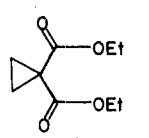
A Spiroactivated Vinylcyclopropane

Summary: The spiroactivated vinylcyclopropane, 6,6-dimethyl-2-vinyl-5,7-dioxaspiro[2.5]octane-4.8-dione is readily available. It reacts with nucleophiles cleanly at carbon 2. A much faster rate of racemization is observed in the optically active compound than was observed for the optically active dimethyl 2-vinylcyclopropane-1,1-dicarboxylate.

Sir: Recently we described the preparation of the spiroacylal **2** and its reactions with nucleophiles.[1] The enormous facility of the ring-opening reactions of compound **2** relative to its diester analog, **1**, is presumably a consequence of the enhanced stabilization provided by the conformationally constrained cyclic acylal system for the anionic leaving group. We have, for some time, been interested in the multiple electrophilic capabilities of activated vinylcyclopropanes.[2,3] For instance, compound **3** is susceptible to nucleophilic attack in both the 1,5 and 1,7 modes. The former pathway is the predominant one, in the most obviously nucleophilic cases.[4-6] However, the two pathways are somewhat competitive under the relatively vigorous reaction conditions required to rupture the cyclopropane ring. This behavior sharply compromises the utility of system **3** for synthetic purposes.



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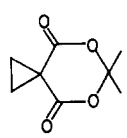

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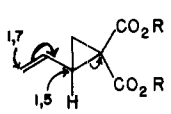
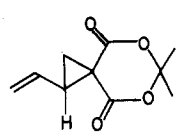


3 R = Et
4* R = Me (optically active)
5 R = H (**5*** optically active)



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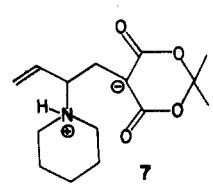
Accordingly, the behavior of the spiroactivated vinylcyclopropane, **6**, was investigated. This compound, mp 51–53°,[7a,b] was prepared in 60% yield by the reaction of diacid **5** with isopropenyl acetate under the influence of concentrated sulfuric acid. Below it is shown that compound **6** reacts with nucleophiles exclusively in the 1,5 sense under very mild conditions, and in high yield. Furthermore the effects of spiroactivation on the thermal fragmentation of the three-membered ring has also been demonstrated by the remarkably facile racemization of optically active **6*** relative to optically active **4***.

Compound **6** reacts with piperidine (room temperature, 4 hr) in benzene to give a 95% yield of **7**,[7a,b] mp 168–170°. It will be noted that the analogous reaction with **3**[3,4] is achieved only by heating at 105°.

Compound **6** reacts with dimethyl sodiomalonate in dimethoxyethane at room temperature, whereas the analogous reaction with compound **3** requires temperatures of 75–85°.[3,5] Moreover, while the reaction in the case of **3** occurs via competitive 1,5 and 1,7 addition (5:1),[3,5] in the case of compound **6** only 1,5 addition occurs, leading to compound **8**,[7a,b] mp 109–111°, in 83% yield. Compound **6** reacts with sodium thiophenoxide in DME at room temperature to give **9**,[7a,b] mp 72–74°. The corresponding reaction in the case of **3**, produces ~20% 1,7 product.[3,5] As in the case of **2**,[1] hydrogenolysis of the cyclopropane in **6** is achieved under relatively mild conditions. Thus, compound **6** reacts with 2 mol of hydrogen (5% Pd/C–EtOAc, atmospheric pressure, room temperature, 3 hr) to give *n*-butyl Meldrum's acid, **10**.[7b]



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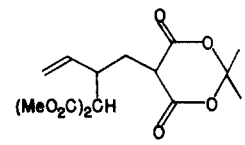

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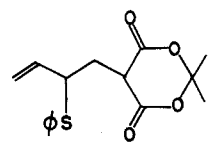

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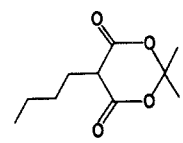

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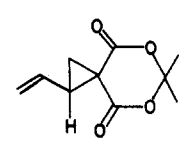
Previously we had prepared[8] optically active **4*** by esterification of the resolved (brucine salt), of diacid **5***. It was of interest to compare the relative rates of racemization of **4*** and **6***, thereby assessing the effects of spiroactivation on unimolecular ionization. Optically active **6***, $[\alpha]D$ (benzene) −18.80°, was prepared from resolved **5**[8a,b] by reaction with isopropenyl acetate in the usual fashion.

At 80° in benzene, the racemization of **6*** is cleanly first order with $t_{1/2} = 1.2 \times 10^2$ min. At 100°, $t_{1/2rac}$, in toluene, is 9 min. We have repeated, for comparison, the racemization of **4***. At 140°, $t_{1/2}$ (xylene) for the racemization of **4*** is 2.7×10^3 min. It would appear that the massive[9] accelerating effect of the spiroacylal system on the racemization rate involves stabilization of the transition state leading to the presumed intermediate, **11**.[10] This must reflect stabilization of intermediate **11** itself[11] (cf. enhanced acidity of Meldrum's acid[12] relative to acylic malonic esters).



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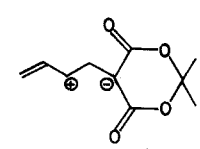

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The effect of spiroactivation, in promoting 1,5 addition to the exclusion of the 1,7 mode, may be a consequence of specific structural features of the system. Alternatively, it may arise from the mild reaction conditions which suffice for **6**. These serve to obscure other processes[3,8] (free-radical reactions, rearrangements, etc.) which compete with the purely nucleophilic reactions of **3**. In any case, the phenomenon of clean 1,5 attack, exhibited by **6**, will increase the value of activated vinylcyclopropanes in synthesis. The use of **6** as a synthetic equivalent of $CH_2{=}CHCH^+\text{-}CH_2CH(CO_2R)_2$, which reacts predictably at the secondary center, will be demonstrated shortly.

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Supplementary Material Available. Experimental procedures for these reactions will appear following these pages in the microfilm edition of this volume of this journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3807.

References and Notes

(1) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, **97**, 3239 (1975).
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(6) For predominant terminal attack upon **3** by cuprates in possible electron transfer processes, see (a) G. Daviaud and P. Miginak, *Tetrahedron Lett.*, 997 (1972); (b) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973). For a recent "cuprate" addition to a monoactivated vinylcyclopropane, see N. Miyaura, M. Itoh, N. Sasaki, and A. Suzuki, *Synthesis*, 316 (1975).
(7) (a) The formula of this compound is established by (a) combustion analysis and (b) spectral properties. The data are provided in the Experimental section which appears in the microfilm edition.
(8) (a) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 821 (1972); (b) G. Rovnyak, Ph.D. Thesis, University of Pittsburgh, 1970.
(9) Unfortunately we are unable to measure the rates for **4*** and **6*** at the same temperature. While the temperature dependence of k_{rac} has not been measured, the minimum ratio would appear to be 10^4.
(10) Cf. A. B. Chmurny and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 4237 (1973), and papers cited therein.
(11) The possibility that this type spiroactivation arises from additional strain imposed on the three-membered ring seems to us unlikely but has not been disproven.
(12) K. Pihalaja and M. Seilo, *Acta. Chem. Scand.*, **23**, 3003 (1969).
(13) An Andrew Mellon Fellow.

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Selective Fluorination of Hydroxy Amines and Hydroxy Amino Acids with Sulfur Tetrafluoride in Liquid Hydrogen Fluoride

Summary: At −78° and atmospheric pressure sulfur tetrafluoride in liquid hydrogen fluoride selectively replaces alcoholic hydroxyl groups in hydroxy amines and hydroxy amino acids by fluorine.

Sir: Sulfur tetrafluoride, SF_4, is the most frequently employed reagent for transforming organic compounds containing certain oxygen functionalities into the corresponding organofluorine compounds. It is regarded as the standard reagent for converting aldehydes, ketones, and carboxylic acids into difluoro and trifluoro compounds, respectively.[1,2] However, fluorination of alcohols by SF_4 was found to be restricted to those containing "acidified" hydroxyl groups.[3] Owing to its low reactivity, SF_4 is employed in high pressure apparatus, generally at temperatures of 50–200°.

We have found that the reactivity of SF_4 toward a variety of alcohols is dramatically and selectively increased when employing liquid hydrogen fluoride (HF) as solvent. Surprisingly, the reactivity of SF_4 with carbonyl compounds and carboxylic acids is not concomitantly increased and thus the SF_4–HF solution becomes a selective fluorinating system toward alcohols.[4] Moreover, the protection of amino groups against electrophilic reagent by use of liquid HF solvent, observed in the C-chlorination[5] and C-fluorination[6] of amines and amino acids, also obtains in this system. (In the absence of this protection amino groups react with SF_4 to form imino sulfur difluorides.[7])

Sulfur tetrafluoride, taken as a gas from a cylinder and measured as a liquid in a graduated trap at −78° (dry ice–acetone bath, ≃2.5 ml, 0.042 mol) was bubbled into 40 ml of liquid HF, kept at −78°. (The HF was taken as a gas from a cylinder, liquefied directly by passing into the cooled reactor, made of polyethylene or KEL-F®.[5]) Threo-β-phenylserine monohydrate (1.99 g, 0.01 mol) was added. (Throughout slight positive pressure of N_2 was maintained.) After a 45-min reaction period at −78°, the solvent was blown off by a stream of N_2, concentrated HCl was added, and the solution was evaporated to dryness in vacuo to give the HCl salt of β-fluorophenylalanine. The free amino acid was liberated in water–pyridine (mp 173–74° dec, yield 65%). Spinco amino acid analysis showed a single symmetrical peak.[8] Also, by a similar procedure, L-threonine was transformed into L-2-amino-3-fluorobutyric acid. The results on free amino acids indicated that there was no protection needed for –COOH groups.[9,10]

The mechanism of the SF_4–ROH reaction has been extensively discussed and it is commonly felt that an alkoxysulfur trifluoride, $ROSF_3$, is the key intermediate and that this intermediate collapses to product via an SNi or SN2 pathway.[1] However in the liquid HF–SF_4 system a carbonium ion mechanism is suggested by the following: (1) The product from the most stable carbonium ion seems to be obtained [the quantitative rearrangement of 3-hydroxypiperidine to 4-fluoropiperidine was observed (indicating a shift of the carbonium ion away from the positive $-NH_2^+-$)]; (2) 2-methylserine affords in addition to a 23% yield of the expected 2-fluoromethylalanine, a 40% yield of 1-aminocyclopropane carboxylic acid (this type of insertion into a C–H bond has been well documented in the literature of carbonium ions[11,12]); (3) in the case of simple alcohols (*n*-hexanol), the products are complex (branched chain fluorides, olefins, and dimers). Since fluorination is not observed in the absence of HF (choline chloride afforded no 2-fluoroethyl trimethyl ammonium product when it was reacted with SF_4 in diglyme at −5°), it is important to consider the role of this acid. It is proposed that HF not only induces the well-known dissociation of SF_4 to the much more electrophilic SF_3^+ (eq 1)[13] but also plays an important role in the ionization of the alkoxysulfur trifluoride (eq 3) by providing a solvent of high dielectric constant and possibly engendering an ionization analogous to the one in eq 1. The latter would provide a better leaving group (eq 4).

$$SF_4 + HF \rightleftharpoons SF_3^+ + HF_2^- \quad (1)$$

$$ROH + SF_3^+ \rightarrow ROSF_3 + H^+ \quad (2)$$

$$ROSF_3 \rightarrow R^+ + SOF_2 + F^- \rightarrow RF \quad (3)$$

$$ROSF_3 + HF \rightarrow ROSF_2^+ + HF_2^- \rightarrow R^+ + SOF_2 \rightarrow \text{etc} \quad (4)$$

This method for the C–OH → C–F transformation[14] (formally "fluorodehydroxylation") is considered a promising tool of antimetabolite synthesis. The physicochemical similarity of the C–OH and C–F bonds has been recognized