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gem-DIFLUOROCYCLOPROPENES BY [1+2] CYCLOADDITION REACTIONS BETWEEN DIFLUOROCARBENE AND ACETYLENES HAVING TERMINAL OR INTERNAL TRIPLE BONDS

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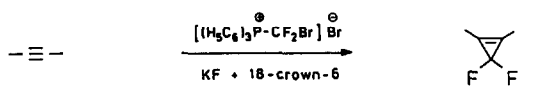
Summary Difluorocarbene, generated by the Burton method, *i.e.* by the dissociation of (triphenylphosphonio)difluoromethanide, was found to add to terminal or internal acetylenes with astonishing ease Actually, it reacts roughly 10 times faster with 4-octyne than with *cis*-4-octene. The *gem*-difluorocyclopropenes resulting from the [1+2] cycloaddition process can be isolated with good to excellent yields. They are perfectly stable under anhydrous conditions while in aqueous media they are quantitatively converted to cyclopropenones - Unsubstituted olefinic ring positions rapidly undergo a base catalyzed hydrogen/deuterium exchange The acidity of such 2-alkyl- or 2-aryl-1,1-difluorocyclopropenes is estimated to be higher than that of terminal acetylenes.

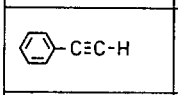
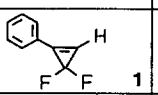
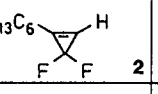
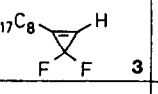
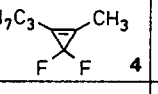
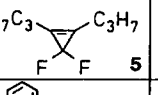
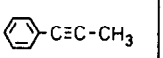
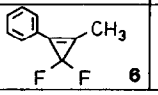
Carbenes or carbenoids generated from diazoalkanes [1] or haloforms [2] appear to undergo [1+2] cycloaddition reactions much less readily with alkynes rather than with alkenes With this as a background, the number of known difluorocarbene/acetylene cycloadducts is quite impressive Besides the parent compound 3,3-difluorocyclopropene [3], notably derivatives carrying electronegative substituents have been prepared 3,3-difluoro-1,2-bis(trifluoromethyl)cyclopropene [4], 3,3-difluoro-1-(pentafluoroethyl)-, -1-(heptafluoropropyl)- and -1-(nonafluorobutyl)cyclopropene [5], 1,2-dibromo-, 1,2-dichloro- and 1,2-diiodo-3,3-difluorocyclopropene [6], 3,3-difluoro-1,2-dimethoxycyclopropene [7], 3,3-difluoro-1-trifluoromethyl-2-(trimethylsilyl)- and -2-(trimethylstannyl)cyclopropene [8] On the other hand, examples of alkyl substituted 3,3-difluorocyclopropenes are scarce and all belong to a fairly uniform series of steroid derivatives [9] Furthermore, the yields were generally poor and extensive hydrolysis or dehydrofluorination occured during work-up and isolation

Recently we have disclosed a considerably improved entry into the class of *gem*-difluorocyclopropanes on the basis of a modified Burton protocol. [10] Encouraged by this experience, we wanted to apply the same method to the synthesis of *gem*-difluorocyclopropenes and we indeed obtained quite satisfactory results



Regardless whether alkynes having terminal or internal triple bonds were used, the products were formed with unexpected ease. The yields were generally high, sometimes close to quantitative (see Table). The *gem*-difluorocyclopropenes **1** - **6** were obtained analytically pure and could then be stored indefinitely. In the presence of moisture, however, they were rapidly hydrolyzed to give cyclopropenones.

Table. *gem*-Difluorocyclopropenes **1** - **6** by [1+2] cycloaddition reactions between difluorocarbene and a variety of alkynes.

alkyne	*gem*-difluoro-cyclopropene	yield [a]
	 **1**	79%
$H_{13}C_6$-C≡C-H	 **2**	77% [b]
$H_{17}C_8$-C≡C-H	 **3**	80% [b]
H_7C_3-C≡C-CH_3	 **4**	46%
H_7C_3-C≡C-C_3H_7	 **5**	80% [c]
	 **6**	66%

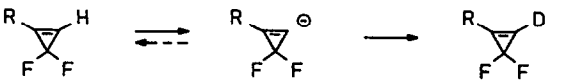
a) Yields of isolated, pure products using 3 equivalents of the difluorocarbene source (bromodifluoromethyl)triphenylphosphonium bromide, unless otherwise stated.

b) Using 6 equivalents of the difluorocarbene source

c) Using 2 equivalents of the difluorocarbene source

The presence of non-hydroxylic functional groups is tolerated Thus, methyl stearolate was smoothly converted into the difluoro analog of sterculic acid methyl ester (**7**)

When the *gem*-difluorocyclopropene **1**, **2** or **3** was dissolved in a catalytic amount of containing methoxide per-deuteromethanol, the ring attached hydrogen was rapidly replaced by the heavier isotope. Presumably the transient carbanion **8** acts as the turntable



8

Cyclopropene itself and simple alkylated derivatives exhibit already an unusually high CH acidity which lies roughly halfway between that of ethylene and acetylene [11]. As a comparison between the acidities of benzene and fluorobenzene demonstrates, one neighboring fluorine atom stabilizes a vicinal negative charge to the extent of roughly 10 kcal/mol, both in the gas phase [12] or in solution [13]. Therefore, we estimate the deprotonation enthalpy of the *gem*-difluorocyclopropenes **1** - **3** to be smaller than that of acetylene, though still bigger than that of cyclopentadiene (respectively 375 and 356 kcal/mol in the gas phase [12]).

In order to quantify the extraordinary reactivity of difluorocarbene towards acetylenes, we have carried out a few competition experiments. In contrast to what has been reported for dichlorocarbene [14], difluorocarbene was found to react faster with alkynes than with alkenes The relative rates of 1-octyne and 4-octyne approximate 2 and 10, respectively, if *cis*-4-octene serves as the reference.

One may feel inclined to attribute the anormal substrate selectivity to a nucleophilic [15] character of the difluorocarbene. However, the complete inertness of the latter divalent species towards dimethyl acetylenedicarboxylate argues against this assumption. All attempts to explain why alkynes outperform alkenes in the cycloaddition reaction with difluorocarbene must remain speculative as long as nothing is known about the temperature dependence [16]. Cycloaddition processes involving difluorocarbene rather than singlet methylene should be less exothermical by roughly 60 kcal/mol, which is a crude estimate for the resonance stabilization of the sextet center due to the electron donation by the two halogen atoms. [17] Combining difluorocarbene with an acetylene should produce a particulary small reaction enthalpy (of approximately "only" 20 kcal/mol) Hence the transition complex will be considerably less reactant like than in the halogen-free model case. In this context it should be kept in mind that the activation barriers of typical carbene cycloadditions are largely entropy (probability) determined while their enthalpy terms are negligeably small [18].

The trajectory of the carbene approaching the unsaturated substrate has also to be considered Possibly the difluorocarbene benefits from a change in mechanism, switching from a "tilted" transition state geometry [17,19-20] employed with olefines to a perpendicular one with acetylenes.

EXPERIMENTAL PART

1. General Remarks

For standard laboratory practice, see related articles [10, 21].

The *gem*-difluorocyclopropenes 1 - 7 slowly decompose at 25 °C. Since samples have to be sent to external services, combustion analytical data were ordered in a single case (product 7). As far as to be judged from nmr spectroscopy, however, all products were perfectly pure.

2. *gem*-Difluorocyclopropenes

a) *Working procedure* : A white precipitate was formed instantaneously when dibromodifluoromethane (15 mL, 34 g, 0.16 mol) was added to a solution of triphenylphosphine (42 g, 0.16 mol) in ethylene glycol dimethyl ether (0.15 L). About one third of this slurry was poured into a mixture of the acetylene (50 mmol), potassium fluoride (20 g, 0.34 mol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (2.0 g, 7.6 mmol) in ethylene glycol dimethyl ether (50 mL). After 4 and 8 h of vigorous stirring the second and third portion of the (bromodifluoro)triphenylphosphonium bromide suspension were added. (Occasionally a smaller or a larger excess of the difluorocarbene source was employed; see footnotes to the Table). After additional 12 h of stirring, always at 25 °C, the dark reaction mixture was diluted with pentane (0.30 L) and filtered (or centrifuged). The organic layer was rapidly washed with an ice-cold, 2% aqueous solution of sodium hydroxide (5 × 0 10 L), dried with potassium carbonate and evaporated. The residue was distilled under reduced pressure.

3,3-Difluoro-1-phenylcyclopropene (1) : 79%, mp -14 to -12 °C; bp 87 - 88 °C/20 mmHg; n_D^{20} 1.5070. - IR : 1800 (s, ν[C=C]). - ^{1}H-NMR *: 7.7 (2 H, m), 7.5 (4 H, m). - ^{19}F-NMR : -43.8 (d, *J* 2). - MS : 152 (5%, M^+), 151 (8%), 133 (77%), 130 (100%).

3,3-Difluoro-1-hexylcyclopropene (2) : 77%; mp -55 to -53 °C; bp 59 - 60 °C/10 mmHg; n_D^{20} 1.4028. - IR : 1840 (s, ν[C=C]). - ^{1}H-NMR *: 7.21 (1 H, s-like), 2.52 (2 H, symm. m), 1 65 (2 H, pent, *J* 7.3), 1.4 (6 H, m), 0.89 (3 H, t, *J* 6.8). - ^{13}C-NMR (H-decoupled) : 138.0 (t, *J* 10), 116.7 (t, *J* 11), 103.2 (t, *J* 269), 31.1 (s), 28.4 (s), 26.1 (s), 23.3 (s), 22.1 (s), 13.5 (s). - ^{19}F-NMR : -41.5 (q, *J* 2). - MS : 141 (6%, M^+ - F), 138 (100%).

3,3-Difluoro-1-octylcyclopropene (3) : (80%); mp -38 to -36 °C; bp 87 - 88 °C/10 mmHg; n_D^{20} 1.4142. - IR : 1830 (s, ν[C=C]). - ^{1}H-NMR *: 7.10 (1 H, s-like), 2.6 (2 H, m), 1.75 (2 H, pent, *J* 7.4), 1.4 (10 H, m), 1.01 (3 H, t, *J* 6.9). - ^{19}F-NMR : -41.6 (q, *J* 2). - MS : 169 (11%), M^+ - F), 166 (100%).

3,3-Difluoro-1-methyl-2-propylcyclopropene (4) : 46%; bp 67.0 - 67.5 °C/80 mmHg; n_D^{20} 1.3890. - IR : 1850 (s, ν[C=C]). - ^{1}H-NMR *: 2.40 (2 H, symm. m), 2.0 (3 H, m), 1.63 (2 H, hex, *J* 7.3), 1.00 (3 H, t, *J* 7.3) - ^{19}F-NMR . 44.5 (hex, *J* 3). - MS : 132 (0.3%, M^+), 117 (3%), 113 (100%).

3,3-Difluoro-1,2-dipropylcyclopropene (5) : 80%; bp 66 0 - 66.5 °C/20 mmHg; n_D^{20} 1.4030. - ^{1}H-NMR *: 2.51 (4 H, symm. m), 1.75 (4 H, hex, *J* 7.2), 1.12 (6 H, t, *J* 7.2). - ^{19}F-NMR : -43.5 (pent, *J* 3). - MS : 160 (0.3%, M^+), 141 (100%).

3,3-Difluoro-1-methyl-2-phenylcyclopropene (6) : 66%; mp 4.0 - 5.5 °C; bp 49 - 51 °C/0.5 mmHg; n_D^{20} 1.5055. - IR : 1830 (s, ν[C=C]). - ^{1}H-NMR *: 7.6 (2 H, m), 7.5 (3 H, m), 2.29 (3 H, t. *J* 3.0). - ^{19}F-NMR : -46.8 (q, *J* 3). - MS : 166 (7%), M^+), 151 (10%), 147 (100%).

Methyl 9,10-Difluoromethylene-9-octadecenoate (7) : 92% [from methyl 9-octadecynoate [22] with two equivalents of (bromodifluoromethyl)phosphonium bromide in *di*ethylene glycol dimethyl ether]; mp -24 to -22 °C; bp 142 - 143 °C/0.06 mmHg; n_D^{20} 1.4489. - IR : 1810 (s, ν[C=C]), 1740 (s, ν[C=O]). - ^{1}H-NMR : 3.67 (3 H, s), 2.41 (4 H, symm. m), 2.32 (2 H, t, *J* 7.5), 1.6 (6 H, m), 1.3 (16 H, m), 0.89 (3 H, t, *J* 6.5). - ^{19}F-NMR : -43.5 (pent, *J* 3). - MS : 344 (0.8%, M^+), 325 (100%, M^+ - F) - Analysis : calc. for $C_{20}H_{34}F_2O_2$ (344 49) C 69.73, H 9.95; found C 69.80, H 10.12%.

b) *Base catalyzed hydrogen/deuterium exchange experiment* : The sample (0 1 mmol of **2**) was dissolved in perdeuteromethanol (1.0 mL) containing sodium methoxide (0.1 mmol). After 15 min at 25 °C, the olefinic proton (δ 7.21) had completely disappeared from the ^{1}H-NMR spectrum and the ^{19}F-quadruplet (δ -41.9) had changed to a triplet (J 3)

c) *Competition experiments* . The carbene was generated in the presence of an acetylene/olefin mixture as previously done with pairs of different olefins [19, 23]. Relative rates were calculated using the standard logarithmic expression of concentrations [24].

3 Cyclopropenones

a) **2-Hexylcyclopropenone** : 3,3-Difluoro-1-hexylcyclopropene (**2**) was dissolved in a 1 : 1 (v/v) mixture of dimethoxymethane and water saturated with sodium carbonate. After 15 h at 25 °C, repetitive extraction with pentane and distillation gave the ketone: 68%. Alternatively, compound **2** may be submitted to hydrolysis by eluting it from a silica gel column using wet diethyl ether as the eluent : 95%. - ^{1}H-NMR : 8.42 (1 H, s), 2.67 (2 H, t, J 7.4), 1.71 (2 H, pent, J 7.5), 1.3 (6 H, m), 0.88 (3 H, t, J 6.8). - ^{13}C-NMR : 170.6 (s), 158.6 (s), 147.4 (s), 31 4 (s), 28 8 (s), 27.9 (s), 25 9 (s), 22.6 (s), 14 3 (s) - MS (c.i.) · 156 (100%, M^{+} + NH_4), 139 (77%).

b) **2,3-Diphenylcyclopropenone** · An attempt was made to prepare 3,3-difluoro-1,2-diphenylcyclopropene as described above (Section 2). When the crude reaction mixture was washed with diluted aqueous sodium hydroxide, complete hydrolysis occurred and the ketone was isolated; 92%, mp 119 - 121 °C [25].

c) **Methyl-8-(2-octyl-3-oxo-1-cyclopropenyl)octanoate** : The *gem*-difluorocyclopropene **7** was dissolved in wet diethyl ether and filtered through a bed of silica gel. After evaporation of the solvent, a colorless oily liquid was collected; 89%; mp 10 - 11 °C; n_D^{20} 1.4688. - IR : 1840 (s, ν[C=C]) + 1740 (s, ν[(O)C=O]), 1630 (s, ν[C=O]) - ^{1}H-NMR · 3.65 (3 H, s), 2.57 (4 H, t, J 7.2), 2.29 (2 H, t, J 7.5), 1.65 (6 H, symm m), 1.3 (16 H, m), 0.87 (3 H, t, J 6 5). - MS · 322 (0.3%, M^{+}), 294 (3%), 264 (7%), 211 (15%), 95 (66%), 81 (100%).

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