

Fluorinated Heterocycles

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Fluorinated Heterocycles

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Foreword

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Preface

This book is based on a symposium held at the fall 2006 meeting of the American Chemical Society in San Francisco, California. The purpose of the symposium was to bring together chemists with an interest and expertise in various aspects of the chemistry of fluorinated heterocyclic compounds. In the initial chapter we have outlined some of the issues and problems that were addressed in this symposium. We gratefully acknowledge the enthusiastic and talented work of the authors of the chapters that follow. In this preface, we have chosen to reveal personal stories describing how fluorinated heterocyclic chemistry became the focus of our own work. We feel that these personal stories might be of interest within the context of the book.

The path of the science is conventionally presented as a history of ideas, yet the human factor can hardly be discounted as irrelevant. Perhaps the key to understand this intertwined relationship is through the acknowledgment that the science is in fact the human science, embedded in the human society among other tools to understand and to transform the outside world. And while the facts of the science would remain the same regardless of an observer, their interpretation and—more importantly—their inner meaning critical for the selection of future research directions are inherently the subjects of a personal choice. We would never know what modern chemistry would look like had Alexei Yevgrafovich Favorskii decided to investigate the reaction between the methyl iodide with the magnesium in ether instead of the rearrangement of α -halo ketones in the presence of a base, and what François Auguste Victor Grignard would select as a subject of his research under these circumstances. The personal choice is critical because there are (and there always will be) many more unknown reactions than known ones

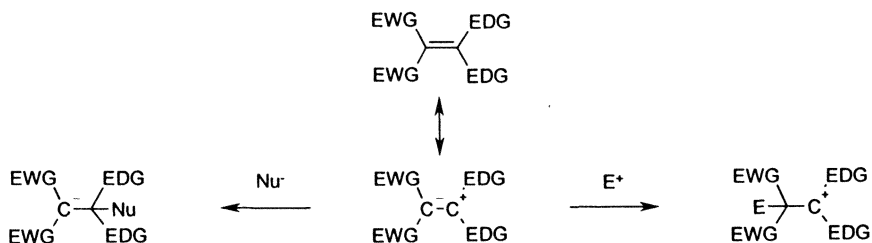
and the direction of the path forward would always be more important than the results acquired along the way. Some of these choices in direction will lead to open new areas yielding results at every fork and turn in the discovery road, and others will lead to dead ends and eventually will be abandoned after the consumption of valuable resources. Cold Fusion is one of the most notable recent examples, but chemistry of the past was also not immune from its own fiascos. The search for the Philosopher's Stone and the Phlogiston theory are notable examples.

The review of existing literature helps little to understand the inner human logic behind the scientific motivations of the past. This book is not an exception, because it is easy to understand *what* was done and *how*, but not always *why* it was done to begin with. After all, the chemistry of fluorinated heterocycles is hardly even close to 1% of modern chemistry, and other, perhaps more exciting opportunities are waiting for a motivated chemist to join. This preface will provide in our own cases answers to *why* our science was pursued, an issue that comes into play before the questions *what* and *how* were even raised.

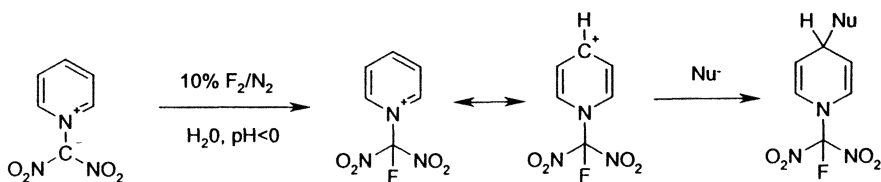
Andrei A. Gakh's Story

It would be easy to state that fluorinated heterocycles was the first area of my research interests and it is natural to stay on the known path rather than to start all over again in the middle of the scientific career. This would be a true statement (my first journal publication was indeed devoted to the reactions of *N*-fluoropyridinium salts), but not the whole truth. My interest in fluorinated heterocycles was developed during the third year of the graduate research from a seemingly unrelated pursuit toward synthetic applications of polarized double bonds. Any polarized double bond [the double bond having electron-withdrawing groups (EWG) on one end and electron-donating groups (EDG) on the other end] can also be considered as an ylide, or a betaine, depending on a chosen convention. Polarized double bonds can be activated by addition of both an electrophile E^+ (on the electronegative end) or a nucleophile Nu^- (on the electropositive end) thus yielding either a conjugated carbocation or a carbanion, respectively. Unfortunately, aliphatic systems

in many cases produce very reactive ionic intermediates that can be investigated only indirectly, based on the structures of the final reaction products.



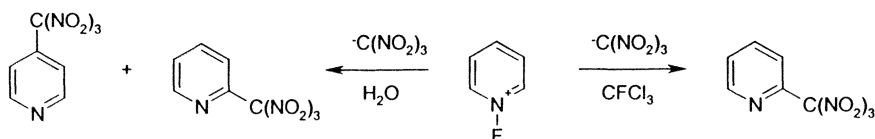
At that time a colleague of mine was working with *N*-dinitromethyl ylides of pyridine. It seemed logical that these systems should also react with an electrophile to yield similar conjugated cations. It was expected that the presence of a strong electron-withdrawing group would force the charge distribution toward the resonance structure having a cationic center at the 4-position rather than at the nitrogen atom (see below). Indeed, fluorination of the ylides gave *N*-fluorodinitromethylpyridinium salts that were stable in water at low pH and that reacted easily with conjugated carbanions. The reactions with the nitroform anion ($pK_a \sim 0$) and the dinitroacetonitrile anion ($pK_a < -5$) were of particular interest. In the first case the expected 4-substituted product was produced in almost quantitative yield, whereas in the second case no reaction between the anion and the cation was detected. Clearly, *N*-fluorodinitromethylpyridinium cation had enough power to heterylate the nitroform anion, but not enough power to react with the dinitroacetonitrile anion.



Perhaps more research could have been done with these cations, but their synthetic availability was a problem: the three-step synthesis from pyridine entailed the use of bromoacetone. In addition, safety precautions were required to work with these cations since they have two nitro groups and—while perfectly stable up to 200 °C with non-nucleophilic counter-anions such as BF₄ or PF₆—could decompose exothermically under certain conditions.

The next logical step was to remove the unnecessary dinitromethyl group by shifting the research focus from *N*-fluorodinitromethylpyridinium salts to *N*-fluoropyridinium salts. These salts can theoretically be produced in one step from pyridine. A quick check of the literature prior to 1983 (when all these events were taking place) revealed that *N*-fluoropyridinium fluoride is unstable at room temperature. It was a disappointment, but the synthesis was still worth repeating with a hope that exchanging the fluoride counter-ion with less nucleophilic BF₄⁻ would produce the reagent with an adequate stability. This proved to be the case.

The *N*-fluoropyridinium salts were a source of initial frustration because—unlike *N*-fluorodinitromethyl analogs—they failed to react instantly with the nitroform anion. Only an accidental discovery of a crystalline product from the left-alone reaction mixture prevented abandonment of this cation and perhaps all future fluoroheterocyclic research altogether. But even with the pure compound at hand it took almost 3 weeks to establish the structure. First of all, two protons in 2-trinitromethylpyridine had the same chemical shift, and its deceptive non-first order ¹H NMR spectrum easily confused even NMR professionals. In addition, the same reaction performed in water yielded 4-trinitromethylpyridine as the major product together with 2-trinitromethylpyridine as the minor product. This was clarified only later in subsequent experiments.



The importance of the intriguing chemistry of fluorinated heterocycles did not receive instant recognition, even though other fluorinated heterocycles, such as *N*-fluoroquinolines, displayed similar reactivity patterns. After several deliberations, it was finally agreed to include *N*-fluoropyridinium chemistry in the dissertation thesis, to publish a short note, and to deposit the rest of the experimental data in the provisional patent and the report.

It was sheer luck that this short publication was apparently noted and perhaps indirectly prompted initial interest in the chemistry of *N*-fluoropyridinium salts of an independent research group across the continent. Otherwise it might have taken another 10 years until the chemistry of *N*-fluoropyridinium salts would find a devoted researcher. This could well be a likely scenario taking into consideration that there were no published reports on this subject between 1972 and 1983.

Opportunities for the substantial expansion of the research effort in the area of fluoroheterocycles presented itself only several years later, with the synthesis of *N*-fluorobenzotriazole and *N*-fluorosaccharine, but the driving force behind this expansion was more pragmatic, and related to the synthesis of compounds with already determined practical application potential. This practical interest eventually shaped this effort during the next twenty years - but this is a completely different story.

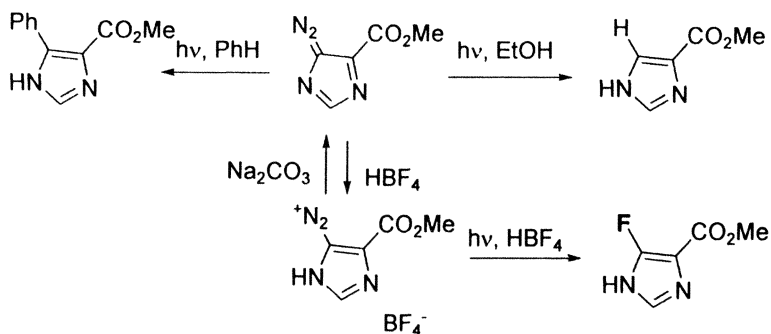
Should this account of actual events be considered as a demonstration of a random sequence of seemingly logical steps leading to an eventual match between the capabilities presented by a chemist and opportunities presented by the chemistry? The answer to this question might be found within the context of the next real story of fluoroheterocyclic chemistry engagement.

Kenneth L. Kirk's Story

I joined the group of the late Louis A. Cohen in the Laboratory of Chemistry (now Laboratory of Bioorganic Chemistry), NIAMD (National Institute of Arthritis and Metabolic Diseases, now National Institute of Diabetes and Digestive and Kidney Diseases—NIDDK) as a postdoctoral fellow in 1965. Initially I carried out some interesting work

synthesizing new compounds as potential peptide reagents and had moved on to other projects. In the mid 1970s, these projects were not going particularly well. During this time period, other postdocs in the group had been trying to put a fluorine atom on an imidazole ring. Lou Cohen had correctly assumed that the resulting fluoroimidazoles not only would be a new class of fluorinated heterocycle, but also, because of the importance of the imidazole ring, this substitution could have a big payoff in biological results. However, all attempts in the lab had been unfruitful. These included repeated attempts with the Schiemann reaction (thermal or metal-catalyzed) and Halex reactions of activated halogens. In all cases, intractable tars and no fluorinated compounds resulted. In one instance, attempts to recrystallize a diazonium salt led to a small explosion, a powdered flask, and one frightened postdoc. These experiences went on for some time, almost a right of passage in Lou's group.

Because of dissatisfaction with my current projects, I asked Lou in mid summer if I could have a try at making fluoroimidazoles, and he agreed. One of the compounds that had been isolated was the diazo ester shown below, prepared by treatment of the diazonium fluoroborate with bicarbonate. I had been trained in photochemistry in graduate school and had additional experience in this area as a postdoctoral fellow in Professor G. Quinkert's group (Braunschweig). It was apparent that the diazo ester would offer interesting photochemistry, so just to see what would happen, I began doing small-scale photochemical reactions, mini-zaps in a mini-zapper. As expected, nitrogen was lost readily upon irradiation with UV light, and, depending on the solvent, a new substituent was installed in the 4-position (e.g., phenyl, hydrogen). A logical question arose. Could a reaction medium be chosen that would provide a source of fluorine? Indeed, a convenient fluorine-containing solvent was at hand, and the diazo ester was dissolved in fluoroboric acid, regenerating the diazonium salt. Irradiation of this solution was accompanied by slow nitrogen evolution with the formation of a new compound less polar than the unsubstituted imidazole carboxylic ester. This was isolated by preparative thin-layer chromatography and a mass spectrum gave the correct molecular weight for methyl 4-fluoro-5-imidazole carboxylate.



That event, in August 1970, marked the real beginning of my research career at the National Institutes of Health (NIH) and propelled me headlong into the exciting field of organofluorine chemistry, with an emphasis on fluorinated heterocyclic compounds, especially imidazoles. The chemistry and biology of ring-fluorinated imidazoles became a very rewarding focus of our research that continues to this day. It is fortunate for me that NIH and NIDDK provided an ideal environment and resources to pursue this research, and I remain grateful for the support and freedom I had to follow leads as my research progressed. I also acknowledge the many colleagues with whom I have been associated and who have supported me in my career. It has been a fantastic ride.

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Fluorinated Heterocycles

Chapter 1

Fluorinated Heterocycles

Andrei A. Gakh¹ and Kenneth L. Kirk²

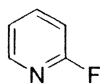
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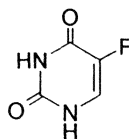
This introductory chapter is a quick overview of almost 100 years of fluoroheterocyclic chemistry, with particular attention to modern synthetic methods and applications presented in this book. Critical discussions regarding various synthetic procedures including nucleophilic and electrophilic fluorination, metal-catalyzed heterocyclization, cine- and tele- substitution in *N*-fluoroheterocycles, fluorodenitration, water-based chemistry, as well as applications of fluorinated heterocycles in medicine and agriculture are presented along with the examples of fluoroheterocyclic compounds of particular interests.

Historical Perspective

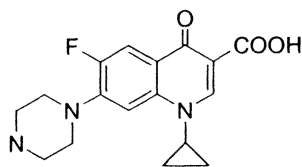
The history of ring-fluorinated heterocycles can be traced back to the seminal work of Chichibabin who carried out the synthesis of 2-fluoropyridine (**1**) over 90 years ago (1). However, real progress in this field did not gain momentum until about four decades later, in the 1950s, with the development of new synthetic methods and more readily handled fluorinating agents. It was in this period that 5-fluorouracil (**2**) was prepared in a rational approach to new anti-cancer agents (2). The effectiveness of this drug heralded the development of many related anti-cancer agents that still have important clinical applications 50 years after the original discovery (3). Another major success story followed shortly thereafter with the discovery of the fluoroquinolone family of antibiotics in the early 1970s (4). A particularly important member of this group, ciprofloxacin (**3**), was approved for human use in the US in late 1980s. There continues to be extensive work being done in the development of new fluoroquinolones (4,5). In addition to these examples, there is an ever-growing inventory of important clinical agents derived from fluorinated heterocyclic compounds. These and other applications will be discussed briefly in this introductory chapter.



2-Fluoropyridine

1

5-Fluorouracil

2

Ciprofloxacin

3

The Status of the Field

Despite these and other important early breakthroughs, not limited to biomedical applications, the status of development of the field of fluorinated heterocyclic chemistry as a whole can be characterized as “evolving.” This is particularly true when this specialized field is compared to the more mature areas of related chemistry, such as the chemistry of fluoroaromatic compounds or the chemistry of non-fluorinated heterocycles. There are many contributing factors for this relatively under-developed status of fluorinated heterocyclic chemistry.

Synthetic Challenges

One factor which clearly amplifies synthetic problems associated with preparation of certain classes of fluorinated heterocycles is the combination of special properties of a heteroatom and special properties of the fluorine atom. The failure of the thermal Schiemann reaction to produce ring-fluorinated imidazoles is one example (6). Many other examples exist.

Three major approaches can be highlighted in an attempt to provide a general overview of existing synthetic methodology for the preparation fluorinated heterocycles: (i) synthesis from fluorinated building blocks, (ii) chemical modification of fluorinated heterocycles with the retention of fluorine atom, and (iii) introduction of fluorine (or fluorine-bearing fragments) into an already formed heterocyclic moiety. All three methods have their advantages and disadvantages, so modern synthetic methodology is best contemplated with the consideration of all approaches, even though the first method is far more widely used than the last two combined.

The ready availability of a wide variety of fluorine-containing building blocks, many on an industrial scale, is one major reason for the popularity of the fluorinated synthon approach to the synthesis of fluorinated heterocycles. The relative ease of carbon-heteroatom bond formation as the key step of the heterocyclization process, and the plurality of excellent, well-developed heterocyclization procedures suitable for fluorinated components also are important factors. It is not a coincidence that this synthetic methodology is being used exclusively or in combination with other approaches in a preponderance of the papers presented in this book (7-12). Due to inherent predilections of this synthetic method, it is most suitable for the synthesis of fluoroalkyl- and fluoroaryl-substituted heterocycles (including annulated benzazole(azine) fluorinated heterocycles), and, to a lesser degree, ring-fluorinated heterocycles. Among these, fluoroalkyl and fluoroaryl fragments, trifluoromethyl and mono-fluorinated *o*-, *m*- and *p*-fluorophenyl fragments are the most popular ones (availability of appropriate building blocks being an obvious driving factor). Lately, some other fluorinated groups, such as trifluoromethoxy (11) and pentafluorosulphonyl (12) groups, have begun to occupy a permanent place in the pool of available fluorinated sub-fragments. Some examples of heterocyclic compounds prepared via this methodology are presented below (Figure 1) (7-12).

One of the notable variants of the above methodology employs carbocyclization instead of heterocyclization. This synthetic approach typically entails transition metal mediated carbon-carbon bond formation (via Diels-Alder reactions or intramolecular methathesis-type transformations). One of the clear advantages of this method is easy access to ring-fluorinated annulated fluoroheterocycles that are difficult to prepare by other means. Examples of fluorinated heterocycles prepared by this method are presented below (Figure 2) (8,13).

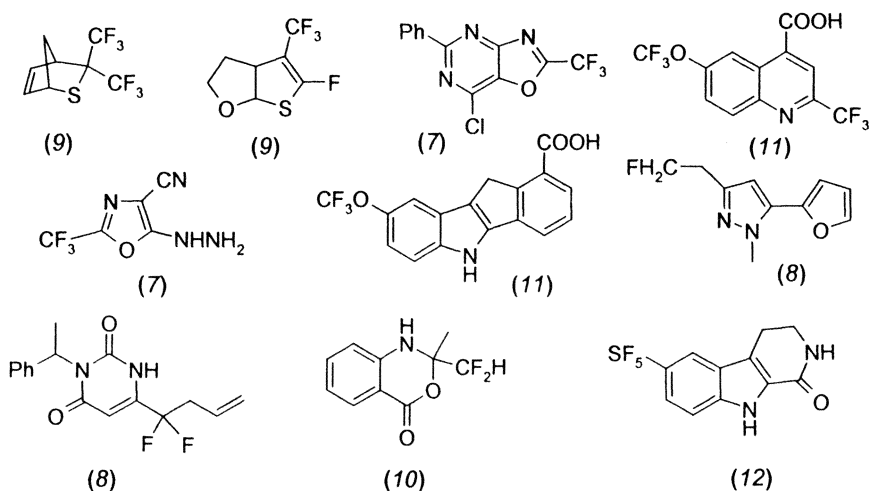


Figure 1. Examples of fluorinated heterocycles prepared from fluorinated building blocks.

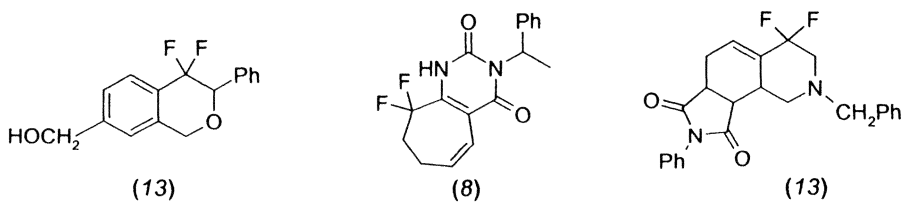


Figure 2. Examples of fluorinated heterocyclic compounds prepared by carbocyclization reactions.

Another popular synthetic strategy involves modification of fluorinated heterocycles with at least partial retention of fluorine to produce a new fluorinated heterocyclic compound. (A special case is represented by fluorine migration reactions, notably exemplified by the reactions of *N*-fluoropyridinium salts with strong bases discussed below.) This widely used approach to fluorinated heterocycles can also be found in almost all previously mentioned chapters of this book (7-13). Although transformations of fluorinated heterocycles can be achieved by many modern synthetic methods, lithiation and subsequent reactions of lithiated fluoroheterocycles deserves special attention since the reaction is both facilitated and directed by the presence of the strongly electron-withdrawing fluorine atom (14).

Finally, introduction of fluorine (or fluorine-bearing fragments) into an already formed heterocyclic moiety is a third widely used synthetic method. Two complimentary approaches are used routinely to accomplish this transformation – electrophilic replacement of a hydrogen atom with “electrophilic” fluorine (including an addition-elimination pathway similar to the one used for the synthesis of 5-fluorouracil 2), and nucleophilic replacement of a good leaving group using a source of fluoride anion. (Installation of the trifluoromethyl group also can be carried out by either electrophilic or nucleophilic procedures.) A less common synthetic methodology entails substitution of a hydrogen atom via transient formation and subsequent rearrangement of halogen-heteroatom compounds (such as *N*-fluorinated heterocycles), but these examples are rare.

The presence of heteroatoms amplifies problems associated with direct fluorination, and has hindered widespread use of this approach for the preparation of *C*-fluorinated heterocycles. With respect to electrophilic substitution, there is generally reduced reactivity of heterocycles compared to carbocycles due to the electron-withdrawing properties of two ubiquitous heteroatoms (N and/or O). Combined with low regioselectivity of elemental fluorine, a commonly used electrophilic fluorinating agent in earlier studies, these factors often resulted in poor regioselectivity in the *C*-fluorination process. In the preponderance of cases a mixture of fluorinated isomers is produced accompanied by unreacted non-fluorinated substrate. Separation and purification is difficult because of the small differences in physical properties (boiling points) of fluorinated heterocycles and their non-fluorinated hydrogen-bearing analogues. The situation improved somewhat with the advent of modern electrophilic fluorinating agents including commercially available *N*-fluorinated reagents such as N^+-F DABCO derivatives and *N*-F sulfonimides, as well as industrially important fluoroxyulfate salts $M^+ \cdot OSO_2OF$ and more exotic ones such as fluorinated fullerenes $C_{60}F_{48}$ (15), fluorine nitrate $FONO_2$ (16), or even noble gas reagents such as $FXeOSO_2CF_3$ (17). However, an adequate resolution of problems associated with electrophilic fluorination of heterocycles has not been realized. So far the best results have been achieved in cases where a

heterocycle (for example – N-methylpyrazole) possesses only one strongly preferred reactive site in the specific reaction conditions (18).

In the case of nucleophilic substitution, regioselectivity is usually not an issue because this is usually determined by the position of a leaving group (notwithstanding rare cases of cine/tele substitution), but other challenges exist. For example, desolvation of fluoride and/or inhibition of coordination are required to expose the latent nucleophilicity of fluoride, but “naked” fluoride is a relatively strong base. This can be particularly problematic with base-sensitive heterocycles or with heterocycles bearing, for example, an acidic N-H functionality. In addition, in comparison to other common nucleophiles, even under such conditions fluoride is not impressively nucleophilic. A variety of new sources of fluoride anion and reaction conditions designed to address these issues have been developed (including systems containing weakly coordinated fluoride ion such as anhydrous tetrabutylammonium fluoride (19) in aprotic solvents), but it did not solve all the problems completely. For example, a supposedly textbook reaction between 2-chloropyridine and KF proceeds only in harsh conditions (200 °C, dimethylsulfone, 21 days) with only moderate yield (ca. 50%) of expected 2-fluoropyridine (20). A variety of additional workaround approaches have been employed to improve kinetic characteristics of these reactions by using less-common leaving groups, such as a nitro group – “fluorodenitration” (21,22), and other groups (23). A very promising approach entails the use of positively charged leaving groups, such as trimethylammonium and dimethylsulfonium. These leaving groups allow syntheses of fluorinated heterocycles by nucleophilic displacement using hydrated fluoride ion and fluorination reactions can be performed even in water-based mixed solvents. Nucleophilic fluorination in water can be considered as the Holy Grail of not only the chemistry of fluoroheterocyclic compounds, but also general organic fluorine chemistry as well (see also the discussion on “Nucleophilic Fluorination in Water” below).

Perhaps the only class of fluoroheterocycles where direct fluorination appears to be a relatively reliable process providing adequate regioselectivity in the preponderance of cases is the unique class of *N*-fluoroheterocycles (24).

Some examples of fluoroheterocycles prepared by electrophilic and nucleophilic fluorination are presented below (Figure 3) (18,19,21,23,24,25).

It appears that these and other problems associated with fluorination of heterocyclic systems can be cited as reasons for the presence of gaps in the family of fluoroheterocycles. For example, while almost all possible isomers of fluoropyridines are known and many of them are available from commercial sources, a search of available literature revealed no simple, reliable synthetic procedures for the synthesis of such simple fluoroheterocycles as 5-fluorotetrazole and 3-fluorothiophene, even though both compounds are registered in the CAS database, and synthetic procedures for preparation of the isomeric 2-fluorothiophene and derivatives of 5-fluorotetrazole are known. The

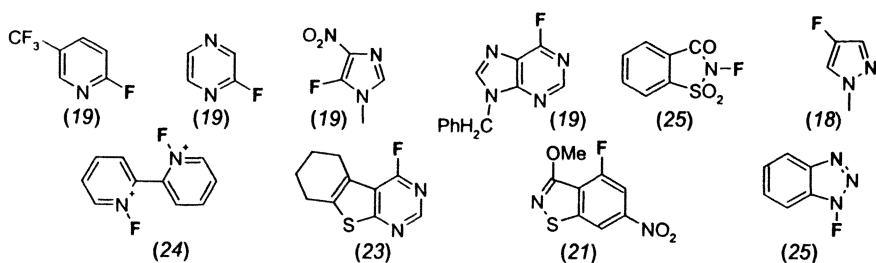
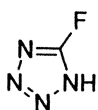
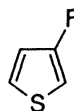


Figure 3. Examples of fluorinated heterocyclic compounds prepared by direct introduction of fluorine (nucleophilic or electrophilic).



5-Fluorotetrazole



3-Fluorothiophen

situation is somehow better for perfluorinated heterocycles, but they clearly represent a special case, as discussed in more detail below.

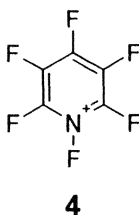
Polyfluorinated Heterocycles: A Special Case

With respect to ease of synthesis, polyfluorinated heterocycles represent a rare exception since these compounds are more readily accessible than their mono- and difluorinated analogs. Available routes include gas-phase polyfluorination of heterocycles with CoF_3 or other metal-based electrophilic fluorine-transfer reagents (26) - procedures now mainly of historic interest - as well as electrochemical fluorination (27), and, finally, Halex-type reactions from the corresponding polyhalogenated heterocycles (28). The last method now provides industrial scale access to these chemicals.

Early synthetic successes with these perfluorinated compounds could be attributed to several factors. One of them is the absence of regioselectivity problems for the synthesis of perfluorinated heterocycles. Another particularly important factor is the improved reaction kinetics of Halex-type reactions due to the presence of several halogen atoms in a molecule. This is the key consideration for current industrial production schemes of polyfluorinated heterocycles.

The presence of multiple fluorine atoms in polyfluorinated heterocycles alters their physical and chemical properties quite substantially, so it would be

prudent to classify them as a stand-alone family of fluoroheterocycles. One unique feature is the cumulative effect of multiple fluorine atoms which manifests itself in (i) the extreme ease of nucleophilic substitution reactions, sometimes proceeding towards complete elimination of all fluorine atoms, (ii) strong electron acceptor properties which are critical for the formation of various charge-transfer complexes, and (iii) the high C/F ratio which is an important parameter affecting applications of non-aromatic perfluoroheterocycles as oxygen carriers in artificial blood systems. Despite better development, some residual challenges still remain in this area. For example, the synthesis of fully-fluorinated symmetrical hexafluoropyridinium cation **4**, a heterocyclic analog of hexafluorobenzene, has yet to be completed.



Specific properties of polyfluorinated heterocycles as well as the sheer volume of available literature prevent us from providing adequate coverage of this special case here. In addition none of the chapters of this book is directly related to the synthesis, transformations and applications of these compounds. Readers are directed elsewhere for an adequate coverage of chemistry of polyfluorinated heterocycles (see, for example, refs. 26-28).

Chemical Behavior and Reactivity of Fluorinated Heterocycles

One of the major factors contributing to the relative lack of comprehensive understanding of fluoroheterocyclic chemistry is the complexity of many aspects of the chemical behavior of these compounds. Fluorinated heterocycles have markedly different behavior when compared to their fluoroaromatic relatives due to a unique interplay between fluorine atoms (having an unusual combination of strong $-I$ and $+M$ effects) with ring-bonded heteroatoms. In addition, strong local dipole moments associated with the presence of the fluorine atoms or perfluoroalkyl groups influence the electronic properties of the heterocyclic ring and its environment. *N*-Fluorinated heterocycles (both positively charged and neutral) have very distinctive features (oxidants and electrophilic fluorinating agents) and therefore warrant separate consideration. One of the chapters of this book is devoted solely to the synthesis and chemistry of *N*-fluoropyridinium salts (24).

A quick review of other materials presented in this book (which could serve as a snapshot of the current state of development of the field) paints a relatively healthy picture wherein almost all modern synthetic methodologies, including such processes as transition metal mediated synthetic methodology, fluororous, combinatorial and microwave-assisted synthesis, as well as domino reactions, have been applied or at least tried with a varied level of success in the chemistry of fluorinated heterocycles (8,13,23,29). While we are not trying to predict the most productive future synthetic venues in this area, we feel that some less-developed approaches presented below deserve further consideration.

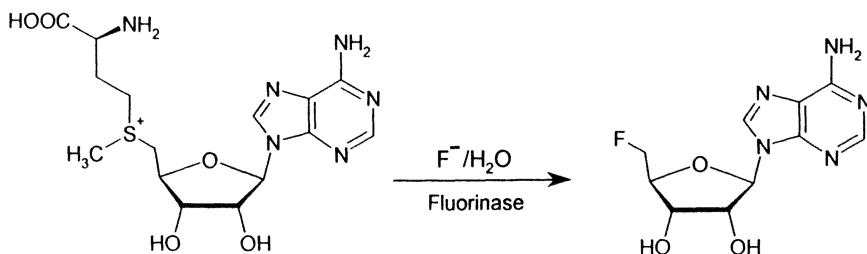
New Areas for Development

We would like to discuss here two areas of research that we feel might have particularly good potential for further growth. It is clear that these are just representative of many new directions of research related to the chemistry of fluoroheterocycles, and are discussed here as two highlighted examples.

Nucleophilic Fluorination in Water

Nucleophilic substitution with the fluoride anion requires special techniques. Strong solvation/hydration of the anion in protic solvents or in the presence of even small amounts of water greatly decreases the nucleophilicity of fluoride. In aprotic solvents, formation of tight ion pairs likewise reduces the nucleophilicity, an effect that can be mitigated by the use of sterically demanding cations that delocalize the positive charge. The formation of solvolysis/hydrolysis by-products presents another potential problem due to the pronounced basic properties of the anion. As a result of these special properties of fluoride, it can be very difficult to achieve good yields of fluorinated heteroaromatic compounds using nucleophilic substitution methodology without employing expensive water-free reaction conditions and anhydrous fluorides (19,21,23). However, a conceptually different approach has been developed that allows the use of non-anhydrous or even protic solvents for nucleophilic fluorination reactions. This employs the use of quaternary salts as the substrates for displacement, wherein solvation of the fluoride anion is effectively mitigated by electrostatic interactions between the cationic reactant and anionic nucleophile (see NMR evidence of such interactions in ref. 30). This approach is so effective that reactions can be performed in non-anhydrous (31) and even water-based solvent systems (1,32) largely unsuitable for displacement reactions involving fluoride/hydrofluoride anions and non-ionic reactants. It is perhaps no surprise that the only well-studied nucleophilic fluorination reaction in living organisms involves nucleophilic substitution of a charged leaving group in a modified

nucleoside by the fluoride anion (Scheme 1). In this case the enzyme-catalyzed reaction employs amplification of this synthetic methodology by additional dehydration of the fluoride anion at the catalytic center. Energetic compensation for dehydration is produced by hydrogen bonding of fluoride with the surface of the active center of the enzyme (33).



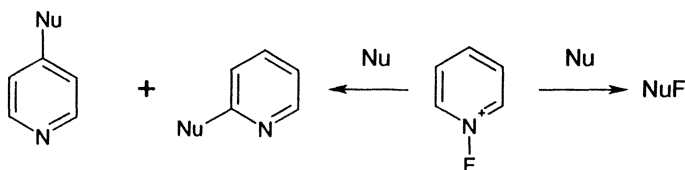
Scheme 1. An enzyme-catalyzed nucleophilic fluorination in aqueous media.

***N*-Fluoroheterocyclic Compounds**

N-Fluorinated heterocycles make up a unique class of compounds that has no analogy among non-fluorinated heterocyclic derivatives. The majority of the compounds in this class have been prepared using elemental fluorine (23), but other electrophilic fluorinating agents such as fluoroxy sulfate salts ($M^+ \text{OSO}_2\text{OF}$) (25) and fluorine nitrate (FONO_2) (16) can also be used. In addition to being good electrophilic fluorinating agents (a quite expected reaction pathway), many reactions of *N*-fluoropyridinium species with nucleophiles result in unexpected products, illustrated for the *N*-fluoropyridinium species in Scheme 2. These include products of hydrogen replacement (cine- and tele- substitution pathways), or α -hydrogen abstraction leading to very reactive species (stabilized α -carbene or stabilized α -cation), the structures of which are still a subject of scientific debate (24,34). The course of the reaction depends not only on the nature of the nucleophile, but also on reaction conditions, such as the solvent used (34). Further efforts in this area are definitely warranted to better characterize these reactive intermediates and their synthetic potential, with possible extension of this approach toward the chemistry of *N*-fluorinated five-membered heterocycles, *N*-fluoroazoles (25).

Analytical and Physical Chemistry of Fluorinated Heterocycles

A similar “evolving” state of development can be used to describe the progress of spectroscopy and computer simulation of ring-fluorinated hetero-



Scheme 2. Two potential reaction directions of an N-fluoropyridinium salt.

cycles. One notable exception is NMR spectroscopy which benefits from the presence of the $\frac{1}{2}$ nuclear spin combined with good NMR sensitivity and strong scalar couplings that are easily detectable even at long-range distances (35). There are several reports regarding the effects of heteroatoms on NMR parameters of fluorinated heterocycles, but a compilation that would summarize these results in a form of a comprehensive review is not yet available. The same is true for Karplus-like correlations between 3J -coupling constants and dihedral torsion angles in the cases of F and H, or F and F nuclei. While parameterization of this equation for H-H constants was accomplished more than 40 years ago, the corresponding equation for F-H and F-F constants were developed only recently (see a relevant discussion in ref. 36).

Mass-spectrometric studies and X-ray analyses of many fluoroheterocycles have been reported in the literature, but only in a few cases were distinctive features associated with the presence of a fluorine atom analyzed. Perhaps some of the better-analyzed fields in the area of X-ray crystallography are related to the topic of coordination properties of a fluorine atom in organic molecules (37,38), and, to some extent, conformational differences between fluoroorganic molecules and their non-fluorinated analogs (39). However, in all cited publications fluorinated heterocycles were not analyzed as a stand-alone class, but only within the context of these studies.

Applications of Fluorinated Heterocyclic Compounds

Biomedical Applications of Fluorinated Heterocyclic Compounds

Heterocyclic chemistry is a major component of the field of medicinal chemistry. This is due in part to the prevalence of heterocyclic rings in naturally occurring biologically important molecules—DNA and RNA bases, carbohydrates, alkaloids, etc. In addition, the effects on such properties as solubility and hydrogen bonding characteristics that are realized by the presence of heterocyclic moieties frequently is an important strategy used to impart “drug-like” qualities to synthetic molecules. Since heterocyclic rings are particularly

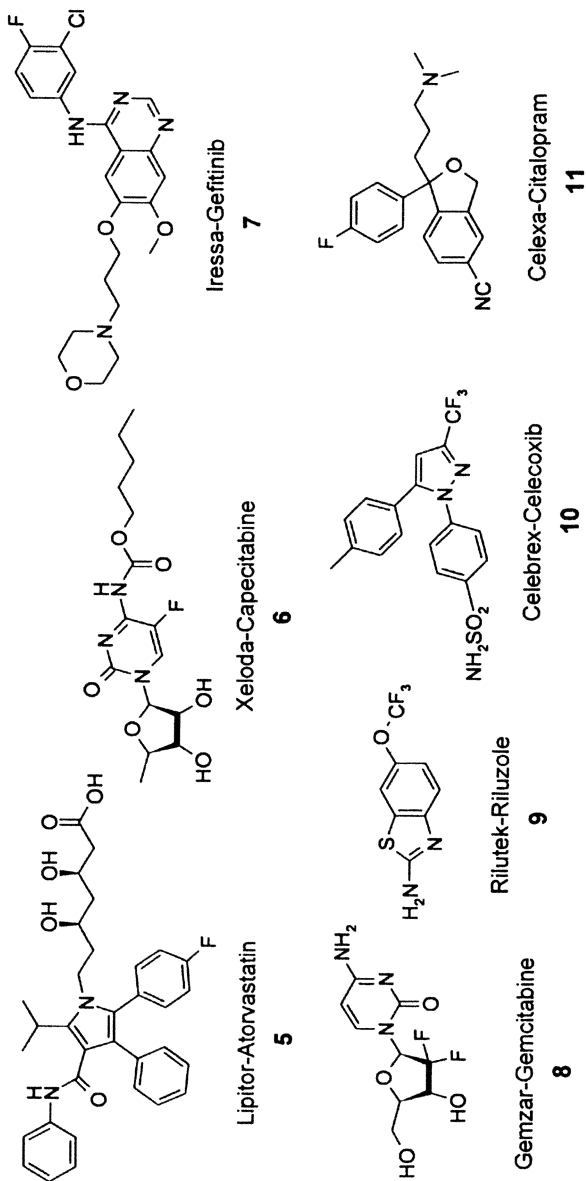
susceptible to the special properties of fluorine, selective fluorine substitution can be used to further tweak the physico-chemical properties of potential drugs, often with dramatic impact on biological properties. Both rational and empirical approaches have been taken to exploit fluorine in drug design and the role of fluorinated heterocycles is particularly notable. The aforementioned 5-fluorouracil (2) and fluoroquinolones are well known examples of successful applications of fluorinated heterocyclic rings. The growing impact of fluorine in drug design - it has been estimated that up to 20% of new drugs contain fluorine (39) - and the prevalence of heterocyclic rings in medicinal chemistry readily explain the important role of fluorinated heterocycles in rational drug design and development. A very similar trend has been observed in the area of agricultural chemistry where the relative share of new fluorinated products is even higher (40). Some of the notable examples of fluorinated heterocyclic compounds as commercial drugs and agrochemicals include (on the drug side) the popular hypolipidemic drug Lipitor-Atorvastatin (5); anti-cancer compounds such as Xeloda-Capecitabine (6), Iressa-Gefitinib (7) and Gemzar-Gemcitabine (8); the amyotrophic lateral sclerosis drug Rilutek-Riluzole (9); the anti-inflammatory COX-2 inhibitor Celebrex-Celecoxib (10); and the anti-depressant Celexa-Citalopram (11). With respect to agrochemicals, notable examples include the acaricide Fluazuron (12); fungicides Thifluzamide (13), Flutriafol (14) and Fluquinconazole (15); herbicides Flufenacet (16) and Prosulfuron (17); insecticides Fipronil (18) and Hydramethylnon (19). The last of these (19) is an active ingredient of the popular Combat pest control systems. More examples can be found in refs (8,11).

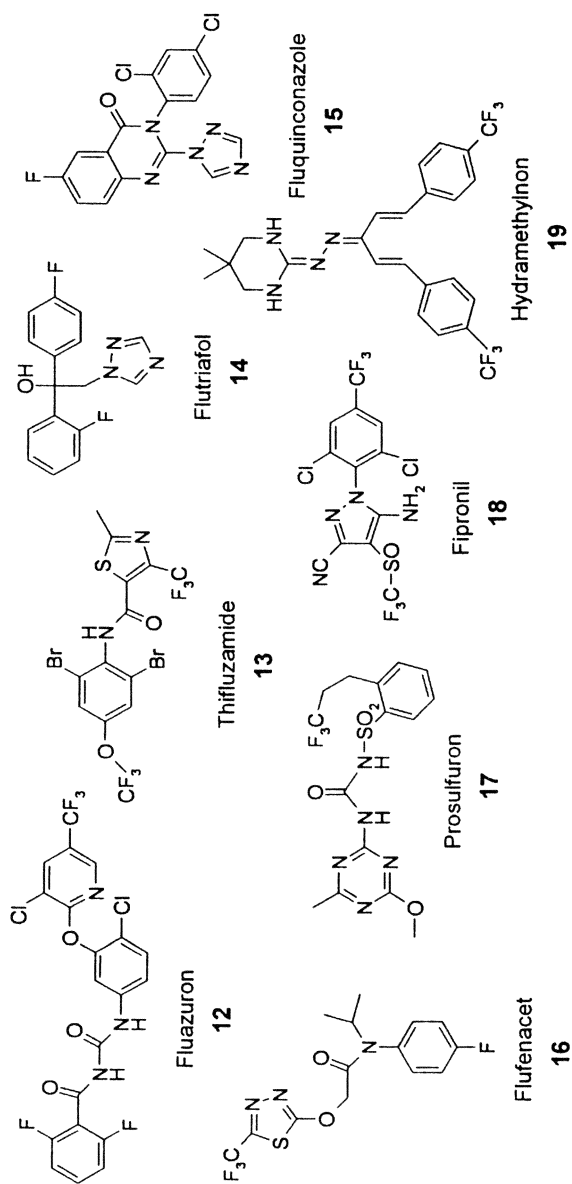
Additional Applications

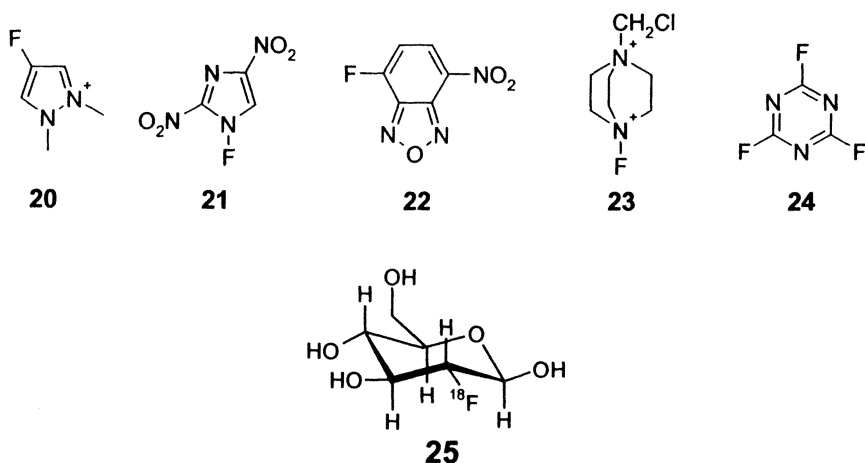
Agriculture and medicine remain the two most important areas of application for ring-fluorinated heterocycles, but uses in other fields are becoming increasingly important. Ionic liquids (17, 20), liquid crystals (41), energetic materials (42, 21), fluorescent probes (43, 22), electrophilic fluorinating agents (42,44, 21,23), and peptide coupling reaction activators (45, 24) are a few areas of application that deserve note. Representative examples of these ring-fluorinated heterocycles of interest are presented below.

¹⁸F-Labelled Fluorinated Heterocyclic Compounds in PET

The positron-emitting isotope ¹⁸F decays with a half-life of 110 min. This convenient half-life and the availability of both electrophilic and nucleophilic radiofluorinating agents are among the factors that have contributed to the many important applications of [¹⁸F]-labeled Positron Emission Tomography (PET)-







scanning agents in medicine. One of the most popular PET agents is the fluorinated heterocycle, [^{18}F] 2-fluoro-2-deoxy-D-glucose **25** (46,47).

The ACS Symposium Book: A Report on Current Topics

The current book is not intended to be a comprehensive survey of chemistry and applications of fluorinated heterocycles, but rather an overview of current activities in this field, both in the US and worldwide. Our hope is that the readers will get a clear snapshot of these intriguing, vibrant areas of research. It is quite obvious that, despite almost 100 years of history, major discoveries (and challenges) still lie ahead for the researchers who are only now entering the field of fluoroheterocyclic chemistry.

Acknowledgements

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Chapter 2

Site Selective Functionalization of Fluorinated Nitrogen Heterocycles

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Functional groups are prerequisites for the assembly of building blocks to more elaborate structures for research work in the life sciences field. Functionalization can be most conveniently and efficaciously accomplished by generating an organometallic derivative of the aromatic or heterocyclic starting material and subsequently treating it with the electrophile of choice. The presence of heterosubstituents facilitates immensely the introduction of the metal (by permutational halogen/metal or hydrogen/metal interconversion) and at the same time enables a perfect control of the desired regioselectivity as will be illustrated by typical examples selected from the indole, pyrazoles, pyridine and quinoline fields.

Manoeuvrable functional groups are indispensable in order to integrate a substructure into a larger target compound having pharmaceutical or agricultural potential. The desired functionality can be very easily fitted into a heterocyclic core compound if the latter, yet "naked", is converted into an organolithium or other organometallic intermediate which eventually is allowed to react with an appropriate electrophile, for example with carbon dioxide if one wants to create a carboxy substituent. This approach is not only extremely simple but also unparalleled in flexibility (1). It can be employed for the attachment of any kind of functional group at any vacant position. Regiochemical selectivity and exhaustiveness can be readily achieved by recurring to the "toolbox methods", (2), a self-consistent set of new or modified organometallic techniques.

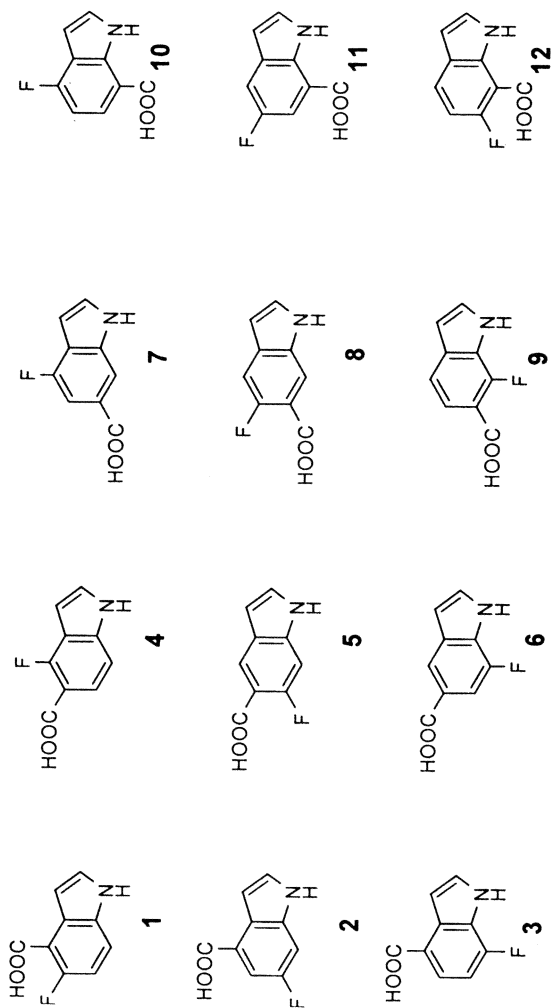
Fluorine or trifluoromethyl bearing heterocycles, in particular nitrogen-containing ones, play a privileged role in medicinal chemistry (3). As the lightest halogen is exceptionally effective in stabilizing C-lithiated derivatives thereof, the latter open a versatile entry to a great variety of attractive novel building blocks. The present summary focuses on two five-membered and two six-membered *N*-heterocycles.

Indoles

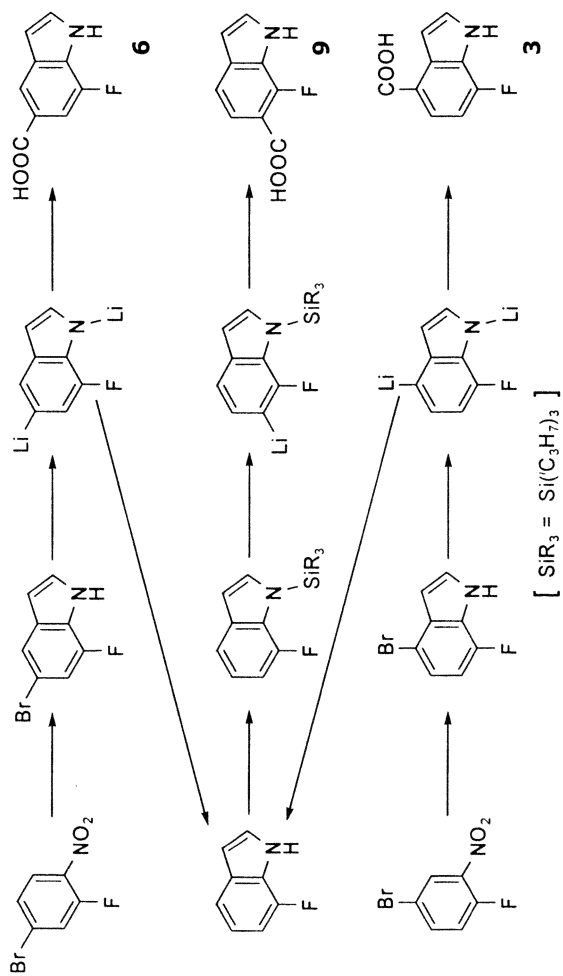
Simple indoles are preferentially metalated at the 2-position of the five-membered ring (4). However, electron-withdrawing substituents may sufficiently increase the kinetic acidity of the six-membered ring to deflect the metalation there. In this way all twelve fluorindolecarboxylic acids (Scheme 1, **1** - **12**) harboring both the halogen and the functional group in the benzo part can be prepared (5).

Thus, NH-protection of 7-fluoroindole with triisopropylsilyl (TIPS) followed by metalation with *sec*-butyllithium, carboxylation and protodesilylation affords the 7-fluoroindole-6-carboxylic acid (**9**). 7-Fluoroindole is obtained from the readily accessible 4- or 5-bromo-7-fluoroindole by reductive debromination. The same intermediates serve also as precursors to the acids **3** and **6** which can be made by consecutive bromine/lithium permutation (using two equiv. of butyllithium), reaction with carbon dioxide and neutralization (Scheme 2) (5).

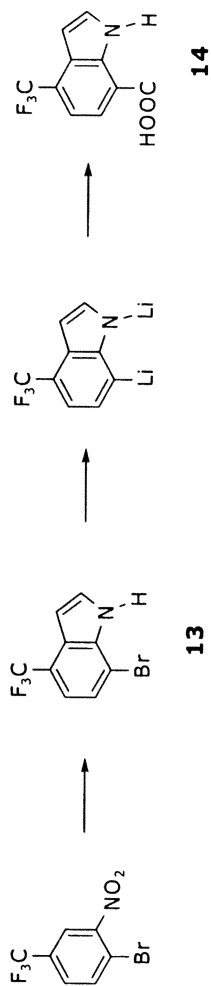
Even if the Bartoli cyclization (6) tends to give only moderate if not poor yields, it represents the most convenient route leading to indoles provided that the nitroarene to be treated with vinylmagnesium bromide is readily available. This happens to be the case with 4-bromo-3-nitrobenzotrifluoride. Treatment of the resulting 7-bromo-4-(trifluoromethyl)indole (**13**) with butyllithium (two equivalents) followed by carboxylation and neutralization affords 4-trifluoromethyl)indole-7-carboxylic acid (**14**; Scheme 3) (7).



Scheme 1. All twelve benzo-substituted fluorindolecarboxylic acids.



Scheme 2. Synthesis of the acids **3**, **6** and **9** from 4- and 5-bromo-7-fluoroindole and 7-fluoroindole.



Scheme 3. A straightforward access to 4-(trifluoromethyl)indole-7-carboxylic acid (**14**).

Pyrazoles

Depending on the work-up conditions, the condensation of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with methylhydrazine produces either one of two regioisomers (8). One of them, 1-methyl-3-(trifluoromethyl)pyrazoles (15) undergoes clean metalation with *sec*-butyllithium at the 5-position to provide the corresponding acid 16 after carboxylation. Heating with elemental bromine in the presence of iron powder gives 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (17) which, when treated either with butyllithium or lithium diisopropylamide (LDA) before being poured on dry ice and neutralized with hydrochloric acid, affords 1-methyl-3-(trifluoromethyl)pyrazoles-4-carboxylic acid (18) and 4-bromo-1-methyl-3-(trifluoromethyl)pyrazoles-5-carboxylic acid (19), respectively. Acid 19 can be readily reduced to 1-methyl-3-(trifluoromethyl)pyrazoles-5-carboxylic acid (16) which, as mentioned above, can also be directly prepared from pyrazole 17 (Scheme 4) (8).

Metalated species derived from fluorinated pyrroles or imidazoles have not yet been reported. Therefore we turn now to six-membered heterocycles, in particular pyridines and quinolines.

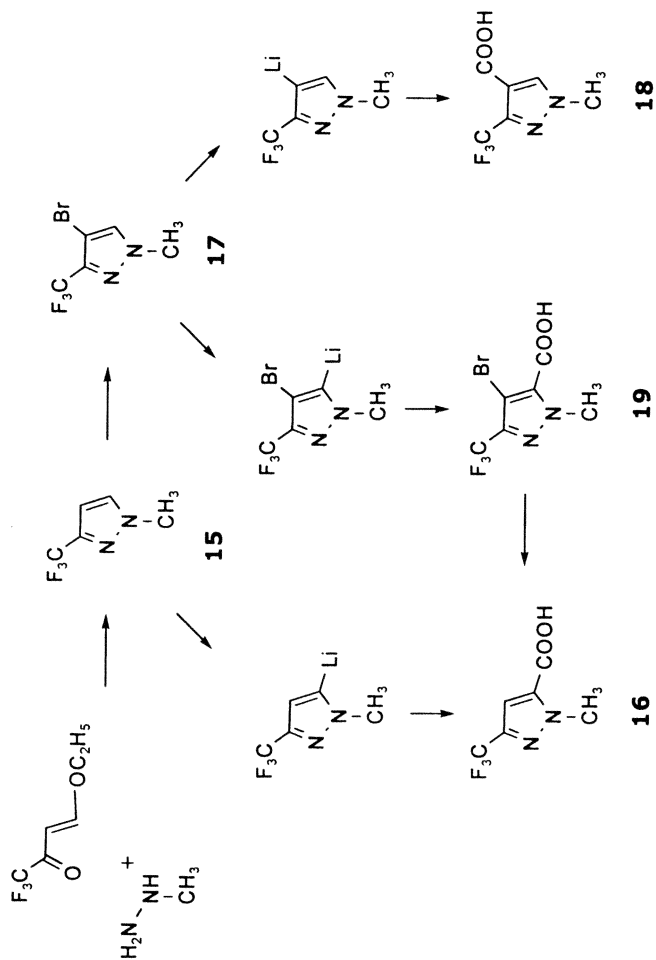
Pyridines

While the medium- and large-scale metalation of pyridine itself still causes trouble, lithium can be conveniently attached to the ring of fluoropyridines (9,10) and (trifluoromethyl)pyridines (11) using alkyllithiums or lithium dialkylamides such as lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) as reagents. In several cases one even benefits from the so-called "optional site selectivity" (12), that is either one of two or three vacant positions may be attacked selectively and alternatively at will (Scheme 5).

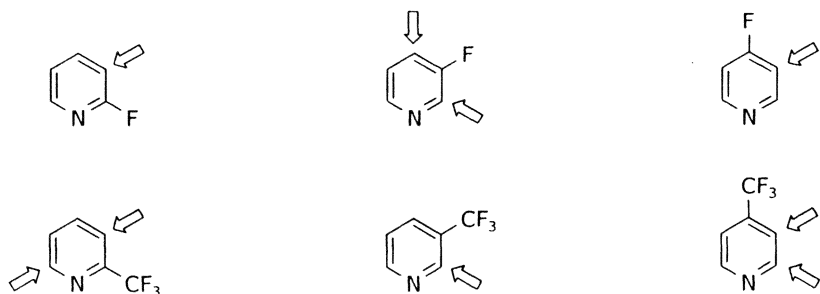
There is one exception, however. Contrary to literature claims (13), 3-(trifluoromethyl)pyridine provides only trace amounts (0.5 – 1.5 %) of 3-(trifluoromethyl)pyridine-2-carboxylic acid when consecutively exposed to butyllithium (at -75 °C), dry ice and hydrochloric acid. Nucleophilic addition of the organometallic reagent followed by nucleofugal fluoride elimination occurs as a major reaction pathway instead. This is evidenced by the formation of 2-butyl-5-(difluoromethyl)pyridine (20) as the main product (Scheme 6) (11b).

Quinolines

The site selective metalation of 2-, 3-, 5- and 7-fluoroquinoline has been briefly reported (Scheme 7) (14). 6-Fluoroquinoline was found to react



Scheme 4. Three 1-methyl-3-(trifluoromethyl)pyrazolecarboxylic acids through organometallic intermediates generated by deprotonation or halo-gen/lithium permutation.



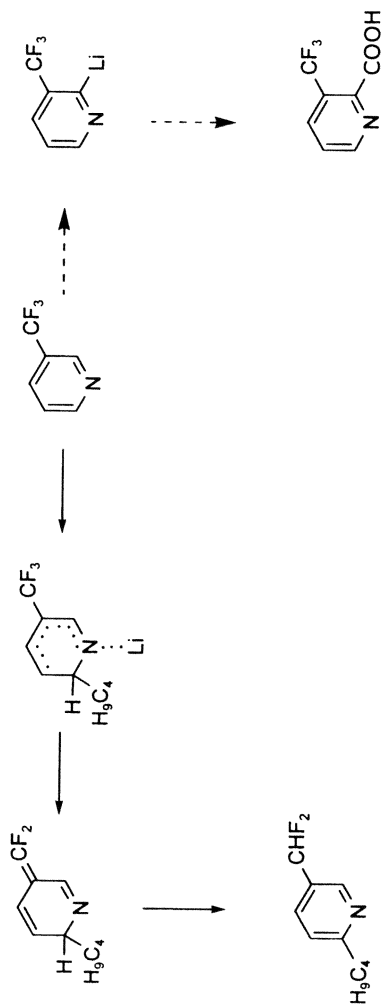
Scheme 5. Sites in fluoropyridines and (trifluoromethyl)pyridines where selective deprotonation and lithiation can be brought about.

concomitantly at the 5- and 7-position (14). 2-, 3- and 4-(Trifluoromethyl)-quinoline offer the bonus of optional deprotonation at either of two competing sites (Scheme 7) (11b).

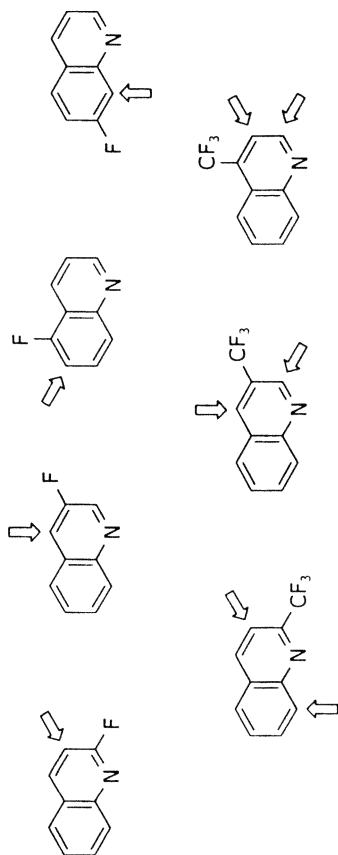
The extension of such systematic investigations to substrates containing an additional heterosubstituent, in particular a bromine atom, is both challenging and rewarding from a practical point of view. The heavy halogen is susceptible to be replaced with hydrogen by a reductive process or with any nucleophile by nucleophilic heteroaromatic substitution or with lithium by permutational halogen/metal interconversion (15). The latter possibility can be exploited to introduce sequentially two different functional groups as exemplified with the readily accessible 2-bromo-4-fluoroquinolines (**21**) (16). Immediate treatment with butyllithium produces a 2-lithio species which, upon trapping with dry ice, provides the corresponding 2-carboxylic acids (**22**) (Scheme 8). In contrast, when LDA is used as the reagent, the 4-position is deprotonated and thus becomes amenable to a first electrophilic substitution (Scheme 8) providing, for example, a 2-bromo-3-fluoro-quinoline-4-carboxylic acid (**23**). The second functionalization can take place when the latter product is exposed to the action of two equivalents of butyllithium thus generating a 2-lithio carboxylate which, when intercepted for example with dimethylformamide, furnishes the corresponding 3-fluoro-2-formylquinoline-4-carboxylic acid (**24**; Scheme 8) (16).

Summary and Outlook

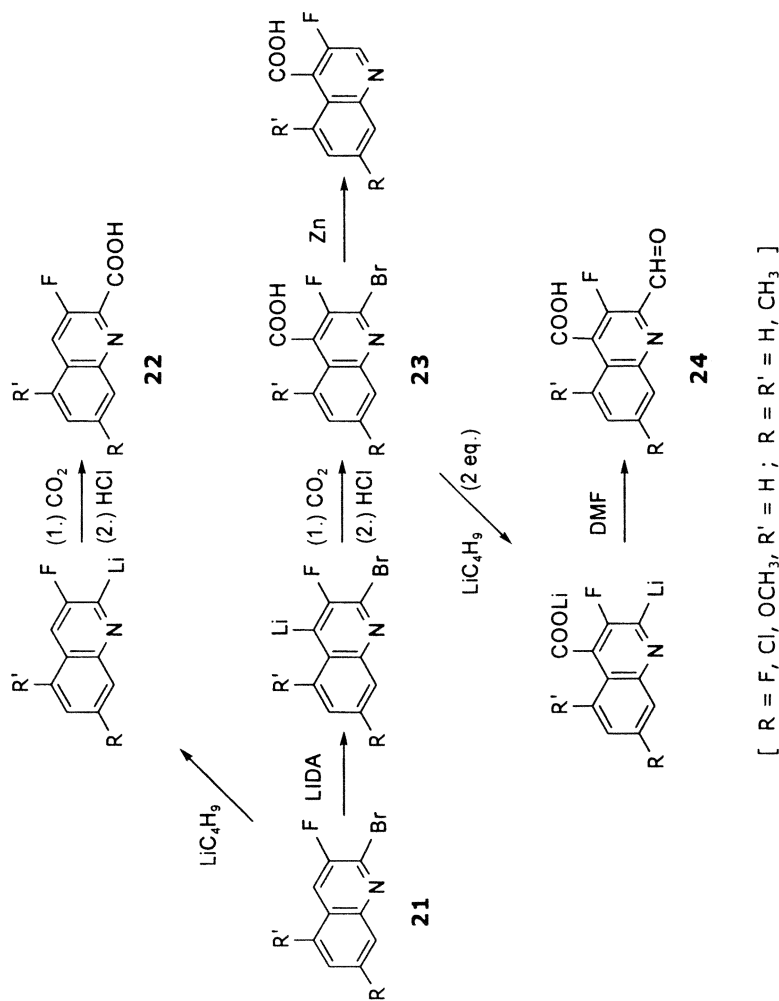
As outlined above, it is very easy to introduce functional groups into heterocyclic core structures by passing through organometallic derivatives of the latter. For simplicity carbon dioxide was used as the standard electrophile in almost all of the described reactions. However, it has to be emphasized once



Scheme 6. Reactions between 3-(trifluoromethyl)pyridine and butyllithium.



Scheme 7. Regioselective metalation (and subsequent electrophilic substitution) of 2-, 3-, 5- and 7-fluoroquinoline and 2-, 3- and 4-(trifluoromethyl)quinoline.



Scheme 8. Simple and double functionalization of 2-bromo-3-fluoro-quinolines featuring halogen/metal and hydrogen/metal permutation processes.

more that the choice of trapping reagents is virtually unrestricted. Thus, the key intermediate can be transformed not only into carboxylic acids. Aldehydes, alcohols, phenols, thiols, amines, phosphorus compounds and countless other valuable derivatives are equally accessible easily and efficaciously (17).

The organometallic approach to the site selective substitution has been applied to five- and six-membered heterocycles other than those specified above, for example also to pyrimidines (18). Without doubt further applications will appear in the future.

Acknowledgment

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Chapter 3

Preparation, Reactivity, and Applications of *N*-Fluoropyridinium Salts

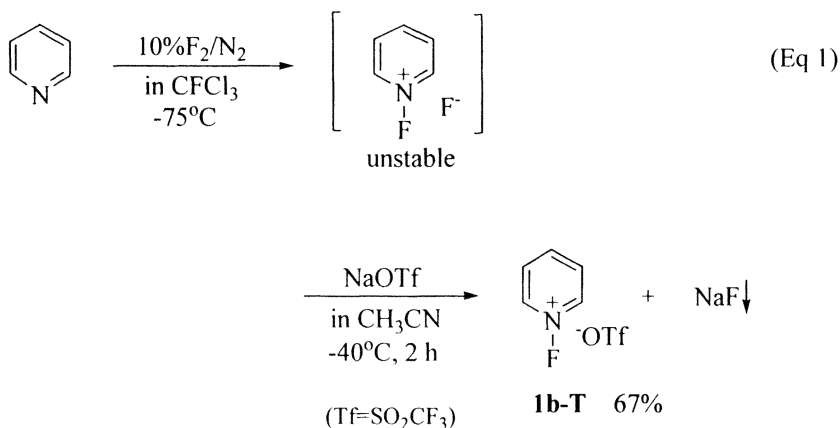
Teruo Umemoto

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Reactions of *N*-fluoropyridinium salts with bases and the carbene mechanism involved are discussed. Applications to new synthetic strategies in heterocyclic chemistry are described. Methods of synthesis of various 2-substituted pyridines from *N*-fluoropyridinium salts or from pyridines via unstable *N*-fluoropyridinium salts are reviewed and discussed. New synthetic methods for fused heterocyclic compounds are also reviewed. Recent advancements in fluorination with *N*-fluoropyridinium salts are discussed.

Introduction

The chemistry of the pyridine ring has been enriched by the development of many significant transformations. These include addition, addition-elimination, elimination-addition, and ring-opening reactions, as well as proton-abstraction reactions followed by nucleophilic reactions. The course of the reaction depends on the nature of the pyridine rings and bases employed (1,2). New reactions involving *N*-fluoropyridinium salts have now been added to the field of pyridine chemistry. In 1986, stable *N*-fluoropyridinium salts were isolated and fully characterized by the author and his coworker (3-5). As shown in Eq 1, the salts were synthesized by the counteranion replacement reaction of unstable pyridine-F₂ compounds (6) which violently decompose above -2 °C. The isolation of the stable salts followed shortly after Gakh's earlier report that the pyridine-F₂ compound, proposed as an *N*-fluoropyridinium structure, reacted in situ with a trinitromethane salt to form 2-(trinitromethyl)pyridine in a 14% yield (7). The



results of these research efforts, including the discovery of the stable *N*-fluoropyridinium salts, have opened up a new area in pyridine chemistry (8,9).

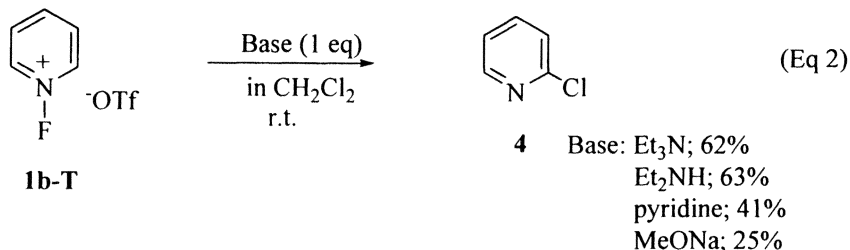
The *N*-fluoropyridinium salts are the first stable 1:1 salts of the pyridine nucleus and halogen, which is in sharp contrast to stable 2:1 salts formed with other halogens. The reactions of *N*-fluoropyridinium salts can be classified into two categories; non-fluorinative reactions and fluorinations. The former include base-induced reactions involving a new carbene mechanism and other transformations. These will be reviewed and discussed in the first several sections of this chapter. The latter involves attack of the electrophilic fluorine of the N-F bond on electron-rich centers. Research to study this process has resulted in the development of many useful fluorinating agents. Recent advances in this area will be discussed in the last section of this chapter.

Reactions of Stable *N*-Fluoropyridinium Salts with Bases

In 1987, the author and coworker reported novel base-induced reactions of the stable *N*-fluoropyridinium salts as shown in Eq 2 (10). Addition of triethylamine (1 eq) to a solution of stable *N*-fluoropyridinium triflate (**1b-T**) in methylene chloride at room temperature brought about an immediate exothermic reaction which produced an unexpected compound, 2-chloropyridine (**4**), in a 62% yield. Other products were 2-(trifluoromethanesulfonyloxy)pyridine (**5**) (21%) and 2-fluoropyridine (**6**) (5%). It was surprising that chlorine atoms of the solvent molecule, which have absolutely no nucleophilicity under basic conditions, were involved in the reaction. The formation of **5** was also unexpected because it is the extremely low nucleophilicity or non-nucleophilicity of the triflate anion that is responsible for the high stability of the *N*-fluoropyridinium triflate.

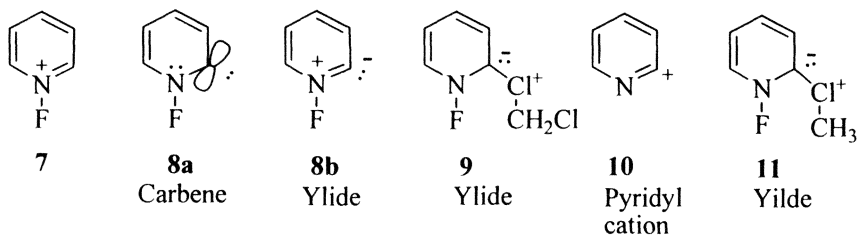
The products **4**, **5**, and **6** were produced regardless of bases. There was little or no formation of base derived 2-substituted or 4-substituted pyridines, which

might be formed by 1,2- or 1,4-addition-elimination reaction involving the base. The function of the base is abstraction of 2-protons of *N*-fluoropyridinium salts.



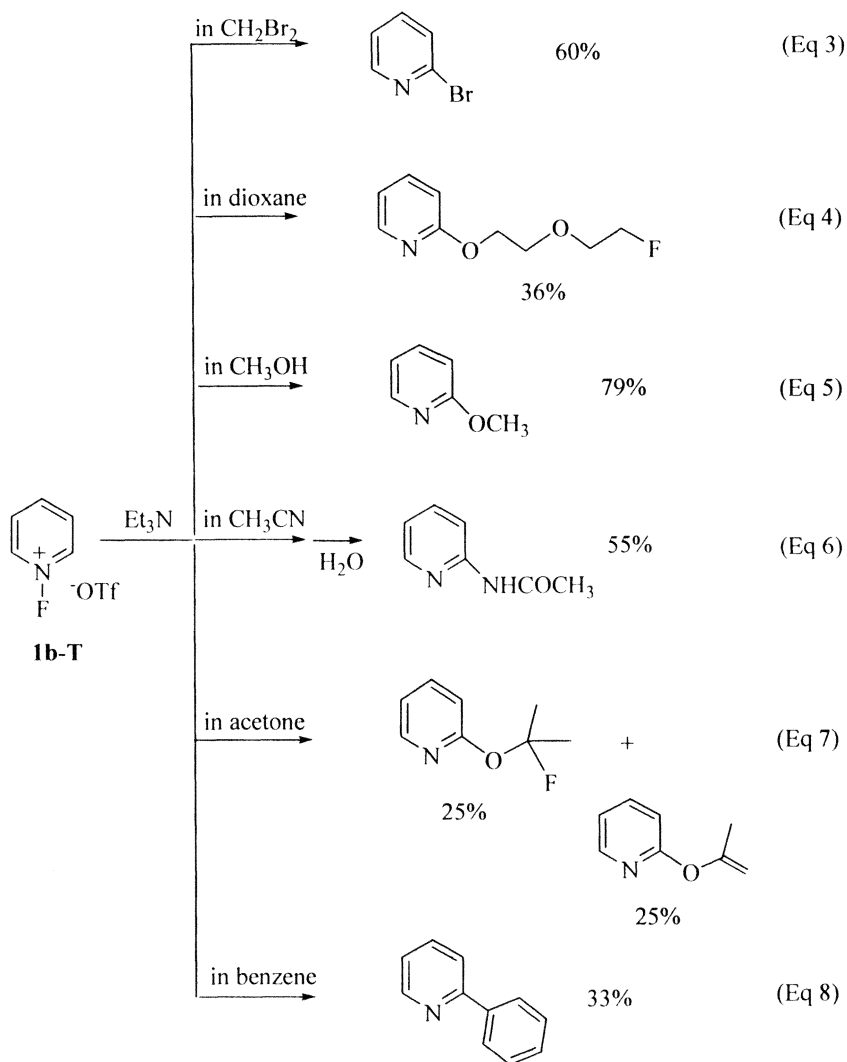
The reactions were conducted in various solvents such as CH₂Br₂, dioxane, methanol, acetonitrile, acetone, benzene, and others as shown in Eqs 3-8 (10, 11). Many unexpected 2-substituted pyridines were produced.

To explain the formation of these products, the formation of a new cyclic carbene **8a**, formed via 2-proton abstraction from *N*-fluoropyridinium cation **7** with a base, was proposed (10). The carbene mechanism involves formation of **8a** followed by reaction with a chlorine atom of CH₂Cl₂ to give ylide **9**, which produces 2-chloropyridine.



Gakh et al. reported reactions of *N*-fluoropyridinium tetrafluoroborate (**1b-B**) with carbanions (12). In their studies, they isolated 2-ethoxypyridine and 2-(acetamido)pyridine and suggested the intermediate formation of 2-pyridyl cation **10**, formed through elimination of a fluoride anion from the deprotonated intermediate **8a** or **8b**, as a possible mechanism.

Ab initio MO calculations on the novel base-induced reactions of *N*-fluoropyridinium salts were conducted (11). The reaction of an *N*-fluoropyridinium cation **7** with CH₃Cl was postulated and calculated. The calculations



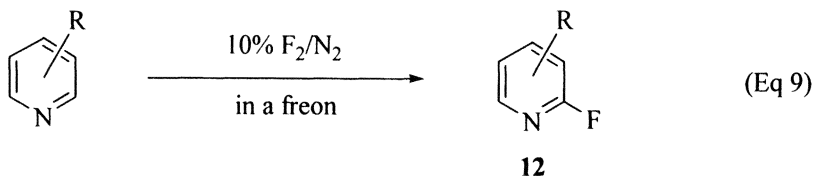
supported formation of ylide **11** from intermediate **8** (route *A*) rather than formation of the pyridyl cation **10** from intermediate **8** (route *B*) because the total energy change for route *B* is extremely large (+143.6 kcal/mol), as compared to the energy change for route *A* ($\mathbf{8} \rightarrow \mathbf{11}$, -2.1 kcal/mol; $\mathbf{8} \rightarrow$ transition state for **11**, +18.4 kcal/mol). The calculation also showed the deprotonated intermediate **8** to have the nature of a carbene given by formula **8a** rather than its resonance structure, ylide **8b**. Therefore, the carbene reaction route $\mathbf{7} \rightarrow \mathbf{8a} + \text{CH}_3\text{Cl} \rightarrow \mathbf{11} \rightarrow 2\text{-chloropyridine and CH}_3\text{F}$ (products) is most likely. Similar calculation results were described by Streckowski et al. (13).

Carbene reactions may be involved in the reactions of pyridines with F_2 and other fluorinating agents such as CH_3COOF and $CsSO_4F$ and in many other reactions of *N*-fluoropyridinium salts, as described below.

A New Synthetic Strategy in Heterocyclic Chemistry

Synthetic Methods for 2-Substituted Pyridines

In 1987, Van Der Puy et al. reported the preparation of 2-fluoropyridine derivatives by direct fluorination of pyridines in a freon solvent ($CF_2ClCFCl_2$) with 10% F_2/N_2 at $-25\text{ }^\circ\text{C}$ - room temperature (14). By this method, substituted 2-fluoropyridines **12** were prepared from pyridines in 25-61% yields, as shown in Eq 9.

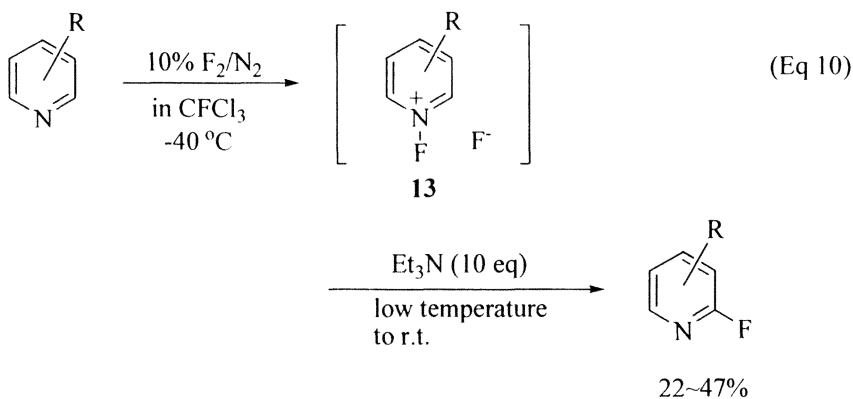


R=4-Me (31%), 4-Et (32%), 4-*i*-Pr (47%), 4-Benzyl (25%),
3-Me (43%), 3,5-diMe (37%), 3,5-diCl (46%), 4-acetyl (26%),
4-COOMe (61%), 3-COOMe (36%)

In 1989, the preparation of 2-fluoropyridine derivatives by the base-induced reaction of unstable *N*-fluoropyridinium fluorides **13** was reported by the author and coworker. The unstable salts **13** were treated in situ with an excess of triethylamine at low temperature to give 2-fluoropyridines in 24-47% yields (Eq 10) (15). The results are similar to those reported by Van Der Puy mentioned above (14). Thus, an efficient method for preparation of 2-fluoropyridines via base-induced reactions of stable *N*-fluoropyridinium tetrafluoroborates was developed (15).

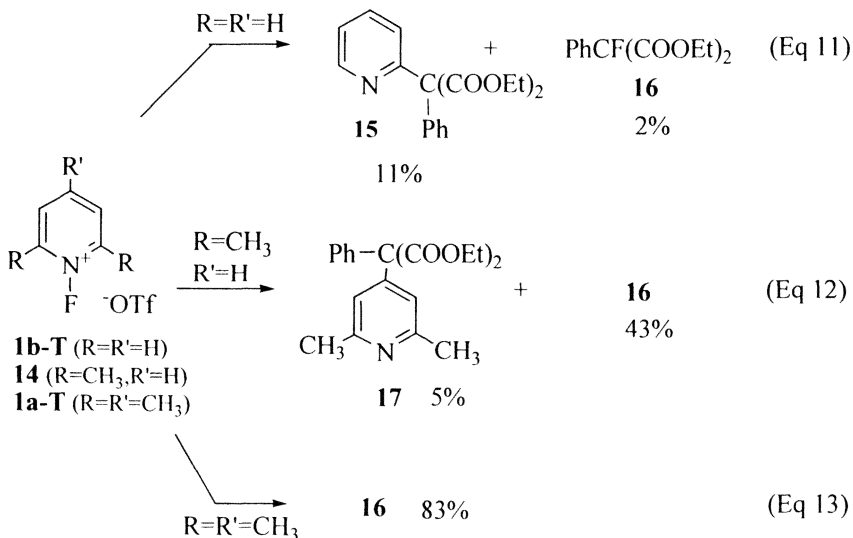
These experiments reveal that the decomposition of the dark brown solid generated by the reaction of liquid pyridine with F_2 at $-40\text{ }^\circ\text{C}$, described by Simons in his book in 1950 (16), and the decomposition of the pyridine- F_2 solid described by Meinert in 1965 (6) involve base-induced reactions of unstable *N*-fluoropyridinium fluoride where pyridine or fluoride anion acts as a base. In both cases, it was reported that 2-fluoropyridine was detected as one of the products.

The novel base-induced reactions take place with bases such as *N*- and *O*-bases and fluoride anion. A large number of fluorination reactions of *C*-bases with different *N*-fluoropyridinium salts were conducted by the author and



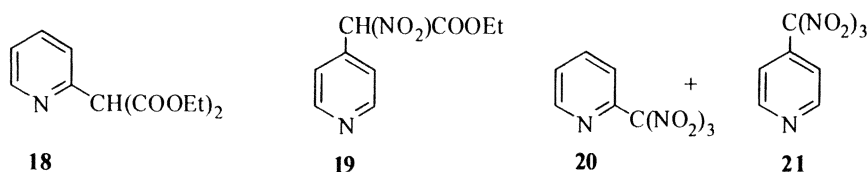
R=H (35%), 4-Me (26%), 4-*t*-Bu (47%), 2-OMe (24%),
4-COOMe (24%), 3-COOEt (2-F, 22%; 6-F, 9%)

coworkers (17, 18). In these studies, 2- and 4-substituted products **15** and **17** with a *C*-base were observed in the reactions of sodium phenylmalonate ester with **1b-T** and **14** as shown in Eqs 11 and 12. Another product was a fluorination product **16**. Reagent **1a-T** exclusively produced **16** in high yield (Eq 13). A single electron transfer (SET) mechanism was proposed (18).



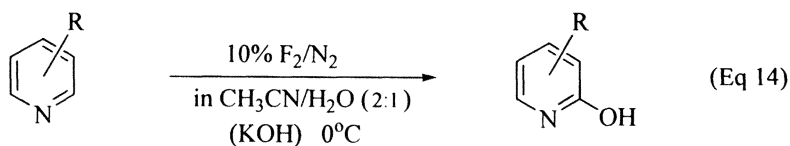
Reaction conditions; PhC(Na)(COOEt)₂ in THF at r.t.

Gakh et al. reported reactions of *N*-fluoropyridinium tetrafluoroborate (**1b-B**) with some *C*-bases (*12*). The formation and ratio of 2- and 4-substituted products changed with *C*-bases and solvents. The reaction of sodium diethyl malonate with **1b-B** in ethanol produced 2-substituted compound **18** in a 22% yield, while the salt of ethyl nitroacetate in water gave 4-substitution product **19** in a 46% yield. The salt of trinitromethane gave a mixture of 2- and 4-substitution products **20** and **21**. A mechanism involving 1,2- and 1,4-addition-elimination or the pyridyl cation intermediate **10** was suggested.



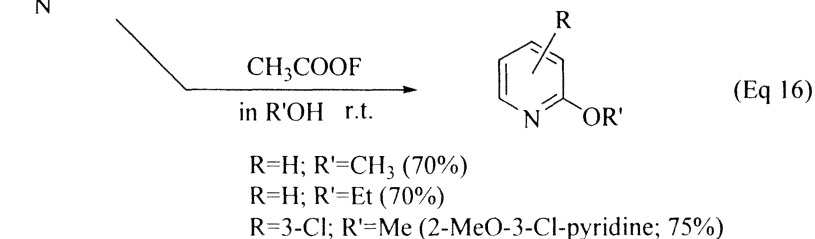
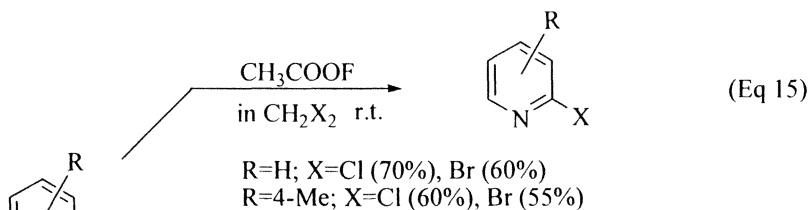
The reactions of *N*-fluoropyridinium salts are complex. The mechanism changes dramatically with the nature of substrates or bases (*C*, *N*, *O*-bases etc.) in addition to the change of *N*-fluoropyridinium salts.

Hydroxylation of pyridinecarboxylic acids and esters with F_2/N_2 in a 2:1 mixture of acetonitrile and water was reported by Van Der Puy et al. (Eq 14) (*19*). For reactions involving the carboxylic acids, potassium hydroxide (2 eq) was added. 2-Hydroxypyridine derivatives were obtained in 51-73% yields. The carbene mechanism was suggested. Similarly, quinoline-4-COOME was converted to 2-OH-4-COOME-quinoline in a 65% yield.



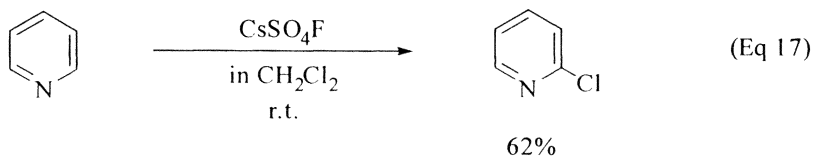
$R=4\text{-COOH (62\%), 3-COOH (73\%), 2-COOH (51\%), 2,3-di(COOME) (56\%), 3,5-di(COOME) (60\%)}$

Rozen et al. reported 2-halogenation and 2-alkoxylation of pyridines with acetyl hypofluorite (CH_3COOF) (*20,21*) as shown in Eqs 15 and 16. Reaction of pyridine with CH_3COOF in CH_2Cl_2 gave 2-chloropyridine and 2-acetoxypyridine in 70% and 15% yields, respectively. When the reaction was carried out in methanol, 2-methoxypyridine was produced in a 70% yield together with a small amount of 2-acetoxypyridine. A 1,2-addition-elimination was proposed to explain the reaction. However, the carbene mechanism again seems to be a



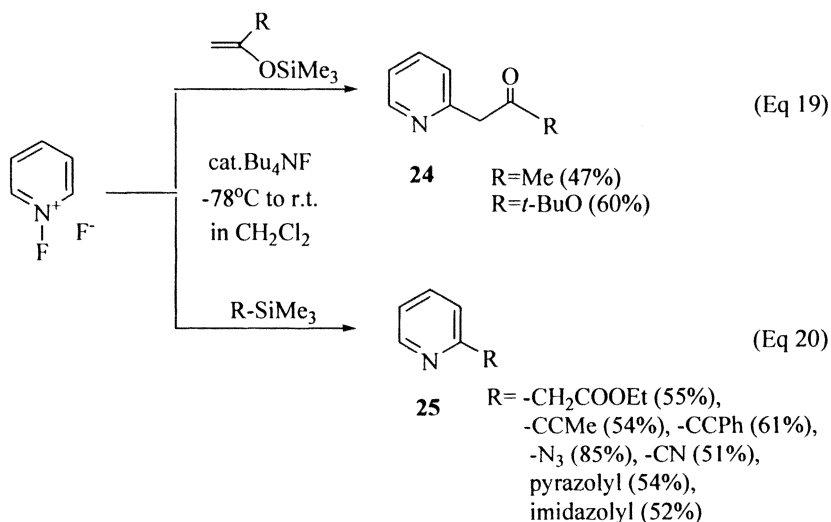
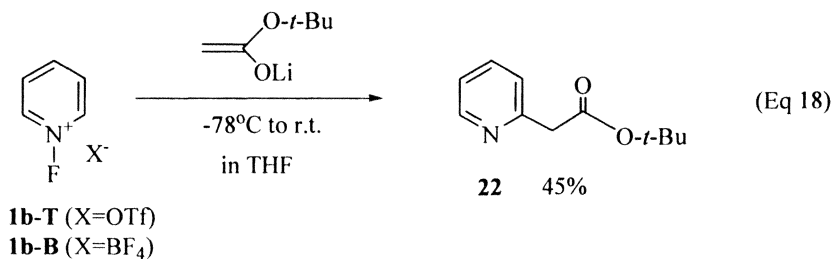
reasonable alternative. This may be initiated by abstraction of the 2-proton of the unstable *N*-fluoropyridinium acetate, formed as an intermediate, by its own counteranion, the acetate anion. It has been shown that acetate can act as a base for the carbene reaction (11). Quinoline was 2-methoxylated in >60% yield in methanol, but in methylene chloride and bromide, only acetoxylation, not halogenation, was observed.

Stavber et al. reported the reaction of pyridine with CsSO_4F (Eq 17) (22). When pyridine was treated with CsSO_4F in CH_2Cl_2 at room temperature, an instantaneous reaction took place and 2-chloropyridine was obtained in a 62% yield together with 2-fluoropyridine (26%) and 2-(fluorosulfonyloxy)pyridine (12%). The use of methanol as solvent gave 2-methoxypyridine quantitatively. The carbene mechanism seems likely. The *N*-fluoropyridinium CsSO_4 salt formed as an intermediate undergoes base-induced reaction, with its counteranion SO_4^{2-} or coexisting pyridine presumably acting as base. Actually, the *N*-fluoropyridinium BF_4 salt (**1b-B**) was isolated in a 48% yield by the reaction of pyridine with CsSO_4F in acetonitrile at 0-5 °C followed by the counteranion exchange reaction with NaBF_4 (23).



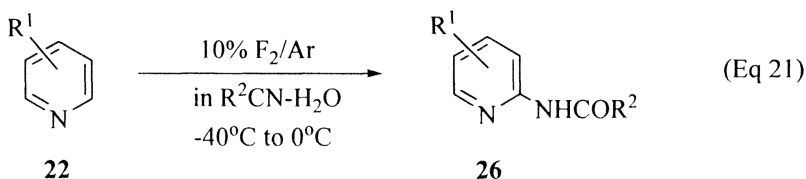
Strekowski et al. reported reactions of **1b-T** and **-B** with lithium enolates of an ester and a ketone (24). As shown in Eq 18, 2-(*t*-butoxycarbonylmethyl)pyridine (**22**) was produced in a 45% yield in the reaction with lithium enolate of *t*-butyl acetate in THF. The reaction in THF was accompanied by the formation

of 2-(4'-fluorobutyloxy)pyridine (**23**) (22-40%). This method was applied to the reactions of the unstable *N*-fluoropyridinium fluoride, prepared in situ at low temperature, with various trimethylsilyl derivatives in methylene chloride in the presence of a catalytic amount of tetrabutylammonium fluoride as shown in Eqs 19 and 20 (24). 2-Substituted pyridines **24** and **25** including 2-oxoalkyl-, -alkoxycarbonylmethyl-, -alkynyl-, -azido-, -cyano-, -pyrazolyl-, and -imidazolylpyridines were prepared in moderate to good yields. These reactions were accompanied by the formation of 2-chloropyridine (10-30%) and 2-fluoropyridine (2-5%). A 1,2-addition-elimination mechanism was proposed as a major pathway for formation of products **24** and **25**. Formation of 2-chloro- and 2-fluoropyridines and ether **23** were explained by the carbene mechanism. They also reported the preparation of 2-(1'-fluoro-2'-oxopropyl)pyridine and 2-(1'-ethoxycarbonyl-1'-fluoromethyl)pyridine by the reaction of **1b-B** with α -diazocarbonyl compounds (25).

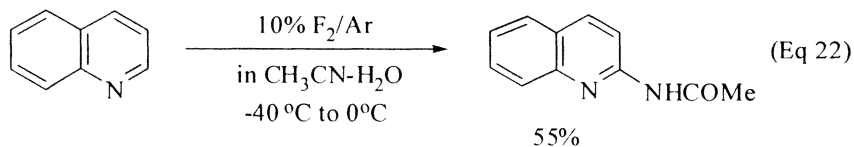


A useful alternative method to the Chichibabin amination was developed by Strekowski et al. as shown in Eq 21 (26). Pyridine and its derivatives were

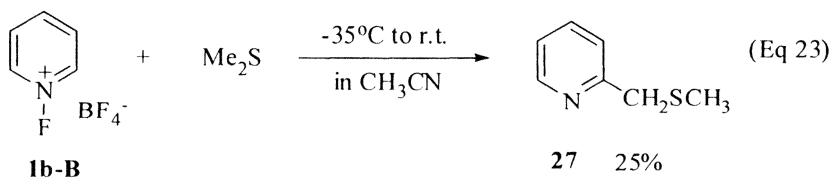
treated with 10%F₂/90%Ar in a wet acetonitrile or butyronitrile at -40 °C to room temperature. Many 2-amidopyridine derivatives **26** were prepared in 27-67% yields. R¹ of **26** includes H, 3-Me, 4-Me, 5-Me, 3-Br, and 3-CN and R² includes methyl and *n*-propyl groups. The corresponding 2-fluorinated pyridine derivatives as byproducts were produced in 9-23% yields.



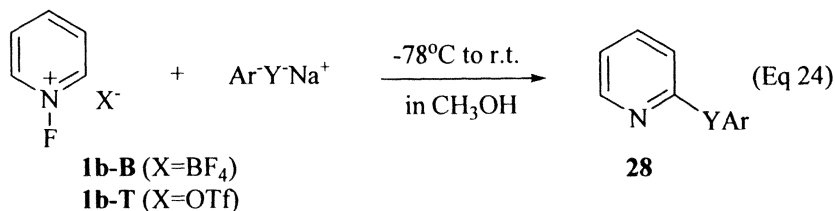
Similar treatment of quinoline and isoquinoline gave 2-(acetamido)quinoline (Eq 22) and 1-(acetamido)isoquinoline in 55% and 44% yields, respectively.



Reactions of **1b-B** with various dialkyl sulfides and aryl alkyl sulfides were reported (27). As shown in Eq 23, pyridyl sulfide **27** was produced in a 25% yield in the reaction with dimethyl sulfide. Ethyl phenyl sulfide gave 2-[1'-(phenylthio)ethyl]pyridine in a 20% yield. A considerable amount of byproducts such as dialkyl disulfides were obtained. These products were explained by a mechanism involving a single electron transfer.



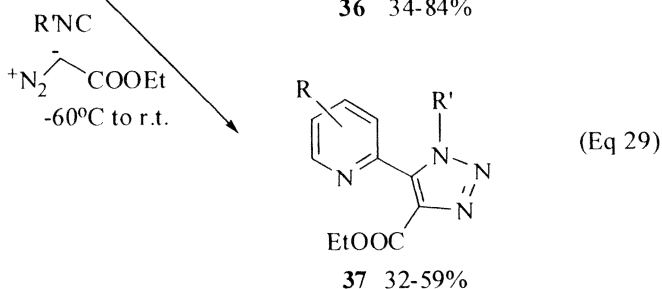
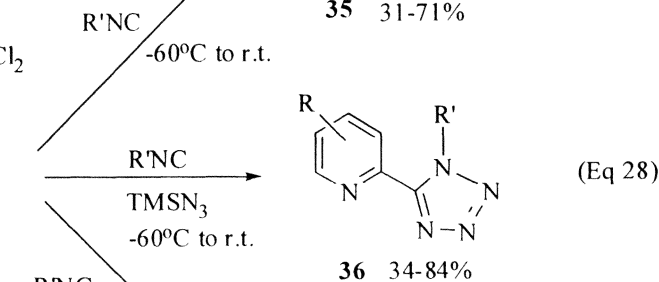
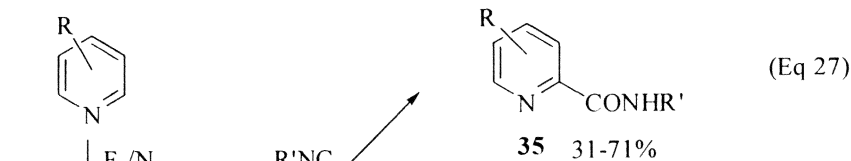
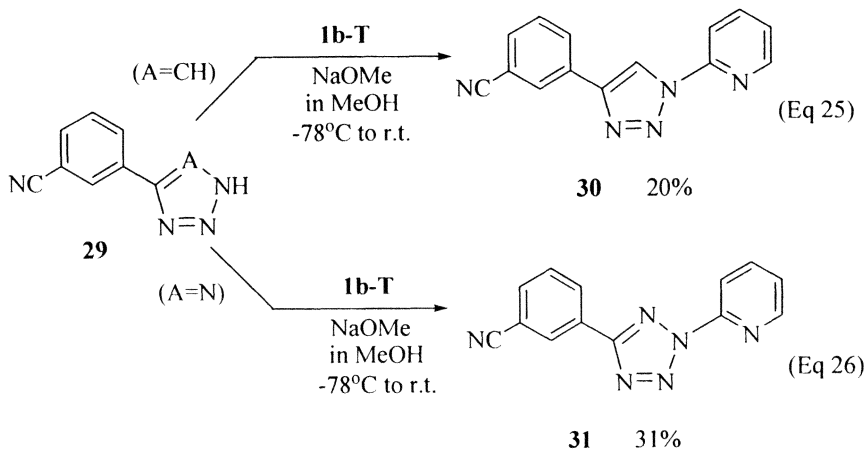
A convenient synthetic route to pyridines having sulfur, oxygen, and nitrogen substituents at the 2-position was developed as shown in Eq 24 (28). Reagents **1b-B** and **1b-T** reacted with anions derived from benzenethiols, phenols, and azoles in methanol at -78 °C to room temperature to produce 2-substituted pyridines **28** in moderate to high yields. The products **28** include 2-arylthio-, -aryloxy-, -imidazolyl- and -triazolyl-pyridines.



ArY ⁻ Na ⁺		28
Y	Ar	
S	Ph	48%
S	o-NO ₂ -Ph	72%
S	p-NO ₂ -Ph	80%
S	o-MeOCO-Ph	58%
O	Ph	56%
O	o-NO ₂ -Ph	76%
O	p-NO ₂ -Ph	80%
O	o-MeOCO-Ph	68%
O	p-MeOCO-Ph	72%
		40%
		43%
		65%
		60%

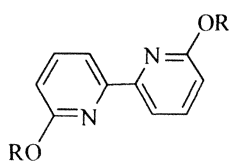
Similarly, sodium azide and sodium cyanamide reacted with **1b-B** or **1b-T** to give 2-azidopyridine and 2-(cyanoamino)pyridine in 80% and 48% yields, respectively. This method was applied to the preparation of heteroaryl triazole **30** and tetrazole **31** (Eqs 25, 26) (29).

Kiselyov developed a one-pot synthetic method for the preparation of heterocycles from pyridines via *N*-fluoropyridinium fluorides **13**. Pyridine derivatives were allowed to react with F₂/N₂ in methylene chloride at -60 °C, and then the solutions were treated with R'NC (Eq 27), R'NC and TMSN₃ (Eq 28), and R'NC and N₂CHCOOEt (Eq 29) at -60 °C to room temperature to produce picolinamides **35**, tetrazol-5-ylpyridines **36**, and (pyridin-2-yl)-1*H*-1,2,3-triazoles **37**, respectively, in fair to good yields (30,31,32).

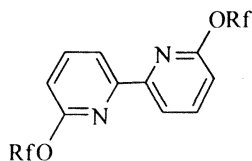


Shreeve et al. reported efficient routes to 6,6'-disubstituted 2,2'-bipyridines from *N,N'*-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) (**3d-B**). No other isomers were produced. Alcohols reacted with **3d-B** under neat conditions at 60 °C for 24 h to give 6,6'-dialkoxybipyridines **32** in excellent isolated yields (33).

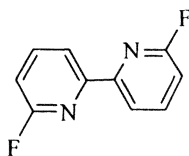
Polyfluorinated alcohols such as 2,2,2-trifluoroethanol did not react with **3d-B** under the same conditions. However, the fluorinated alcohols reacted with **3d-B** under the action of base, producing 6,6'-di(polyfluoroalkoxy)bipyridines **33** in high yields (34). Many kinds of *N*-bases were used for the reaction. Reagent **3d-B** was heated in trifluoroethanol in the presence of an equimolar amount of triethylamine at 60 °C for 15 h to give 6,6'-bis(trifluoroethoxy)-2,2'-bipyridine in a 82% yield. Further, treatment of **3d-B** with excess of triethylamine without solvent at 0 °C produced 6,6'-difluoro-2,2'-bipyridine (**34**) in a 82% yield (34). The formation of products **33** and **34** was explained by a 1,2-addition-elimination mechanism. However, the carbene reaction is applicable to formation of all the products **32-34**. The 6,6'-fluorination of **3d-B** should be analogous to the base-induced reaction of *N*-fluoropyridinium tetrafluoroborates with triethylamine, which produced 2-fluoropyridines in high yields (15). In this case, the formation of 2-fluoropyridines was explained by the reaction of carbene **8a** with a fluorine atom of BF_4^- as a key step (15).

**32**

R=Me 95%, Et 92%,
Pr 92%, Bu 90%,
Hexyl 90%,
H(OCH₂CH₂)₂ 88%

**33**

Rf=CF₃CH₂ 82%
FCH₂CH₂ 80%
CF₃CF₂CH₂ 75%
CHF₂CF₂CH₂ 72%
(CF₃)₂CH 72%

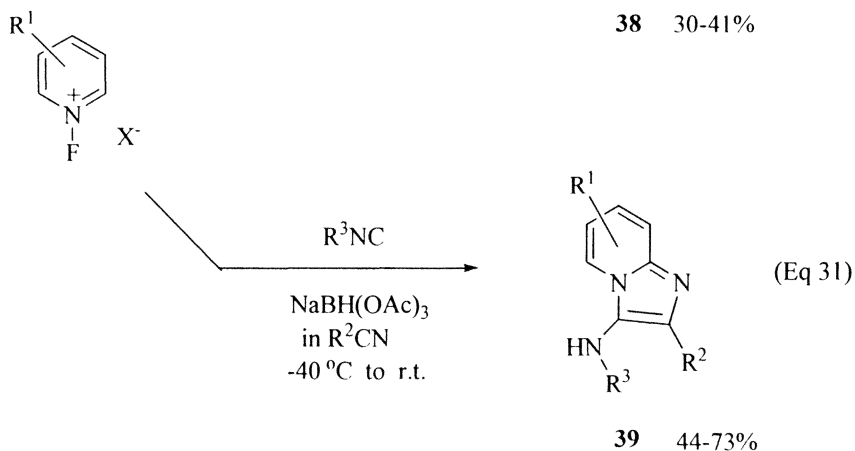
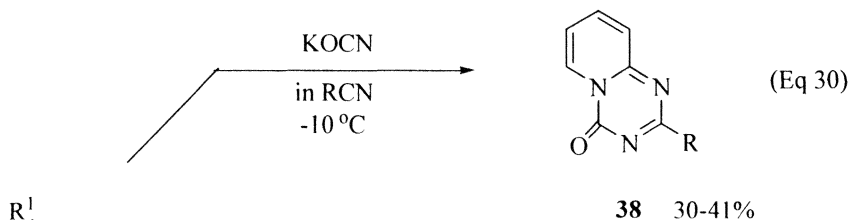
**34**

82%

Synthetic Methods for Fused Heterocyclic Compounds

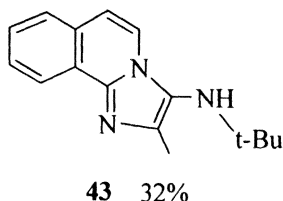
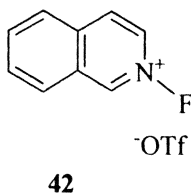
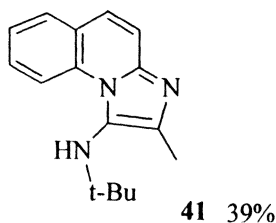
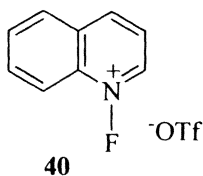
Strekowski et al. applied the base-induced reactions of *N*-fluoropyridinium salts to the synthesis of fused heterocyclic systems. As shown in Eq 30, *N*-fluoropyridinium tetrafluoroborate or triflate (**1b-B** or **1b-T**) was treated with potassium cyanate in RCN solvent to give 2-substituted pyrido[1,2-*a*]-1,3,5-triazin-4-ones **38**, a previously unknown class of heterocyclic compounds (13). Butyronitrile, pivalonitrile, and benzonitrile solvents were used for the reaction. By this method, three pyridotriazinones **38** (R = *n*-propyl, *t*-butyl, and phenyl)

were synthesized in 30-41% yields. These products were accompanied by the corresponding 2-(RCONH)pyridines (12-30%). Interestingly, acetonitrile solvent gave 2-(acetamido)pyridine in a 30% yield, not **38** (R=Me). These products were explained by the carbene mechanism via **8a**.



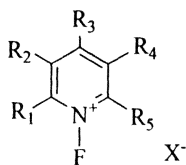
Kiselyov reported that reactions of *N*-fluoropyridinium triflates with isonitriles in acetonitrile and propionitrile in the presence of NaBH(OAc)_3 led to the formation of imidazo[1,2-*a*]pyridines **39** as shown in Eq 31 (35). By this method, many imidazopyridines **39** were synthesized in 44-73% yields. R^1 of **39** includes H, 2-Me, 3-Me, 4-Me, 4-*i*-Pr, 2-phenyl, 2-OMe, and 3-Cl, R^2 includes Me and Et, and R^3 includes *i*-Pr, *t*-Bu, phenyl, *m*- and *p*-tolyl, *p*-nitrophenyl, cyclohexyl, and ethoxycarbonyl. In these reactions, the corresponding 2-(R^2CONH)pyridine derivatives as byproducts were produced in 9-26% yields.

This method was applied to *N*-fluoroquinolinium and *N*-fluoroisoquinolinium triflates (**40** and **42**) (35). Triflate **40** reacted with *t*-butyl isonitrile in acetonitrile in the presence of NaBH(OAc)_3 at $-40\text{ }^\circ\text{C}$ to room temperature to give a triple ring fused heterocyclic compound **41** in a 39% yield. As other products, 2-(acetamido)quinoline and 2-(*N*-*t*-butylcarbonyl)quinoline were produced in 25% and 13% yields, respectively. Similar treatment of triflate **42** gave **43** in a 32% yield. The other products were 1-(acetamido)isoquinoline (21%) and 1-(*N*-*t*-butylcarbonyl)isoquinoline (18%).

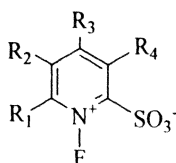


Recent Advance in Fluorination with *N*-Fluoropyridinium Salts

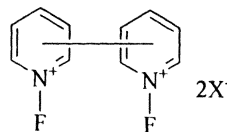
Three series of *N*-fluoropyridinium salts **1-3** shown below have been developed (3-5,17,18,36,37). Using these reagents, a wide range of selective fluorinations of organic compounds differing in reactivity have been carried out. Syntheses of *N*-fluoropyridinium salts and fluorination chemistry with them were reviewed previously (38). Newer results thereafter and results unreported in the review are the focus of this discussion.



Series 1



Series 2



Series 3

1a; R^{1,3,5}=Me, R^{2,4}=H: **T**; X=OTf: **B**; X=BF₄

1b; R¹⁻⁵=H: **T**; X=OTf: **B**; X=BF₄

1c; R^{2,4}=Cl, R^{1,3,5}=H: **T**; X=OTf: **B**; X=BF₄

1d; R^{1,5}=Cl, R²⁻⁴=H: **T**; X=OTf: **B**; X=BF₄

1e; R¹⁻⁵=Cl: **T**; X=OTf: **B**; X=BF₄

2a; R^{1,3}=Me, R^{2,4}=H

2b; R³=Me, R^{1,2,4}=H

2c; R²=CF₃, R^{1,3,4}=H

2d; R¹=CF₃, R²⁻⁴=H

2e; R^{1,3}=CF₃, R^{2,4}=H

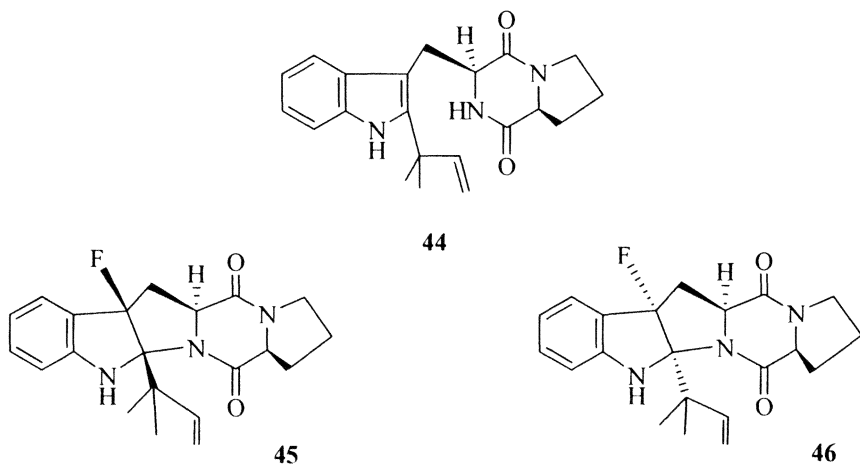
3a; 4,4'-bonding: **T**; X=OTf: **B**; X=BF₄

3b; 3,3'-bonding: **T**; X=OTf: **B**; X=BF₄

3c; 2,4'-bonding: **T**; X=OTf: **B**; X=BF₄

3d; 2,2'-bonding: **T**; X=OTf: **B**; X=BF₄

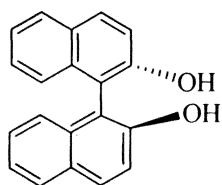
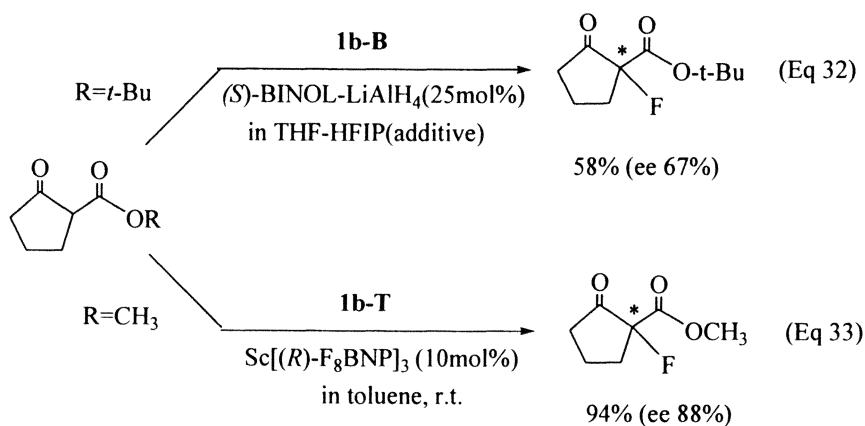
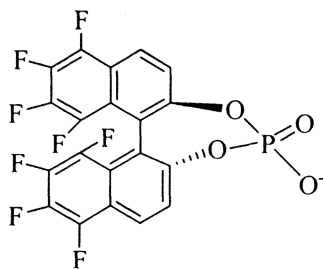
It was reported that tryptophan derivative **44** undergoes highly effective fluorination-cyclization with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**1a-T**) (1.5 eq) in THF solvent at 65 °C to give a 1:1.6 mixture of anti-isomer **45** and syn-isomer **46** in a quantitative yield (39). Reagent **1a-T** is the least powerful fluorinating agent of (**1a-T**)-(1e-T) (power order; **a**<**b**<**c**<**d**<**e**). The report

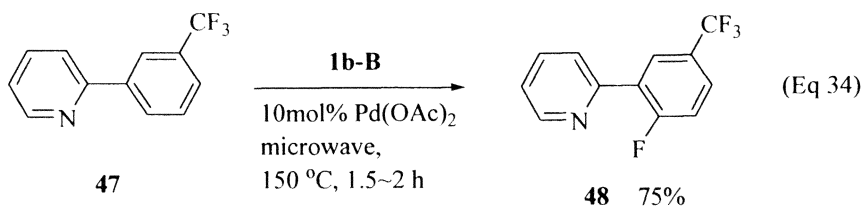


showed that THF is a very suitable solvent for the fluorination of the reactive heteroaromatic compound **44** with **1a-T**. The strong coordination of THF solvent greatly decreases the power of *N*-fluoropyridinium salts (18). Thus, the high reactivity of **44** is modulated by use of a non-powerful fluorinating agent (**1a-T**), the power of which is further decreased by the use of THF as solvent, an illustration of concept for power-variable *N*-fluoropyridinium salts (17,18,36,38).

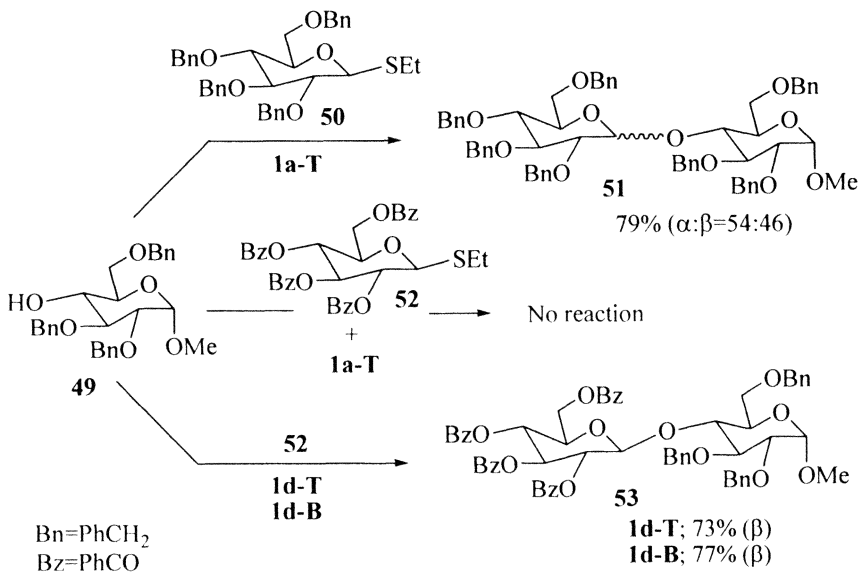
Asymmetric fluorinations catalyzed by chiral catalysts have been actively studied from the time these easy-to-handle fluorinating agents became commercially available. It has been reported that **1b-B** is particularly suited for fluorination with the chiral Al-Li-bis(binaphthoxide) complex (Eq 32) (40). Fluorination with **1b-T** using 10 mol% Sc[(*R*)-F₈BNP]₃ as catalyst provides a higher chemical and enantioselective yield as shown in Eq 33 (41).

Recently, palladium-catalyzed fluorinations of non-activated C-H bonds with **1b-B** and **1a-B** were reported. As shown in Eq 34, substrate **47** was treated with 10 mol% Pd(OAc)₂ and 2.5-4.5 eq **1b-B** in CH₃CN-CF₃C₆H₅ at 150 °C for 1.5-2 h using microwave (300W) irradiation, giving fluoro product **48** in a 75% yield (42).

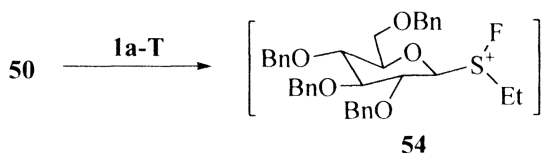
*(S)*-BINOL*(R)*-F₈BNP



Scheme 1.

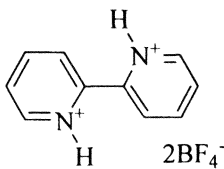
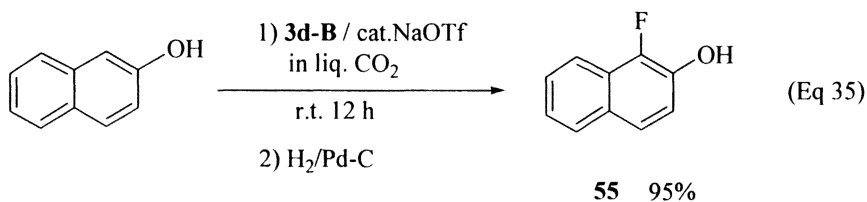


Transformation of thioglycosides into *O*-glycosides is an important chemical method for synthesis of oligosaccharides. As shown in Scheme 1, powerful *N*-fluoro-2,6-dichloropyridinium triflate and tetrafluoroborate (**1d-T** and **1d-B**) can activate the less reactive sulfide **52** for reaction with **49** and transformation into *O*-glycoside **53**. On the other hand, the less powerful **1a-T** does not react with **52**, but does react with reactive sulfide **50** to give *O*-glycoside **51**. With **1d-T** and **1d-B**, an exclusive β -selectivity is obtained (43). The activation of thioglycosides is caused by the transfer of an electrophilic fluorine atom onto the sulfur atom, giving the fluorosulfonium cation intermediate **54**.



A microwave-assisted fluorination of anisole with *N,N'*-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) (**3d-B**) was reported (44). [Ti(TADDOLato)]-catalyzed fluorination/chlorination competition experiments of a β -keto ester were conducted (45). The halogenation ratio (k_F/k_{Cl}) of **3d-B** and *N*-chlorosuccinimide (NCS) was determined to be 0.06. The fluorination with **3d-B** is slow compared to chlorination with NCS.

2-Naphthol was treated with **3d-B** in liquid CO₂ at room temperature for 12 h in the presence of a catalytic amount of sodium triflate (19 mol %). Subsequent hydrogenation with H₂/Pd-C produced 1-fluoro-2-naphthol **55** in an overall 95% yield (Eq 35) (46). With a counteranion-bound *N*-fluoropyridinium salt **2d**, **55** was produced in an overall 99% yield (47). Since liquid CO₂ is a clean solvent, this technology has environmental advantages.



Fluorinations with **3d-B** produce *N,N'*-dihydro-2,2'-bipyridinium bis(tetrafluoroborate) (**56**) together with fluorinated products. Since **56** precipitates almost quantitatively from the reaction mixture with addition of such solvents as ether, it is easily separated from the fluorinated products and re-converted to **3d-B** almost quantitatively by fluorination with F₂/N₂. The recycling is so easy and effective that **3d-B** is a quite suitable fluorinating agent for commercial applications (46).

Recently, H/D isotope effects with the NF type reagents, including *N,N'*-difluoro-2,2'-bipyridinium salt **3d-B**, were studied for the fluorination of benzene, mesitylene, and naphthalene of which ionization potentials are higher than that of durene (48). The study showed that the results of fluorination of the aromatic compounds having high ionization potentials are consistent with a polar S_EAr mechanism.

Summary

In this chapter, reactions of *N*-fluoropyridinium salts with bases and their reaction mechanism involved were discussed, and applications to new synthetic methodologies in heterocyclic chemistry were reviewed. In addition, recent advancements in the fluorination with *N*-fluoropyridinium salts were discussed. Thus, the findings of the novel base-induced reactions have significantly broadened the scope of the reactions of heterocycles. Many new synthetic methods for heterocyclic compounds have been found. Further explorations in this new field should result in significant advancements in the field of heterocyclic chemistry. Additionally, through the use of the fluorinating agents developed, many new and novel fluoroorganic compounds, which may have utility in medical, agricultural, electronic and other areas of chemistry, should now be accessible.

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Chapter 4

Efficient One-Pot Synthesis of Novel Fluorinated Heterocycles Using Trimethylsilyl Trifluoromethanesulfonate as a Metal-Free Homogeneous Lewis Acid Catalyst

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Inessa Bychinskaya, Habiba Vaghoo, Thomas Mathew,
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Metal free homogeneous catalysis is highly significant and advantageous in the design of various therapeutic drugs in the pharmaceutical industry. The presence of organofluorine substituents in drug molecules can highly affect their physicochemical and pharmacokinetic properties. This chapter describes the one-pot synthesis of biologically active fluorinated heterocycles such as benzimidazolines, benzothiazolines, benzoxazolines, dihydrobenzoxazinones, 1,2,3,4-tetrahydroquinazolines, 4H-3,1-benzoxazines and 3,1-benzoxathiin-4-ones using trimethylsilyl trifluoromethyl-sulfonate as a metal free catalyst.

Introduction

Heterocyclic compounds such as benzimidazolines, benzothiazolines, benzoxazolines, dihydrobenzoxazinones, 1,2,3,4-tetrahydroquinazolines, 4H-3,1-benzoxazines and 3,1-benzoxathiin-4-ones are important classes of compounds. Benzimidazolines, often referred to as organic hydrides, can act as good reducing agents and good hydrogen storage materials in many organic reactions [1]. Benzothiazolines and benzoxazolines are used as plant growth regulants, herbicides, anticonvulsants, in photochromic dyes and for the treatment of ADD (Attention Deficiency Disorder) [2]. Dihydrobenzoxazinones are used in analgesics and also as useful building blocks for drugs and pharmaceuticals, which possess antiviral, antifungal, antibacterial and antiparasitic properties [3]. 1,2,3,4-Tetrahydroquinazolines, 4H-3,1-benzoxazines and 3,1-benzoxathiin-4-ones also show similar biological activities [4]. In addition, 4H-3,1-benzoxazines are used in lithium ion batteries [5], as anti-knock agent for gasoline [6], and as stabilizers, especially for jet fuels and turbine fuels [7].

Fluorinated heterocycles are becoming increasingly important in the pharmaceutical industry and development of new reaction methodologies for their convenient and efficient synthesis has attracted the efforts of a large number of synthetic chemists in recent years. It is well known that the presence of fluorine can result in substantial functional changes in the biological as well as physicochemical properties of organic compounds [8]. Incorporation of fluorine into drug molecules can highly affect their physicochemical properties, such as bond strength, lipophilicity, bioavailability, conformation, electrostatic potential, dipole moment, pK_a etc; pharmacokinetic properties, such as tissue distribution, rate of metabolism; and pharmacological consequences, such as pharmacodynamics and toxicology. Considering the increasing importance of fluorinated heterocycles and knowing the effect of fluorine substitution, we became interested in synthesizing the fluorinated analogs of the above-mentioned classes of compounds.

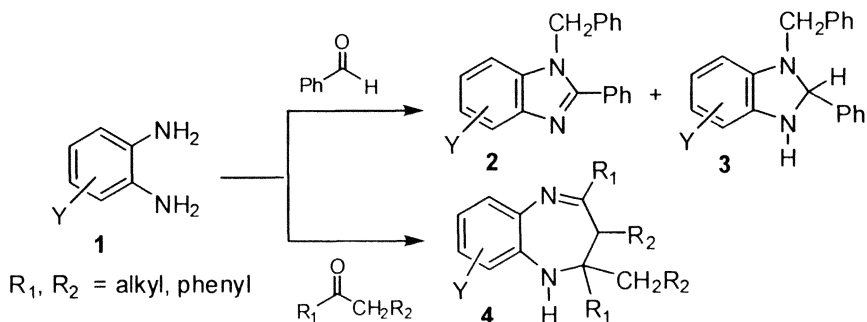
Recently [9], we have shown that gallium triflate in dichloromethane is the best catalyst-solvent combination for the effective condensation-cyclization reaction of fluorinated ketones with *ortho*-aniline derivatives for the synthesis of fluorinated heterocycles such as fluorinated benzimidazolines **7a**, benzothiazolines **7b**, benzoxazolines **7c**, and dihydrobenzoxazinones **8**. However, cognizant of the fact that metal-free organocatalysis [10] has drawn considerable attention of chemists in recent times and metal-free homogeneous catalysis is highly significant and advantageous for designing suitable drugs completely devoid of any metal content, we realized it would be very useful to perform similar reactions using metal-free Lewis acid catalysts.

Since the late 1970s, trimethylsilyl trifluoromethanesulfonate (TMSOTf) is known to be an efficient silylating agent as well as a strong Lewis acid [11]. In the late 1980s our group has successfully carried out the reductive coupling of ketones, to produce the corresponding symmetrical ethers using TMSOTf as the catalyst [12]. In the last decade, varieties of organic transformations, including Friedel-Crafts reactions, Diels–Alder reactions, C–O couplings, epimerizations etc. have been carried out successfully using TMSOTf as a homogeneous Lewis acid catalyst [13,14]. Recently, we have accomplished the direct three component Strecker reaction of aldehydes, ketones and fluorinated ketones using TMSOTf as the catalyst [15]. Considering all these facts, we envisioned TMSOTf as a good metal-free, homogeneous Lewis acid catalyst for the condensation-cyclization reaction of various bifunctional arenes with aldehydes and ketones. Also, in our previous studies we have shown that the synthesis of four different kinds of fluorinated heterocycles from aniline derivatives can be carried out using gallium triflate as the catalyst. In our current studies, we succeeded in expanding our methodology to other possible 1,2-disubstituted benzene derivatives such as thiosalicylic acid, anthranilic acidamides, *o*-hydroxybenzyl amine, etc., showing the versatility of this condensation-cyclization methodology. Hence we could easily prepare 3,1-benzoxathiin-4-ones **12** and similar derivatives under relatively mild conditions. Herein, we report in detail the results of our studies for the efficient synthesis of many previously unknown fluorinated heterocycles using catalytic amounts of trimethylsilyl triflate as the Lewis acid catalyst.

Synthesis of Fluorinated Benzimidazolines, Thiazolines, Oxazolines and Oxazinones

Benzimidazolines **3** are generally synthesized from the reaction of 1,2-phenylenediamines **1** and benzaldehyde (Scheme 1) [16]. However, when ketones (R_1 , R_2 = alkyl, phenyl) were used under similar conditions, 1,5 benzodiazepine derivatives **4** were formed as the major products (Scheme 1) [17]. This reaction proceeds through the diimine intermediate **10a** (Scheme 3), which then undergoes an internal Michael type addition reaction to give rise to the corresponding 1,5-benzodiazepine derivatives **4** (Scheme 1).

Reports on the direct synthesis of fluorinated benzimidazolines are very rare [18]. To our best knowledge, an easy and convenient method was not available until we recently communicated our preliminary results on condensation-cyclization [9]. Funabiki et al. [19] have prepared fluorinated benzimidazolines from fluorinated alkynyl carboxylic acids **5** (Scheme 2). Synthesis of more diverse and functionalized starting materials for this reaction is tedious. Since the reaction conditions and chemical yields are not very impressive in all cases,



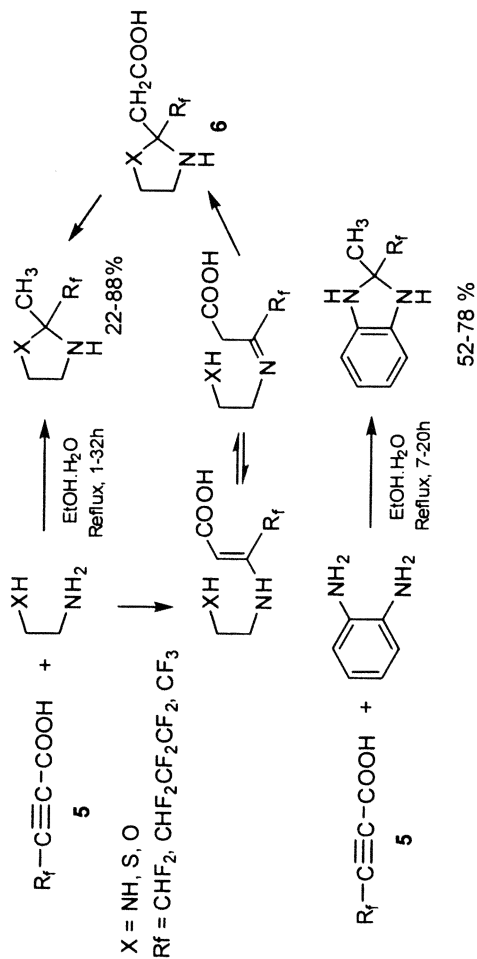
Scheme 1. Reactions of benzaldehyde and ketones with 1,2-phenylenediamines

finding a convenient and efficient method feasible under ambient conditions has been an important goal.

We explored the synthesis of fluorinated benzimidazolines directly from fluorinated ketones and diamines using gallium triflate as the Lewis acid catalyst (Scheme 3). In our previous communication [9] we have discussed the results of our studies. We found that $\text{Ga}(\text{OTf})_3$ is a very unique and highly efficient catalyst for this transformation under mild conditions. High efficiency and greater versatility of this reaction, including high selectivity and purity of the products, reveal the significance of using $\text{Ga}(\text{OTf})_3$ as a highly suitable catalyst for these reactions.

It is clear from our earlier results that the number of fluorine atoms present in the fluorinated ketone has a significant governing effect on the path of the reaction. This is because the electrophilicity at the carbon center of the monoimine intermediate **9** depends strongly on the number of fluorine atoms attached to the α -carbon. An increase in the number of fluorine atoms significantly increases the electrophilicity at the carbon center of the monoimine intermediate. Because of this the non-bonding electron pair on the nitrogen atom of the second amino group rapidly attacks the highly electrophilic carbon center of the internal fluorinated imine. This is followed by a 1,3-proton transfer, which leads to the formation of the corresponding 5-membered ring (Scheme 3).

On the other hand, when the number of fluorine atoms in the ketone drops to one or zero, the electrophilicity at the carbon center of the monoimine **9a** is not sufficient to facilitate internal attack by the electron pair on the nitrogen atom of the second amino group. Thus, the second amine moiety reacts faster with another molecule of ketone to form the diimine intermediate **10a**, which undergoes further rearrangement to give rise to the corresponding 7-membered ring (Scheme 3).



Scheme 2. Synthesis of fluorinated benzimidazolines from fluorinated alkyne carboxylic acids and vicinal-diamines

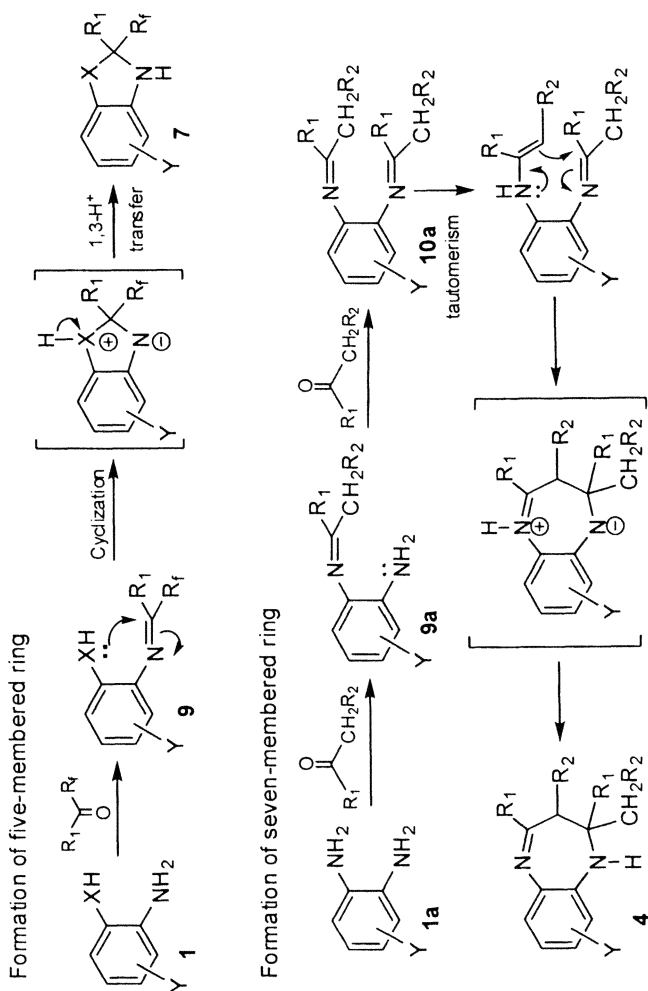
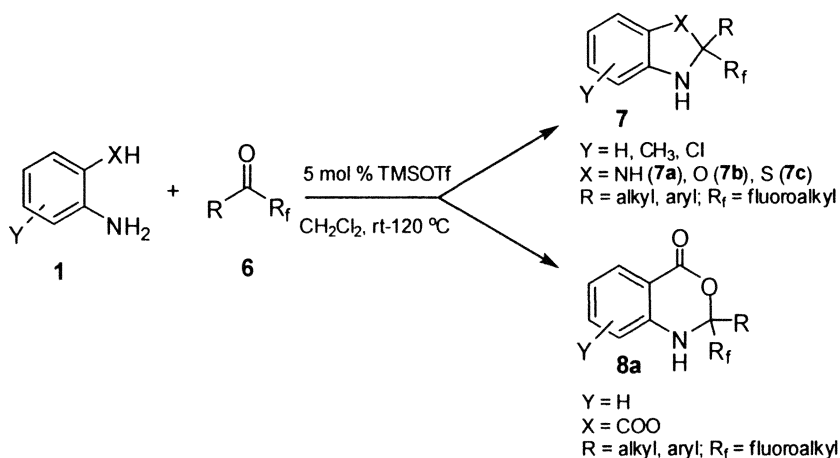


Table 1. Reaction of 1,2-phenylenediamine with 1,1,1-trifluoroacetone using various metal triflates and TMSOTf as the catalysts

entry	catalyst	yield (%)
1	Ga(OTf) ₃	97
2	Yb(OTf) ₃	93
3	Y(OTf) ₃	87
4	Sc(OTf) ₃	96
5	Sm(OTf) ₃	88
6	La(OTf) ₃	32
7	Cu(OTf) ₂	75
8	TMSOTf	92

Our detailed investigation on the potential of other metal triflate catalysts towards this condensation-cyclization reaction shows that most of the metal triflate catalysts bring out this reaction efficiently when dichloromethane is used as solvent, except for lanthanum triflate (Table 1, entry 6). However, gallium triflate was found to be superior, giving the maximum yield of 2-trifluoromethylbenzimidazoline (Table 1, entry 1). During our search for a metal free, homogeneous and efficient organocatalyst for these reactions, we found that trimethylsilyl triflate can serve this purpose effectively (Table 1, entry 8). In reactions which require the complete absence of metal catalysts (strong interaction of metal catalysts with other functional groups by chelation and complex formation can cause significant decrease in reactivity), trimethylsilyl triflate is found to be an ideal substitute. The homogeneous nature of this organocatalyst in organic media is an added advantage, as already mentioned. We have explored the potential of the catalyst by carrying out a similar study for the condensation-cyclization reaction as we did in the case of reactions catalyzed by metal triflates (Scheme 4). Our present work also involves the successful extension of this methodology beyond the synthesis of the four classes of fluorinated heterocycles that were covered in our previous communication [9].

When the condensation-cyclization reaction was carried out with the diamine derivatives and fluorinated ketones using TMSOTf, the results were found to be similar as in the gallium triflate catalyzed reactions. However, the reaction conditions and yields of the products were slightly different. 1,2-Phenylenediamines bearing electron withdrawing and electron donating groups reacted with aliphatic, aromatic and benzylic trifluoromethyl ketones under TMSOTf catalyzed conditions. In all cases, yields of the products were found to be high (Table 2). As with the gallium triflate-catalyzed reaction, higher temperature and more reaction time were required for the reaction of 1,1,1-trifluoromethylacetophenone using TMSOTf as the catalyst (Table 2, entry 7).



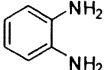
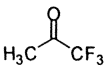
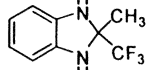
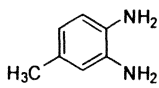
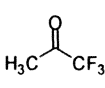
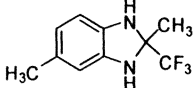
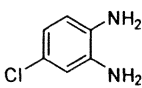
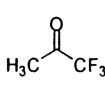
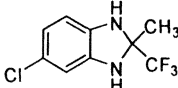
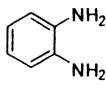
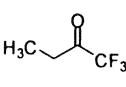
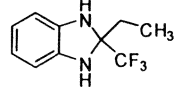
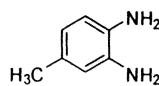
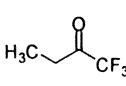
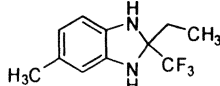
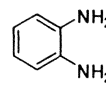
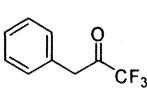
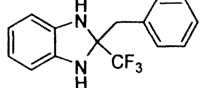
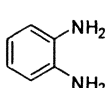
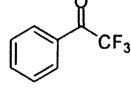
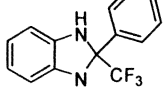
Scheme 4. Condensation of ketones with *o*-aminoarenes using TMSOTf as catalyst

Fluorinated thiazolines **7b**, oxazolines **7c** and oxazinones **8a** (Scheme 4) were also prepared using the corresponding *o*-amino derivatives and trimethylsilyl triflate as the catalyst (Table 3). 1,1-Difluoroacetone also gave clean products with many of these *o*-amino derivatives. In general, it has been found that reactions using anthranilic acid (Table 3, entries 8 and 9) or aromatic trifluoromethyl ketones (Table 3 entries 1, 2 and 7) require higher temperatures. On the other hand, when the substrates were changed to *o*-aminophenol/*o*-aminothiophenol and difluoromethyl ketone (Table 3, entries 4-6) reactions proceeded smoothly under very mild conditions. Similar to the gallium triflate-catalyzed reactions, monofluoroacetone always gave a mixture of the corresponding seven and five membered ring systems (Scheme 3, R = F) [9].

Synthesis of 1,2,3,4-tetrahydroquinazolines, 4H-3,1-benzoxazines and 3,1-benzoxathiin-4-ones

Syntheses of various other important classes of heterocycles such as 1,2,3,4-tetrahydroquinazolines **8b**, 2,3-dihydro-4(1H)-quinazolinones **8c**, 4H-3,1-benzoxazines **8d**, and 3,1-benzoxathiin-4-ones **12** have been achieved in good yields by further extension of the present methodology (Schemes 5 and 6 and Tables 4 and 5). This makes their access easier compared to previous methods. As mentioned earlier, many of these compounds possess interesting biological activities. Hence building a library of new fluorinated analogs of such compounds and studying their biological activities and their potential uses in the pharmaceutical arena would be of great interest.

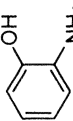
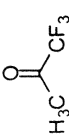
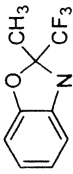
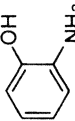
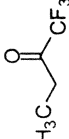
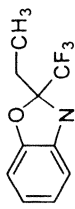
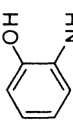
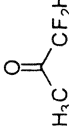
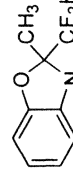
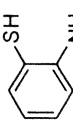
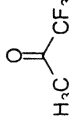
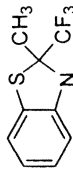
Table 2. Preparation of 2-fluoroalkyl benzimidazolines using TMSOTf as the catalyst

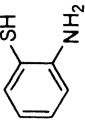
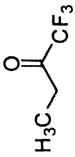
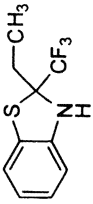
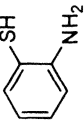
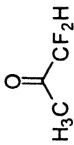
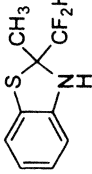
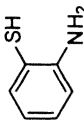
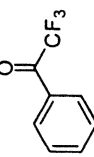
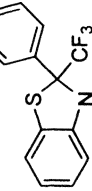
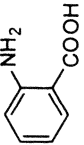
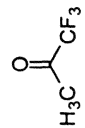
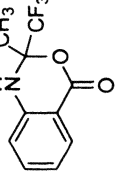
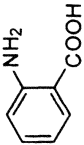
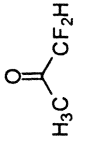
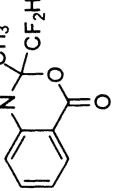
entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yields (%)
1			4	50		92
2			4	50		85
3			4	50		78
4			4	50		78
5			4	50		80
6			4	50		87
7			5	120		89

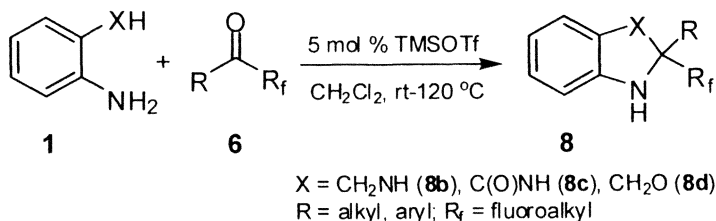
Anthranilic acid and the corresponding amides were less reactive and required higher temperature for higher conversion. 2-Aminobenzyl amine and its hydroxy analog also undergo the condensation-cyclization reaction with fluorinated ketones to yield the corresponding fluorinated 6-membered heterocycles in high yields (Table 4a, entries 1-7). However, reactions with aromatic and benzylic trifluoromethyl ketones were found to be slow.

Reaction of thiosalicylic acid (**11**) gave the corresponding fluorinated oxathiinones **12** in good yield and purity showing the synthetic utility and versatility of this method (Scheme 6 and Table 5). Hence the scope of this methodology can be broadened to a greater spectrum despite low conversions and yields for the reaction of salicylic acid itself. The acidity of TMSOTf as a Lewis acid may not be sufficient to carry out the condensation-cyclization reaction of salicylic acid successfully.

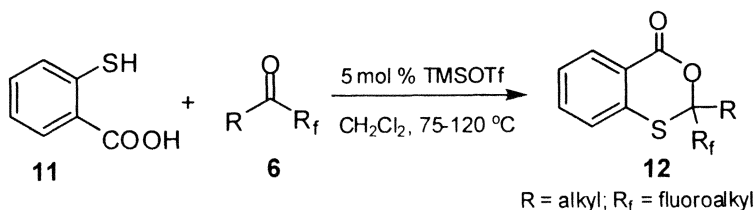
Table 3. Preparation of fluorinated benzothiazolines, benzoxazolines and dihydrobenzoxazinones using TMSOTf as the catalyst

entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yields (%)
1			4	75		87
2			4	75		75
3			4	rt		78
4			6	rt		88

5			4	50		82
6			4	rt		90
7			4	100		80
8			7	100		70
9			7	75		66



Scheme 5



Scheme 6

Interestingly, when 2-hydroxythiophenol (**13**) was subjected to the condensation-cyclization reaction under TMSOTf conditions, instead of the desired intramolecular cyclization, the corresponding intermolecular dithioether formation took place (Scheme 7). Thiols are known to undergo similar reactions under acid catalyzed conditions [20]. Since the nucleophilicity of the thio group is greater than that of the hydroxyl group, formation of thioketal is preferred rather than ketal formation. Further condensation of thioketal with another molecule of 2-hydroxythiophenol at the thio function gives rise to the product **14**. Therefore, in this case, we did not observe the formation of the expected cyclized product **15**.

For further investigation, we performed the reaction with 1,2-benzenedithiol **16** and catechol **18** under similar conditions (Scheme 7). When dithiol **16** was subjected to similar treatment, a significant amount of product **17** was observed (by NMR) in the reaction mixture. However, catechol **18** never gave a clean reaction, but a complex mixture of products was always observed.

These results prompted us to reinvestigate the mechanism of these reactions further. In our previous studies, a mechanism involving mainly a monoimine intermediate has been suggested for the formation of the heterocycles from the *o*-amino substrates (Scheme 3). However, considering all the current studies and observation of the formation of the intermolecular reaction product, we now also

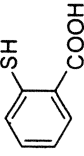
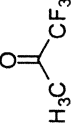
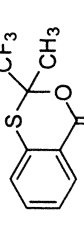
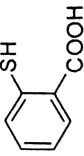
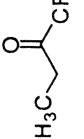
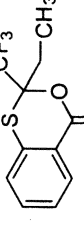
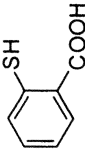
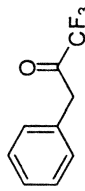
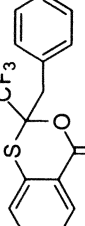
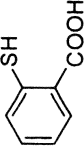
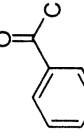
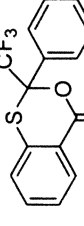
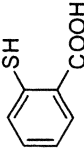
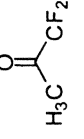
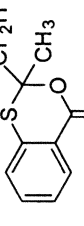
Table 4a. Preparation of fluorinated 1,2,3,4-tetrahydroquinazolines and 4H-3,1-benzoxazines using TMSOTf as the catalyst

entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yields (%)
1			12	50		84
2			12	50		75
3			12	75		86
4			3	rt		75
5			2	50		60
6			3	rt		79
7			4	rt		73

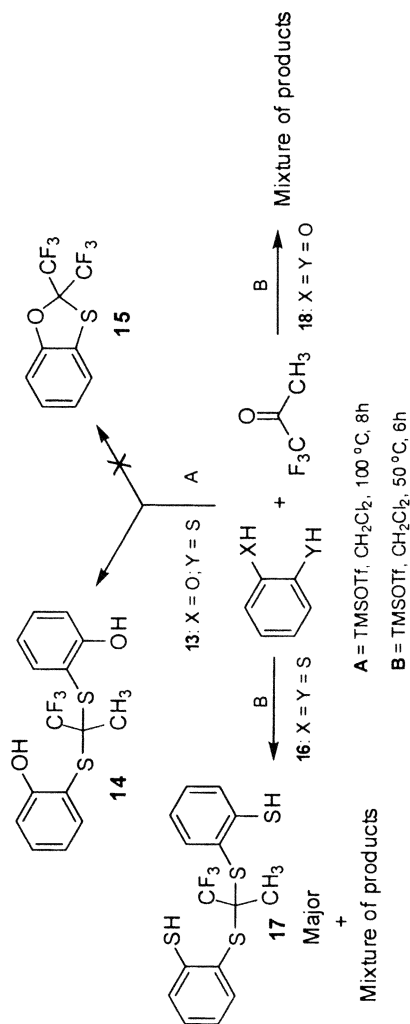
Table 4b. Preparation of fluorinated 2,3-dihydro-4(1H)-quinazolinones using TMSOTf as the catalyst

entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yields (%)
1			12	100		85
2			3	60		86
3			12	100		83
4			12	120		76

Table 5. Preparation of fluorinated 3,1-benzoxathiin-4-ones using TMSOTf as the catalyst

entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yield (%)
1			12	100		75
2			12	75		80
3			12	100		91
4*			12	120		65
5			6	75		96

* Unreacted acid was removed by bicarbonate treatment



Scheme 7

consider the “aminal” route. The reaction has been repeated with *N*-methyl-1,2-phenylenediamine **19** with the view that the methyl group should make the amino group attached to it more nucleophilic than the other amino group favoring the initial aminal formation at the methylamino function. The initial attack of the amino function can give rise to the aminal intermediate **20**, which on activation by the Lewis acid can then undergo either an intermolecular or intramolecular attack depending on the nature of the other nucleophile (Scheme 8). In the case of compound **19**, we obtained the cyclized product **21** only (Scheme 8a).

The formation of product **14** from 2-hydroxythiophenol (**13**) can also be explained on the basis of this “aminal” type mechanism. Intermolecular attack on the aminal type of intermediate **22** could give rise to product **14** with the elimination of one molecule of water (Scheme 8b). Since the C-O bond cleavage is more feasible than S-C (aromatic) bond cleavage under the reaction conditions, product **14** is formed resulting from the C-O bond cleavage. In the case of **16** and **18**, the situation may be more complicated and thus a complex mixture of products was formed.

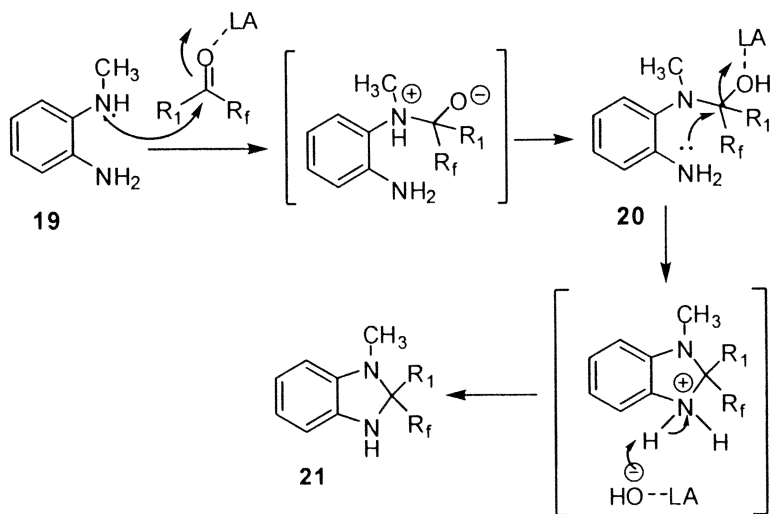
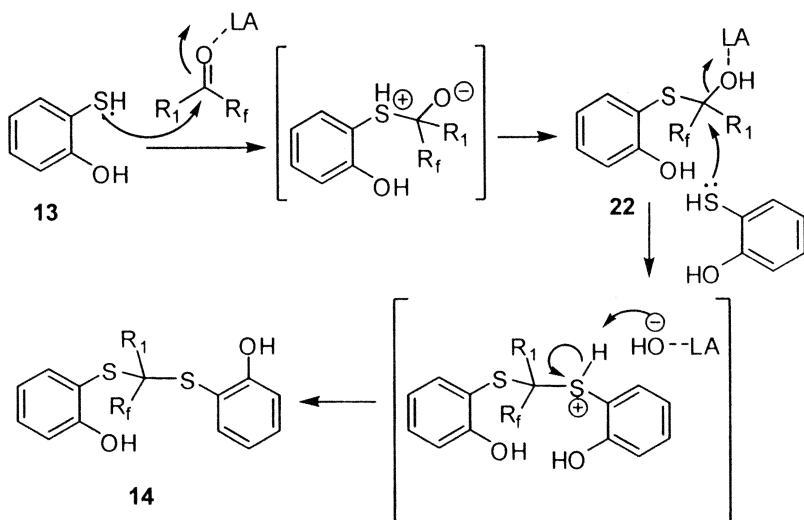
General procedure for the TMSOTf catalyzed cyclization-condensation

Fluorinated ketone (3 mmol) and *o*-amine derivative (2 mmol) were placed in a pressure tube and dissolved in 4 mL of CH₂Cl₂. To this mixture was added TMSOTf (22 mg, 5 mol%) and the pressure tube was closed. The mixture was stirred at the required temperature till the completion of the reaction, with monitoring at different time intervals by TLC and NMR. The mixture was then quenched with water and extracted with CH₂Cl₂ (3x15 mL). All the organic layers were collected, washed with brine solution (15 mL), dried over anhydrous Na₂SO₄ and then the solvent was removed under reduced pressure to obtain the product in NMR pure grade in most cases. Further purification can be carried out by trituration of the residue with excess hexane followed by evaporation of hexane or by column chromatography using 4:1 hexane-ethyl acetate solvent mixture. Products were fully characterized by spectral analysis (¹H, ¹³C, ¹⁹F NMR and HRMS data) and comparison of the spectral data with those of the authentic samples [9,21].

Conclusion

Syntheses of various fluorinated heterocycles such as benzimidazolines, benzothiazolines, benzoxazolines, dihydrobenzoxazinones, 1,2,3,4-tetrahydroquinazolines, 4H-3,1-benzoxazines and 3,1-benzoxathiin-4-ones were achieved under mild conditions using TMSOTf, an effective metal-free, homogeneous Lewis acid catalyst. Even when used in catalytic amounts, this reagent

(a) The "aminal" route

(b) Formation of product **14** following the "aminal" type route

Scheme 8. Modified mechanism

provides the optimum Lewis acidity required for the synthesis of fluorinated heterocycles. This current methodology can be considered as a general procedure for the efficient synthesis of many of the above mentioned heterocycles under metal-free conditions. In most cases, reactions are clean and easy to work up, require mild conditions and provide the corresponding products in high yield and purity. The current study also highlights detailed mechanistic aspects of the condensation-cyclization reaction.

Acknowledgment

Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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21. **Spectral data of new compounds**

2-Methyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline (Table 4a, entry 1): $^1\text{H NMR}$ δ 1.49 (q, $J = 1.21$ Hz, 3H), 1.87 (brs, 1H), 3.87 (d, $J = 16.61$ Hz, 1H), 4.03 (d, $J = 16.67$ Hz, 1H), 4.08 (brs, 1H), 6.54 (dd, $J = 8.00, 0.87$ Hz, 1H), 6.72 (dt, $J = 7.41, 1.14$ Hz, 1H), 6.92 (dd, $J = 7.48, 0.83$ Hz, 1H), 7.05 (dt, $J = 8.06, 1.61$ Hz, 1H); $^{13}\text{C NMR}$ δ 22.7, 42.3, 68.2 (q, $2\text{JC-F} = 28.83$ Hz), 114.7, 118.4, 120.1, 125.52 (q, $1\text{JC-F} = 287.4$ Hz), 125.78, 127.5, 140.4; $^{19}\text{F NMR}$ δ -82.46; HRMS (EI) m/z 216.0878, calculated for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{N}_2$ 216.0874.

2-Ethyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline (Table 4a, entry 2): $^1\text{H NMR}$ δ 0.93 (dd, $J = 7.86, 7.21$ Hz, 3H), 1.92-1.69 (m, 3H), 3.81 (d, $J = 16.33$ Hz, 1H), 4.00 (s, 1H), 4.04 (d, $J = 16.45$ Hz, 1H), 6.53 (dd, $J = 7.98, 0.90$ Hz, 1H), 6.68 (dt, $J = 7.40, 1.10$ Hz, 1H), 6.89 (d, $J = 7.42$ Hz, 1H), 7.03 (dt, $J = 7.99, 1.43$ Hz, 1H); $^{13}\text{C NMR}$ δ 6.2, 28.0, 42.3, 70.3 (q, $2\text{JC-F} = 27.50$ Hz), 114.0, 117.9, 120.3, 125.6, 126.8 (q, $1\text{JC-F} = 289.3$ Hz), 127.4, 141.0; $^{19}\text{F NMR}$ δ -80.38; HRMS (EI) m/z 230.1028, calculated for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{N}_2$ 230.1031.

2-Benzyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline (Table 4a, entry 3): $^1\text{H NMR}$ δ 3.09 (s, 2H), 3.79 (d, $J = 16.71$ Hz, 1H), 4.07 (d, $J = 16.76$ Hz, 1H), 6.57 (dd, $J = 7.99, 0.92$ Hz, 1H), 6.67 (dt, $J = 7.41, 1.12$ Hz, 1H), 6.84 (dd, $J = 7.46, 0.73$ Hz, 1H), 7.03 (dt, $J = 8.01, 1.41$ Hz, 1H), 7.33-7.21 (m, 5H); $^{13}\text{C NMR}$ δ 40.9, 42.4, 70.16 (q, $2\text{JC-F} = 27.46$ Hz), 114.4, 118.3, 120.0, 125.61, 125.72 (q, $1\text{JC-F} = 289.42$ Hz), 127.46, 127.71, 128.7, 130.9, 132.8, 140.6; $^{19}\text{F NMR}$ δ -79.74; HRMS (EI) m/z 292.1193, calculated for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2$ 292.1187.

2-(Difluoromethyl)-2-methyl-1,2,3,4-tetrahydroquinazoline (Table 4a, entry 4): $^1\text{H NMR}$ δ 1.34 (t, $J = 1.69$ Hz, 3H), 1.80 (brs, 1H), 3.85 (d, $J = 16.86$ Hz, 1H), 3.92 (d, $J = 16.86$ Hz, 1H), 4.07 (brs, 1H), 5.64 (t, $J = 56.30$ Hz,

1H), 6.51 (dd, $J = 8.00, 0.91$ Hz, 1H), 6.68 (dt, $J = 7.41, 1.13$ Hz, 1H), 6.88 (dd, $J = 7.46, 0.90$ Hz, 1H), 7.02 (dt, $J = 8.02, 1.52$ Hz, 1H); ^{13}C NMR δ 20.4, 41.7, 67.1 (t, $2\text{JC-F} = 21.9$ Hz), 114.76, 115.1 (dd, $1\text{JC-F} = 249.80, 246.60$ Hz), 117.9, 119.8, 125.8, 127.4, 141.0; ^{19}F NMR δ -131.33 (dd, $J = 279.24$ Hz, $J = 56.46$ Hz, 1F), -135.64 (dd, $J = 277.71$ Hz, $J = 56.46$ Hz, 1F); HRMS (EI) m/z 198.0971, calculated for $\text{C}_{10}\text{H}_{12}\text{F}_2\text{N}_2$ 198.0969.

2-Methyl-2-(trifluoromethyl)-2,4-dihydro-1H-benzo[d][1,3]oxazine (Table 4a, entry 5): ^1H NMR δ 1.62 (s, 3H), 4.30 (s, 1H), 4.84 (d, $J = 14.43$ Hz, 1H), 5.01 (d, $J = 14.40$ Hz, 1H), 6.70 (d, $J = 8.01$ Hz, 1H), 6.87 (t, $J = 7.38$ Hz, 1H), 6.99 (d, $J = 7.50$ Hz, 1H), 7.17 (t, $J = 7.67$ Hz, 1H); ^{13}C NMR δ 22.2, 63.8, 82.46 (q, $2\text{JC-F} = 30.37$ Hz), 115.1, 119.37, 119.68, 124.63 (q, $1\text{JC-F} = 290.62$ Hz), 124.64, 128.1, 138.7; ^{19}F NMR δ -81.56; HRMS (EI) m/z 217.0715, calculated for $\text{C}_{10}\text{H}_{10}\text{F}_3\text{NO}$ 217.0714.

2-(Difluoromethyl)-2-methyl-2,4-dihydro-1H-benzo[d][1,3]oxazine (Table 4a, entry 6): ^1H NMR δ 1.43 (t, 1.83 Hz, 3H), 4.18 (s, 1H), 4.79 (q, $J = 14.80$ Hz, 2H), 5.64 (dd, $J = 56.57, 55.48$ Hz, 1H), 6.60 (dd, $J = 8.01, 0.70$ Hz, 1H), 6.76 (dt, $J = 7.44, 1.10$ Hz, 1H), 6.89 (dd, $J = 7.55, 0.88$ Hz, 1H), 6.99-7.18 (m, 1H); ^{13}C NMR δ 18.8, 62.5, 82.4 (t, $2\text{JC-F} = 24.67$ Hz), 113.9 (dd, $1\text{JC-F} = 252.51, 246.44$ Hz), 115.6, 119.08, 119.65, 124.7, 128.0, 139.2; ^{19}F NMR δ -132.32 (dd, $J = 283.81$ Hz, $J = 56.46$ Hz, 1F), -134.74 (dd, $J = 283.81$ Hz, $J = 54.93$ Hz, 1F); HRMS (EI) m/z 199.0812, calculated for $\text{C}_{10}\text{H}_{11}\text{F}_2\text{NO}$ 199.0809.

2-Ethyl-2-(trifluoromethyl)-2,4-dihydro-1H-benzo[d][1,3]oxazine (Table 4a, entry 7): ^1H NMR δ 0.96 (dd, $J = 7.73, 7.20$ Hz, 3H), 1.67-1.78 (m, 1H), 2.02-1.91 (m, 1H), 4.08 (s, 1H), 4.74 (d, $J = 14.09$ Hz, 1H), 4.95 (d, $J = 14.21$ Hz, 1H), 6.61 (d, $J = 7.99$ Hz, 1H), 6.76 (dt, $J = 7.45, 1.05$ Hz, 1H), 6.90 (d, $J = 7.48$ Hz, 1H), 7.08 (t, $J = 7.68$ Hz, 1H); ^{13}C NMR δ 6.1, 28.3, 64.2, 84.1 (q, $2\text{JC-F} = 28.91$ Hz), 114.5, 119.00, 119.65, 124.6, 125.0 (q, $1\text{JC-F} = 292.41$ Hz), 128.1, 139.4; ^{19}F NMR δ -80.26; HRMS (EI) m/z 231.0878, calculated for $\text{C}_{11}\text{H}_{12}\text{F}_3\text{NO}$ 231.0871.

2-Methyl-2-(trifluoromethyl)-2,3-dihydroquinazolin-4(1H)-one (Table 4b, entry 1): ^1H NMR δ 1.68 (s, 3H), 6.42 (brs, 1H), 6.74 (dd, $J = 13.42, 7.55$ Hz, 2H), 7.27 (t, $J = 7.04$ Hz, 1H), 7.79 (d, $J = 7.39$ Hz, 1H), 8.21 (s, 1H); ^{13}C NMR δ 22.0, 68.8 (q, $2\text{JC-F} = 30.34$ Hz), 112.8, 113.2, 117.7, 124.8 (q, $1\text{JC-F} = 293.82$ Hz), 127.2, 133.6, 145.1, 163.8; ^{19}F NMR δ -85.33; HRMS (EI) m/z 230.0678, calculated for $\text{C}_{10}\text{H}_9\text{F}_3\text{N}_2\text{O}$ 230.0667.

2-(Difluoromethyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one (Table 4b, entry 2): ^1H NMR δ 1.58 (d, $J = 1.56$ Hz, 3H), 5.79 (t, $J = 56.41$ Hz, 1H), 6.65 (d, $J = 8.12$ Hz, 1H), 6.77 (brs, 1H), 6.86 (t, $J = 7.50$ Hz, 1H), 7.26 (s, 1H), 7.33 (t, $J = 7.32$ Hz, 1H), 7.87 (d, $J = 7.80$ Hz, 1H); ^{13}C NMR δ 69.2 (t, $2\text{JC-F} = 25.09$ Hz), 113.9 (dd, $1\text{JC-F} = 253.76, 251.40$ Hz), 114.09, 114.32, 119.7, 128.6, 134.7, 144.7, 163.7; ^{19}F NMR δ -130.97 (dd, $J =$

279.24 Hz, $J = 56.46$ Hz, 1F), -135.02 (dd, $J = 279.24$ Hz, $J = 56.46$ Hz, 1F); HRMS (EI) m/z 212.0772, calculated for $C_{10}H_{10}F_2N_2O$ 212.0761.

2-Ethyl-2-(trifluoromethyl)-2,3-dihydroquinazolin-4(1H)-one (Table 4b, entry 3): 1H NMR δ 1.14 (t, $J = 7.41$ Hz, 3H), 1.86 (m, 1H), 1.97 (m, 1H), 4.46 (brs, 1H), 6.67 (d, $J = 8.12$ Hz, 1H), 6.84 (dt, $J = 7.82$, 0.96 Hz, 1H), 7.26 (s, 1H), 7.34 (ddd, $J = 8.14$, 7.33, 1.56 Hz, 1H), 7.87 (dd, $J = 7.81$, 1.42 Hz, 1H); ^{13}C NMR δ 6.8, 27.0, 72.79 (q, 2JC-F = 29.71 Hz), 112.7, 113.7, 119.4, 125.09 (q, 1JC-F = 293.28 Hz), 128.3, 134.8, 145.2, 164.8; ^{19}F NMR δ -85.45; HRMS (EI) m/z 244.0829, calculated for $C_{11}H_{11}F_3N_2O$ 244.0823.

2-Benzyl-2-(trifluoromethyl)-2,3-dihydroquinazolin-4(1H)-one (Table 4b, entry 4): 1H NMR δ 3.18 (d, $J = 14.47$ Hz, 1H), 3.31 (d, $J = 14.47$ Hz, 1H), 4.62 (s, 1H), 6.63 (d, $J = 8.13$ Hz, 1H), 6.79 (t, $J = 7.55$ Hz, 1H), 7.24-7.36 (m, 6H), 7.80 (d, $J = 7.80$ Hz, 1H), 8.12 (s, 1H); ^{13}C NMR δ 39.5, 72.46 (q, 2JC-F = 29.12 Hz), 112.4, 113.5, 118.2, 124.9 (q, 1JC-F = 294.44 Hz), 127.25, 127.54, 128.2, 131.0, 132.4, 134.0, 145.1, 164.1; ^{19}F NMR δ -83.95; HRMS (EI) m/z 306.0992, calculated for $C_{16}H_{13}F_3N_2O$ 306.0980.

2-Methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]oxathiin-4-one (Table 5, entry 1): 1H NMR δ 1.96 (q, $J = 1.01$ Hz, 3H), 7.27 (dd, $J = 7.78$, 0.94 Hz, 1H), 7.33 (ddd, $J = 7.68$, 7.68, 1.17 Hz, 1H), 7.53 (ddd, $J = 7.68$, 7.68, 1.51 Hz, 1H), 8.18 (dd, $J = 7.89$, 1.48 Hz, 1H); ^{13}C NMR δ 23.0, 84.4 (q, 2JC-F = 32.81 Hz), 121.8, 123.7 (q, 1JC-F = 286.36 Hz), 126.6, 127.0, 132.2, 133.7, 134.5, 160.7; ^{19}F NMR δ -79.92; HRMS (EI) m/z 248.0132, calculated for $C_{10}H_7F_3O_2S$ 248.0119.

2-Ethyl-2-(trifluoromethyl)-4H-benzo[d][1,3]oxathiin-4-one (Table 5, entry 2): 1H NMR δ 1.22 (t, $J = 7.52$ Hz, 3H), 1.97-2.08 (m, 1H), 2.27-2.38 (m, 1H), 7.24-7.33 (m, 2H), 7.50 (dt, $J = 7.78$, 1.57 Hz, 1H), 8.17 (dd, $J = 7.87$, 1.52 Hz, 1H); ^{13}C NMR δ 7.8, 28.1, 87.7 (q, 2JC-F = 31.14 Hz), 121.3, 124.0 (q, 1JC-F = 287.31 Hz), 126.6, 131.9, 133.9, 134.323, 160.7, 218.6; ^{19}F NMR δ -78.6; HRMS (FAB) m/z 263.0366, calculated for $C_{11}H_9F_3O_2S$ 263.0354.

2-Benzyl-2-(trifluoromethyl)-4H-benzo[d][1,3]oxathiin-4-one (Table 5, entry 3): 1H NMR δ 3.19 (d, $J = 14.64$ Hz, 1H), 3.61 (d, $J = 14.64$ Hz, 1H), 7.04 (d, $J = 7.91$ Hz, 1H), 7.12 (dt, $J = 7.71$, 1.25 Hz, 1H), 7.24-7.37 (m, 6H), 8.00 (dd, $J = 7.94$, 1.52 Hz, 1H); ^{13}C NMR δ 40.7, 87.5 (q, 2JC-F = 30.61 Hz, 1C), 121.3, 123.9 (q, 1JC-F = 287.94 Hz), 124.7, 126.42, 126.63, 128.00, 128.33, 131.45, 131.91, 133.8, 134.3, 160.5; ^{19}F NMR δ -78.12; HRMS (FAB) m/z 325.0526, calculated for $C_{16}H_{11}F_3O_2S$ 325.0510.

2-Phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]oxathiin-4-one (Table 5, entry 4): 1H NMR δ 7.18-7.23 (m, 1H), 7.30 (dd, $J = 7.88$, 1.19 Hz, 1H), 7.31-7.36 (m, 3H), 7.42 (dt, $J = 7.44$, 1.50 Hz, 1H), 7.73-7.77 (m, 2H), 8.04

(dd, $J = 7.89, 1.47$ Hz, 1H); ^{13}C NMR δ 90.33 (q, $2\text{JC-F} = 32.41$ Hz), 122.34 (q, $1\text{JC-F} = 284.95$ Hz), 123.27, 127.41, 127.78, 127.85, 128.7, 130.5, 132.3, 133.35, 133.40, 134.7, 160.9; ^{19}F NMR δ -77.09; HRMS (FAB) m/z 311.0339, calculated for $\text{C}_{15}\text{H}_9\text{F}_3\text{O}_2\text{S}$ 311.0354.

2-(Difluoromethyl)-2-methyl-4H-benzo[d][1,3]oxathiin-4-one (Table 5, entry 5): ^1H NMR δ 1.85 (t, $J = 1.53$ Hz, 3H), 5.87 (dd, $J = 56.04, 54.89$ Hz, 1H), 7.28-7.36 (m, 2H), 7.53 (dt, $J = 7.49, 1.51$ Hz, 1H), 8.18 (dd, $J = 7.94, 1.53$ Hz, 1H); ^{13}C NMR δ 21.0, 85.4 (t, $2\text{JC-F} = 25.0$ Hz), 113.07 (dd, $1\text{JC-F} = 254.37, 250.97$ Hz), 122.6, 127.00, 127.39, 132.3, 134.22, 134.49, 161.3; ^{19}F NMR δ -125.10 (dd, $J = 280.76$ Hz, $J = 54.93$ Hz, 1F), -130.06 (dd, $J = 282.29$ Hz, $J = 56.46$ Hz, 1F); HRMS (EI) m/z 230.0212, calculated for $\text{C}_{10}\text{H}_8\text{F}_2\text{O}_2\text{S}$ 230.0213.

Chapter 5

Rapid Preparation of Fluorinated Aromatic Heterocycles

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Nucleophilic aromatic substitution (S_NAr) reactions are typically used for fluoride introduction into heterocyclic aromatic compounds, but substitution occurs sluggishly with unactivated substrates. This chapter discusses new reagents and methods for fluorination of key heterocyclic pharmacophores. Purines, pyrimidines, pyridines, and even imidazoles are fluorinated readily with anhydrous tetraalkylammonium fluorides in DMSO. Though the tetraalkylammonium fluoride reagents themselves are prone to decomposition, the presence of substrate protects these fragile reagents and permits rapid fluorination of relatively reluctant substrates at high temperature. Use of anhydrous fluorinating reagents in radiochemistry is facilitated by a fluoride-relay process that quickly converts hydrated potassium fluoride into anhydrous, exceptionally nucleophilic tetraalkylammonium fluorides.

Introduction

Though naturally-occurring fluoroorganic compounds are rare (1-3), fluorine substitution is a remarkably ubiquitous and powerful tool in organic chemistry. The chemical inertness, dipolar charge distribution, short length and small total volume of the C-F bond (4,5) have made C-F substitution attractive for replacement of a number of functional groups, including C-OH, C-H, and C=O (6). Fluorine incorporation into biologically active compounds can alter drug metabolism (7-13) or enzyme-substrate recognition (14-20). The hydrophobic nature of fluorinated compounds is also cited for their improved transport across the blood brain barrier (21-24). Better oral bioavailability is seen in some systems where fluorine substitution leads to increased hydrolytic or oxidative stability (23,25-28). Review articles appear regularly on these subjects; some recent examples are cited here (9,13,29-39).

One goal of our research effort is to develop selective methods for late-stage introduction of fluorine into natural products or biologically active compounds. Such methods would be particularly helpful where "fluorinated building block" synthetic approaches could not be used, or where desirable aromatic or heterocyclic aromatic fluorination targets reside at the core of complex natural products. In addition to providing an efficient means to modulate the pharmacological profiles of target molecules, late-stage fluorination methods enable ^{18}F -labeling of such compounds for positron emission tomography (PET) based imaging and diagnostic applications.

Fluorinated aromatic heterocycles are frequently found pharmacophores (Figure 1) (40). The discovery of the antitumor activity of fluorinated pyrimidines in the 1950s led to intensive investigation of the anticancer drug 5-fluorouracil and its derivatives (41). Extensive studies on naphthyridine and quinolone cores resulted in the first new classes of antibacterial drugs after the advent of the penicillin age (42). Many fluorinated naphthyridine and fluorinated quinolone derivatives, including Enoxacin (43), Tosufloxacin (44,45), and Mefloquine (46) are critical to the treatment of infections caused by β -lactam- and tetracycline-resistant bacteria. Synthetic methods based upon fluorinated building blocks are used primarily in the preparation of these drugs, but late-stage or direct fluorination would be useful to permit facile radiolabeling of these compounds for pharmacokinetic studies.

From the preceding discussion, pyridine, pyrimidine, and pyridone core structures can be seen to be attractive fluorination targets. Current electrophilic and nucleophilic fluorination methods and reagents, and their application to heterocyclic chemistry are reviewed briefly here.

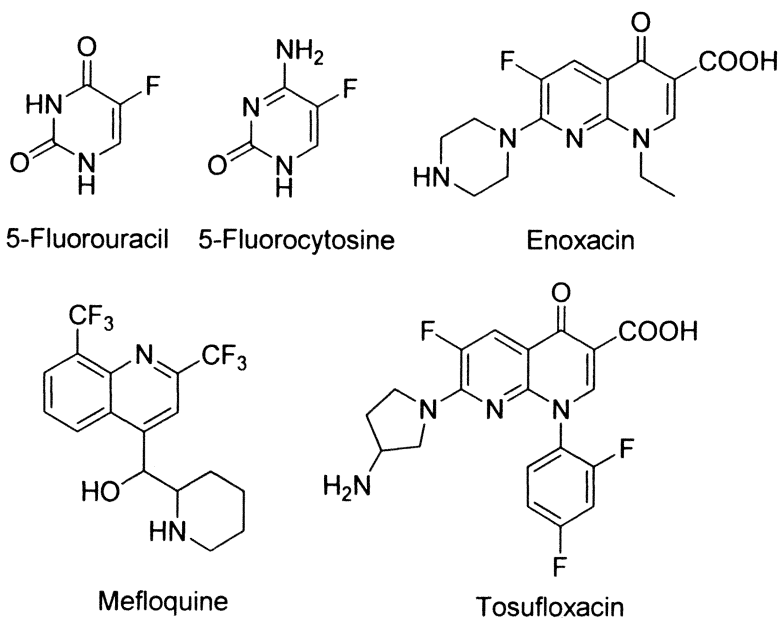


Figure 1. Selected examples of bioactive fluorinated heterocyclic compounds

Fluorination Methods

Electrophilic Fluorinating Agents

Recent advances in fluorine microreactor technology notwithstanding (47-50), the perceived hazards and lack of selectivity in direct fluorinations with F_2 , and the special techniques, equipment, and precautions required for handling anhydrous HF, have stimulated the development of alternative fluorinating agents. The development of electrophilic fluorinating agents requires that one temper the oxidizing power of F_2 to engineer “F⁺” donors. Perchloryl fluoride, xenon difluoride, and perfluoroalkyl and perfluoroacyl hypofluorites have been used as sources of “tamed” electrophilic fluorine, although caution must still be exercised with these strongly oxidizing reagents. Most recently developed “F⁺” reagents for organic synthesis feature N-F (51) bonds (Figure 2). The decreased electronegativity of nitrogen and the increased N-F bond energy (58.5 kcal/mol in NF_3 (52)) compared to O-F (39.1 kcal/mol in F_2O (53)) or F-F (38.4 kcal/mol(52)) attenuates the electrophilicity sufficiently for N-F reagents to be stable, easily handled “F⁺” sources. Such reagents are capable of fluorinating diverse organometallic reagents, enolates, and electron rich aromatic rings.

Direct, transition metal catalyzed fluorination of aromatic and heteroaromatic compounds are uncommon. A more common two step transformation involves metalation of the aromatic compound (metal = Li, Sn) followed by treatment with an electrophilic fluorinating agents or elemental fluorine (54-58). This approach permits exploitation of directing group abilities in the metalation reactions to achieve regioselective fluorination. Substituted benzenes, naphthalenes, indoles, thiophenes, pyrroles, and purines have been fluorinated in this manner. A recent report from Sanford shows that directed oxidative addition of palladium into a C-H bond, followed by treatment with an electrophilic fluorinating agent, is a useful direct route into fluorinated phenyl pyridines (59). Metal-mediated/catalyzed fluorination of unactivated aromatic or heteroaromatic compounds using nucleophilic fluoride sources is a highly sought goal. Preliminary studies of aryl palladium fluorides show that aryl fluoride reductive elimination from these complexes is not the preferred pathway for decomposition of these salts (60,61).

Selective fluorination of heteroaromatic compounds by electrophilic aromatic substitution tends to be difficult except in the case of highly activated aromatic systems like pyrroles (62). Fluorination of indoles using SelectfluorTM resulted in fluorinated oxindoles (63) that could be reduced to the fluorinated indoles by fluoroboranes (64). Selective, direct electrophilic fluorination of pyridines can be challenging (65).

Nucleophilic Fluorinating Agents

In contrast to the strategy employed for developing electrophilic fluorination reagents, the challenge in nucleophilic fluorination is to enhance, rather than attenuate, solution phase reactivity. Gas phase fluoride ion is a strong base (proton affinity of fluoride: $\Delta H^\circ = 371.4$ kcal/mol) (66) and a potent nucleophile. For example, F⁻ fluorodenitrates nitrobenzene rapidly in the gas phase (67). However, fluoride is strongly solvated in water ($\Delta G^\circ_{\text{(solv)}} = -104.3$ kcal/mol) (68) and other protic solvents, and it forms tight ion pairs with most cations in aprotic media. Solvation so attenuates the nucleophilicity of F⁻ that it is considered a poor nucleophile in protic solvents ($n_{\text{MeI}} = 2.7$ for F⁻, 5.8 for Br⁻, 6.5 for HO⁻ in methanol (69)). In anhydrous polar aprotic solvents, strong ion pairing interactions must be overcome to liberate a potent fluoride nucleophile from its cation. Two general approaches have been advanced to frustrate F⁻•••M⁺ ion pairing. The first is to prepare a coordination compound in which the relatively hard Lewis base F⁻ is paired with a soft Lewis acid. The hard/soft mismatch strategy is exemplified by late transition metal fluorides (Pd, Sn, Hg) (70-72), various S-F reagents (SF₄ (73), (diethylamino)sulfur trifluoride (74)), and BrF₃ (75-77). The second approach is to prepare fluoride salts featuring shielded, sterically demanding, or simply large cations. The goal here is to reduce the

extent of ion pairing by delocalizing the positive charge over a larger surface area. Salts featuring nucleophilic, “weakly coordinated” fluoride include tetramethylammonium fluoride (TMAF) (78), 1-methylhexamethylenetetramine fluoride (MHAF) (79), and tetramethylphosphonium fluoride (TMPF) (80). The phosphonium salts are typically less desirable, because the longer P-C bonds and the less hindered environment around phosphorus permit formation of neutral coordination compounds (R_4PF) in lower polarity solvents (80). Schwesinger and coworkers have synthesized a series of peralkylated polyamino-phosphazene cations as potentially stable sources of weakly coordinated fluoride (81,82). Based upon studies of competing E2/S_N2 reactions of primary alkyl halides, these authors argue that these cations are the sources of the most weakly coordinated fluoride salts reported to date.

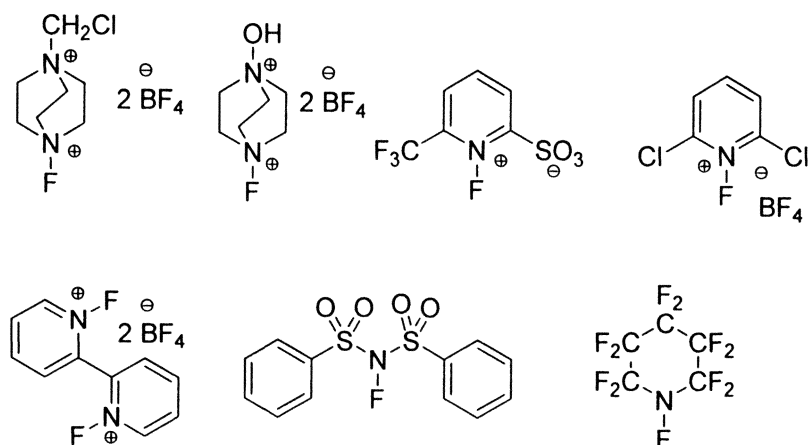


Figure 2. Commercially available N-F electrophilic fluorinating agents.

Tetraalkylammonium or phosphonium fluorides are commonly prepared in a hydrated state by ion exchange, and are dried subsequently by heating under dynamic vacuum or by azeotropic distillation. The conditions used to dry these salts are often incompatible with a variety of desirable cations. For example, drying of tetrabutylammonium fluoride (TBAF) (83) results in Hofmann elimination; the isolated salt is heavily contaminated with bifluoride ion (HF_2^-) and tributylamine (84). These considerations had led to the belief that “it is very unlikely that pure, anhydrous tetraalkylammonium fluoride salts have ever, in fact, been produced in the case of ammonium ions susceptible to E2 eliminations” (84). In practice, only tetraalkylammonium salts featuring methyl groups, quaternary β -carbon atoms, non carbon atoms at the β -positions, and/or bicyclic systems that would give rise to a Bredt’s rule (85) violation upon

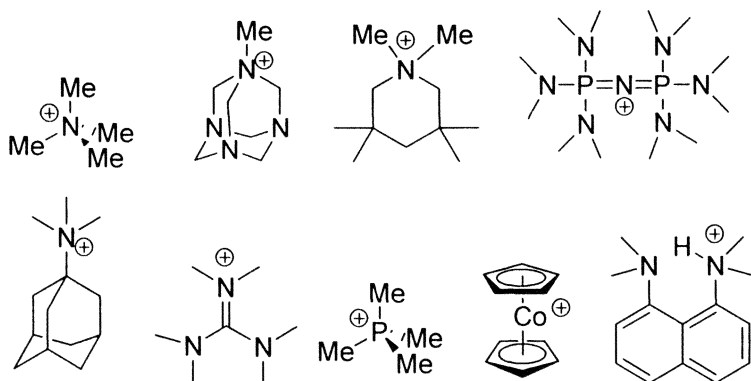


Figure 3. Cations used for the preparation of anhydrous fluoride salts.

elimination have been isolated in an anhydrous state. Representative examples are shown in Figure 3.

The restrictions on cation structure outlined above limit severely the diversity of anhydrous tetraalkylammonium salts. Moreover, the reliance on methyl blocking groups leads to poorly soluble, less nucleophilic fluoride sources, because the methyl C-H bonds are unshielded, bear substantial positive charge, and tend to form good electrostatic contacts with fluoride ion (86).

We sought to develop a versatile set of anhydrous fluoride reagents to expand the “fluorination toolbox” for nucleophilic reactions; much like the advent of N-F reagents increased the scope and utility of electrophilic fluorination. To accomplish this goal, synthetic methods were required to generate diverse anhydrous fluorides directly, thereby circumventing the rather harsh dehydration procedures that lead to Hofmann degradation of simple tetraalkylammonium fluorides.

Preparation of Anhydrous Fluorides

Low-temperature nucleophilic aromatic substitution (S_NAr) of fluorinated aromatic compounds is a convenient and experimentally forgiving method to generate anhydrous tetraalkylammonium fluorides, including those with cations featuring alkyl chains bearing β -hydrogen atoms (87). Treatment of hexafluorobenzene with tetrabutylammonium cyanide (TBACN) (in 1:1 to 1:6 molar ratios) in the polar aprotic solvents THF, acetonitrile, or DMSO at or below room temperature gave excellent yields of anhydrous tetrabutylammonium fluoride, hereafter abbreviated as TBAF* to differentiate it from its commercially available hydrate (Figure 4). (The hexacyanobenzene generated

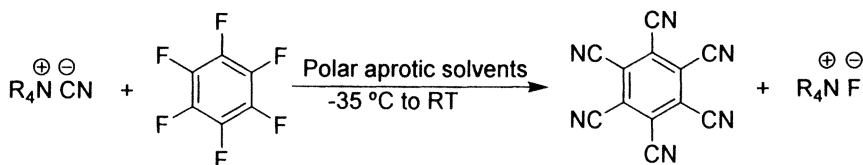


Figure 4. The S_NAr approach to anhydrous tetraalkylammonium salts.

during this reaction scavenges any adventitious water in the solvent, forming the corresponding pentacyanophenolate and 2 moles of bifluoride ion per mole of water.)

Colorless to light yellow TBAF* precipitates from cooled (-35 °C) THF solutions; yields of the isolated salt ranged from 40% to 70%. TBAF* decomposes slowly in THF by E2 elimination if the solution is warmed above 0 °C. TBAF* is stable for hours in CD₃CN and for several days in DMSO at 25 °C. Further refinements in the isolation procedure since the initial publication led us to discover that TBAF* is stable in the solid state for months at room temperature, provided all residual solvent is removed. It is robust enough to be shipped. The stability of the salt is of practical significance because batch scale synthesis of the salt (10-20 g) can be performed in our laboratories and TBAF* can be stored for use or distribution at a later date.

Tetramethylammonium fluoride (TMAF), benzyltributylammonium fluoride (BTBAF), and approximately 30 other tetraalkylammonium fluoride salts have been synthesized in the DiMugno and Koch laboratories using S_NAr reactions. The S_NAr approach to anhydrous fluorides appears to be general and straightforward; these preparations have been reproduced or initiated by undergraduate researchers.

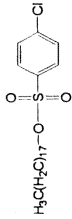
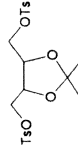
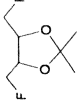
Benchmark reactions employing TBAF* generated *in situ* are summarized in Table 1. For nucleophilic substitution, anhydrous TBAF* exceeds the reactivity of other nucleophilic fluorinating agents. In head-to-head comparisons, TBAF* exhibits dramatically enhanced rates of fluorination compared to dynamic vacuum dried "anhydrous" TBAF (83), CoCp₂F (88), TBAT (89), TMAF, and KF-Kryptofix 222. Neither heating nor a gross excess of TBAF* is required to effect substitution.

Anhydrous Fluorides in Heterocycle Substitutions

Halex Reactions

The rapid rates observed for S_N2 reactions featuring TBAF* prompted us to investigate nucleophilic aromatic substitution (S_NAr) reactions with this reagent.

Table 1. S_N2 reactivity of TBAF*.

Substrate	Reagent	Solvent	Time/Temp	Product	Yield
PhCH ₂ Br	TBAF*	CD ₃ CN	<5 min, -35 °C	PhCH ₂ F	100%
PhCH ₂ Br	TBAF	THF	8 h, RT	PhCH ₂ F	>90%
CH ₃ I	TBAF*	CD ₃ CN	<5 min, -40 °C	CH ₃ F	100%
CH ₃ I	CoCp ₂ F	THF	6 h, RT	CH ₃ F	100%
CH ₃ (CH ₂) ₇ Br	TBAF*	THF	<5 min, RT	CH ₃ (CH ₂) ₇ F	~50%
CH ₃ (CH ₂) ₇ Br	TBAT	CH ₃ CN	24 h, reflux	CH ₃ (CH ₂) ₇ F	85%
CH ₃ (CH ₂) ₇ Br	TBAF	THF	1 h, RT	CH ₃ (CH ₂) ₇ F	48%
	TBAF*	THF	<5 min, RT	CH ₃ (CH ₂) ₁₇ F	100%
	TBAF*	THF	<5 min, RT		>90%

*Yields were calculated by integration of starting material and product signals in the ¹H and/or ¹⁹F NMR spectra.

Chlorinated aromatic compounds undergo halogen exchange (Halex) (90-93) reactions at room temperature in DMSO, CH₃CN, or THF upon exposure to TBAF*. In a typical preparation, TBAF* (1.3 eq.) and the chloroaromatic compound were simply stirred together in DMSO (94). Representative substrates that were successfully fluorinated by TBAF* at room temperature are shown in Figure 5.

TBAF* fluorinates 2-chloropyridine relatively slowly at room temperature; conversion to the corresponding 2-fluoropyridine requires about 14 days. The less activated 3-chloropyridine is completely inert under these conditions; the chlorinated heterocycle is recovered unchanged after 2 weeks. In contrast, if additional electron-withdrawing substituents are present, fluorination occurs rapidly at room temperature. For example, 2,3-dichloropyridine is fluorinated in > 95% yield within an hour to yield 2-fluoro-3-chloropyridine. Similarly, 2-chloro-5-trifluoromethylpyridine and 2,6-dichloropyridine are fluorinated in 20 minutes and 1.5 hours, respectively. Rapid fluorination (30 minutes) of 2-chloro-5-(2-(ethoxycarbonyl)benzoyl)pyridine occurs without hydrolysis of the ethyl ester; hydrolysis of labile esters is a frequent side reaction if hydrated fluoride sources are employed.

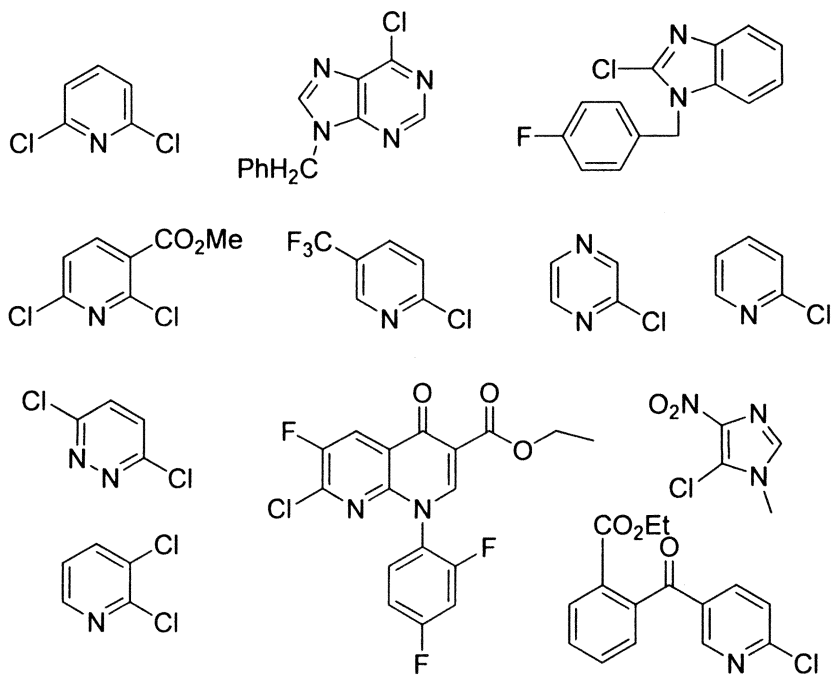


Figure 5. Chlorinated Halex substrates for room temperature fluorination.

A second nitrogen atom in the heterocyclic ring is a potent activator for the Halex reaction. 2-Chloropyrazine, 3,6-dichloropyridazine, 9-benzyl-6-chloropurine, and 2-chloro-1-(4-fluorobenzyl)benzimidazole are all fluorinated within 30 minutes at room temperature in DMSO.

Impact of reaction temperature

Early studies with TBAF* convinced us that, though it could be synthesized readily and isolated as a stable salt, dissolution of TBAF* in relatively nonpolar solvents like benzene, or heating solutions of TBAF* dissolved in polar protic solvents like acetonitrile or DMSO still led to decomposition of the salt by E2 elimination. Thus, initial studies focused on reactions performed under conditions at which the salt was stable. However, if TBAF* is premixed with an aromatic substrate before the reaction mixture is heated, the presence of the excess aromatic substrate is protective, and the cation does not decompose. Apparently, complexation of relatively weakly coordinated fluoride ion by the electron deficient aromatic compound attenuates the basicity of fluoride ion. In such cases, even relatively unactivated substrates may be fluorinated effectively simply by heating the reaction mixture to 100-150 °C. For example, 4-chlorobenzonitrile is fluorinated (90% yield) in 2 days at room temperature, but fluorination is complete in less than 20 minutes at 150 °C in DMSO (Figure 6). Similarly, 2-chloropyridine is fluorinated in 14 days at room temperature, but fluorination requires only 10 minutes heating at 150 °C (35% yield (unoptimized) based on TBAF*). In cases where fluoride is the limiting reagent and the presence of excess substrate presents no experimental difficulties, as in the preparation of fluorinated radiotracers, exceptionally rapid fluorination reactions may be performed with TBAF*.

Anhydrous Fluorides in Heterocycle Fluorodenitration

Fluorodenitration is often superior to halogen exchange as a method for preparing fluorinated aromatic compounds by S_NAr reactions (90,93). In keeping with these published results, we found that nitroaromatic compounds are fluorinated much more rapidly than their chlorinated counterparts with TBAF* under similar conditions (Figure 7). All nitrobenzonitriles (*ortho*, *meta*, and *para*) are fluorodenitrated easily with TBAF*; even the relatively unactivated *m*-nitrobenzonitrile can be fluorinated at room temperature, although the reaction requires 24 hours to reach completion. At elevated temperature (150 °C) this reaction is completed (70% yield) within 10 minutes.

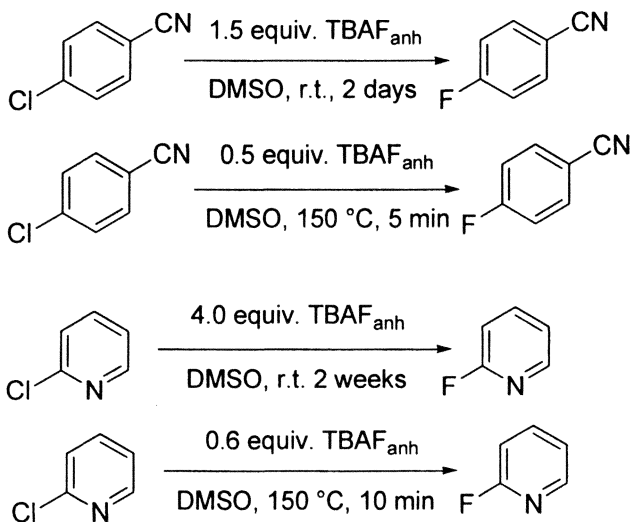


Figure 6. Rate acceleration of Halex reactions upon heating DMSO solutions of TBAF* and substrates.

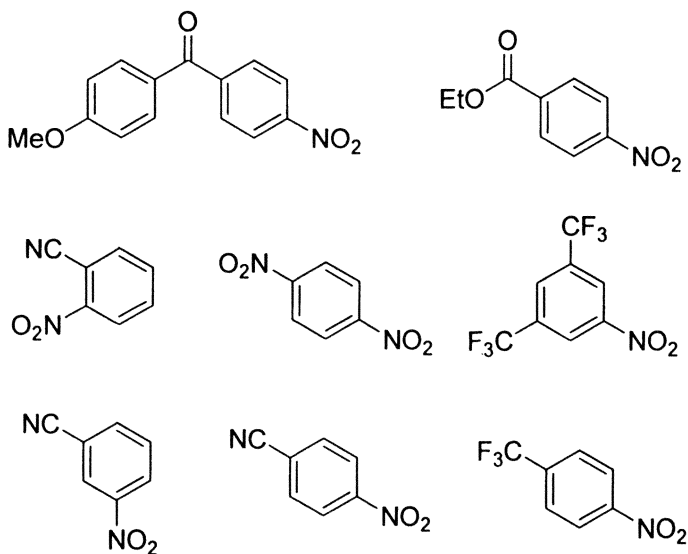


Figure 7. Aromatic substrates for fluorodenitration with TBAF*

Unfortunately, no similar rate acceleration is seen in the attempted fluorination of nitropyridines with TBAF*. ^{19}F NMR spectra show quantitative formation of tetrabutylammonium bifluoride from TBAF* and 3-nitropyridine. Apparently, the exceptionally electron-withdrawing nitro group renders the C-H bond at the pyridine 2-position so acidic that it is cleaved heterolytically under these relatively basic conditions. Once the anion is formed, no further substitution chemistry is possible.

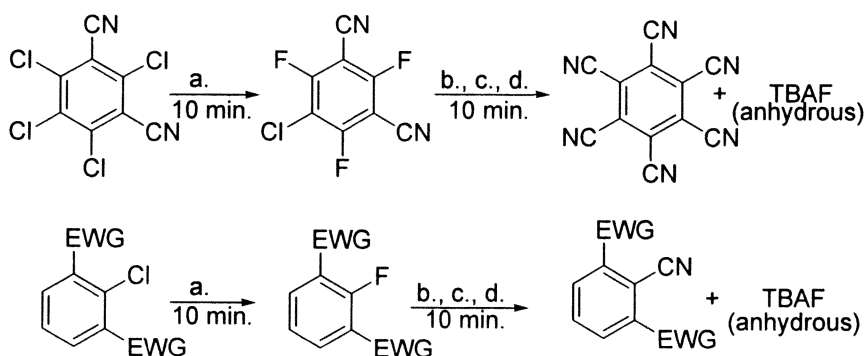
Modifications for Radiotracer Synthesis

Positron emission tomography (PET) is a powerful imaging technique that permits mm-scale resolution of drug location or diagnostic agents *in vivo* (95-98). The exquisite sensitivity of PET (imaging can be performed with minute quantities of labeled compounds under tracer conditions) makes it a useful diagnostic tool to assess the pharmacokinetics, partitioning, and modes of action of new and currently prescribed drugs (99,100). An isotope of fluorine (^{18}F , $\tau_{1/2} = 109.7$ min.) is a common positron emitter used for the labeling of organic molecules. This isotope is generally obtained by proton bombardment of the [^{18}O] H_2O cyclotron target. Nucleophilic fluorination is generally the reaction of choice for [^{18}F] radiotracer synthesis, (90,101) because of the convenience and high yield of the nuclear reaction ($^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$) (102). A fundamental challenge for the synthetic radiochemist is the transformation of [^{18}F]-labeled alkali metal fluorides obtained from the cyclotron target into a highly active nucleophilic fluoride source. In practice, [^{18}F]-labeled potassium fluoride is often dried to the extent possible and activated by addition of a cryptand, such as Kryptofix 222. In competitive reactions, we have found that KF-Kryptofix 222 is a poor reagent, both in terms of its nucleophilicity and selectivity, compared to TBAF*. Thus, we hoped to develop a process by which anhydrous fluoride salts of various compositions, including TBAF*, could be prepared directly and rapidly from hydrated potassium fluoride. Such a process has the potential to expand the scope of ^{18}F -labeled heterocyclic aromatic compounds available for PET imaging studies.

We developed a straightforward “Fluoride Relay” procedure to prepare anhydrous nucleophilic tetraalkylammonium fluoride sources directly from KF. This process, shown in Figure 8, permits simultaneous capture and drying of ^{18}F fluoride by simple electron-deficient aromatic carrier compounds. The sole function of these carriers is to sequester and dissolve the radioactive fluoride in easily dehydrated organic solvents. Subsequent to water removal, the fluoride ion is liberated from the aromatic carrier using standard $\text{S}_{\text{N}}\text{Ar}$ reactions with tetraalkylammonium cyanide salts.

In 2007, we reported the first implementation of the “Fluoride Relay” process (103). Electron-deficient chlorobenzenes of various types are cleanly

and rapidly (10 min.) fluorinated with KF in polar aprotic solvents. We selected 2,6-dicyanochlorobenzenes to enhance the reaction rate, and elected to investigate initially only those compounds in which the 3- and 5-positions were blocked by halogen substituents. Blocking these positions prevents arene deprotonation at the carbon atoms adjacent to the electron-withdrawing cyano groups. Following rapid halogen exchange, the fluorinated isophthalonitrile is extracted into a hexane or ethyl acetate and passed through an activated silica gel column to remove any residual water. The dried fluoroisophthalonitrile is treated with anhydrous tetrabutylammonium cyanide to liberate the anhydrous tetraalkylammonium fluoride salt. This final reaction generates tetraalkylammonium fluoride salts in good yields from KF (>60%), but also suffers the disadvantage of generating potentially large amounts of anhydrous tetraalkylammonium chloride. Currently we are investigating the reactivity of these cogenerated anhydrous tetraalkylammonium halides.



a. KF, DMF, reflux; b. EtOAc/H₂O extraction; c. flash chromatography, evaporation; d. TBACN, DMSO, room temperature.

Figure 8. The Fluoride Relay procedure for generation of anhydrous fluoride salts.

Fluorination of relatively challenging heterocyclic naphthyridine, pyridine, and imidazole substrates was performed following the fluoride relay procedure. Anhydrous TBAF, generated *in situ* and used without isolation or purification, was synthesized within 10 minutes from KF. Equimolar ratios of TBAF* and substrate (0.2 mmol) were simply mixed together in 0.5 mL of DMSO-*d*₆ and the progress of the reaction was followed by ¹H NMR spectroscopy. In evaluating the yields of the process, it was convenient to use the signals from the TBA cation as an internal standard. Following fluorination of the naphthyridine antibiotic precursor ethyl 1-(2,4-difluorophenyl)-6-fluoro-7-chloro-1,4-dihydro-

4-oxo-1,8-naphthyridine-3-carboxylate (104), the product was isolated to confirm that the yields calculated from the NMR experiments were, in fact, accurate.

An important observation from the synthetic studies of these substrates is that TBAF* generated from KF is compatible with relatively delicate methyl ester functionality. Because fluoride ion is a relatively strong base in polar aprotic media, any residual water can lead to saponification of sterically undemanding methyl esters. This point is amply demonstrated by the comparison of the crude ^1H NMR spectra of the fluorination of methyl 2,6-dichloronicotinate with TBAF* and KF-Kryptofix 222 (Figures 9 and 10). The large number of products ensuing from the latter reaction is largely a result of ester hydrolysis.

The facile fluorination of the commercially available compound 5-chloro-1-methyl-4-nitroimidazole to form the previously unknown, water-sensitive 5-fluoro-1-methyl-4-nitroimidazole provides a further example of the power of the Fluoride Relay technique. This hitherto unknown fluorinated heterocycle enables synthesis of diverse unusual 4-substituted-5-fluoroimidazoles in two subsequent steps (reduction/diazotization) (105).

Finally, while most of the preliminary results describing the Fluoride Relay process have featured DMSO as the polar aprotic solvent for $\text{S}_{\text{N}}\text{Ar}$ fluorinations,

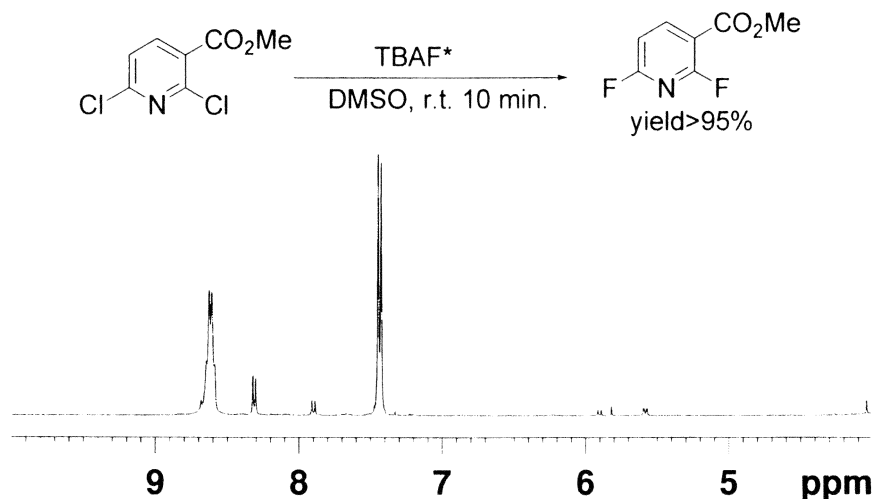


Figure 9. ^1H NMR spectrum of the reaction mixture of methyl 2,6-dichloronicotinate and TBAF* in DMSO-d_6 after 10 minutes.

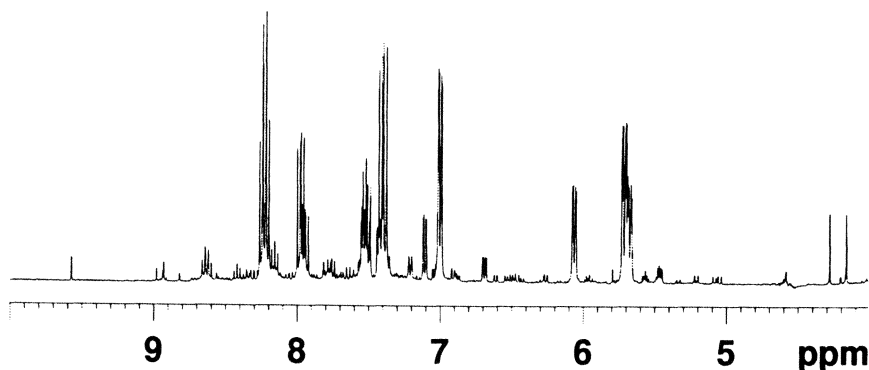
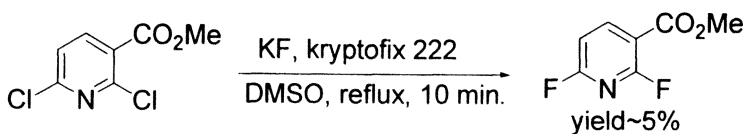


Figure 10. ^1H NMR spectrum of the reaction mixture of methyl 2,6-dichloronicotinate and Kryptofix KF in $\text{DMSO-}d_6$ after 10 minutes.

it is worthwhile to note that this technique works equally well in other, more volatile polar aprotic solvents such as THF or acetonitrile. Thus, there is little obstacle to the use of the Fluoride Relay process or the anhydrous fluoride reagents derived therefrom for the preparation of radiolabeled compounds.

Conclusions

Recent work with anhydrous fluoride salts of tetraalkylammonium fluorides show that these reagents are potent, yet selective sources of nucleophilic fluoride in room temperature halogen exchange reactions of heterocyclic aromatic compounds. Despite the relatively fragile nature of these cations and their propensity for undergoing E2 (Hofmann) elimination, the presence of substrates lends protection and enables fluorination reactions to be performed successfully at elevated temperatures. Finally, a two step Fluoride Relay process enables potassium fluoride to be used as the ultimate fluoride source for anhydrous fluoride reagents. This process opens a potential avenue into generating a wide array of ^{18}F -labeled anhydrous fluoride salts for radiotracer synthesis.

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Chapter 6

Cycloaddition Reactions of Hexafluorothioacetone and Halogenated Thiocarbonyl Compounds: Chemical Transformations of Fluorinated Sulfur-Containing Heterocycles

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This chapter summarizes data on chemical transformations of halogenated thiocarbonyl compounds, focusing mostly on different aspects of the cycloaddition reactions of hexafluorothioacetone. The first part gives an overview of cycloaddition reactions of monomeric hexafluorothioacetone. The second part contains information on the use of 1,1,3,3-tetrakis(trifluoromethyl)-2,4-dithiane as a synthetic equivalent of hexafluorothioacetone in cycloaddition processes. The last section covers different chemical transformations of sulfur-containing cycloadducts.

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Introduction

The discovery of polyfluorinated thiocarbonyl compounds in the early 1960s led to rapid development of this area of organic chemistry, resulting in the synthesis of a large number of new compounds. The unique ability of polyfluorinated thiocarbonyls to undergo cycloaddition reactions with a variety of organic substrates was immediately recognized by W. Middleton, who discovered this class of fluorinated materials. A few years later the ability of 1,1,3,3-tetrakis(trifluoromethyl)-2,4-dithiane to generate monomeric hexafluorothioacetone under the action of fluoride ion in polar solvents was reported. This procedure bypassed the laborious preparation and handling of gaseous and unstable-at-ambient-temperature hexafluorothioacetone, and significantly simplified the preparation of hexafluorothioacetone-based polyfluorinated heterocyclic materials.

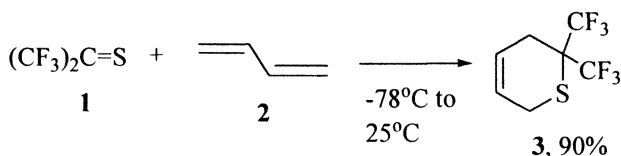
Although hexafluorothioacetone has been studied for over 45 years, the chemistry of this material has not previously been reviewed. This article is an attempt to summarize data on cycloaddition reactions of hexafluorothioacetone and, to a lesser extent, some other halogenated thiocarbonyls, such as $\text{Cl}_2\text{C}=\text{S}$ or $(\text{CF}_3)_2\text{C}=\text{C}=\text{S}$. A somewhat more comprehensive summary of the chemical transformations of various cycloadducts of polyfluorinated thiocarbonyl compounds is also presented.

Cycloaddition Reactions of Hexafluorothioacetone

Diels–Alder Reactions of Hexafluorothioacetone

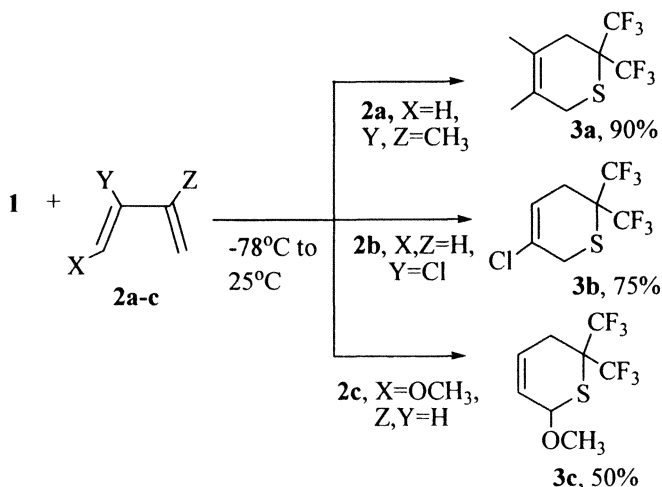
The discovery of polyfluorinated thiocarbonyl compounds (1,2) opened a new page in the chemistry of organic polyfluorinated derivatives of sulfur and made accessible a wide variety of fluorinated sulfur-containing materials (2-5). The most distinctive representative of this group is hexafluorothioacetone (**1**), a blue gas with boiling point 6 °C (2), originally prepared by the reaction of bis(perfluoroisopropyl)-mercury with boiling sulfur or high temperature pyrolysis of 1,1,3,3-tetrakis(trifluoromethyl)-2,4-dithiane (3). Thioketone **1** has unique reactivity (1-8). Cycloaddition reactions are of special interest, because **1** is one of the best dienophiles for Diels–Alder reactions, being in third place after *N*-methylmethyleammonium cation and tetracyanoethylene (9). Indeed, the thioketone reacts rapidly with various dienes already at low temperature and often in the absence of solvent. For example, the addition of **1** to buta-1,3-diene (**2**) resulted in an instantaneous reaction to give cycloadduct **3** in a high yield even at -78 °C. The reaction was so fast that in the paper it was suggested “to

titrate butadiene in an inert solvent, using the appearance of the blue color of the thioketone as the end point of the titration” (3).



Eq.1

Other reported examples of Diels-Alder chemistry involved reactions of **1** with 2,3-dimethyl- (**2a**), 2-chloro- (**2b**) and 3-methoxy- (**2c**) buta-1,3-dienes leading to high yield formation of the corresponding cycloadducts **3a-c** (Eq.2).

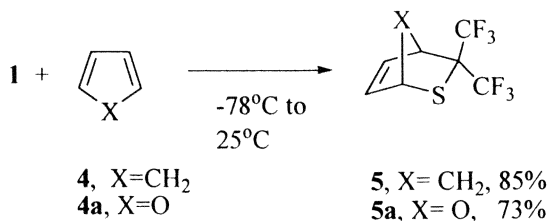


Eq.2

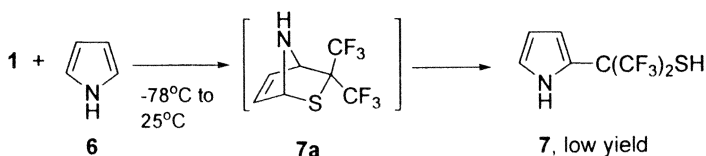
Cyclopenta-1,3-diene (**4**) and furan (**4a**) both react with **1** at low temperature giving the corresponding cycloadducts **5** and **5a** in high yield (Eq. 3).

Although compound **5** is stable and can be distilled under reduced pressure without decomposition (3), the cycloadduct **5a** at room temperature underwent polymerization to give a clear, glassy homopolymer (3).

Despite the fact that the reaction of pyrrole (**6**) and **1** gave a tarry material as the main product, a 1:1 adduct **7** was isolated from this reaction in low yield (Eq. 4).



Eq. 3



Eq.4

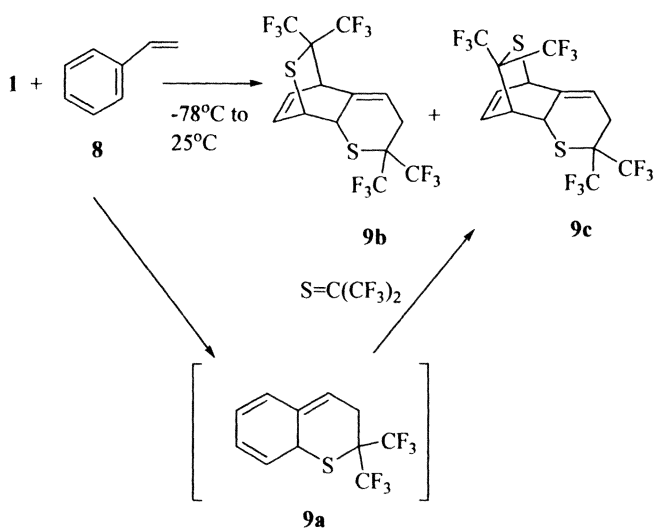
The proposed mechanism suggests isomerization of cycloadduct **7a** under the reaction conditions (3). The structure **7** was assigned to the 1:1 adduct based on combined data of NMR and IR spectroscopy wherein both methods confirmed the presence of $-\text{NH}$ and $-\text{SH}$ functions in the molecule (3).

The reaction between **1** and **8** results in the formation of two isomeric 2:1 adducts **9b,c** (Scheme 1). The mechanism of the reaction between **1** and **8** was described in terms of a Diels-Alder-type reaction involving two conjugated double bonds of styrene (Scheme 1) (3). In the original work the structure was not assigned to the second isomer, but in light of recently published data on cycloaddition reactions of **1** with other cyclohexa-1,3-dienes (10), it is safe to assume that isomers **9b,c** differ by orientation of the $-\text{C}(\text{CF}_3)_2\text{-S-}$ fragment relative to the sulfur in the six-membered ring and are formed through cycloaddition of a second mole of **1** to the non-symmetrical intermediate **9a** (Scheme 1).

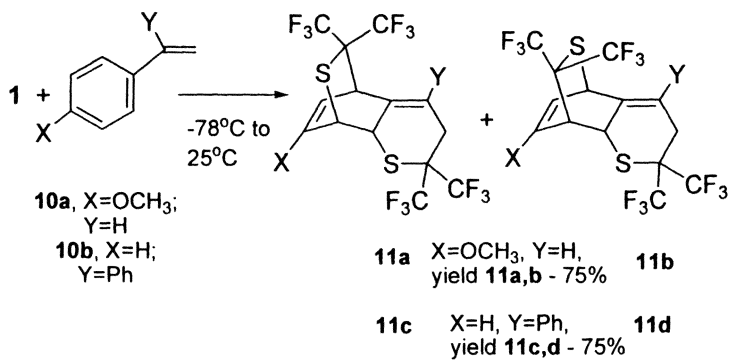
High affinity to cyclohexa-1,3-diene systems is a characteristic feature of hexafluorothioacetone. For example, the reaction of 4-methoxystyrene (**10a**) and 1,1-diphenylethylene (**10b**) with **1** at low temperature resulted in high yield formation of 2:1 adducts **11a,b** and **11c,d**, respectively (Eq. 5) (3).

Anthracene (**12**) seems to be less reactive towards **1** although it forms the corresponding 1:1 cycloadduct **13** quantitatively upon the addition of **1** to a suspension of **12** in CCl_4 at 0°C (3).

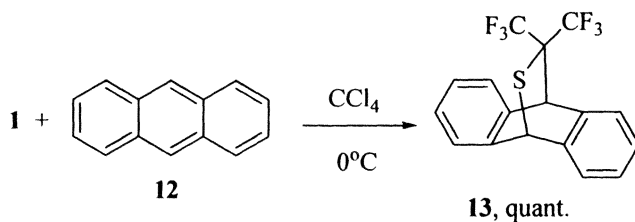
Polyhalogenated thiocarbonyl compounds are also highly reactive towards **12** and electron-rich dienes. The corresponding cycloadducts were obtained in reaction of $\text{Cl}_2\text{C}=\text{S}$ (**14**) (11), $\text{CF}_3\text{C}(\text{S})\text{F}$ (**15**) and **12** with $\text{C}_2\text{F}_5\text{C}(\text{S})\text{F}$ (**16**) (3)



Scheme 1



Eq. 5



Eq. 6

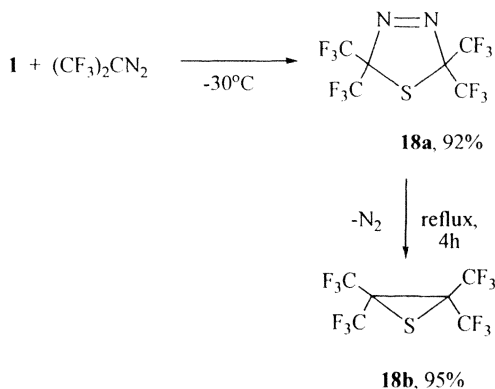
[for pentacene adduct with **14** see (12)]. The list of other thiocarbonyl substrates involved in the reaction with different dienes includes $F_2C=S$ [**16a**; reaction with **4**, and hexachlorocyclo-1,3-pentadiene (**3**)], **14** [reaction with spiro[2.4]hepta-4,6-diene (13,14), cyclohexa-1,3-diene (**17**) (15), (1Z,3Z,5Z)-cyclohepta-1,3,5-triene (**18**) (16), **15** [reaction with **2**, **2a**, **4** (3)] and cycloaddition of $(CF_3)_2C=S$ and **4** (3).

It should be pointed out that $(CF_3)_2C=C=S$ has reactivity similar to the reactivity of **1** and undergoes selective cycloaddition with a variety of dienes through the $C=S$ bond. Reported examples involving $(CF_3)_2C=C=S$ include cycloadditions with 2,3-dichloro-1,3-butadiene, compounds **2**, **4**, **17**, (1Z,3Z,5Z,7Z)-cycloocta-1,3,5,7-tetraene (**18**) and quadricyclane (**19**) (Eq. 15) (13). Data on cycloaddition of $R_fC(S)-X$ ($X=Cl, NR_2, -SR'$) were summarized in two recently published review articles (17,18).

[2+1]-, [2+2]-, [3+2]- Cycloaddition and Ene- Reactions of Hexafluorothioacetone

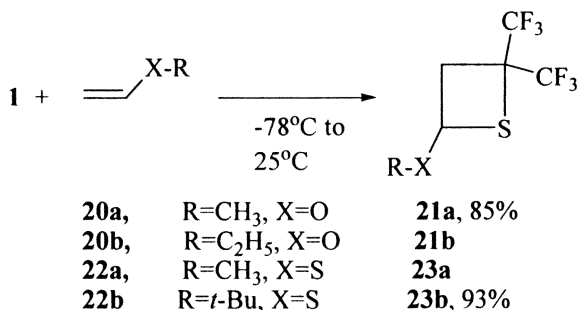
There are very few examples of [2+1] cycloaddition reactions reported for **1**. For example, interaction with diphenyldiazomethane or ethyldiazoacetate in pentane at low temperature was reported to give the corresponding thiiranes in moderate to high yield (5). On the other hand, the reaction of diazomethane involves two moles of **1** leading to 2,2,5,5-tetrakis(trifluoromethyl)-1,3-dithiolane (5).

The reaction of **1** with bis(trifluoromethyl)diazomethane is reported to proceed as a [3+2] cycloaddition (8), leading to thermally unstable thiadiazoline **18a**, which underwent nitrogen elimination with formation of tetrakis(trifluoromethyl)thiirane **18b** upon heating (Scheme 2).



Scheme 2

Electron-rich olefins not containing allylic hydrogens combine with **1** to produce 2+2 cycloadducts. Both vinyl ethers (**20a,b**) and vinyl sulfides (**22a,b**) were found to react with **1** under mild conditions forming the corresponding thietanes **20a, 20b** and **21a, 21b**, respectively (4) (Eq. 7).

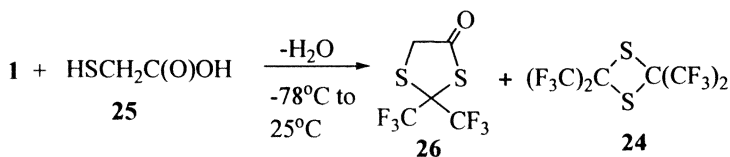


Eq. 7

The corresponding 2+2 cycloadducts were also isolated from the reaction of **1** with dihydropyran and dioxene (4).

Compound **1** is highly sensitive to the action of base undergoing rapid 2+2 cyclodimerization to form 1,1,3,3-tetrakis(trifluoromethyl)-2,4-dithiane (**24**) (2) (for reactions of **24** see the next section). Cyclodimerization is a typical transformation and was observed for all perfluorinated thiocarbonyl compounds (5).

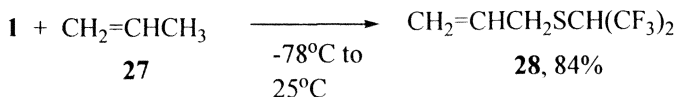
The addition of mercaptoacetic acid (**25**) to **1** results in moderate yield formation of **26** along with dimer **24** byproduct (5) (Eq. 8).



Eq. 8

The interaction with olefins containing allylic hydrogens proceeds through insertion of **1** into C-H bonds. For example, the reaction of propene (**27**) and **1** was reported to give sulfide **28** (4) as a result of an ene-reaction (Eq. 9).

Using nonsymmetrical olefins, it was demonstrated that insertion of **1** into a C-H bond involves migration of the double bond and is likely to have a concerted mechanism (19,20).



Eq. 9

It should be pointed out that a similar reaction of hexafluoroacetone (HFA) and **27** proceeds with the formation of allylhexafluoro-*iso*-propanol (*21*). Thus, the process involving **1** and **27** has different regiochemistry leading to exclusive formation of sulfide **28**, rather than the corresponding thiol. This can be a result of opposite polarization of C=S in **1** vs. C=O in HFA.

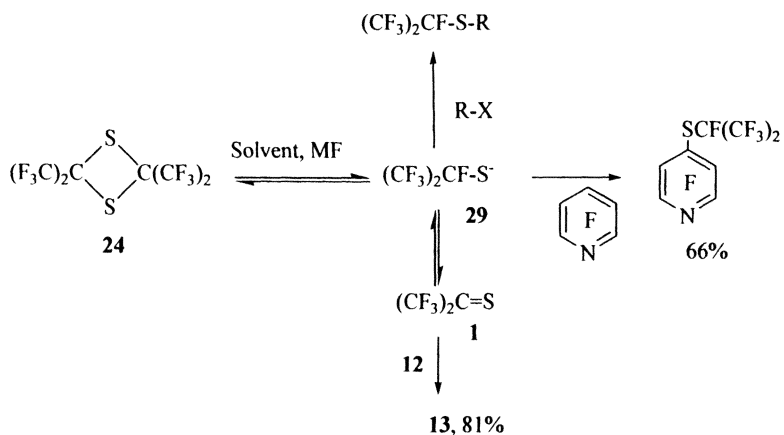
1,1,3,3-Tetrakis(trifluoromethyl)-2,4-dithiane (**24**) as a Synthetic Equivalent of Hexafluorothioacetone

Hexafluorothioacetone (**1**) has limited thermal stability and undergoes cyclodimerization forming 1,1,3,3-tetrakis(trifluoromethyl)-2,4-dithiane (**24**) at ambient temperature. This process is accelerated significantly by base (*2,5*). The combination of low thermal stability and base sensitivity makes handling of **1** difficult.

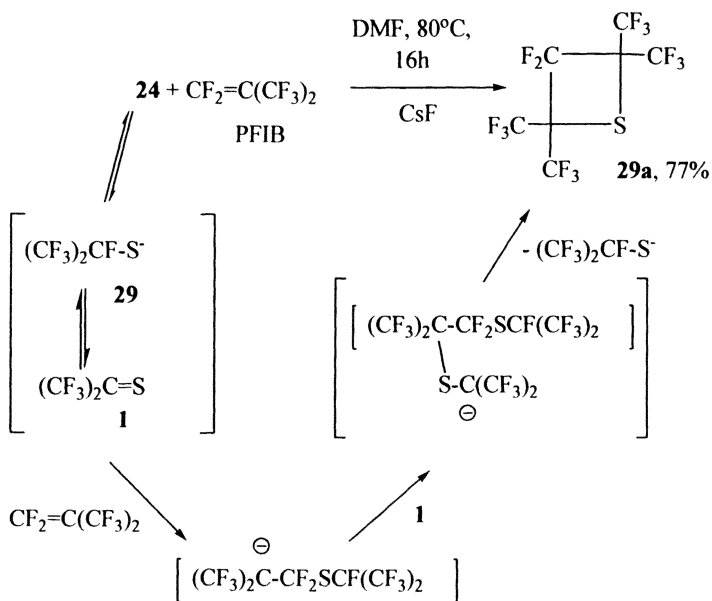
In contrast to gaseous **1**, the dimer **24** is a liquid with b.p. 101-102 °C (*22*). Relatively simple synthesis of **24** by the reaction of hexafluoropropene (HFP) and sulfur in the presence of KF, first reported by Dyatkin (*23,24*) and later modified by England (*22*), made **24** readily available. An important property of this compound is the ability to regenerate **1** upon treatment with a catalytic amount of fluoride anion in polar solvent. This process leads to the formation of **1** in equilibrium with anion **29** through the attack of fluoride anion on sp³ carbon of **24** (*25*) (Scheme 3).

Interception of **1** by anthracene (**12**) and **29** by a number of electrophiles is reliable proof of the presence of both intermediates in this reaction system (*25,26*).

The first example of KF-catalyzed reactions of **24** and vinyl ethers **20a,b** leading to thietanes **21a,b** was reported in 1976 (*27*). Later was discovered the [2+2] cycloaddition of diphenylketene and **1** (generated "*in situ*" from **24**) that results in selective formation of 2,2,4,4-tetrakis(trifluoromethyl)thietan-3-one (*28*). The unusual reaction of **24** and perfluoroisobutene (PFIB) catalyzed by fluoride anion leads to the formation of the only known representative of perfluorinated thietanes - compound **29a** (*25*). This transformation is believed to have a nucleophilic stepwise addition-elimination mechanism (Scheme 4).



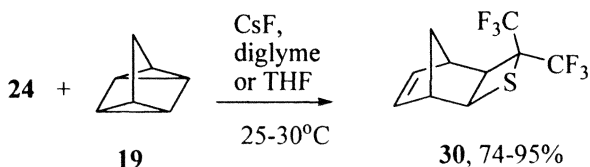
Scheme 3



Scheme 4

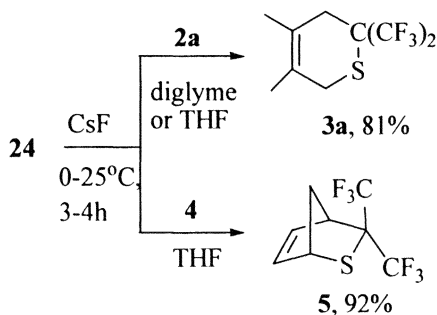
It should be pointed out that this process is limited to PFIB and the fluoride anion catalyzed reaction of HFP with **24** selectively produces $(\text{CF}_3)_2\text{CFSC}(\text{CF}_3)=\text{CFCF}(\text{CF}_3)_2$ (**22**).

Recently, it was shown that cycloadduct **30** is formed in the CsF catalyzed reaction of **24** and quadricyclane (**19**) (**29**) (Eq. 10). It is interesting that the formation of **30** was also observed *in the absence* of the catalyst. Despite a significantly slower rate (50% conversion of **24** after 1 week at 25 °C) the process still was highly selective leading to **30** as a single product (**29**). The uncatalyzed process is believed to have a SET (single electron transfer) mechanism (**29**).



Eq. 10

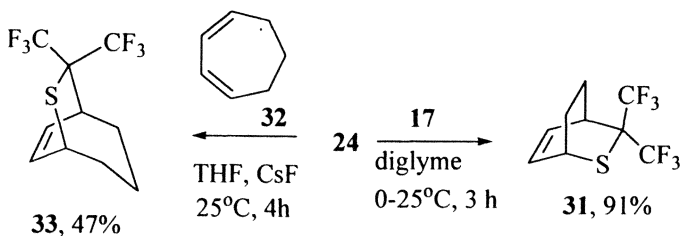
Several dienes were successfully involved in Diels-Alder reactions when compound **24** was used as a source of **1** (**10**), for example, dienes **2a** and **4** (Eq. 11).



Eq. 11

In reaction of cyclohexa-1,3-diene (**17**) or (1*Z*,3*Z*)-cyclohepta-1,3-diene (**32**) (**10**) (Eq. 12) with a mixture of **24**/CsF the adducts **31** and **33** were isolated (Eq. 12).

Recently it was found that compound **1** is also able to react with nonconjugated cyclic dienes (**10**). Treatment of cyclohexa-1,4-diene (**34**) with **24**/CsF in THF solvent resulted in the mixture of two isomeric 1 : 2 adducts (**35a** and **35b**, Eq. 13), while (1*Z*,5*Z*)-cycloocta-1,5-diene (**36**) under similar



Eq. 12

conditions gave diene **37** as a result of a double ene- reaction (Eq. 13). The structures of adducts **35a** and **37** were confirmed by single crystal X-ray diffraction (10).

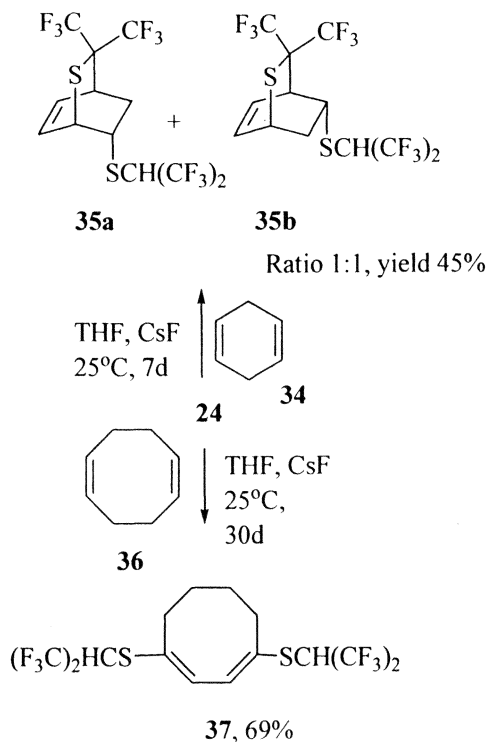
It should be pointed out that neither **36** nor **37** gave the corresponding cycloadducts in this process. Lower reactivity of dienes **32**, **36** and **37** towards cycloaddition is in agreement with a general trend observed for cyclic dienes - the reduction of the reactivity with increasing size of the ring (30).

When (1*Z*,3*Z*,5*Z*)-cyclohepta-1,3,5-triene (**38**) was treated with **24**/CsF in THF as solvent, selective formation of cycloadduct **40** was observed (Eq. 14). Although the reaction of (1*Z*,3*Z*,5*Z*,7*Z*)-cycloocta-1,3,5,7-tetraene (**39**) with **24** was significantly slower it gave cycloadduct **41** (Eq. 14). Isolated adducts **40** and **41** were thoroughly characterized by ¹H, ¹³C, ¹⁹F NMR spectroscopy and correct structural assignments for both products having *endo*-orientation of the three- and four- membered rings were confirmed by single crystal X-ray diffraction (10).

The formation of compound **40** (or **41**) results from the equilibrium between **38** and bicyclo[4.1.0]hepta-2,4-diene (or between **39** and bicyclo[4.2.0]octa-2,4,7-triene). Bicyclic isomers have significantly higher reactivity towards **1** and despite their relatively low equilibrium concentration, selectively undergo 4+2 cycloaddition with **1** producing adducts **40** and **41**, respectively (10). Reaction of bis(trifluoromethyl)thioetene (**42**) with **39** was reported to give cycloadduct **43** (see Eq. 15).

Reaction of compound **42** with diene **17** gave a mixture of cycloadduct **44a** and the product **44b** (31) (Eq. 15) and in reaction with quadricyclanes **19**, **45a** and **45b** the corresponding cycloadducts **46a-c** were isolated (Eq.15). The assignments of *exo*- orientation of the thietane ring in **46a-c** and *anti*- orientation of the substituent connected to one-carbon bridge in adducts **46b** and **46c** were made based on NMR data. (32)

Although compounds **1** and **42** have a similar reactivity pattern (*cf.* reactions of **1** and **42** with **19**, **39** or **20b**), often these two behave differently. For example, in contrast to compound **1** which gives 2 : 1 adducts in reaction with

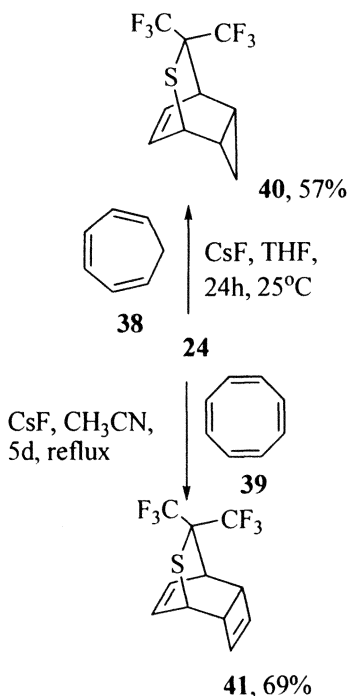


Eq. 13

styrenes, thioketene **42** reacts with **8** and **10b** selectively producing the corresponding 2+2 cycloadducts (**32**) (see Eq. 5 and Scheme 1 for reactions of **1**).

Compound **42** undergoes [2+2] cycloaddition with ketenes and carbodiimides (**32**). A variety of [3+2] cycloadducts were prepared in reaction of **42** with HN_3 , benzonitrile oxide, nitrones and aryl oximes (**31**). Additional information on the chemistry of this interesting heterocumulene can be found in original publications (**31-33**).

Among other transformations of **24** are the cycloaddition reactions with cyanamides (**34,35**), $\text{P}(\text{CN})_3$ and $\text{As}(\text{CN})_3$ (**36**), KNCS (**37**), leading to the formation of various five- and six- membered nitrogen/sulfur- containing heterocycles.

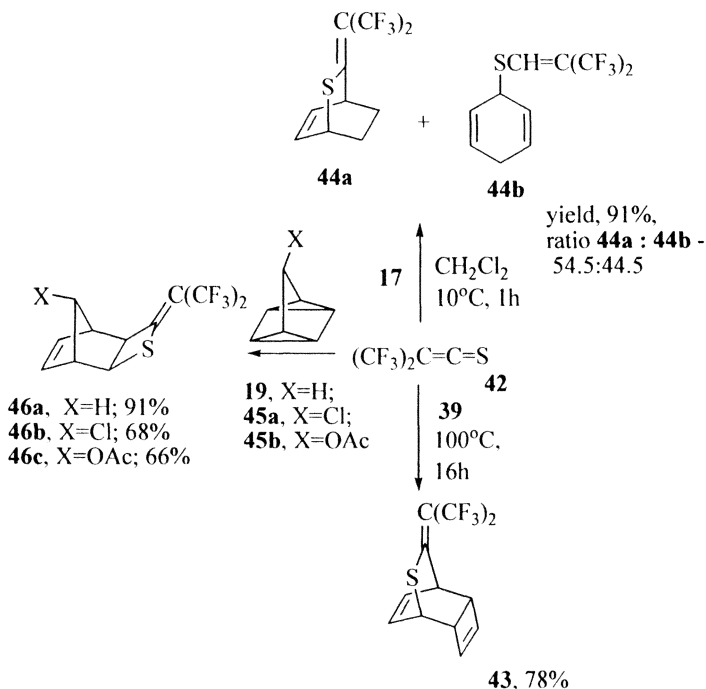


Eq.14

Chemical Transformations of Halogenated Sulfur-Containing Heterocycles

Synthetic applications of dithietane **24** are not limited to its use as a source of hexafluorothioacetone or anion **29**. This compound also is a valuable precursor for the synthesis of a variety fluorinated sulfur-containing derivatives. For example, the pyrolysis of **24** at 325 °C results in the high yield formation of $(\text{CF}_3)_2\text{C}=\text{C}(\text{CF}_3)_2$ (**38**). The reaction of **24** with Ph_3P was found to be a convenient route to $(\text{Ph})_3\text{P}=\text{C}(\text{CF}_3)_2$, which was used for the preparation of 1,1-bis(trifluoromethyl) alkenes (**20**, **39**) and $\text{CF}_2=\text{C}(\text{CF}_3)\text{P}(\text{O})(\text{OR})_2$ (**40**, **41**).

The cycloadduct **24** can be selectively oxidized to tetrakis(trifluoromethyl)-1,4-dithietan-S-oxides **47a-c** (**42-45**). Oxides **47a** and **47b** (Eq. 16) have been used for generation of $(\text{CF}_3)_2\text{C}=\text{S}=\text{O}$ (**48a**) and $(\text{CF}_3)_2\text{C}=\text{SO}_2$ (**48b**), respectively - reactive dienophiles involved in various cycloadditions (Eq. 16) (**42,45**). Compound **49a**, prepared by selective oxidation of **13** (**45**), was used as a source



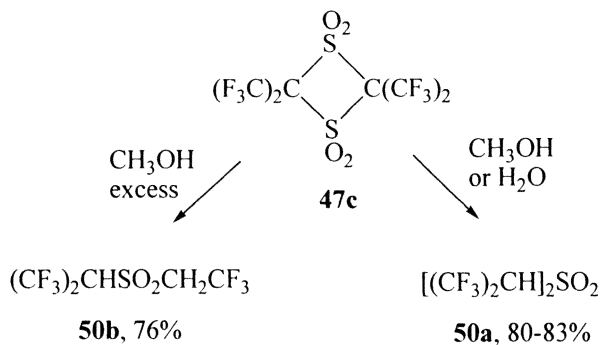
Eq. 15

of $(\text{CF}_3)_2\text{C=S=O}$, since at elevated temperature it underwent retro Diels-Alder reaction with extrusion of **48a** (45). The pyrolysis of fluorinated 1,1-dioxo-1,3-dithietanes provides a general route for the synthesis of fluorinated thiiiranes, for example, compound **47b** was converted into thiiirane **18b** in 90% yield (6).

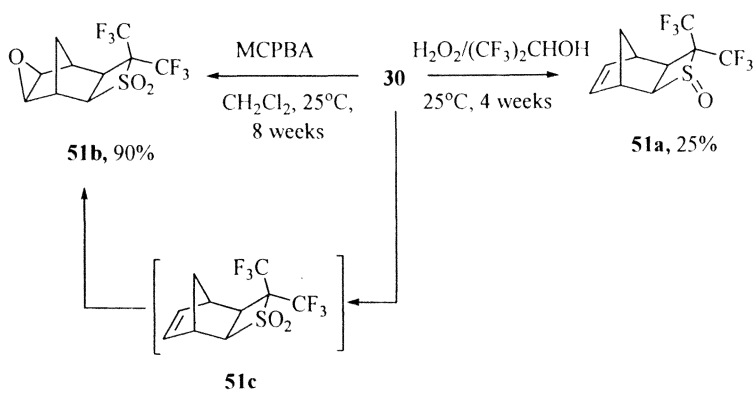
2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane-1,1,3,3-tetraoxide (**47c**, Eq. 17) is extremely sensitive to nucleophilic attack and rapidly reacts with an equimolar amount of water to form bis(hexafluoro-*iso*-propyl)sulfone (**50a**). The reaction with an excess of methanol results in the hydrolysis of one CF_3 group leading to sulfone **50b** (44).

Cycloadducts of **1** were reported to undergo selective oxidation. For example, the reaction of **30** with 30% H_2O_2 in hexafluoro-*iso*-propanol solvent resulted in the formation of sulfoxide **51a** (46) (Eq.18), while rather slow oxidation by an excess of *m*-chloroperoxybenzoic acid (MCPBA) led to epoxysulfone **51b** (Eq. 18).

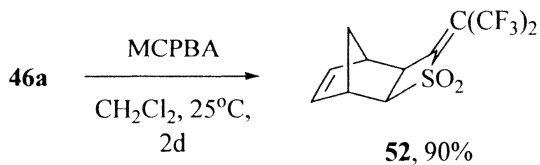
The double bond oxidation in intermediate **51c** was found to be the slowest step of the process (46). This conclusion is consistent with the result of the oxidation of cycloadduct **46a** by MCPBA reported to give the corresponding sulfone **52** at shorter reaction time (13) (Eq.19).



Eq. 17

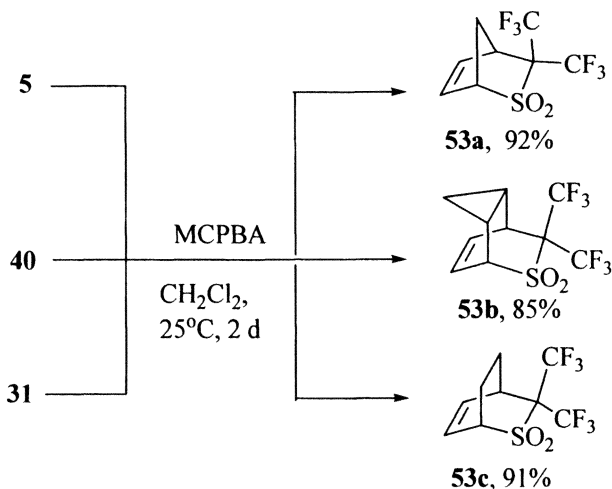


Eq. 18



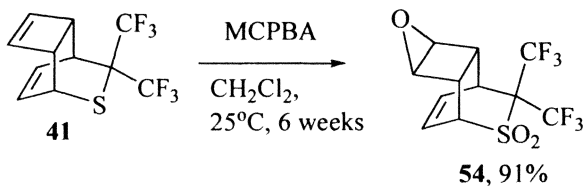
Eq. 19

On the other hand, cycloadducts **5**, **40** and **31**, each containing a sulfur atom in the six-membered ring, have different reactivity. Surprisingly selective oxidation of all three compounds by MCPBA (25 °C, 2 d) resulted in formation of the corresponding unsaturated sulfones **53a-c** (46, 47).



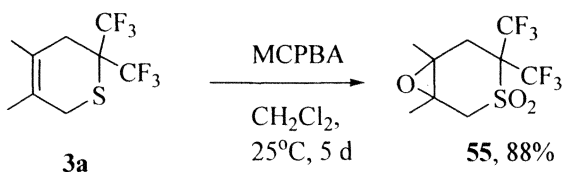
Eq. 20

The high stability of the C=C fragment towards oxidation in sulfones **53a-c** is believed to be a result of a strong electron withdrawing effect of the -SO₂-C(CF₃)₂- moiety, resulting in higher electron deficiency of the norbornene double bond and its reduced reactivity in electrophilic Prilezhaev oxidation. It should be pointed out that sulfones **53a-c** are kinetic products, since further oxidation of these materials was observed when the reaction was carried out for a longer time (5 weeks at 25 °C) (46). The “electron deficiency of the double bond” hypothesis also agrees well with data on the oxidation of adduct **41** by MCPBA. This process led to high yield formation of monoepoxide **54** as the result of selective oxidation of the remote C=C bond of **41** (Eq. 21) (46).



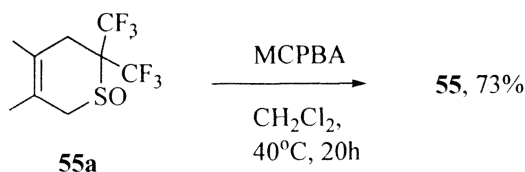
Eq. 21

On the other hand, the oxidation of **3a** having relatively electron-rich double bond proceeds with formation of the expected epoxy sulfone **55** (Eq. 22) (46).



Eq. 22

Significantly faster oxidation of sulfoxide **55a** was observed at elevated temperature (Eq. 23) (48).



Eq. 23

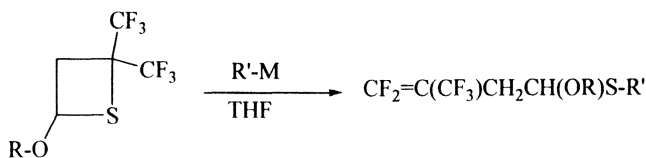
It should be mentioned that the structures of compounds **51a,b**, **53b**, **54** and **55** were firmly established by single crystal X-ray diffraction (46).

Due to substantial positive charge on the sulfur atom generated by the strong electron-withdrawing effect of the two neighboring trifluoromethyl groups, fluorinated thietanes have very unusual reactivity compared to hydrocarbon analogs. For example, compounds **21a,b** were reported to react with Grignard reagents or *n*-C₄H₉Li to produce the corresponding unsaturated sulfides **56a-e** (27) as the result of a ring opening reaction (Eq. 24), which certainly starts with attack of the corresponding reagent on sulfur.

A similar process was reported recently for compound **30**. The reaction with Grignard reagents proceeds with preservation of the *exo*-geometry of the starting material, leading to high yield formation of *exo*-, *exo*-substituted norbornenes **57a-c** (49) (Eq. 25).

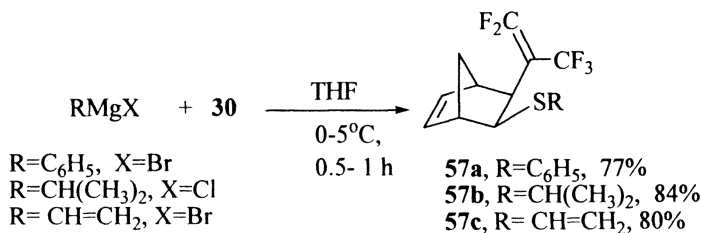
The interaction of **30** with lithium reagents carried out at low temperature resulted in selective formation of norbornenes **57c-f** (49) (Eq. 26).

The selectivity in the reaction of **30** with fluoroalkylsilanes **58a-c** was found to be significantly lower due to side reactions involving the double bond of the products **57g-i** (Eq. 27) (49).

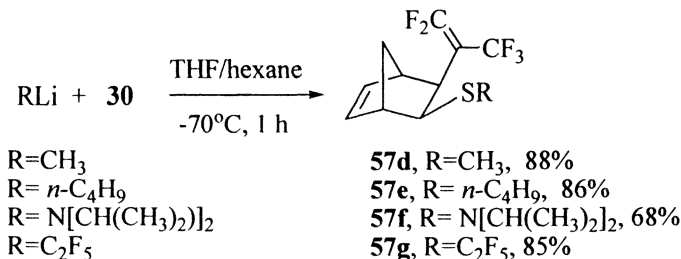


21a , R=CH ₃	R'-M= <i>n</i> -C ₄ H ₉ -Li (-60°C)	56a , R=CH ₃ R'= <i>n</i> -C ₄ H ₉ , 59 %
21a , R=CH ₃	R'-M= <i>n</i> -C ₄ H ₉ -MgBr (20°C)	56a , R=CH ₃ R'= <i>n</i> -C ₄ H ₉ , 56 %
21a , R=CH ₃	R'-M=Ph-MgBr (20°C)	56b , R=CH ₃ R'=Ph, 63 %
21b , R=C ₂ H ₅	R'-M= <i>n</i> -C ₄ H ₉ -Li (-60°C)	56c , R=C ₂ H ₅ R'= <i>n</i> -C ₄ H ₉ , 53 %
21b , R=C ₂ H ₅	R'-M=Ph-MgBr (20°C)	56d , R=C ₂ H ₅ R'=Ph, 67 %
21b , R=C ₂ H ₅	R'-M=C ₂ H ₅ -MgI (20°C)	56e , R=C ₂ H ₅ R'=C ₂ H ₅ , 37 %

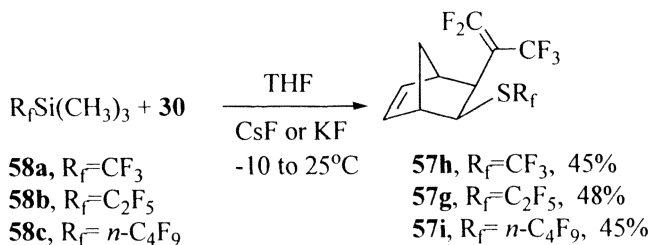
Eq. 24



Eq. 25

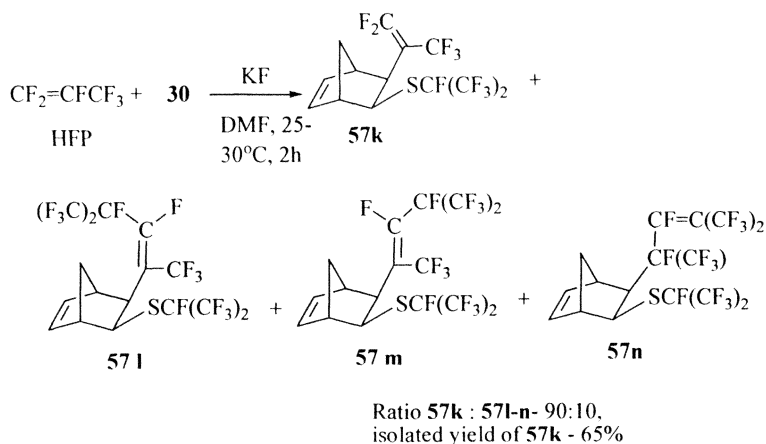


Eq. 26



Eq. 27

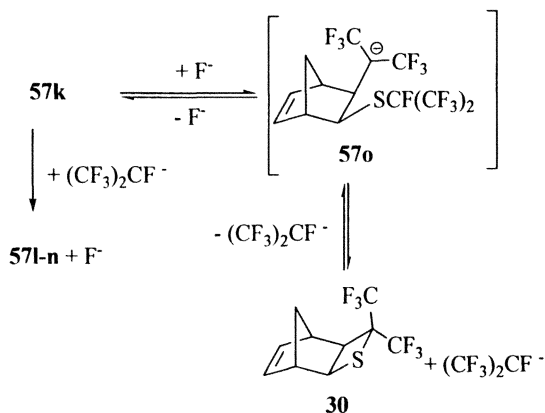
It should be pointed out that compound **30** has surprisingly high resistance to the action of hard nucleophiles, such as fluoride anion. For example, unchanged **30** was recovered after treatment with CsF at elevated temperature (DMF, 70 °C, 8h) (49). On the other hand, this material is much more susceptible to the action of soft nucleophiles, such as (CF₃)₂CF⁻. The addition of hexafluoropropene (HFP) to a mixture of **30** and dry KF catalyst in DMF solvent at ambient temperature results in a spontaneous exothermic reaction leading to the formation of ring opened product **57k** (29,49), along with smaller amount of 2:1 adducts **57 l-n** (49).



Eq. 28

The mixture of isomers **57 l-n** was isolated from the reaction of **30** with excess of HFP (76% yield, ratio **57l** : **57m** : **57n** - 60:43:6) (29,49). Based on ¹⁹F NMR spectroscopy the structures of *trans*- and *cis*- isomers were assigned to compounds **57l** and **57m**, respectively (Eq.28). Compound **57n** is believed to form from **57 l,m** as result of well-known migration of the double bond catalyzed by fluoride anion.

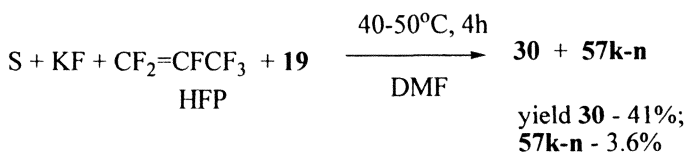
It is interesting that the reaction of **30** and HFP is reversible, since the treatment of **57k** with CsF (DMF, 25 °C, 2h) resulted in the formation of equimolar mixture of **30** and **57l-n** (29,49) (Scheme 5).



Scheme 5

The proposed mechanism of this process (29,49) involves the generation of anion **57o** through the attack of F^- on the electrophilic double bond of **57k**, followed by the attack of the carbanion on the positively charged sulfur leading to **30** (Scheme 5). The $(CF_3)_2CF^-$ liberated in this process is consumed by reaction with **57k** to give **57l-n** and F^- .

A simplified procedure for the synthesis of **30** reported recently is based on direct reaction of sulfur, HFP and **19** catalyzed by KF (conditions used for the preparation of **24**) (29) (Eq.29).

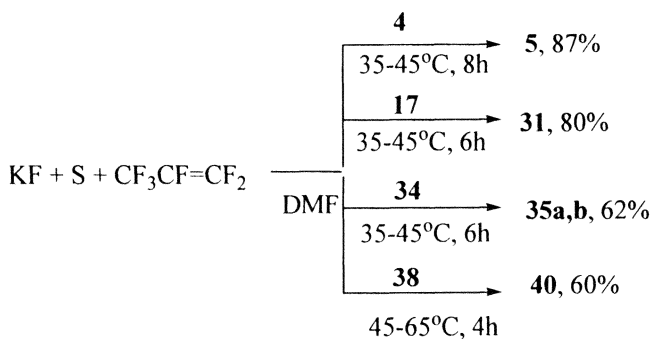


Eq. 29

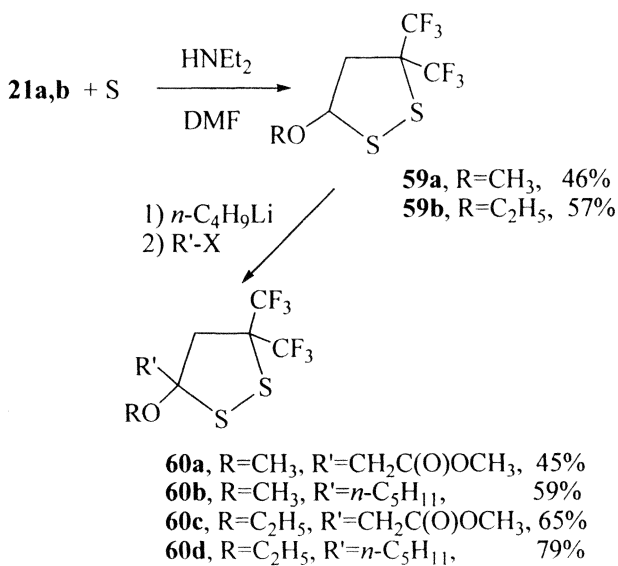
This simple protocol is general and has been used for the preparation of compounds **5**, **31**, **35a,b** and **40** (10).

Another example of nucleophilic reaction involving electron-deficient sulfur of thietane ring is the reaction of thietanes **21a,b** with sulfur leading to the formation of products **59a,b** (27) (Eq. 31).

Due to the presence of the relatively acidic hydrogen connected to the carbon bearing sulfur and oxygen, both **59a** and **59b** can be lithiated by *n*-



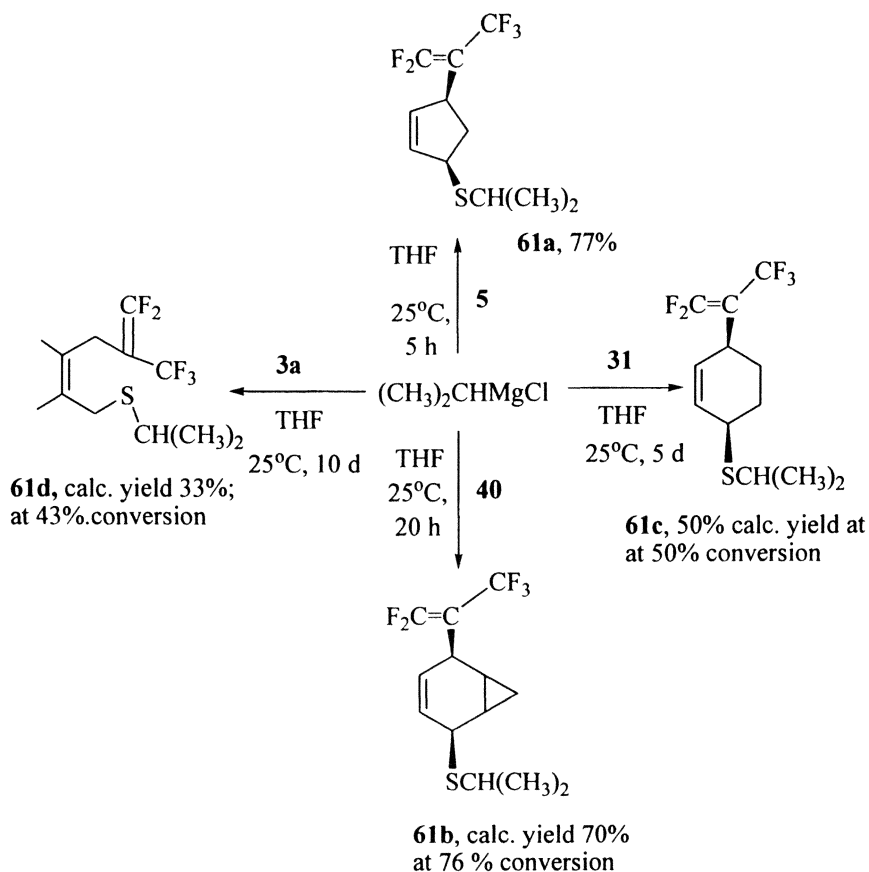
Eq. 30



Eq. 31

butyllithium. Subsequent treatment of the lithium derivative with the appropriate electrophile was employed for the preparation of 1,2-dithiolanes **60a-d** (27) (see Eq.31).

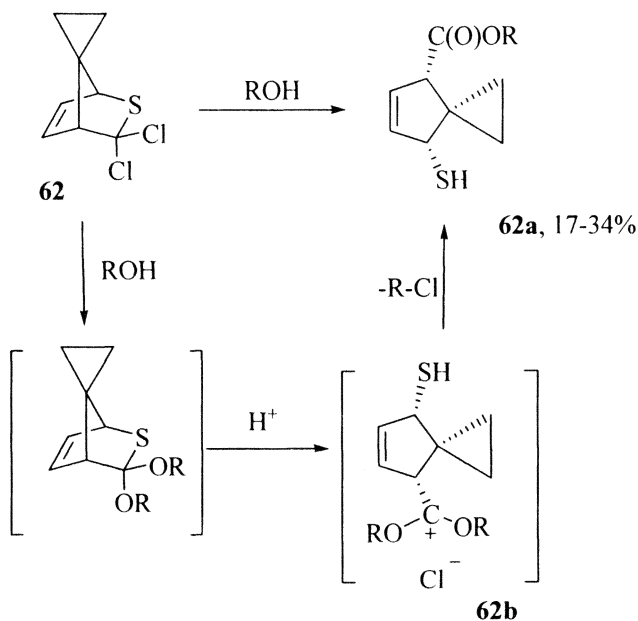
The ability to undergo ring-opening reactions involving positively charged sulfur atom is a typical feature of fluorinated sulfur-containing heterocycles. However, as was demonstrated recently, the relative reactivity depends strongly on the strain energy of heterocycle bearing sulfur (46). While the addition of $(\text{CH}_3)_2\text{CHMgCl}$ to a solution of **30** in THF at 0 °C results in a fast, high yield formation of **57b** (see Eq. 25) the conversion of **5** into **61a** is slower (5 h, 25 °C, 77 % yield) (Scheme 6).



Scheme 6

The reaction of compound **40** under similar conditions was significantly slower and was not completed after 20h at 25 °C. Finally, the reaction of monocyclic compound **3a** having the least strained heterocyclic ring was the slowest and least selective (Scheme 6) (46).

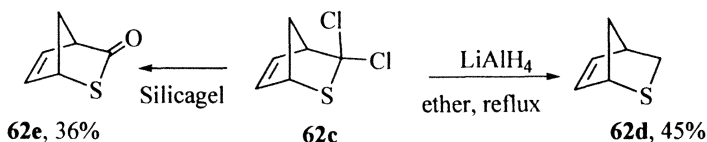
The ring opening reactions described above are believed to have a mechanism similar to the one represented by Scheme 5. The first step involves either electron transfer to (or nucleophilic attack on) positively charged sulfur atom of the heterocycle. In a sense, this mechanism is a “mirror” image of the mechanism proposed for ring opening processes of hydrocarbon sulfur-containing heterocycles (14). The mechanism of the reaction of cycloadduct **62** with alcohols involves consecutive displacement of chlorines by alkoxy groups, followed by an *electrophilic* ring opening step involving protonation of sulfur and resulting in intermediate **62b**, which is converted into the final product **62a** by elimination of alkyl chloride (14) (Eq. 32).



Eq. 32

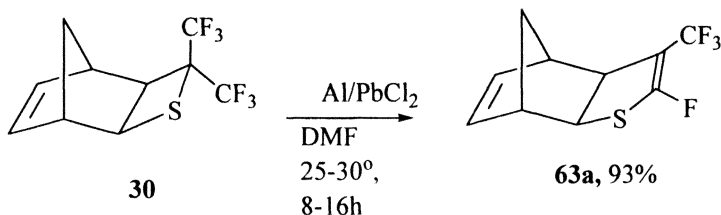
It should be pointed out that the nucleophilic displacement of chlorines (*vs.* nucleophilic attack on sulfur atom of **62**) is characteristic for all cycloadducts of dichlorothiophosgene (**14**). For example, adducts of **14** and cyclohexa-1,3-diene (11,50), substituted butadienes (51), compounds **4a** (52-54), **38** (16), **17** (15), all were converted into the corresponding hydrocarbons either through selective

reduction of the CCl_2 group by LiAlH_4 (15,16) or a combination of $-\text{CCl}_2$ hydrolysis (optionally oxidation of sulfur), followed by a reduction step (11,50-54). Representative examples of these transformations are given below (Eq. 33).



Eq. 33

Recently, an interesting transformation was reported which involves *reductive ring expansion* of fluorinated thietanes. The treatment of compound **30** with aluminum powder in the presence of a catalytic amount of PbCl_2 resulted in an unprecedented ring expansion with high yield formation of compound **63a** (55).

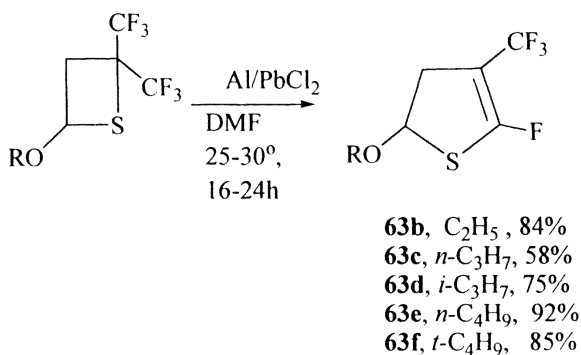


Eq. 34

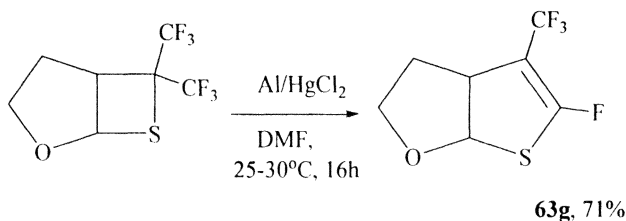
This reaction was extended to other fluorinated thietanes. Under similar conditions readily available cycloadducts of vinyl ethers and **1** were converted into dihydrothiophenes **63b-g** (Eq. 35, 36) (55).

The mechanism of this transformation involves single electron transfer from the metal to the molecule of thietane, resulting in the formation of radical-anion **64a**, which subsequently undergoes ring opening isomerization into intermediate **64b** (Scheme 7).

The elimination of fluoride anion and the reduction of the sulfur radical to the corresponding anion leads to **64e**. Intramolecular *5-endo-trig* nucleophilic cyclization [for review on cyclization of *gem*-difluoroolefins see (56)], leads to the formation of the final product. The intermediacy of sulfur-centered radical **64c** proposed in this mechanism is supported by isolation of the corresponding disulfide **64d** ($\text{R}=\textit{n}\text{-C}_4\text{H}_9$ and $\textit{t}\text{-C}_4\text{H}_9$) in the reduction of sterically hindered thietanes **63e** and **63f**.



Eq. 35

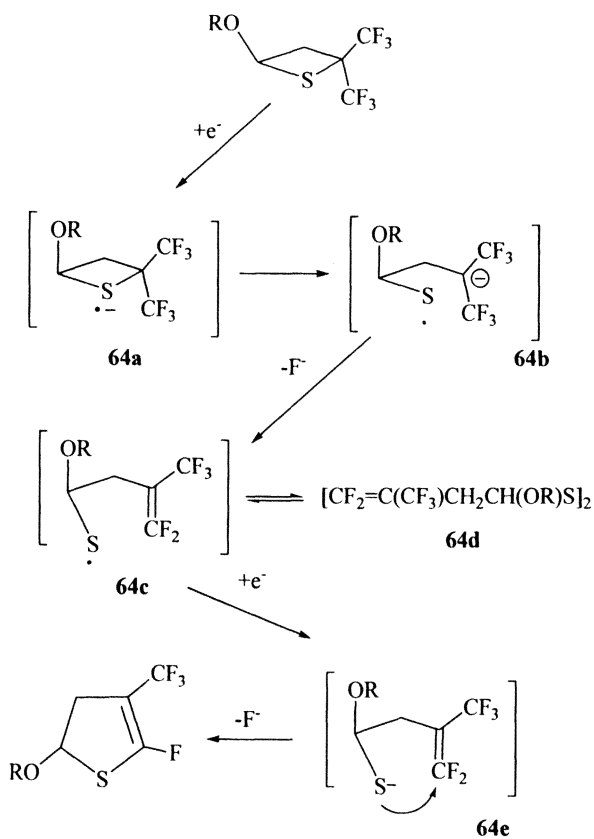


Eq. 36

Conclusion

The remarkable ability of fluorinated thiocarbonyls to undergo cycloaddition reactions with both electron-rich and electron-deficient substrates was utilized for the preparation of a wide variety of polyfluorinated cycloadducts. Several new modifications to the methods of generation of hexafluorothioacetone significantly simplify the preparation of the corresponding cycloadducts and make most of them readily available on a preparative scale. In sharp contrast to oxygen analogs, cycloadducts of hexafluorothioacetone and other fluorinated thiocarbonyl compounds are often more stable and can be involved in a much wider range of chemical transformations including oxidation into S(IV) and S(VI) derivatives.

The ring opening and ring expansion transformations of fluorinated thiethanes are new and interesting processes with significant synthetic potential.



Scheme 7

Acknowledgement

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Chapter 7

Synthesis of *gem*-Difluorinated Heterocycles Using a Difluoropropargyl Molecular Scaffold

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The practical syntheses of *gem*-difluorohomopropargyl-alcohols, -ethers, -esters, -amides and -ketones are reported. The fluorinated alcohols cyclize under AgNO₃ catalysis to give substituted tetra-, dihydrodifluorofurans and fluorofurans; they also yield tri-substituted fluorofurans under basic conditions and iodine trapping followed by a cross-coupling reaction. *gem*-Difluorohomopropargyl ethers furnish difluoroisochromans after a rhodium-catalyzed [2+2+2] cycloaddition, whereas *gem*-difluoroamides are converted to the corresponding β- or γ-lactams selectively via a 4-*exo-digonal* or 5-*endo-digonal* cyclization modes, respectively. Alternatively these amides could be converted into 4,4-difluoro-3-oxoisoquinolines using enyne ring closing meta-thesis followed by a Diels-Alder reaction. These isoquinolines, in turn, react in a Diels-Alder fashion to yield a heterotricyclic system. Finally, *gem*-difluoroamides yield difluoro-1,4-dihydro-3(2*H*)-isoquinolinones via a [2+2+2] rhodium-catalyzed cycloaddition.

Introduction

Interest in cyclic, non-benzenoid organofluorine compounds has increased in recent years due to their increased applications in the pharmaceutical research (1). Specifically, α,α -difluoromethylene-containing heterocycles are highly relevant because there are no general methods for their synthesis, or for generating structural diversity. Occasionally, a CF_2 moiety can be installed on a ring via selective fluorination of the carbonyl group employing fluorinating agents such as (diethylamino)sulfur trifluoride (DAST) or related reagents; however these fluorinating reagents are highly reactive and often do not tolerate other functionalities. During the last decade there has been a concerted effort to utilize transition metals capable of activating the triple bond to form new carbon-carbon bonds and carbon-heteroatom bonds (2). We entered this field by investigating the synthesis and cyclization chemistry of a functionalized *gem*-difluoroallene (3), and only recently we began a rational study of *gem*-difluoropropargyl systems (Figure 1). Our group has sought to increase the structural diversity of cyclic and heterocyclic fluorinated systems using a molecular building block approach that hinges on a combination of an unsaturated π -system and a transition metal. This juxtaposition has demonstrated that it is capable of promoting useful synthetic transformations with less steps than traditional methodologies. The reactions reported in this chapter are those in which the nucleophilicity of X-H (X=N, O) is activated with a stoichiometric amount of base or through the activation of unsaturated bonds using catalytic amounts of transition metals.

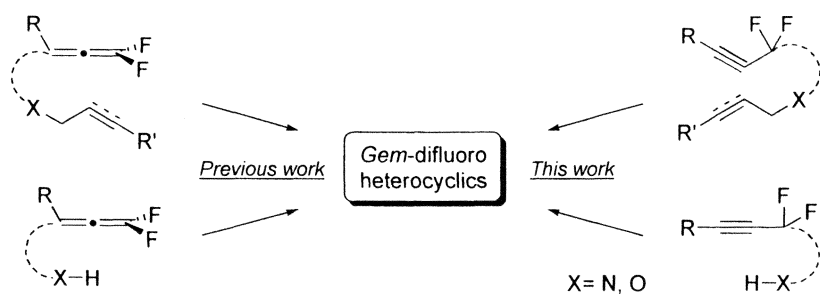


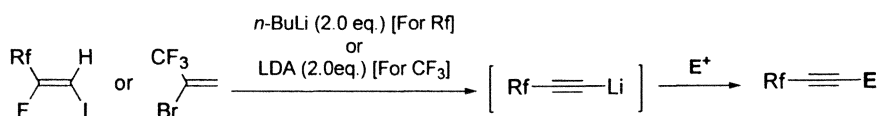
Figure 1. Possible complementary synthetic approaches toward *gem*-difluorocyclic compounds

Practical synthesis of *gem*-difluorohomopropargyl alcohols

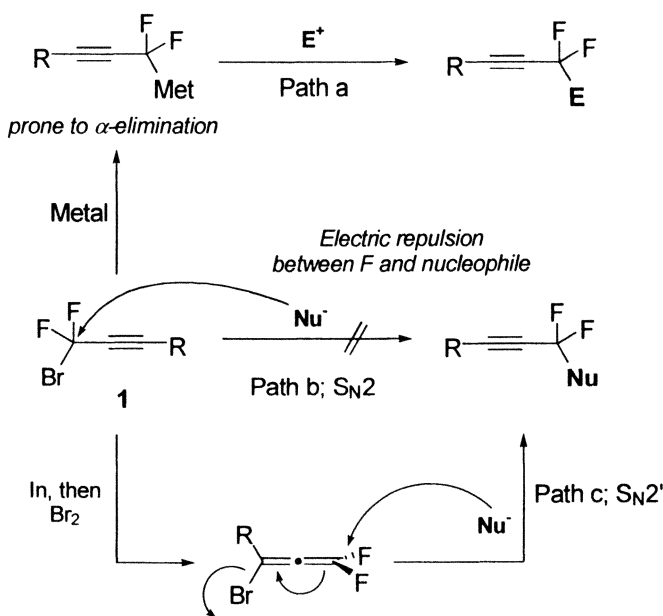
By placing a *gem*-difluoromethylene carbon on a propargylic position we can modify the electronic properties of the resulting alkyne, leading to unique

reactivity on the triple bonds. There are two possible fluorine locations surrounding a triple bond, either on the terminal end of the alkyne as shown in Scheme 1, or in between an sp carbon and an introduced substituent (such as an electrophile or nucleophile) as shown in Scheme 2. The former has been prepared from fluoroiodoolefins or trifluorobromopropene and have been used to prepare fluorinated isoquinolines (4a-c) and other medicinal targets such as panomifene (4d).

There are fewer methodologies available for the synthesis of internally fluorinated acetylenes. This is due to the inherent difficulty of executing nucleophilic substitutions on a CF₂ group due to the electronic repulsion between the fluorine atoms and the incoming nucleophile (Path b, Scheme 2); or because



Scheme 1. Synthetic approaches to externally substituted acetylenes



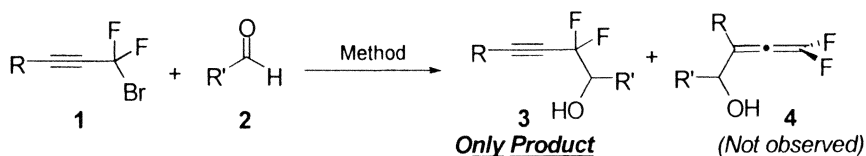
Scheme 2. Synthetic approaches to internally substituted acetylenes

this system is prone to form carbenoid intermediates—through α -elimination of fluoride in the presence of metals—which has led to decomposition and by-products (Path a, Scheme 2).

Our group has recently overcome the problem of nucleophilic substitution on a difluoromethylene carbon using a functionalized difluoroallene acting as a CF_2 cation equivalent with both hard and soft nucleophiles in good yields (Path c, Scheme 2) (5). However this reaction is not yet amenable for large scale synthesis. Homopropargyl alcohols are versatile building blocks in organic synthesis (6). *Gem*-difluorohomopropargyl alcohol **3** has been synthesized using a Barbier reaction between difluoropropargyl bromide **1** and aldehyde **2** (7), but this protocol requires anhydrous conditions.

A green chemistry alternative is the Barbier reaction of **1** with aldehydes **2** using indium in an aqueous environment. Indium has shown potential for such

Table 1. Barbier reaction of difluoropropargyl bromide **1 and aldehyde **2** in the aqueous media**



Method A: In (1.0 eq.), $\text{Eu}(\text{OTf})_3$ (5 mol%),
 $\text{H}_2\text{O}/\text{THF}$ (4/1) (0.3 M), 40 °C, 20 h,)))

Method B: In (0.1 eq.), Zn (0.9 eq.), I_2 (0.1 eq.),
 $\text{H}_2\text{O}/\text{THF}$ (4/1) (0.3 M), 40 °C, 12 h,)))

Entry	R	R'	Isolated yield of 3 (%) Method A / Method B
1	TES (1a)	Ph (2a)	72 / 55 [3aa]
2		4-Me-C ₆ H ₄ (2b)	65 / 48 [3ab]
3		3-MeO-C ₆ H ₄ (2c)	60 / 48 [3ac]
4		2,4-(MeO) ₂ -C ₆ H ₃ (2d)	73 / 53 [3ad]
5		4-Cl-C ₆ H ₄ (2e)	71 / 42 [3ae]
6		4-NO ₂ -C ₆ H ₄ (2f)	No Rxn
7		2-F-C ₆ H ₄ (2g)	65 / 47 [3ag]
8	<i>n</i> -Hex (1b)	Ph (2a)	55 / 41 [3ba]
9	Ph (1c)		35 / 0 [3ca]

reactions; notable examples include the Reformatsky reaction (8); Barbier-type alkylation (9), allylation (10) and propargylation (11) of carbonyl compounds. We and others reported the synthesis of **3** using difluoropropargyl bromide **1** and aldehyde **2** in a predominantly aqueous media in good yields (12).

We also reported that the use of catalytic amounts (5 mol%) of $\text{Eu}(\text{OTf})_3$, as a water-tolerant Lewis acid, is a reproducible alternative to obtain **3** (Method A, Table 1) (13). Although this reaction system was effective in aqueous media, an intrinsic drawback of indium is the need for almost stoichiometric amounts of this relatively expensive metal. In response to the cost factor, a number of groups have tried various combinations containing catalytic amounts of indium and a secondary cheaper metal (such as Al, Zn, Sn or Mn) (14). We screened the effects of other readily available metals (Mg, Al, Fe, Cu, Zn, Mo, Sn, and Sb) and found that a catalytic amount of indium and zinc was the most effective metal combination (15). Some metal halide complexes, including zinc halides and indium halides (16) are well known water-tolerant Lewis acid catalysts, but available at a fraction of the cost. Thus, an economical solution is the *in situ* generation of a metal halide complex by addition of iodine to the reaction. This led us to discover a very inexpensive synthesis of **3** that relies on the utilization of zinc (0.9 eq.) combined with catalytic amounts of indium (0.1 eq.) and iodine (0.1 eq.) (Method B, Table 1) (15). Although the resulting *gem*-difluorohomopropargyl alcohols **3** are obtained in moderate yields, those reactions are highly regioselective as the isomeric *gem*-difluorohomoallenyl alcohol **4** was not detected using either method (Table 1). A six-membered transition state in which the indium complex coordinates with the carbonyl oxygen of aldehydes has been invoked to explain the allenyl-propargyl regiocontrol in nonfluorinated systems (17). If our reaction had followed a similar six-membered transition state pathway, then we would have observed the corresponding *gem*-difluorohomoallenyl alcohols. The fact that we did not observe such a byproduct led us to ponder whether a radical pathway was in effect, in which case, water would play a crucial role in the generation of radical species (18). Further studies are needed to probe the reaction mechanism of this unusual regioselectivity.

Selective synthesis of fluorinated furan derivatives via the AgNO_3 catalyzed cyclization or iodocyclization followed by Suzuki coupling of *gem*-difluorohomopropargyl alcohols

The furan ring is an ubiquitous unit in natural products, pharmaceuticals, agricultural compounds, fragrances, and synthetic precursors (19). A concise

synthetic methodology for multi-substituted furans derivatives remains an important task in modern organic chemistry (20). A particularly underdeveloped area of furan chemistry is the synthesis of its fluorine congeners (21). Notable advances include the anti-HIV agent 3,3-*gem*-difluoromethylenated nucleosides (22), and the anticancer drug Gemcitabine (2'-deoxy-2'-difluorocytidine), recently approved for the treatment of pancreatic cancer (23). With a convenient large-scale synthesis of *gem*-difluorohomopropargyl alcohols **3** in hand, we investigated the synthesis of fluorinated furan derivatives (24,25). DFT calculations (Figure 2) showed that the triple bond of **5a** (Figure 2, A) is electronically deficient compared with the corresponding non-fluorinated homopropargyl alcohol (**B**), hence it is expected that the triple bond of **3** and **5** will react easier with nucleophiles than with electrophiles.

Complexes of group 11 metals (Cu, (26) Ag, (27) Au (28)) are known to activate triple bonds to induce nucleophilic attack on the triple bond; thus we proceeded to screen group 11 metals that would catalyze the cyclization of alcohol **5a** (Table 2). In striking contrast to non-fluorinated systems (29), gold(I) or (III) complexes did not give satisfactory results (Table 2, entries 1-2). Instead, we found that AgNO₃ was the best catalyst for obtaining 3,3-difluoro-4,5-dihydrofuran **6a** (Table 2, entries 4-5). This reaction exhibited a remarkable solvent effect, THF is the best solvent for obtaining dihydrofuran **6a** selectively (Table 2, entry 9). Product **6a** could not be isolated by silica gel chromatography or distillation, both purification methods yielded 3-fluorofuran **7a** (30). It is

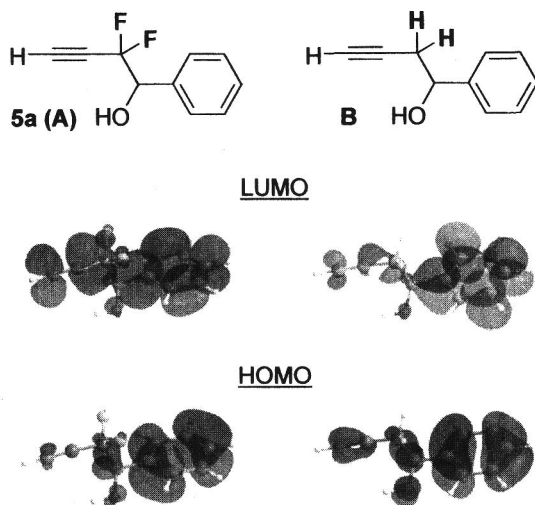
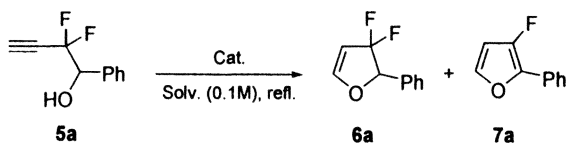


Figure 2. Comparison of the electronic states of the triple bond of *gem*-difluorohomopropargyl alcohol **5a** (A) and its non-fluorinated counterpart (**B**). [b3lyp/6-311g(d, p) 5d] (See page 1 of color insert.)

worth noting that our attempts to obtain furan **7a** by inducing aromatization of dihydrofuran **6a** using basic (NaOH, *t*-BuOK and NaH) or acidic (BF₃•Et₂O and BCl₃) conditions failed.

In order to explore the scope and limitations of the new Ag(I) catalyzed cyclization, various *gem*-difluorohomopropargyl alcohols **3** and **5** were treated with AgNO₃ (10 mol%) in THF (Table 3).

Table 2. Screening of metal complexes of group 11 metals



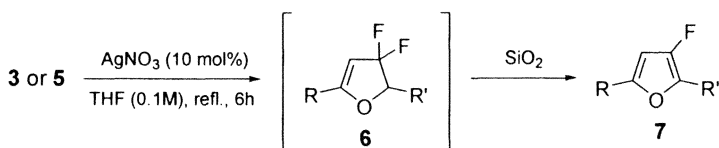
Entry	Cat. (X mol%)	Solv.	Time (h) ^{a)}	Yields of 6a/7a (%) ^{b)}
1	AuBr ₃ (5)	CH ₂ Cl ₂	24	0/34
2	Me ₃ PAuCl (5)		24	No Rxn
3	AgOTf (5)		12	0/34
4	AgNO ₃ (5)		24	60/11
5	AgNO ₃ (10)		24	45/31
6	Ag ₂ CO ₃ (5)		24	No Rxn
7	CuI (5)		24	0/34
8	CuOTf (5)		24	No Rxn
9	AgNO ₃ (10)	THF	6	94/0
10		Et ₂ O	6	No Rxn
11		Benzene	6	72/5

a) The reaction time was determined by consumption of **5a** as monitored by TLC. b) Yields were determined by ¹⁹F NMR.

In all cases ¹⁹F NMR monitoring indicated an excellent conversion to 4,5-dihydrofurans **6** regardless of substrate R' used [electron-donating (Table 3, entries 2-5), electron-withdrawing (Table 3, entries 6-8), and aliphatic substituents (Table 3, entry 9)]. After eluting through a silica gel column, 4,5-dihydrofurans **6** furnished the corresponding 3-fluorofurans **7** in good isolated yields (Table 3, entries 1-5 and 9); electron-withdrawing substituents (Table 3, entries 6-8) produced furans **7** in low to moderate yields. In the case of internal alkynes, a Ag(I) catalyzed cyclization furnishes 3-fluorofurans **7** directly, albeit in low to moderate yields (Table 3, entries 10, 11 and 13). The reaction did not take place when R = TIPS (Table 3, entry 12).

Although 3,3-difluoro-4,5-dihydrofuran **6** could not be isolated, we were able to prepare 3,3-fluorotetrahydrofuran **8** by catalytic hydrogenation of dihydrofuran **6** (Table 4, entries 1-8). This reaction gave high ^{19}F NMR yields and satisfactory isolated yields with all substrates tested. The reaction mechanism proposed for the cyclization of alcohols **3** and **5** to dihydrofurans **6** contemplates activation of the triple bond through coordination with AgNO_3 , followed by a 5-*endo-dig* cyclization and proton shift to produce 4,5-dihydrofuran. Our AgNO_3 catalyzed cyclization does not permit installing a synthetic handle on the 4-position to access other multi-substituted fluorinated furans. But if a reactive halide could be placed on the 4-position, it could be functionalized using cross-coupling reactions (Scheme 3) (31), therefore the iodocyclization of *gem*-difluorohomopropargyl alcohol **3** was investigated (25). After screening various iodine sources and bases we found that the combination of iodomonochloride (ICl) and Na_2CO_3 under microwave irradiation gave the desired iodocyclization product in satisfactory yield with little decomposition.

Table 3. Synthesis of 3,3-difluoro-4,5-dihydrofurans **6 and 3-fluorofurans **7****



Entry	R	R'	Yields of products (%) ^{a)}	
1	H	Ph (5a)	94 (6a)	55 (7a)
2		4-Me-C ₆ H ₄ (5b)	70 (6b)	55 (7b)
3		4-MeO-C ₆ H ₄ (5c)	>99 (6c)	65 (7c)
4		3-MeO-C ₆ H ₄ (5d)	>99 (6d)	79 (7d)
5		2,4-(MeO) ₂ -C ₆ H ₃ (5e)	>99 (6e)	62 (7e)
6		4-Cl-C ₆ H ₄ (5f)	>99 (6f)	32 (7f)
7		4-CF ₃ -C ₆ H ₄ (5g)	>99 (6g)	52 (7g)
8		2-F-C ₆ H ₄ (5h)	91 (6h)	49 (7h)
9		BnOCH ₂ (5i)	81 (6i)	68 (7i)
10 ^{b)}	<i>n</i> -Hex (3ba)	Ph	--	58 (7j)
11	Ph (3ca)		--	20 (7k)
12	TIPS (3da)		--	No Rxn.
13	BnOCH ₂ (3ea)		--	65 (7l)

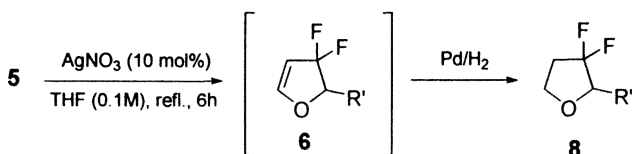
a) Yields of **6** were determined by ^{19}F NMR; yields of **7** were calculated after isolation of pure product. b) Reaction time was 24h.

Aryl substrates with both electron-donating and withdrawing groups at the homopropargyl position gave the corresponding 4-iodofurans **10** in good isolated yields (Table 5, entries 1-3). Interestingly, when silica gel was deactivated with triethylamine (Et₃N), **9** was isolated instead of the aromatized derivative **10** (Table 5, entries 4-6) (**32**).

The proposed mechanism of this reaction is depicted in Scheme 4. Initial deprotonation of **3** by a base gives rise to an oxyanion, which can then attack on the CF₂ carbon in a 3-*exo-tet* fashion (Scheme 4, Path a) (**33**) or on the triple bond in a 5-*endo-dig* fashion (Path b) (**34**).

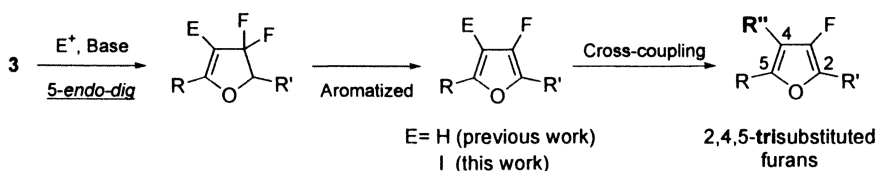
Acetylenic epoxide intermediates have been converted into furans via their cumulene intermediates in the presence of bases; however for this transformation to occur alkyl substrates are required on R (**35**). Fortunately, we were able to recrystallize **9f** and obtain an X-ray analysis, which cemented our

Table 4. Synthesis of 3,3-difluorotetrahydrofuran **8**



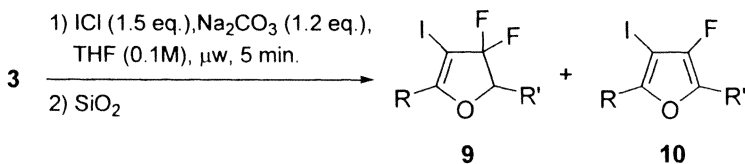
Entry	R'	Yields of 8 (%) ^{a),b)}
1	Ph (5a)	74 [81] (8a)
2	4-Me-C ₆ H ₄ (5b)	41 [52] (8b)
3	3-MeO-C ₆ H ₄ (5d)	63 [71] (8d)
4	2,4-(MeO) ₂ -C ₆ H ₃ (5e)	52 [68] (8e)
5	4-Cl-C ₆ H ₄ (5f)	49 [53] (8f)
6	4-CF ₃ -C ₆ H ₄ (5g)	68 [92] (8g)
7	2-F-C ₆ H ₄ (5h)	67 [73] (8h)
8	BnOCH ₂ (5i)	50 [57] (8i)

a) Isolated yields. b) The values in brackets correspond to ¹⁹F NMR yields.



Scheme 3. Synthetic access to multi-substituted fluorinated furans

Table 5. Microwave mediated iodocyclization of *gem*-difluorohomopropargyl alcohols **3**



Entry	R	R'	Isolated yields of 9 or 10 (%)	
1	<i>n</i> -Hex	Ph	-	66 (10a)
2		4-MeO-C ₆ H ₄	-	62 (10b)
3		4-CF ₃ -C ₆ H ₄	-	76 (10c)
4		BnOCH ₂	46 (9d) ^a	-

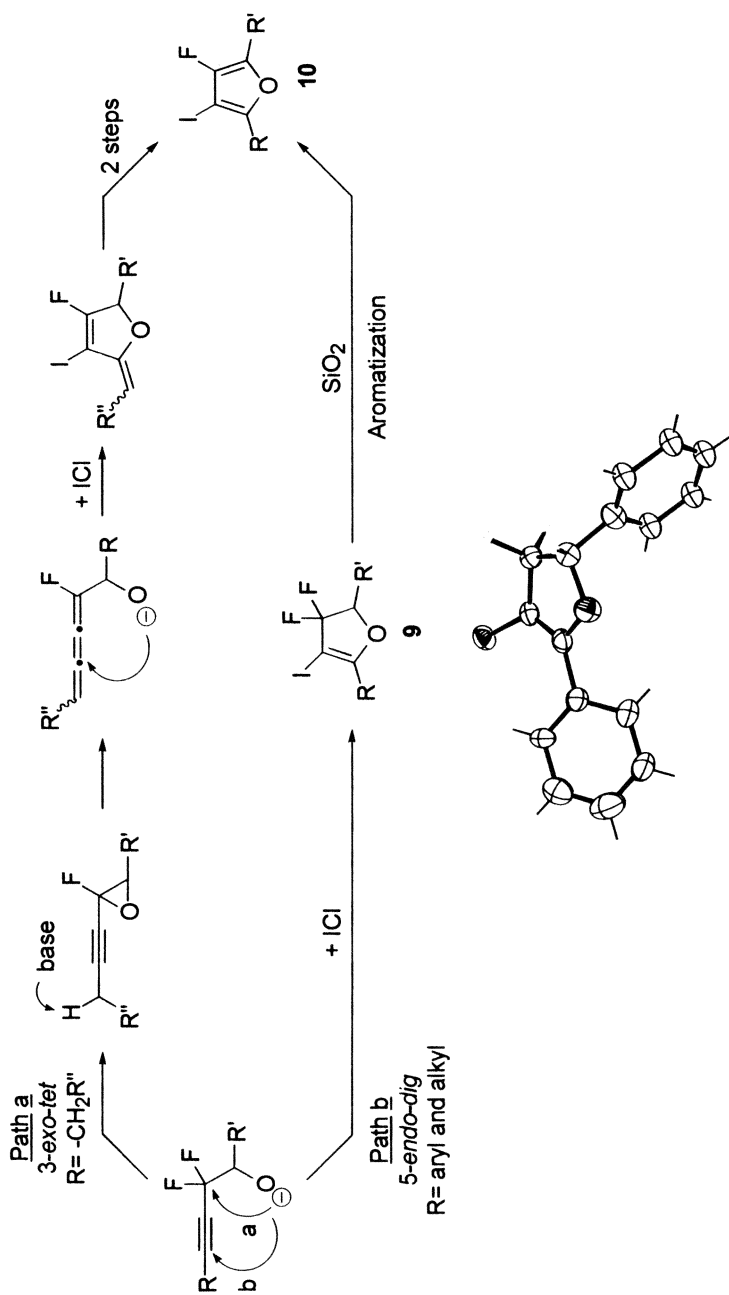
5	BnOCH ₂	Ph	56 (9e) ^a	-
6	Ph		49 (9f) ^a	-

a) SiO₂ was deactivated by Et₃N.

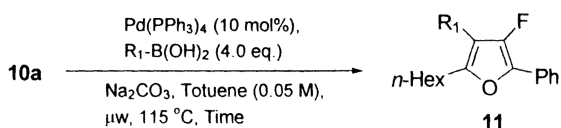
characterization of **9** and allowed us to use the ¹⁹F NMR spectral data of crude **9** (prior to aromatization) to confirm that in all cases, 3,3-difluoro-4-iodo-4,5-dihydrofurans **9** were obtained regardless of substrates on R and R'. The origin of the unusual electronically deficient nature of the alkyne moiety in **3** was supported by our previous DFT calculations illustrated in Figure 2.

There are several reports dealing with the synthesis of 2,5-substituted-3-fluorofurans, but none of them permits functionalization at the 4-position of 3-fluorofurans (**36**). One important synthetic application of **9** and **10** is that both could, in principle, allow functionalization at the 4-position using a Suzuki cross-coupling. We explored this route in order to construct multi-functional 3-fluorofurans (Table 6).

It should be pointed out that microwave irradiation was critical for the efficiency of this reaction. Indeed, phenylboronic acid reacted readily with **10a** to furnish **11aa** in excellent yield in only 0.5 h (Table 6, entry 1), whereas the reaction at reflux failed to consume **10a** even after 12 h, and led to the formation of by-products. Both electron-rich and electron-deficient aryl boronic acids reacted with **10a** in satisfactory yields (Table 6, entries 2-6). Furthermore, 3-thienylboronic acid (Table 6, entry 7) and (*E*)-cinnamylboronic acid (Table 6, entry 8) gave the corresponding sp²-sp² coupling products in good and moderate yields respectively, with only a slight change of the reaction time. 4-Iodofuran



Scheme 4. Reaction mechanism for the formation of iodofluorofurans **10**. (See page 1 of color)

Table 6. Microwave mediated Suzuki coupling of 10a with several boronic acids

Entry	R ₁	Time (h)	Isolated yields of 11 (%)
1	Ph	0.5	98 (11aa)
2	3,4-(OCH ₂ O)-C ₆ H ₃	0.5	78 (11ab)
3	4-CHO-C ₆ H ₄	1.5	72 (11ac)
4	4-CN-C ₆ H ₄	1.0	63 (11ad)
5	4-F-C ₆ H ₄	0.5	66 (11ae)
6	4-CF ₃ -C ₆ H ₄	0.5	63 (11af)
7	3-Thienyl	1.0	71 (11ag)
8	(E)-PhCHCH ₂	1.5	58 (11ah)

analogues **9** and **10** were also investigated in the coupling reaction with phenylboronic acid (Table 7). The Suzuki coupling of 4-iodofurans **10** was carried out smoothly to give 2,4,5-trisubstituted 3-fluorofurans **11** in good yields (Table 7, entries 1 and 2). Interestingly, the Suzuki coupling between 4-iodo-4,5-dihydrofurans **9** spontaneously yielded only **11** (Table 7, entries 3-5) with no trace of the corresponding 4,5-dihydrofurans. In this manner, we were able to obtain the first crystallographic characterization of a fully substituted 3-fluorofuran (i.e., **11fa**) (37). If the substrate possesses a benzyl ether group, the product yield was relatively low, perhaps due to the instability of this group (Table 7, entries 3 and 4).

Synthesis of 4,4-difluoroisochromans

Despite the fact that isochromans are biologically attractive compounds (Figure 3) (38), to our knowledge there have been no reports on the preparation of 4,4-difluoroisochromans derivatives. We decided to investigate the synthesis of 4,4-difluoroisochromans **14** using a rhodium-catalyzed [2+2+2] cycloaddition of 3,3-difluoro-1,7-diyne **12** with monosubstituted acetylene **13**. The starting material **12** was easily prepared in three steps from difluoropropargyl bromide **1d** (Scheme 5).

Table 7. Preparation of multi-substituted 3-fluorofuran 11 via Suzuki coupling of 9 or 10 with phenylboronic acid

Entry	R	R'	Time ^a (h)	Isolated yields of 11 (%)
1	<i>n</i> -Hex	4-MeO-C ₆ H ₄ (10b)	2.0	85 (11ba)
2		4-CF ₃ -C ₆ H ₄ (10c)	1.0	75 (11ca)
3		BnOCH ₂ (9d)	1.5	50 (11da)
4	BnOCH ₂	Ph (9e)	1.0	51 (11ea)
5	Ph	(9f)	1.5	77 (11fa)

a) Reaction progress was monitored by TLC or GC-MS.

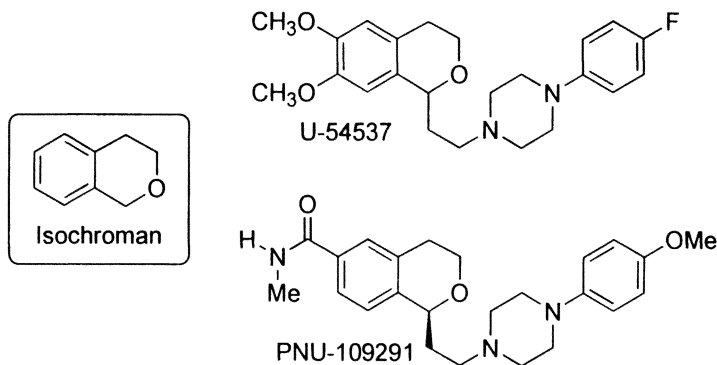
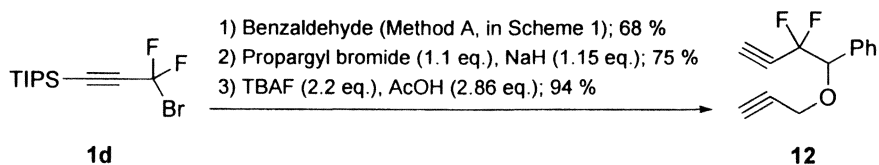


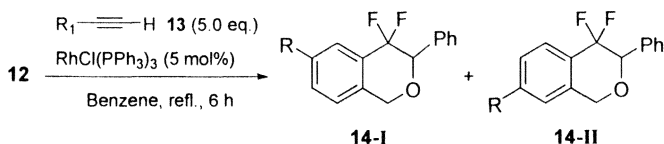
Figure 3. Examples of biologically active isochroman congeners



Scheme 5. Preparation of 3,3-difluoro-1,7-diyne **12**

This cycloaddition produced a mixture of regioisomers **14-I** and **14-II** in moderate to good yields with the exception of **14c**, **14f**, and **14g** (Table 8). TMS acetylene did not give the desired product, probably due to steric hindrance (Table 8, entry 3), and when the substituent R contained an electron-withdrawing group, the mass balance of products **14** decreased (Table 8, entries 5-7). This may be due to the formation of complex fluorinated by-products, visible in the ^{19}F NMR spectrum of the reaction mixture. In all cases examined, the dominant products were the regioisomers **14-II**, even though both alkyne groups in **12** are terminal; these results may imply that the regiochemistry of the reaction might be controlled by electronic rather than steric effects.

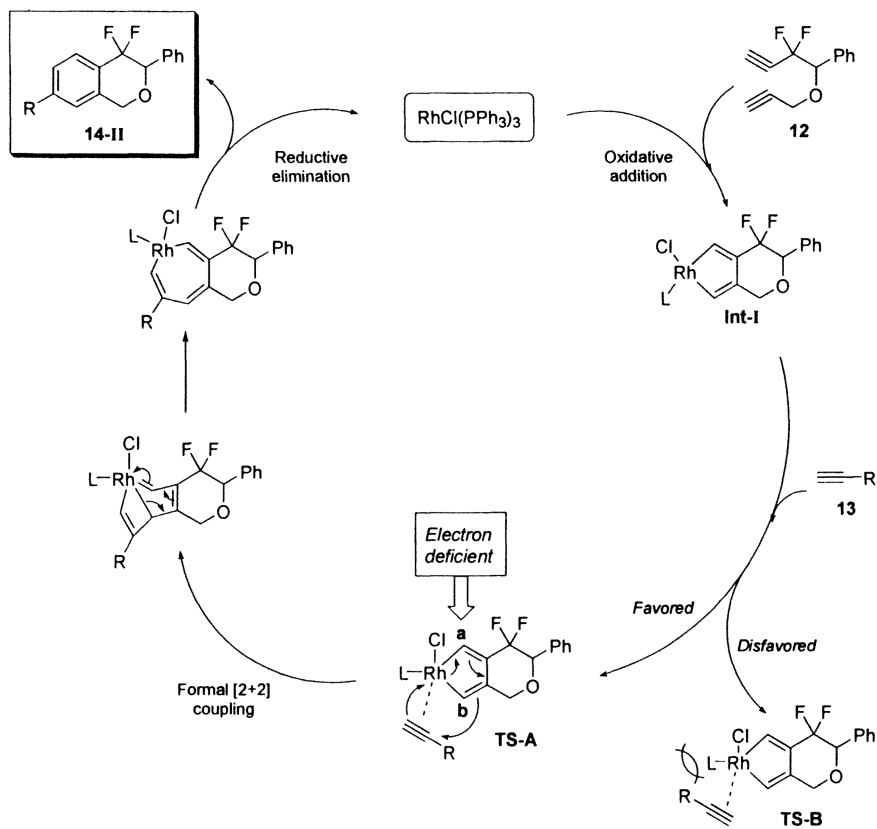
Table 8. Synthesis of 4,4-difluoroisochromanes **14 via $\text{RhCl}(\text{PPh}_3)_3$ catalyzed [2+2+2] cycloaddition of diyne **12****



Entry	R	Yields of products (%) ^a 14-I / 14-II
1	CH ₂ OH (13a)	31 / 59 (14a)
2	<i>n</i> -Hex (13b)	39 / 55 (14b)
3	TMS (13c)	No Rxn (14c)
4	Ph (13d)	15 / 68 (14d)
5	<i>p</i> -F-C ₆ H ₄ (13e)	14 / 47 (14e)
6	<i>p</i> -CF ₃ -C ₆ H ₄ (13f)	19 / 20 (14f)
7	C ₆ F ₅ (13g)	0 / 15 (14g)

a) Yield was determined by ^{19}F NMR.

Based on the widely accepted mechanism of [2+2+2] alkyne cycloaddition (39), we proposed the pathway outlined in Scheme 6 to explain the regioselectivity found in our experiments. Initially, two triple bonds coordinate to the metal to give metallacyclopentadiene **Int-I** through an oxidative coupling, followed by a third triple bond insertion to the intermediate metallacyclopentadiene and a final reductive elimination to yield products **14-I** and **14-II**. The rationale for this regioselectivity can be traced to the steric hindrance that exists between the metal ligands and the substituent R of the third acetylene, and the electronic density differences between C-a and C-b (see **TS-A** and **TS-B** in Scheme 6).



Scheme 6. Plausible reaction mechanism for [2+2+2] cycloaddition of **12** leading to 4,4-difluoroisochromans **14**

The electronic deficiency in C-a may be due to the strong electron-withdrawing effect of fluorine, and therefore the insertion of the third acetylene to the metallacyclopentadiene would take place from the C-b side (40).

Intramolecular hydroamination of difluorohomopropargyl amides. Regioselective synthesis of fluorinated β - and γ -lactams

The synthesis of 2,2-difluorohomopropargylic esters has been reported by Kobayashi via DAST fluorination of homopropargylic ketoester (41), or through the reaction of an iododifluoroacetate-copper complex with alkynyl iodides (42). However, both methods suffer from scale-up limitations. First we screened the reaction of difluoropropargyl bromide **1** and alkyl chloroformate **15** (43),

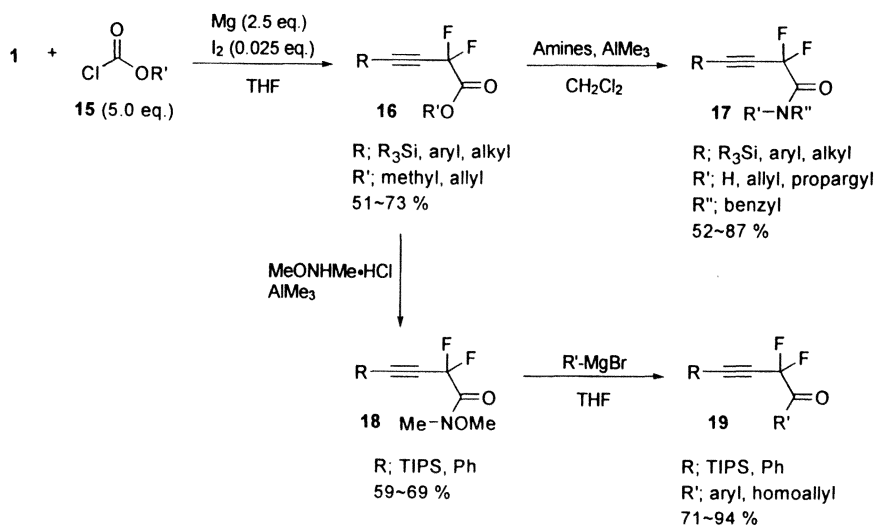
because the methyl ester group in the desired product could be converted to the corresponding amide and ketone. To prevent possible α -defluorination we chose the Barbier protocol instead of using a Grignard reaction. The Barbier reaction furnished *gem*-difluorohomopropargylic esters **16** in satisfactory yields after distillation of the product at molar scale (Scheme 7). Next, the transformation from methyl 2,2-difluorohomopropargyl ester to the corresponding amide was explored. This reaction was successfully carried out with aminoaluminum reagents generated from AlMe_3 with primary and secondary amines for homopropargylic amides **17**, as well as with a $\text{MeONHMe}\cdot\text{HCl}$ salt for the synthesis of Weinreb amide **18** respectively, in moderate to good yields. The Weinreb amide **18** was readily transformed into ketone **19** (Scheme 7) in good to excellent yields. If necessary, desilylation of TIPS on triple bonds can be conducted smoothly with TBAF and $\text{CH}_3\text{CO}_2\text{H}$.

Catalytic hydroamination of multiple carbon-carbon bonds constitutes one of the most efficient methodologies to create carbon-nitrogen bonds (44). The intramolecular version of this process is an attractive method to generate nitrogen heterocycles, converting starting materials into desired products in a single operation, without the formation of side products and with high atom efficiency. To overcome the high activation energy required for the direct addition of amines or their derivatives across multiple carbon-carbon bonds, a variety of catalytic and non-catalytic methods have appeared in the literature (45). We decided to study the construction of these small fluorinated heterocycles using *gem*-difluorohomopropargylic amides **17** as their synthetic applications (46). Depending on the reaction points of the triple bond, it is possible to synthesize β -lactams **20** via a 4-*exo-digonal* cyclization mode and formation of γ -lactams **21** via a 5-*endo-digonal* cyclization mode (Scheme 8).

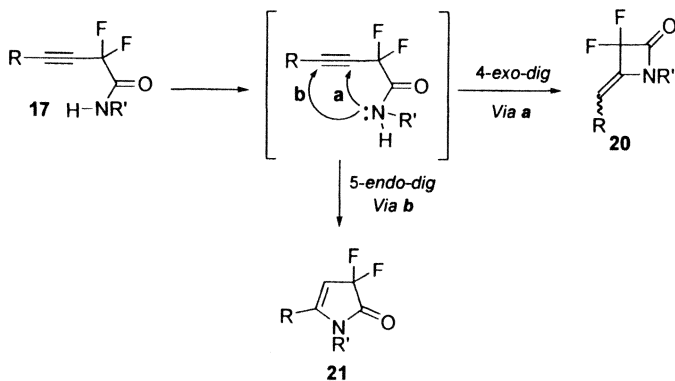
Our initial intramolecular hydroamination studies were carried out with alkyne **17b** using several palladium catalysts (47). With palladium acetate in the presence of Et_3N in THF, a diastereomeric mixture of (*Z*)-**20b** and (*E*)-**20b** was obtained in 63% yield (13:1) (Table 9, entry 2) (48). The extension of this protocol to other amides **17**, led to the formation of the corresponding β -lactams (*Z*)-**20** and (*E*)-**20** in moderate yields and good selectivities (Table 9).

A plausible mechanism (Scheme 9) may involve initial alkyne activation through coordination of the triple bond with palladium(0). Literature reports suggest (49) that the p character of triple bond increases through this interaction, thus resembling the sp^2 -like bond. This pseudohybridization, could favor both, 4-*exo-trig* and 5-*exo-trig*, modes of cyclization, but the presence of the *gem*-difluoro moiety should predispose the α -position for the intramolecular nucleophilic attack by the amidic nitrogen, thus favoring its 4-*exo-dig* cyclization mode.

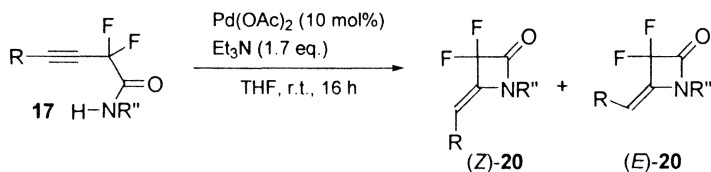
We also investigated the base-mediated activation of the amidic nitrogen to produce γ -lactams **21** (Table 10).



Scheme 7. Synthesis of 2,2-difluorohomopropargylic carbonyl analogues

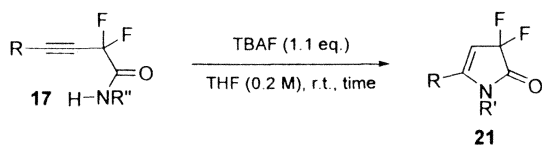


Scheme 8. Synthetic strategy to construct β - and γ -difluorolactams

Table 9. Synthesis of fluorinated β -lactams 20

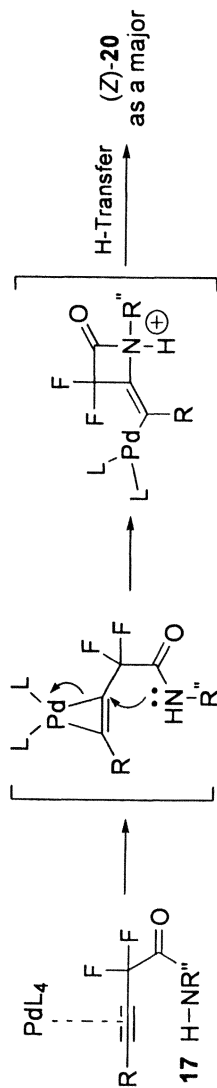
Entry	R	R'	Yields of products (%) ^a [(Z)- 20 / (E)- 20]
1	TIPS	Bn	(17a) No Rxn
2	Ph	Bn	(17b) 63 [13/1] (20b)
3	Ph	PMP ^b	(17c) 54 [>50/1] (20c)
4	Ph	Allyl	(17d) 33 [14/1] (20d)
5	Ph	(s)-PhCH(Me)Bn	(17e) 40 [10/1] (20e)
7	3-Thienyl	Bn	(17f) 34 [10/1] (20f)
8	MMP ^c	Bn	(17g) 34 [10/1] (20g)

a) Isolated yield. b) PMP=*p*-MeOC₆H₄. c) MMP=2-Me-4-MeO-C₆H₃.

Table 10. Hydroamination mediated by TBAF

Entry	R	R'	time	Isolated yield of 21 (%)
1	Ph	Bn	(17b) 1.5	61 (21a)
2	Ph	PMP ^a	(17c) 2	60 (21b)
3	Ph	Allyl	(17d) 3	64 (21c)
4	Ph	(s)-PhCH(Me)Bn	(17e) 0.5	62 (21d)
5	3-Thienyl	Bn	(17f) 1	66 (21e)
7	MMP ^b	Bn	(17g) 3	67 (21f)
8	H	Bn	(17h) 3	78 (21g)

a) PMP=*p*-MeOC₆H₄. b) MMP=2-Me-4-MeO-C₆H₃.



Scheme 9. Possible mechanism for the Pd-catalyzed 4-exo-dig cyclization

Of all bases tried (DBU, NaH, *i*-Pr₂NEt, LiN(TMS)₂, KOH, *t*-BuOK, TBAF), the best results were obtained using 1.1 equiv of TBAF at r.t. (Table 10). In this case, the triple bond is electron deficient, so a base-promoted nucleophilic addition occurs easily, and since a 5-*endo-digonal* cyclization is favored, the formation of γ -lactam **21** is expected.

Synthesis of 4,4-difluoroisoquinolinone congeners

The importance of 3-oxoisoquinoline derivatives as synthetic intermediates or pharmaceuticals is well documented (50). Our difluorohomopropargylic carbonyl building block could also serve to construct the fluorinated counterpart of oxoisoquinolines. First, we investigated an enyne metathesis reaction with ruthenium carbene complexes (43), whose reaction will transform the 1,7-enyne into a six-membered ring structure bearing a diene moiety, which can then be used to build a bicyclic compound through a Diels-Alder reaction (51).

On the course of screening this reaction (Table 11), the Hoveyda-Grubbs-II catalyst (Figure 4) proved to be the most reactive, yielding moderate yields of the product. At 110 °C, this reaction produced **22a-iso** as the major compound, through the isomerization of **22a** (Table 11, entry 3). The synthesis of **22a** in good yield was attained when the reaction was carried out at 70 °C in toluene (Table 11, entry 4). Other solvents (1,2-dichloroethane or THF) were not as effective (Table 11, entries 5 and 6). It became clear that ethylene gas was crucial additive for this reaction (Table 11, compare entries 4 and 7) (52). Although 2,6-dichloro-1,4-benzoquinone has been employed elsewhere (53) to prevent isomerizations, this additive did not give the desired effect (Table 11, entry 8). When our optimized conditions were applied to other fluorinated 1,7-enynes, the desired six-membered compounds could be isolated only when amide substrates were employed (Table 12, entry 1-3) and a higher temperature was required with non-terminal alkynes (Table 12, entry 2-5). Enyne ester **16a**

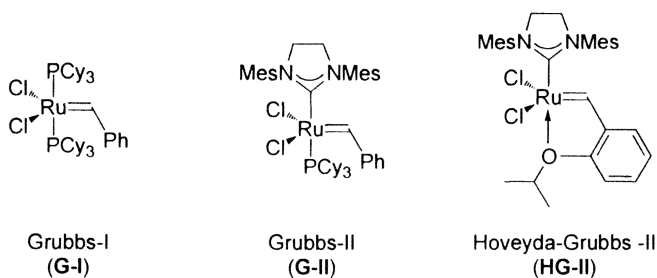
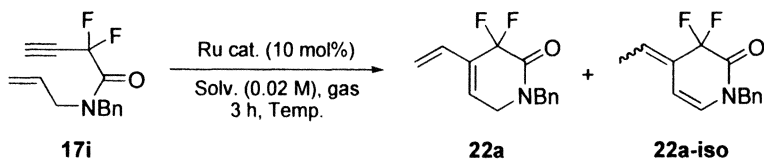


Figure 4. Ruthenium carbene metathesis complexes

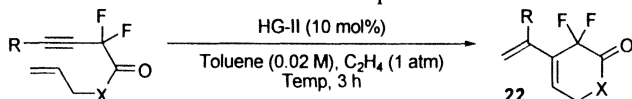
Table 11. Screening of the enyne metathesis of **17i**

Entry	Solvent	Ru cat.	gas	Temp. (°C)	Yields of product (%) ^a 17i / 22a / 22a-iso
1	Toluene	G-I	C ₂ H ₄	110	53 / 0 / 0
2	Toluene	G-II	C ₂ H ₄	110	0 / 34 / 0
3	Toluene	HG-II	C ₂ H ₄	110	0 / 6 / 66 (60)
4	Toluene	HG-II	C ₂ H ₄	70	0 / 85 (70) / 0
5	1,2-Dichloroethane	HG-II	C ₂ H ₄	70	No Rxn.
6	THF	HG-II	C ₂ H ₄	70	30 / 25 / 0
7	Toluene	HG-II	Argon	70	28 / 34 / 0
8 ^b	Toluene	HG-II	C ₂ H ₄	110	0 / 20 / 11

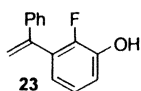
a) Yield was determined by ¹⁹F NMR and the value in parenthesis is the isolated yields.

b) 20 mol% of 2,6-dichloro-1,4-benzoquinone was used.

Table 12. Several metathesis reactions with fluorinated 1,7-enyne carbonyl compounds



Entry	X	R	Temp. (°C)	Yields of 22 (%) ^a
1	NBn	H (17i)	70	70 [85] (22a)
2		<i>n</i> -Hex (17j)	110	52 [78] (22b)
3		Ph (17k)	110	69 [95] (22c)
4	O	Ph (16a)	110	- [33] ^b (22d)
5	C	Ph (19a)	110	- [97] ^c (22e)

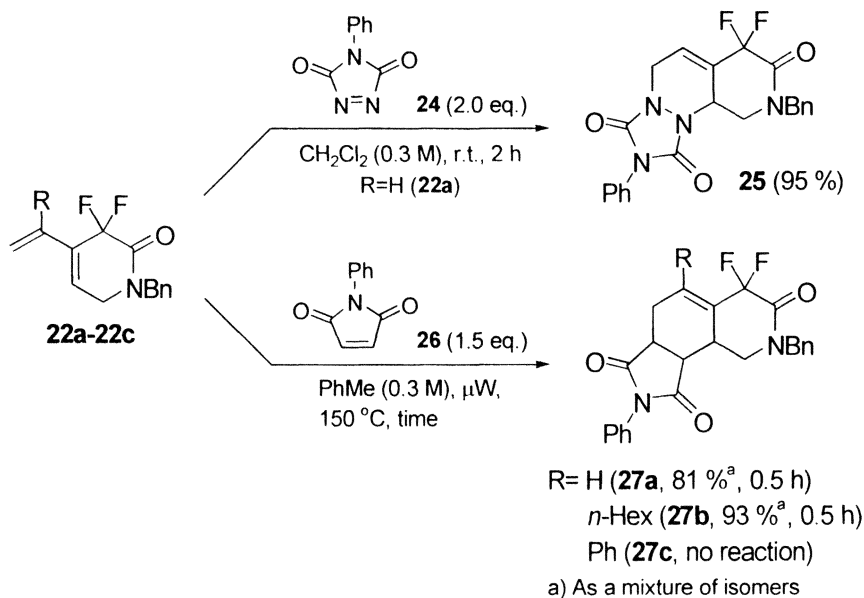


a) The values in brackets were determined by ¹⁹F NMR. b) The compound could not be isolated due to the complexity of the reaction products.

c) Compound **23** was isolated in 84 % after silica gel chromatography.

did not give a satisfactory result, but the corresponding ketone **19a** gave a good ^{19}F NMR yield [97 %, δ : -103.99 ppm (s, 2F)] of the six-membered-ring product **22e**. The monofluorinated aromatic compound **23** was obtained in good yield after silica gel chromatography (Table 12, entry 5).

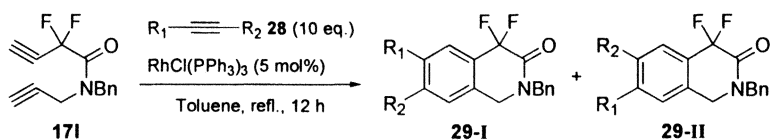
As shown in Scheme 10, the diene moiety of **22** could be transformed further by a Diels-Alder reaction with dienophiles **24** or **26** to give the bicyclic products **25** and **27**, respectively, in excellent yields.



Scheme 10. Diels-Alder reaction of dienes **22** with **24** and **26**

As described earlier, we synthesized 4,4-difluoroisochromans **14** using a [2+2] cycloaddition strategy. We applied a similar approach to the synthesis of 4,4-difluoro-1,4-dihydro-3(2*H*)-isoquinolinones using 1,7-diyne amide **171** (**43**). The reaction proceeded smoothly using various alkyne substrates **28** and catalytic amounts of $\text{RhCl}(\text{PPh}_3)_3$ (5 mol%) in good to excellent yields (Table 13). It is worth mentioning that an interesting regioselectivity of products **29-I/29-II** was observed with the terminal alkynes **28a-28g** (Table 13, entry 1-7). The product **29-II** was obtained as major isomer in all cases, regardless of the substituents on the terminal alkyne **28**. This regioselectivity can be explained by the mechanism illustrated in Scheme 6; that is through the cooperative effects of

Table 13. Synthesis of 4,4-difluoro-1,4-dihydro-3(2*H*)-isoquinolinone derivatives **29 by [2+2+2] cycloaddition of **171** with **28****



Entry			Yields of product (%) [29-I : 29-II] ^a	
1	CH ₂ OH	H	(28a)	92 [1:4] (29a)
2	<i>t</i> -Bu	H	(28b)	10 [1:3] (29b)
3	TMS	H	(28c)	85 [1:3] (29c)
4	C ₆ H ₅	H	(28d)	85 [1:6] (29d)
5	<i>o</i> -NO ₂ -C ₆ H ₄	H	(28e)	37 [1:1.5] (29e)
6	OEt	H	(28f)	55 [1:2.5] (29f)
7	CO ₂ Me	H	(28g)	40 [1:2] (29g)
8	CH ₂ OH	CH ₂ OH	(28h)	52 (29h)
9	CO ₂ Et	CO ₂ Et	(28i)	45 (29i)

a) The isomer ratio was determined by ¹⁹F NMR.

the electron-withdrawing effect of fluorine and steric hindrance between ligand and substrate on alkyne **28** in the transition state.

Conclusions

In summary, we have described the practical synthesis of *gem*-difluorohomopropargyl-alcohols, -ethers, -esters, -amides and -ketones capable of generating structurally diverse fluorinated heterocycles such as furans, isochromans, isoquinolines and lactams, using cyclization reactions catalyzed mostly by transition metals including Ag, Rh, Ru or Pd.

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Chapter 8

Pentafluorosulfanyl Serotonin Analogs: Synthesis, Characterization, and Biological Activity

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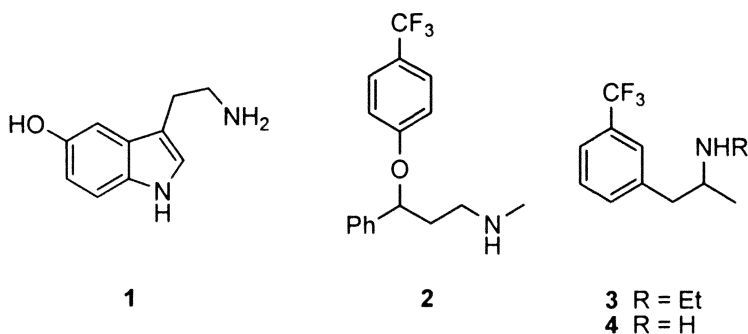
The synthesis of a pentafluorosulfanyl containing analog of serotonin by functionalization of 4-pentafluorosulfanylaniline is described. In addition the preparation of pentafluorosulfanyl analogs of fluoxetine, norfenfluramine and fenfluramine are reported and the relative affinity of these compounds for tryptamine receptors is reported. The pentafluorosulfanyl group replacement facilitates discrimination between receptor subtypes.

Introduction

Serotonin (5-hydroxytryptamine)

Contemporary chemotherapy for mood and psychotic disorders is highly dependent upon our understanding of the molecular biology of serotonin (**1**; 5-HT; 5-hydroxytryptamine) receptors (*1*). 5-HT receptors may be classified as belonging to at least 15 different subtypes. Most antipsychotic drugs or serotonin-selective reuptake inhibitors (SSRI) may interact with a multiplicity of receptors. Currently with few subtype-selective compounds available, new approaches to the design of selective ligands are important. We have focused our attention on the preparation of pentafluorosulfanyl analogs of fluoxetine **2**

and substrate-type 5-HT-releasing agents such as fenfluramine **3** or norfenfluramine **4** (Scheme 1) where the activity of these compounds can be contrasted with the parent compounds or (\pm)-3,4-methylenedioxy-methamphetamine ((\pm)-MDMA, "ecstasy"), and *m*-chlorophenylpiperazine (mCPP), compounds with both therapeutic and adverse effects (2, 3).



Scheme 1. Serotonin, fluoxetine and fenfluramine

Receptors

Given their importance to the activity of potentially therapeutic compounds, an understanding of the chemical structure of 5-hydroxytryptamine receptors has been the subject of several investigations (4). Models for the receptor-binding site can be derived from structures of active analogs or the known structures of regulatory proteins (5). 5-HT receptor function can be further classified using tryptamine analogs and the binding sites delineated using tryptamine-based receptor classifications (6, 7). Seven distinct receptor families, for example 5-HT₁–5-HT₇, comprised of at least 15 sub-families have been cloned. Serotonin itself binds to all receptor subtypes. Investigation of the role of these subtypes is hindered by a lack of receptor selectivity, very few agents possess significant selectivity for a particular population of 5-HT receptors. Of particular interest to us is the tendency of specificity for a specific subpopulation or even agonist vs. antagonist activity to be a function of substituent type, this in spite of the general observation that tryptamine analogs are notoriously indiscriminant.

Biological Responses

The mediation of a wide range of physiologic functions as well as a sense of well being is associated with serotonin levels. The behavioral responses

resulting from excess stimulation of postsynaptic 5-HT receptors were known in the late 1940's and the relative risk of these occurrences on treatment with different drug combinations has been reported. The first human data were described in 1955 and by 1958 work with animal models had defined characteristic response patterns (8).

Mood. Serotonin levels may be modulated by inhibiting uptake in pre-synaptic cells. However, this effect can be complicated by competing effects when there is a flood of serotonin on other receptors. Selective serotonin reuptake inhibitor (SSRI) antidepressants inhibit serotonin reuptake, and consequently increase serotonin availability. These effects are responsible for the relief of depressive symptoms and also for some of the adverse effects of this class of drugs (9). Although the SSRIs share a common mechanism of action, they differ substantially in their chemical structure, metabolism, and pharmacokinetics (10, 11). While chemically different structures may have similar antidepressant efficacy and similar side effect profiles, differences may be found in pharmacokinetic properties (12).

Appetite. Agonists of the serotonin 5-HT_{2C} receptor have found importance in anti-obesity drug development. The importance of 5-HT in appetite was formally proposed nearly 30 years ago. In particular, endogenous hypothalamic 5-HT was implicated in satiety. Of the numerous 5-HT receptor subtypes, 5-HT_{1B} and 5-HT_{2C} receptors are believed to mediate the 5-HT induced satiety (13). The precise role of serotonin in human appetite is less well understood than in animal studies. However, the 5-HT_{2C} receptor has been implicated in human eating, although any role for the 5-HT_{1Db} (5-HT_{1B}) receptor has yet to be determined (14).

Before their removal from the market, fenfluramine and the more active enantiomer dexfenfluramine were considered to be among the most effective of weight loss agents. Much of the weight loss produced by fenfluramine was attributed to the direct activation of serotonin 5-HT_{2C} receptors in the central nervous system via the desethyl-metabolite of fenfluramine, norfenfluramine. Norfenfluramine, however, is non-selective, activating additional serotonin receptors, such as 5-HT_{2A} and 5-HT_{2B}, which likely mediate the heart valve hypertrophy seen in many patients.(15-17)

Cardiovascular. 5-Hydroxytryptamine released from platelets in the human cardiovascular system can produce harmful acute and chronic effects. The acute cardiac effect of 5-HT consists primarily of tachycardia. Chronic exposure to high levels of 5-HT, the anorectic drug fenfluramine and its metabolites, as well as the ecstasy drug 3,4-methylenedioxymethamphetamine (MDMA) and its metabolite 3,4-methylenedioxyamphetamine (MDA) have been associated with thickening of cardiac valves, mediated through 5-HT_{2B} receptors (18, 19).

50 years ago, serotonin was identified as a circulating neurohormone acting on the central nervous system regulating cerebral blood flow as well as vascular permeability through direct and indirect effects. Among the various 5-

hydroxytryptamine receptors which mediate these effects, the preferred targets of modern antimigraine agents are 5-HT_{1B} and 5-HT_{1D} subtypes (20).

Gastrointestinal Of the multiple 5-hydroxytryptamine receptor subtypes in the gastrointestinal tract, e.g., 5-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄, the 5-HT₄ receptor is the most important (21).

Pentafluorosulfanyl arenes

Properties of the pentafluorosulfanyl group. The relative steric demand and symmetry of the SF₅ group can be compared and contrasted with both the *tert*-butyl and trifluoromethyl groups.

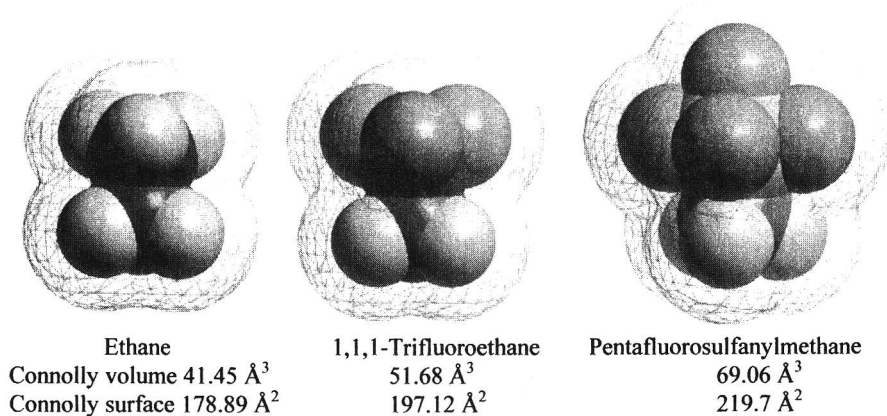


Figure 1. Relative volumes and areas C₂H₆, CF₃CH₃, and SF₅CH₃
(See page 2 of color insert.)

The volume of the SF₅ group is slightly less than that of a *tert*-butyl group (22, 23) and therefore considerably greater than that of a trifluoromethyl group (CF₃). However the electrostatic surface presented by SF₅ is comparable to CF₃ in that it presents a highly fluorinated surface, a pyramid of electron density as opposed to the inverted cone of density associated with CF₃ group. The electron withdrawing effect as assessed by the carbon 1s photoelectron spectra suggest these electron withdrawing groups are similar in magnitude (24, 25). The electronegativity of the SF₅ group has been proposed to be as high as 3.65 in comparison to a value of 3.36 for the CF₃ group (26). In electrophilic substitution reactions the Hammett σ_p value for SF₅ was determined to be 0.68 in contrast to σ_p value for CF₃ of 0.54 (27). This has been further refined to a σ_1 value for SF₅ of 0.55 and a σ_{R^+} value of 0.11 (27) in contrast to σ_1 value for CF₃

of 0.39 and a σ_R value of 0.12 (28, 29). It is important to note the decreased resonance and increased inductive contributions, a trend that is consistent with the electronic effects observed in the estimation of electronegativity (24, 25).

The organic chemistry of the SF₅ group, previously reviewed (23, 30) and extensively developed by Gard, has only recently come under more widespread investigation with the ready availability of previously difficultly accessible building blocks or reagents (31). Pentafluorosulfanylarene chemistry is largely based on the development of modern synthetic reactions which makes possible the commercial availability of arene building blocks. In particular it was the availability of kilogram quantities of arylpentafluorosulfanyl compounds such as 4-nitro-pentafluorosulfanylbenzene by direct fluorination methods that facilitated exploration of their utility (32).

However these building blocks would have had much less impact without the basic understanding and chemical explorations provided by Thrasher who revealed the potential of pentafluorosulfanylarene compounds (33). Pentafluorosulfanyl groups are hydrolytically and chemically relatively stable (34-37). "Hydrolytic stability of aromatic pentafluorosulfanyl group equals or exceeds that of the trifluoromethyl group. Aromatic SF₅ groups withstand attack of Bronsted acids and bases and are stable under conditions required for Ni, Pd, or Pt hydrogenation." "The weak point of the SF₅ group is reactivity toward alkyl lithium reagents such as *n*-butyllithium. However reagents such as *tert*-butyllithium are compatible with the SF₅ group."

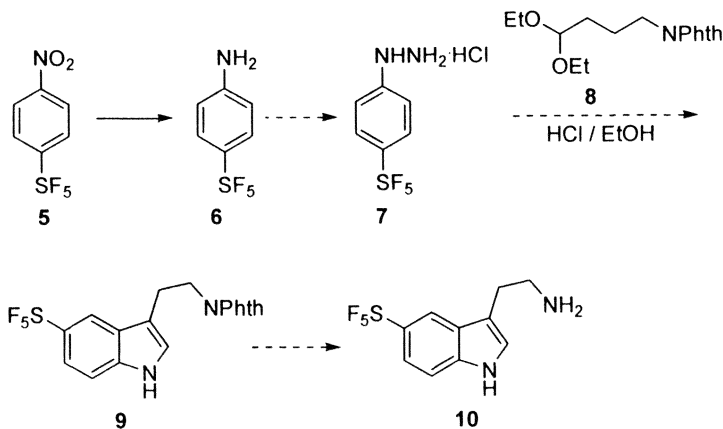
Kirsch has extensively explored not only the preparation of arylpentafluorosulfanyl compounds but also the stability of this functional group to a variety of reaction conditions (34, 35, 37).

The utility of aromatic SF₅ compounds is only today being revealed (38). These materials have found applications in liquid crystalline displays (39, 40) and in agrochemicals (33, 41). The recent report on the preparation of pharmaceutical compositions containing arylpentafluorosulfanyl groups is particularly exciting as this report of the preparation of kinase inhibitors seems to be one of the first reports where the unique geometry and electrostatic surface of the pentafluorosulfanyl group has been employed by design (42).

Synthesis

5-Pentafluorosulfanyltryptamine

Two alternative approaches to the synthesis of the pentafluorosulfanyl containing analog of tryptamine **10** were explored. The first was based upon the classic Fischer indole synthesis (Scheme 2) and the second on the Japp-Klingmann approach (Scheme 3).



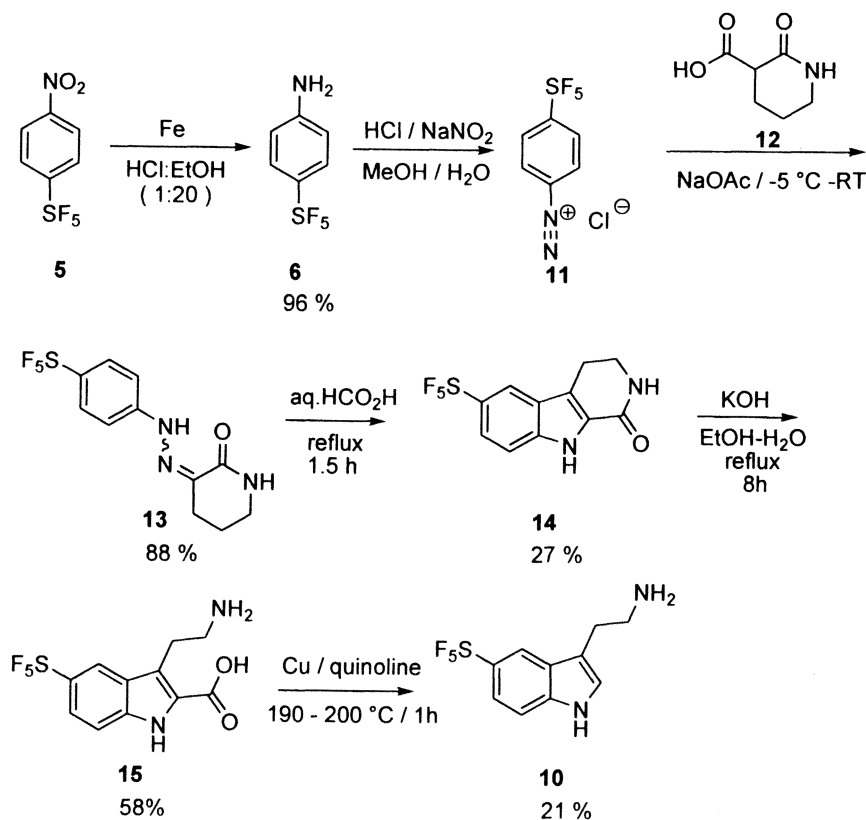
Scheme 2. Fischer Indole Synthesis

The reduction of **5** to aniline **6** was uneventful. However, all attempts to form the necessary hydrazine **7** failed. Nonetheless, it remains likely that suitable conditions for this transformation can be identified. Formation of the diazonium salt **11** required for the alternative Japp-Klingmann synthesis was successful (Scheme 3).

Diazotization of **6** was effected by slow addition of aqueous sodium nitrite to an acidic methanolic solution. The addition of a solution of 2-oxopiperidine-3-carboxylic acid **12** followed by buffering of the solution with sodium acetate produced the desired 3-(2-(4-(pentafluorosulfonyl)phenyl)hydrazono)piperidin-2-one **13** as a solid (43-45). On dissolution in aqueous formic acid (88%) and heating under reflux for 1.5 hours the cyclized lactam **14** was formed in modest but unoptimized yield (44). The lactam was saponified to yield the carboxylic acid **15** (46). Decarboxylation to the desired tryptamine analog **10** was effected on heating to 200 °C in quinoline in the presence of copper powder.

Synthesis of Fluoxetine Analog

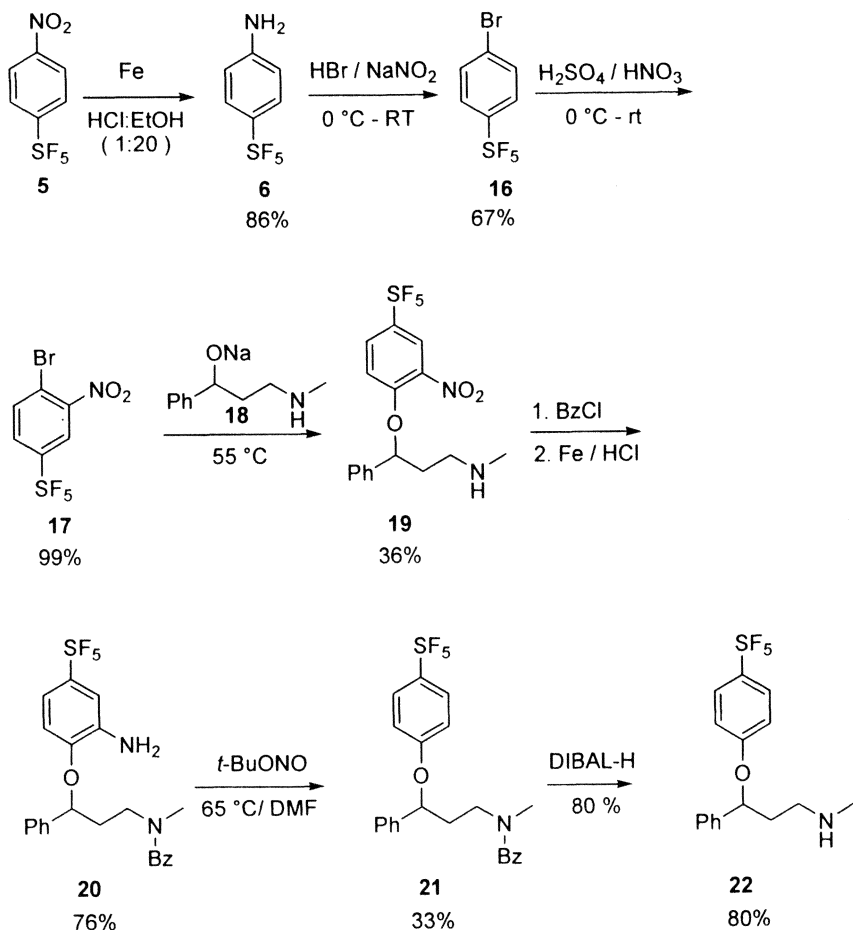
The synthesis and pharmacological efficacy of fluoxetine, **2**, have been reviewed (47, 48) and the clinical utilities of this compound are summarized regularly (49-53). The complexity of the profile of positive and negative effects of fluoxetine on 5-HT receptors (9) suggested that the simple replacement of the trifluoromethyl group by the pentafluorosulfonyl group could lead to a different pattern of response (54).



Scheme 3. Japp-Klingmann Synthesis

Synthesis

Commercially available 1-nitro-4-pentafluorosulfanylbenzene **5** was easily reduced to 1-amino-4-pentafluorosulfanylbenzene **6** under classic conditions with iron powder and concentrated hydrochloric acid (33). Diazotization and Sandmeyer reaction were uneventful. In contrast to reactions of 4-chlorotrifluoromethylbenzene that undergoes a ready nucleophilic aromatic displacement reaction with **18** (55), **16** did not react in our hands. However following introduction of the sacrificial auxiliary nitro group, 1-bromo-2-nitro-4-pentafluorosulfanylbenzene **17** did undergo the desired displacement reaction. Protection of the methylamine group of **19**, necessary for successful reduction of the reactive amine group, by benzylation, *tert*-butoxycarbonylation, benzyloxycarbonylation, trimethylsilylation or *tert*-butyldimethylsilylation all failed to lead to the desired reduction product. Fortunately benzylation to form



Scheme 4. Synthesis of Fluoxetine analog 22

20 suppressed undesired side reactions. Diazotization and reductive dediazotiation of **21** with *tert*-butylnitrite in DMF proceeded smoothly. Deprotection of **21** with diisobutylaluminum hydride resulted in formation of the desired pentafluorosulfonyl fluoxetine analog **22** (Scheme 4).

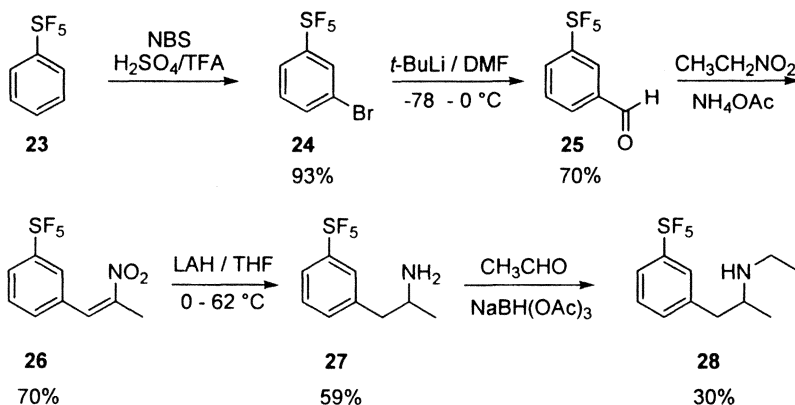
Synthesis of Fenfluramine Analog

A side effect of the anorectic fenfluramine is the development of cardiac valvulopathy (56, 57) an effect that lead to the withdrawal of this compound from the marketplace. The influence of fenfluramine on appetite was first

reported in the late 1970s (58). The clinical effects of fenfluramine and the metabolite norfenfluramine on appetite suppression have been documented in numerous reviews (13, 59-62). Following these early reports, the long term efficacy of fenfluramine in the treatment of obesity was established (63). However, adverse effects of both fenfluramine **3** and the metabolite norfenfluramine **4** have appeared (2, 3, 64, 65). From these findings it is apparent that separation of these detrimental side effects from efficacy is essential (15). The efficacy of fenfluramine as an anorectic is proposed to be derived principally from activation of the 5-HT_{2C} receptor (66) whereas interaction with the 5-HT_{2B} receptor is associated with the side effect heart valve hypertrophy (67). The 5-HT_{2B} receptor associated with pulmonary hypertension (18) has also been associated with overgrowth valvulopathy (68). It is in this context that the pentafluorosulfonyl analogs of fenfluramine and norfenfluramine were prepared (54).

Synthesis

The pentafluorosulfonyl analogs of fenfluramine and norfenfluramine were prepared from readily available pentafluorosulfonylbenzene **23** (Scheme 5). Bromination after the method of Dolbier (69) produced 1-bromo-3-pentafluorosulfonylbenzene **24**. Metallation with *tert*-butyllithium was followed by quenching of the resultant anion with dimethylformamide which on workup afforded the desired aldehyde **25**. Condensation with nitroethane formed the olefin **26** which was subsequently reduced with lithium aluminum hydride. The pentafluorosulfonyl analog of norfenfluramine, **27**, was reductively alkylated with acetaldehyde and sodium triacetoxyborohydride to form the desired fenfluramine analog **28**.



Scheme 5. Synthesis of fenfluramine analog **28**.

The arylpentafluorosulfanyl group was stable toward strong Bronsted acids such as trifluoroacetic or sulfuric acids and reductants such as LAH, diisobutylaluminium hydride, iron powder-HCl or sodium triacetoxyborohydride. Metallation with *tert*-butyllithium proceeded smoothly and the resultant aryllithium reagent exhibited no evidence of unusual instability.

Biological Activity

The binding and inhibition assays of the materials prepared above were performed as described previously using the resources of the National Institute of Mental Health Psychoactive Drug Screening Program (56). In initial screening, compounds were tested at concentrations of 10 $\mu\text{mol/L}$; K_i determinations using seven concentrations of unlabeled ligand spanning four orders of magnitude were obtained with compounds that gave 50% inhibition at 10 $\mu\text{mol/L}$. K_i values were calculated with the LIGAND program (56).

As seen in Table 1, the pentafluorosulfanyl analogs selectively inhibited binding of the 5-HT receptors. These results confirmed the viability of the pentafluorosulfanyl group as a substituent in a medicinal chemical application.

Table 1. Percent inhibition of receptor binding from initial screening^a

Compd	22	28	27
Receptor			
5-HT _{1a}	-3 ^b	85.5	50
5-HT _{1b}	3.4	63.5	62.9
5-HT _{1d}	12.7	15.2	73.7
5-HT _{1e}	77.8	7.3	23.4
5-HT _{2a}	97.3	53.2	85.9
5-HT _{2b}	71.9	85.3	89.6
5-HT _{2c}	75.8	72.8	94.6
,5-HT ₃	6.8	14.6	-6.1 ^b
5-HT _{5a}	25	62.7	31.3
5-HT ₆	1.5	50	50
5-HT ₇	12	50	50

Data represent mean % inhibition (N = 4 determinations) for 10 μm of compound tested at receptor subtypes (56).

^b Negative inhibition(-) represents a stimulation of binding. Compounds at high concentrations non-specifically may increase binding.

In secondary screening, the K_i values were determined for those receptors where at the original test concentration of 10 nM, there was greater than 50% inhibition. For **22**, substitution of the trifluoromethyl group diminished the affinity for 5-HT_{2a} and 5-HT_{2c} by 17% and 12% respectively but had no effect on 5-HT_{2b}.

However substitution of the trifluoromethyl group of **3** and **4** by the pentafluorosulfanyl group had a much more dramatic effect on the selectivity of the substituted compounds for the receptors examined. As shown in Fig. 2 it is evident that the pentafluorosulfanyl group enhances the affinity of **28** for 5-HT_{2b}, 5-HT_{2c}, and 5-HT₆. Of especial note is the increased affinity for 5-HT_{2b} and 5-HT₆, with binding increasing nearly 10 fold (Fig. 3). It was binding to 5-HT_{2b} that has been associated with the adverse valvulopathy (68). Unfortunately the increase in affinity for the 5-HT_{2c} receptor is much less, and thus it is likely that the analog **28** would be less safe than the current clinical agent. In contrast, as shown in Figure 4, while the affinity of **27** relative to **4** for the 5-HT_{2b} is enhanced the increase is much less than in the case of **28** relative to **3** (Fig. 5). Perhaps more strikingly, the pentafluorosulfanyl group substitution in the norfenfluramine structure showed the same general pattern of selectivity observed with the parent compound. As determined in the primary inhibition assays there was little affinity for 5-HT_{1a}, 5-HT_{1c}, 5-HT₃, or 5-HT_{5a} and this selectivity was unaffected by substitution.

Conclusion

During the preparation of the pentafluorosulfanyl analogs of fluoxetine, fenfluramine, and norfenfluramine (**22**, **28**, and **27**, respectively) it was shown that the pentafluorosulfanyl group tolerates a wide variety of reaction conditions normally associated with synthetic organic chemical manipulations. Included are those involving alkyllithium reagents, diazotization and dediazonation, strong Bronsted acids or reducing conditions. The intermediate pentafluorosulfanyl organolithium reagent formed on metallation of 1-bromo-3-(pentafluorosulfanyl)benzene **24** underwent reactions in the expected manner and uneventfully.

During the course of inhibition and binding studies the pentafluorosulfanyl group, a novel non-natural octahedral substituent, exhibited totally conventional substituent influences. All the synthetic materials had some degree of activity while showing discrimination between different receptors. In the case of the fenfluramine and norfenfluramine analogs, the affinity for the 5-HT_{2B} and 5-HT₆ receptors was enhanced. The ten-fold increase in affinity for the 5-HT₆ was equally true for both the fenfluramine and norfenfluramine analogs **28** and **27** respectively. Enhanced affinity for the 5-HT₆ receptor may be useful in research into the uniqueness and clinical significance of the 5-HT receptor subfamily.

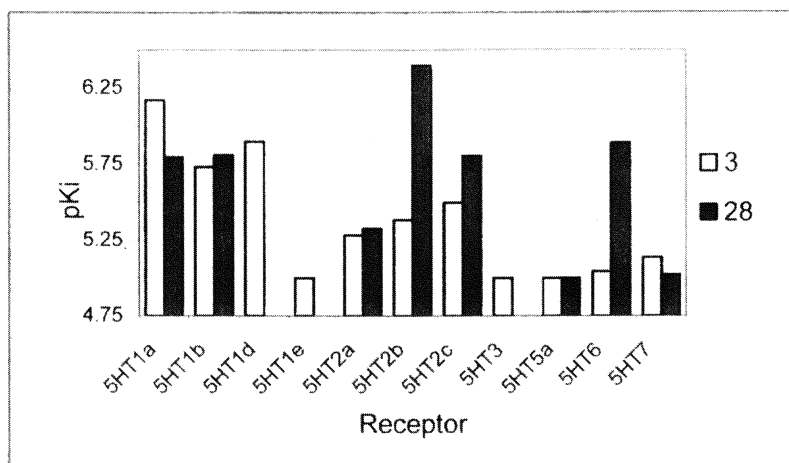


Figure 2. Influence of substitution on receptor binding. Replacement of the trifluoromethyl group of fenfluramine **3** by pentafluorosulfanyl group **28**.⁽⁵⁶⁾ Reproduced with permission from reference (54). Copyright 2007 Elsevier.

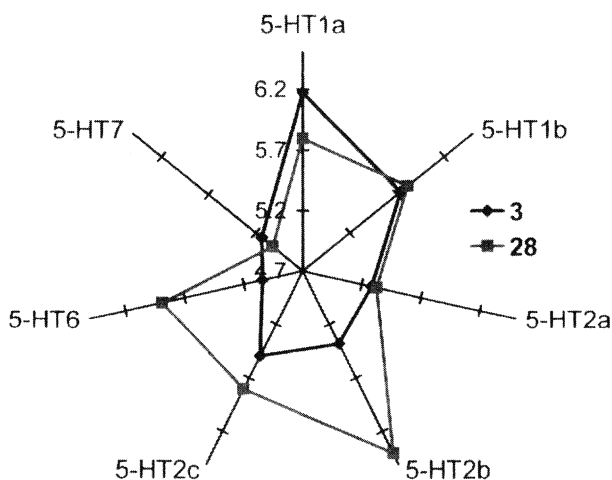


Figure 3. A comparison of pK_i values of **3** and **28** for a series of 5 HT receptors (56). Additional data in Fig. 3. Reproduced with permission from reference (54). Copyright 2007 Elsevier.

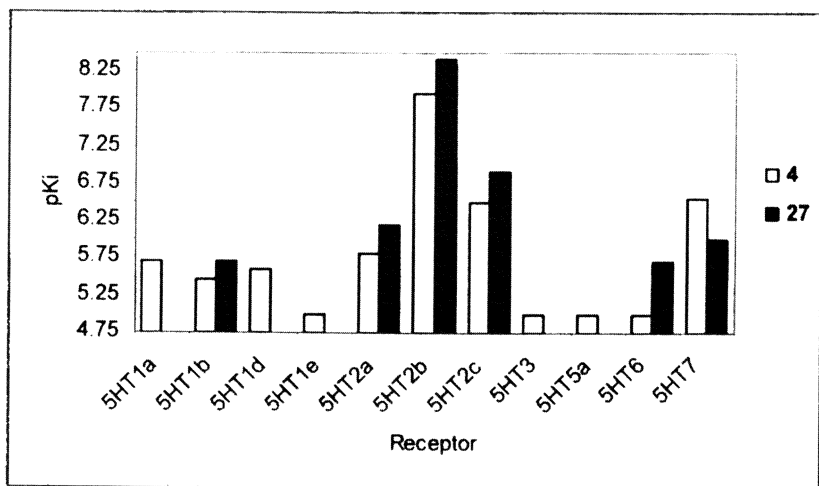


Figure 4. Influence of substitution on receptor binding. Replacement of the trifluoromethyl group of norfenfluramine 4 by pentafluorosulfanyl group 27 (56). Reproduced with permission from reference (54). Copyright 2007 Elsevier.

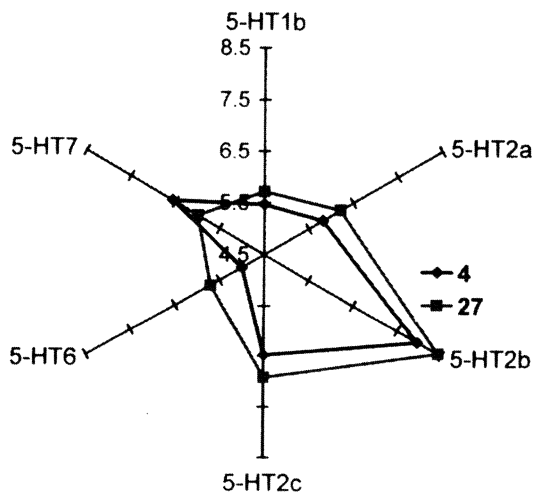


Figure 5. A comparison of pKi values for 4 and 27 with a series of 5 HT receptors (56). Additional data in Fig. 5. Reproduced with permission from reference (54). Copyright 2007 Elsevier.

Thus, ligands for 5-HT₆ receptors might be useful to treat such conditions as motor disorders, depression, anxiety, mood disorders, memory disorders, Huntington's disease, Parkinson's disease and Alzheimer's disease (70).

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Chapter 9

New Fluorinated Pyrazol and Uracil Derivatives: Synthesis and Biological Activity

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Both fluorinated pyrazoles and uracils are compounds that display very interesting biological activities. This chapter reviews recent work of our group in the development of synthetic strategies for the preparation of new examples of these two kinds of compounds.

Introduction

It is widely accepted that the introduction of fluorine atoms into organic molecules causes significant changes in their physicochemical as well as biological properties (1). As a consequence, organofluorine chemistry has reached a fundamental value in several areas including materials science, agrochemistry, and, most importantly, medicine. Besides, the fact that organofluorine compounds are practically unknown in Nature is remarkable, thus limiting their accessibility to synthetic approaches. These can be based on both electrophilic and nucleophilic direct fluorination methodologies or the use of fluorinated building blocks (2). It is significant that fluorinated nitrogen-containing derivatives have received less attention than other fluorinated compounds, in spite of the importance of this class of compounds. It is thus readily appreciated that *the development of new methods of synthesis for this class of derivatives is a fundamental objective in fluoroorganic chemistry.*

In the last few years the interest of our research group has focused on the chemistry of fluorinated nitrogen compounds. In this sense, we have developed new synthetic strategies that allow for the synthesis of several fluorinated nitrogen heterocycles such as uracils, pyrimidines and pyrazoles among others. The aim of this review is to discuss our most recent applications for preparing fluorinated nitrogen heterocycles, with a special focus on the synthesis of fluorinated derivatives of the commercial pyrazole acaricide *Tebufenpyrad* and fluorinated uracils.

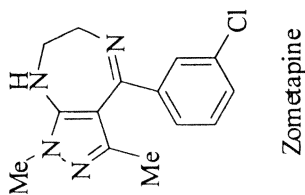
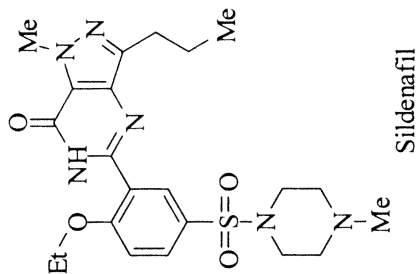
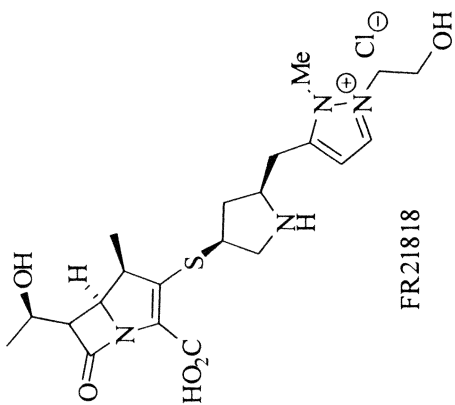
Synthesis of fluorinated pyrazoles

In the past few years, interest in pyrazole derivatives has increased due to their proven usefulness as intermediates in the preparation of new biological materials. The pyrazole moiety is present in many pharmacologically and agrochemically important compounds, some of which have been found to inhibit HIV-1 reverse transcriptase (3), the sodium hydrogen ion exchanger NHE-1 (4), or dipeptidyl peptidase IV (DPP-IV) (5). Others act as antagonists of the $\alpha_v\beta_3$ receptor present on the surface of many tumor cells (6) and as insecticides (7). In particular, the *N*-methylpyrazole unit forms part of several well-known pharmaceuticals (e.g. the antidepressant *Zometapine* (8), the inhibitor of type 5 cGMP phosphodiesterase *Sildenafil* (9), and the antibacterial agent *FR21818* (10)) and agrochemicals, including the pesticides *Tebufenpyrad* (11), *Tolfenpyrad* (12), *Cyanopyrafen* (13), and *Fenpyroximate* (14) (Figure 1).

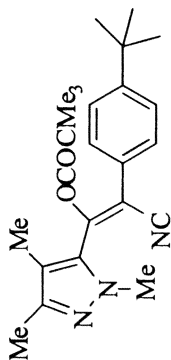
Specifically, *Tebufenpyrad* is an *N*-methylpyrazole derivative with important acaricidal activity. Acaricides play a major role in the management of the two-spotted spider mite, *Tetranychus urticae* Koch, which causes significant yield losses in many field and greenhouse crops worldwide. Numerous chemical pesticides have been used intensively to control *T. urticae*, but the species has developed resistance to widely different classes of acaricides. This resistance to so many established compounds has resulted in a demand for new, resistant-free acaricides with novel modes of action (14).

The introduction of fluorine atoms or fluorine-containing groups into heterocyclic rings has facilitated the development of new bioactive products (15). Pyrazoles with fluoroalkyl groups (Figure 2) are especially interesting due to their agrochemical and pharmaceutical properties (16).

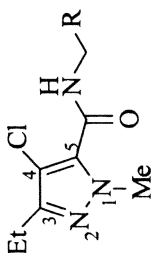
The aim of our work was to prepare fluorinated pyrazoles derived from *Tebufenpyrad* incorporating several different fluorinated substitution patterns (R_F) on the C-3 of the heterocyclic ring. Two different strategies were developed to take into account variations in the availability of the starting materials (Scheme 1). When $R_F = CF_3, CF_3CF_2, CH_3CF_2$ (strategy A), the fluorinated 1,3-diketones **1a-c** were either commercially available or synthesized in one step from the appropriate fluorinated esters and ketones. In contrast, when $R_F = CF_3CH_2, CHF_2CH_2, CH_2FCH_2, CH_3CHF, CF_3CHF$ (strategy B), ethyl 4-(2-furyl)-2,3-dioxabutanoate **2** was used as the 1,3-dicarbonylic system; the fluorine atoms were incorporated at a later stage of the sequence.

Pharmaceuticals

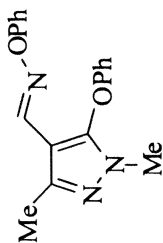
Agrochemicals



Cyanopyrafen



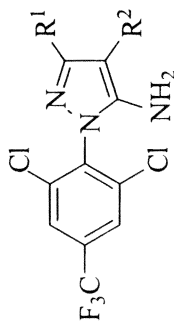
R = *p*-*t*-BuC₆H₄ (Tebufenpyrad)
R = 4-C₆H₄-O-(4-Me)C₆H₄ (Tolfenpyrad)



Fenpyroximate

Figure 1. *N*-Methylpyrazole derivatives as pharmaceuticals and agrochemicals.

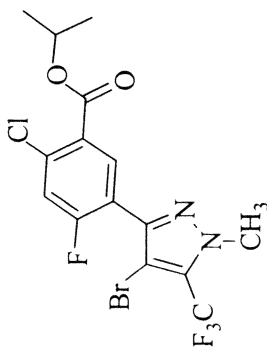
Agrochemicals



$R^1 = \text{COCH}_3$; $R^2 = \text{SOCH}_3$ Acetoprole
(acaricide, insecticide, nematocide)

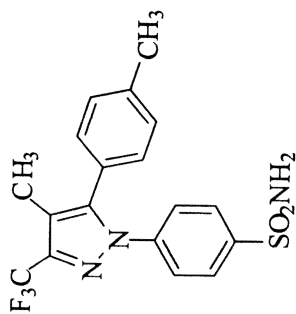
$R^1 = \text{CN}$; $R^2 = \text{SOCF}_3$ Fipronil
(acaricide, insecticide)

$R^1 = \text{CN}$; $R^2 = \text{SOCH}_2\text{CH}_3$ Ethiprole
(acaricide, insecticide)

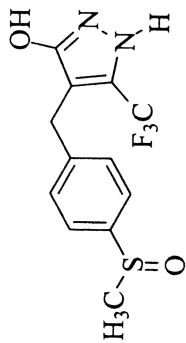


Isopropozol
(herbicide)

Pharmaceuticals

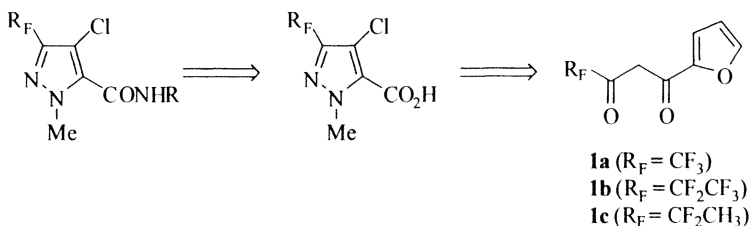
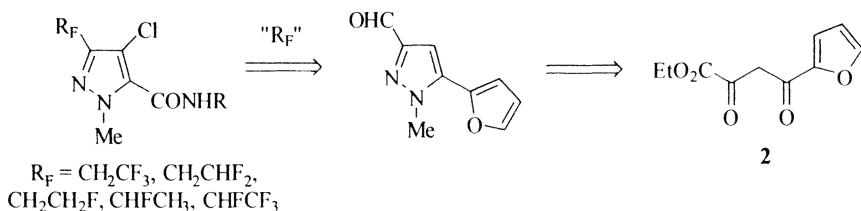


Celecoxib
(antiinflammatory)



Antihyperglycemic agent

Figure 2. Fluorinated pyrazole derivatives as agrochemicals and pharmaceuticals.

Strategy A**Strategy B**

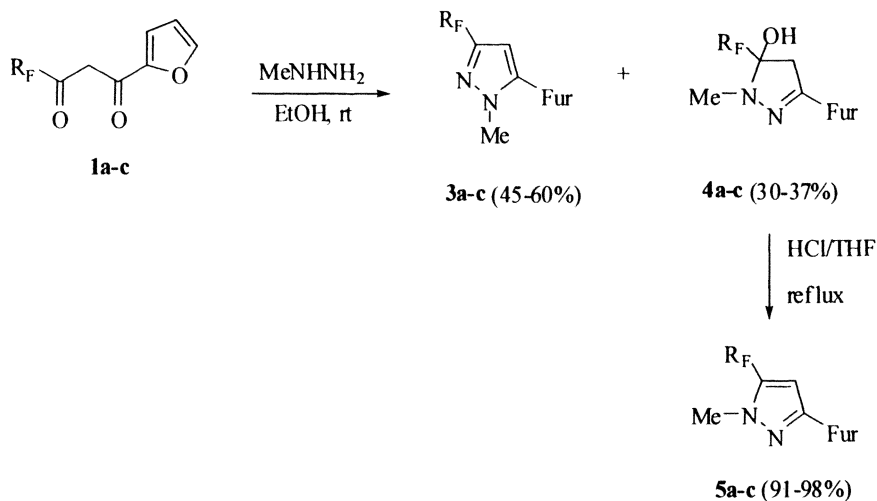
Scheme 1. Synthetic strategies for the preparation of fluorinated analogues of Tebufenpyrad.

A common synthetic method for forming the *N*-methylpyrazole ring entails the cyclocondensation of an appropriate 1,3-diketone with methylhydrazine in ethanol as solvent. However, this method has serious limitations in the synthesis of substituted *N*-methylpyrazoles as it leads to the formation of a mixture of the 3- and 5-regioisomers. Thus, in the reaction of fluorinated 1,3-diketones **1a-c** with methylhydrazine in ethanol at room temperature, mixtures of the targeted 5-furylpyrazoles **3a-c** as major products and hydroxydihydropyrazoles **4a-c** were obtained. Both were easily separated by means of flash chromatography and **4a-c** were subsequently converted in good yields into the corresponding 3-furylpyrazoles **5a-c** through treatment with HCl in THF (Scheme 2).

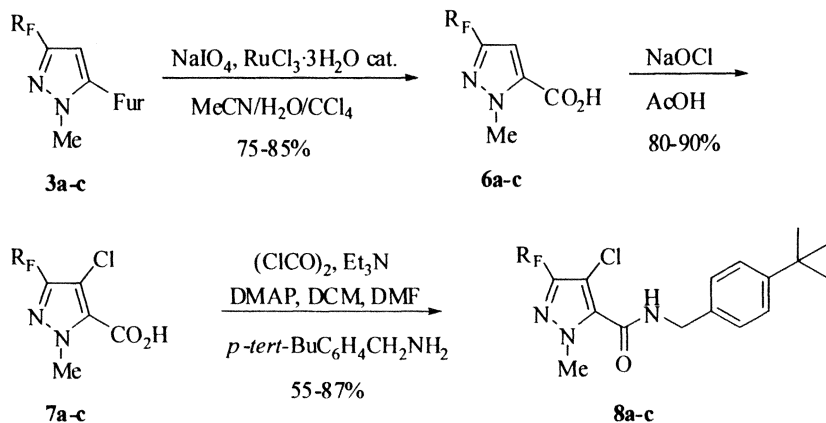
5-Furylpyrazoles **3a-c** were then transformed into the carboxylic acids **6a-c** in good yields through oxidation of the furyl ring (Scheme 3). The next step involved the C-4 chlorination to derivatives **7a-c** and, finally, the formation of the amides **8a-c** under standard conditions.

Starting with the 1,3-diketone **2**, the reaction with methylhydrazine in ethanol at room temperature afforded an almost 1:1 mixture of the two 5-furyl **9** and 3-furyl **10** regioisomers, which were easily separated by means of flash chromatography (Scheme 4).

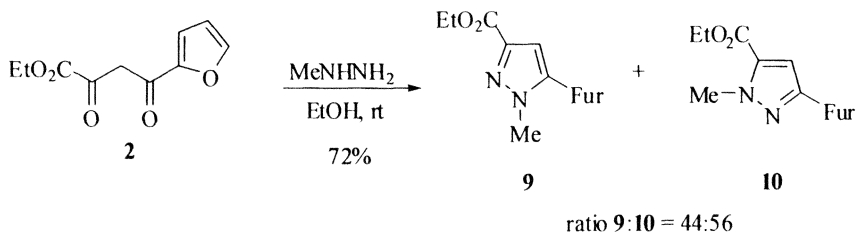
Still, the formation of mixtures of regioisomers seriously limits the usefulness of this process (17). A variant of the general method for the synthesis



Scheme 2. Reaction of fluorinated 1,3-diketones (**1a-c**) with methylhydrazine.



Scheme 3. Synthesis of the amides (**8a-c**), analogues to Tebufenpyrad.



Scheme 4. Reaction of ethyl 4-(2-furyl)-2,3-dioxabutanate(2) with methylhydrazine.

of *N*-methylpyrazoles described above is a two-step process with hydrazine, which first provides the *N*-H pyrazole, which then is subjected to methylation with methyl iodide or dimethyl sulfate. It had been previously found (17) that *N*-methylation of a 3-trifluoromethyl-5-arylpyrazole derivative with methyl iodide under basic conditions afforded a 30:70 mixture of two regioisomers in favor of the unwanted 3-furyl derivative, and that if the methylation reaction was carried out with dimethyl sulfate, the ratio increased to 4:96. In an effort to find simple regioselective routes toward the 5-furyl isomer **9**, we thus carried out the cyclocondensation reaction using a fluorinated solvent instead of ethanol.

Fluorinated solvents, in particular fluorinated alcohols, are known to be useful in organic synthesis as media for selective and clean reactions. This is because the presence of fluoroalkyl groups endows fluorinated alcohols with specific properties that their non-fluorinated counterparts do not share. The electron withdrawing character of CF_3 , for example, confers high acidity to the hydrogen of the hydroxyl group, with pK_a values of 12.4 for trifluoroethanol (TFE) and 9.3 for hexafluoroisopropanol (HFIP) ($\text{pK}_a = 15.9$ for EtOH). TFE and HFIP are polar solvents and they possess a high ionizing power: Y (TFE) = 1.80 and Y (HFIP) = 3.82; for EtOH, $\text{Y} = -1.75$. In addition, fluorinated alcohols differ from non-fluorinated alcohols and other protic solvents in that they are neither nucleophiles nor hydrogen bonding acceptors (18).

In a first assay using TFE as solvent at room temperature, **2** reacted with methylhydrazine to afford once again the mixture of 5- and 3-furyl regioisomers **9** and **10**, respectively, but in an 89:11 ratio in favor of the desired 5-furyl derivative. The regioselectivity was enhanced to a ratio of 93:7 when the condensation reaction was carried out in HFIP. Subsequent assays with two trifluoromethyl 1,3-diketones and methyl- and phenyl hydrazine confirmed the influence of the fluorinated alcohols on the regioselectivity of the reaction, especially that of HFIP, with which the 5-arylpyrazole derivatives were obtained almost exclusively in all cases. The results are summarized in Table 1. Although the reasons for this selectivity are not totally clear, it is likely that the fluorinated solvents, because of their high hydrogen bonding donor ability and low nucleophilicity, considerably increase the electrophilicity of the carbonyl group that contains withdrawing groups as substituents.

Table 1. Results for the reaction of *N*-methyl and *N*-phenylhydrazine with 1,3-dicarbonyl derivatives in EtOH, TFE and HFIP.

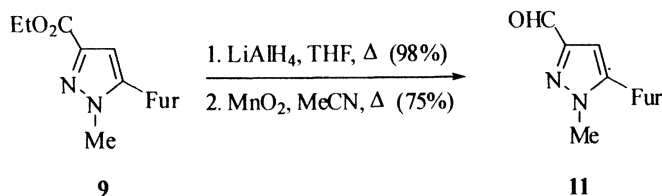
Reaction scheme: 1,3-dicarbonyl compound (2) + R²NHNH₂ → Pyrazole I + Pyrazole II (72-95% yield, solvent, rt, 1h)

<i>R</i> ¹ / <i>Ar</i>	<i>R</i> ²	Solvent / <i>I:II</i> ratio ^a		
		EtOH	TFE ^b	HFIP ^c
CF ₃ / Furyl	Me	36:64	85:15	97:3
	Ph	48:52	87:13	97:3
CF ₃ / Phenyl	Me	36:64	79:21	92:8
	Ph	24:76	81:19	>99:1
CO ₂ Et / Furyl	Me	44:56	89:11	93:7
	Ph	49:51	89:11	96:4

^a Ratios measured by means of GC and/or ¹⁹F NMR. ^b TFE = 2,2,2-trifluoroethanol.

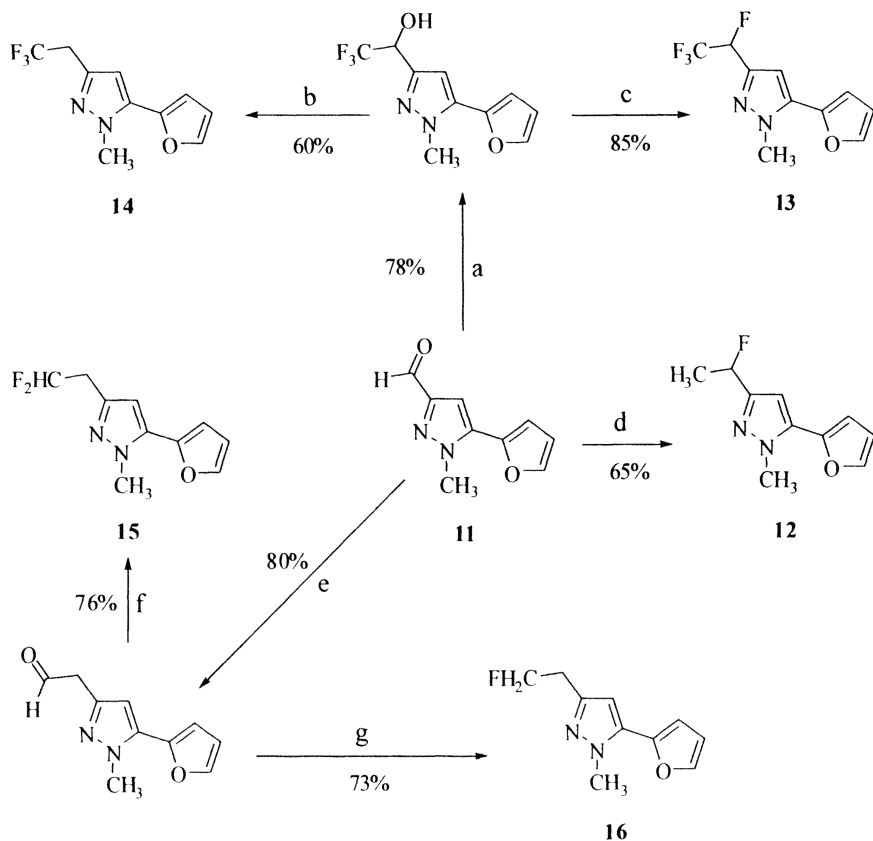
^c HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

3-(Ethoxycarbonyl)-5-(2-furyl)-*N*-methylpyrazole **9** was then converted into aldehyde **11** through a two-step sequence involving LiAlH₄ reduction to the corresponding alcohol and subsequent oxidization with MnO₂ (Scheme 5).



Scheme 5. Preparation of 3-formyl-5-(2-furyl)- N-methylpyrazole (11).

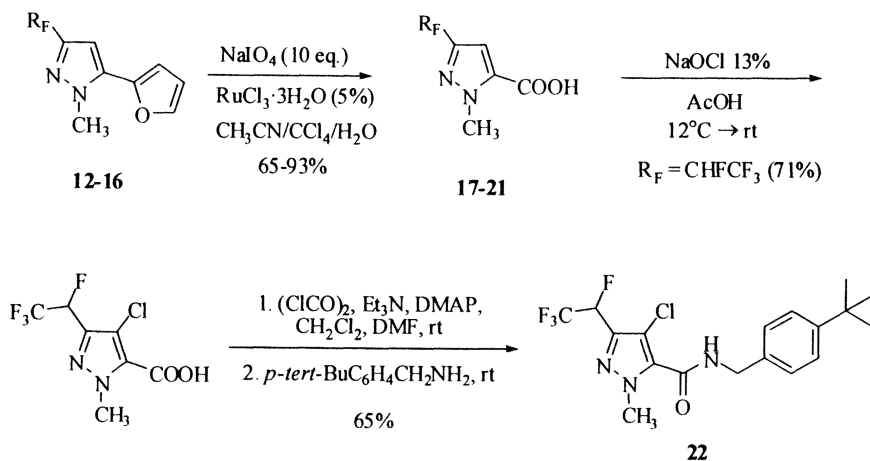
This compound constitutes the starting point for obtaining the other fluorinated analogs of *Tebufenpyrad* (Scheme 6). Reaction of **11** with MeMgBr followed by treatment with Deoxofluor afforded the monofluorinated derivative **12** (R_F = CH₃CHF). Treatment of **11** with Ruppert-Prakash's reagent (CF₃SiMe₃) followed by reaction with Deoxofluor or dehydroxylation provided the tetrafluorinated and trifluorinated derivatives **13** (R_F = CF₃CHF) and **14** (R_F = CF₃CH₂), respectively. Homologation of **11** followed by treatment with Deoxofluor, or previous reduction of the homologue aldehyde and subsequent treatment with Deoxofluor, afforded the di- and monofluorinated derivatives **15** (R_F = CHF₂CH₂) and **16** (R_F = CH₂FCH₂), respectively.



(a) i) CF_3SiMe_3 , THF, TBAF cat., rt. ii) HCl, H_2O . (b) i) PhOCSCl , DMAP, Tol, $50\text{--}60^\circ\text{C}$. ii) Bu_3SnH , AIBN cat., Tol, 80°C . (c) Deoxofluor®, CH_2Cl_2 , rt. (d) i) MeMgBr , THF, 0°C . ii) Deoxofluor®, CH_2Cl_2 , rt. (e) i) $\text{MeOCH}=\text{PPh}_2$, NaHMDS, THF, rt. ii) 12N HCl, CH_2Cl_2 , rt. (f) Deoxofluor®, CH_2Cl_2 , rt. (g) i) NaBH_4 , MeOH, 0°C to rt. ii) Deoxofluor®, CH_2Cl_2 , rt.

Scheme 6. Synthesis of fluorinated *N*-methylpyrazoles (12-16).

Subsequent oxidation of the furyl ring of **12-16** under the same conditions described above provided the corresponding carboxylic acids **17-21** in good yields. However, the next step, which involved the chlorination of the C-4 of the pyrazole ring, presented several difficulties. For example, while the reaction was successful with carboxylic acid **18** ($\text{R}_\text{F} = \text{CF}_3\text{CHF}$), eventually providing the targeted amide **22** (Scheme 7), in all other cases and under various reaction conditions, only complex mixtures were obtained.

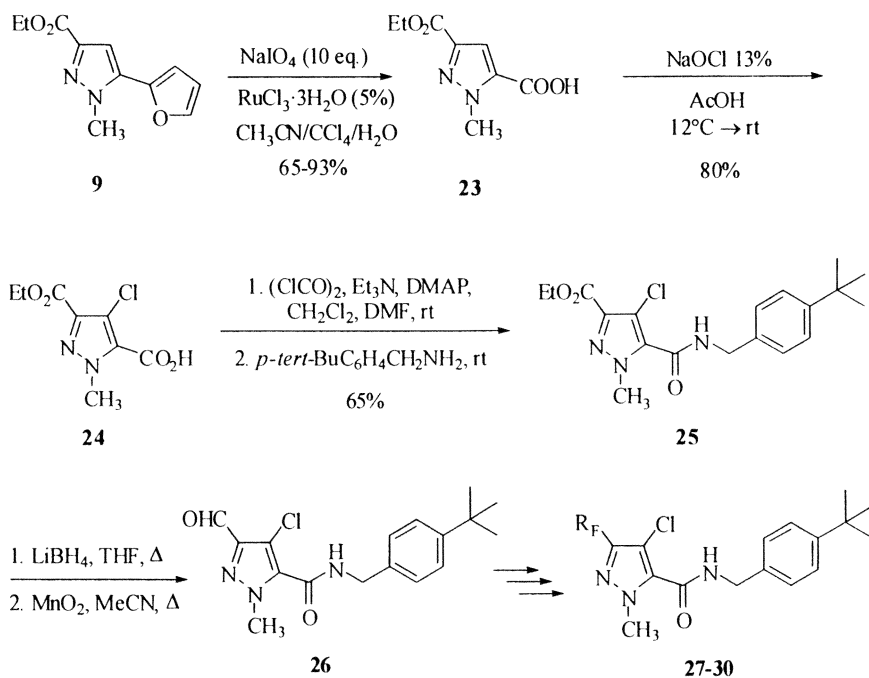


Scheme 7. Preparation of carboxylic acids (17-21) and synthesis of the fluorinated analogue of Tebufenpyrad (22)

To avoid this inconvenience, we changed our strategy slightly and performed the chlorination at an earlier stage. The furyl ring of 3-(ethoxycarbonyl)-5-(2-furyl)-*N*-methylpyrazole **9** was thus oxidized in high yield and the resulting carboxylic acid **23** was successfully chlorinated (Scheme 8). Conversion of **24** into the amide **25** occurred after chemoselective reduction of the ester group; subsequent oxidation afforded the aldehyde **26** in good yield. This compound, in turn, constituted the starting point for obtaining the targeted molecules. The subsequent steps are similar to those previously described and provided the fluorinated analogues of *Tebufenpyrad* **27-30**. Fluorinated amides **8a-c**, **22**, and **27-30** were all tested on *Tetranychus urticae* Koch to evaluate their potential acaricidal activity with preliminary results showing interesting activity for several of them (19).

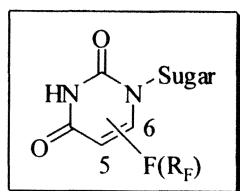
Uracils, in particular those with fluorine or fluorinated groups at positions 5 or 6 on the ring, represent another class of compounds with interesting biological properties. Derivatives in which the substituent appears on C-5 have proven to be useful drugs, the most notable being the well known antitumorals 5-fluorouracil and gemcitabine, along with the antiviral trifluridine (20). In contrast, derivatives with C-6 fluorinated substituents, particularly CF₃ derivatives, are commonly used as agrochemicals, especially as herbicides, insecticides, and acaricides (Figure 3) (21).

One of the most common methods for the preparation of fluorinated uracils involves the reaction between carbamates or isocyanates with the CF₃ β-amino ester as depicted in Scheme 9. Several *N*-3 substituted uracils have been prepared in this way and used as agrochemicals. Our group has long been

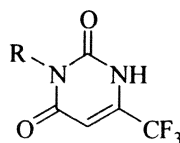


Scheme 8. Synthesis of fluorinated analogues of Tebufenpyrad (27-30).

Synthesis of fluorinated uracils



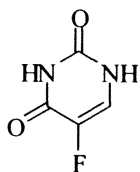
Fluorinated uracils



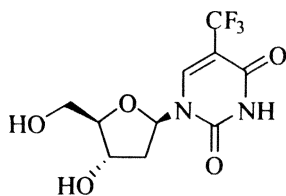
Agrochemicals

C-6 CF₃-Uracils

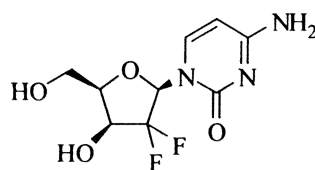
R = Ar, CH₂Ar, CH₂CH₂X



5-Fluorouracil



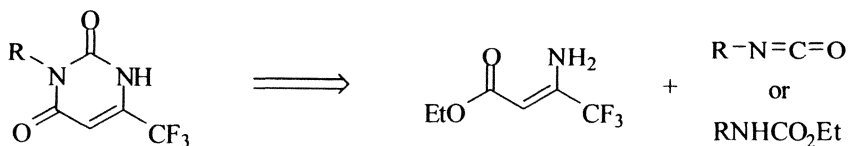
Trifludine



Gemcitabine

Figure 3. Examples of fluorinated uracils.

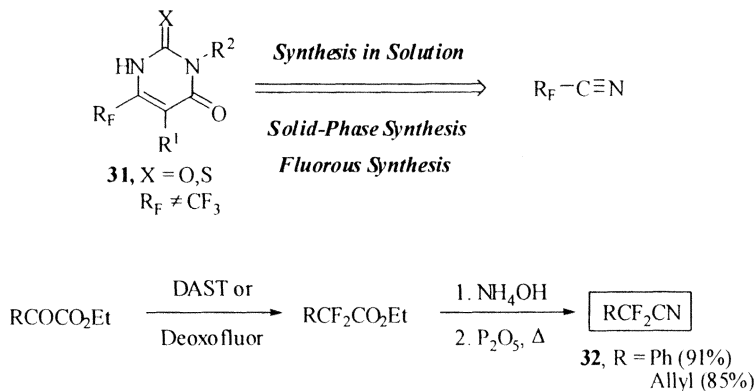
General Synthesis



Scheme 9. General synthetic approach to uracils.

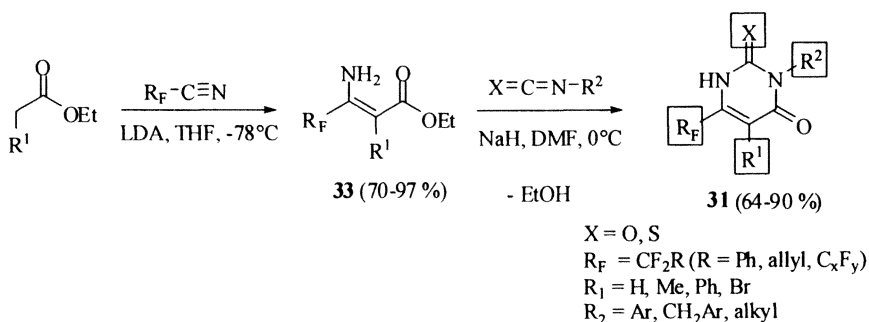
interested in the development of new strategies for the synthesis of this type of compounds, and we have now extended this methodology to the synthesis of derivatives other than those with a CF_3 group.

We have developed two complementary strategies for the preparation of C-6 fluorinated substituted uracils and thiouracils **31**. Both methodologies were initially developed in solution, but one was later adapted to solid phase and fluorous techniques. The starting materials for both syntheses are fluorinated nitriles **32**, which contain a CF_2 group in the α position. These starting nitriles can be easily prepared through initial treatment of α -keto esters with DAST or, for better results, with Deoxofluor (22), to produce difluorinated esters (Scheme 10). These are then converted into the desired nitriles **32** through standard procedures. We have thus been able to prepare several CF_2 aromatic and aliphatic nitriles in good yields (Scheme 10) (23,24).



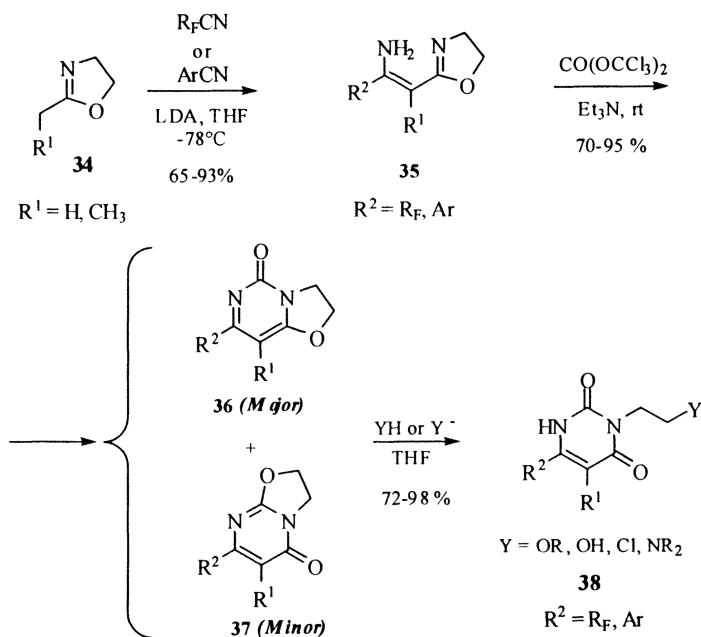
Scheme 10. Fluorinated nitriles as starting materials for the preparation of fluorinated uracils.

The first strategy for the preparation of C-6 fluorinated substituted uracils and thiouracils in solution uses esters and fluorinated nitriles as starting materials. These are first converted into β -enamino esters **33** in excellent yields through condensation with ester enolates (Scheme 11). These β -enamino esters are then converted into fluorinated uracils and thiouracils by means of reaction with isocyanates and isothiocyanates in the presence of sodium hydride and DMF as solvent. The process appears to be general and works well on a multigram scale. We were thus able to obtain a significant number of examples with several different R^1 , R^2 , R_F , and X groups (25). The possibility of introducing structural diversity in these positions, together with the excellent yields in the intermediate steps, make this synthesis suitable for solid phase and fluorous synthesis, as can be seen below. Indeed, the only limitation we found



Scheme 11. First strategy for the preparation of C-6 fluoroalkyl uracils.

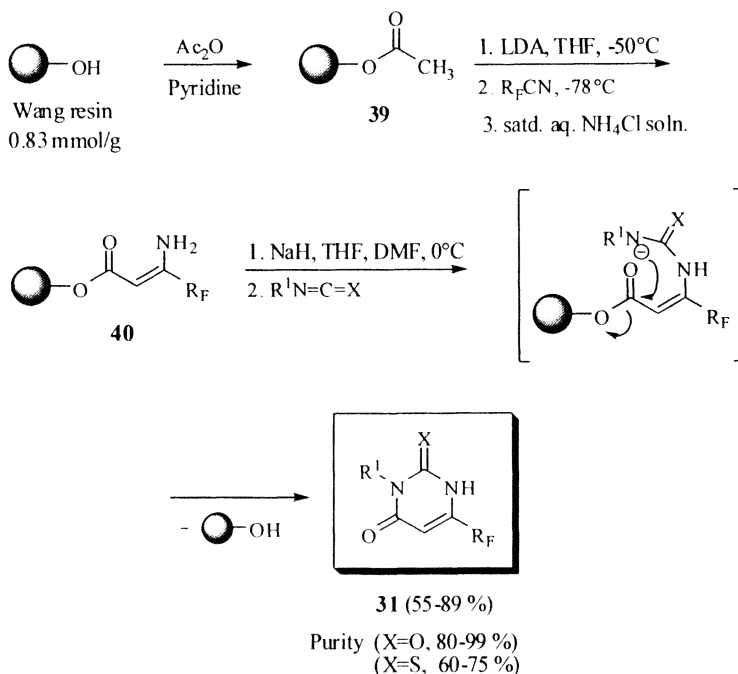
with this procedure appeared when R² was a CH₂CH₂Y substituent. In this case, the desired fluorinated uracils could not be prepared. Because this class of compounds generally has interesting biological properties and offers many possibilities for introducing different functionalities in the N-3 position, we decided to develop a different, more specific strategy for obtaining them (Scheme 12).



Scheme 12. Second strategy for the preparation of C-6 fluoroalkyl uracils.

In our second approach, we used oxazolines **34** as starting materials, reacting them with fluorinated nitriles **32** to furnish β -enamino oxazolines **35** in good yields. These compounds were then reacted with triphosgene to afford a mixture of isomeric oxazolopyrimidinones **36** and **37**, which were easily separated by means of flash chromatography. Both compounds were identified through X-ray diffraction analysis. Finally, **36** and/or **37** (separately or as a mixture) were reacted with different nucleophiles to afford the desired uracils **38** in good yields (Scheme 12) (26). The key step for this synthesis was the opening of the oxazoline ring by means of a nucleophile.

As mentioned above, our first method for synthesizing fluorinated uracils allows for the introduction of diversity in four different positions, which makes it suitable for the preparation of small chemical libraries. With this purpose in mind, we decided to adapt our procedure to solid-phase techniques using the approach given in Scheme 13. First, acetic anhydride was coupled with Wang resin to afford the acetate ester **39**. This resin-bound ester reacted first with LDA and then with fluorinated nitriles to yield the corresponding enamino esters **40**, which were then converted into uracils **31** after treatment with sodium hydride and isocyanates. In this process, the targeted uracils and thiouracils were obtained directly after cyclization-cleavage from the resin and, in general, in high yields and purities (Scheme 13) (25).



Scheme 13. Solid-phase synthesis of C-6 fluoroalkyl uracils.

Figure 4 shows a small library of uracil and thiouracil derivatives that was prepared with the aid of solid-phase methodology with the procedure described above. Both yields and purities (in parentheses) are shown. Although both are, in general, high for uracil derivatives, they are only moderate in the case of thiouracils, as indicated in the corresponding examples.

Once we had successfully adapted the uracil synthesis to solid-phase techniques, our next challenge was to extend this methodology to fluorous synthesis (27) in order to prepare small libraries of fluorinated uracils and thiouracils in a simple and efficient manner (28). This would also give us the opportunity to compare the solid-phase and fluorous methodologies. Following the same strategy as before, we first tried to prepare the tagged β -enamino esters

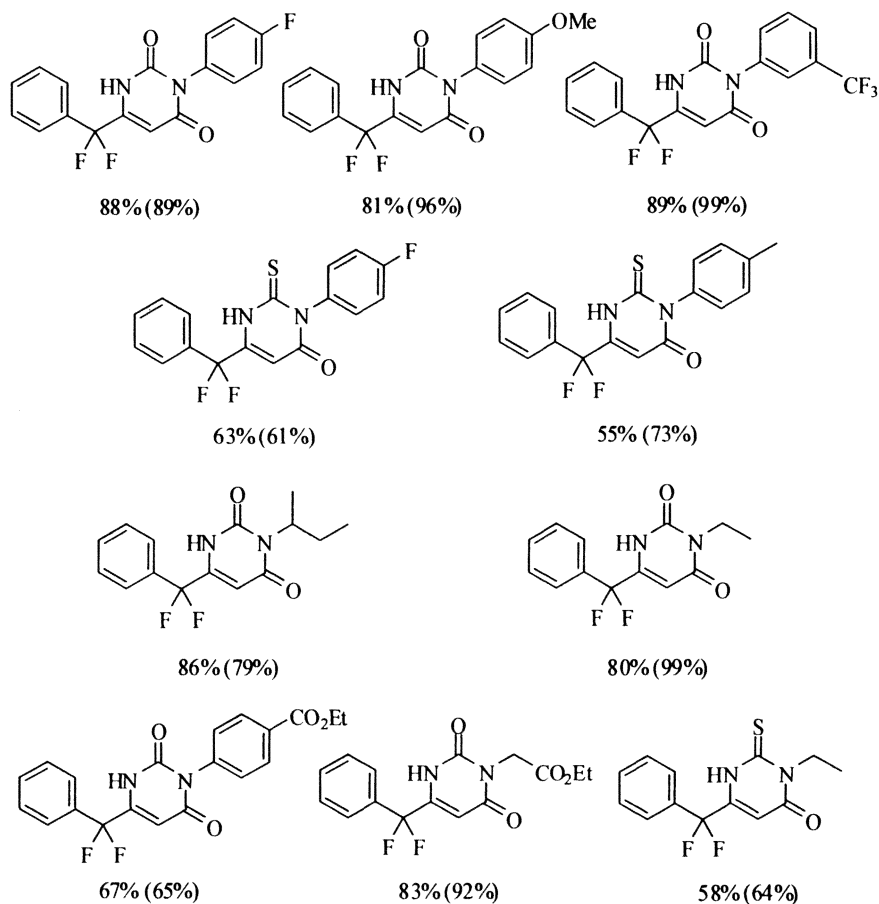


Figure 4. A small library of fluorinated uracils prepared by means of solid-phase synthesis. Both yields and purities (in parentheses) are shown.

41 as shown in Scheme 14. The actual synthesis begins with the preparation of the starting fluororous ester **42**. To this end, fluororous alcohol **43** was acetylated with acetic anhydride, triethylamine, and DMAP to afford the desired ester **42** in 60% yield.

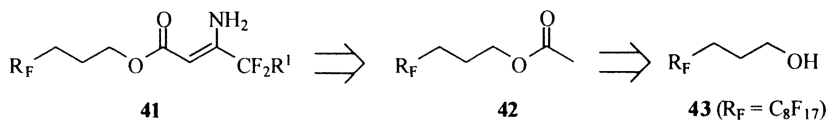
Surprisingly, and in stark contrast with our previous experience, the condensation of ester **42** with fluorinated nitriles **32** was difficult to achieve. While this reaction, which constitutes the key step of the process, takes place easily in solution and on solid-phase, it proved to be very elusive in the fluororous version. Thus, when the previously applied conditions were employed to generate the enolate of fluororous esters **42**, only the corresponding starting alcohols **43** were obtained, with no trace of the desired β -enamino ester **41**.

The deacetylation process may occur *via* ketene formation once the ester enolate is formed, as shown in Scheme 15. This would suggest that the fluororous chain imparts an unexpected reactivity to fluororous esters **42**.

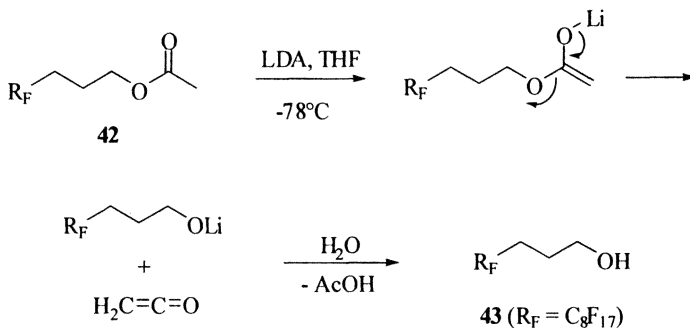
A study with several different solvents, bases, temperatures, and other variables was carried out in order to optimize the reaction conditions for the preparation of the tagged β -enamino esters **41**. When the enolate was generated with a base and followed by a subsequent addition of the nitrile, the reaction did not furnish the desired β -enamino esters **41**; instead, only the fluororous alcohol **43** was recovered. In contrast, when sodium bis(trimethylsilyl)amide was used as a base at 0 °C in fluororous solvents such as perfluorobutyl methyl ether and especially benzotrifluoride (BTF), and when the addition was a Barbier-type, with the base being added to the nitrile, **41** was produced in satisfactory yields (Scheme 16). Once these tagged β -enamino esters **41** had been prepared, the final step of the synthetic sequence consisted of their reaction with sodium hydride in DMF, followed by addition of the corresponding aliphatic and aromatic isocyanates and isothiocyanates at 0 °C (Scheme 16).

The desired uracils **4** were thus obtained in good yields and purities and with concomitant elimination of the fluororous tag. The fluororous tag can be easily removed from the reaction mixture through fluororous solid phase extraction (FSPE) and successfully recovered in 60-80% yield. Figure 5 shows a small library of the uracils and thiouracils **31** (18 examples) obtained through fluororous synthesis.

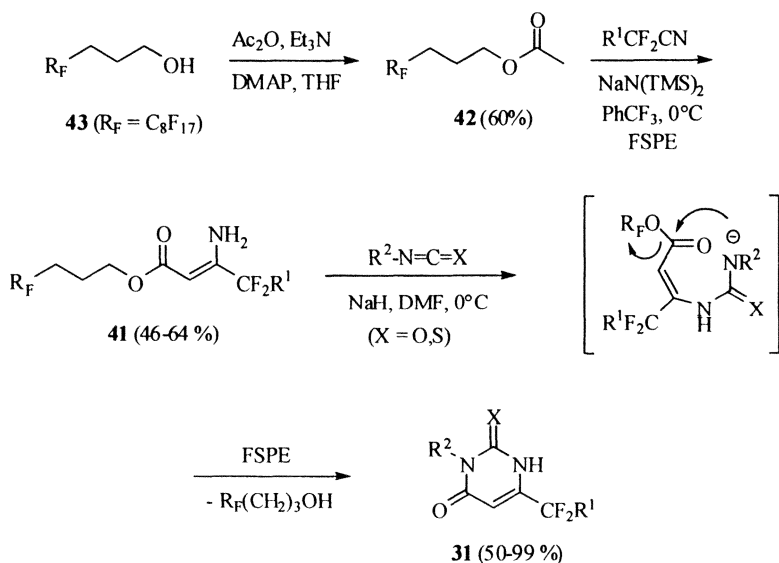
When all three methods for the preparation of fluorinated uracils **31** are compared, it is clear that while fluororous and solution syntheses produce similar yields and have similar reaction times (approx. 2 hours), the separations are considerably faster and easier with the fluororous technique. As for solid phase synthesis, while the ease of purification and the obtained yields are comparable with those of fluororous synthesis, the kinetics of the solid-phase reactions are much less favorable, as considerably longer reaction times are required (15 hours) and a twofold excess of nitrile (3 or more equivalents) is needed to complete them. This is clearly unfavorable, as nitrile is by far the most expensive reagent in this synthesis.



*Scheme 14. Retrosynthetic analysis for the fluororous synthesis of β -enamino esters **41**.*



Scheme 15. Initial difficulties in the generation of a fluororous ester enolate.



Scheme 16. Fluororous synthesis of fluorinated uracils.

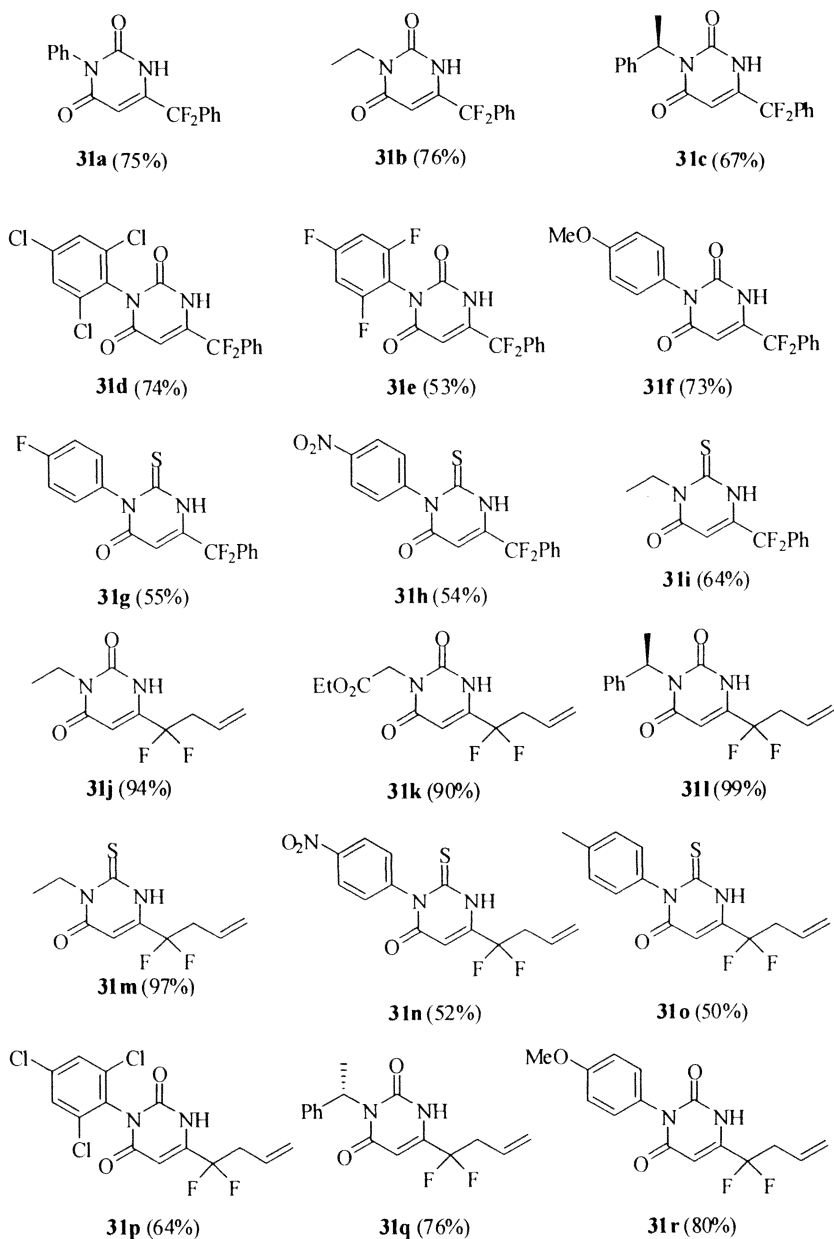
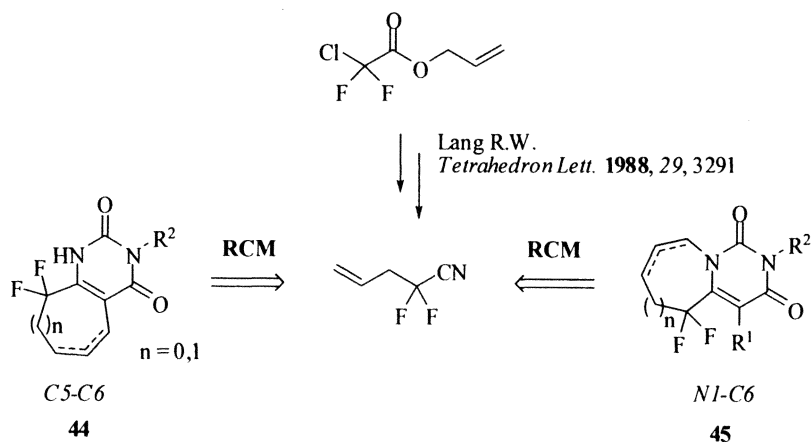


Figure 5. A small library of fluorinated uracils prepared by means of fluororous synthesis. Yields are shown in parentheses.

We also tested the acaricidal activity against *Tetranychus urticae* of more than 30 fluorinated uracils and thiouracils and compared it with that of Tebufenpyrad. Some of the compounds show an acaricidal activity similar or even slightly better than that of the commercially available product, while their *acute oral toxicity* in mice is considerably lower than that of Tebufenpyrad (19).

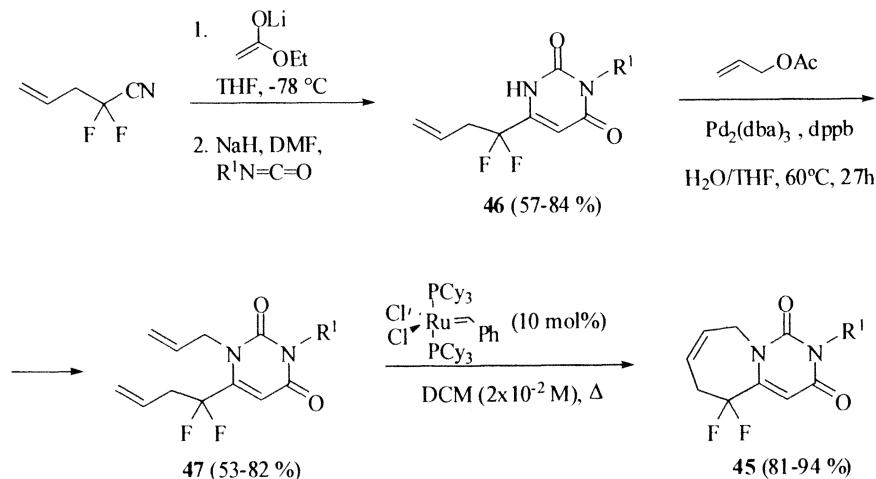
Yet another synthetic strategy allowed us to prepare two new families of fused bicyclic fluorinated uracil derivatives **44** and **45** (Scheme 17) (29). The starting material for these syntheses was α,α -difluoro-4-pentenitrile, which was prepared from commercially available allyl chlorodifluoroacetate in accordance with Lang's method (30). In both cases the key step of the process was a ring-closing metathesis reaction (Scheme 17) (31).



Scheme 17. Synthetic strategy for the preparation of bicyclic uracils with an RCM reaction as the key step.

The strategy that we used for the synthesis of the N1-C6 bicyclic fluorinated uracils **45** is shown in Scheme 18. α,α -Difluoro-4-pentenitrile reacted with ester enolates at -78°C to afford intermediate β -enaminoesters **46**, which could then be reacted with several isocyanates in the presence of sodium hydride in DMF-THF as solvent. In this way, several intermediate uracils **47** were prepared in good yields.

The synthetic strategy for the preparation of these compounds requires the introduction of an allyl group into the uracil NH group. We discovered that the use of allyl acetate as alkylating agent in the presence of Pd(0) as catalyst provided the best results, affording the N-allyl derivatives **47** as the only reaction products and in good yields. Finally, these dienes reacted with the first generation Grubbs catalyst to afford the bicyclic seven-membered derivatives **45** in excellent yields.

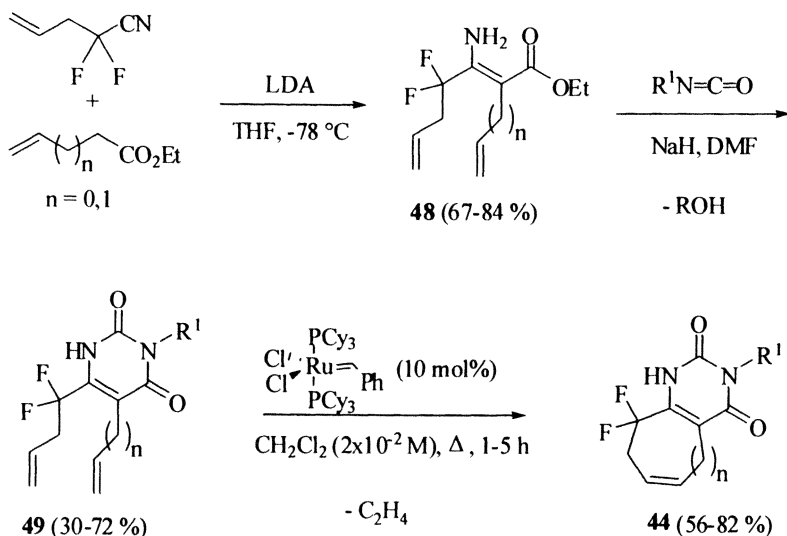


Scheme 18. Synthesis of N1-C6 fused bicyclic uracils.

A slightly different strategy was used for the synthesis of the C5-C6 fused bicyclic uracils **44** (Scheme 19), for which alkenoic esters and α,α -difluoro-4-pentenitrile served as the starting materials. The reaction of pentenoic and butenoic ester enolates with this nitrile initially provided β -enamino esters **48**, which then reacted with isocyanates to afford C5-C6 disubstituted uracils **49** in variable yields. These uracils were in turn transformed into the new family of fused bicyclic six- and seven-membered uracils **44** by means of treatment with first generation Grubbs catalyst under the same conditions as described above, also in good yields (Scheme 19).

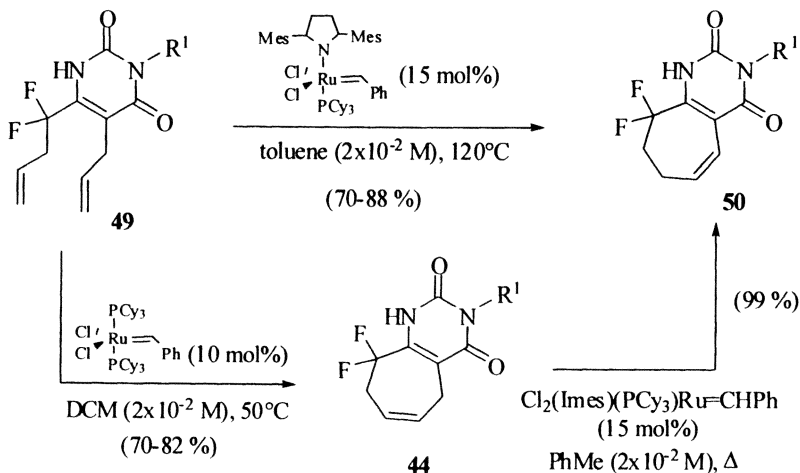
With these new bicyclic fluorinated uracils in hand, we next focused our attention on the preparation of new isomeric uracils **50** by applying a tandem RCM-isomerization sequence (Scheme 20). When the reaction of the acyclic uracils **49** was performed with the second generation Grubbs catalyst in refluxing toluene and subjected to a tandem RCM-isomerization sequence, we regioselectively obtained the isomeric fused bicyclic seven-membered uracils **50** as the only product and in good yields (Scheme 20). It is also possible to obtain these compounds in a two-step sequence, as shown in Scheme 20: the first generation catalyst provides the expected bicyclic uracils **44** and the second generation catalyst, at high temperature and in toluene, acts as a ruthenium hydride, causing complete isomerization to afford **50** in very high yields.

We were thus able to prepare a small library of two different families of fused bicyclic fluorinated uracils using a very simple methodology (Figure 6). In this process, the synthetic utility of the tandem RCM-isomerization sequence was amply demonstrated.



Scheme 19. Synthesis of C5-C6 fused bicyclic uracils.

Tandem RCM-Isomerization



Scheme 20. Tandem RCM-Isomerization.

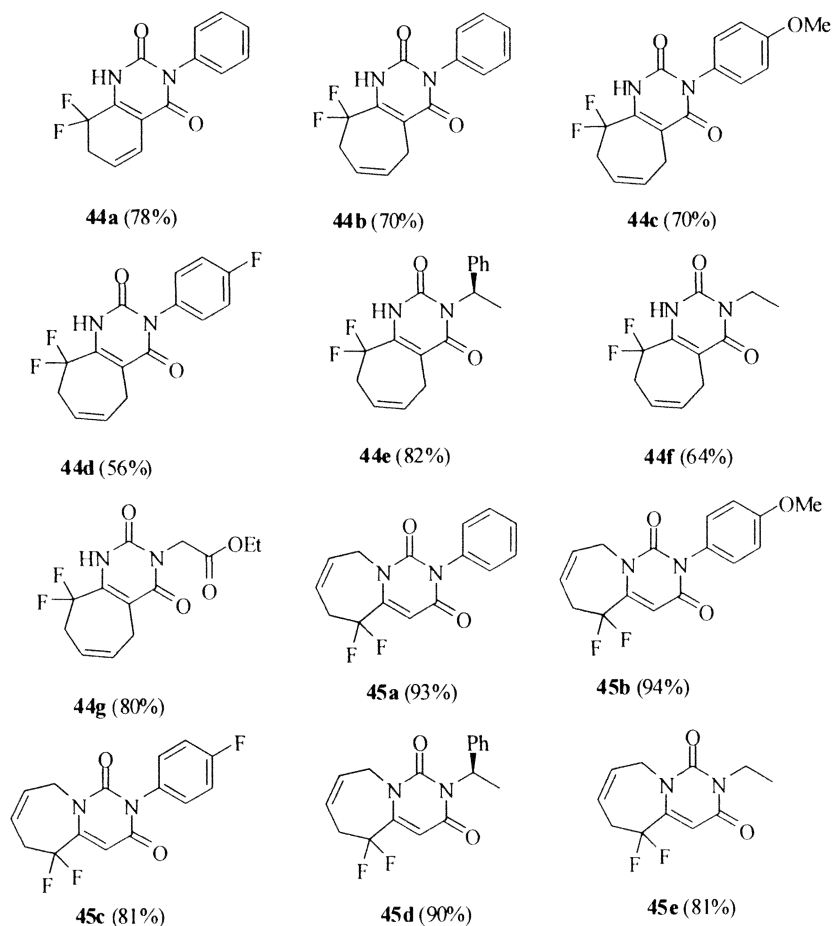


Figure 6. A small library of bicyclic fluorinated uracils prepared by means of fluorous synthesis. Yields for the RCM reactions are indicated in parentheses.

We then went on to test the acaricidal activity of these new families of uracils and their precursors against *Tetranychus urticae*. Preliminary results showed that the best results for these compounds were slightly inferior than those for Tebufenpyrad.

Conclusions

In summary, we have developed a simple strategy for the preparation of fluorinated derivatives of Tebufenpyrad, some of which have shown promising

activity as acaricides. We have also described two new synthetic approaches to fluorinated uracils. One of them has been adapted to solid-phase and fluororous methodologies, thus allowing for the preparation of small libraries of these compounds, some of which also display acaricidal activity.

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Chapter 10

Reactivity and Selectivity of F₂ Toward 3,4,6-Tri-*O*-acetyl-D-Glucal in Anhydrous HF: Synthesis of [¹⁸F]2-Fluoro-2-deoxy-β-D-allose and Its Use for the Detection of a Breast Tumor

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Because of growing interest in the biological properties of D-allose, its ¹⁸F-labeled analogue, [¹⁸F]2-fluoro-2-deoxy-β-D-allose ([¹⁸F]2-FDβA), was synthesized to probe its biological activity. A fast and efficient two-step, regio-, and stereoselective synthesis of [¹⁸F]2-FDβA was achieved by electrophilic fluorination of 3,4,6-tri-*O*-acetyl-D-glucal in anhydrous HF using [¹⁸F]F₂ and [¹⁸F]CH₃COOF. The fluorocarbohydrate was characterized by multi-NMR spectroscopy and mass spectrometry. Small animal PET imaging was used to study the *in vivo* behavior of [¹⁸F]2-FDβA. Preliminary studies using Polynoma Middle T mice showed that [¹⁸F]2-FDβA is a promising radiotracer for the detection of breast tumors.

Introduction

Rare sugars are defined by the *International Society of Rare Sugars (ISRS)* as monosaccharides that are infrequently encountered in nature. Because of their rarity and their laborious and expensive chemical syntheses, the biological properties of rare sugars have not been investigated in detail. Recently, an effective strategy for the large-scale production of these sugars has been developed (1,2) and interest in studying their properties is rapidly growing.

Recent studies on the biological properties of one such rare sugar, D-allose (Figure 1), the C3 epimer of D-glucose, show that it provides very effective protection against neutrophil-related postischemic injury of liver tissue (3), inhibits segmented neutrophil production (4), and lowers platelet count without detrimental side effects (4). Such characteristics suggest that D-allose may be a potential therapeutic agent against cancer. Significant advances in our understanding of the biochemical behavior of D-allose can be made using its ^{18}F -labeled analogue, namely [^{18}F]2-fluoro-2-deoxy-D-allose, in conjunction with Positron Emission Tomography (PET). Deoxyfluorinated analogues allow studies of the transport and metabolism of the corresponding parent sugars and aid in isolating specific biochemical reaction sequences from general metabolic pathways, especially in the functional imaging sciences (5). For example, the ^{18}F -labeled analogue of D-glucose, [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]2-FDG), is a well-established tracer in PET that is used to measure the glucose utilization rates in normal tissue and tumors. By analogy with D-glucose and [^{18}F]2-FDG, it is anticipated that [^{18}F]2-fluoro-2-deoxy-D-allose should be an excellent tracer for the study of the *in vivo* behavior of D-allose (Figure 1). The first synthesis of 2-fluoro-2-deoxy-D-allose was reported by Johansson and Lindberg (Scheme 1) (6). Their lengthy, multi-step synthesis, however, is not suitable for the synthesis of [^{18}F]2-fluoro-2-deoxy-D-allose owing to the short half-life of ^{18}F ($t_{1/2} = 109.7$ min).

The design and synthesis of [^{18}F]2-fluoro-2-deoxy-D-allose was initially confronted by three major hurdles: [1] D-allose is a rare sugar and therefore a suitable precursor for fluorination is also scarce. [2] An efficient method for the regio- and stereospecific introduction of fluorine at C2 in D-allose is not known. [3] The successful synthesis should also be applicable to radio-labeling with ^{18}F . These challenges were overcome by the judicious application of two previously known synthetic methodologies: [1] electrophilic fluorination of 3,4,6-tri-*O*-acetyl-D-glucal (TAG) in CFCl_3 (7-10), one of the most commonly used methods for the introduction of fluorine at C2 in carbohydrate molecules that results in 2-FDG and its C2 epimer, 2-fluoro-2-deoxy-D-mannose (2-FDM) (Scheme 2); and [2] treatment of TAG with aHF (11-13), which results in epimerization at C3 (Scheme 3).

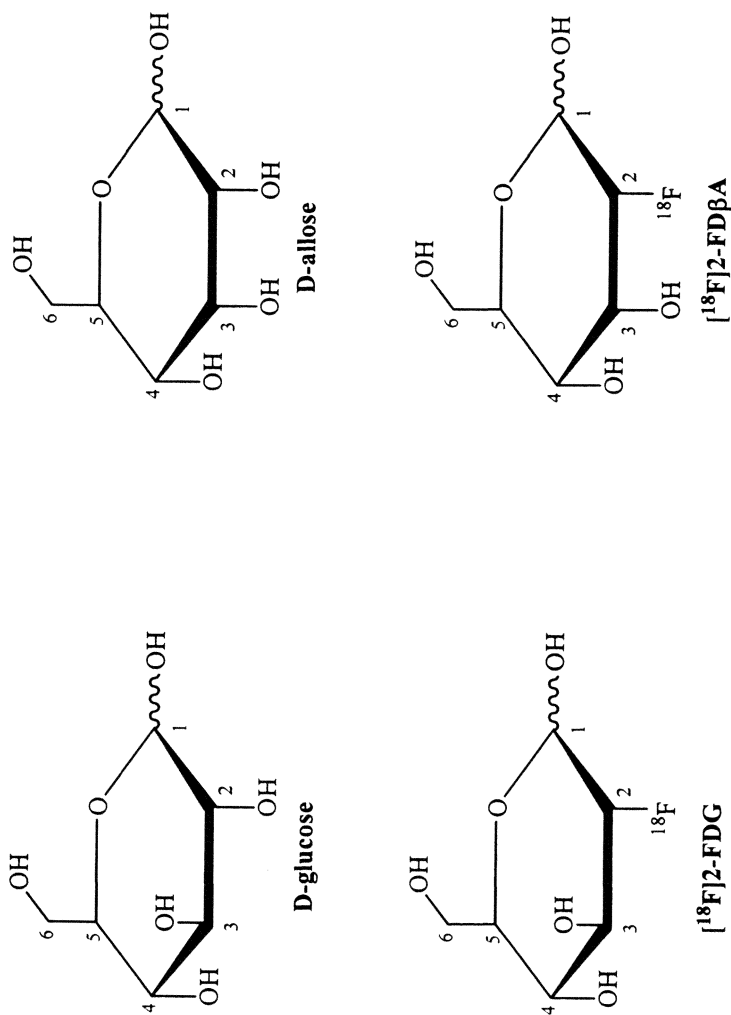
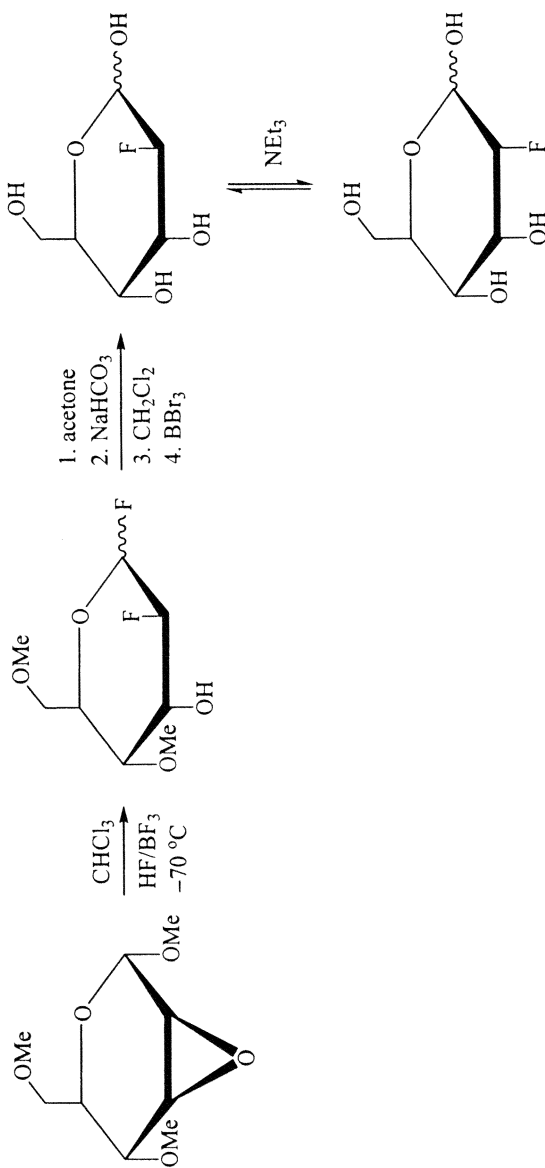
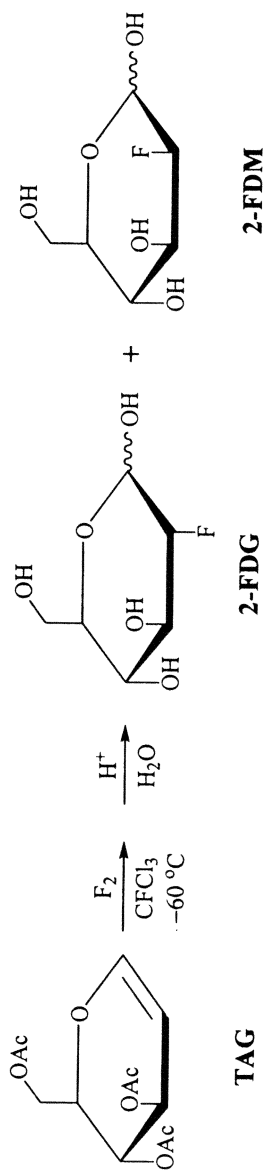


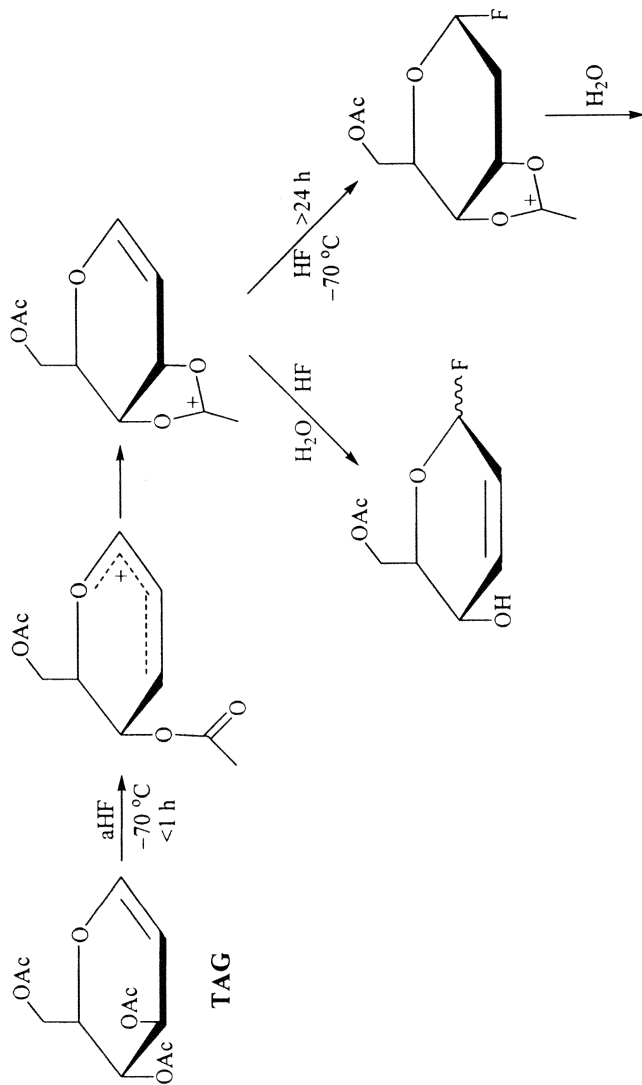
Figure 1. The structures of [¹⁸F]2-FDG, a well-established tracer for D-glucose, and [¹⁸F]2-FDβA, a potential tracer for D-allose.

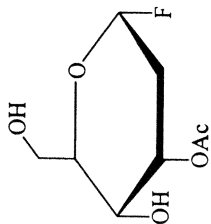


Scheme 1. The synthesis of 2-fluoro-2-deoxy-D-allose according to Johansson and Lindberg (6).



Scheme 2. Introduction of fluorine at C2 position of carbohydrate molecules by direct fluorination (7-10).





Scheme 3. Epimerization induced at C3 when TAG is reacted with aHF (12).

Such a rapid and efficient two-step synthesis of 2-(*R*)-fluoro-2-deoxy- β -D-allose (2-FD β A) by direct fluorination of TAG in aHF, that combines reaction Schemes 2 and 3, has recently been developed in our laboratory (14). The synthesis of [18 F]2-FD β A and preliminary findings relating to its implications for PET imaging are reported here.

Regio- and Stereoselective Syntheses of 2-FD β A and [18 F]2-FD β A

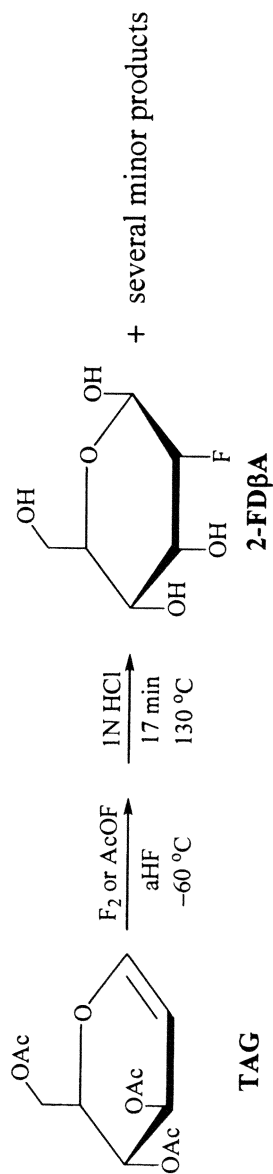
The synthesis of 2-FD β A was accomplished by electrophilic fluorination of commercially available TAG with F₂ or CH₃COOF in aHF at -60 °C, followed by acid catalyzed hydrolysis and purification using liquid chromatography (Scheme 4).

The synthesis of [18 F]2-FD β A was accomplished by electrophilic fluorination of TAG with [18 F]F₂ or [18 F]CH₃COOF in aHF according to Scheme 4. The decay-corrected radiochemical yields (RCY) in the final product solutions were 33 \pm 3 and 9 \pm 2%, respectively, with respect to [18 F]F₂. The RCY of 33 \pm 3% is excellent in view of the theoretical maximum RCY, which is 50% for electrophilic fluorinations using [18 F]F₂. The RCY is the highest achieved to date for electrophilic fluorination of TAG using [18 F]F₂ in any solvent system. This is not surprising because aHF has been shown to be an excellent solvent for the direct fluorination of organic compounds using [18 F]F₂ (15,16). It is important to note that neither [18 F]2-FDG nor [18 F]2-FDM was produced in this reaction, whereas electrophilic fluorination of TAG with [18 F]F₂ and [18 F]CH₃COOF in other solvent media reported to date result in both [18 F]2-FDG and [18 F]2-FDM (7,9,17-20). The absence of these 18 F-labeled carbohydrates is a significant feature of the reaction in the context of PET imaging because the presence of either or both contaminants would reduce the signal-to-noise ratio of the image by contributing to background noise, unnecessarily increasing the radiation dose to the patient.

Characterization of 2-FD β A

Structural Characterization by NMR Spectroscopy

The characterization of 2-FD β A by NMR spectroscopy included 1-D 1 H, 13 C, 19 F, selective 1-D 1 H, 2-D 1 H- 1 H, and 1 H- 13 C correlation spectroscopy (14). The 1 H, 13 C, and 19 F NMR spectra of the products resulting from fluorination of TAG in aHF (Figures 2-4) established that 2-FD β A was the major product. The 1 H and 13 C NMR parameters for 2-FD β A are summarized in Tables I and II, respectively.



Scheme 4. Synthesis of 2-FDβA by electrophilic fluorination of TAG in aHF (14).

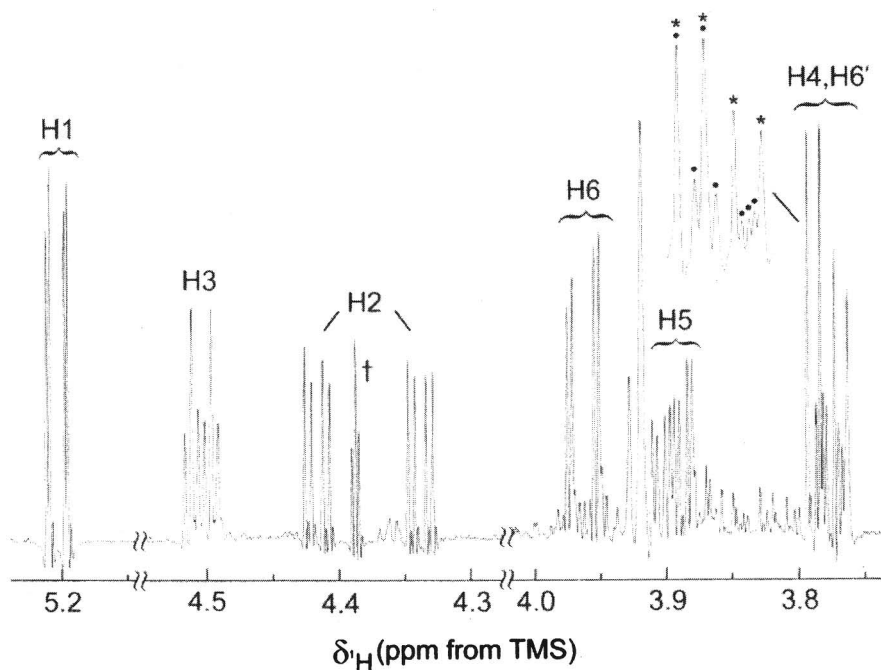


Figure 2. The ^1H NMR spectrum (D_2O solvent at 25 $^\circ\text{C}$) of the products resulting from the electrophilic fluorination of TAG in aHF. Dots (•) and asterisks (*) and denote H4 and H6' resonances, respectively. The dagger (†) denotes an unassigned "triplet" ($\delta(^1\text{H})$ 4.39 ppm; 1.6 Hz splitting). (Reproduced with permission from ref 14. Copyright 2006 Elsevier.)

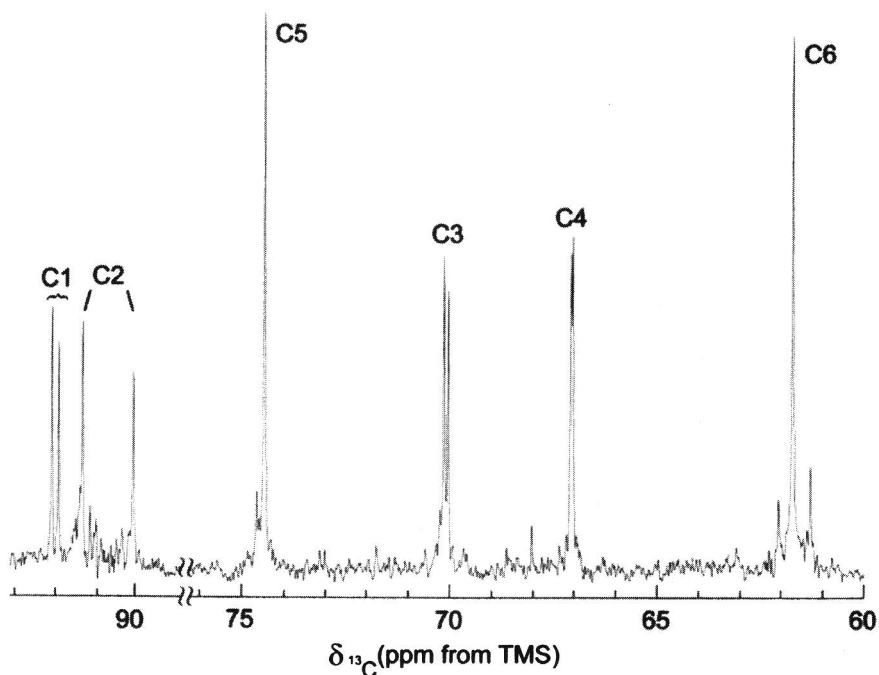


Figure 3. The ^{13}C NMR spectrum (D_2O solvent at 25 $^\circ\text{C}$) of the products resulting from the electrophilic fluorination of TAG in aHF. (Reproduced with permission from ref 14. Copyright 2006 Elsevier.)

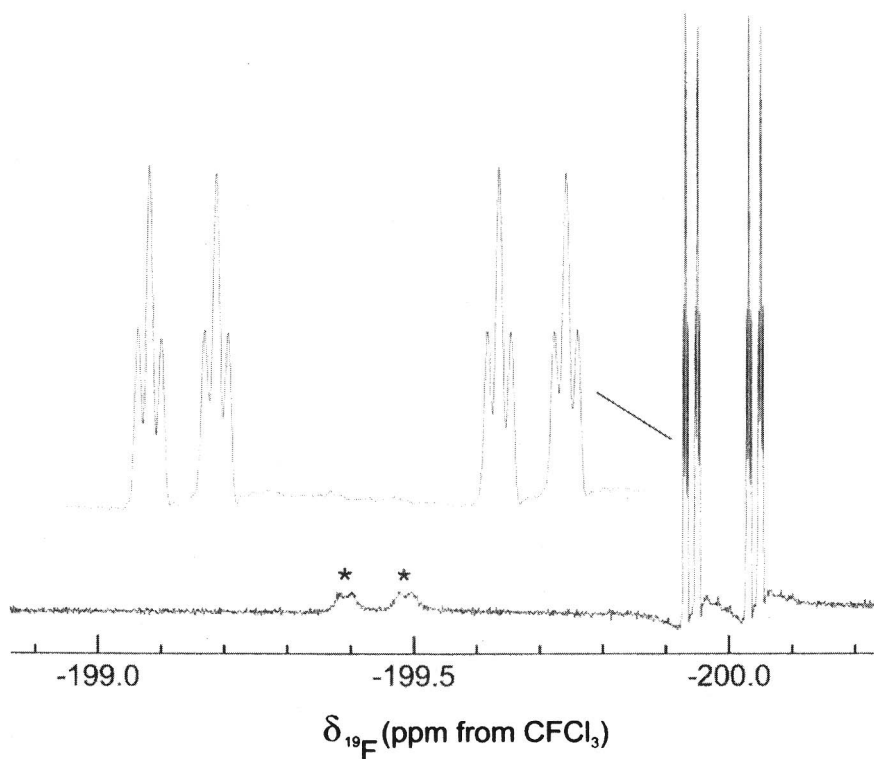


Figure 4. The ^{19}F NMR spectrum (D_2O solvent at 30°C) of the products resulting from the electrophilic fluorination of TAG in aHF. Asterisks (*) denote an unassigned resonance (“doublet of doublets”) arising from a minor component ($\delta(^{19}\text{F})$, -199.44 ppm; $^2\text{J}_{\text{F,H}}$, 44.35 Hz and $^3\text{J}_{\text{F,H}}$, 7.67 Hz) characteristic of a fluorocarbohydrate. (Reproduced with permission from ref 14. Copyright 2006 Elsevier.)

Table I. ^1H NMR Parameters for 2-FD βA

^1H chemical shift (ppm)		multiplicity ^a	coupling constant (Hz)	
H1	5.21	dd	$^3J_{\text{H1,F}}$, 1.4	$^3J_{\text{H1,H2}}$, 8.2
H2	4.38	ddd	$^2J_{\text{H2,F}}$, 47.0	$^3J_{\text{H2,H3}}$, 3.1
H3	4.51	ddd ^b	$^3J_{\text{H3,F}}$, 8.9	$^3J_{\text{H3,H4}}$, 3.0
H4	3.78	ddd	$^4J_{\text{H4,F}}$, 1.6	$^3J_{\text{H4,H5}}$, 10.0
H5	3.90	ddd	$^3J_{\text{H5,H6}}$, 2.3	$^3J_{\text{H5,H6'}}$, 5.8
H6	3.97	dd	$^2J_{\text{H6,H6'}}$, 12.3	
H6'	3.78	dd		

^aThe abbreviations denote doublet of doublets (dd) and doublet of doublets of doublets (ddd). ^bThis multiplet appears as a doublet of "triplets" because $^3J_{\text{H3,H4}} \approx ^3J_{\text{H2,H3}}$. Reproduced with permission from ref 14. Copyright 2006 Elsevier.

Table II. ^{13}C NMR Parameters for 2-FD βA

^{13}C chemical shift ^a (ppm)		multiplicity ^b	Coupling constant (Hz)
C1	91.93 (96.4)	d	$^2J_{\text{C1,F}}$, 24.5
C2	90.67 (74.2)	d	$^1J_{\text{C2,F}}$, 185.5
C3	70.09 (74.3)	d	$^2J_{\text{C3,F}}$, 15.9
C4	67.05 (69.5)	d	$^3J_{\text{C4,F}}$, 5.5
C5	74.47 (76.5)	s	
C6	61.75 (64.1)	s	

^aChemical shifts in parentheses are those of $\beta\text{-D-allose}$ (21).

^bThe abbreviations denote doublet (d) and singlet (s).

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Mass Spectrometric Characterization

Negative ion electrospray ionization (ESI) mass spectrometry of the reaction products resulting from Scheme 4 corroborated the NMR findings showing that 2-FD β A was the major product. The ESI mass spectrum showed the deprotonated molecular ion, $[M-H]^-$ at m/z 181. However, the base peak in the spectrum appeared at m/z 217, which corresponds to the chloride adduct of neutral 2-FD β A. It is noteworthy that 2-FD β A gave a fragmentation pattern that was very similar to the combined fragmentation patterns of 2-FDG and 2-FDM formed by the fluorination of TAG in $CFCl_3$.

Chromatographic Properties of [^{18}F]2-FD β A

It is imperative to establish the identity, chemical purity, and radiochemical purity of any tracer used for *in vivo* and *in vitro* studies. The identity of [^{18}F]2-FD β A was established by 1H , ^{13}C , and ^{19}F NMR spectroscopy and mass spectrometry, after samples were allowed to decay for a minimum of 48 h. For routine use, only radio-HPLC (stationary phase: Waters Carbohydrate Analysis Column, 3.9×300 mm, 10μ ; mobile phase: a 95% CH_3CN and 5% H_2O solvent mixture at 2.0 mL/min) and radio-TLC (stationary phase: Alltech silica gel 60 TLC aluminium sheet, 200μ ; mobile phase: a 95% CH_3CN and 5% H_2O solvent mixture) were used to determine the identity and radiochemical purity of [^{18}F]2-FD β A. As expected from their structural similarities, [^{18}F]2-FD β A had chromatographic properties very similar to those of [^{18}F]2-FDG and [^{18}F]2-FDM. Figures 6 and 7 show the radio-HPLC and radio-TLC chromatograms, respectively, of [^{18}F]2-FD β A and a mixture of [^{18}F]2-FDG and [^{18}F]2-FDM. The retention time (t_R) of [^{18}F]2-FD β A was 3.83 min (Figure 5a), whereas those of [^{18}F]2-FDG and [^{18}F]2-FDM were 3.75 min (Figure 5b). The dark spots on the TLC plates (Figure 6) correspond to the ^{18}F radioactivity, which gave rise to the peaks on the TLC chromatograms. The R_f -value of [^{18}F]2-FD β A, 0.37, was also very close to those of [^{18}F]2-FDG and [^{18}F]2-FDM (0.36). The radiochemical purity of [^{18}F]2-FD β A was 96 ± 3 and $85 \pm 7\%$, as determined by radio-HPLC and radio-TLC, respectively.

Proposed Mechanism for the Synthesis of 2-FD β A Using F_2

Fluorinations of TAG and D-glucal by F_2 in polar solvents and aqueous solutions usually result in difluorinated intermediates in which F_2 is added across the double bond to give a *syn*-arrangement (8,9,22). The absence of an *anti*-arrangement is attributed to the inability of fluorine, in contrast with other halogens, to form a halonium ion. Therefore, the initial fluorocarbonium ion intermediate, formed by electrophilic attack of F_2 at C2, is not bridged (23). The

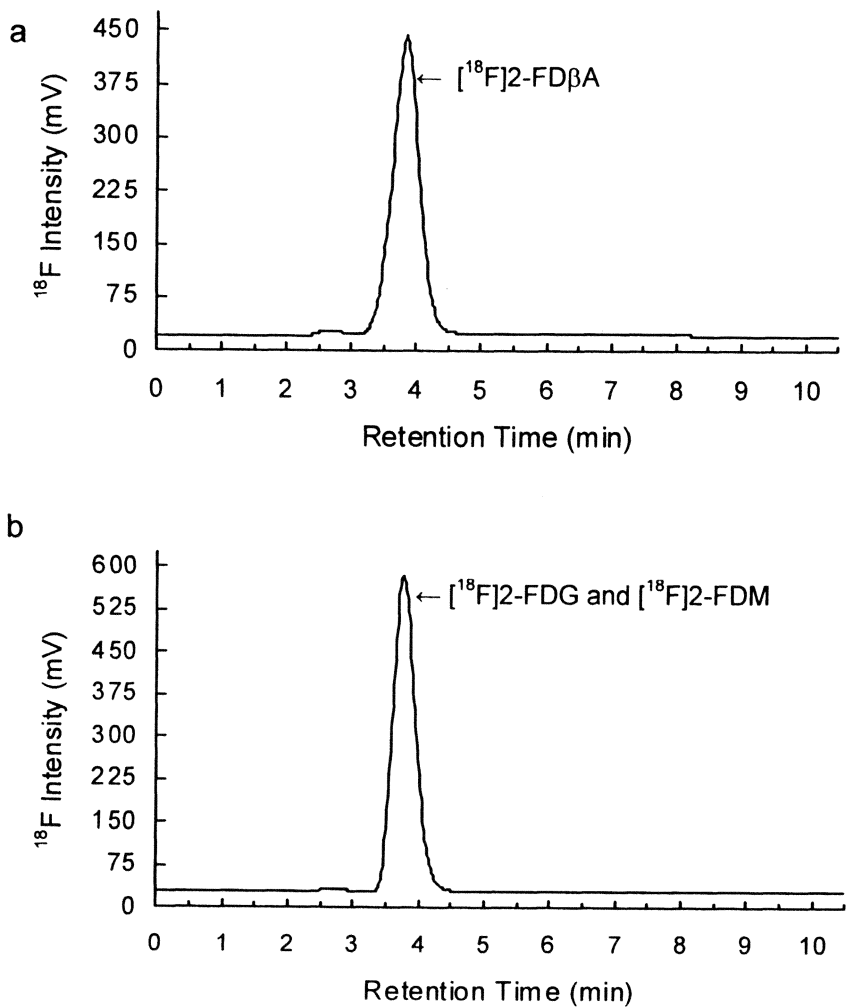


Figure 5. Radio-HPLC chromatograms of (a) the products resulting from the electrophilic fluorination of TAG in aHF and (b) a mixture of $[^{18}\text{F}]2\text{-FDG}$ and $[^{18}\text{F}]2\text{-FDM}$ resulting from the electrophilic fluorination of TAG in CFCl_3 .

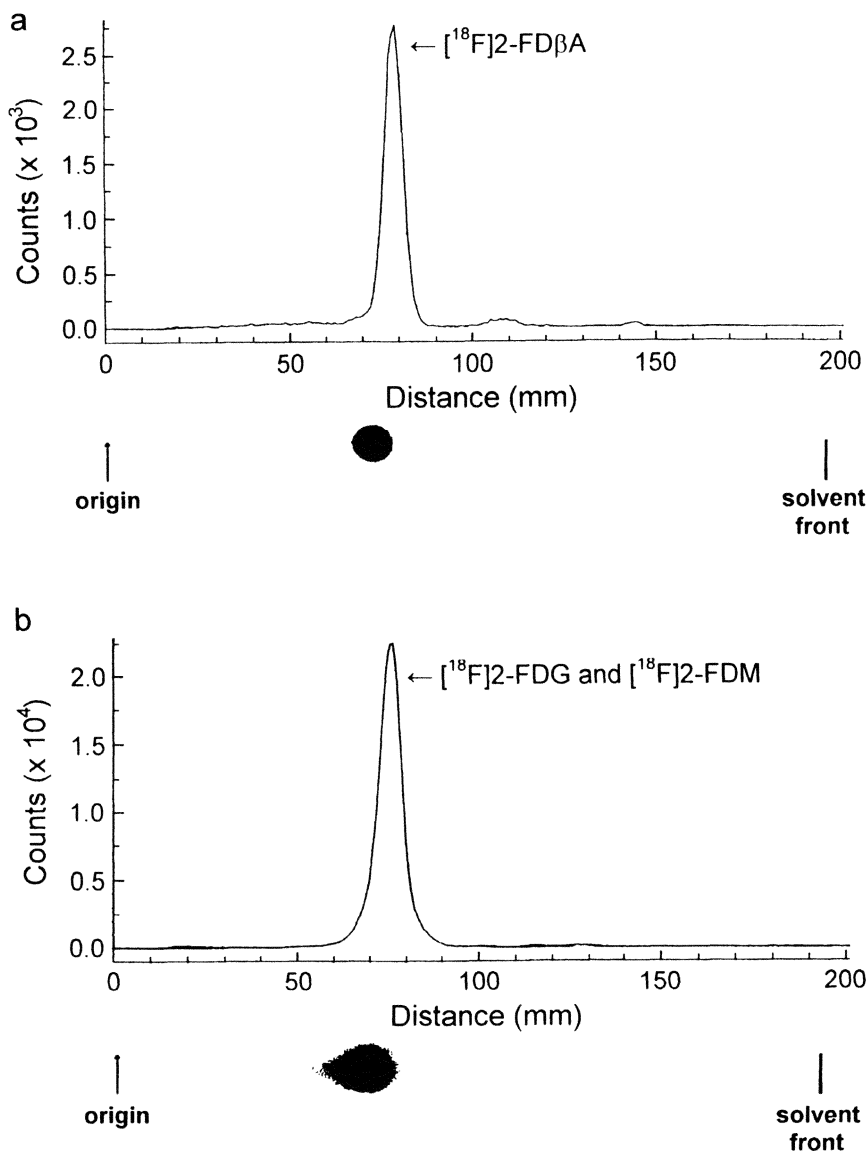


Figure 6. Radio-TLC chromatograms and plates of (a) the products resulting from the electrophilic fluorination of TAG in aHF and (b) a mixture of $[^{18}\text{F}]2\text{-FDG}$ and $[^{18}\text{F}]2\text{-FDM}$ resulting from the electrophilic fluorination of TAG in CFCl_3 .

fluorocarbenium ion rapidly combines with the F^- counter ion to form the difluorinated intermediate in which the fluorine ligand on C1 is susceptible to hydrolysis in dilute acid media.

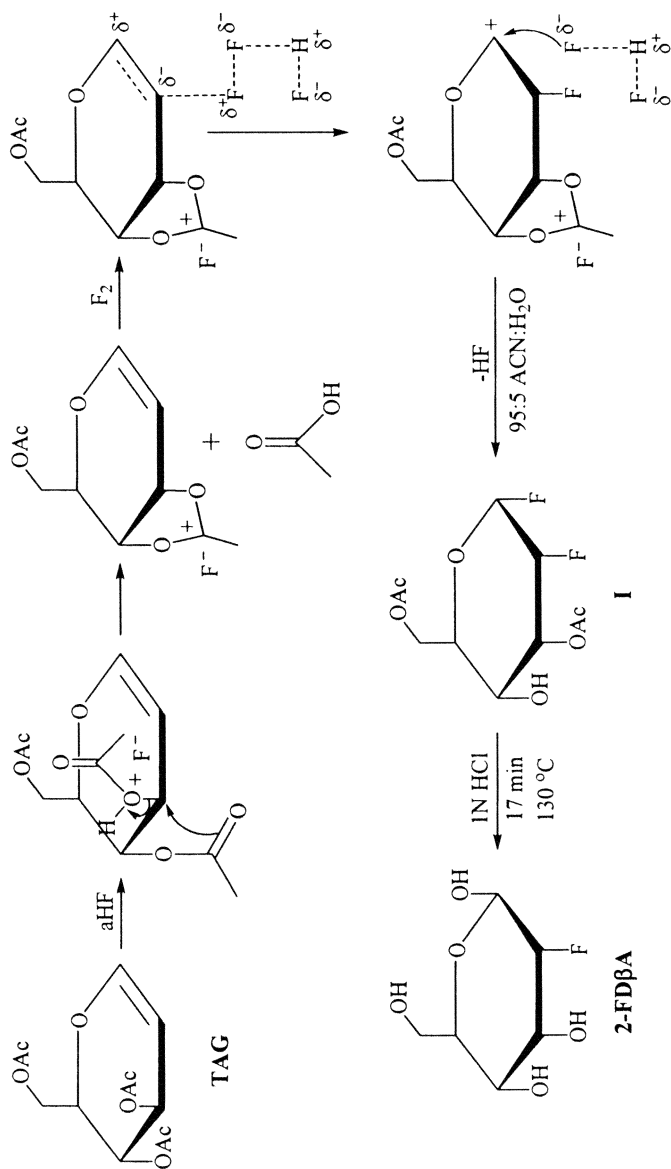
Lundt and Pedersen (12) proposed that the reaction of TAG with aHF (Scheme 3) proceeded by protonation of the *O*-acetyl oxygen atom bonded to C3. Subsequent cleavage of the *O*-acetyl group to form acetic acid was likely assisted by attack from the acyloxy group at C4. These workers showed, from a freshly prepared aHF solution of TAG, that the double bond of the corresponding 1,2-unsaturated 3,4-dioxolenium ion was initially intact at -70°C . The ^1H NMR spectrum obtained after a period of 24 h showed that HF had added across the double bond of the dioxolenium ion in a Markovnikov fashion. The introduction of a small amount of water into the reaction medium resulted in hydrolysis of the dioxolenium ion and subsequent epimerization at C3.

Fluorinations of TAG in the present study were routinely carried out at -60°C within 30 min following addition of aHF, thus avoiding significant HF addition to the double bond of the 1,2-unsaturated dioxolenium ion prior to fluorination. It is expected that the formation of 2-FD β A takes place through a difluorinated intermediate, 3,6-di-*O*-acetyl-2-deoxy-2-fluoro- α -D-allopyranosyl fluoride (Scheme 5; **I**), similar to that formed during the reaction of TAG with F_2 in CFCl_3 (7,8,24). Epimerization at C3 takes place in aHF followed by the addition of F_2 across the double bond in TAG and subsequent removal of HF, resulting in **I**. The hydrolysis of **I** then yields 2-FD β A.

Because of the predominance of 2-FD β A in the final product solution, it was anticipated that **I** would be the major reaction intermediate, and would thus give rise to the most intense signals in ^{19}F NMR spectrum. The ^{19}F - ^{19}F COSY spectrum of the reaction mixture recorded immediately following fluorination (Figure 7), showed strong cross-peaks between the resonances at -147.8 and -205.2 ppm. These resonances were assigned to the fluorine ligands of the difluorinated intermediate (**I**) because their chemical shifts were very similar to those observed for the intermediate resulting from the electrophilic fluorination of TAG in CFCl_3 (-151.3 and -205.1 ppm) (24).

Biological Studies Using [^{18}F]2-FD β A

All animal experiments were conducted in accordance with the guidelines of the Institutional Review Board, McMaster University. For studies involving biodistribution and the time course of [^{18}F]2-FD β A, male PMT mice were bred with commercial FVB (inbred strain) control females. The mice developed tumors at approximately 5 weeks of age. The results obtained using [^{18}F]2-FD β A were compared with those using [^{18}F]2-FDG.



Scheme 5. A proposed partial reaction mechanism for the synthesis of 2-FDβA by electrophilic fluorination of TAG in aHF. (Reproduced with permission from ref 14. Copyright 2006 Elsevier.)

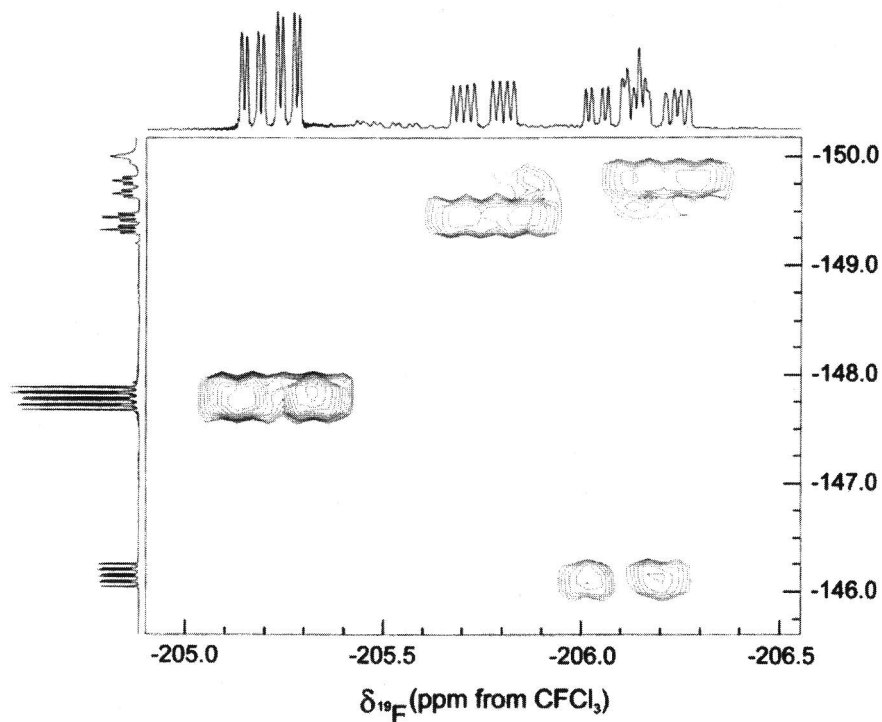


Figure 7. The ^{19}F - ^{19}F gradient COSY spectrum (CD_3CN solvent at 25 $^\circ\text{C}$) of the intermediates resulting from the electrophilic fluorination of TAG in aHF.

The mice were injected with 10–18 mBq (0.3–0.5 mCi) of either [^{18}F]2-FD β A or [^{18}F]2-FDG in about 0.2 mL of saline solution through the tail vein. Animals were sedated and maintained with 1–2% isoflurane and whole body dynamic PET scans were acquired from 5 min before to 120 min after injection using a Philips Mosaic small animal PET scanner.

Biodistribution studies were carried out by euthanizing the mice by cardiac puncture using 0.03 mL of Euthanol followed by dissection and the removal of the tissue samples. Tissue samples were weighed and their ^{18}F content measured using a Packard Cobra II Auto-Gamma Counter. The tissue uptake indices were calculated by dividing activity per gram of tissue by injected activity per body weight. Tissue : blood ratios were calculated by dividing the tissue uptake index by the blood uptake index.

The whole body PET image of an FVB control mouse 45 min after injection of [^{18}F]2-FD β A (Figure 8) showed significant uptake in the kidney and bladder and no uptake in the brain. The time course of ^{18}F in a control mouse after administering [^{18}F]2-FD β A showed that almost all of the ^{18}F activity was present in the bladder within 60 min after injection (Figure 9). Moreover, ^{18}F uptake in the bone was not observed even after 120 min, which proved that [^{18}F]2-FD β A was not catabolised *in vivo* to free $^{18}\text{F}^-$.

Because of the very similar structures of D-glucose and D-allose, one would expect very similar biological properties for both tracers. A comparison of the biodistribution of [^{18}F]2-FD β A with that of [^{18}F]2-FDG in control mice, sacrificed at different times (30–90 min; Table III), however, showed the *in vivo* properties of the two tracers to be markedly different, that is, the ^{18}F organ distribution data (Table III) showed significant differences in the uptake in the heart, brain, and bone. The standard errors in the uptake indices (values in parentheses) are rather large because they are average values obtained from different experiments in which the animals were sacrificed at different times.

The time course of ^{18}F in a tumor-bearing PMT mouse after injection of [^{18}F]2-FD β A is shown in Figure 10. The tumor can be clearly visualized within 30 min after tracer injection. Biodistribution studies showed a high level of [^{18}F]2-FD β A uptake in the tumor when compared with the non-targeted tissues (Table IV). The tumor : blood ratio was 10 ± 6 ; the high standard error results from the differences in sacrifice time (80 ± 20 min). Figure 11 compares the ^{18}F uptake between [^{18}F]2-FD β A and [^{18}F]2-FDG using a tumor-bearing PMT mouse, which was injected with each tracer on two consecutive days. Although uptakes of both tracers were clearly visible in the tumor, unlike that of [^{18}F]2-FDG, accumulation of [^{18}F]2-FD β A was not visible in the non-targeted tissues, except the bladder. Hence, [^{18}F]2-FD β A has the potential to provide a better signal-to-noise ratio for tumors.

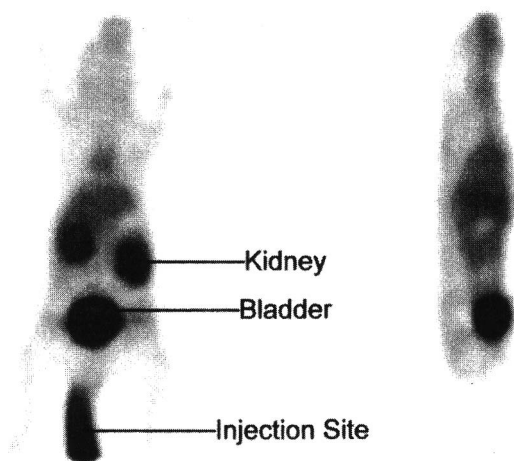


Figure 8. Whole body PET image of a FVB control mouse (coronal view on the left and sagittal view on the right) 60 min after injection of [^{18}F]2-FD β A.

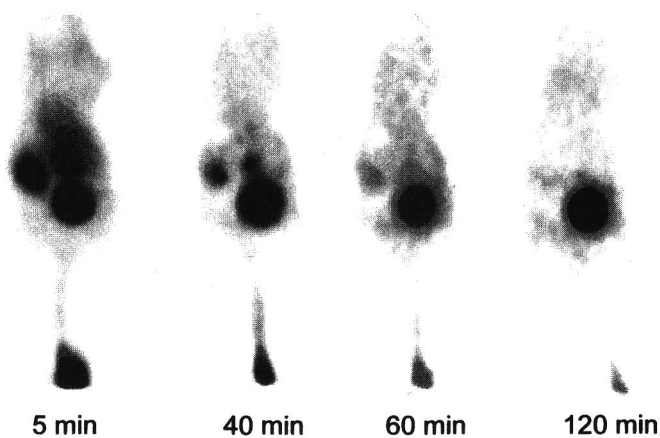


Figure 9. Time course of ^{18}F in a FVB control mouse after injection of [^{18}F]2-FD β A.

Table III. Biodistribution of [¹⁸F]2-FDβA vs. [¹⁸F]2-FDG in Control Mice^a

Tissue	[¹⁸ F]2-FDβA		[¹⁸ F]2-FDG	
	Uptake Index	Tissue : Blood	Uptake Index	Tissue : Blood
Lung	0.16 (0.03)	2.7 (1.1)	0.20 (0.03)	6.6 (0.4)
Liver	0.16 (0.07)	2.1 (0.5)	0.08 (0.01)	2.48 (0.09)
Kidney	0.3 (0.2)	2.0 (0.2)	0.20 (0.05)	6.2 (1.1)
Heart	0.23 (0.01)	4.0 (1.8)	2.5 (0.6)	81 (13)
Brain	0.041 (0.001)	0.8 (0.3)	0.34 (0.04)	11 (2)
Bone	0.08 (0.04)	1.0 (0.2)	0.4 (0.1)	14 (4)
Blood	0.13 (0.08)	1.0 (0.0)	0.031 (0.005)	1.0 (0.0)

^aAverage values obtained using a sample population of three. Standard errors in the values are shown in parentheses.

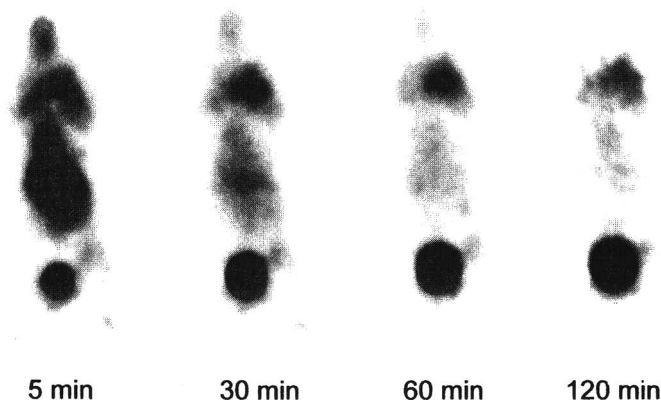


Figure 10. Time course of ¹⁸F in a tumor-bearing PMT mouse after it was injected with [¹⁸F]2-FDβA.

Table IV. Biodistribution of [¹⁸F]2-FDβA in Tumor-bearing PMT Mice^a

Tissue	Uptake Index	Tissue : Blood
Lung	0.18 (0.04)	3.3 (0.7)
Liver	0.12 (0.02)	2.5 (0.6)
Kidney	0.16 (0.04)	3.3 (1.007)
Heart	0.30 (0.06)	8.2 (3.4)
Brain	0.045 (0.009)	0.8 (0.2)
Bone	0.10 (0.02)	1.9 (0.4)
Blood	0.06 (0.02)	1.0 (0.0)
Tumor	0.3 (0.1)	10 (6)

^aAverage values obtained using a sample population of six. Standard errors in the values are shown in parentheses.

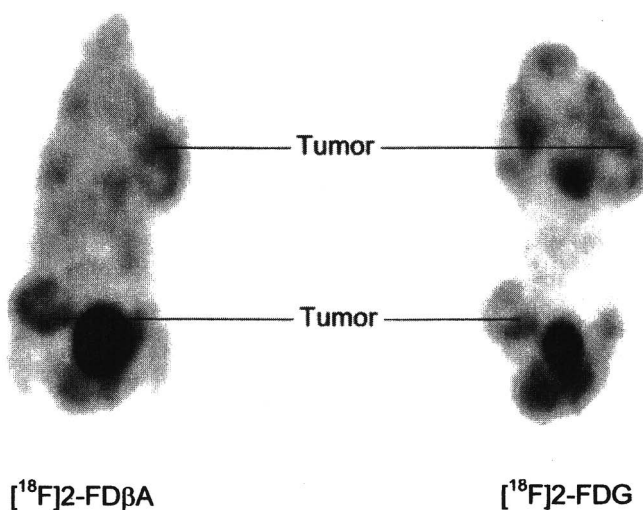


Figure 11. Whole body PET image of a tumor-bearing PMT mouse that was first injected with [¹⁸F]2-FDβA (left) and then with [¹⁸F]2-FDG (right) on two consecutive days.

Conclusion

The present study has employed F_2 and CH_3COOF to develop reliable and rapid two-step highly regio- and stereoselective syntheses of 2-FD β A by electrophilic fluorination of TAG in aHF. The salient features of these reactions are: (1) high regioselectivity, (2) high stereoselectivity, which is unique for electrophilic fluorination, (3) *in situ* epimerization at C3, (4) high RCY (in the case of [^{18}F] $_2$) for electrophilic fluorinations, (5) short syntheses times, which are ideal for ^{18}F -labeling, and (6) no formation of [^{18}F]2-FDG or [^{18}F]2-FDM. It is noteworthy that the chromatographic properties of [^{18}F]2-FD β A are almost identical to those of [^{18}F]2-FDG and [^{18}F]2-FDM, both of which, however, show markedly different *in vivo* behaviors. Therefore, high regio- and stereoselectivity of the reaction is essential and underscores one of the advantages of using aHF as the reaction medium.

Preliminary *in vivo* studies using FVB control and tumor-bearing PMT mice showed significant differences between the uptakes of [^{18}F]2-FD β A and [^{18}F]2-FDG. Whole body PET images of PMT mice showed retention of [^{18}F]2-FD β A in the tumor with corresponding high tumor to blood ratios, indicating that [^{18}F]2-FD β A is a promising tracer for the detection of breast tumors.

Acknowledgement

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Chapter 11

Structural Studies of Biologically Interesting Fluorinated Nucleosides

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The use of fluorine as a surrogate for hydrogen and/or a hydroxyl group in synthetic nucleoside analogues has proved to be invaluable in the discovery of exciting new drug agents with novel biochemical properties. Being the most electronegative atom of all nonmetals, fluorine exerts distinct effects on nearly all structural elements in nucleosides and these effects are highly dependent on both the region and the stereochemistry of the fluorine substitution. Despite the dramatic influence that fluorine incorporation often has on the conformational and pharmacological properties of nucleoside analogues, there is a relatively small community of research groups that study the structural effects of fluorine substitution in detail. This review will concentrate on the current research on these effects, paying particular attention to fluorine substitution in the furanose portion of both nucleoside and nucleotide analogues.

Introduction

It would be virtually impossible for any researcher in life sciences to overestimate the biological importance of nucleosides and their phosphorylated metabolites, nucleotides. These molecules are the precursors to the code of all life, being the building blocks of nucleic acids and hence date to the origins of our species itself. In addition, it was discovered early on that “tinkering” with nucleoside metabolism and hence with the synthesis of DNA or RNA was highly relevant to intervention in many disease processes. Organisms can be “tricked” into incorporating nucleoside analogues into a growing DNA chain and in effect, halt synthesis at opportune times in the cell cycle. In addition, inhibition of critical steps in nucleoside metabolism can have an equally devastating effect on the growth of or life cycle of cells, leading to death and/or cellular stasis. These mechanisms have been exploited by nucleoside analogues for the treatment of various cancers (1) and many viral diseases (2,3).

Nucleosides are relatively simple molecules that are comprised of two structural elements: 1) A furanose ring (ribose or deoxyribose) and 2) a pyrimidine- or purine-derived base yielding molecules with a maximum molecular weight of 283 amu (ribo-guanosine). Examination of the literature will reveal that essentially every atom of both the furanose and base units of the endogenous nucleosides have been replaced by other atoms, mostly through synthetic manipulations. These investigations have shown that many of these analogues have potent biological activity, well surpassing those of the parent nucleoside. Some of these substitutions have resulted in the preclinical and clinical development of interesting analogues, such as carbocyclic (4), unsaturated, aza (5), conformationally “locked” (6,7) and base-modified nucleosides (8,9). Some derivatives synthesized as “transition state” inhibitors of enzymatic processes can have inhibitory constants in the low picomolar to femptomolar range (10,11).

When speaking of atom replacement in nucleosides, fluorine has arguably been one of the most valuable atoms to use as a surrogate for any hydrogen and/or hydroxyl group in this template. The survey given in this review will primarily cover the conformational or electronic effects that fluorine has on nucleoside structure and what that effect has on the biological activity of the specific analogue in question. The material will concentrate on the past decade of work, with an introduction that dates back to early work in an attempt to specifically orient the reader to the origins of interest in fluorine in nucleoside analogue design.

Structural Elements in Nucleosides and How Fluorine Affects Them

There are three main structural elements that define the conformations of the components of a nucleoside in its entirety: The angle χ , which defines the

relative position of the base with the remainder of the molecule; 1) the angle γ , which defines the position of the methylene hydroxyl group (C5') to the base and the glycone portion and 3) the pucker of the furanose sugar ring which itself is described by the concept of pseudorotation (12), quantitatively defined by the phase angle of pseudorotation P and the maximum out-of-plane puckering amplitude v_{\max} . Figure 1 illustrates these features and defines the pseudorotational cycle (PC) for nucleosides. Each designation of ring pucker around the wheel signifies a movement of 18° around the cycle. The letters "T" and "E" respectively represent twist and envelope conformations about the five membered ring, the true "North" (N , 0° by convention) and true "South" (S , 180°) being twist forms while "east" and "west" forms are envelope. An early survey of neutron diffraction and X-ray structures revealed that most nucleosides reside either in the N or S quadrants of the PC (13) (shaded areas of Figure 1).

Structural studies on nucleosides involve examining some or all of these elements. Years of studies involving the analysis of NMR coupling constant data showed that in solution, nucleosides exist as an equilibrium mixture between the two antipodal forms (N and S), although one may be populated to a much higher extent than the other. Not surprisingly, there seems to be a distinct interplay between sugar pucker and other structural parameters, and hence it is useful to study the complete set when approaching a particular conformational analysis. In addition, it is highly advantageous to use all of the various structural techniques at one's disposal, i.e., solid state (X-ray crystallography), solution state (NMR spectroscopy) and theory/modeling (*ab initio*, molecular mechanics) to compare results as it is oftentimes the case where the solid and solution state conformations may differ significantly or "violate" certain trends seen in closely related analogues (see for example (14,15) and *vide infra*). Being the most electronegative atom, substitution of furanose hydrogen atoms or hydroxyl groups by fluorine obviously exerts distinct effects on ring pucker conformation and these effects in turn modulate the two rotamer populations about the anomeric and C4'-C5' bonds. In particular, the position and stereochemistry of the fluorine atom in the 2' or 3' position of a nucleoside has a tendency to "pull" that particular carbon in the direction the fluorine points—a consequence of a strong gauche effect (16,17) between the fluorine atom and the endocyclic O4' oxygen. Fluorine substitution at the 2'-position is also known to stabilize the anomeric center to hydrolysis as a result of the destabilization of the developing positive charge at C1' due to the powerful fluorine inductive effect (18). Hence, there is a rich history of the synthesis and comparative SAR of fluorinated nucleosides, primarily in the antiviral and anticancer drug discovery arenas. The following sections will outline only the studies that have included some type of [atomic resolution] structural or conformational analysis in the research. Two excellent reviews on the design and synthesis of fluorinated nucleosides have recently appeared (19,20) and the reader is referred to these for comprehensive information on this methodology.

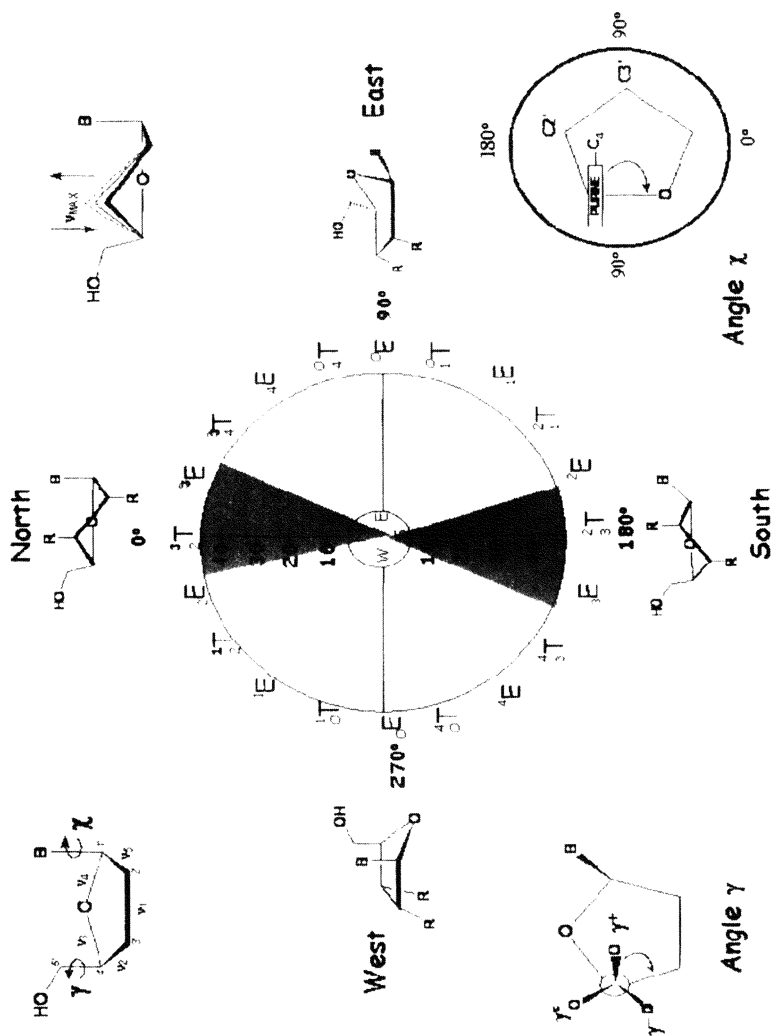


Figure 1. Structural features of nucleosides. The center describes the pseudorotation wheel and the corresponding puckering at 90° intervals.

Fluorine in Nucleosides: Early Structural Work

Substitution of fluorine for hydrogen or hydroxyl groups as part of a drug discovery effort dates back to the early 1960's, where Fox and coworkers synthesized uridine and thymidine fluorinated at the α -2' ("down") position along with the 2', 5-difluoro analogue of uridine in an effort to explore the effect of halogen replacement for hydroxyl in standard ribo-nucleosides (21,22). In a remarkably comprehensive study for the time, this group also studied the conformational effects of halogens, including fluorine, on the ring pucker of the furanose by NMR. They performed 60 and 100 MHz NMR studies and determined H-H and H-F coupling constants, developed crude Karplus relations with these and proposed defined ring puckers for 2'- α -fluorouridine (**1**) and 3'- α -fluoro-*ara*-uridine (**2**). These conformations are shown in Figure 2.

The tabulation and analysis of the data on several halogenated nucleosides without access to more refined pseudorotational analysis set the stage for all future studies. In the early 1970's, the Langen group prepared 3'-fluoro- and chlorothymidine (3'-FLT (**3**) and 3'-CLT (**4**), Scheme 1) and tested them as cytostatic agents against Ehrlich ascites tumors (23,24). Although no formal

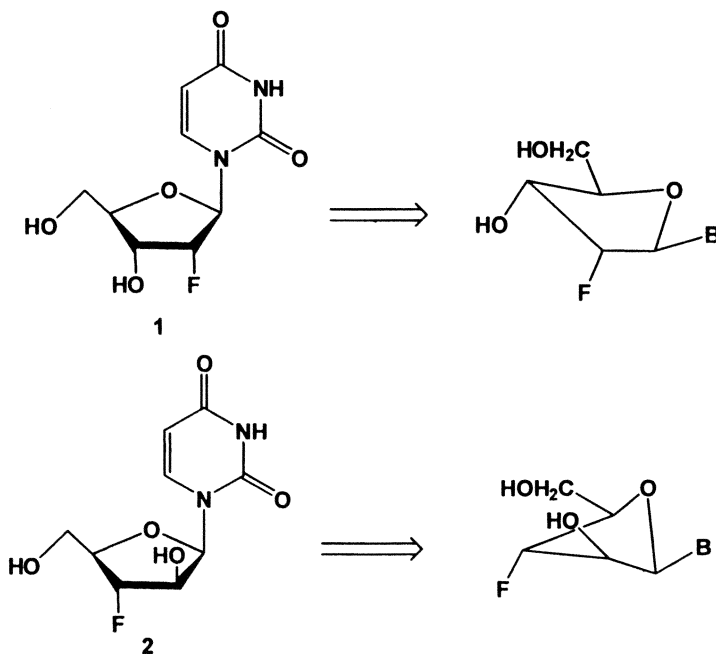
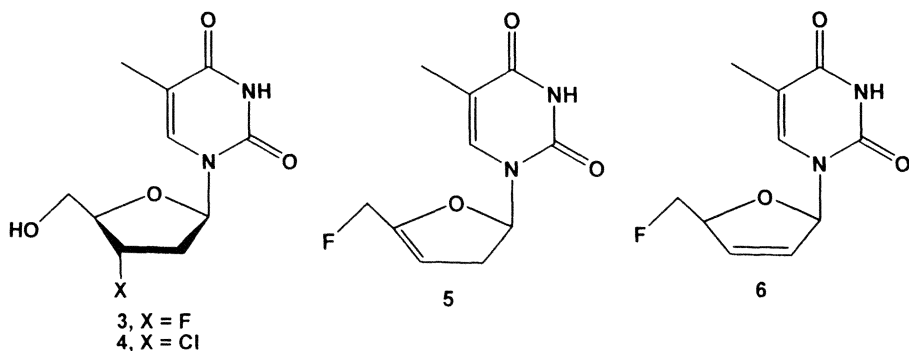


Figure 2. Chemical structures (left) and predicted ring conformations (right) of compounds **1** and **2**.

structural work was performed, they found that the halogen, although it was placed in a “distant” position from the anomeric center, slowed hydrolysis of the thymine base (*vide supra*) and was readily eliminated to the 2',3' unsaturated compounds (24). They also determined the Cotton effects of 3 and 4 from CD spectra. They took the work with the unsaturated compounds further and prepared the 5'-F-2',3'-unsaturated derivatives 5 and 6. In this study, H-F coupling constants were measured and tabulated for both 2- and 3-bond couplings. Analogues 5 and 6 were found to be potent inhibitors of thymidylate kinase (E.C. 2.7.4.9) (23).

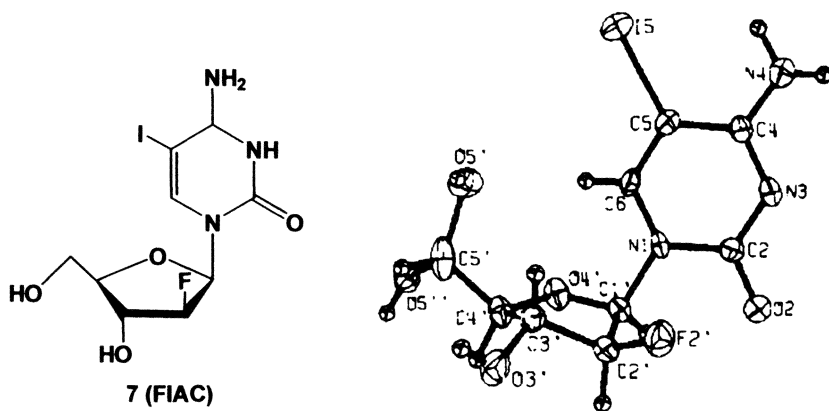
Scheme 1



Spawmed by the potent antitumor activity of compounds like *ara*-cytidine (*ara*-C) and *ara*-adenosine (*ara*-A), this decade saw several other synthetic studies on fluorinated nucleosides with *ara*-disposed fluorine in the 2'-position. Fox and coworkers synthesized many of these (25) including 2'-fluoro-5-iodo-arabinosylcytosine (FIAC, 7), a very potent anti-herpetic agent which also inhibited human cytomegalovirus and many cancer cell lines (Scheme 2).

The solution conformation of this drug was determined by 270 MHz NMR experiments and the results suggested that FIAC, along with the 5-bromo and 5-chloro derivatives existed in approximately a 50:50 mixture of 3'-*endo*/2'-*endo* (*N/S*) conformers (26). A subsequent crystal structure of FIAC, the first of a fluoroarabinosyl nucleoside, showed that contrary to other recent studies (27,28) that suggested the aforementioned F-O4' GE would operate strongly in this molecule to bias the ring pucker to the South, the X-ray structure was almost pure North (Scheme 2, $P = 10$ deg). The fluorine atom and 3'-hydroxyl group are pseudoequatorial, and hence the 2'F-3'OH GE seems to override the *S*-driving F2'-O4' GE. It is possible that crystal packing forces or the influence of the 5-halogen on the *N*-driving anomeric effect may contribute to the conformational preference.

Scheme 2



It is well known that different forms of DNA and RNA are constructed of nucleotides with specific sugar puckers. Standard B-DNA furanoses pucker *S* while A-DNA and RNA sugars pucker *N*. The use of replacement atoms in nucleotide building blocks that bias the conformation toward one pucker or another may act as efficient surrogates for the standard base pair monomers or can be incorporated into the growing oligonucleotide (ON) chain to act in a variety of therapeutic ways. An extensive NMR study of 2'- α -fluoroadenosine and several phosphorylated monomers and dimers was performed by Ikehara's group (29) and coworkers who showed that, similar to the pucker of a standard RNA, replacing the 2'-hydroxyl group with fluorine maintained a 3'-*endo* envelope (3E) conformation. The pKa of phosphates in the fluorinated nucleotides were found to be similar to those of the standard monomer, indicating that this analogue may be an excellent substitute for 2-deoxyadenosine. In addition, ^{19}F linewidth analysis could be used to study helix-coil transitions of homopolymers comprised of the 2-fluorinated building blocks with other complementary ON's. This study showed that fluorine could be an extremely useful probe for the study of ODs in complex systems.

The 1980's: PSEUROT and the Start of the AIDS Era

The synthesis and structural research on fluorinated nucleosides increased dramatically in this decade for two primary reasons: 1) The advent of the program PSEUROT discovered and developed by the Altona group in Leiden for the conformational analysis of the ring pucker of nucleoside glycones (30,31) and 2) The start of the AIDS epidemic which sparked a flurry of synthetic work

on nucleoside derivatives after the discovery of the anti-HIV activity of 3'-azidothymidine (AZT). PSEUROT is a program that takes as input furanose ring coupling constants and iteratively calculates the $N \leftrightarrow S$ equilibrium values P and v_{\max} . The program uses an extended version of the generalized Karplus equation to help relate the endocyclic torsion angles to the exocyclic proton-proton torsions from the NMR data (32-35). This program was a major advance in the analysis of furanose ring pucker. The most comprehensive description of the use of PSEUROT in nucleoside conformational analysis was published by Chattopadhyaya and coworkers (36), who have used the program most extensively throughout the past 15 years. An extension of this program to include proton-fluorine vicinal couplings constants was also published by this group, and paved the way for further refinement of the conformational analysis of ring-fluorinated nucleoside analogues (37).

Throughout this decade, it had been consistently shown that nucleosides with 2',3'-dideoxy nucleosides with 3'-*ribo*- or 2'-*ara* electronegative substituents often displayed antiviral activity (38-40). From the arguments above, these should all pucker preferably in the S hemisphere of the PC. A rationale for the anti-HIV activity of the known compounds was put forth by Van Roey, et al. (41) and Taylor et al. (42) stating that the S form was the preferred sugar ring pucker for the known active compounds. The following examples illustrate some of the features of some of these analogues with fluorine in the furanose ring.

Herdewijn, et al. prepared a series of 2',3' substituted nucleosides with fluorine and various other groups in different stereochemical dispositions (39,43-46). Crystallographic analysis of some of these derivatives showed the expected ring puckers from the arguments stated above. For example, 3'-fluoro-5-iodouridine (**8**) crystallized (47) in a true S conformation ($P = 184^\circ$), as well as 3'-fluorothymidine (**3**) whose crystal structure showed an 2E south pucker ($P = 164^\circ$) (48). In contrast but following from electronegativity arguments, 2'-*ribo*-fluorothymidine (**9**) was a true N pucker ($P = 8^\circ$) (49) (Figure 3). Compound **8** was ~40 times more active than **9**, most likely owing to S -driven sugar pucker.

The 1990's and FLUOROT

The first comprehensive study of a fluorinated nucleoside using PSEUROT was that of Plavec, et al. (50) on 3'- α -fluorothymidine (FLT, **10**). This group compared the crystal structures of FLT (48) and AZT to the conformations obtained by NMR-aided molecular mechanics calculations. They clearly showed that FLT prefers to be in a S pucker ~90% of the time, while AZT is a 1:1 mixture in solution by PSEUROT and MNDO calculations. This was in contrast to the crystal structure of AZT which shows a distinct S pucker. The authors point out the dangers of using solely crystal structures of small molecule

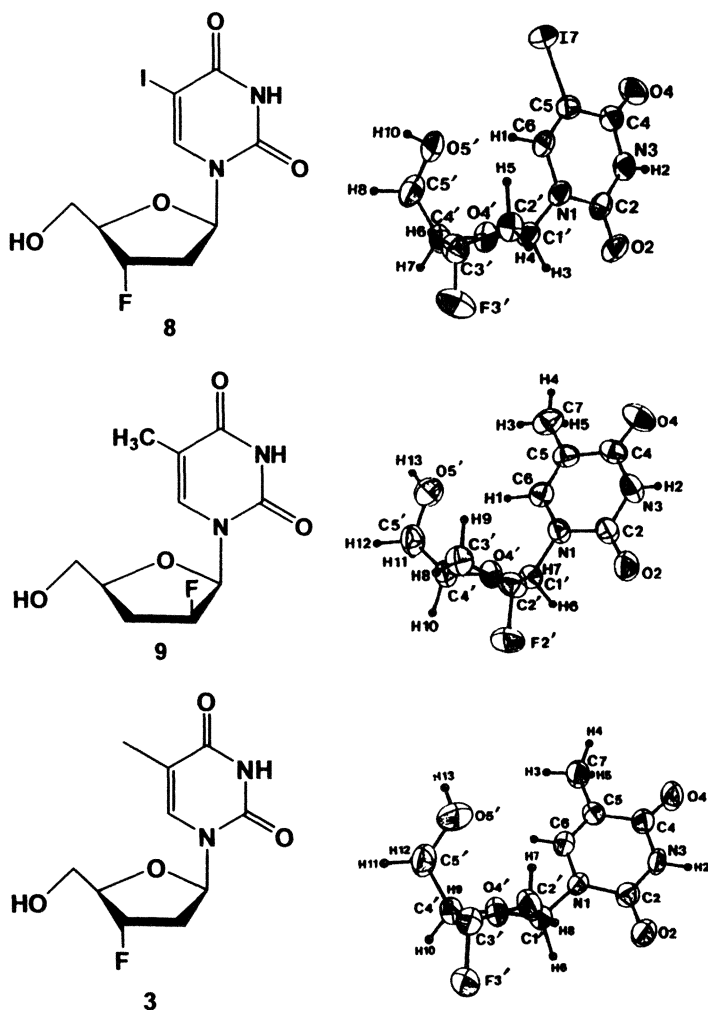


Figure 3. Chemical structures (left) and X-ray-derived ORTEP drawings (right) for compounds 3, 8 and 9.

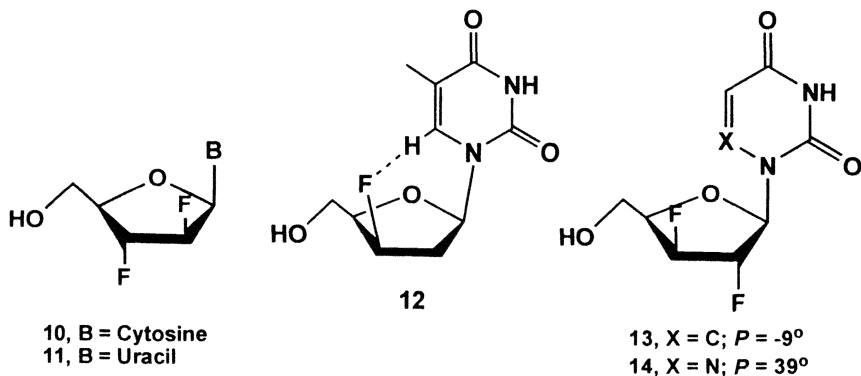
therapeutic agents since the overall solution structure is what is active “biologically”.

About this time, the Laboratory of Medicinal Chemistry at the NCI became interested in exploring the conformational properties of some of the fluorinated nucleosides that we had prepared (18,38,51). In a study performed using the early version of PSEUROT, we calculated the preferred conformations of two monofluorinated 2',3'-dideoxy- and three 2',3'-difluorinated 2',3'-dideoxy nucleosides by NMR analysis with PSEUROT (52). One of the compounds was

the 2'- β -3'- α -difluorinated cytidine **10**, synthesized by Martin, et al., (53) to take advantage of the two favorable F-O4' GE's that would drive the pseudorotational equilibrium toward the *S*, and produce what was thought to be a "super" anti-HIV compound. This compound proved to be much less active than either of the potent monofluorinated analogues (with single 2'- β -F or 3'- α -F substituents). The similar difluorouridine analogue **11** was inactive as well. Prior to this work in a separate structural study, Bergstrom performed MNDO calculations on the 3'-"up" (β) fluoro-2',3'-dideoxythymidine derivative **12**. This compound was locked heavily in the *N* conformation, and due to the distance and geometry between the 3'-fluorine and the H6 hydrogen, he proposed a "strong attractive" interaction is present between these two atoms. We set out to determine the preferred ring pucker to possibly explain the inactivity of these analogues. In addition, we prepared the 6-azauridine analogue in the difluoroxyuridine case in an attempt to find additional evidence for the β -F3'-H6 interaction, since no such interaction is possible with this analogue.

Our initial results followed from those outlined above: The F-O4' GE was the overriding factor in driving the *N/S* equilibrium in all the compounds studied. However, **10** and **11** "stray" from a pure *S* pucker and angle closer to the *N*, a possible suggestion for their inactivity. The 2',3'-difluoroxylo-disposed uridines **13** and **14** both show *N* puckers, however **13** seems virtually "locked" in that conformation according to PSEUROT calculations but the RMS deviations of the calculated to experimental coupling constants were abnormally high. The 6-aza compound **14** was handled much more accurately, and the trend was toward

Scheme 3

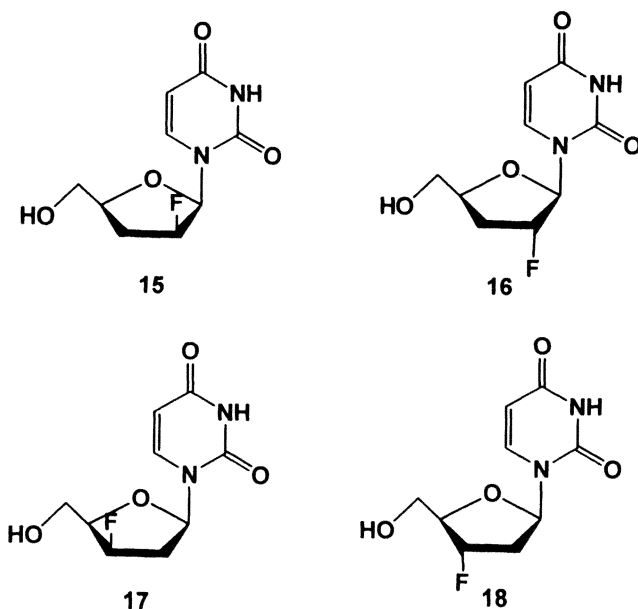


a more "*S*" conformation, offering more evidence that the putative 3'F-H 6 interaction is operational in **13** (Scheme 3). We have recently refined these data for three uridine analogues **11**, **13** and **14** with crystal structures and high level *ab initio* calculations (Barchi, et al., unpublished).

Our lab continued to explore the puckering preferences of furanoses by critically examining the solution structures of compounds **15-18** which constitutes the complete set of 2' or 3' monofluorinated dideoxyuridines. (Scheme 4) by NMR and PSEUROT analysis, complemented by single point energy calculations at the *ab initio* level (54). The data were consistent with previous observations that the F-O4' GE drove the pseudorotational preference for each compound. However, it was also found that the anomeric effect "tempers" the mole fraction of each pseudorotamer as calculated by PSEUROT, by counteracting the *S*-driven structures (**15** and **18**) to assume a higher degree of *N* conformer in their calculated equilibrium. In addition, the position of the fluorine atom, either above or below the ring, affects the distribution of the angle γ about the C4'-C5' bond. *Ab initio* calculations are in good agreement with the NMR calculated structures, with the exception of the 3'-"up" fluoro derivative **17**. Vacuum calculations at the 3-21 g* level suggested that the *S* conformer is more stable than the *N* pucker, although temperature-dependent NMR data shows a 100% population of the *N* pucker at equilibrium ($P = 27^\circ$). These discrepancies may be due to the level of theory used and the fact that solvation models were not employed in this work.

The data we generated on compounds **15-18**, along other structural data on conformationally "fixed" fluorinated molecules other than nucleosides, were used to quantitatively "reparameterize" the original PSEUROT Karplus equation (34) to include expressions for the effect of J_{HF} coupling constants and H-C-C-F

Scheme 4



torsion angles on the pseudorotational equilibrium of fluorinated nucleosides. The work by the Chattopadhyaya group extended the Karplus equation to seven parameters which include coefficients for the torsion angle dependence of $^3J_{\text{HF}}$, dependence on electronegativity and relative orientation of substituents in the H-F pathway, and a seventh term to describe the dependence of $^3J_{\text{HF}}$ on F-C-C and H-C-C bond angle changes. This last term was required due to the wide discrepancy in fits for the first six parameters due to the changes in bond angles (and hence the H-F coupling constants) with substituents along the coupling pathway. This new equation was incorporated into the PSEUROT program and used to recalculate data on several fluorinated nucleosides. The addition of $^3J_{\text{HF}}$ coupling constants increased the parameter set which serves to “overdetermine” the system and provide refined analyses for these types of structures. The authors were also able to calculate the N/S equilibrium of 2',2" difluorocytidine (gemcitabine) and the corresponding nucleosides containing the other DNA bases (guanine, adenine and thymine) using both $^3J_{\text{HH}}$ and $^3J_{\text{HF}}$ data offering five 3-bond couplings constants where only one $^3J_{\text{HH}}$ would be available ($^3J_{\text{H3',H4'}}$).

The preceding paragraph mentions the compound gemcitabine (trade name Gemzar® 19), which is a powerful antitumor agent that has been approved for the treatment of several cancers including first line defense against advanced stage adenocarcinoma of the pancreas (55). This compound was first synthesized in 1988 (56) and has been studied structurally by X-ray crystallography. In the first study (57), an X-ray structure of gemcitabine was compared to *ab initio* calculated structures at the 63-1 G* level of theory. The crystal data indicated a C2'-*endo* pucker for the sugar, a conformation in the *S* hemisphere. The second study done 7 years later was on the gemcitabine-hydrochloride salt. This structure showed a C3'-*endo*/C4'-*exo* conformation, a pucker in the *N* hemisphere (shown in Figure 4). The data from NMR analysis with the J_{HF} version of PSEUROT calculates the ring pucker between 62° and 76°, again in the *N* quadrant but heavily biased toward the “east” (O4'-*endo*). These studies point out that all manners of structural techniques need to be considered and the proper context considered when studying the effect of fluorine on nucleoside structures. It is interesting to note that in the structure of the complex of gemcitabine with deoxycytidine kinase, the enzyme that converts this prodrug to its monophosphate form, the nucleoside is in the *S* conformation with a ring pucker of 138° (C1'-*exo*), which is about 36° offset from the crystal structure conformation and nearly 70° from the NMR calculated ring pucker.

The New Millennium: The Same but Different: Bases Bring Surprises

In 1999, Chattopadhyaya and coworkers published an extended treatise on the how stereoelectronic effects influence the conformation of nucleos(t)ides which they updated in 2005 (36). This was the most comprehensive and useful treatment of the subject at the time, and they included their work on the

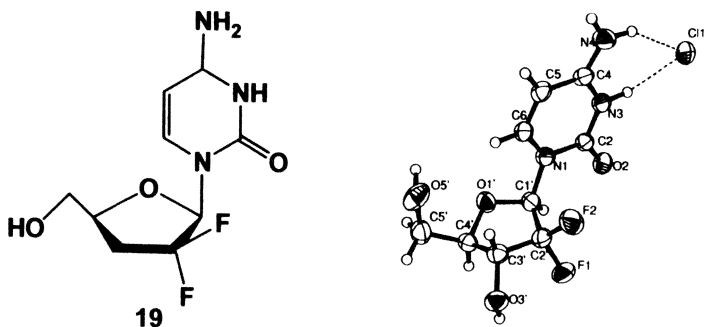


Figure 4. Chemical structure (left) and ORTEP drawing of the conformation derived from X-ray data (right) of Gemcitabine (19).

incorporation of J_{HF} into PSEUROT calculations along with guidelines to performing these analyses. Their work had run the gamut of nucleoside derivatives (e.g., 4-thio-, carbocyclic, C-nucleosides) and their detailed analyses have “set the bar” for this type of research. Subsequent to this guide, several other studies of fluorinated nucleosides have revealed some novel trends when specific changes are made, especially to the nucleobase. The groups of Altona, Mikhailopulo and Seela have dominated these studies from 2000-2007, and many other groups had begun to incorporate fluorinated analogues into DNA and RNA structures and studied their high resolution structures along with the effect that fluorine substitution in various positions has on hybridization potential and melting temperatures of duplexes formed with these modified ON's. This section will begin by describing some of our work and progress to some work that “shifted” the paradigm of fluorine’s effect on ribose conformation. The review will conclude with a brief description of some of the oligonucleotide work that has been reported in the last 10 years.

Adenosine deaminase (ADA) is an enzyme of the purine metabolic pathway that converts adenosine and 2'-deoxyadenosine to their inosine derivatives. It is critical to immune system development and in addition, ADA is overexpressed in many haematological cancers, and its inhibition has been associated with potentiating the potency of anticancer nucleosides that are targets of ADA catabolism. In 2000, we published on the structural analysis of several mono-fluorinated nucleosides that were potential inhibitors of ADA to further define the structural requirements of the enzyme’s substrates/inhibitors (58). Using NMR and PSEUROT we were able to assign preferred ring puckers to these compounds and molecular modeling helped us to dock the best inhibitors into the active site of the enzyme. We found that ADA greatly preferred the *N* sugar pucker over the *S*, and docking an *S*-puckered sugar into the enzyme active site pocket actually caused the molecule to “flip” to the more preferred *N*-conformation during extended molecular dynamics simulations (Figure 5).

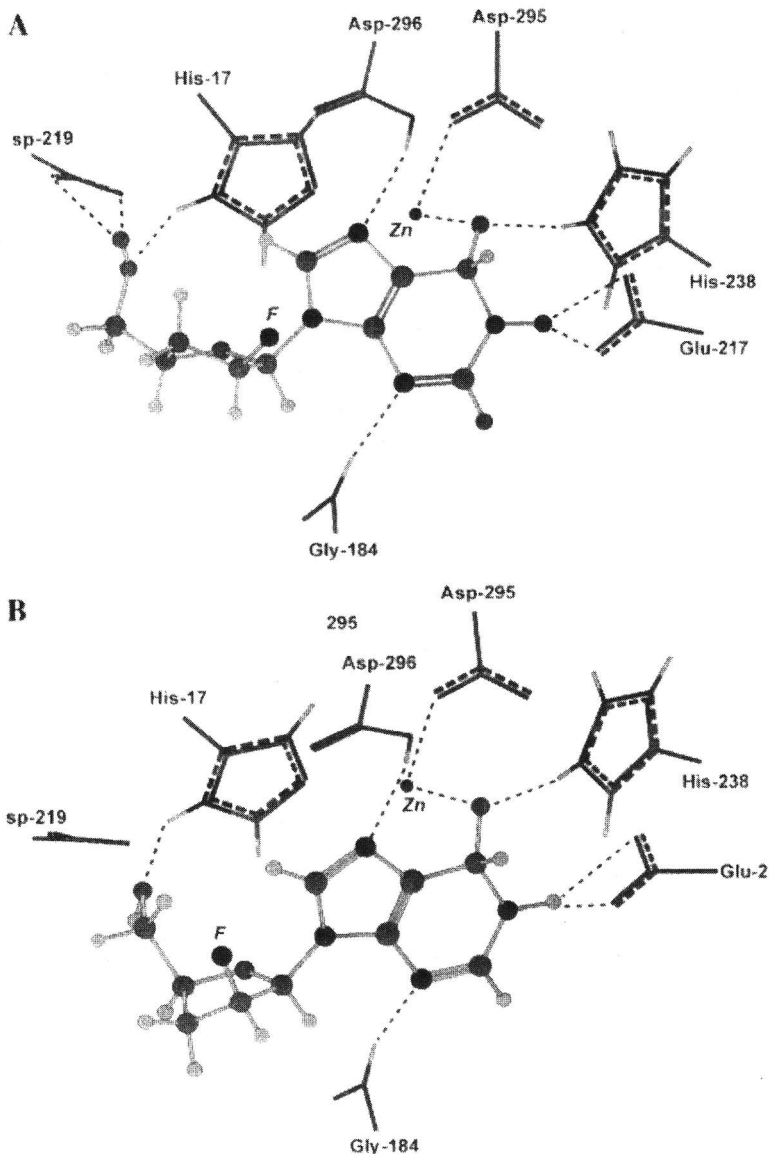


Figure 5. 2'- β -F-dideoxyadenosine (Lodenosine) docked into the active site of ADA. In (A) all atoms were allowed to adjust during the simulation and in (B) the S-preferred sugar pucker was "locked" in place. It is clear in (A) that the sugar ring has now a standard N-twist conformation. (from (58))

In 1999, the Seela group in Osnabrück published a study on the effect of some unusual bases on the structural features of the 2-deoxyribose sugar in these derivatives (59). Compounds **20** and **21**, with 7-halogeno-7-deaza, 8-aza purine bases (Figure 6) were shown to exhibit a high-*anti* disposition about the glycosyl bond and were puckered *N* in their solid state structures. In addition, their solution state ring puckers as calculated by PSEUROT 6.2 were shown to favor the *N* 8-10% more than the standard purine nucleosides. Here there were both stereoelectronic and steric effects working to drive these derivatives to favor *N* puckers. This study set the stage for follow up work with fluorinated nucleosides. The first example of this effect was published in 2003 and showed that 2'-*ara*-fluoro-2'-deoxy-3-bromopyrazolo (3,4-*d*)pyrimidines **22** and **23** also favor the *N* sugar pucker, as opposed to the same compounds with standard adenine or guanine bases (60). The sugar puckers as calculated by PSEUROT

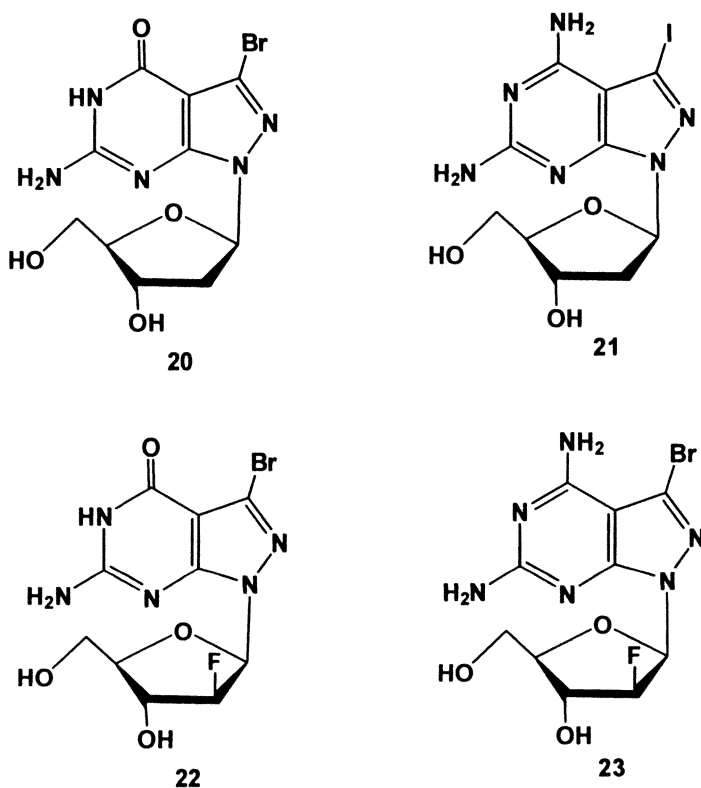


Figure 6. The four 8-aza-7-halogeno-7-deazapurines that all pucker in the *N* hemisphere from the work of Seela et al. (59,60)

were 98% in the N hemisphere, with P angles almost pure North (358°). This was also true for the solid state structures of **22** and **23**.

Several observations led to the determination of the unusual N conformations for the pyrazolo ($3,4-d$)pyrimidines described above. Only one vicinal H-F coupling was observed suggesting a nearly 90° disposition of the fluorine atom and a vicinal hydrogen (i.e., H1'). In most 2'-*ara*-fluoro nucleosides, the $^3J_{\text{H1}',\text{F2}}$ coupling constant is 15-20 Hz. In addition, the antiperiplanar arrangement of the F2' and C4' atoms yields a large $^3J_{\text{C4}',\text{F2}}$ coupling constant of 10-11 Hz. This study was remarkable in the fact that these derivatives showed nearly identical solution and solid state conformations, which has not always been observed, especially in the case of 2'-*ara*-fluoro nucleosides (vide supra and (60)). Other than an increase in the strength of the anomeric effect in these molecules, there is a here-to-for unmentioned GE between the F2' atom and the base nitrogen (N9) that also may play a role in stabilizing the N ring pucker.

Another interesting study by Mikhailopulo and Altona defined the solution conformations of a series of 2'-chloro-3'-fluoro nucleosides where various bases, stereochemistries and aglycones were compared in the context of the NMR data and the latest PSEUROT 6.3 version with parameters for refinement of both $^3J_{\text{HH}}$ and $^3J_{\text{HF}}$ coupling constants (61). Both 5'-protected and unprotected compounds were studied. The conformational analysis showed that there were varied sugar puckers in these derivatives depending on the nature of the sugar substituents. In all, fluorine did drive the pseudorotational equilibrium toward the S , since the GE of chlorine is not nearly as powerful as that of fluorine. Of interest in the analysis was the implementation of the Brunck and Weinhold (62) interpretation of the GE which deviates from that of Wolfe (17). The premise is that there is maximum antiperiplanar $\sigma \rightarrow \sigma^*$ stabilization when the donating bond is the least polar one and the acceptor orbital is at the most polarized bond. This interpretation was suggested to offer explanations for the relative conformational bias in the derivatives that were as good or better than invoking the earlier definition related to the gauche preference for vicinal electronegative atoms. It should be noted that many of the apparent "discrepancies" in the analyses of ring pucker based on the 2',3'(X)-O4' GE's may be explained by this theory, and its use is becoming more prevalent in these studies.

A whole series of diverse nucleosides with a 2'-*ara*-fluorine substitution synthesized by Seela's group were shown to "defy" the GE of the F2'-O4' drive toward the S and display sugar puckers that are highly biased to the N pucker both in solution and the solid state. Some of these are shown in Figure 7. Although the 2'-*ara*-F atom drives the overall ring pucker of most of these to the S , there is an increased proportion of N conformer when the base changes to increase the contribution of the anomeric effect to the overall equilibrium. Thus, 5-aza-7-deazaguanine nucleosides (63), 7-deazapurines (64), 6-azauridine (65) or tubercidin derivatives (66-68) (Figure 7), all with the 2'-fluoroarabino-

furanosyl sugars either pucker exclusively in the *N* hemisphere or shift the conformational equilibrium toward the *N*-puckered sugars. This work definitively showed that specific changes on the base moiety can dramatically influence the ring conformation of fluorinated nucleosides.

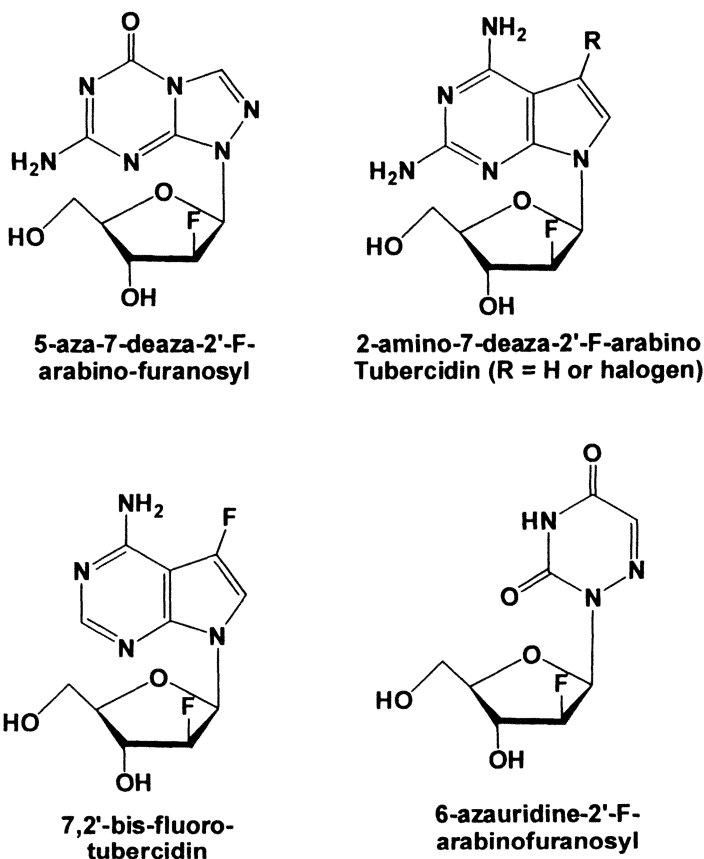


Figure 7. Various structures from the Seela group that pucker preferentially or partially toward the *N* furanose conformation.

Other than our work cited above, there have been very few studies on 2',3'-difluorinated nucleoside analogues. A very recent paper by Sivets et al. (69) described the synthesis of several fluorinated nucleosides with various substituents at either C3' or C1' (different aglycones, Figure 8). Although this study did not include biological data, families of molecules cited therein (3'-

amino-2'-F-adenosine, **24**) are important in the preparation of N(3')- P(5') phosphoramidate oligonucleotides (*70*) which can inhibit cancer cell growth by their complementarity to the RNA template region of human telomerase (*71*). The 2',3'-ribo-difluoroadenosine **25** was synthesized and subjected to complete structural analysis in solution. All of the 3'-substituted 2'-fluoro-nucleosides favored the *N* pucker, and the percentage of *S* pucker increased with increasing electronegativity of the 3'-substituent.

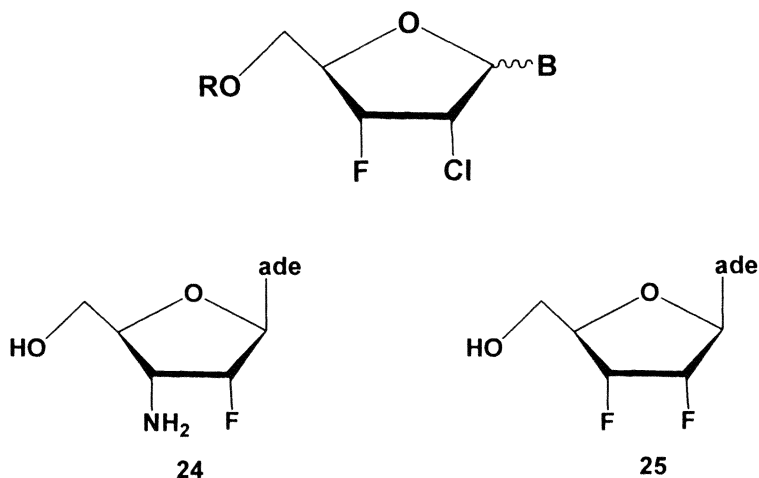


Figure 8. General structure of compounds synthesized by Sivets, *et al.* (*68*) (top) and structures of compounds **24** and **25**. All these compounds favor a *N*-type pucker

4'-Thio Fluorinated Nucleosides

A handful of research groups have synthesized and studied the structures and biological activities of fluorinated nucleosides where the O4' oxygen is replaced with sulfur. This interesting series of compounds were originally prepared as surrogates of standard O4'-nucleosides that may be more resistant to phosphorylases and nucleases (*72*). Although several compounds have been prepared since the early 1990s, very few contain fluorine. The majority of this work came from the groups of Secrist (*73-75*), Marquez (*765-78*), Chu (*79*) and Jeong (*72,80*). Crystal structures of the entire series of monofluorinated-dideoxy uridine analogues, similar to those shown in Scheme 4 but substituting sulfur for the ring oxygen, were obtained by Jeong and Marquez. The ring puckers all correspond to the "standard" conformation for each fluorinated derivative: The

F-S4' GE evidently takes charge of the ring conformation and the rings follow a common trend outlined previously, at least in the solid state (Figure 9).

One recent study has explored the solution conformation of a fluorinated 4-thio nucleoside 4'S-FMAU (2'-fluoro-5-methyl-*ara*-uridine) and compared it to that of the oxygenated counterpart FMAU (81). The authors found that the thio-derivative puckered in the pure *N* conformation ($P = -4^\circ$), again, counter to what would be predicted if invoking the concept of the GE of the ring substituents. The corresponding oxygen derivative remained in the southern hemisphere with a *P* value of $\sim 120^\circ$.

Some Thoughts on F-nucleosides Incorporated into Oligonucleotides

There is a wealth of information in the literature that expounds upon the effect of incorporating a fluorinated nucleoside into a DNA or RNA chain. As is evident from the information contained in this review, inserting a surrogate for a hydroxyl group that may modulate the conformational properties of the monomer should by inference have a direct influence on the structure of the oligomer. This undoubtedly is the case and has been shown by several groups. At present, there are a host of different constructions (without fluorine) that have been designed into monomer nucleotides effectively to "lock" the conformation into one ring pucker or another, and incorporated into DNA, hybridized with RNA and tested for activity as antisense, antigene or RNAi-based therapeutics. Without going into great detail, the following paragraph will simply outline selected studies that have been catalysts for other more intricate design models.

In 1997, Reif et al. (821), published an outstanding piece of work comparing the structures of RNA oligomers with and without incorporation of 2'-ribofluoropyrimidine building blocks by NMR spectroscopy. A full battery of biophysical methods were used to probe the solution structures including H-H NOESY spectra edited to observe only protons close to fluorine and H-F HSQC-E-COSY spectra used to obtain H-F coupling constants for pseudorotation analysis. The authors showed that the fluorinated ON existed in a mixture of hairpin/duplex forms whereas in the unmodified ON, only a hairpin conformation was detected. Using the H-F coupling constant data, they were also able to show that in the sugar puckers in the stem region of the hairpin conformation equilibrated between two conformations in both a uridine and cytidine base unit. The following year, we published a study where we incorporated 2'-*ara* and 2'-*ribo*-oriented monofluorinated nucleotides into a standard B-type DNA (*S* ring pucker) to study the effect of the fluorine on DNA conformation and hybridization (83). We found that adding 2'-*ara*-fluoro nucleotides stabilized the Dickerson Drew dodecamer, a prototype "all B DNA" duplex. Destabilization was realized with 2'-fluoro-"down" (*ribo*) configured

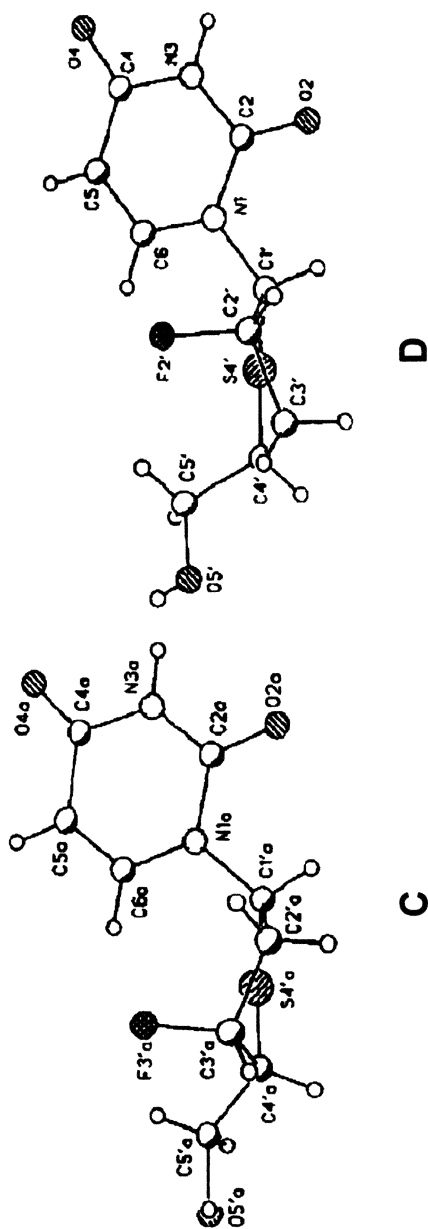


Figure 9. ORTEP drawings of the solid state structures of dideoxy-monofluorouridines: (A) 3'-F-'down'; (B) 2'-F-'up' and (D) 2'-F-'up'.

nucleotides, suggesting that the *N*-driving fluorine at C2' destabilized this B-form DNA. Crystal structures of the DNA having the thymidines replaced with 2'-*ara*-fluorothymidine showed a very stable duplex that was partially "preorganized" to fold into a B-DNA helix. The fluorinated base pairs puckered in the east quadrant of the PC, completely acceptable conformational space for B-DNA (84). Around the same time, Dahma et al., published a landmark study of the conformation and duplex stability of 2'-arabinonucleosides (F-ANA) in several different DNA duplex sequences and showed that these oligos efficiently formed RNA/F-ANA hybrids and took the form of an A-like DNA conformation (85). These hybrids were capable of activating RNase H which subsequently cleaves the RNA strand (86). These constructs were taken to commercial use by the company Topigen to be used in gene silencing and other therapeutic oligonucleotide applications.

Conclusions

This limited review of the literature has outlined some of the more unique effects that fluorine substitution can impart to nucleoside structure and function. Fluorine is an atom that always makes things interesting. It has properties that are rarely benign, but it works as an almost perfect replacement for hydroxyl or hydrogen in specific applications. The electronic properties of fluorine impart intriguing properties to almost any molecule where it resides—this is especially evident from the work described above. In most medicinal chemistry programs, when deciding on "what changes" to make in the lead molecule, fluorine substitution invariably comes to mind. In nucleosides it has dramatic effects on the ring pucker, which in turn can cascade to the other physical and structural properties of the molecule. The effects of fluorine substitution can often be predicted, but more often one is astounded with what is actually observed, and hence we continue to utilize, and marvel at the unexpected activity-imparting, potency-enhancing or conformation-modulating properties of this "simple" substitution. Although not a comprehensive list, this manuscript should serve to excite the community who has not been introduced to the "wonders" of fluorine and the fascinating therapeutic potential for the many fluorinated nucleoside derivatives that are now being evaluated.

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Chapter 12

Synthesis and Reactions of Fluorinated Nicotinonitriles

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The first part of the review describes methods of synthesis of substituted 2-fluoronitriles of nicotinic acid utilizing simple and readily available reagents such as halogenated pyridines, pyridine-2(1*H*)-thiones, potassium fluoride, and TBAF. The second part encompasses a one-pot synthetic method for preparation of difluoro- and trifluoro-substituted 2-mer-captonitriles of nicotinic acid. The described method allows facile synthesis of diverse di- and trifluoropyridines in one pot and does not require purification and isolation of any reactive intermediates. These fluoromethylated 3-cyanopyridinethiones were demonstrated to be convenient reagents for domino-type reactions leading to diverse polyannulated heterocyclic systems.

2-Fluoronicotinonitrile and Its Derivatives: Direct Nucleophilic Fluorination of Pyridine Ring

2-Fluoropyridines are an important class of biologically active compounds that include potent kinase inhibitors, potassium channel inhibitors, and CNS active agents (Figure 1) (1-3). In addition, fluorinated pyridines can be potentially used as labeling agents for various spectroscopic techniques such as positron emission tomography, X-ray photoelectron spectroscopy, and NMR spectroscopy.

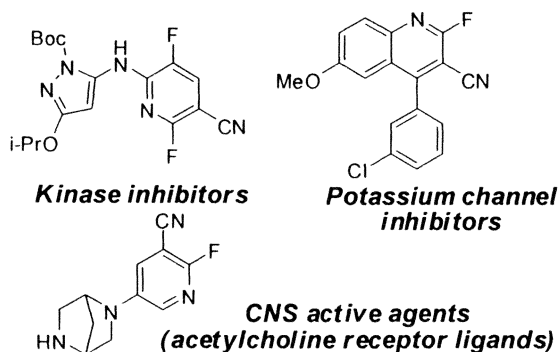
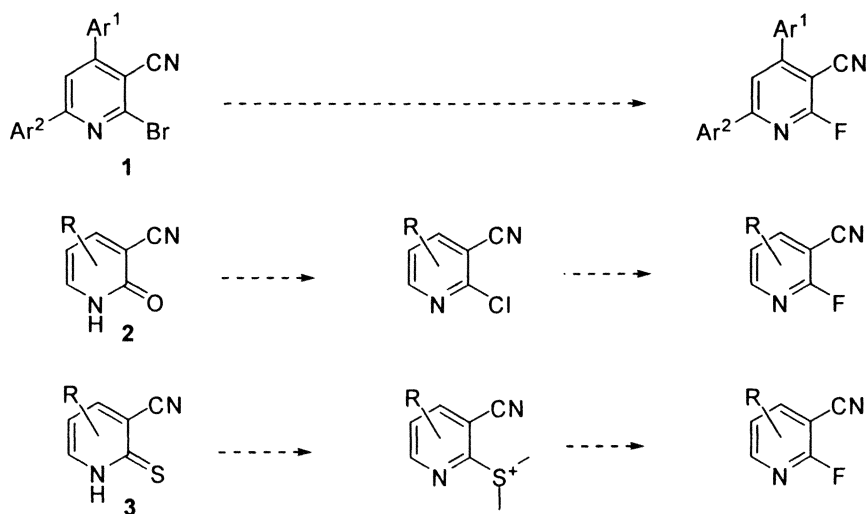


Figure 1. Examples of biologically active fluorinated pyridines.

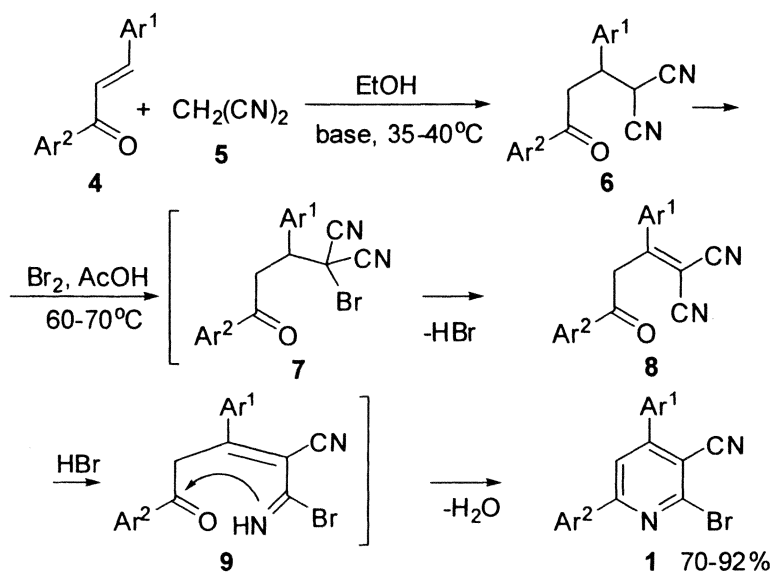
Known methods of synthesis of 2-fluoropyridines, such as the Balz-Schiemann reaction and nucleophilic substitution in activated pyridines, have several limitations. They usually put significant restrictions on the functional groups that can be present in the pyridine ring, and often require special conditions, as well as laborious work up and purification procedures. Other methods of synthesis of 2-fluoropyridines include direct fluorination of substituted pyridines (4), decomposition of N-fluoropyridinium salts (5), and transformation of azirindifluoromethanides into fluoropyridines (6).

We decided to investigate several new strategies that potentially could yield 2-fluoropyridines in high yields utilizing simple synthetic techniques. As our precursors to fluoropyridines we chose 2-bromo-3-cyanopyridines **1**, 3-cyano-2-pyridinones **2**, and 3-cyano-2-pyridinethiones **3** (Scheme 1). All these reagents can be readily prepared directly from the commercially available compounds, and they all have the 2-position activated for nucleophilic substitution.

Following a previously developed protocol several 2-bromo-3-cyanopyridines **1** were prepared from 1,3-unsaturated ketones **4** and malononitrile **5** in two simple steps (Scheme 2) (7,8). First, reaction of **4** and **5** in ethanol in the presence of base gave Michael adduct **6**, which was then treated with Br₂ in acetic



Scheme 1. Starting compounds for synthesis of 2-fluoropyridines.

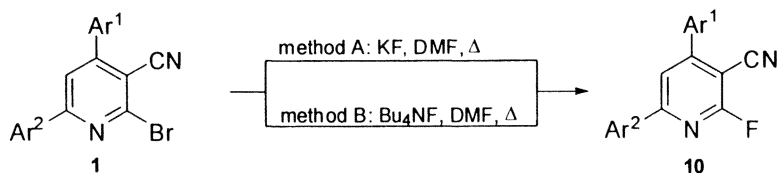


$\text{Ar}^1, \text{Ar}^2 = \text{C}_6\text{H}_5$; $\text{Ar}^1 = \text{C}_6\text{H}_5, \text{Ar}^2 = 4\text{-F-C}_6\text{H}_4$; $\text{Ar}^1 = 4\text{-Cl-C}_6\text{H}_4, \text{Ar}^2 = \text{C}_6\text{H}_5$;
 $\text{Ar}^1 = 4\text{-CH}_3\text{-C}_6\text{H}_4, \text{Ar}^2 = \text{C}_6\text{H}_5$; $\text{Ar}^1 = 4\text{-CH}_3\text{O-C}_6\text{H}_4, \text{Ar}^2 = \text{C}_6\text{H}_5$;
 $\text{Ar}^1 = 2\text{-C}_4\text{H}_3\text{S}, \text{Ar}^2 = \text{C}_6\text{H}_5$.

Scheme 2. Synthesis of 2-bromo-3-cyanopyridines.

acid at 60–70 °C and cyclized into 2-bromopyridine **1** in 70–92 % yields via possible formation of transient intermediates **7**, **8**, and **9**.

Substituted 2-bromo-3-cyanopyridines **1** were successfully converted into substituted 3-cyano-2-fluoropyridines **10** (Scheme 3). A nucleophilic replacement of bromine with fluorine was achieved in heated DMF with dry KF (Method A) or with dry TBAF (Method B). The yields of 2-fluoropyridines **10** were 15–20 % higher in Method B (Scheme 3).



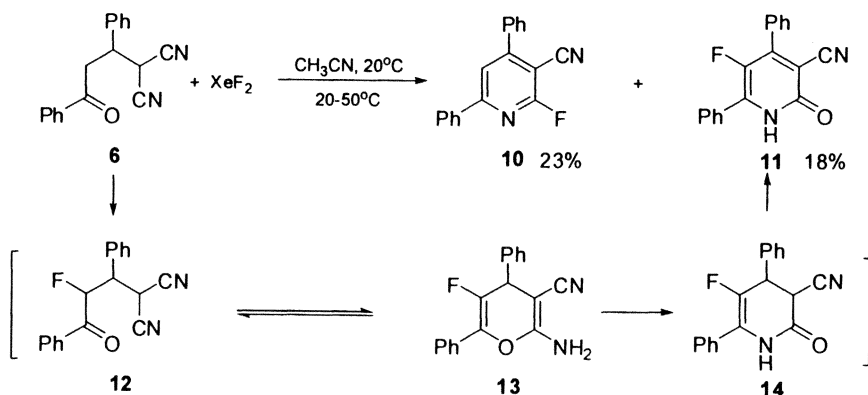
Ar ¹	Ar ²	Yield (method A)	Yield (method B)
C ₆ H ₅	C ₆ H ₅	62	90
C ₆ H ₅	4-F-C ₆ H ₄	62	82
4-Cl-C ₆ H ₄	C ₆ H ₅	68	76
4-CH ₃ -C ₆ H ₄	C ₆ H ₅	76	87
4-CH ₃ O-C ₆ H ₄	C ₆ H ₅	76	90
2-C ₄ H ₃ S	C ₆ H ₅	63	76

Scheme 3. Synthesis of 3-cyano-4,6-diaryl-2-fluoropyridines from 2-bromo-3-cyanopyridines.

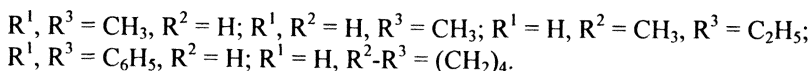
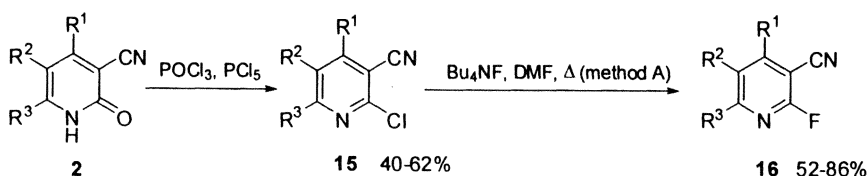
Similar to the bromination reaction of 4-ketonitriles (Scheme 2), we utilized ketonitriles **6** in a fluorination reaction using XeF₂ as a fluorinating agent. We discovered that this reaction proceeds at room temperature in acetonitrile and gives a mixture of 2-fluoro- and 5-fluoropyridines **10** and **11**, which were separated by column chromatography. The low regioselectivity of the fluorination reaction can be explained by the high reactivity of XeF₂, which fluorinates ketonitriles **6** at the 1- and 3-positions at approximately equal rates (Scheme 4).

Substituted pyridine-2(1H)-ones **2** were transformed into 2-fluoropyridines **16** via 2-chloropyridines **15**, which were synthesized from compounds **2** by a chlorination reaction using a mixture of POCl₃ and PCl₅ (Scheme 5). The subsequent transformation of **15** into 2-fluoropyridines **16** was achieved with TBAF in heated DMF.

A transformation of hydroxyheterocycles into chlorinated heterocycles is often used in organic synthesis (9). Using this reaction as a key step, we



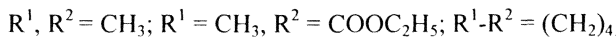
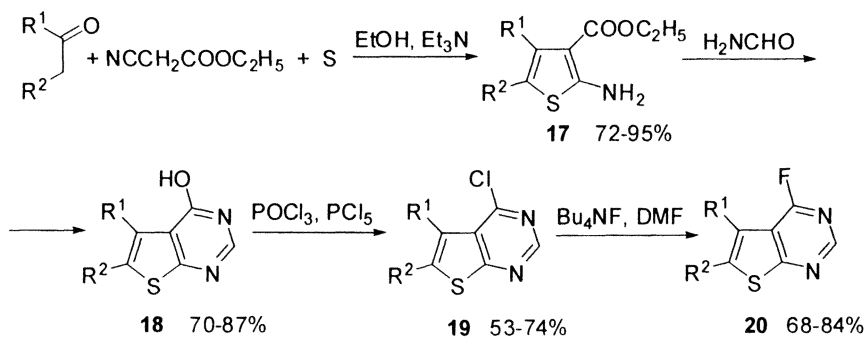
Scheme 4. Fluorination of 4-ketonitrile with XeF_2 .



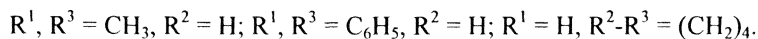
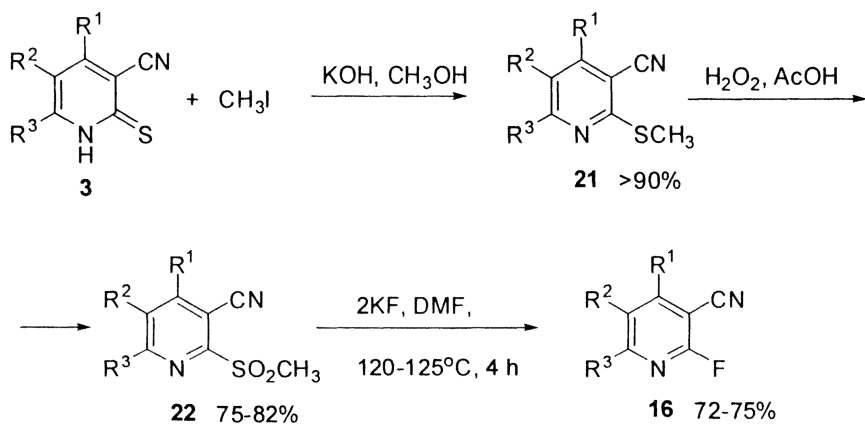
Scheme 5. Synthesis of 3-cyano-2-fluoropyridines from pyridine-2(1H)-ones.

synthesized annulated 7-fluorothienopyrimidines. First, we synthesized 2-amino-3-ethoxycarbonylthiophenes **17** by the Gewald reaction from α -methyl-eneketones, cyanoacetic ester, and elemental sulfur (**10**). The subsequent condensation of **17** with formamide produced 7-hydroxythienopyrimidines **18**, which were converted into chlorinated pyrimidines **19**. Finally, a fluorination reaction of **19** with TBAF in DMF afforded fluorothienopyrimidines **20** in 68–84 % yields (Scheme 6).

We also demonstrated that 3-cyanopyridine-2(1H)-thiones can be transformed into 3-cyano-3-fluoropyridines via two different pathways. As such, pyridinethiones **3** were alkylated with methyl iodide to afford 2-methylthiopyridines **21**, which were subsequently oxidized with an excess of hydrogen peroxide in acetic acid into 2-methylsulfonylpyridines **22** in 75–82 % yields. Reaction of the resulting pyridines **22** with two equivalents of dry KF in heated DMF produced substituted 2-fluoropyridines **16** in 72–75 % yields (Scheme 7).

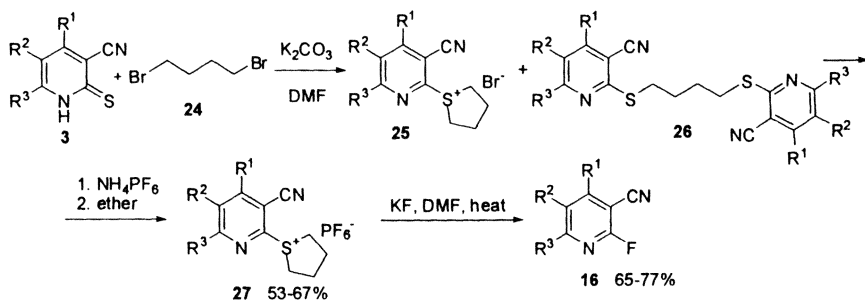


Scheme 6. Synthesis of substituted 7-fluorothienopyrimidines.



Scheme 7. Synthesis of 3-cyano-2-fluoropyridines from pyridine-2(1H)-thiones.

Alternatively, pyridinethiones **3** were first treated with 1,4-dibromobutane **24** to produce sulfonium salts **25** and bipyridines **26** as byproducts (~ 10–12 %). Next, **24** and **25** were separated by converting the bromonium salts **25** into hexafluorophosphonium salts **27** and selectively precipitating resulting compounds **27** by the addition of ether. Lastly, salts **27** were treated with KF in heated DMF to give 2-fluoropyridines **16** (Scheme 8).



$\text{R}^1, \text{R}^3 = \text{CH}_3, \text{R}^2 = \text{H}; \text{R}^1, \text{R}^2 = \text{H}, \text{R}^3 = \text{Ad}^1; \text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2 = \text{H}, \text{R}^3 = 4\text{-F-C}_6\text{H}_4;$
 $\text{R}^1 = 4\text{-CH}_3\text{O-C}_6\text{H}_4, \text{R}^2 = \text{H}, \text{R}^3 = \text{C}_6\text{H}_5;$

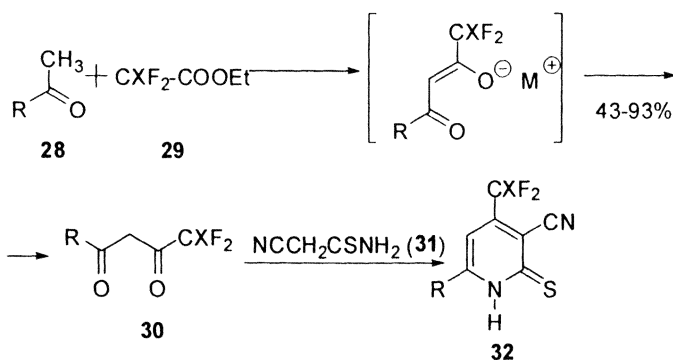
Scheme 8. Synthesis of 3-cyano-2-fluoropyridines from sulfonium salts.

In conclusion, we have demonstrated that various 3-cyano-2-fluoropyridines can be synthesized from readily available reagents such as 2-bromo-(hydroxy-, thio-)pyridines via simple reaction steps using KF and TBAF as fluorinating agents.

Synthesis of Anneleted Fluoroheterocycles Based on 4-Trifluoro(difluoro)methyl-3-cyanopyridine-2-(1H)-thiones

Fluoromethylpyridines were previously identified as potential herbicides (11–14) and medically important compounds (15–19). Apart from the useful biological properties, 6-methyl-4-trifluoromethyl-3-cyanopyridine-2(1H)-thiones and 4-methyl-6-trifluoromethyl-3-cyanopyridine-(1H)-thiones have been effectively utilized in the past as versatile building blocks suitable for preparation of diverse libraries of annulated and non-annulated heterocycles (14). These reasons motivated us to develop a new efficient method to synthesize diverse 3-cyanopyridine-2(1H)-thiones containing the di(tri)fluoromethyl group and to demonstrate that these compounds are effective building blocks suitable for fast derivatization.

In most cases, fluoromethylated 3-cyanopyridine-2(1*H*)-thiones **32** are obtained by the reaction of fluoromethylated 1,3-diketones **30** with cyanothioacetamide **31** (14,20-22). Unfortunately, synthesis, isolation, and purification of the fluoromethylated 1,3-diketones as starting materials often involve laborious multistep procedures, resulting in poor yields (*Scheme 9*) (23-25). Hence, the diversity of the accessible fluoromethylated 3-cyanopyridine-2(1*H*)-thiones was usually determined by the commercial availability of the corresponding fluoromethylated 1,3-diketones **30** (14,21,22,26,27), the majority of which are aroyltrifluoroacetones. Here, we report a new regioselective one-pot method of synthesis of 4-difluoro(trifluoro)methyl-3-cyanopyridine-2(1*H*)-thiones which obviates the isolation and the purification of the fluoromethylated 1,3-diketones.



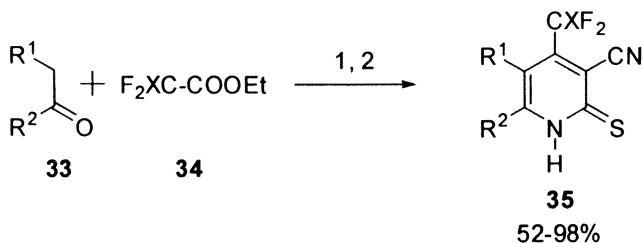
R = Ar, Het, Me; X = H, F.

*Scheme 9. Synthesis of 4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thiones.*

The developed method allows the entire synthesis of the final pyridine-2(1*H*)-thiones to be carried out in a single reaction vessel, without isolation or transfer of the fluoromethylated intermediates. First, the Claisen condensation between corresponding methyl(methylene)ketone **33** and ethyl difluoro(trifluoro)acetate **34** is conducted in ether in the presence of sodium ethoxide. Then, after evaporation of ether, the reaction mixture is treated with cyanothioacetamide at 50–60 °C in ethanol, quenched with acetic acid, and refluxed for a short period of time to produce final pyridine **35** (*Scheme 10*). The yields of prepared 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones **35** vary from 50 % to 98 % and strongly depend on other substituents present in the pyridine ring.

The described procedure not only permits synthesis of diverse 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones with virtually any possible

aryl- or heteroaryl-substituents in the 6-position, but also allows preparation of various 6-alkyl substituted pyridines, including sterically hindered and constrained adamantyl and cyclopropyl fragments. Moreover, the same method can be used to obtain 5,6-dialkyl- and 5,6-cycloalkylpyridine-2(1*H*)-thiones. The regioselectivity of the reaction was confirmed by the synthesis of known 6-methyl-4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thione, the structure of which was established by X-ray analysis (22,27).

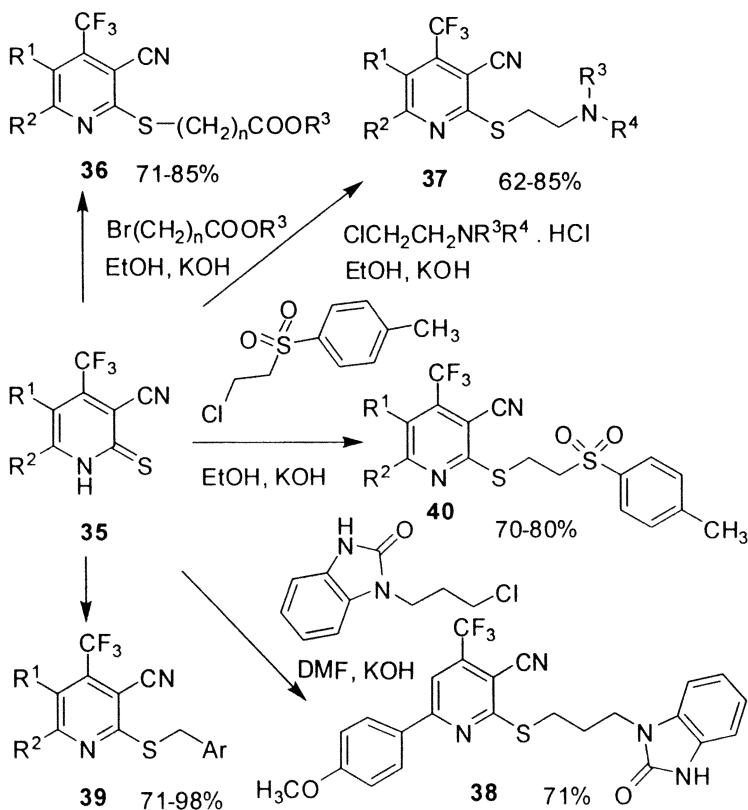


1 - EtONa, Et₂O, 0°C, 3h, evaporation of solvent;
 2 - NCCH₂CSNH₂ (31), EtOH, AcOH, 50-60 °C.

R ¹	R ²	X	R ¹	R ²	X
H	2-Cl-C ₆ H ₄	F	-(CH ₂) ₃ -		F
H	2-C ₄ H ₃ O	F	-(CH ₂) ₄ -		F
H	4-CH ₃ O-C ₆ H ₄	F	-(CH ₂) ₄ -		H
H	2,5-(CH ₃ O) ₂ -C ₆ H ₃	F	H	CH ₂ -	H
H	3,4-(CH ₃ O) ₂ -C ₆ H ₃	F	H	4-Cl-	H
H	3-C ₃ H ₄ N	F	H	4-F-	H
H	<i>i</i> -C ₃ H ₇	F	H	3-C ₅ H ₄ N	H
H	Ad ¹	F	H	2-C ₄ H ₃ S	H
CH ₃	CH ₂ CH ₃	F			

Scheme 10. Synthesis of 4-trifluoro(difluoro)methyl-3-cyanopyridine-2(1H)-thiones.

The prepared fluoromethylated pyridinethiones were used as precursors in the synthesis of diverse 2-alkylthienopyridines containing CF₃- or CHF₂-groups (Scheme 11). Accordingly, compounds 35 can be regioselectively alkylated by halogenated carboxylic acids and their esters in ethanol in the presence of equimolar amount of KOH to give pyridyl-2-thiocarboxylic acids and esters 36. Similarly, pyridines 35 can be alkylated with β-chloroethylamines in ethanol or DMF in the presence of KOH to produce compounds 37 and 38. The same



36: $n = 2$, $\text{R}^3 = \text{H}$; $n = 2, 3$, $\text{R}^3 = \text{Et}$.

37: $\text{R}^3-\text{R}^4 = \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$; $(\text{CH}_2)_4$; $(\text{CH}_2)_5$; $(\text{CH}_2)_6$.

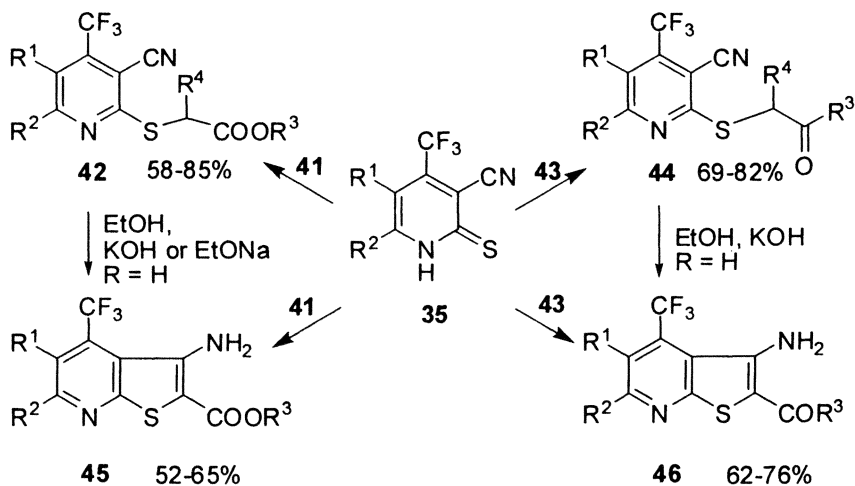
39: $\text{Ar} = 4\text{-COOH-C}_6\text{H}_4$; $2\text{-C}_3\text{H}_4\text{N}$; Bz ; $o\text{-CH}_3\text{-Bz}$.

Scheme 11. Synthesis of 2-alkylthieno-4-trifluoromethyl-3-cyanopyridines.

reaction can be also used to produce 2-arylmethylenethiopyridines **39** from benzyl halides, and substituted pyridines **40** from β -chloroethylsulfonylchlorides.

α -Halogen carbonyl compounds **41,43** can also react with substituted pyridine-2(1*H*)-thiones **35** giving *S*-substituted pyridines **42,44**. In this reaction we did not observe formation of unsaturated elimination products. Most likely the alkylation reaction proceeds via an $\text{S}_{\text{N}}2$ mechanism (Scheme 12).

In the presence of excess base (KOH) the reaction of pyridinethiones with α -halogen carbonyl compounds proceeds further and gives 3-aminothieno-[2,3-*b*]pyridines **45** and **46** in a two step cascade process (nucleophilic substitution,



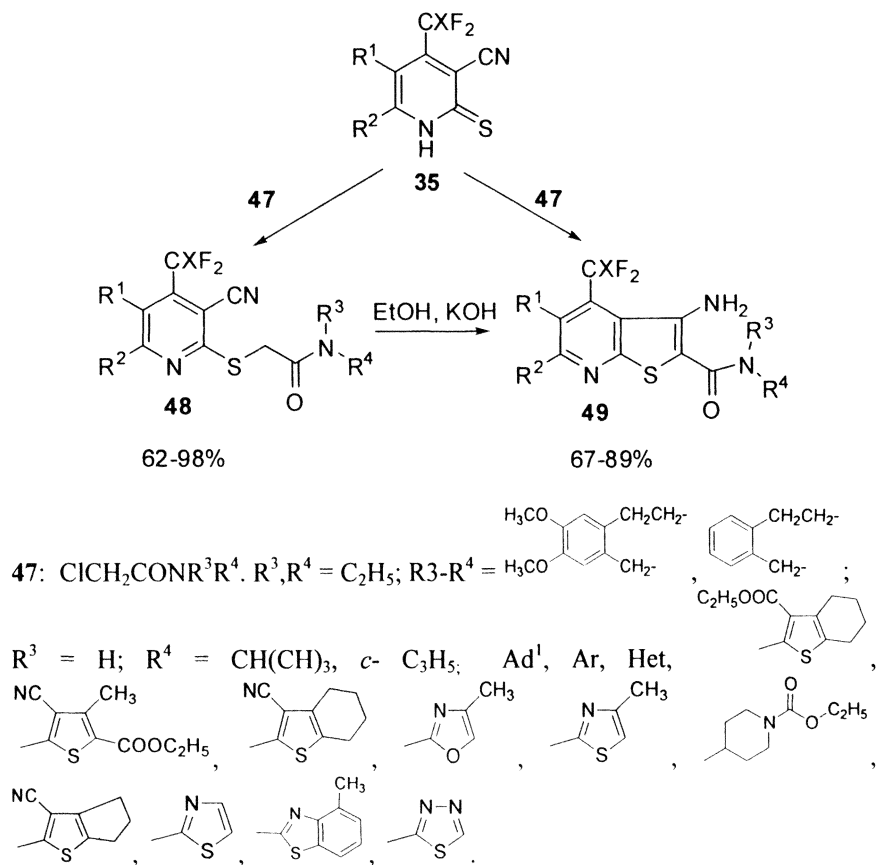
41: ClCH₂COOH; BrCH(C₆H₅)COOH; ClCH₂COOC₂H₅;
 BrCH₂COOCH₂C₆H₅; BrCH(CH₃)COOC₂H₅.

43: ClCH₂COCH₃; ClCH(CH₃)COCH₃; 3,4-(OCH₂O)-C₆H₃-COCH₂Br;
 3,4-(OH)₂-C₆H₃-COCH₂Br; 3,4-(OCH₂CH₂O)-C₆H₃-COCH₂Br; 3,4-(OCH₃)₂-C₆H₃-COCH₂Br.

*Scheme 12. Synthesis of 4-trifluoromethyl-3-aminothieno-[2,3-*b*]pyridines.*

followed by the Thorpe-Ziegler reaction). Reactions of substituted pyridinethiones with α -halogen acetamides **47** have broad synthetic potential. A variety of *N*-substituted chloroacetamides can be used, including reagents containing pharmacophoric fragments, leading to the preparation of a series of pyridyl-2-thioacetamides **48** and 2-carbamoyl-3-aminothieno[2,3-*b*]pyridines **49** (*Scheme 13*).

Substituted pyridine-2(1*H*)-thiones **35** were used as starting materials for synthesis of a previously unknown heterocyclic system: pyridothienobenzo-diazocinone **53** (*Scheme 14*). These compounds were first prepared stepwise by a reaction of **35** with chloroacetamide **50** in DMF in the presence of an equimolar amount of KOH, followed by the subsequent treatment of compound **51** with an excess of KOH, and by the subsequent cyclization of the resulting thieno[2,3-*b*]pyridine **52** into diazocine **53** under reflux in ethanol in the presence of KOH. Diazocines **53** also can be obtained in one step directly from chloroacetamides **50** and pyridinethiones **35** by a domino reaction: S_N2 reaction – the Thorpe-Ziegler reaction – the Thorpe-Guareschi reaction. Both methods gave comparable yields (~52-55%).

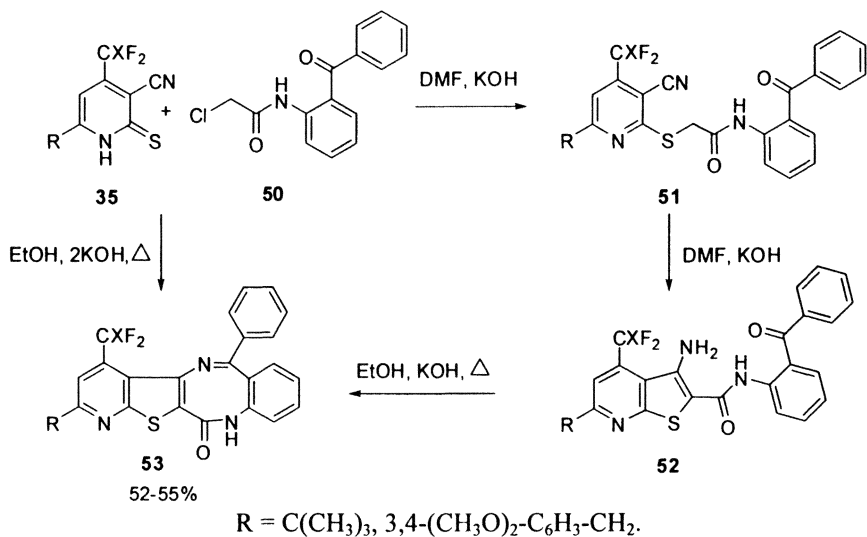


Scheme 13. Synthesis of 4-trifluoro(difluoro)methylpyridyl-2-thioacetamides and 2-carbamoyl-3-aminothieno[2,3-b]pyridines.

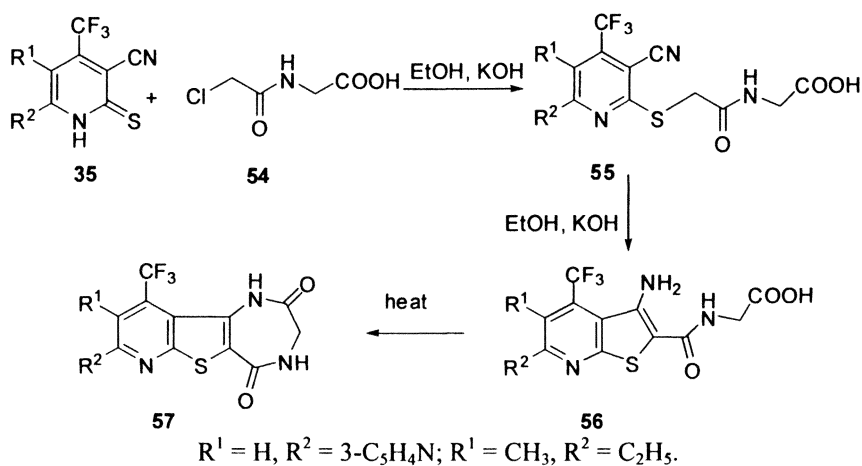
Using pyridinethiones **35** and chloroacetyl aminoacetic acids **54** we developed a method of synthesis of poly-annulated diazepines **57** (Scheme 15). Accordingly, pyridinethiones **35** were first alkylated to yield compounds **55**, which were then cyclized into thienopyridines **56** by the Thorpe-Ziegler reaction, which in turn were heated slightly above their melting points without solvent to give diazepines **57**.

Using this reaction we prepared annulated pyrrolo diazepine **61**, analogues of which were previously identified as antibiotics and anti-cancer compounds (Scheme 16).

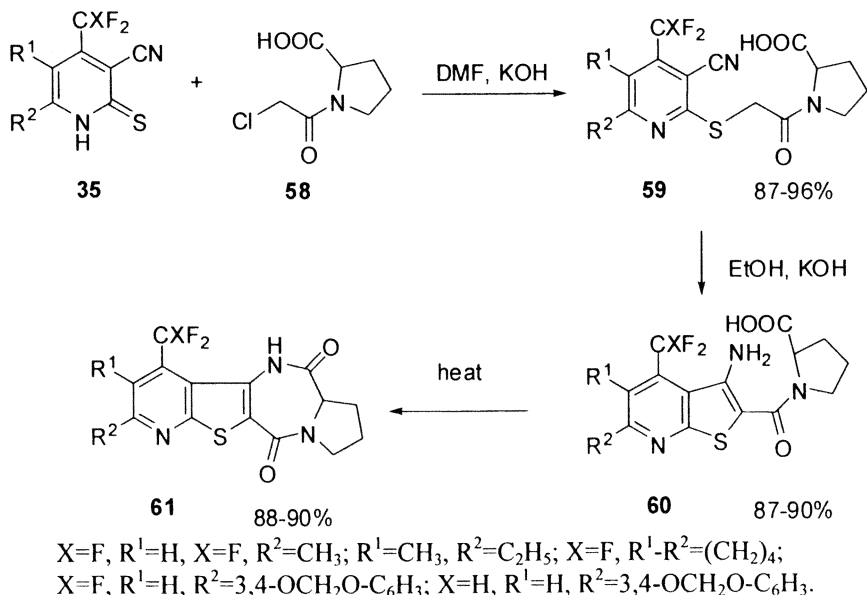
Pyridinethiones **35** were used in domino-type reactions with 4-chloroacetoacetic ester **62** ($\text{Y}=\text{CH}_2$) and chloroacetylurethane **62** ($\text{Y}=\text{NH}$) to



Scheme 14. Synthesis of pyridothienobenzodiazocinones.



Scheme 15. Synthesis of diazepines.



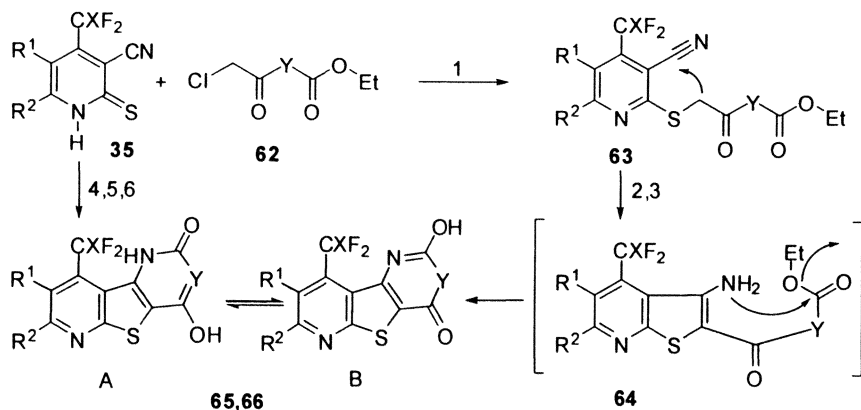
Scheme 16. Synthesis of pyrrolodiazepines.

prepare in high yields dipyridothiophenes **65** (Y=CH) and pyridothienopyrimidines **66** (Y=NH) (*Scheme 17*). Most likely, the reaction proceeds by a sequential $\text{S}_{\text{N}}2$ -substitution, a Thorpe-Ziegler reaction, and a Thorpe-Guareschi reaction. This sequence was partially supported by the isolation of intermediates **63** and by the introduction of these intermediates into the subsequent reaction step.

Dihydroxydipyridothiophenes **65** were subsequently utilized as convenient reagents for the synthesis of annulated 2-amino-4H-pyrans **70**, which were obtained by the reaction of compounds **65** and unsaturated nitriles **67**, or by the three-component condensation of **65**, corresponding aldehydes, and malononitrile (*Scheme 18*).

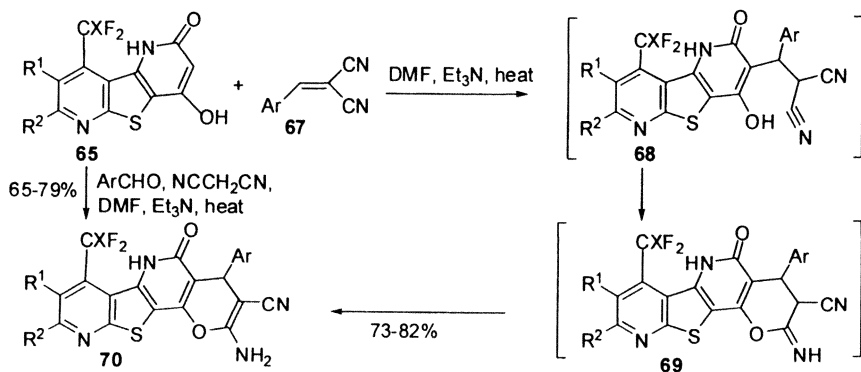
Previously it was demonstrated that esters of pyridylcyanoacetic acid **63** react with electrophilic reagents (28). We discovered that esters **63** regioselectively react with only one methylene group of arylmethylenemalononitrile **71** (CH_2COOR), exclusively giving substituted 2-amino-4H-pyrans **73** (*Scheme 19*).

Compounds **73** were also obtained by the direct alkylation of pyridinethiones **35** with pyran **74**.



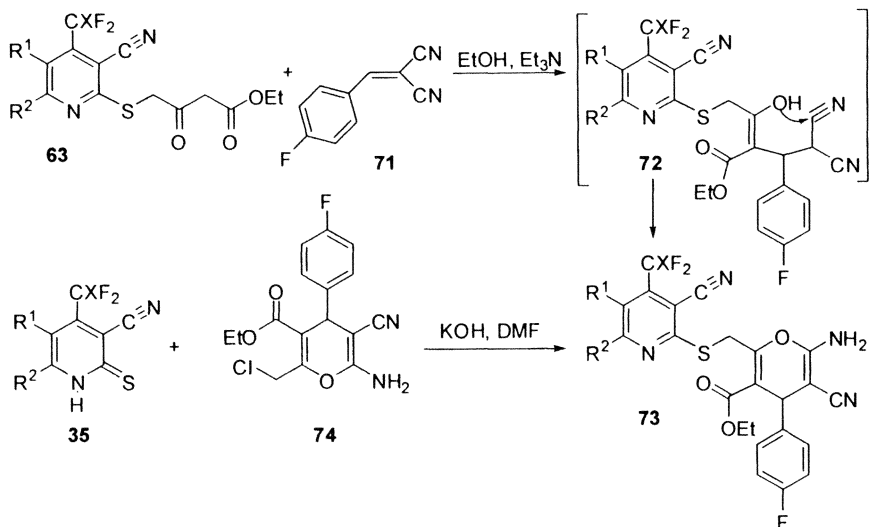
1 - DMF or EtOH, KOH; 2 - **2B**, EtOH, heat; 3 - H₂O, HCl; 4 - **62**, KOH, EtOH, r.t.; 5 - **2B**, heat; 6 - H₂O, HCl. **B** = KOH, EtONa. Y = CH₂, NH.

Scheme 17. Synthesis of dipyridothiophenes and pyridothienopyrimidines.



70: X = F, R¹ - R² = (CH₂)₅, Ar = 4-Cl-C₆H₄; X = H, R¹ = H, R² = 3,4-OCH₂O-C₆H₃, Ar = 4-Cl-C₆H₄; X = H, R¹ = H, R² = 4-OCH₃-C₆H₄, Ar = 4-CH₃O-C₆H₄; X = H, R¹ = H, R² = 3,4-(OCH₃)₂-C₆H₃, Ar = 4-F-C₆H₄.

Scheme 18. Synthesis of annulated 2-amino-4H-pyrans.



$X=\text{R}^1=\text{H}$, $\text{R}^2=3,4\text{-(CH}_3\text{O)}_2\text{-C}_6\text{H}_3$; $X=\text{F}$, $\text{R}^1\text{-R}^2=\text{CH}_2\text{CH(C(CH}_3\text{)}_3\text{)CH}_2\text{CH}_2$

Scheme 19. Synthesis of 2-amino-4H-pyrans.

Acknowledgment

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Chapter 13

Syntheses of Fluorinated 1,3-Oxazoles, 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, and Oxazolo[4,5-*d*]pyrimidines

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The preparation of fluorine-containing azole and azine heterocyclic systems that possess additional pharmacophoric groups is often a difficult process. As our approach, we have carried out cyclization of fluorinated 2-acylamino-3,3-dichloroacrylonitriles. The sequence allows retention of the nitrile group, or this group can be used for further transformation.

In order to obtain fluorine-containing analogues of heterocyclic substances designed for the study of different types of bioactivity, mainly two basic approaches are used. These include reaction of halogen-substituted heterocycles with inorganic nucleophilic fluorinating agents or, alternatively, cyclization of fluorinated organic precursors.

Areas of applications for the two approaches in general do not overlap and they are developed independently. During the last few years, cyclization of various fluorine-containing reagents have been studied with special intensity. Electrophilic reagents for this application were synthesized recently in our laboratory through addition of fluorine-containing carboxamides to chloral (Figure 1).

The sequence of reactions (1)→(2)→(3)→(4)→(5) is similar to transformations of ordinary non-fluorinated chloral amides, which were synthesized and studied previously (1). Of special interest here is the obtaining of fluorinated 2-acylamino-3,3-dichloroacrylonitriles (2), which we have abbreviated ADAN_F.

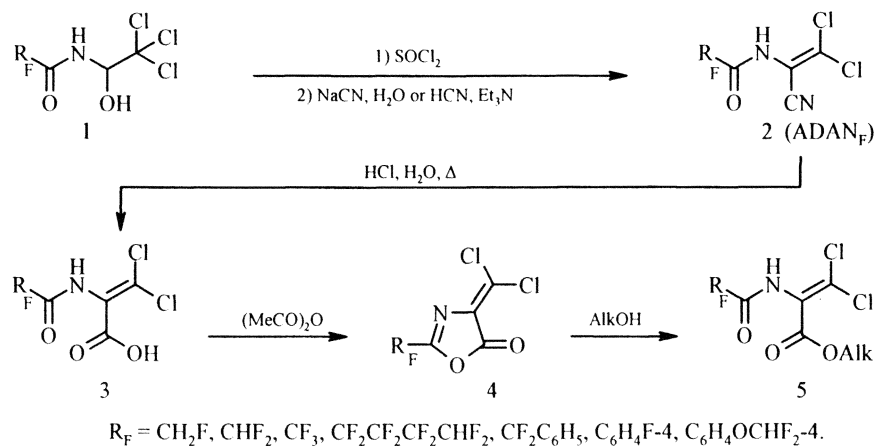


Figure 1

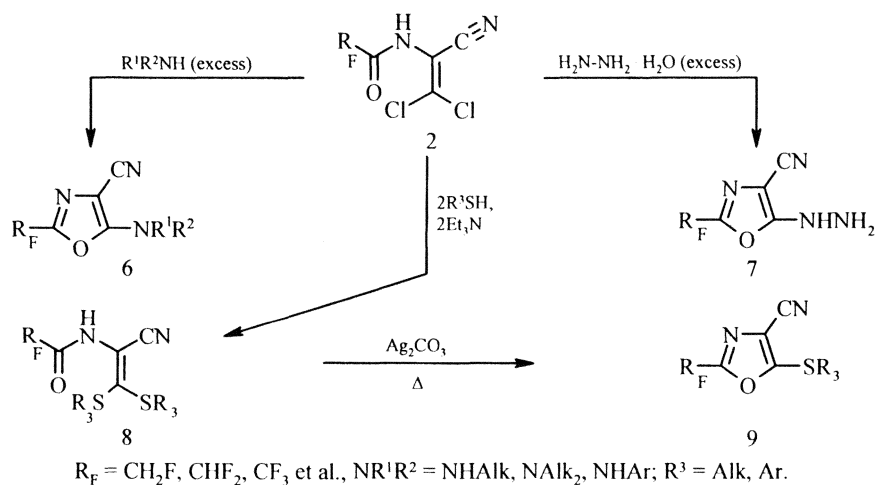
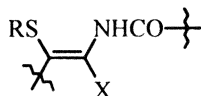


Figure 2

Although derivatives (3-5) are also suitable for the syntheses of heterocyclic compounds, they are not considered in this article in detail, and our main attention is devoted to cyclization reactions based on ADAN_F. We have established that ADAN_F, like non-fluorinated 2-acylamino-3,3-dichloroacrylonitrile (1-3), react under ordinary conditions with various primary and second amines to give substituted 5-amino-4-cyano-1,3-oxazoles (6). These heterocycles contain fluorinated alkyl or aryl residues in position 2 of the oxazole rings (Figure 2).

The ADAN_F reaction with a hydrazine hydrate proceeds in a similar manner to produce the 5-hydrazino-4-cyano-1,3-oxazole derivatives (7). We also successfully synthesized the fluorine-containing derivatives of 5-mercapto-4-cyano-1,3-oxazoles using the sequence of transformations (2)→(8)→(9), presented on the Figure 2.

Formation of oxazole rings as a result of removal of a alkylthio- or arylthio-groups from the generalized structure



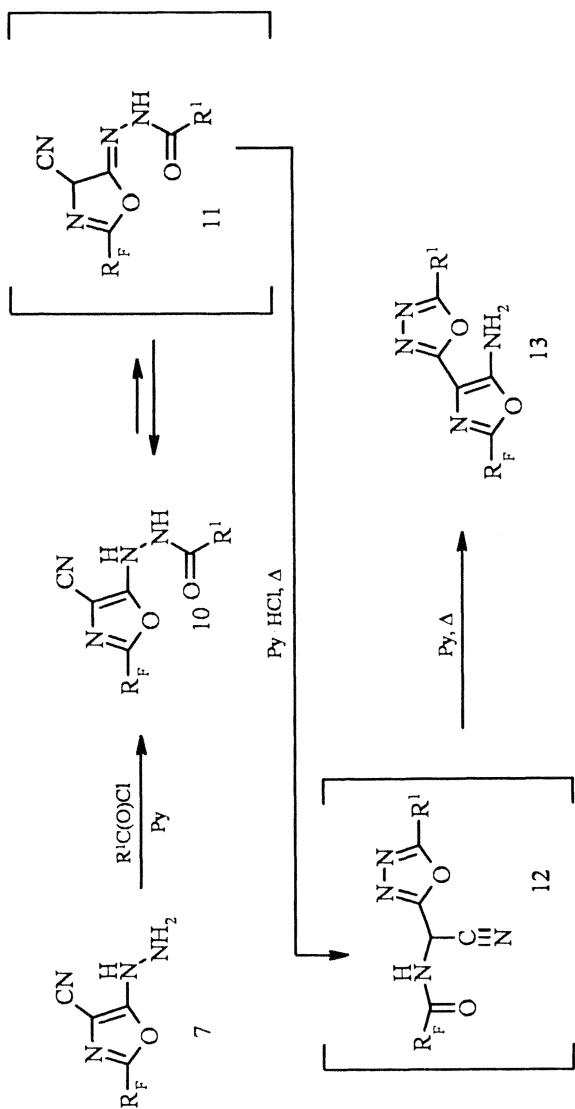
where X=CN, CO(O)OAlk, P(O)(OAlk)₂ and other electron-withdrawing substituents, has been studied recently with several non-fluorinated enamides (4,5). Such cyclocondensations are also characteristic for several of the fluorinated amidonitriles [see transformation (8)→(9) in Figure 2, unpublished results].

The readily accessible reagents ADAN_F were applicable not only for the synthesis of substituted oxazoles, but also for the preparation of new types of fluorine-containing derivatives of 1,3,4-oxadiazoles. Reagents (2) were first converted into substituted 5-hydrazino-4-cyano-1,3-oxazole (7) and their analogues (14). Subsequent treatment with acylating agents initiates the successive transformations: (7)→(10)→(11)→(12)→(13) (Figure 3).

Similar transformations (14)→(15)→(16)→(17) or (18) are shown in Figure 4.

Formation of the 1,3,4-oxadiazole system presented in Figures 3 and 4 occurs due to ring transformation (10)→(13) (15)→(17) and (15)→(18). An important factor in this rearrangement is prototropic destabilization of the oxazole ring. Intermediate prototropic tautomers (11) and (16) contain a non-aromatic oxazoline ring and are capable of ring transformations at elevated temperatures in pyridine or acetic acid. The structure of the recyclization products (13,17,18) were confirmed by combination of spectral methods, by X-Ray analysis of compounds (13) and (18) (6), and also by chemical transformations presented on the Figure 5.

We tried to convert compounds (17) into amino acids (19), but they are easily decarboxylated. However, we did manage to modify compounds (17) by



R_F = CH₂F, CHF₂, CF₃, CF₂CF₂, CF₂CHF₂, CF₂C₆H₅, C₆H₄F-4, C₆H₄OCHF₂-4; R¹ = Alk, Ar, R_p.

Figure 3

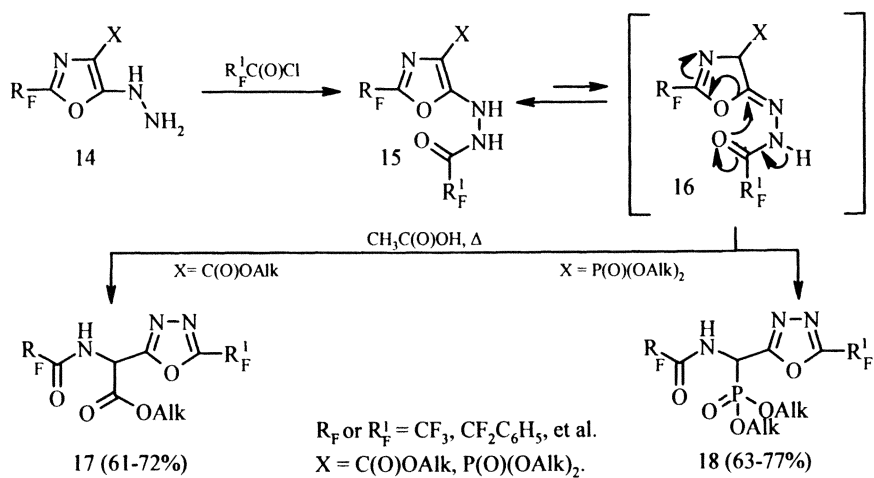


Figure 4

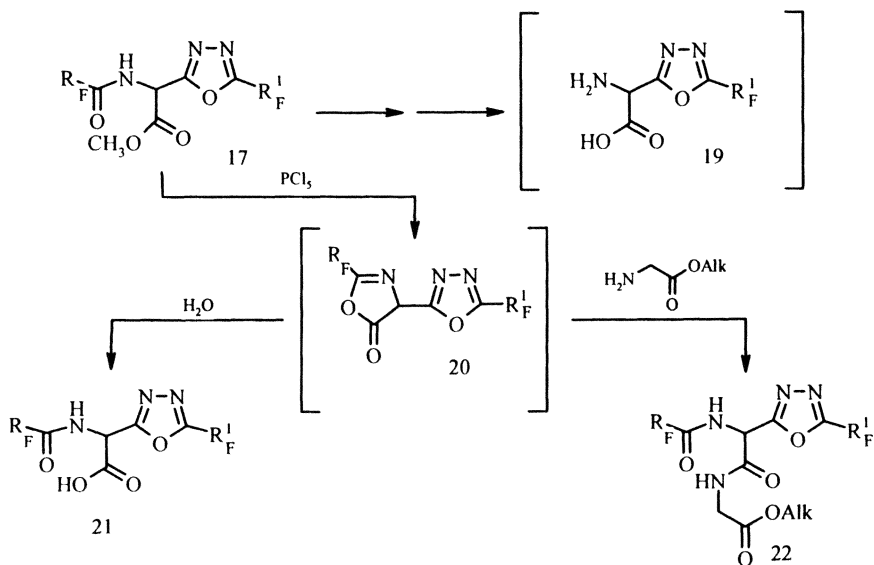


Figure 5

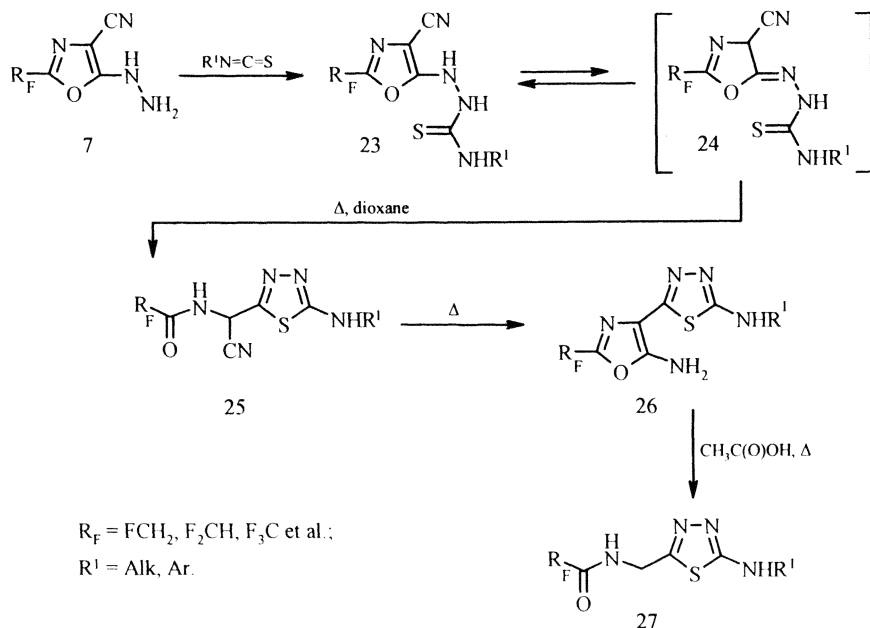


Figure 6

their conversion into (21) and (22). As is shown in Figure 5, these transformations involve intermediate (20) containing an azlactone ring which is readily cleaved by water or alkyl esters of glycine to give derivatives of alpha-amino acids (21, 22).

Starting from 5-hydrazino-4-cyanooxazoles (7), we synthesized not only the 1,3,4-oxadiazole derivatives but also the related derivatives of 1,3,4-thiadiazole (Figure 6).

For this purpose, compounds (7) were heated in dioxane with alkyl- or arylisothiocyanates. The resulting compounds (25) are then converted into compounds (26). The latter, when heated in acetic acid, gave compounds (27). We propose that initial cleavage of the 5-aminooxazole ring of compound (26) occurs and that this is followed by decarboxylation.

It is interesting that ADAN_F (2) reacts with benzamidine in a totally different way compared to the reaction with amines. Here, [2+3] condensation takes place resulting in compounds (28) which after acid hydrolysis produces imidazolones (29). When heated in pyridine compounds (29) are converted to substituted oxazo[4,5-*d*]pyrimidines (31). Probably, in such an intricate transformation, intermediate spiro-compounds play an important part [see transformations (29)→(30)→(31) on Figure 7].

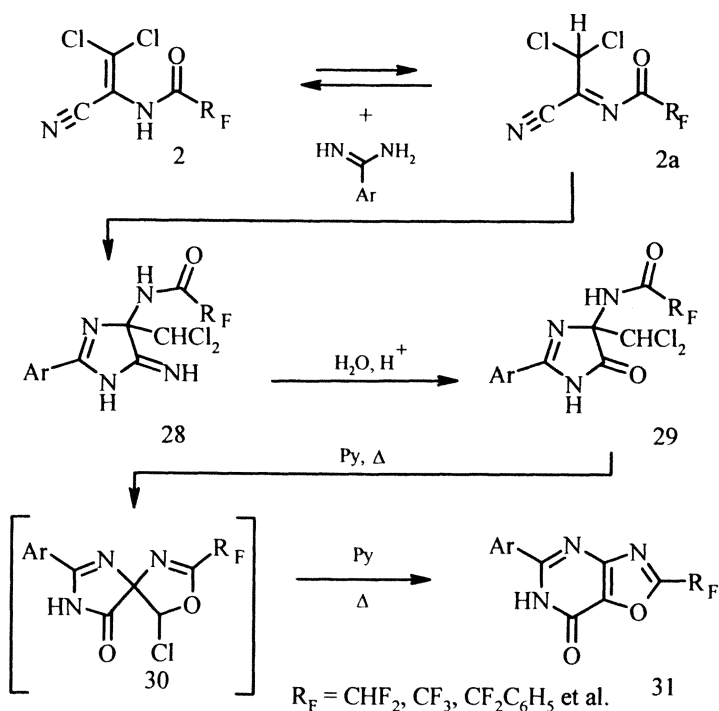
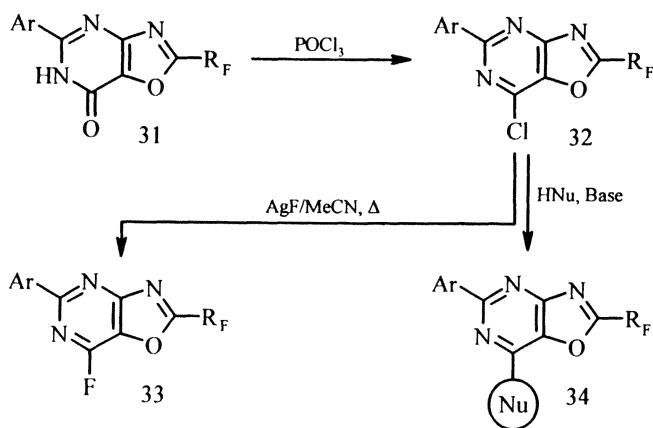


Figure 7



$\text{R}_F = \text{CHF}_2, \text{CF}_3, \text{CF}_2\text{C}_6\text{H}_5$ et al. Nu = AlkNH, Alk₂N, ArNH, AlkS, ArS.

Figure 8

It should be noted that compounds (**31**) have been little investigated and are unlikely to be obtained by other methods.

The presence of the oxazopyrimidine fragment in the final products (**31**) is supported by the fact that the structures of similar non-fluorinated compounds analogous to (**31**) were confirmed by X-ray analysis (7).

Compounds (**31**) are attractive starting points for the synthesis of other derivatives of oxazolo[4,5-*d*]-pyrimidine using simple transformation (**31**)→(**32**)→(**33**) or (**34**) presented on Figure 8.

Thus, based on the availability of reagents ADAN_F, we have successfully synthesized a series of derivatives of oxazole (**A**, **B**), 1,3,4-oxadiazole (**C**), 1,3,4-thiadiazole (**D**) and oxazolo-[4,5-*d*]pyrimidines (**E**, **F**, **G**) containing fluorinated substituents. These compounds should be of interest as leads for the development of various bioregulators (see Figure 9).

In conclusion, we have reviewed briefly the most recent results of our research on heterocyclizations of fluorinated 2-acylamino-3,3-dichloroacrylonitriles. Only a small portion of this work has been previously published (8,9), but more detailed publications will be forthcoming.

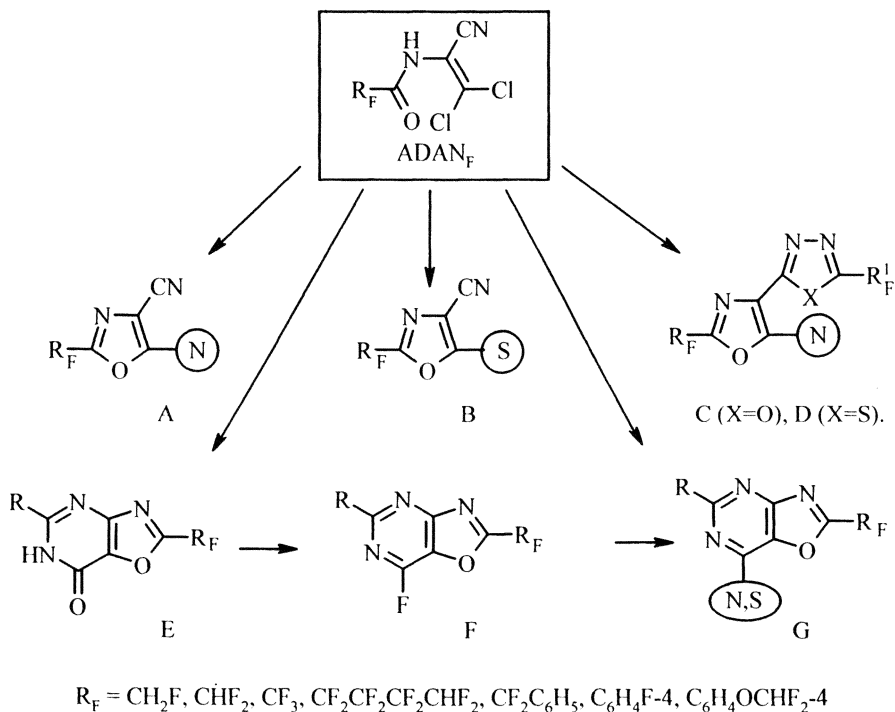


Figure 9

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Chapter 14

Synthetic Utilization of Polynitroaromatic Compounds: Synthesis of Fluorinated Fused Heterocycles from Polynitroaromatic Compounds

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Methods for the preparation of fluorinated benzo[*d*]-isothiazoles, benzo[*d*]isothiazol-3(2*H*)-ones and benzo[*b*]-thiophenes from available 2,4-di- and 2,4,6-trinitrotoluenes are described. One of them entails fluoro- or trifluoroethoxydenitration of corresponding nitro- or dinitroheterocycles obtained from polynitrotoluenes. An alternative approach is based on a stepwise regioselective substitution of nitro groups in polynitrotoluenes or polynitrobenzoic acid derivatives (amides, nitriles) with S-, O- and F-nucleophiles followed by heterocyclic ring closure. The methods were applied for the conversion of polynitroaromatic compounds to pharmacologically-useful fused heterocycles.

2,4,6-Trinitrotoluene **1** is a widespread energetic material – a principal component of gun powders and explosives (1). Another important polynitroaromatic compound, 2,4-dinitrotoluene **2**, (produced by the chemical industry in million of tons as a mixture with isomeric 2,6-dinitrotoluene) is used for the synthesis of 2,4-diaminotoluene **3** (2) and polycondensation polymers (3). Reduction of nitro groups in compound **1** affords 2,4,6-triaminotoluene **4** that has potential applications as a valuable monomer for the polymer industry (4). Recently, polynitroaromatic compounds **1** and **2** have shown promise as intermediates in fine chemical organic synthesis. Their conversion to 2,4,6-trinitrobenzoic acid **5** and 2,4-dinitrobenzoic acid **6**, respectively, followed by substitution of the *ortho*-nitro group by other atoms and groups opens up routes to the synthesis of pharmacology-useful fused heterocycles (5–10) (Figure 1).

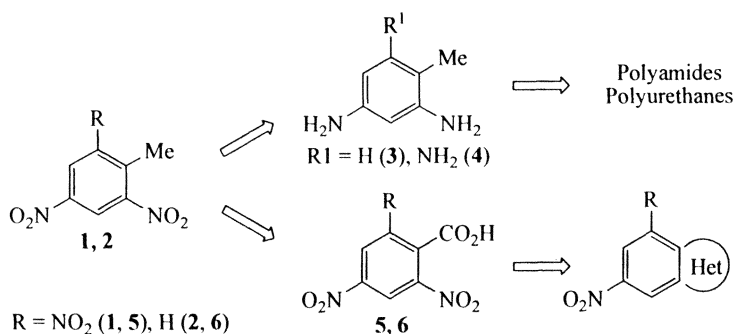


Figure 1. Transformations of polynitroaromatic compounds into useful products.

Among these heterocycles, 3-aminobenzo[*b*]thiophene **7** and 1,2-benzo[*d*]isothiazol-3(2*H*)-one derivatives **8** are of particular interest. Compounds **7** bearing the 3-aminobenzo[*b*]thiophene moiety serve as intermediates for the synthesis of various biologically active compounds, such as protein kinase (11) and other enzyme inhibitors (12–14), adrenoceptor antagonists (15), and medications for the treatment of allergies (16) (Figure 2).

1,2-Benzisothiazole derivatives have been extensively studied over the last decade due to their favorable biological activity profile. For example, compound PD 161374 is capable of removing zinc from HIV nucleocapsid protein (NCp7), thereby inhibiting viral replication in infected cells (17–21). Other compounds act as irreversible inhibitors of serine protease (22) and human leukocyte elastase (23, 24). They influence potent, dose-dependent inhibition of an interleukin IL-1 β -induced breakdown of proteoglycan in a cartilage organ culture assay and binding of interleukin-5 (IL5) to hIL5Ra and are being considered as nonpeptidic agents for the treatment of arthritic diseases (25, 26). Some benzisothiazol-3(2*H*)-one-1,1-dioxides, in particular compound

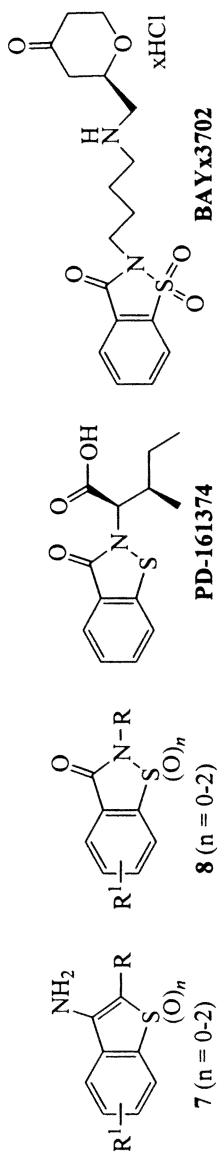


Figure 2. Pharmacologically active sulfur-containing fused heterocycles.

BAYx3702 (Repinotan hydrochloride), were recognized as selective high affinity 5-HT_{1A} receptor agonists with neuroprotective, anxiolytic, and antidepressant effects in animal models (27) and inhibitors of apoptosis caused by serum deprivation in cultured neurons (28) (Figure 2).

A majority of these biologically active 3-aminobenzo[*b*]thiophenes and 1,2-benzisothiazol-3-ones do not contain functional groups in the aryl moiety, presumably due to a lack of affordable synthetic approaches. On the other hand, introduction of such functional groups with diverse electronic and spatial properties should enhance the selectivity of the interactions between compounds and receptors and accordingly influence the biological activity profile. In particular, it might be expected that fluorination would enhance a heterocycle "acceleration factor (AF)" characterizing its potential biological activity as an anti-cancer agent. For this purpose, the C-F fragment seems to be preferable to other common fluorinated fragments (29).

In this paper we briefly review synthetic approaches to benzo[*d*]isothiazoles, benzo[*d*]isothiazol-3(2*H*)-ones and benzo[*b*]thiophenes bearing a fluorine atom or 2,2,2-trifluoroethoxy group in the aromatic ring, from available polynitrotoluenes **1** and **2** (Figure 3).

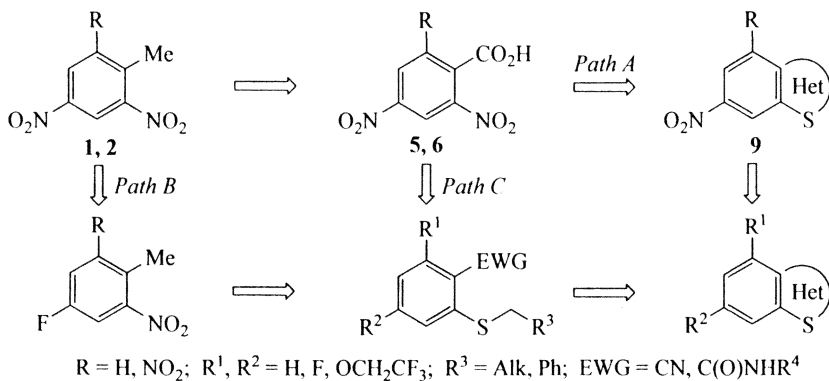


Figure 3. Synthetic approaches to fluorinated sulfur-containing fused heterocycles from polynitroaromatic compounds.

One strategy entails the synthesis of the corresponding fused heterocyclic 6-nitro- and 4,6-dinitro derivatives **9** followed by the replacement of the nitro group(s) with the fluorine atom or trifluoroethoxy group (Path A). An alternative approach is based on a stepwise regioselective substitution of nitro groups in polynitroaromatic compounds **1**, **2** (Path B) or **5**, **6** (Path C) followed by heterocyclic ring closure.

Synthesis of Fluorinated Fused Heterocycles Based on Nitroheterocycles Obtained from Polynitrotoluenes

Simple and efficient procedures for the synthesis of polynitro benzoic acids **5** and **6** by high-temperature oxidation of the corresponding polynitrotoluenes **1** or **2** with dilute nitric acid have been recently developed. The experiments were run in a thin-wall pipe autoclave (60-100 ml volume) made of high purity titanium. It was designed specially for carrying out explosion-prone thermo-oxidative processes at high temperatures and pressures. In addition, the equipment enabled rapid reaction mixture heating and cooling to allow kinetic measurements (30).

Acid **6** was obtained in high yield ($\geq 95\%$) by reaction of dinitrotoluene **2** with 30% HNO_3 at 210 °C. A high yield of acid **5** (70–75%) was achieved at a 35 to 45% conversion of trinitrotoluene **1** at a narrow range of conditions (80% HNO_3 , 194 °C, 20 min) (31). Minor by-products under these conditions were 2,4,6-trinitrobenzene **10** (15%) and 1,3-dinitrobenzene **11** (1%) respectively (Figure 4).

A technical-grade mixture of 2,4- (**2**) and 2,6-dinitrotoluenes (**12**) (3 : 2) may be used as industrially available low-cost feedstock for the synthesis of acid **6** (Figure 5). Along with the acid **6** (80% calcd. on **2**) 1,3-dinitrobenzene **11** (50% calcd. on **12**) was obtained by decarboxylation of unstable 2,6-dinitrobenzoic acid **13** produced *in situ* from compound **12** under the reaction conditions. A somewhat higher reaction time (1 h) compared to oxidation of pure **2** is required to attain a better **6/11** ratio. The acid **6** can be easily separated from by-product **11** through the conversion to the sodium salt.

Reactions of polynitrobenzamides **14**, **15** and -nitriles **16**, **17** with S-nucleophiles followed by the ring closure of the resulting substitution products **18** – **21** *via* oxidative chlorination or a sequence of oxidation and Thorpe-Ziegler reactions afforded the corresponding benzo[*d*]isothiazol-3(2*H*)-one **22**, **23**, benzo[*d*]isothiazole **24**, **25**, or benzo[*b*]thiophene **26**, **27** nitro derivatives (5, 7, 8, 32, 33) (Figure 6).

As a rule, polynitrobenzonitriles **16**, **17** reacted with S-nucleophiles less selectively than did the corresponding primary or secondary polynitrobenzamides **14**, **15**. This resulted in mixtures of *ortho*- and *para*-isomers of compounds **20**, **21** in 3/1 to 5/1 ratios depending on reaction conditions. However, selectivity could be enhanced (up to 20/1 *o/p* ratio) by running the reaction in a non-polar solvent (benzene) in the presence of a phase-transfer catalyst *n*-Bu₄NBr. It is conceivable that tetrabutylammonium thiolate which formed under the proposed conditions coordinated with the cyano group of polynitrobenzonitrile thus facilitating nucleophilic attack at the *ortho*-position.

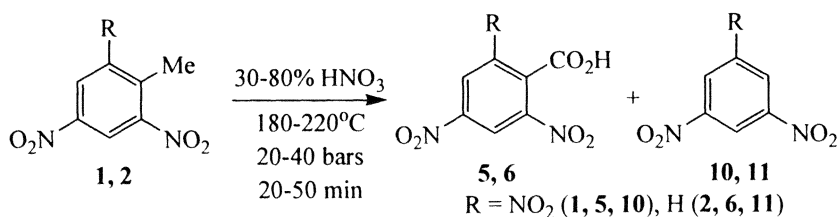


Figure 4. High temperature oxidation of polynitrotoluenes **1** and **2**.

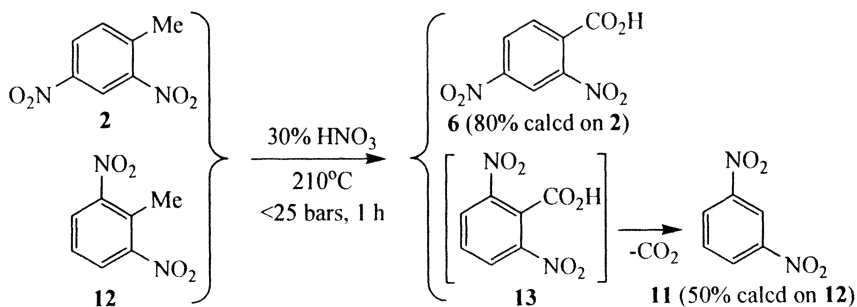


Figure 5. High temperature oxidation of isomeric dinitrotoluenes **2** and **12** technical-grade mixture.

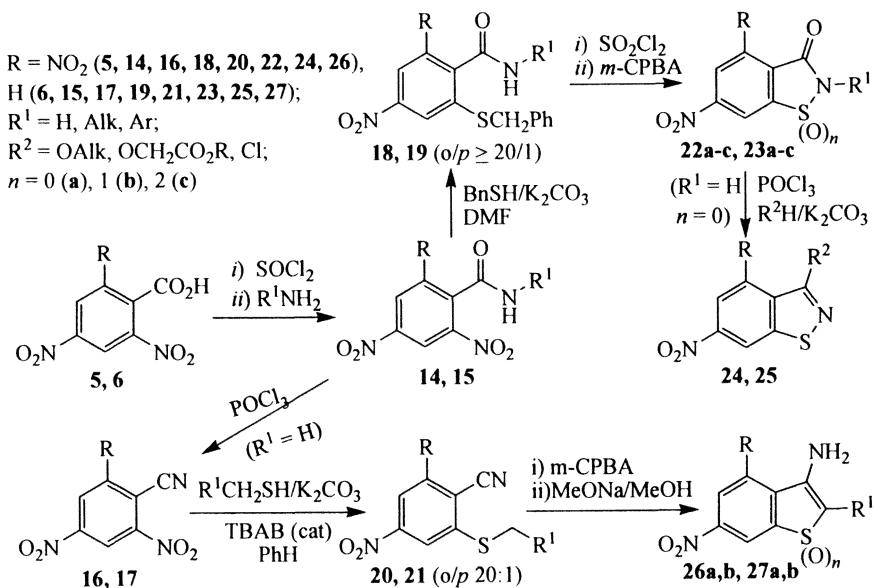


Figure 6. Synthesis of fused heterocyclic nitro derivatives (Path A).

2-[Alkyl(benzyl)thio]benzothionitrile nitro derivatives **20**, **21** did not afford 3-aminobenzo[*b*]thiophenes under Thorpe-Ziegler reaction conditions (MeONa/MeOH). Nonetheless, ring closure readily occurred in the corresponding S-oxides and S,S-dioxides (**8**).

Nitro heterocycles **22** – **24** reacted with metal fluorides and with the 2,2,2-trifluoroethanol/ K_2CO_3 system. 4-Fluoro-6-nitro-1,2-benzisothiazol-3(2*H*)-ones **28** and 4-fluoro-6-nitro-1,2-benzisothiazoles **29** were prepared in moderate to high yield and high selectivity by reactions between the corresponding 4,6-dinitro heterocycles **22**, **24** and carefully dried CsF in CH_3CN . The nitro group at C-6 remained intact under the reaction conditions in spite of an excessive amount of the fluorinating agent (**33**) (Figure 7). A few other examples of selective fluorodenitration of fused heterocyclic nitro derivatives have been reported in the literature (**34**–**39**).

Reactivity of the 2,2,2-trifluoroethanol/ K_2CO_3 system towards nitro heterocycles depended on the structure of the heterocycle. Reactions with 4,6-dinitro-1,2-benzisothiazoles **24** and 6-nitro-1,2-benzisothiazol-3(2*H*)-on-1,1-dioxide **23c** afforded the corresponding trifluoroethoxy denitration products **30**, **31**. Substitution of both nitro groups in compound **24** was achieved by using the reagent in excess (**33**) (Figure 8).

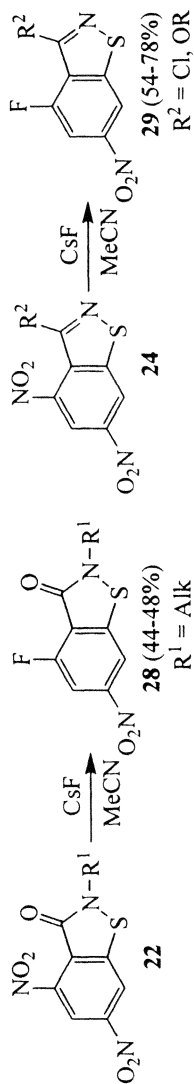


Figure 7. Fluorodenitration of benzo[d]isothiazol-3(2H)-one and benzo[d]isothiazole 4,6-dinitro derivatives.

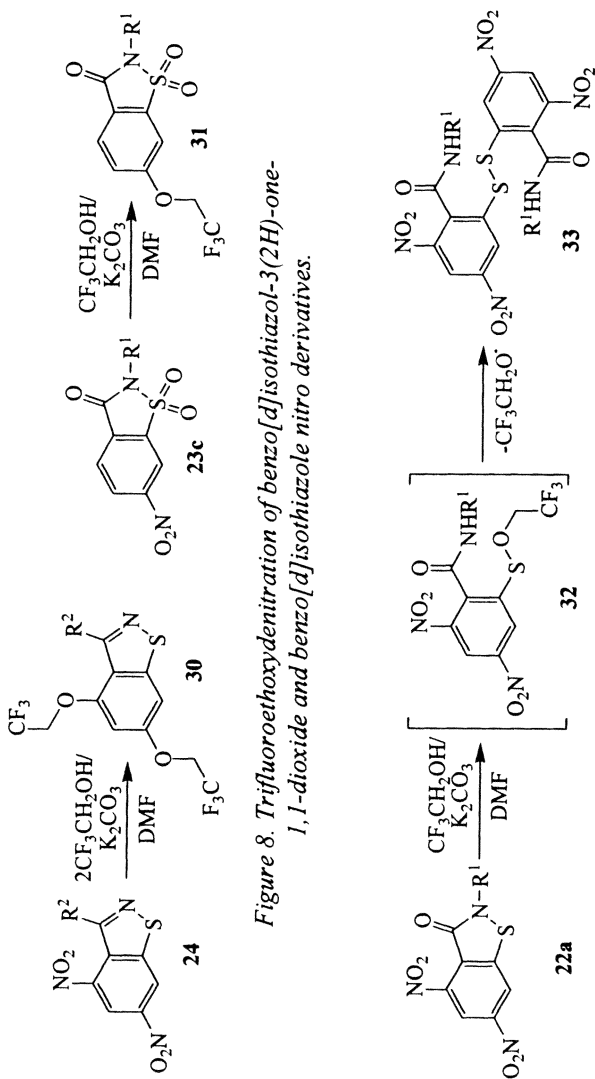


Figure 8. Trifluoroethoxydenitration of benzo[d]isothiazol-3(2H)-one-1,1-dioxide and benzo[d]isothiazole nitro derivatives.

Figure 9. Reaction of 4,6-dinitrobenzo[d]isothiazol-3(2H)-ones with 2,2,2-trifluoroethanol/ K_2CO_3 system.

In contrast, reactions between 4,6-dinitro-1,2-benzisothiazol-3(2*H*)-ones **22a** and 2,2,2-trifluoroethanol/ K_2CO_3 system proceeded in another direction yielding bis(dinitrophenyl)disulfides **33**, which presumably are derived from unstable S-trifluoroethoxy derivatives **32** (Figure 9).

Synthesis of Fluorinated Fused Heterocycles Based on Fluoroaromatic Compounds Obtained from Polynitrotoluenes

Additional opportunities for the synthesis of fluorinated fused heterocycles are offered by an alternative reaction scheme that consists of a stepwise regioselective replacement of nitro groups in polynitroaromatic compounds **1**, **2**, or **5**, **6** followed by heterocyclic ring closure (Figure 3). 4-Fluoro-2-nitrobenzoic acid **34** can be prepared from 2,4-dinitrotoluene **2** by initial regioselective reduction of the *para*-nitro group followed by a Schiemann reaction and oxidation of the methyl group to the carboxylic acid (40) (Figure 10). Compound **34** is a valuable building-block for the synthesis of fluorinated 3-aminobenzo[*b*]thiophenes and 1,2-benzisothiazol-3(2*H*)-ones.

Reactions of 4-fluoro-2-nitrobenzamides **35** with alkyl(benzyl)thiol/ K_2CO_3 system afforded the corresponding 2-alkyl(benzyl)thio-4-fluorobenzamides **36** in high yields. The reactions occur regioselectively, and the amount of fluorine-free by-product was less than 5%. Oxidative chlorination of amides **36** by SO_2Cl_2 afforded 2-substituted 6-fluoro-1,2-benzisothiazol-3(2*H*)-ones **37**. Dehydration of amides **36** bearing primary amino group to the corresponding nitriles **38** followed by oxidation with *m*-CPBA and the Thorpe-Ziegler cyclization of the oxidation products yielded 6-fluoro-3-aminobenzo[*b*]thiophene 1-oxides and 1,1-dioxides **39** (Figure 11).

6-Fluoro-1,2-benzisothiazol-3(2*H*)-ones **40** bearing aminoacid moiety incorporated into the heterocycle and their amides **41** (Figure 12) were recognized as fluorinated analogs of the compound PD 161374 (Figure 2) which has been studied for anti-HIV-1 activity (17–21). It might be expected that fluorinated analogs **40** and **41** would exhibit significantly modified and even strengthened anti-HIV activity.

1,2-Benzisothiazol-3(2*H*)-one and 3-aminobenzo[*b*]thiophene trifluoroethoxy derivatives were synthesized by replacement of one or two nitro groups in 2-(benzylthio)benzamide **18** or 2-(alkylthio)benzimidazole derivatives **20**, **21** with trifluoroethoxy group(s) followed by ring closure. Reactions of 2-benzylthio-4,6-dinitrobenzamides **18** with the 2,2,2-trifluoroethanol/ K_2CO_3 system proceeded regioselectively affording ortho-trifluoroethoxy benzamides **42**, whereas more active 2-benzyl(alkyl)thio-4,6-dinitro- **20** and 2-benzylthio-4-nitrobenzimidazoles **21** yielded products of exhaustive substitution of the nitro

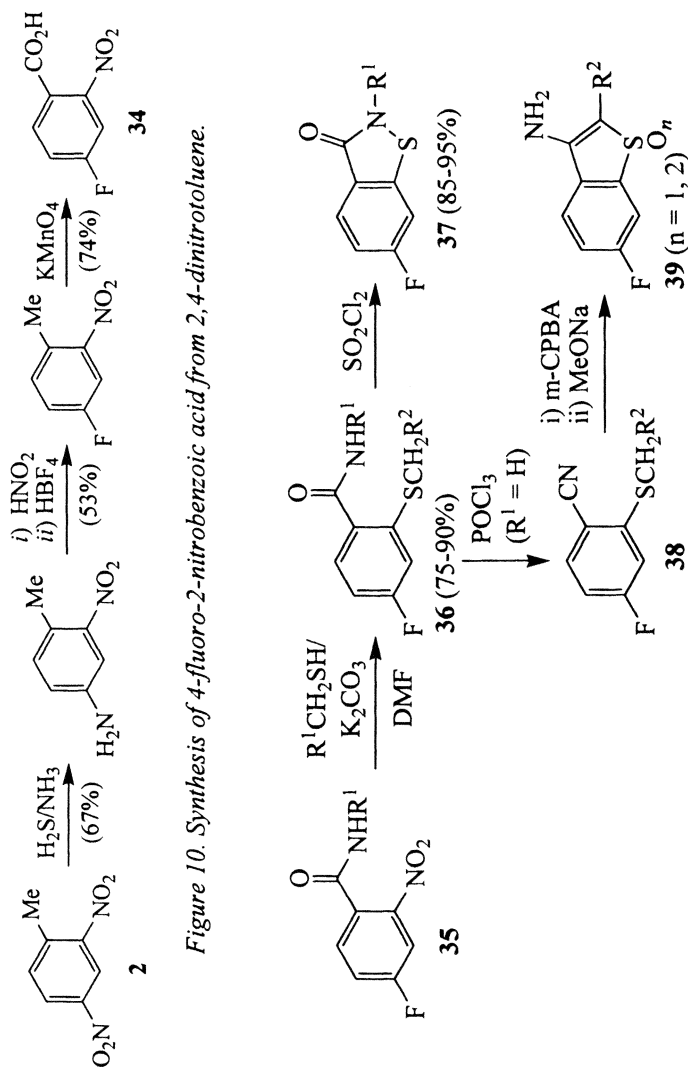


Figure 10. Synthesis of 4-fluoro-2-nitrobenzoic acid from 2,4-dinitrotoluene.

Figure 11. Synthesis of fluorinated 1,2-benzisothiazol-3(2H)-one and 3-aminobenzo[b]thiophene derivatives from 4-fluoro-2-nitrobenzyl thioacetamide.

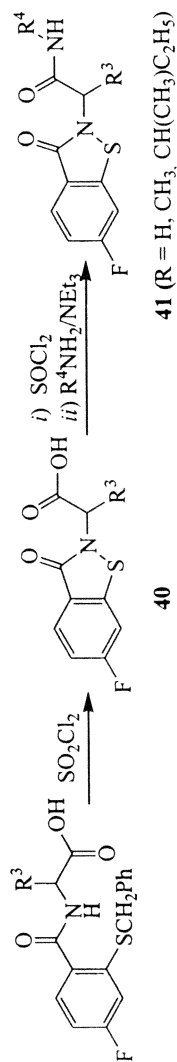


Figure 12. Synthesis of fluorinated PD 161374 analogues

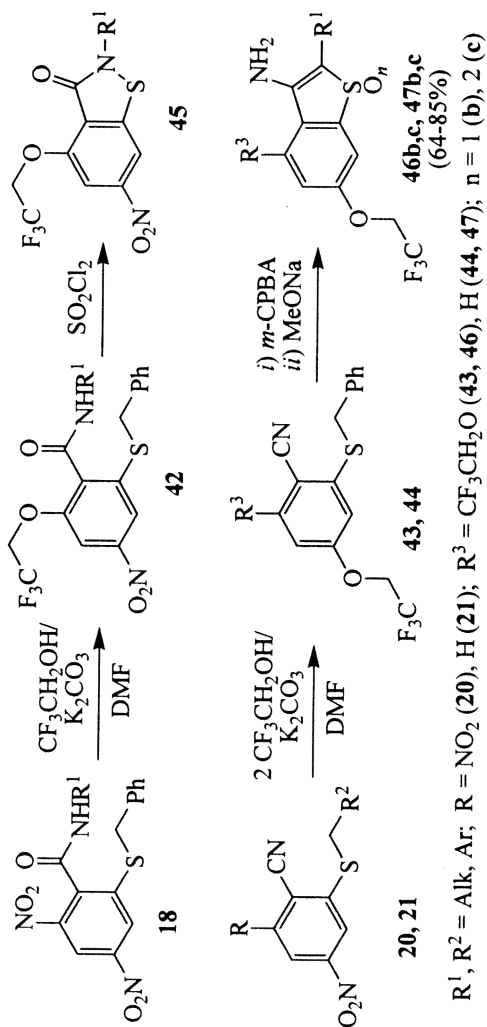


Figure 13. Synthesis and heterocyclization of 2-(benzylthio)benzamide and 2-(alkylthio)benzimidazole trifluoroethoxy derivatives

groups (**43** and **44**). The formation of the corresponding fluorinated heterocycles **45** – **47** from polynitroaromatic compounds was accomplished by oxidative chlorination or by a sequence of oxidation and Thorpe-Ziegler reactions (*Figure 13*).

Conclusion

In summary, the results described in this brief review show that polynitroaromatic compounds, in particular 2,4-di- and 2,4,6-trinitrotoluenes, can be used as industrially available, low-cost feedstock for the synthesis of benzo[*d*]isothiazoles, benzo[*d*]isothiazol-3(2*H*)-ones and benzo[*b*]thiophenes bearing fluorine atom or 2,2,2-trifluoroethoxy group in the aromatic ring. Some of the prepared heterocycles show promise as fluorinated analogs of biologically active compounds. The proposed methods can be considered as methods for synthetic utilization of explosive polynitroaromatic compounds (including 2,4,6-trinitrotoluene).

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Chapter 15

Trifluoromethoxy Containing Azoles and Azines: Synthesis and Biological Activity

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The synthesis and biological properties of trifluoromethoxy-containing azoles and azines are discussed and analyzed systematically in this review. Recent literature reports including results from the authors' research are covered.

Introduction

Fluorine-containing functional groups are widely used as unique tools for fine-tuning the biological activity of organic compounds. Due to its unique properties fluorine is frequently introduced as a substituent in biologically active compounds. Fluorine-containing compounds have a wide spectrum of activities and are extensively used as insecticides, fungicides, and herbicides in agrochemical applications, and have broad applications in medicine for example as anti-cancer agents, corticoids, neuroleptics or cardiovascular agents. The presence of fluorine-containing functional groups often leads to higher lipophilicity and increased metabolic stability of biologically active compounds. Trifluoromethyl containing compounds are currently being used as synthetic reagents (1), biologically active compounds and advanced materials (2-5). Of

special interest are the heterocyclic compounds bearing trifluoromethoxy group, some of which showed remarkable biological activity and have been applied as pro-insecticides (Indoxacarb) (6), acaricide (Flufenimer) (7), plant growth regulator (Fluprimidol) (8) and neurologic agents (Riluzole) (9). These practical applications clearly indicate that trifluoromethoxy derivatives of azines and azoles are prospective biologically active compounds and drug candidates. This review summarizes for the first time the scattered literature data on synthesis and biological activities of trifluoromethoxy derivatives of five and six membered nitrogen containing heterocycles.

Synthesis

The chemistry of trifluoromethoxy containing compounds was initiated in 1957 by the pioneering research of Prof. L. Yagupolskii who synthesized 4-trifluoromethoxyaniline (10) from the corresponding amide through the Hoffman reaction. The same compound was resynthesized by Prof. W. Shepard in 1964 by reduction of 4-trifluoromethoxynitrobenzene (11).

In 1963, the Prof. L. Yagupolskii team developed a synthesis of 2-amino-6-trifluoromethoxybenzthiazole (Riluzole) (12) from 4-trifluoromethoxyaniline. Riluzole is a neuroprotective agent used to slow the progress of amyotrophic lateral sclerosis (ALS). The beneficial properties of this drug stimulated further investigation in the area and attracted considerable research attention to heterocyclic compounds containing trifluoromethoxy and trifluoromethoxy phenyl groups. Over the last five years over 60 articles have been published dealing with the search for biologically active heterocyclic compounds that contain the trifluoromethoxy group.

A retrosynthetic approach applied to the development of synthetic strategies for preparation of heterocyclic compounds containing the trifluoromethoxy group identifies four starting materials. These consist of two nucleophilic compounds, including 4-trifluoromethoxyaniline (13) (1) and 4-trifluoromethoxyphenyl-hydrazine (14) (2) and two electrophilic reagents – 4-trifluoromethoxyphenyl-isothiocyanate (15) (3) and 4-trifluoromethoxyphenylisocyanate (4) (16). Despite the fact that these compounds are commercially available their methods of synthesis were not optimized and required the use of toxic intermediates. Therefore the elaboration of convenient and safe synthetic methods constituted an important synthetic challenge. Our group has synthesized aniline **1** through the reduction of the corresponding nitrobenzene with tin(II) chloride. Amine **1** was used for the synthesis of hydrazine **2** in high yield. We have also developed a facile method for synthesizing 4-trifluoromethoxyphenylisothiocyanate **3** which does not require the use of thiophosgene (Scheme 1) (17).

Pyrroles

The generation of diverse libraries of nitrogen-containing heterocyclic structures bearing trifluoromethoxy groups represents an important contribution to the drug discovery process. We have developed a facile method for the synthesis of previously unknown trifluoromethoxy-containing pyrroles that can be used for the synthesis of large combinatorial libraries. Condensation of trifluoromethoxyaniline **1** with diketone **5** followed by functionalization at the 3-position of pyrrole **6** with chloroacetonitrile resulted in compound **7** which was hydrolyzed to give active chloroketone **8**. The Hantsch reaction of compound **8** with thiureas and thioamides led to the library of compounds **9** containing pharmacophore thiazole structural unit (Scheme 2) (17).

It was established that chloroacetylpyrrole **8** is an effective alkylating agent for nitrogen-, sulfur- and oxygen-containing compounds. Experimental conditions were optimized for N-alkylation of imidazole, thiazole, and triazole, for S-alkylation of thiadiazole, oxadiazole, and tetrazole derivatives, and for O-alkylation of izoxazole carboxylic acids and pyridylacetic acids to afford new pyrrole compounds **10-12** in good preparative yields (Scheme 3) (17).

Indoles

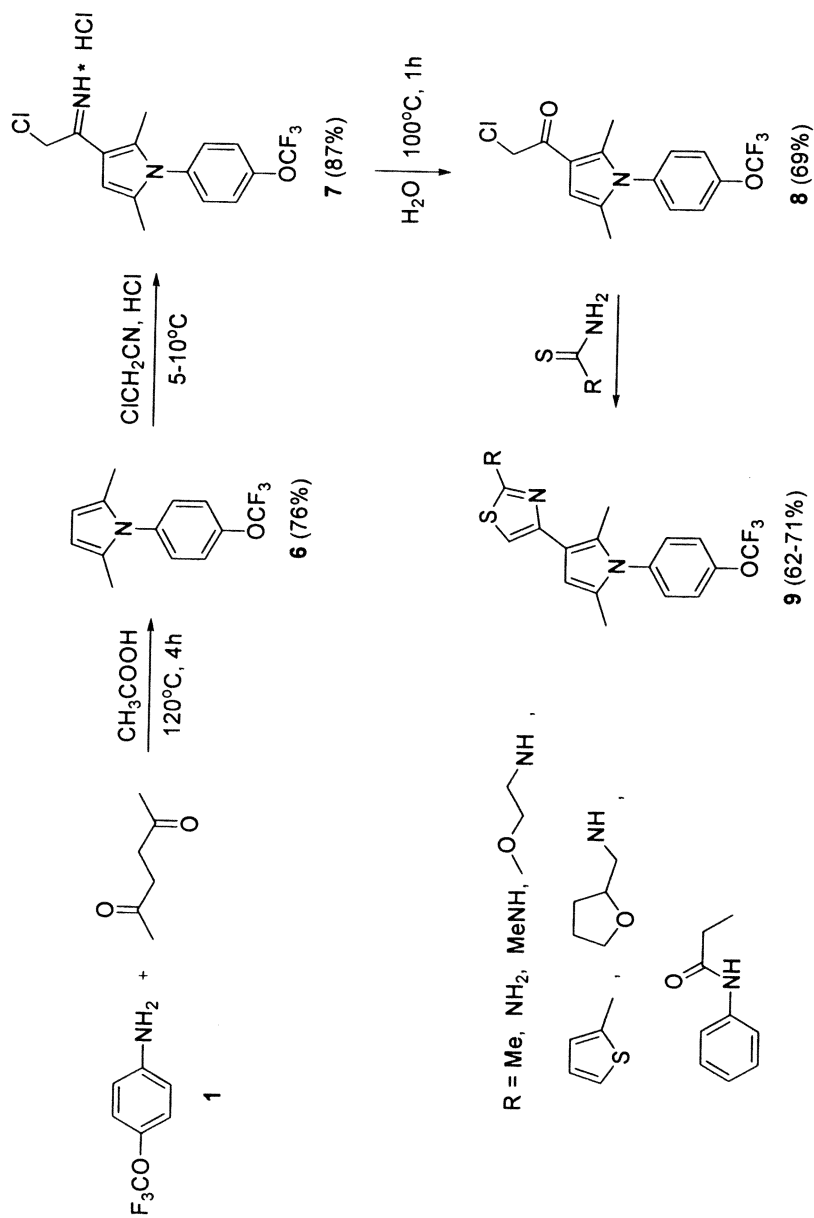
The classical Fisher method was used for the synthesis of 5-trifluoromethoxy indoles **13-15**, functionalized with carboxylic (18), carboxymethyl (19) and benzyl groups (20) (Scheme 4).

5-Trifluoromethoxyindole **16** bearing a pendant amide substituent at the 3-position was obtained through a polymer supported synthetic procedure shown in Scheme 5 (21). These compounds were investigated as NK₁ antagonists.

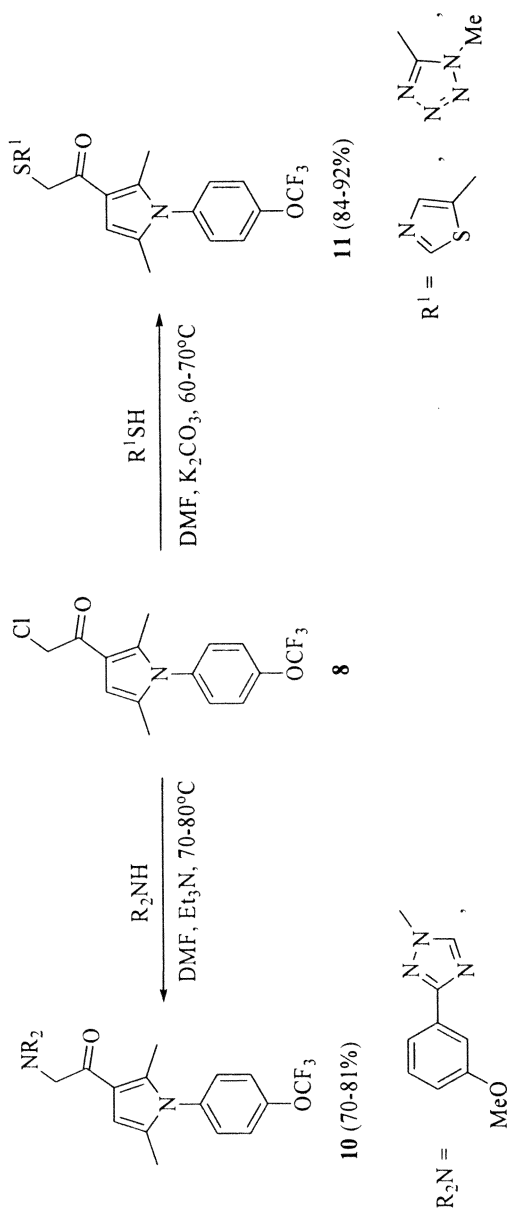
As part of a program to develop potassium channel activators, Buterea and coworkers prepared the trifluoromethoxy derivative **19** of 5,10-dihydroindeno[1,2-b]indole-1-carboxylic acid by condensation of hydrazine **2** with indone carboxylic acid **17** followed by the microwave-facilitated Fisher cyclization of hydrazone **18** (Scheme 6) (22).

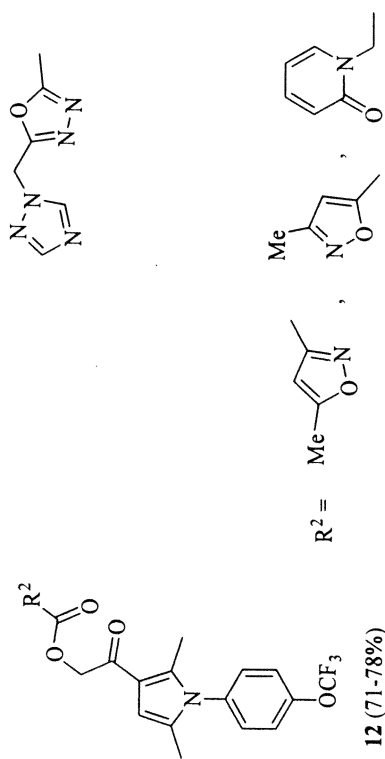
The reaction of hydrazone **20** with anthranilic acid lead to quinazolino- β -carbolin-5-one **21** – a potential antiproliferative agent (Scheme 7) (23).

2-Methyl-6-trifluoromethoxyindole (**23**) was used as a starting material for the synthesis of metabolically robust N-benzyl-indols with either a 3-benzoyl or 3-benzisoxazolyl moiety that function as selective peroxisome proliferator-activated receptor gamma (PPAR γ) modulators (24). Compound **23** was prepared by treatment of 3-trifluoromethoxyaniline with *t*-butyl hypochlorite, thiomethyl acetone and triethylamine followed by reduction of 3-thiomethylindole **22** by Raney Ni in ethanol (Scheme 8).

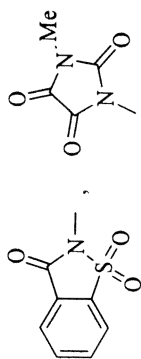


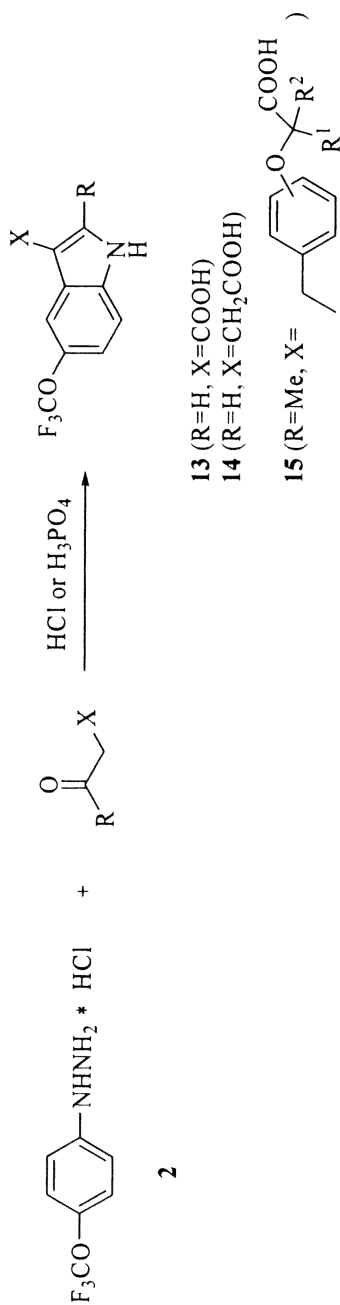
Scheme 2



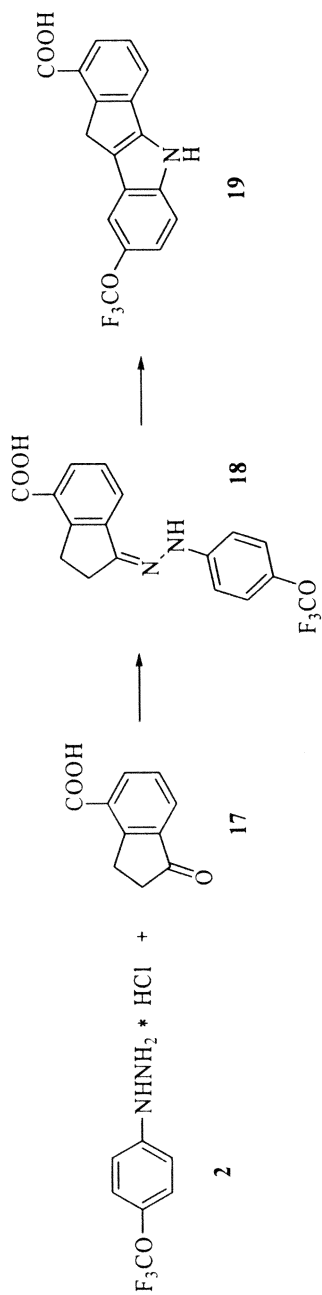


Scheme 3

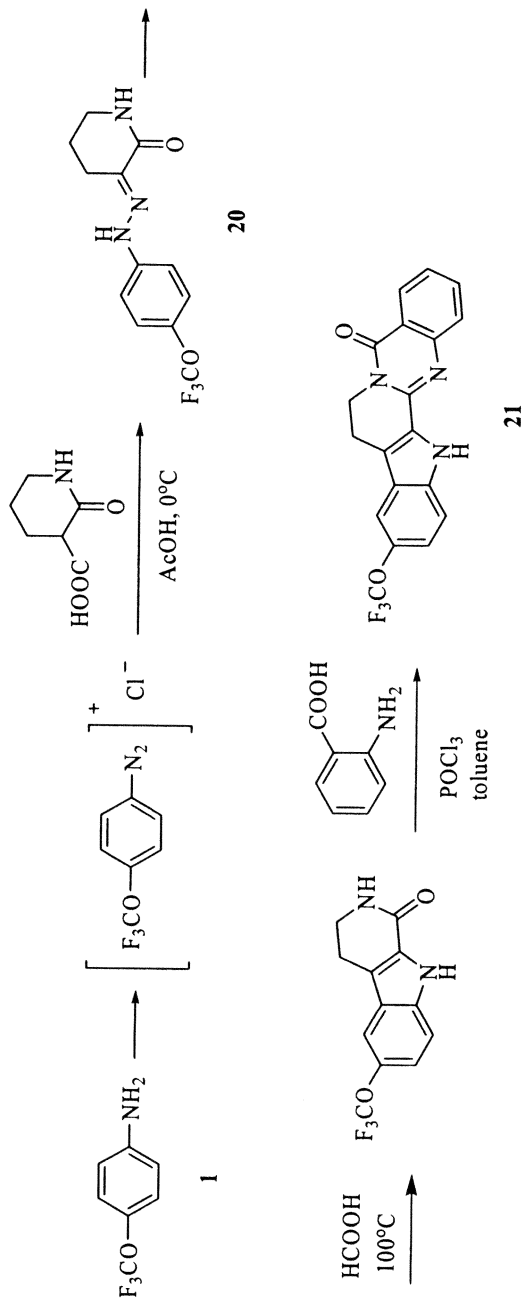




Scheme 4



Scheme 6



Scheme 7

The Fisher reaction of **2** with cyclic ketones **24** gave trifluoromethoxy indoles **25** in 80% yield. The structural diversity of compounds **25** makes them useful for systematic of structure-activity relationships (Scheme 9) (17).

Azoles

There are only a few examples of F₃CO-containing pyrazoles described in the literature. 1-(4-Trifluoromethoxy)-phenyl pyrazoles (25,26) functionalized at position 5 were obtained through the condensation of diketoethers **26** with 4-trifluoromethoxyphenylhydrazine hydrochloride **2**. The intermediate esters of pyrazole-3-carbonic acids **27** were transformed into acid **28**, alcohol **29**, bromide **30** and ether **31** (25) (Scheme 10).

The reaction of compound **2** with beta-dicarbonyl compound **32** and ester **33** resulted in the benzodipyrazole (27) **34** and pyrazolo[3,4-d]pyridine (28) **35**, respectively representing a new class of potent CDK2 inhibitors (Scheme 11).

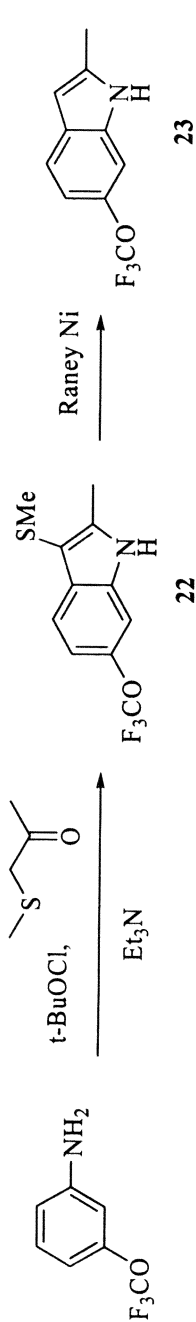
Trifluoromethoxy benzimidazole **37** containing a chloromethyl group in the 2-position was synthesized through acid catalized condensation of 4-trifluoromethoxyortho-phenylene diamine **36** with chloroacetic acid (29). Compound **37** was used as an efficient alkylating agent for the preparation of pharmacologically active derivatives of piperazine (Scheme 12).

It has been shown that the presence of the trifluoromethoxy group in diamine **36** influences the formation of the imidazole ring. For example, 2-methylbenzimidazole **38** can be obtained only through the condensation with acetic anhydride. On the other hand the condensation with hydroxyacetic and propionic acids was shown to be the optimal method for the synthesis of 2-hydroxymethyl- and 2-ethylbenzimidazoles **39**, respectively, whereas 2-aryl- and 2-heteroaryl benzimidazoles **40** can be synthesized via the reaction with the corresponding aldehydes in the presence of nitrobenzene as an oxidizer (Scheme 13) (17).

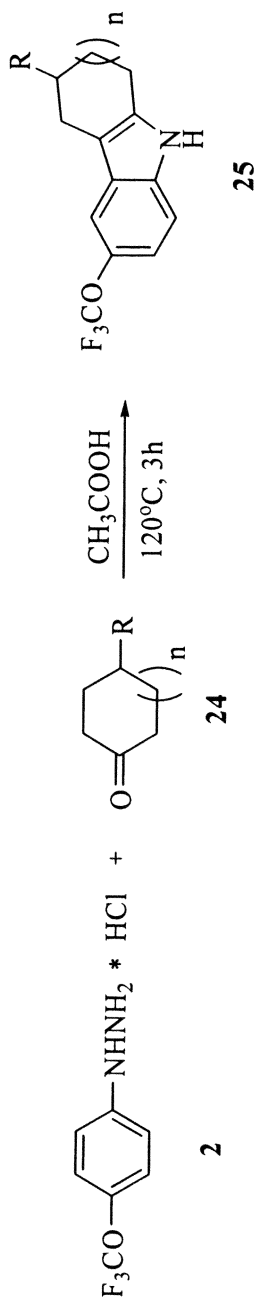
Some trifluoromethoxy derivatives of thiazole and benzthiazole showed remarkable biological activity. The syntheses of 2-amino-5-trifluoromethoxy benzthiazole (12) **41** (Riluzole (9)), and thiazolo-5-carboxylic acid **42** (fungicide Thifluzamide), are shown in Scheme 14 (30).

It is known that 2-thiohydantoin is starting material for the synthesis of many therapeutic substances, fungicides and herbicides. The S-alkylated hydantoins exhibit activity against herpes simplex virus (31) (HSV) and human immunodeficiency virus (32) (HIV). In an attempt to modify biological activity of 2-thiohydantoin the trifluoromethoxy derivative **43** was prepared through the reaction of methyl ester of N-ethylglycine with isothiocyanate **3** (Scheme 15) (33).

A facile method for the synthesis of thiohydantoin **44** containing the F₃CO group is presented in Scheme 16. Further modification of compounds **44** with pharmacophore heteroarylaldehydes afforded 4-ylidene substituted thiohydantoin **45**. Alkylation of these compounds provides an easy access to various derivatives **46** (Scheme 16) (17).

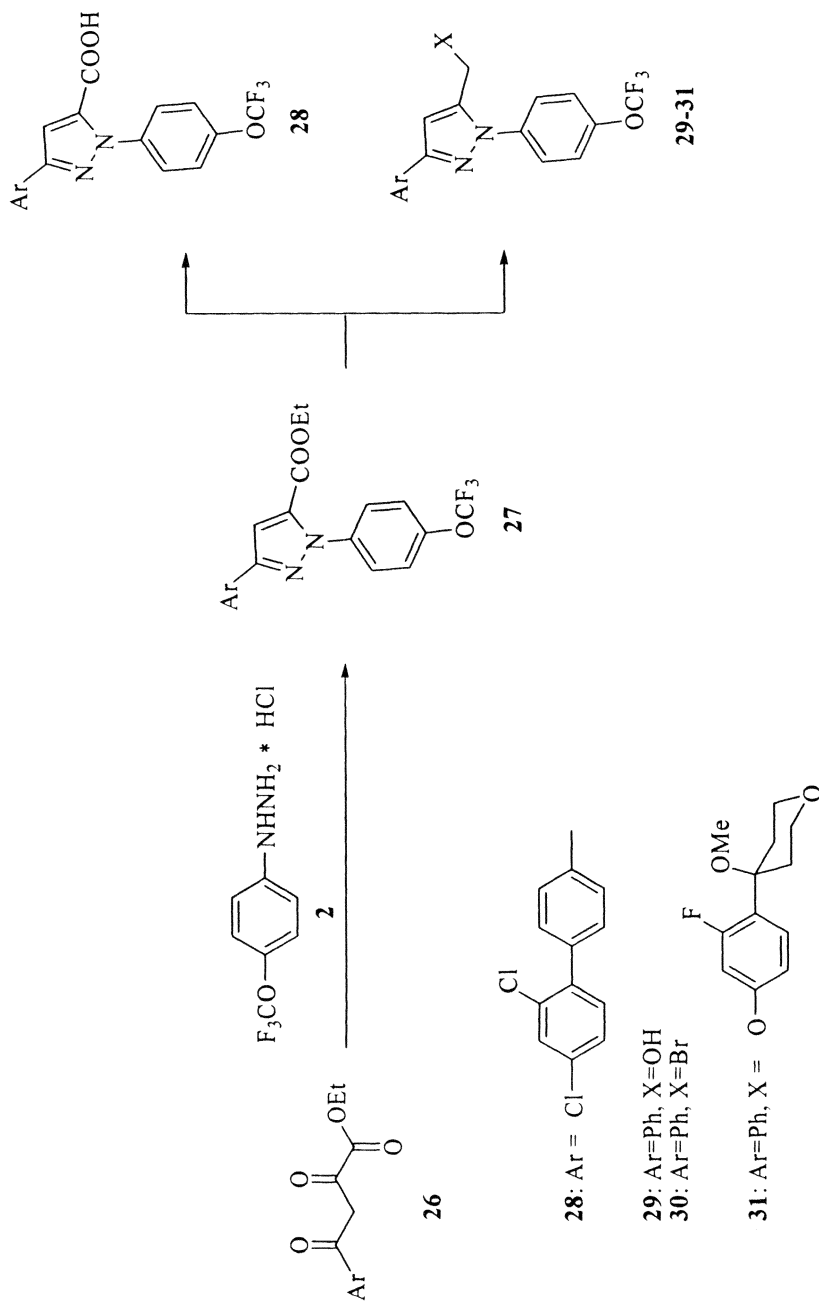


Scheme 8

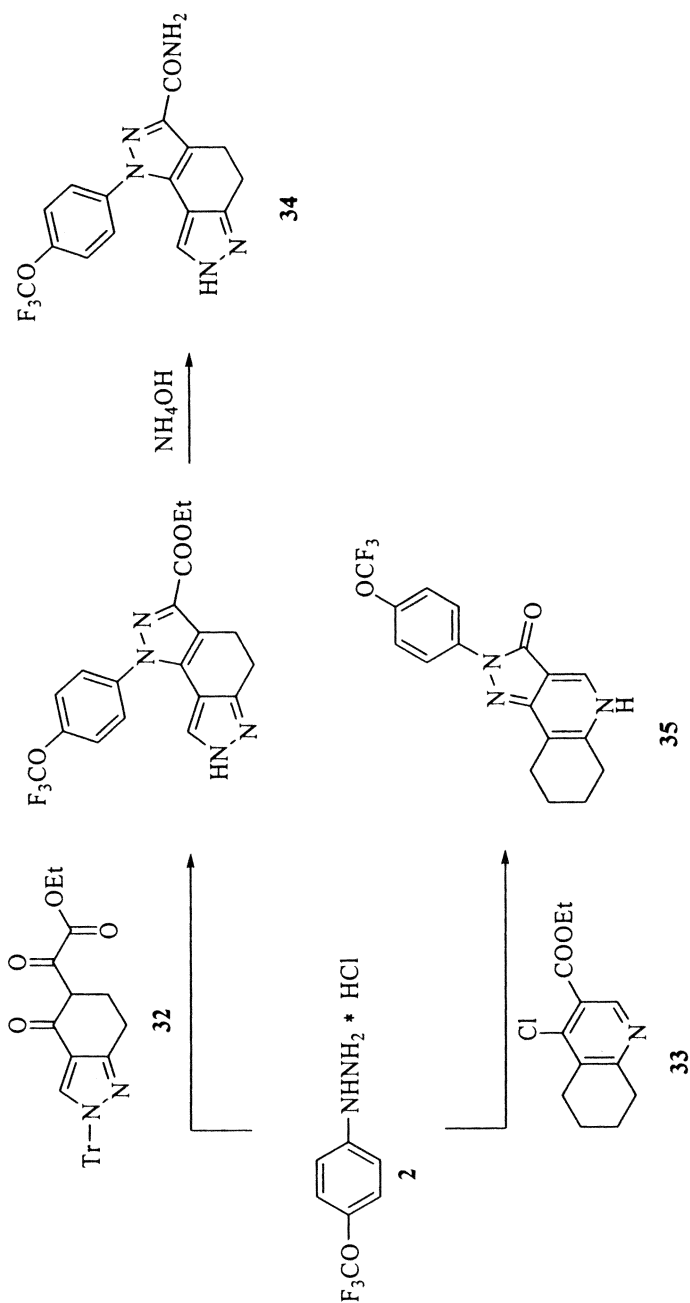


$n=0, \text{R}=\text{H}; n=1, \text{R}=\text{H}, \text{Me}, \text{Et}, \text{Ph}$

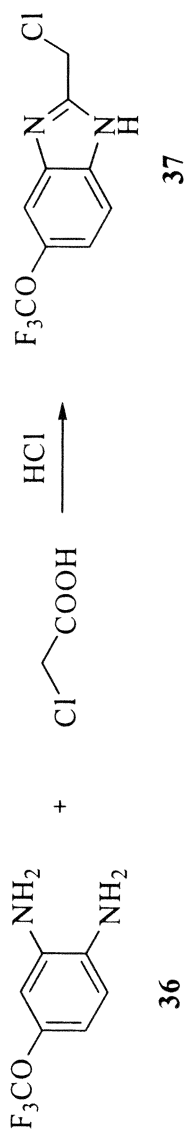
Scheme 9



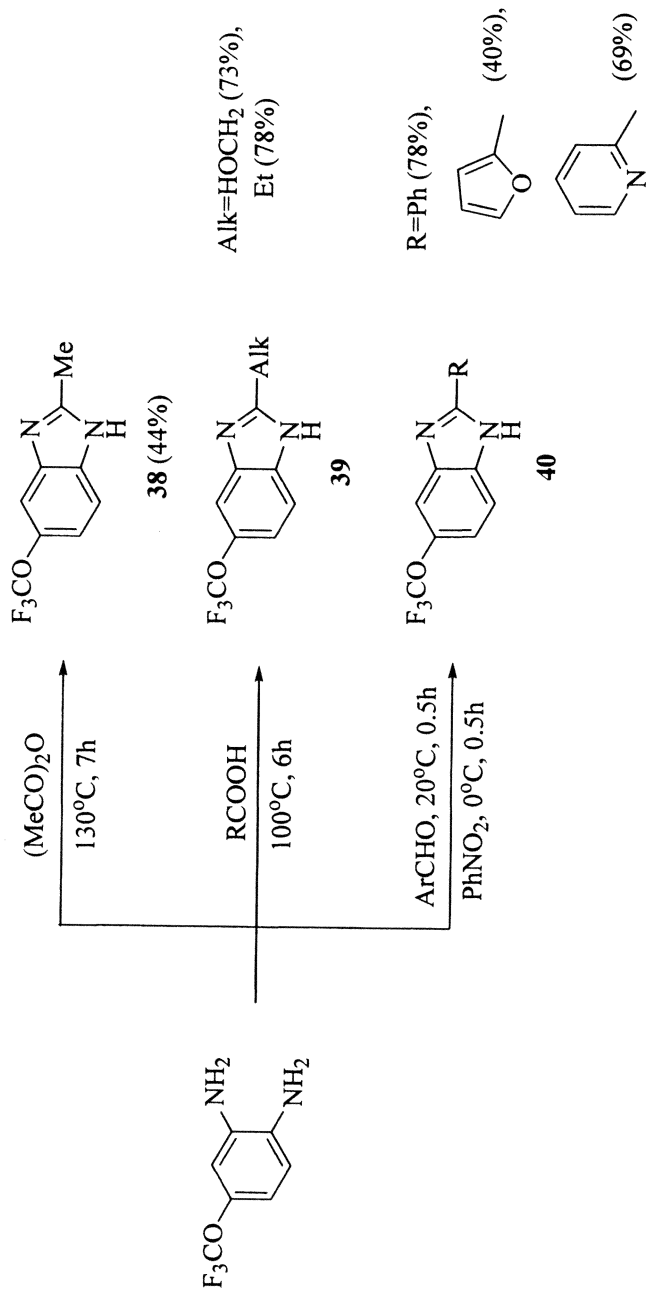
Scheme 10



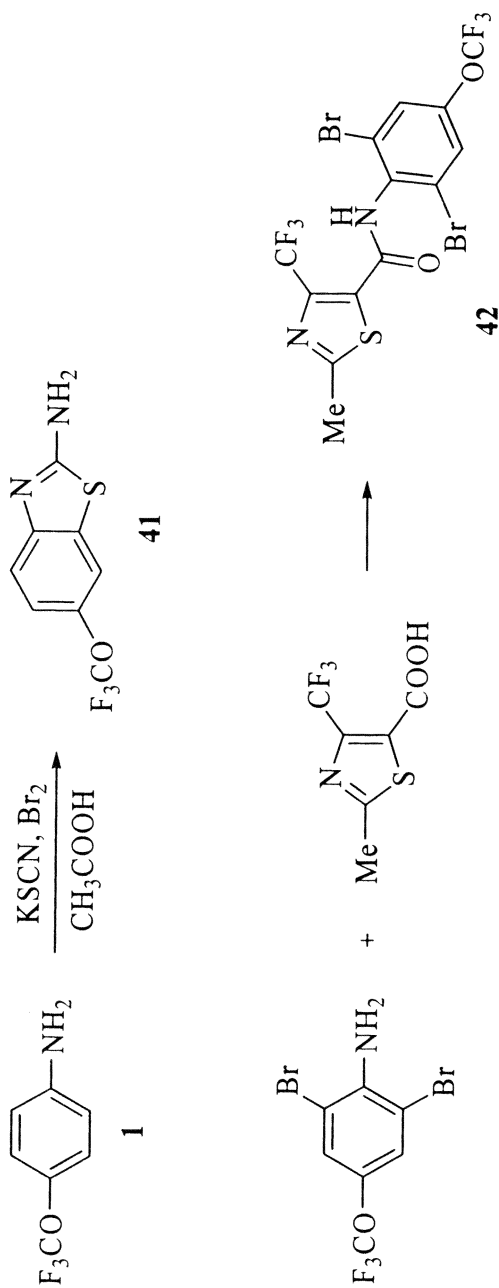
Scheme 11



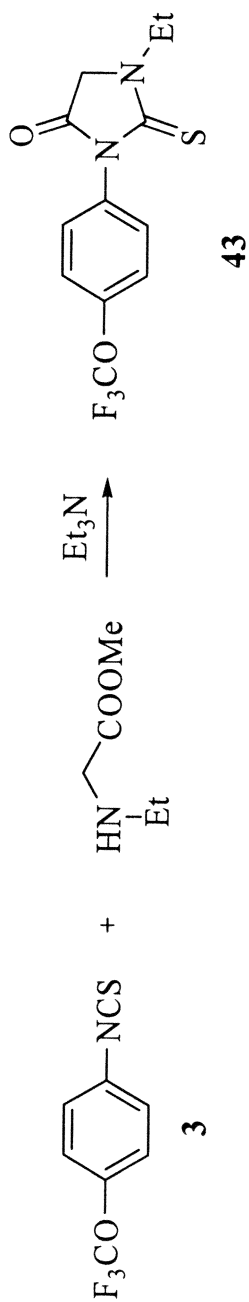
Scheme 12



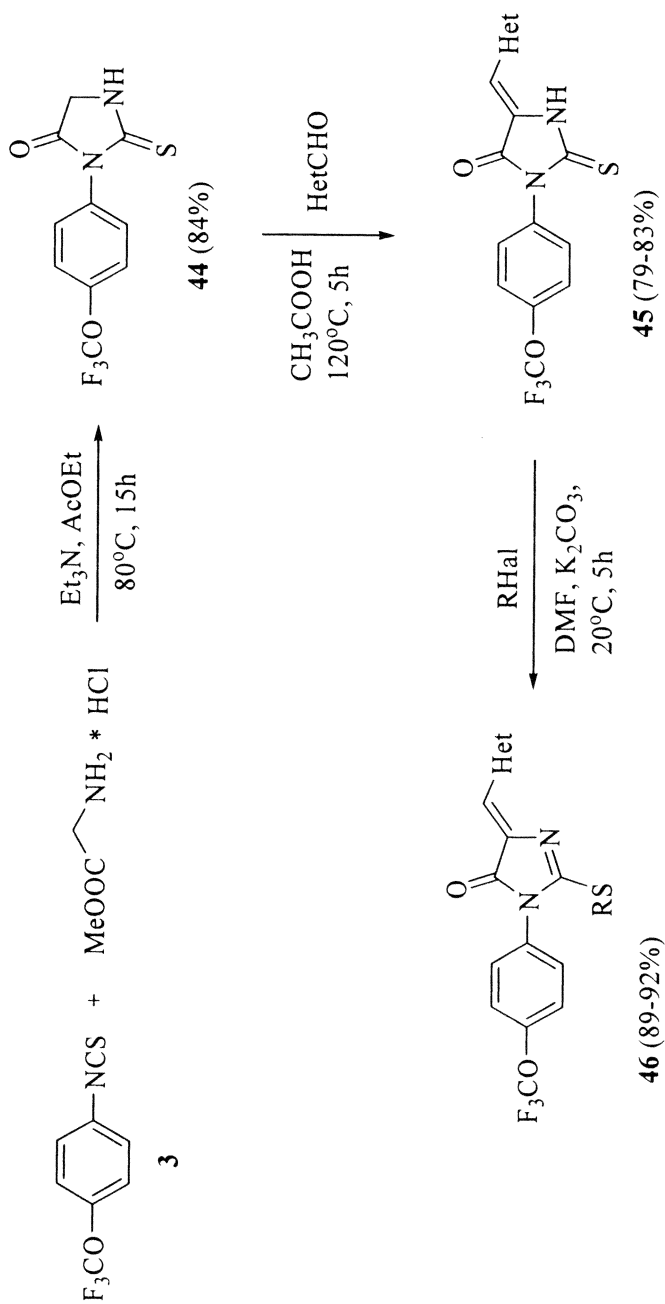
Scheme 13



Scheme 14



Scheme 15



Scheme 16

The synthetic potential of 4-(trifluoromethoxy)phenylthioisocyanate **3** was tested in the synthesis of other sulfur-containing azoles. For example 1,3,4-thiadiazolthione **47** was used for preparation of a mini-library of compounds **48** bearing the original acyclic and heterocyclic fragments (Scheme 17) (17).

Other azoles, namely 1,3,4-triazol-5-thiones, have been shown to have anti-inflammatory activity (34). Thus, it was of interest to synthesize a set of trifluoromethoxyphenyl substituted triazoles **50** by condensation of the corresponding thiosemicarbazides **49** in the presence of alkali. Further reaction of compounds **50** with alkyl halides, alkenyl halides and with haloid carbonyl compounds resulted in small library of S-alkylated derivatives **51** (Scheme 18) (17).

The previously unknown trifluoromethoxyphenyl substituted tetrazolthione **52** was synthesized through the addition of HN_3 to the C=N bond of isothiocyanate **3**. This compound was modified at the nitrogen atom in the 4-position of the heterocyclic ring and at the exocyclic sulfur atom to give a set of potentially biologically active compounds **53** and **54** (Scheme 19) (17).

Azines

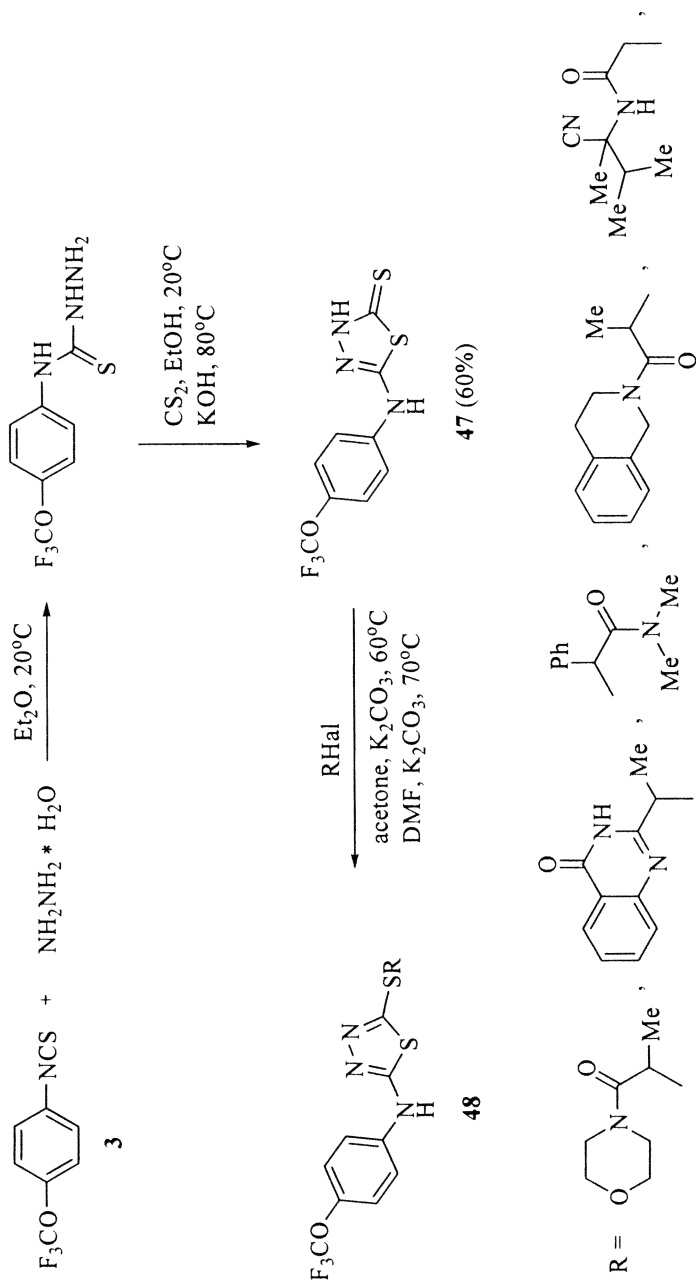
A trifluoromethoxy group has been shown to strongly influence pharmacological activities of quinolines and pyrimidines. Quinolines containing a CF_3O substituent in position 6 (35-37) and 7 (38) of the cycle have been described in the literature as well as compounds bearing 4-trifluoromethoxyphenylthiocarbamoyl group at the 3-position (39). 4-Hydroxy-6-trifluoromethoxyquinoline-2-one **55** was prepared through high temperature condensation of aniline **1** with a substituted acetoacetic ester (35). Alkylation of compound **55** with cyclopentylbromide resulted in quinolone **56** (Scheme 20).

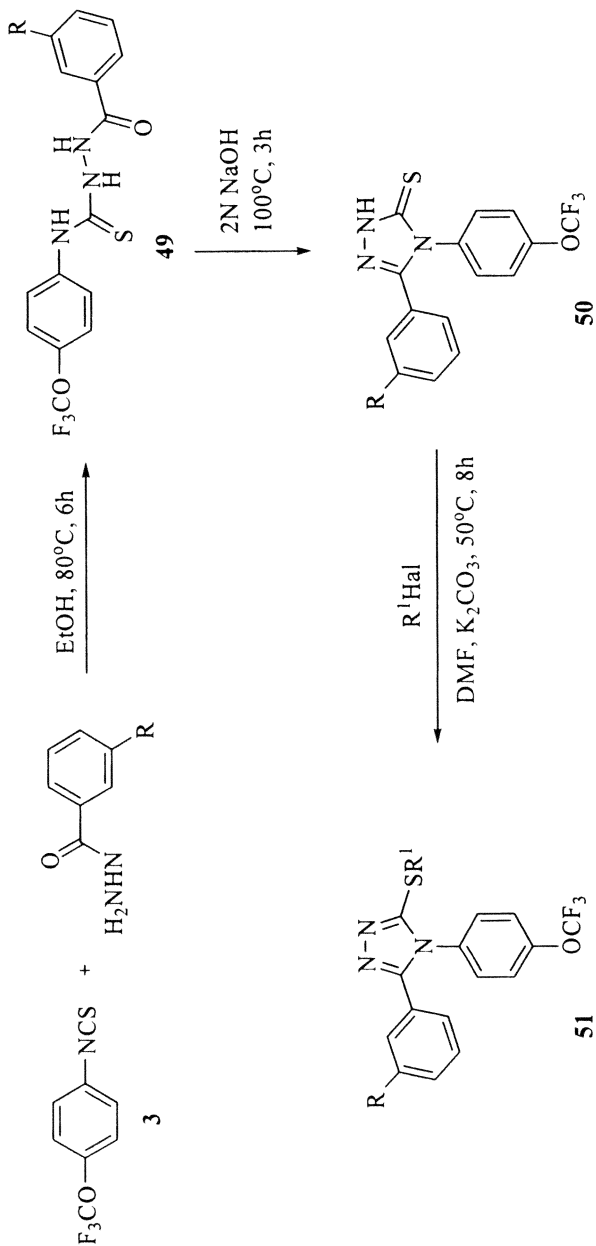
Similar reactions of β -ketoesters, such as 4,4,4-trifluoroacetoacetate, gave 2-trifluoromethyl-4(1H)-quinolinone **57**, which could be readily converted into 4-quinoline carboxylic acid **58** (Scheme 21) (36).

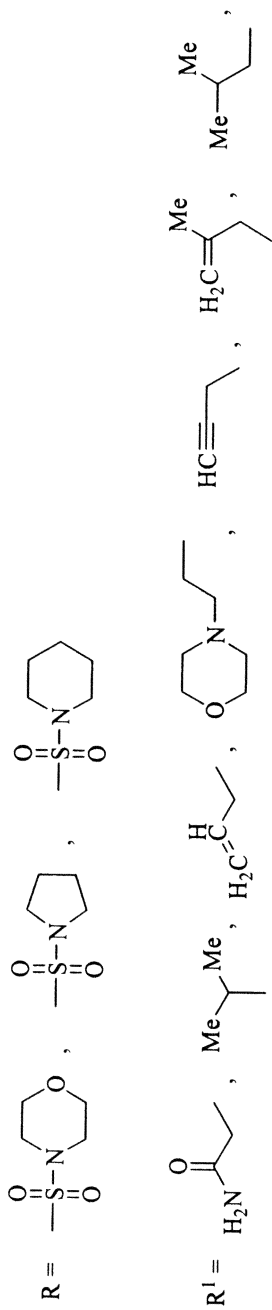
Condensation of aniline **1** with Meldrum's acid and trimethyl orthoformate resulted in 4-chloro-6-trifluoromethoxyquinoline **59** (36) which was used for the synthesis of compound **60** – a trifluoromethoxy derivative of antimalarial agent Chloroquine (Scheme 22) (40).

A 4-trifluoromethoxyphenyl group can be attached to the pyrimidine cycle using expensive and hard to synthesize 4-(trifluoromethoxy)phenyl containing building blocks for the pyrimidine ring closure. For example, oxidation of cinnamyl chloride **61** resulted in epoxide **62**, which was reacted with 4-trifluoromethoxy benzamidine to give 1,4,5,6-tetrahydropyrimidin-5-ol **63** (Scheme 23) (41).

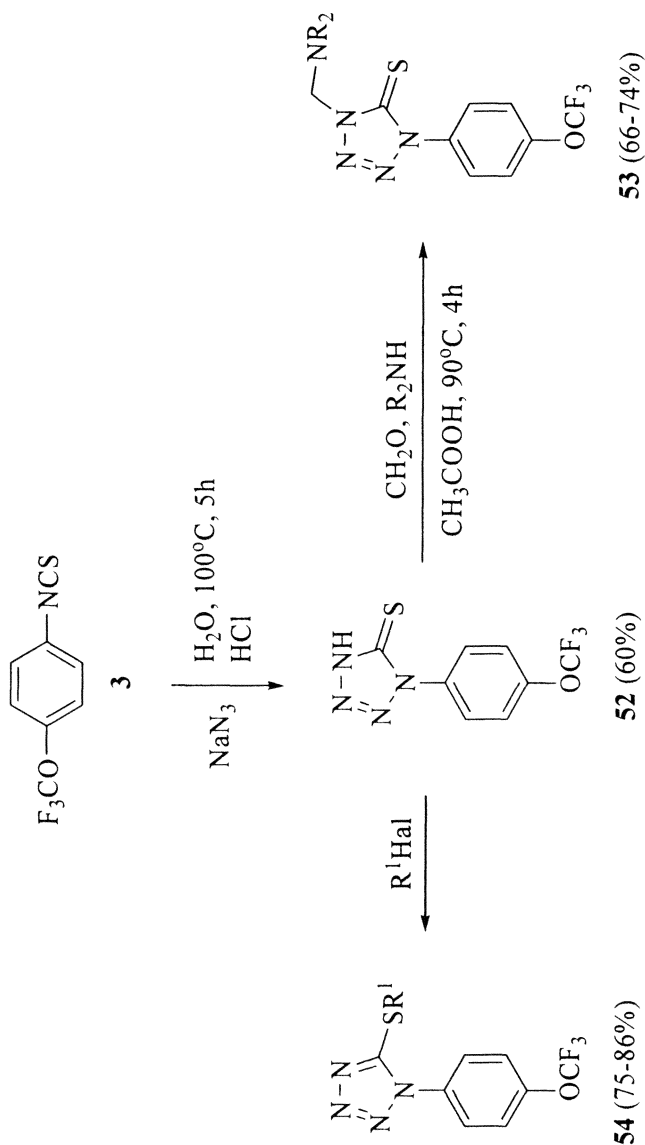
The condensation of (2H-indol-2-ylidene)malonate **64** with hydrazine **2** produced 2-[4-(trifluoromethoxy)phenyl-2H-pyridazino[4,3-b]indole-4-carboxylic acid **65** (Scheme 24) (42).

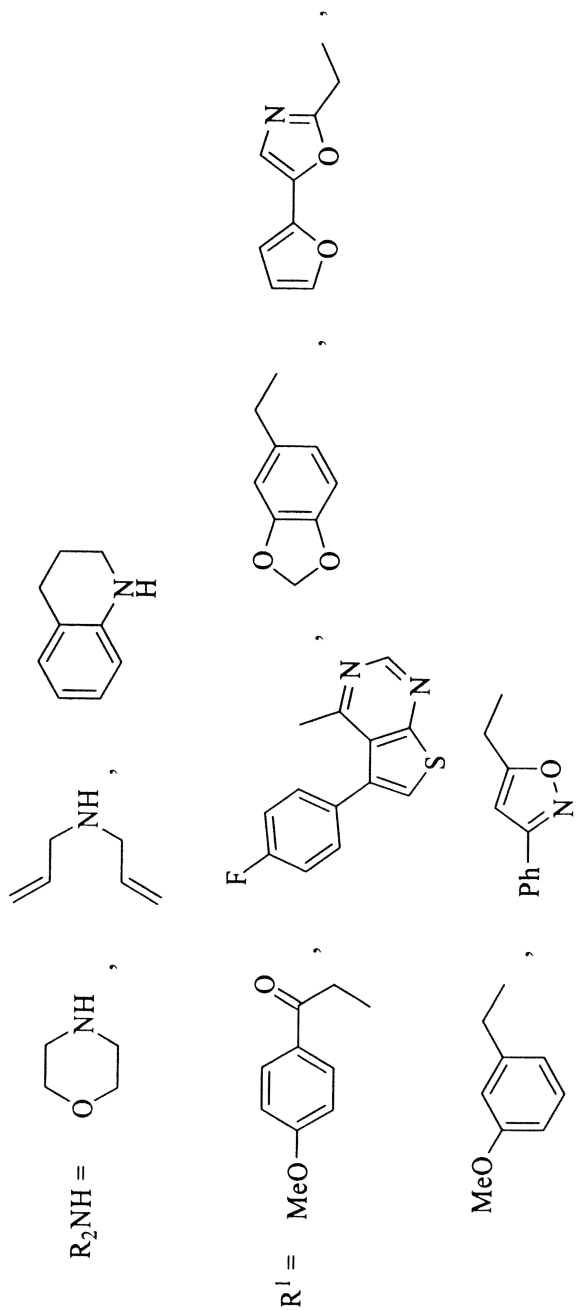




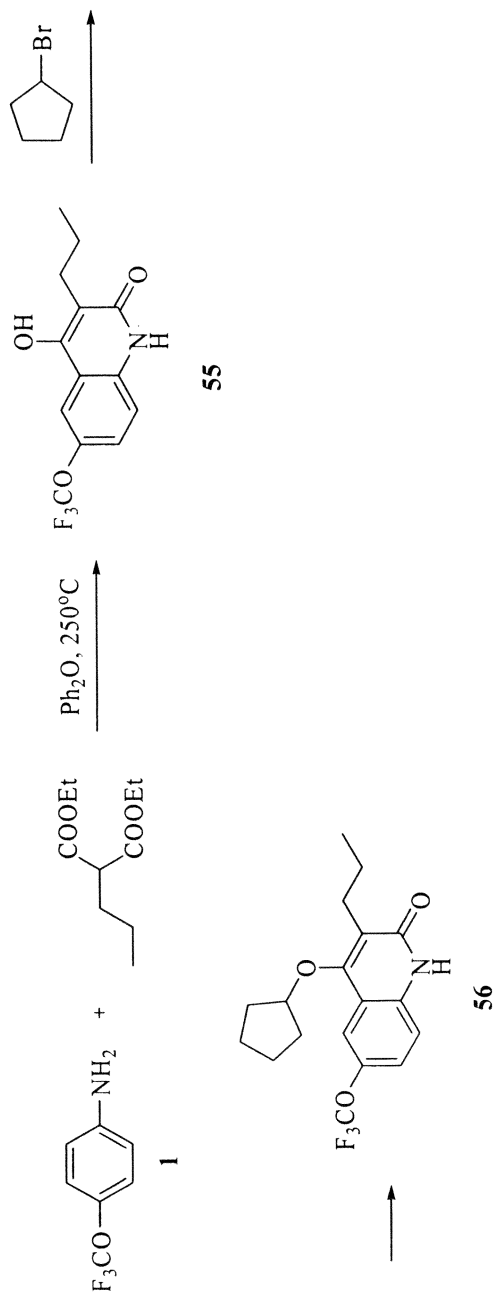


Scheme 18

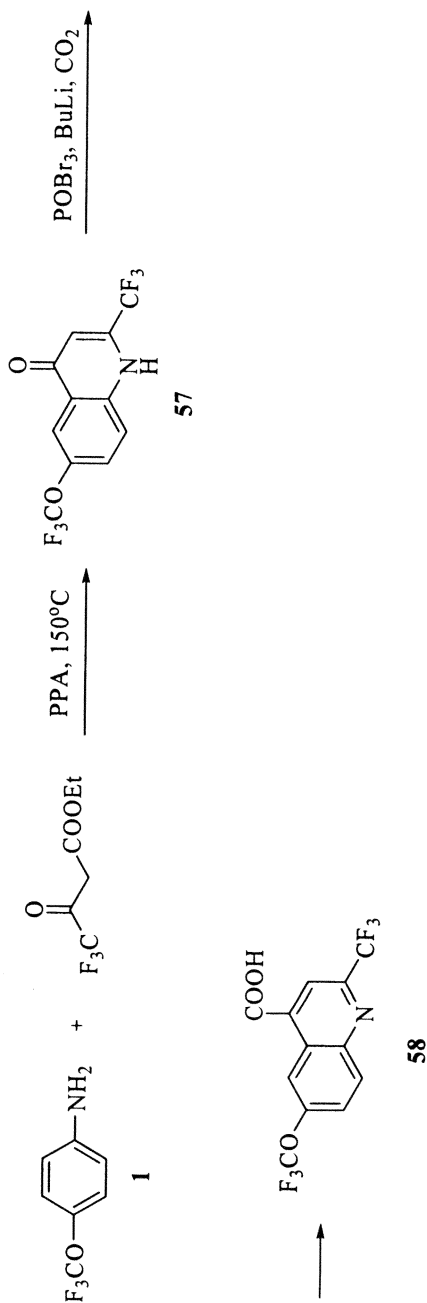




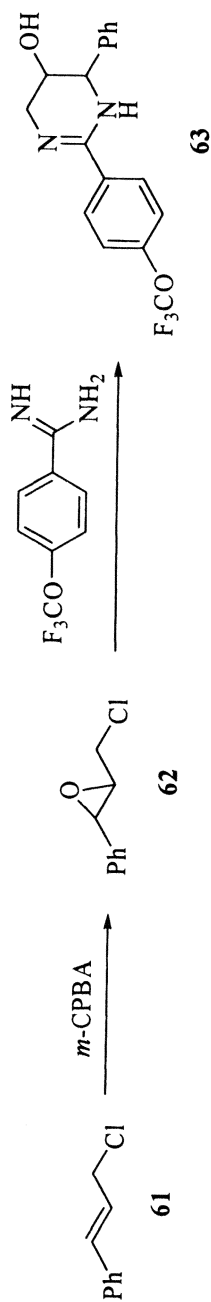
Scheme 19



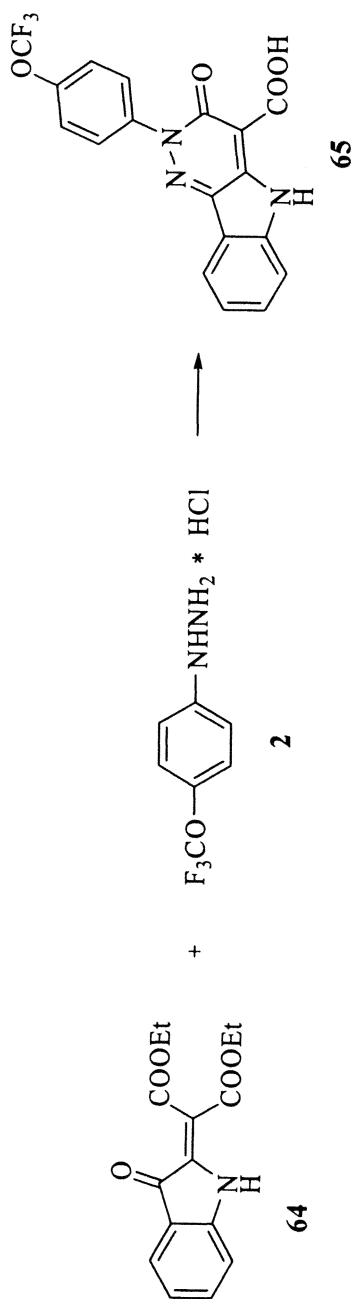
Scheme 20



Scheme 21

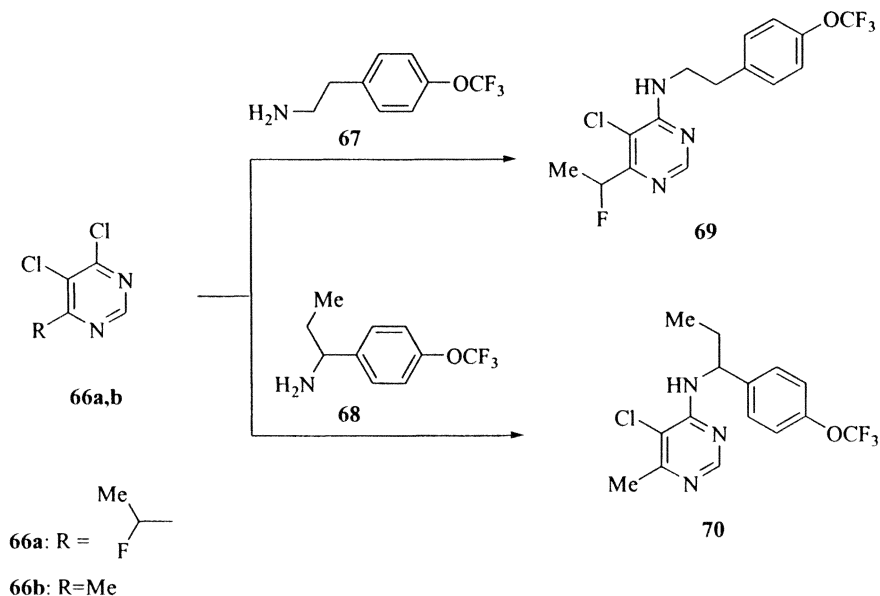


Scheme 23



Scheme 24

Reactive 4-chloropyrimidines **66a,b** readily underwent nucleophilic substitution with 4-(trifluoromethoxy)phenylalkylamines **67** and **68** to give the acaricide Flufenimer **69** and fungicide Diflumerimor **70**, respectively (Scheme 25) (43).



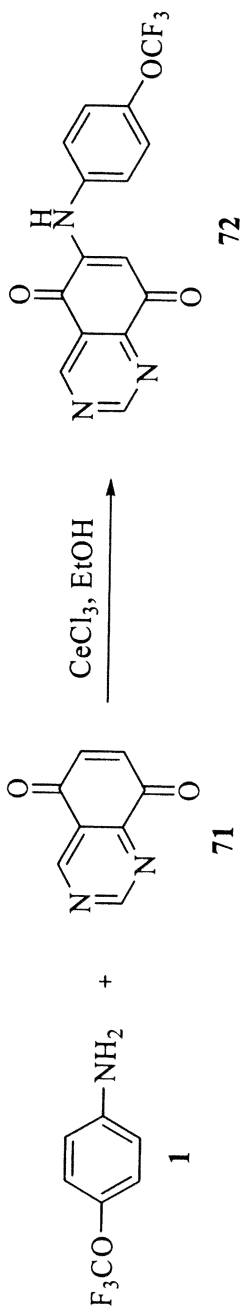
Scheme 25

6-[4-(Trifluoromethoxy)phenyl]amino-5,8-quinazolinodione **72** was synthesized through the regioselective reaction of aniline **1** with 5,8-quinazolinodione **71** in the presence of Ce(III) ions (Scheme 26) (44).

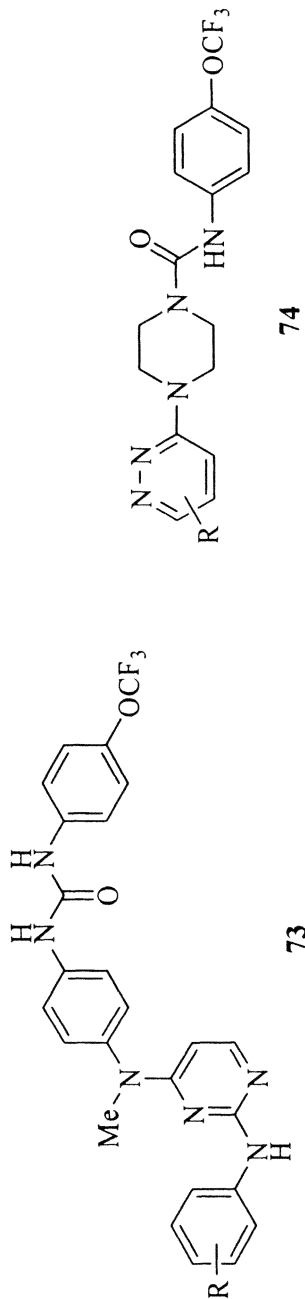
Azine structures containing nucleophilic nitrogen atoms can be functionalized with the 4-trifluoromethoxyphenyl moiety through carbonylation with 4-(trifluoromethoxy)phenylisocyanate **4**. This method was used for the synthesis of biologically active ureas **73-75** containing pyrimidine (45), pyridazine (46) and 1,3,4-oxadiazine (6) structural units.

Biological activity

Over the last decade considerable research effort has been dedicated to systematic studies of biological activity and structure-activity relationships of trifluoromethoxy containing heterocyclic compounds. These studies resulted in the discovery and commercial production of the insecticide Indoxacarb (**6**) **75**,

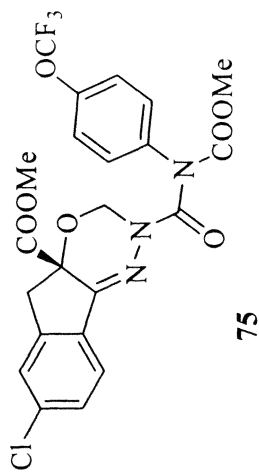


Scheme 26



R = 3-H₂NSO₂, 3-MeSO₂CH₂, 4-H₂NSO₂, 4-H₂NSO₂

R = H, 4-Cl, 4-Me, 5-Me, 4-MeO, 4-Ph



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the acaricide Flufenimer (7) **69**, the fungicide Thifluzamid (30) **42**, the plant growth regulator Flupimidol (8) **76**, as well as the neurologic agent Riluzole (9) **40**, which is the first drug approved for the treatment of amyotrophic lateral sclerosis.

Trifluoromethoxyindoles exhibit a wide spectrum of biological activity. For example trifluoromethoxyindole-3-acetic acid **14** was found to be an oxidatively activated prodrug with potential for targeted cancer therapy (19). Benzoyl-2-methyl indoles **15** were proposed as effective peroxisome proliferator-activated receptor gamma (PPAR γ) modulators (20). Biological evaluation of amide **16** revealed its high affinity for the human neurokinin-1 (hNK₁) receptor **20**. Indeno[1,2-*b*]indole-1-carboxylic acid **19** was shown to possess potent bladder-selective smooth muscle relaxant properties and thus is potentially useful for the treatment of urge urinary incontinence (22). Quinazolino- β -carbolinone derivative **21** has shown good in vitro cytotoxic activity in the concentration range of 1-8 μ M (23).

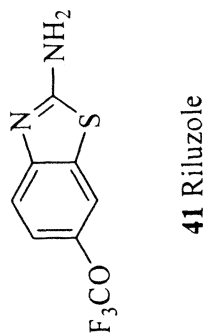
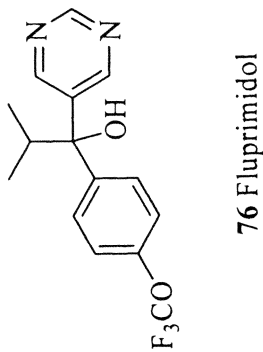
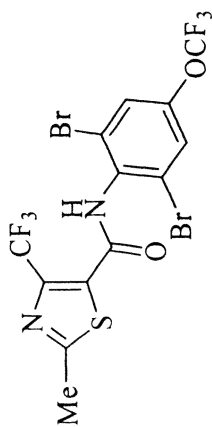
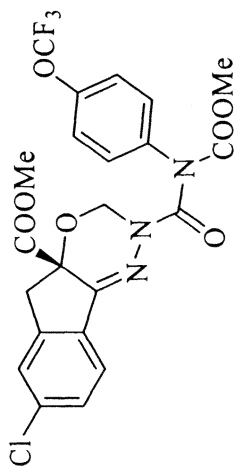
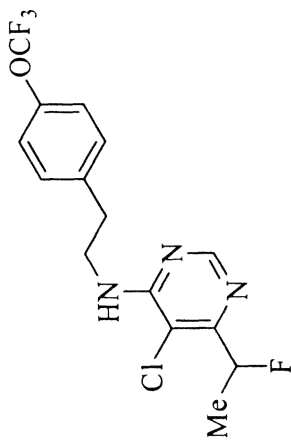
Pyrazole-3-carboxylic acid **28** was identified as an inhibitor (25) of methionyl-*t*-RNA synthetase (MetRS) and ether **31** as cyclooxygenase-2 (COX-2) and lipoxygenases (LOX) inhibitor (26), a property that makes it potentially useful in prostate cancer chemotherapy. Benzodipyrzazole amide **34** is a new class representative of potent cyclic dependent kinase 2 (CDK2) inhibitors (27).

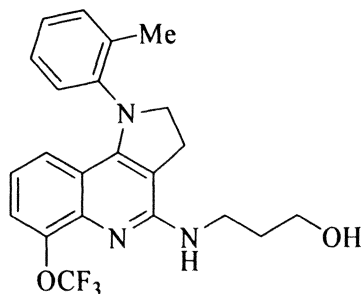
Trifluoromethoxyquinolines have proven to be pharmacologically prospective compounds. For example, quinolone **56** showed remarkable inhibitory activity towards HIV-1 reverse transcriptase (35) whereas the trifluoromethoxy analogue of the known antimalarial drug Chloroquine is active against chloroquine-resistant *P. Falsiparum* (37). Pharmacological studies revealed that quinoline derivative **77** prevents gastric lesions induced by orally administered 95% ethanol (30-300 mg/kg) (38).

Azines containing the trifluoromethoxy group also have been shown to have potential for pharmacological applications. Tetrahydropyrimidin-5-ol **63** was shown to be an efficient antagonist of NR2B-subtype selective N-methyl-D-aspartate (NMDA) (41). 5,8-Quinazolinedione **72** is a potent inhibitor of acetylcholine (Ach)-induced vasorelaxation of rat aorta with endothelium (44). For the last three years biological activity of trifluoromethoxy containing ureido azines has been systematically studied. As result of these efforts effective tyrosine kinase inhibitors **73** (45), antagonist of vanilloid receptor 1 (46) **74** and antibacterial agent **65** (42) were discovered.

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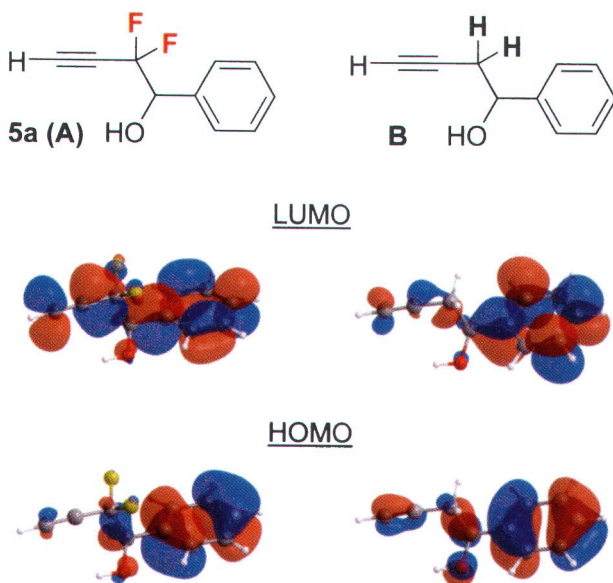
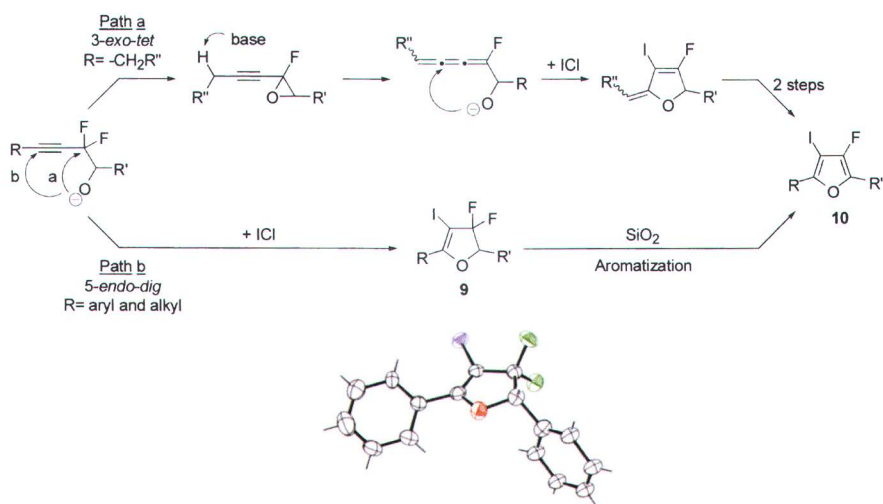


Figure 7.2. Comparison of the electronic states of the triple bond of gem-difluorohomopargyl alcohol **5a (A)** and its non-fluorinated counterpart (**B**). [b3lyp/6-311g(d, p) 5d]



Scheme 7.4. Reaction mechanism for the formation of iodofluorofurans **10**.

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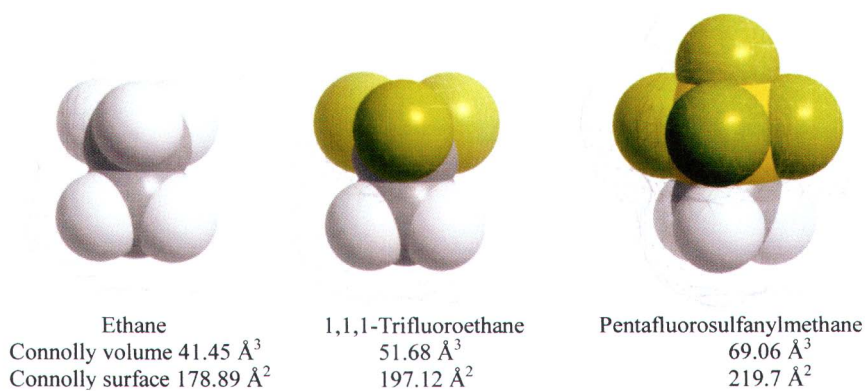


Figure 8.1. Relative volumes and areas C₂H₆, CF₃CH₃, and SF₅CH₃