New Molecular Rearrangement of 1,3-Oxathioles via Thiocarbonyl Ylides

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Abstract: 2,5-Diphenyl-2-benzoyl-4-acetyl-1,3-oxathiole (**11**) and 2-phenyl-2,4-dibenzoyl-5-methyl-1,3-oxathiole (**12**) are in an equilibrium relationship even under the mild conditions including those found in biological systems. Kinetic experiments revealed that the intermediate of this equilibration is thiocarbonyl ylide **10**. By rotation or inversion of the S^+–C^- bond of **10**, 1,3-oxathioles **11** and **12** were converted to each other via 6π electrocyclization. On the other hand, equilibration between thiocarbonyl ylide **10** and thiirane **14** through 4π electrocyclization proceeds at higher temperatures, above 140 °C. Inflammatory activities of these 1,3-oxathioles may be attributed to the results of the equilibrium between these species and thiocarbonyl ylide **10**.

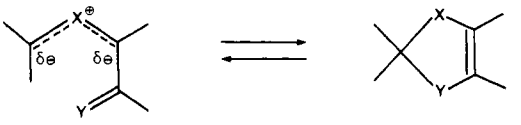
Potential biological activities of oxiranes **1a**, thiiranes **1b**, and

1 2

a b c
X = O ; S ; NH

aziridines **1c** have been widely attributed to the results of nucleophilic substitution reactions in vivo on these small ring systems. On the contrary, several experimental observations have been made concerning the chemical conversions of these ring systems into open-chain systems[1] such as carbonyl ylides **2a**,[2] thiocarbonyl ylides **2b**,[3] and azomethine ylides **2c**.[4] The chemical species **2** are in equilibrium with the ring systems **1**, and the position of the equilibria lies on the side of the ylide when the species contain strong π-electron-accepting substituents[5] or are stabilized by effective charge delocalization.[2,6] Furthermore, the polar species **2** exhibit characteristic, strong chemical reactivities with protic reagents, dienophiles, and dipolarophiles.[3,7,8] Thus we might expect the broad biological activities of these ylide systems in comparison with the corresponding cyclic systems.

For the chemical reactivities of the ylides for biological applications to be maintained, some intramolecular masking mechanism, other than the 4π electrocyclization mentioned above, may be required to protect such highly reactive and unstable species which have to be reproduced in vivo. One potential example of this type is suggested by the intramolecular cyclization of the vinyl carbonyl ylides **3a** to dihydrofurans **4a**,[7] benzoylthiocarbonyl ylides **3b** to 1,3-oxathioles **4b**,[8a,9] and benzoylcarbonyl ylides **3c** to 1,3-dioxoles **4c**.[10] The observed isomerizations reveal that the equilibrium leans to one side which is stabilized by the bonding array of atoms into five-membered heterocycles **4** under mild conditions. In this paper we will report a molecular design



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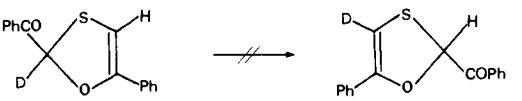
	X	Y
a	O	C
b	S	O
c	O	O

which will provide an appropriate equilibration rate between thiocarbonyl ylide **3b** and 1,3-oxathiole **4b** and the manifestation of biological activities.

Results and Discussion

Recently, Norin examined deuterium scrambling by using 2-benzoyl-2-deuterio-5-phenyl-1,3-oxathiole (**5**).[9] No isomerization of **5** to its isomer **6** was observed below 120 °C, while



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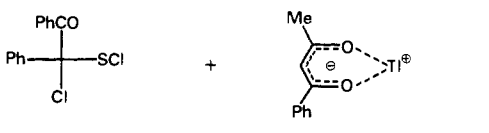
desulfurization to form 1,2-dibenzoylethylene was detected at higher temperatures. The results suggest that the substituent with more effective electron-withdrawing capacity may be required on the 1,3-oxathiole ring to facilitate C_2–O bond opening to form the thiocarbonyl ylide.

A synthetic procedure for the preparation of such 1,3-oxathioles has been suggested in our preceding paper.[5] For example, sulfenyl chloride **7**[11] when treated with thallium(I) benzoylacetonate **8** gives



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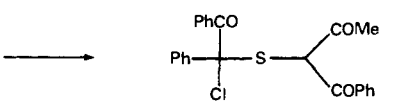

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an unstable sulfide **9**. This sulfide upon treatment with triethylamine affords two 1,3-oxathioles. Isomeric **11** and **12** were separated by HPLC using silica gel in yields of 39.1 and 31.1%, respectively. The structural assignments for **11** and **12** were distinguished by the following: (1) IR spectroscopy, the acetyl–carbonyl stretching band at 1691 cm^{-1} for **11** and benzoyl–carbonyl inserted between two aryl groups at 1643 cm^{-1} for **12**; (2) UV spectroscopy, the bathochromic shift (7–8 nm) for absorption of **11** attributed to the linear arrangement of the conjugated system; and (3) NMR spectroscopy, the acetyl–methyl singlet of **11** appeared at a lower magnetic field than the vinyl–methyl singlet of **12**. Another potential mode of cyclization to afford a 1,3-oxathiole **13** was not observed.

The pure isomers **11** and **12** isomerized slowly even at room temperature in organic solvents. The kinetic experiments were carried out in the deuteriochloroform solution by using a 100 MHz NMR apparatus. Typical spectra are shown in Figure 1. The concentration of the two isomers as a function of time was monitored by integrating the methyl singlets at δ 2.06 for **11** and δ 1.97 for **12** at 42 and 70 °C, respectively. The approach to equilibrium is first order, and the rate data are summarized in Table I. It is difficult to account for this isomerization without proposing a mechanism involving thiocarbonyl ylide **10** as an intermediate which would then yield another isomer through the S^+–C^- bond rotation or inversion.[2] On the other hand, equilibration between thiocarbonyl ylide **10** and thiirane **14** proceeds at higher temperatures, so that desulfurization with triphenylphosphine occurred in refluxing xylene to afford the mixture of alkenes **15** and **16** which were separated by silica gel HPLC.

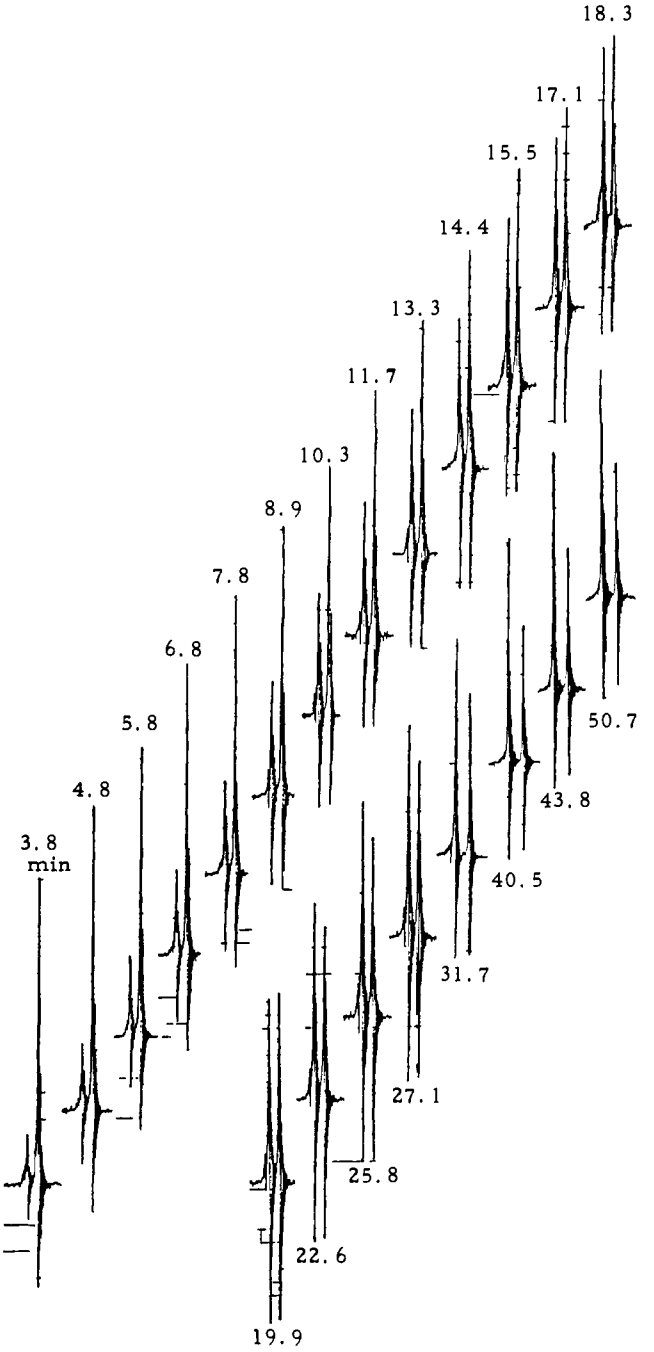

Figure 1. Equilibrium of the 1,3-oxathioles **11** and **12** in $CDCl_3$ solution at 70 °C starting from isomer **12**. The areas of the methyl proton singlets of **11** at δ 2.06 and **12** at δ 1.97 ppm were shown. It can be seen isomer **11** grows steadily with time.

Table I. Rate Data for Isomerization between 1,3-Oxathioles **11** and **12**

temp, °C	equilibrium constant K (NMR)	rate constant, s^{-1} k_1	k_{-1}
42	0.63	3.1×10^{-5}	5.2×10^{-5}
70	0.62	4.6×10^{-4}	7.8×10^{-4}
activation parameter		11 to 12	12 to 11
E_{act}, kcal/mol		20.7	19.5
ln A		22.7	21.5
$\Delta H^{\ddagger}$, kcal/mol		20.1	18.9
$\Delta S^{\ddagger}$, cal/deg		−16.8	−19.2
$\Delta G^{\ddagger}$, kcal/mol		21.4	19.5

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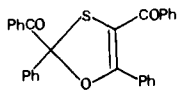
The structural assignments for **15** and **16** depended on their NMR spectra. Careful examination of CPK molecular models of the two alkenes compelled us to consider that the stereostructure of the trans-isomer **16** is more crowded than the cis-isomer **15**. Bond rotation of the trans isomer is difficult, while, in the cis isomer, two benzoyl groups can rotate freely so that the four ortho protons of the benzoyl substituents may be found at a lower field than that of the trans isomer. Rotation of the olefinic double bond proceeds at higher temperatures in the presence of triphenylphosphine as described in the Experimental Section.

In conclusion, we would like to suggest that the strong π-electron interaction with the carbonyl groups shifts the equilibrium to the thiocarbonyl ylide side even under mild conditions including those found in biological systems. From a viewpoint of structure–biological activity relationships, it may be worth mentioning that the 1,3-oxathioles described herein and their congeners **17** and **18** which contain two benzoyl[5] and three benzoyl[12] groups, respectively, showed strong inflammatory activities which are a function of the number of carbonyl groups.[13] The stabilities of the thiocarbonyl ylides may also depend upon the number of carbonyl substituents.[5] Thus our results provide a prototype of drug design involving the thiocarbonyl ylide and, probably, other isoelectronic systems.



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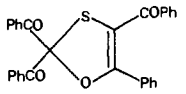

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Experimental Section

Melting points were determined on a micro hot-plate melting point apparatus. All melting points were uncorrected. Infrared (IR) spectra were determined on a Hitachi 260-100 grating infrared spectrophotometer, and ultraviolet (UV) spectra were recorded on a Hitachi Model 200-10 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded at 100 MHz (JEOL PS-100): chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00 ppm) as an internal standard. Low-resolution mass (MS) spectra were recorded on a Hitachi RMU-7L instrument.

Reactions were run under an atmosphere of argon and monitored by thin-layer chromatography on Merck Silica Gel 60-F-254 plates. Dry benzene and xylene were distilled from sodium metal; tetrahydrofuran (THF) was distilled from lithium aluminum hydride; triethylamine was distilled from sodium hydroxide. Other solvents and reagents are of reagent grade purities. Liquid chromatography was performed by HPLC techniques using 50 μm irregularly shaped silica gel packed in CIG glass column tube (Kusano, Tokyo).

Thallium(I) Benzoylacetonate (8). To a solution of benzoylacetone (1.11 g, 6.85 mmol) in 10 mL of benzene was added a solution of thallium ethoxide (1.71 g, 6.85 mmol) in 10 mL of benzene. After the mixture was allowed to stand at room temperature for 1 h, 30 mL of hexane was added dropwise and the resulting precipitates were collected and washed with hexane to give 2.15 g (86%) of yellow needles, mp 103–104 °C (dec). This material was used in the next stage without purification.

2,5-Diphenyl-2-benzoyl-4-acetyl-1,3-oxathiole (11) and 2-Phenyl-2,4-dibenzoyl-5-methyl-1,3-oxathiole (12). To a solution of 832 mg (2.81 mmol) of α-chloro-α-(chlorosulfenyl)benzyl phenyl ketone (**7**) in 10 mL of THF was added a solution of 1.03 g (2.81 mmol) of **8** in 10 mL of THF at −40 °C. The mixture was allowed to stand at the same temperature for 10 min and then at room temperature for 30 min. The precipitated thallium salts were filtered off through Celite powder and washed with benzene. The combined filtrate was concentrated to dryness in vacuo to give an unstable slightly yellow residue of α-chlorosulfide **9**. To a solution of this sulfide in 10 mL of benzene was added dropwise a mixture of 284 mg (2.81 mmol) of triethylamine and 5 mL of benzene at 5–10 °C. The resulting mixture was passed through a short silica gel column to remove triethylamine hydrochloride. The column was washed with benzene, and the combined eluate was concentrated to dryness in vacuo to give a mixture of the two 1,3-oxathioles. These components were separated by HPLC using 30 g of silica gel and hexane–ethyl acetate (20:1) mixtures. The first eluate contained 424 mg (39.1%) of **11**, which was recrystallized from the acetone–hexane mixture to give yellow prisms: mp 130–132 °C; IR (KBr) 3055, 3017, 2908, 1691, 1683, 1623, 1599, 1592, 1580, 1572, 1486, 1445, 1425, 1370, 1330, 1304, 1282, 1250, 1231, 1186, 1180, 1169, 1150, 1083, 1071, 1059, 1038, 1028, 1020, 996, 974, 942, 898, 856, 845, 782, 762, 728, 708, 702, 685, 678, 664 cm^{-1}; UV (EtOH) 251 (ϵ 17 300), 344 (4200) nm; NMR ($CDCl_3$) δ 2.06 (s, 3 H), 7.15–7.50 (m, 11 H), 7.55–7.79 (m, 4 H); MS *m/e* (%) 386 (M^+, 0.6), 354 (0.6), 343 (1.5), 281 (59), 105 (100). The second eluate contained 337 mg (31.1%) of **12** as yellow glass: IR (KBr) 3055, 3013, 2904, 1683, 1643, 1618, 1612, 1588, 1572, 1488, 1446, 1418, 1360, 1331, 1308, 1281, 1230, 1179, 1156, 1145, 1108, 1071, 1043, 1033, 1020, 997, 960, 932, 920, 908, 863, 838, 776, 768, 753, 696, 685, 665, 655 cm^{-1}; UV (EtOH) 244 (ϵ 26 400), 336 (6970) nm; NMR ($CDCl_3$) δ 1.97 (s, 3 H), 7.15–7.52 (m, 9 H), 7.54–7.88 (m, 6 H); MS *m/e* (%) 386 (M^+, 0.4), 354 (0.3), 343 (1.0), 281 (42), 105 (100).

Kinetics of the Isomerization of 1,3-Oxathioles 11 and 12. A crop of 10 mg of freshly isolated 1,3-oxathiole was dissolved in 0.3 mL of $CDCl_3$ immediately before use. The rate of isomerization was measured by using the areas of the methyl proton NMR singlets of **11** and **12**. Typical spectra are shown in Figure 1, where it can be seen the acetyl isomer **11** (downfield singlet) grows steadily with time. NMR measurements in the region of interest were repeated until the fractions of isomers were constant and the equilibrium spectra were obtained at 42 and 70 °C. There is no coalescence of methyl singlets which allows the observed rate constants k_{obsd} to be calculated. The approach to equilibrium is first order, and knowledge of the equilibrium constant ($K = k_1/k_{-1}$, Table I) for the isomerization

$$\mathbf{11} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{12}$$

allows calculation of the individual rate constants, since $k_{obsd} = k_1 + k_{-1}$. Values for k_1 and k_{-1} are given in Table I.

Desulfurization of 11 and 12. To a solution of 100 mg (0.259 mmol) of 1,3-oxathiole **11** in 5 mL of xylene was added 205 mg (0.782 mmol) of triphenylphosphine, and the mixture was heated at reflux temperature for 8 h. The resulting solution was injected into a column containing 30 g of silica gel and eluted with 15% ethyl acetate–hexane mixture. The first eluate contained 73 mg (96%) of triphenylphosphine thioxide, and the second eluate contained 41 mg (44.7%) of *cis*-1,2-dibenzoyl-1-acetyl-2-phenylethylene (**15**) which was recrystallized from acetone–hexane mixture to give prisms: mp 147–148 °C; IR (KBr) 3073, 3057, 3020, 2910, 1687, 1667, 1655, 1595, 1591, 1583, 1571, 1492, 1451, 1443, 1415, 1358, 1312, 1308, 1282, 1270, 1251, 1223, 1204, 1200, 1193, 1172, 1160, 1095, 1076, 1069, 1050, 1028, 1022, 1018, 992, 974, 972, 933, 922, 903, 852, 814, 783, 768, 758, 710, 701, 690, 682, 653 cm^{-1}; UV (EtOH) 256 (ϵ 40 010) nm; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 6.98–7.15 (m, 2 H), 7.20–7.52 (m, 9 H), 7.80–7.98 (m, 4 H); MS *m/e* (%) 354 (M^+, 21), 338 (3), 312 (2), 261 (8), 249 (18), 207 (10), 129 (12), 105 (100), 77 (63). The third eluate contained 13 mg (14.2%) of *trans*-1,2-dibenzoyl-1-acetyl-2-phenylethylene (**16**) which was recrystallized from the acetone–hexane mixture to give prisms: mp 102–104 °C; IR (KBr) 3052, 3023, 2963, 2915, 1677, 1666, 1655, 1598, 1580, 1490, 1448, 1355, 1315, 1310, 1301, 1290, 1275, 1257, 1250, 1237, 1203, 1174, 1170, 1154, 1091, 1071, 1067, 1030, 1011, 995, 979, 953, 933, 927, 839, 814, 795, 767, 751, 730, 700, 695, 683, 671 cm^{-1}; UV (EtOH) 256 (ϵ 38 000) nm; NMR ($CDCl_3$) δ 2.54 (s, 3 H), 7.20–7.60 (br s, half-width = 4 Hz, 11 H), 7.65–7.83 (m, 4 H); MS *m/e* (%) 354 (M^+, 14), 338 (4), 312 (2), 261 (6), 249 (14), 207 (7), 129 (7), 105 (]00), 77 (36).

Isomerization of 15 and 16. Pure isolated alkene **15** (20 mg, 56 nmol) was treated with triphenylphosphine (5 mg, 19 nmol) in 2 mL of xylene at the reflux temperature for 1 h. Separation of the mixture by HPLC afforded 12 mg of **15** and 4 mg of **16**.

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(13) The results will be published elsewhere in detail.