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SYNTHESIS OF PARTIALLY FLUORINATED HETEROCYCLES FROM 4,4-BIS(TRIFLUOROMETHYL) SUBSTITUTED HETERO-1,3-DIENES *VIA* C-F BOND ACTIVATION AND THEIR APPLICATION AS TRIFLUORO-METHYL SUBSTITUTED BUILDING BLOCKS*[1]

Klaus Burger,*[a] Lothar Hennig,[a] Jan Spengler,[b] and Fernando Albericio[b]

[a)]Department of Organic Chemistry, University of Leipzig, Johannisallee 29, 04103 Leipzig, Germany
[b)]Department de Quimica Orgànica, Universitat de Barcelona, Parc Cientific, Josep Samitier 1-5, 08028 Barcelona, Spain
E-mail: burger@organik.chemie.uni-leipzig.de

Abstract – Bis(trifluoromethyl) substituted hetero-1,3-dienes can be transformed into partially fluorinated five-membered heterocycles by a new reductive cyclization protocol. Certain members of the new class of heterocycles represent versatile building blocks. α-Trifluoromethyl α-amino acids, trifluoromethyl substituted butenolides and α-trifluoromethyl-γ-keto acids are readily available via 5-fluoro-4-trifluoromethyloxazoles and 2-fluoro-3-trifluoromethylfurans, respectively.

CONTENTS

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* Dedicated to Prof. Dr. Satoshi Omura on the occasion of his 70th birthday

1. Introduction

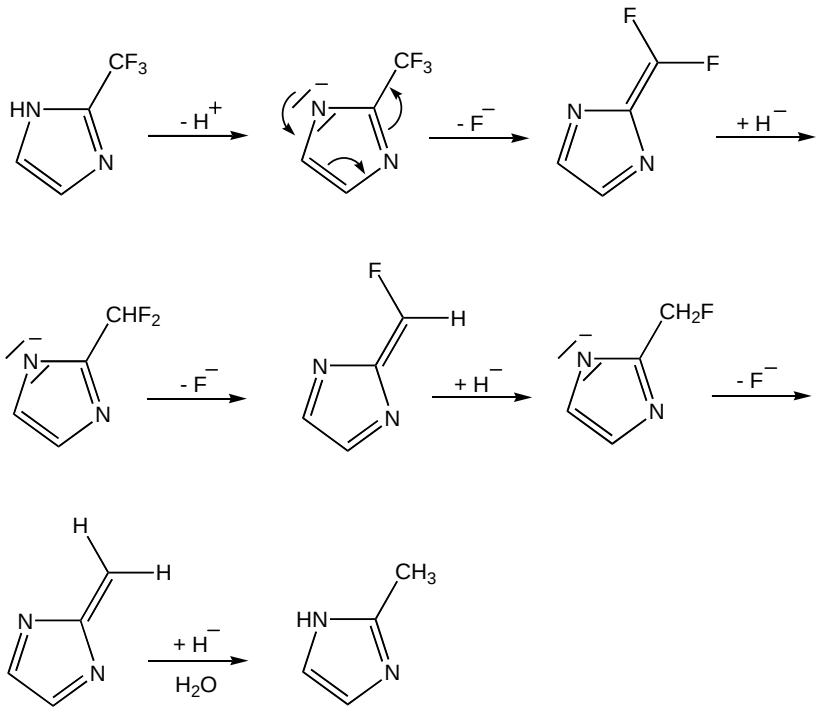
1.1. Influence of Fluorine and of Trifluoromethyl Groups on the Reactivity of Molecules

Fluorine and/or perfluoroalkyl groups placed in strategical positions of target molecules may modify chemical properties, biological activity and selectivity in a favorable way.[2] The number of patents concerning fluoro-containing compounds in medicinal and agricultural chemistry as well as in material science is still growing.[3] The exchange of hydrogen by fluorine does not alter steric bulk much because of the similarity of the Van der Waals radii (H: 1.20 Å; F: 1.47 Å)[4] and therefore may be regarded as isosteric replacement. The postulated quasi-isosterism between CH_3 and CF_3 groups proved untenable.[5] The Van der Waals radii of a trifluoromethyl and of a methyl group are 2.7 Å and 2.0 Å, whereas the Van der Waals volumina are 42.6 $Å^3$ and 16.8 $Å^3$. Therefore, the steric demand of a trifluoromethyl group seems to be close to that of an isopropyl group.[6]

The important differences in chemical reactivity of fluorinated compounds and their unfluorinated pendants are based on the difference in carbon-fluorine (456-486 kJ/mol) and carbon-hydrogen bond energies (356-435 kJ/mol), on the difference in electronegativity (Pauling scale: F 4.0 / H 2.1) and on the ability to participate in hydrogen bonding as an electron pair donor.[7,8] The high carbon-fluorine bond energy renders the fluorine substituent a bad leaving group in S_N2 reactions. Incorporation of trifluoromethyl groups stabilizes molecules. This phenomenon is unique among halogens.[9] For example the CC-bond in 1,1,1-trifluoroethane or hexafluoroethane is 59 and 42 kJ more stable than that of ethane.[10]

Fluorine incorporated into key positions of biologically active molecules can block certain metabolic pathways. It improves lipophilicity[11] (lipophilicity scale: $F < CF_3 < OCF_3 < SCF_3$) enhances absorption rates and improves transport rates of drugs in vivo. In contrast, in addition / elimination processes (e.g. Sanger reagent[12]) fluorine is superior to other halogens. These properties led to the development of efficient mechanism-based enzyme inhibitors.[13] Although the trifluoromethyl group originally was considered to be chemically inert,[14] it is known to undergo a variety of reactions.

The stability of a trifluoromethyl groups depends on the position in a molecule. For example, trifluoromethyl groups bound to aromatic systems, e.g. trifluorotoluene, undergo hydrolysis, but only in strong acidic media at elevated temperatures. A trifluoromethyl group attached to carbon atoms possessing acidic hydrogen atoms like 3,3,3-trifluoroalanine is unstable in basic media. Above pH 8.5 the trifluoromethyl group is degraded to give the corresponding carboxylate[15] (C-F bond activation *via* anion formation[16]). Trifluoromethyl groups attached to certain positions of heterocyclic systems like 2-trifluoromethylimidazole, undergo facile base-catalyzed hydrolysis[17] (Scheme 1).



Scheme 1

Primary and secondary perfluoroalkyl amines are relatively unstable, but the situation is not as extreme as that of the corresponding alcohols.[18] The ability to eliminate fluoride ions from trifluoromethyl and perfluoroalkyl groups after transformation into an anionic species allows *i.a.* the *in situ* generation of useful fluorine-containing building blocks.[19,20] Recently, a low-valent niobium-mediated double activation strategy was disclosed, in which a C-F and a C-H bond in close proximity in the same molecule are jointly activated, leading to ring-closing and formation of a polycyclic system (Scheme 2). Differently substituted o-phenyl-α,α,α-trifluorotoluenes, $NbCl_5$ and $LiAlH_4$ were heated in DME under reflux for several hours to give fluorenes with variable substituent pattern in good yields.[21-23]

Scheme 2

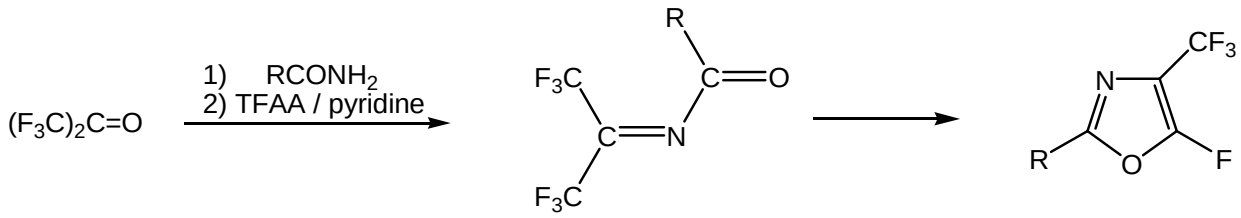
1.2. Strategies for the Introduction of Fluorine and Trifluoromethyl Groups

There are two fundamentally different strategies by which fluorine and/or perfluoroalkyl groups can be introduced into target molecules:

1) Direct introduction – by substitution of hydrogen or functional groups by fluorine or perfluoroalkyl groups in a later step of the reaction sequence;
(2) Introduction of fluorine and/or perfluoroalkyl groups via fluorine-containing building blocks.
Although the first approach is more straightforward, provided that suitable fluorinating and perfluorinating reagents are available, control of site selectivity and stereoselectivity is often difficult to achieve. Because of the high reactivity of most fluorinating reagents many functional groups already present in a molecule also may be transformed in an undesired way, and therefore have to be protected. Protection and deprotection of these groups require additional steps. Furthermore, many reagents currently used for direct introduction of fluorine are expensive, toxic, corrosive, and sometimes explosive. Consequently, the building block strategy for introduction of fluorine and perfluoroalkyl groups into organic molecules still represents an attractive alternative concept.[24,25]

2. Trifluoromethyl Substituted Five-membered Heterocycles from 4,4-Bis(trifluoromethyl) Substituted Hetero-1,3-dienes

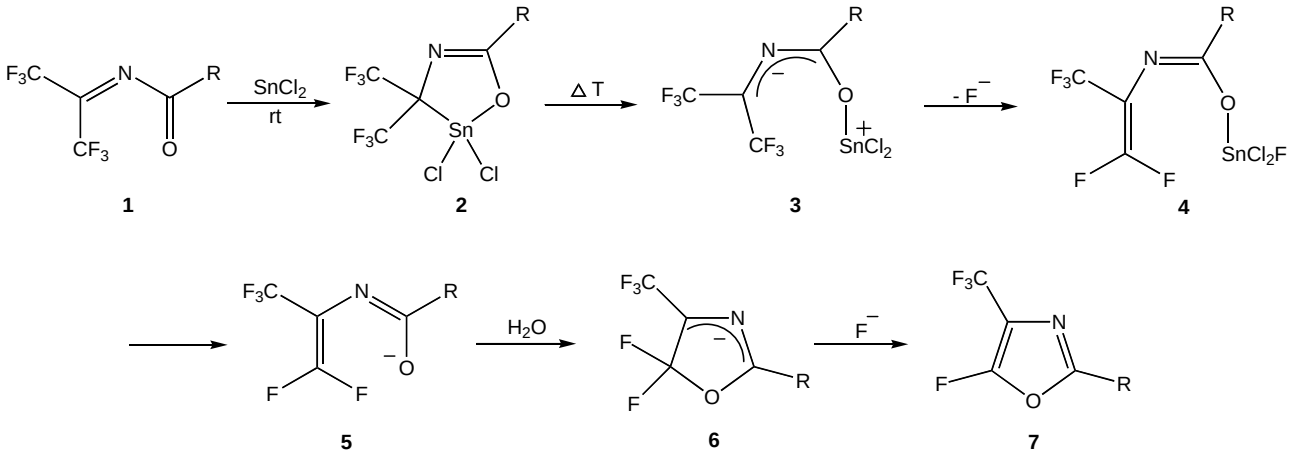
Hexafluoroacetone (bp – 28 °C) is commercially available. It represents a versatile, highly reactive building block for organofluorine as well as heterocyclic chemistry and can be applied as bidendate protecting/activating reagent for peptide and depsipeptide chemistry.[1b] 4,4-Bis(trifluoromethyl) substituted 1,3-heterodienes, obtained from hexafluoroacetone and carboxamides on elimination of water,[26] were used as model compounds to develop new routes to partially fluorinated heterocycles. In this context, we studied the possibility of transforming bis(trifluoromethyl) substituted hetero-1,3-dienes into five-membered ring systems, where one trifluoromethyl group of the geminal pair remains unaffected, while the second trifluoromethyl group reacts like an "orthofluoride" being degraded and incorporated as –CF= fragment into the newly formed five-membered ring system (Scheme 3).



Scheme 3

4,4-Bis(trifluoromethyl)-1-oxa-3-azabuta-1,3-dienes (**1**)[26] belong to the most reactive hetero-1,3-dienes known in organic chemistry, being highly sensitive even toward weak nucleophiles like water. To switch on the reactivity of one of the trifluoromethyl groups, an anionic species has to be generated from **1** *via*

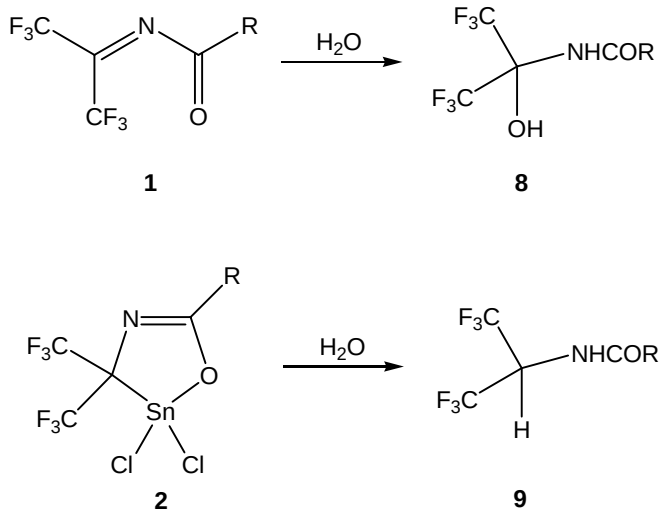
electron transfer.[16,27] An efficient way to achieve this redox process is a [4+1] cycloaddition of carefully dried $SnCl_2$ to hetero-1,3-dienes of type (**1**)[28] in dry acetone at room temperature (Scheme 4).



1 **2** **3** **4** **5** **6** **7**

Scheme 4

In the newly formed five-membered heterocycle the tin moiety is present as Sn^{4+}. Consequently, two electrons have been transferred from the metal centre to the heterodiene skeleton during the cycloaddition process. In solution, at room temperature compounds (**2**) are stable enough to be characterized spectroscopically.[29] Different products (**8**, **9**) were isolated, when **1** and **2** were treated with water demonstrating unambigously that the [4+1] cycloaddition includes an "Umpolung" (Scheme 5).



1 **8**

2 **9**

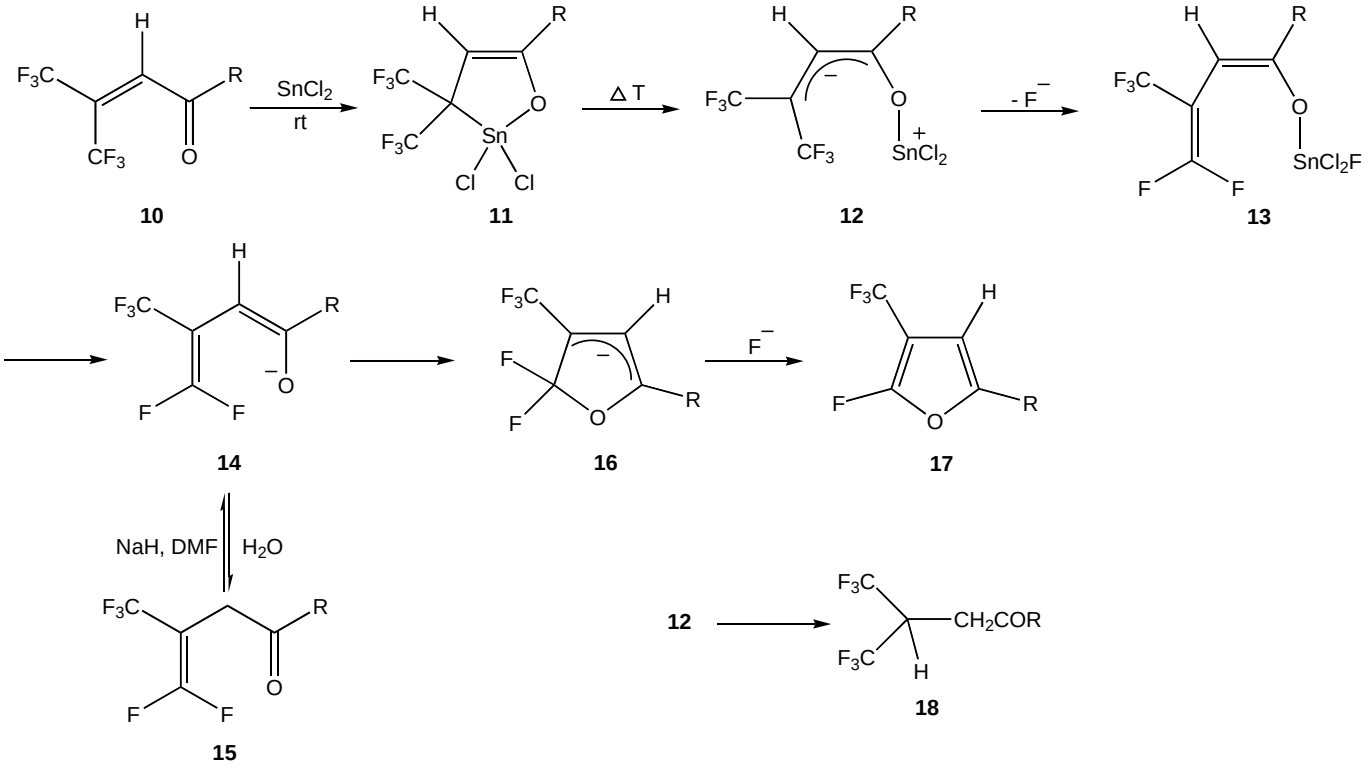
Scheme 5

Syntheses of metallacycles *via* [4+1] cycloaddition of carbene analogues e.g. SnR_2 and GeR_2 to 1,3-dienes and hetero-1,3-dienes are well-known.[30,31] In general the divalent species is generated in situ.[32]

However, to transform **2** into oxazoles elevated temperatures are required. Compound (**2**), on heating in toluene, undergoes a heterolytic ring cleavage providing a dipolar species (**3**) with an azaallyl anion substructure accomodating the negative charge, while the positive charge is located at the metal centre (Scheme 4). The heteropentadienyl anion (**5**) formed after splitting off a fluoride ion and the tin fragment (**4** → **5**) undergoes an electrocyclic ring closure with fluoride elimination (**5** → **6** → **7**). Driving force for this multistep procedure is heteroaromatization.[33] Intermediates (**5** and **6**) have been trapped and characterized as protonated species.[29]

2.1. Variation of the Skeleton Atoms

The reaction **1** → **7** can be performed as one-pot procedure, by heating the bis(trifluoromethyl) substituted hetero-1,3-diene (**1**) in the presence of dry $SnCl_2$ in toluene under reflux for 12 – 36 h. The progress of the reaction can be monitored by ^{19}F-NMR spectroscopy. The reaction was also applied to other bis(trifluoromethyl) substituted hetero-1,3-dienes like 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-dienes (**10**)[34], which are stable on contact with water. Therefore, commercially available $SnCl_2 * 2\ H_2O$ can be used for the [4+1] cycloaddition process.

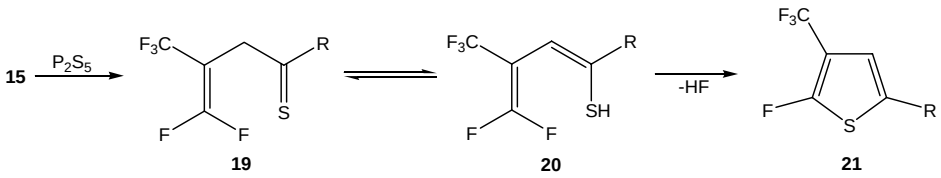


Scheme 6

Based on the spectroscopic data, we ascribe the newly formed products the structure of 1-aryl-4,4-difluoro-3-trifluoromethyl-3-buten-1-ones (**15**) (Scheme 6). The reaction sequence parallels that of compounds (**1**).

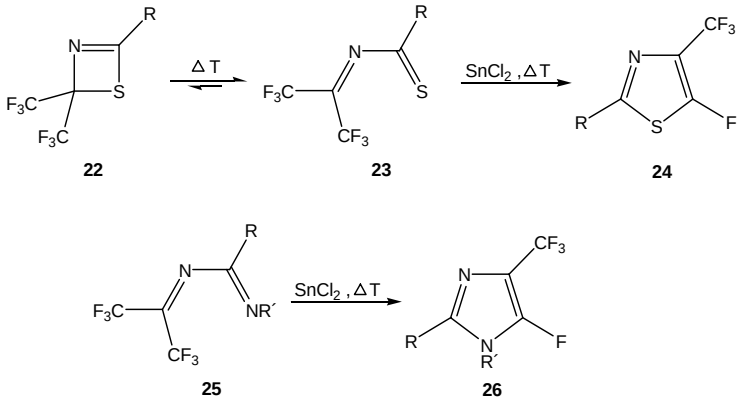
However, in the presence of water, protonation of the oxapenta-2,4-dienyl anion (**14**) is faster than the electrocyclic ring closure with fluoride elimination. Therefore, protonation stops the reaction sequence providing compounds (**15**). We interpret the formation of by-product (**18**) (5-6%) as an additional argument that an "Umpolung" takes place in an early stage of the reaction sequence. Compounds (**15**) can be transformed into 2-fluoro-3-trifluoromethylfurans (**17**) on treatment with NaH in dry DMF. The reaction sequence (**15**) → (**14**) → (**16**) → (**17**) is very capricious and extremely sensitive to changes of solvent and base.

When compounds (**15**) and phosphorus pentasulfide are heated up to 120 – 140 °C without solvent an oxygen/sulfur exchange takes place. The thioketone (**19**) formed first, exists in an equilibrium with **20** which undergoes ring closure with HF elimination to give 5-aryl-2-fluoro-3-trifluoromethylthiophenes (**15**) → (**19**) → (**20**) → (**21**)[35] (Scheme 7).



Scheme 7

At the first view it is surprising that 2,2-bis(trifluoromethyl)-2*H*-1,3-thiazetes (**22**) readily react with $SnCl_2$. However, when we assume that **22** exists in a thermally mobile valence tautomeric equilibium with 1-thia-3-azabuta-1,3-dienes (**23**),[36] the reaction can be readily explained as a [4+1] cycloaddition of the $SnCl_2$ to give a tin-heterocylce which is transformed further into a thiazole (**24**).[37] Analogously, 1,3-diazabuta-1,3-dienes (**25**)[38] are transformed into the corresponding imidazoles (**26**).[37]

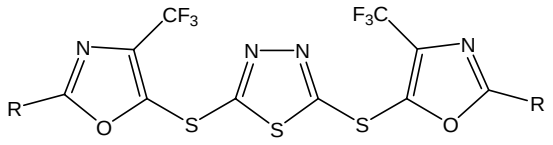


Scheme 8

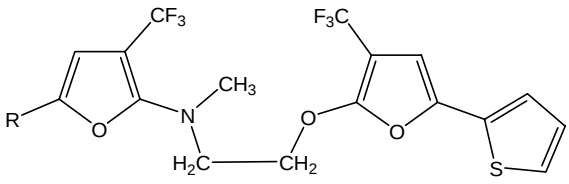
Compounds (**7**) can be obtained also via direct electron transfer from certain metals like Zn, Ga, Cd, In, Sn, Tl and Pb to the hetero-1,3-dienes (**1**) on heating in an ultrasound bath,[39] but the isolated yields are lower than from the $SnCl_2$ reaction.

2.2. Variation of the Substituent Pattern

Further structural diversity can be generated on replacement of the single fluorine atom adjacent to the trifluoromethyl group by O-, S-, N- and C-nucleophiles.[40] The rate of the nucleophilic substitution process depends very much on the nature of the ring skeleton atoms (oxazoles > thiazoles > imidazoles) and on the electron withdrawing capacity of the substituent R. For example nucleophilic substitution of the single fluorine bound to C-(5) of oxazoles (**7**) by ethanol was complete at room temperature within two h for R = p-$NO_2C_6H_4$, while in the case of R = p-$CH_3OC_6H_4$ the sample has to be heated for 6 h up to 100 °C. Addition of bases to generate the conjugated base of the nucleophiles, to trap the hydrogen fluoride formed during the nucleophilic substitution process as well as the application of lithium salts, addition of crown ethers in the case of potassium salts and finally application of O-trimethylsilyl derivatives are accelerating the nucleophilic substitution process. A large number of structural different five-membered trifluoromethyl substituted heterocycles including bridged symmetrical and unsymmetrical systems of type (**27**) and (**28**) (Scheme 9) have been synthesized.



27

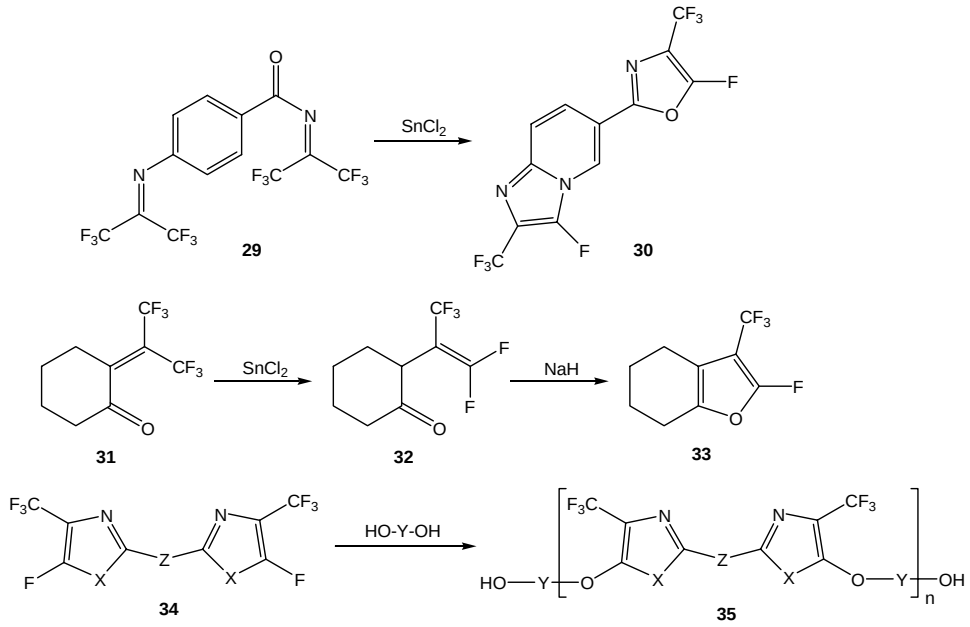


28 R = 4-Cl-C_6H_4

Scheme 9

2.3. Annelation, Oligomerization and Polymerization

The above discussed domino reaction can also be used for annelation procedures (**29** → **30**)[41] and (**31** → **33**)[42] (Scheme 10). Furthermore, bifunctional systems of type (**34**) are readily accessible and can be used as monomers for oligomer and polymer syntheses (**34** → **35**).[43,44]

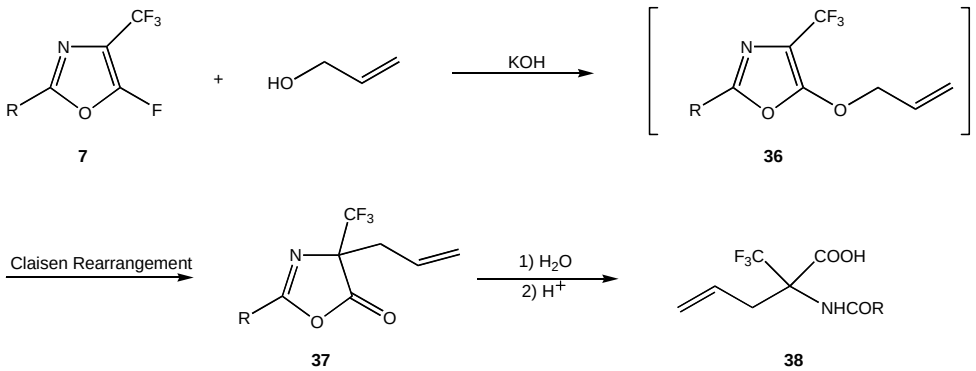


Scheme 10

3. 5-Fluoro-4-trifluoromethyloxazoles as Trifluoromethyl (Tfm) Glycine Equivalent

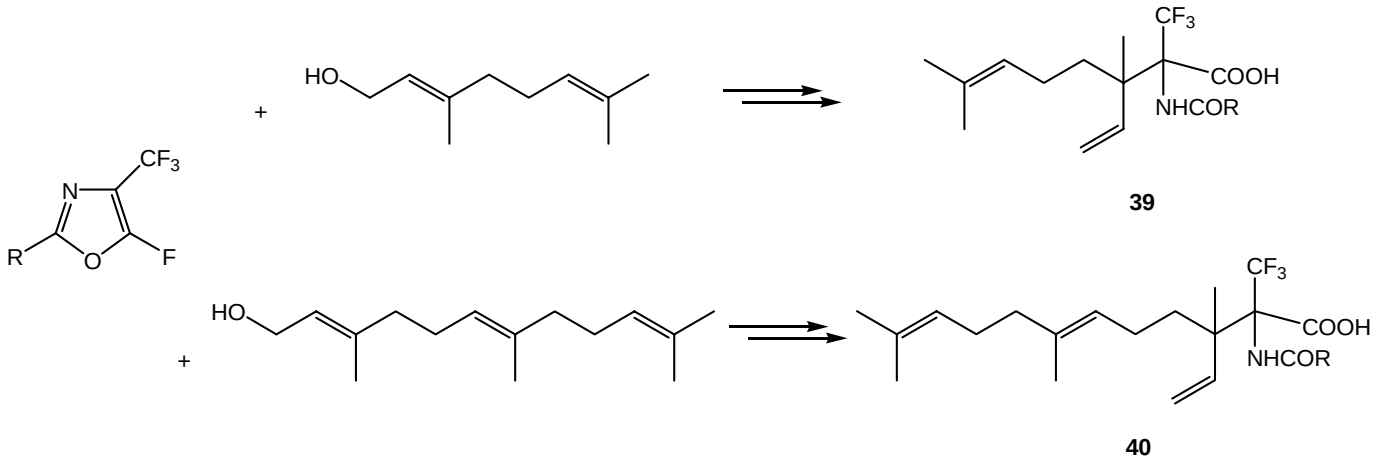
3.1. Unsaturated α-Trifluoromethyl Amino Acids

Different strategies have been developed for the synthesis of α-Tfm amino acids.[45] The most general approach is the amidoalkylation of carbon nucleophiles with alkyl 2-(alkoxycarbonylimino)-3,3,3-trifluoropropionates.[46] Recently, we found that 5-fluoro-4-trifluoromethyloxazoles (**7**) exhibit the synthetic potential of Tfm Gly equivalents. Various side-chains can be introduced on reaction with allyl alcohols. When compound (**7**) was treated with the allyl alcohol the expected nucleophilic substitution product (**36**) could not be isolated. The Claisen system present in compounds (**36**) is responsible for a spontaneously proceeding rearrangement to give 5(*4H*)oxazolone (**37**) with a characteristic IR-absorption around 1830 cm^{-1} [47] (Scheme 11). Ring cleavage to give the *N*-protected α-Tfm amino acids (**38**) was achieved on addition of water.



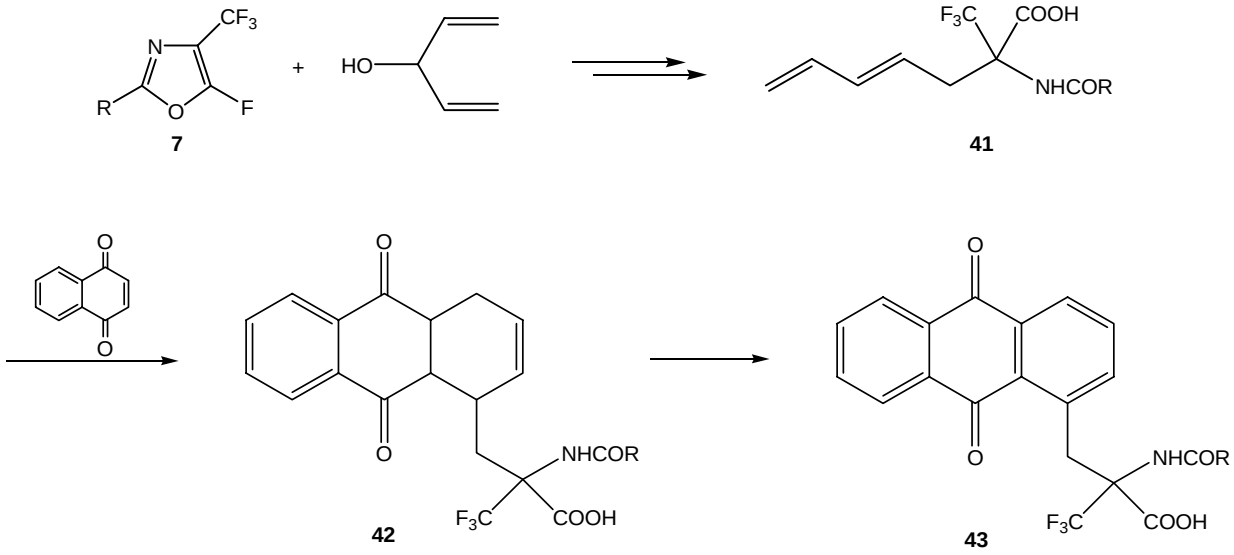
Scheme 11

Since a broad selection of allyl alcohols is available this reaction sequence provides a rather general synthesis for α-Tfm amino acids with unsaturated side-chains, which can be functionalized further or cross-linked after being incorporated into a peptide backbone to generate rigid domains. In this context, the reaction with terpene alcohols like geraniol, nerol, farnesol and phythol is noteworthy. α-Tfm amino acids (**39**, **40**) with lipophilic side chains now are readily available (Scheme 12).



Scheme 12

Furthermore, the new approach allows the incorporation of a 1,3-diene substructure into the side-chain (**7**) → (**41**) which includes the option of applying Diels-Alder chemistry[48] to decorate peptides and depsipeptides with carbocycles (**41** → **42** → **43**), e.g., constructing fluorescence markers in the side chains of peptides.

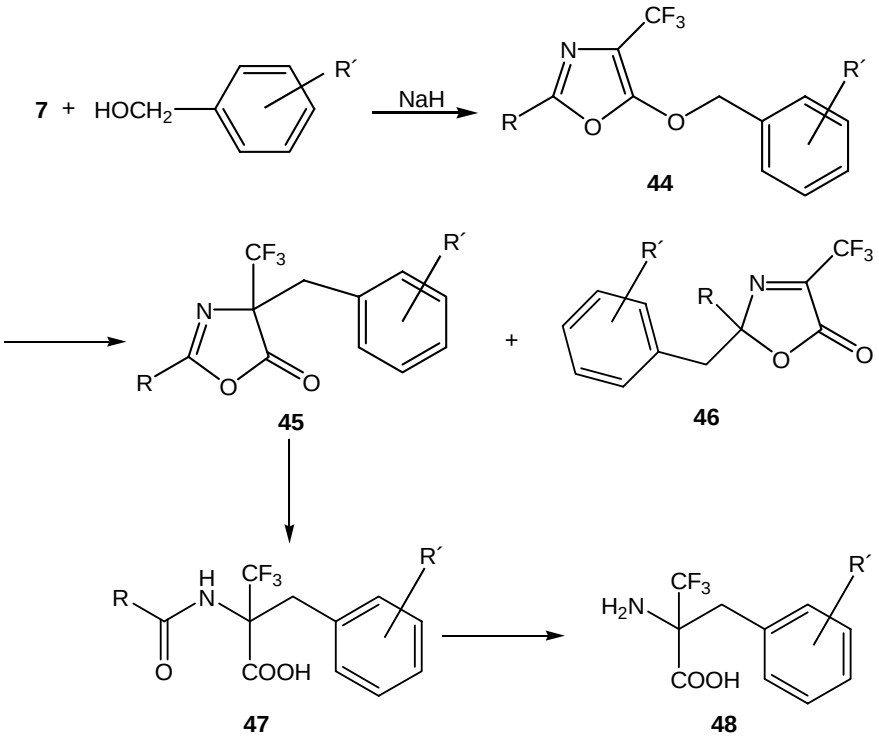


Scheme 13

When propargyl alcohols are used as nucleophiles α-Tfm amino acids with 1,2-diene subunits in the side-chain are obtained. [47]

3.2. Aromatic α-Trifluoromethyl α-Amino Acids

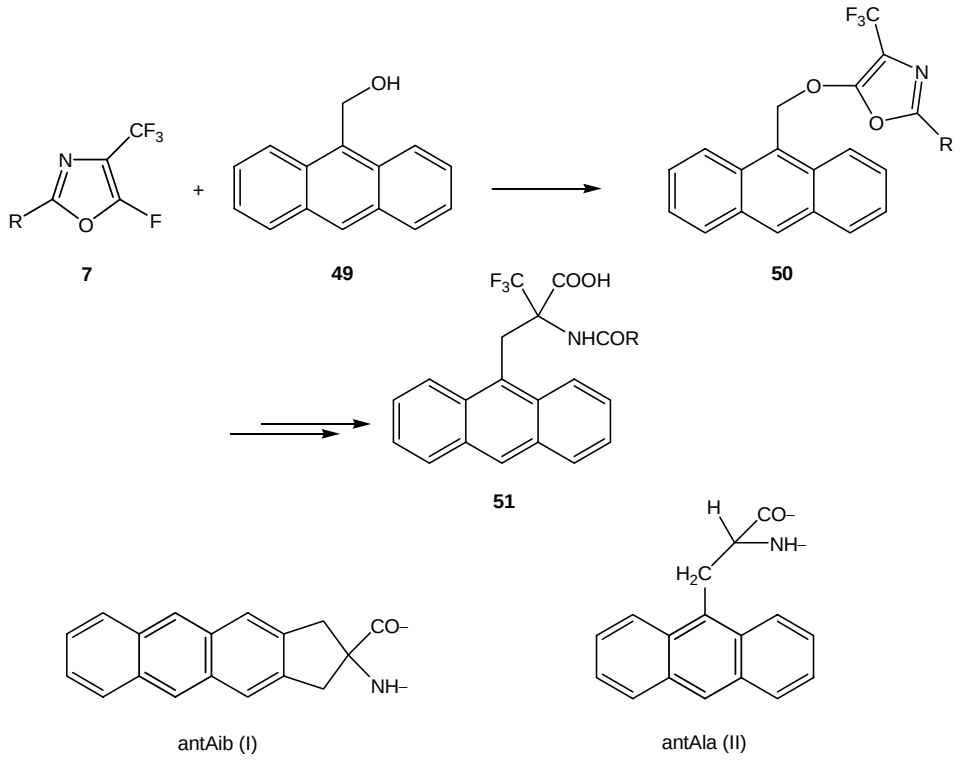
5-Fluoro-4-trifluoromethyl-oxazoles (**7**) react with benzyl alcohols in the presence of a base to give benzyl ethers (**44)**, which are stable at room temperature. At elevated temperatures they rearrange to give lactones. Two pathways are possible:[49] Claisen rearrangement or 1,3-benzyl group migration. Products formed via 1,3-benzyl group migration are characterized by the formation of a methylene group, while Claisen products show signals for methyl groups. The progress of the reaction can be monitored by ^{19}F-NMR spectroscopy. Intercrossing experiments revealed that the 1,3-benzyl shift is a non-concerted process.[50]



Scheme 14

Compounds of type (**45**) have been transformed into *N*-protected α-Tfm phenylalanines (**47**) on treatment with 6N HCl. The unprotected amino acids (**48**) were obtained on heating in conc. HCl and finally by crystallization at the isoelectric point.

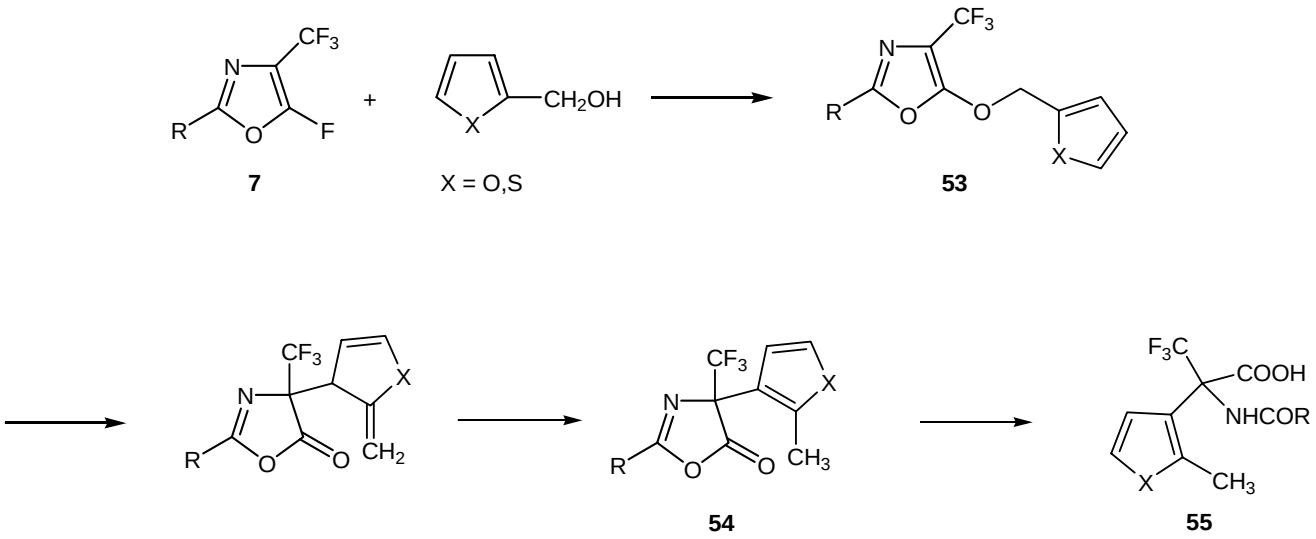
Recently, Wakselman et al. proposed antAib (I) and antAla (II) as fluorescent amino acids for conformational studies.[51] Compound (**51**), now readily available from **7** and 9-hydroxymethylanthracen, represents an α-Tfm analogue of antAla (II) (Scheme 15).

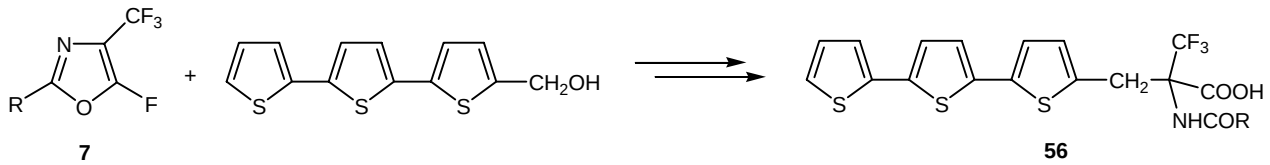


Scheme 15

3.3. Heteroaromatic α-Trifluoromethyl Amino Acids

Analogously, heteroaromatic systems possessing a hydroxymethyl group can be transferred as side-chain into α-Tfm amino acids. Remarkably, we observed different pathways for hydroxymethylfuran and hydroxymethylthiophene and on the other hand [2,2′:5′,2′′-terthiophen]-5-methanol. While substitution products of furan and thiophene undergo a Claisen rearrangement (**53**) → (**54**) → (**55**) the oligo-thiophene derivative gives products of a 1,3-shift (**56**)[52] (Scheme 16).

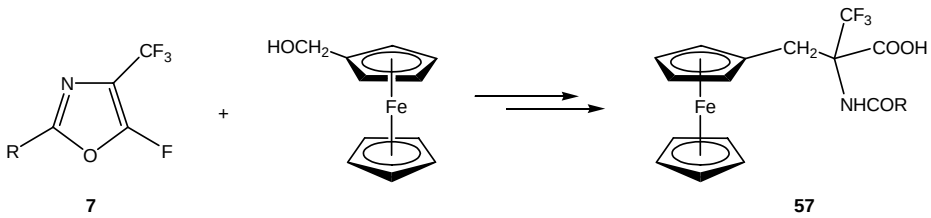




Scheme 16

3.4. Metal-containing α-Trifluoromethyl Amino Acids

Since cis-platin was introduced as antitumor drug[53] the development of new methodology for the synthesis of metal-containing amino acids is of current interest. Cancer activity of several metallocene derivatives[54] has been reported. Metal-containing amino acids like **57** can be readily incorporated into various biomolecules like peptides, depsipeptides and glycopeptides (Scheme 17).

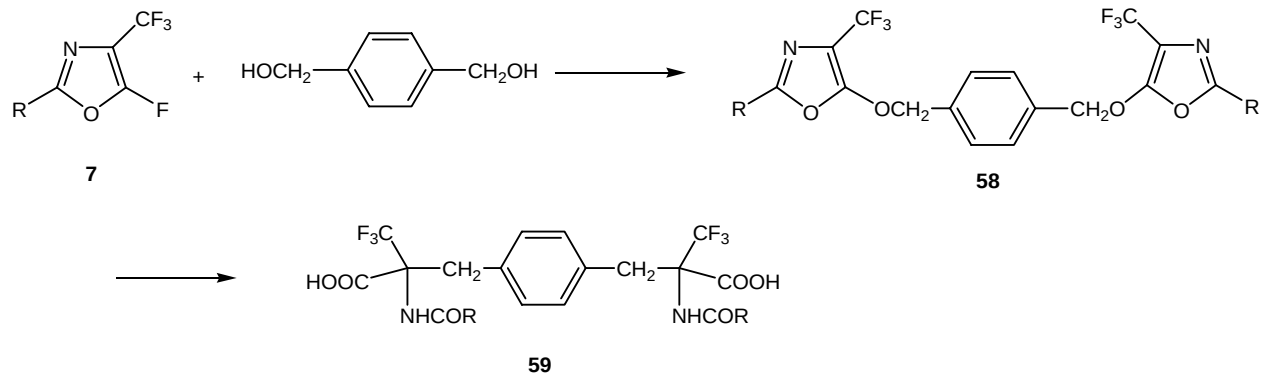


Scheme 17

3.5. Bis-armed α-Trifluoromethyl Substituted Amino Acids

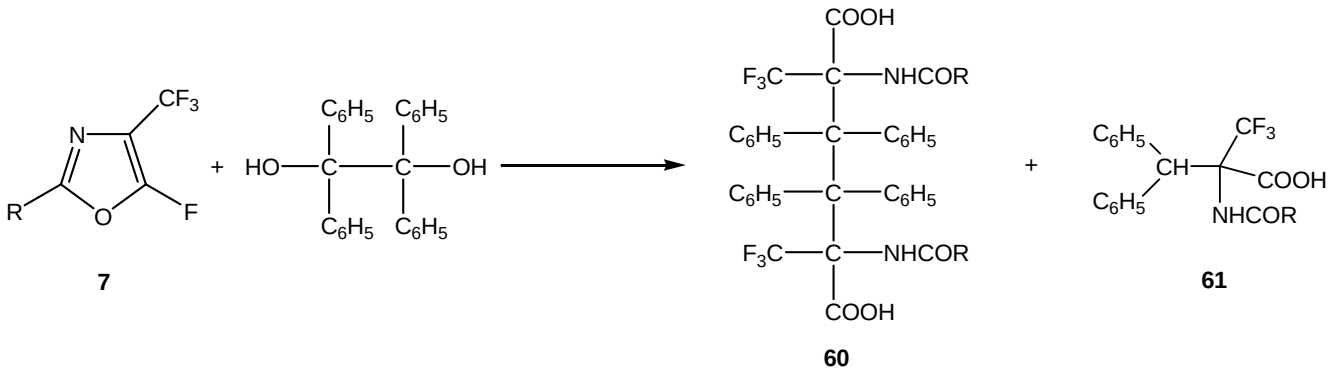
The design and synthesis of bis-armed α-amino acids has attracted considerable interest[55] mainly due to their presence as structural subunits in peptide antibiotics that disrupt microbial cell wall synthesis.[56]

In principle, every aromatic and heteroaromatic compound bearing two hydroxymethyl groups should be capable to react with two equivalents of the Tfm Gly moiety. Using this strategy new types of bis-armed α-Tfm amino acids become available on reaction of **7** with starting materials like 1,4-di(hydroxy-methyl)benzene (**7**) → (**58**) → (**59**) and benzopinacol (Scheme 18).



Scheme 18

Especially the concise synthesis of 2,5-di(trifluoromethyl)-2,5-diaminoadipic acid (**60**) is remarkable. [52] As by-product 2-benzhydryl-3,3,3-trifluoroalanine (**61**) was isolated (Scheme 19).

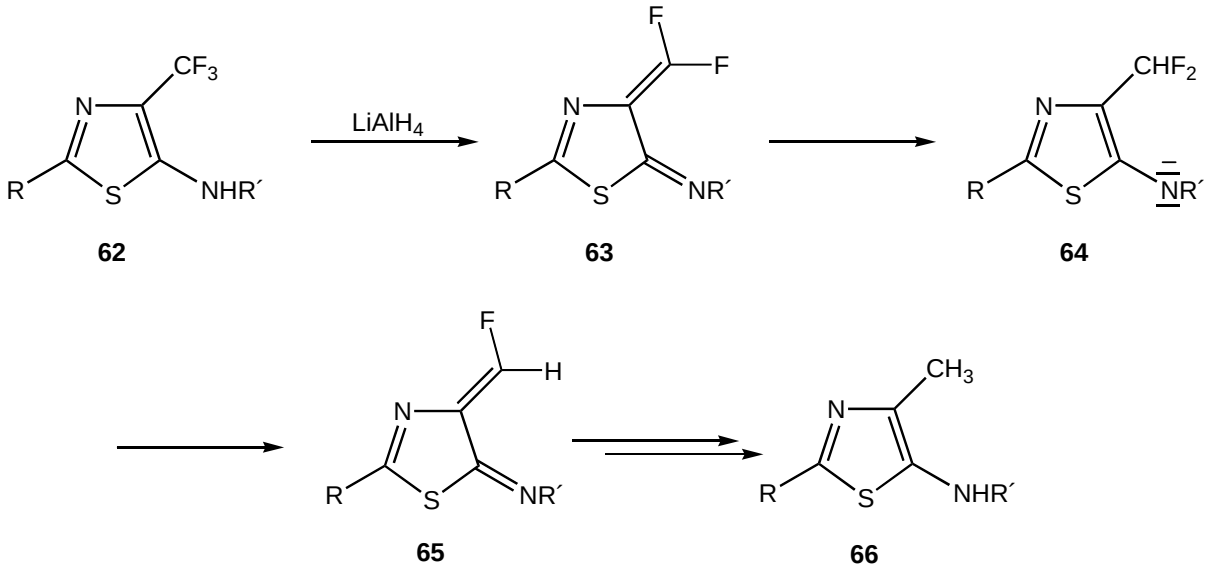


Scheme 19

4. Six Step Domino Reactions

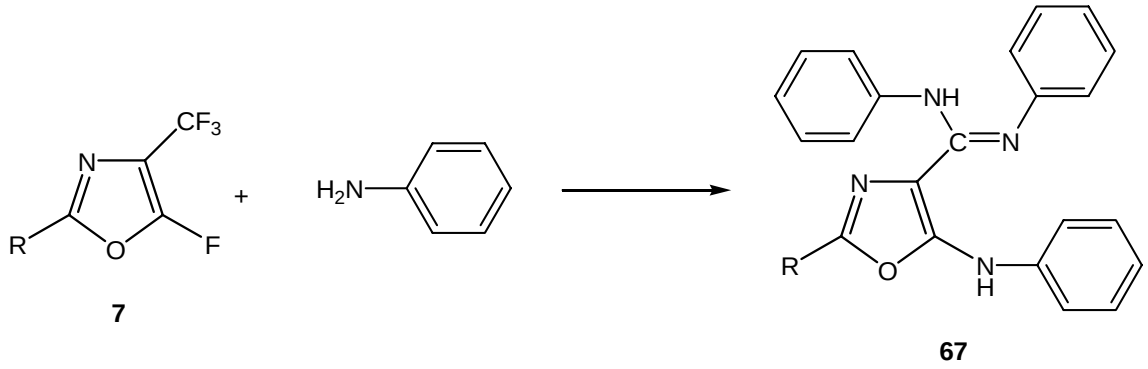
Compounds containing subunits like CF_3-C=C-NH-R readily undergo elimination / addition reactions which can be linked together and performed as domino reactions. 5-Amino-4-trifluoromethyl-1,3-thiazoles[57] have been applied as model compounds to develop new types of domino reactions.[58]

Under mild conditions a complete F/H-exchange of the trifluoromethyl group can be achieved on treating compounds (**62**) with $LiAlH_4$. Three cycles, each consisting of two steps, namely [1,4] HF-elimination followed by Michael addition of a hydride ion are linked together to give a six-step domino reaction (**62**) → (**66**) (Scheme 20).



Scheme 20

This reaction sequence can be applied for an efficient decoration of open-chain and cyclic systems bearing the subunit $CF_3CH=CHNH$- with interesting substituent pattern. When 5-fluoro-4-trifluoromethyl-1,3-oxazole (**7**) was heated with an excess of freshly distilled aniline compound (**67**) was formed in a six step domino reaction [59] (Scheme 21). The domino reaction should be suitable for deuterium labelling.



7 **67**

Scheme 21

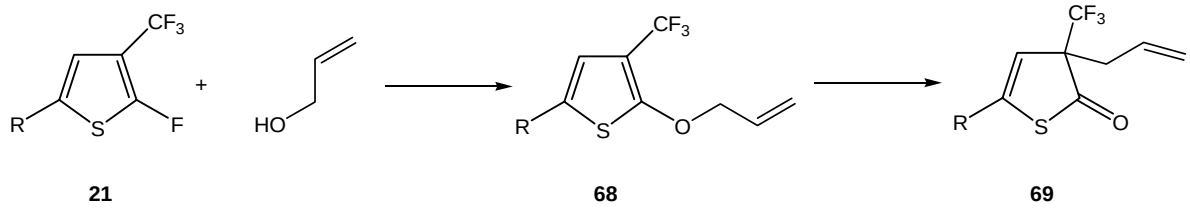
5. 2-Fluoro-3-trifluoromethylfurans and –thiophenes

α-Trifluoromethyl Substituted Butenolides and γ-Ketoacids

Butenolides[60] - 2(*5H*)-furanones - are of interest to medicinal and agricultural chemists because of their broad biological activities.[61] Consequently, numerous routes to this interesting class of compounds have been described.[62] However, trifluoromethyl-containing butenolides are still rare.

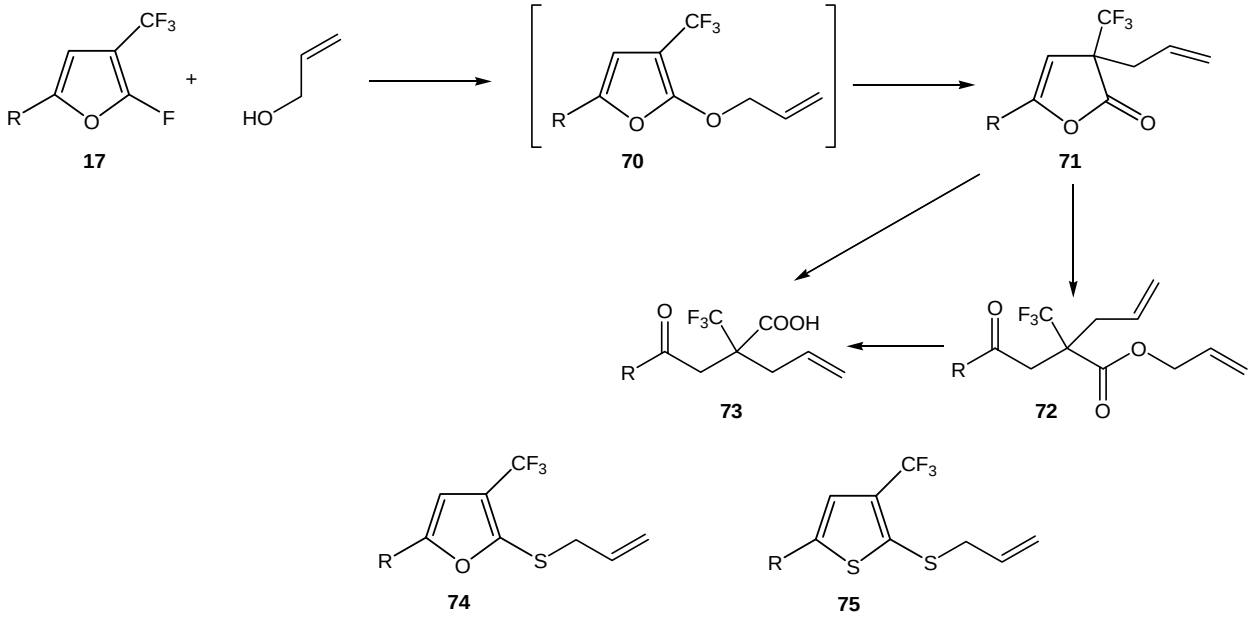
5.1. Domino Reactions: Nucleophilic Substitution / Claisen Rearrangement

The reaction behavior of 2-fluoro-3-trifluoromethylfurans (**17**) and –thiophenes (**21**) should be similar to that of 5-fluoro-4-trifluoromethyl-1,3-azoles (**7**). The fluorine bound to C-(2) is activated by the adjacent trifluoromethyl group and therefore readily displaceable by various O-, S- N- and C-nucleophiles. When NaH was added at 0 ^oC to a solution of 2-fluoro-3-trifluoromethylthiophenes (**21**) and allyl alcohol (1-2 equiv.) in THF a nucleophilic substitution of the single fluorine readily takes place to give the allyl ether (**68**) in excellent yield. The presence of a Claisen system in **68** is the reason for its instability. After storage for three weeks at room temperature the rearrangement **68** → **69** was complete. The newly formed product again has a 1,5-hexadiene subunit. However, at room temperature a second [3,3] sigmatropic process was not observable (Scheme 22).[63]



Scheme 22

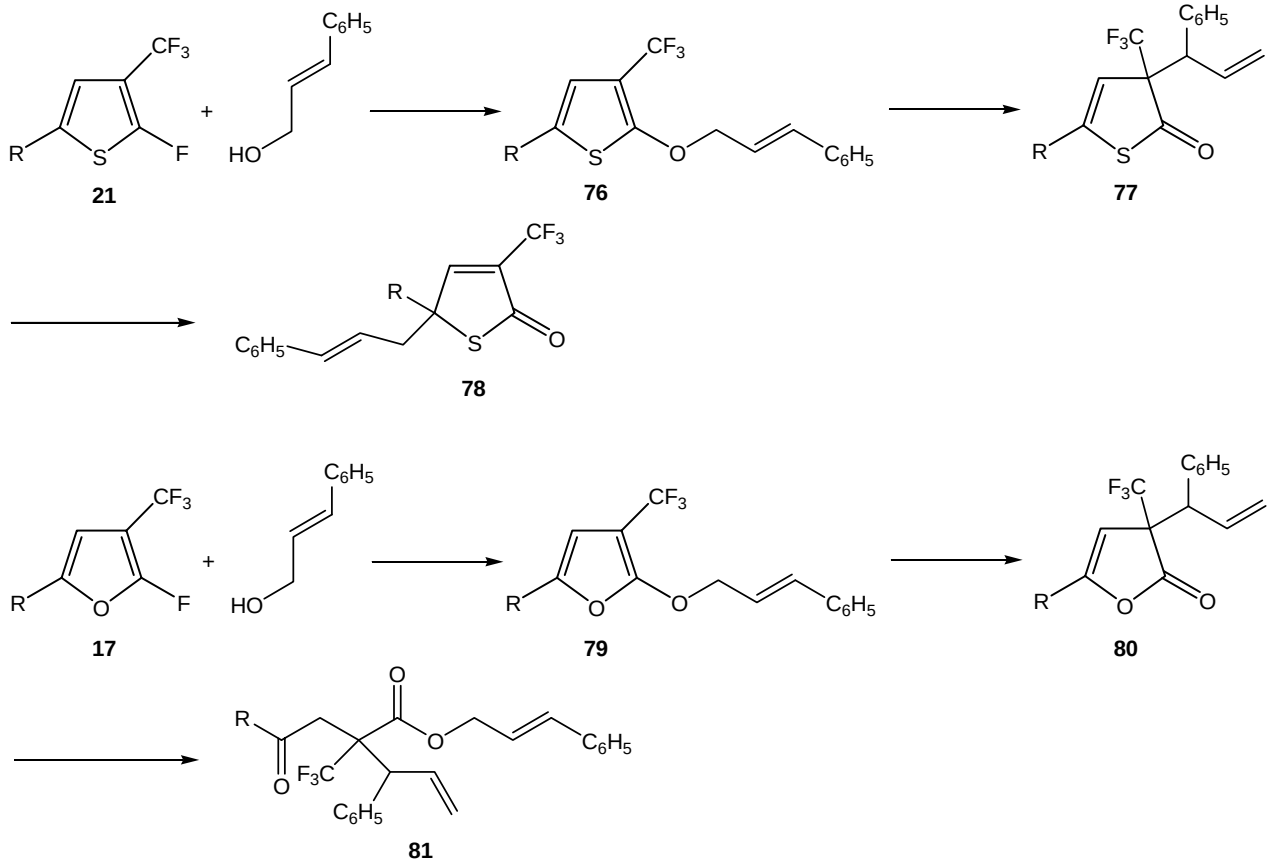
When 2-fluoro-3-trifluoromethylfuran (**17**) was treated with allyl alcohol under the same reaction conditions the product of the nucleophilic substitution (**70**) could not be detected even on monitoring the progress of the reaction by ^{19}F NMR spectroscopy because the Claisen rearrangement **70** → **71** is extremely fast. If an excess of allyl alcohol is used a transesterification occurs to give the allyl ester (**72**) of the α-trifluoromethyl substituted γ-keto acid. **71** and **72** on hydrolysis with diluted HCl give the unprotected α-trifluoromethyl-γ-keto acid (**73**) (Scheme 23). In contrast, the corresponding thioallyl ethers (**74, 75**) are stable up to 140 ^{o}C.[63]



Scheme 23

To activate the Cope system we studied systematically the reaction with a series of allyl alcohols having different substitution pattern at C-(3). For example. thiophene (**21**) reacted with cinnamic alcohol to give the Claisen product (**77**), which could be isolated, but it underwent a Cope rearrangement (**77** → **78**) on storage at room temperature. Under the same reaction conditions the furan (**17**) was transformed into the

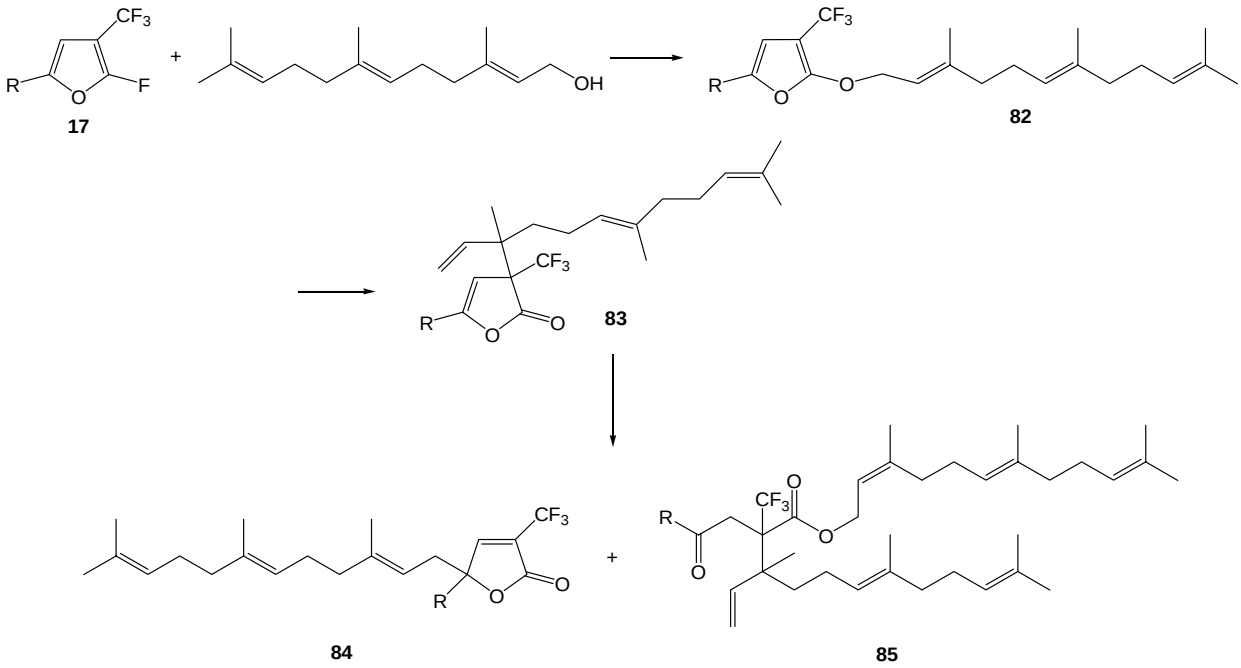
Claisen product (**80**) which spontaneously underwent cleavage of the lactone ring by the alcoholate (**80** → **81**), demonstrating that the transesterification is faster than the Cope rearrangement (Scheme 24).



Scheme 24

5.2. Domino Reactions: Nucleophilic Substitution / Claisen Rearrangement / Cope Rearrangement

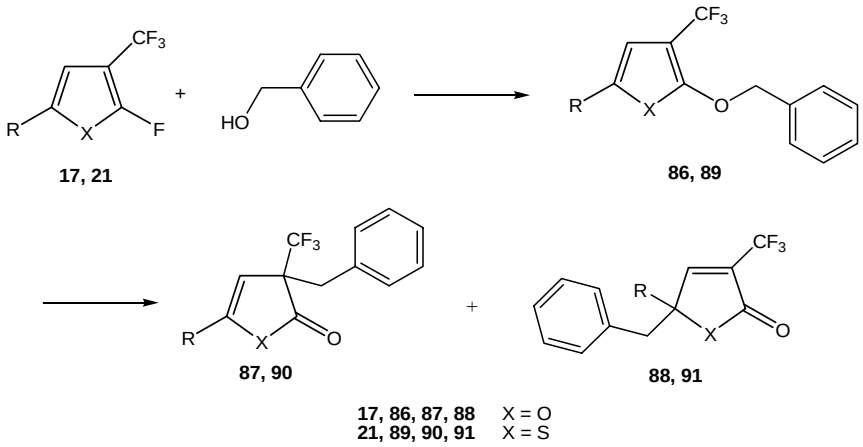
Finally, with two alkyl groups in C-(3) position of the allyl alcohol we succeeded in running the desired three step procedure consisting of nucleophilic substitution, Claisen rearrangement, Cope rearrangement as domino reaction (**17**) → (**82**) → (**83**) → (**84**). The development of methodology for the incorporation of lipidic anchors into biologically relevant compounds is a challenge for preparative bioorganic chemists.[64] Therefore, the applicability of the new domino reaction for introduction of lipidic side chains into α-trifluoromethyl substituted butenolides using commercially available C-10 and C-20 building blocks like geraniol, nerol farnesol, and phytol are of current interest[63b] (Scheme 25). Compounds (**84**) should be able to dock at membranes with its lipidic tail. The presence of the trifluoromethyl group allows to monitor the interaction of the butenolides with membranes by ^{19}F-NMR spectroscopy.



Scheme 25

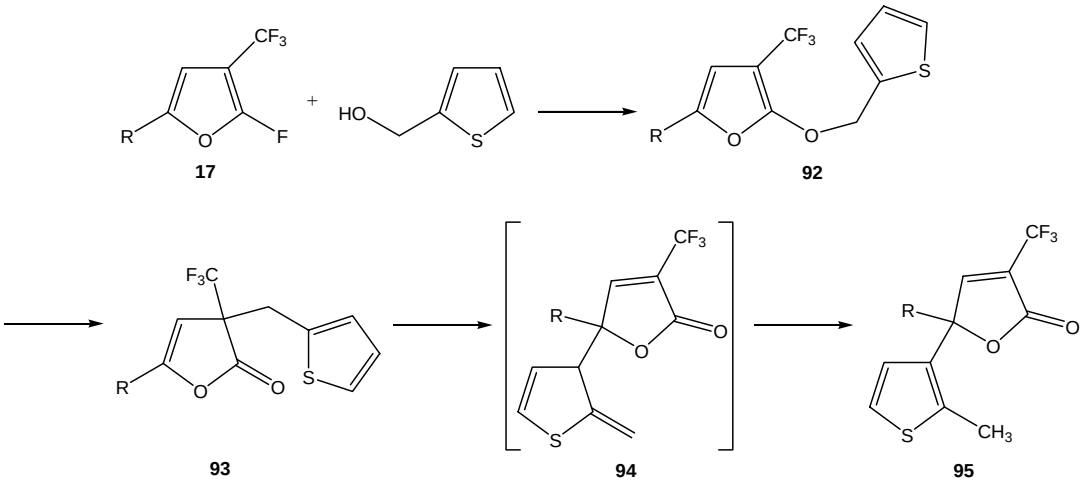
5.3. Nucleophilic Substitution with Benzyl Alcohols

2-Fluoro-3-trifluoromethyl-furans (**17**) and –thiophenes (**21**) undergo nucleophilic displacement reactions with benzyl alcohols at room temperature in the presence of sodium hydride.[65] While compound (**86**) rearranges slowly under the reaction conditions (**86** → **87** + **88**), **89** is stable at room temperature. At 120 ^{o}C both compounds (**86**) and (**89**) rearrange to give products of a 1,3- (main product) and a 1,5-benzyl group migration (by-product) (Scheme 26). The higher the temperature, the higher is the amount of the by-product. Intercrossing experiments revealed that the rearrangement is a non-concerted process. The 2(*3H*)furanones (**87**) show a characteristic IR-absorption around 1810 cm^{-1}, while 2(*5H*) furanones (**88**) with a conjugated lactone moiety absorb around 1765cm^{-1}.



Scheme 26

Surprisingly, we observed different reaction pathways when we reacted 5-fluoro-4-trifluoromethyloxazol (**7**) and 2-fluoro-3-trifluoromethylfuran (**17**) with 2-hydroxymethylthiophene and 2-hydroxymethylfuran, respectively. While in the oxazol series the nucleophilic substitution product (**53**) undergoes a Claisen rearrangement (**53**) → (**54**) (Scheme 16),[52] compound (**92**) stabilizes via 1,3-thienylmethyl group migration.[65] The complete reaction sequence (**92**) → (**93**) → (**94**) → (**95**) can be carried out as a one-pot reaction (Scheme 27).



Scheme 27

Scope of the review is to draw attention of synthetic chemists to new methodologies for fluoromodification of organic molecules. Anion activation of bis(trifluoromethyl)-substituted hetero-1,3-dienes is a powerful concept for the synthesis of partially fluorinated heterocycles, which are interesting compounds on their own, furthermore they can serve as versatile building blocks for the construction of complex trifluoromethyl substituted molecules.[52, 63b]

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