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PREPARATION OF TRIFLUOROMETHYL KETONES AND RELATED FLUORINATED KETONES

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CONTENTS

1 INTRODUCTION

Fluorinated compounds have been of great interest to synthetic and medicinal chemists for a considerable time due to the unique physical and biological properties imparted by fluorine.[1,2] Fluoroorganic compounds have become a very important part of organic chemical research, because of their utilisation in the pharmaceutical, agrochemical and polymer fields: drugs, pesticides, dyes, surfactants, textiles, etc.. .[2]

Among these numerous and various compounds, fluorinated ketones are the subject of renewed interest by organic chemists. This focus is derived not only from their roles as synthons in the preparation of more complex molecules, but also from their own biological properties as enzyme inhibitors.

A review on monofluoroketones has been recently published,[3] but the last report on polyfluoromethyl ketones was published thirteen years ago.[4] Another review has been devoted to the preparation of biologically active fluorine compounds.[5] However, this comprehensive review does not describe the synthetic procedures for the preparation of fluoromethyl ketones. In fact, the synthesis of these ketones has, for a long time, not been trivial because the original methods were limited. The success of new improved synthetic approaches, now makes fluorinated ketones, in most cases, readily available.

After a short survey of the typical properties of fluoroalkyl ketones, this Report describes the synthetic problems and methods for their solution. In most cases, general methods described for the preparation of trifluoromethyl ketones can be used for the preparation of hemiperfluoroalkyl and α,α-difluoro ketones: a separate part of this Report will be devoted to specific approaches to the latter compounds. The last section of this Report describes the preparation of α-functionalized fluoroketones.

2 BRIEF SURVEY OF THE PROPERTIES OF TRIFLUOROMETHYL AND RELATED KETONES

The strong electron-withdrawing character of fluoroalkyl groups alters the properties of the carbonyl group. The most important factor is the exceptionally high electrophilicity of fluorinated ketones.[6]

A perfluoroalkyl group also significantly reduces the basicity of carbonyl group of fluorinated ketones. The difference in proton affinity between trifluoroacetone and acetone is about 17 Kcal/mol.[7] This diminishes protonation or complexation of fluoroketones by metal cations or soft Lewis acids. On the other hand, the

presence of fluorine on the carbon adjacent to the carbonyl enhances the reactivity of the ketone towards nucleophiles. Stabilization of the tetrahedral adduct between a nucleophilic entity and the carbonyl group is amply illustrated by the ability of fluorinated ketones to form stable hydrates in aqueous media or hemiketals.[8,9,10,23b] These phenomena can be explained as a stabilization of the anionic tetrahedral intermediate by the electron-withdrawing R_f group, which diminishes the reversibility of the nucleophilic addition (Fig. 1).[11,12]

These tetrahedral adducts serve as ideal mimics of the tetrahedral transition state[13] involved in enzymatic peptide or ester hydrolysis. When the nucleophilic agent that adds the fluoroketone is the active site of a nucleophilic enzyme then the fluoroketone can act as inhibitor.[14]

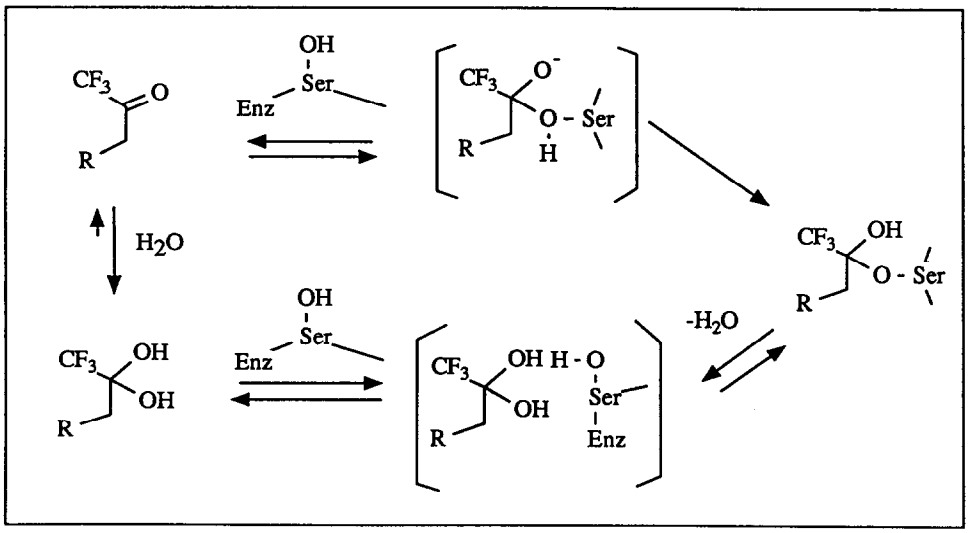


Fig. 1

Fluoromethyl ketones have been proven to inhibit the action of a variety of esterases or proteases[14] (Table 1 and 2). Serine esterases (acetylcholinesterase[14-17,23b], insect juvenile hormone esterase and mammalian carboxyl esterases[16-25], phospholipase A_2[26,27]) are efficiently inhibited by fluoromethyl ketones. Serine proteases (α-chymotrypsin and elastase[11,18,29-33], trypsin and blood-coagulation serine protease[34]) and cysteine proteases[30,35,36,37] are reversibly inhibited by α-amino or peptidyl fluoromethyl ketones.

Covalent bonding between the active site of serine and the carbonyl group of fluoro ketones has been established by kinetic analysis and NMR spectroscopy.[11,28,29,30,32,38] The crystal structures of the covalent

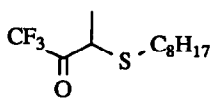
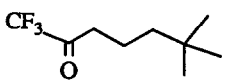
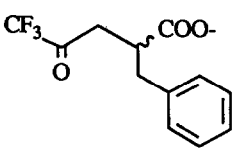
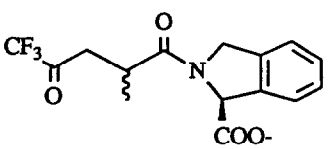
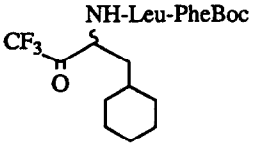
Table 1: Esterases and proteases inhibited by fluoromethyl ketones

Enzyme family	Enzymes	References
Esterases	Phospholipase A_2	26,27
	Lipase	16,18
	Porcine Liver Carboxy Esterase	16,18,25
Serine esterases	Acetyl cholinesterase	14,15,16,17,23b,42
	Insect juvenile hormone Esterase	16,17,19,21,22 23,24,42,43
Serine proteases	α-Chymotrypsin	11,28,32,33a
	Pig pancreatic Elastase	28,30
	Human Leukocyte Elastase	29,30,31,33b,44
	Bovin Trypsin	24,34
	Factor XIa	34
	Thrombin	34
	Pig pancreatic Kallekreine	34
Cysteine proteases	Rat Cathepsin G	30
	Human Cathepsin G	30
	Bovin Cathepsin D	35
	Bovin Cathepsin B	36
	Papain	37
Metalloproteases	Carboxypeptidase A	31,45
	Angiotensin converting enzyme	14
Aspartic proteases	Pepsin	14,35
	Renin	20,35,47,48,49,50

complexes formed between a peptidyl fluoromethyl ketone with porcine pancreatic elastase[12,39], or with α-chymotrypsin,[40] demonstrate the tetrahedral geometry of the carbon atom which results from the addition of Ser 195 to the ketonic carbonyl group. The strong stability of the covalent adduct may involve not only the electronegativity of the fluorinated groups but also hydrogen bonding between the fluorine atoms and acidic hydrogens of the enzyme.[12,39,41] Fluoromethyl ketones can inhibit the action of zinc metalloproteases (carboxy-peptidase A,[31,45] angiotensin converting enzyme[14]) but in these cases, the mechanism of inhibition is different. Lipscomb and Christianson have proposed that the fluoromethyl ketone hydrate gives a gem-diolate adduct with Zn cation at the active site.[46]

Aspartic proteases (pepsin and renin) are also inhibited by fluoromethyl ketones[14,20,35,47,48,49,50] but the mechanism of inhibition has not been fully elucidated. The inhibitor could interact with a water molecule which is bound to the two aspartic acid residues of the catalytic site at the enzyme as is observed with pepstatin derivatives.[51]

Table 2: Some examples of trifluoromethyl ketones as proteolytic enzyme inhibitors.[14,19,48]

	Insect JH esterase	IC_{50} 9.10^{-10} M
	Acetylcholine esterase	K_i 16.10^{-9} M
	Carboxypeptidase A	K_i 2.10^{-7} M
	Angiotensin Converting Enzyme	K_i 12.10^{-9} M
 NH-Leu-PheBoc	Renin	IC_{50} 25.10^{-8} M

3 PREPARATION OF FLUOROMETHYL AND HEMIPERFLUOROALKYL KETONES

The earliest reports on the preparation of fluorinated ketones were based on direct fluorination or halogen exchange reactions. These methods were not of great synthetic interest because these reactions are not selective and require drastic conditions. Moreover, trichlorinated starting materials are not easily available. Fluorination is nowadays used only for the preparation of some particular α,α-difluoroketones.

A major approach to the preparation of fluoromethyl and hemiperfluoroalkyl ketones has been based on two organometallic reactions (i) reactions of a non-fluorinated organometallic reagent with a fluorinated carbonyl compound, or (ii) reactions of a fluorinated organometallic reagent with a carbonyl compound. The first method was for a long time one of the most practical for the preparation of trifluoromethyl ketones because reactions on trifluoroacetic acid derivatives form trifluoromethyl ketones directly. The presence of the electron-withdrawing CF_3 group stabilizes the tetrahedral adduct between the organometallic reagent and the carbonyl group so that the formation of a ketone during the reaction is suppressed, so further addition of the organometallic reagent does not occur. Fluoroketones were obtained in variable yields along with by-products (secondary and tertiary alcohols) which depend critically upon reaction conditions and structure including that of the Rf groups. Since the yield of tertiary alcohol increases with the size of Rf group this method is not good for hemiperfluoroalkyl ketone preparation. In the case of aromatic fluoroalkyl ketones, Friedel-Crafts reactions are an alternative to method (i).

Method (ii) is limited by the instability or the decreased nucleophilicity of fluorinated organometallic reagents. However, perfluoroalkyl organometallic compounds react with aldehydes, or activated carbonyl compounds yielding fluorinated alcohols. However this leads to another problem because until recently good methods for the oxidation of fluorinated alcohols have not been available. Recently great effort has been devoted to the improvement of these organometallic methods. Moreover, new approaches to fluorinated ketones were based upon the enhanced electrophilicity of carbonyl carbon. Wittig reactions have been successfully effected on trifluoroacetic derivatives, including esters, anhydrides, and amides. Various fluorinated synthons, including fluoroalkyl ketones, could be prepared in this way.

Another new approach was based on the unique reactivity of ethyl trifluoroacetoacetate which is now commercially available. The presence of CF_3 group modifies the reactivity of this β-ketoester but with careful selection of reaction conditions, C-alkylation can lead to various trifluoromethyl ketones. The Carroll reaction has also been employed for the preparation of homoallylic trifluoromethyl ketones.

3-1 Organometallic reagents and trifluoroacetic acid (or perfluoroalkanoic) derivatives

Reactions between organometallic reagents and trifluoroacetic acid derivatives have been extensively used for the synthesis of fluoroketones. This approach is limited by the availability of the organometallic reagent and the formation of by-products such as secondary and tertiary alcohols. The excellent study of Tamborski *et al.*[52] has shown that the stability of the initial tetrahedral adduct of the organometallic compound governs the subsequent formation of different products (Fig. 2). In some cases, this intermediate is sufficiently stable to be isolated[52] or trapped by silylation or acetylation (Fig. 3).[53] Its stability depends on the nature of the substituents and reaction conditions. This explains the low yields of fluorinated ketones which are often encountered and the variety of procedures examined since the pioneering work in the 1950's.[54-61]

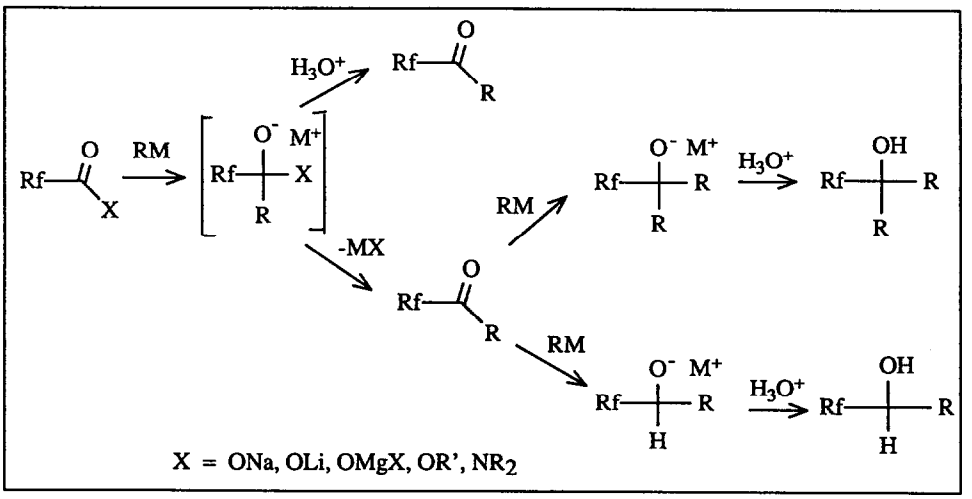


Fig. 2

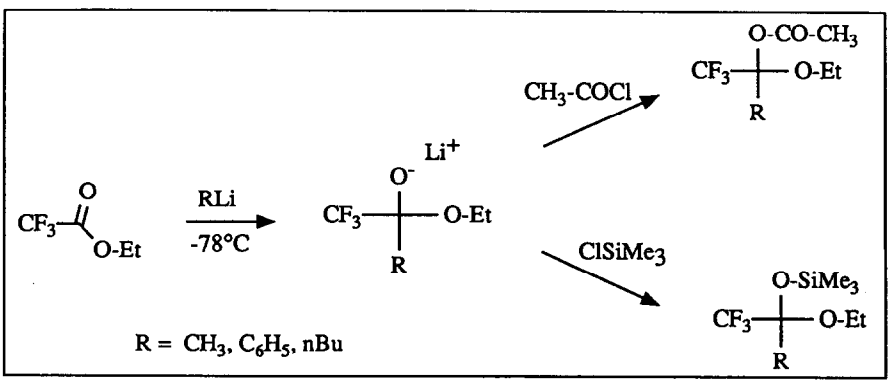


Fig. 3

1) Organometallic reagents:

Grignard or organolithium reagents have often been used but organozinc[56] or organocadmium reagents have also been employed.[62] More interesting are the organomanganous reagents. These reagents are easily prepared from cheap manganese (II) salts and acylation by trifluoroacetic anhydride affords the trifluoromethyl ketones (Table 3).[63]

Table 3: CF_3-CO-R by acylation of organomanganese (II) iodides with trifluoroacetic anhydride.[63]

R	Yield
R = *n*-$C_{10}H_{21}$-	70 %
R = $(n\text{-}C_4H_9)_2C{=}CH$-	89 %
R = *n*-C_6H_{13}-C≡C-	85 %
R = *p*.MeO-C_6H_4-	84 %

2) *Trifluoroacetic derivatives*

Starting trifluoroacetic acid derivatives are often metallic salts (Li, Na, Mg), either formed directly *in situ* from trifluoroacetic acid and organolithium (or Grignard) reagents, or preformed in order to avoid use of a large excess of organometallic reagents.[56,60,64-67] Alkyl trifluoroacetates,[57] various amides ,[7,53,68-71] trifluoroacetic anhydride[72,73] or trifluoroacetonitrile [56,74,75] can also be used.

3) *Procedures*

Among different variables,[57-59] the mode of addition and the reaction temperature are important factors in determining the stability of the tetrahedral intermediates. Low temperature stabilizes the adduct and reverse introduction of the organometallic reagent leads to increased formation of alcohols (table 4).

The best yields of trifluoromethyl ketones are based upon the conclusions of Tamborski *et al.*,[52] and this is illustrated by Creary's recent procedure for the addition, at low temperature, of Grignard or organolithium reagents to ethyl trifluoroacetate.[53] The same procedure can be applied to the α,α-difluoroesters with success.[76]

Table 4: Addition of C_6H_5Li on Rf-COOEt.[52]

Rf-COOEt	Temp °C/Time	Rf-CO-Ph	Rf-CHOH-Ph	Rf-COH-$(Ph)_2$
CF_3-COOEt	A -78 (10 min)	98	0	2
	20 (10 min)	82	0	18
	20 (10 min) → 20 (72h)	79	3	18
	B -40 (10 min)	96	0	4
	-40 (10 min) → 20 (72h)	94	2	4
	20 (10 min)	1	1	98
C_2F_5-COOEt	A -78 (10 min)	98	1	1
	-40 (10 min)	88	1	11
	-40 (10 min) → 20 (72h)	1	87	12
	B -40 (10 min)	53	1	46
	-40 (10 min) → 20 (72h)	4	49	47
	20 (10 min)	0	2	98
n-C_3F_7-COOEt	A -78 (10 min)	98	1	1
	-40 (10 min)	86	1	13
	-40 (10 min) → 20 (72h)	0	87	13
	B -40 (10 min)	37	1	62
	-40 (10 min) → 20 (72h)	0	37	62
	20 (10 min)	0	2	98

A: C_6H_5Li added on ester; B: reverse addition

4) *Nature of R group of organometallic reagents*

If the R group in the organometallic reagents is a good electron-donor such as 2-thienyl group then the tetrahedral intermediate is destabilized and considerable formation of tertiary alcohol is observed.[53] Acetylenic organometallic reagents provide the corresponding acetylenic trifluoromethyl ketones easily.[77,78] Yields and reproductibility can be improved by the presence of boron trifluoride etherate[79] (Table 17, part 6).

Table 5: CF_3-CO-R from reaction of CF_3-COOEt with organometallic reagents RM at -78°C.[52,53]

RM	Ketone
Ph-MgBr	86 %
$p$$CH_3C_6H_4$-MgBr	68 %
$p$$CH_3O$-$C_6H_4$-MgBr	69 %
$p$$CF_3$-$C_6H_4$-MgBr	72 %
Ph-Li	88 %
$p$$Me_2N$-$C_6H_4$-Li	85 %
1-Naphtyl-Li	75 %
pBr-C_6H_4-Li	73 %
Ph-CH_2-MgCl	70 %
cyclo-C_6H_{11}-MgCl	66 %
n-C_6H_{13}-MgBr	63 %
2-thienyl-MgBr	51 % (37 % of tertiary alcohol)

5) Nature of Rf group

The thermal stability of the tetrahedral adduct is a function of steric and electronic character of the R_f group. From systematic studies,[52] it appears that the stability of the tetrahedral adduct decreases in the following order: $CF_3 > C_2F_5 > n$-$C_3F_7 > i$-C_3F_7. Consequently, the yields of hemiperfluoroalkyl ketones are often low.[52,57,80]

3-2 Fluoroorganometallic reagents and carboxylic esters

A more direct approach to the synthesis of fluorinated ketones is based on the condensation of fluoroorganometallic reagents with carboxylic esters. However, until recently, there have been few successful reports of the introduction of small perfluoroalkyl groups.Trifluoromethyllithium,[81] trifluoromethyl Grignard reagent[82] are not synthetically useful because they readily decompose, apparently to difluorocarbene, even when formed at low temperature in the presence of a suitable electrophile. Trifluoromethylzinc, -cadmium, -mercury and -copper are stable but poorly reactive towards carboxylic esters.[83,84,85] Nevertheless when the ester function is activated by an electron-withdrawing group, as in the case of ethyl oxalate, then the Barbier procedure is effective (fig. 4).[84,86,87]

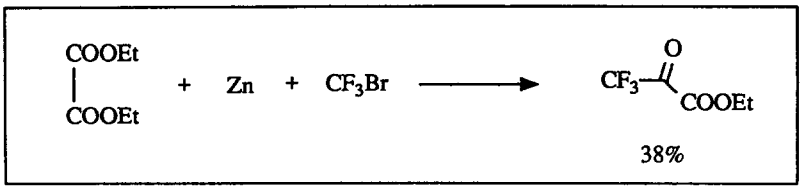


Fig. 4

Due to their low nucleophilicity, perfluoroalkylzinc[88-91] or - copper[92] can hardly be used for the perfluoroalkylation of unactivated esters. Perfluoroalkylmagnesium reagents are more stable than the trifluoromethyl Grignard reagent and lead to perfluoroalkyl ketones in only low yields.[93-94] In contrast, perfluoroalkyllithium reagents have been widely used for the preparation of perfluoroalkyl ketones.[95-98] However, difficulties are encountered with C_2F_5Li, which often leads to tertiary alcohols but even in this case, some pentafluoroethyl ketones have recently been prepared in good yields at low temperature (Table 6).[99]

New reagents such as perfluoroalkyltrimethylsilanes[100,103b] or the complexes RfI,$P(NR)_3$,[100,101] have been reported as efficient fluoroalkylating agents of some acyl derivatives. Thus the addition of Ruppert's reagent (CF_3-TMS)[100] to activated di-*t*-butyl oxalate affords the trifluoropyruvic acid in its hydrated form (Fig 5).[102] A patent describes the preparation of aryl perfluoroalkyl ketones using a homologous perfluoroalkyl trimethyl silanes and aroyl fluorides or anhydrides.[103a] Recently perfluoroalkyl ketones have been obtained in moderate yields, by the reaction of the complex between Rf-I and hexamethyl tris-amino phosphine with aroyl chlorides.[101,103a]

Table 6: Reaction of C_2F_5Li (about 5 equiv) with ethyl esters at -78°C.[99]

Ester	Ketone	Tertiary Alcohol
Benzoate	-	62%
Phenyl acetate	74%	-
Hexanoate	-	66%
Pivalate	-	93%
Cyclohexylcarboxylate	39%	24%
Methylthio acetate	62%	-
Nicotinate	71%	-
(2-Pyridine) carboxylate	78%	-
(2-Pyridine) acetate	100% (enol form)	-

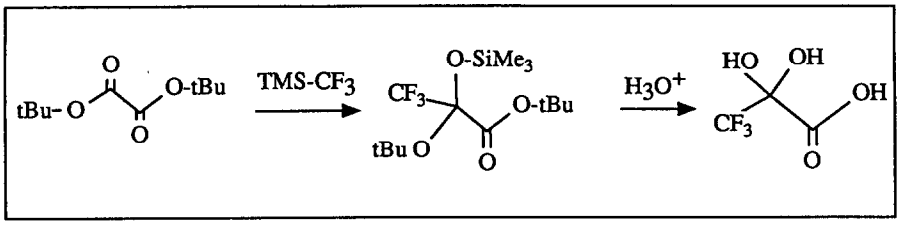


Fig. 5

3-3 Oxidation of secondary fluoroalkyl carbinols

Unsuccessful attempts to introduce, *via* organometallic reagents, small perfluoroalkyl groups to relatively unreactive carboxylic esters have led to a study of this reaction with more reactive carbonyl compounds such as aldehydes. Two shortcomings of this approach had to be resolved: firstly, organometallic reactions had to be optimized (see above), and secondly, methods for the oxidation of secondary trifluoromethyl carbinols into ketones had to be developed.

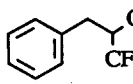
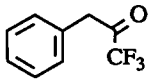
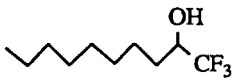
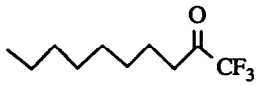
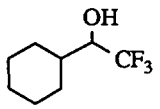
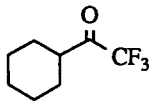
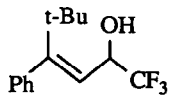
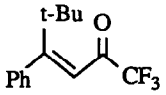
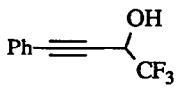
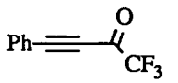
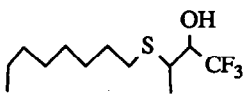
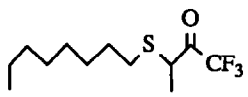
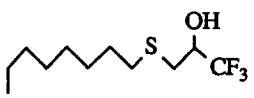
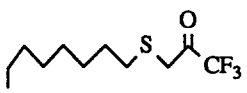
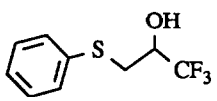
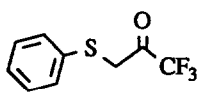
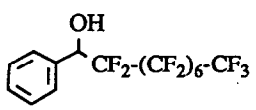
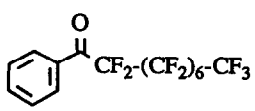
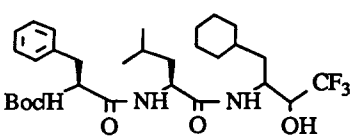
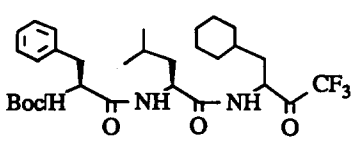
1) Preparation of secondary trifluoromethyl carbinols by organometallic process

Secondary trifluoromethyl carbinols can be prepared by the reaction of an organometallic reagent with trifluoroacetaldehyde[104,105] or by the reaction of a trifluoromethyl reagent with an aldehyde.[84,86,87,103b,106-111] The second strategy has received much attention in recent years. Now trifluoromethyl secondary alcohols are readily available by the use of zinc reagents, formed from CF_3Br and Zn, with activation techniques such as ultrasonic irradiation, pressure and electrochemistry.[84,87,106-110] Recently, CF_3-$SiMe_3$ has been identified as a good alternative reagent.[103b,111]

2) Oxidation

Classical procedures for the oxidation of secondary trifluoromethyl carbinols require severe conditions.[27,33a,105,112] Swern oxidation has been used, but reactions were not easily reproducible.[35b,105,113] The same difficulties are encountered in permanganate oxidations in basic aqueous media.[11,105,113,114]

Table 7 : Oxidation of secondary trifluoromethyl carbinols by the Dess-Martin reagent.[48,113]

Carbinol	Ketone	yield
		95 %
		93 %
		75 %
		76 %
		90 %
		79 %
		0 %
		96 %
		86 %
		92 %

The Dess-Martin periodinane[115] (Fig. 6) is an excellent reagent for the oxidation of fluoroalkyl carbinols.[113,114] An extensive study by Linderman[114] shows that this procedure is efficient (Table 7). It can be carried out in the presence of other functional groups, such as peptidyl substituents,[20,39,48] and proceeds without racemization of chiral centers.[39,114]

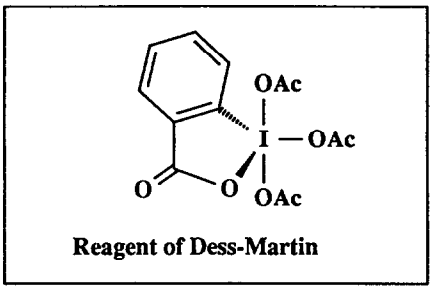


Fig. 6

3-4 Alkylation of ethyl trifluoroacetoacetate

A very useful preparative method for the synthesis of methyl ketones is the C-alkylation of enolates of ethyl acetoacetate followed by decarboxylation. Similarly this method could be appropriate for preparing the trifluoromethyl ketones from the commercially available ethyl trifluoroacetoacetate (ETFAA).

1) Preparation of C-alkylated Ethyl Trifluoroacetoacetate

Before 1985, only two scattered examples of alkylation of ETFAA had been described. Methyl tosylate did react with the cesium enolate of ETFAA in HMPA but this led exclusively to O-alkylation products.[116] This result was not surprising since all factors, a dissociating solvent, a large cation and a good leaving group (O-Ts) favorable for the O-alkylation are combined.[117] Chloroacetone leads exclusively to the corresponding C-alkylated product, when reacted with sodium enolate of ETFAA in acetone (dissociating solvent) in presence of a catalytic amount of KI.[118]

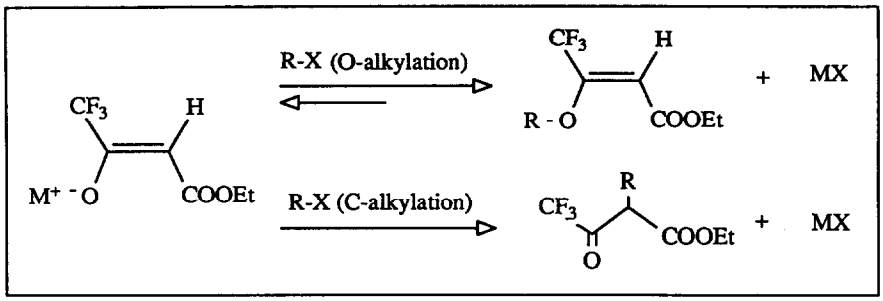


Fig. 7

Extensive studies on alkylation of trifluoroacetoacetate enolates have been made.[119,120,121] The following conclusions can now be drawn. When factors favorable for the C-alkylation process are combined (especially the use of small cations and non-dissociating solvents) then ETFAA enolates are very poorly reactive . Consequently, in order to improve the reactivity of these enolates, the use of dissociating solvents is absolutely necessary. Under these conditions, the O-alkylation process is kinetically favored but reversibility of this process has been demonstrated so this leads eventually to the C-alkylated product (Fig. 7).[119] When reactive halides in acetone are employed, the reversibility is so efficient that the C-alkylated trifluoroacetoacetates can be obtained in good yields, provided that reaction times are long[118,119,120] (Fig. 8; Table 8).

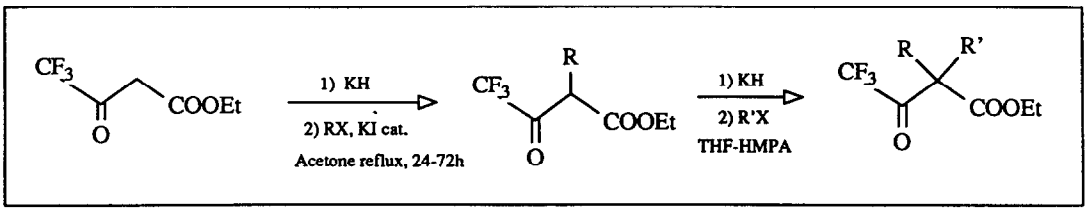
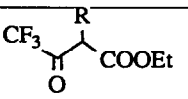


Fig. 8

Table 8: Mono C-alkylation of sodium enolate of ETFAA in boiling acetone in presence of KI.[118,120]

RX (equiv.)	Time (h)	
n-Propyl I (1)	72	9%
n-Propyl I (3)	72	15%
n-Octyl I (1)	120	13%
C_6H_5-CH_2Br (1)	48	74 % (62%)*
C_6H_5-CH=CH-CH_2Br (1)	72	56 % (49%)
CH_2=CH-CH_3-Br (1.1)	48	75% (64%)
CH_3I (1.1)	72	75% (50%)
C_6H_5-CO-CH_2Br (1)	72	57% (30%)
BrCH_2-COOEt (1)	72	47% (37%)
CH_3-CO-CH_2Cl (1)	72	(64%)

*Values in parentheses are yields in isolated products.

The failure of C-alkylation of ETFAA enolate with non-activated halides required a new route to these C-alkylated ETFAA compounds. Recently, alkylation of the anions of the dioxolane or the N,N-methyl hydrazone of ETFAA followed by deprotection, has been reported. The mild conditions required for the deprotection of N,N-dimethyl hydrazones make this last route particularly attractive (Fig. 9, Table 9).[121]

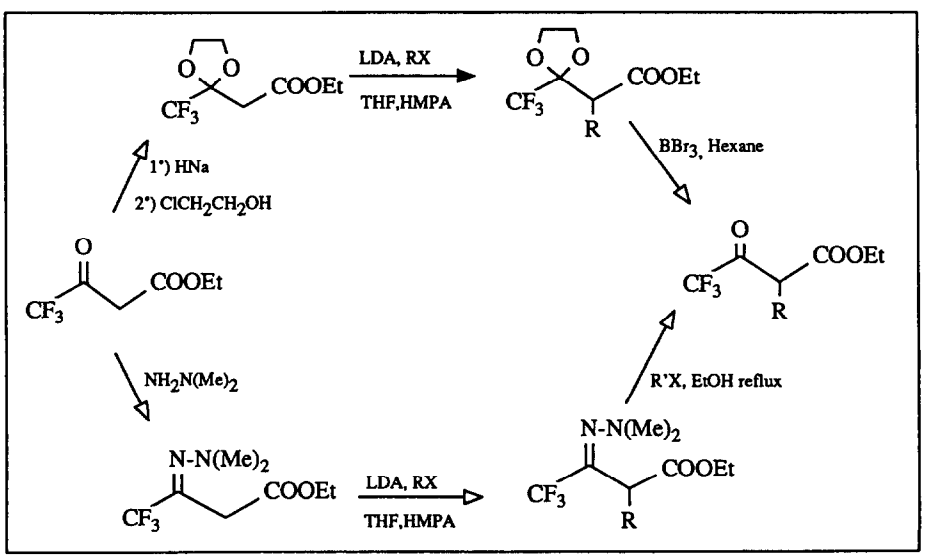
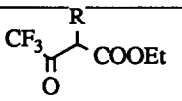


Fig. 9

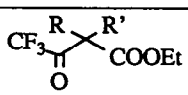
Table 9: Monoalkylated Ethyl Trifluoroacetoacetate from alkylation of ETFAA dimethylhydrazone (THF/HMPA 3 equiv.) at room temperature. Deprotection performed with R'X (15 equiv.).[121]

RX (1 equiv.)	Alkylated hydrazone		Deprotection R'X/time
n-Propyl I	90% (75)	(80)	(EtBr, 48 h)
C_6H_5-CH_2Br	>95% (80)	(90)	(EtBr, 48 h)
C_6H_5-CH_2CH_2I	25% (18)	(80)	(EtBr, 48 h)
$C_6H_5CH_2CH_2CH_2$I	80% (68)	(80)	(EtBr, 72 h)
C_6H_5-CH=CH-CH_2Br	80% (65)	(70)	(Allyl Br, 1.5 h)
Dimethylallyl Br	95% (77)	(80)	(MeI, 48 h)
(5-Phenyl 5-hexenyl)I	65% (47)	(70)	(Allyl Br, 1.5 h)
		(60)*	(Allyl Br, 7.5 h)
(4-Phenyl 4-pentenyl)I	60% (45)	(80)	(Allyl Br, 1.5 h)
		(70)*	(Allyl Br, 7.5 h)

Values in parentheses refer to isolated products.
*Under these conditions, the isomerization of the double bond occurred.

Dialkylated compounds can be obtained by alkylation of the first prepared monoalkylated ETFAA , provided that a very dissociating medium (THF/HMPA) and an active halide are used (Fig. 8, Table 10).

Table 10 : Alkylation of potassium enolate of monoalkylated ETFAA in THF-HMPA (2 equiv.) at boiling point.[119,120]

R	R'X (equiv)	Time (h) 
C_6H_5-CH_2-	CH_2=CH-CH_2Br (1)	8 45% (28)
C_6H_5-CH_2-	C_6H_5-CH_2Br (1,5)	16 42% (21)
C_6H_5-CH_2-	CH_3-C(=CH_2)CH_2Cl (4)	24 50% (40)
$CH_3CH_2CH_2$-	CH_2=CH-CH_2Br (2)	19 75% (58)
$CH_3CH_2CH_2$-	CH_3-C(=CH_2)CH_2Cl (2)	22 63% (48)
$CH_3CH_2CH_2$-	CH_3-CH=CH-CH_2Cl (3)	24 50% (42)

Values in parentheses refer to isolated products.

2) Trifluoromethyl ketones from decarbethoxylation of alkylated ethyl trifluoroacetoacetates

Trifluoromethyl ketones are easily obtained from alkylated ETFAA using Krapcho's decarbethoxylation methodology[122] under neutral conditions (LiCl, DMF) (Table 11)[121]. This procedure is more convenient than classical acidic conditions.[123-128]

Table 11: CF_3-CO-CH_2-R from decarbethoxylation of alkylated ETFAA (LiCl/DMF).[121]

R	Isolated yield
n-Octyl-	65%
Benzyl-	85%
Phenylethyl-	85%
3-Phenylpropyl-	90%
Cinnamyl-	77%
Dimethylallyl-	62%
5-Phenyl 5-hexenyl	44%
4-Phenyl 4-pentenyl	38%
5-Phenyl 5-hexenyl	52%
4-Phenyl 4-pentenyl	56%

3) Carroll reaction from alkyl trifluoroacetoacetate. Preparation of γ,δ-unsaturated trifluoromethyl ketones

The Carroll reaction of an alkyl β-ketoester with an allylic alcohol in presence of sodium acetate leads to γ,δ-ethylenic ketones. The first step, a transesterification, is followed by a Claisen-type thermal transfer of the allylic group.[129] This reaction has been successfully applied to ethyl trifluoroacetoacetate (Fig. 10).[129,130,131]

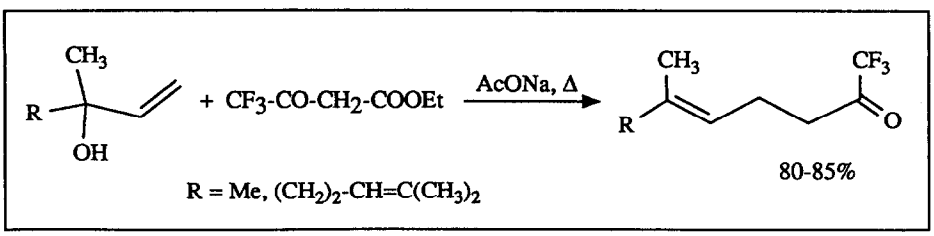


Fig. 10

The same reaction, catalyzed by palladium (II), has recently been applied to allylic esters of trifluoroacetoacetic acid obtained by transesterification with distannoxane catalyst Cl-, or SCN-(n-Bu)$_2$Sn-O-Sn(n-Bu)$_2$OH (Fig. 11).[132]

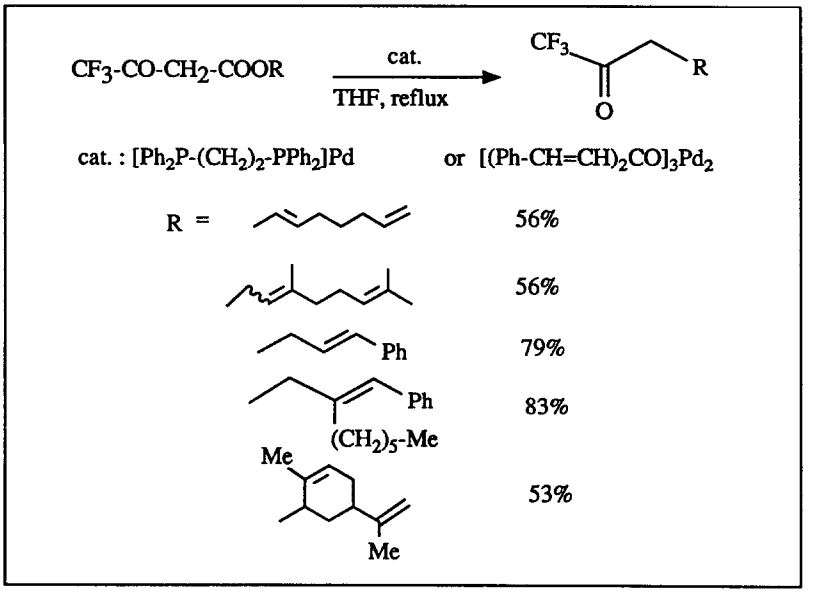


Fig. 11

3-5 Claisen and related reactions of ethyl fluoroalkanoates

The Claisen condensation of ester enolates with ethyl trifluoroacetate is an alternative route to the formation of alkylated ETFAA. Besides some literature examples,[80,123-128] this reaction has been industrially used for preparation of ETFAA from ethyl acetate and ethyl trifluoroacetate. It can also be carried out with ethyl perfluoroalkanoates.[80] In addition CF_3-COOEt can be condensed with lactones leading to ω-hydroxy trifluoromethyl ketones.[133] Classical methods for decarbethoxylation require heating in an acidic medium but, as described above (part 3-4), Krapcho's procedure might be more convenient.[121]

When performed with ketone enolates, the Claisen condensation with Rf-COOEt leads to fluorinated β-diketones.[125,134,135] Discussion of this important class of fluorinated ketones is not included in this Report.

β-Diketones are converted to fluoromethyl ketones in good yield by cleavage in an alkaline medium.[125] A related reaction is the condensation of an anion of a nitrile with CF_3-COOEt (Fig. 12).[136,137]

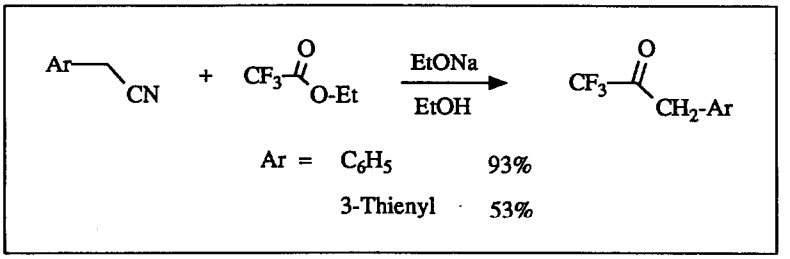


Fig 12

The condensation between anions of activated methylene compounds and ethyl fluoroalkanoates have been developed in order to synthesize α-functionalized fluoroalkyl ketones (part 7).

Condensation of α-sulfinyl anions with alkyl perfluoro alkanoates affords α-sulfinyl hemiperfluoroalkyl ketones (part 7-4).

The addition of α-nitro anions or carboxylic acid dianions to trifluoroacetaldehyde is used in the synthesis of α-amino trifluoromethyl ketones (part 7-5).

3-6 Wittig reaction: Phosphonium ylides and trifluoroacetic derivatives

During the past few years, the Wittig reaction has been successfully applied to trifluoroacetic acid derivatives for the preparation of various fluorinated synthons, by several groups[138-147,161] including Shen's group in Shanghai.[148-157] This approach is one of the most versatile approaches to fluorinated ketones.[138,141,142,149,157]

1) Wittig reaction from trifluoroacetamides

No example of an intermolecular Wittig reaction of amides had been reported, but the peculiar addition

of phosphoranes to a β-lactam is known.[158] This is clearly due to the very poor electrophilic character of the carbonyl carbon of amides. However, due to the strong electron-withdrawing effect of the CF_3 group, the Wittig reaction can be performed on trifluoroacetamides leading to a E:Z (~50:50) mixture of 1-(trifluoromethyl)-enamines. The best yields are obtained from the less basic morpholino-amide (Fig 13, Table 12).

These enamines are easily hydrolyzed to trifluoromethyl ketones by HCl/Et_2O (1.5M) in high yields (95-100%).

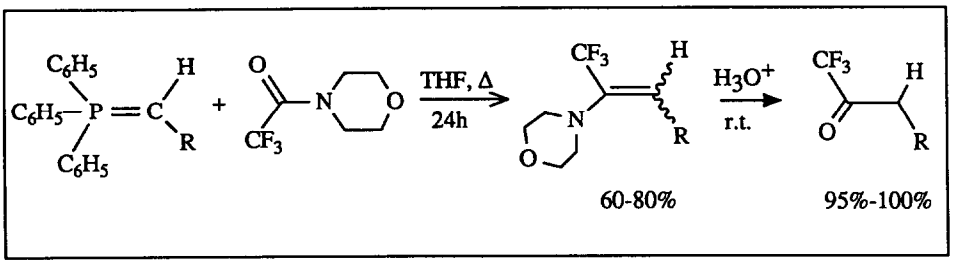


Fig 13

Table 12: 1-(Trifluoromethyl)-enamines from phosphonium ylides Ph_3P=CH-R and trifluoroacetamides.[141]

R_1R_2NH	R	Isolated Yields
Morpholine	n-C_6H_{13}-	76%
Morpholine	Phenyl	62%
Morpholine	C_6H_5-CH_2-CH_2-	66%
Morpholine	*p*MeO-C_6H_4-CH_2-CH_2-	59%
Piperidine	*cyclo*-C_6H_{11}-CH_2-	36%
Piperidine	C_6H_5-CH_2-CH_2-	46%
1-Phenylethylamine	C_6H_5-CH_2-CH_2-	37%
1-Phenylethylamine	*cyclo*-C_6H_{11}-CH_2-	55%

2) Wittig reaction from perfluoroalkanoic anhydrides and chlorides

A phosphonium ylide addition to carboxylic anhydrides or chlorides does not lead to the olefinic compounds. However α-acylphosphonium salts,[159,160] are potential precursors of ketonic compounds (Fig.

14) andthis approach has been successfully used by Shen *et al.* for the preparation of trifluoromethyl and hemiperfluoroalkyl ketones (Fig. 14 and Table 13).[157]

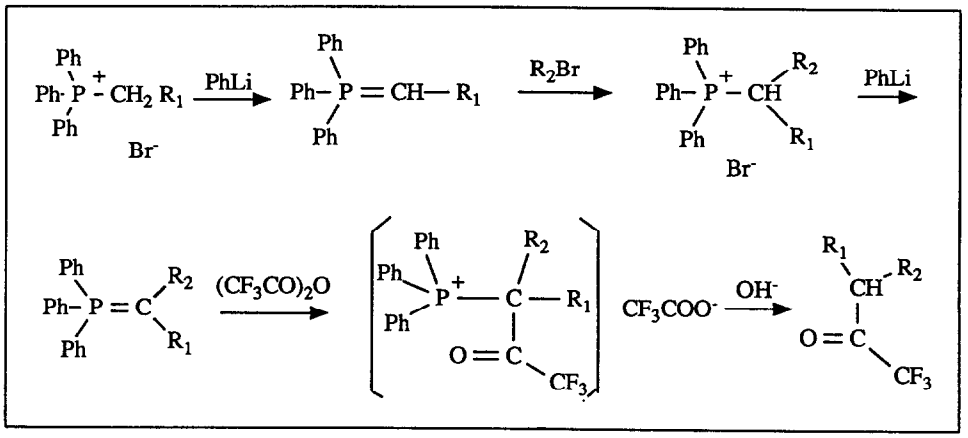


Fig. 14

Table 13 : Rf-CO-CHR$_1$R$_2$ prepared from phosphonium ylides and (Rf-CO)$_2$O (Fig.14).[157]

R_f	R_1	R_2	Yield
CF_3	Me	Ph-CH_2	78%
C_2F_5	Me	Ph-CH_2	67%
C_3F_7	Me	Ph-CH_2	75%
CF_3	Et	Ph-CH_2	66%
CF_3	*n*-Pr	Ph-CH_2	70%
CF_3	*n*-Bu	Ph-CH_2	70%
CF_3	Ph	Me	40%
CF_3	*i*-Hept	Me	54%
CF_3	Ph-CH=CH-CH_2	Me	34%

Perfluoroalkyl carboxylic chlorides react with phosphoranes stabilized by an electron-withdrawing group (EWG) to form fluoroacetylated phosphonium salts (Fig. 15)[143,148,149] (see part 6-1).

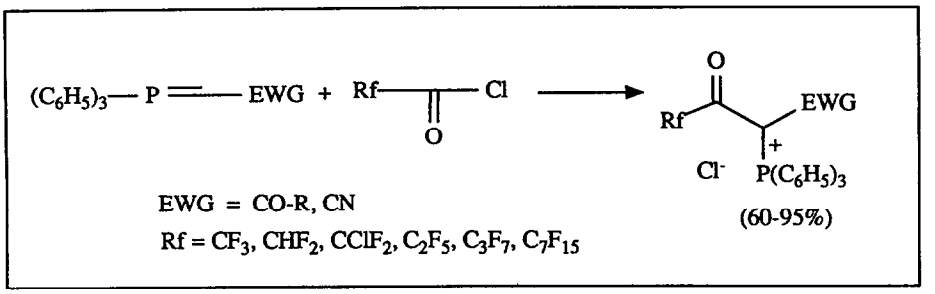


Fig. 15

3°) Wittig reaction with perfluoroalkyl carboxylic esters

The Wittig reaction of activated esters has been studied by several groups.[160,163] The reaction is highly dependent on the structure of the ester (especially the nature of O-R_1 group), of the phosphorane reagent, and also on the medium (presence of salts or not). The Wittig reaction can lead to two different processes: the first (a) allows the formation of the enol ethers, and the second (b) leads to the α-acyl phosphonium salts (Fig. 16). The competition between these two processes is still under investigation.[162] Clearly, a poor leaving group in the intermediate oxaphosphetane makes the process (b) unfavorable, as is observed with amides.

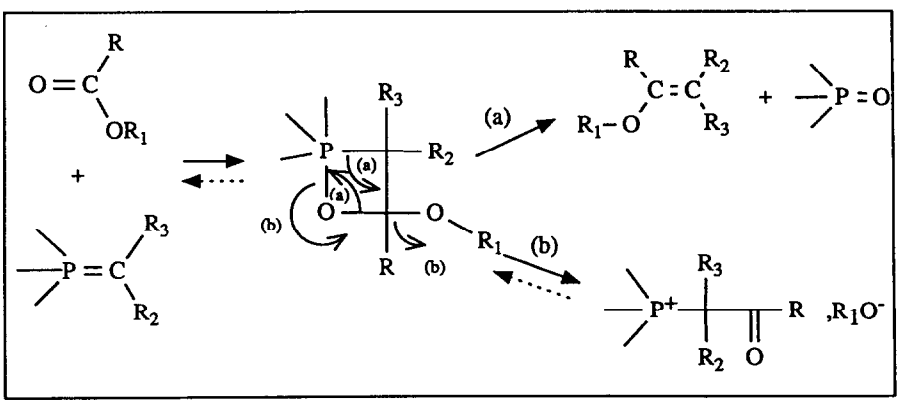


Fig. 16

In 1970, Bestmann[163] showed that ethyl trifluoroacetate can react with phosphoranes to provide the enol

ethers (process a), but these ethers were quite stable toward hydrolysis even in HI. However, in other studies,[142] these enol ethers could be transformed into the corresponding ketones using BBr_3.

In order to circumvent this hydrolysis problem, the Wittig reaction has been performed on trimethylsilyl trifluoroacetate.[142] The corresponding silyl enol ethers are isolated in good yield and are then hydrolysed under very mild conditions yielding the trifluoromethyl ketones (Fig. 17 and Table 14). This method is particularly useful when an isomerizable double bond is present in the molecule.

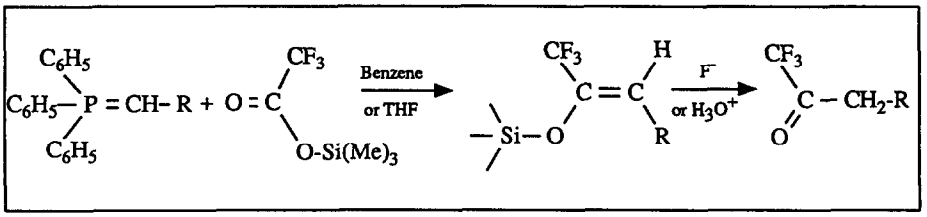
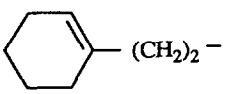
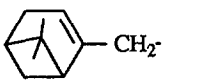
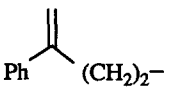
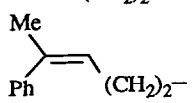


Fig 17.

Table 14: Trifluoromethyl ketones from phosphonium ylide Ph_3P=CH-R and trimethylsilyl trifluoroacetate.[142]

R	Silyl enol ether*	CF_3-CO-CH_2-R*
C_6H_5-	48%	95%
C_6H_5-CH_2-CH_2-	50%	90%
3,4-diMeO-C_6H_4-CH_2-CH_2-	40%	90%
Cyclohexyl-	46%	95%
Cyclohexyl-CH_2-	78%	95%
n-Hexyl-	70%	92%
	51%	80%
	58%	90%
	35%	95%
	17%	95%

* Isolated yields

4) Wittig reaction with perfluoronitriles

Perfluoronitriles react with phosphoranes stabilized by a carbonyl group giving the corresponding iminophosphoranes. Their acidic hydrolysis leads easily to perfluoroalkyl 1-3-dicarbonyl compounds in high yield (Fig. 18).[144-146]

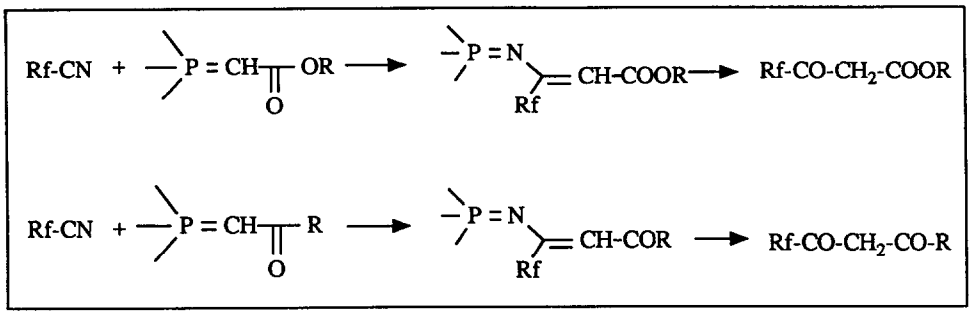


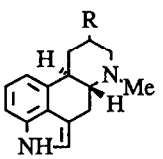
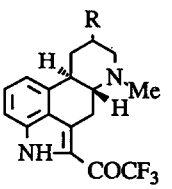
Fig. 18

3-7 Electrophilic fluoroacylation (Friedel-Crafts reaction)

Acylation of aromatic compounds with electrophilic trifluoroacetylating reagents was one of the earliest routes to aromatic trifluoromethyl ketones. As early as 1943, trifluoroacetophenone was prepared by the action of trifluoroacetyl chloride on benzene, in the presence of $AlCl_3$.[164-166] Since then, classical Friedel-Crafts conditions have been used for various aromatic compounds, mostly, using trifluoroacetic anhydride[73a,167-170]; trifluoroacetyl chloride is hard to handle. Yields are sometimes low because of the formation of arylated by-products arising from further reaction of the resulting fluoromethyl ketone with the aromatic compound.[165,171] The high electrophilicity of trifluoroacetic anhydride, or trifluoroacetyl triflate[172] makes possible the uncatalyzed reaction with nucleophilic aromatic compounds. This is a very good procedure for the preparation of aromatic and heterocyclic trifluoromethyl ketones (Table 15).[173-178,180,181] However, highly nucleophilic aromatic compounds are required as is demonstrated by the failure of resorcinol dimethylether[173] and phenol to be trifluoroacetylated.[179]

Trifluoroacetonitrile has also been used as trifluoroacetylating reagent but a catalyst is required in addition to highly nucleophilic aromatic substrates.[182]

Table 15: Trifluoroacetylation of aromatic compounds with trifluoroacetic anhydride.

ArH	Relative rates Ar-CO-CF_3 (at 75°C)		Yield	Ref.
Thiophen	1	(2-CO-CF_3)		173,175
Selenophen	6.5	(2-CO-CF_3)		
Furan	$1.5x10^2$	(2-CO-CF_3)	75%	175,177
2-Methylthiophen	$3x10^2$	(2-CO-CF_3)		175
2-Methylfurane	$3.5x10^4$	(2-CO-CF_3)	58%	175,177
2-Methoxythiophen	$1x10^6$	(2-CO-CF_3)		175
Pyrrole	$1x10^8$	(2-CO-CF_3)	66%	173,174,175
N-Methylpyrrole	$2x10^8$	(2-CO-CF_3)		175
Indole		(3-CO-CF_3)	90%	173
3-Methyl Indole		(2-CO-CF_3)	32%	173
Azulene		(1-CO-CF_3)	91%	178
Resorcinol Dimethyl ether		-	0%	173
Dimethylaniline		(4-CO-CF_3)	40%	173
Pyrogallol Trimethyl ether		(1-CO-CF_3)	76%	173
1-Dimethylamino naphthalene		(4-CO-CF_3)[a]	95%	180
			63%[b]	181

[a] When 2.5 equiv. of $(CF_3\text{-}CO)_2O$ are used, the 2- and 4-diacylation products are obtained.
[b] In presence of BF_3,Et_2O as catalyst.

Very recently 2-(trifluoroacetoxy) pyridine has turned out to be an effective reagent for trifluoroacetylation of a variety of aromatic compounds, provided that aluminium chloride is used as catalyst (Fig. 19).[183]

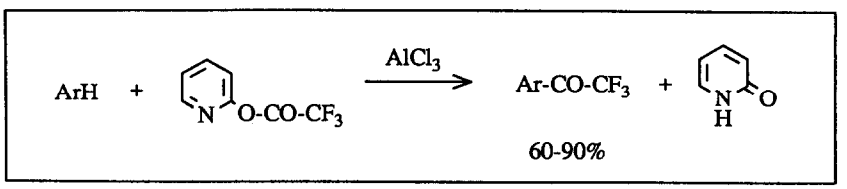


Fig. 19

Some examples of trifluoroacetylation of olefinic compounds have been described. An isolated example has been reported in 1973 by Wenkert[184] in the course of the Polonovski-Potier reaction of N-methyl piperidine oxide (Fig. 20).

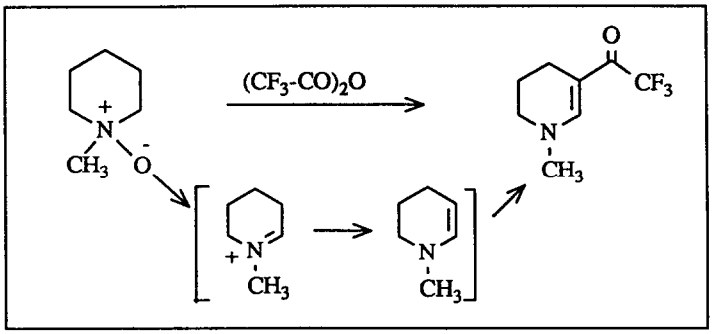


Fig. 20

More recently, Hojo *et al.* have reported the very facile trifluoroacetylation of electron-rich olefins. Figure 21 shows an example.[185] These reactions will be described later (part 6-2).

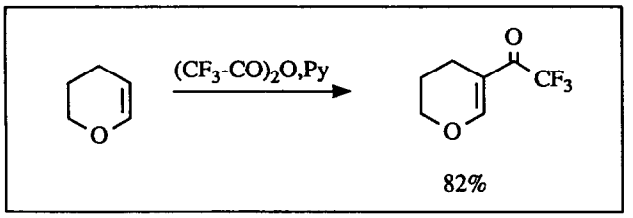


Fig. 21

A peculiar example of acylation of a bicyclic diene, has recently been reported (Fig. 22).[186]

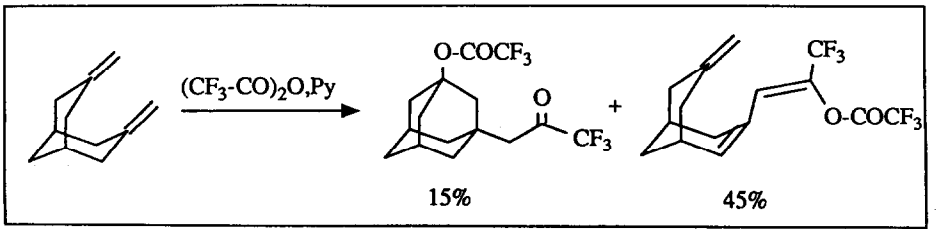


Fig. 22

4 SPECIFIC METHODS FOR PREPARATION OF α,α-DIFLUORO KETONES

1) Electrophilic fluorination of enolic compounds

By employing electrophilic fluorinating agents such as perchloryl fluoride, enolic compounds (enol ethers, enamines, enolates of β-dicarbonyl compounds) can be easily converted to the α-fluoro derivatives, and in some cases to the difluoroketones, and even trifluoromethyl ketones. This method has been efficiently applied in the steroid field[187-189] (Fig. 23).

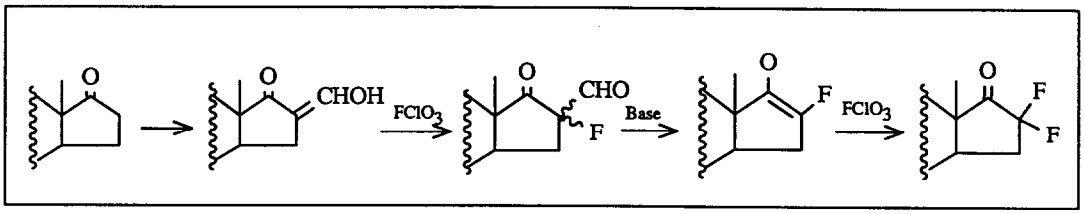


Fig. 23

New fluorinating agents, such as an N-fluorosultam,[190] can replace the classical reagents. The potassium enolate of ketones can be selectively converted the α,α-difluoro ketones (Fig. 24).[191]

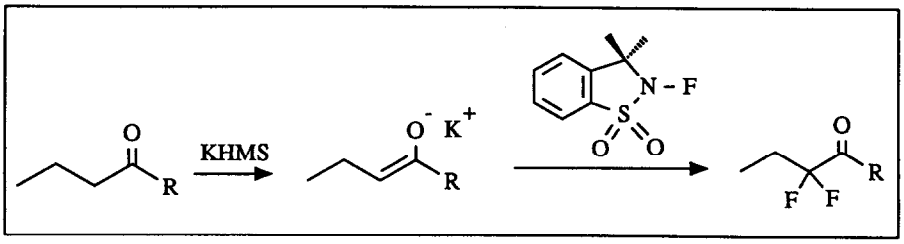


Fig. 24

2) Anodic fluorination of benzylic ketones

In acetonitrile, in the presence of $Et_3N,3HF$, anodic oxidation of benzylic ketones bearing a electron-donating substituent at the para position yields selectively the corresponding difluoro ketones (Fig.25).[192,193]

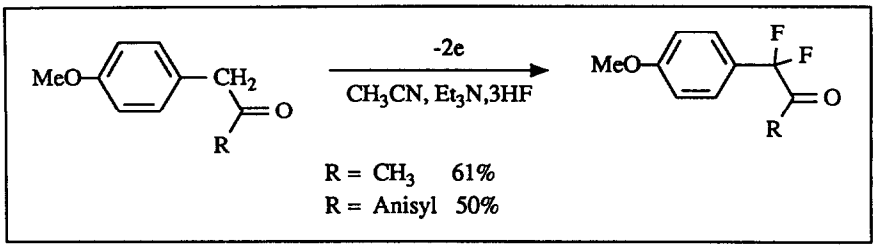


Fig. 25

3) Difluoroalkenyl boranes as precursors

Difluoroalkenyl boranes are easily obtained by treatment of trifluoroethyl tosylate with LDA followed by addition of trialkyl boranes. The corresponding difluoromethyl ketones are obtained by classical alkaline hydrogen peroxide treatment in presence of sodium methanolate (Fig. 26).[194]

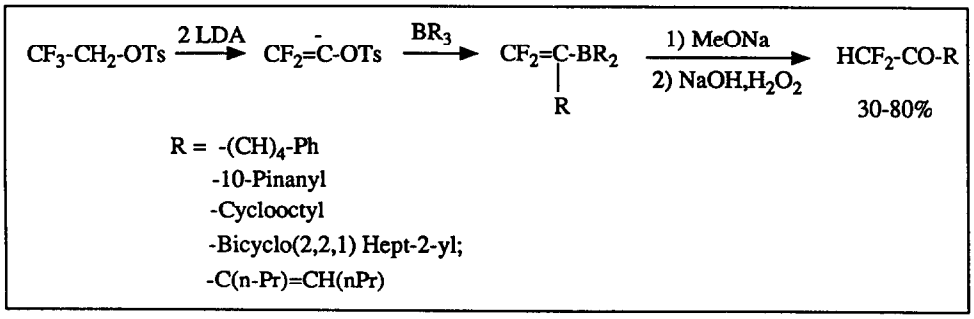


Fig. 26

4) Reduction of chlorodifluoroketones

As fluorine atoms are more resistant to reduction than other halogens, chlorodifluoro ketones can be reduced with zinc to the corresponding difluoromethyl ketones (Fig. 27).[2,195] The hypothesis of an intermediate zinc enolate has been etablished by the isolation of the difluoro silyl enol ethers when the reaction is performed in the presence of trimethyl silyl chloride in an aprotic medium (Fig. 27).[195] Hydrolysis of these difluoro silyl enol ethers into the difluoromethyl ketones, although not reported, should be easy (see part 3-6).[142]

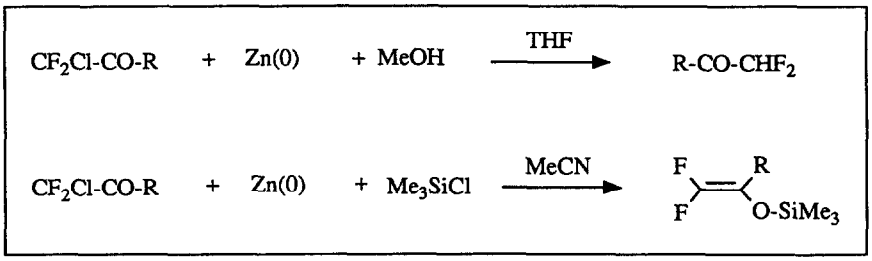


Fig. 27

5) From difluorovinyl ether by Claisen rearrangement

The Claisen rearrangement of allylic difluorovinyl ethers offers a novel way to difluoroallyl ketones. The difluorovinyl allyl ethers are easily prepared by dehydrofluorination (LDA or BuLi) of allyl ethers of trifluoroethanol (Fig. 28).[196]

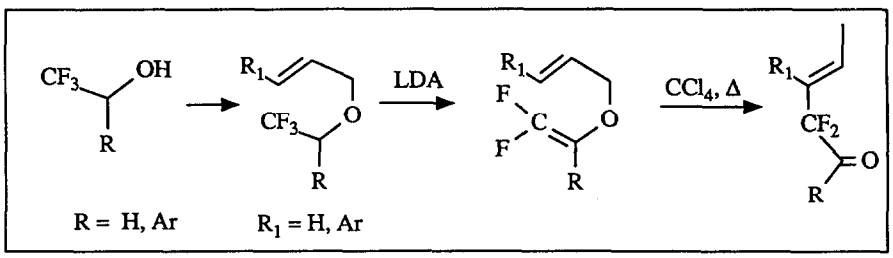


Fig. 28

This approach has been extended to the preparation of difluoroallyl aldehydes starting from the allylic hemiketal of trifluoroacetaldehyde.[196] One example is given (Fig. 29).

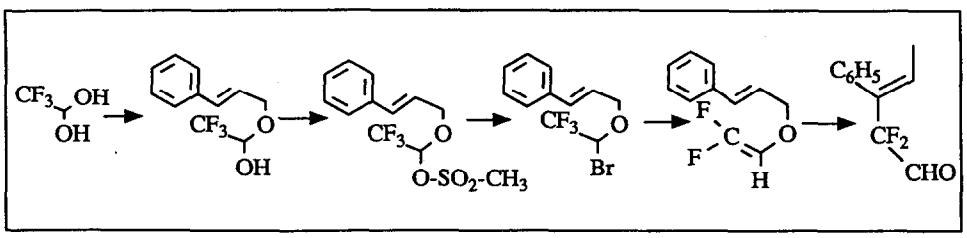


Fig. 29

6) Fluorosilyloxirane as precursors

Opening of α,β-difluorosilyloxiranes with pyridine/HF has been studied.[197] When R = *n*-heptyl, the corresponding difluoromethyl ketone is obtained in moderate yield (Fig. 30). The mechanism of this reaction is still under investigation.

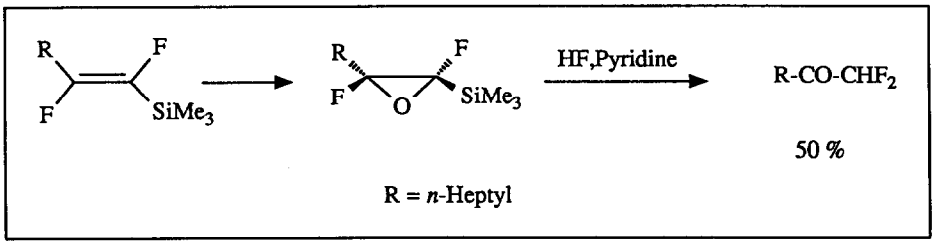


Fig. 30

5 SPECIFIC METHODS FOR PREPARATION OF HEMIPERFLUOROALKYL KETONES

1) Collman's coupling

Collman's reaction is used to couple perfluoroacyl anhydrides or chlorides with alkyl or acyl halides in presence of disodium tetracarbonyl ferrate.[198,199] Perfluoroalkyl ketones, even with possibly functional groups, are obtained in good yields (Fig. 31 ; Table 16). This procedure has also been applied to the preparation of trifluoromethyl ketones, but with erratic results.[24]

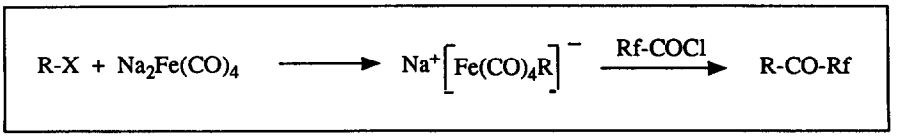


Fig. 31

Table 16: Hemiperfluoroalkyl ketones Rf-CO-R obtained by Collman's coupling.[199]

RX	Rf compounds	Yields
C_6H_5-CH_2Br	n-C_7F_{15}-COCl	59%
n-$C_8H_{17}Br$	(n -C_3F_7-CO)$_2$O	75%
C_6H_5-COCl	n-C_7F_{15}-COCl	76%
C_6H_5-CH_2COCl	n-C_7F_{15}-COCl	70%
Cl-CH_2-$(CH_2)_3$-CH_2-Br	n-C_7F_{15}-COCl	76%
NC-CH_2-$(CH_2)_3$-CH_2-Br	n-C_7F_{15}-COCl	76%
C_5H_{11}-O-C-C_5H_{11}-Br	n-C_7F_{15}-COCl	78%

2) Pd catalyzed coupling of acyl chlorides and allyl perfluoro alkanoates.

A palladium-catalyzed reaction of an allylic ester of a perfluoroalkanoic acid, in presence of alkyl or aryl acyl chloride, leads to the formation of perfluoroalkyl enol acetates.[200,201] Hydrolysis (concentrated H_2SO_4) of these products provides the perfluoroalkyl ketones. This procedure has been described for only one particular Rf group but might be extended to other Rf groups (Fig. 32).

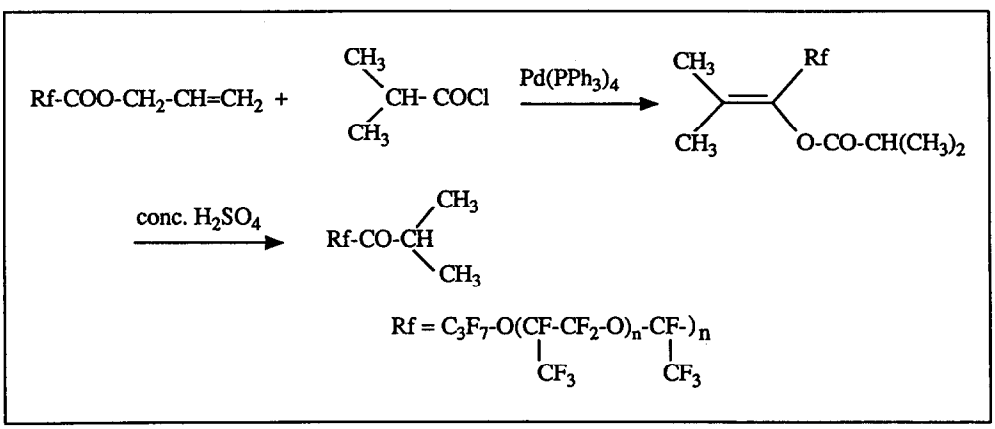


Fig. 32

3°) Perfluoroalkyl alkyne hydration.

Easy access to perfluoroalkynes[202] has provoked studies concerning their hydration as a potential route to perfluoroalkyl methyl ketones.[203] This route has been recently illustrated by the formation of methyl

perfluorohexyl ketone as the sole product, by hydration of 1-Hydro-F-1-octyne, in the presence of mercuric sulfate (Fig. 33).[94]

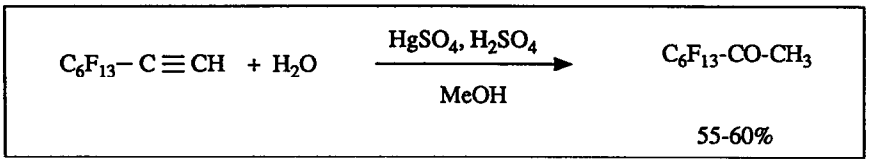


Fig. 33

4°) Transformation of a CF_2 group to a C=O group in a Rf chain

The basic methanolysis of perfluoroalkyl resorcinols leads to the formation of benzylic acetals which, under acidic deacetalization conditions, give the perfluoroalkyl resorcinol ketones (Fig. 34).[204]

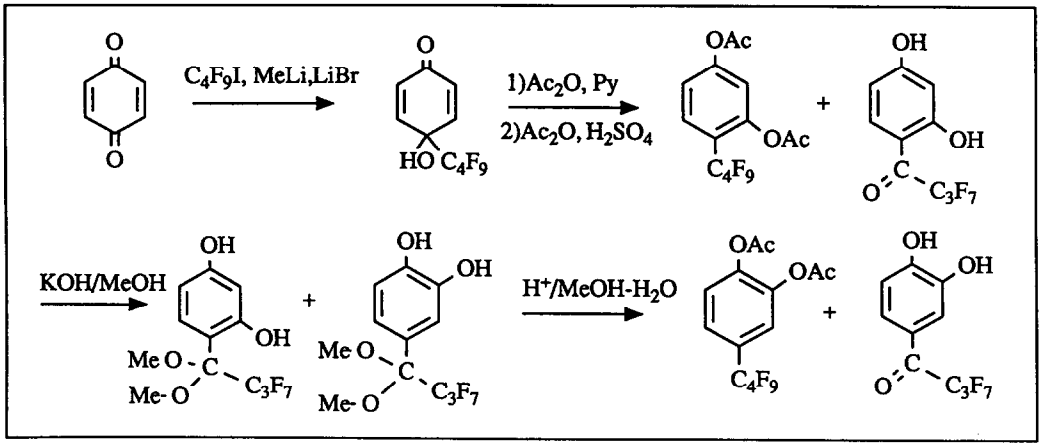


Fig. 34

6 UNSATURATED FLUOROMETHYL AND HEMIPERFLUOROALKYL KETONES

6-1 αβ-Acetylenic fluoromethyl and hemiperfluoroalkyl ketones

αβ-Acetylenic trifluoromethyl ketones can be used as the precursors of trifluoromethyl substituted heterocycles[205,226] or vinylic trifluoromethyl ketones.[79,206] These ketones and the corresponding

difluoromethyl ones may be prepared by condensation of acetylide anions with ethyl tri- or di-fluoroacetate.[66,77,78,207,208,209] Catalysis by BF_3,Et_2O improves the yields and the reproducibility of the reaction (Fig. 35 and Table 17).[79]

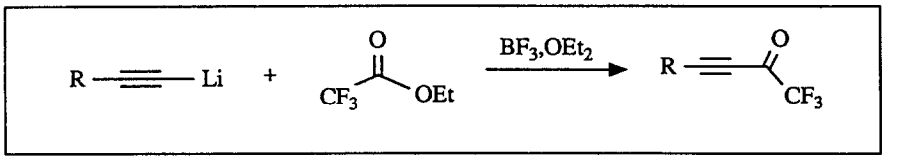


Fig. 35

Table 17: Rf-CO-C≡C-R from ethyl tri- or di-fluoroacetate and lithium acetylides.[79]

Rf	R	Yield
CF_3	C_6H_5	81%
CF_3	n-C_4H_9	71%
CF_3	n-C_6H_{13}	69%
CF_3	n-C_8H_{17}	81%
CF_3	n-$C_{10}H_{21}$	83%
CF_3	n-$C_{12}H_{25}$	91%
CF_3	$(CH_2)_2$-CH_2-OTHP	72%
CF_3	$(CH_2)_2$-CH_2-OSi(Me)$_3$	71%
HCF_2	C_6H_5	77%
HCF_2	n-C_4H_9	74%
HCF_2	n-C_7H_{15}	71%
HCF_2	n-C_8H_{17}	66%
HCF_2	n-$C_{10}H_{21}$	64%

An interesting example of the addition of an unsaturated organolithium, generated *in situ*, to CF_3-COOEt is illustrated by direct transformation of a gem-dibromo olefin to the corresponding trifluoromethyl ynone (Fig. 36).[208]

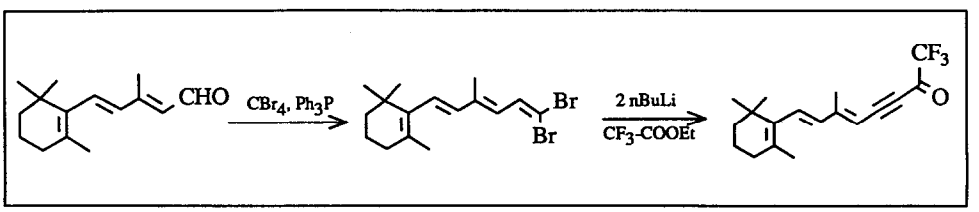


Fig. 36

Finally, isomeric fluorinated αβ-ynones are obtained by pyrolysis of diacyl phosphonium salts prepared by the acylation of acyl phosphoranes with perfluoroalkanoyl chlorides (fig. 37)[149,153] (see part 3-6-2).

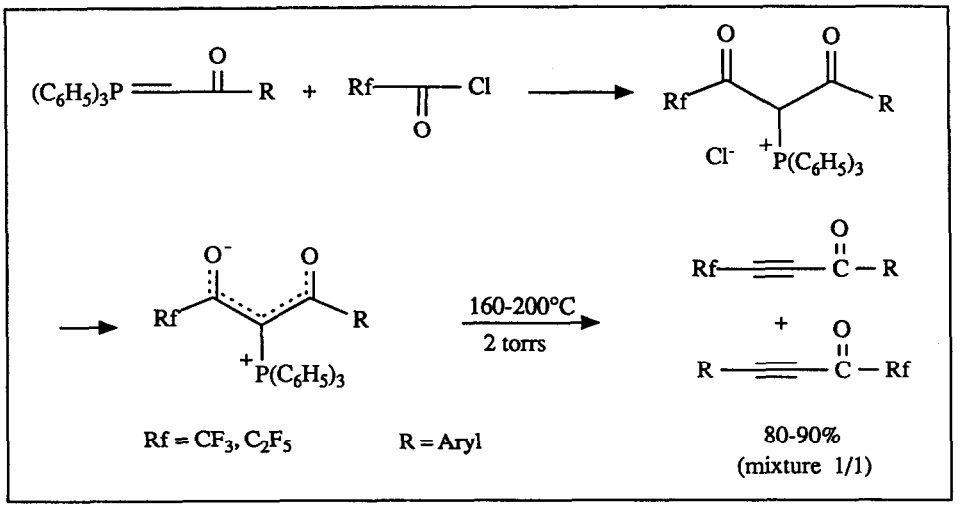


Fig. 37

6-2 αβ-Ethylenic fluoromethyl ketones

αβ-Ethylenic fluorinated ketones have not been readily accessible. Conventional procedures for the synthesis of ethylenic ketones have not been applicable to the preparations of their fluorinated analogues.

1) Perfluoroalkyl organometallic reagents and unsaturated esters

The addition of an ethylenic organometallic compound to fluoroalkyl acid derivatives has been attempted but without success.[61] To prepare αβ-ethylenic fluoromethyl ketones, condensation of perfluoroalkyl organometallic compounds with αβ-unsaturated esters was investigated (see part 3-2). Grignard reagents[94] or organolithium compounds, generated *in situ* by reaction of perfluoroalkyl iodide with methyllithium[97b,98] have been shown to react with unsaturated esters affording the αβ-ethylenic perfluoroalkyl ketones in high yields.

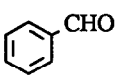
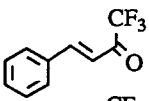
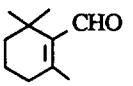
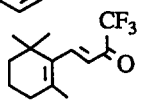
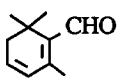
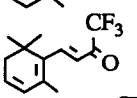
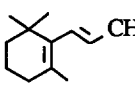
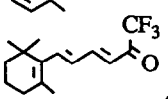
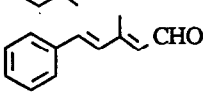
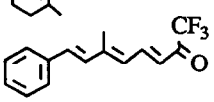
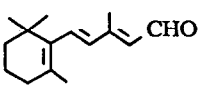
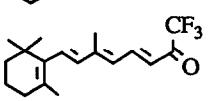
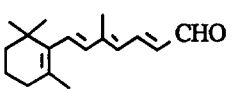
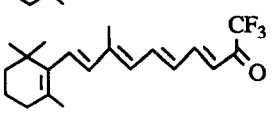
2) Oxidation of allylic fluoromethyl (or perfluoroalkyl) carbinols

Allylic fluoromethyl- or perfluoroalkyl carbinols can be prepared by organometallic methods. Vinyl anions may be added to trifluoroacetaldehyde,[104] or trifluoromethyl (and perfluoroalkyl) organometallic compounds may be added to unsaturated aldehydes.[87,106,210] The resulting secondary carbinols are oxidized with the Dess-Martin reagent to the αβ-ethylenic trifluoromethyl ketones (see part 3-3).[113]

3) Aldol condensation-dehydration

The aldol condensation-dehydration route has been reported for trifluoroacetone and unsaturated or aryl aldehydes using piperidine/acetic acid as the catalyst (Table 18).[207-209] However, this procedure failed in reaction with other aldehydes.[207]

Table 18: αβ-Ethylenic trifluoromethyl ketones by aldol condensation of aromatic or ethylenic aldehydes with CF_3-CO-CH_3.[207]

R-CHO	Products	Yields
		55%
		40%
		28%
		85%
		67%
		80%
		70%

4) Iminophosphorane route

Fluoroalkyl αβ-enones may be prepared from β-iminophosphonates, accessible in four steps from perfluoroalkanoyl chlorides (*via* phosphinyloxy F-alkene phosphonates). The β-iminophosphonate anions when condensed with an aldehyde, lead to the corresponding fluoroalkyl enones after acidic hydrolysis (Fig. 38).[138]

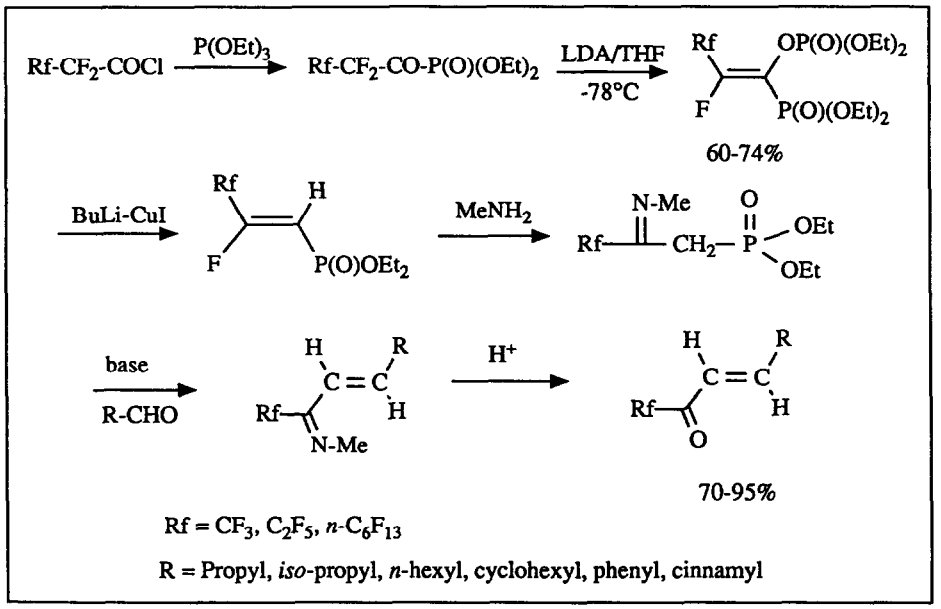


Fig. 38

5) 1-4 Addition of organocuprates to acetylenic trifluoromethyl ketones

A general route for the synthesis of fluorinated enones requires the 1,4- addition of organocuprate reagents to acetylenic ketones.[79,206] With higher order cyanocuprate reagents, very good 1,4-addition regioselectivity is observed. However stereoselectivity is variable and yields are moderate (Fig. 39; Table 19).

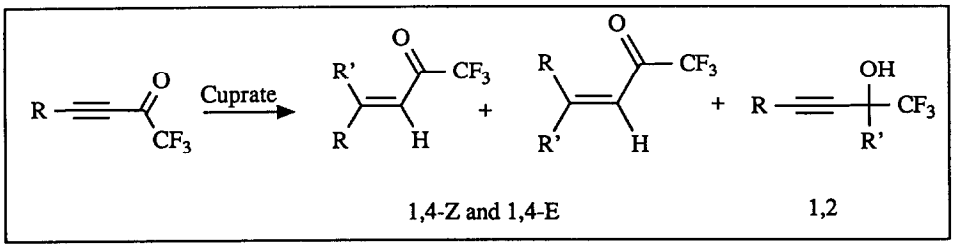


Fig. 39

Table 19: Organocuprate addition to acetylenic fluoro ketones CF_3-CO-C≡C-R.[79,206]

Ketone R	Ketone Rf	Cuprate (*)	1,4:1,2	E:Z	Yield 1,4E	Yield 1,4Z	Yield 1,2
C_6H_5	CF_3	1a	88:12	76:24			
		2a	100:0	53:47	12	3	0
		3a	100:0	71:29	51	1	0
		1b	61:39	52:48	15	5	16
		2b	91:9	69:31	34	22	7
		3b	81:19	59:41	37	14	16
C_4H_9	CF_3	1b	82:18	100:0	64	0	25
		2b	100:0	100:0	44	0	0
		3b	100:0	100:0	55	0	0
$C_{10}H_{21}$	CF_3	3a	100:0	55:45	21	23	0
C_8H_{17}	CF_3	3a	100:0	45:55	15	14	0
$C_{10}H_{21}$	CHF_2	3a	100:0	50:50	11	12	0

(*) 1 $(R')_2CuLi$ 2 R'Cu(CN)Li 3 $(R')_2Cu(CN)Li$ a Me b n-Bu

It should be noted that a direct reduction of acetylenic fluoro ketones ($NaBH_4$ or Red-Al) leads mainly to allylic alcohols and requires a reoxidation step.[209] Microbial reductions are also ineffective.[78]

6) Acylation of enolic compounds

a) Hojo's group has shown β-functionalized α,β-unsaturated trifluoromethyl ketones may be easily generated by reaction of trifluoroacetic anhydride with electron-rich ethylenic compounds[211-221] (Fig. 40) (see Part 3-7). These compounds are versatile synthons, especially for building fluorine-containing heterocycles.[221-225,226]

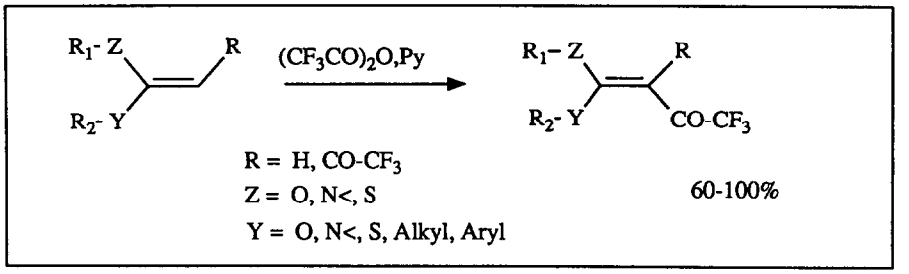


Fig. 40

Two examples are illustrated in Fig. 41.

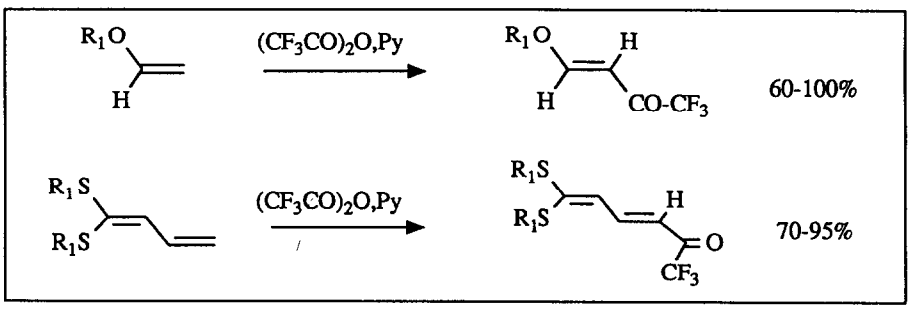


Fig. 41

b) The synthons (Z = N< and Y = H; Fig. 40) are also easily prepared by 1,4-addition of an amine to αβ-acetylenic trifluoromethyl ketones.[226]

7) Vinyl trifluoromethyl ketones

Trifluoromethyl or pentafluoroethyl vinyl ketones are not accessible by the procedures described thus far. They have been prepared by the dehydrohalogenation of β-halogeno ketones[112,227] (Fig. 42).

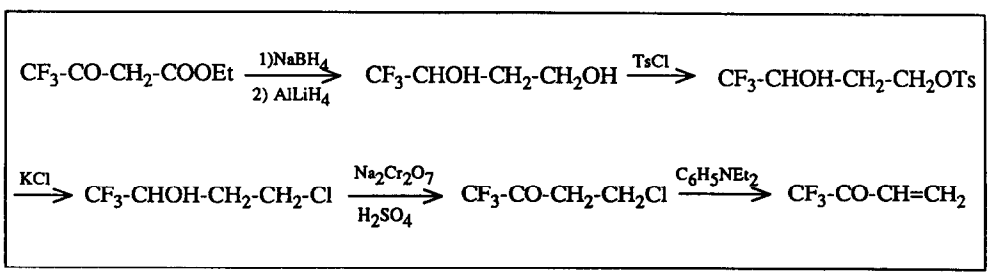


Fig. 42

6-3 γδ-Ethylenic trifluoromethyl ketones

Three methods have recently been described for the construction of γδ-ethylenic trifluoromethyl ketones which are interesting substrates for potential cyclizations,[228] and building blocks for the synthesis of biologically active compounds.[130,131]

a) Alkylation of ETFAA by allylic halides, followed by a decarbethoxylation process, see part 3-4-1.[120,121]

b) The Carroll reaction performed on alkyl trifluoroacetoacetate, see part 3-4-3.[129-132]

c) The Wittig reaction performed on trimethylsilyl trifluoroacetate with an homoallylic phosphonium ylide (see part 3-6-3).[142]

d) An elegant synthesis of γδ-ethylenic trifluoromethyl ketones by a Wittig reaction between (3-trifluoroacetyl) allylidene triphenyl phosphorane and a ketone, has recently been described (Fig. 43).[229]

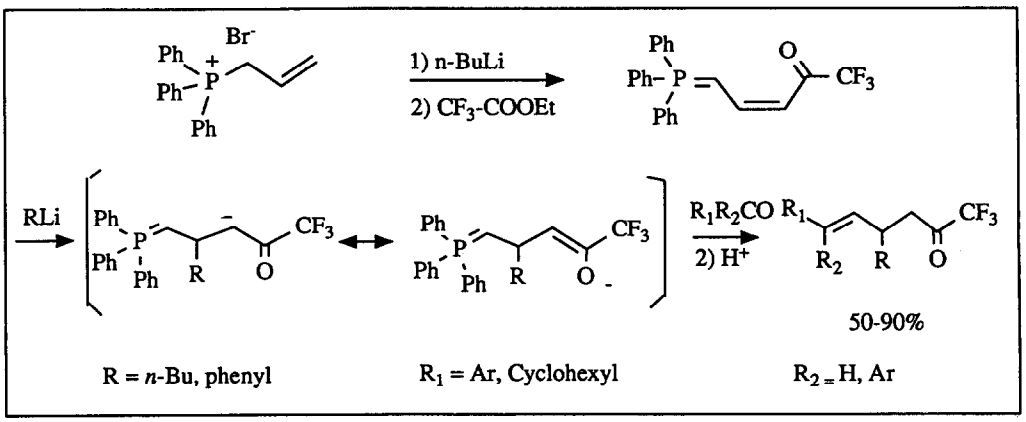


Fig. 43

7 α-FUNCTIONALIZED FLUOROMETHYL KETONES

7-1 α-Bromo (and α-Chloro) trifluoromethyl ketones

α-Bromo trifluoromethyl ketones have great potential as synthons, but only bromo trifluoroacetone has been widely used to date. Until now, bromination of fluoromethyl ketones was difficult to achieve since drastic conditions were required.[19,60a,124,136,230] Reactions were carried out in concentrated sulfuric acid for protonation of the ketone. This avoids reaction with hydrogen bromide and hence disproportionation of the α-bromoketone.[124]

Bromination of ethyl trifluoroacetoacetate occurs under mild conditions, but yields of the α-bromo ketone (after acidic decarbethoxylation)[231] are low. Some α-chloro trifluoromethyl ketones have been prepared by similar methods.[231,232]

All these difficulties have been recently overcome by performing the bromination, under very mild conditions (no excess of bromine, 20°C, CH_2Cl_2), on trimethylsilyl trifluoromethyl enol ethers (see part 3-6). This general method allows for preparation of many kinds of α-bromo ketones in very high yields (Fig. 44 and Table 20).[11,142]

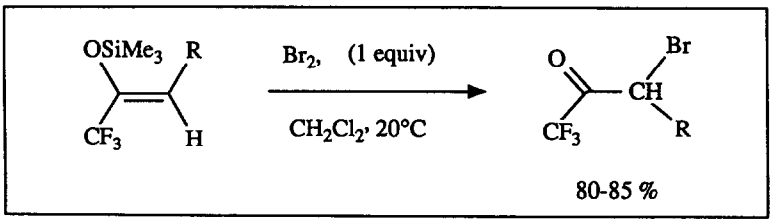


Fig. 44

Table 20: α-Bromo trifluoromethyl ketones R-CHBr-CO-CF_3 by bromination of trifluoromethyl silyl enol ethers.[142]

R	Yield
Phenyl	85%
Cyclohexyl	85%
n-Hexyl	80%
Cyclohexylmethyl	85%
2-Phenylethyl	85%

7-2 α-Fluoro perfluoroalkyl ketones

Besides direct fluorination (see part 4-1), α-fluoro perfluoroalkyl ketones can be prepared by oxidation under phase transfer conditions of the corresponding fluorohydrins using $Na_2Cr_2O_7/H_2SO_4$.[233] These fluorohydrins are easily obtained via opening of the fluoroalkyl epoxides with diisopropylamine/hydrogen fluoride complex fluorohydrate[234] (Fig. 45).

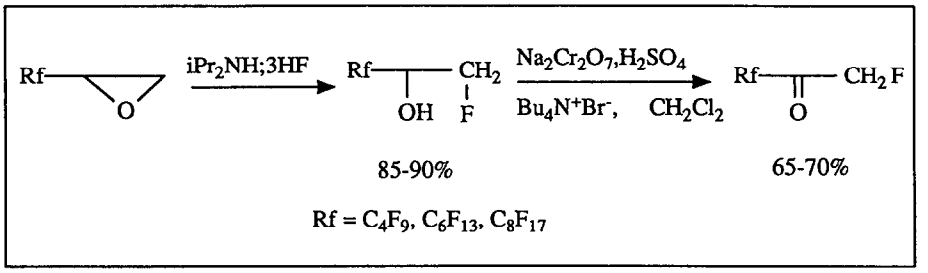


Fig. 45

The α-fluorotrifluoroacetone has been prepared by the Claisen condensation between ethyl monofluoroacetate and ethyl trifluoroacetate followed by acidic decarbethoxylation.[123,232]

7-3 α-Sulfenyl trifluoromethyl ketones

Many α-sulfenyl trifluoropropanones have been prepared as potential selective inhibitors of insect juvenile hormone esterase[18,19,23] and mammalian carboxyl esterases.[23] These compounds are easily obtained by reaction of alkanethiols and bromo trifluoropropanone in presence of triethylamine or sodium bicarbonate (Fig.46).[16,19,23]

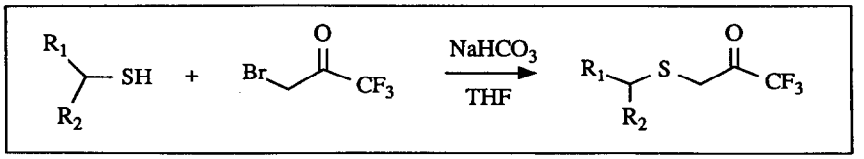


Fig. 46

7-4 α-Sulfinyl fluoroalkyl ketones

α-Sulfinyl fluoroalkyl ketones are interesting building blocks. They can be precursors of fluorinated vinylic sulfoxides which can be used as Michael acceptors.[235] α-Sulfinyl fluoroalkyl ketones can be obtained by addition of lithiated aryl alkyl sulfoxide on ethyl (or lithium) trifluoroacetate (see. part 3-5),[235-237] and are available in an enantiomerically pure form (Fig. 46).[237,238]

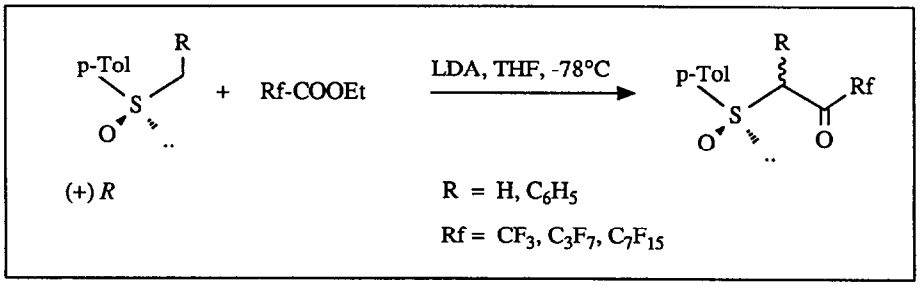


Fig. 47

7-5 α-Amino and α-Peptidyl fluoromethyl ketones

α-Amino fluoromethyl ketones and α-peptidyl fluoromethyl ketones are a very important class of protease inhibitors. This interest, especially in the aspartyl protease field (see part 2), has stimulated a lot of attention. However, the classical substitution of a bromoketone by a nucleophilic nitrogen group has not often been used.[3,11] In fact, until recently α-bromo trifluoromethyl ketones were not easily accessible.

In the literature three important works have been reported, using two strategies:

1) *Oxidation of α-amino trifluoromethyl carbinols, resulting from condensation of anions on trifluoroacetaldehyde.*

a) The key-step of the Abeles method[105] is based on the alkaline condensation of trifluoro (or difluoro) acetaldehyde with a nitroalkane. The resulting α-nitro fluoromethyl carbinol is reduced to the α-aminoalcohol (H_2, Raney nickel), and coupled to the peptidyl residues. Oxidation leads to α-peptidyl fluoromethyl ketone. This last step should be easier now using Dess-Martin reagent [113] (Fig. 48).

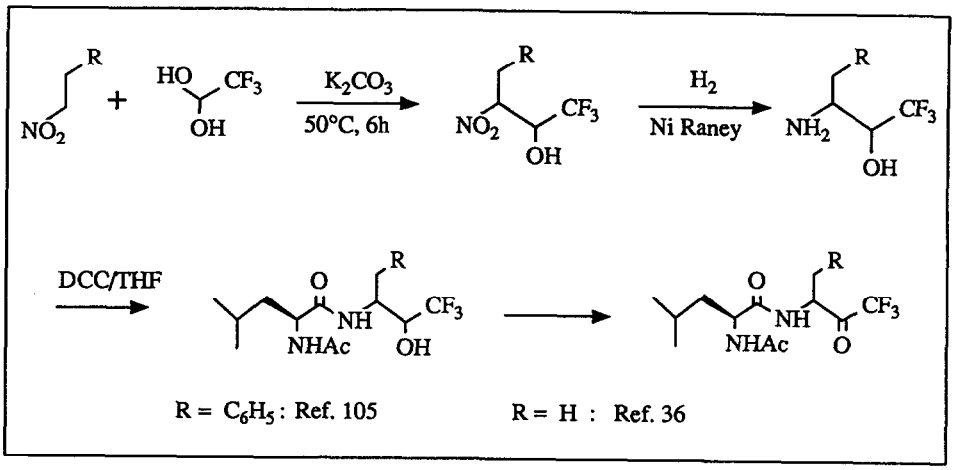


Fig. 48

b) A group at Squibb has described another route to the α-amino trifluoromethyl carbinols.[48] Condensation of the lithium dianion of the carboxylic acid with trifluoroacetaldehyde provides the β-carboxy trifluoromethyl carbinol. Protection of hydroxyl group as a silyl ether is followed by a Curtius rearrangement to afford the protected amino trifluoromethyl carbinol. Deprotection, peptidic coupling and Dess-Martin oxidation lead to the desired peptidyl trifluoromethyl ketone (Fig. 49).

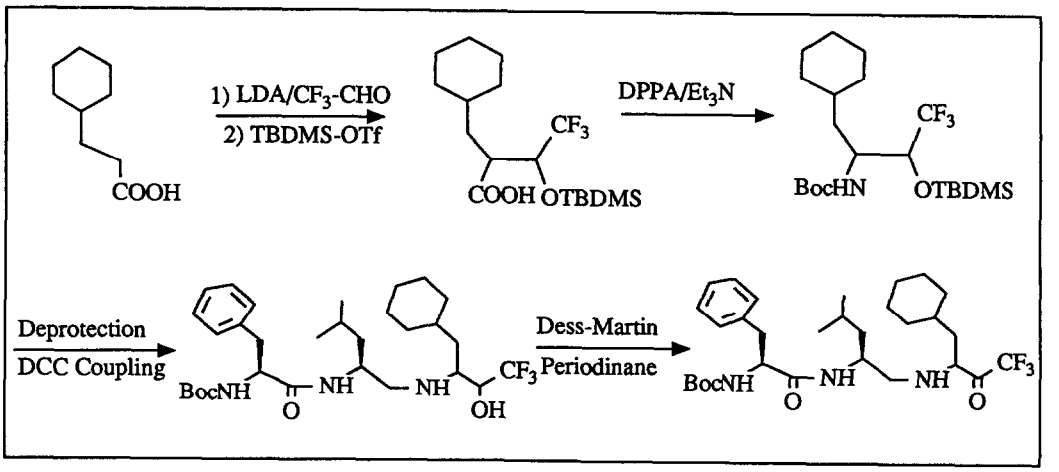


Fig. 49

2) *A direct preparation of α-amino trifluoromethyl ketones from aminoacids using a Dakin-West reaction.*

The pioneering works of Steglich[239,240] and Tatlow [241] on the Dakin-West reaction,[245] have described the preparation of 4(5H)-oxazolones and thus α-amino ketones, from aminoacids. In this connection Kolb *et al.*,[30,34,242-244] have proposed a very short one-pot synthesis of α-amino fluoromethyl ketones. The oxazolones are acylated by trifluoroacetic anhydride (or other fluoralkyl acylating reagent), and further decarbonylated with anhydrous oxalic acid leading to the fluorinated α-amino ketones. Unfortunately, the peptidic coupling could not be performed directly from α-amino ketones, but only from α-aminoalcohols. After reduction, coupling and oxidation, the peptidyl fluoromethyl ketones are obtained[30] (Fig. 50).

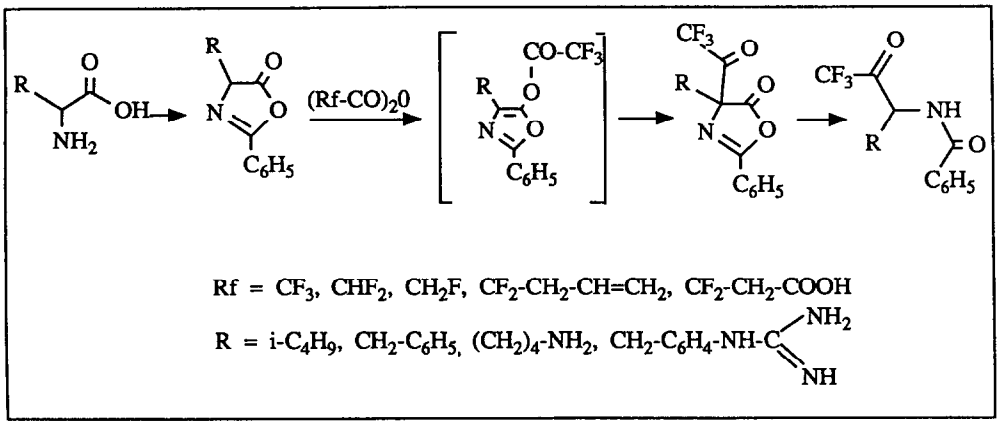


Fig. 50

Acknowlegments

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