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DEFLUORINATION REACTIONS OF *gem*-DIFLUORO- AND MONOFLUOROOLEFINS. NOVEL METHODS FOR ONE-CARBON HOMOLOGATIONS OF CARBONYL COMPOUNDS LEADING TO ALDEHYDES, CARBOXYLIC ACIDS, AND ESTERS[1)]

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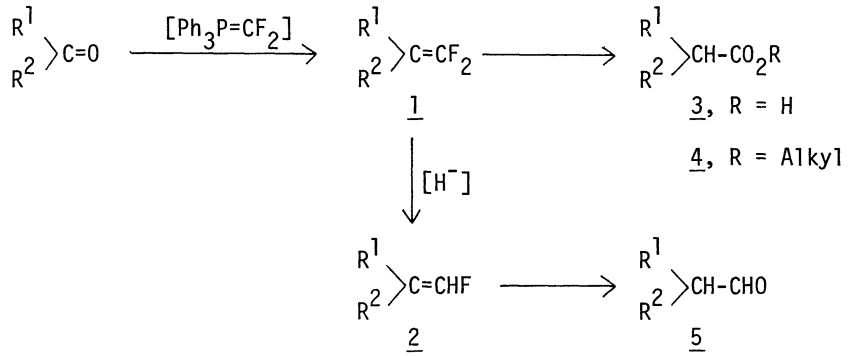
Defluorinative hydrolysis (or alcoholysis) of *gem*-difluoroolefins (1) easily prepared via the facile difluoromethylenation of carbonyl compounds afforded the carboxylic acids (or esters). The homologation method was applied to the synthesis of anti-inflammatory *ibuprofen*. Furthermore, defluorinative hydrolysis of monofluoroolefins obtained via the reduction of 1 gave the aldehydes.

Recently we have reported convenient procedures for the conversion of carbonyl compounds to *gem*-difluoroolefins (1) via the *in situ* Wittig reaction with difluoromethylene ylides and for the selective reduction of 1 to monofluoroolefins (2).[2)] In our continuing investigation of new applications of organofluorine compounds in *fluorine-free* organic synthesis, we now wish to report facile defluorination reactions of 1 and 2 which eventually provide novel, versatile methods for one-carbon homologations of carbonyl compounds leading to carboxylic acids (3), esters (4), and aldehydes (5), as depicted below.



While a number of synthetic methods have become available for effecting one-carbon homologations of carbonyl compounds to aldehydes[3,4)] and carboxylic acids (or esters)[3,5)] in recent years, the present procedures are the first examples of fluorine-mediated one-carbon homologa-

tions[6] and certainly additions to the host of existing methods. Notable features of the present methods are as follows; (i) the ylide precursor (CBr_2F_2) is commercially available and inexpensive, (ii) the Wittig reaction can be accomplished in one operation requiring no isolation of the phosphonium salt, (iii) the carboxylic acid precursors (1) can be readily converted to the aldehyde precursors (2), and (iv) some of defluorination reactions of 1 and 2 described below are relatively quite simple.

First, the transformations of *gem*-difluoroolefins (1) to carboxylic acids (3) and esters (4) were examined. We found that simple treatment of arylsubstituted difluoroolefins with conc. sulfuric acid (method *A*) afforded the corresponding arylacetic acids in high yields (entries 1,3, 5 and 6, Table 1). Use of a mixture of conc. sulfuric acid and an alcohol (method *B*) gave the corresponding arylacetic esters in good yields (entries 2 and 4). Unfortunately, however, neither method *A* nor *B* was successful for aliphatic difluoroolefins. After many attempts, we found that treatment of aliphatic difluoroolefins with mercury(II) acetate in trifluoroacetic acid (TFA)[7] followed by successive treatments with aqueous sodium hydrogencarbonate and hydrogen sulfide gas (method *C*) gave rise to the corresponding acids in high yields (entries 7 and 8). On treatment with mercury(II) acetate in TFA followed by alcoholysis (method *D*), on the other hand, aliphatic difluoroolefins were directly converted to the corresponding esters (entry 9).

A simple synthesis of α-(*p*-isobutylphenyl)propionic acid (so called *ibuprofen*), a potent anti-inflammatory agent,[8,9] serves to illustrate the applicability of the homologation method leading to arylacetic acid derivatives (entry 6).

Next, the transformation of monofluoroolefins (2) to aldehydes (5) were studied. We found that simple acid treatments of 2 did not afford any defluorinative products. Thus mercury-assisted hydrolysis[7] was examined. We found that treatment of aliphatic monofluoroolefins with mercury(II) acetate in TFA followed by hydrolysis (method *E*) gave rise to the corresponding aldehydes in excellent yields (entries 10 and 11). However, application of method *E* to aryl-substituted monofluoroolefins resulted in the formation of complicated mixtures which probably arises from the great instability of the corresponding arylacetaldehydes once formed under acidic conditions (entries 12 and 13).

In summary, combinations of the facile difluoromethylenations of carbonyl compounds via the *in situ* Wittig reactions with appropriate defluorination reactions provide convenient methods for one-carbon homologations of carbonyl compounds leading to carboxylic acids (or esters) and aldehydes. In addition, this work serves to illustrate an example of the potential applicability of organofluorine compounds in *fluorine-free* organic synthesis.

The following procedure is illustrative of hydrolysis of *gem*-difluoroolefins (method *A*). *p*-Isobutyl-α-methyl-β,β-difluorostyrene (1 mmol) was added to conc. sulfuric acid (2 ml) with

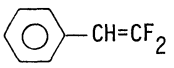
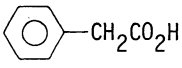
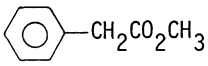
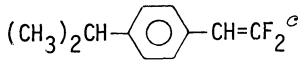
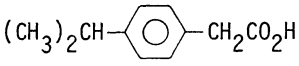
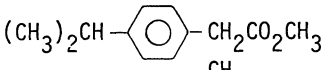
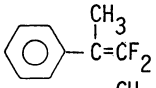
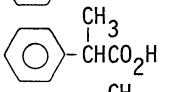
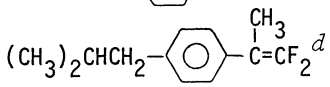
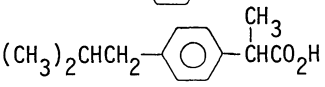
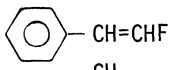
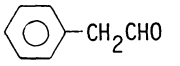
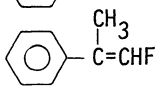
Table 1. Hydrolysis and Alcoholysis of *gem*-Difluoro- (1) and Monofluoroolefins (2)

Defluorination Methods:

A : Conc. H_2SO_4 *B* : Conc. H_2SO_4 - ROH

C : $Hg(OAc)_2$ - TFA - (aq. $NaHCO_3$) $\longrightarrow$ H_2S (gas)

D : $Hg(OAc)_2$ - TFA - (ROH) *E* : $Hg(OAc)_2$ - TFA - (aq. $NaHCO_3$)

Entry	Fluoroolefin[a]	Method	Defluorinative Product[b]	Isolated Yield
1		*A*		93%
2	〃	*B*		80%
3	 [c]	*A*		70%
4	〃	*B*		81%
5		*A*		94%
6	 [d]	*A*		80%
7	n-$C_6H_{13}CH{=}CF_2$	*C*	n-$C_7H_{15}CO_2H$	69%
8	n-$C_{10}H_{21}CH{=}CF_2$	*C*	n-$C_{11}H_{23}CO_2H$	88%
9	〃	*D*	n-$C_{11}H_{23}CO_2C_2H_5$ [e]	(40%)[f]
10	n-$C_6H_{13}CH{=}CHF$	*E*	n-$C_7H_{15}CHO$	80%
11	n-$C_{10}H_{21}CH{=}CHF$	*E*	n-$C_{11}H_{23}CHO$	95%
12		*E*		(37%)[f]
13		*E*	*g*	

[a] Unless otherwise noted, optimal preparations of these fluoroolefins have been described in ref. 2. [b] All products exhibited spectral (IR, NMR and/or MS) data in accord with the assigned structures and/or the reported literature values. [c] Prepared in 83% yield via the *in situ* Wittig reaction with *p*-isopropylacetophenone following the ylide generation method *C* described in ref. 2; bp 94-96 °C/39 mmHg. [d] Prepared in 53% yield via the *in situ* Wittig reaction with *p*-isobutylacetophenone following the ylide generation method *D* in ref. 2; bp 102-104 °C/12 mmHg. [e] Also prepared in a high yield from the same difluoroolefin via the reaction with sodium ethanolate followed by acid hydrolysis (our unpublished results). [f] Determined by GLC. [g] The arylacetaldehyde was not isolated (see the text).

stirring at -10°C and the mixture was stirred at room temperature for 3 h. The resultant mixture was poured onto ice and extracted with ether. Usual work-ups of the ethereal extracts followed by column chromatography on silica gel (benzene) gave *ibuprofen* (80%).

The following procedure is illustrative of hydrolysis of monofluoroolefins (method *E*). A mixture of 1-fluoro-1-dodecene (1.1 mmol) and mercury(II) acetate (1.5 mmol) in TFA (5 ml) was stirred overnight at room temperature. After evaporation of TFA, the residue was treated with saturated aqueous sodium hydrogencarbonate solution and then extracted with ether. Usual work-ups of the ethereal extracts followed by column chromatography on silica gel (*n*-hexane) gave dodecanal (95%).

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References and Notes

1) Part VII on "Application of Organofluorine Reagents in Organic Synthesis". Part VI : ref. 2.

2) S. Hayashi, T. Nakai, N. Ishikawa, D.J. Burton, D.G. Naae, and H.S. Kesling, *Chem. Lett.*, 1979, 983.

3) For leading previous references of one-carbon homologations of carbonyl compounds, see the most recent review: S.F. Martin, *Synthesis*, 1979, 673.

4) For more recent examples, see A.F. Kluge and I.S. Cloudsdale, *J. Org. Chem.*, 44, 4847 (1979), and references cited therein.

5) For more recent examples, see S.E. Dinizo, R.W. Freerksen, W.E. Pabst, and D.S. Watt, *J. Am. Chem. Soc.*, 99, 182 (1977), and references cited therein.

6) For fluorine-mediated bis-homologation of carbonyl compounds leading to α-keto acids, see K. Tanaka, T. Nakai, and N. Ishikawa, *Tetrahedron Lett.*, 1978, 4809.

7) S.F. Martin and T.S. Chou (*Tetrahedron Lett.*, 1978, 1943) have recently reported that mercury(II) acetate in TFA was quite effective for the conversion of vinylic chlorides to the corresponding ketones.

8) For physiological activities and synthesis of *ibuprofen* and the related propionic acids, see D. Lednica and L.A. Mitscher, "The Organic Chemistry of Drug Synthesis", John Wiley, New York, 1977, Chap. 6.

9) For more recent syntheses of *ibuprofen*, see K. Kogure, K. Nakagawa, and H. Furukawa, *Agr. Biol. Chem.*, 39, 1427 (1975).

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