

Notes

Trifluoromethyl Group Effect in Chlorination of Dihydro-1,4-oxathiin-3-carboxanilide : Unusual Non-Stereospecific Addition

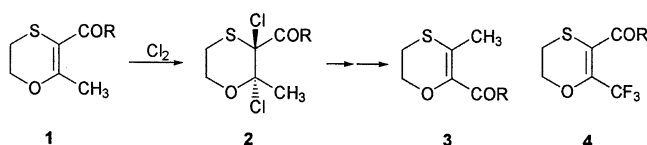
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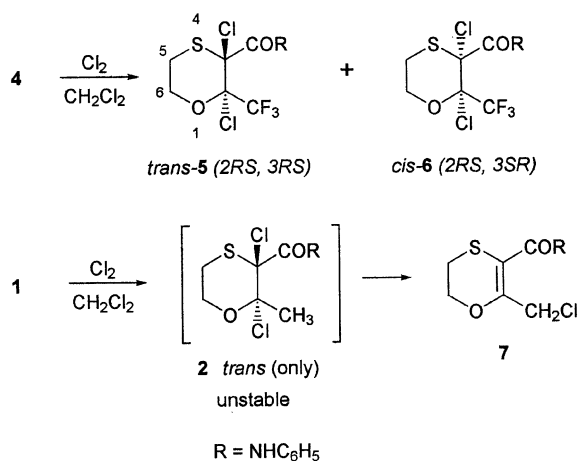
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In our previous papers,¹ we reported that the conversion of dihydro-1,4-oxathiin **1** to isomeric dihydro-1,4-oxathiin **3** through dichloro-1,4-oxathiane **2**. Trifluoromethyl group has received increasing interest owing to its unique nature for material sciences and potential biological activities for pharmaceuticals and agrochemicals. In the course of our studies of the development of new agrochemical fungicides, we reported² that the synthesis of trifluoromethylated dihydro-1,4-oxathiin **4** which is an analogue of a systemic fungicide, carboxin used for seed treatment. Here we describe an unanticipated result in the chlorination of trifluoromethylated dihydro-1,4-oxathiin **4** and compare the results with those reported previously.^{1,3} R = NHC₆H₅



Results

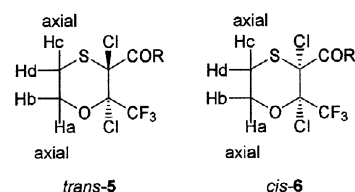
The starting trifluoromethylated dihydro-1,4-oxathiin **4** was obtained by the previously reported method.² Chlorination of **4** was carried out in a methylene chloride solution at



Scheme 1

Table 1. Chemical shifts and coupling constants of *trans*-**5** and *cis*-**6** isomers

Isomer	Chemical shifts (δ , in CDCl ₃)				Coupling constants (Hz)
	Ha	Hb	Hc	Hd	
<i>trans</i> - 5	4.60	4.39	3.62	2.68	$J_{ab}=12.2$, $J_{ac}=12.8$, $J_{ad}=2.6$, $J_{bc}=3.9$, $J_{bd}=1.7$, $J_{cd}=14.3$
<i>cis</i> - 6	4.64	4.43	4.28	2.50	$J_{ab}=12.1$, $J_{ac}=12.5$, $J_{ad}=2.9$, $J_{bc}=4.2$, $J_{bd}=1.5$, $J_{cd}=13.5$

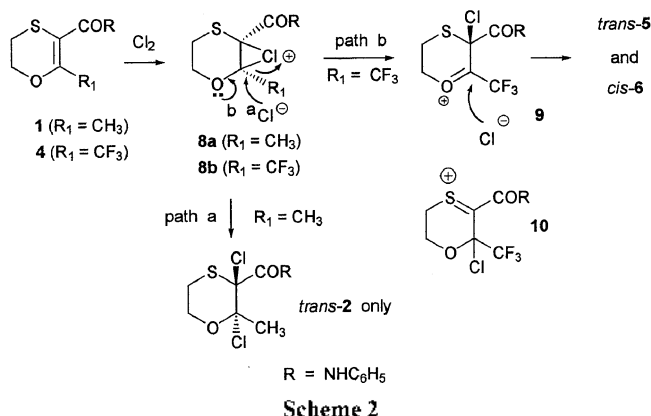


room temperature to give a 1 : 1 mixture of *trans*-**5** (2*RS*, 3*RS*) and *cis*-**6** (2*RS*, 3*SR*) dichloro-1,4-oxathianes, which were separated by flash chromatography (Scheme 1).

Both the *trans*-**5** and *cis*-**6** isomers were white crystalline solids and fairly stable under refluxing benzene, while the **2** was slowly converted to chloromethyl compound **7** at room temperature ($t_{1/2} = 3\text{h}$) by anchimeric assistance of anilide as reported previously.^{3a} Assignment of the stereochemistry of the *trans*-**5** and *cis*-**6** isomers was based on the ¹H NMR data by comparison with the similarity of the structures to those of previously reported dichloro-1,4-oxathiane **2**,¹⁻³ *trans*-2,3-dichloro-1,4-oxathiane and 2,3,3-trichloro-1,4-oxathiane.⁴ In the ¹H NMR spectra, four protons of the C-5 and C-6 of the both isomers showed ABCD spin system respectively (Table 1). The characteristic feature was that the axial proton on C-5 of *cis*-**6** isomer appeared at considerable lower (δ 4.29 ppm) field than that in the *trans*-**5** isomer (δ 3.62 ppm). This phenomenon is attributable to the anisotropic effect by neighboring carbonyl group, which will be discussed later.

Discussion

Although a halogenation of olefins with halogens affords to a stereospecific *trans*-addition, the presence of some substituents which can stabilize an adjacent carbonium ion lead to increased ionic character in the intermediate.⁵ As the



reaction intermediate becomes more ionic in nature, the stereochemistry of the halogen addition has been found to change so that either *cis*-addition to the olefin or a non-stereospecific addition is observed.⁵ Formation of an unusual *cis*-addition product of chlorine to the double bond of **4** suggested that the reaction pathway is different from that of the chlorination dihydro-1,4-oxathiin **1**.

Without a doubt, the chloronium ion **8** was initially formed by electrophilic attack of the chlorine on the double bond (Scheme 2). It was known that carbocation intermediates are destabilized by strongly electron-withdrawing substituent such as trifluoromethyl and cyano group.⁶ Recently, the presence of an ion pairs generated from α -(trifluoromethyl)tosylates related to neighboring double bond due to destabilizing effect of CF₃ group on carbocation were reported.⁷ In case of methyl dihydro-1,4-oxathiin **1**, nucleophilic attack of chloride from the side opposite to the large chloronium ion **8a** yielded the dichloro-1,4-oxathiane *trans*-**2** isomer as a sole product (path a). In comparison, the strong electron withdrawing effect of trifluoromethyl group in **8b** led to increased ionic character by involvement of the lone pair electron of oxygen to form oxonium ion intermediate **9** (path b). The oxonium ion **9** is more plausible than an alternative intermediate involving thiuranium ion **10**.⁸ Nucleophilic attack of chloride from both side to the α -carbon of oxonium ion **9** resulted in the mixture of *trans*-**5** and *cis*-**6**.

To compare the thermodynamic stability and conformational behavior of the both isomers by molecular mechanics (MM) and semi-empirical molecular calculations we undertook an inspection by the calculation of MM2 and Discover

2.97 package (MSI Inc.) with CVFF (Consistent Valence Force Field).⁹ The results demonstrated that the both isomers have almost same stability (Figure 1).

According to the most stable conformation of *cis*-**6**, the axial hydrogen at C-5 is close to the amide carbonyl oxygen (2.427 Å by MM2 calculation or 2.7 Å by CVFF data) which was consistent with experimental facts of downfield shift (see Table 1) of that proton in NMR by carbonyl anisotropy.¹⁰

Experimental Section

Chlorination of Dihydro-1,4-oxathiin 4. To a solution of 5,6-dihydro-2-trifluoromethyl-1,4-oxathiin-3-carboxanilide (**4**) (288 mg, 1 mmol)² in methylene chloride (10 mL) was added a solution of chlorine (707 mg, 1 mmol) dissolved in methylene chloride (1.51 mL) at room temperature and stirred for 10 min. The reaction mixture was washed with aqueous saturated sodium bicarbonate solution and water and dried (MgSO₄). Evaporation of the solvent gave a yellow solid (0.35 g), which was a 1 : 1 mixture of *cis*-**6** and *trans*-**5** dichloride by ¹H NMR spectroscopy. Flash chromatography on silica gel (GF254, 230-400 mesh) using *n*-hexane and ethyl acetate (4 : 1) yielded *cis*-**6** (*R_f* 0.58) (116 mg) and *trans*-**5** (*R_f* 0.39) (32 mg) isomers.

For *trans*-**5** isomer: mp 105.9-107.3 °C; ¹H NMR (CDCl₃, 300 MHz) δ 2.68 (m, *J* = 1.7, *J* = 2.6, *J* = 14.3, 1H, SCH equatorial), 3.62 (m, *J* = 3.9, *J* = 12.8, *J* = 14.3, 1H, SCH axial), 4.39 (m, *J* = 1.7, *J* = 3.9, *J* = 12.2, 1H, OCH equatorial), 4.60 (m, *J* = 2.6, *J* = 12.2, *J* = 12.8, 1H, OCH axial), 7.20-7.54 (m, 5H, ArH), 8.45 (s, 1H, NH); FT-IR (KBr) 3402 (NH), 1686 (C=O) cm⁻¹; GC/MS *m/z* (relative intensity), 360 (unobserved), 289 (M⁺-2Cl, 38), 197 (M⁺-2Cl-NHC₆H₅, 100), 141 (80).

For *cis*-**6** isomer: mp 151.7-153.0 °C; ¹H NMR (CDCl₃, 300 MHz) δ 2.50 (m, *J* = 1.5, *J* = 2.9, *J* = 13.5, 1H, SCH equatorial), 4.28 (m, *J* = 4.2, *J* = 12.5, *J* = 13.5, 1H, SCH axial), 4.43 (m, *J* = 1.5, *J* = 4.2, *J* = 12.1, 1H, OCH equatorial), 4.64 (m, *J* = 2.9, *J* = 12.1, *J* = 12.5, 1H, SCH axial), 7.19-7.53 (m, 5H, ArH), 8.59 (s, 1H, NH); IR (KBr) 3404 (NH), 1686 (C=O) cm⁻¹; HRMS for C₁₂H₁₀NO₂F₃Cl₂S Calcd 358.9762. Found, 358.9762.

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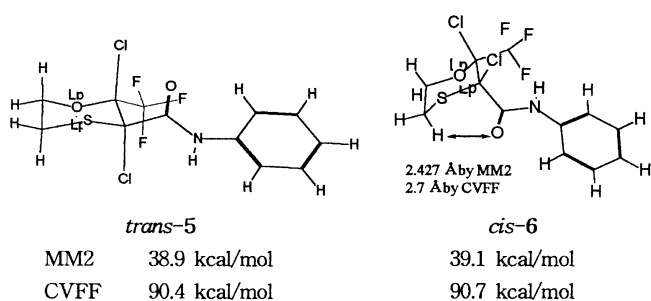


Figure 1. The optimized structures by MM2 and minimized energies of *trans*-**5** and *cis*-**6** isomers calculated by MM2 and CVFF.

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 9. All rotatable bonds were searched from 0 to 360° in 30° increments. The lowest energy conformer was minimized using *va09a* minimizers until maximum energy are less than 0.00001 kcal/Å. All conformation searches and molecular mechanics calculations were carried out using Discover 2.97 package (MSI Inc.) with CVFF (Consistent Valence Force Field).
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