Radical Additions to Alkenylidenecyclopropanes[1]

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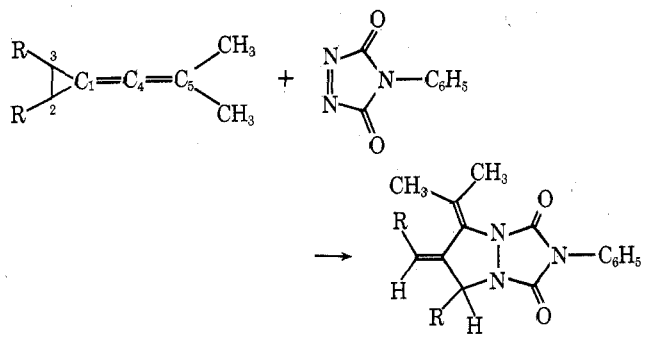
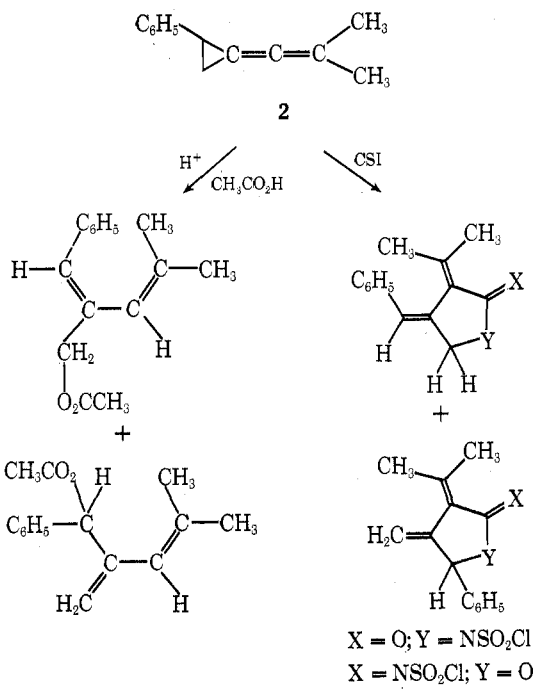
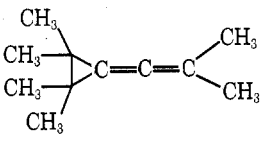
Recent studies in our laboratories have been directed toward gaining an understanding of the electronic structure of alkenylidenecyclopropanes and factors which determine reactivity and mode of reaction. Alkenylidenecyclopropanes (1) undergo cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) across the methylenecyclopropane portion of 1 regardless of the nature and number of groups attached to the three-membered ring.[2] Kinetic[3] and theoretical studies[4] have provided a detailed understanding of the bonding in 1



and of the mechanism of the cycloaddition reaction. In contrast to the uniform situselectivity exhibited in the cycloaddition reactions of 1 with PTAD, the site of attack by electrophilic reagents depends on the number and nature of the groups attached to the three-membered ring.[5] For example, the phenyl-substituted derivative 2 undergoes attack exclusively at the p orbital on C_4 of the C_1–C_4 double bond by electrophilic reagents such as proton and chlorosulfonyl isocyanate (CSI).[5] The incipient cyclopropyl cation undergoes ring opening subsequently producing substituted butadienes. The presence of a methyl group on the ring of 1 results in a predominant shift of electrophilic attack to C_5 (85%) to produce a β-lactam derivative, while with the tetramethyl derivative 3 electrophilic attack occurs exclusively at C_5.[5] In the



X = O; Y = NSO_2Cl
X = NSO_2Cl; Y = O



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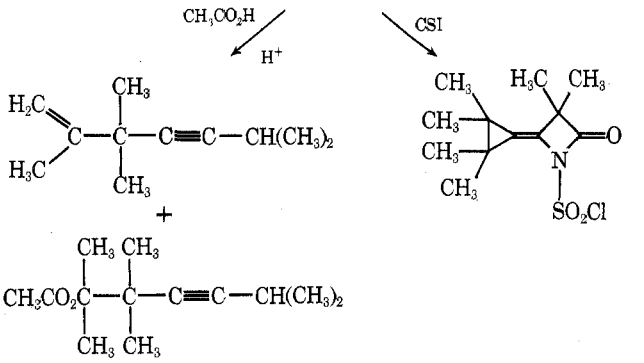
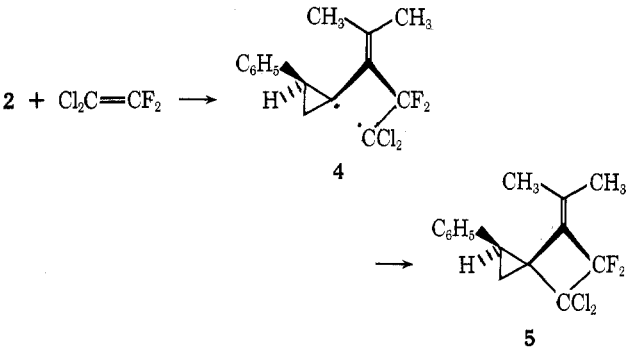


only study of the chemistry of alkenylidenecyclopropanes involving the formation of a radical intermediate 2 was found to react with 1,1-dichloro-2,2-difluoroethene to produce essentially only 5 via the diradical intermediate 4.[6] The present



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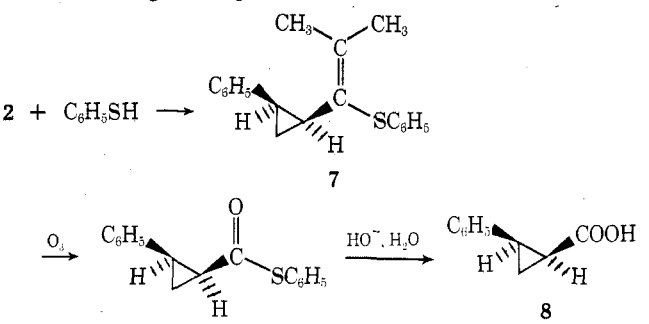
paper describes the course of reaction of substituted alkenylidenecyclopropanes in radical chain addition reactions with thiophenol.

Alkenylidenecyclopropanes 2, 6, and 3 rapidly react (15 min at 25 °C) with thiophenol either neat or in benzene solution open to the laboratory light and atmosphere. Measurement of the rates of reactions (by NMR) shows the presence of an induction period, and the addition of dissolved sulfur and freeze-degassing result in longer reaction times, all characteristic of typical free-radical chain addition reactions of thiophenol.[7] Also, the products formed in the reactions of 2, 6, and 3 with thiophenol do not possess structures typically derived in electrophilic additions to these substrates,[5] but are similar to that derived from 2 with 1,1-dichloro-2,2-difluoroethene.[6]

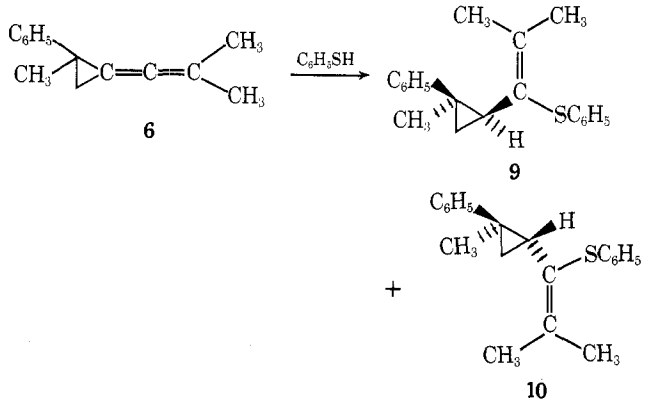
Thiophenol reacts with 2 to produce only 7. The complexity of the NMR spectrum of 7 precluded assignment of the stereochemistry and stereochemical purity of the adduct. Ozonolysis of the product followed by basic hydrolysis gave pure (>98%) *cis*-2-phenylcyclopropanecarboxylic acid (8) demonstrating that 7 possesses the cis stereochemistry.



7

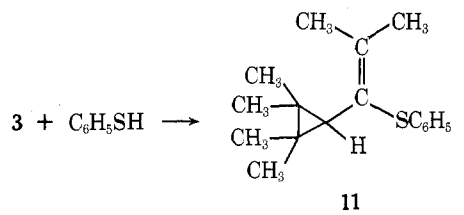
8

Reaction of **6** with thiophenol produces a mixture of **9** and **10** (65:35 ratio) which could not be separated. The stereochemistry of the two adducts is clearly indicated by the long-range shielding effects of the ring phenyl on the isopropylidene methyls, and of the thiophenyl group on the ring methyl.[8] In **9** the isopropylidene methyls appear at δ 1.84 and

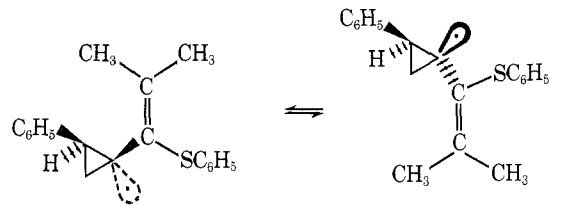


1.88, whereas in **10** they appear at δ 1.87 and 2.08. Similarly, the ring methyl of **9** appears at lower field (δ 1.47) than in **10** (δ 1.33). The ring hydrogens of the major isomer **9** are clearly evident as an ABX system, but those of **10** are obscured by the resonances of **9** and the methyl groups.

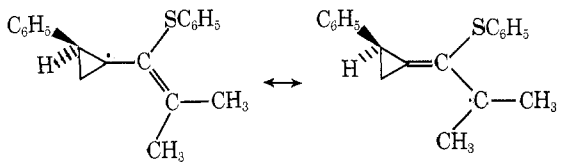
Reaction of **3** with thiophenol produces only **11**, which on ozonolysis produces 1 equiv of acetone.



In contrast to the different modes of reaction of **2, 3,** and **6** with CSI, attack by thiophenoxy radical occurs at the same position to give products of similar structure. The structures of the products, however, do not indicate whether attack occurs on the C_1–C_4 double bond to initially produce radical **12,** or the C_4–C_5 double bond to give radical **13,** both of which are initially non-resonance-stabilized radicals. (Resonance stabilization of the radical centers in **12** and **13** requires an internal rotation of 90°, a process which may or may not be occurring simultaneously with attack by the thiophenoxy radical). Whether the radical center in the ultimate radical intermediate is nonplanar and non-resonance-stabilized, or is planar and resonance stabilized (i.e. **14**), is difficult to assess. Estimation of the relative energies of the two radicals leads to similar values. Addition to produce the nonplanar radical involves a reduction of ring strain from ~38.2 kcal/mol (42 kcal/mol ring strain for the methylenecyclopropane[9] minus the resonance energy of the alkenylidenecyclopropane system of 3.8 kcal/mol[4]) to ~27 kcal/mol (assumed to be the same as the ring strain of cyclopropane), a change of ~11.2 kcal/mol. Formation of the planar radical results in retention of the methylenecyclopropane ring strain and the resonance energy of the alkenylidenecyclopropane ring system, but yields an allyl radical possessing a resonance energy of ≥11.6 kcal/mol.[10] The stereochemistry of **7** is undoubtedly determined in the hydrogen atom abstraction step. Whether a rapidly inverting pair of nonplanar radicals[11] or a planar radical is involved, approach to the radical must occur highly preferentially at the face opposite the phenyl group on the ring thus producing **7.**



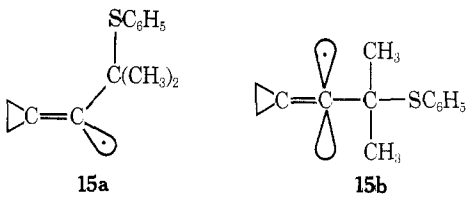
rapidly inverting, nonplanar radical



planar linear radical

In the radical derived from **6** the larger steric effect of the phenyl relative to the methyl group directs dominant hydrogen atom abstraction at the face opposite the phenyl to produce the major product **9.**

In view of the substantial directive effects exerted by alkyl groups attached to the three-membered ring on the position of electrophilic attack (i.e., exclusively at C_5 in **3**),[2,5] it is at first somewhat surprising that no radical attack occurs at C_5 of **3** to produce radical intermediate **15.** This would appear to be



due to the fact that vinyl cations prefer linear geometries[12] which would provide for excellent overlap of the vacant p orbital on C_4 with the orbitals of the three-membered ring,[4] whereas vinyl radicals prefer nonlinear geometries[13] (i.e., **15a**) in which overlap of the sp^2 hybrid orbital on C_4 with the orbitals of the three-membered ring would not be as favorable as in the linear radical **15b.**

Experimental Section

Reaction of 2 with Thiophenol. A solution of 500 mg (2.96 mmol) of **2** and 325 mg (2.96 mmol) of thiophenol in 10 ml of benzene was allowed to stand at 25 °C until no further reaction occurred as indicated by NMR analysis (0.5 h). The benzene solution was washed with 10% sodium hydroxide and water, and was dried ($MgSO_4$). The NMR spectrum of the residue obtained after removal of the solvent indicated the presence of **2** and **7.** A 200-mg portion of the residue was chromatographed on activity III alumina with hexane as eluent giving 17 mg of **2,** 24 mg of diphenyl disulfide (identified by its melting point

and NMR spectrum), and 116 mg of 7 as a pale yellow, viscous oil: NMR ($CDCl_3$) δ 1.25 (m, 2 H), 1.68 (bs, 3 H), 1.82 (d, J = 0.9 Hz, 3 H), 2.17 (m, 2 H), and 7.04 and 7.11 (s's, 5 H each); mass spectrum M.+ 280.1257, (calcd for $C_{19}H_{20}S$, 280.1254).

Conversion of 7 to *cis*-2-Phenylcyclopropanecarboxylic Acid (8). A solution of 80 mg of 7 in 2 ml of 1:1 dichloromethane–pyridine was cooled in a dry ice–acetone bath and was treated with a slight excess of ozone.[14] The reaction mixture was allowed to warm to 25 °C, poured into 25 ml of ether, and washed several times with 1 N hydrochloric acid. The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure, giving a yellow, viscous oil (ir 1702 cm^{-1}).

The residue was dissolved in 10 ml of 10% sodium hydroxide in 50% aqueous ethanol. The mixture was refluxed for 40 min, cooled, poured into 20 ml of water, and extracted with ether. The aqueous layer was acidified with hydrochloric acid and was extracted with two 10-ml portions of ether. The ether extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure, leaving 15 mg of a tan solid whose NMR spectrum was identical with that of *cis*-2-phenylcyclopropanecarboxylic acid (8).[15] No peaks representing *trans*-2-phenylcyclopropanecarboxylic acid were present.

Reaction of 6 with Thiophenol. To a solution of 200 mg of 6 in 0.5 ml of hexadeuteriobenzene in an NMR tube was added 120 mg of thiophenol. The reaction mixture was thoroughly mixed and the rate of reaction was monitored with time by NMR. The reaction displayed an induction period of ~2 min, being essentially complete in 15 min at 39 °C. The resulting mixture was poured into 10 ml of ether and was extracted twice with 5-ml portions of 1 M sodium hydroxide, washed with water and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was distilled in a microstill at 115 °C (0.07 mm), giving a pale yellow, viscous oil: NMR of 9 ($CDCl_3$) δ 0.88 (dd, J = 5.0 and 8.1 Hz), 1.08 (dd, J = 2.3 and 8.1 Hz), 1.47 (s), 1.63 (dd, J = 2.3 and 5.0 Hz), 1.84 and 1.88 (broadened s's), 7.18; **10**, δ 1.33 (s), 1.87 and 2.08 (broadened s's), 71.8 (the AMX double doublets are obscured by the more intense resonances of 9); mass spectrum M.+ 294.1426 (calcd for $C_{20}H_{22}S$, 294.1442).

Reaction of 3 with Thiophenol. A solution of 430 mg (2.86 mmol) of 3 in 5 ml of benzene was added to 314 mg (2.86 mmol) of thiophenol dissolved in 5 ml of benzene. The reaction mixture was allowed to stand at room temperature for 3 h, at which time analysis by NMR indicated complete reaction. The benzene solution was washed with 15 ml of 10% sodium hydroxide and water, and was dried ($MgSO_4$). The benzene was removed under reduced pressure giving 656 mg of a pale yellow oil (11): bp ~50 °C (0.05 mm) in a molecular still; NMR ($CDCl_3$) δ 0.90 (s, 6 H), 0.98 (s, 6 H), 1.13 (m, 1 H), 1.83 (d, J = 1.6 Hz, 3 H), 1.92 (d, J = 2.2 Hz, 3 H), and 7.07 (m, 5 H); mass spectrum M.+ 260.1597 (calcd for $C_{17}H_{14}S$, 260.1608).

Ozonolysis of 11. A solution of 76 mg (0.30 mmol) of 11 in 1.75 ml of dichloromethane and 0.25 ml of pyridine[14] was cooled in a dry ice–acetone bath and ozone was bubbled through the solution for 15 s. The reaction mixture was allowed to warm to 25 °C and was analyzed directly by GLC on a Carbowax 20M column showing the presence of acetone by comparison of retention time with authentic material and admixture.

Registry No.—2, 4544-23-4; 3, 13303,30-5; 6, 40922-91-6; 7, 58873-30-6; 8, 939-89-9; 9, 58873-31-7; 11, 58873-32-8; thiophenol, 108-98-5.

References and Notes

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Trichloromethyl Chloroformate. Reaction with Amines, Amino Acids, and Amino Alcohols

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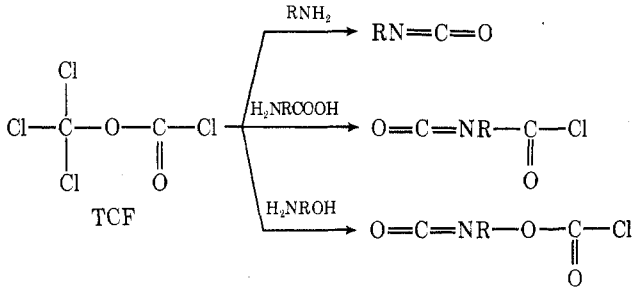
The title compound, trichloromethyl chloroformate (TCF), is of interest in that it is a potential substitute for phosgene, which presents a severe hazard in laboratory use because of its volatility and high toxicity. Although TCF is also toxic,[1] it is a dense liquid (bp 128 °C, d_{15}^{15} 1.65) with vapor pressure of only 10 mm at 20 °C. Thus TCF is more easily handled with safety, and seems to have significant advantages over phosgene.

Hentschel studied the decomposition of TCF and reactions with some organic compounds and found that phenyl isocyanate was formed by the action of TCF on 1,3-diphenylurea.[2] The reaction with alcohols to give carbonates has also been reported.[3] TCF was recently reported to be used as a substitute for phosgene in the preparation of *N*-carboxy-α-amino acid anhydrides; 1 mol of TCF provided the equivalent of 2 mol of phosgene in the NCA synthesis.[4]

To extend our knowledge of the reactivity of TCF, it was of interest to compare other reactions of TCF with those of phosgene. This paper describes the reaction of TCF with amines, amino acids, and amino alcohols to give the corresponding isocyanates, isocyanato acid chlorides, and isocyanato chloroformates.



The reactions of TCF with aniline were carried out under conditions similar to those employed in the phosgene method. As expected, phenyl isocyanate was obtained in high yields (78–89%) either from the hydrochloride or the free base. It was also confirmed that 0.5 mol of TCF was sufficient to convert 1 mol of the amine to the isocyanate.

Treatment of *p*-phenylenediamine hydrochloride with TCF in dioxane, on the other hand, gave only poor yields (23% or less) of the diisocyanate, even though the reaction was carried out under almost the same conditions used with phosgene. When the free base was used instead of the hydrochloride, the yield of the diisocyanate was improved to 47%. An attempted reaction of hexamethylenediamine hydrochloride with TCF in dioxane was unsuccessful and the hydrochloride was recovered. This result is presumably due to the high basicity of hexamethylenediamine compared to that of aromatic amines,