J. Org. Chem. **1986**, *51*, 4899–4905

Polysulfide-Promoted Conversions of Ene Carbonyls. Arrangements of *o*-Methoxy-Substituted Chalcone Units Incorporated into Product Thiolanes

Robert T. LaLonde,*[1a] LynnMarie Codacovi,[1a] He Cun-heng,[1b] Xu Cang-fu,[1b] Jon Clardy,[1b] and Bala S. Krishnan[1c]

Departments of Chemistry, SUNY-College of Environmental Science and Forestry, Syracuse, New York 13210, and Cornell University, Ithaca, New York 14853-1301, and Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York 13221

Received April 28, 1986

Stereo- and regiochemistry are used as probes for learning how thiolanes are formed. The location of substituents on the thiolane ring and the configuration of these substituents were determined by X-ray crystallography or ^{1}H and ^{13}C NMR correlations for seven thiolanes resulting from the treatment of *o*-methoxychalcones with sodium polysulfide. 2-Methoxychalcone and 2,2′-dimethoxychalcone produce the cis,trans,trans and the all-trans diastereomeric thiolanes in which the two chalcone units combined in a side-by-side fashion. Both cis,trans,trans diastereomers are transformed under reaction conditions to the corresponding all-trans diastereomers. The cis,trans,trans thiolane resulting from 2-methoxychalcone appeared in the product before its all-trans diastereomer. The dynamic stereochemical results give evidence for the succession of thiolane product formation and, combined with evidence for the regiochemistry of the thiolanes, restrict further the mechanistic interpretations of the bond-forming processes.

The facile room-temperature reactions of conjugated enals and enones with alkali polysulfides result in the formation of complex mixtures containing carbon-bonded polysulfides, thiolanes, and thiophenes.[2-4] Thiophenes resulting from these reactions have been viewed as secondary products generated from either the dehydrogenation of initially formed thiolanes or the base-promoted dehydration of β-hydroxy aldehydic and ketonic thiolanes followed by hydrogen shift.[4] However, the thiophene content is virtually nil when the ene carbonyl is a chalcone.[3,4] This observation gave us the opportunity to gain information about the initial carbon–sulfur and carbon–carbon bonding occurring in sulfur heterocycle formation. Two questions were of concern. What is the configuration of the thiolane product? How do the two ene carbonyl units combine; do they align themselves in a top-to-bottom fashion or side-by-side, as previously assumed?[4,5] Conceivably, these two possible modes for combining chalcone units may occur by a number of different routes all based on precedents. Two such routes, from among the many, are compared in Scheme I for the purpose of showing that both top-to-bottom and side-by-side regiochemistry are reasonable. A common intermediate is chosen as the starting point in the interest of economy of illustration. *trans*-Thiirane **1** may arise from a *trans*-chalcone and polysulfide in a process analogous to the well-known conversion of Michael acceptors to epoxides with alkaline hydrogen peroxide.[6] Thermal conrotatory opening of the *trans*-thiirane,[7] formation of the thiocarbonyl ylide **2**, and dipole–dipolarophile reaction[8] of the latter with a second mole of chalcone would result in the top-to-bottom mode of combination. Alternatively, the strongly basic conditions resulting from the use of alkali polysulfide may favor removal of the proton α to the carbonyl and the formation of the intermediate thioenolate **3**, which reacting with another molecule of chalcone would account for the side-

Scheme I

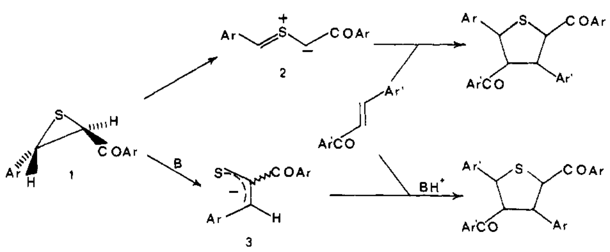
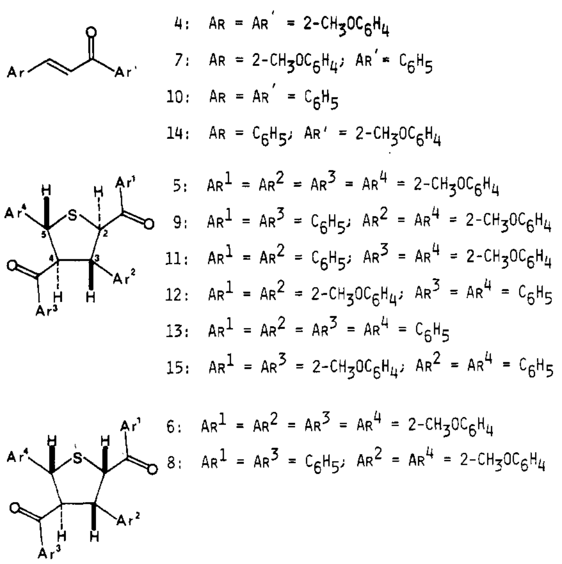


Chart I



4: $AR = AR' = 2\text{-}CH_3OC_6H_4$
7: $AR = 2\text{-}CH_3OC_6H_4$; $AR' = C_6H_5$
10: $AR = AR' = C_6H_5$
14: $AR = C_6H_5$; $AR' = 2\text{-}CH_3OC_6H_4$

5: $AR^1 = AR^2 = AR^3 = AR^4 = 2\text{-}CH_3OC_6H_4$
9: $AR^1 = AR^3 = C_6H_5$; $AR^2 = AR^4 = 2\text{-}CH_3OC_6H_4$
11: $AR^1 = AR^2 = C_6H_5$; $AR^3 = AR^4 = 2\text{-}CH_3OC_6H_4$
12: $AR^1 = AR^2 = 2\text{-}CH_3OC_6H_4$; $AR^3 = AR^4 = C_6H_5$
13: $AR^1 = AR^2 = AR^3 = AR^4 = C_6H_5$
15: $AR^1 = AR^3 = 2\text{-}CH_3OC_6H_4$; $AR^2 = AR^4 = C_6H_5$

6: $AR^1 = AR^2 = AR^3 = AR^4 = 2\text{-}CH_3OC_6H_4$
8: $AR^1 = AR^3 = C_6H_5$; $AR^2 = AR^4 = 2\text{-}CH_3OC_6H_4$

---

(1) (a) SUNY-College of Environmental Science and Forestry. (b) Cornell University. (c) Bristol-Myers Company.

(2) Reinecke, M. G.; Morton, D. W.; Del Mazza, D. *Synthesis* **1983**, 160.

(3) LaLonde, R. T.; Horenstein, B. A.; Schwendler, K.; Fritz, R. C.; Florence, R. A.; Ekiel, I.; Smith, I. C. P. *J. Org. Chem.* **1983**, *48*, 4049.

(4) LaLonde, R. T.; Florence, F. A.; Horenstein, B. A.; Fritz, R. C.; Silveira, L.; Clardy, J.; Krishnan, B. S. *J. Org. Chem.* **1985**, *50*, 85.

(5) Del Mazza, D.; Reinecke, M. G. *J. Org. Chem.* **1981**, *46*, 128.

(6) (a) Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327. (b) Lutz, R. E.; Weiss, J. O. *J. Am. Chem. Soc.* **1955**, *77*, 1814. (c) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428. (d) Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108.

(7) Synder, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 5005.

(8) Huisgen, R.; Fulka, C.; Kalwinsch, I.; Xingya, L.; Mloston, G.; Moran, J. R.; Profstl, A. *Bull. Soc. Chim. Belg.* **1984**, *93*, 511.

0022-3263/86/1951-4899$01.50/0

Table I. Chemical Shifts ($\delta^{\text{H-}n}$) (ppm) Relative to Me_4Si (δ 0.00) and Splitting Patterns (SP) and Coupling Constants ($^3J_{\text{H-H}}$) (Hz) for Thiolane Ring Protons Located at Position *n*

compd	parameter	*n*			
		2	3	4	5
5	$\delta^{\text{H-}n}$	5.46	4.75	5.30	5.49
	SP	d	dd	t	d
	$^3J_{\text{H-H}}$	(2–3) 8.2	(3–4) 10.6	(4–5) 10.4	
6	$\delta^{\text{H-}n}$	5.47	4.75	5.89	5.31
	SP	d	dd	dd	d
	$^3J_{\text{H-H}}$	(2–3) 6.6	(3–4) 12.1	(4–5) 10.4	
8	$\delta^{\text{H-}n}$ [a]	5.63	4.93	5.41	5.43
	SP	d	m	m	m
	$^3J_{\text{H-H}}$	(2–3) 6.1	(3–4) 11.0	(4–5) 9.8	
9	$\delta^{\text{H-}n}$	5.65	4.81	5.31	5.55
	SP	d	dd	t	d
	$^3J_{\text{H-H}}$	(2–3) 9.3	(3–4) 11.0	(4–5) 10.1	
11	$\delta^{\text{H-}n}$	5.18	4.72	5.19	5.47
	SP	d	dd	t	d
	$^3J_{\text{H-H}}$	(2–3) 9.2	(3–4) 11.2	(4–5) 10.7	
12	$\delta^{\text{H-}n}$ [b]	5.60	4.74	5.01	5.12
	SP	d	dd	t	d
	$^3J_{\text{H-H}}$	(2–3) 8.2	(3–4) 10.8	(4–5) 10.6	
13	$\delta^{\text{H-}n}$ [c]	5.28	4.78	4.73	5.12
	SP	d	dd	dd	d
	$^3J_{\text{H-H}}$	(2–3) 8.7	(3–4) 11.9	(4–5) 10.3	
15	$\delta^{\text{H-}n}$ [d]	5.21	4.58	4.94	5.03
	SP	d	dd	dd	d
	$^3J_{\text{H-H}}$	(2–3) 7.5	(3–4) 10.9	(4–5) 10.5	

[a] Parameters obtained by simulation. See discussion in subsection entitled Spectra. [b] A first-order spectrum was obtained at 250 MHz. [c] Data taken from ref 3. [d] A first-order spectrum was obtained at 360 MHz.

by-side orientation of chalcone units.[9] We report below results giving answers to the fundamental questions that we have posed above.

Results

The *o*-methoxy-substituted chalcones were chosen for this study since preliminary work had suggested that the presence of the *o*-methoxy group, unlike several other explored, would assist product analysis in such aspects as chromatographic separations, crystallinity required for X-ray structure determinations, and first-order ^1H NMR signals needed for making stereochemical assignments. Thus the treatment of 2,2′-dimethoxychalcone (**4**) with an ethanolic solution, saturated with sodium polysulfide, for 48 h at 30 °C yielded a crude product mixture in which unconverted **4** and tetramethoxythiolanes **5** and **6** were present in a ratio of 1.5:3.6:1.0 as determined by HPLC. The all-trans diastereomer **5** was obtained in 32% yield from the crude product mixture by crystallization. Extensive chromatography of a portion of the material recovered from the mother liquors afforded a much smaller sample of the cis,trans,trans diastereomer **6**. The structures of both **5** and **6** were determined by their spectral properties and X-ray crystallographic studies, from which the models shown in Figures 1a and 1b were obtained. The chemical shifts and $^3J_{\text{H-H}}$ values for the four adjacent thiolane ring protons are compared in Table I with the other thiolanes of the series. The first step in making specific assignments for the the thiolane ring protons was made on the basis of the splitting patterns, which distinguished H-2 and H-5 on the one hand from H-3 and H-4 on the other. The ^1H–^1H 2D correlation for **5** allowed the distinction of severely overlapping H-2 and H-5 signals. Further distinction in the case of **5** rested on the ^1H–^{13}C, direct bond, heteronuclear 2D correlation, in which the starting point for assigning the ^{13}C and ^1H signals was the C-4 resonance identified as the lowest field signal in the saturated carbon region based on chemical shift considerations, which are discussed further below. Thus, H-3 and H-4 were distinguished from one another. Once H-3 and

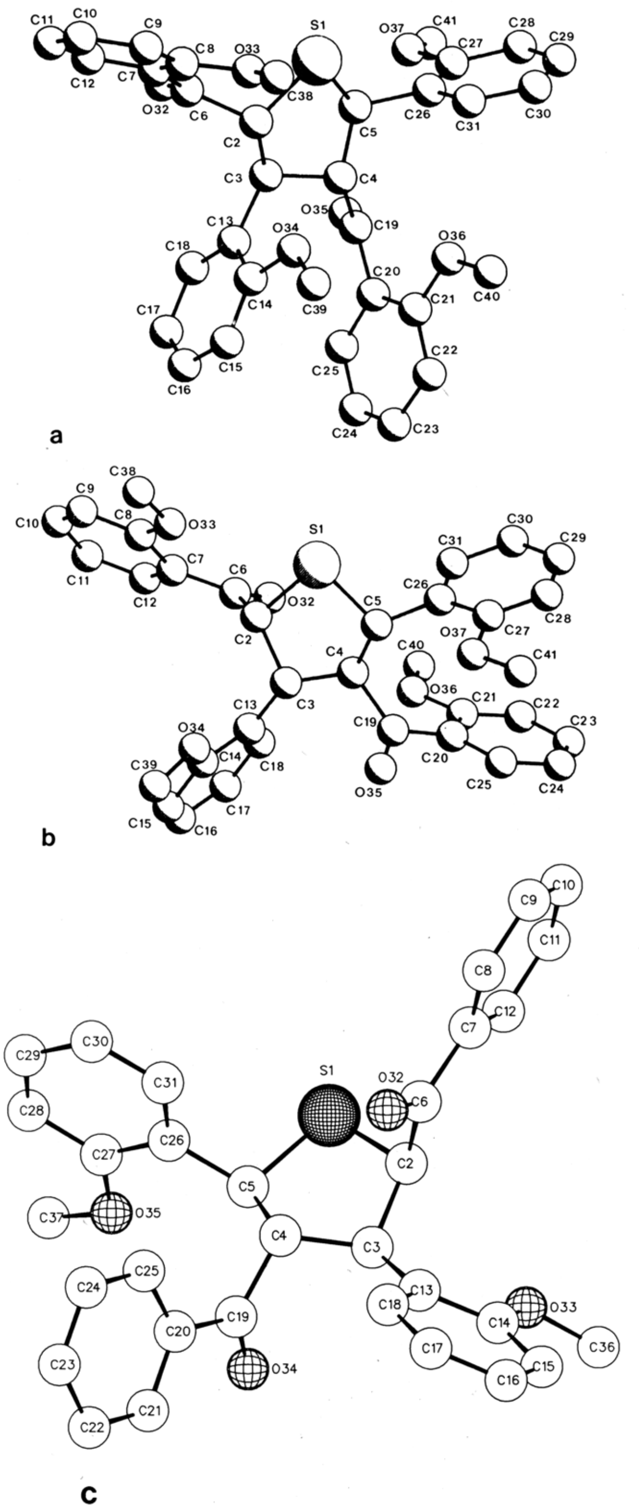


Figure 1. Computer-generated drawings of **5** (a), **6** (b), and **8** (c). Hydrogens are omitted. Compounds **5** and **6** are depicted as the enantiomers of the representations given elsewhere.

---

[9] The dual pathways offered here for thiiranes have an established parallel in oxirane chemistry. Oxiranes undergo thermal conrotatory opening with formation of carbonyl ylides, which are trapped by dipolarophiles (Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572), but some, exemplified by chalcone oxide, when treated with base undergo conversion to 1,3-diphenylpropane-1,2-dione (Widman, O. *Chem. Ber.* **1916**, *49*, 477).

H-4 had been distinguished, their different $^3J_{H-H}$ values (Table I) allowed the further distinction of C-2 from C-5. Regarding proton assignments in the spectrum of cis,trans,trans-**6**, doublets having the smaller and larger $^3J_{H-H}$ values were assigned to H-2 and H-5, respectively, in order that the magnitude of the $^3J_{H-H}$ values would correspond to the dihedral angles revealed by the X-ray structures. Accordingly, the doublet of a doublet at δ 4.75 was assigned to H-3 of **6**. Likewise, the doublet of a doublet or the triplet resonance appearing near δ 4.75 was assigned to H-3 in the spectra of all the other members of the thiolane series. The H-3 assignments are in agreement with other $^1H-^{13}C$ 2D heteronuclear correlations, described below,[10] and earlier[3] NMR studies of 3,5-$^2H_2$-labeled **13**. In the case of **15**, identification of the H-3 signal was based on the observation that for all compounds in the series H-3 is coupled to H-2 by the lowest $^3J_{H-H}$ value.

Under the same conditions whereby the mixture of **5** and **6** had resulted from treating **4** with polysulfide, the cis,trans,trans diasteromer **6** was converted completely to *all-trans*-**5** as ascertained by TLC. However, **5** underwent no change when similarly treated with polysulfide.

These results were significant in the following respects. Firstly, the complete stereochemistry was established unequivocally for the first time for thiolane products resulting from a chalcone. Secondly, the results made possible the correlation of all three $^3J_{H-H}$ values with the relative configurations of hydrogen atoms. Furthermore, the chemical shift assignments of the thiolane ring protons provided the first data for correlating chemical shift with the nature of the thiolane ring substituents. These correlations would assist later structure determinations when crystals appropriate for X-ray structure determination were unattainable. Thirdly, the results established the relative stability of **5** and **6** under conditions for thiolane formation and thereby suggested that the cis,trans,trans diastereomer **6** was formed initially but in time it isomerized to the all-trans diastereomer **5**. Indeed, the initial formation of a cis,trans,trans thiolane and later appearance of the all-trans diastereomer could be followed readily when *trans*-2-methoxychalcone (**7**) was treated on the same scale and in the same manner as the chalcone **4**. Equal volume aliquots were withdrawn at half-hour intervals starting one-half hour after the addition of chalcone **7** to the saturated polysulfide solution. Each aliquot was analyzed by TLC for the presence of starting chalcone **7**, cis,trans,trans-**8**, and *all-trans*-**9**. The presence of *cis,trans,trans,*-**8** was first detected in the third aliquot while the presence of *all-trans*-**9** was not detected until the ninth aliquot, which also contained **8**. Isolation of *all-trans*-**9** from a crude product mixture could be achieved in 30% yield by careful crystallization while isolation of *cis,trans,trans*-**8** required extensive chromatography of product materials enriched in this isomer. Under standard reaction conditions **8** isomerized to *all-trans*-**9**.

The structure of *cis,trans,trans*-**8** was secured by the X-ray crystallographic study, which yielded the model shown in Figure 1c. The structure of *all-trans*-**9** rested not only on its base-promoted formation from **8** but also on the $^1H-^{13}C$ direct-bond and long-range heteronuclear 2D correlations, as well as the $^1H-^1H$ 2D correlation. Again, the starting point for identifying the ^{13}C and ^1H signals was the C-4 resonance. Through the help of the direct-bond $^1H-^{13}C$ 2D and the $^1H-^1H$ 2D correlations, the five-membered ring ^{13}C and ^1H signals were identified. The long-range $^1H-^{13}C$ 2D correlation, as depicted in Figure 2a, showed that C-3 and C-5 were long-range coupled to aromatic protons. Thus, the attachment of 2-methoxyphenyl groups to C-3 and C-5 is justified. Moreover, the distinction of C-3 from C-5 is confirmed by the number of long-range couplings: two in the case of C-5 but three in the case of C-3.

The relatively more rapid formation of the cis,trans,trans-substituted thiolane **8** from two *trans*-chalcone units means that the configuration of one unit must have been lost in its combination with the second. However, the results of the following study advise us that a side-by-side combination of chalcone units and sulfur atom affords the thiolanes. thus, a mixture containing equal molar amounts of chalcone **10** and 2,2′-dimethoxychalcone (**4**) was treated with sodium polysulfide under the usual conditions. Small samples of all-trans hybrid thiolanes **11** and **12** were isolated by chromatography of the crude reaction mixture, which also yielded, as expected, quantities of the thiolanes **5** and **13**.[5]

Since attempts to obtain either **11** or **12** in crystalline form appropriate for an X-ray study were unsuccessful, ^1H and ^{13}C NMR were utilized to determine the ring carbon atoms to which the four different substituents were attached. The $^1H-^{13}C$ direct-bond heteronuclear 2D correlation was determined for hybrid **12**. This 2D correlation gave the assignments of the four ^{13}C and ^1H signals on the basis of considerations as explained above in the case of **5**. The long-range 2D correlation, Figure 2b, showed that C-5 was coupled through three bonds to more aromatic protons than C-3.[12] Thus, a phenyl group was attached to C-5 and a 2-methoxyphenyl attached to C-3, giving a partial structure in agreement with ^1H chemical shift correlations discussed below. To ascertain where the benzoyl and 2-methoxybenzoyl group were attached, it was necessary to rely on ^1H and ^{13}C NMR chemical shift correlations, which not only allowed the complete structure determination of hybrid **12** but hybrid **11** as well. The following analysis shows how the chemical shift correlations were established and used.

---

(10) Still another confirmation of the proton assignments comes from the lower field doublet of a doublet at δ 5.89 appearing in the spectrum of **6**. This resonance was attributed to H-4 because the X-ray model showed that this proton was located uniquely in a strongly deshielding region of the C-2 carbonyl oxygen (ref 11). Accordingly, the remaining doublet of a doublet at δ 4.75 was assigned to H-3, an assignment conforming to that given in the text. Although the downfield shift is not as striking for H-4 in the *cis,trans,trans*-**8**, this resonance does appear nonetheless as the second-most downfield signal of the H-4 group.

(11) Jackman, L. M.; Sternhell, S. *Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergammon Press: New York, 1969; pp 88–92.

(12) Long-range correlation of C-3 with a one-proton peak and C-5 with a two-proton peak in the aromatic region could not be achieved by separate ^1H integrations because of the severe overlapping of signals. However, the correlation was made on the basis that the spot for C-5 was recognizably much more intense than the spot for C-3 and, therefore, C-5 must be long-range coupled to a larger number of aromatic protons than C-3. This conclusion is justified provided the delay times, Δ_1, and Δ_2, are appropriately chosen. These delay times depend on the magnitude of the long-range coupling of protons to a given ^{13}C, the complexity of the $^1H-^1H$ multiplet structure and the transverse ^1H relaxation time (ref 13). Thus, having all these facotrs the same, we would expect the spot intensity to be the same for equal numbers of $^{13}C-^1H$ long-range couplings. In the case of compound **12**, we expect each of the three-bond couplings of C-5 to aromatic protons to be the same order of magnitude as that of C-3 to an aromatic proton. Further, we expect all three aromatic protons to have the same complexity of coupling patterns and transverse relaxation times. Thus, the correlation is solely dependent on the number of protons having three-bond couplings to the particular ^{13}C since the delays Δ_1 and Δ_2 used in this experiment were the same ($^1/_2J = 41.7$ ms, where $J_{CCCH} = 12$ Hz).

(13) Bax, A. "Two dimensional NMR Spectroscopy" in *Topics in Carbon-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1984; Vol. 4, pp 199–227.

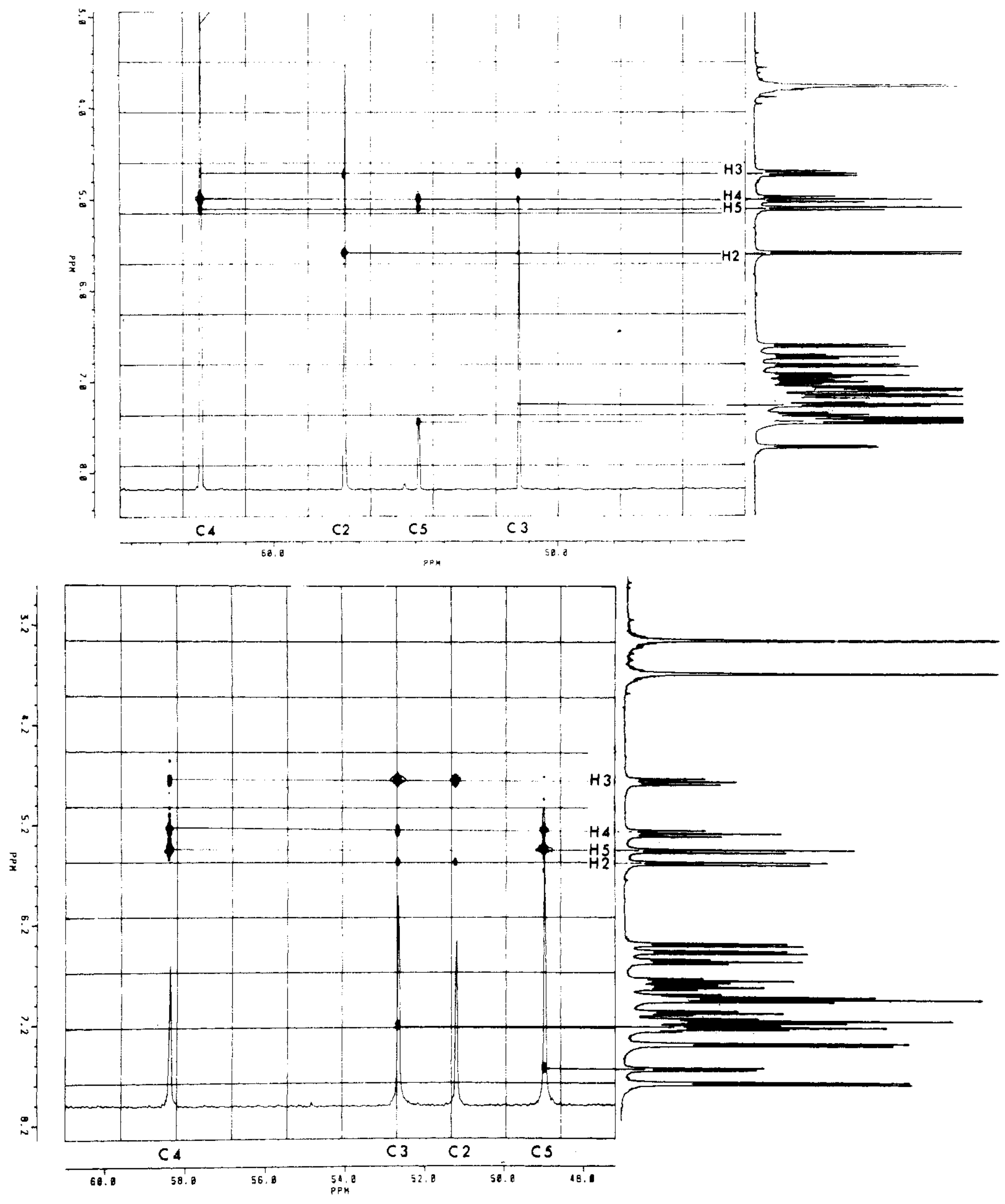


Figure 2. ^1H–^{13}C 2D long-range correlation plots for **9** (a, top) and **12** (b, bottom).

Table I reveals that δ^{H-5} falls into two value sets.[14] The one, 5.03–5.12 ppm, results from phenyl substitutions at C-5. The second, 5.31–5.55 ppm, results from 2-methoxyphenyl substitutions. Plotting δ^{H-5} in three dimensions against the type of geminal substituent, phenyl or 2-methoxyphenyl, and against the vicinal substituent, benzoyl or 2-methoxybenzoyl gives Figure 3a, which shows clearly that δ^{H-5} varies along the geminal axis but not along the vicinal axis. Since δ^{H-5} for hybrid **12** is influenced predominantly by geminal substitution and δ^{H-5} falls into the lower value set, a phenyl group is attached to C-5. This partial structure assignment is in accord with the interpretation of the 2D NMR of **12**. Since δ^{H-5} for **11** falls into the higher value set, a 2-methoxyphenyl group is attached to C-5 in this hybrid thiolane.

A similar grouping of the δ^{H-2} values is noted. One group occurs at 5.18–5.28 ppm, the second at 5.46–5.65 ppm. Figure 3b shows, however, that the predominant influence on δ^{H-2} is not the geminal substituent on C-2 but the vicinal substituent on C-3. Since δ^{H-2} of **11** falls into the lower value set, a phenyl group must be located at C-3. Because δ^{H-2} of **12** occurs in the higher value set, a 2-methoxyphenyl group is located at C-3 in this hybrid thiolane. The attachment of a 2-methoxyphenyl group at C-3 of **12** is also in accord with the 2D NMR. To summarize the results of the preceding analysis, **11** is substituted by phenyl and 2-methoxyphenyl groups at C-3 and C-5, respectively. In relation to **11**, **12** has the location of the same two substitutents reversed.

There is a similar relation between ^{13}C NMR δ^{C-4} values and the type of substituent at C-4 and the adjacent C-3 and C-5 carbons. The δ^{C-4} is the lowest field signal in the saturated carbon region and is separated by 5–10 ppm from the next lowest field signal for all thiolanes examined. It can be identified by accounting for the number of α and β substituents attached to each of the thiolane ring carbons and the greater downfield contribution of an α benzoyl than an α phenyl group, as demonstrated by simpler

---

(14) The effects of geminal and vicinal substitution on the proton chemical shift value of a given thiolane ring proton (δ^{H-n}) were sought. The only clear systematic patterns were observed in the case of geminal substitution on δ^{H-5} and vicinal substitutions n δ^{H-2}. Nothing in the other relations between δ^{H-n} and geminal and vicinal substitution is inconsistent with the systematic patterns for δ^{H-2} and δ^{H-5}. Charts illustrating the relation of geminal and vicinal substitution to δ^{H-3} and δ^{H-4} are made available as supplementary material.

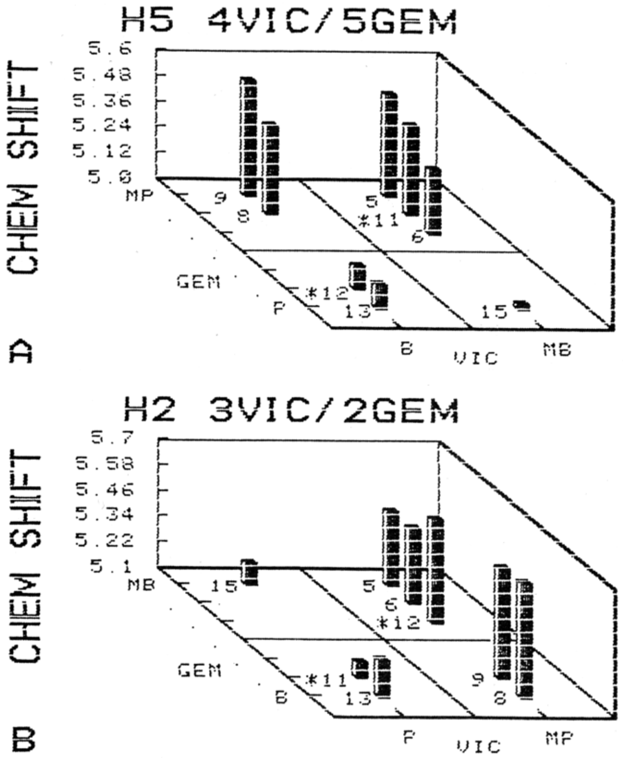


Figure 3. Three-dimensional plots illustrating the change in the ^{1}H chemical shift value (δ^{H-n}) for (a) H-5 and (b) H-2 resulting from the geminal and vicinal substituent changes of phenyl (P), 2-methoxyphenyl (MP), benzoyl (B), and 2-methoxybenzoyl (MB) groups at C-5 and -4 (Figure 3a) and C-2 and -3 (Figure 3b). the δ^{H-n} are taken from Table I. The designation * indicates compounds whose C-5 and C-3 substituents were to be determined with the help of the chemical shift correlations illustrated in this figure.

models.[15] In the case of the parent thiolane **13**, δ^{C-4} had been identified earler[3] through the ^{13}C NMR of the 3,5,-^{2}H$_2$ labeled thiolane. Relative to **13**, δ^{C-4} is shifted upfield by 6.7 ppm for the (3,5-dimethoxyphenyl)thiolane **9** but downfield by 3.3 ppm for the (2,4-dimethoxybenzoyl)thiolane **15**. Both **11** and **12** have one *o*-methoxyphenyl group adjacent to C-4. Therefore, in comparing δ^{C-4} values for **11** and **12**, the observation that δ^{C-4} occurs 2.9 ppm further downfield for the former compound relative to the latter means an *o*-methoxybenzoyl group is attached to C-4 in **11** and a benzoyl group at the same carbon in **12**. The structures of **11** and **12** are given in accord with the preceding interpretation of the NMR chemical shift data. The all-trans configuration of hybrids **11** and **12** follows from the $^3J_{H-H}$ values.

Conclusions

At least as far as the *o*-methoxychalcones are concerned, our results give clear answers to the questions posed in the introduction: cis,trans,trans and all-trans diastereomers are formed in the side-by-side combination of chalcone units. Therefore, hypothetical routes requiring top-to-bottom orientation of enone units, such as the dipole–dipolarophile process given in Scheme I, are inconsistent with the observed regiochemistry of the product thiolanes. The cis,trans,trans diastereomers are less stable and isomerize to the all-trans diastereomers under the conditions of the reaction. These observations suggest that it is the cis,trans,trans diastereomers that are the kinetically favored products. This suggestion becomes a clear indication in the case of the formation of *cis,trans,trans*-**8**, which was observed to appear in the product before its diastereomer, all-*trans*-**9**. Although these regio- and stereochemical results are consistent with the thioenolate route of Scheme I, they are also consistent with several other hypothetical routes leading to the side-by-side combination of chalcone units. Further investigations of the bond-forming reactions are now being planned on the basis of the information gained from the studies reported here.

Experimental Section

Spectra. ^{1}H NMR were determined in CDCl$_3$ solution in 5-mm tubes on Varian XL-100, Mohawk 250, Bruker WM360, and GE (Nicolet) 500-MHz spectrometers. Spectra of thiolanes were determined first at 100 MHz and then at higher field until first-order signals for all the thiolane ring protons were obtained. The δ^H and $^3J_{H-H}$ values are given in Table I. The thiolane proton region of the spectra determined at all field strengths were simulated by Apple IIe computer program (BINSIM) and plotted in order to confirm the measured δ^H and $^3J_{H-H}$ values by comparison with determined spectra. Only in the case of thiolane **8** were first-order signals for all the thiolane protons unattainable at any field strength. Therefore, the spectrum was simulated iteratively at 360 MHz by variation of $^3J_{H-H}$ and δ^H values until the simulated and determined resonance patterns agreed. Spectra simulated at lower field strength (100 and 250 MHz), using the values from the 360-MHjz simulation, agreed with the determined spectra. The 360.13-MHz ^{1}H shift correlated 2D NMR (COSY-90) for compounds **5** and **9** were carried out on the Bruker WM360 NMR spectrometer. the 2D parameters were 256 × 1 K data points; $W_1 = \pm 1000$ Hz, W2 = 2000 Hz, recycle delay 3 s, $\Delta t_1 = 0.5$ ms acquisitions ca. 13 h, transformed with sine-bell in both domains. Totally decoupled ^{13}C NMR were determined in 5-mm tubes in CDCl$_3$ solution on a Varian XL-100 spectrometer at 25.2 MHz. δ^H and δ^C values are relative to Me$_4$Si (δ 0.00). Contour plots for direct-bond and long-range 2D ^{1}H–^{13}C heteronuclear shift correlated spectra were obtained in CDCl$_3$ solution at 90.6 MHz on a Bruker WM360 spectrometer. Direct-bond correlations for compounds **5**, **9**, and **12** were determined by using the respective spectra widths [$W_1(+)$, W_2 in Hz] and number of free induction decays for each value of t_1 as follows: **5**, 2000, 2000, 112; **9**, 2000, 1250, 23; **12**, 2000, 2000, 192. The recycle delay was 1.5 s, $\Delta t_{1/2} = 0.25$ ms, $\tau_1 = 3.3$ ms, $\tau_2 = 1.67$, phase cycling for quad detection in F$_1$. FIDs were transformed with sine-bell squared-shifted $\pi/5$ in t_1 and $\pi/3$ in t_2. Long-range correlations for compounds **9** and **12** were determined by using the pulse sequence optimized to provide the maximum polarization for $J = 12$ Hz and simultaneously suppressed $_1J = 144$ Hz interactions. Spectra widths [W_1 (+), W_2 in Hz] and number of free induction decays for each value of t_1 were as follows: **9**, 2000, 1250, 96; **12**, 2000, 2000, 192. The data set consisted of 256 points in the t_1 dimension and 2048 points in the t_2 dimension. The recycle delay was 1.5 s, $\Delta t_{1/2} = 0.25$ ms, τ_1, $\tau_2 = 41.7$ ms, with phase cycling for quad detection in F$_1$. FIDs were transformed with sine-bell square-shifted $\pi/5$ in t_1 and $\pi/3$ and t_2. EIMS were obtained from a Finnigan 4020 spectrometer by solid bombardment. IR were determined in CHCl$_3$ solution on Perkin-Elmer 1310 spectrometers.

TLC. TLC was performed on Baker-flex silica gel 1B2-F strips, 7.5 × 2.5 cm, with low boiling (30–60 °C) petroleum ether (PE) and ethyl acetate (EtOAc) mixed in the proportions indicated within parentheses appearing after the designation "TLC". Spots were visualized by UV irradiation.

Michael Acceptor Chalcones. Chalcones **4**, **7** [mp 56–58 °C (lit.[16] mp 58–59 °C); ^{1}H NMR (100 MHz) δ 3.85 (s, OCH$_3$), 8.14 (d, $^3J_{H-H} = 15$ Hz, CH═CCO)], and **14**[3] [^{1}H NMR (100 MHz) δ 3.82 (s, OCH$_3$), 7.64 (d, $^3J_{H-H} = 16$ Hz, CH═CCO)] were prepared by common hydroxide ion catalyzed condensations of the appropriate benzaldehyde and acetophenone. Properties of **4** are as follows: mp 100–102 °C; ^{1}H NMR (100 MHz) δ 3.87 (s, OCH$_3$), 3.89 (s, OCH$_3$), 7.98 (d, $^3J_{H-H} = 16$ Hz, CH═CCO); MS, *m/e* 268 (M$^+$), 237 (base peak), 161, 135, 121, 91, 77. Anal. Calcd. for

---

[15] Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; pp 58, 98, 147.

[16] Stobbe, H.; Wilson, F. J. *J. Chem. Soc.* **1910**, *97*, 1722.

$C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.75; H, 5.94.

Conversion of 2,2′-Dimethoxychalcone (4) to *trans,trans,trans*- and *cis,trans,trans*-2,4-Bis(*o*-methoxybenzoyl)-3,5-bis(*o*-methoxyphenyl)thiolane (5 and 6). The standard procedure for the conversion of chalcone to thiolane consisted of the following. A 14.4-mmol quantity of 4 was added in one portion to 30 mL of a stirred 95% ethanolic solution saturated with sodium polysulfide, which had been prepared by stirring 225 mmol of powdered Na_2S H_2O with 270 mmol of sulfur for 30 min. After stirring for and additional 2 days at 30 °C, the bulk of the ethanol was removed from the viscous mixture with a rotary evaporator. A 50-mL quantity of CH_2Cl_2 was added to the red residue and the resulting mixture was filtered. Quantities of CH_2Cl_2 (50 mL), water (25 mL), and CH_2Cl_2 (20 mL) were consecutively passed through the filter cake and added to the original filtrate. The CH_2Cl_2 layer was separated and the aqueous layer was back-washed with three 20-mL portions of CH_2Cl_2, which were combined and added to the original CH_2Cl_2 solution. The combined solution was washed first with two 40-mL and then three 25-mL portions of 20% aqueous $(NH_4)_2S$. The CH_2Cl_2 solution was washed repeatedly with 50-mL portions of water until the water wash was neutral and then with brine. After further drying of the orange solution over anhydrous $MgSO_4$, the CH_2Cl_2 was removed with a rotary evaporator to obtain 3.4 g of a deep orange residue that was taken up in 2000 mL of EtOAc. Obtained as a result of slow evaporation of solvent over several days was a 520-mg quantity of well-formed crystals of 5: mp 166–169 °C; TLC (2:1) R_f 0.22; IR 1670 cm^{-1}; MS, *m/e* 568 (M$^+$), 433, 415, 503, 299, 297, 281, 269, 267, 237, 165, 135 (base peak), 92, 91, 77; ^{13}C NMR δ 201.9, 198.0, 64.6 (C-4), 57.6, 50.0, 46.5; CH_3O ^1H NMR (100 MHz) δ 3.55 (s), 3.72 (s), 3.74 (s). Anal. Calcd for $C_{34}H_{32}O_6S$: C, 71.81; H, 5.67; S, 5.64. Found: C, 71.62; H, 5.74; S, 5.99.

Further slow evaporation from EtOAc yielded an additional 810 mg of crystalline 5; mp 156–161 °C.

The solution remaining after the removal of 5 yielded 1.6 g of solid residue after removal of the solvent. Flash chromatography on SiO_2 using PE–EtOAc (2:1) followed by HPLC of fractions enriched in 6 gave nearly pure 6. Dissolving the combined fractions in the minimum quantity of EtOAc followed by the slow evaporation of the solvent resulted in the formation of 19 mg of crystalline 6: mp 149–151 °C; TLC (2:1) R_f 0.48; IR 1665 cm^{-1}; MS, *m/e* 568 (M$^+$), 433, 415, 299, 297, 281, 269, 237, 135 (base peak) 92, 91, 77; ^{13}C NMR δ 203.4, 201.5, 61.0 (C-4), 54.0, 50.0, 45.9; CH_3O ^1H NMR (100 MHz) δ 3.49 (s), 3.67 (s), 3.72 (s), 3.83 (s); HRMS, calcd mass for $C_{34}H_{32}O_6S$ 568.1920, found 568.1917.

Isomerization of 6 to 5. A 2-mg quantity of 6 was added to 0.7 mL of a stirred 95% ethanolic solution saturated with sodium polysulfide, which had been prepared from 130 mg of Na_2S H_2O and 190 mg of S. The resulting mixture was stirred for 2 days at 30 °C, at the end of which time it was processed in a manner similar to that described in the immediately preceding subsection. TLC (2:1), comparing the components of the CH_2Cl_2 solution against pure 6 and 5, showed the presence of both stereoisomers (5, R_f 0.22, and 6, 0.48) in the CH_2Cl_2 solution. ^1H NMR showed the OMe resonances from both stereoisomers.

Similarly, a 5-mg sample of 6 was treated with a saturated sodium polysulfide solution. TLC (2:1), comparing the components of the CH_2Cl_2 solution against pure 6 and 5, showed the presence of only the starting stereoisomer 5.

Conversion of 2-Methoxychalcone (7) to *cis,trans,trans*- and *trans,trans,trans*-2,4-Dibenzoyl-3,5-bis(*o*-methoxyphenyl)thiolane (8 and 9). According to the standard procedure, the first transformation of a 14.4-mmol quantity of chalcone 8 produced after the usual workup 2.96 g of a light orange residue, whose TLC (2:1) showed R_f 0.35 and 0.23. Stirring the residue with 50 mL of EtOAc gave a solution, which was set aside for further use (see below), and 1.1 g (30%) of an insoluble powder, 9: mp 162–165 °C (recrystallized from 95% EtOH); TLC (2:1) R_f 0.23; IR 1680 cm^{-1}; MS, *m/e* (508 (M$^+$), 403, 297, 270, 269, 265, 251, 239, 207, 105, 91, 77; CH_3O ^1H NMR (100 MHz) δ 3.59 (s), 3.85 (s); ^{13}C NMR δ 199.2, 194.5, 58.8 (C-4), 52.9, 51.6, 49.3. Anal. Calcd for $C_{32}H_{28}O_4S$: C, 75.57; H, 5.55; S, 6.30. Found: C, 75.71; H, 5.37; S, 6.20.

A second transformation was carried out by using the same scale and conditions as described directly above, except that nine 0.5-mL aliquots were withdrawn at 0.5-h intervals. After the ninth aliquot had been taken, the solvent was removed from the reaction flask by rotary evaporation. Each aliquot was centrifuged immediately after removal from the reaction flask to remove insoluble sulfur. The supernatant was analyzed by TLC (2:1) for the presence of starting chalcone 7 (R_f 0.48), cis,trans,trans diastereomer 8 (R_f 0.35), and trans,trans,trans diastereomer 9 (R_f 0.23). This analysis showed the first presence of 8 in the third aliquot, which had been taken at 1.5 h. The diastereomer 9 was observed in the ninth aliquot, which was taken at 4.5 h.

The residue remaining after rotary evaporation of the solvent was processed in CH_2Cl_2 solution according to the usual workup procedure previously described. Rotary evaporation of the solvent gave a crude product mixture (2.8 g) that was combined with the previously described, EtOAc-soluble material obtained in the first transformation. The resulting mixture (4.45 g) enriched in the cis,trans,trans stereoisomer was then flash chromatographed on SiO_2 in five consecutive 500-mg portions. Fractions containing only the desired stereoisomer were combined. Resulting was 30 mg of 8: mp 165–169 °C; TLC (2:1) R_f 0.35; IR 1680 cm^{-1}; MS, *m/e* 508 (M$^+$), 403, 285, 297, 295, 270, 269, 265, 251, 239, 207, 105, 91, 77; CH_3O $_1H$ NMR (360 MHz) δ 3.25 (s), 3.81 (s). Anal. Calcd for $C_{32}H_{28}O_4S$: C, 75.57; H, 5.55; S, 6.30. Found: 75.83; H, 5.68; S, 6.15.

Isomerization of 8 to 9. A 3-mg quantity of 8 was treated with the corresponding molar and volume amounts of saturated polysulfide solution in the manner described for the isomerization of 6 to 5. Thereafter the recovered thiolane was analyzed by TLC and ^1H NMR (100 MHz) for the presence of 8 and 9: TLC (2:1) R_f 0.23 (R_f 0.35 absent); CH_3O ^1H NMR δ 3.59 (s), 3.89 (s) [δ 3.25 (s), 3.81 (s) absent].

A 5-mg quantity of 9 was treated similarly. The recovered thiolane was analyzed by TLC and ^1H NMR (100 MHz). TLC (2:1) R_f 0.23; CH_3O ^1H NMR δ 3.59 (s), 3.85 (s).

Conversion of a Mixture of Chalcone (10) and 2,2′-Dimethoxychalcone (4) to 2-Benzoyl-3-phenyl-4-(*o*-methoxybenzoyl)-5-(*o*-methoxyphenyl)thiolane (11) and 2-(*o*-Methoxybenzoyl)-3-(*o*-methoxyphenyl)-4-benzoyl-5-phenylthiolane (12). A mixture containing 7.2 mmol of 4 and 7.2 mmol of 10 was added in one portion to a saturated polysulfide solution by using the standard procedure except that the reaction was allowed to proceed 1 day. After standard workup, 3.33 g of a red glass-like solid was obtained. An MS search for *m/e* 478 and 538, M$^+$ values corresponding respectively to mono- and trimethoxy-substituted thiolanes, failed to show the presence of these peaks in the MS of the crude product mixture. A small portion of the crude in EtOAc solution was streaked on a 20 × 20 cm silica gel TLC plate that was developed three times with PE–EtOAc (4:1). Streaks were removed, extracted with CH_2Cl_2, and, after evaporation of the solvent from the resulting solutions, were analyzed by MS for the appearance of *m/e* 508 (M$^+$, 11 and 12) and the absence of M$^+$ values for 5, 6, and 13. Material from streaks having M$^+$, *m/e* 508, were then used to monitor by TLC comparison the flash chromatography (PE–EtOAc, 4:1) of five 100-mg samples of the crude product. Fractions rich in 11 and 12 were selected for HPLC, which yielded 3.7 mg of light yellow powder, 11: mp 144–152 °C; TLC (3.5:1) R_f 0.33; IR 1685 cm^{-1}; MS, *m/e* 508 (M$^+$), 490, 473, 457, 403, 356, 300, 285, 269, 267, 251, 237, 135 (base peak), 105, 91, 77; CH_3O ^1H NMR (100 MHz) δ 3.60 (s), 3.73 (s); ^{13}C NMR δ 65.8 (C-4), 55.0, 53.4, 48.8; HRMS, calcd mass for $C_{32}H_{28}O_4O$ 508.1708, found 508.1713.

Also from HPLC was obtained 4.3 mg of white crystalline 12: mp 178–180 °C; TLC (3.5:1) R_f 0.29; IR 1724 cm^{-1}; MS, *m/e* 508 (M$^+$), 491, 473, 457, 403, 355, 300, 269, 267, 251, 238, 237, 135, 105 (base peak) 91, 77; CH_3O ^1H NMR (100 MHz) δ 3.78 (s), 3.79 (s); ^{13}C NMR δ 62.8 (C-4), 57.7, 55.6, 51.6; HRMS, calcd mass for $C_{32}H_{28}O_4S$ 508.1708, found 508.1698.

Conversion of 2′-Methoxychalcone (14) to 2,4-Bis(*o*-methoxybenzoyl)-3,5-diphenylthiolane (15). A 14.4-mmol quantity of 14 was treated with sodium polysulfide according to the standard procedure and worked up in the normal manner. After removal of 1.2 g of rearranged thiolane product, whose formation from 14 was previously described,[4] the 330-mg residue from the mother liquors was flash chromatographed on silica gel to obtain 161 mg of glasslike material, which when dissolved in glacial acetic acid deposited solid 15: mp 122–124 °C; TLC (2:1) R_f 0.35; IR 1680 cm^{-1}; MS, *m/e* 508 (M$^+$), 373, 269, 251, 239, 237, 135 (base peak), 92, 77; CH_3O ^1H NMR (100 MHz) δ 3.45 (s), 3.74 (s); ^{13}C NMR δ 68.8 (C-4), 60.3, 55.5, 53.8. Anal. Calcd for $C_{32}H_{28}O_4S$: C, 75.57; H, 5.55: S, 6.30. Found: C, 75.29, H, 5.54; S, 6.13.

Single-Crystal X-ray Analysis of 5, 6, and 8.[17] Compound **5** crystallized in the monoclinic space group *Cc* with $a = 8.461$ (1), $b = 23.159$ (2), and $c = 14.862$ (2) Å, and $\beta = 89.08$ (1)°. All unique diffraction maxima with $2\theta \leq 144°$ were collected by using a computer-controlled four-circle diffractometer and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.5478 Å) with variable speed, 1° ω-scans. Of the 1967 reflections surveyed in this fashion, 1835 (93%) were judged observed. The structure was solved routinely and refined by block-diagonal least-squares refinements to a conventional crystallographic residual of 0.0545 for the observed reflections. Additional crystallographic data are available and are described in the paragraph entitled Supplementary Material Available at the end of this paper.

Compound **6** crystallized in the orthothrombic space group $P2_1nb$ with $a = 9.199$ (2), $b = 11.251$ (3), and $c = 28.593$ (8) Å. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer with graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å) and variable speed, 1° ω-scans. Of the 2139 reflections collected in this manner, 2006 (94%) were judged observed and used in subsequent refinements. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.0795 for the observed reflections. Additional crystallographic data are available and are described in the paragraph entitled Supplementary Material Available at the end of this paper.

In the case of **8**, preliminary X-ray photographs displayed only Friedel's law symmetry and belonged to the triclinic crystal class. Lattice constants were obtained from a least-squares fitting of 15 moderate angle 2θ values and were α 9.9507 (20), $b = 12.8833$ (29), and $c = 11.8464$ (27) Å, $\alpha = 117.97$ (2)°, $\beta = 99.398$ (17)°, $\delta = 83.331$ (17)°. A rough density measurement indicated that two molecules of composition $C_{32}H_{28}O_4S$ were in the unit cell. The space group was assumed to be $P\bar{1}$, and this assumption was verified by successful refinement. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer with graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å) and variable speed, 1° ω-scans. Of the 3554 reflections measured in this fashion, 3212 (90%) were judged observed ($|F_0| \geq 3\sigma(F_0)$) after correction for Lorentz, background, and polarization effects. A phasing model was found easily by using a multisolution sign determining approach. All of the non-hydrogen atoms were clearly visible on the resulting E-synthesis. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.0595 for the observed reflections. Additional crystallographic parameters are available and are described in the paragraph entitled Supplementary Material Available at the end of this paper.

Acknowledgment. We thank Dr. Philip Borer and Mr. Gene Bailey of the NIH Resource for Multi-Nuclei NMR and Data Processng, Department of Chemistry, Syracuse University, for the 500-MHz ^1H NMR spectra. We thank Mr. Bruce Prosser of Bristol-Myers Company and Mr. Timothy Ullman of Corporate Research and Development Center, General Electric Company, for elemental and HRMS analyses. We also thank Dr. Ronald Eby and Dr. Francis Webster, who provided us with the NMR simulator program. The Cornell authors thank NSF INT14133 for financial support.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for compounds **5**, **6**, and **8**, the direct-bond ^1H–^{13}C 2D heteronuclear-correlated spectra for compounds **5**, **9**, and **12**, 2D ^1H–^1H NMR (COSY) spectra for compounds **5** and **9**, and three-dimensional plots illustrating the relation of δ^{H-3} and δ^{H-4} to vicinal and geminal thiolane substitution (29 pages). Ordering information is given on any current masthead page.

---

[17] All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978 and 1980; DIRDIF written by P. T. Beurskens et al., University of Nijmegen, Netherlands, 1981; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

Factors Affecting the Regioselection of the Allylic Imidates Iodocyclization

Alessandro Bongini, Giuliana Cardillo,* Mario Orena, Sergio Sandri, and Claudia Tomasini

Istituto Chimico "G. Ciamician", 40126 Bologna, Italy

Received December 24, 1985

The regiochemistry of the iodocyclization reaction of allylic imidates leading to 4,5-dihydro-1,3-oxazoles or to 4,5-dihydro-1,3-oxazines strongly depends on the configuration of the double bond: (*E*)-allylic imidates afford preferentially 4,5-dihydro-1,3-oxazines through a 6-endo closure, whereas (*Z*)-allylic imidates afford preferentially 4,5-dihydro-1,3-oxazoles through a 5-exo closure. Furthermore a study on the effect of an oxygen atom vicinal to the double bond is reported.

Cyclic intermediates have been widely utilized in the total synthesis of complex molecules.[1] The use of cyclic systems in asymmetric induction relies on the propensity of a cyclic transition state to assume a configuration compatible with the smallest interaction among the substituents.[2]

In this field we have developed methods for functionalization of double bonds of allylic and homoallylic alcohols and amine derivatives, through iodonium-initiated cycli-

---

[1] Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

[2] (a) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829. (b) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (c) Pauls, H. W.; Fraser-Reid, B. J. *J. Am. Chem. Soc.* **1980**, *102*, 3956. (d) Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett.* **1981**, *22*, 4611.

0022-3263/86/1951-4905$01.50/0 © 1986 American Chemical Society