Chemistry of Fluorinated Pyrroles

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Contents

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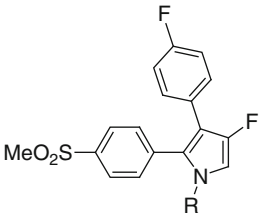
Abstract Synthetic approaches towards pyrroles, bearing fluorine atoms and trifluoromethyl group, are overviewed in this chapter. Literature data are surveyed accordingly to reaction type used to obtain the fluorinated pyrrole moiety. Properties as well as some applications of fluorinated are also reviewed.

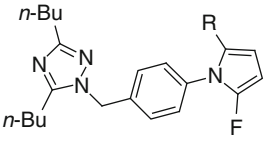
Keywords Pyrroles • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

1 Introduction

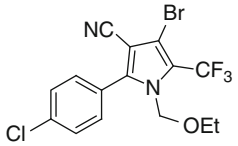
Pyrroles constitute the core of a large number of alkaloids and many other physiologically active compounds, which make them strongly attractive as synthetic targets for further investigation. Fluoropyrrole derivatives are important anti-inflammatory agents [1], stable GnRH receptor antagonists [2], inhibitors of HCV NS5B polymerase [3], Angiotensin II receptor antagonists used in therapy for treating hypertension [4]. Fluorinated pyrrole derivative chlorfenapyr, discovered in 1988, was commercialized in 1995 as a broad-spectrum insecticide [5].



Antiinflammatory Activity



Angiotensin II Antagonist Activity



Chlorfenapyr

This chapter summarizes the major synthetic pathways towards fluoro- and trifluoromethylpyrroles. Biological properties and applications of these compounds are also included. The chapter is organized according to the reaction type used to gain the target fluorinated pyrrole.

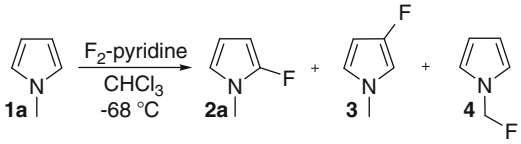
2 Synthesis of Fluorinated Pyrroles

2.1 Fluorination/Trifluoromethylation Methods

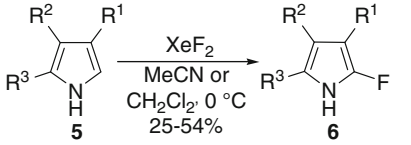
2.1.1 Electrophilic Fluorination

Direct fluorination of pyrrole ring was examined in several works to give a simple pathway to fluoropyrroles. However, high reactivity of pyrrole ring towards electrophiles, resulting in their easy polymerization, leads to fluoropyrroles obtained in low or moderate yields, which is a disadvantage of this approach. Except the

fluorination with elemental fluorine, this method provides regioselectively 2-fluoropyrroles. Thus, treatment of N-methylpyrrole **1a** with F_2 under carefully controlled conditions in $CHCl_3$ afforded both 2- and 3-fluoropyrroles **2,3** together with fluoromethylpyrrole **4** (the yields are not given) [6].



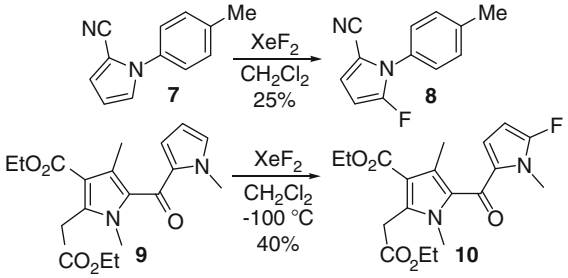
Direct fluorination of pyrroles **5** without NH-protection can be performed with substrates bearing electron-withdrawing substituents, using xenon difluoride. The transformation gives substituted 2-fluoropyrroles **6** in moderate yields [7].



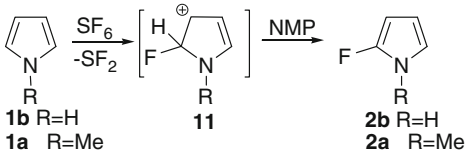
R^1,R^2 = H, CH_2CO_2Me, $CH_2CH_2CO_2Me$

R^3 = CHO, CO_2CH_2Ph, $COCCl_3$, $CONMe_2$

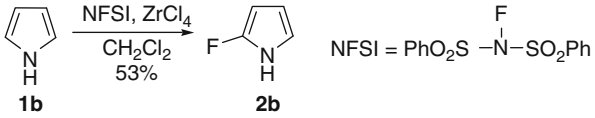
Fluorination of N-substituted pyrroles **7,9** with xenon difluoride was also performed to give substituted products at α-position **8,10** in moderate yields [8].



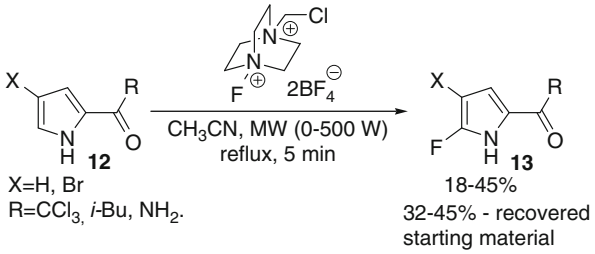
The first synthesis of 2-fluoropyrrole **2b** and N-methylated analogue **2a** was performed in gas phase by electron ionization of SF_6. SF_3^+ species are formed under these conditions providing approach to generate a gentle and effective electrophilic monofluorinating reagent for five-membered heterocyclic compounds [9].



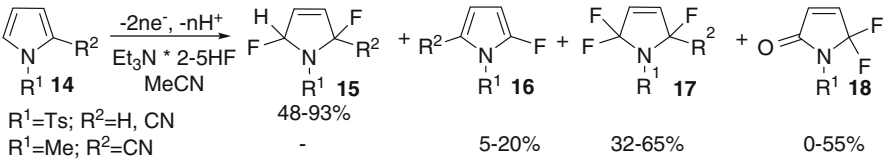
A more convenient method of fluorination is based on the Lewis acid catalyzed reaction with N-fluorobenzenesulfonimide (NFSI). The reaction is catalyzed by $ZrCl_4$ and gives 2-fluoropyrrole **2b** in 53 % yield. The use of a large amount of catalyst can increase the yield of the product; but the amount of unknown by-products also increases [10].



Fluorination of a series of 2-acylpyrroles **12** was also performed using Selectfluor. Treatment of mono- and nonbrominated 2-acylpyrroles **12** with Selectfluor in MeCN under microwave irradiation leads to fluorination of the pyrrole ring at the 5-position. The corresponding fluoropyrroles **13** were isolated in moderate yields. However noticeable amounts of starting materials were also isolated, making real yields much higher [11]. Fluoropyrroles thus obtained were used for the synthesis of fluoroanalogue of hymenidin (see Sect. 3 of this chapter).

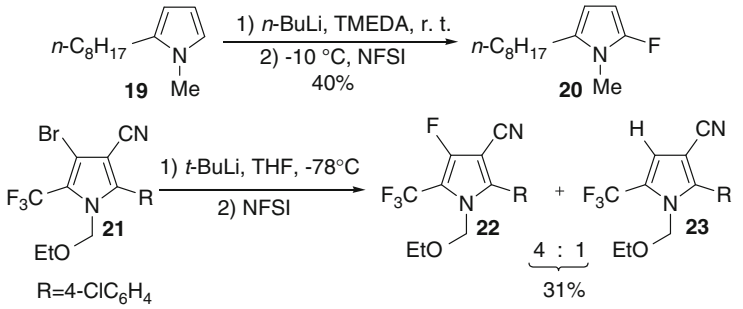


Direct anodic fluorination of 1,2-disubstituted pyrroles **14** gives 5-fluoropyrroles **16** and/or fluorinated adducts **15**, **17**, pyrrolin-2-ones **18**. The transformation is performed with platinum plate electrode in acetonitrile containing supporting fluoride salts Et_3N-nHF [12]. The structure of product depends on supporting fluoride salts.

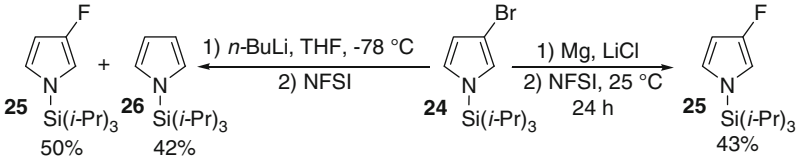


It is known, that convenient approach to fluorinated five-membered heterocycles, including pyrroles, is based on the metallation-fluorination reactions [13]. Thus, 100 % regioselective lithiation of the starting N-methylpyrrole **19** followed by a treatment of the corresponding organolithium derivative with NFSI gives 2-fluoro-5-*n*-octyl-N-methylpyrrole **20** in 40 % yield [13]. Similarly, starting from

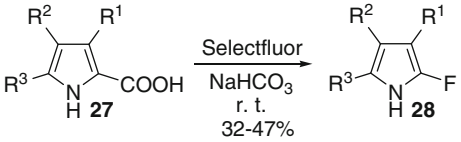
bromopyrrole **21**, highly substituted fluoropyrrole **22** was prepared with admixture of pyrrole **23** [14].



Reaction of NFSI with lithiopyrrole derivative obtained by Br-Li exchange from 3-bromopyrrole **24** afforded the desired 3-fluoro-l-(triisopropylsilyl)pyrrole **25** in 50 % yield and 1-(triisopropylsilyl)pyrrole **26** as a major by-product [14, 15]. The conversion of Grignard reagents into the corresponding fluorinated products using a Br–Mg exchange and a subsequent fluorination procedure with NFSI represents convenient modification of this method providing the fluoropyrrole **25** in 43 % yield [16].

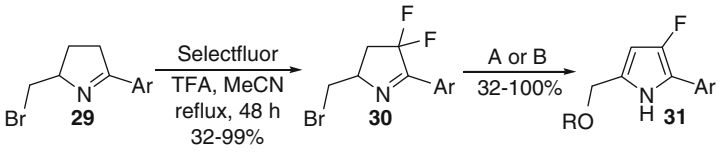


All methods above described are based on the direct fluorination of heterocycle or lithiation followed by fluorination via formal substitution of hydrogen. However, various pyrrole derivatives such as carboxylic acids and halopyrroles can be also used as starting compounds for electrophilic fluorination-decarboxylation. Thus, reaction of α-pyrrolecarboxylic acids **27**, in which the ring is highly substituted by electron-withdrawing or electron-donating groups, with Selectfluor gives the corresponding α-fluoropyrroles **28** in 32–47 % yields [17].



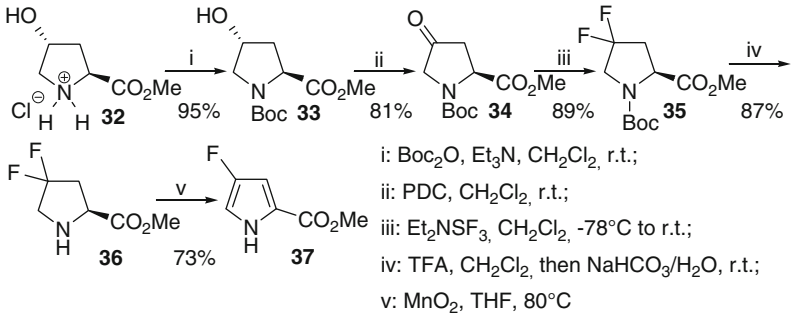
R^1=Me, CH_2CO_2Me, $CH_2CH_2CO_2Me$.
R^2=H, Me, CH_2CO_2Me, $CH_2CH_2CO_2Me$.
R^3=Cbz, CHO, Me.

Another possibility for the synthesis of fluorinated pyrroles is the use of their nonaromatic precursors. Thus, 3,3-difluoro-1-pyrrolines **30** were prepared via electrophilic fluorination of the corresponding 1-pyrrolines **29** by Selectfluor. Reaction of the difluoropyrrolines **30** with sodium alkoxides yielded fluorinated 5-(alkoxymethyl) pyrroles **31** in good yields [18].



Ar = Ph, 4-F-C_6H_4; A: 2M aq. NaOH, ROH, 1h; B: 1M NaOR, ROH, 1h

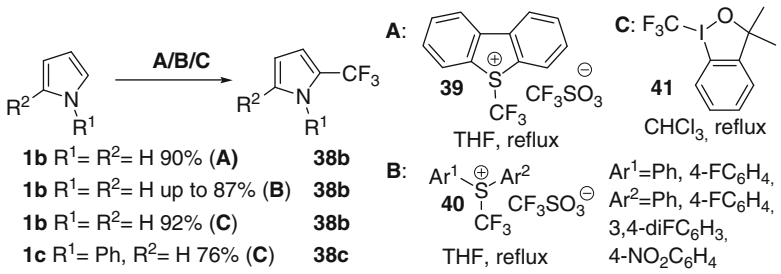
Effective pathway towards 3-fluoropyrrole **37** was elaborated on the base of easily available methyl *trans*-4-hydroxy-L-prolinate **32**. After Boc-protection of this compound followed by oxidation with PDC, ketone obtained **34**, was converted into difluoride **35** by the reaction with DAST. N-Boc deprotection of **35** with trifluoroacetic acid afforded, after basic treatment, free base **36** which was aromatized by activated manganese dioxide into methyl 4-fluoro-1H-pyrrole-2-carboxylate **37** [15, 19].



2.1.2 Electrophilic Trifluoromethylation

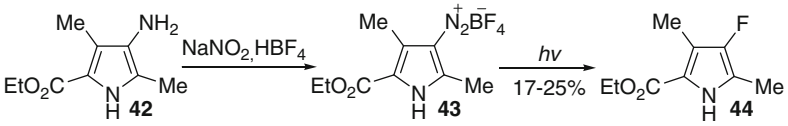
Electrophilic aromatic substitution is also a general method towards trifluoromethylated pyrroles. Umemoto et al. investigated a variety of sulfonium, telluronium, selenonium and oxonium salts as sources of the trifluoromethyl cation. Thus, the sulfonium salt **39** was applied for pyrrole trifluoromethylation. The 2-CF_3-pyrrole **38b** was obtained regioselectively in 90 % yield [20]. Several other sulfonium salts **40** were also used for pyrrole trifluoromethylation [21]. Highest yields were obtained with the most electrophilic salts bearing electron-withdrawing groups in the benzene rings. Perfect regioselectivity was also achieved then hypervalent iodine reagent **41** was used for electrophilic trifluoromethylation of pyrroles [22].

High yields of the target pyrroles and simplicity of experimental technique are significant advantages of electrophilic trifluoromethylation.

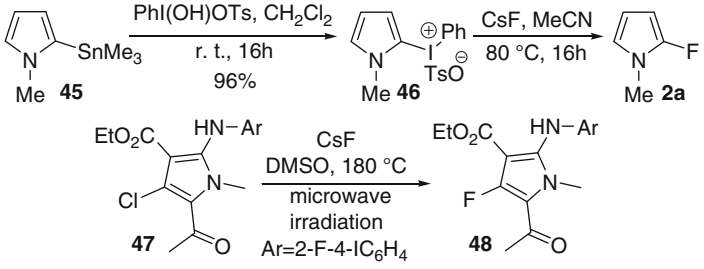


2.1.3 Nucleophilic Fluorination

In contrast to fluorination using electrophiles, nucleophilic fluorination is much rarely presented in the literature. A photochemical modification of the Schiemann reaction has been used for the preparation of 3-fluoropyrroles. Thus, treatment of aminopyrrole derivative **42** with $NaNO_2$ in fluoroboric acid afforded the diazonium tetrafluoroborate **43**. Irradiation of this compound with a high pressure mercury lamp gave 3-fluoropyrrole **44** in 17–25 % yield [23].

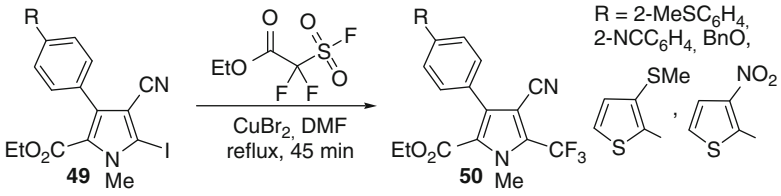


2-Fluoropyrrole **2a** was obtained in good yield through the intermediate iodonium salt **46**, starting from stannane **45** [24]. The reaction represents an example of nucleophilic substitution in iodonium salts by fluoride ion. Similarly, chlorine atom in pyrrole **47** activated by electron-withdrawing CO_2Et and acyl groups was substituted by fluoride in DMSO under microwave irradiation to give fluoropyrrole **48** [25]. The yields of products obtained were not reported.

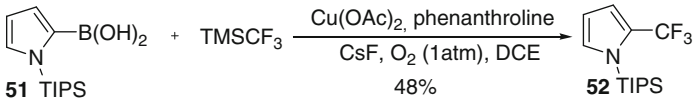


2.1.4 Nucleophilic Trifluoromethylation

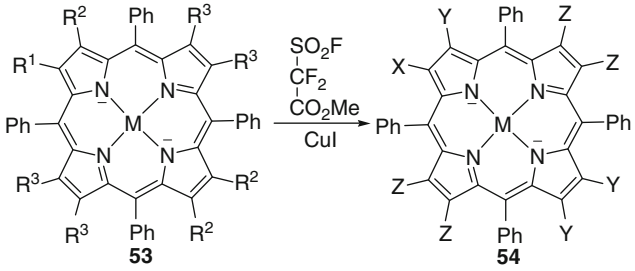
2-Triflurомethyl pyrroles can be also synthesized by nucleophilic trifluoromethylation. In few works the *ipso*-substitution of iodide in compounds **49** by the trifluoromethyl group was reported using a mixture of $FSO_2CF_2CO_2Et$ and $CuBr_2$ as the source of the unstable intermediate trifluoromethyl anion [26]. No yields of compounds **50** were given.



Copper-mediated oxidative cross-coupling of 2-pyrrolylboronic acid **51** with $TMSCF_3$ provided another selective approach to 2-trifluoromethylpyrrole. Reaction proceeds in mild conditions to give *N*-TIPS-2-trifluoromethylpyrrole **52** in 48 % yield [27].



Various trifluoromethylated metalloporphyrins **54** were prepared in high yields by the reaction of brominated metalloporphyrins **53** (copper and nickel complexes) with stoichiometric amounts of FSO_2CF_2COOMe/CuI in the presence of catalytic amounts of a palladium catalyst [28]. Similarly, the $(CF_3)_2Cd$-CF_3CdBr-CuBr system was used as a source of trifluoromethyl anion in the synthesis of some porphyrin derivatives [29].



R^1= Br, R^2= R^3= Y = Z = H, X = CF_3 M = Cu^{2+} 65%; M = Ni^{2+} 70%
R^1= R^2= Br, R^3= Z = H, X= Y = CF_3 M = Cu^{2+} 95%; M = Ni^{2+} 95%
R^1= R^2= R^3= Br, X = Y = Z = CF_3 M = Cu^{2+} 85%; M = Ni^{2+} 90%

Table 1 Synthesis of regioisomeric trifluoromethylpyrroles

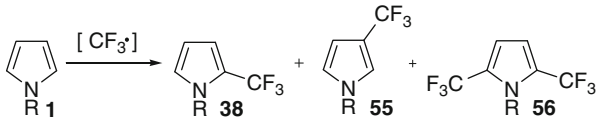
Entry	Educt **1**	R	CF_3 source	CF_3	Yield **38** (%)	Yield **55** or **56**, (%)	References
2	**1a**	Me	CF_3I	CF_3	36	7 (**56**)	[31]
1	**1b**	H	CF_3I	CF_3	33	–	[31]
3	**1d**	Bn	CF_3I	CF_3	71	–	[32]
4	**1e**	*p*-Tol	CF_3I	CF_3	91	–	[32]
5	**1b**	H	CF_2I_2	CF_3	42	2 (**55**)	[33]
6	**1a**	Me	CF_2I_2	CF_3	46	3 (**55**)	[33]
7	**1b**	H	$(CF_3CO_2)_2$	CF_3	72	–	[34]
8	**1b**	H	**70**	CF_3	51	–	[35]
9	**1b**	H	$Te(CF_3)_2$	CF_3	(25:	1(**38b**))[a]	[36]
13	**1a**	Me	CF_3Br	CF_3	52[b]	–	[37]
10	**1b**	H	CF_3Br	CF_3	15[b]	–	[37]
11	**1b**	H	CF_3Br	CF_3	47[c]	–	[37]
12	**1b**	H	CF_3Br	CF_3	65[d]	8 (**55**)	[38]

[a]Yield not given

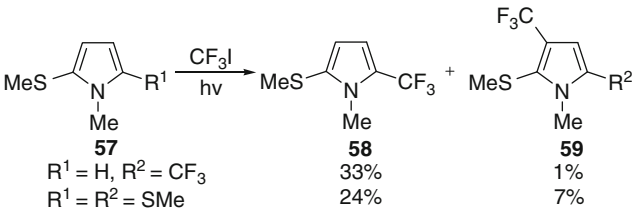
Reducing systems: [b]Zn/SO_2, [c]$Na_2S_2O_4$, [d]HCO_2Na/SO_2

2.1.5 Radical Trifluoromethylation

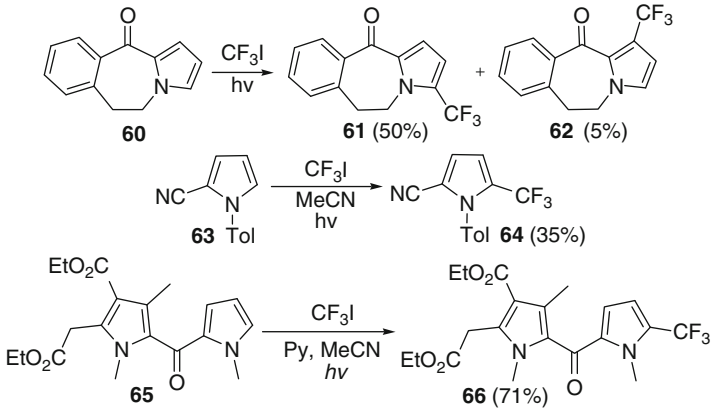
The direct trifluoromethylation of the pyrrole ring is a widely used approach to synthesize trifluoromethylated products [30]. The *N*-methylpyrrole **1a** reacted regioselectively with CF_3Br in acetonitrile under UV irradiation (Hg lamp) giving the 2-CF_3-pyrrole **38a** in 6 % yield. Under similar conditions, the reactions of pyrroles **1a,1b** with CF_3I in acetonitrile [31] resulted in higher yields. Trifluoromethylation of **1b** proceeded regioselectively in 2-position to give **38b** in 33 % yield, while **38a** was isolated in 36 % yield [31] (Table 1, entries 1 and 2). However, excess of CF_3I (2.5 equiv.) was needed to complete the conversion of **1a**. This resulted in the admixture of the bis-trifluoromethylation product **56a** (7 %). In contrast, *N*-benzyl- and *N*-(*p*-tolyl)substituted pyrroles **1d** and **1e** afforded the corresponding derivatives **38d** and **38e** in 71 % and 91 % yields, respectively [32] (Table 1, entries 3 and 4).



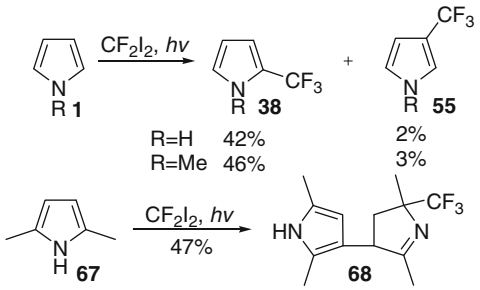
Similarly, in case of the methylthio derivatives **57** maximal yields of **58** were obtained using 2.5 equiv. of CF_3I. However, full consumption of starting material was not achieved and formation of side products **59** was observed [31].



Several other photochemical trifluoromethylations by CF_3I were reported. The regioisomeric substitution products **61** and **62** were formed [32] from the tricyclic pyrrole **60,** whereas regioselective α-trifluoromethylation was observed for pyrroles **63** and **65** to give 2-CF_3-pyrroles **64** [4] and **66** [8] in moderate and good yields.

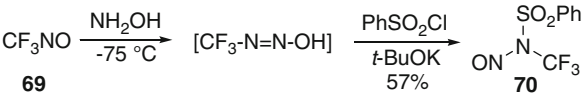


Surprisingly, the reaction of CF_2I_2 with pyrrole (**1b**) and *N*-methylpyrrole (**1a**) gave the trifluoromethylated products **38b** and **38a** in moderate yields under UV irradiation in DMF (Table 1, entries 5 and 6) [33]. In contrast the related reaction with 2,5-dimethylpyrrole **67** gave the trifluoromethylated dimer **68** instead of the desired 2,5-dimethyl-3-trifluoromethylpyrrole.



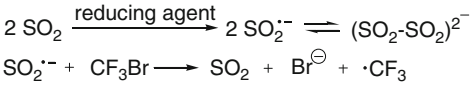
Bis(perfluoroalkanoyl)peroxides were also applied for radical trifluoromethylation of pyrrole **2b** [34]. Performing the reaction in freon 113 at −30 °C was found to be optimal for all peroxides. In this way 2-CF_3-pyrrole **38b** was regioselectively synthesized in 72 % yield (Table 1, entry 7). Lower yields were obtained both at higher temperature and in diethyl ether as a solvent.

The *N*-nitrososulfonamide **70** was shown to be a convenient reagent for radical trifluoromethylation. UV irradiation of **1b** with **70** in the presence of diacetyl as a sensitizer led to **38b** in 51 % yield (Table 1, entry 8). Distinct advantage of this method is easy handling of the solid **70** instead of gaseous CF_3I or of the quite unstable bis(perfluoro-alkanoyl)peroxides. **70** is assessable from trifluoronitroso-methane **69** in a one-pot procedure [35]. $Te(CF_3)_2$ was also used as a trifluoromethyl radical source for trifluoromethylation. The reaction proceeded under UV irradiation and led to a 25:1 mixture of pyrroles **1b** and **2b** (Table 1, entry 9) [36].

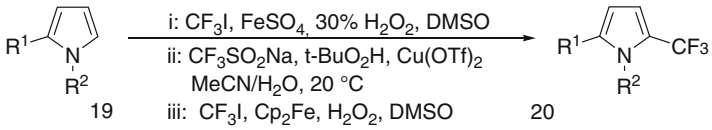


69 **70**

Besides UV irradiation, different reductive systems (Zn/SO_2 couple or $Na_2S_2O_4$) can be used for the initiation of trifluoromethyl radical formation [37]. Using these systems, compound **38b** was synthesized in low or moderate yields (Table 1, entries 10 and 11). **38a** was prepared analogously (entry 13). Initiation by HCO_2Na/SO_2 improved the yield of **38b** up to 65 %, but the admixture of 8 % of the regioisomer **55b** was found (entry 12) [38].



Trifluoromethylation of pyrroles under oxidative conditions was also reported. Thus, the DMSO-CF_3I-$FeSO_4$-H_2O_2 and DMSO-CF_3I-Cp_2Fe-H_2O_2 systems were applied to prepare the 2-CF_3-pyrroles **71** [39], **72** [40], **2b, 73** [41] regioselectively in good to high yields. Similarly, using the combination CF_3SO_2Na/*t*-BuOOH/$Cu(OTf)_2$ in acetonitrile/water, the 2-trifluoromethyl-*N*-acylpyrrole **38f** was prepared in 35 % yield [42].



19 20

71 R^1 = 4-$MeSO_2C_6H_4$, R^2 = 4-FC_6H_4
72 R^1 = 2-MeO-5-ClC_6H_3, R^2 = 4-$MeCO_2C_6H_4$
2f R^1 = H, R_2 = Ac
2b R^1 =R^2=H
73 R^1 =Ac, R^2=Me,

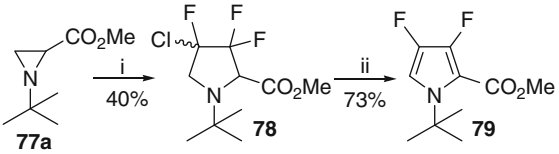
(i) **74** 43%
(i) **75** 43%
(ii) **38f** 35%
(i) **38b** 96%
(iii) **76** 79%

Direct fluorination/trifluoromethylation are very synthetically attractive approaches to prepare fluorinated pyrroles due to it is not necessary to construct the heterocyclic core. Especially this methods are convenient for the synthesis of fluoropyrroles. In contrast, synthesis of trifluoropyrroles is restricted by lower regioselectivity, moderate yields and the application of gaseous CF_3I or quite unstable (bis(trifluoroacetyl)peroxides).

2.2 *Heterocyclizations Leading to Fluorinated Pyrroles*

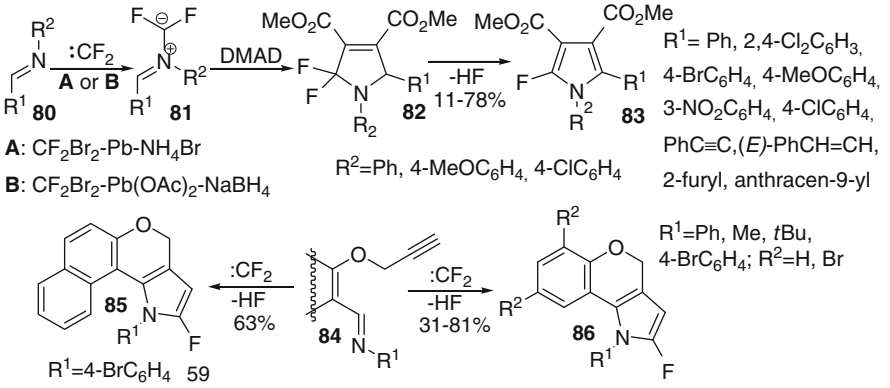
2.2.1 Synthesis of Fluoropyrroles by [3+2] Cycloaddition Reactions

Application of cycloaddition reactions is one of the most prominent strategies in synthesis of cyclic systems. 1,3-Dipolar cycloaddition of azomethine ylides to unsaturated compounds gives rise to a number of pyrrole syntheses. For example, azomethine ylide, generating by the thermal ring-opening of 2-carbomethoxyl-t-butyl-aziridine **77a**, reacts with chlorotrifluoroethene to give a mixture of diastereoisomeric chlorofluoropyrrolidines **78**. Treatment of those with sodium methoxide resulted in formation of 3,4-difluoropyrrole derivative **79** in high yield [43].



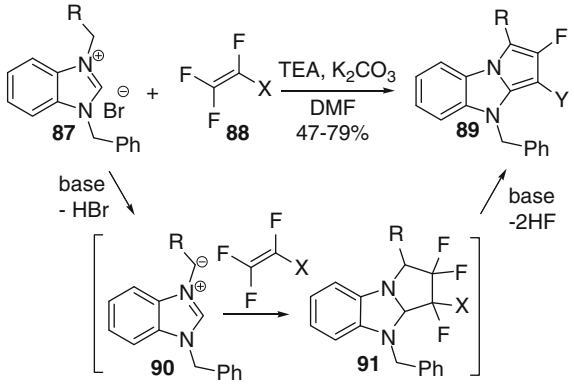
i: FClC=CF_2, 200 °C, 2 h; ii: MeONa, MeOH

Imines **80** react with difluorocarbene in the presence of dimethyl acetylenedicarboxylate (DMAD) producing 2-fluoropyrroles **83** in 11–78 % yields. This domino process was assumed to occur via difluorocarbene attack on the nitrogen lone pair resulting in formation of azomethine ylides **81**, 1,3-dipolar cycloaddition of the latter one to DMAD, and dehydrofluorination of pyrrolines **82** thus formed [44]. Difluorocarbene can be generated by reduction of dibromodifluoromethane with lead powder in the presence of tetrabutylammonium bromide (Method A) or using active lead obtained by reduction of aqueous lead acetate with sodium borohydride (Method B). This reaction can be also performed as intramolecular version to form substituted 2-fluoropyrroles **85**, **86** [45].



Benzimidazolium N-ylides **90**, generated in situ from bromides **87**, react with fluoroalkenes **88** in DMF in the presence of K_2CO_3 and Et_3N, to give fluorinated H-pyrrolo[1,2-a]benzimidazoles **89**. The mechanism of the reaction includes

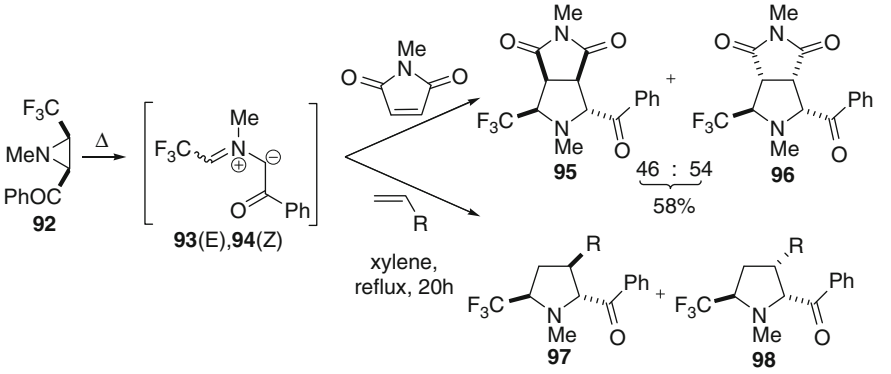
1,3-dipolar [3+2] cycloaddition with formation of pyrrolines **91**, followed by base induced elimination-aromatization [46].



X = Cl, Br, F, CF_3; R = COPh, COOEt, CN; Y=F, CF_3

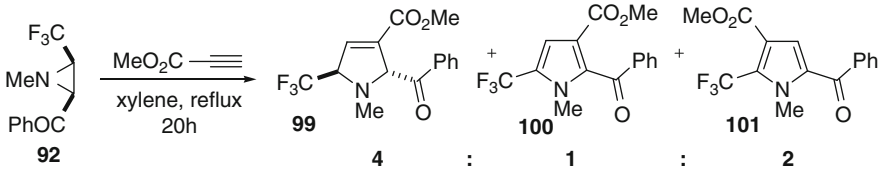
2.2.2 Synthesis of Trifluoropyrroles by [3+2] Cycloaddition Reactions

Azomethine ylides were also used as dipols for the preparation of CF_3-pyrroles by 1,3-dipolar cycloaddition. The ylides **93** and **94** prepared *in situ* from aziridine **92** in refluxing xylene, with excess of *N*-methyl-maleimide gave an 1:1 mixture of the diastereomeric pyrrolidines **95** and **96**. The reactions of **92** with monosubstituted ethenes (styrene, methyl acrylate, acrylonitrile) proceeded regio- and stereoselectively giving only one of the possible isomers. In contrast, the electron-rich vinyl butyl ether led to both possible stereoisomers **97** and **98** in almost 1:1 ratio [47].

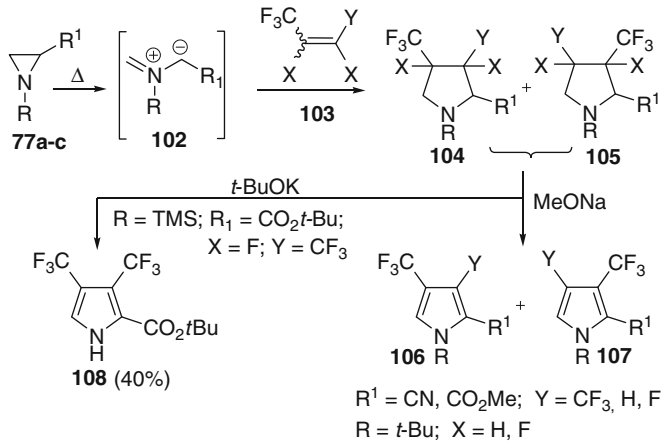


The reaction of **92** with methylpropiolate was not regioselective and led to a 4:1:2 mixture of the pyrroline **99** and the isomeric pyrroles **100** and **101**. The pyrroline **99**

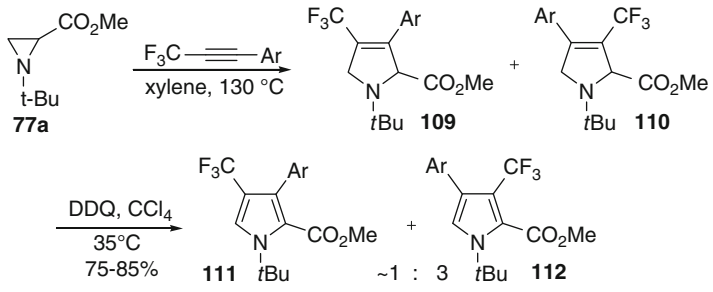
was shown to be an intermediate, which on refluxing in xylene was aromatized into **100**. The regioisomeric pyrroline leading to **101** was not isolated [47].



The addition of azomethine ylides **102** formed by heating of the aziridines **77a,b** (R = *t*-Bu) to the trifluoromethylated alkenes **103** led to mixtures of the diastereomeric pyrrolidines **104** and **105**. Subsequent elimination of HF by treatment with sodium methoxide in methanol gave predominantly the pyrrole **106** and minor amount of the regioisomer **107** [43]. 3,4-Bis(trifluoromethyl)pyrrole **108** with a free nitrogen atom was obtained using *N*-trimethylsilyl aziridine **77c** [48].

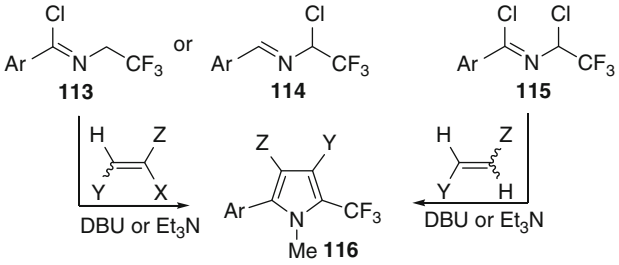


The reaction of azomethine ylide formed from the aziridine **77a** with trifluoromethylaryl acetylenes gave a mixture of dihydropyrroles **109** and **110**, which formed a 1:3 mixture of pyrroles **111** and **112** by oxidation with DDQ [49].



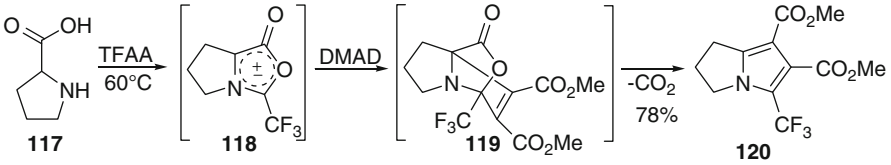
This methodology was further developed using imidoylchlorides **113** as precursors of azomethine ylides [50], which were generated by treatment with bases.

Application of the isomeric chloroimines **114** led to the same pyrroles **116** [51]. The generation of ylides was also possible from dichloroimines **115**, that allowed to involve alkenes without any vinylic halogen atoms. The yields were not given [52].

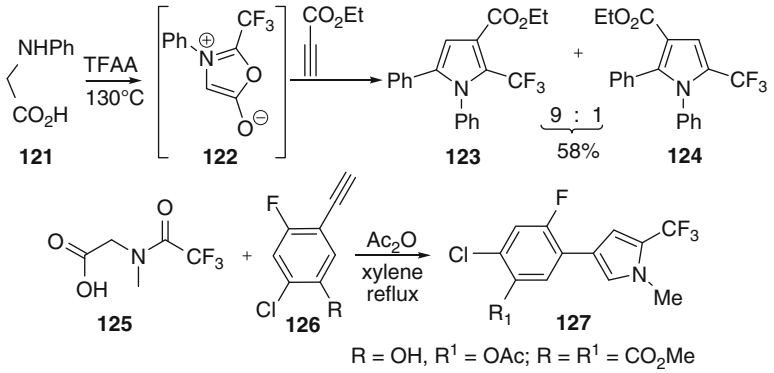


Ar = 4-ClC$_6$H$_4$; X = Cl, Br, I; Y = H, C$_n$F$_{2n}$$^{+1}$; Z = CN, NO$_2$, CO$_2$R

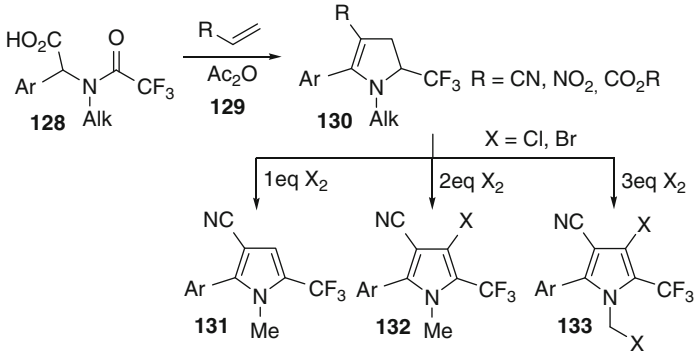
The 1,3-dipolar cycloaddition of acetylenes and alkenes with oxazolones is widely used for the construction of the pyrrole ring. The presence of a CF_3-group in the 1,3-dipolar component opens a pathway to 2-CF_3-pyrroles, while the application of trifluoromethylated dipolarophiles provides 3-CF_3-pyrroles. For example, the dimethyl pyrroledicarboxylate **120** was synthesized in 78 % yield by the reaction of the CF_3-containing oxazolone **118**, prepared from proline **117** and trifluoroacetic anhydride (TFAA), with dimethyl acetylene dicarboxylate (DMAD) [53].



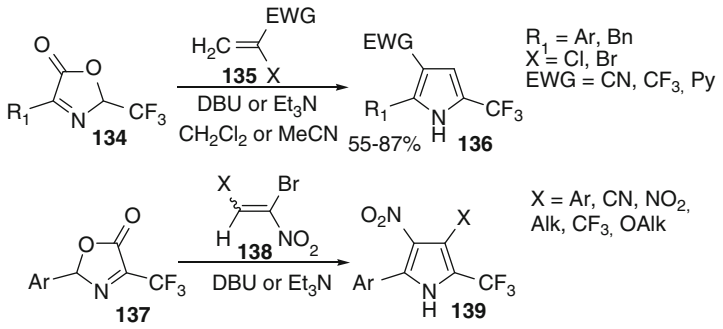
Derivatives of other amino acids were also used for the preparation of pyrroles [54]. Accordingly, the reaction of the unstable **122**, generated in situ from *N*-phenylglycine **121**, with ethyl propiolate gave an inseparable 9:1 mixture of **123** and **124** in 58 % yield. Similarly, the pyrroles **127** were synthesized from trifluoroacetylated sarcosine **125** and the acetylenes **126** [55].



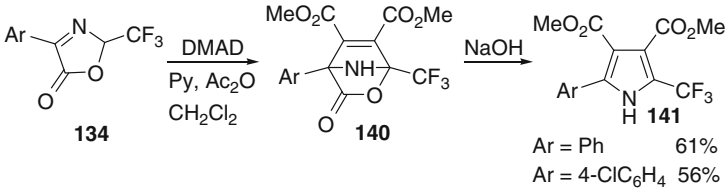
If electron deficient terminal alkenes **129** as dipolarophiles were treated with appropriately protected arylglycine derivatives **128**, the dihydropyrroles **130** were formed as cycloadducts [56]. However, aromatization was easily possible by treatment with oxidants such as bromine or chlorine. Depending on the amount of halogen, pyrroles **131**, monohalopyrroles **132** or dihalopyrroles **133** can be synthesized. Using that strategy, compound **131** (Ar = 4-ClC_6H_4, X = Br) was prepared starting from the corresponding **128** in three steps in 30 % overall yield. This compound is a useful starting material to synthesize the broad-spectrum insecticide chlorfenapyr and analogues [57].



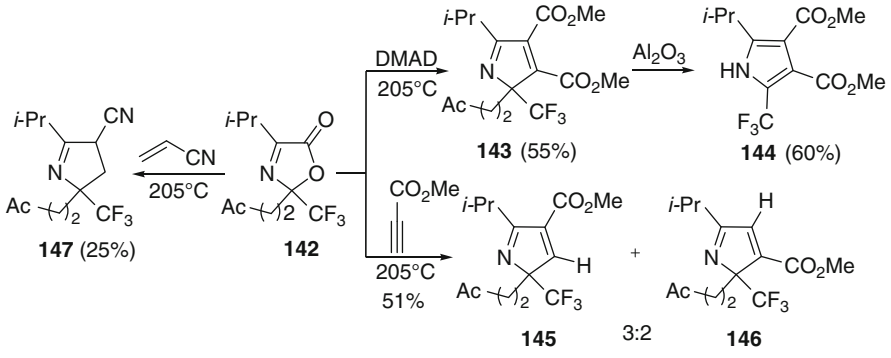
The reaction of oxazolones **134** with electron-deficient alkenes **135** in the presence of a base (DBU or Et_3N) gave the pyrroles **136** in good yields [58]. These base promoted cyclocondensations involve a tandem Michael addition of oxazolones **134** to electron-deficient alkenes **135** followed by intramolecular cyclization and decarboxylation. This method opened up a convenient pathway to synthesize 2-trifluoromethylpyrroles containing electron-withdrawing groups in 4-position. When the reactions were performed in MeCN and Et_3N at reflux, yields rose up to 86–94 % in case of the 4-chlorophenyl substituent [59]. Instead of the alkenes their saturated bromo precursors were also successfully applied [60]. The synthetic scope of this reaction was significantly expanded using reactions of oxazolones **137** with nitroalkenes **138.** The 2-CF_3-pyrroles **139** bearing numerous combinations of aryl, alkyl, alkoxy, nitro and cyano groups can be prepared by this method [61].



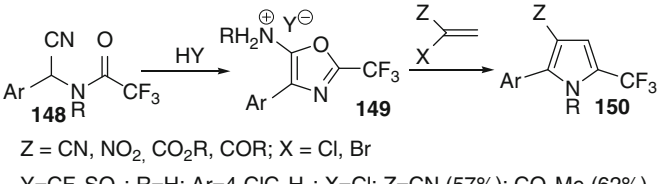
The reaction of oxazolones **134** with DMAD led to adducts **140**, which were transformed into pyrroles **141** after decarboxylation [58].

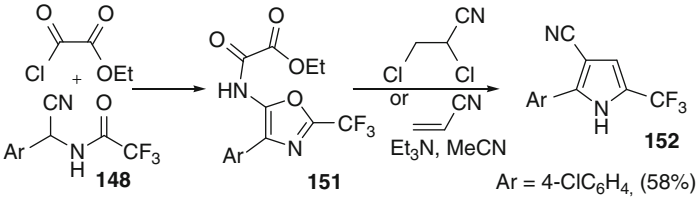


The reaction of the oxazolone **142** (bearing two substituents at C-2 atom) with DMAD led to the nonaromatic pyrroline **143**, which after passing through a column with active Al_2O_3 gave the pyrrole **144** by elimination of methyl vinyl ketone with aromatization. Treatment of **142** with methyl propargylate produced a 3:2 mixture of the regioisomers **145** and **146**, while the reaction with acrylonitrile led to the pyrroline **147** in 25 % yield [62].

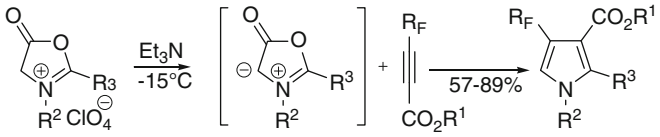


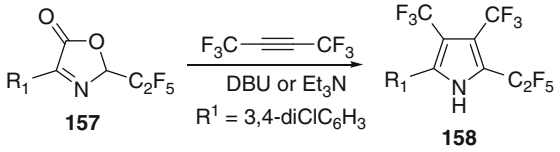
Besides alkyl and aryl oxazolones and their salts, also 5-aminooxazoles **149** [63] as well as the amides of aminooxazoles **151** [64] were used to synthesize trifluoromethylated pyrroles by cycloaddition. This is not surprising taking into account that the aminooxazoles **149** and amides **151** are formal tautomers of the oxazolone imines. Accordingly, a number of CF_3-pyrroles **150** and **152** bearing electron-withdrawing groups at the 4-position have been prepared by this method.





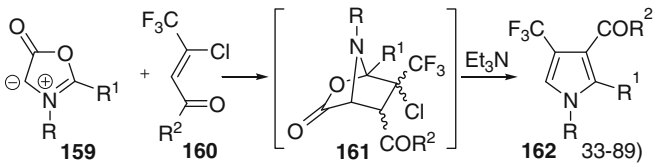
Mesoionic oxazolones **154**, prepared from **153**, allowed the synthesis of 3-CF_3-pyrroles. Thus, their reactions with fluorinated derivatives of ethyl propiolate **155** led to the alkyl pyrrole-3-carboxylates **156** [65]. Similarly, the reaction of compound **157** with hexafluorobut-2-yne gave the pyrrole **158** [66].





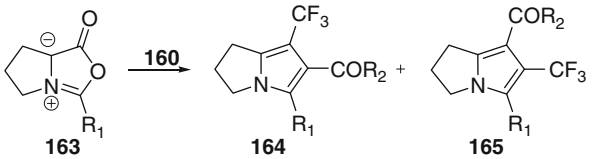
The reaction of the oxazolones **159** with the trifluoromethylated chloroalkenones **160** proceeded regioselectively via the intermediate bicyclic pyrrolidines **161**,

which in the presence of triethylamine eliminated HCl and CO_2, forming the pyrroles **162** in moderate to high yields [67].

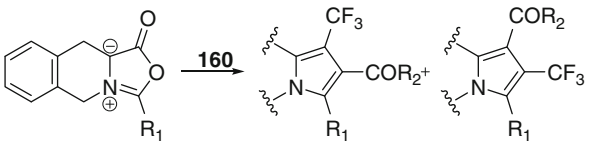


R=Me, Ph; R^1=Ph, Me; R^2=Ph, OBu

Starting from the analogous fused-ring oxazolones **163** and **166** derived from cyclic amino acids, the reaction with the ketone **160** (R^2 = Ph, OBu) afforded mixtures of the regioisomeric dihydropyrrolizines **164** and **165** and the dihydropyrrolo[1,2-b]isoquinolines **167** and **168**, respectively, in high overall yields [67]. In all cases the isomers **164** and **167** dominate in the mixtures.

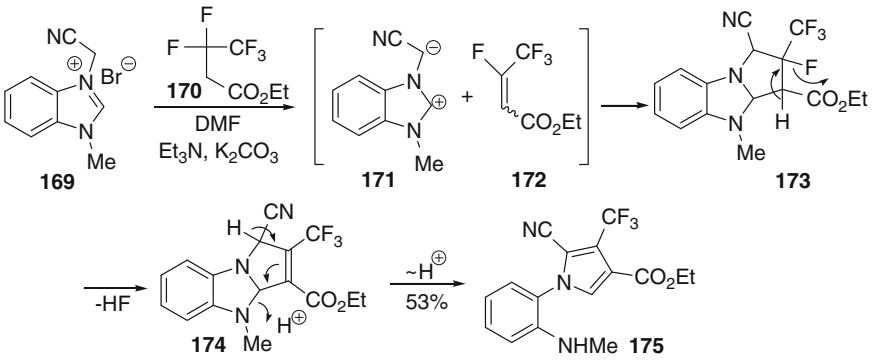


R_1 = Ph; R_2 = Ph	49%	15%
R_1 = Me; R_2 = Ph	56%	12%
R_1 = Ph; R_2 = OBu	49%	36%
R_1 = Me; R_2 = OBu	9%	7%

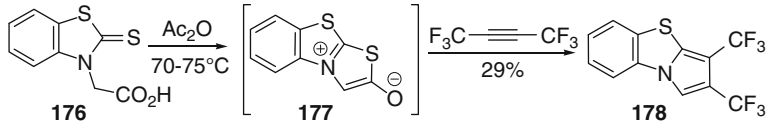


R_1 = Ph; R_2 = Ph	17%	-
R_1 = Me; R_2 = Ph	65%	21%
R_1 = Ph; R_2 = OBu	50%	24%

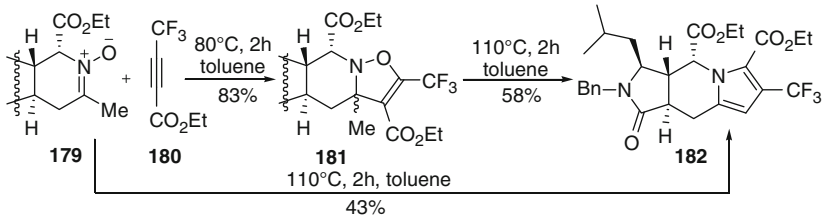
An interesting approach to *N*-[2-(alkylamino)aryl]-3-trifluoromethylpyrroles **175** was elaborated by Zhang et al. [68]. The benzimidazolium salt **169** gave the pyrrole **175** in 53 % yield by treatment with ethyl 3,3,4,4,4-pentafluorobutyrate **169**. Initially the ylide **171** and the activated alkene **172** are formed, which subsequent 1,3-dipolar cycloaddition forms **173**. Elimination of HF continues the reaction to give the intermediate **174**, which by proton migration and ring opening leads to the final pyrrole **175** [68].



Another mesoionic system used as dipolarophile was a cyclic system of anhydro-2-hydroxythiazolo[1,3-b]benzothiazol hydroxide **177**. This compound was prepared *in situ* from thionobenzothiazole **176** by reaction with acetic anhydride. The subsequent reaction with hexafluorobut-2-yne led to the tricyclic 3,4-bis(trifluoromethyl) pyrrole **178** [69].

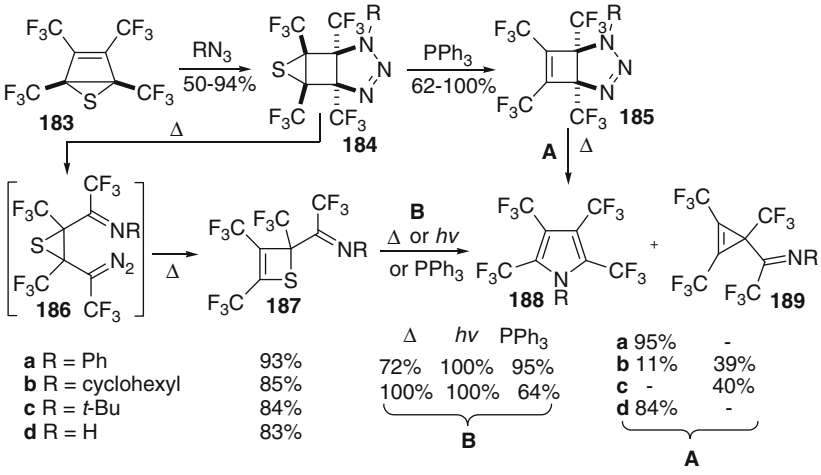


An elegant approach to the "alkaloid-like" heterocycle **182** with a pyrrole moiety was developed using the nitrone **179** in a [3+2]-cycloaddition with ethyl 4,4,4-trifluorobut-2-ynoate (**180**) to give first the 3-methyl-2,3-dihydroisoxazole **181** at 80 °C in toluene. Refluxing in toluene converted **181** to the 3-trifluoromethylpyrrole **182** through a sequence of ring-opening and ring-closure steps with an azomethine-type ylide as a key intermediate. This reaction can also be performed in one step without isolation of **181** [70].

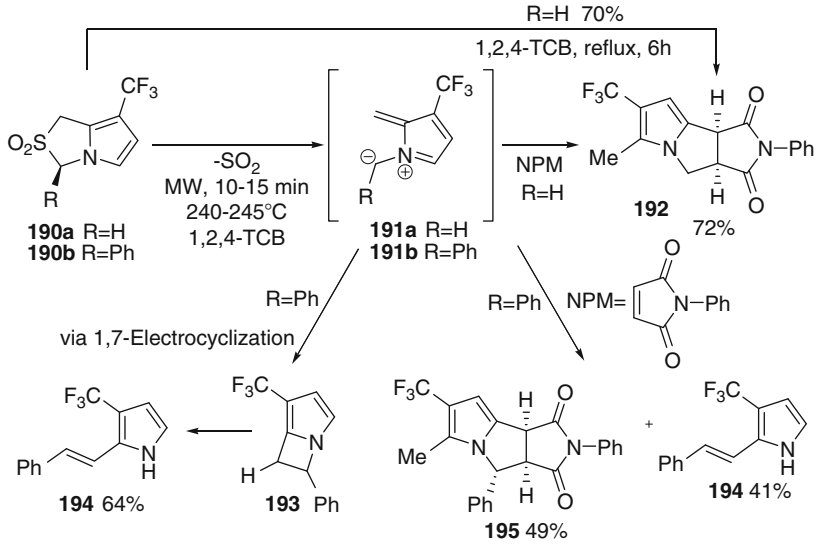


A number of approaches to tetrakis(trifluoromethyl)-pyrroles was developed using tetrakis(trifluoro-methyl)-Dewar-thiophene (**183**) [71]. The 1,3-dipolar cycloaddition with azides led to the tricyclic thiiranes **184**. Subsequent desulfurization by treatment with PPh_3 afforded the cyclobutenes **185** in good to quantitative yields. The result of thermolysis of **185** was strongly depended on the substituent on the amine nitrogen. Pyrroles **188** were formed in high yields (cases **a** and **d**), while only cyclopropene **189**, or a mixture of **188** and **189** (cases **b** and **c**) were isolated. Pyrrole **188a** was also synthesized by the reaction of **183** with aniline in 19 % yield [72].

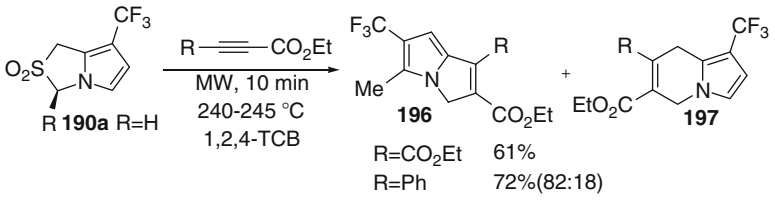
An alternative approach to the pyrroles **188** is based on thermolysis of compounds **184** [71]. The thietimines **187** were formed in high yields via the thiirane **186**, which was isolated and characterized in case of the phenyl compound **186a**. The conversion of the thietimines **187** into the pyrroles **188a** and **188b** was performed by thermolysis, photolysis or by treatment with triphenyl phosphine.



Generated by thermally induced SO_2 extrusion from dioxothiazoles **190** (for the synthesis of **190** see Sect. 2.2.7) under microwave irradiation, azafulvenium methides **191** reacts with dipolarophiles to give CF_3-pyrroles **192**–**195**. Thus, reaction of **191a** with N-phenylmaleimide (NPM) leads to polycyclic CF_3-pyrrole derivative **192** in high yield. Phenyl substituted azafulvenium methide **191b** reacts with NPM to give pyrrole **195** and admixture of 2-styrylpyrrole **194**, which is formed via competitive 1,7-electrocyclization process and can be obtained exclusively by decomposition of **190b** in the absence of NPM [73].



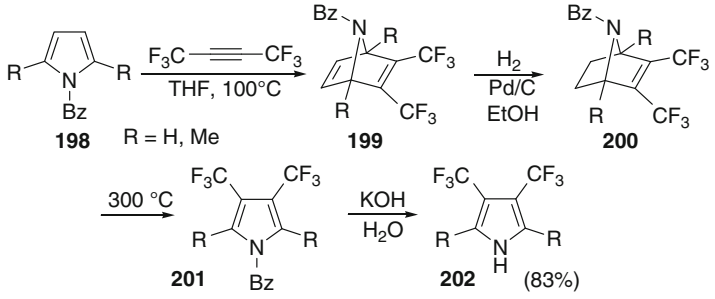
Addition of azafulvenium methides to the triple bond was also realized. Thus, reaction with DMAD afforded bicyclic CF_3-pyrrole **196** in 61 % yield. In case of unsymmetrical ethyl 3-phenylpropiolate the reaction gives a mixture of 1,3- and 1,7-cycloadducts **196** and **197**, respectively, in 72 % overall yield with a ratio of 82:18 [73].



[3 + 2] Cycloaddition reactions open an access to both 2- and 3-trifluoromethylated pyrroles with wide range of additional substituents in pyrrole ring, therefore the method is very useful and general for synthesis of fluorinated pyrroles.

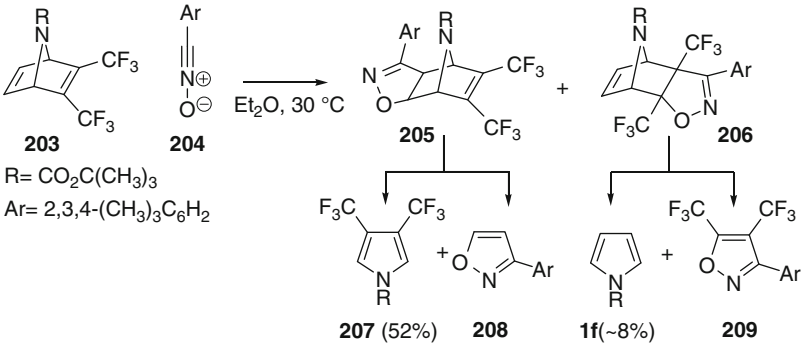
2.2.3 Synthesis of Trifluoromethyl Pyrroles by [4 + 2] Cycloaddition: Cycloreversion Reactions

The sequence of Diels-Alder reactions of nonfluorinated pyrroles with hexafluorobut-2-yne followed by retro Diels-Alder reactions (extrusion of acetylene) was also used for trifluoromethylpyrrole synthesis. However, the 7-azanorbornadiene system was found to be quite thermostable [74], which undergoes cycloreversion only at very high temperature resulting in low yields of trifluoromethylated pyrroles. Hence, additional steps were necessary. For instance, the reduction of the bicyclo[2.2.1] hepta-2,5-diene **199** (formed from **198** and hexafluorobut-2-yne) to **200**, followed by a cycloreversion, afforded the 3,4-bis(trifluoromethyl)pyrrole **201**. Subsequent basic hydrolysis gave the target pyrrole **202**. All reactions proceeded almost quantitatively to give **202** in 83 % overall yield [75].

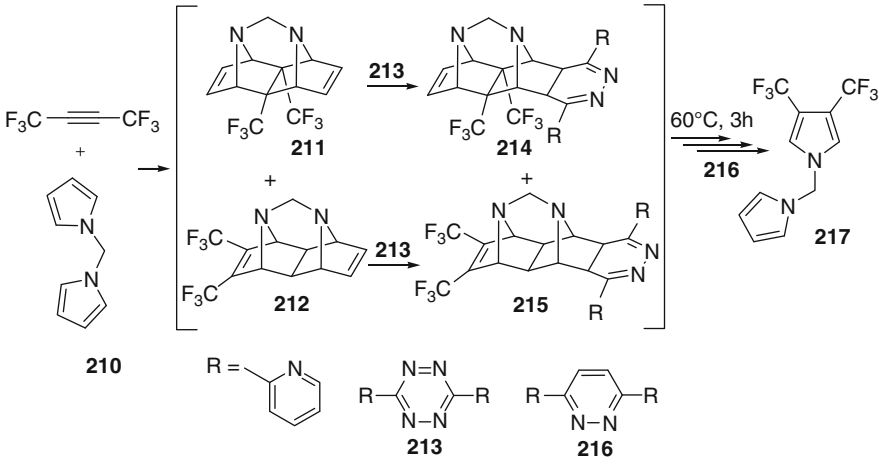


Another variation to facilitate the cycloreversion of trifluoromethylated 7-azabicyclo[2.2.1]heptadienes is their transformation to polycyclic isoxazolines by 1,3-dipolar cycloaddition with nitrile oxides followed by elimination of isoxazole.

Accordingly, the reaction of **203** with benzonitrile oxide (**204**) led to the isoxazolines **205** and **206.** Subsequent retro Diels-Alder reaction of **205** afforded the desired pyrrole **207** in 52 % yield by elimination of the isoxazole **208**. The isomeric isoxazoline **206** gave the pyrrole **1f** in very low yield [48].



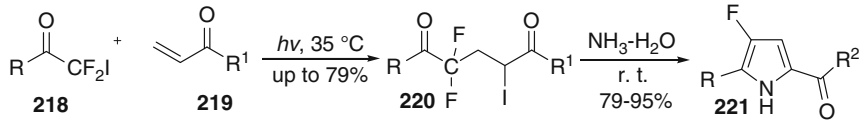
An analogous pathway was used for the synthesis of the pyrrole **217** [76]. The "double" Diels-Alder adducts **211** and **212** of dipyrrolomethane (**210**) were treated with the electron-deficient diene 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**213**) to give the cycloadducts **214** and **215**. The decay of these compounds proceeded with extrusion of 3,6-di(2-pyridyl)-1,2-pyridazine (**216**) and gave the pyrrole **217**. No yield was given.



2.2.4 Synthesis Based on Carbonyl Compounds

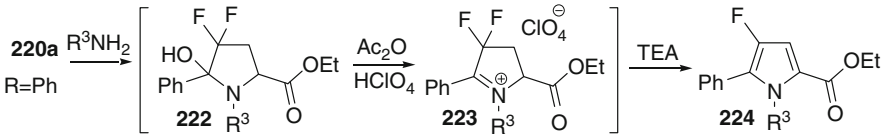
The use of carbonyl function is classic approach in heterocyclic synthesis. In case of fluorinated pyrroles this approach was frequently used. Convenient method for synthesis of pyrroles **221** is based on the reaction of fluorinated δ-keto acid esters or amides **220** with ammonia. In case of methyl and ethyl esters amidolysis was

observed to give the corresponding amides [77]. Starting dicarbonyl compounds **220** are easily available through the radical addition of CF_2I-ketones **218** to alkyl acrylates **219** [78]. Similarly, the reaction of ethyl-4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate **220a** with primary amines in a one-pot scheme produces a series of β-fluoropyrrole derivatives **224** at ambient temperature. The mechanism is presented below [79]. It includes nucleophilic substitution of I- with amine followed by heterocyclization and aromatization as key steps.



218 **219** **220** **221**

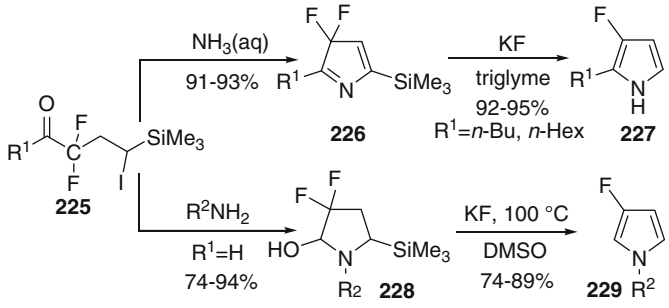
R = Ph, *n*-Bu, *n*-Hex; R^1=NMe_2, R^2=NMe_2; R^1=OEt, OMe; R^2= NH_2



222 **223** **224**

R^3 = H, Me, Et, *cyclo*-Pr, *n*-Bu, *cyclo*-Pn, *cyclo*-Hex, Bn

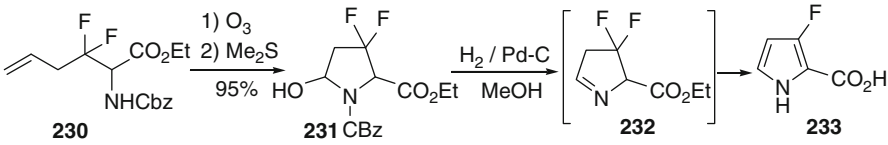
Using α,α-difluoro-γ-iodo-γ-iodotrimethylsilyl ketones or aldehyde **225** as starting compounds, 3,3-difluoro-5-trimethylsilyl-1-pyrrolines **226, 228** were obtained in high yields. Further treatment of them with potassium fluoride gave 4,5-unsubstituted 3-fluoropyrroles **227, 229** in yields up to 95 % [80].



225 **226** **227** **228** **229**

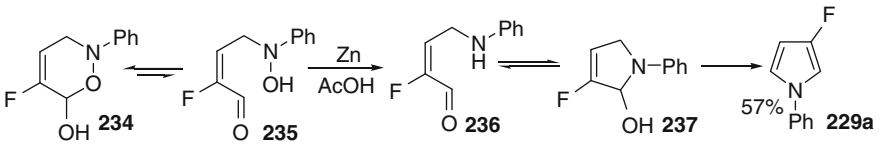
R^2=H,*n*-Bu, *cyclo*-Hex, Bn, Ph, $PhCH_2CH_2$, PMB, 4-Pyridyl

Neutral ozonolysis of compound **230** afforded the cyclic hemiaminal **231** in 95 % yield. Catalytic hydrogenation of **231** in the absence of the acid led to the formation of the pyrrole derivative **233** as a major product [81].

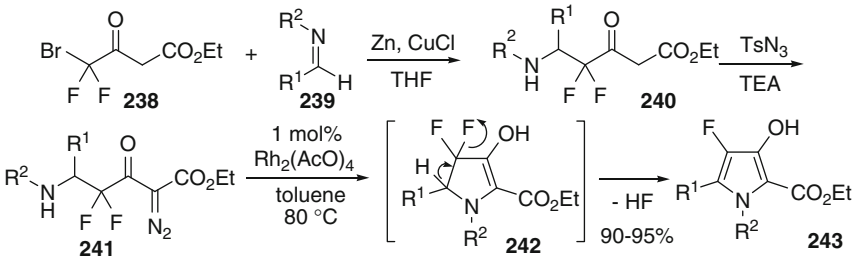


230 **231** **232** **233**

3-Fluoro-1-phenylpyrrole **229a** was effectively prepared starting from compound **234**. Cyclic hemiacetal **234**, existing in equilibrium with its open form **235**, was reduced into amine **237**, which transformed easily into pyrrole **229a** via acid catalyzed cyclization and dehydration [82].

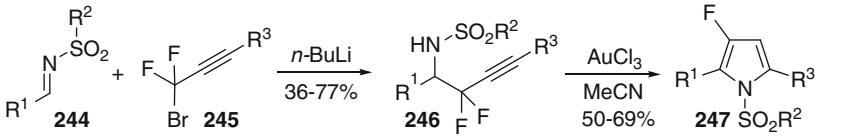


A convenient method for the synthesis of polyfunctionalized 3-fluoropyrroles **243** by $Rh_2(OAc)_4$-catalyzed intramolecular N-H insertion reaction of difluorinated diazo compounds **241** was reported [83]. The starting compounds can be synthesized by Zn-CuCl-promoted Reformatsky-imine addition reaction of 4-bromo-4,4-difluoroacetoacetate **238** with aldimines **239**. Subsequent diazotransfer reaction and $Rh_2(OAc)_4$-catalyzed intramolecular N-H insertion allow the preparation of 3-fluoropyrroles **243** in almost quantitative yield.



R^1=Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Naphthyl, 2-Furyl; R^2=Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, Bn

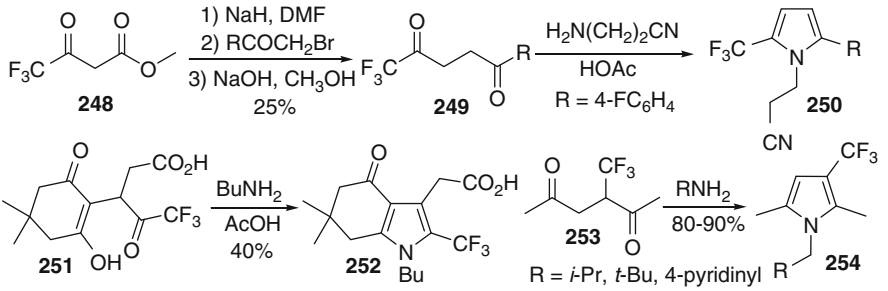
A valuable method for the synthesis of 2-aryl-3-fluoropyrroles **247** is based on a gold-catalyzed cyclization and dehydrofluorination of gem-difluorohomopropargylamines **246**. Difluorinated homopropargylamines **246** can be prepared by the addition of gem-difluoropropargyllithium reagents to arylated *N*-tosylimines **244** [84].



R^1= 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2= Ph, 4-MeC_6H_4; R^3= Ph, TMS

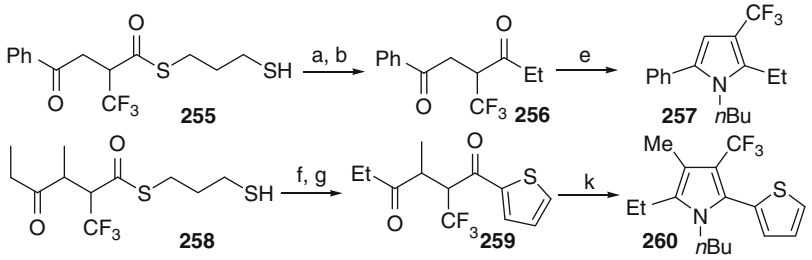
The Paal-Knorr reaction was used for the synthesis of the pyrrole **250** from methyl 4,4,4-trifluoroacetoacetate (**248**) in two steps [85]. Alkylation of **248** with 4-fluorophenacyl bromide gave the 1,4-diketone **249** in 25 % yield after decarboxylation. Its cyclization with 2-cyanoethylamine in acetic acid provided **250**,

which was used without purification in next step. Similarly, the 1,4-diketones **251** and **253** gave the pyrrole derivatives **252** [86] and a series of N-substituted pyrroles **254**, respectively [87].



248 **249** **250** **251** **252** **253** **254**

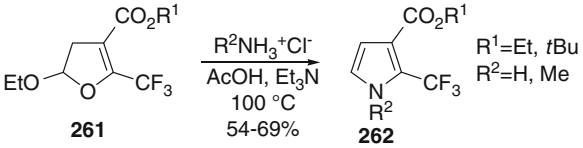
Thiol esters **255** and **258** have proved to be versatile precursors of 3-trifluoromethylpyrroles. Methylation of the mercapto groups of **255** and **258,** followed by subsequent cross-coupling reactions of the resulting thiol esters with organozinc reagents yielded 2-trifluoromethyl-1,4-diketones **256** and **259**, respectively. Classic Paal–Knorr condensation of **256** and **259** afforded highly substituted 3-trifluoromethyl five-membered heteroaromatics **257** and **260** in high yields [88].



255 **256** **257** **258** **259** **260**

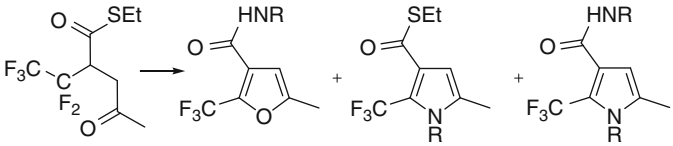
a) MeI (2 equiv), iPr$_2$EtN (2 equiv), acetone, 25°C, 8h, 80%;
b) [PdCl$_2$(PPh$_3$)$_2$] (10 mol%), EtZnI (2 equiv), toluene, reflux, 12h, 65%;
e) nBuNH$_2$ (2 equiv), Ti(OiPr)$_4$ (1.5 equiv), toluene, reflux, 10h, 81%;
f) MeI (2 equiv), iPr$_2$EtN (2 equiv), acetone, 25°C, 8h, 78%;
g) [PdCl$_2$-(dppf)] (10 mol%), (2-thienyl)ZnI·LiCl (5.6 equiv), toluene, 0°C, 1h, 87%, d.r.=3:2;
k) nBuNH$_2$ (4 equiv), Ti(OiPr)$_4$ (3 equiv), toluene, 25°C, 4h, 83%.
dppf=1,1'-bis(diphenylphosphanyl)ferrocene

A versatile approach to 2-CF$_3$-pyrroles was elaborated using dihydrofurans as masked 1,4-dicarbonyl compounds. Condensation of the dihydrofurans **261** with primary amine hydrochlorides gave the corresponding N-substituted pyrroles **262** in good yields [89].



261 **262**

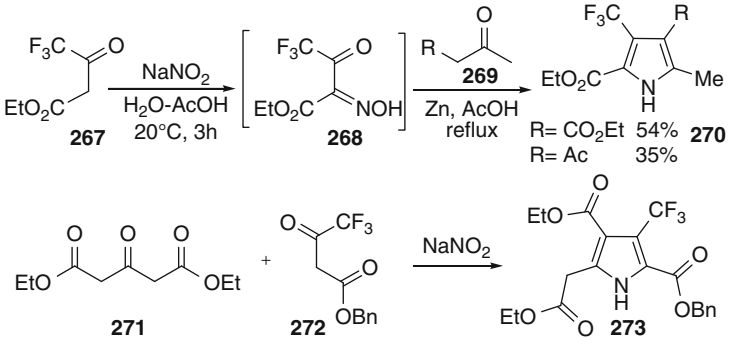
The reactions of the diketone **263** with a number of rather basic amines ($pK_a \sim 9–10$) under different conditions gave mixtures of the furans **264** and the pyrroles **265** and **266** [90]. The reactions with two equivalents of primary amines in ether afforded mixtures of products **264** and **265** (method A). Large excess of pentylamine (8 eq.) increased the yield of furan **264c** and produced the pyrrole **265c** and **266c** as minor products. Without solvent the furan **264c** was not formed and the pyrrole **266c** became the major product. Maintaining the furan **264** in excess amine without solvent at r.t. resulted in its conversion into the corresponding pyrrole **266** in 67 % yield.



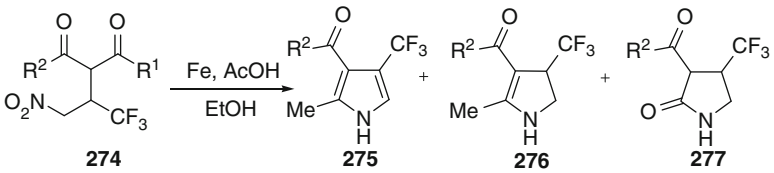
263	**264**	**265**	**266**
A: $PhCH_2$	25%	48%	-
A: *i*Pr	57%	24%	-
A: nC_5H_{11}	40%	35%	-
B: nC_5H_{11}	54%	9%	17%
C: nC_5H_{11}	-	7%	67%

A: 2 eq RNH_2, Et_2O, r.t.; B: 8 eq RNH_2, Et_2O, r.t.; C: 8 eq RNH_2, r.t.

The Knorr pyrrole synthesis was also employed for the synthesis of 3-trifluoropyrroles [91]. Treatment of ethyl trifluoroacetoacetate **267** with sodium nitrite in acetic acid led to the oxime **268**. Refluxing with zinc dust and addition of 1,3-dicarbonyl compounds **269** afforded the 3-trifluoromethylpyrroles **270** in moderate yields. Using more acidic trifluoroacetic acid allowed to lower the reaction temperature to 70 °C [92]. Using a similar approach, the tricarboxylic acid ester **273** was prepared starting from the acetone dicarboxylic acid ester **271** and the fluorinated keto ester **272** [93].

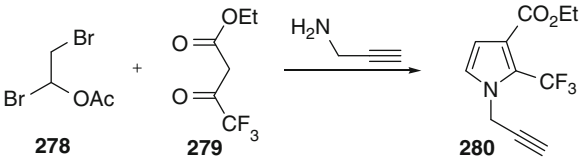


The γ-nitro ketones **274** were also used as precursors in pyrrole synthesis. The reduction of the nitro compounds **274** by iron depending on the conditions and the substrate can give pyrroles **275a,b**, dihydropyrroles **276b** or pyrrolidinones **277c**. It was also found that the di-hydropyrrole **276b** can be transformed into pyrrole **275b** in 25 % yield at reflux in nitrobenzene [94].

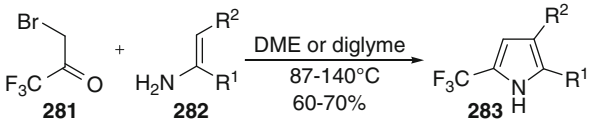


	274		**275**	**276**	**277**
a	R^1=R^2=Me	70°C	27%	-	-
b	R^1=Me, R^2=MeO	70°C	21%	36%	-
	R^1=Me, R^2=MeO	100°C	47%	-	-
c	R^1=R^2= OEt	70°C	-	-	67%

The classic Hantzsch pyrrole synthesis is based on the reaction of ketones bearing electron-withdrawing group in α-position with α-haloketones or aldehydes in the presence of amine or ammonia. For example, the condensation of the masked bromoacetaldehyde **278** with ethyl 4,4,4-trifluoroacetoacetate (**279**) and propargyl amine gave the pyrrole **280** [95]. The yield of pyrrole **280** was not given.

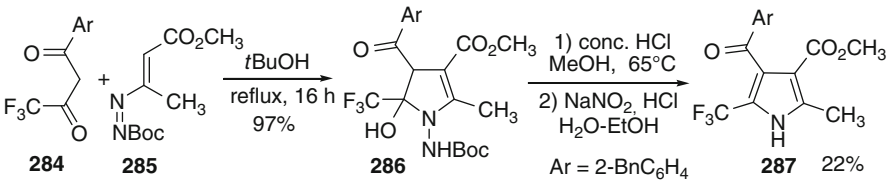


In contrast, the reaction of α-halotrifluoromethyl ketones due to the high electrophilicity of these ketones led to furans [96]. However, in order to synthesize pyrroles, the reaction of such α-haloketones has to be carried out with previously prepared enamines. So, based on reactions of the bromoketone **281** with enamines **282**, a series of 2-CF_3-pyrroles **283** was obtained in good yields [96].

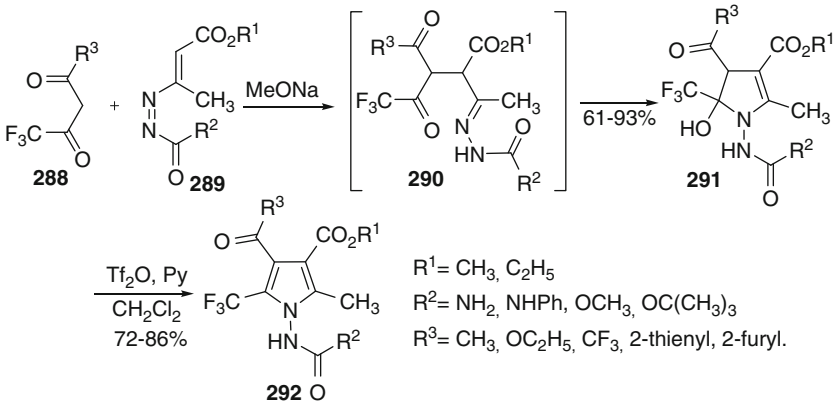


R^1= Me, Ph, 4-ClC_6H_4, 4-MeC_6H_4; R^2= CN, CO_2Me

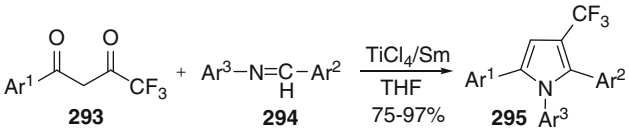
The aim of the following work [97] was the synthesis of the trifluoromethyl analogue **287** of FPL 64176, which is a calcium channel activator. Key step of the synthesis was the reaction of diketone **284** with the azoalkene **285** in refluxing *tert-butanol*. The reaction gave the hydroxypyrroline **286** in quantitative yield. Subsequent treatment with hydrochloric acid followed by reaction with $NaNO_2$ converted the hydroxypyrroline **286** into the target pyrrole **287**.



The reaction of the 1,3-diketones **288** with the azoalkenes **289** led regioselectively to the dihydropyrroles **291** in high yields via the intermediates **290** [98]. The compounds **291** are stable and can be isolated in pure form, but they lost easily water by treatment with triflic anhydride to form the pyrroles **292** [99].

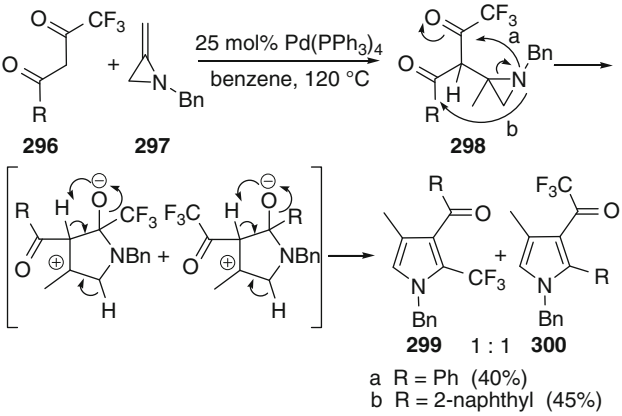


A novel coupling cyclization reaction of 1,3-diketones with imines was applied for the synthesis of polyaryl substituted 3-trifluoromethylpyrroles. The reaction was promoted by a low-valent titanium reagent and afforded the pyrroles **295** in high to quantitative yields. A number of 1,3-diketones **293** and imines **294** provided a variety of pyrroles **295**, bearing different combinations of electron-donating, as well as electron-withdrawing substituents in aromatic rings [100].

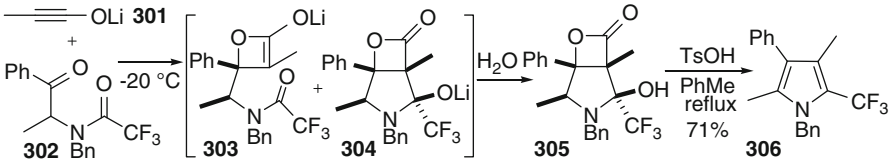


Ar^1=Ph, 2-thienyl; Ar^2, Ar^3=4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3,4-di$MeOC_6H_3$, 4-ClC_6H_4, 4-FC_6H_4, 3-Cl-4-$MeOC_6H_3$, 4-MeC_6H_4

The Pd(0)-catalyzed reaction of the unsymmetrical 1,3-diketones **296a** and **296b** with *N*-benzylmethyleneaziridine **297** produced the corresponding 2-trifluoromethylpyrroles **299a** or **299b** in moderate yields as 1:1 mixture with trifluoroacetylpyrroles **300a** or **300b** via the intermediate aziridine **298**, which rearrange on pathway **a** or **b** to pyrroline cations to give the products **298** and **300** [101].

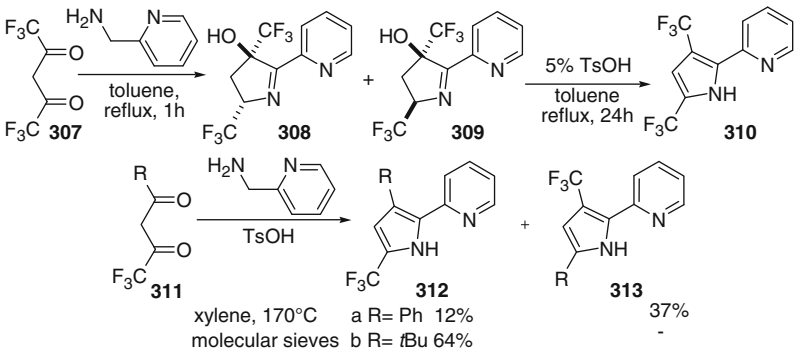


An efficient synthetic method for the preparation of polysubstituted furans, thiophenes and pyrroles using ynolates was developed by Shindo et al. [102]. The cycloaddition of ynolate **301** to amidoketone **302** gave the oxetene **303**, which formed the bicyclic β-lactone **304** by cyclization. Aqueous workup afforded **305**, which was converted to the final 2-trifluoromethylpyrrole **306** in 71 % yield by dehydration with TsOH. The ynolate **301** was prepared *in situ* by treatment of ethyl 2,2-dibromopropanoate with *t*-BuLi at −78 °C.

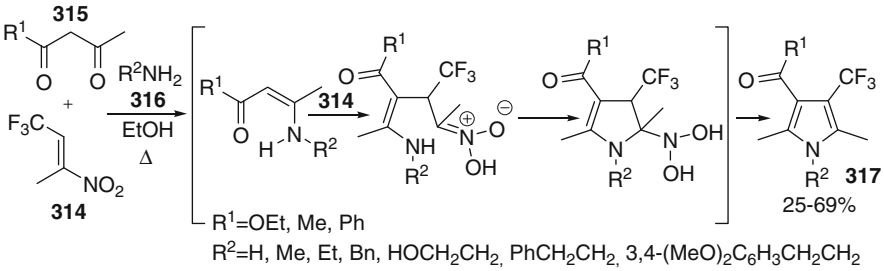


Furthermore, bistrifluoroacetylmethane (**307**) at heating with 2-picolylamine gave a mixture of the diastereomeric dihydropyrroles **308** and **309** in high overall yield [103]. The ratio of the diastereomers depends on the acidic catalyst and the reaction time. Complete dehydration of **308** and **309** resulted in the formation of the pyrrole **310** after 24 h at reflux using *p*-toluenesulfonic acid as catalyst. Similarly, the 1,3-diketone **311a** (R = Ph) gave an 1:3 mixture of the pyrroles **312a** and **313a**, while **311b** (R = *t*-Bu) gave **312b** as the sole product [104]. It should be noted, that 2-(aminomethyl)pyridine appears to be the only amine, which participated in such

a transformation. Neither other isomeric (aminomethyl)-pyridines nor benzylamine reacted in this way.

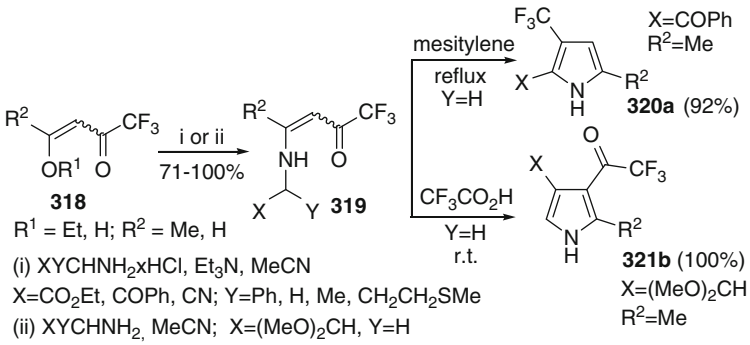


It was shown that the three-component Grob cyclization of (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **314** with 1,3-dicarbonyls **315** and primary aliphatic amines **316** provides a simple and convenient approach to substituted 4-(trifluoromethyl)pyrroles **317** bearing different electron-withdrawing substituents at the 3-position. Mild conditions and readily available starting materials are distinct advantages of the approach [105].

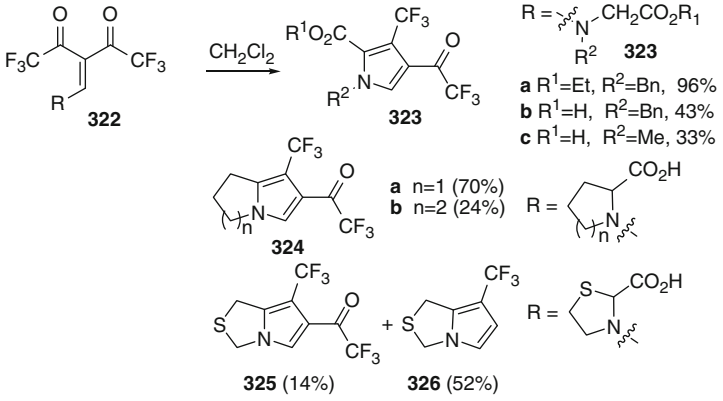


2.2.5 Synthesis Based on α,β-Unsaturated Trifluoromethyl Ketones

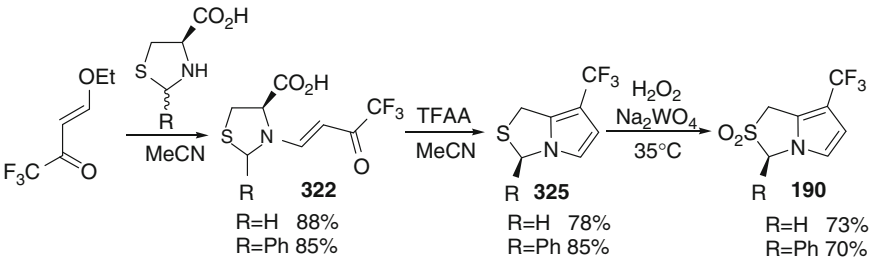
α,β-Unsaturated trifluoromethyl ketones such as **319** were found to be very useful building blocks for the construction of pyrroles [106]. For example, the enaminoketones **319**, which can be prepared in high yields from the enol ethers **318**, gave the 3-trifluoromethylpyrroles **320** or 3-trifluoroacetylpyrroles **321** depending on the reaction conditions [107]. Thus, the cyclization of **319a** afforded the pyrrole **320a** in high yield at reflux in mesitylene, while at standing in trifluoroacetic acid at room temperature the pyrrole **321b** was formed. It should be mentioned, that non-fluorinated analogs of **319** gave 1:1 mixtures of the corresponding pyrroles under these conditions.



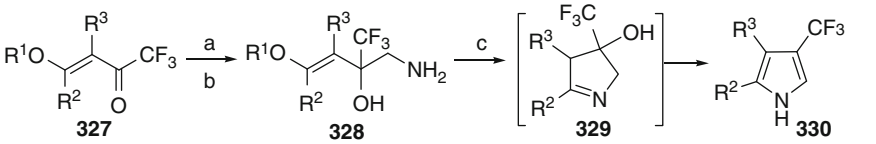
A convenient pathway towards the 3-trifluoromethyl-pyrroles **323** starts from enaminodiketones **322** prepared *in situ* from amino acid derivatives. The derivative of *N*-benzylglycine ethyl ester gave the pyrrole **323a** quantitatively [108]. In the case of *N*-methyl- and *N*-benzylglycine the corresponding pyrroles **209b** and **209c** were obtained in 43 % and 33 % yields. Cyclic amino acid derivatives afforded the bicyclic derivatives **324a** (from proline) and **324b** (from pipecolic acid). In both cases decarboxylation occurred in the aromatization step. Finally, the reaction of a thioproline derivative gave a mixture of pyrroles **325** and **326** [109].



A simple changing of solvent from dichloromethane to acetonitrile allowed to prepare **325** exclusively in higher yield. Compounds **212** were converted into dioxothiazoles **190** by catalytic oxidation and then used as a precursor for generation of azafulvenium methides acting as 1,3-dipols (see Sect. 2.2.3) [73].



Another example dealing with α,β-unsaturated ketones was reported by Gerus et al. [110]. Ketones **327** were smoothly converted to cyanohydrins by treatment with TMSCN, which on reduction with $LiAlH_4$ afforded the aminoalcohols **328**. Acid catalyzed intramolecular cyclization gave **329**, which by dehydration gave the pyrroles **330** generally in good yields.



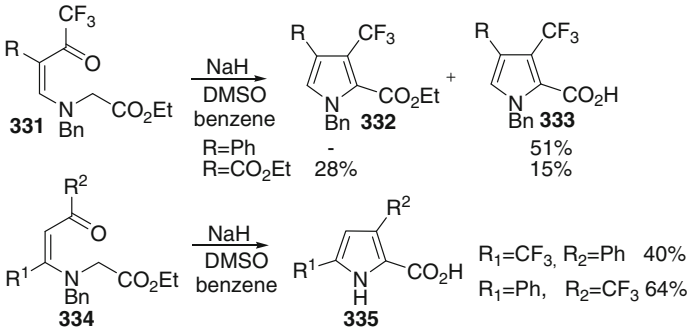
R^1=Me, Et

a: TMSCN, Et_3N, 0-10 °C R^2=H, R^3=H 65%; R^2=Me, R^3=H 55%

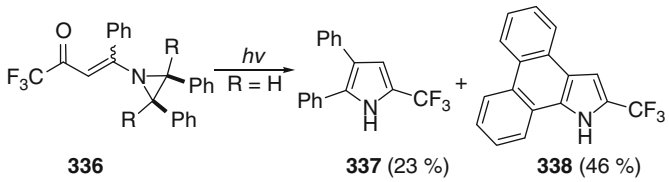
b: $LiAlH_4$, ether, 0-5 °C R^2=H, R^3=Br 5-10%; R^2=Ph, R^3=H 90%

c: HCl, H_2O, MeCN, r.t.

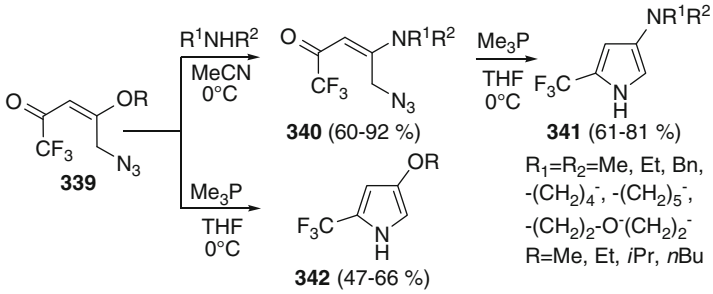
A number of *N*-benzylated 2- and 3-trifluoromethylated pyrroles were prepared using enaminoketones. Accordingly, the treatment of **331** or **334** with NaH-DMSO in benzene led to the corresponding pyrroles **332** and **333** or **335**, respectively, in moderate yields [111].



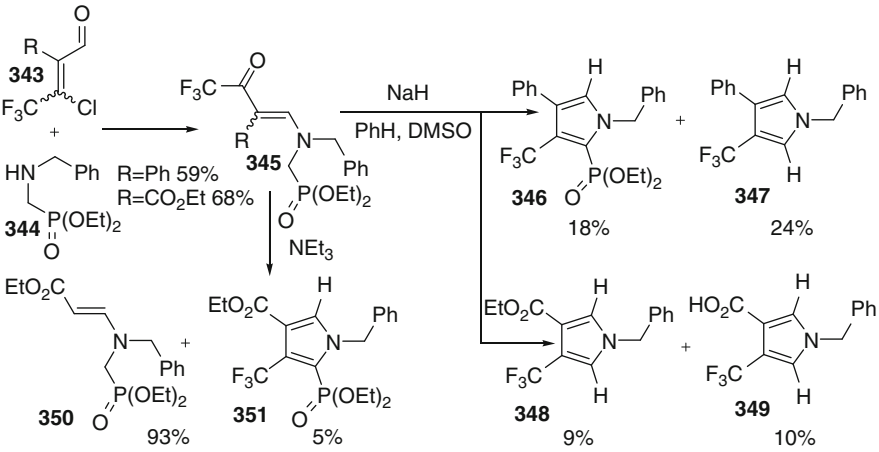
The photolytic rearrangement of aziridine derived enaminoketones **336** was used for the synthesis of a mixture of diphenylpyrrole **337** and dibenzoindole **338** [112].



The 2-trifluoromethylpyrroles **341** and **342** were obtained in high yields starting from **339**. Reaction of the alkoxy azide **339** with a variety of secondary amines formed **340**. Subsequent reduction with trimethylphosphine and cyclizing dehydration gave **341**, while direct reduction of **339** and cyclization led to **342** [113].

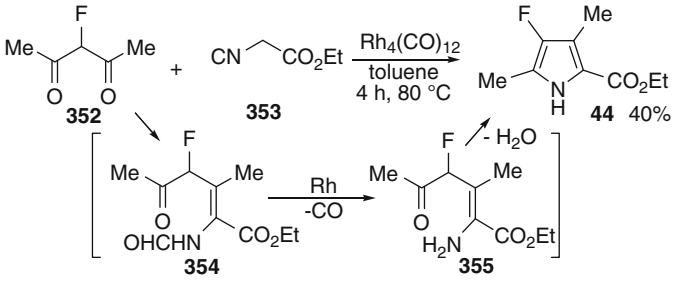


The reaction of ketones **343** with phosphorus analogue of *N*-benzylglycinate **344** allowed to prepare the enaminoketones **345** in good yields. Treatment of **345** with bases led to 3-trifluoromethyl-2-phosphonopyrroles **346** and **351** in low yields via 5-exo-trig cyclization. Formation of nonphosphorylated pyrroles **347** and **349** was also observed making this method less synthetically valuable [114].

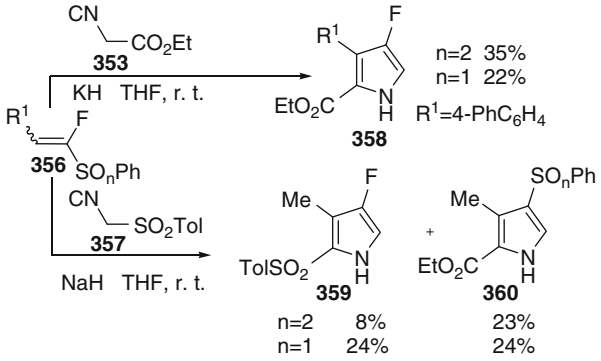


2.2.6 Synthesis Based on Isocyanides

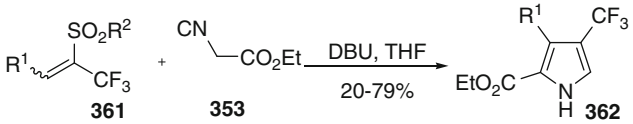
Rhodium catalyzed reactions of ethyl isocyanoacetate **353** with 3-fluoroacetylacetone **352** provides a new facile method for the catalytic synthesis of substituted pyrroles. The key step of the reaction is the activation of the C-H bond of isonitrile **353** induced by the α-heteroatom effect. 3-Fluoropyrrole **44** was obtained in 40 % by this method [115]. The mechanism of the transformation includes rhodium promoted decarbonylation of formamide **354** followed by cyclocondensation of intermediate **355** to form the corresponding pyrrole **44**.



3-Fluoropyrroles **358, 359** were synthesized using addition of isocyanomethylide anions to α-fluoroalkenyl sulfones and sulfoxides **356**. The addition of isocyanoacetate **353** led regioselectively to ethyl 3-fluoropyrroles **358** in moderate yields. In contrast, the addition of tosylmethylisocyanide **357** afforded a mixture of 4-fluoro-3-methyl-2-tosyl-1H-pyrrole **359** with non-fluorinated pyrrole derivative **360** [116].

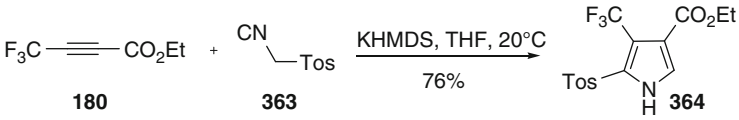


Convenient approach to 3-CF_3-pyrroles is also based on the condensation of electron-deficient alkenes with isocyanomethylide anions. A wide range of pyrroles **362** was synthesized from α-trifluoromethyl(vinyl-sulfones) **361** and ethyl isocyanoacetate **353** [117].

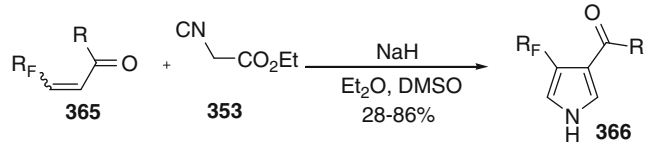


R^1=Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, C_6F_5, 2,6-$Cl_2C_6H_4$, 2-thiophene, CO_2Et, CN; R^2=Ph, *n*-C_6H_{13}

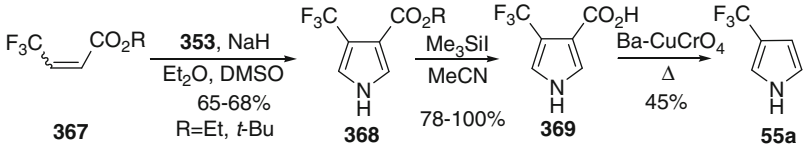
Ethyl 3-trifluoromethylacetylenecarboxylate (**180**) and toluenesulfonylmethyl isocyanide (TOSMIC) **363** provided the 3-CF_3-pyrrole **364** containing a tosyl group in 2-position [118].



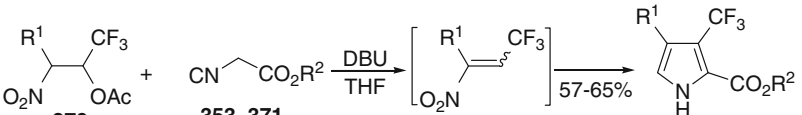
The reaction of perfluoroalkyl substituted α,β-unsaturated ketones **365** or β-trifluoromethylacrylates **367** with ethyl isocyanoacetate **353** gave 3-acylpyrroles **366** [119] or 3-pyrrolylcarboxylates **368** [120] in one step. Subsequent treatment of **368** with trimethylsilyl iodide afforded the acid **369**, which after pyrolysis at copper chromite gave the unsubstituted 3-trifluoromethylpyrrole **55a**.



R=Ph, 4-$CO_2MeC_6H_4$, 4-$CO_2HC_6H_4$, Me, MeO; R_F= CF_3, $CF_2CF_2CF_3$



The reaction of trifluoromethyl substituted β-acetoxy-α-nitroalkanes **370** with isocyanoacetates **353, 371** in the presence of DBU gave the 3-trifluoromethylpyrroles **373** in good yields via the nitroalkenes **372** [121]. The yield was increased up to 100 % employing two equivalents of an even stronger non-nucleophilic base [122].

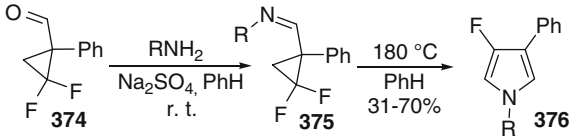


R^1=Me, Et; R^2=Et, *t*-Bu

So, application of isocyanides is one of the best methods for synthesis of fluorinated pyrroles due to high yields, simplicity and mild reaction conditions.

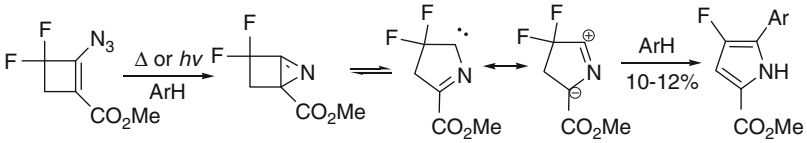
2.2.7 Miscellaneous Approaches to Fluoropyrroles

Thermal rearrangement of N-alkyl- and N-aryl-(2,2-difluoro-1-phenylcyclopropyl) methyleneamines **375** into N-substituted 3-fluoropyrroles **376** was reported by Kagabu. The transformation at high temperature gave regioselectively the corresponding 3-fluoropyrroles **376** in moderate to good yields. Using this method both N-alkyl- and aryl derivatives of pyrrole can be prepared [123].



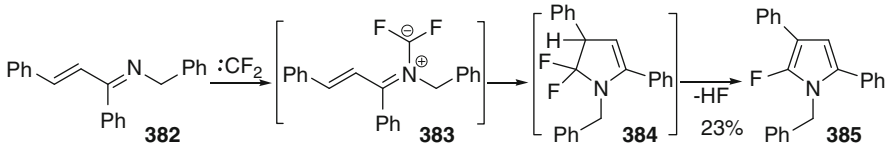
R= Ph, *n*-Bu, *t*-Bu, *cyclo*-Hex, 1-Naphtyl, $Ph(CH_3)_2C$, $4\text{-}MeOC_6H_4CH_2$

An interesting cyclobutene ring expansion reaction was found by Buhr. Being heated or irradiated by UV light, methyl 2-azido-3,3-difluorocyclobut-1-enecarboxylate **377** extrudes nitrogen to give highly strained azirine **378**, which transforms into azomethine ylide **380** through the carbene **379**. The last step of the transformation is the reaction of ylide **380** with solvents leading to methyl 4-fluoro-5-aryl-1H-pyrrole-2-carboxylates **381** in low yield [124].

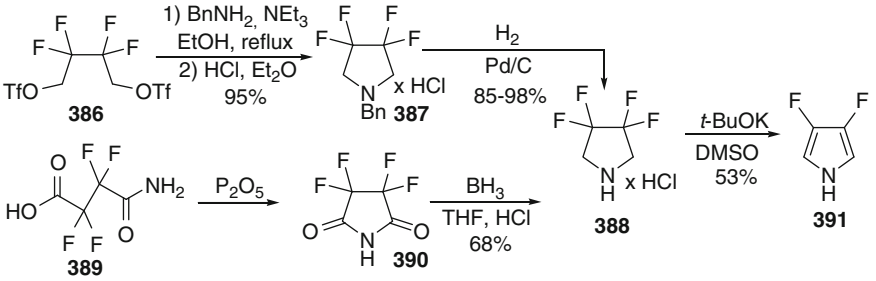


ArH= PhH, furan, mesitylene, 1,4-dimethoxybenzene

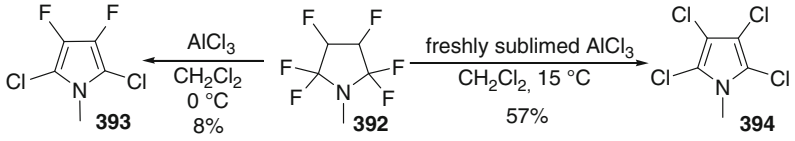
The reaction of azadiene **382** with difluorocarbene gives fluoropyrrole **385** as a major product. Difluorocarbene was generated by reduction of dibromodifluoromethane with active lead in dichloromethane in the presence of tetrabutylammonium bromide under ultrasound irradiation. A possible mechanism includes the formation of difluoroazomethine ylide **383**, 1,5-cyclization of the latter into difluoropyrroline **384**, and subsequent HF elimination [125].



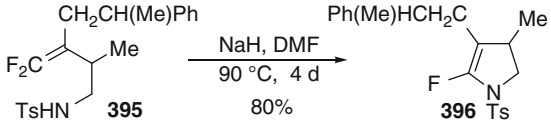
t-BuOK in DMSO was found to be the most efficient basic system for the elimination of HF from **388** to prepare 3,4-difluoropyrrole **391** [43]. Tetrafluoropyrrolidine **388** was prepared starting from **386** or **389**. Thus, **386** was converted into **387** by nucleophilic substitution with benzylamine. Next, **387** was debenzylated by treatment with hydrogen on Pd/C to give **388** [126]. Another pathway to **388** is reduction of tetrafluoromaleimide **390** obtained by cyclization of **389** under P_2O_5 [127].



An interesting transformation was found by Tatlow et al. 1-Methyl-2,5-dichlorodifluoropyrrole **393** was obtained in low yield by treatment of 1-methyl-3H,4*H*-hexafluoropyrrolidine **392** with "old" aluminium chloride, which was of a normal reagent grade. In contrast, using freshly sublimed aluminium chloride gave 1-methyltetrachloropyrrole **394** in good yield [128].



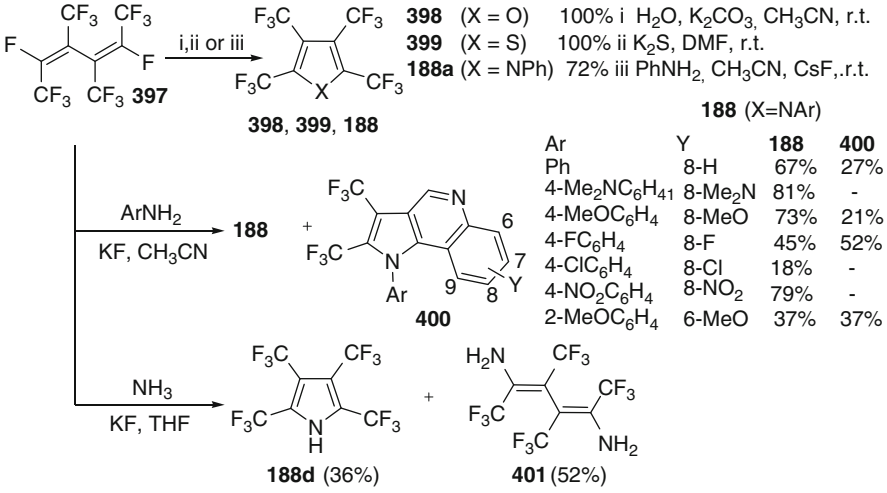
5-Endo-trig cyclizations can be applied for 2-fluoropyrroles synthesis. Thus, treatment of *N*-(3-(difluoromethylene)-2-methyl-5-phenylhexyl)-4-toluenesulfonamide **395** with base provided 5-fluoro-3-methyl-4-(2-phenylpropyl)-1-tosyl-2,3-dihydro-1*H*-pyrrole **396** in 80 % yield [129].



2.2.8 Miscellaneous Approaches to Trifluoromethylpyrroles

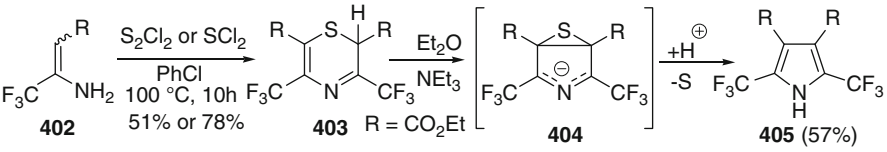
The perfluorohexa-2,4-diene **397** was revealed to be a very useful building block for the preparation of tetrasubstituted pyrroles, thiophenes and furans. Thus, the derivatives **398**, **399**, and **188a** were formed at room temperature [130]. Replacement of the

base by potassium fluoride (in the case of anilines) led to the pyrroloquinolines **400** among other reaction products [131]. Surprisingly, the reaction of the diene **397** with ammonia in the presence of potassium fluoride gave the pyrrole **188d** besides open chain the diaminodiene **401** [130].

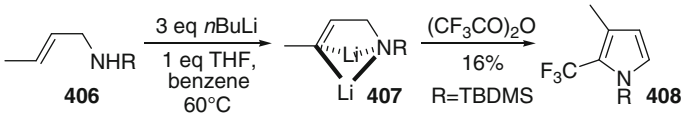


Ar	Y	188	400
Ph	8-H	67%	27%
4-$Me_2NC_6H_{41}$	8-Me_2N	81%	-
4-$MeOC_6H_4$	8-MeO	73%	21%
4-FC_6H_4	8-F	45%	52%
4-ClC_6H_4	8-Cl	18%	-
4-$NO_2C_6H_4$	8-NO_2	79%	-
2-$MeOC_6H_4$	6-MeO	37%	37%

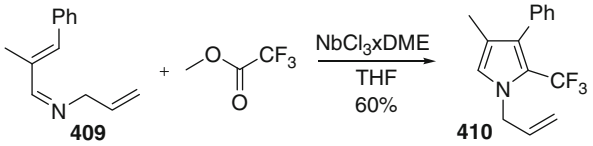
An interesting approach to polysubstituted pyrroles was elaborated based on the enamine **402**, which on heating with S_2Cl_2 or SCl_2 in chlorobenzene led to the thiazine **403** in good yields [132]. Subsequent refluxing of **403** with triethylamine in ether afforded the pyrrole **405** in 57 % yield by sulfur extrusion from the intermediate **404** and acidic workup. Employing one pot technique, the pyrrole **405** was synthesized in 56 % overall yield calculated on the enamine **402**. Other bases (LDA, *s*-BuLi, KH, EtONa) can also be used for conversion of **403** to **405** [133].



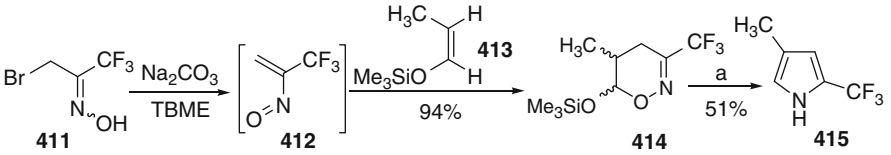
The allylamine **406** was deprotonated with three equiv. of *n*-BuLi using one equivalent of THF as accelerator (benzene, 60 °C) to give the intermediate **407**, which on treatment with trifluoroacetic acid anhydride led to the pyrrole **408** in 16 % overall yield [134].



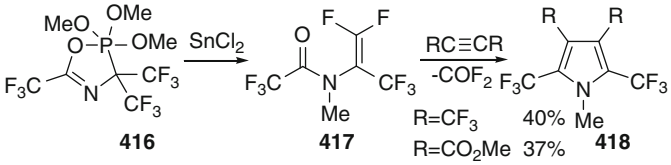
Coupling of the imine **409** with 500 fold excess of methyl trifluoroacetate proceeded smoothly at room temperature in the presence of equimolar amount of the $NbCl_3 \cdot DME$ complex, giving the pyrrole **410** in 60 % yield [135].



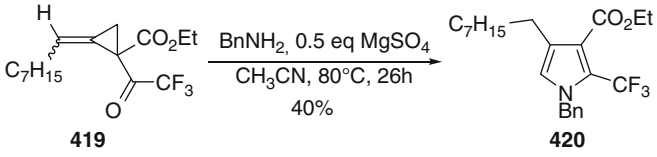
The 1,1,1-trifluoro-2-nitroso-2-propene **412** generated *in situ* by treatment of the α-bromooxime **411** with sodium carbonate, on reaction with the silyl ether **413** gave the 5,6-dihydro-4*H*-1,2-oxazine **414**, which was transformed to the target pyrrole **415** in 51 % yield by treatment with $Mo(CO)_6$ in acetonitrile in the presence of trifluoroacetic acid [136].



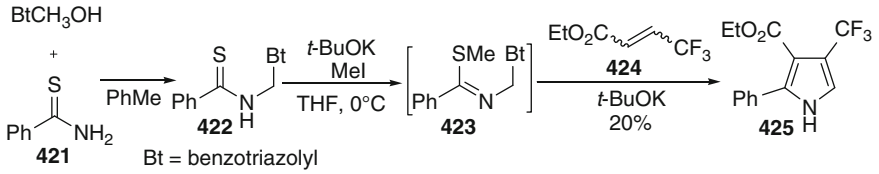
Furthermore, the reaction of the orthophosphonate **416** with $SnCl_2$ gave the trifluoroacetic enamide **417**, which reacted with acetylenes to afford the 2,5-bistrifluoro-methylpyrroles **418** in moderate yields [137].



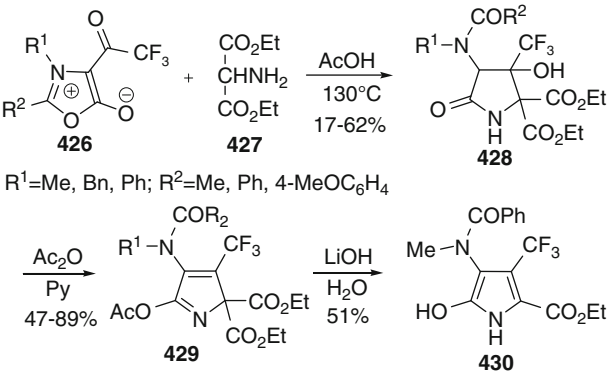
The 2-trifluoromethylpyrrole **420** connected with a long-chain alkyl group in 4-position was obtained in one step in 40 % yield from alkylidenecyclopropyl ketone **419** with excess of benzylamine in the presence of $MgSO_4$ as an additive [138].



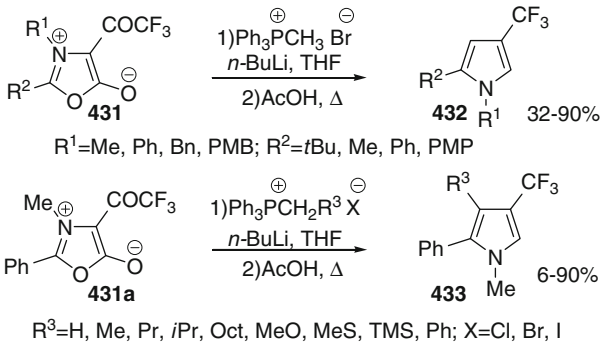
An efficient one-pot pyrrole synthesis was elaborated by Katritzky et al. [139]. The addition of *S*-methylthioimidate **423** to ethyl β-trifluoromethylacrylate **424** was the key step of the reaction leading to **425**. The intermediate **423** was readily prepared from thioamide **421** in two steps via **422**.



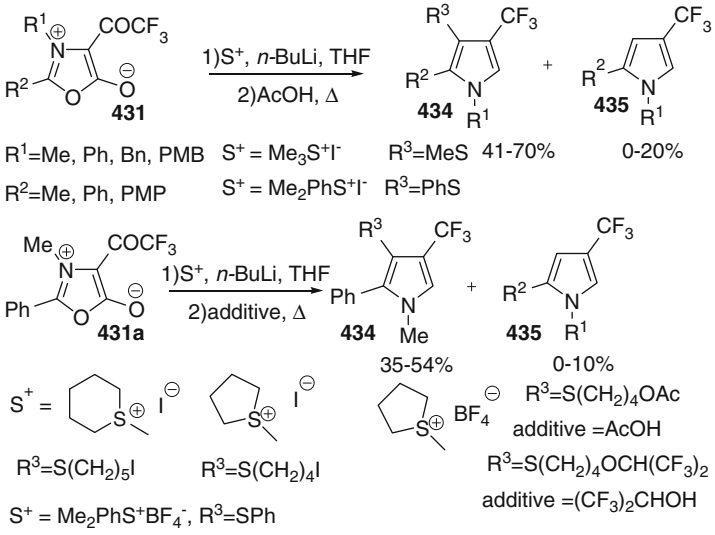
As it was mentioned previously, mesoionic oxazolones were used as dipolarophiles in the synthesis of 2-CF_3-pyrroles. A tandem addition of 1,2-binucleophiles to oxazolones also led to pyrroles, but bearing the CF_3-group in 3-position. For instance, the reaction of the oxazolones **426** with aminomalonate **427** gave the pyrrolidine derivative **428**, which formed **429** by reaction with acetic anhydride. Treatment of **429** with lithium hydroxide resulted in a decarboxylation giving the pyrrole **430** [140].



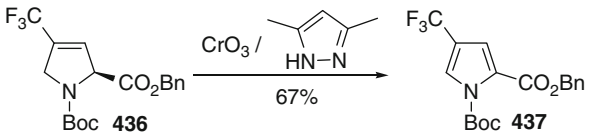
Efficient pathway towards 3-CF_3-pyrroles was elaborated using condensation of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **431** with phosphorus ylides. Target pyrroles **432**,**433** with big variety of substituents were easily obtained in the yields up to 90 %. The principal advantage of the method is flexibility in the type of substituents in the pyrrole ring which can be readily achieved by choosing the appropriate N-acyl-N-alkylglycines (precursors of **431**) as the starting material and also the ylides [141].



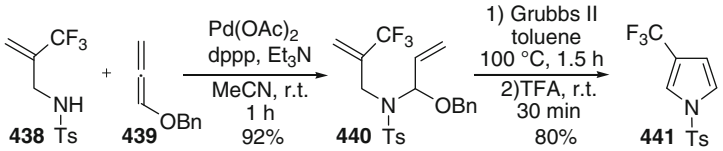
The use of sulfur ylides in the synthesis of trifluoromethylpyrroles from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **431** is prove to be also valuable. Reactions proceed to give alkyl(aryl)thio-4-trifluoromethylpyrroles **434** in good yields with an admixture of non-sulfur pyrroles **435** in small amounts [142].



Qiu and co-workers failed to oxidize the dihydropyrrole **436** to the α,β-unsaturated lactam with CrO_3 in pyridine. Instead, the oxidation in the presence of dimethylpyrazol provided the 3-trifluoromethyl-pyrrole **437** in good yield [143].

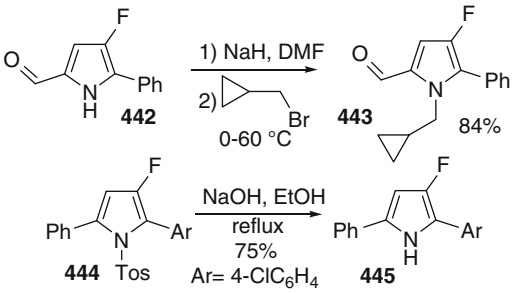


An interesting pathway towards the *N*-tosylated 3-trifluoromethylpyrrole **441** was developed by Rutjes et al. [144]. The palladium catalyzed addition of benzyloxyallene **439** to sulfonamide **438** led to the *N*,*O*-acetal **440** in excellent yield. Subsequent, treatment of **440** with the Grubbs II catalyst followed by acid workup gave the *N*-tosylpyrrole **441** in 80 % yield.

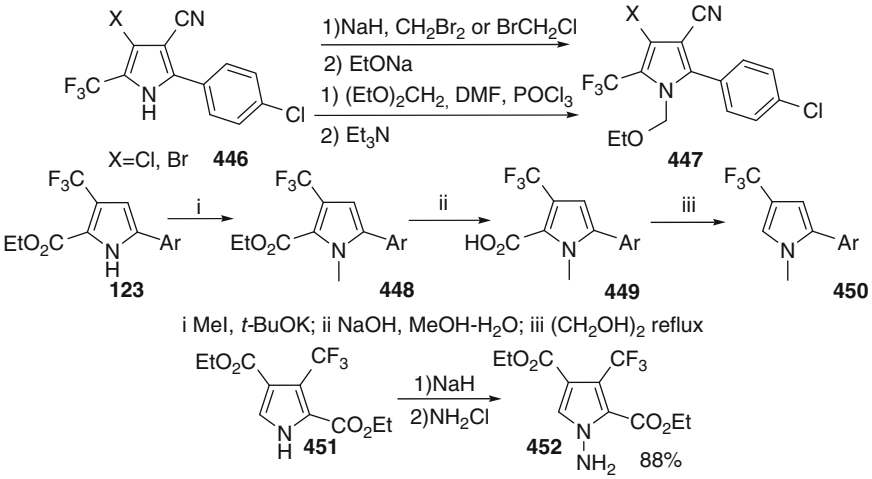


3 Properties and Some Applications of Fluorinated Pyrroles

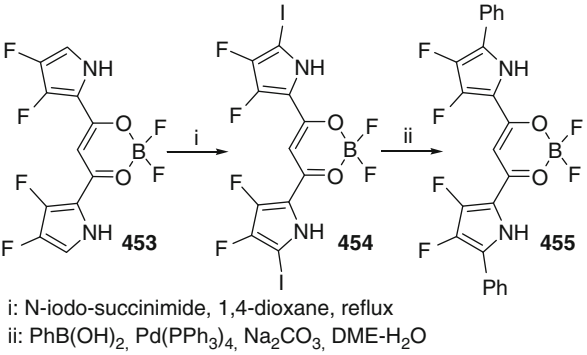
There are not too much examples of fluorinated pyrroles reactivity. Nevertheless one can easily conclude that fluoropyrroles have very similar chemistry in comparison to other pyrroles. Thus, fluorinated pyrrole **442** can be N-alkylated by treatment with alkyl bromides [18]. Inverse process is possible for N-tosyl derivative **445** under basic workup [84].



Trifluoromethylpyrroles were also alkylated. Alkylation of pyrroles **446** led to N-ethoxymethyl derivatives **447** [145, 146]. Similarly, N-methyl derivative of pyrrolecarboxylic ester **448** was obtained, which was further hydrolyzed and decarboxylated [55]. Reaction of **451** with NH_2Cl afforded N-aminopyrrole **452** in 88 % yield [147].

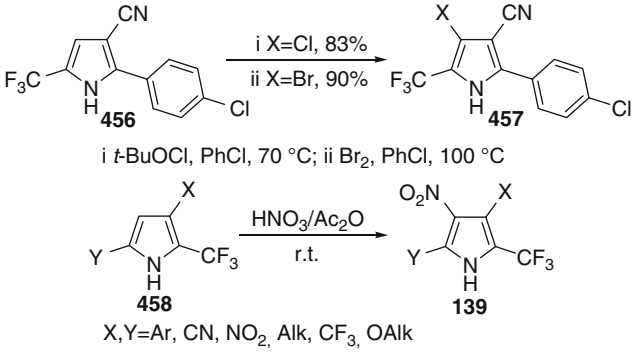


Due to electron-donating properties of pyrrole ring, fluorinated pyrroles react smoothly with electrophiles to give the corresponding functionalized derivatives. Thus, iodination of **453** was carried out under treatment with N-iodo-succinimide in refluxing 1,4-dioxane. Diiododerivative **454** prepared in this way was coupled with phenylboronic acid to give the corresponding polyaromatic compound **455** in 20 % yield under Suzuki reaction conditions [148].

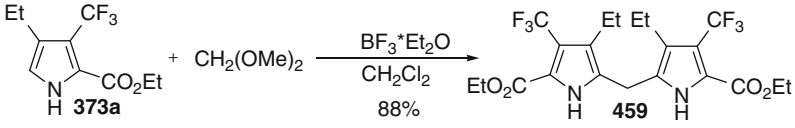


Chlorination and bromination of trifluoromethylpyrroles were carried out by treatment with *t*-BuOCl and Br_2 correspondingly. Deactivating influence of CF_3- and

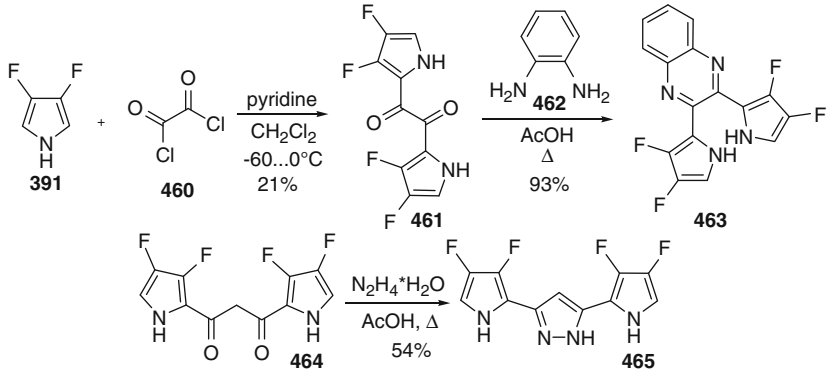
cyano groups explains, why heating was used for halogenation of pyrrole **456** [149]. Nitration of **458** was achieved using acetylnitrate [61].



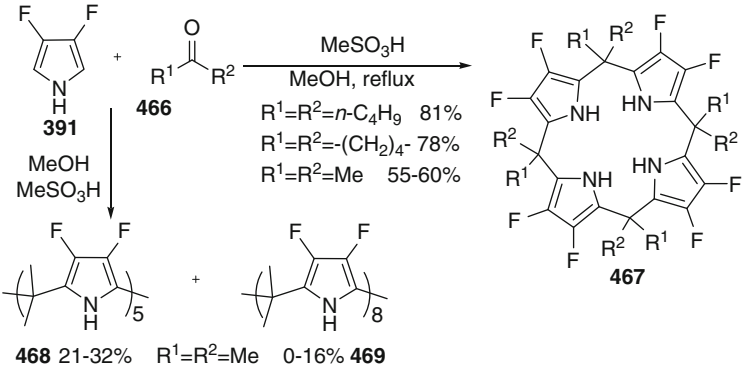
Several efforts were done to perform C-alkylation of pyrrole **373a** by dimethoxymethane [122]. Then PTSA was used as catalyst, about 10 days are needed for full conversion. Using of $(CH_2O)_n$ in EtOH does not lead to pyrrole **459** at all. Nevertheless, using of BF_3xEt_2O in dichloromethane allowed to prepare compound **459** in high yield.



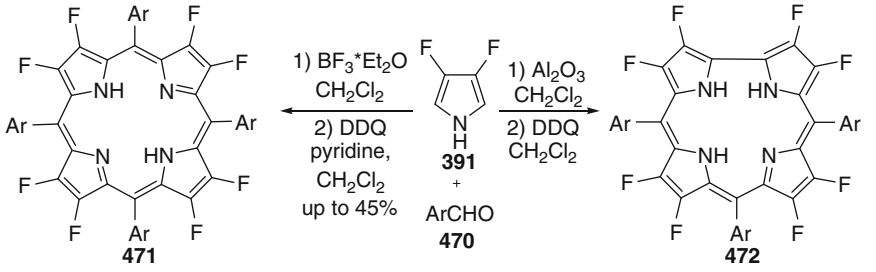
Reaction of 3,4-difluoropyrrole **391** with oxalyl chloride **460** led to the corresponding 1,2-diketone **461**, which was transformed into quinoxaline **463** in high yield by the reaction with 1,2-phenylenediamine **462** [150]. Using reaction of 1,3-diketone **464** with hydrazine, fluorinated dipyrrolylpyrazole **465** was prepared in good yield [151].



The reaction of 3,4-difluoropyrrole **391** with aliphatic ketones **466** afforded fluorinated calix[n]pyrroles. Different fluorinated macrocyclic compounds of this type were prepared using this approach by careful variation of concentration, temperature, and reaction time. Calix[4]pyrrole **467** and calix[5]pyrroles **468** can be prepared as sole products. In contrast, calix[8]pyrrole **469** is always obtained as a mixture with calix[5]pyrrole **468**. Calix[4]pyrroles **467** act as neutral anion receptors and were found to bind anions such as fluoride, chloride, or dihydrogen phosphate with an enhanced affinity compared to their non-fluorinated analogues [150, 152].

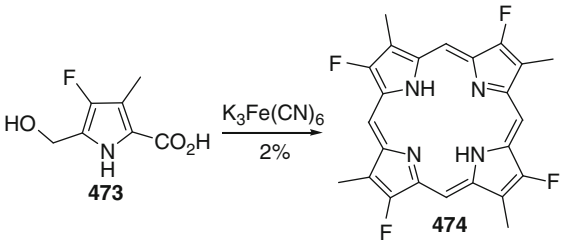


Reaction of 3,4-difluoropyrrole **391** with benzaldehydes **470** followed by oxidation with DDQ led to tetraarylporphyrins **471**. On the base of that reaction sequence a convenient and common pathway towards β-octafluoroporphyrins **471**, bearing meso-tetraaryl substituents, including perfluorinated tetraarylporphyrin was elaborated [153]. In the case of Al_2O_3 catalysis the first step of above mentioned sequence afforded β-octafluorocorroles **472** instead of porphyrins **471** [154].

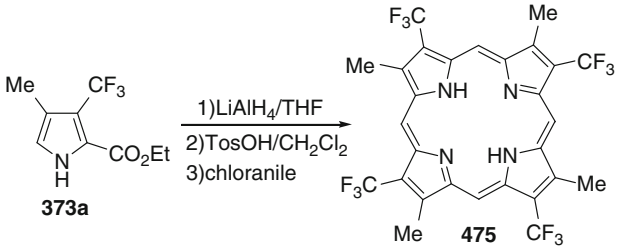


Alternatively fluorinated porphyrin **474** was synthesized by oxidation of 4-fluoropyrrole **473** with $K_3Fe(CN)_6$. The target tetrafluoroporphyrin **474** was prepared in poor yield, however [23]. It should be noted, that due to the high

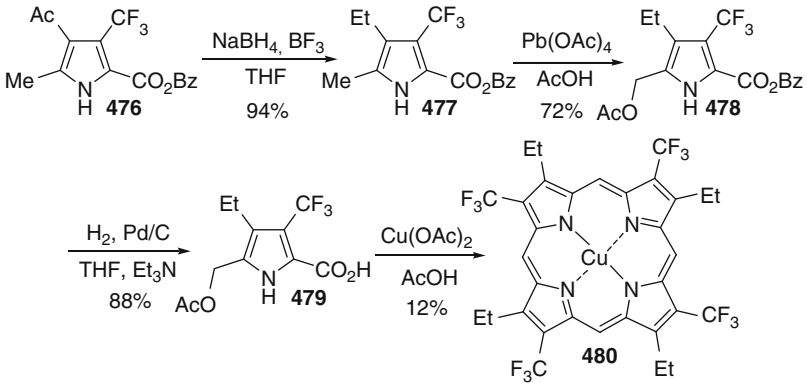
electronegativity of fluorine, fluorinated porphyrins became a valuable tool for the investigation and understanding of the electronic effects in porphyrin structure, opening new horizons for their application.



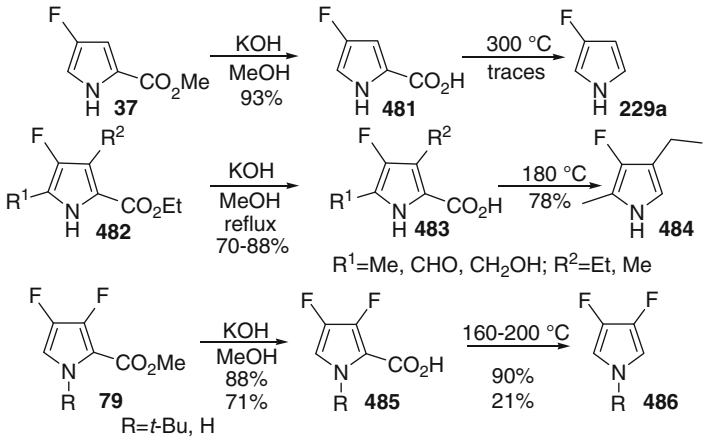
3-Trifluoromethylpyrroles were also used in the fluorinated porphyrins synthesis [121]. Thus, porphyrin **475** was prepared in three steps starting from pyrrole **373a**. At first step reduction of carboxyethyl group was performed. Next, intermolecular alkylation takes place to form CH_2-bridged precursor of porphyrin under PTSA catalysis. The last step is aromatization under treatment with chloranile.



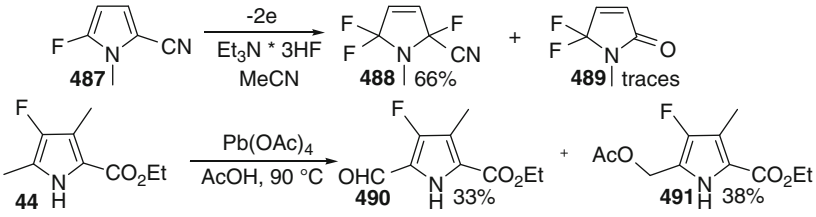
The key step of another porphyrin synthesis is template assembling of the porphyrin core at copper acetate, accompanying with decarboxylation. Starting from pyrrole **476**, porphyrin **480** was prepared in few steps [155, 156].



Other part of fluorinated pyrroles chemistry is connected with chemistry of functional groups transformation attached to fluorinated pyrrole ring. Pyrrole carboxylic acid esters can be easily transformed into acids by alkaline hydrolysis. Pyrrole carboxylic acids undergo decarboxylation at 160–200 °C [23, 157] 3,4-Difluoropyrrole **79** with nitrogen atom, protected with *tert*-butyl group, gave higher yield at decarboxylation step to compare with non-protected one. Unfortunately, only traces of parent 3-fluoropyrrole **229a** were isolated using this method [15]. Nevertheless, this two step transformation represents simple and straightforward approach to fluoropyrroles with unoccupied α-position, which are useful starting materials in synthesis of porphyrins [43].

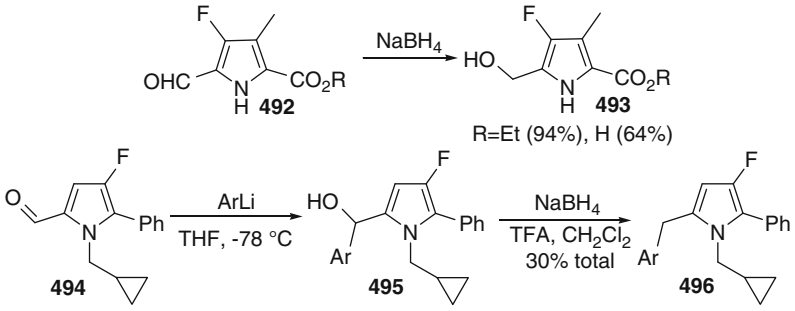


Oxidation and reduction reactions in series of fluorinated pyrroles were also reported. Anodic oxidation of 5-fluoro-1-methyl-1H-pyrrole-2-carbonitrile **487** in acetonitrile in the presence of $Et_3N \cdot 3HF$ complex afforded 2,5,5-trifluoro-1-methyl-2,5-dihydro-1H-pyrrole-2-carbonitrile **488** with traces of 5,5-difluoro-1-methyl-1H-pyrrol-2(5H)-one **489**. α-Methyl group in ethyl 4-fluoro-3,5-dimethyl-1H-pyrrole-2-carboxylate **44** can be selectively oxidized by $Pb(OAc)_4$ in the presence of β-methyl group. The reaction led to a mixture of aldehyde **490** and acetate of the corresponding alcohol **491** in high total yield [23].

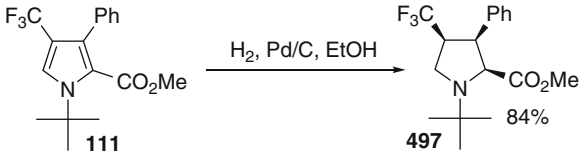


Reduction of 2-formylpyrroles **492** was carried out using $NaBH_4$ in THF to give alcohols **493** in good to high yields [23]. Such alcohols can be further reduced by

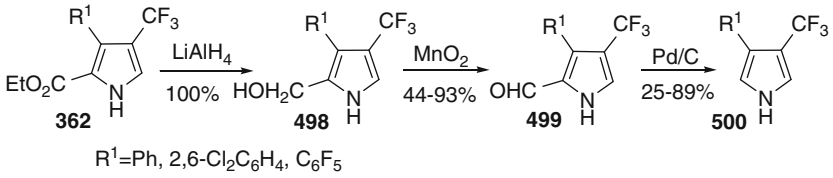
treatment with $NaBH_4$ in CH_2Cl_2 in the presence of TFA. Thus, alcohol **495** obtained by addition of aryllithium to fluorinated pyrrole carbaldehyde **494**, was converted into pyrrole **496** in 30 % total yield [18].



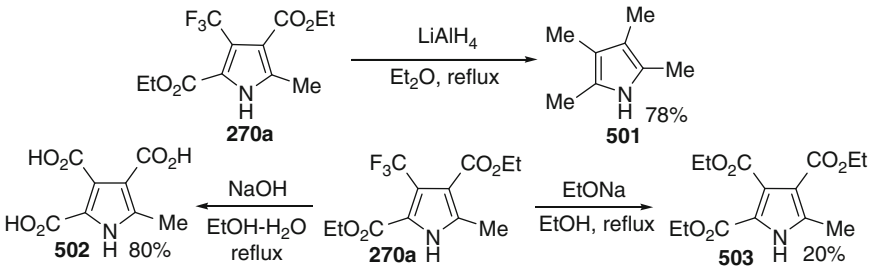
Heterocyclic core of trifluoromethylpyrrole **111** was smoothly reduced by hydrogen under Pd catalysis in EtOH. Pyrrolidine **497** was isolated as the only diastereomer [49].



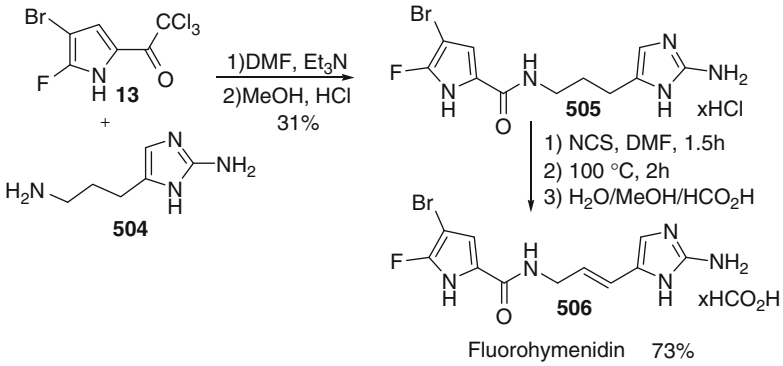
A series of pyrroles **500** with unsubstituted second positions was synthesized using pyrroles **362** as starting materials [158]. Reduction of esters **362** with $LiAlH_4$ afforded alcohols **498**, which were converted into aldehydes **499** by treatment with activated MnO_2. Decarbonylation under Pd/C gave target pyrroles **500**.



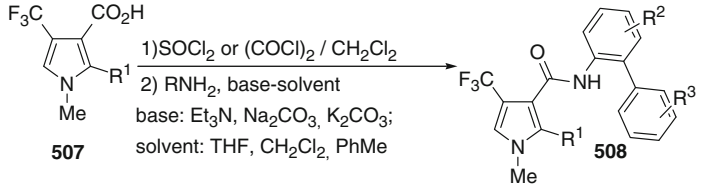
There are few examples of reactions, leading to the loss of fluorine. Thus, treatment of trifluoromethylpyrrole **270a** with excess of $LiAlH_4$ led to reducing of all functional groups to give tetramethylpyrrole **501** in high yield [91]. Another example is basic hydrolysis of pyrrole **270a** in water-ethanol mixture, which led to pyrroletricarboxylic acid **502**. Similarly, its ester **503** was obtained in the reaction of **270a** with sodium ethoxide.



5-Fluorinated trichloromethylketone **13** was used for the synthesis of fluorohymenidin **506**. Hymenidin is bromopyrrole marine alkaloid isolated from the Okinawan marine sponge, and found to be is an antagonist of serotonergic receptors [159]. Coupling of diamine **504** with the **13** led to fluorodihydrohymenidin **505**. Next, vinyl double bond was created via electrophilic chlorination of the 2-aminoimidazole moiety, followed by dehydrochorination. Addition of NCS to **505** in DMF at room temperature selectively formed the corresponding chloroimidazole. Elimination of HCl was induced by heating to 100 °C to give fluorohymenidin formate **506** after reversed phase chromatography (H_2O/MeOH/HCOOH) [11].

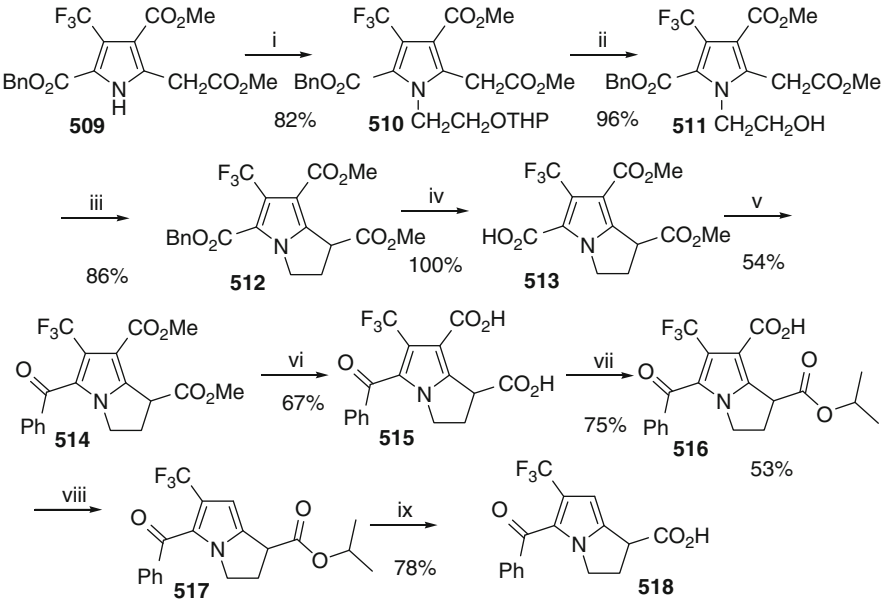


Most applications of trifluoromethylpyrroles connected with pesticide candidates synthesis. In some cases, however, compounds having the 3-trifluoromethyl core posses the fungicidal properties as well. For example amides **508** prepared from **507** was found to reveal such activity [160].



R^1=H, F; R^2=H, F; R^3=H, Cl, F, Br, Me, CF_3, OCF_3, SCF_3

Ketorolac is a non-steroidal anti-inflammatory drug, often used as an analgesic. Fluorinated analogue of ketorolac (compound **518**) was synthesized in nine steps in 11 % total yield starting from **509** [161].



i $BrCH_2CH_2OTHP$, K_2CO_3, NaI, DMF; ii AcOH-H_2O; iii a) Et_3N, $MeSO_2Cl$, CH_2Cl_2; b) NaH, DMF; iv H_2, 10% Pd/C, AcOEt; v $(COCl)_2$, PhMe, PhMgBr, $Fe(acac)_3$; vi EtSLi, HMPTA; vii i-PrOH, HCl; viii CuO, quinoline, 215 °C; ix HCO_2H, $MeSO_3H$

4 Conclusions

Fluorinated pyrroles have been studied intensively in recent years. As a result, a significant number of synthetic approaches to these compounds was elaborated. The most general methods involve direct fluorination/trifluoromethylation of the parent pyrroles, both the [3 + 2]- and the [4 + 2]-cycloaddition reactions, the applications of carbonyl compounds as well as TOSMIC and isocyanoacetates. Though variety of methods are already known, the elaboration of novel preparative pathways towards fluorinated pyrrole derivatives is still ongoing, which is due to the manifold of biological activities of this structural motive and the use as precursors for porphyrins synthesis. It is no doubt, that this branch of synthetic organic chemistry will enjoy a much attention, giving rise to sustainable flow of novel convenient pathways to the synthesis of fluorinated pyrroles.

Acknowledgments Financial support from the Russian Foundation for Basic Research (grants no. 12-03-00292-a and 13-03-01129) are gratefully acknowledged.

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