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Chemistry of Heterocyclic Compounds **2021**, *57*(12), 1149–1154

REVIEWS

Synthesis of five-membered heterocycles by [3+2] cycloaddition reactions of sulfur-containing 3,3,3-trifluoropropene derivatives

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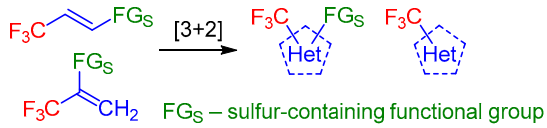


The present minireview provides a survey of literature reports on the application of 3,3,3-trifluoropropene derivatives bearing sulfur-containing functional groups at positions 1 or 2 in the synthesis of functionalized five-membered heterocycles – pyrroles, pyrrolines, pyrrolidines, tetrahydrothiophenes, pyrazoles, pyrazolines, pyrazolidines, isoxazoles, isoxazolines, isoxazolidines, and triazoles *via* [3+2] cycloaddition reactions with 1,3-dipolarophiles.

Keywords: sulfur-containing functional group, 3,3,3-trifluoropropene, cycloaddition, dipolarophile, 1,3-dipole.

[3+2] Cycloaddition reactions are among the most versatile tools for the synthesis of five-membered heterocycles.[1] Utilization of 3,3,3-trifluoropropene derivatives, bearing electron-withdrawing substituents – trifluoromethyl and sulfur-containing groups at the C=C bond, in combination with heteroatomic 1,3-dipoles in such cyclization reactions provides an efficient synthetic route to various types of five-membered heterocycles featuring both a CF_3 group and a heteroatom moiety, as compounds with potential biological activity. The nature of substituents and their spatial arrangement in the alkene substrates of [3+2] cycloadditions directly affect the product structure, as well as the stereochemical outcome of the reactions. Furthermore, the ability of functionalities, such as a sulfonyl substituent, to act as a leaving group can produce a broader range of possible cycloaddition products, in contrast, for example, to the cyclizations of dipolarophiles containing an ester group. In such reactions, accompanied by the elimination of a sulfur-containing moiety, the starting substituted 3,3,3-trifluoropropene derivative can be considered as an equivalent of 3,3,3-trifluoropropyne.

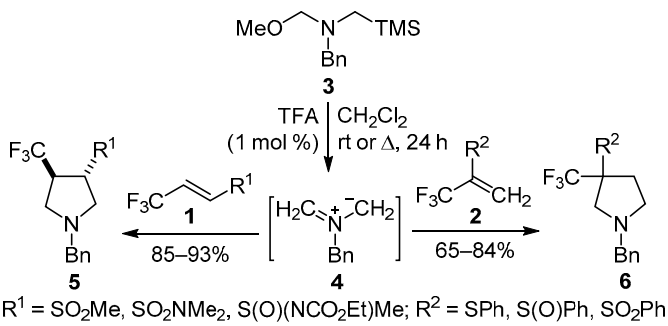
In this review article, the syntheses of five-membered heterocycles *via* [3+2] cycloaddition reactions of 3,3,3-trifluoropropene derivatives bearing sulfur-containing substituents at positions 1 or 2 are classified according to the obtained types of heterocyclic products formed. In some cases, synthetic or biological applications of the obtained heterocycles are also discussed.

* Here and further the corresponding author is marked with *.

Cycloaddition to azomethine ylides. Synthesis of pyrrolidines

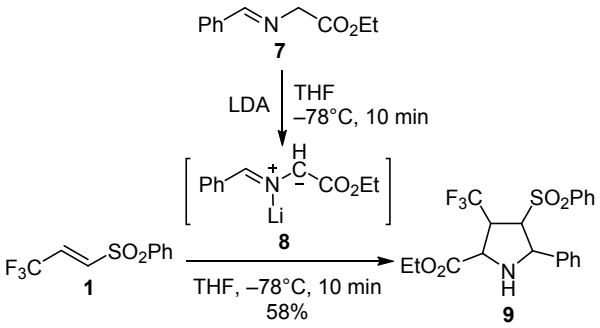
The cycloaddition reaction of *N*-benzyl azomethine ylide **4**, generated *in situ* at room temperature from (methoxymethyl)(trimethylsilylmethyl)-*N*-benzylamine (**3**) in the presence of catalytic amounts of TFA in CH_2Cl_2, to 3,3,3-trifluoropropene derivatives bearing a sulfur-containing functional group at position 1 (compound **1**)[2] or 2 (compound **2**)[3] led to the formation of *N*-benzyl-4-(trifluoromethyl)- and *N*-benzyl-3-(trifluoromethyl)-pyrrolidines **5**, **6** in 85–93 and 65–84% yields, respectively (Scheme 1). In the case of *trans*-alkenes **1**, the cycloaddition leading to the formation of adducts **5** proceeded stereospecifically. Reductive debenzylation of compounds **5** using molecular hydrogen on palladium catalyst provided the respective *NH*-pyrrolidines.[2]

Scheme 1



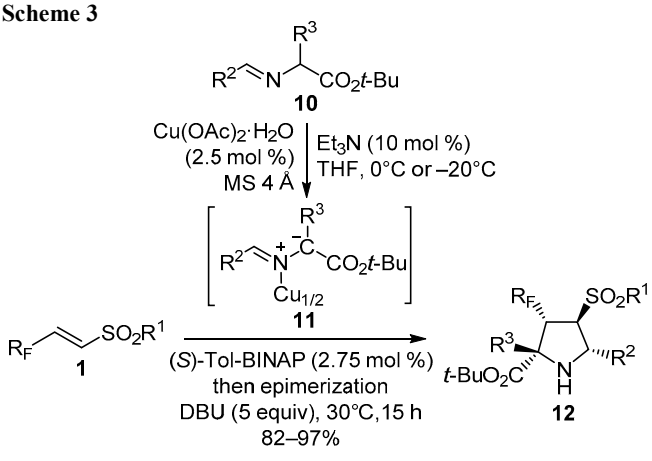
When 1-phenylsulfonyl-3,3,3-trifluoropropene (**1**) was reacted with azomethine ylide – *N*-benzylideneglycinate **8**, generated from imine **7** by the action of LDA in THF at –78°C, regioselective formation of 2,3,4,5-tetrasubstituted *NH*-pyrrolidine **9** was observed, giving rise to a mixture of stereoisomers in 58% yield (Scheme 2).[4]

Scheme 2



Chiral Cu(II) complexes and (*S*)-Tol-BINAP were used in asymmetric cycloaddition protocol involving reactions of various (β-polyfluoroalkyl/alkenyl)arylsulfones **1** in the presence of Et_3N in THF with glycine and alanine iminoesters **10** as precursors of azomethine ylide **11**. This proved to be a practical approach for the generation of a wide range of polysubstituted polyfluoroalkyl pyrrolidines **12** bearing four adjacent chiral centers in high yields (82–97%) and good enantio- and diastereoselectivity (Scheme 3).[5]

Scheme 3

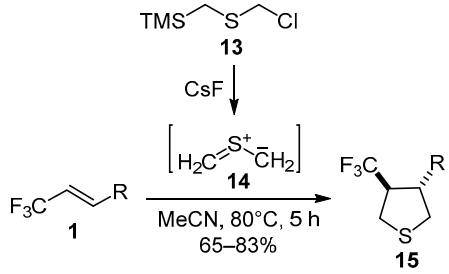


R_F = CF_3, CF_3CF_2, HCF_2, R^1 = Ph, 2-Py; R^2 = Ar, Het; R^3 = H, Me

Cycloaddition to thiocarbonyl ylide. Synthesis of tetrahydrothiophenes

Cycloaddition of thiocarbonyl ylide **14** generated *in situ* from chloromethyl trimethylsilyl methyl sulfide (**13**) in the presence of CsF in MeCN at reflux temperature, to (*E*)-3,3,3-trifluoropropene derivatives **1** containing a sulfonyl, sulfamide, or sulfoximine substituent at position 1, proceeded in a stereospecific manner, with the formation of 4-(trifluoromethyl)tetrahydrothiophenes **15** in 65–83% yields (Scheme 4).[6] Subsequent oxidation and oxidative imination reactions of thiolanes **15** allowed to synthesize functionalized cyclic 4-(trifluoromethyl)tetrahydrothiophenyl *S*-oxides, *S*,*S*-dioxides, as well as *S*-imino-*S*-oxides.[6]

Scheme 4

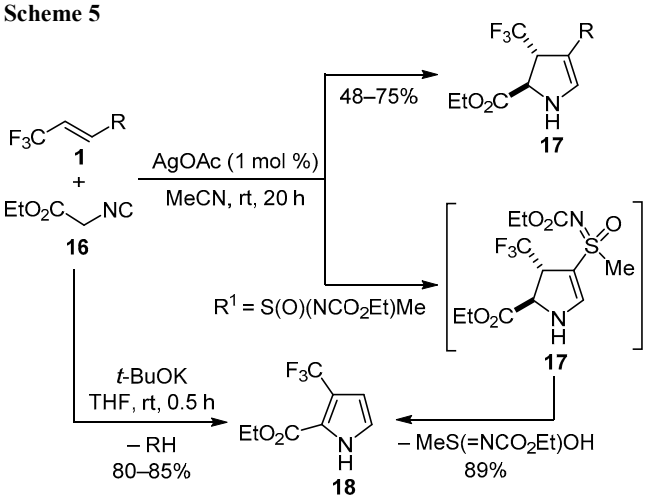


R = SO_2Me, SO_2NMe_2, S(O)(NCO_2Et)Me

Cycloaddition to isocyanomethylides and nitrile ylides. Synthesis of pyrrolines and pyrroles

The reaction of 1-sulfonyl- and 1-sulfamoyl-(*E*)-3,3,3-trifluoropropenes **1** with isocyanoacetic ester **16** in MeCN, with a catalytic amount of AgOAc added, proceeded regioselectively at room temperature, to give 3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrroles (Δ^2-pyrrolines) **17** in 48–75% yields (Scheme 5).[7] In the case of a reaction between alkene **1** bearing an iminosulfonyl substituent (R^1 = S(O)(NCO_2Et)Me), the intermediate sulfoximine-substituted pyrroline **17** underwent ring aromatization with elimination of methane(*N*-carbethoxy)imidosulfinic acid, resulting in the formation of ethyl 2-pyrrolecarboxylate **18** (Scheme 5). When the reaction of alkenes **1** and isocyanide **16** was performed in the presence of a base (*t*-BuOK) in THF, the *in situ* elimination of sulfur-containing fragment from cycloadducts **17** resulted in one-pot formation of pyrrole **18** (Scheme 5).[7] Pyrazoline derivative **17** containing a methylsulfonyl group was used in the synthesis of 4-methanesulfonyl-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid that can be considered as a fluorine- and sulfur-containing analog of proline.[7]

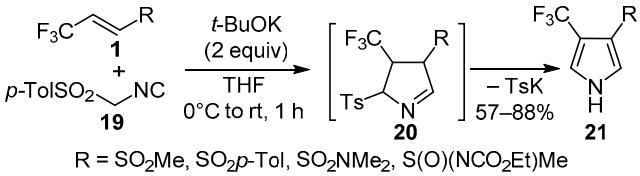
Scheme 5



R = SO_2Me, SO_2p-Tol, SO_2NMe_2

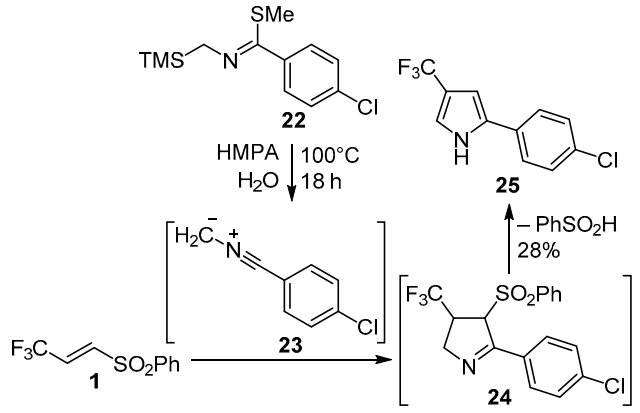
The reactions of alkenes **1** with isocyanomethylide anion obtained from tosylmethyl isocyanide **19** in the presence of a base (*t*-BuOK, 2 equiv) in THF proceeded with the formation of 4-(trifluoromethyl)-1*H*-pyrroles **21** in 57–88% yields (Scheme 6).[7] α-Tosylpyrroline intermediates **20** formed in this reaction underwent *in situ* elimination of toluenesulfonate, yielding pyrroles **21** (the Van Leusen reaction) (Scheme 6).

Scheme 6



Cycloaddition of 1-phenylsulfonyl-3,3,3-trifluoropropene (**1**) with nitrile ylide **23** generated from methyl 4-chloro-*N*-[(trimethylsilyl)methyl]benzimidothioilate (**22**) upon heating in hexamethylphosphoramide (HMPA) in the presence of H_2O gave 2-(4-chlorophenyl)-4-(trifluoromethyl)pyrrole (**25**) in 28% yield as a desulfonylation product derived from the sulfonylated pyrroline intermediate **24** (Scheme 7).[8]

Scheme 7

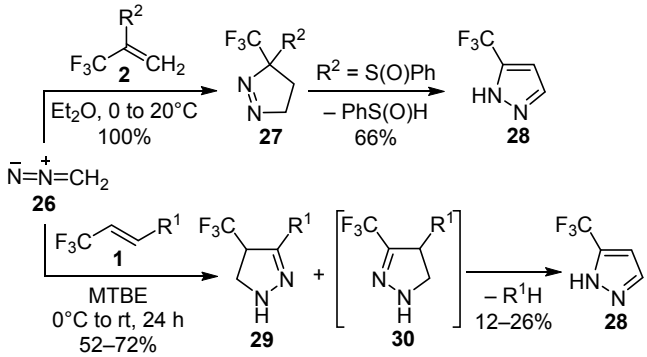


Cycloaddition to diazo compounds, nitrile imines, and azomethine imines. Synthesis of pyrazolines, pyrazoles, and pyrazolidines

Cycloadditions of diazomethane (**26**) with 3,3,3-trifluoropropene derivatives **2** bearing sulfanyl, sulfinyl, or sulfonyl group at position 2 proceeded regioselectively in Et_2O at room temperature, affording isolable 3-substituted 3-(trifluoromethyl)-4,5-dihydro-3*H*-pyrazole derivatives (Δ_1-pyrazolines) **27**, which differ in thermal stability depending on the nature of sulfur-containing substituent (Scheme 8).[3] Pyrazoline thioether **27** (R^2 = SPh) is so stable that it can be distilled. Sulfinylated pyrazoline **27** (R^2 = S(O)Ph) underwent elimination of phenylsulfenate on thermolysis at 80°C, affording 3-(trifluoromethyl)pyrazole (**28**). Sulfonylpyrazoline **27** (R^2 = SO_2Ph) can be isolated as individual compound, but the thermolysis led to a complex mixture of products.[3]

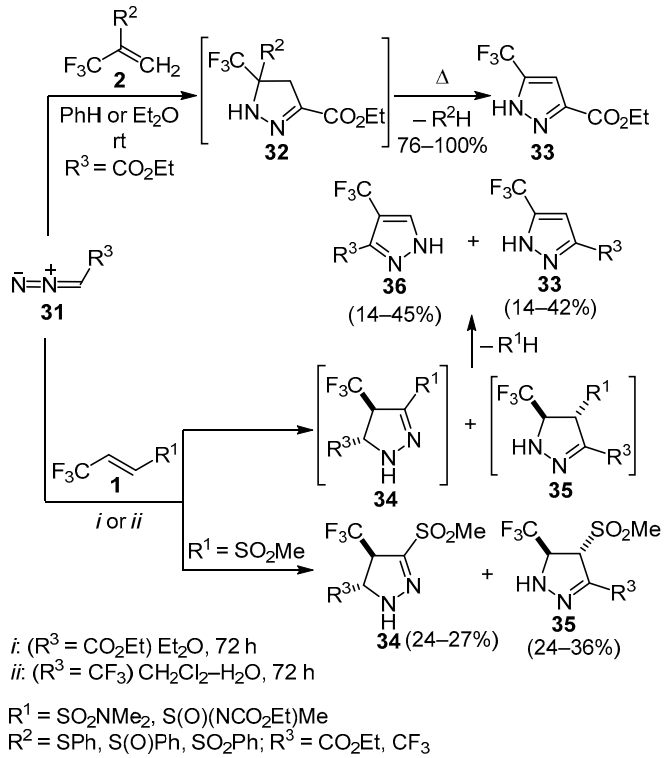
The reactions of diazomethane (**26**) with sulfur-containing 1-substituted 3,3,3-trifluoropropene derivatives **1** in *t*-BuOMe at room temperature led to the formation of regioisomeric cycloadducts – 4-(trifluoromethyl)- and 3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazoles (Δ^2-pyrazolines) **29** and **30** (Scheme 8).[9] The sulfur-containing substituent in regioisomers **30** was eliminated under the reaction conditions, giving pyrazole **28** (Scheme 8).[9]

Scheme 8



Cycloaddition of diazoacetic ester **31** (R^3 = CO_2Et) with alkenes **2** in Et_2O or PhH at room temperature proceeded regioselectively, with the formation of 5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole derivatives (Δ^2-pyrazolines) **32**, which underwent ring aromatization upon heating, forming pyrazole **33** (Scheme 9).[3]

Scheme 9

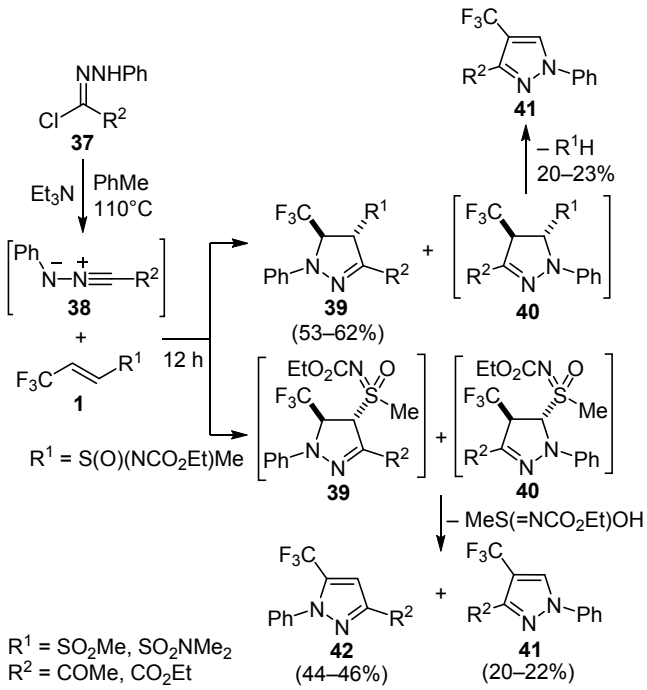


The reactions of alkenes **1** with diazoacetic ester **31** ($R^3 = CO_2Et$) in Et_2O and with 2,2,2-trifluorodiazoethane **31** ($R^3 = CF_3$) that was generated *in situ* from 2,2,2-trifluoroethylamine hydrochloride by the action of $NaNO_2$ in biphasic CH_2Cl_2–H_2O system proceeded with the formation of isomeric 5(3)-substituted 4-trifluoromethyl-3,4(4,5)-dihydro-2(1)*H*-pyrazoles **34** and 4-substituted 5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazoles **35**. Yet, depending on the nature of the sulfur-containing substituent, the initial cycloadducts could undergo further transformations. Pyrazolines **34** and **35** bearing a sulfonyl substituent were stable, while pyrazolines **34** and **35** having a sulfamide or sulfoximine substituent underwent spontaneous ring aromatization in the reaction mixture, leading to the formation of pyrazole derivatives **36** and **33**, respectively (Scheme 9).[9]

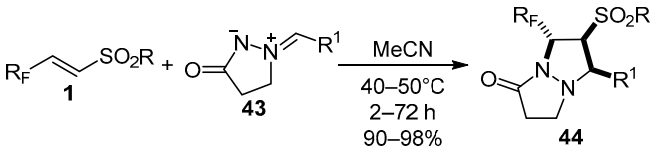
Cycloaddition of 1-sulfonyl- and 1-sulfamoyl-(*E*)-3,3,3-trifluoropropenes **1** with *N*-phenylnitrile imine **38** generated *in situ* from phenylhydrazinylidene chlorides **37** in the presence of an excess of Et_3N, was performed by heating in PhMe and resulted in the formation of regioisomeric cyclodducts – 5-(trifluoromethyl)- and 4-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole derivatives (Δ^1-pyrazolines) **39** and **40**. The latter, under the reaction conditions, were converted to 1-phenyl-4-(trifluoromethyl)-1*H*-pyrazoles **41** *via* the loss of the sulfur-containing moiety (Scheme 10).[9] When nitrile imine **38** was reacted with alkene **1** bearing an iminosulfonyl substituent (R^1 = S(O)(NCO$_2$Et)Me), both intermediate regioisomeric pyrazolines **39** and **40** underwent elimination of methane(*N*-carbethoxy)imidosulfinic acid to give pyrazoles **42** and **41**, respectively (Scheme 10).[9]

Cycloaddition reactions of (*E*)-α,β-unsaturated β-fluoroalkyl-2-pyridyl- and phenylsulfones **1** with a series of aromatic, heteroaromatic, and aliphatic azomethine imines **43** were accomplished under mild conditions (heating in MeCN) in the absence of catalysts, resulting in regioselective formation of trifluoromethylated *N,N'*-bicyclic pyrazolidinones **44** that were isolated as racemic mixtures in high yields, with a good to high degree of *exo* selectivity (Scheme 11).[10]

Scheme 10



Scheme 11



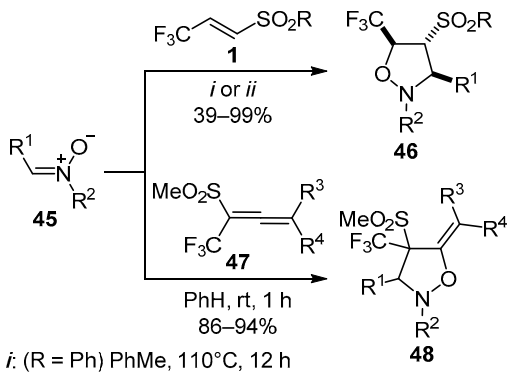
R_F = CF_3, HCF_2, H_2CF, C_2F_5, CF_2Cl, CF_2Br
R = Ph, 2-Py; R^1 = Alk, Ar, Het

Cycloaddition to nitrones and nitrile oxides. Synthesis of isoxazolidines, isoxazolines, and isoxazoles

Cycloaddition of (*E*)-1,1,1-trifluoro-3-phenyl- and 2-pyridylsulfonylpropene **1** to nitrones **45** proceeded regioselectively upon refluxing in PhMe[11] or heating in MeCN[10] and led to highly stereoselective formation of substituted 4-sulfonyl-5-(trifluoromethyl)isoxazolidines **46** that were isolated in 39–99% yields (Scheme 12). Analogous reactions involving 1-(methanesulfonyl)-1-(trifluoromethyl)allenes **47** as active 1,3-dipolarophiles occurred readily without catalyst in PhH at room temperature providing high yields (86–94%) of polysubstituted isoxazolidine derivatives **48** containing an exocyclic C=C bond as single isomers (Scheme 12).[12] Isoxazolidines **46** have been used as precursors of various acyclic compounds for the preparation of the respective trifluoromethylated *syn*-3-amino alcohols through a sequence of reductive desulfonylation and catalytic hydrogenation reactions.[11]

For the asymmetric variant of cycloaddition to nitrones **45**, optically active α,β-unsaturated trifluoromethyl-

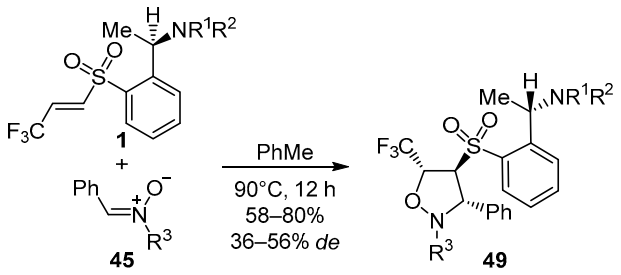
Scheme 12



i: (R = Ph) PhMe, 110°C, 12 h
ii: (R = 2-Py) MeCN, 40°C, 24 to 48 h
1, **45**, **46** R = Ph, 2-Py; R^1 = H, Me, Ph, 4-$MeOC_6H_4$
R^2 = Me, Bu, Ph
45, **47**, **48** R^1 = Ph; R^2 = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$
R^3/R^4 = Me, Et, $(CH_2)_5$

arylsulfones **1**, containing a chiral *N*,*N*-dialkylaminoethyl group at the *ortho* position, were used. In this case, the respective 5-(trifluoromethyl)isoxazolidines **49** were obtained regioselectively from nitrones **45** upon heating in PhMe, with 58–80% yields and 36–56% diastereoselectivity (Scheme 13).[13]

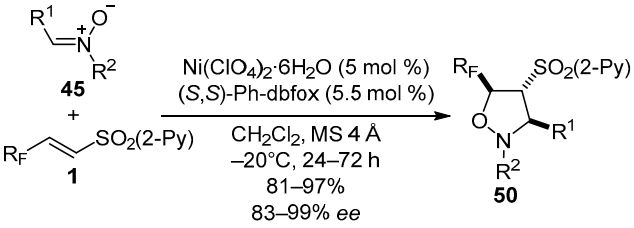
Scheme 13



$R^1 = R^2 = Me$; $R^1 + R^2 = (CH_2)_5$; $R^1 = Me$; $R^2 = Pr$; $R^3 = Me$, Bu, Ph

The asymmetric version of cycloaddition has also been achieved by the use of chiral catalysts. Thus, a wide range of optically pure 5-(fluoroalkyl)isoxazolidines **50** were obtained in high yields (81–97%), as well as with high diastereo- and enantioselectivity (83–99% *ee*) *via* asymmetric cycloaddition reactions between a series of α,β-unsaturated fluoroalkyl-2-pyridylsulfones **1** and various aromatic and aliphatic nitrones **45** in the presence of Ni(II) bis(oxazoline) catalyst (*S*,*S*)-Ph-dbfox (Scheme 14).[14] Products **50** have found applications in asymmetric synthesis of enantiomerically enriched α-trifluoromethylated γ-amino alcohols, as well as for the preparation of chiral trifluoromethyl-substituted 1,3-oxazinan-2-one derivatives as compounds with potential antiviral activity.[14]

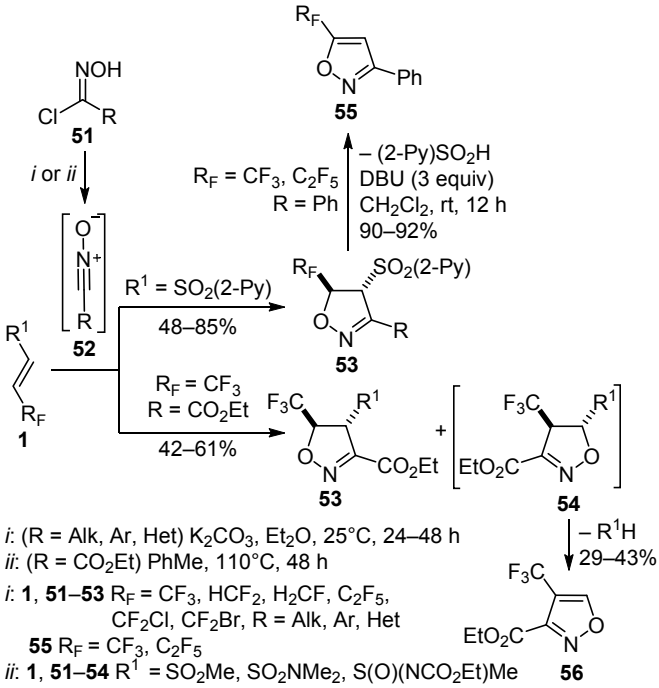
Scheme 14



$R_F = CF_3$, C_4F_9, C_6F_{13}; R^1 = Ph, Bn; R^2 = Ar, Alk

The cycloaddition reactions of β-fluoroalkylvinylpyridylsulfones **1** with various nitrile oxides **52** (R = Alk, Ar, Het) formed from the appropriate *N*-hydroxyimidoyl chlorides **51** by the action of a base (K_2CO_3) in Et_2O at room temperature proceeded with the formation of 5-(trifluoromethyl)-4,5-dihydroisoxazole derivatives **53** in 48–85% yields with high regio- and diastereoselectivity (*dr* >99:1) (Scheme 15).[15] Compounds **53** can be easily converted by treatment with DBU into the respective 5-fluoroalkyl-2-isoxazoles **55** *via* the cleavage of pyridylsulfonyl substituent (Scheme 15).[15] In analogous reactions between (*E*)-3,3,3-trifluoropropene derivatives **1** ($R_F = CF_3$) containing sulfonyl, sulfoximine, or sulfamide

Scheme 15



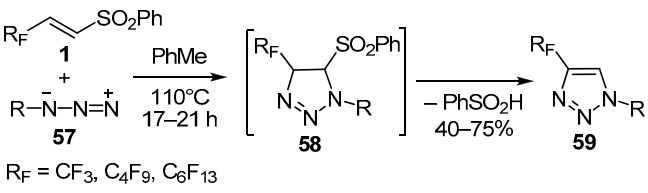
i: (R = Alk, Ar, Het) K_2CO_3, Et_2O, 25°C, 24–48 h
ii: (R = CO_2Et) PhMe, 110°C, 48 h
i: **1**, **51**–**53** $R_F = CF_3$, HCF_2, H_2CF, C_2F_5, CF_2Cl, CF_2Br, R = Alk, Ar, Het
55 $R_F = CF_3$, C_2F_5
ii: **1**, **51**–**54** $R^1 = SO_2Me$, SO_2NMe_2, S(O)(NCO$_2$Et)Me

substituent at position 1 and ethyl cyanocarboxylate *N*-oxide **52** (R = CO_2Et) generated *in situ* from ethyl oximinochloroacetate **51** upon refluxing in PhMe, a mixture of regioisomeric cycloadducts – 5-(trifluoromethyl)- and 4-(trifluoromethyl)-4,5-dihydroisoxazoles **53** and **54** was formed (Scheme 15).[16] The latter were converted under the reaction conditions into isoxazole **56**, which arose from spontaneous elimination of sulfur-containing fragment from isoxazolines **54** (Scheme 15).[16]

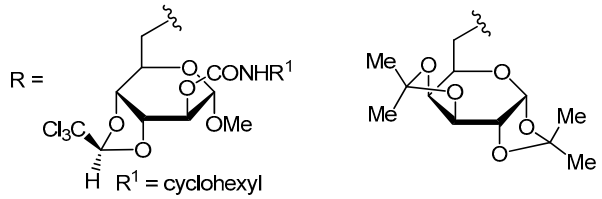
Cycloaddition to azides. Synthesis of 1,2,3-triazoles

Cycloaddition of (*E*)-perfluoroalkyl-2-phenylsulfonylethenes **1** to 6-azido-α-D-galactose and -altrose **57** upon refluxing in PhMe was accompanied by desulfonylation of 1,2,3-triazoline intermediates **58** and formation of 1,2,3-triazole derivatives **59** as a single regioisomer, isolated in 40–75% yields (Scheme 16).[17] These reactions

Scheme 16



$R_F = CF_3$, C_4F_9, C_6F_{13}



were used for obtaining reverse nucleosides of fluoroalkyl-substituted 1,2,3-triazoles linked to the C-6 atom of sugars as potentially biologically active compounds.[17]

In the present review, we have summarized for the first time the literature data on the synthesis of trifluoromethyl-substituted sulfur-containing five-membered heterocycles using the methodology of 1,3-dipolar [3+2] cycloaddition of functionalized 3,3,3-trifluoropropene derivatives, as well as highlighted the effect of the nature of substituents in the initial substrates on the regioselectivity of reactions and the structure of cycloadducts. The practical value of this synthetic approach, by employing fluorine- and sulfur-containing alkene substrates as dipolarophiles, lies in the possibility of the simultaneous introduction of both a fluoroalkyl group and an exocyclic sulfur-containing fragment into the heterocycle molecule. The heterocycles obtained in this manner are promising targets for biological investigations, and some of them, due to the revealed biological activity, have already found practical application. To conclude, the wide range of available 1,3-dipoles suggests an undoubted development of the synthetic strategy illustrated in this review for the preparation of novel barely accessible heterocyclic compounds.

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