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CIS-TRANS ISOMERIZATION OF AN α,α-DIFLUOROOLEFIN CATALYZED BY BROMINE

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Summary: The cis-trans isomerization of 1 by Br_2 in CCl_4 is described. A bridged bromonium cation α to CF_2 is destabilized resulting in a carbocation bromide ion pair at the β-carbon capable of free rotation and loss of bromine to form 2. A CF_2 group appears to be more effective in promoting isomerization than aryl in the case of stilbenes.[2]

We recently described a synthesis of (Z)-7,7-difluoro-8-dodecenyl acetate (1), a fluoro derivative of the sex pheromone of the oriental fruit moth and its photo isomerization to the E-isomer 2.[1] The procedure, which makes these fluoro olefins available for the first time, promises to be of general applicability. One of the objectives of this work was to learn whether the biological activity of this pheromone which requires the Z-structure was dependent on the geometry or the chemical reactivity of the double bond or both. The presence of two fluorine atoms in α-position should have significant effects on its reactions with electrophiles.

We report here on the reaction of 1 and 2 with bromine at different concentrations. The reaction of 1 with 35 equivalents of 1M Bromine in CCl_4 room temperature in the dark for 1 hour gave as the major product (79% yield) a dibromide to which we have assigned the threo structure 3[2] in accordance with the classical anti-addition mechanism based on the intermediacy of a bromonium cation. The erythro dibromide 4[3] was isolated from this reaction in 4% yield. Bromination of 2 under the same condition was much slower and yielded the erythro dibromide 4 as the sole product in 90% yield after 21 hours. Treatment of the dibromides 3 and 4 with 2.5% KOH in 50% aqueous dioxane followed by reacetylation gave the products of anti-elimination 5[4] and 6[5], respectively, in quantitative yield. These assignments were confirmed by the position of the ^1H NMR signal for the vinyl proton for 5, which is found 0.16 ppm downfield from that for 6 due to deshielding by fluorine. Debromination of both 5 and 6 with Bu_3SnH and AIBN produced the trans olefin 2, as did 1, rendering this procedure useless for confirming the nature of the double bond in 5 and 6.

Radically different results were obtained in the bromination reaction with low concentrations of Br_2 in CCl_4. These results are summarized in Table 1. The major product at all concentrations was the trans-olefin 2, which was obtained in better than 50% yield.[6] The second most abundant product at 0.04 M Br_2 was recovered 1 and at the higher concentrations its anti-bromination product 3. The erythro-dibromide 4 derived from 2 was always a minor product, reflecting the significantly slower rate of bromination of 2. Another minor constituent of the mixture was the allylic bromination product 10[7] derived from 2. The posi-

tion and trans chemistry of the double bond and the location of the bromine atom in 10 was established by double irradiation experiments. A single experiment with 0.06 M Br_2 in $CHCl_3$ gave similar results.

TABLE 1

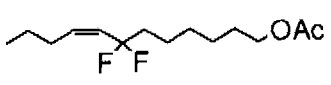
Reaction of 1 with Br_2 in CCl_4 at 25° in the Dark for 4 Hours[a]

		Reaction Products (%)				
$[Br_2]$	Molar Ratio, Br_2: 1[b]	2	1	3	4	10
0.04 M	21	53	28	10	3	6
0.08 M	47	58	11	18	4	8
0.11 M	63	54	14	20	11	8

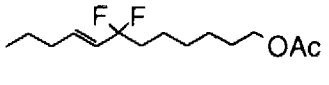
a) To obtain reproducible results it was essential to prepare solutions freshly in anhydrous CCl_4. b) Molar ratios of 4:1 at 1M initial bromine concentration gave similar but less reproducible results.

The data presented in Table 1, including the unprecedented isomerization in high yield, can be rationalized according to Scheme 1. The bridged bromonium ion 7 is isomerized via the open carbocation 8, to 9, which by reversal of the bromine addition step yields 2. Alternatively, 7 and 8 collapse to the dibromides 3 and 4. This scheme is analogous to that proposed to explain the formation of meso-α,α'-dibromobibenzyl from cis-stilbene[8,9] by invoking the intermediacy of an open carbocation stabilized by the aryl substituent. The reversal of the formation of the bridged bromonium ion pair has recently been demonstrated.[10] The driving force for the formation of the open carbocation in the two cases is, of course, of opposite origin: in the stilbene case a carbocation is stabilized α to the phenyl substituent, while the difluoromethylene group strongly destabilizes positive charge at the α-carbon, leading to localization of charge at the β-carbon. The almost exclusive formation of the threo product 3 from 1 at high bromine concentrations may be the result of an increase in the rate of the collapse of 7 to form 3, which now exceeds that of the formation of the carbocation 8. It may also be the result of the intervention of a more stable bridged intermediate involving two molecules of bromine.[10]

Comparing the data for the isomerization of stilbene with those reported here, it



1



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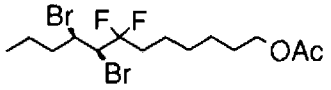

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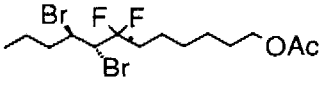

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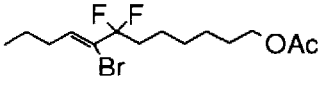

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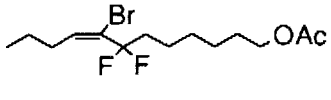
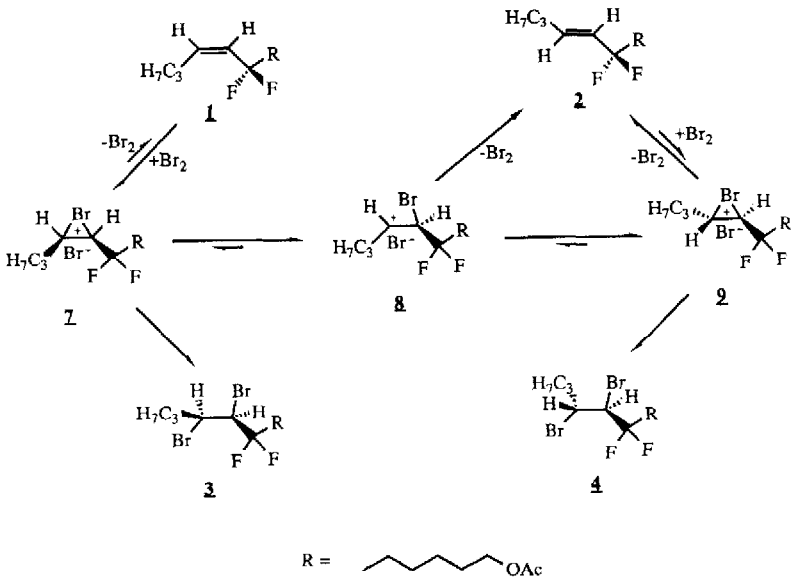


6

Scheme 1



becomes evident that the effect of the CF_2 substituent is more powerful than that of the phenyl group. Thus, in the cis-stilbene case only 5% of the trans-isomer was present after 4 hours exposure to 2.5×10^{-3} M Br_2 in dichloroethane (D = 10.7).[10] Moreover, only in solvents more polar than CCl_4 has evidence for isomerization of stilbene been obtained.[9] This is in contrast to the present work, all of which was carried out in CCl_4. The powerful destabilization of positive charge α to a CF_2 group has been described in quantitative terms.[11]

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2. **3**: ^{1}H NMR (500 MHz, $CDCl_3$); 4.32-4.23 (m, 2H, H-8, H-9), 4.06 (t, 2H, J = 6.7 Hz, H-1), 2.27-2.05 (m, 2H, H-6) 2.05 (s, 3H, $COCH_3$), 2.09-2.00 (m, 1H, H-10), 1.92-1.85 (m, 1H, H-10), 1.69-1.36 (m, 10 H, H-2, H-3, H-4, H-5, H-11), 0.97 (t, J = 7.4 Hz, H-12); ^{19}F NMR (376 MHz, $CDCl_3$): Φ 97.89 (ddt, J = 244.1, 26.8, 7.3 Hz), 100.27 (ddt, J = 244.1, 24.4, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 171.18 (s, $COCH_3$), 122.10 (t, J = 246.1 Hz, C-7), 64.39 (s, C-1), 56.88 (t, J = 29.6 Hz, C-8), 50.43 (bs, C-9), 39.78 (s, C-10), 34.72 (t, J = 24.5 Hz, C-6), 28.80 (s, C-2 or C-3), 28.42 (s, C_2 or C_3), 25.86 (s, C-4), 21.43 (t, J = 5.3 Hz, C-5), 20.99 (s, $COCH_3$), 20.73 (s, C-11), 13.16 (s, C-12). $C_{14}H_{24}O_2F_2Br_2$: Calcd.: C, 39.83; H, 5.73; Found: C, 40.17; H, 6.42.

3. **4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.49-4.40 (m, 2H, H-8, H-9), 4.06 (t, 2H, J = 6.7 Hz, H-1), 2.21-2.0 (m, 2H, H-6), 2.05 (s, 3H, $COCH_3$), 2.00-1.92 (m, 2H, H-10), 1.72-1.35 (m, 10 H, H-2, H-3, H-4, H-5, H-11), 0.97 (t, 3H, J = 7.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): Φ 100.58 (dddd, J = 244.2, 22.0, 17.1, 7.3 Hz), 101.86 (ddt, J = 244.2, 19.5, 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 170.97 (s, $COCH_3$), 122.46 (dd, J = 251.5, 245.4 Hz, C-7), 64.35 (s, C-1), 59.61 (t, J = 26.5 Hz, C-8), 51.80 (d, J = 8.8 Hz, C-9), 37.56 (d, J = 5.6 Hz, C-10), 35.57 (t, J = 24.6 Hz, C-6), 28.78 (s, C-2 or C-3), 28.47 (s, C-2 or C-3), 25.72 (s, C-4), 21.68 (t, J = 6.8 Hz, C-5), 21.23 (s, C-11), 21.10 (s, $COCH_3$), 13.55 (s, C-12).

4. **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (t, 1H, J = 7.0 Hz, H-9), 4.06 (t, 2H, J = 6.7 Hz, H-1), 2.24 (qu t, 2H, J = 7.3, 2.4 Hz, H-10), 2.13-2.05 (m, 2H, H-6), 2.05 (s, 3H, $COCH_3$), 1.64 (m, 2H, H-2), 1.50 (sext, 2H, J- 7.4 Hz, H-11), 1.49-1.35 (m, 6H, H-3, H-4, H-5), 0.97 (t, 3H, J = 7.4 Hz, H-12); ^{19}F NMR (376 MHz, $CDCl_3$): Φ 96.48 (t, J = 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 171.17 (s, $COCH_3$), 133.79 (t, J = 4.8 Hz, C-9), 120.57 (t, J = 244.1, C-7), 119.76 (t, J = 28.1 Hz, C-8), 64.43 (s, C-1), 35.54 (t, J = 24.4 Hz, C-6), 32.75 (s, C-10), 28.72 (s, C-2 or C-3), 28.43 (s, C-2 or C-3), 25.69 (s, C-4), 22.17 (t, J = 3.7 Hz, C-5), 21.25 (s, C-11), 21.01 (s, $COCH_3$), 13.71 (s, C-12); $C_{14}H_{23}O_2F_2Br$: Calcd: C, 49.27; H, 6.79; Found: C, 49.22; H, 6.80.

5. **6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 (t, 1H, J = 7.8 Hz, H-9), 4.06 (t, 2H, J = 6.7 Hz, H-1), 2.25 (qu t, J = 7.5, 2.5 Hz, H-10) 2.14-2.03 (m, 2H, H-6), 2.05 (s, 3H, $COCH_3$), 1.65 (m, 2H, H-2), 1.55-1.35 (m, 8H, H-3, H-4, H-5, H-11), 0.94 (t, 3H, J = 7.4 Hz, H-12); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 170.98 (s, $COCH_3$), 139.78 (s, C-9), 121.65 (t, J = 245.6 Hz, C-7), 116.04 (t, J = 30.2 Hz, C-8), 64.42 (s, C-1), 36.66 (t, J = 25.2 Hz, C-6), 31.93 (t, J = 5.7 Hz, C-10), 28.86 (s, C-2 or C-3), 28.71 (s, C-2 or C-3), 25.80 (s, C-4), 22.63 (s, C-11), 22.03 (bs, C-5), 21.11 (s, $COCH_3$), 13.71 (s, C-12).

6. Chromatographic separation of **1** and **2** was unsuccessful. However, pure **2** was obtained, when the crude reaction mixture was rebrominated with 1M Br_2 in CCl_4 for 40 min., followed by chromatography.

7. **10**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.17 (ddt, 1H, J = 15.6, 9.1, 2.4 Hz, H-9), 5.72 (ddd, 1H, J = 15.6, 10.7, 10.1 Hz, H-8), 4.42 (qu, J = 7.6 Hz, H-10) 4.06 (t, J = 6.7 Hz, H-1) 2.05 (s, 3H, $COCH_3$), 2.00-1.86 (m, 2H, H-6), 1.68-1.60 (m, 2H, H-2), 1.60-1.34 (m, 6H, H-3, H-4, H-5), 1.04 (t, 3H, H-12); ^{19}F NMR (376 MHz, $CDCl_3$): 95.33 (dm, J = 241.3 Hz), 97.80 (dm, J = 241.3 Hz).

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