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γ-Chloroallyl Sulfoxides as Latent α,β-Unsaturated Carbonyl Compounds. A New Approach to Steroid Synthesis

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Received December 8, 1975

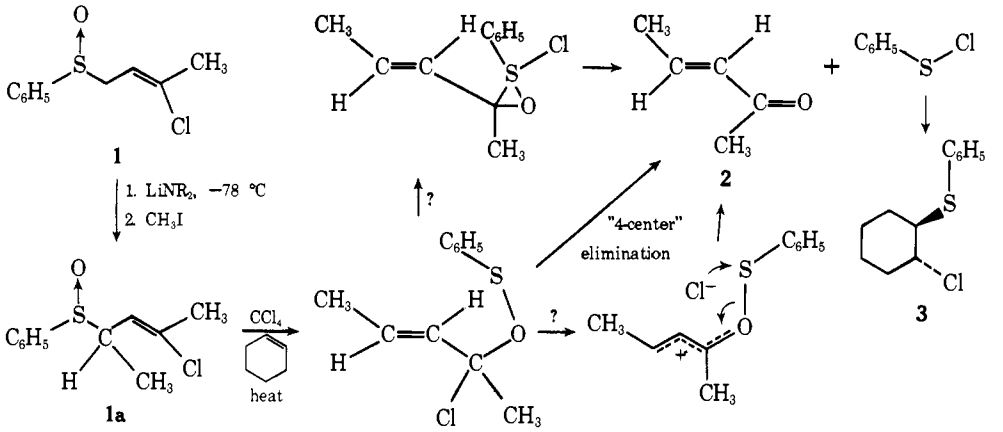
Abstract: γ-Chloroallyl sulfoxides undergo [2,3] sigmatropic rearrangement and "self-immolative" fragmentation of α-chloro sulfenates with great ease. α,β-Unsaturated carbonyl compounds with varying substitution patterns can thus be generated at an appropriate stage of a multistep synthesis. The approach is illustrated with construction of potential steroid precursors **17** and **18**.

Chloro olefin annelation has proven to be versatile for construction of five- through seven-membered carbocyclic rings, especially in the steroid and terpene areas.[1] Likewise, chloroalkene units can be successfully employed in electrocyclic reactions proceeding via cyclic transition states, but not resulting directly in ring formation ("chloro olefin pseudoannelation").[2,3] Thus, [3,3] sigmatropic alkylations employing β-chloroallyl vinyl ethers played a key role in hirsutane synthesis,[2] while exploratory [2,3] sigmatropic rearrangements of γ-chloroallyl sulfoxides and amine oxides, followed by further decomposition (vide infra), indicated their capabilities as latent α,β-unsaturated carbonyl compounds.[3]

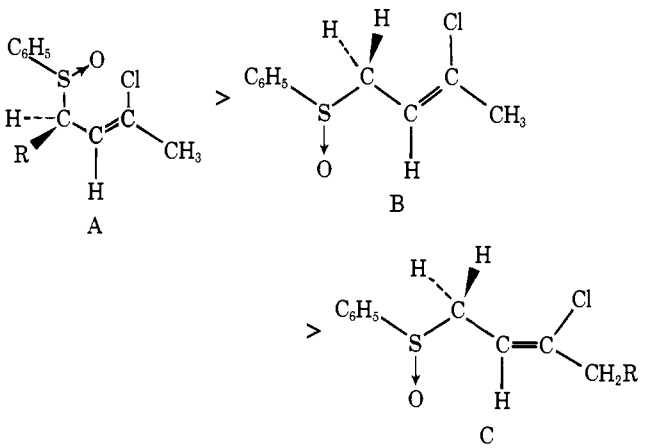
The present paper concerns potential applications of γ-chloroallyl sulfoxide rearrangements to steroid synthesis. Related synthetic utilization of allyl sulfoxide-sulfenate equilibria[4] involve thiophile-assisted conversions of sulfenates into allyl alcohols.[5] Regiospecific generation of synthetically versatile α,β-unsaturated ketones from latent precursors, as we discuss herein, complements extensive recent work of others on enone synthesis. Some examples are 1,3-alkylative carbonyl transposition,[6] alkylative elimination of α-sulfinyl esters,[7] and introduction of α,β-unsaturation into existing ketones[8a,b] and esters[8c] via selenoxide eliminations.

From the outset of our studies with γ-chloroallyl sulfoxides,[3] it was clear that such species would in some cases rearrange so rapidly that deprotonation and alkylation prior to "self-immolative" rearrangement-elimination[9] might be problematic. Thus, sulfoxide **1**[10] can be methylated and the crude **1a** (estimated yield ca. 65%) completely transformed during 2 h of refluxing in carbon tetrachloride-cyclohexene to *trans*-3-pentene-2-one (**2**) and the phenylsulfenyl chloride adduct **3** (Scheme I). However, **1a** and comparably alkylated

Scheme I



sulfoxides prepared directly from the corresponding sulfides are so prone to rearrange that further alkylation (as in Scheme I) cannot be efficiently carried out.[11] Conversely, further substitution of **1** only at the methyl group not surprisingly slows down rearrangement to a rate facilitating experimental manipulation, while not diminishing the realization of excellent yields. Qualitatively, the ease of rearrangement[12] follows the order shown with the most stable type of substrate (C) of primary concern herein. At least three mechanisms for arylsulfenyl chloride extrusion can be envisaged (see Scheme I) with nonpolar pathways (e.g., episulfuranes or four-center) probably more likely in the solvents used (primarily carbon tetrachloride).

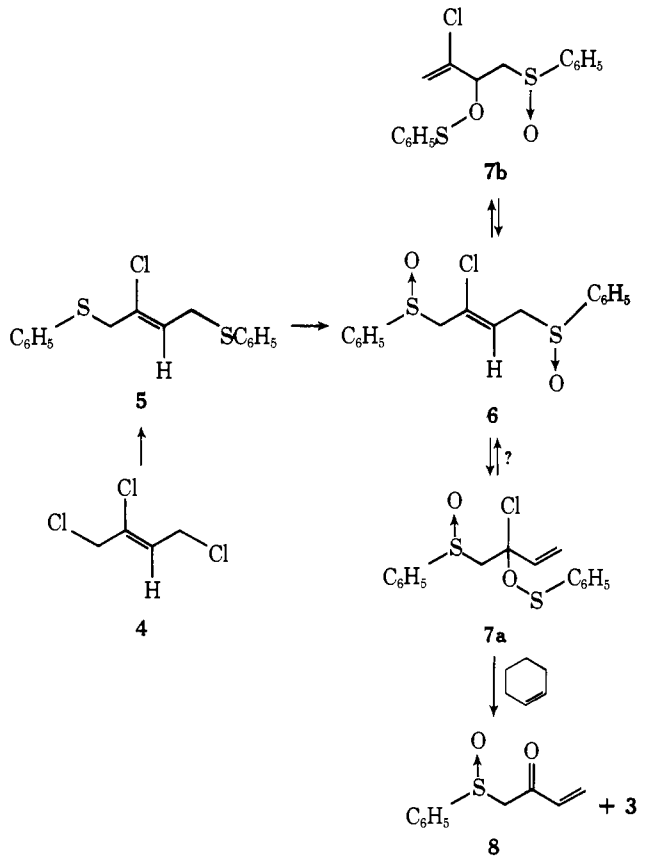


(*Z*)-1,2,4-Trichloro-2-butene[13] (**4**) provides an opportunity to sequentially and selectively consume each chlorine atom.[14] The two allylic chlorines are obviously much more reactive than the vinyl chlorine. Moreover, our earlier experiences with carbon alkylation, using 2,3-dichloropropene and 1,3-dichloro-2-butene, convinced us that the allylic chlorines in **4** might have significantly different reactivities in bimolecular nucleophilic substitution, as has been observed with other nucleophiles.[15] We shall see that this information can be used to advantage in synthesis.

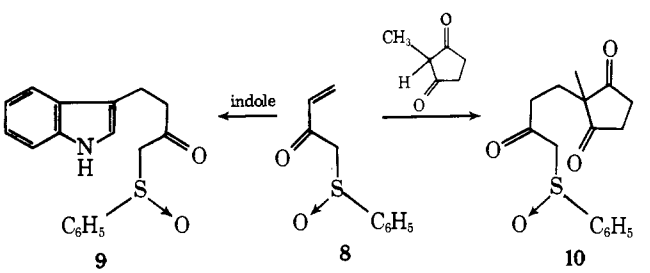
In initial experiments, excess thiophenoxide reacted with **4** to provide **5** in 86% yield. *m*-Chloroperbenzoic acid oxidation of **5** proceeded virtually quantitatively, giving bis sulfoxide **6,** as a mixture of stereomers. As formulated in Scheme II, reversible [2,3] sigmatropic rearrangement[4] of **6** can proceed in both possible modes when this substance is heated in carbon tetrachloride–cyclohexene. However, without thiophilic trapping[5] of sulfenate **7b,** only intramolecular decomposition[9] of **7a** to **8** occurs (85% yield from **6**).

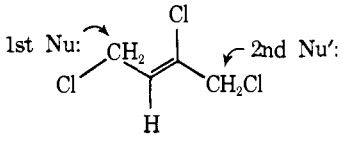
1-Phenylsulfinyl-3-buten-2-one (**8**) possesses the usual properties of both an electrophilic Michael acceptor and an

Scheme II



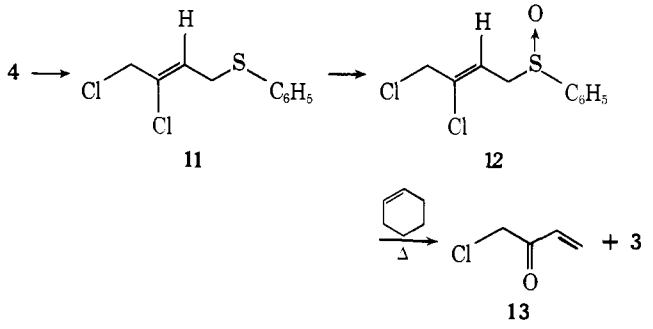
active methylene compound capable of undergoing electrophilic substitution[16] as well as Pummerer reactions.[17] The first property is exemplified by successful conversions of **8** to adducts **9** (in 80% yield) and **10** (nearly quantitative, but difficult to purify because of aldolization, etc.). These conjugate additions have potential relevance to alkaloid and steroid synthesis. Further transformations of **10,** for the latter purpose,[18] were curtailed in favor of a more promising approach involving stepwise regiospecific attack of nucleophiles upon **4**.





4

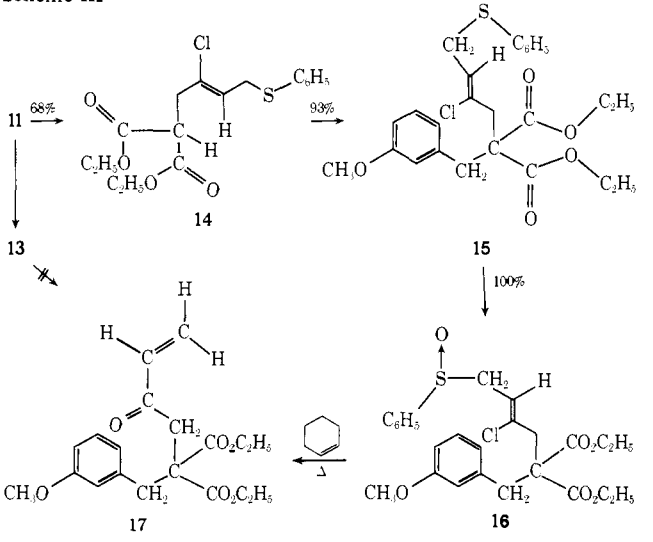
Thiophenoxide (1 equiv) converts **4** to (*Z*)-1,2-dichloro-4-phenylthio-2-butene[10] (**11**), whose derived sulfoxide **12** (quantitative yield) is a latent equivalent of 1-chloro-3-buten-2-one (**13**). The actual conversion of **12** to **13** was easily



11 12 13

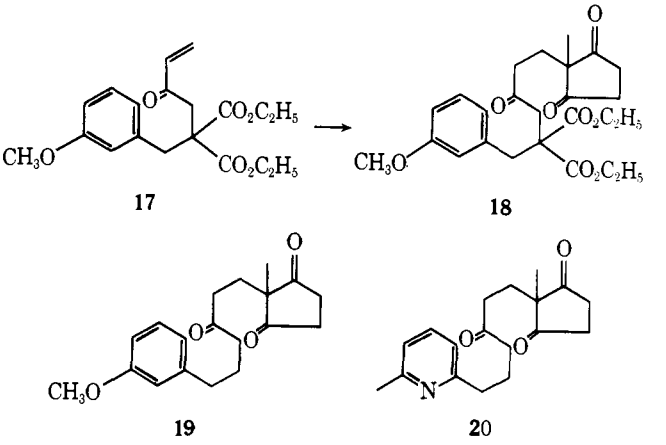
realizable (ca. 90% yield, based on isolated **3**), thus providing further evidence for the regiospecific nucleophilic displacement leading to **11**. However, **13** is an ambident electrophile whose expected reaction course with a particular nucleophile might be unpredictable and capricious in practice. Thus it became preferable to replace the labile chlorine in **11** by a group which would render the resultant enone electrophilic at only one position and usefully nucleophilic as well. To illustrate, we successfully reacted **11** with diethyl malonate, which at this stage could not react with the *latent* enone grouping in **11**. The resulting monoalkylated malonic ester **14** provides the opportunity for further electrophilic substitution. In practice, alkylation of **14** with *m*-methoxybenzyl bromide proceeded in high yield to give **15** (a sequence preferable to attacking **11** with a bulkier benyzl malonate anion). It is extremely unlikely that **13** could have provided **17** free of competitive, unwanted Michael addition, as was accomplished in the sequence **14** → **17** depicted in Scheme III. When **15** was oxidized to sulfoxide

Scheme III



14 15 17 16

16, the latter was found to be quite resistant toward rearrangement at room temperature (see above), raising the possibility of further α alkylation if desired. In refluxing carbon tetrachloride–cyclohexene for ca. 8 h, **16** rearranged and eliminated phenylsulfenyl chloride (→**3**), affording the relatively stable vinyl ketone **17** in 84% yield. Once **17** had been obtained, an intended conjugate addition with other nucleophiles was, of course, possible. Thus, 2-methyl-1,3-cyclopentanedione smoothly reacted with **17** to give the prochiral, polyfunctional trione **18** (52% overall from **15** without isolation

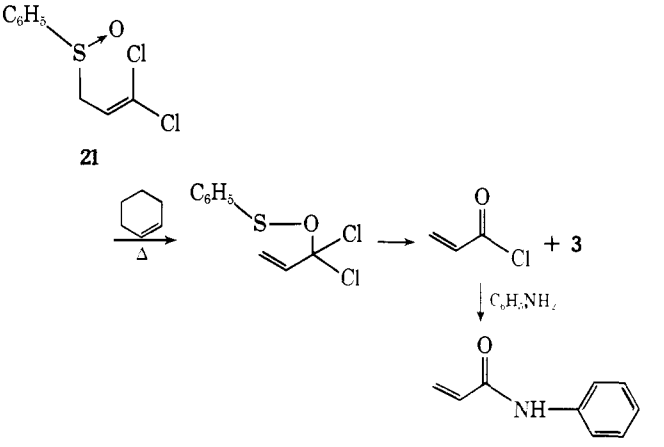


17 18 19 20

of intermediates). It can be seen that **18** (or analogous derivatives originating from **11** and active methylene compounds other than malonate) has potential capabilities similar to firmly established Torgov–Smith estrane intermediates[19] such as **19** as well as the pyridine trione **20**, which has been cyclized with high asymmetric specificity.[20]

At this stage, the synthetic utility of γ-chloroallyl sulfoxides, which can be assembled in various ways, is clearly indicated. During the sequence proceeding from **4** to **18**, we have kept the latent enone system of **17** unavailable (**11, 14**) while malonate displacements and alkylations were performed at another electrophilic site. It is clear that active methylene compounds other than malonic esters can react with **11**, providing access to a variety of analogues of **17** and **18** having potential as steroid intermediates.

Finally, we have also observed that γ,γ-dichloroallyl sulfoxides can lead to α,β-unsaturated acid chlorides, as predicted by the transformations in Scheme I. Conversion of **21** to acrylanilide in 65% yield illustrates[21] the possibilities for nucleophilic quenching, although we have not extended investigations in this direction and do not plan to.



21

In future publications, we will report on the utility of **18** and related compounds in steroid synthesis.

Experimental Section

General Considerations. Melting points, determined on a "Mel-Temp" capillary tube apparatus, and boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-5A (or Perkin-Elmer Model 267) spectrometer and were calibrated using the 1603 cm^{-1} band of polystyrene. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 instrument. NMR spectra were obtained with Varian T-60 or Joelco 100-MHz spectrometer, using Me_4Si as internal

standard in chloroform-*d* or other solvents as noted. Mass spectra were obtained on a Perkin-Elmer RMU-6E mass spectrometer at 70 eV ionization potential. Elemental analyses were performed by Instranal Laboratories (Renssalear, N.Y.) or Atlantic Microlab (Atlanta, Ga.). When referring to "standard workup", a reaction mixture was partitioned between organic and aqueous layers; the former was washed with saturated sodium chloride solution, dilute acid or base where necessary, and finally dried over anhydrous sodium sulfate or magnesium sulfate. After solvent removal, product mixtures were subjected to GLC, TLC, and column chromatography as noted. Recorded temperatures in "kugelrohr" bulb-to-bulb distillation refer to the heating oven.

1,2,4-Trichloro-2-butene[22] **(4).** A mixture of 2,3,4-trichloro-1-butene (160 g, 1 mol), triphenylphosphine (8.0 g, 0.031 mol), and hydroquinone (1 g) was stirred under argon at 150–160 °C for 6 h. The dark solution was then distilled, giving 134.5 g (84% recovery) of trichlorobutenes, bp 55–90 °C (10 Torr). VPC analysis indicated this to be a 75:25 mixture of 1,2,4-trichloro-2-butene (**4**) and 2,3,4-trichloro-1-butene, respectively. Fractionation with a 30-cm jacketed, helices-packed column afforded 86.9 g (54%) of pure **4**, bp 89 °C (30 Torr) (lit.[13] 65–67 °C (10 Torr)): ir (neat) 1648 cm^{-1}; NMR ($CDCl_3$) δ 6.12 (tt, J = 7.4 and 0.8 Hz, 1 H), 4.18 (d, J = 7.4 Hz, 2 H), and 4.18 (d, J = 0.8 Hz, 2 H).

2-Chloro-1,4-bis(phenylthio)-2-butene (5). An ethanolic thiophenoxide solution was obtained by dropwise addition of 6.8 ml (66 mmol) of freshly distilled thiophenol in 30 ml of ether to freshly prepared sodium ethoxide (from 1.52 g, 0.066 g-atom, of sodium) in 30 ml of anhydrous ethanol under argon. 1,2,4-Trichloro-2-butene (4.78 g, 30 mmol) in 10 ml of ether was gradually added to the above thiophenoxide and the resultant solution was stirred overnight. Aqueous hydrolysis and ether extraction, followed by standard workup gave 7.92 g (86%) of **5** as a pale yellow oil, bp 148 °C (0.01 Torr), pure by TLC: ir (neat) 1642 (w), 738 (s), and 689 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.7 (br s, 10 H), 5.62 (br t, J = 7 Hz, 1 H), 3.58 (br s, 2 H), and 3.53 (d, J = 7 Hz, 2 H).

For analytical purposes, a sample of **5** in methylene chloride was oxidized (100% yield) with *m*-chloroperbenzoic acid to the crystalline bis sulfone, mp 149–150 °C (from methanol).

Anal: ($C_{16}H_{15}S_2ClO_4$) C, H.

Preparation of 1-Phenylsulfinyl-3-buten-2-one (8). *m*-Chloroperbenzoic acid (5.18 g, 30 mmol) in 250 ml of methylene chloride was gradually added to 15 mmol (4.60 g) of **5** (in methylene chloride) during 2 h at room temperature. After 1 h more, the reaction mixture was poured into 50 ml of 10% sodium sulfite and then subjected to standard workup. Solvent removal in vacuo afforded 5.09 g (~100%) of crude bis sulfoxide **6**, which was suitable for preparing **8**. However, if the oily **6** was dissolved in 15 ml of carbon tetrachloride containing 1 ml of cyclohexene and kept overnight at 0°, **6** could be obtained as a waxy white solid (ca. 70% of theory, perhaps mainly the less soluble of the two diastereomeric forms of **6**): ir (KBr) 1640 (w, >C=C<) and 1035 (s, >S→O) cm^{-1}.

Bis sulfoxide **6** (678 mg, 2 mmol) dissolved in 10 ml of carbon tetrachloride containing cyclohexene (330 mg, 4 mmol) and a trace of hydroquinone was refluxed for 3 h under argon. Solvent evaporation afforded 820 mg (quantitative yield) of an oily mixture of **8** and *trans*-2-chloro-1-thiophenylcyclohexane (**3**). This oil was dissolved in several milliliters of ether and stored in a freezer for ca. 2 days, whereupon rosette-like crystals of pure **8** were obtained (332 mg, 85% yield), mp 43.5 °C (from methylene chloride–ether): uv λ_{max} (95% C_2H_5OH) 216 nm (ϵ 14 600): ir (neat) 1675 (>C=O), 1613 (>C=C<), and 1040 cm^{-1} (>S→O); NMR ($CDCl_3$) δ 7.53 (m, 5 H), 6.37–5.77 (m, ABC system, 3 vinyl H), and 4.08 (AB quartet with J_{AB} = 13.7 Hz); mass spectrum (70 eV) *m/e*, M^+ at 195, 178, and 125 (base peak).

Anal: ($C_{10}H_{10}SO_2$) C, H.

Reaction of 1-Phenylsulfinyl-3-buten-2-one (8) with Carbon Nucleophiles. A. With 2-Methyl-1,3-cyclopentanedione. A mixture of 2-methyl-1,3-cyclopentanedione (224 mg, 2 mmol), pyridine (0.2 ml, 2.6 mmol), and **8** (388 mg, 2 mmol) in 10 ml of benzene was refluxed under argon for 6 h. The cooled mixture was filtered to remove a trace of unreacted dione, and then the solvent was evaporated to leave 635 mg of crude Michael adduct **10**: ir (neat) 1758, 1720 (>C=O), 1034 (>S→O), and 747 and 688 cm^{-1} (aryl); NMR ($CDCl_3$), δ 7.54 (s, 5 H), 3.80 (s, 2 H), 2.77 (s, 4 H), 2.48 (t, J = 7 Hz, 2 H), 1.82 (t, J = 7 Hz, 2 H), and 1.05 (s, 3 H).

A sample of **10** was reduced with aluminum amalgam in 10% aqueous tetrahydrofuran[23] and the product worked up to provide mainly 2-(3′-oxobutyl)-2-methyl-1,3-cyclopentanedione, identical with an authentic sample.[24]

B. With Indole. 1-Phenylsulfinyl-3-buten-2-one (**8**) (388 mg, 2 mmol), indole (234 mg, 2 mmol), and 2 mg of hydroquinone in 15 ml of benzene were refluxed under argon for 8 h. Cooling afforded 501 mg (80%) of crude product, which was recrystallized from acetone–hexane to give tan crystals, mp 134–135 °C dec: uv λ_{max} (95% C_2H_5OH) 222 (ϵ 34 500), 284 (ϵ 8400), and 292 nm (ϵ 6300); ir (KBr) 3378 (N–H), 1703 (>C=O), and 1030 cm^{-1} (S→O).

Anal: ($C_{18}H_{17}NO_2S$) C, H, N.

Ethyl 2-Carbethoxy-4-chloro-6-phenylthio-4-hexenoate (14). An ethanol solution of sodium thiophenoxide (50 mmol), prepared as above, was added to a cold (−78°) ether solution containing 8.37 g (53 mmol) of 1,2,4-trichloro-2-butene (**4**) under argon. After warming to −20° during 5 h, the reaction mixture was hydrolyzed and worked up in the usual manner. Short-path distillation of the oily product (containing some unreacted **4** and disulfide **5**) afforded 10.065 g (86%) of **11**, bp 79–80 °C (0.01 Torr): ir (neat) 1645, 740, and 690 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (br s, 5 H), 5.98 (br t, J = 7.4 Hz, 1 H), 4.10 (br s, 2 H), and 3.67 (br d, J = 7.4, 2 H).

For analytical purposes, a 1-g sample of **11** was oxidized with excess *m*-chloroperbenzoic acid in methylene chloride to the crystalline sulfone, mp 74 °C (from C_2H_5OH).

Anal: ($C_{10}H_{10}SO_2Cl_2$) C, H.

Diethyl sodiomalonate (40 mmol) was prepared from sodium hydride and diethyl malonate in 20 ml of 1,2-dimethoxyethane (DME), and the solution was cooled to −78°. A DME solution of **11** (4.66 g, 20 mmol) was gradually added, the solution was allowed to warm to room temperature, and was kept there for 40 h. Hydrolysis and standard workup gave a colorless oil, which was distilled to provide 5.36 g (68%) of malonic ester **14**, bp 148–150 °C (0.01 Torr), pure by GLC and TLC: ir (neat) 1733, 1652, 1232, 1156, 1030, 858, 741, and 691 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (br s, 5 H), 5.73 (t, J = 7.2 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 4 H), 3.67 (t, J = 7.6 Hz, 1 H), 3.62 (br d, J = 7.2 Hz, 2 H), 2.88 (d, J = 7.6 Hz, 2 H), and 1.20 (q, J = 7.2 Hz, 6 H).

The crystalline sulfone, prepared from **14** by *m*-chloroperbenzoic acid oxidation, had mp 57–59 °C (from ether–hexane).

Anal: ($C_{12}H_{21}ClO_6S$) C, H.

Alkylation of 14 with *m*-Methoxybenzyl Bromide. Conversion of **14** (5.35 g, 15 mmol) to its conjugate base was accomplished with sodium hydride (695 mg of 57% Nujol dispersion, 16.5 mmol) in DME at 0° under argon. After hydrogen evolution had ceased, 3.7 g (20 mmol) of *m*-methoxybenzyl bromide[25] in DME was added and the reaction mixture was kept overnight at room temperature prior to hydrolysis and standard workup. The crude oily product (three components by TLC) was chromatographied over Florisil, using 1:1 hexane–ether as eluent, providing 6.62 g (93%) of pure (TLC) **15**: ir (neat) 1733, 1640, 1265, 1206, 1184, 860, 780, 743, and 695 cm^{-1}; NMR ($CDCl_3$) δ 7.40–6.53 (br m, 9 H), 5.72 (t, J = 7 Hz, 1 H), 4.12 (q, J = 7 Hz, 4 H), 3.72 (s, 3 H), 3.68 (d, J = 7 Hz, 2 H), 3.25 (s, 2 H), 2.97 (s, 2 H), and 1.18 (t, J = 7 Hz, 6 H).

The crystalline sulfone, derived from **15** by *m*-chloroperbenzoic acid oxidation, had mp 64–65 °C (from ether–pentane).

Anal: ($C_{25}H_{29}ClO_7S$) C, H.

5,5-Dicarbethoxy-6-(3′-methoxy)phenyl-1-hexen-3-one (17). Quantities of *m*-chloroperbenzoic acid (1 mmol) and sulfide **15** (477 mg, 1 mmol) were reacted in methylene chloride and the reaction was worked up as usual to provide 499 mg (quantitative) of crude sulfoxide **16** (ir showed sulfoxide at 1037 cm^{-1}), which was immediately used for the rearrangement step. Refluxing **16** in carbon tetrachloride under argon with 4 mmol of cyclohexene and 2 mg of hydroquinone for 8 h, followed by solvent removal at 50 °C (1 Torr) afforded 582 mg of enone **17** and *trans*-2-chloro-1-thiophenylcyclohexane (**3**). Gradient elution chromatography of this mixture over Florisil with hexane–ether, ultimately (with pure ether) provided 291 mg (84%) of pure **17**; uv (95% C_2H_5OH) λ_{max} 215 nm (ϵ 15 300): ir (neat) 1730, 1698, 1680, and 1607 cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.47 (br m, 4 H), 6.35–5.67 (m, ABC system, 3 H), 4.22 (q, J = 7 Hz, 4 H), 3.72 (s, 3 H), 3.42 (s, 2 H), 3.15 (s, 2 H), 1.25 (t, J = 7 Hz, 6 H); mass spectrum (70 eV) *m/e*, M^+ at 348, base peak at 121 (methoxytropylium ion).

The analytical sample of **17** was prepared by "kugelrohr" bulb-to-bulb distillation (160 °C (0.01 Torr)).

Anal: ($C_{19}H_{24}O_6$) C, H.

Addition of 2-Methyl-1,3-cyclopentanedione to Vinyl Ketone 17 (→18). Sulfide **15** (954 mg, 2 mmol) was converted to sulfoxide **16** and the latter rearranged as above to the mixture of **17** and **3**. This, in turn, was dissolved in 10 ml of toluene and 1 ml of pyridine and 250 mg (2.2 mmol) of 2-methyl-1,3-cyclopentanedione was added; the resulting solution was stirred at 100° for 48 h under argon. After removal of solvent in vacuo, the residue was triturated with cold methylene chloride and unreacted dione was recovered by filtration. Florisil chromatography of the filtrate, with gradient elution employing ether–hexane mixtures, eventually afforded 479 mg (52%) of **18**, which was further purified for analysis by "kugelrohr" distillation (210 °C (0.01 Torr)): ir (neat) 1750, 1730, 1720, 1262, 1183, 860, 784, and 700 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.25 (t, J = 7 Hz, 6 H), 1.83 (t, J = 6 Hz, 2 H), 2.37 (t, J = 6 Hz, 2 H), 2.77 (s, 4 H), 2.88 (s, 2 H), 3.33 (s, 2 H), 3.75 (s, 3 H), 4.18 (q, J = 7 Hz, 4 H), and 6.5–7.3 (complex m, 4 H).

Anal: ($C_{25}H_{32}O_8$) C, H.

Acknowledgment. We are grateful to the National Science Foundation for support of this research and for providing funds to the Chemistry Department to help purchase the Varian T-60 NMR spectrometer. We also appreciate a gift of chemicals and unpublished data from Dr. C. A. Stewart, Jr.

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(11) For example, 1-chloro-3-phenylsulfinylcyclohexene and 4-chloro-2-phenylsulfinyl-3-heptene begin to rearrange *while* the precursor sulfides are being oxidized (*m*-chloroperbenzoic acid in CH_2Cl_2 at 0°), and they are approximately half converted to ketones (ir) within 30 min after careful, low-temperature workup. In contrast, 2-chloro-3-phenylsulfinylcyclohexene is readily prepared and handled without apparent change (unpublished observations by L. P. Sendlak).
(12) It is not unreasonable to assume that once an α-chloro sulfenate is produced its fragments *intramolecularly* without reverting to sulfoxide, although we have no evidence bearing on this point. Even *intermolecular* trapping of allylic sulfenates by external thiophiles can effectively prevent their return to sulfoxides (ref 5).
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Molecular Rearrangements with Ethoxycarbonyl Group Migrations. 1. The Rearrangement of Epoxides

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Abstract: A superficial analysis of the reaction products for the boron trifluoride catalyzed isomerization of 2-substituted-3-phenyl-3-methylglycidates led to an acceptable sequence of migratory aptitudes, phenyl > ethyl and ethoxycarbonyl > methyl and hydrogen. However, its predictive value was nil, since the actual course of most rearrangement reactions was dependent on the temperature as well as on the solvent used. With **1h**, **1m**, and **1e**, the products formed with lowest activation energy were the allylic alcohols **4**, and next the α-keto esters **2**. The β-keto esters **3**, which were the most stable products, required the highest activation energy for their formation. This appears to be the first study of the effect of the temperature on the course of a pinacol-like rearrangement, and leads to the hope that in many cases it will be possible to achieve a selective control of the products formed in a competitive set of rearrangements by the proper selection of the solvent and reaction temperature.

Introduction

Several years ago, we observed the unexpected acid-catalyzed rearrangement of glycidic esters with ethoxycarbonyl group migration, which yielded β-keto esters rather than pyruvic esters which were then anticipated.[1] The novelty of this rearrangement encouraged us to pursue a study in this area, and we now wish to describe the results of this work.

Our initial observations of the ethoxycarbonyl group migration in epoxide rearrangements were made with a series of glycidic esters which did not all have the same substituents at the 3 position, the initial site of carbonium ion formation, and the sequence of migratory aptitudes established then was therefore questionable. The esters **1** were subsequently examined because the substitution at the 3 position theoretically favored the initial formation of a stabilized tertiary, benzylic,