, we examined reactions of **1** with 42% HBF_4 and 70% $HClO_4$ whose anion parts, BF_4^- and ClO_4^-, respectively, lack nucleophilicity. In all cases, the benzothiazinium salts **3** were isolated in high yields (Table 1, entries 9—11).[3] Treatment of **1a** with 1.1 eq of Me_3OBF_4 in CH_2Cl_2 at −20 °C to room temperature overnight gave the sulfonium salt **3aC** in 74% yield (entry 12). The results suggest that (*Z*)-allyl halides **2** would be stereoselectively formed by nucleophilic ring-opening of **3** with a halide ion. In order to confirm this assumption benzothiazinium salts **3** were treated with concentrated HCl and HBr (Table 2). In fact, reactions with an excess amount of concentrated HCl gave (*Z*)-allyl chlorides [(*Z*)-**2**] stereoselectively (entries 1, 3 and 4) and allyl bromide **2aB** was formed as a mixture of geometrical isomers by the use of concentrated HBr (entry 2).

The reaction of vinylcyclopropane **1** may proceed as follows. Protonation at the carbonyl oxygen causes attack of the sulfur atom on the terminal olefinic methylene with opening of the cyclopropane ring to form a sulfonium salt **3**. In the cases of nucleophilic anions, namely X = Cl and Br, the allylic carbon undergoes S*N*2 reaction with C-S bond cleavage to give (*Z*)-allyl halides **2**. The greater acidity of HBr than HCl allows isomerization of the (*Z*)-allyl bromide to the thermodynamically more stable (*E*)-isomer, (*E*)-**2aB**.[6]

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 NOE were obtained on a JEOL EX-400 spectrometer. The *J* values are given in 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.

Reactions of Vinylcyclopropanes (1) with an Acid General Procedure: Method A: An acid (0.5 mmol or 1.0 ml for an excess amount of an acid) was added to a stirred solution of **1** (0.5 mmol) in a solvent (10 ml), and the whole was stirred at room temperature for 12 or 72 h. The reaction mixture was extracted with chloroform (5 ml × 2). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate–hexane (1 : 5) to give an allyl halide. The reaction conditions and the yields are summarized in Table 1.

Method B: An acid (0.5 ml) was added to a stirred solution of **1** (0.5 mmol) in ether (10 ml) and the whole was stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure. The resultant solid was washed with ether to give a pure sulfonium salt. The yields are summarized in Table 1.

Method C: A solution of **1a** (2.31 g, 10 mmol) in dry CH_2Cl_2 (25 ml) was treated with Me_3OBF_4 (1.68 g, 11 mmol) under stirring at −20 °C (cooled by ice-NaCl). The mixture was stirred at room temperature overnight and evaporated under reduced pressure. The resultant solid was purified by recrystallization from CH_3CN–ethyl acetate to give the benzothiazinium salt **3aC** (1.72 g, 74%).

2-[(*Z*)-4-Chloro-2-butenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**2aA**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.35—2.47 and 2.62—2.73 (each 1H, m, 1′-H), 3.45 (3H, s, NMe), 3.45—3.52 (1H, m, 2-H), 4.01 (2H, d, J=8 Hz, 4′-H), 5.66 (1H, dt, J=11, 7 Hz, 2′-H), 5.78 (1H, dt, J=11, 8 Hz, 3′-H), 7.01—7.10 (2H, m, ArH), 7.24—7.37 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 26.9 (t), 32.3 (q), 38.9 (t), 42.7 (d), 117.2 (d), 121.1 (s), 123.5 (d), 127.3 (d), 128.4 (d), 128.7 (d), 129.5 (d), 139.5 (s), 166.5 (s). MS (rel. int. %) *m/z*: 267 (M^+, 17), 232 (M^+ − Cl, 100). IR (NaCl) cm^{-1}: 1660 (C=O). HRMS Calcd for $C_{13}H_{14}ClNOS$: 267.0485. Found: 267.0491.

2-[(*Z*)- and (*E*)-4-Bromo-2-butenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**2aB**): Pale yellow oil as a mixture of (*Z*)- and (*E*)-isomers. ^{1}H-NMR ($CDCl_3$) δ: 2.46 and 2.70 (each 1H, dt, J=14, 7 Hz, (*Z*)-1′-H), 2.39—2.48 and 2.62—2.73 (each 1H, m, (*E*)-1′-H), 3.41—3.47 (total 2H, m, (*Z*)- and (*E*)-2-H), 3.44 (3H, s, (*E*)-NMe), 3.45 (3H, s, (*Z*)-NMe), 3.83 and 3.86 (each 1H, dd, J=8, 12 Hz, (*Z*)-4′-H), 3.91 (2H, d, J=7 Hz, (*E*)-4′-H), 5.66 (1H, dt, J=11, 7 Hz, (*Z*)-2′-H), 5.72 (1H, dt, J=15, 7 Hz, (*E*)-2′-H), 5.79 (1H, dt, J=15, 7 Hz, (*E*)-3′-H), 5.86 (1H, dt, J=11, 8 Hz, (*Z*)-3′-H), 7.01—7.37 (total 4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: (*Z*)-isomer: 26.4 (t), 26.7 (t), 32.3 (q), 42.6 (d), 117.2 (d), 121.1 (s), 123.5 (d), 127.3 (d), 128.4 (d), 128.7 (d), 129.8 (d), 139.5 (s), 166.5 (s); (*E*)-isomer: 26.3 (t), 31.7 (t), 32.3 (q), 42.6 (d), 117.2 (d), 121.4 (s), 123.4 (d), 127.1 (d), 128.6 (d), 129.6 (d), 130.8 (d), 139.5 (s), 166.6 (s). MS (rel. int. %) *m/z*: 311 (M^+, 3), 232 (M^+ − Br, 100). IR (NaCl) cm^{-1}: 1665 (C=O). HRMS Calcd for $C_{13}H_{14}BrNOS$: 310.9979. Found: 310.9969.

2-[(*Z*)-4-Chloro-2,3-dimethyl-2-butenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**2bA**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.74 and 1.79 (each 3H, s, 2′- and 3′-Me), 2.42 (1H, dd, J=9, 14 Hz, 1′-H), 2.59 (1H, dd, J=6, 14 Hz, 1′-H), 3.45 (3H, s, NMe), 3.59 (1H, dd, J=6, 9 Hz, 2-H), 3.65 and 3.89 (each 1H, d, J=15 Hz, 4-H), 5.78 (1H, dt, J=11, 8 Hz, 3′-H), 7.01—7.10 (2H, m, ArH), 7.24—7.37 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 26.9 (t), 32.3 (q), 38.9 (t), 42.7 (d), 117.2 (d), 121.1 (s), 123.5 (d), 127.3 (d), 128.4 (d), 128.7 (d), 129.5 (d), 139.5 (s), 166.5 (s). MS (rel. int. %) *m/z*: 295 (M^+, 6), 260 (M^+ − Cl, 100). IR (NaCl) cm^{-1}: 1660 (C=O). *Anal.* Calcd for $C_{15}H_{18}ClNOS$: C, 60.90; H, 6.13; N, 4.73. Found: C, 60.62; H, 6.16; N, 4.64.

6-Methyl-4,4a,5,6-tetrahydro-5-oxo-1*H*-thiopyrano[1,2-*a*]-1,4-benzothiazinium tetrafluoroborate (**3aC**): Colorless prisms (CH_3CN–ethyl

acetate), mp 179—180 °C. ^{1}H-NMR (CD_3CN) δ: 2.85 and 3.45 (each 1H, br d, J=19.5 Hz, 4-H), 3.48 (3H, s, NMe), 4.10 (1H, br d, J=16 Hz, 1-H), 4.18 (1H, dd, J=5.4, 16 Hz, 1-H), 4.74 (1H, br d, J=4.9 Hz, 4a-H), 5.84—5.85 and 6.10—6.12 (each 1H, m, 2- and 3-H), 7.41 (1H, t, J=8 Hz, ArH), 7.49 (1H, d, J=8 Hz, ArH), 7.88 (1H, t, J=8 Hz, ArH), 7.92 (1H, d, J=8 Hz, ArH). ^{13}C-NMR (CD_3CN) δ: 23.2 (t), 32.3 (q), 33.3 (t), 41.6 (d), 104.1 (s), 115.6 (d), 119.6 (d), 124.8 (d), 128.7 (d), 133.2 (d), 136.5 (d), 141.7 (s), 159.9 (s). IR (KBr) cm^{-1}: 1665 (C=O), 1060 (BF_4). *Anal.* Calcd for $C_{13}H_{14}BF_4NOS$: C, 48.78; H, 4.40; N, 4.38. Found: C, 48.72; H, 4.43; N, 4.48.

Reactions of Benzothiazinium Salts (3) with Acid General Procedure: An acid (1.0 ml) was added to a suspension of **3** in a solvent (10 ml) and the whole was stirred at room temperature for 12 or 72 h. The reaction mixture was extracted with chloroform (5 ml × 2). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate–hexane (1 : 5) to give an allyl halide. The reaction conditions and the yields are summarized in Table 2.

Acknowledgments This work was supported in part by grants No. 06303002 and 07672423 from the Ministry of Education, Science, Sports and Culture.

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6) Isomerization of (*Z*)-**2aB** to (*E*)-**2aB** was observed. A mixture of (*Z*)-**2aB** (16 mg, 0.05 mmol, obtained from the reaction of **1a** with concentrated HBr, Table 1, entry 4) and concentrated HBr (0.1 ml) in tetrahydrofuran (THF) (1 ml) was stirred for 12 h at room temperature and evaporated under reduced pressure. The oily residue was analyzed by ^{1}H-NMR spectroscopy and the ratio of (*Z*)-**2aB** : (*E*)-**2aB** was ca. 4 : 1.