Preparation of Fluorine-Containing Heterocyclic Compounds *via* Cycloaddition Reactions

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Abstract: This account deals with recent progress in the study on the synthesis of fluorine containing heterocycles *via* the cycloaddition reactions of some fluorine-containing dienophiles or dipolarophiles. It includes two main parts: (1) the 1,3-dipolar cycloaddition reactions to five-membered fluorinated heterocycles; (2) the (hetero) Diels-Alder reactions to six-membered fluorinated heterocycles.

Keywords: Fluorinated heterocycles, cycloaddition, 1,3-dipolar addition, (hetero) Diels-Alder reaction.

1. INTRODUCTION

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It's equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds. Since the isolation of elemental fluorine by H. Moissan in 1886, the amount of fluorine-containing compounds was over 6% of the 10 million compounds registered in Chemical Abstracts [1]. It is well documented that the replacement of a hydrogen atom by a fluorine atom or a fluoroalkyl group in an organic molecule may profoundly influence its physical and biological properties [2]. Especially, the fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activities for their potential applications in medicinal and agricultural fields [3-5]. Germane to the growth and application of fluorinated compounds is the development of new synthetic methods in fluorine chemistry. Cycloaddition reactions figure prominently in both synthetic and mechanistic organic chemistry. In recent years, numerous natural and unnatural products have been prepared by synthetic routes that have a cycloaddition reaction as a crucial step in their synthesis. Consequently, this reaction has become recognized as an extremely important transformation in the repertoire of the synthetic organic chemistry. Since 1990, several research groups at the Shanghai Institute of Organic Chemistry have made great efforts to exploit the cycloaddition reactions to synthesize the fluorine-containing heterocyclic compounds.

This review deals with advances in the synthetic chemistry for the preparation of fluorinated heterocyclic compounds, which contain one or more fluorine atoms. This article concentrates on the application of cycloaddition reactions to prepare the fluorine-containing heterocyclic compounds. In this mini-review, we wish to summarize these results.

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2. PREPARATIONS OF FLUORINE-CONTAINING HETEROCYCLES *VIA* 1,3-DIPOLAR ADDITIONS

1,3-dipolar cycloaddition provides an excellent method for constructing a five-membered ring because a wide variety of 1,3-dipoles is available and undergo addition to carbon-carbon or carbon-heteroatom multiple bonds to produce five-membered heterocycles. There are two choices in the synthesis of fluorine-containing heterocycles using this methodology, one of which is the application of fluorinated 1,3-dipolar compounds as dipole precursors to cycloadd to multiple-bond compounds; another one is the application of fluorine containing olefins and acetylenes as dipolarophiles to add to a great amount of 1,3-dipoles.

2.1 Preparations of Fluorinated Heterocycles *via* 1,3-Dipolar Cycloaddition Using Fluorinated Dipolarophiles

2.1.1 Application of the Fluorinated Dipolarophiles and Azomethine Ylides to Synthesis of Fluoro-Containing Indolizines

Indolizine is an important ring system in view of its similarity to indole. Numerous researches on indolizines concerning the search for drugs, for dyestuffs and for special sensitizers have been reported previously [6]. There are many synthetic cases about indolizine's analog fluorine-containing compounds. In 1985, Banks *et al*. [7] once reported the cycloaddition reaction of pyridinium N-ylide generated *in situ* from a pyridinium salt in the presence of a base with perfluoroalkenes or alkynes afforded a series of fluorine-containing indolizines.

At the end of the last century, Huang *et al*. [8] had studied thoroughly the preparation of fluorine-containing indolizines. For example, in the presence of a mixed organic and inorganic base, the reaction of pyridinium ylides with 1-iodo-2-(polyfluoroalkyl)ethenes gave the indolizine derivatives **3** with a fluoroalkyl group at the 1-position. When R_f = $Cl(CF_2)_4$ and $Cl(CF_2)_6$, the defluorinated cycloadducts **4** were obtained as the major products accompanied by a trace of the expected ones **3**.

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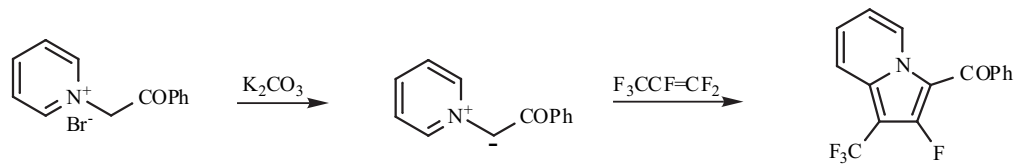
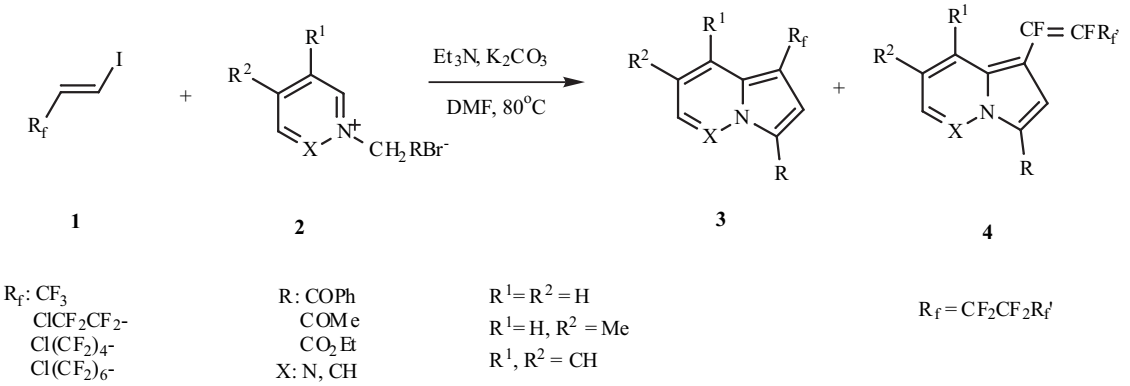


Scheme 1.

Meanwhile, they also found that upon treatment of 2-bromo-3,3,3-trifluoropropene **5** with pyridinium ylides, the corresponding 1-(trifluoromethyl)-substituted indolizines derivatives **6** were also obtained successfully.

anhydride in large scale, was a good dipolarophile due to the pull-push action of the ethoxyl and trifluoroacetyl groups. The reactions of **15** were studied in detail in our laboratory. We found that **15** reacted readily with pyridinium or

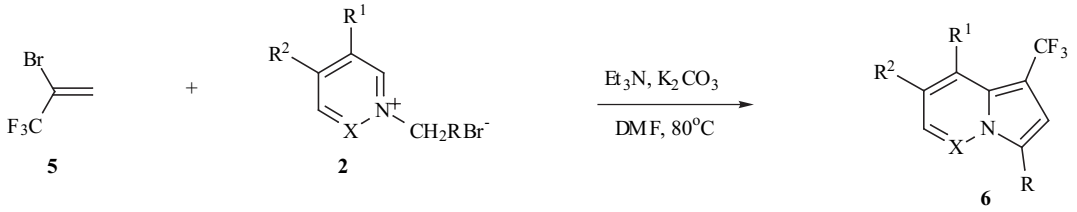


Scheme 2.

They found that 2,2-dihydropolyfluoroalkanoates of type $R_fCF_2CH_2CO_2Et$ **7** could react smoothly with pyridinium and isoquinolinium ylides to give the corresponding indolizine derivatives **8** and **10** under the similar reaction conditions. The similar defluorinated cycloadducts **9** and **11** were obtained when R_f was $Cl(CF_2)_4$ and $Cl(CF_2)_6$, respectively [9].

isoquinolinium N-ylides to give the corresponding 1-trifluoroacetyl substituted indolizines derivatives **16**, **17** and **18** [11].

Not much attention was paid to the N-(methylene)ylide with an electron-withdrawing group such as CO_2Et, CN, COPh *etc.* by now. In continuation of our work on the fluorine-containing indolizines, the reactions of N-

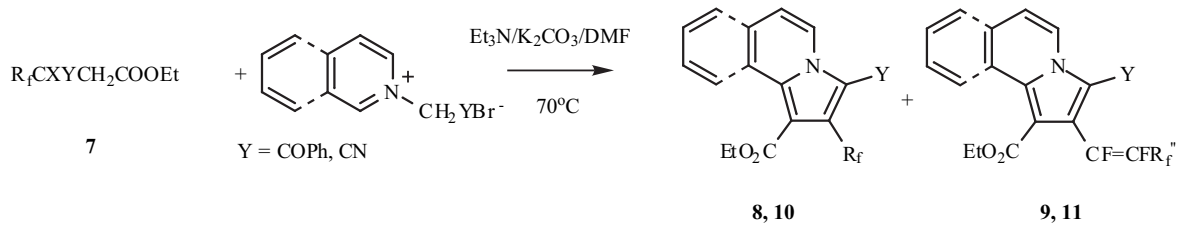


Scheme 3.

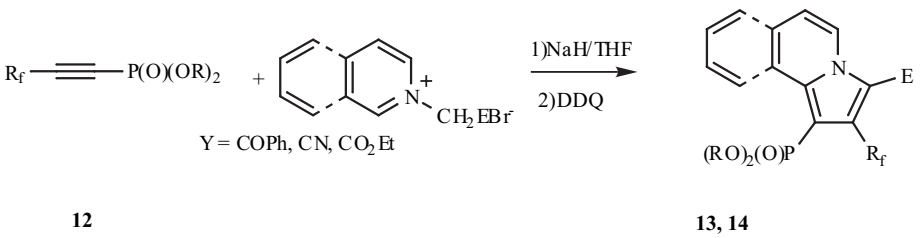
Recently, Shen *et al.* [10] reported a convenient method for the synthesis of perfluoroalkylated indolizinyl phosphonates **13** and **14** *via* the 1,3-cycloaddition of pyridinium and isoquinolinium N-ylide and perfluoroalkynyl phosphonate **12**.

4-Ethoxyl-1,1,1-trifluorobut-3-en-2-one **15**, easily prepared by the treatment of vinyl ethers with trifluoroacetic

benzylpyridinium and N-benzylisoquinolinium ylides with fluorinated acrylates were investigated [12]. N-pyridinium ylides reacted smoothly with ethyl 3-fluoro-3-fluoroalkyl-acrylates **19** to give the major fluoroalkylated indolizine derivatives **21** through 1,3-dipolar cycloaddition followed by an oxidative aromatization process accompanying the minor product **22** formed from a 1,3-H-shift aromatization process.



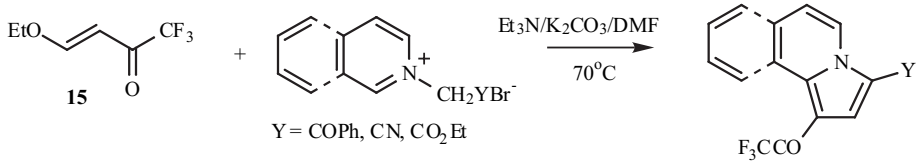
Scheme 4.



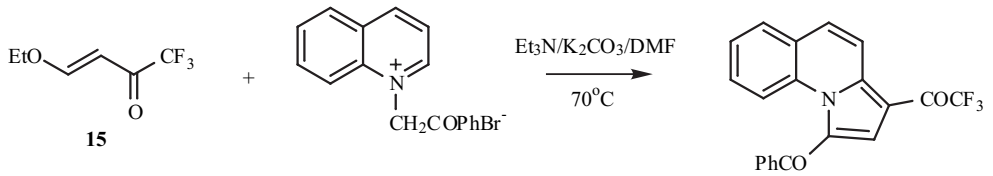
12 **13, 14**

Scheme 5.

While treating **19** with N-benzylisoquinolinium **23**, only product **24** obtained *via* an oxidative aromatization process, the similar 1,3-H-shift product was not found.



16, 18



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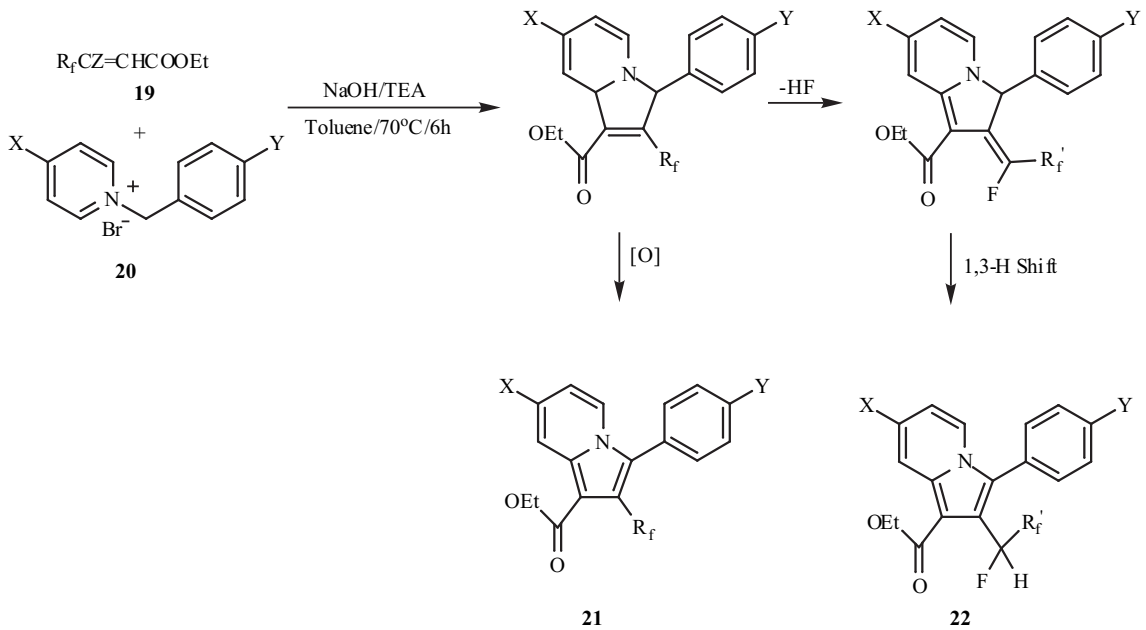
Scheme 6.

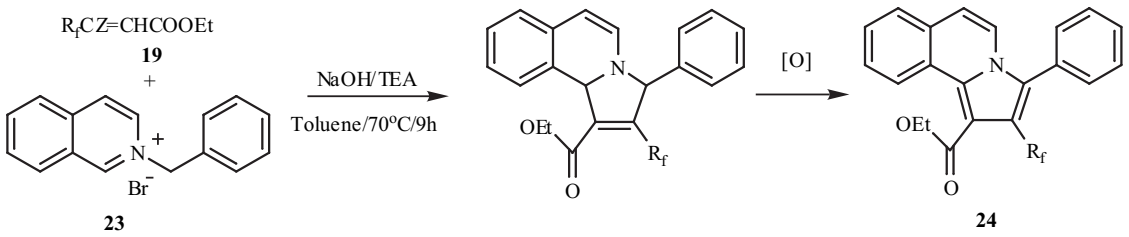
In particular, in the case of the reaction of ethyl 3-bromodifluoromethyl-3-fluoroacrylate and N-isoquinolinium, an unexpected 2-fluorocarbonyl-substituted pyrrolo[2,1-a] isoqulinoline derivative **25** was successfully isolated, which was fully characterized by spectroscopic methods and X-ray diffraction analysis, in addition to the 1,3-H-shift aromatization product (Fig. **1**).

In compound **25**, the planar pyrrolo[2,1-a]isoquinoline system is conjugated with the fluorocarbonyl group, the planes of the ethoxycarbonyl and phenyl substituents are inclined to the pyrrolo[2,1-a]isoquinoline plane by 75° and



21 **22**

Scheme 7.



Scheme 8.

70˚, respectively, probably due to steric repulsion from the fluorocarbonyl group.

Recently, Wu *et al*. [13] reported an efficient synthesis of monofluorine-substituted indolizines derivatives **27** by the treatment of 2,2-difluorovinyl *p*-toluenesulfonate **26** with N-ylides generated *in situ* in high yields.

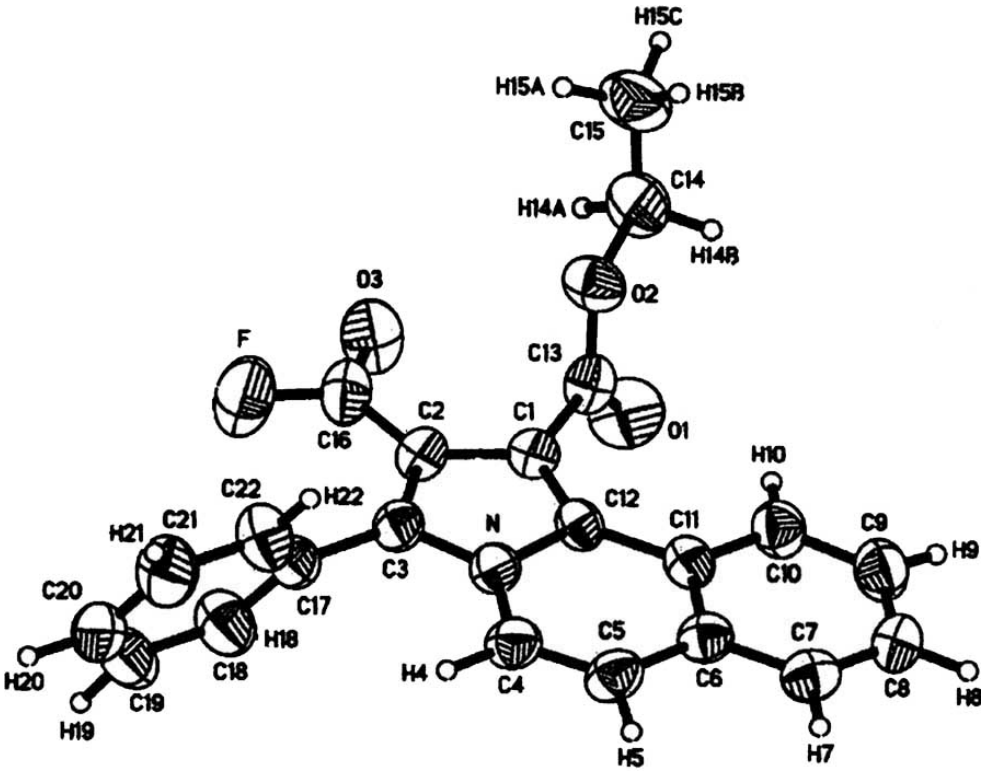
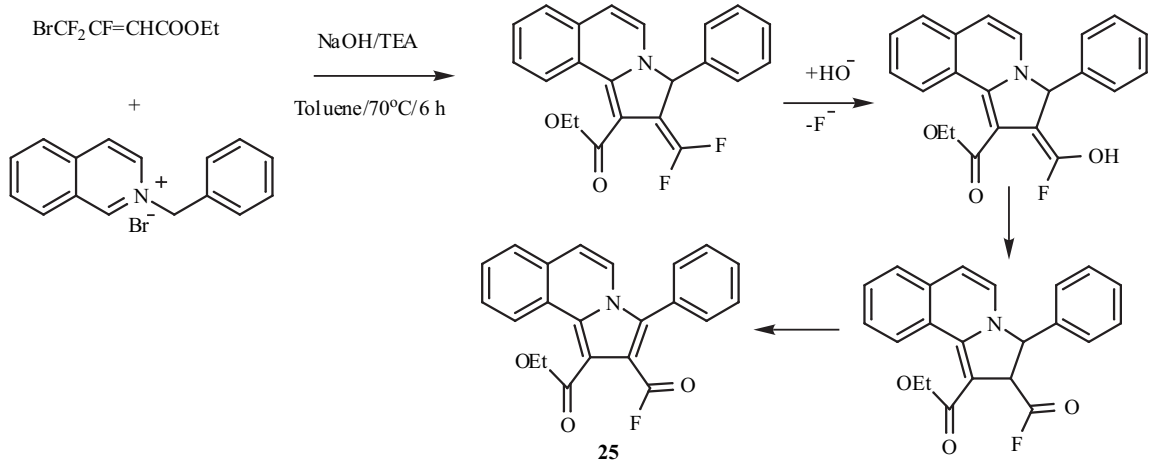
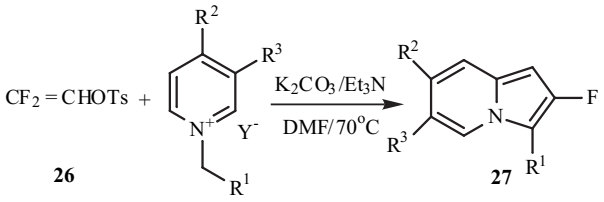


Fig. (1). Molecular structure of compound **25**.

The possible formation process of the compound **25** was proposed as follows:



Scheme 9.

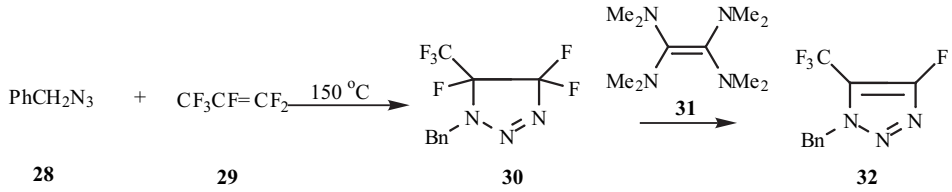


Scheme 10.

2.1.2. Application of the Fluorinated Dipolarophiles and Azides to Synthesis of Fluoro-Containing Triazoles

Up to now, no natural products containing a 1*H*-1,2,3-triazole heterocycle moiety have been isolated. Although numerous applications have been found widely in organic synthesis, as well as in medicine, industry and agrochemicals [14], the use of 1,3-dipolar cycloaddition reactions between fluorine-containing alkenes or alkynes and azides to synthesize the 1*H*-1,2,3-triazoles has been reported rarely.

In 1966, Donald *et al*. [15] found that benzyl azide reacted slowly with perfluoropropene at 150ºC to produce the corresponding triazolines **30** in relative low yields. By treatment of tetrakis(dimethylamino)ethylene **31, 30** were smoothly defluorinated to the corresponding triazoles **32**.



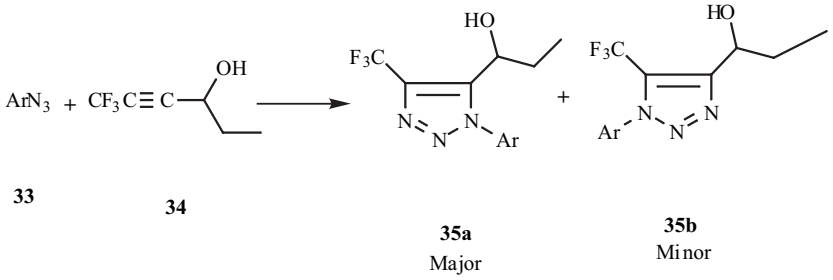
Scheme 11.

In 1985, Petrov *et al*. [16] once reported their study on the 1,3-dipolar addition of aromatic azides to fluorine-containing acetylenes and diacetylenes. They found that the reactions are poorly regioselective and two regioisomers were normally obtained, *i.e.*, the reaction gave the 4-fluoroalkylated triazoles **35a** as major derivative while the 5-fluoroalkylated triazoles **35b** was the minor one.

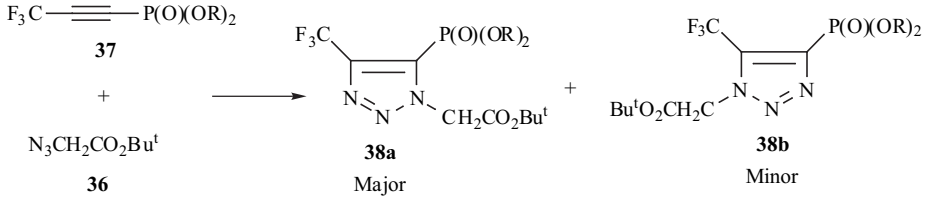
In 1995, Shen *et al*. [17] reported that by treatment of *tert*-butyl azidoacetate **36** with perfluoroalkylated alkynylphosphonates **37**, the corresponding perfluoroalkylated triazolylphosphonates **38a** and **38b** (ratio **38a**: **38b** 75:25) were obtained in good to excellent yields with high regioselectivity.

Recently, a new class of building blocks perfluoroalkyl substituted β-chlorovinyl aldehydes **39** was studied by Greif *et al*. [18] to synthesis of fluorinated heterocycles. When reacting **39** with sodium azide, they found that a 1*H*-1,2,3-triazole without substituent on 1 position **40** was isolated successfully. The possible mechanism of formation of 5-CF_3-substituted triazoles was proposed, *i.e.*, an intramolecular 1,3-dipolar cycloaddition occurred in the process.

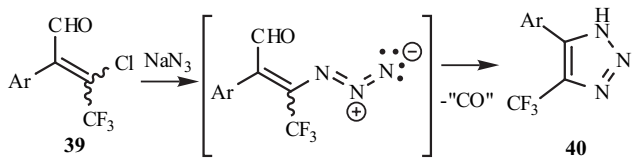
To prepare the multi-functional 1*H*-1,2,3-triazole, the reactions of 3-fluoroalkyl-3-pyrrolidino-acrylate **41** with phenyl or benzyl azides were studied in detail in our group [19]. We found that the influence of solvent is very important. Either low or high boiling point solvent could furnish the triazoles successfully. Finally, solvent free conditions were tried. A series of 5-fluoroalkylated 1*H*-1,2,3-triazoles **42** was prepared in good yields by the regiospecific 1,3-dipolar cycloaddition reaction of the (Z) ethyl 3-fluoroalkyl-3-pyrrolidino-acrylates with aryl or benzyl azides.



Scheme 12.



Scheme 13.

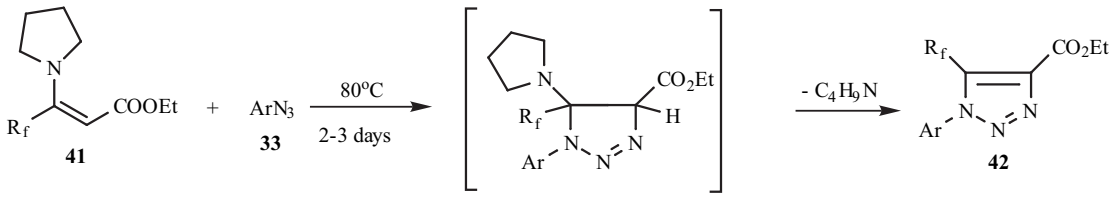


Scheme 14.

In the case of benzyl azides, addition of Na_2CO_3 was crucial for a high yield of the triazoles.

pyrano[3,4-d][1,2,3]-triazol-4-one compounds **46** in good yields.

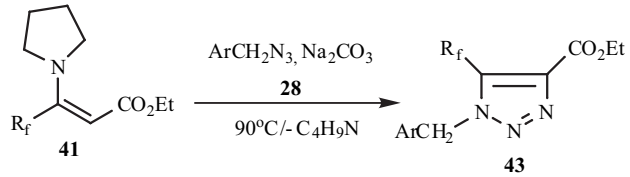
In addition, the 1,3-dipolar cycloaddition of aryl (or benzyl) azides with 1,1,1-trifluoro-4-ethoxyl-3-butene-2-one **15** proceeded smoothly under the similar conditions [21]. 1-Aryl (or benzyl)-4-trifluoroacetyl-1*H*-1,2,3-triazoles **47** were formed regiospecifically in good yields. In contrast, in the case of benzylazide, **15** reacted smoothly in the absence of Na_2CO_3. Due to the presence of the trifluoroacetyl group,



R_f = $ClCF_2$-, $BrCF_2$-, CF_3-
Ar = Ph-, Ar = 4-$CH_3OC_6H_4$- , Ar = 4-$NO_2C_6H_4$-

Scheme 15.

It is noteworthy that the pyrrolidino group plays two important roles in the course of the reaction: (1) acting as an electron-donating group (EDG) to completely control the regioselectivity in the initial 1,3-dipolar cycloaddition reaction of the acrylate with azide; (2) acting as a leaving group (LG) to prevent the formation of triazoline intermediate from decomposing, by ready elimination of pyrrolidine.



R_f = $ClCF_2$-, R_f = $BrCF_2$-, R_f = CF_3-

Ar = Ph-, 4-$CH_3OC_6H_4$-, 4-$NO_2C_6H_4$-

Scheme 16.

Meanwhile, the further chemical transformations of the bromodifluoromethylated 1*H*-1,2,3-triazoles **44** were also studied [20]. Treatment of **44** with aldehydes in the presence of tetrakis(dimethylamino)ethylene (TDAE) under mild conditions afforded a new class of *β,β*-difluoro-*β*-triazolyl alcohol derivatives **45**, which were lactonized with a catalytic amount of p-toluenesulfonic acid in toluene at 80-90ºC to give a series of novel bicyclic *gem*-difluorinated 1*H*-

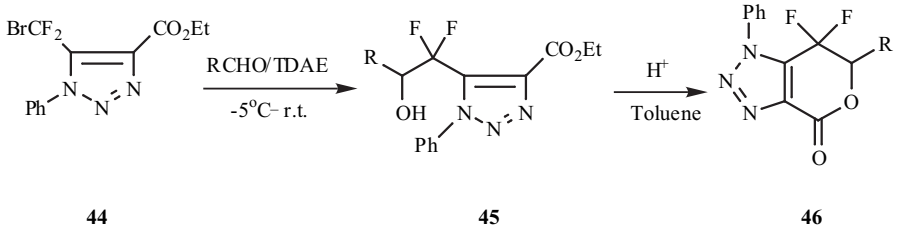
these compounds obtained were readily hydrated, when exposed to the atmospheric moisture, in different rates, which are correlated with the substituents on the 1 position.

2.1.3 Application of the Fluorinated Dipolarophiles and Nitrile Imines to Synthesis of Fluoro-Containing Pyrazoles and Pyrazolines

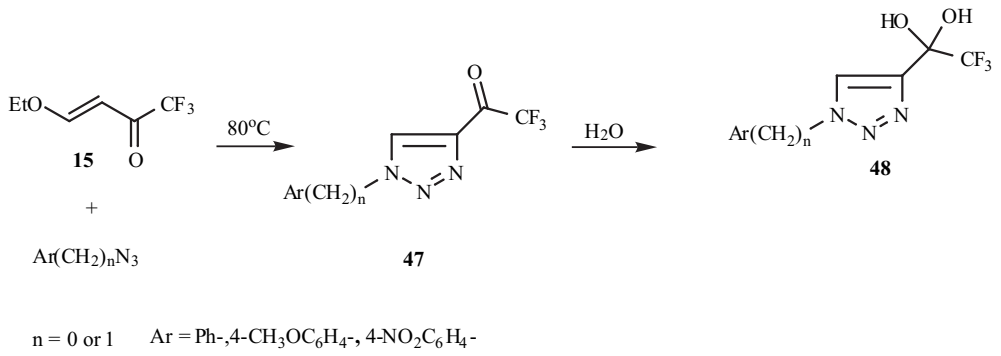
Variously substituted nitrile imines are easily available and react readily with a wide range of double and triple bonds. Intermolecular cycloaddition is therefore an area of major interest, and a large proportion of the papers on the use of nitrile ylides in synthesis are concerned with the exploitation of this reaction.

Tanaka *et al*. [22] reported their studies on N-phenyl-trifluoroacetohydrazonoyl halides **49**, the precursors of trifluoroacetonitrile phenylimine. The reactions of N-phenyl-C-(trifluoromethyl)nitrilimines with a series of dipolarophiles such as olefins, acetylenes and some activated methylene compounds were studied extensively, which provided a regiospecific synthesis of 3-trifluoromethyl-pyrazolines and pyrazoles with a wide variety of substituents, respectively. In most cases, two regioselective isomers were obtained though the conformation of double bond could be retained in the formed heterocyclic compounds.

Recently, Song and Zhu [23] reported that under mild reaction conditions, oxidation 4-chloro-2,3,5,6-



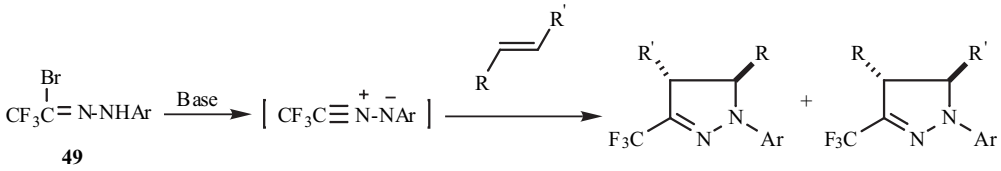
Scheme 17.



Scheme 18.

tetrafluorophenylhydrazones of aldehydes (**50**) with [bis(acetoxy)iodo]benzene led to the formation of nitrile imines, which reacted *in situ* with acrylonitrile **51** to regioselectively produced 1-(4-chloro-2,3,5,6-tetrafluorophenyl)-3-substituted-5-cyano-4,5-dihydropyrazoles **52** in moderate to good yields.

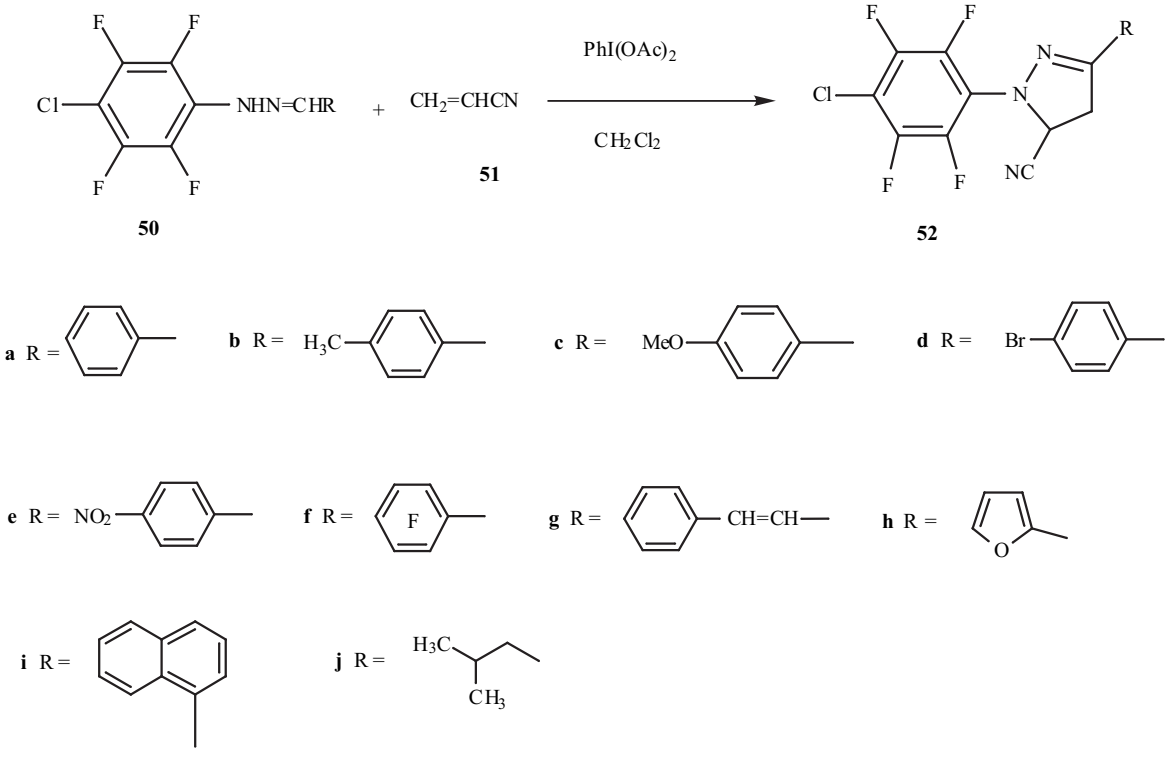
Ethyl 3-fluoroalkyl-3-halo-acrylate **19**, easily prepared by dehydrohalogenation from ethyl α-fluoroalkyl acetate **7**, was used as an excellent dipolarophile to react with various dipoles to afford some novel fluorine-containing



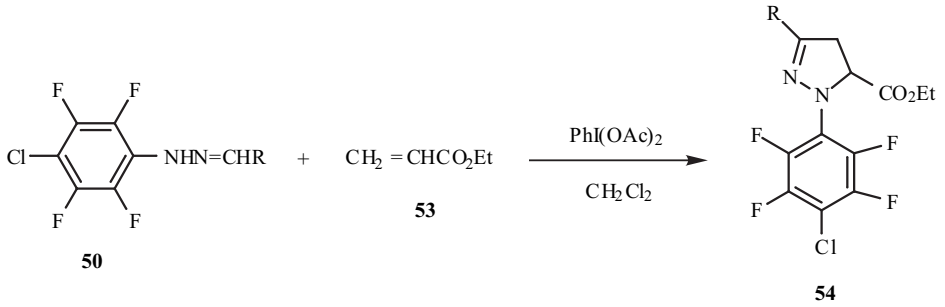
Scheme 19.

Under the same conditions, we also successfully obtained the 1-(4-chloro-2,3,5,6-tetrafluorophenyl)-3-substituted-5-ethoxycarbonyl-4,5-dihydropyrazoles **54** by the treatment of

heterocycles. Hu and his co-workers [25] found that when **19** was treated with excess diazomethane, 1-methyl-3-ethoxycarbonyl-4-fluoroalkylpyrazoles **55a** and 1-methyl-5-



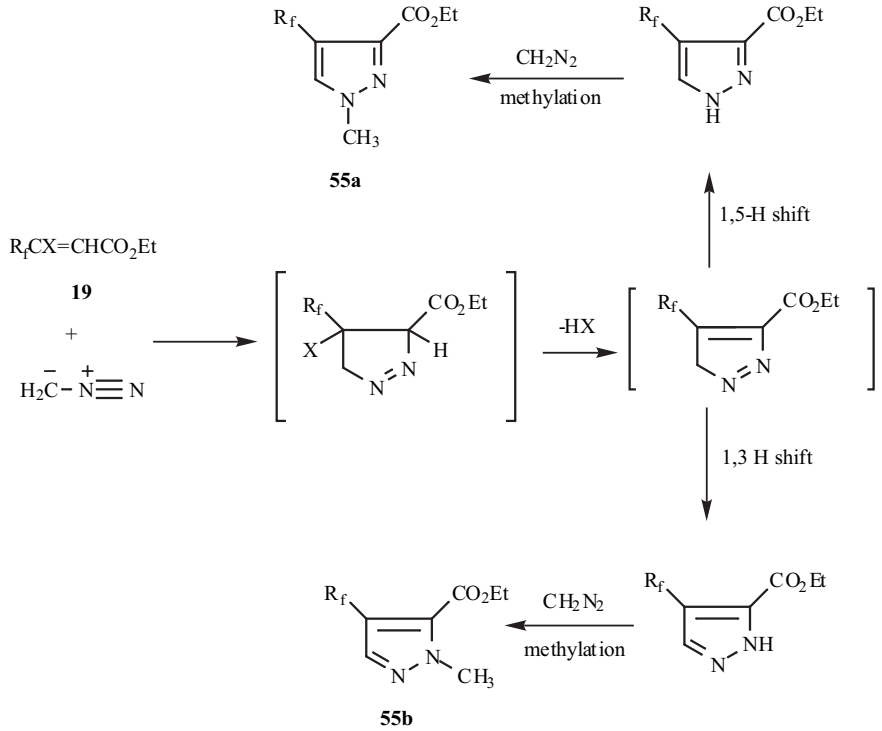
Scheme 20.



Scheme 21.

ethoxycarbonyl-4-fluoroalkylpyrazoles **55b** were obtained with a ratio of 90-95:10-5 in good yields. They proposed the two isomers were formed due to the methylation at different nitrogen atoms as illustrated below (Scheme **22**):

with fluoride ion. In the latter case, stable carbanions have been observed. For example, compound **56** reacted readily with diazomethane to give a mixture of the Δ^1 and Δ^2 pyrazolines **57** and **58**, in the ratio of 3:5, respectively.

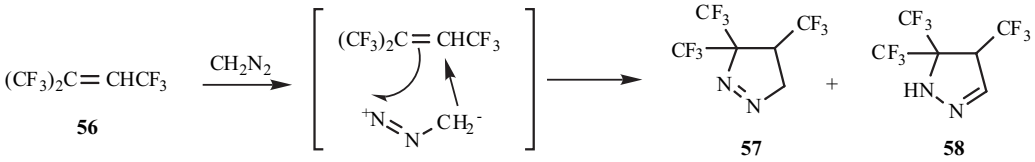


Scheme 22.

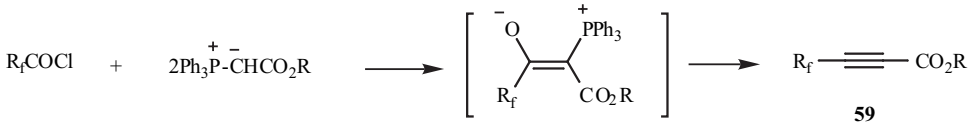
At the same time, Chambers [26] reported novel fluorinated mono-enes and di-enes synthesized *via* telomerisation reactions of $(CF_3)_2CFI$ with CF_2=CH_2 or CF_2=CFH. Cycloaddition with diazomethane occurred readily to give Δ^1or Δ^2 pyrazolines, depending on the system, and nucleophilic attack occurred with methanol and

Recently, Shen *et al*. [27] reported a convenient method for the synthesis of a series of 3-fluoroalkylated acetylenes **59** *via* an intramolecular Wittig reaction.

They found that the fluoroalkylated acetylenes could be used as an excellent dipolarphile to react with ethyl diazoacetate affording a series of 4-fluoroalkylated pyrazoles



Scheme 23.



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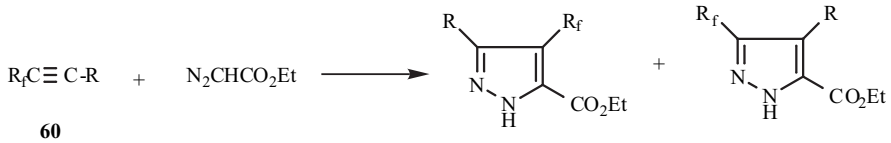
Scheme 24.

61a in high yields [28]. In addition, small amounts of 3-fluoroalkylated isomers **61b** were also isolated.

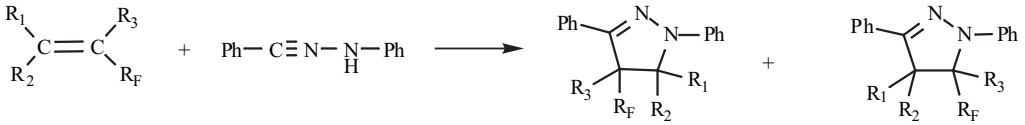


60 **61a** **61b**

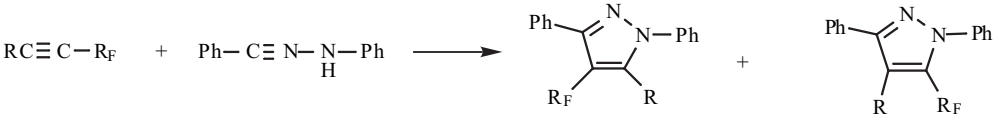
Scheme 25.

By use of theoretical calculations, regioselectivity of the 1,3-dipolar cycloaddition products can be predicated reliably. Kabbaj *et al*. [29] reported their studies on the 1,3-dipolar cycloaddition reactions of diphenylnitrilimine with various fluorinated dipolarophiles with the use of ab initio molecular orbital calculation. It elucidated the mechanistic aspects of the reaction based on the kinetic and frontier molecular orbital (FMO) theoretical points of views.

By dehydrobromination of hydroximoyl bromides containing CF_3 group $CF_3C(Br)=NOH$ (**62**), the cycloaddition reactions of the *in situ* nitrile oxides were studied in detail by Tanaka *et al*. [30]. The nitrile oxides reacted readily with various dipolarophiles such as alkenes, acetylenes and some activated methylene compounds *etc.* in the presence of a base, which provided an efficient method for the synthesis of the fluorinated isoxazoles and



R_F= C_6F_{13}; R_1 = H; R_2 = H; R_3 = H.
R_F= $CH_2C_6F_{13}$; R_1 = H; R_2 = H; R_3 = H.
R_F= C_5F_{11}; R_1 = $COCH_3$; R_2 = H; R_3 = F.



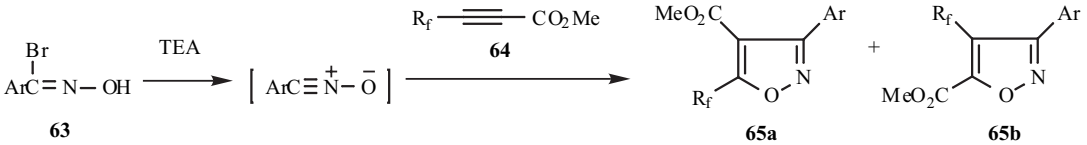
R_F= C_6F_{13}; R = H.
R_F= C_6F_{13}; R = $CH(OH)CH_3$.

Scheme 26.

2.1.4. Application of the Fluorinated Dipolarophiles and Nitrones to Synthesis of Fluoro-Containing Isoxazoles and Isoxazolidines

As one of the most thoroughly investigated 1,3-dipoles, nitrones are arguably the most useful through their ability to generate nitrogen- and oxygen-based functionality from the isoxazolidines. In most cases only regiospecific products were obtained except when treated **62** with double substituted alkenes and alkynes, a regioisomeric mixture in nearly 1:1 ratio was formed. The conformation of the double bond could be retained in the cycloadducts.

As a continuous investigation of the methyl perfluoro-2-

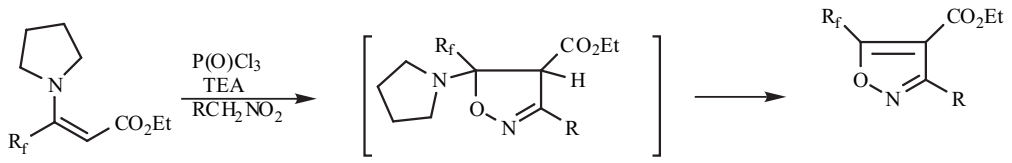


63 **64** **65a** **65b**

Ar = Ph, 2-ClC_6H_4-, 4-ClC_6H_4-, 4-$CH_3C_6H_4$-
R_f= CF_3-, C_2F_5-, *n*-C_3F_7-.

Major Minor

Scheme 27.

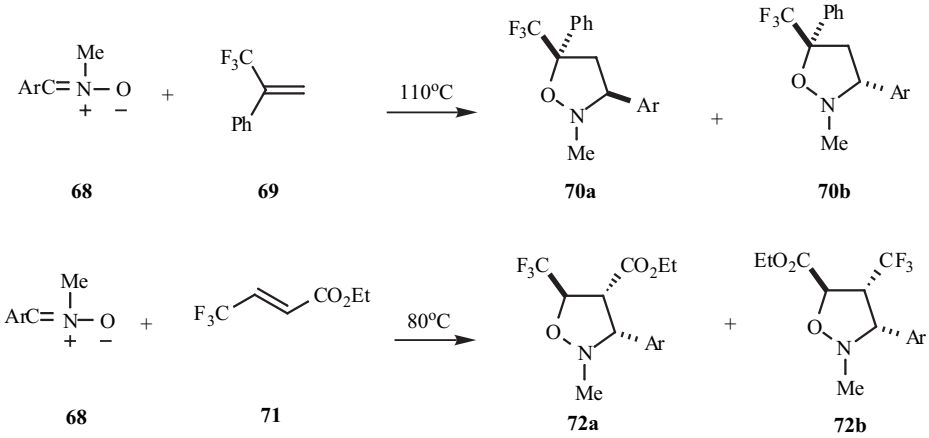


41 **66** **67**

Scheme 28.

alkynoates **64** reactivity, Shen *et al*. [31] found that it could lead to 5-perfluoroalkyl-4-methoxycarbonyl-3-aryl-1,2-oxazoles **65a** in good yields by treatment of **64** with aromatic nitrile oxides generated *in situ* from aryl hydroximoyl bromides **63**, accompanying a small amount of regioisomer in 4-position **65b**. The ratio of the isomers was about 9:1.

Recently, Liu *et al*. [35] found that the ethyl 2-hydropoly(per)fluoroalk-2-enoates **19** proceeded smoothly with various nitrile oxides affording a series of 5-fluoroalkyl substituted isoxazolines **73** as a mixture of two diastereoisomers (*trans* and *cis*) in high yields. Although the



68 **69** **70a** **70b**

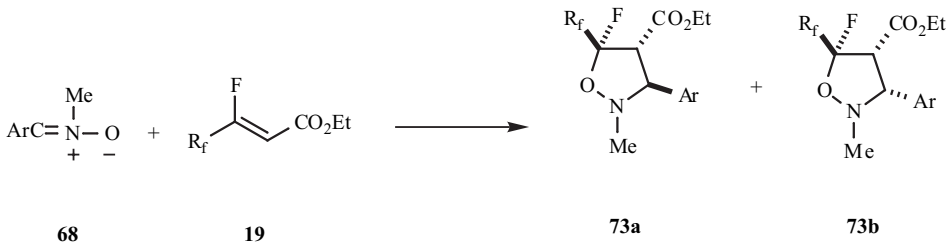
68 **71** **72a** **72b**

Scheme 29.

From the above descriptions, it is obvious that the problems of regio- and stereoselectivities are necessary to be solved. So how to synthesize the regio- and stereospecific heterocycles is now becoming the emphasis during our studies of the cycloaddition reactions. Based on this principle, we developed a convenient method to synthesize the regiospecific 5-perfluoroalkylsubstituted isoxazoles **67**, which were prepared readily from the 1,3-dipolar cycloaddition reactions of nitrile oxides generated *in situ* from RCH_2NO_2, TEA and $POCl_3$ with ethyl 3-perfluoroalkyl-3-pyrrolidino-acryl-ates **41** [32].

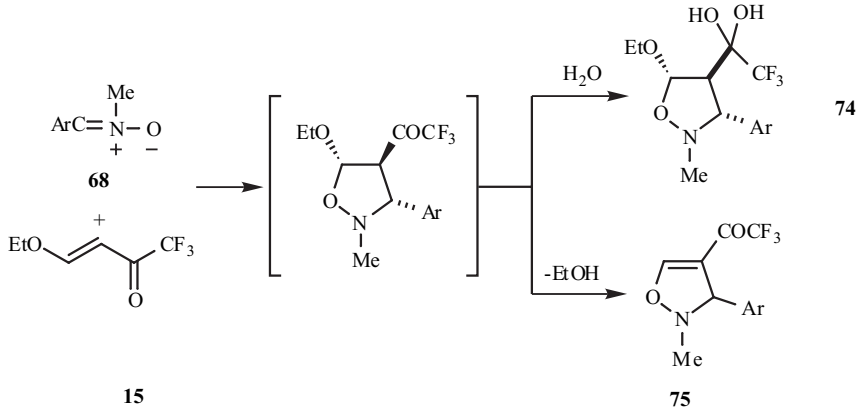
In 1995, Bonnet-Delpon and co-workers [33] reported the reactions of 2-trifluoromethyl styrene with N-(benzylidene)-methylamine-N-oxides **68** performed in the absence of solvent, affording a stereoisomeric mixture of trifluoro-methylisoxazolidines **70**, though high regiospecifity was found in the process. However, when **68** was treated with ethyl 3-trifluoromethyl acrylates, two regioisomers **72a** and **72b** were isolated [34].

In continuation of our study on the 1,1,1-trifluoro-4-ethoxyl-3-butene-2-one **15**, we found that 1,3-dipolar cycloaddition of **15** with C-arylnitrones ArCH=N(O)Me proceeded smoothly *via* a Z-*endo* transition state to give regio- and stereospecific 4-trifluoroacetyl substituted isoxazolidines and their derivatives [36]. It was found that the 4-trifluoroacetyl isoxazolidines were easily hydrated or eliminated to give compounds **74** and **75** during the purification process by column chromatography on silica gel. The conformation of **15** was retained for the *trans* relation of aryl and trifluoroacetyl group.



68 **19** **73a** **73b**

Scheme 30.

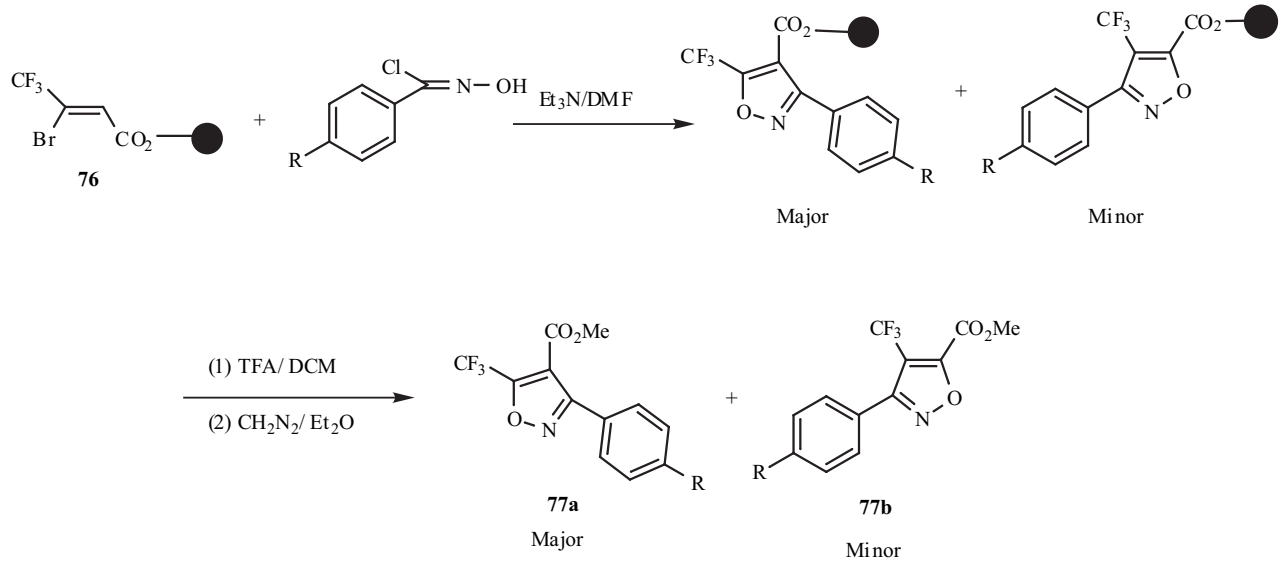


Scheme 31.

Solid-phase organic synthesis (SPOS) has attracted much attention over the past decade, as a powerful tool for the rapid synthesis of small molecule libraries for drug discovery. Recently, a novel resin-bond CF_3-containing building block (Z)-Wang 3-bromo-4,4,4-trifluoro-2-butenoate **76** was prepared by Lü *et al*. [37]. 1,3-dipolar cycloaddition of compound **76** with the precursors of aryl nitrile oxides followed by cleavage with TFA led to methyl 3-aryl-5-trifluoromethyl-4-isoxazolecarboxylate **77a** regioselectively, which was determined by ^{19}F NMR analysis.

Pyrrolidines have been prepared *via* the reaction of an azomethine ylide with a range of trifluoromethylalkenes. α-Trifluoromethylstyrene reacted smoothly to afford cycloadduct **78** in good yields. α-Methylstyrene failed to react under the same conditions.

The formal [2+2] cycloaddition between fluoroketene, generated *in situ* from fluoroacetyl chloride and triethylamine, and the optically-pure imine **79** was exploited in an efficient asymmetric synthesis of a fluorinated β-lactam [39]. Lactam **80** was obtained in moderate chemical yield though in high e.e. (≥ 99%). Lactam **81** was converted into

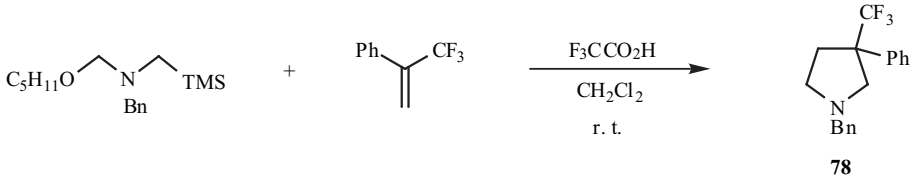


Scheme 32.

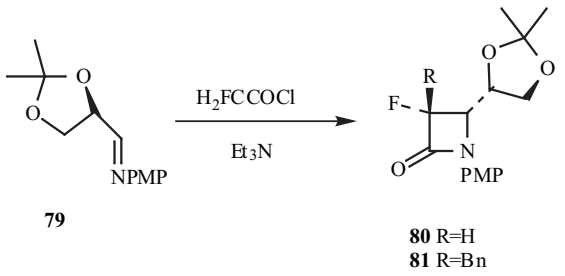
2.1.5 Other Dipolar Cycloaddition for the Preparation of Fluorine-Containing Heterocyclic Compounds

The LUMO-lowering effects exerted by the trifluoromethyl and carboxylic ester groups are similar [38]. a configurationally fixed alkylmalonamide component of an HIV protease inhibitor [40].

Treatment of phenylhydrazone of a methyl ketone or a cyclohexanone with N-aryl trifluoroacetimidoyl iodide **82** in



Scheme 33.

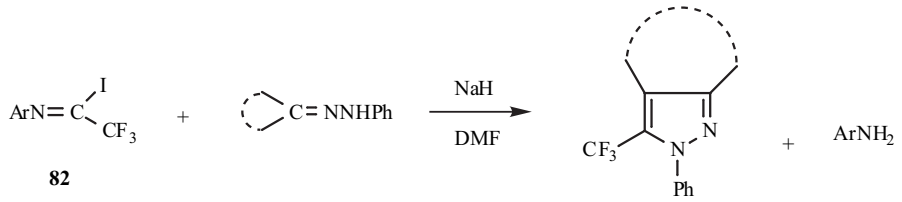


79

80 R=H
81 R=Bn

Scheme 34.

the presence of excess sodium hydride resulted in a [1+4] cyclization to give 5-trifluoromethyl pyrazoles **83** regioselectively [41].

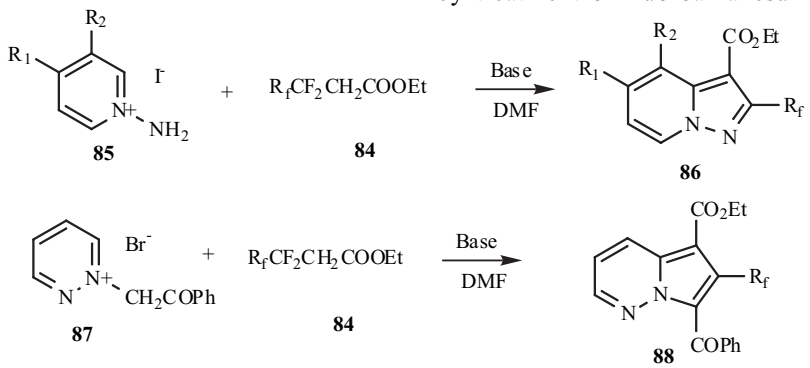


82

83

Scheme 35.

In the presence of base, the reactions of ethyl 2,2-dihydropolyfluoroalkanoates **84** were studied extensively by Huang *et al*. For example, basic treatment of **84** in the presence of N-aminopyridinium iodide **85** or N-phenacylpyridazinium bromide **87** in DMF afforded a series of the corresponding poly(per)fluoroalkyl substituted pyrazolo[1,5-a]pyridine **86** and pyrrolo[1,2-b]pyridazine **88** derivatives, respectively [9b].



85

84

86

87

84

88

Scheme 36.

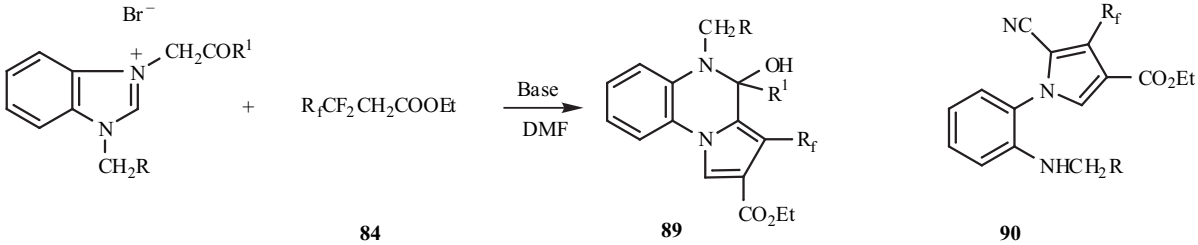
Meanwhile, the reaction of **84** with 1-arkylbenzimidazolium 3-ylides generated *in situ* under the similar conditions formed the pyrrolo[1,2-a]quinoxaline derivatives **89** in good yields [42]. However, when **84** was treated with N-cyanomethyl benzimidazole bromides, fluoroalkyl substituted 1-aryl pyrrole derivatives **90** were formed as major products accompanying a minor product **89**.

2.2 Preparations of Fluorinated Heterocycles *via* 1,3-Dipolar Cycloaddition Using Fluorinated Dipoles

2.2.1 Preparations of Fluorinated Heterocycles Using Fluorine-Containing Azides

Organic azides belong to the propargyl-allenyl category of dipoles, and are popular for synthetic transformations because of their ready availability. Since the discovery of triazole formation from phenyl azide and dimethyl acetylenedicarboxylate in 1893, synthetic applications of azides as 1,3-dipoles for the construction of heterocyclic frameworks and core structures of natural products have progressed steadily. Herein we wish to summarize the developments of 1,3-dipolar cycloaddition reactions of azides in recent years, with an emphasis on the synthesis of fluorine-containing heterocycle.

Recently we prepared the fluoroalkanesulfonyl azides **91** by treatment of fluoroalkanesulfonyl fluoride or chloride with sodium azide NaN_3 in methanol or acetonitrile at 0°C or room temperature [43].

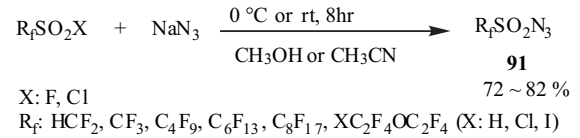


84

89

90

Scheme 37.

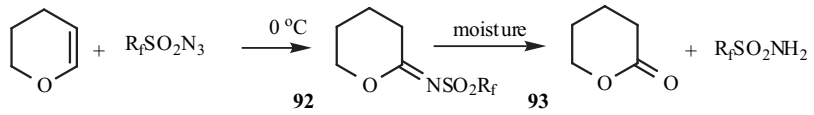


Scheme 38.

Due to the strong electron-withdrawing properties of fluoroalkanesulfonyl group, per (poly)-fluoroalkanesulfonyl azides are more reactive than non-fluorinated organic azides, especially in reactions with electron -rich olefins, such as enamines, silyl enol ethers *etc*. In our group, the dipolar cycloadditions of the fluoroalkanesulfonyl azides have been studied extensively. In most cases, we did not obtain the dipolar cycloadduct successfully but the decomposition products with the elimination of nitrogen gas due to the introduction of fluoroalkyl groups in the molecules. However, in some cases, we also successfully obtained the heterocycles *via* 1,3-dipolar cycloaddition reactions.

For example, 3,4-dihydro-2*H*-pyran reacted easily with azides at 0°C afforded the corresponding sulfonylimines **92**, which were moisture sensitive and were readily hydrolysed to the corresponding δ-valerolactone **93** and perfluorosulfonylamine [44].

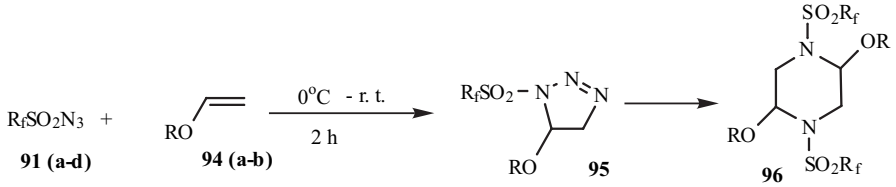
Recently, the reactions of fluoroalkanesulfonyl azides **91** with some electron-rich olefins have been studied [45]. Reaction of alkyl vinyl ethers with **91** at 0°C or room temperature failed to give the corresponding N-fluoroalkanesulfonyl aziridines but regiospecifically products



Scheme 39.

1-fluoroalkanesulfonyl 1,2,3-triazolines **95** were formed which decomposed slowly at room temperature to form 1,4-fluoroalkanesulfonyl-2,5-alkoxyl-piperazines **96** with elimination of nitrogen gas. The compound **96ca** was confirmed by X-ray diffraction analysis and the corresponding molecular structure is shown in (Fig. **2**).

Lermontov *et al*. [46] once reported their studies on the reaction of α,α-difluoroazides with acetylenic compounds.



Scheme 40.

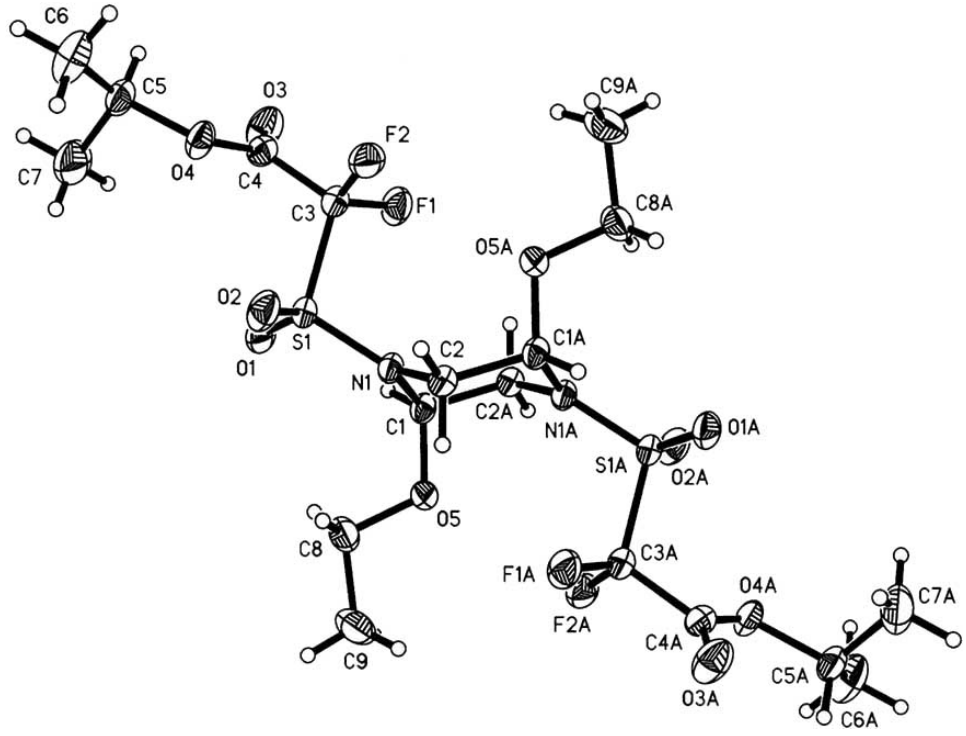
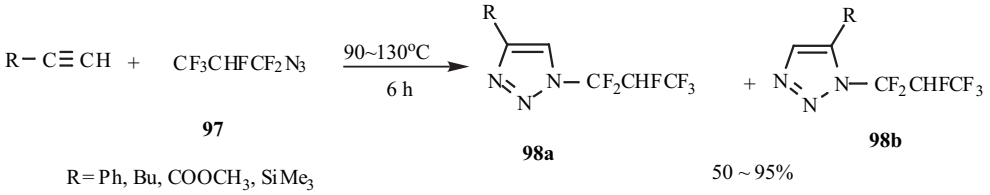


Fig. (2). The molecular structure of compound **96ca**.

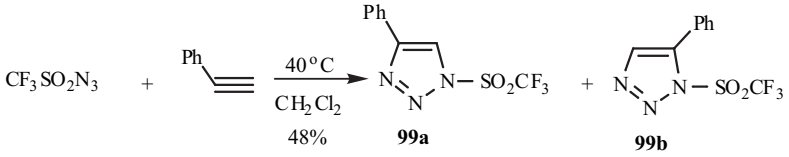


Scheme 41.

Treatment of α,α-difluoroazides, 2*H*-perfluoropropyl azide **97** and methyl ester of 3-azidoperfluoropropionic acid, with different acetylenes afforded a mixture of 1-fluoroalkyl substituted 1,2,3-triazoles **98a** and **98b** in high yields. Thermal decomposition of some triazoles led to products of oxidative aminofluorination.

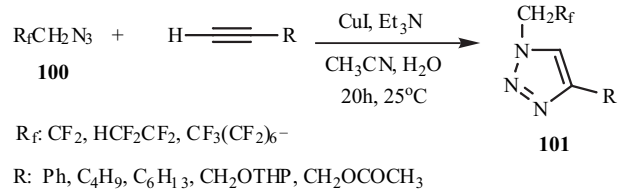
substantial progress with 1,3-dipolar cycloaddition chemistry of the intact diazo function with π-bonds of novel dipolarophiles.

During the studies on the perfluoroalkanesulfonyl azides **91**, we found that in the presence of triethylamine, diazo transfer reaction of **91** with 1,3-dicarbonyl compounds



Scheme 42.

The reactions of trifluoromethanesulfonyl azide as a convenient reagent for the synthesis of triazole were also investigated by Shainya *et al*. [47] in recent years. Trifluoromethanesulfonyl azide reacted with phenylacetylene in CH_2Cl_2 at 40 °C to give the mixture of 4-phenyl and 5-phenyl-1-trifluoromethansulfonyl-1*H*-1,2,3-triazoles **99a** and **99b** in moderate yields. Further chemical transformation proceeded well in ethanol to afford the corresponding defluorination products 4- and 5-phenyl-1*H*-1,2,3-triazoles.



Scheme 43.

Recently, Wu *et al*. [48] found that fluoroalkylated 1,4-disubstituted [1,2,3]-triazoles **101** were regiospecifically synthesized by 1,3-dipolar cycloaddition of fluoroalkylated azides **100** with terminal alkynes in the presence of Cu(I) salts as catalysts at room temperature.

2.2.2. Preparations of Fluorinated Heterocycles via 1,3-Dipolar Cycloaddition of the Potential Fluoro-Containing Dipoles α-Diazo Carbonyl Compounds

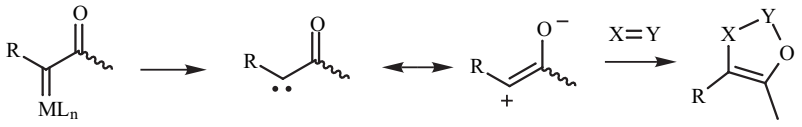
During the past two decades, diazo compounds have been extensively used as substrates for transition metal catalyzed reactions. These include both intra- and intermolecular reactions with multiple-bond systems. In addition,

proceeded smoothly to yield a series of diazo group transfer products 2-diazo-1,3-dicarbonyl compounds in good yields under mild conditions [49]. Encouraged by these results, using the per(poly)fluoroalkanesulfonyl azides as diazo transfer reagent, by treatment of **91** with ethyl fluoroalkylacetoacetate R_fCOCH_2COOEt allowed us to obtain a series of ethyl 2-diazo-fluoroalkylacetoacetate **103** in fair to good yields [50].

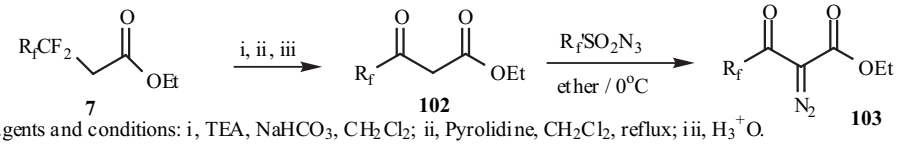
By use of the potential 1,3-dipoles α-diazo dicarbonyl compounds **103**, in the presence of catalytic amounts of rhodium (II) acetate, it reacted readily with nitriles *via* carbenoid intermediates to afford a series of 5-fluoroalkyl substituted 1,3-oxazoles **104** with high regioselectivity in fair to good yields [50]. From the obtained results, we found that the nitrile substrate with a conjugated alkenyl or aryl group gave the highest yields of oxazoles, whereas simple alkyl-substituted nitrile typically gave lower yields of the products.

Recently, we also found that the electron-efficient 1,3-dipoles generated *in situ* by treatment of ethyl 2-diazo-fluoroalkylacetoacetate with the catalyst rhodium (II) acetate proceeded smoothly with electron-rich acyclic or cyclic alkyl vinyl ether, which afforded a series of fluoroalkyl-substituted 2,3-dihydrofuroates **105** *via* a [3+2] cycloaddition process in good to excellent yields [51]. Further transformation of the dihydrofuroates by an acid catalyzed alcohol elimination yielded α-fluoroalkyl-β-furoates **106** readily.

In 1993, Hoffmann *et al*. [52] once reported that dirhodium tetraacetate catalyzed decomposition of trifluoromethyl acetyl diazoacetates in ethyl vinyl ether gave



Scheme 44.

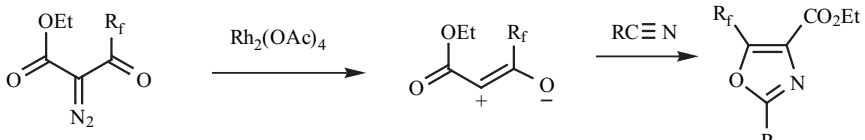


Reagents and conditions: i, TEA, $NaHCO_3$, CH_2Cl_2; ii, Pyrolidine, CH_2Cl_2, reflux; iii, H_3^+O.

Scheme 45.

rise to the dihydrofuroates, which can be converted into the corresponding 2-(trifluoromethyl) pyrroles **107** in the presence of β-alanine ethylester hydrochloride in acetic acid and triethylamine.

vinyldiazomethanes **109** in moderate yields according to Guillaume. **109** were indefinitely stable at room temperature, which might be attributed to the fact that the two adjacent electron-withdrawing groups, trifluoromethyl and

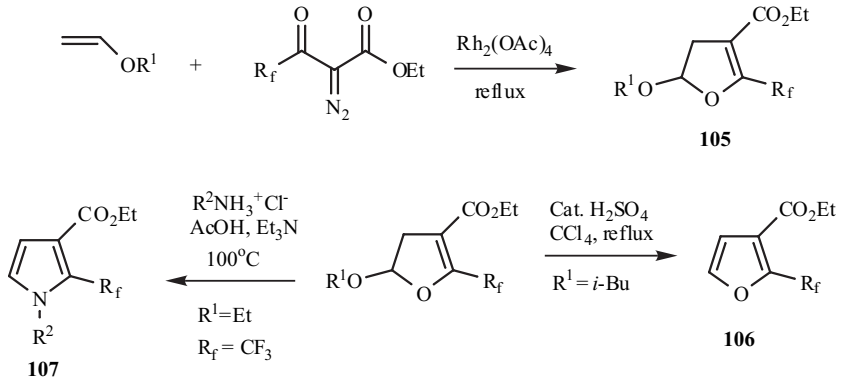


R = C_6H_5, m-$CH_3C_6H_4$, $CH_2C_6H_5$, E and -Z-CH=$CHCH_3$ and $ClCH_2$, R_f= CF_3, ClC_3F_6, C_5F_{11}.

Scheme 46.

Similarly, **103** reacted with cyclic vinyl ethers to give the expected 1,3-dipolar cycloaddition products. Interestingly, only vinyl C-H insertion compound **108** was obtained concerning the reaction of **103** with 2,5-dimethylfuran.

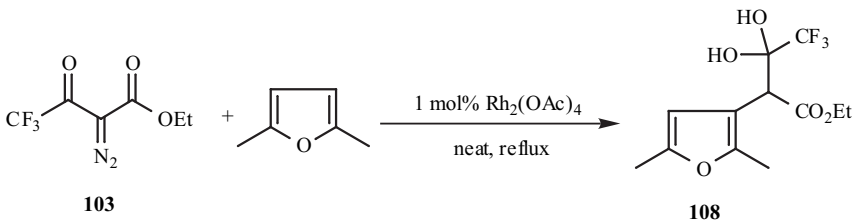
ethoxycarbonyl, greatly stabilized the vinyldiazomethanes and inhibited the formation of 3*H*-pyrazole. An efficient method where the rhodium (II) acetate catalyzed decomposition of **109** in the presence of furans resulted in the formation of a series of 3-trifluoromethylated 8-



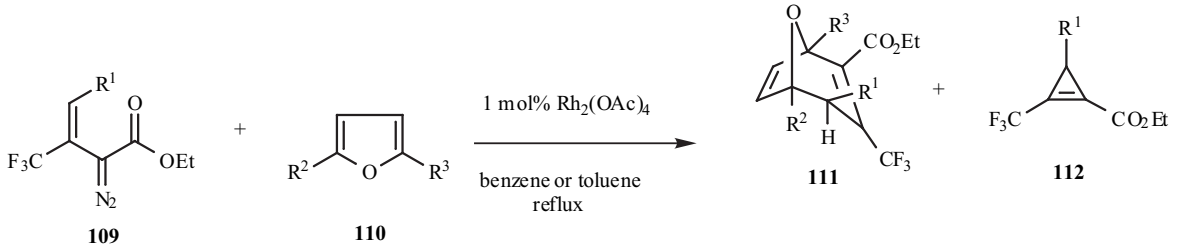
Scheme 47.

Recent research by Davies Huw M. L and co-workers [53] found that a formal [3+4] cycloaddition reaction between vinylcarbenes with stabilized groups and dienes such as dienes, substituted furans and pyrroles *etc*. represented a general and stereoselective method for the synthesis of seven-membered rings. The synthesis of new vinyldiazomethanes from ethyl 2-diazo-4,4,4-trifluor-acetoacetate and Wittig or Horner-Emmons-Wadswoth (HWE) reagents was developed by Guillaume *et al*. [54]. Recently, we successfully synthesized 3-trifluoromethylated

oxabicyclo [3.2.1] octa-2,6-dienes was developed by us. The 4-substitutent on the vinyldiazomethanes had great effects on the product distribution and the stereo- and regiochemistry of the [3+4] annulation products. The rhodium (II) acetate catalyzed reaction of 4-carbonyl substituted vinyldiazo-methanes with furans resulted in cyclopropenes **112** and [3+4] annulation products **111**, while in the case of cyano-substituted vinyldiazomethane, only cycloaddition products were obtained. A tandem cyclopropanation/Cope rearrange-ment mechanism was proposed [55].



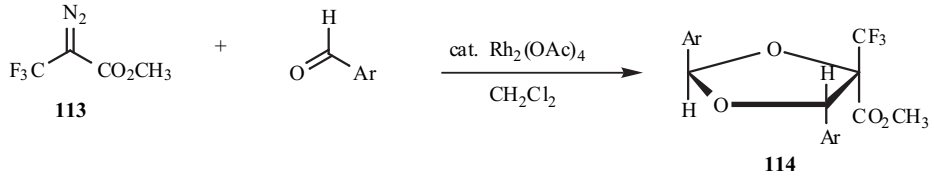
Scheme 48.



$R^2 = R^3 = Me$; $R^2 = Bu$, $R^3 = H$; $R^1 = CO_2Et$ (a), CO_2Me (b), COMe (c), CN(d),

Scheme 49.

Recently, Jiang *et al*. [56] reported that the $Rh_2(OAc)_4$–catalyzed reaction between methyl diazo(trifluoromethyl)acetate **113** and aryl aldehyde afforded the 1,3-dioxolane **114** bearing a C-4 trifluoromethyl group with remarkable diastereoselectivity in excellent yields.



Scheme 50.

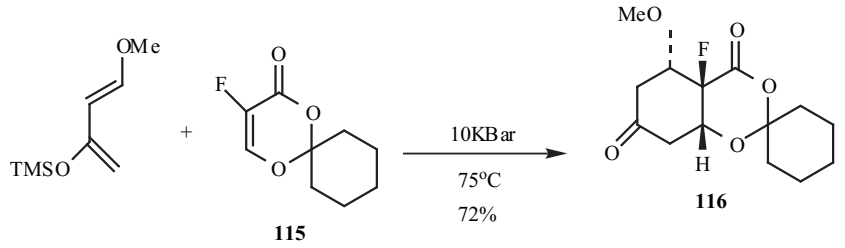
3. PREPARATIONS OF FLUORINE-CONTAINING HETEROCYCLES *VIA* DIELS-ALDER AND HETERO-DIELS-ALDER REACTIONS

The Diels-Alder reaction has proven to be an exceptionally powerful method for carbon-carbon bond formation in organic synthesis. Its widespread application arises from the versatility and predictability of the stereochemical and regiochemical outcome of the reaction based on well-defined rules. Modification of the diene and dienophile components led to significant extension of synthetic utility of the Diels-Alder reaction. The conspicuous success encountered by dienes bearing lone pair electron-containing heteroatom substituents is certainly worth emphasizing.

Dienophiles bearing fluorine atoms attached directly to the carbon-carbon double bond are rare; the propensity for thermal [2+2] cycloaddition displayed by fluoroalkenes is well known. 5-Fluorodioxinone **115** employed as a component in a Diels-Alder reaction; **115** reacted with Danishefsky's diene to afford the expected cycloadduct **116** in moderate yields under high-pressure conditions (Scheme **51**). A more efficient reaction was reported with the more electron-deficient trifluoromethyl congener [57].

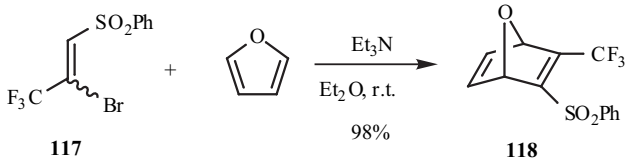
A reactive dienophile, prepared from **117**, has been prepared *in situ* from bromotrifluoropropene *via* an efficient sequence. Cycloadducts were obtained in high yields with electron rich dienes. For example, with furan under mild conditions **118** was obtained in almost quantitative yield (Scheme **52**) [58].

Tipping and co-workers [59] have reported the smooth cycloaddition reactions of trifluoromethyl propiolate derivative **119** with furan. Pyrolysis of the cycloadduct **120** led to the elimination of ethane, setting the stage for a second cycloaddition reaction between furan **121** and hexafluorobutyne (Scheme **53**).

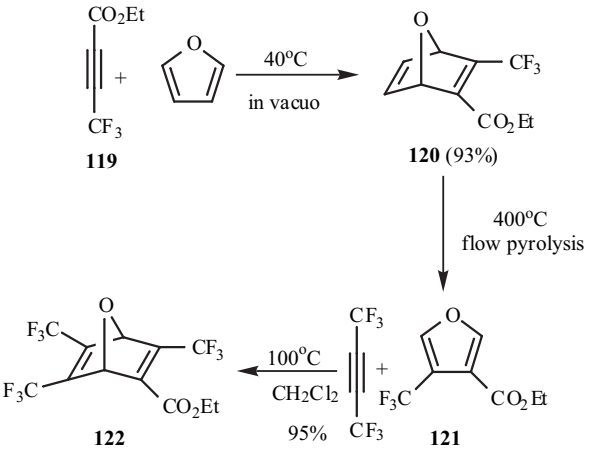


Scheme 51.

The application of Diels-Alder reaction using suitable fluorinated dienophiles selectively provided the fluorinated cyclohexenes that serve as versatile synthetic intermediates for the construction of complex-fluorinated compounds. Despite their importance, the successful [4+2] cycloaddition reactions of fluorinated dienophiles are scarce. Accordingly, the development of mono-fluorinated dienophiles as well as di- or tri-fluorinated is limited. The reason seemed to be the difficulty with introduction of fluorine onto olefins.

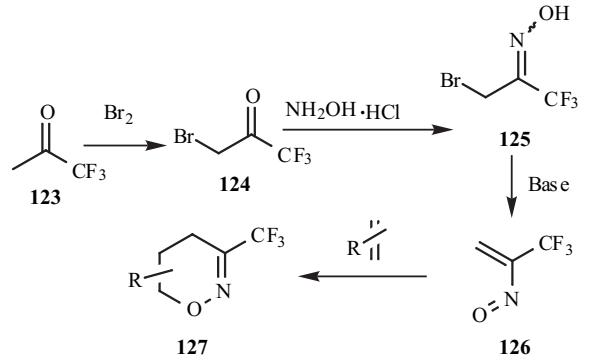


Scheme 52.



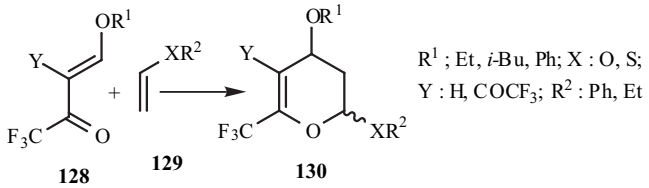
Scheme 53.

In 1992, Zimmer and Reissig [61] reported their studies on the 1,1,1-trifluoro-2-nitoso-2-propene **126**, a highly reactive nitroso alkene, was generated *in situ* by treatment of the α-bromo oxime **125** with base. Moderate to excellent yields of the 3-trifluoromethyl-substituted 1,2-oxazines were obtained from the reaction of **126** and the activated alkene. This reaction provides flexible and efficient access to a large variety of trifluoromethyl-substituted 1,2-oxazines **127**. The results demonstrated that **126** are probably the most reactive heterodiene that has so far been employed in this type of Diels-Alder reaction (*i.e.*, Diels-Alder reaction with inverse electron demand).



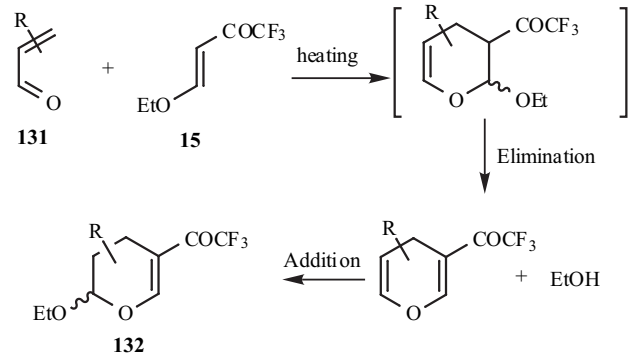
Scheme 54.

Recently, Hojo *et al*. [62] reported reactions of β-(trifluoroacetyl)vinyl ethers or β,β-bis(trifluoroacetyl)vinyl ethers, which were prepared by acylation of vinyl ethers with trifluoroacetic anhydride, with electron-rich alkene such as vinyl ethers, ethyl vinyl sulfide and 1,1-diphenoxyethylene proceed quite easily under mild conditions to afford a series of 6-trifluoromethyl-3,4-dihydro-2*H*-pyrans **130** in excellent yields.



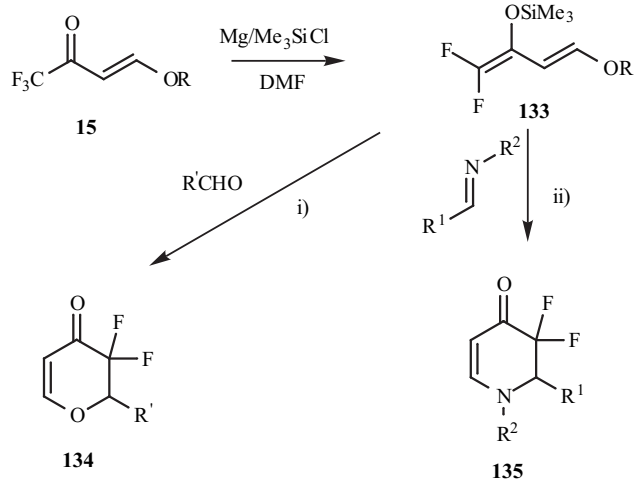
Scheme 55.

However, the Diels-Alder reaction of β-trifluoroacetyl vinyl ethers **15** as the dienophiles with the heterodienes has not been studied until now. During our investigations on pull-push olefins, we found that **15** reacted readily as dienophiles with α,β-unsaturated carbonyl compounds to give the unexpected 2-alkoxyl- 5-trifluoroacetyl-3,4-dihydro-2H-pyrans **132** [36]. These products are formed by elimination and addition of the alcohol to the products of the normal hetero Diels-Alder reaction (2-alkoxyl-3-trifluoroacetyl-2,3-dihydro-2*H*-pyrans).



Scheme 56.

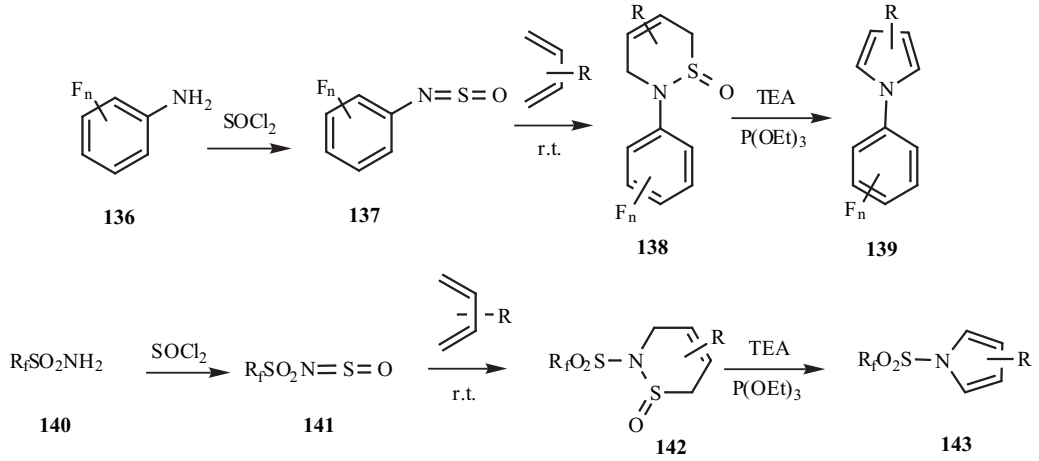
Recently, Uneyama *et al*. [63] found that a Mg(0)/Me_3SiCl system was effective for the first preparation of difluoro Danishefsky's diene **133**, which involves selective C-F bond cleavage of trifluoromethyl ketones **15**. The synthetically useful application of difluoro Danishefsky's diene has been made for the hetero Diels-Alder reaction. Subsequent hetero Diels-Alder reaction of **133** with aldehydes and imines gave a variety of fluorinated six-membered dihydropyrones **134** and dihydropyridones derivatives **135**. Moreover, enantioselective hetero Diels-Alder reaction of **133** is also studied in detail.



i) 1. $ZnBr_2/CH_2Cl_2$ 2. cat. CF_3COOH/CCl_4
ii) ZnI_2/CH_3CN

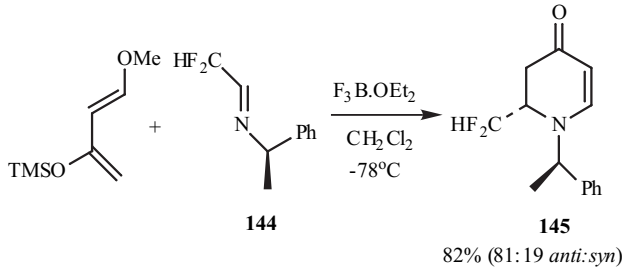
Scheme 57.

Hetero-Diels-Alder reaction of N-sulfinyl per-(poly)fluoroaniline **136** and N-sulfinylfluoroalkanesulfonyl amine **140** with 1,3-dienes afforded the corresponding cycloadduct 3,6-dihydro-1,2-thiazine-1-oxide which was readily converted to N-per(poly)fluorophenyl pyrrole **139** and N-fluoroalkanesulfonyl pyrrole **143** under mild reaction conditions in good yields [64].



Scheme 58.

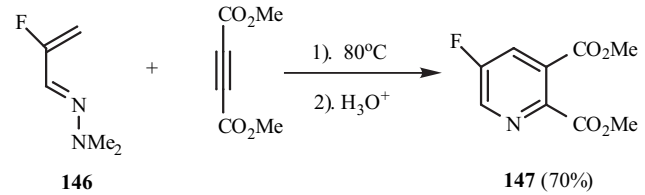
Fluoroalkyl imines have been explored as building blocks for the synthesis of nitrogen heterocycles with fluoroalkyl substituents. In the presence of boron trifluoride etherate, **144** added efficiently to Danishefsky's diene to afford a separable mixture of dihydropyridinones **145** [65]. The chemical yield and diastereoisomeric purity of each adduct were high.



Scheme 59.

Homo- and hetero-dienes, displaying useful reactivity have been described. Azadiene **146** was prepared from readily-available 2-fluoroacrolein by Schlosser and Ghosh [66] and added smoothly to DMAD to afford fluoropyridine **147** after hydrolysis.

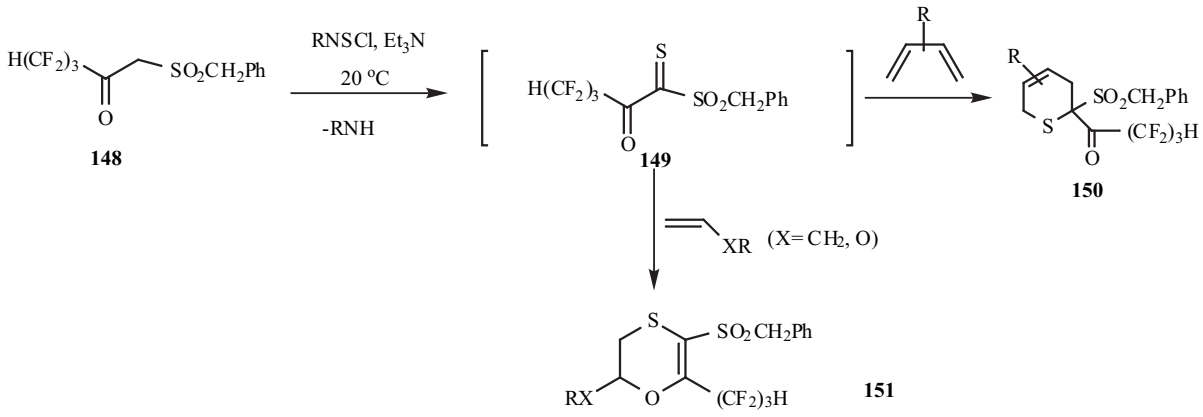
1-Benzylsulfonyl-1,1-dihydropolyfluoroalkan-2-ones **148** react with phthalimidosulfenyl chloride or succinimido-sulfenyl chloride to form the sulfenylated products on the active methylene group, 1-benzylsulfonyl-1-phthalimido (succinimido)thiopolyfluoralkan-2-ones [67]. Decomposition of the latter leads to formation of 1-benzylsulfonyl-1-thioxopolyfluoroalkan-2-ones **149**. These compounds easily undergo the hetero Diels-Alder reaction with electron-rich 1,3-dienes as dienophiles and with electron-rich olefins as hetero-1,3-dienes. Polyfluoroalkyl substituted derivatives of six-membered sulfur-containing heterocylces, 5,6-dihydro-2*H*-thiins **150** and 2,3-dihydro-1,4-oxathiins **151**, are obtained as a result of these reactions.



Scheme 60.

4. CONCLUSION

In the last decade our institute has made great efforts on the study of the cycloaddition reactions and their applications in the synthesis of heterocycles using various fluorine-containing dipolarophiles and dienophiles. It is becoming an important strategy for the construction of



Scheme 61.

versatile fluorinated compounds due to its higher selectivity, milder reaction conditions and ready to scale up. It is believed that significant achievements and great progress in this area may be expected in the future.

ACKNOWLEDGEMENT

We are grateful to the National Natural Science Foundation of China and Innovation Foundation of the Chinese Academy of Science for the financial support (20032010, 20372077).

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Received: 12 November, 2003 **Accepted: 6 February, 2004**