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Fluorine-containing ketimines

S N Osipov, A F Kolomiets, A V Fokin
A N Nesmeyanov Institute of Heteroorganic Compounds, Russian Academy of Sciences

ABSTRACT. **Data appearing in the last ten years have been correlated for the methods of synthesis of fluorine-containing imines, their reactions with N-, O-, S-, P- and C-nucleophiles, with aromatic and heteroaromatic π-donors and in cycloaddition and cyclocondensation processes involving these compounds. The principal theoretical ideas on the reactivity of fluorine-containing ketimines are discussed.**

The bibliography contains 132 references.

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I. Introduction

The chemistry of fluorine-containing imines may rightfully be considered as one of the most interesting areas of fluorine chemistry. The diversity of the effects of a fluorine atom and of fluoroalkyl groups is shown most completely in these compounds due to the presence of the highly polarisable C=N bond. The mutual effects of fluorine-containing and other substituents on the azomethine bond prove to be extremely prominent. This has caused compounds to appear in the fluoroimine series with contrasting properties, from the very stable chemically inert to the extremely reactive.

Of the great variety of fluorine-containing compounds with a C=N bond the *N*-fluoroimines, imidoyl halides, fluoroazomethines including aldimines and ketimines, ketenimines and acylimines have been studied fairly well. Each type of compound is characterised by special methods of preparation and by a set of specific properties which determine both the features of their chemistry and their area of use. The search for effective components of high-energy fuels and combustion accelerators is linked with *N*-fluoroimines. The fluoroazomethines have attracted attention as potential precursors of heat-transfer agents, greases, other valuable materials and additives. Imidoyl halides, ketenimines and acylimines are most interesting as synthons for fluorine-containing biologically active compounds.

The vast literature on fluorine-containing compounds with a C=N bond is correlated in a series of publications. The principal data on *N*-fluoroimines have been discussed in reviews,[1,2] the chemistry of fluorine-containing ketenimines has been illustrated in a review[3] and in a dissertation,[4] the general state of the chemistry of fluorine-containing imines up to the early eighties is described in review articles.[5–7]

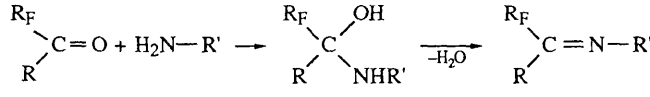
Interest in the various fluorine derivatives of the azomethines has grown during the last ten years. Particular attention has been attracted by the functionally substituted fluorine-containing ketimines, including the acylimines of polyfluoroketones, the imines of various α- and β-ketocarboxylic acids, the imines of unsaturated fluoro-carbonyl compounds and other bi- and trifunctional compounds which are interesting synthons of fluorine-containing biologically active compounds. The present paper is devoted to the correlation of this experimental material and to some of the theoretical investigations carried out in this area.

II. Methods of synthesis

From the multitude of methods developed previously for the synthesis of fluorine-containing ketimines[7] most attention has continued to be paid in the last ten years to the development of methods based on the condensation of fluorocarbonyl compounds with amino compounds. Somewhat less attention has been paid to methods based on cycloaddition–elimination reactions, including the Staudinger reaction. Interesting new approaches to the synthesis of fluorine-containing ketimines have been developed by studying the reaction of fluorine-containing nitriles and ketenimines with HCN, of geminal isocyanatohalo compounds with various nucleophilic reagents and amino compounds with fluoroalkenes and alkynes. Methods specfic for fluorine compounds have also been developed further.

1. Condensation of fluorine-containing ketones with amino compounds

The condensation of fluorine-containing ketones with amino compounds usually leads readily to geminal aminohydroxy compound (hemiaminal or hemiamidal) which is converted into a ketimine either by the elimination of water or (in the case of highly stable hydroxy compounds) by the action of strong dehydrating agents.

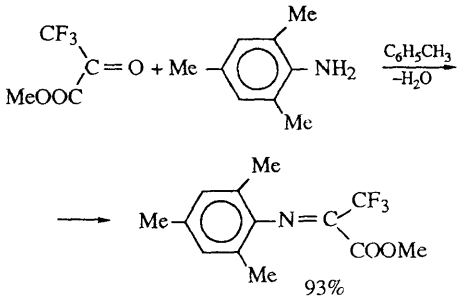


According to recent data[7] the dehydration conditions for a hemiaminal are directly dependent on the electron-accepting properties of the substituents at the ketone carbonyl carbon atom and the basicity of the amino compound. New data summarised in Table 1 define these concepts more precisely.

It turned out that aminals obtained from fluorine-containing α-ketocarboxylic acids (Table 1, No. 1–4) and alkyl(aryl) ketones (Table 1, Nos. 5–8) are readily dehydrated to imines under solvation conditions or by azeotropic distillation of the water formed.[8–18] This is in agreement with previous ideas,[7] since the carbonyl compounds listed contain only one electron-accepting group.

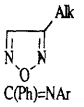
However anils are obtained from methyl trifluoropyruvate under practically the same conditions.[19,20,21] In the reaction of the latter

with mesidine the corresponding anil is formed almost quantitatively (93%).[19]



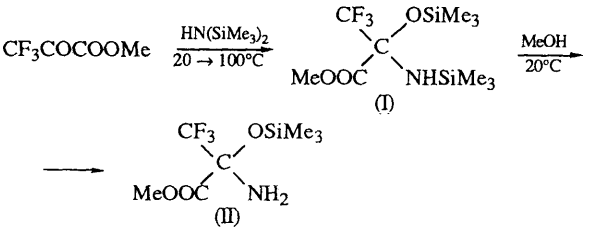
Reaction with aniline under conditions for the azeotropic distillation of water gave 35% yield. The relatively low yield of anil in this case is caused by the occurrence of several side reactions, the nature of which has been discussed.[21] Only the weakly basic nitroanilines did not give anils on reaction with methyl trifluoropyruvate. The hemiaminals formed in this case are not dehydrated even at 200 °C.[21] It must be noted that hexafluoroacetone does not form anils with either aniline[22] or with mesidine[23] under azeotropic distillation conditions. On heating, the hemiaminals are decomposed into the starting materials.

Table 1. Features of the formation of imines from fluorocarbonyl and amino compounds.

No.	R_F	R	R′	Dehydration conditions	Refs.
1	CFHCOOH	COOH	Alk	–	[8]
2	$CFAlk_2$	COOH	Alk	–	[9]
3	CFH_2	COOH	CH(Me)Ph	0–25 °C, EtOH	[10]
4	CFHAr	COOH	Alk	Δ, alcohol	[11]
5	CFH_2	Me	Alk	$K_2CO_3(MgSO_4)$, CCl_4	[12, 13]
6	CF_3	Alk	$(CH_2)OAlk$	Boiling benzene	[14]
7	C_8F_{17}	Me	Alk	Δ, $CHCl_3$	[15, 16]
8	CF_3	Ph	CH(Me)Ph	Δ, toluene *p*-TsOH	[17, 18]
9	CF_3	COOMe	Ar	Boiling benzene	[19, 20, 21]
10	$CF(CF_3)_2$	$C(O)CF(CF_3)_2$	Alk	Δ, $CHCl_3$	[24]
11	CF_3	Ph		$(CF_3CO)_2O$, Py	[25]
12	CF_3	CF_3	C(Ph)=NAr	$POCl_3$, Py	[26]
13	CF_3	COOMe	COOAlk	$(CF_3CO)_2O$, Py	[27]
14	CF_3	COOMe	$C(O)CF_3$	$POCl_3$, quinoline	[28, 29]
15	CF_3	COOMe	SO_2Me, SO_2Ph	$SOCl_2Py$	[28, 30, 31]

The adducts of perfluoro-α-diketones, for example the product of reacting diperfluoro-isobutyroyl with amines (Table 1, No. 10), are readily dehydrated under conditions of azeotropic distillation of water. Carbalkoxy and perfluoroacyl groups, in spite of their high electron-accepting properties, assist the dehydration of an adjacent hemiaminal function. The stabilisation of the intermediate carbocation and of the final azomethine bond by conjugation with the adjacent C=O group is probably decisive in this case.

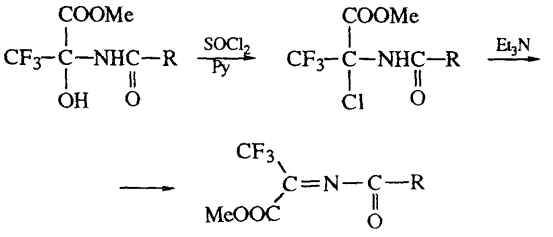
It must be noted that the positive effect of carbalkoxy groups on the dehydration of an adjacent hemiaminal function is not extended to their *N*- and/or *O*-silylated derivatives.[27–31] The silylated hemiaminals (I) and (II), obtained from methyl trifluoropyruvate and hexamethyldisilazane are not converted successfully into the imine of methyl trifluoropyruvate.[32]



The hemiaminal obtained by the desilylation of (II) is also not dehydrated. Under the conditions of its formation this compound undergoes an intramolecular condensation involving the NH_2 and COOMe groups giving oligomers.

Dehydrating agents known previously are used to obtain the new imines of hexafluoroacetone (Table 1, Nos. 11, 12) and the acylimines of methyl trifluoropyruvate (Table 1, Nos. 13, 14).[25,26] More rapid formation and high stability were recorded for the hemiamidal of methyl trifluoropyruvate compared with the hemiamidals of hexafluoroacetone together with more forcing conditions for their dehydration.[28,29]

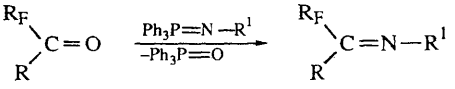
The readily formed highly stable adducts of methyl trifluoropyruvate with sulphonamides are readily dehydrated by boiling $SOCl_2$ in the presence of catalytic amounts of pyridine (Table 1, No. 15). Under these conditions the hemiaminals of methyl trifluoropyruvate are quantitatively converted into the unusually stable geminal amidochloro compounds, which turned out to be smooth precursors of methyl trifluoropyruvate acylimines.[32,33]



R = Me, OEt, CF_3.

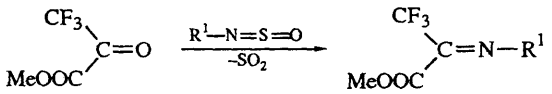
2. Cycloaddition–elimination reactions

Cycloaddition–elimination reactions have been used for obtaining new alkyl-, aryl- and acylimines using the Staudinger reaction.[17,34–38] The data obtained confirm the value of this method which enables any phosphazo compound to react with fluorine-containing aldehydes, ketones and α-ketoacid derivatives.



$R_F = CF_3$; R = H, Me, Ph, COOMe, CF_3; R^1 = Bu, Ph, CH_2Ph, CH(Me)Ph, 4-$MeOC_6H_4$, COOMe.

It is also possible to use thionyl imines for the synthesis of imines and acylimines from esters of fluorine-containing α-ketoacids.[39]

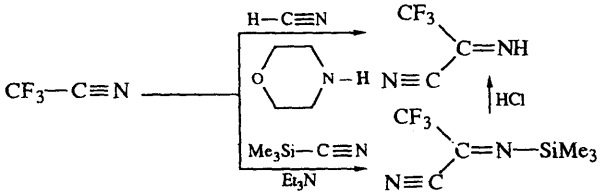


R^1 = Ph, C(O)Ph .

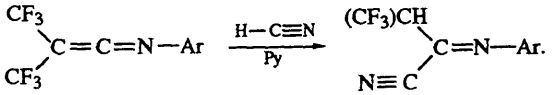
In this case the reaction occurred more readily than for hexafluoroacetone, even in the absence of a catalyst.

3. Addition of HCN to trifluoroacetonitrile

The reaction of HCN with CF_3CN has been carried out under base catalysis conditions,[5] raising the prospect of synthesising α-iminofluorocarboxylic acids. The possibility of using trimethylsilyl cyanide in place of HCN in this reaction is of particular interest,[40] since the *N*-trimethylsilylimines of α-ketoacid nitriles formed are efficienct precursors of a variety of *N*-substituted imines.



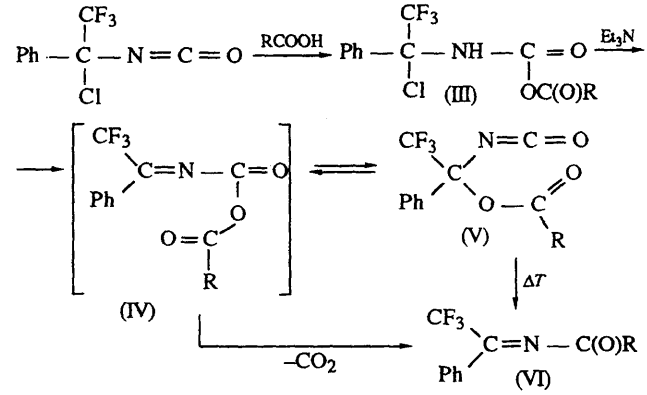
Nitriles of α-iminofluorocarboxylic acids are also formed readily by nucleophilic addition of HCN to fluorine-containing ketenimines.[41]



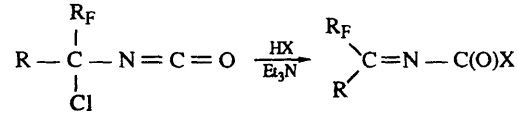
The applicability of this method is limited by the stability of the monomeric fluoroketenimines.

4. Conversion of fluorine-containing geminal chloroisocyanato compounds

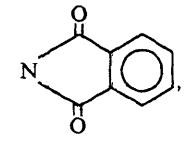
The reaction of $R_FRClCN{=}C{=}O$ with nucleophilic reagents opens broad prospects for the synthesis of various fluoroacylimines. Two types of reaction are used. Carboxylic acids are used as nucleophiles in the first reaction type and form mixed anhydrides with the chloroisocyanato compounds. These undergo rearrangement with decarboxylation on dehydrochlorination.[42] For example, 1-chloro-1-trifluoromethyl-1-phenylmethyl isocyanate reacts vigorously with carboxylic acids giving the corresponding addition products (III), which eliminate HCl above 20 °C. Compounds (III) are converted in the presence of triethylamine into the unstable mixed anhydrides (IV) which are stabilised in one of two ways. One is by decarboxylation and the formation of *N*-acylimines (VI) and the other is by a 3,3-sigmatropic shift of the acyloxy group in the C–N=C triad with the formation of 1-(acyloxy)alkyl isocyanates (V). The latter eliminates CO_2 on thermolysis (above 120 °C) giving the *N*-acylimines (VI).



The second type of reaction of chloroisocyanato compounds includes reaction with O-, N- and S-nucleophiles, such as alcohols,[43,44] imines, diphenylsulphinimine, diphenylamine,[45] potassium *O*-alkyldithiocarbonates,[46] and amides of carboxylic acids[47] in the presence of a dehydrochlorinating agent. The addition of nucleophile at the C=N bond and dehydrochlorination of the geminal chloroamino compound to the acylimines occurs under mild conditions.

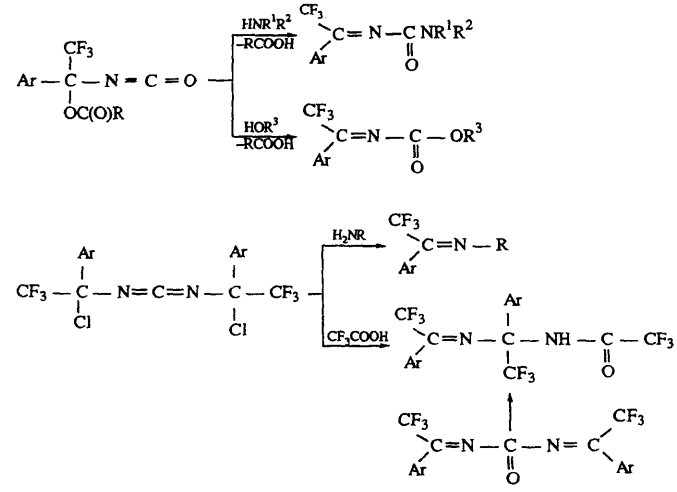


$R_F = CF_3$; R = R_F, Ar; X = OAlk, N=CAlk$_2$, N=SPh$_2$,



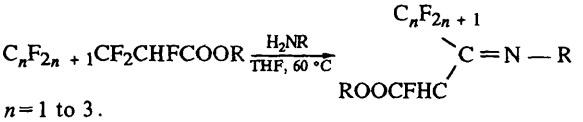
NPh_2, S — C(S)OAlk, N(Ar)C(O)Alk.

1-(Acyloxy)alkyl isocyanates,[48,49] *N,N*-bis(1-chloroalkyl)carbodiimides[42,50,51] and *N,N*-bis(alkylidene)ureas[42] react similarly to the geminal chloroisocyanato compounds. They are readily converted into the corresponding acyl- or alkylimines on reaction with alcohols, acids and amines.



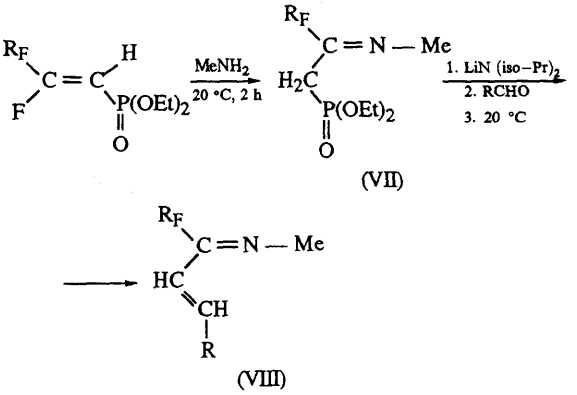
5. Reactions of fluoroalkenes and fluoroalkynes with amines

An original method has been developed for obtaining imines of β-ketofluorocarboxylic acids from esters of α-hydroperfluorocarboxylic acids and primary aliphatic amines. The reaction comprises dehydrofluorination of the initial ester, vinylic replacement of a fluorine atom by an alkylamino group and enamine–imine rearrangement. In spite of being so complex these processes lead to the corresponding imines in 70–82% yield.[52]



$n = 1$ to 3.

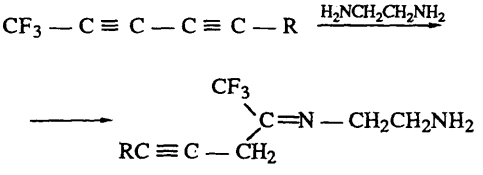
Fluoroalkenylphosphonates are used successfully to obtain fluorine-containing imines with alkenyl substituents at the carbon atom of the C=N bond.[53,54] The vinylic replacement of a fluorine atom by an alkylamino group and subsequent enamine–imine rearrangement lead to the highly reactive CH-acids (VII). Treatment of these with lithium diisopropylamine in ether at −78 °C with subsequent addition of an aldehyde leads to the *trans* isomer of (VIII) in high yield.



(VII)

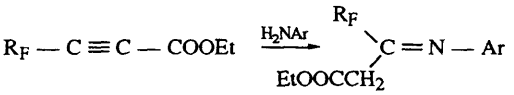
(VIII)

Fluorine-containing imines are obtained by traditional methods by reacting fluorinated diacetylenes with nitrogen-containing binucleophiles.[55]



R = iso-Pr, t-Bu, CMe_2OH.

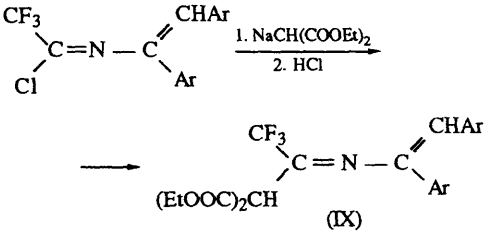
Imines of β-ketocarboxylic acids are obtained by condensing esters of fluoroalkyl substituted acetylenecarboxylic acid with substituted anilines.[56]



$R_F = C_4F_9$, C_6F_{13}, C_8F_{17}; Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$.

6. Reactions of fluorine-containing imidoyl chlorides with CH-acids

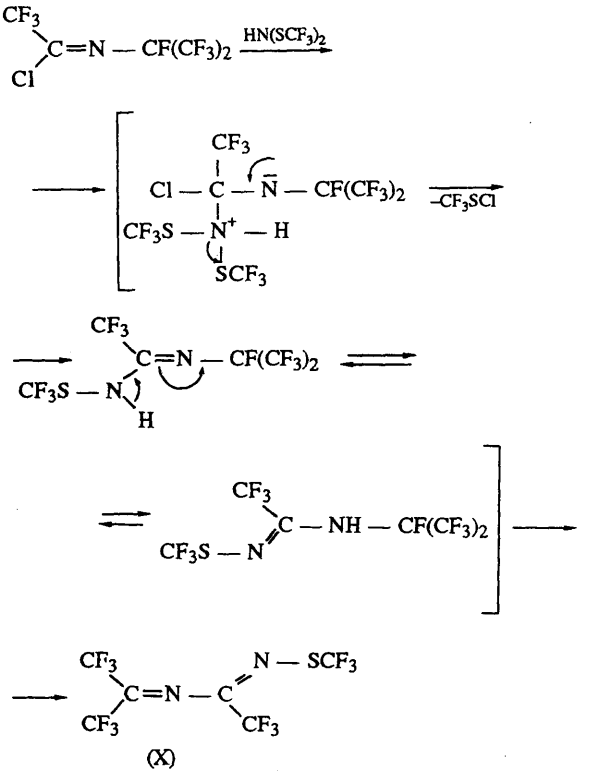
The reaction of imidoyl chlorides with CH-acids is one of the promising routes for synthesising fluorine-containing *N*-alkenylketimines. For example, the ketimines (IX) are obtained in preparative yield by reacting *N*-(1,2-diarylvinyl)trifluoroacetimidoyl chlorides with sodiomalonic ester.[57]



(IX)

Ar = 4-RC_6H_4 (R = H, OMe, Cl)

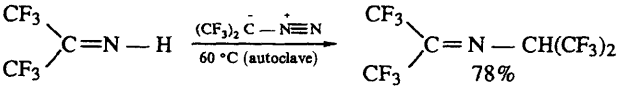
The perfluoroketimine (X) is obtained by the reaction of *N*-perfluoroisopropyltrifluoroacetimidoyl chloride with bis(trifluoromethylthio)amine.[58]



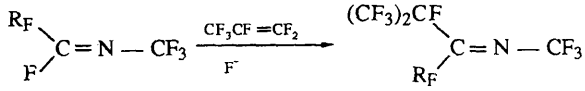
(X)

7. Other reactions

There are few examples of methods of synthesis of ketimines which are specific for fluorine compounds. The preparative value of the reaction of hexafluoroacetone imine with bis(trifluoromethyl)-diazomethane has been shown.[59]

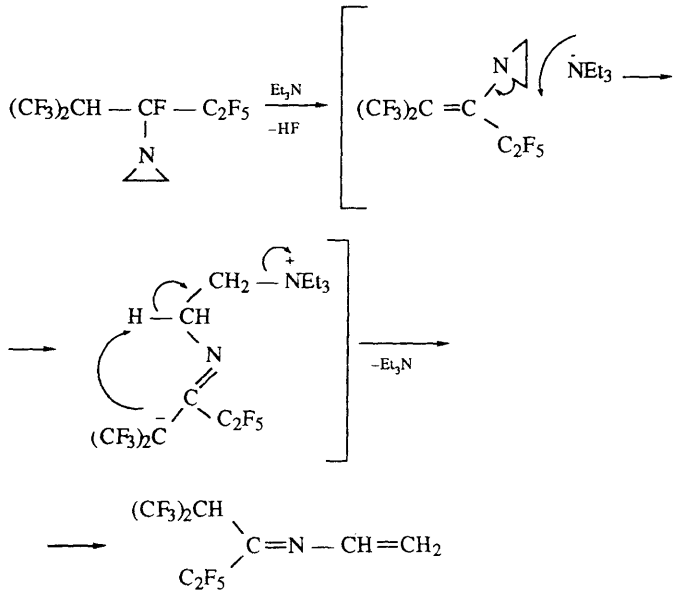


Homologues of perfluoro-2-azapropene form codimerisation products with fluoroolefins in the presence of fluoride ion.[60]

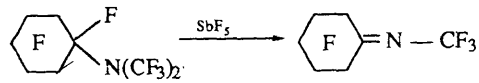


$R_F = CF_3, C_2F_5, C(CF_3)_3$

The addition products of an ethylenimine to an internal fluoroolefin formed under dehydrofluorination conditions undergo an unusual rearrangement with the formation of *N*-vinylpolyfluoroketimines.[61]



Under cationotropic conversion conditions tertiary fluoroamines, such as perfluorodimethylcyclohexylamine, eliminate CF_4 with the formation of a perfluoroketimine.[62]



80%

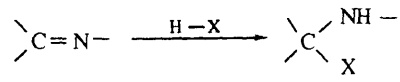
By comparing the data (of the last decade) discussed above on the methods of synthesising fluorine-containing ketimines with the results of previous work,[7] it is easy to see that the investigations in this area have acquired a distinctly applied character. Fundamental attention is now paid to the search for methods of synthesising functionally substituted ketimines. These include the imines of fluorine-containing, α-, β-, and γ-ketocarboxylic acids and their derivatives and various polyunsaturated derivatives, formally belonging to the hetero-1,3-dienes and conjugated heteropolyenes. They are all efficienct precursors of fluorine-containing compounds of various types possessing biological activity.[63,64]

III. Reactivity

At present studies are being vigorously continued on the reactions of fluorine-containing ketimines with nucleophilic reagents and on the cyclocondensation of mono- and bifunctional ketimines with mono- and binucleophiles. A new route has been developed for the polyfluoroalkylamino- and polyfluoroalkylamidoalkylation of aromatic and heteroaromatic π-systems of the donor type by fluorine-containing imines and acylimines. New data have been obtained on various cycloaddition reactions involving ketimines and acylimines.

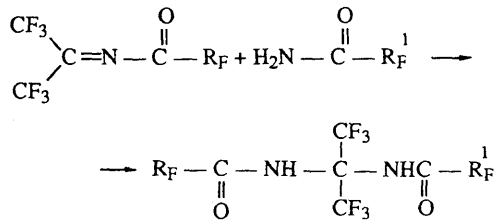
1. Reactions with nucleophilic reagents.

Fluorine-containing ketimines usually react readily with proton-containing nucleophiles giving the corresponding products of addition at the azomethine bond.[7,65–70] Electron-accepting properties and in some cases the structure of the substituent on the nitrogen atom of the C=N bond have a decisive effect on the addition conditions. Sulphonyl- and perfluoroacylimines of polyfluorocarbonyl compounds display the maximum reactivity in these reactions. Reaction of them with O-, N-, S- and P-nucleophiles is effected selectively either on cooling or in dilute solution. It is necessary to carry out the reaction with strong bases under strictly controlled conditions.



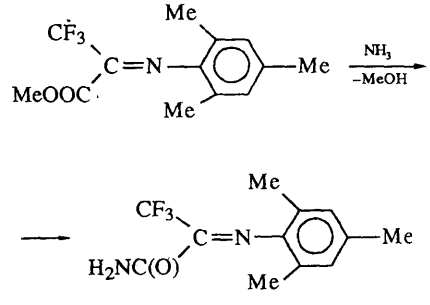
X = OH, OR, OPh, SPh, SR, NH_2, NHR, NR_2, $NHC(O)R$, $NHSO_2R$, PH_2, PHR, $P(O)R^1R$, $P(O)(OR)_2$, P(O)(OR)R.

The nature of the nucleophile used also affects the reaction conditions significantly. Reaction with imines is more difficult with a reduction in nucleophilic basicity. For example, even such highly reactive compounds as the perfluoroacylimines of hexafluoroacetone react with perfluorocarboxylic acid amides only on heating (100–150 °C) in a sealed tube.[71,72]

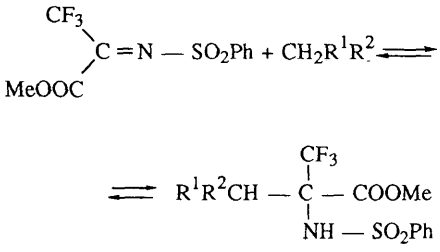


$R_F = CF_3$; $CH(CF_3)_2$; $R_F^1 = CF_3$, $CH(CF_3)_2$, C_4F_9.

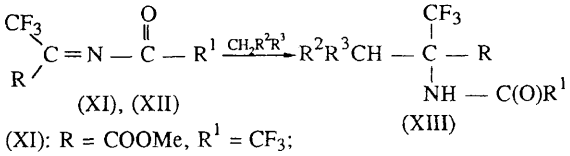
The reaction of nucleophilic reagents with functionally substitued imines occasionally lead to side products. For example, the anils of methyl trifluoropyruvate are converted on treatment with ammonia into anils of trifluoropyruvate amide.[32]



The reactions of sulphonyl- and acylimines of methyl trifluoropyruvate with CH-acids proved to be interesting.[32,70] Products of *C*-alkylation are formed in 25–30% yield on reacting a sulphonylimine with malonic or acetoacetic acid esters or with acetylacetone. The reactions are carried out at room temperature as equilibrium processes.



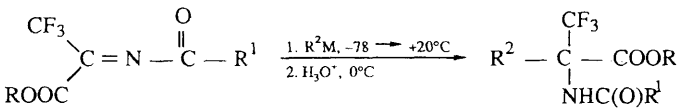
The reaction of the trifluoroacetylimine (XI) with malonic ester is even more difficult and the *C*-amidoalkylation product (XIII) was successfully obtained in 30% yield only on catalysis with toluene-4-sulphonic acid. Furthermore, reaction of the imine (XI) and the benzoylimine of hexafluoroacetone (XII) with CH-acids capable of enolisation, such as acetylacetone, acetoacetic ester and acetophenone, was effected at 20–80 °C leading to the *C*-amido-alkylation product (XIII) in up to 90% yield.[70] It is quite probable that in the latter case the process occurs by a [2 + 4] cycloaddition mechanism with an asymmetrical transition state.



(XI): R = COOMe, $R^1 = CF_3$;

(XII): R = CF_3, R^1 = Ph.

Organometallic compounds of Li, Cd and Mg react extremely vigorously with methyl trifluoropyruvate acylimines. These reactions occur selectively only under strong cooling and lead to derivatives of α-trifluoromethyl-α-amino-acids.[35,73,74]

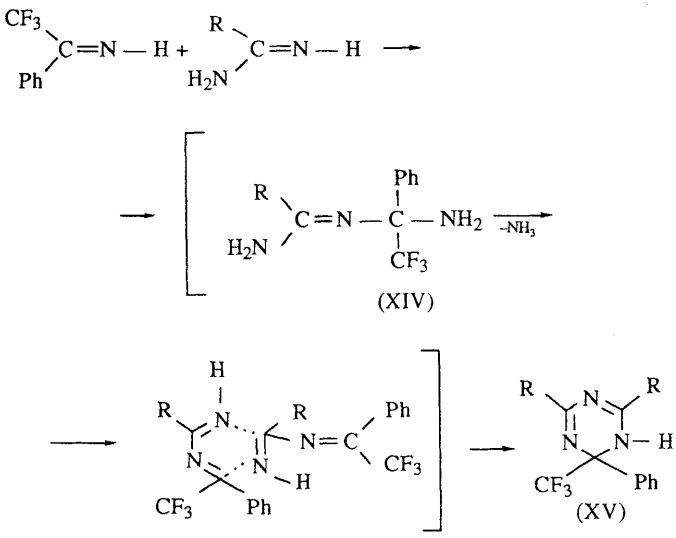


R = Me, Et; R^1 = OAlk, CF_3; R^2 = Me, Pr, Bu, iso-Bu, Ph, $PhCH_2$,

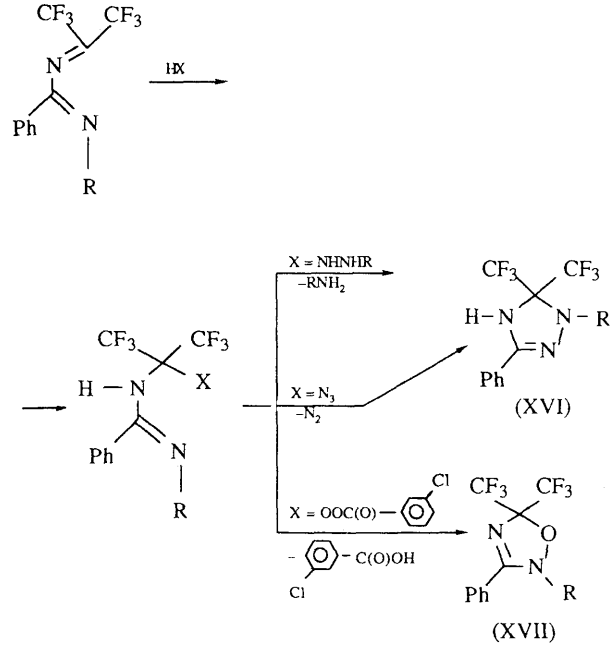
$CH_2=CH-(CH_2)_n$ (n = 0 to 4), ; M = Li, CdR^2, MgHal.

The reaction of fluorine-containing ketimines with nucleophilic reagents accompanied by heterocyclisation or cyclocondensation is particularly interesting. Such conversions take place on reaction of functionally unsubstituted ketimines with binucleophiles. For example, reaction of the imine of trifluoroacetophenone with amidines leads to unstable adducts (XIV) which dimerise after elimination of ammonia to the corresponding dihydrotriazines (XV).

An unstable adduct (XIV) is formed with trifluoroacetamidine and is transformed into the triazine only on heating to 200 °C.[75]

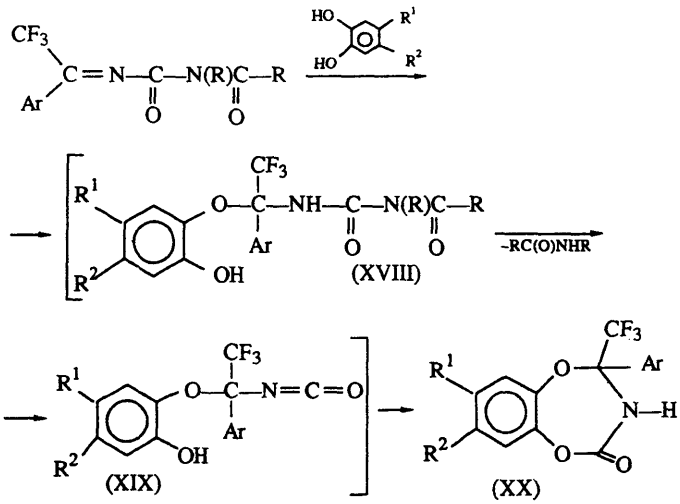


Functionally substituted ketimines also react with mono- and binucleophiles. Burger and collaborators[76–78] showed that the adducts of the iminoacylimines of hexafluoroacetone formed initially with hydrazines,[76] hydrazoic acid[77] and 3-chloroperbenzoic acid[78] cyclise spontaneously into the triazolines (XVI) and the isoxadiazolines (XVII).

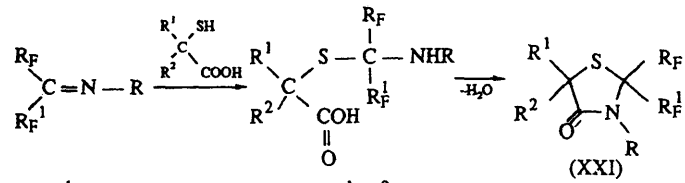


Poorly stable geminal amino-aryloxy compounds (XVIII) are also formed initially on reacting ureidoimines with *o*-dihydroxybenzenes. On boiling in benzene these compounds are converted through the

intermediate isocyanates (XIX) into the 1,3,5-benzodioxazepines (XX).[79]

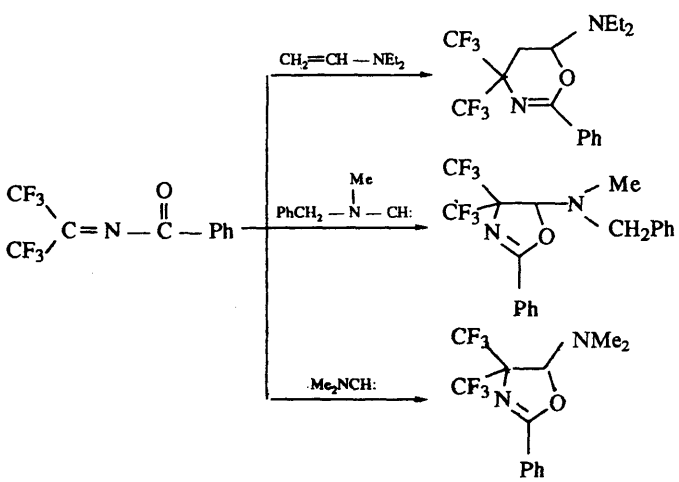


Recently Dupont patented the synthesis of the thiazolidones (XXI) which are plant growth regulators.[80] The method is based on the reaction of various polyfluoroketimines with α-mercaptocarboxylic acids, the first step of which is attack of the S-nucleophile on the C=N bond.

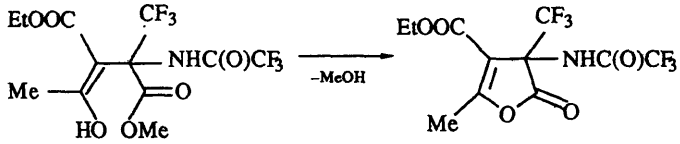


$R_F = R_F^1 = CF_3$, CF_2Cl, C_2F_5, CF_2H; $R^1 = R^2$ = H, Me, CH_2COOH.

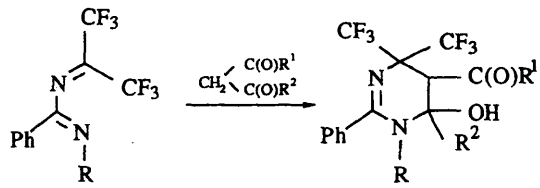
Ring formation also occurs in the reaction of acylimines with tertiary amines. The benzoylimine of hexafluoroacetone, which is an efficient acceptor of hydride ion,[7] converts triethylamine into *N,N*-diethylvinylamine, dimethylbenzylamine into the aminocarbene $PhCH_2(Me)NCH$: and tetramethyldiaminomethane into the aminocarbene Me_2NCH:, which are then stabilised by a second molecule of the benzoylimine as the corresponding [2 + 4] and [1 + 4] cyclic adducts.[81]



Various heterocyclic compounds may be obtained by reacting functionally substituted ketimines with CH-acids. The Michael addition products of acylimines of methyl trifluoropyruvate to enolisable CH-acids cyclise (slowly at 20 °C and rapidly on heating) to butenolides.[70] The mild conditions for the heterocyclisation are due to the stabilisation of the initial compounds in the enolic form.



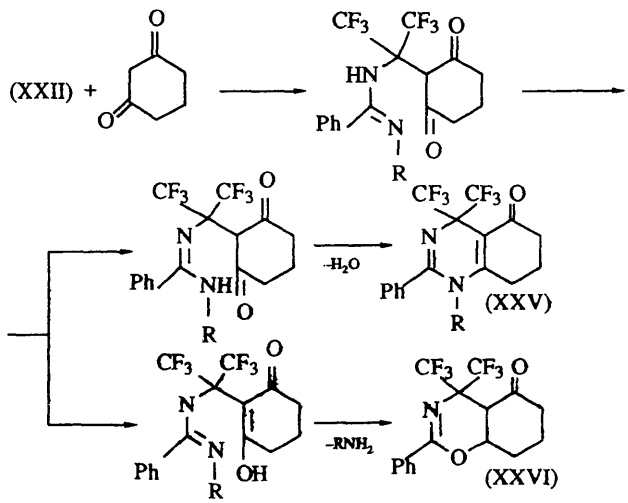
The adducts of CH-acids with acylimines of hexafluoroacetone are not subject to intramolecular heterocyclisation. However, the reaction of the iminoacylimines (XXII) with CH-acids capable of enolisation gives the [2 + 4] cyclic adducts (XXIII) and (XXIV) exclusively.[81]



(XXIII): $R^1 = R^2$ = Me;
(XXIV): R^1 = OEt, $R^2 = CH_2X$.

These differences are explained by the higher nucleophilicity of the terminal nitrogen in the iminoacylimines (XXII) compared to the carbonyl oxygen in the acylimines since the reaction of the acylimines stops at the stage of forming Michael adducts and the initial *C*-amidoalkylation products of (XXII) are transformed further into (XXIII) and (XXIV).

Cyclic 1,3-diketones, the enolic forms of which are not stabilised by an intramolecular hydrogen bond, undergo cyclocondensation with (XXII) giving a mixture of 1,4-dihydropyrimidines (XXX) and 1,3-oxazines (XXVI).[82]

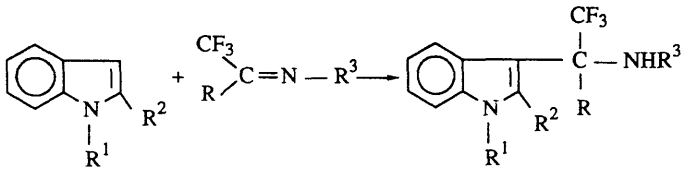


2. Reactions with aromatic and heteroaromatic compounds

A systematic study of the reactions of the imines, sulphonyl- and acylimines of hexafluoroacetone and of methyl trifluoropyruvate with aromatic and heteroaromatic compounds led to the design of a

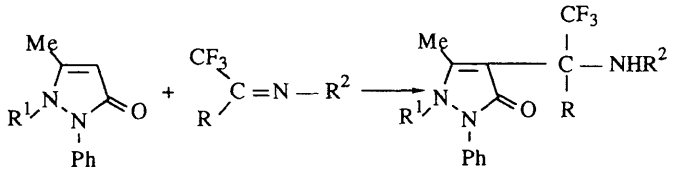
general method for polyfluoroalkyl-α-amino(amido)alkylation of aromatic systems of the donor type. These reactions proved to be closely similar to the known aminomethylation reaction, particularly with several heterocyclic π-donors.

Indole and certain 1- and 2-substituted indoles are almost quantitatively amino(amido)alkylated at position 3. The alkylating properties of $CF_3(R)C=N-R^3$ increase in the following series of R^3: H < $XC_6H_4C(O)$ < RSO_2 < $R_FC(O)$. The optimum reaction temperature in this series is thereby reduced from +120 to −50 °C.[28,83–85]



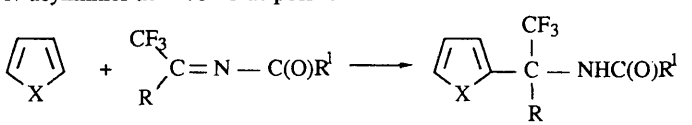
R = CF_3, COOMe; R^1 = H, Me, Ph; R^2 = H, Me, Ph; R^3 = H, 4-$FC_6H_4C(O)$, 2-$FC_6H_4C(O)$, SO_2Me, SO_2Ph, $CF_3C(CO)$, $CF_3(CF_2)_3C(O)$.

Hexafluoroacetone imine, its *N*-acyl derivatives and also the acyl- and sulphonylimines of methyl trifluoropyruvate also display similar properties when reacting with *N*-phenyl-3-methylpyrazol-5-ones.[85,86] Aminoalkylation is effected at the point of maximum π-electron density in the system.



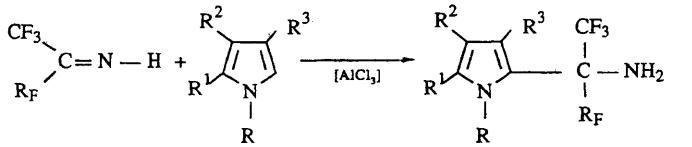
R^1 = H, Me; R = CF_3, COOMe; R^2 = H, SO_2Me, SO_2Ph, $CF_3C(O)$.

Furan, pyrrole and *N*-methylpyrrole are amidoalkylated by *N*-acylimines at −78 °C at position 2.[85,87]

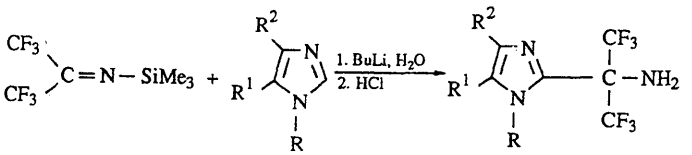


X = O, NH, NMe; R = CF_3 COOMe; R^1 = CF_3, $CH(CF_3)_2$.

According to the patent data the aminoalkylation of substituted pyrroles by imines of polyfluoroketones may be effected in the presence of Lewis acids.[88] The trimethylsilylimines of hexafluoroacetone reacts readily with 2-lithioimidazoles.[89] The *C*(2)-alkylation products formed in both cases possess nonsteroidal antiinflammatory activity.

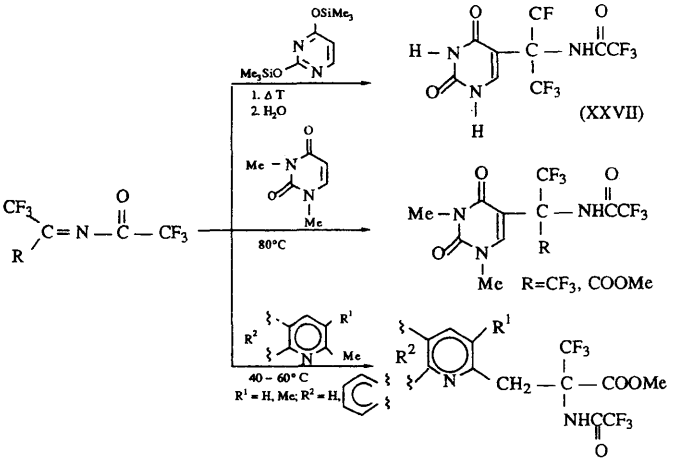


R^1H, Me; R^2 = R^3 = 4-FC_6H_4; R_F = CF_3, CF_2H CF_2Cl.

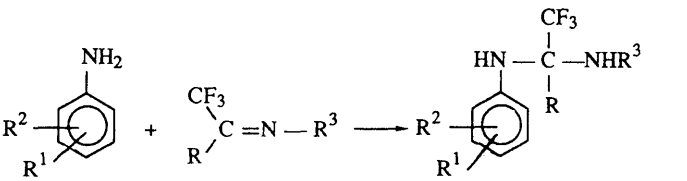


R^1 = R^2 = 4-$MeOC_6H_4$; R = CH_2OMe.

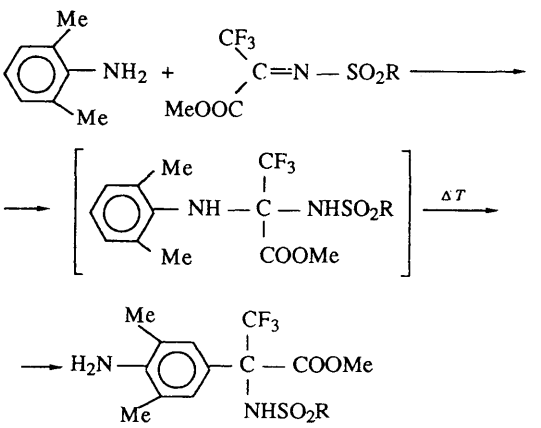
Only the highly electrophilic trifluoroacetylimines of hexafluoroacetone and methyl trifluoropyruvate react successfully with electron-deficient heterocyclic compounds. Thus the trimethylsilyl derivative of uracil forms the *C*(5)-aminoalkylation product (XXVII) on moderate heating.[90] 1,3-Dimethyluracil reacts readily.[91] 2-Methylpyridines and quinolines react at the methyl group with the trifluoroacetylimine of methyl trifluoropyruvate.[32,92]



A systematic study of the reactions of the sulphonyl- and acylimines of hexafluoroacetone and methyltrifluoropyruvate with primary and secondary arylamines[31,32,93–96] led to the conclusion that the *C*-amidoalkylation of these compounds is controlled by the probability of formation and the stability of the *N*-amidoalkylation products. Stable adducts at the nitrogen atom are formed exclusively with primary amines of various structure.

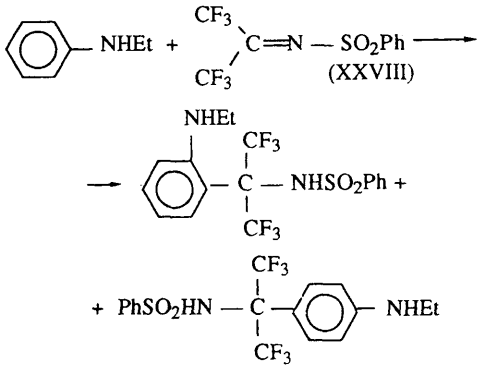


Steric hindrance to the formation of geminal diamino compounds exists in the reaction of the sulphonylimine of methyl trifluoropyruvate with 2,6-dimethylaniline. The initially formed unstable adducts at the nitrogen atom are isomerised quantitatively on boiling for 1–2 h in CCl_4 into products of *C*(4)-amidoalkylation.[32]



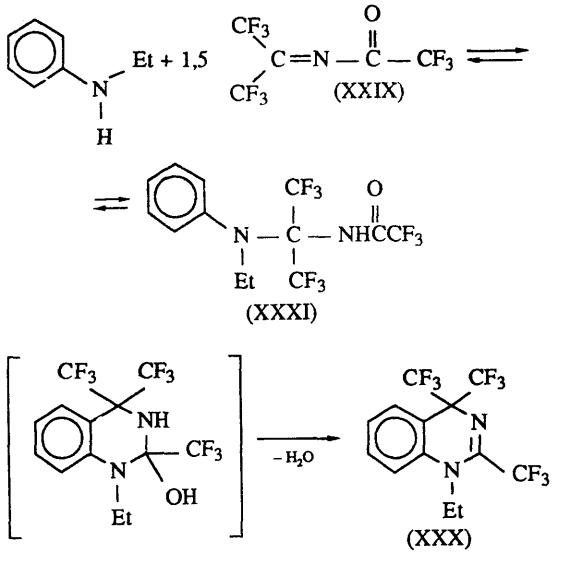
R = Me, Ph.

The probability of *C*-amidoalkylation of secondary arylamines is higher than for primary arylamines. *N*-ethylaniline reacts at 20 °C with the benzenesulphonylimine of hexafluoroacetone (XXVIII) forming products of *C*(2)- and *C*(4)-alkylation in low yield.[95]

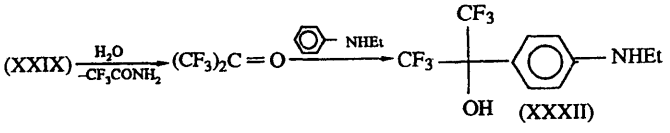


Boiling indoline with the imine (XXVIII) in $CHCl_3$ leads to a complex mixture of products from which the *C*(7)-alkylation product was successfully isolated in low yield (17%). It must be noted that this result is in agreement with the regioselective *C*(7)-alkylation of indoline by hexafluoroacetone described previously.[96]

The reaction of the trifluoroacetylimine of hexafluoroacetone (XXIX) with secondary arylamines is unusual and was studied in detail using *N*-ethylaniline as an example. The reaction unexpectedly leads to the 1,4-dihydroquinazoline (XXX) in 87% yield, i.e. the product of simultaneous *C*(2)-amidoalkylation and cyclocondensation involving the NH and $NHC(O)CF_3$ groups.

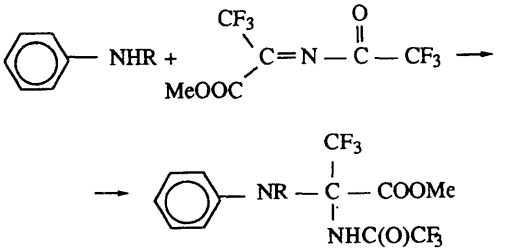


It was shown that the unstable *N*-alkylation product (XXXI) is formed first after mixing the reagents and disappears as compound (XXX) accumulates. The aniline (XXXII) is a side product of the reaction. Its appearance is linked with the decomposition of the acylimine by the water eliminated during cyclocondensation.

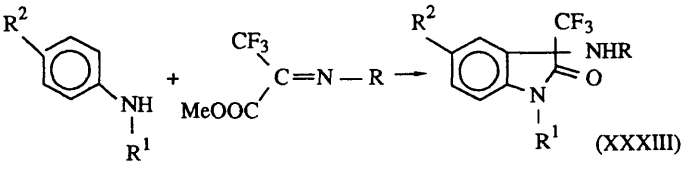


N-Methyl-, *N*-isopropyl- and *N*-phenylanilines and their 4-methoxy and 4-chloro derivatives react like the acetylimine (XXIX).[95] The reaction time was reduced as the volume of the substituent at nitrogen increased in the series of *N*-alkylanilines studied.

The sulphonyl- and acrylimines of methyl trifluoropyruvate give more stable *N*-amidoalkylation products with secondary arylamines. The *C*-amidoalkylation of methyl- and ethylanilines does not take place.

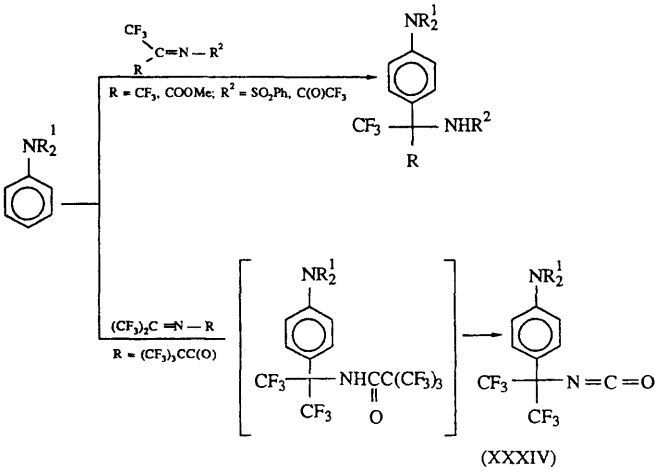


However, the products of simultaneous *C*(2)-amidoalkylation and *N*-acylation, the corresponding indolinones (XXXIII), are obtained in moderate yield with *N*-isopropylaniline, *N*-isopropyl-*p*-toluidine, *N*-isopropyl-*p*-anisidine and diphenylamine.[31]



R_2 = H, Me, OMe; R^1 = iso-Pr, Ph; R = SO_2Me, SO_2Ph, $C(O)CF_3$.

N,*N*-Dimethyl- and *N*,*N*-diethylaniline are *C*(4)-amidoalkylated quantitatively under strong cooling by the sulphonyl- and acylimines of hexafluoroacetone and methyl trifluoropyruvate.[28,31,97] In the case of the *N*-pivaloylimine of hexafluoroacetone the products of *C*(4)-alkylation formed initially eliminates $(CF_3)_3CH$ and is converted into the isocyanate (XXXIV).[97]



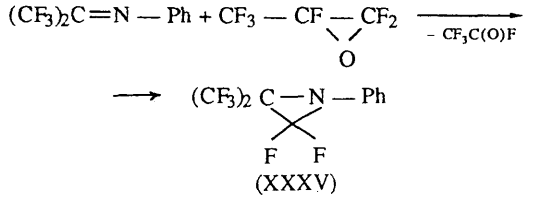
(XXXIV)

3. Cycloaddition reactions

The behaviour of unsaturated compounds in cycloaddition reactions reveals the chemical nature of the fluorine-containing ketimines most completely. It was shown previously[7] that

fluoroketimines with an isolated C=N bond for [1 + 2], [2 + 2], [3 + 2] and [4 + 2] cycloadducts somewhat more readily than their unfluorinated analogues. The sulphonyl-, acryl, thioacyl- and iminoacylimines of hexafluoroacetone are significantly more reactive and react either as activated azomethines or as 1,3-heterodienes in cycloaddition reactions. The new data obtained have extended significantly the concepts of both these reactions and in some cases have enabled electronic models of them to be constructed.

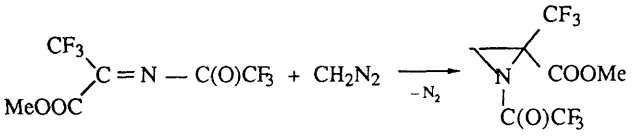
Carbenes, their precursors and the carbenoids usually react unambiguously with fluoroketimines. The reaction of difluorocarbene with fluoroketimines has been demonstrated.[98] The [1 + 2] cyclic adduct, the aziridine (XXXV), was obtained in satisfactory yield by heating a mixture of hexafluoroacetone anil with hexafluoropropylene oxide at 180 °C.



(XXXV)

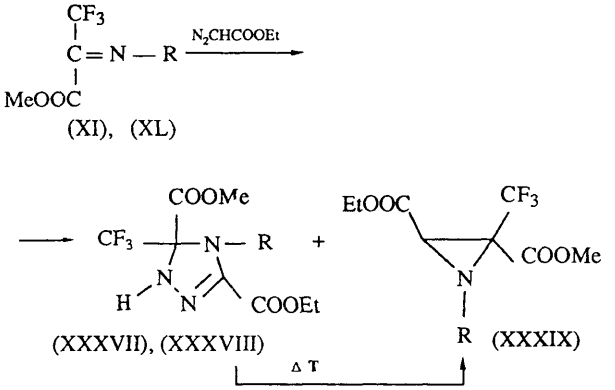
Diazoalkanes are efficient precursors of carbenes in reactions with highly electrophilic fluoroketimines.[7] The behaviour of methyl trifluoropyruvate acylimines in these reactions has been studied.[29,32]

The reaction of trifluoroacetylimine of methyl trifluoropyruvate with diazomethane occurs at −30 °C and is accompanied by elimination of nitrogen and the formation of the aziridine (XXXVI)[29] and not the [1 + 4] cylic adduct as in the analogous reaction with the benzoylimine of hexafluoroacetone.[99]



(XXXVI)

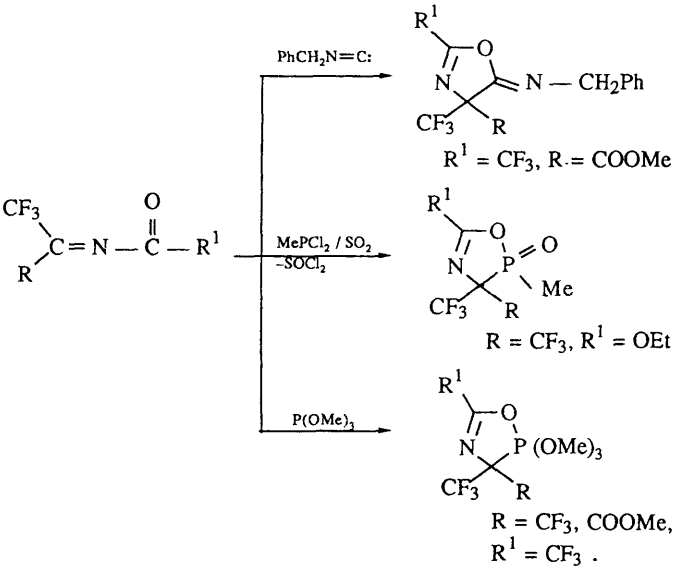
The reaction of the imine (XI) with diazoacetic ester also proceeds in an unusual manner.[29,74] It is effected at 20 °C and leads to a 2:1 mixture of the triazoline (XXXVII) and the aziridine (XXXIX). Thermolysis of (XXXVII) occurs at 180 °C giving the product (XXXIX) in high yield.



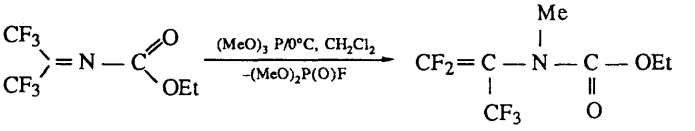
R = C(O)CF$_3$ (XI, XXXVII, XXXIX); SO_2Ph (XL, XXXVIII).

However, diazoacetic ester forms the highly stable [3 + 2] cyclic adduct (XXXVIII) with the sulphonylimine (XL) and no aziridine.[74]

On the other hand, the acylimines of methyl trifluoropyruvate, like the acylimines of hexafluoroacetone,[100] form [1 + 4] cyclic adducts with benzyl isocyanide[32] and with compounds of three-coordinate phosphorus.[74]

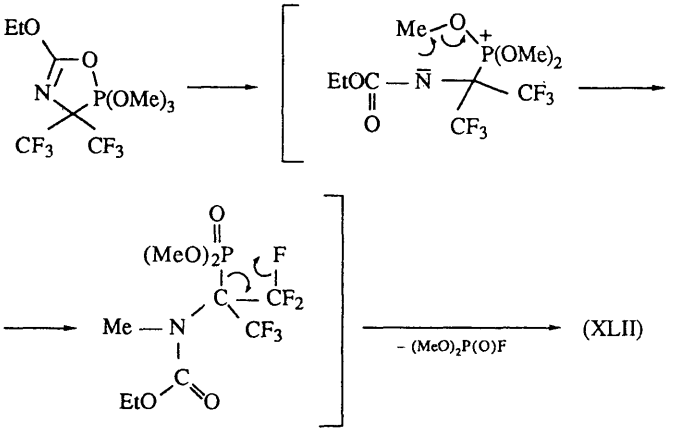


An anomalous course for the reaction was established only when reacting the *N*-ethoxycarbonylimine of hexafluoroacetone (XLI) with trimethyl phosphite.[101] The reaction product proved to be the carbamate (XLII) and not the [1 + 4] cyclic adduct.



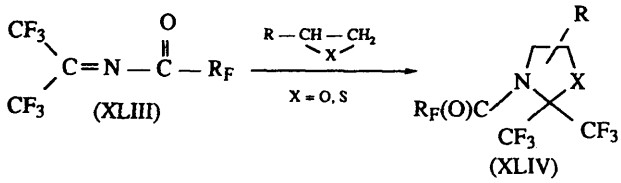
(XLI) (XLII)

Probably the [1 + 4] cyclic adduct formed initially is readily converted into a zwitterion which is stabilised by intramolecular *N*-methylation with subsequent elimination of dimethyl fluorophosphate.



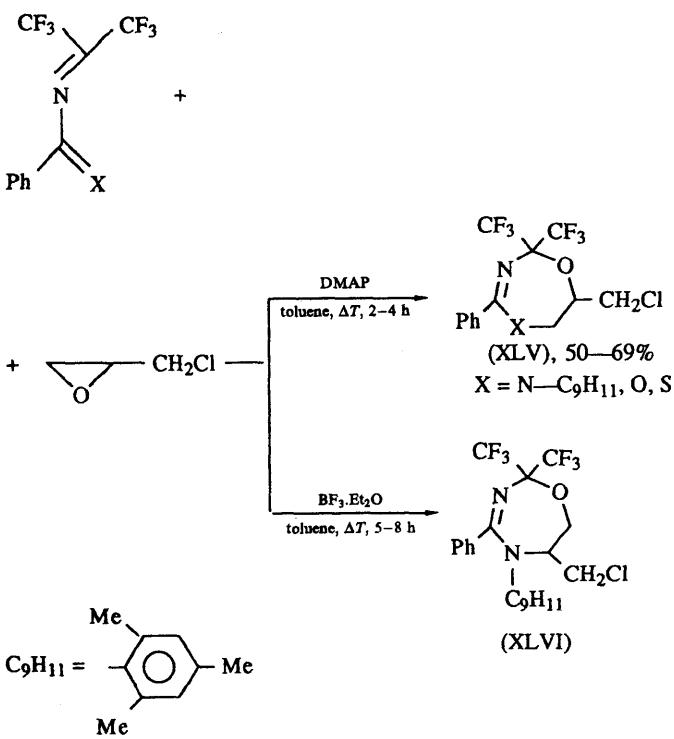
An important feature of the sulphonylimines of hexafluoroacetone is the extremely mild conditions for their reaction with oxiranes and thiiranes with the formation of [3 + 2] cyclic adducts.[7] The acylimines of hexafluoroacetone react even more vigorously with

oxiranes and thiiranes.[102] The reaction of the imines (XLIII) with an oxirane occurs even at −70 °C, being accompanied by much oligomerisation, and the corresponding 1,3-oxazolines (XLIV) are successfully isolated in only small yield (15%). Methyloxirane and methylthiirane smoothly add (XLIII) under analogous conditions forming a mixture of regioisomers in 55–75% yield.[102]



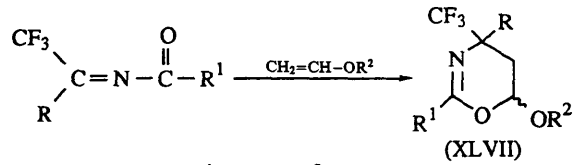
R_F = $CH(CF_3)_2$, CF_3; R = H, Me.

Acyl-, thioacyl- and iminoacylimines of hexafluoroacetone react catalytically with epichlorhydrin[103] giving the [3 + 4] cyclic adducts. On using an equimolar quantity of 4-dimethylaminopyridine (DMAP) as catalyst, the reaction leads to the selective formation of the heterooxazepines (XLV). Conduct of the reaction of the iminoacylimines with a catalytic quantity of boron trifluoride etherate leads to the tetrahydrooxadiazepine (XLVI) in 50% yield. In the absence of catalyst or with an acid catalyst a mixture of compounds is formed.



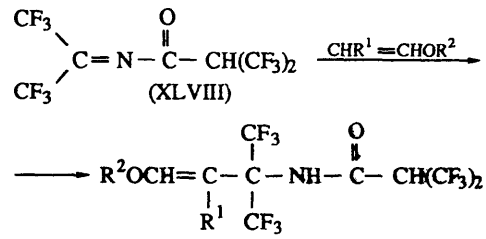
The properties of acylimines as 1,3-heterodienes have been studied widely.[7] Particular attention has been paid to their reactions with alkenes. Interest in them is due first of all to the fact that the 1,3-oxazine derivatives formed are promising synthetic intermediates.[104–106] Recently acylimines with a prochiral centre in the molecule have been used in these reactions.

Vinyl acetate and vinyl butyl ether react under mild conditions with the acylimines of methyl trifluoropyruvate and hexafluoroacetone giving the corresponding dihydrooxazines (XLVII). The reaction is effected regioselectively and in certain cases stereoselectively as well.[29,107]



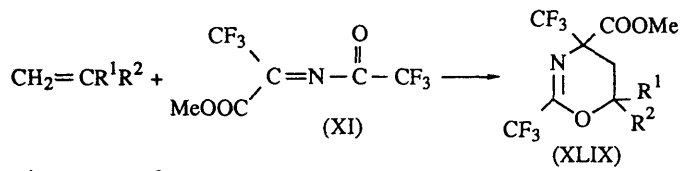
R = COOMe, Ph; R^1 = CF_3; R^2 = Ac, Bu.

The reaction of the *N*-(hexafluoro-α-hydroisobutyroyl)imine of hexafluoroacetone (XLVIII) with alkyl vinyl ethers unexpectedly leads to the product of amidoalkylation of the multiple bond.[108]



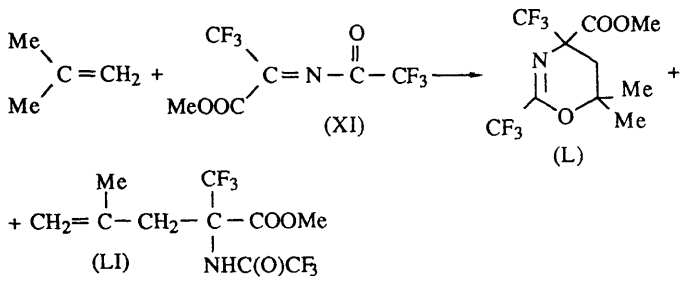
This may be explained by the steric effects of the hexafluoroisopropyl group of the imine (XLVIII) which hinders the formation of the symmetrical transition state.

The reaction of the trifluoroacetylimine of methyl trifluoropyruvate (XI) with other terminal olefins such as 2-chloromethylpropene, propylene, methyl allyl ether, allyl iodide, bromide and chloride and methyl methacrylate also occurs regiospecifically giving the corresponding 1,3-dihydrooxazines (XLIX) in preparative yield. The optimum reaction temperature increases from 10 to 70 °C in the series shown.[109]

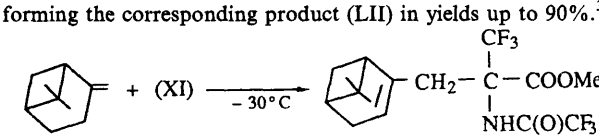


R^1 = H, Me; R^2 = Me, CH_2OMe, CH_2Cl, CH_2Br, CH_2I, COOMe.

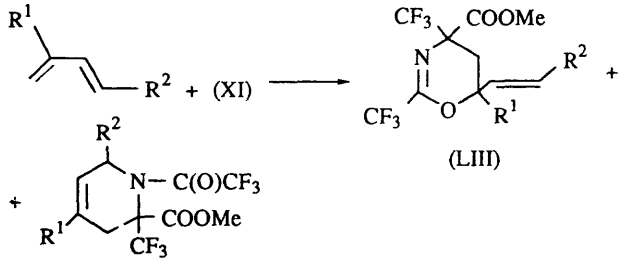
However, the product of the ene reaction (LI) is formed in addition to the 1,3-dihydrooxazine (L) in the reaction of the imine (XI) with 2-methylpropene. The content of (LI) increases from 15 to 25% on increasing the reaction temperature to −78 to 20 °C.[29]



β-Pinene, being extremely reactive in ene reactions, reacts with (XI) forming the corresponding product (LII) in yields up to 90%.[32]

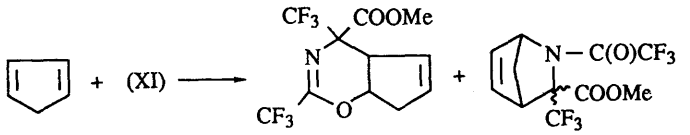


The imine (XI) also displays the properties of a strong 1,3-heterodiene in reactions with 1,3-dienes which is not a characteristic of the perfluoroacylimines of hexafluoroacetone.[110,111] Thus on reacting (XI) with butadiene, isoprene and piperylene the main reaction products proved to be the 1,3-dihydrooxazines (LIII), which are the [2 + 4] cyclic adducts. Products of the Diels–Alder reaction or the [4 + 2] cyclic adducts, which were expected to be the main products, were present only as insignificant contaminants.[109]



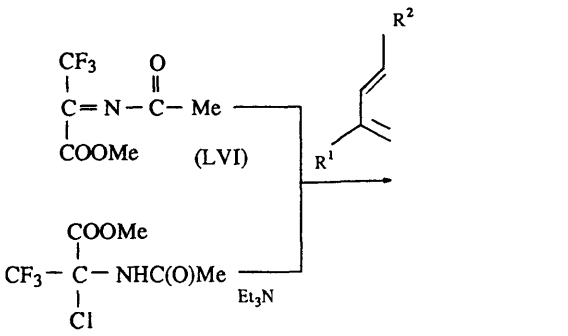
(LIII)

Even such a reactive diene as cyclopentadiene forms with imine (XI) the 1,3-dihydrooxazine (LIV) and the Diels–Alder reaction product (LV) in a ratio of 1 : 3.[109]

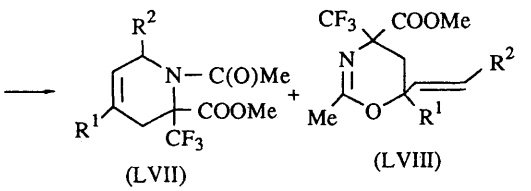


(LIV) (LV)

The character of the reaction of the less electrophilic acetylimine of methyl trifluoropyruvate with 1,3-dienes is reversed. Thus mixtures are formed in the reaction of (LVI) with isoprene and piperylene which contain up to 80% Diels–Alder reaction product (LVII) and no more than 20%, 1,3-dihydrooxazines (LVIII).[32]



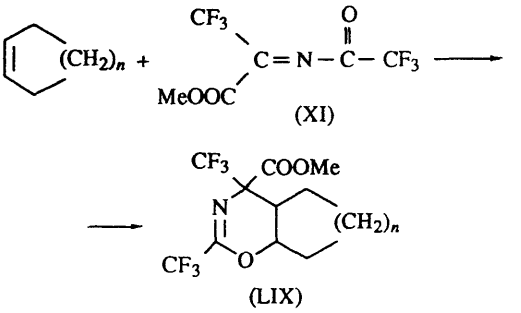
(LVI)



(LVII) (LVIII)

Analogous results were obtained on using the precursor of imine (LVI), the geminal aminochloro compound, and an HCl acceptor (Et_3N) instead of (LVI). The optimum conditions, yield, and product ratio proved to be the same as on using the pure imine.

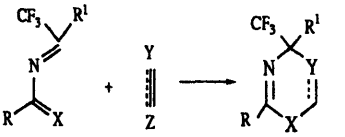
In contrast to the terminal alkenes, cyclopentene and cyclohexene form [2 + 4] cyclic adducts (LIX) with the imine (XI) only under forcing conditions (150 °C, sealed tube).[29]



(XI) (LIX)

$n = 1$ or 2.

Table 2. Reactions of acylimines with aldehydes, ketones and nitriles of carboxylic acids.



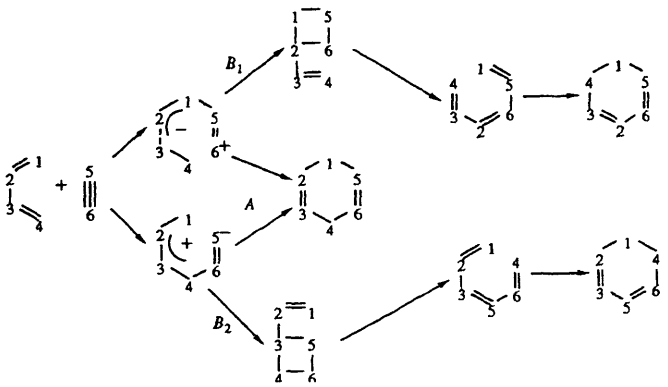
No.	R	R^1	X	Y	Z	Refs.
1	4-ClC_6H_4 Ph	CF_3	O, S, NAr O, S	O N	$C(CF_3)_2$, $CHCCl_3$ $-CCCl_3$, $-CCF_3$	[108]
2	$C(CF_3)=CF_2$	CF_3	O	O	$C(CF_3)_2$ $-CCH_3$	[66]
3	$C(CF_3)_3$	CF_3	O	O	CHPh	[112]
4	4-ClC_6H_4 Ph	CF_3	O, S, NAr	O	$C(R^1)-C(R^2)=CHR^3$, ($R^1=R^2=H$, Me; $R^3=H$, Ph)	[113]
5	Ph	CF_3	NAr	N	$-CCH=CHR$ (R = Me, Ph) $-CC(R_1)=CHR^2$ ($R_1=H$, Me; $R_2=H$, Ph). $-CC\equiv CPh$	[114]
6	C_3F_7 $CH(CF_3)_2$	CF_3	O	N	$-CPh$, $-CMe$, $-CCH=CH_2$, $-CCH_2COOEt$	[115]
7	Ph	CF_3	NAr	N	$-CNMe_2$, $-CMe$, $-CPh$	[116]
8	Ph	CF_3	S	N	$-CC(CN)=C(CN)_2$	[117]
9	CF_3	CF_3	O	N	$-C(NH_2)=C(Me)-NH-C(O)-P(OEt)_2$ (Et)	[118]
10	CF_3	CO_2Me	O	N	$-Cr^1(R^1=Me, CH_2=CH-)$	[29, 32]

The acyl-, thioacyl- and iminoacylimines of hexafluoroacetone and the acylimines of methyl trifluoropyruvate are inclined to form rings even with such weak heterodienophiles as aldehydes, ketones and nitriles. Products (heterocycles) typical of [2 + 4] cycloaddition reactions are formed in several cases. Examples of these reactions are shown in Table 2.

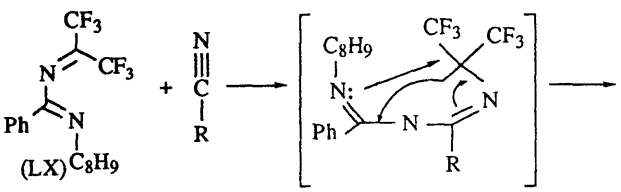
Cases are also known of the formation of compounds of anomalous structure the appearance of which is the result of stepwise conversions. The theoretical aspects of such reactions have

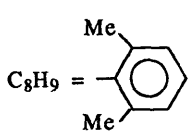
been considered by K Burger and his collaborators.[116] They proceeded from the fact that the reactions of polar 1,3-dienes with polar unsaturated systems usually occur as charge-controlled processes.[119] The stabilisation of the intermediates formed, the 1,X-dipoles (Scheme 1), may be effected by closing either a six- or a four-membered ring. The greater the degree of rotation of the 1,X-dipole the greater its lifetime and the greater the probability of forming a six-membered ring in the reaction. On the other hand, the formation of a four-membered cyclic system is preferred for destabilised 1,X-dipoles and in its turn it may be converted by fission of the 1–2 and 3–4 bonds giving products different from those formed by route *A*.

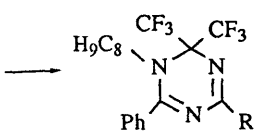
Scheme 1



A similar scheme is proposed for the reaction of the 4,4-bis(trifluoromethyl-1,3-diazabuta-1,3-diene (LX) with carboxylic acid nitriles.[116] The reaction of dimethylcyanamide, aceto- and benzonitriles in this system leads to the expected 1,3,5-triazine (Scheme 1, route *A*). However, in the reaction of the diazobutadiene (LX) with electron-deficient nitriles such as 4-chlorophenylazonitrile, trichloro- and trifluoroacetonitrile, the products proved to be the triazines (LXI) with a reorganised diene skeleton which is only possible via route B_1 (Scheme 1).

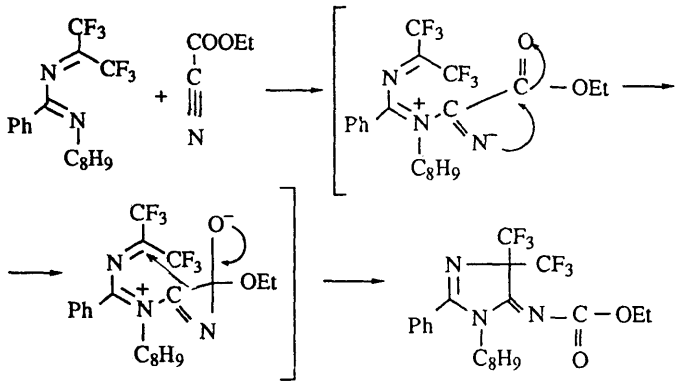


(LX) C_8H_9 = 



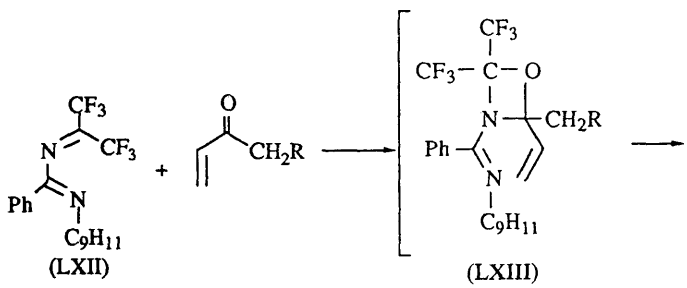
(LXI)

Diazabutadiene (LX) reacts most unusually with ethyl cyanoformate.[120]

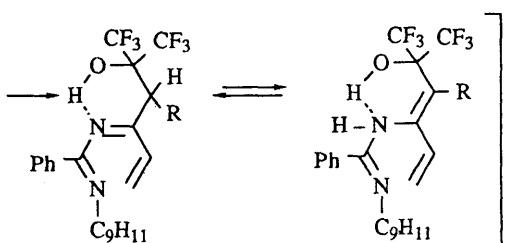


A similar cyclisation was observed previously in the acylation of acetophenone dianion.[121]

The reaction of heterodiene (LXII) with α,β-unsaturated ketones proved to be anomalous in a series of aldehydes and ketones.[122]

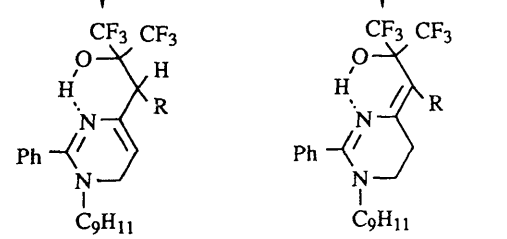


(LXII) (LXIII)



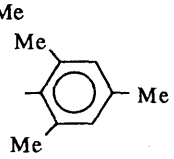
(LXIV) (LXV)

electrocyclisation ene reaction



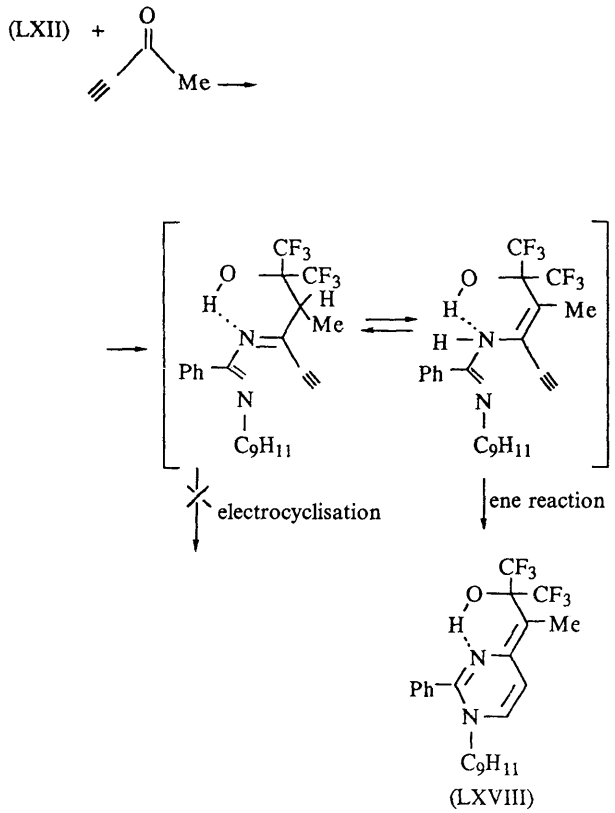
(LXVI) (LXVII)

R = H, Me

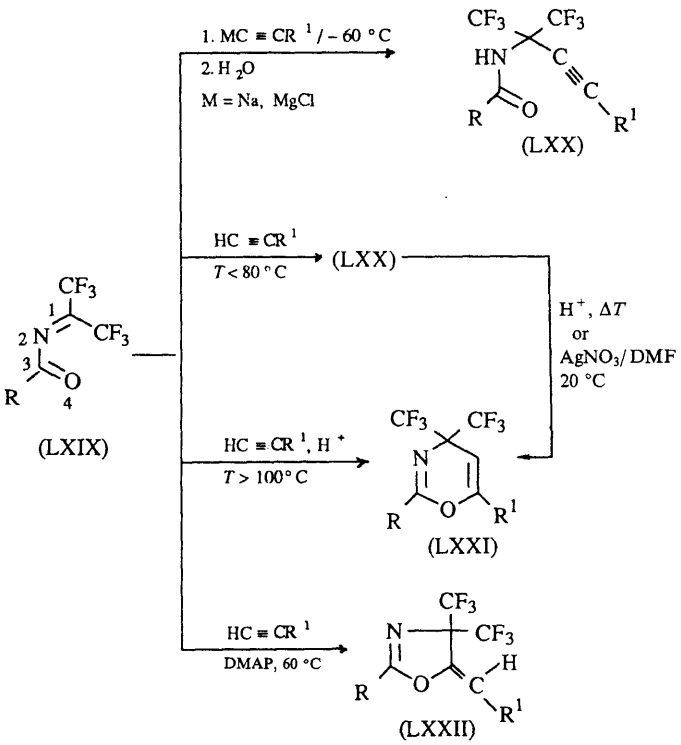
C_9H_{11} = 

It is considered that the four-membered ring intermediate (LXIII) undergoes decomposition to hexafluoroacetone and a 1,3-diaza-1,3,5-triene which react by an ene mechanism giving the product (LXIV) existing in two tautomeric forms (LXIV) ⇄ (LXV). In their turn compounds (LXIV) and (LXV) cyclise to the final products (LXVI) and (LXVII) electrocyclically and according to an intramolecular ene reaction mechanism respectively.

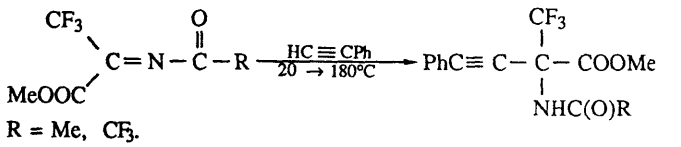
The heterodiene (LXII) also reacts in a similar manner with acetylacetylene giving only one product (LXVIII) since in this case the electrocyclic reaction is hindered.[122]



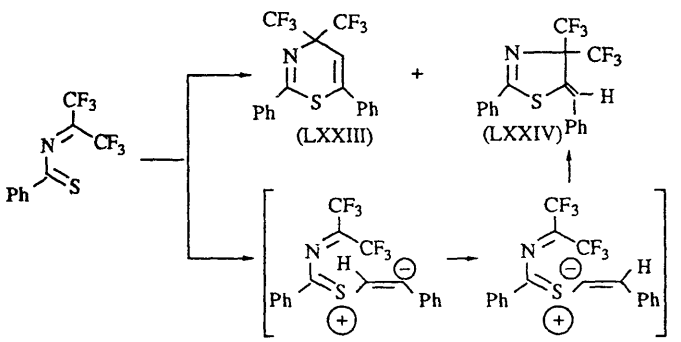
Acetylenes react with fluorine-containing 1,3-heterodienes giving the corresponding trifluoromethyl-substituted *N*-propargylamides,[32,123] 4H-1,3-oxazines[118,123] and 2-oxazolines.[123,124] The selectivity of these processes depends on the reaction conditions. Thus the acylimine (LXIX) reacts with electron-rich terminal acetylenes and alkali metal acetylides forming *N*-propargylamides (LXX). Cyclisation of these compounds under the action of acid catalysts or silver nitrate leads quantitatively to the 1,3-oxazines (LXXI). However, the electron-deficient alkynes form five-membered cyclic systems with (LXIX) including in the ring only the terminal carbon atom of the acetylene. The addition of 4-dimethylaminopyridine (DMAP) to the acylimine (LXIX) leads to the reversible blocking of the electrophilic position 1 in (LXIX) which increases the nucleophilicity of position 4. The oxazoline (LXXII) is therefore formed exclusively.



The acylimine (LXIX) forms adduct (LXX) with phenylacetylene by a Michael reaction. On heating the adduct is transformed into the oxazine (LXXI). This was not observed in the case of the acetyl- and trifluoroacetylimines of methyl trifluoropyruvate.[32]

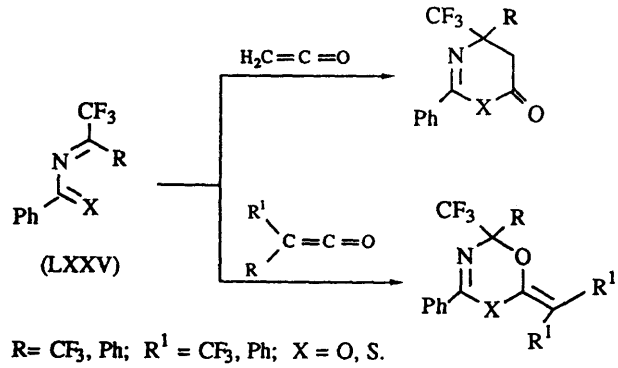


On heating in phenylacetylene (80–90 °C) the thio analogue of the acylimine (LXIX) forms a mixture (1 : 1) of the products (LXXIII) and (LXXIV). The product (LXXIII) is formed by a Michael addition but the product (LXXIV) is formed through a cyclisation in which the skeleton of the dienophile is included in the cyclic system only partially. This occurs according to the following postulated mechanism.[124]



An analogous reaction was observed by Giordano[125,126] in the hydrocarbon series when reacting phenylacetylene with the imine generated *in situ* from thiobenzoic acid amide and benzaldehyde by the action of boron trifluoride ethereate.

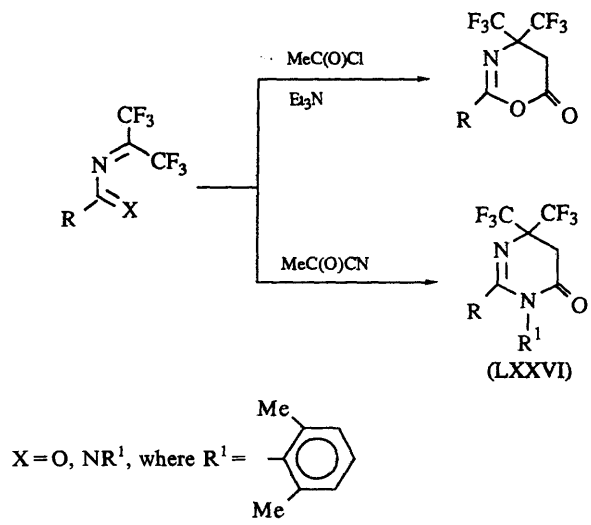
The acylimines of polyfluoroketones react with ketene by a [2 + 4] cycloaddition mechanism forming the corresponding cyclic adducts at the C=C bond.[107,127–129] However, in the reaction of the heterodiene (LXXV) with diphenyl-[127] and bis(trifluoromethyl)-ketenes[129] ring formation occurs at the C=O bond.



R= CF_3, Ph; R^1 = CF_3, Ph; X = O, S.

Desimoni and Tacconi[130] have considered this reaction from the point of view of frontier molecular theory orbitals. They showed by correlation diagrams that the reaction of the benzoylimine of hexafluoroacetone with a ketone occurs as an inverted Diels–Alder reaction, i.e. by a [2 + 4] cycloaddition mechanism. On the other hand the benzoylimine reacts as a π-donor with hexafluorodimethylketene, i.e. a typical [4 + 2] cycloaddition is implemented. This also determines the observed differences in the reaction pathways.

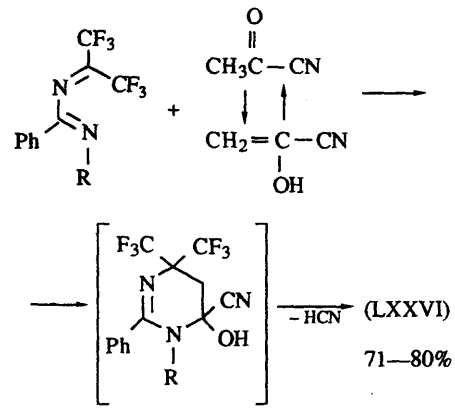
It is also possible to use ketene precursors, such as a mixture of acetyl chloride with triethylamine or nitriles of α-ketocarboxylic acids, in the reaction with acyl- and iminoacylimines.[127]



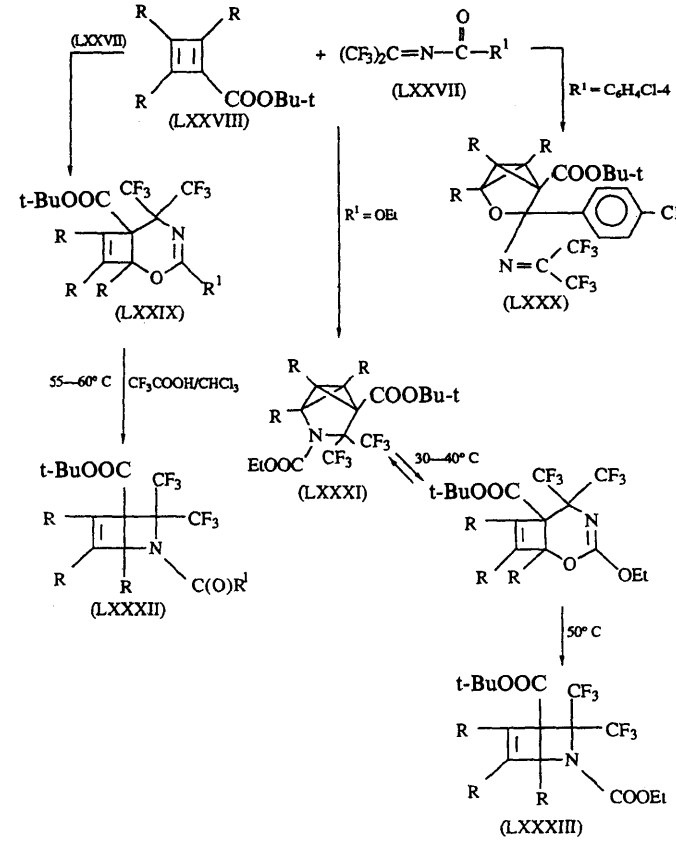
X=O, NR^1, where R^1 =

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4.

Formation of the product (LXXVI) occurs on reaction of the heterodiene with the enolic form of pyruvic acid nitrile. The [2 + 4] cyclic adduct formed initially eliminates HCN spontaneously giving compound (LXXVI) in high yield.



Reaction of the *N*-acylimines (LXXVII) of hexafluoroacetone with cyclobutadiene (LXXVIII) leads to the formation of the oxazabicyclo[4.2.0]octadienes (LXXIX).[131] Exceptions are the reaction of (LXXVIII) with the imine (LXXVII, R^1 = C_6H_4Cl), when the tricyclic isomer (LXXX) is formed, and with the ethoxycarbonylimine of hexafluoroacetone (LXXVII, R^1 = OEt) which leads to the 3-azatricyclo[3.1.0^{2,6}]hexane (LXXXI). Compounds (LXXIX) and (LXXXI) are readily transformed into the bicyclic compounds (LXXXII) and (LXXXIII) respectively.[131]



R = t-Bu; R^1 = iso-Pr, Ph, 4-$MeOC_6H_4$.

(LXXIX) $\xrightarrow[14\ h]{165\ ^\circ C}$ (LXXXII)

The literature data considered in this review suggest that the known methods of synthesising fluorine-containing ketimines may be used for obtaining practically all possible types of these interesting compounds. The broad study of the properties of the various ketimines has increased the preparative accessibility of many biologically active fluorine-containing compounds, particularly fluorine-substituted aminoacids, amines and heterocyclic compounds of various types.

It may be expected that further work on the synthesis and study of the properties of fluorine-containing ketimines will be directed mainly to the development of preparative methods for obtaining various β-fluorine-containing α-aminoacids the biological activity of which is linked with the selective irreversible inhibition of pyridoxal phosphate-dependent enzymes.[132] This will probably trigger research in the least studied areas of the chemistry of these highly reactive synthons, for example, the ene reaction, various heterocyclisation reactions and further conversions of the primary products of cycloaddition reactions.

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