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FACILE SYNTHESIS OF α-FLUORO-β-KETOESTERS FROM POLYFLUOROALKENES

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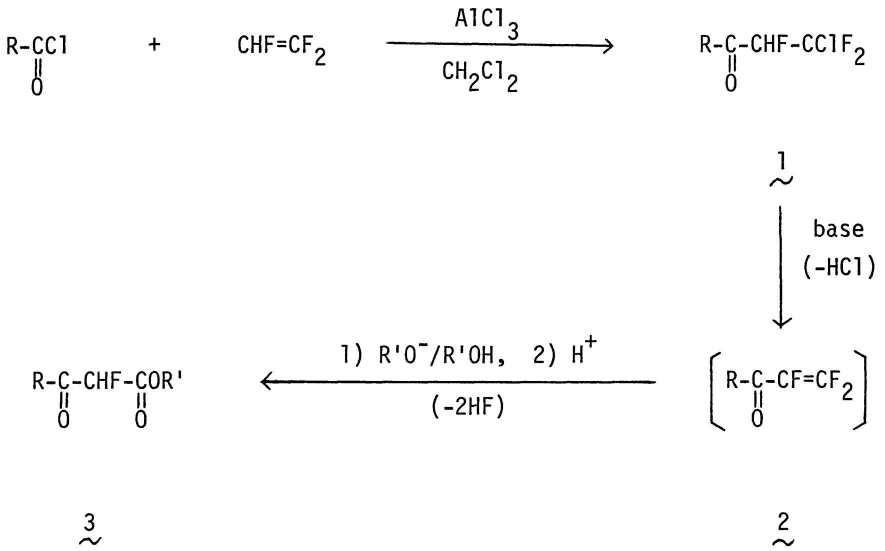
Alkyl 2-chloro-1,2,2-trifluoroethyl ketones and aryl 1,2,2,2-tetrafluoroethyl ketones were respectively prepared by the Friedel-Crafts acylation of trifluoroethene and by the Grignard arylation of N,N-diethyl-1,2,2,2-tetrafluoropropionamide, a hydrolyzed product of hexafluoropropene-diethylamine adduct. These alkyl and aryl polyfluoroalkyl ketones were subjected to base-induced dehydrohalogenation, and resulting trifluorovinyl ketones were hydrolyzed in situ affording α-fluoro-β-ketoesters in good yields.

The compounds carrying active fluoromethylene groups, such as α-fluoro-β-diketones, α-fluoro-β-diesters or α-fluoro-β-ketoesters, are versatile intermediates which may be led to α-fluorocarbonyl or monofluoroheterocyclic compounds which are of interest from the biological point of view.[1)] Reported synthetic routes for these fluoromethylene compounds so far include 1) the Claisen or Reformatsky reactions of monofluoroacetic acid derivatives[2)] and 2) the fluorination of an active methylene group with perchloryl fluoride.[3-5)] However, the former method generally gives only poor yields and the latter uses the fluorinating agent not easily handled. We now wish to report a facile synthetic route for α-fluoro-β-ketoesters by utilizing the reactivity of polyfluoroalkenes, such as trifluoroethene and hexafluoropropene.

Trifluoroethene is known to react with excess acetyl chloride giving an adduct 2-chloro-1,2,2-trifluoroethyl methyl ketone (**1**, R = Me).[6)] We found that the Friedel-Crafts addition could be applied to various aliphatic carboxylic acid chlorides by using dichloromethane as a solvent, though aromatic acid chlorides did not give good results. Dehydrochlorination of the chlorotrifluoroethyl ketones **1** to the unstable trifluorovinyl ketones (**2**) was performed in situ by treating **1** with a base, and the resulting ketones **2** were subjected to base solvolysis affording α-fluoro-β-alkylketoesters (**3**) in good yields (Table 1, Method A).



$$\mathrm{R\text{-}\overset{}{\underset{\|O}{C}}Cl} + \mathrm{CHF{=}CF_2} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{AlCl_3}} \mathrm{R\text{-}\underset{\|O}{C}\text{-}CHF\text{-}CClF_2}\ (\mathbf{1}) \xrightarrow[(-\mathrm{HCl})]{\text{base}} \left[\mathrm{R\text{-}\underset{\|O}{C}\text{-}CF{=}CF_2}\right]\ (\mathbf{2}) \xrightarrow[(-2\mathrm{HF})]{1)\ \mathrm{R'O^-/R'OH},\ 2)\ \mathrm{H^+}} \mathrm{R\text{-}\underset{\|O}{C}\text{-}CHF\text{-}\underset{\|O}{C}OR'}\ (\mathbf{3})$$

For example, a mixture of aluminum chloride (16.0 g, 0.12 mol), acetyl chloride (7.85 g, 0.10 mol) and dichloromethane (100 ml) in a pressure vessel was cooled in a dry ice-acetone bath and trifluoroethene (9.0 g, 0.11 mol) was introduced. The whole was stirred at room temperature for 48 h and was poured onto ice containing conc. hydrochloric acid. An oily layer was separated, washed with aqueous solution of $NaHCO_3$, and dried ($MgSO_4$). After evaporating the solvent, distillation of the residue gave **1** (R = Me) (10.2 g, 64%), bp 98 - 100 °C. A mixture of **1** (R = Me) (0.80 g, 5 mmol) and a sodium ethoxide solution prepared from sodium (0.45 g, 20 mmol) and ethanol (10 ml) was stirred for 2 h at room temperature and the reaction mixture was poured into water. Oily material was extracted with diethyl ether and a few drops of hydrochloric acid (1 N) was added into the ethereal extract. After 15 h of stirring at room temperature, the whole was poured into water and worked up as usual. Distillation (bp 102 °C/ 53 mmHg) gave **3** (R = Me) in 88% yield.

On the other hand, we found that aryl 1,2,2,2-tetrafluoroethyl ketones (**5**) could be obtained by the reaction between arylmagnesium bromides and N,N-diethyl-1,2,2,2-tetrafluoropropionamide (**4**), a hydrolyzed product of hexafluoropropene-diethylamine adduct.[7] The dehydrofluorination of **5** with a base gave aryl trifluorovinyl ketones (**6**) in situ, and the subsequent solvolysis afforded α-fluoro-β-arylketoesters (**7**) (Table 1, Method B).

For example, phenyl 1,2,2,2-tetrafluoroethyl ketone (2.06 g, 10 mmol) prepared by the reaction of phenylmagnesium bromide with **4** in tetrahydrofuran at -30 °C was mixed with methanol (10 ml) and aqueous sodium hydroxide (2 N, 18 ml), and the whole was stirred for 1 h at room temperature. The reaction mixture was treated with conc. HCl and the ethereal extract was subjected to distillation

Table 1 Preparation of α-fluoro-β-ketoesters, 3 and 7

R	R'	Method[b]	Yield[c] %	Bp (^{o}C/mmHg) (Mp ^{o}C)	^{19}F NMR δ ppm (J_{HF} Hz)[d]	IR (C=O) cm^{-1}
Me	Et	A	88	102/53[e]	116 (50.0)	1730, 1760
n-Pr	"	"	95	83-85/8	117.5 (50.4)	1735, 1760
n-C_5H_{11}	"	"	95	83-84/5	117.3 (50.4)	1735, 1760
n-C_9H_{19}	"	"	97	114-116/3	117.1 (51.0)	1735, 1760
Ph	Me	B	87	114-115/10	115 (47.0)	1680, 1750
Ph	Et	"	71	120-121/12[f]	114 (43.2)	1680, 1750
4-ClC_6H_4	Me	"	77	152-153/8	112 (49.8)	1695, 1770
4-MeC_6H_4	"	"	83	135-136/2	112 (47.9)	1690, 1760
4-$Me_2NC_6H_4$	"	"	87	(60-61)	111 (48.9)	1660, 1755

a) The structures were identified or confirmed by ir and nmr spectra. The microanalyses were in satisfactory agreement with the calculated values.

b) Method A : From 1 to 3. Method B : From 5 to 7.

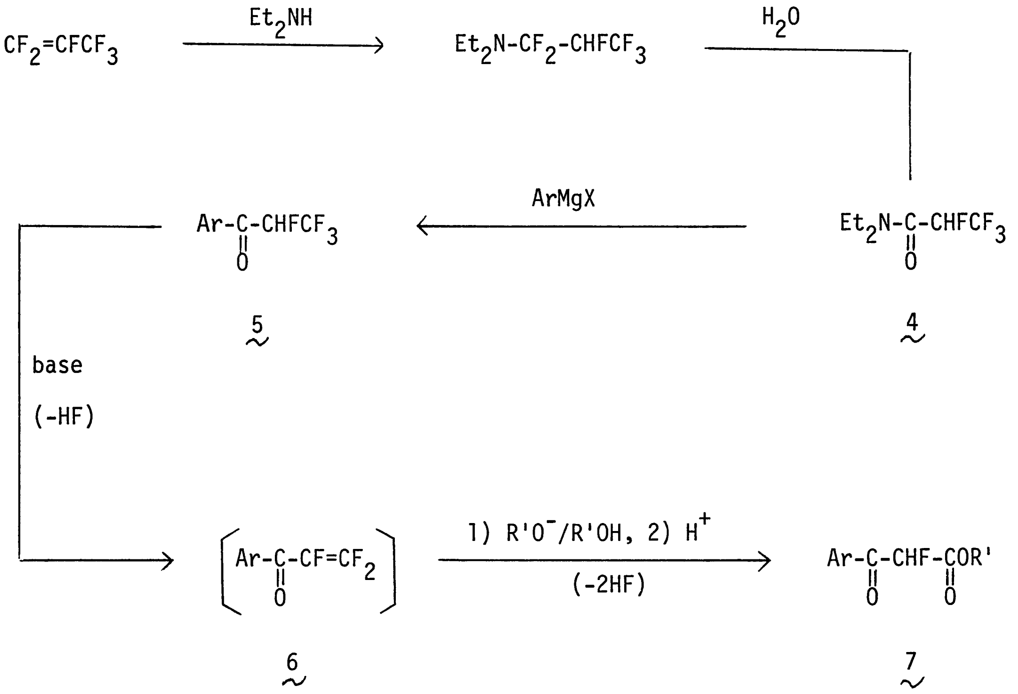
c) Isolated yield.

d) δ ppm upfield from ext. CF_3CO_2H.

e) Lit.[2], bp 83 - 85 ^{o}C/ 19 mmHg.

f) Lit.[2], bp 125 - 128 ^{o}C/ 4 mmHg.

affording **7** (Ar = Ph) (bp 144 - 145 °C/ 10 mmHg) in 87% yield.



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