The Journal of
Organic
Chemistry

VOLUME 56, NUMBER 6 MARCH 15, 1991



# Communications

## Electrophilic Substitution at an Olefinic Carbon Atom. Some Studies of the Mechanism of the Trifluoroacetylation of Aryl Vinyl Sulfides

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*Received October 2, 1990*

*Summary:* A study of the mechanism of the trifluoroacetylation of aryl vinyl sulfides was made. The rates of trifluoroacetylation of ArSCH=$CH_2$, ArSCH=$CD_2$, *cis*-ArSCH=CHD, and *trans*-ArSCH=CHD were determined. The results imply that this electrophilic substitution reaction proceeds by a single-step mechanism.

Upon reaction with electrophilic reagents, olefins characteristically yield products of addition, whereas aromatic compounds characteristically yield products of substitution. The many reported reactions of vinyl sulfides, vinyl ethers, and vinyl amides with electrophilic reagents are all addition reactions.

However, we reported earlier that ketene dithioacetals,[1] vinyl sulfides,[2] and vinyl ethers[3] reacted readily at room temperature with trifluoroacetic anhydride to give the corresponding β-trifluoroacetylated compounds in almost quantitative yield.[4] From a mechanistic standpoint,[5] these examples of electrophilic substitution at an olefinic carbon atom attracted our interest, particularly because they resembled much more familiar aromatic electrophilic substitutions.

**Table I. Pseudo-First-Order Rate Constants for the Trifluoroacetylation of Para-Substituted Aryl Vinyl Sulfides at 35 °C in $CDCl_3$**

| para substituent | $k$ ($s^{-1}$) | para substituent | $k$ ($s^{-1}$) |
|---|---|---|---|
| $NO_2$ | $(1.2 \pm 0.2) \times 10^{-6}$ | $CH_3$ | $(1.5 \pm 0.1) \times 10^{-3}$ |
| Cl | $(2.1 \pm 0.2) \times 10^{-4}$ | $OCH_3$ | $(2.4 \pm 0.1) \times 10^{-3}$ |
| H | $(4.0 \pm 0.2) \times 10^{-4}$ | | |

A number of para-substituted phenyl vinyl sulfides were trifluoroacetylated with a large excess of trifluoroacetic anhydride in $CDCl_3$ at 35 °C in the presence of a small amount of pyridine-$d_5$. The rate of trifluoroacetylation

$$\underset{\mathbf{1}}{\text{ArSCH=CH}_2} \xrightarrow[C_5D_5N,\ (CF_3CO)_2O]{CDCl_3,\ 35\ ^\circ C} \underset{\mathbf{2}}{\text{ArSCH=CHCOCF}_3}$$

was measured by following the disappearance of the =$CH_2$ protons by $^1H$ NMR. The rate was measured in duplicate or triplicate. The mean values of the pseudo-first-order rate constants are listed in Table I. From the data in Table I, the Hammett ρ value was calculated to be −3.0.[6]

The deuterated phenyl vinyl sulfide, PhSCH=$CD_2$, was prepared. Reduction of ethyl phenylthioacetate with lithium aluminum deuteride gave the corresponding dideuterated alcohol. Dehydration of the alcohol in the presence of potassium hydroxide and a small amount of copper powder and pyrogallol[7] gave the deuterated phenyl vinyl sulfide. Duplicate measurements of the rate of trifluoroacetylation of this compound were made in the same manner as described above. The deuterium isotope effect, $k_H/k_D$, was 2.5 ± 0.3. Although the value of $k_H/k_D$ could

(1) Hojo, M.; Masuda, R. *J. Org. Chem.* **1975**, *40*, 963.
(2) Hojo, M.; Masuda, R.; Kamitori, Y. *Tetrahedron Lett.* **1976**, *17*, 1009.
(3) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.
(4) It was reported[3] that the introduction of a powerful electron-withdrawing group, like $COCF_3$, into a possible cationic intermediate (e.g., $ROCHCH_2COCF_3^+$) led to deprotonation of the intermediate to give substitution products, rather than reaction with a nucleophile to afford addition products.
(5) For the application of this reaction in organic synthesis, see: Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016. Hojo, M.; Masuda, R.; Okada, E. *Tetrahedron Lett.* **1987**, *28*, 6199. Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T.; Ohara, S.; Yamada, K.; Yoshikawa, N. *J. Org. Chem.* **1988**, *53*, 519. Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1989**, 215. Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 347. Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 425 and references cited therein.
(6) log ($k_{p\text{-}X}/k_H$) vs σ; correlation coefficient 0.987. Tentative plot, log ($k_{p\text{-}X}/k_H$) vs $\sigma^+$, revealed that *p*-OMe group terribly drifted downward.
(7) Prince, C. C.; Gillis, R. G. *J. Am. Chem. Soc.* **1953**, *75*, 4750.

0022-3263/91/1956-1975$02.50/0 

not be determined with high accuracy, it can be safely said[8] that a primary kinetic isotope effect was observed for the trifluoroacetylation of phenyl vinyl sulfide-2,2-$d_2$.

There appear to be four possible mechanisms for electrophilic substitution at an olefinic carbon atom.[9] Mechanism 1 is analogous to that for the nitration of aromatic compounds, which involves cyclohexadienium ion intermediate. However, if 1 were the mechanism of trifluoroacetylation, a primary isotope effect would not be observed.[10] Mechanism 2 can also be excluded because it cannot explain the observed substituent effect. Mechanism 3 is that accepted for the sulfonation and mercuration of aromatic compounds.[9] It involves the very rapid establishment of an equilibrium between the vinyl sulfide and an intermediate cation, followed by rate-determining deprotonation of the cation. Mechanism 4 is a single-step process in which approach of the electrophile to, and departure of a proton from, the terminal carbon atom of the carbon-carbon double bond occur simultaneously. Both the observed substituent and isotope effects can be explained in terms of either mechanism 3 or mechanism 4. Although for aromatic sulfonation and mercuration a discrimination between 3 and 4 has not yet been achieved experimentally, 3 is now widely accepted as the mechanism for those reactions.[9]

$$1 \xrightarrow[\text{slow}]{COCF_3^+} \underset{3}{ArS\overset{+}{C}HCH_2COCF_3} \xrightarrow[\text{fast}]{-H^+} 2 \quad (1)$$

$$1 \xrightarrow[\text{fast}]{COCF_3^+} 3 \xrightarrow[\text{slow}]{-H^+} 2 \quad (2)$$

$$1 \underset{\text{very rapid}}{\overset{COCF_3^+}{\rightleftharpoons}} 3 \xrightarrow[\text{slow}]{-H^+} 2 \quad (3)$$

$$1 \xrightarrow[-H^+]{COCF_3^+} 2 \text{ (single step)} \quad (4)$$

Fortunately, however, a discrimination between mechanisms because feasible in the present case through the use of pairs of *cis*- and *trans*-aryl vinyl sulfides-2-$d_1$. If the reaction proceeded by mechanism 3, each geometric isomer of a pair would yield the same cationic intermediate, $ArSCHCHDCOCF_3^+$. Any recovered aryl vinyl sulfide would be a mixture of cis- and trans isomers, of which the cis/trans ratio would be the same, due to the very rapid establishment of an equilibrium between the vinyl sulfide and the cationic intermediate.

Two pairs of ArSCH=CHD (Ar = *p*-tolyl, cis/trans = 94:6 and 5:95; Ar = *p*-chlorophenyl, cis/trans = 95:5 and 13:87) were prepared[11] in a stereoselective manner. Each compound was trifluoroacetylated separately under the conditions described above. The progress of the reaction (inside an NMR tube) was followed carefully by $^1H$ NMR. Special attention was paid to the change in intensity of the methylene proton signal of the aryl vinyl sulfide [$\delta$ 5.19 (d, $J$ = 10.2 Hz) and 5.14 (d, $J$ = 16.2 Hz) for the *p*-Me pair; 5.35 (d, $J$ = 9.6 Hz) and 5.25 (d, $J$ = 17.4 Hz) for the *p*-Cl pair] during the reaction. In all four cases, no detectable change in the cis/trans ratio of the aryl vinyl sulfide was observed when the trifluoroacetylation was monitored to at least 75% completion. This meant that there was no rapidly established equilibrium between the aryl vinyl sulfide and a cationic intermediate. Thus, the possibility that the reaction proceeded by mechanism 3 was clearly eliminated. The experimental results obtained so far strongly suggest a single-step concerted process 4 for the trifluoroacetylation of aryl vinyl sulfides.[12] Further work aimed at completely elucidating the mechanism is now under consideration in this laboratory.

In contrast to the trifluoroacetylation of aryl vinyl sulfides, the trifluoroacetylation of aryl vinyl-2,2-$d_2$ ethers did not show any detectable primary isotope effect, although the rate of reaction was accelerated by electron-releasing substituents ($\rho$ = -2.4), as was the trifluoroacetylation of aryl vinyl sulfides. Presumably, the trifluoroacetylation of aryl vinyl ethers proceeds by mechanism 1 which is similar to that for the nitration of aromatic compounds. That vinyl ethers and vinyl sulfides undergo trifluoroacetylation by different mechanisms may be due to the difference in stability between the two cations, $ArOCHCH_2COCF_3^+$ and $ArSCHCH_2COCF_3^+$. Both are stabilized by resonance, by overlap of a 2p orbital of the electron-deficient carbon atom with, in the former, a 2p orbital of the adjacent oxygen atom or, in the latter, a 3p orbital of the adjacent sulfur atom. Stabilization by 2p-2p overlap is surely more efficient. Hence, vinyl ethers can yield stable cationic intermediates, whereas vinyl sulfides cannot.[13]

(8) A similar effect was observed in the competitive trifluoroacetylation of $PhSCH{=}CH_2$ and $PhSCH{=}CD_2$.

(9) For example, see: Hine, J. In *Physical Organic Chemistry*, 2nd ed.; McGraw Hill: New York, 1962; pp 352. Alder, R. W.; Baker, R.; Brown, J. M. In *Mechanism in Organic Chemistry*; John Wiley & Sons: New York, 1971; pp 286.

(10) An addition-elimination mechanism that gives substitution products can also be excluded, because the formation of $ArSCHCH_2COCF_3^+$ would be rate controlling.

(11) Hojo, M.; Masuda, R.; Takagi, S. *Synthesis* **1978**, 284.

(12) A truly concerted reaction should involve no bulid up of charge ($\rho$ = 0) in the transition state. There are degrees of concertedness. Therefore we would prefer it said that the mechanism is closest to option four.

(13) That two mechanisms were involved was implied earlier.[3] Although the rate of trifluoroacetylation of vinyl ethers was only slightly influenced by the presence of $\beta$-substituents, the trifluoroacetylation of vinyl sulfides was greatly inhibited by the presence of $\beta$-substituents.

## A Synthesis of (-)-Slaframine and (-)-1,8a-Diepislaframine

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*Received November 14, 1990*

*Summary:* Reductive cyclization of the optically pure azido epoxides **12** and **13** afforded the indolizidines **14** and **16**, which were converted into (-)-slaframine **1** and (-)-1,8a-diepislaframine **18**.

Forages contaminated with the fungus *Rhizoctonia leguminicola* are responsible for a disease in ruminants

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