STUDIES ON
SYNTHESIS AND REACTION OF
PERFLUOROALKYLATED HETEROCYCLIC AND
ETHYNYLAROMATIC COMPOUNDS

MASAYUKI YOSHIDA

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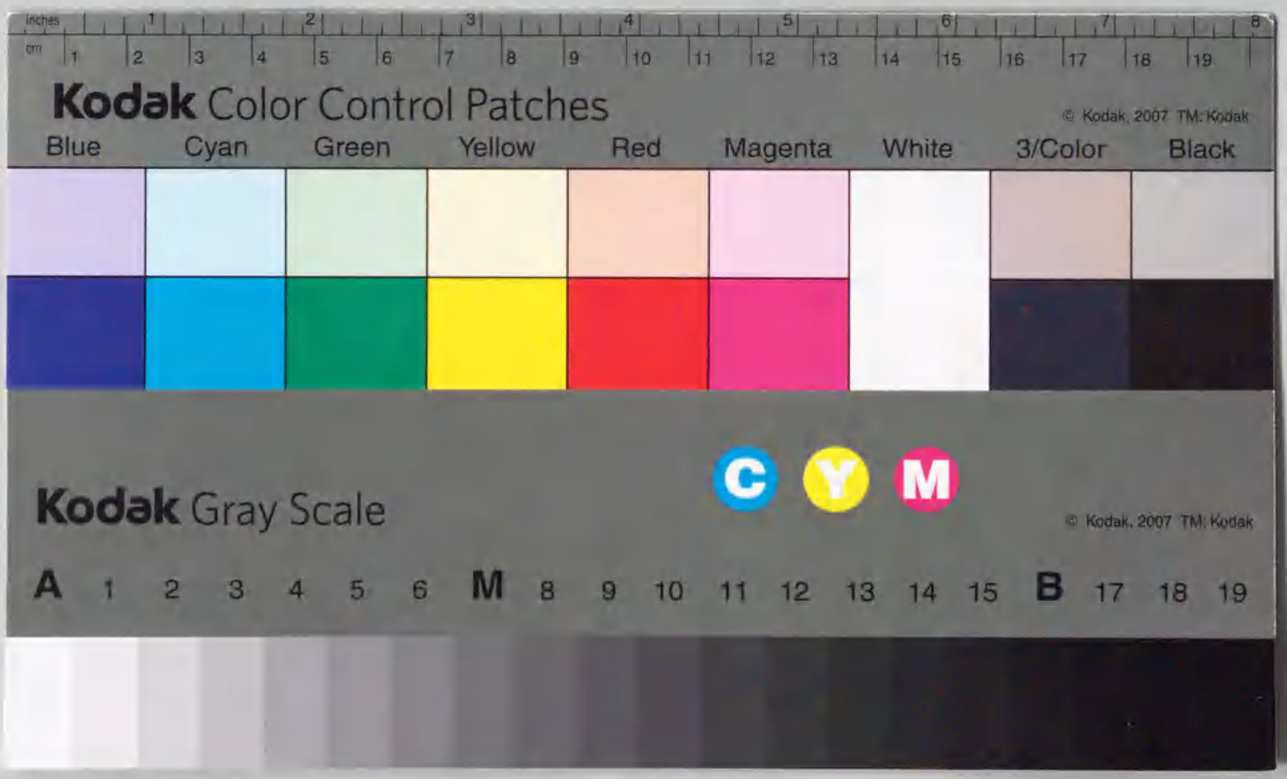

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STUDIES ON

SYNTHESIS AND REACTION OF PERFLUOROALKYLATED HETEROCYCLIC AND ETHYNYLAROMATIC COMPOUNDS

A DISSERTATION
FOR
THE DEGREE OF DOCTOR OF ENGINEERING
TO
DEPARTMENT OF APPLIED CHEMISTRY
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NAGOYA UNIVERSITY

MASAKAZU NISHIDA

1993

PREFACE

The studies described in this dissertation have been carried out at Fluorine Chemistry Division, Department of Chemistry, Government Industrial Research Institute, Nagoya. This dissertation presents the *Studies on Synthesis and Reaction of Perfluoroalkylated Heterocyclic and Ethynylaromatic Compounds*.

The author wishes to express his sincere gratitude to Professor Shoji Eguchi for his kind and fruitful suggestions and encouragement.

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Finally, the author heartily thanks to his wife, Keiko, for her affectionate care and encouragement.

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March, 1993

CONTENTS

CHAPTER 1

INTRODUCTION

Recent years have seen dramatic development in organic fluorine chemistry in both academic and industrial fields. The development in organic fluorine chemistry, however, has been marked with a certain delay as compared with other halogens. This is because very few of organic fluorine compounds occur naturally and no really simple methods exist for the synthesis of carbon-fluorine bonds. Element fluorine was first isolated by Moissan in 1886, although fluorine-containing minerals, such as fluorspar (CaF_2), had been known for a long time. In the period 1892 - 1938, Swarts prepared many simple aliphatic fluorocarbons by the halogen-exchange reaction using antimony and mercurous fluorides (Swarts reaction). As first industrial materials of organic fluorine compounds, Freon was synthesized by Midgley in 1930 using Swarts reaction. Teflon, one of fluoro-polymer used in great quantities now, was discovered as a polymer of decomposition product of chlorofluorocarbons by Plunkett in 1938. The Manhattan project gave a stimulus to organic fluorine chemistry; in order to treat corrosion gas, UF_6 and HF, inert materials were demanded, therefore new fluorinated polymers and fluorocarbons were developed vigorously. Since excellent biological activity of 9α-fluorocortisol was discovered by Fried and Sabo in 1953, organic fluorine chemistry have been broken new fields: drugs, anesthetics, and pesticides. Now, the application of organic fluorine chemistry has reached various industrial fields: engineering, electronic, medicinal, agricultural, and so on.

Table 1.1
Electronic Properties of Hydrogen, Fluorine, and Chlorine.

	H	F	Cl
Electronic configuration	$1s^1$	$2s^22p^5$	$3s^23p^53d^0$
Electronegativity (Pauling)	2.1	4.0	3.0
Ionization energy (kcal/g atom)	315.0	403.3	300.3
Electron affinity (kcal/g atom)	17.8	83.5	87.3
Bond energies of C-X (kcal/g atom)	99.5	116	78
Bond lengths of C-X (Å)	1.091	1.317	1.766
Preference as a leaving group	H^+	F^-	Cl^-

Fluorine has anomalous properties observed for no other elements: (1) fluorine is the most electronegative of all the elements; (2) fluorine is the second smallest atom, closely to hydrogen. Fluorine is different from the other halogens either when in elemental state or bonded in chemical compounds (Table 1.1). The high electronegativity of fluorine causes high oxidation potential, high ionization energy, and high electron affinity. Dissociation energy of molecular fluorine is lower than any other molecules (F_2, 37 kcal/ mol; Cl_2, 58 kcal/mol; Br_2, 46 kcal/mol; N_2, 225 kcal/mol; O_2, 118 kcal/mol). Consequently, elemental fluorine reacts explosively with organic compounds in extremely exothermic reactions. The fluorine atom forms very stable bonds with carbon and hydrogen owing to their high bond strength and short bond length. In addition, it is possible to pack all the fluorines necessary to replace hydrogen by fluorine completely.

The organic fluorine compound divides into two main classes based on contents of fluorine: perfluorinated and polyfluorinated compounds, and partially fluorinated compounds. Each class of organic fluorine compounds exhibits distinctive properties and is used in different industrial fields.
Perfluorinated and polyfluorinated compounds: replacement of all or almost all hydrogen atoms of the hydrocarbons by fluorine atoms lead to change the reactivity and physical properties, such as the boiling point and the surface tension, owing to shielding a center element by fluorine atoms. Because of unusual chemical inertness, perfluorinated and polyfluorinated compounds were applied for a wide range of industrial fields: coolants, inert fluids, fire extinguishers, surface-active agents, and oxygen-carrying blood substitutes.
Partially fluorinated compound: replacement of a few hydrogen atoms of the hydrocarbon by fluorine atoms does not change physical properties markedly but can alter biochemical properties compared with original hydrocarbons. The main applications of the partially fluorinated compounds exist in medicinal and agricultural fields: they display impressive biological activities. Further, because of stability of carbon-fluorine bonds, their applications to dyes and electronic materials are examined.

The unusual properties of fluorine lead to following biologically important effects.
Mimic effect: since fluorine has the closest atomic radii to hydrogen (the van der Waals' radii: F, 1.35 Å; H, 1.1 Å), fluorinated compounds can become

incorporated into metabolic process, especially into enzyme receptor sites, without distinction from their original hydrogen compounds.

Block effect: fluorine imparts increased oxidative and thermal stability because the strength of the carbon-fluorine bond exceeds that of the carbon-hydrogen bond. Therefore, improved stability of the modified compound causes inhibition of further metabolisms.

Polarity effect: the electron inductive effect of fluorine exerts neighboring functional groups of a reactive site to change the reactivity and biochemical equilibrium of the modified compound.

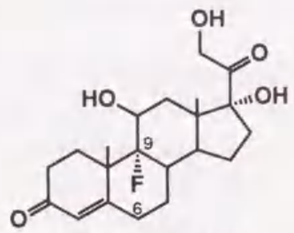
Lipophilicity effect: the presence of fluorine may lead to increased lipid solubility and thereby enhance the rates of absorption and transport of drugs *in vivo*.

The biological activity of partially fluorinated compounds appeared by combination of the four effects of fluorine mentioned above. Important examples in medicinal and agricultural applications of biologically active fluorinated compounds are summarized as follows.

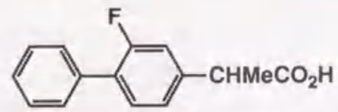
Anti-inflammatory Drugs

Fluorinated steroids cause a wide variety of pharmacological activities in mammalian organism. Studies of structure-activity relationships indicated that 9α- and 6α-fluoro-steroids were effective anti-inflammatory drugs.

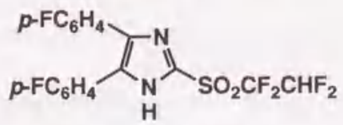
Because of undesirable side-effects of steroids, several fluorine-containing compounds have been examined as non-steroidal anti-inflammatory agents. Flurbiprofen has high analgesic and anti-inflammatory activity. A fluorine-containing imidazole, tiflamizole, is currently undergoing clinical trials.



9α-Fluorocortisol



Flurbiprofen

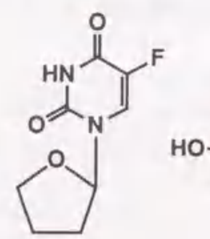


Tiflamizole

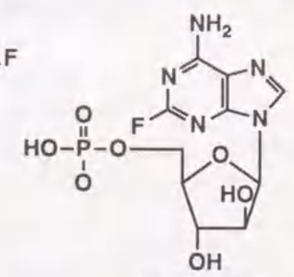
Anticancer and Antiviral Agents

Fluorinated analogs of the naturally occurring nucleic acid component have become established anticancer and antiviral agents. A wide variety of fluorinated uracils and their nucleosides has been studied intensively, since significant tumor-inhibiting activity of 5-fluorouracil was discovered. Several fluorinated uracils, such as ftorafur, are practically used in therapeutic fields.

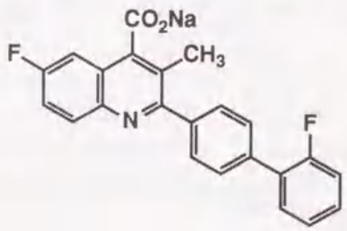
The studies on anticancer and antiviral agents were extended to other nitrogen-containing heterocycles, for example, purines and pyridines. Potentiality of fludarabine and DuP-785 as cancer drugs was discovered.



Ftorafur



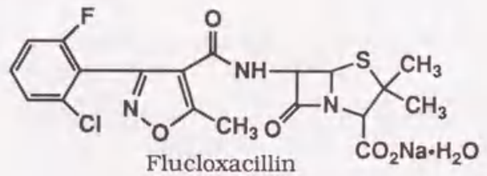
Fludarabine



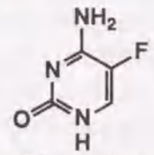
DuP-785

Antibiotics

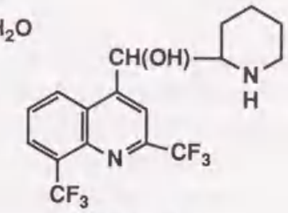
Fluorine-containing compounds are being used selectively in many antimicrobial applications. Flucloxacillin is a specific narrow-spectrum antibiotic, which is stable to penicillinase. Flucytosine is orally-active antifungal agent and less toxic than amphotericin B. Mefloquine is a useful antiprotozoal drug, that is one of the most outstanding antimalarial drugs.



Flucloxacillin



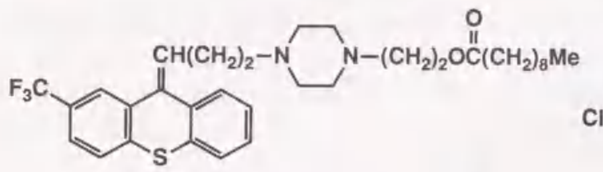
Flucytosine



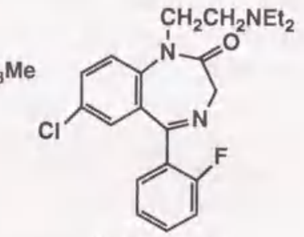
Mefloquine

Central Nervous System (CNS) Agents

Replacement of hydrogen of central nervous system (CNS) agents by fluorine atoms or trifluoromethyl groups causes stronger activity and longer action time. This is because fluorinated substituents increase the rate of absorption and transport of the drug across the blood-brain barrier into the central nervous system. Flupenthixol and flurazepam are used as a tranquilizer.



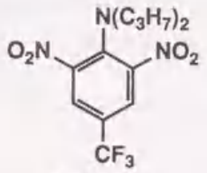
Flupenthixol Decanoate



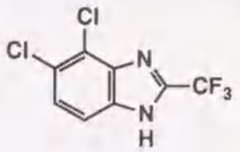
Flurazepam

Agrochemicals

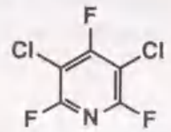
Though the production cost is higher, fluorine-containing organic pesticides were widely used because of a lower dosage, great crop safety, and increased selectivity of action. The most commercially successful fluorine-containing pesticides are aniline derivatives: beginning with trifluralin, many 2,6-dinitro-4-trifluoromethylanilines were synthesized and practically used in relatively large amount. Chlorflurazole and haloxydine were developed as typical examples of herbicides containing heterocyclic rings.



Trifluralin



Chlorflurazole



Haloxydine

As mentioned above, many aromatic and heterocyclic compounds having fluorinated substituents display remarkable biological activities and have potentiality for medicinal and agricultural chemicals. In addition, these fluorinated compounds are applicable for engineering materials, such as electronic materials and functional dyes. The purpose of the present study is to develop new synthetic methods for introduction of perfluoroalkyl

groups into heterocyclic and ethynylaromatic compounds. Furthermore, chemistry of new perfluoroalkylated heterocycles is investigated in the view of the substituent effect of fluorine.

This dissertation describes synthesis and reaction of perfluoroalkylated heterocyclic and ethynylaromatic compounds. In Chapter 2, synthesis of perfluoroalkylated analogs of nitrogen-containing heterocycles which are components of amino acid and nucleic acid is described. These compounds are expected to exhibit biological activity for application to drugs and agrochemicals. In Chapter 3, synthesis of trifluoromethylated heterocycles by ring formation reaction is described. The addition products *via* γ-ray induced addition reaction to hexafluoro-2-butyne are useful intermediates for synthesis of fluorinated heterocycles. Reaction and decomposition of these trifluoromethylated heterocycles are also described. In Chapter 4, synthesis of trifluoromethylated ethynylaromatic compounds is described. These arylacetylenes gave high molecular weight polymers. Polymerization of trifluoromethylated acetylenes and properties of polymers obtained are also described.

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CHAPTER 2

PERFLUOROALKYLATED ANALOGS OF BIOLOGICALLY IMPORTANT NITROGEN HETEROCYCLES

Introduction to Chapter 2

Nitrogen-containing heteroaromatic compounds are widely distributed in nature. Several nitrogen heterocycles are essential components of amino acids or nucleic acids. The nitrogen atom in the ring shows particular importance in bioorganic chemistry. The nitrogen heterocycles are key compounds in biological process, especially in the metabolism.

Introduction of the perfluoroalkyl group into these nitrogen heterocycles significantly changes biochemical activities of the original compound. The strong electron-withdrawing inductive effect of the perfluoroalkyl group influences reactivity and stability of the compound. The perfluoroalkylated compound can inhibit an essential enzyme action by an irreversible reaction with the receptor. Further, improvement of the lipophilicity due to the perfluoroalkyl group enhances absorption and transport of the compound. Perfluoroalkylated analogs of the nitrogen heterocycles, therefore, have potentialities of biological activities as drugs and agrochemicals.

Many methods have been reported concerning with the perfluoroalkylation of aromatic and heteroaromatic compounds. These methods, however, were not suitable for an electron deficient heteroaromatic compound because of the low regioselectivity and low yield. This chapter describes new perfluoroalkylation methods applicable to several nitrogen heterocycles which are biologically important as components of amino acids and nucleic acids.

2.1 Photochemical Trifluoromethylation of 1-Methylimidazoles and 1-Methylpyrroles Containing Methylthio Groups

Summary

The title reaction was achieved by UV (254 nm) irradiation with CF_3I. The methylthio group was introduced to increase electron density and to limit available reactive sites in the rings. Following trifluoromethylation, the methylthio groups were readily removed by hydrogenolysis (Raney Ni) to give the desired trifluoromethyl-substituted heterocycles.

Introduction

Heterocyclic compounds containing the trifluoromethyl group are of considerable interest because of their utility as drugs and agrochemicals. Trifluoromethyl groups on imidazoles and pyrroles possess the additional property of undergoing facile transformations to other functional groups [1 - 4]. Regiospecific introduction of this group has been achieved by reaction of the carboxyl group with SF_4 [5], by reaction of heteroaryl halides with trifluoromethyl organometallics [6 - 13], by ring closure of 1,2-bis(acylamino)ethylenes with trifluoroacetic anhydride [14] and by ring closure involving various ketones [15, 16]. Of these methods, only the latter two can be performed under reaction conditions mild enough for use in polyfunctional or biologically significant systems. Comparably mild are methods involving photochemical [4, 17, 18] or electrochemical [19, 20] generation of trifluoromethyl radicals, or generation from trifluoroacetyl peroxide [21]. These methods often yield isomer mixtures or, when regioselective, may give mainly undesired isomers. In order to provide better routes to specific isomers, the author considered the introduction of reversible blocking groups on ring carbons prior to photochemical trifluoromethylation, and demonstrated here the utility of methylthio groups for this purpose. Such groups are introduced and removed with relative ease. In addition, the mildly electron-donating methylthio group would be expected to help to reverse the deactivation of heteroaromatic rings by electronegative substituents [17], and offers the further possibility of conversion to potentially bioactive sulfoxides and sulfones. In views of author's particular interest in (perfluoroalkyl)imidazoles and pyrroles, these heteroaromatic systems received author's first attention. In this study, the ring NH functions are blocked as *N*-methyl but other photostable protective groups, which are readily removed by acid hydrolysis or by hydrogenolysis, should be equally applicable. Furthermore, previous results [17] have shown that trifluoromethylation is representative of perfluoroalkylation in general.

Results and Discussion

The methylthio group was introduced by selective deprotonations of **1a** [22] and **1b** [23] (Scheme 2.1) with butyllithium and reaction of the resulting carbanions with dimethyl disulfide. The use of an equivalent of butyllithium provided mono(methylthio) derivatives **2** in high yield. Two equivalents of

butyllithium led to the bis(methylthio) derivatives **3** but, even in the presence of excess base or with **2** as the starting material, formation of **3** was never complete. Fortunately, **2** and **3** are readily separated by fractional vacuum distillation. In contrast to author's results, **2a** (containing *N*-methoxymethyl in place of methyl) has been reported to undergo deprotonation at S-CH_3 rather than at a ring position [24]. The preferential formation of the carbanion at C-2 in *N*-methylimidazole (**1a**) [25 - 27] and in *N*-methylpyrrole (**1b**) [23, 28] is governed by the inductive effects of the ring nitrogen atoms. The generation of the second carbanion in **1a** occurs exclusively at C-5 and leads to the single bis(methylthio) product **3a** [22]. This selectivity is determined by the strong repulsion that would exist between adjacent sp^2 lone pairs at N-3 and a C-4 carbanion (the ALP effect) [29, 30].

Photochemical trifluoromethylation was performed according to published procedure [17], samples being irradiated in quartz ampoules for 7 days at ambient temperature. According to the solubility of the starting compound, either methanol or acetonitrile was used as solvent and triethylamine was added to neutralized the hydrogen iodide evolved. As seen from the results in Table 2.1, the choice of solvent has relatively little effect on yield or isomer distribution.

Table 2.1
Yields and Conversions in Trifluoromethylation by UV Irradiation of 1-Methyl-2-methylthioimidazole (**2a**)

CF_3I (equiv)	Solvent	Yield [a] (%)		
		4a	**5a**	**2a**
0.5	CH_3CN	0.8	11.9	31.2
0.5	CH_3OH	2.7	14.1	30.3
1.2	CH_3CN	1.5	25.0	12.7
1.2	CH_3OH	2.8	20.7	47.4
2.5	CH_3CN	2.6	29.3	0.7
2.5	CH_3OH	3.2	30.8	26.1

[a] Isolated yields based on the imidazole, not adjusted for recovered **2a**.

The photochemical trifluoromethylation of 1-methyl-2-(methylthio)imidazole (**2a**) gave mixture of **4a** and **5a**, the latter being the major isomer (Table 2.1). Several criteria were used to assign isomer structure: (a) coupling patterns of the ^{13}C NMR signal for C-4 and C-5 with CF_3 group [31, 32]; (b) the ^{19}F NMR signal for 4-CF_3 appears at higher field than for 5-CF_3 [18]; (c) the ring proton in **5a** (*meta*-like) is found at higher field than that in **4a** (*para*-like) [33]; (d) weak coupling is observed between the N-CH_3 and the adjacent CF_3 group; (e) products were compared with authentic samples following reductive removal of the methylthio group. The direct trifluoromethylation of 1-methylimidazole had given three isomeric products (2-CF_3 : 4-CF_3 : 5-CF_3) in the ratio 43 : 8 : 50, separation requiring the use of both preparative gas and column chromatography [17]. On the other hand, isomers **4a** and **5a** were formed in the ratio 10 : 90, the increased degree of substitution at C-5 probably being due to the electron-releasing effect of the methylthio group.

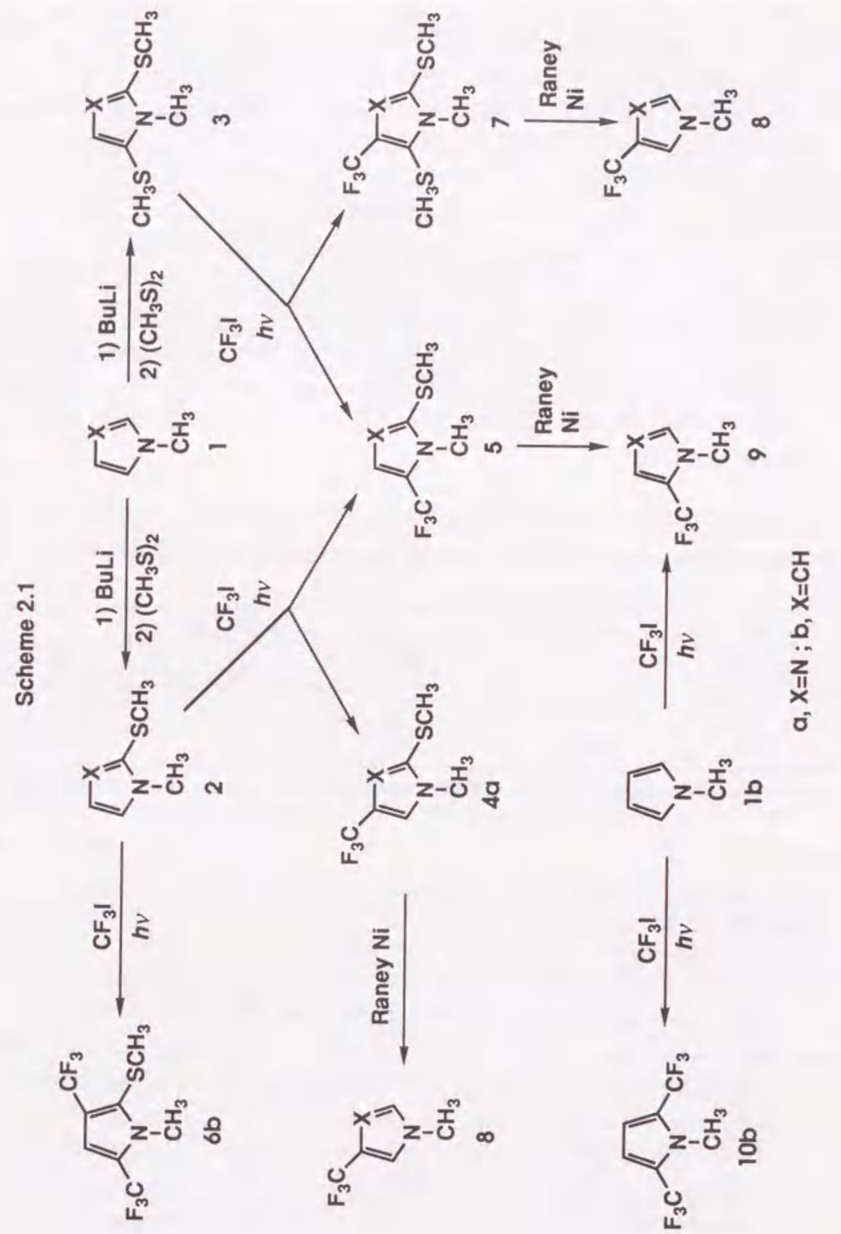
The 4-CF_3 isomer is the most difficult to obtain by photochemical trifluoromethylation of either **1a** or **2a**. Although C-4 is the only vacant ring position in **3a**, yields of **7a** never exceeded 6 - 8% (Table 2.2), even with 2.5 equiv of CF_3I. Interestingly, **7a** was accompanied by smaller amounts of **5a**, which may have arisen due to a slow photochemical conversion of **3a** to **2a**.

Table 2.2

Yields and Conversions in Trifluoromethylation by UV Irradiation of 1-Methyl-2,5-bis-(methylthio)imidazole (**3a**)

CF_3I (equiv)	Solvent	Yield [a] (%)		
		5a [b]	**7a** [c]	**3a** [c]
0.5	CH_3CN	1.3	6.3	43.3
1.2	CH_3CN	2.9	7.8	32.0
1.2	CH_3OH	–	7.2	12.3
2.5	CH_3CN	2.3	8.3	31.1

[a] Based on the imidazole, not adjusted for recovered **3a**. [b] Determined by ^{19}F NMR. [c] Isolated yields.



Photochemical trifluoromethylation of 1-methylpyrrole (**1b**) has been reported to yield the 2-trifluoromethyl derivative (**9b**) in 35% yield [4]. The author has confirmed this result, but found that excess CF_3I also provides a small yield (Table 2.3) of the 2,5-bis(trifluoromethyl) derivative (**10b**). Unfortunately, the boiling points of **9b** and **10b** are too close permit clean separation and yields given in Table 2.3 are based on GC analysis. Although *N*-methylpyrrole undergoes efficient α-perfluoroalkylation with higher bis(perfluoroalkanoyl) peroxides, introduction of the CF_3 group could not be achieved [21]. The results of trifluoromethylation of **2b** are given in Table 2.4. Significant yields of **5b** require the use of at least 2.5 equiv of CF_3I, but small amounts of a bis(trifluoromethyl) derivative, presumably **6b**, are also formed. Fortunately, the methylthio group facilitates the separation of mixtures by increasing boiling points and R_f differences in silica gel chromatography.

Table 2.3
Yields in Trifluoromethylation by UV Irradiation of 1-Methylpyrrole (**1b**)

CF_3I (equiv)	Solvent	Yield [a] (%)		
		9b	**10b**	**1b**
1.2	CH_3CN	36.5	–	10.5
2.5	CH_3CN	32.2	7.4	–

[a] Determined by GC analysis based on the pyrrole, not adjusted for recovered **1b**.

Table 2.4
Yields and Conversions in Trifluoromethylation by UV Irradiation of 1-Methyl-2-methylthiopyrrole (**2b**)

CF_3I (equiv)	Solvent	Yield [a] (%)		
		6b [b]	**5b** [c]	**2b** [c]
0.5	CH_3CN	–	4.2	18.4
1.2	CH_3CN	–	17.7	4.7
2.0	CH_3CN	0.14	18.8	5.0
2.5	CH_3CN	1.24	33.3	5.3

[a] Based on the pyrrole, not adjusted for recovered **2b**. [b] Determined by GC analysis. [c] Isolated yields.

Introduction of the trifluoromethyl group at the β-position of the pyrrole ring has not been achieved by direct or indirect methods. The reaction of 5-methyl-2-pyrrolecarbaldehyde with bis(heptafluorobutyryl) peroxide provide the 3-heptafluoropropyl derivative [21], but this method failed to provide the trifluoromethyl derivative. Photochemical trifluoromethylation of **3b** provided the desired product **7b**. Even at a level of 2.5 equiv of CF_3I, the yield of **7b** was only 7% and was accompanied by 17% of **5b** (Table 2.5). Detection of a trace of **2b** suggested that the apparent replacement of the methylthio group by trifluoromethyl, both in the conversion of **3a** to **5a** and **3b** to **5b**, may actually be due to a prior loss of the methylthio group by irradiation. On the other hand, products devoid of the methylthio group were not detected in the photochemical trifluoromethylation of **2a** or **2b**.

Table 2.5
Yields and Conversions in Trifluoromethylation by UV Irradiation of 1-Methyl-2,5-bis(methylthio)pyrrole (**3b**)

CF_3I (equiv)	Solvent	Yield [a] (%)		
		5b [b]	**7b** [c]	**3b** [c]
0.5	CH_3CN	6.7	2.3	29.5
1.2	CH_3CN	10.2	3.9	38.1
2.5	CH_3CN	23.6	7.0	7.0

[a] Based on the pyrrole, not adjusted for recovered **3b**. [b] Determined by ^{19}F NMR. [c] Isolated yields

Methylthio groups were removed by hydrogenolysis with Raney nickel in refluxing ethanol [34]. The imidazole derivatives provided the expected products in yields of 50 - 90%, and these products were readily isolated and purified by vacuum distillation in a microtube oven. In each case, properties of the sulfur-free imidazole coincided with those of authentic samples [17]. On the other hand, the lower boiling points of (trifluoromethyl)pyrroles (and their closeness to that of ethanol) rendered isolation and purification difficult. Even the use of higher boiling alcohols as reaction solvents did not eliminate this problem. Thus, spectral properties were determined in mixtures containing some solvent. Yields were determined by GC analysis and were found comparable to those of the imidazoles. Reduction at 90 - 100 °C gave somewhat higher yields than at the temperature of refluxing ethanol.

For certain (trifluoromethyl)pyrroles, therefore, it may be necessary to use the materials for further synthetic procedures without recovery of the pure product.

In these test cases, the overall yields of trifluoromethylated products were found to be comparable (or even inferior) to those obtained by direct photochemical trifluoromethylation. On the other hand, laborious isomer separations have been eliminated. Finally, this method provides a route to β-(trifluoromethyl)pyrroles, isomers which have not yet been obtained by direct trifluoromethylation.

2.2 Facile Perfluoroalkylation of Uracils and Uridines at the C-5 Position with Bis(perfluoroalkanoyl) Peroxides

Summary

Perfluoroalkylation at the C-5 position of uracil has been achieved in yields of 38 - 56% by reaction of its bis(trimethylsilyl) derivative with bis(perfluoroalkanoyl) peroxides and the hydrolytic deprotection of the silylated products. A substituent or nitrogen replacement at C-6 does not interfere with perfluoroalkylation at C-5, but no significant reaction occurs at C-6 when C-5 is blocked.

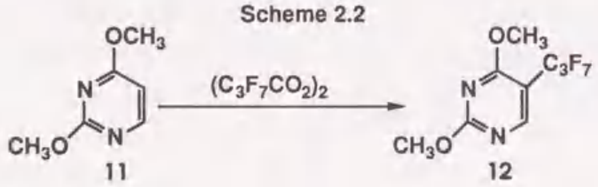
Introduction

The impressive antimetabolic activities of 5-(trifluoromethyl)uracil (**15a**) and its furanosides [35 - 37] have stimulated research into improved methods of synthesis, as well as methods which may provide higher perfluoroalkyl homologs. The author has been interested in improving accessibility to these higher homologs, both for the sake of examining their own biological activities and for their use as precursors to even less accessible functionalities at C-5 [38]. In the presence of copper bronze in DMSO, perfluoroalkyl iodides have been found to perfluoroalkylate uracil, uridine and their derivatives in yields rarely exceeding 3 - 6% [39, 40]. Although 5-iodouracil proved to be unreactive toward replacement of iodine in this work, Lin and Gao [41] succeeded in obtaining the perfluoroethyl derivative of a protected uridine in 17% yield from the 5-iodo compound. Photochemical perfluoroalkylation of the same pyrimidines with bis(perfluoroalkyl)mercury has also been explored [42 - 44]: while yields were significantly better in favorable cases, the results were inconsistent; furthermore, cost and toxicity of the reagent may limit the appeal of the latter method.

Results and Discussion

The perfluoroalkylation of electron-rich heterocycles with bis(perfluoroalkanoyl) peroxides has been described previously, the expected products being obtained in moderately high yields [21, 45, 46]. The author's application of this method to uracil failed (low solubility of uracil in Freon 113). The author then investigated the reactivity of 2,4-dimethoxypyrimidine (**11**), which was anticipated to be more soluble and more reactive toward an electrophilic perfluoroalkyl radical by virtue of its electron-releasing methoxyl groups. Reaction of compound **11** with bis(heptafluorobutyryl) peroxide gave the 5-heptafluoropropyl derivative (**12**) in 47% yield (Table 2.6).

Scheme 2.2

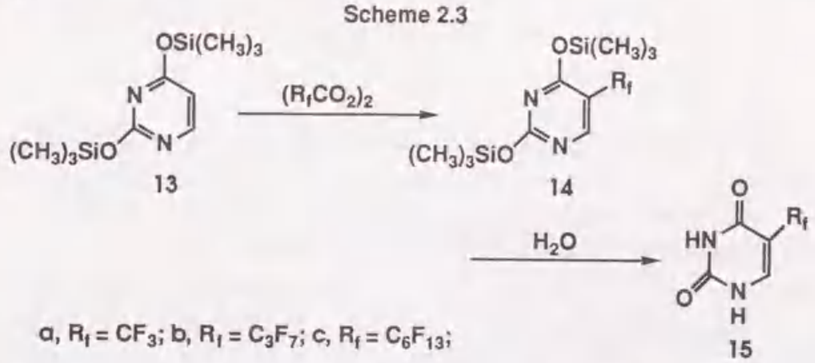


11 12

In contrast, **11** failed to react with perfluorohexyllithium [47]. Encouraged by this first result, the author turned to pyrimidine derivatives from which the uracil might be more easily regenerated than from the dimethoxy derivative [47].

2,4-Bis(trimethylsilyloxy)pyrimidine (**13**) was prepared by reaction of uracil with chlorotrimethylsilane and triethylamine in dioxane [48]. Reaction of the moisture-sensitive **13** with bis(perfluorobutyryl) peroxide gave a mixture which, according to GC-MS, contained the expected product, **14b**. This was hydrolyzed to the uracil derivative (**15b**) prior to purification. Reaction conditions and yields for several runs are given in Table 2.6. At least for the preparation of the perfluoropropyl derivative (**15b**), the optimum yield was realized by the use of 0.5 equiv of the peroxide. Structural assignment is based on the correspondence of the ^{1}H NMR signal for the residual ring CH with that of H-6 (δ 8.01 ppm) in the authentic 5-(trifluoromethyl)uracil (**15a**). In no case did the crude product give evidence for the formation of the isomeric 6-(perfluoroalkyl)uracil (H-5, δ 5.95 ppm [47]) or for perfluoroalkylation on nitrogen or oxygen. In a similar manner, **15c** was obtained in 38% yield. Preparation of the known **15a** by author's method proved more difficult in that a sealed tube was required to achieve a higher reaction temperature (70 °C) and yields were lower than those for **15b** or **15c**.

Scheme 2.3



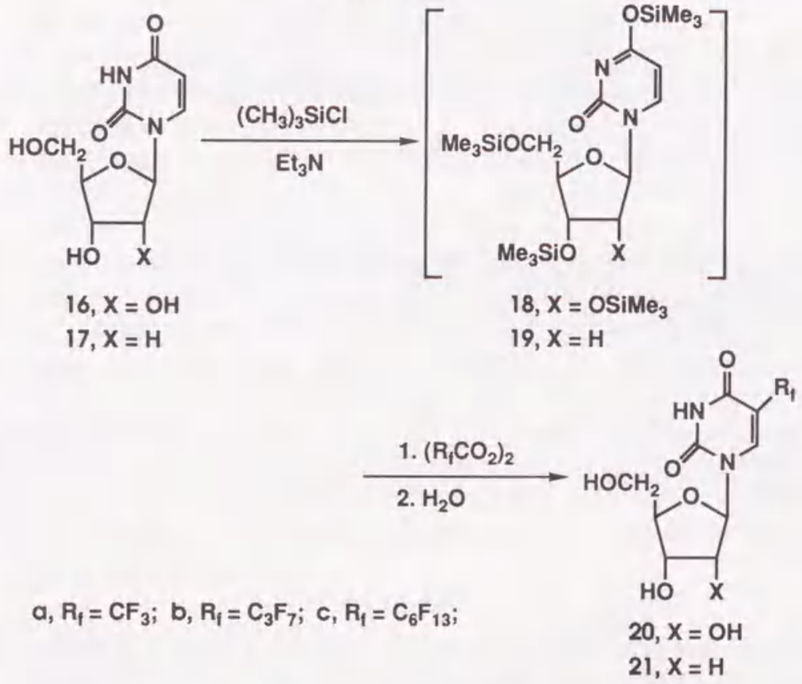
13 14 15

a, $R_f = CF_3$; b, $R_f = C_3F_7$; c, $R_f = C_6F_{13}$;

Analogous reactions with uridine (**16**), 2'-deoxyuridine (**17**), or their sugar-acetylated derivatives, failed; nor did silylation of the pyrimidine ring in the sugar-acetylated derivatives lead to the expected products. After *both* the sugar and pyrimidine moieties had been converted to their silyl derivatives (**18**, **19**) [49], however, reaction did occur and the desired 5-perfluoroalkyl derivatives (**20**, **21**) were obtained in yields of 26 - 42% (Table

2.7). Presumably, the success of the latter route is due to the combination of increased solubility and increased electron density in the pyrimidine ring.

Scheme 2.4



16, X = OH
17, X = H

18, X = $OSiMe_3$
19, X = H

a, $R_f = CF_3$; b, $R_f = C_3F_7$; c, $R_f = C_6F_{13}$;

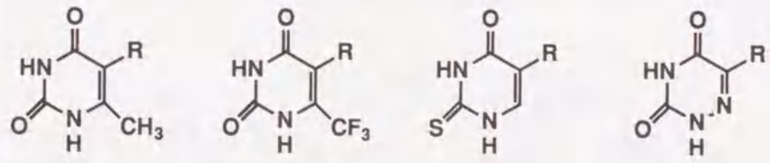
20, X = OH
21, X = H

Substitution at the 6-position of uracil does not interfere with perfluoroalkylation at C-5 *via* the silylated compound. Thus, 6-methyluracil (**22a**) gave the 5-heptafluoropropyl derivative (**22b**) in 36% yield and 6-(trifluoromethyl)uracil (**23a**) gave **23b** in 41% yield (Table 2.6). On the other hand, substitution at C-5 failed to direct perfluoroalkylation to C-6 to any significant extent. Thus, reaction of the bis(trimethylsilyl) derivative of thymine with bis(heptafluorobutyryl) peroxide gave only 3% of a crude product whose MS and ^{19}F NMR spectra were consistent with expectations for 6-(heptafluoropropyl)thymine, but further purification could not be achieved. Somewhat low yields were obtained with 2-thiouracil (**24b**, 20% yield) and with 6-azauracil (**25b**, 13%). In the latter case, further elution of silica gel provided an additional product in comparable yield whose structure is under investigation.

Table 2.6
Reactions of Protected Pyrimidines with Bis(perfluoroalkanoyl) Peroxides [a]

Compd	$(R_fCO_2)_2$		Product	Yield [b] (%)
	R_f	equiv		
uracil	C_3F_7	0.5	no reaction	
11	C_3F_7	0.5	**12**	46.9
13	CF_3	0.5	**15a**	12.7
13	C_3F_7	0.5	**15b**	56.5
13	C_3F_7	0.75	**15b**	50.5
13	C_3F_7	1.2	**15b**	42.8 [c]
13	C_6F_{13}	0.5	**15c**	37.7
22a [d]	C_3F_7	1.0	**22b**	36.1
23a [d]	C_3F_7	1.0	**23b**	41.0
24a [d]	C_3F_7	1.0	**24b**	19.7
25a [d]	C_3F_7	1.0	**25b** [e]	12.9

[a] For reaction conditions, see Experimental Section. [b] Isolated yield based on peroxide. [c] Isolated yield based on pyrimidine. [d] As trimethylsilyl derivative (not isolated). [e] A second product, obtained in comparable yield is still under investigation.



22 23 24 25

a, R = H; b, $R = C_3F_7$

The silylated derivative of 2-hydroxypyrimidine failed to undergo perfluoroalkylation. Results with cytosine were also unrewarding. Direct reaction of unprotected cytosine gave 13% of the N^4-heptafluorobutyryl derivative. Silylation of cytosine with chlorotrimethylsilane was incomplete; the bis(trimethylsilyl) derivative was obtained by the use of the more powerful reagent, *N,O*-bis(trimethylsilyl)trifluoroacetamide, but no perfluoroalkylation was achieved. Similarly, the more stable trimethylsilyl derivative of N^4-acetylcytosine failed to give a product.

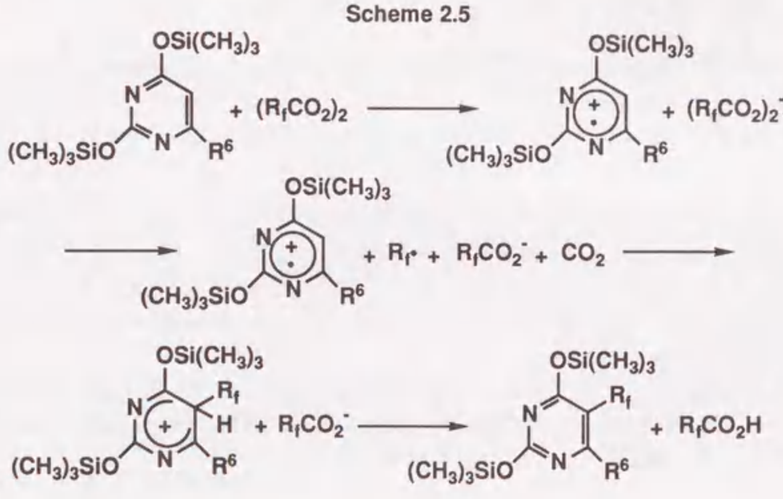
Table 2.7
Reactions of Persilylated Uridines with Bis(perfluoroalkanoyl) Peroxides [a]

Compd	$(R_fCO_2)_2$		Product	Yield [b] (%)
	R_f	equiv		
18	C_3F_7	1.2	**20b**	38.6
18	C_6F_{13}	1.2	**20c**	37.9
19	C_3F_7	1.2	**21b**	26.0
19	C_6F_{13}	1.2	**21c**	41.9

[a] All reactions conducted for 20 h at 30 °C in Freon 113 as solvent. [b] Isolated yield based on pyrimidine.

The single electron transfer (SET) mechanism has been proposed for the perfluoroalkylation of electron-rich heterocyclic compounds [45]. Although the pyrimidine ring is electron deficient, the introduction of trimethylsilyloxy groups increases the level of the HOMO; the ring is now sufficiently electron-rich to participate in the SET mechanism (Scheme 2.5). The trimethylsilyloxy groups not only facilitate the formation of the cation radical by electron donation but also stabilize the carbocation resulting from perfluoroalkyl addition. Thus, the substrates containing two trimethylsilyloxy groups provide ring-perfluoroalkylated compounds in moderate yield.

Scheme 2.5



Although the silylation of cytosines also increases the HOMO level, perfluoroalkylation by the SET mechanism does not occur, not only because the N-TMS bond of the silylated substrate is less stable than the O-TMS bond, but also because the intermediates readily release the hydrogen of the amino group. The attack of a perfluoroalkyl radical at C-6 would lead to an intermediate cation which cannot be stabilized by delocalization with silyloxy group. The author has not determined whether **24a** leads to a mono- or bis-silyloxy derivative, but even a bis-derivative should be less reactive since sulfur is less effective than oxygen in stabilizing a carbocation by delocalization. The yield in perfluoroalkylation of **25a** is reduced because of side reactions involving the nitrogen at C-6. The silylated derivatives of sugar-acetylated uridine are barely soluble in Freon and provided no perfluoroalkylated compounds. Evidently, solubility of the substrate is a critical factor in electron transfer and/or addition of the perfluoroalkyl radical.

2.3 Direct Heptafluoropropylation of Purines with Bis(heptafluorobutyryl) Peroxide

Summary

Some silylated purines react with bis(perfluorobutyryl) peroxide to provide ring-C_3F_7 derivatives. Introduction of the C_3F_7 group occurs predominantly at the C-8 position: 6-methoxypurine gave the C-2 isomer as well in isolable yield. Replacement of the 6-amino group of adenine with dimethylamino or methoxy improved the yields of the C_3F_7 derivatives.

Introduction

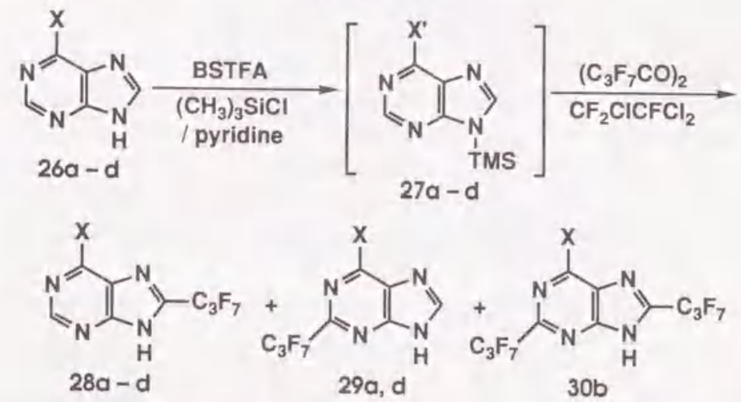
In the preceding section, the author described the facile synthesis of 5-perfluoroalkylpyrimidines and their nucleosides by reaction of the fully silylated derivatives with bis(perfluoroalkanoyl) peroxides. These perfluoroalkylpyrimidines are of interest because of their potential biological activities as well as their use as precursors to other fluorine-containing pyrimidines [38]. For the same reasons, the author have now explored the use of bis-(perfluoroalkanoyl) peroxides for the synthesis of perfluoroalkyl purines. To the best of author's knowledge, the only previous work in this direction involves the replacement of a halogen at the C-8 position of purines and of their nucleosides by the trifluoromethyl group, using trifluoromethyl iodide and copper powder [9]. Since the author had already demonstrated that homologous perfluoroalkyl derivatives of pyrimidines are readily obtained by variation in chain length of the peroxide (Chapter 2.2), the author has limited his present study to the incorporation of the heptafluoropropyl residue as a prototype of the general method.

Results and Discussion

The product of silylation of adenine with chlorotrimethylsilane was treated with bis(heptafluorobutyryl) peroxide, but only starting material was recovered following hydrolytic deprotection. However, more extensive silylation of adenine with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) proved moderately effective and 7.7% of 8-(heptafluoropropyl)adenine (**28a**) was obtained, together with 0.77% of the 2-heptafluoropropyl isomer (**29a**) (Scheme 2.6, Table 2.8) [50, 51]. In contrast to the very low solubility of adenine in both water and organic solvents, introduction of the heptafluoropropyl group increases solubility considerably in organic solvents such as ethyl acetate. The major isomer **28a** could be purified by silica gel chromatography, while the minor isomer **29a** was obtained as a mixture with **28a**, and the yield of **29a** was determined by ^{19}F NMR. Because N-Si bonds are more moisture-sensitive than O-Si bonds, the author could not detect Me_3Si-purine intermediates by MS. Even in cases of silylation by the more stable *t*-$BuMe_2Si$ group, no heptafluoropropylated *t*-$BuMe_2Si$-purines were detected. Accordingly, silylated intermediates were hydrolyzed prior to isolation or purification of products. The reaction formed a considerable

amount of yellow amorphous material which was not further investigated because it showed no fluorine peaks in the ^{19}F NMR.

Scheme 2.6



a, X = NH_2, X'= NHTMS; b, X = X'= NHAc; c, X = X'= NMe_2; d, X = X'=OMe.

Structural assignment is based on the observation that the H-8 signal, in the ^1H NMR spectra of adenine and its derivatives, appears at slightly higher field than that of H-2; however, the difference in δ value is insufficient to inspire confidence and the assignments should be considered tentative. Previously, it was reported that thermal condensation of 4,5,6-triaminopyrimidine with trifluoroacetamide provided only 8-(trifluoromethyl)adenine [52]. In order to confirm the structure of **28a**, the author performed an analogous condensation of 4,5,6-triaminopyrimidine sulfate with heptafluorobutyramide (Scheme 2.7). At 175 - 180 °C, the condensation failed because the amide sublimed out of the reaction mixture. In a glass ampoule under vacuum at 200 - 210 °C, the mixture of the pyrimidine and the amide provided 8-(heptafluoropropyl)adenine in a 7.3% yield; this product coincided with **28a** in all respects.

Scheme 2.7

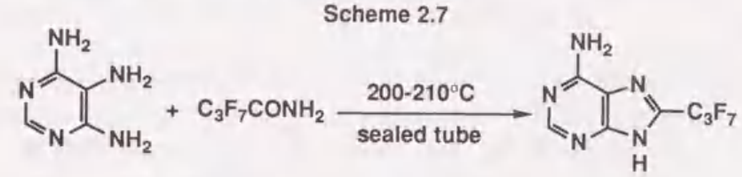
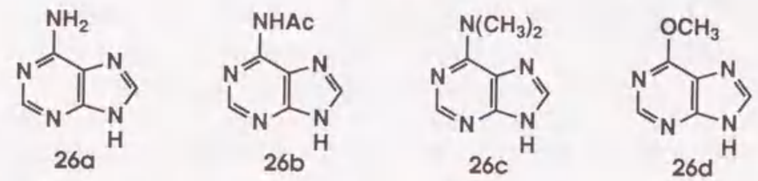


Table 2.8
Reaction of Protected Purines with Bis(perfluorobutyryl) Peroxide [a]

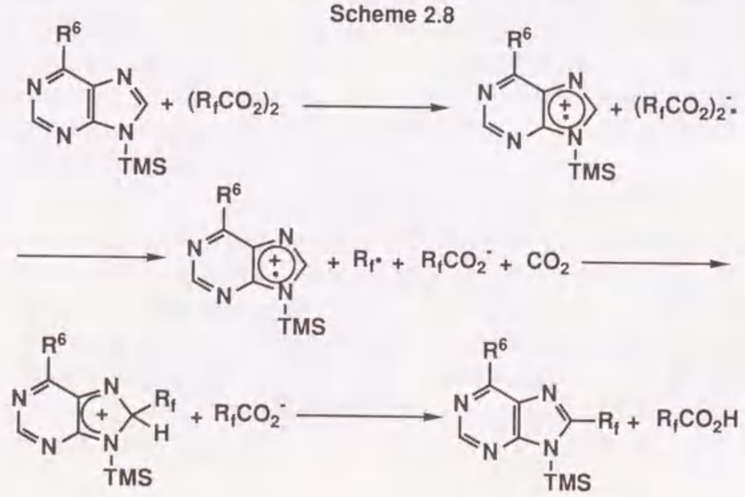
Compd	Yield [b] (%)		
	28	**29**	**30**
26a	7.7	0.77 [c]	–
26b	8.1	–	trace [d]
26c	17.5	–	–
26d	14.7	5.8	–

[a] For reaction conditions, see Experimental Section. [b] Isolated yield based on purine. [c] Determined by ^{19}F NMR. [d] Detected by MS.



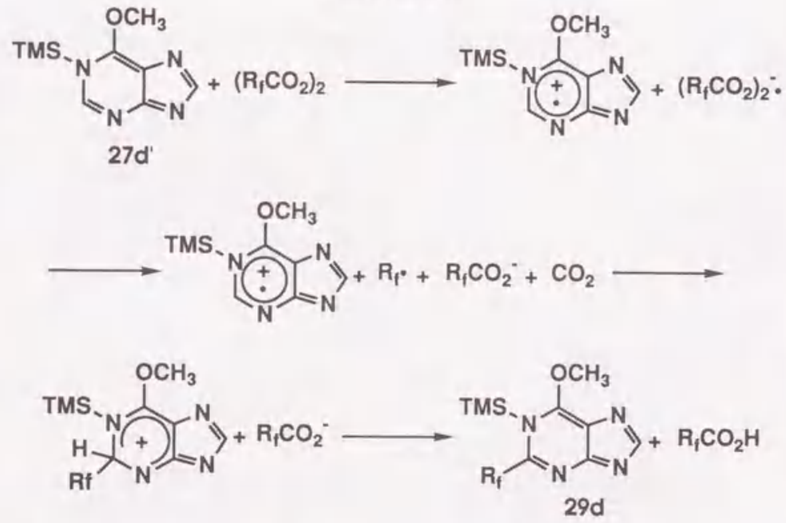
In the case of N^6-acetyladenine (**26b**), perfluoroalkylation occurs at C-8 in 8.1% yield (**28b**); a minor by-product was considered to be the 2,8-bis derivative (**30b**) on the basis of its mass spectrum, but no evidence for the C-2 isomer was found. On the other hand, 6-(dimethylamino)purine (**26c**) gave an 18% yield of the C-8 isomer (**28c**) as the only isolable product.

Scheme 2.8



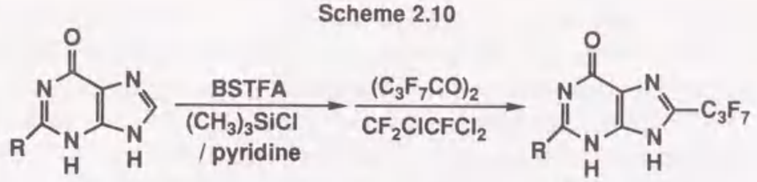
In contrast, 6-methoxypurine (**26d**) gave modest yields of both the C-8 isomer (**28d**) and the C-2 isomer (**29d**). The structures of **28d** and **29d** were assigned by comparison of ^1H and ^{19}F chemical shifts with those of **28a** and **29a**. Protection of the amino group of adenine with acetyl had little effect on product yield, but replacement of the amino group by dimethylamino or methoxy resulted in doubling of the yield of the 8-heptafluoropropyl derivative. By analogy with other heteroaromatic ring systems [45], perfluoroalkylation of silylated purines is considered to begin with a single electron transfer (SET) mechanism (Scheme 2.8). Thus, the availability of a dissociable hydrogen on R^6 (**26a**, **26b**) may lead to reduced reactivity in the subsequent coupling step. The reason for a more competitive yield of **29d** is not obvious, although ^1H NMR suggests the presence of isomeric silyl derivatives (**27d**, **27d'**) in the silylation mixture (Scheme 2.9).

Scheme 2.9



The silylated derivatives of hypoxanthine (**31e**, Scheme 2.10) gave some fluorinated products, but these compounds showed no ring heptafluoropropyl peaks and they could not be separated by silica gel chromatography without decomposition while that of xanthine (**31f**) failed to give any fluorinated product. The product of silylation of guanine (**31g**) provided 8.4% of the 8-(heptafluoropropyl) derivative (**32g**), together with a more complex product whose structure is under investigation.

Scheme 2.10



31e – g

32g: Yield 8.4%

e: R =H; f: R =OH; g: R = NH_2.

Although quite reasonable yields were obtained in the perfluoroalkylation of persilylated uridines (Chapter 2.2), similar efforts in the purine nucleoside series have thus far given only traces of fluorine-containing products according to ^{19}F NMR, but all these products decomposed during silica gel chromatography.

While the overall yields of (perfluoroalkyl)purines are less impressive than those of pyrimidines, the author has demonstrated that such compounds are accessible in sufficient quantity for further transformations and for biological studies.

EXPERIMENTAL

Analytical Methods and Instrumentation

All boiling and melting points are uncorrected. ^1H NMR spectra were measured on a Hitachi R-90H instrument at 90 MHz, with tetramethylsilane as internal reference. ^{19}F NMR spectra were measured on a Hitachi R-90F instrument at 84.68 MHz; positive δ value are downfield from the external reference, trifluoroacetic acid. Gas chromatographic analyses were performed on a Shimadzu GC-4A instrument (column KF-96, 3 m). Mass spectra were obtained on a Hitachi M-80 instrument. IR spectra (in KBr) were obtained with a JASCO IR-810 spectrometer.

Materials

Trifluoromethyl iodide was prepared by reaction of silver trifluoroacetate and iodine [53]. The following methylthio compounds were prepared according to literature methods: 1-methyl-2-(methylthio)imidazole, **2a**, 55% yield, bp 124 - 125 °C / 30 Torr (1 Torr= 133.322 Pa) (Lit., 65 - 70 °C / 0.5 Torr [22]); 1-methyl-2,5-bis(methylthio)imidazole, **3a**, 34% yield, bp 104 - 105 °C / 5 Torr (Lit., 100 - 110 °C / 0.5 Torr [22]); 1-methyl-2-(methylthio)-pyrrole, **2b**, 73% yield, bp 90 - 91 °C / 30 Torr (Lit., 144 - 145 °C / 12 Torr [23]). Raney nickel (Aldrich) was used as a suspension in ethanol after thorough washing of the commercial material with water and ethanol. All bis(perfluoroalkanoyl) peroxides were supplied by Nippon Oil & Fats Co., Ltd.. Other reagents were obtained from commercial sources and were used without further purification.

Photochemical Trifluoromethylation of 1-Methylimidazoles and 1-Methylpyrroles Containing Methylthio Groups

*Preparation of 2,5-Bis(methylthio)pyrrole (**3b**)*

To a solution of 2-(methylthio)pyrrole (**2b**, 2.77 g, 21.8 mmol) and *N,N,N',N'*-tetramethylethylenediamine (3.33 g, 28.7 mmol) in hexane (20 mL), was added dropwise a hexane solution of butyllithium (1.6 M, 18 mL, 1.2 equiv) at 30 °C under nitrogen. The reaction mixture became dark red instantly, and the suspension was stirred for 1 h. To the reaction mixture, cooled in an ice bath, was added dimethyl disulfide (2.70 g, 28.7 mmol) in

hexane (5 mL). The reaction mixture was stirred at 0 °C for 1 h, and was then poured into water (50 mL). The organic layer was separated, washed with water and dried ($MgSO_4$). The water layer was extracted with ethyl acetate (2 × 100 mL) and the organic layer was treated in a similar manner. Vacuum distillation of the combined organic layers afforded 2,5-bis(methylthio)pyrrole (**3b**, 1.58 g, 31.8% yield).

*2,5-Bis(methylthio)pyrrole (**3b**)*

colorless oil; bp 94 - 95 °C/7 Torr; ^{1}H NMR δ ($CDCl_3$)=2.26 (s, 6H, SCH_3), 3.72 (s, 3H, NCH_3), 6.30 (s, 2H, ring); MS (EI, 20 eV) m/z 173 (M^+ 100%), 158 (84), 117 (70). Found: C, 48.78; H, 6.23; N, 8.35%. Calcd for $C_7H_{11}NS_2$: C, 48.52; H, 6.40; N, 8.08%.

*UV-Induced Trifluoromethylation of 1-Methyl-2-(methylthio)imidazole (**2a**)*

Into a solution of **2a** (2.56 g, 20.0 mmol) and triethylamine (2.43 g, 24.0 mmol) in acetonitrile (10 mL), was bubbled gaseous trifluoromethyl iodide until the weight had increased by 4.70 g (24.0 mmol). The solution was placed in a quartz tube and the remaining upper space was filled with argon. The tube was sealed with a glass stopper and then the solution was irradiated for 7 days at ambient temperature, using a 60W low pressure mercury lamp equipped with a Vycor filter.

The dark orange reaction mixture was poured into water and the products were extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was subjected to silica gel chromatography with CH_2Cl_2 and ether as successive eluents to provide, in order, **4a** (1.5%), **5a** (25.0%) and **2a** (12.7%). The eluting solvent was removed and the product purified by vacuum distillation using a glass tube oven. Additional runs are summarized in Table 2.1.

*1-Methyl-2-methylthio-4-(trifluoromethyl)imidazole (**4a**)*

white needles, mp 44 - 46 °C; ^{1}H NMR δ (acetone-d_6)=2.60 (s, 3H, SCH_3), 3.66 (br s, 3H, NCH_3), 7.63 (q, 1H, J=1.1 Hz, H-5); ^{13}C NMR δ_C ($CDCl_3$)= 15.8 (s, SCH_3), 33.3 (s, NCH_3), 121.7 (q, J=267 Hz, CF_3), 121.8 (q, J=4.1 Hz, C-5), 131.9 (q, J=39 Hz, C-4), 145.8 (s, C-2); ^{19}F NMR δ_F (acetone-d_6)=14.8 (s); MS (EI, 20 eV) m/z 196 (100, M^+), 163 (54). Found: C, 36.65; H, 3.57; N, 14.40%. Calcd for $C_6H_7N_2F_3S$: C, 36.73; H, 3.60; N, 14.28%.

*1-Methyl-2-methylthio-5-(trifluoromethyl)imidazole (**5a**)*

colorless oil, bp 98 - 99 °C/30 Torr; ^{1}H NMR δ (acetone-d_6)=2.64 (s, 3H, SCH_3), 3.65 (br s, 3H, NCH_3), 7.42 (q, J=1.5 Hz, H-4); ^{13}C NMR δ_C

($CDCl_3$)=15.3 (s, SCH_3), 31.6 (d, J=1.4 Hz, NCH_3), 121.0 (q, J=266 Hz, CF_3), 123.2 (q, J=39 Hz, C-5), 130.9 (q, J=4.2 Hz, C-4), 149.1 (br s, C-2); ^{19}F NMR δ_F (acetone-d_6)=17.3 (s); MS (EI, 20 eV) m/z 196 (100, M^+), 163 (59). Found: C, 36.30; H, 3.68; N, 14.77%. Calcd for $C_6H_7N_2F_3S$: C, 36.73; H, 3.60; N, 14.28%.

*UV-Induced Trifluoromethylation of 1-Methyl-2,5-bis(methylthio)imidazole (**3a**)*

Trifluoromethylation of **3a**, by the procedure described above, gave **7a** (7.8%), **5a** (2.9%), and unreacted **3a** (32.0%). The mixture of imidazoles was separated by silica gel chromatography with 50% hexane/50% CH_2Cl_2 and 100% CH_2Cl_2 as successive eluents and products were eluted in the order given. Additional runs are summarized in Table 2.2.

*1-Methyl-2,5-bis(methylthio)-4-(trifluoromethyl)imidazole (**7a**)*

white needles, mp 39 - 40 °C; ^{1}H NMR δ (acetone-d_6)=2.33 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 3.65 (br s, 3H, NCH_3); ^{19}F NMR δ_F (acetone-d_6)=16.6 (s); MS (EI, 20 eV) m/z 242 (100, M^+), 227 (46), 209 (45), 186 (37). Found: C, 34.38; H, 3.77; N, 11.52%. Calcd for $C_7H_9N_2F_3S_2$: C, 34.70; H, 3.74; N, 11.56%.

*UV-Induced Trifluoromethylation of 1-Methylpyrrole (**1b**)*

Following the procedure used with **2a**, **1b** gave **9b** and **10b** or **9b** and recovered **1b**. The results are given in Table 2.3. It was difficult to separate **9b**, **10b**, and **1b** because the boiling points are very close to one another, therefore, these materials were identified in a mixture and the yields are based on GC analysis.

*1-Methyl-2-(trifluoromethyl)pyrrole (**9b**)*

^{1}H NMR δ (acetone-d_6)=3.73 (s, 3H, SCH_3), 6.07 (m, 1H, ring), 6.53 (m, 1H, ring), 6.88 (m, 1H, ring); ^{19}F NMR δ_F (acetone-d_6)=18.6 (s); MS (EI, 20 eV) m/z 149 (100, M^+), 130 (36).

*1-Methyl-2,5-bis(trifluoromethyl)pyrrole (**10b**)*

^{1}H NMR δ (acetone-d_6)=3.83 (s, 3H, SCH_3), 6.66 (s, 2H, ring); ^{19}F NMR δ_F (acetone-d_6)=17.6 (s); MS (EI, 20 eV) m/z 217 (100, M^+), 198 (40), 156 (21).

*UV-Induced Trifluoromethylation of 1-Methyl-2-(methylthio)pyrrole (**2b**)*

Following the procedure used with **2a**, **2b** gave **5b** (17.7%) and **2b** (4.7%). The mixture of pyrroles was separated by silica gel chromatography with 90% hexane/10% CH_2Cl_2 and 100% CH_2Cl_2 as successive eluents. The

results of additional runs are given in Table 2.4. At higher ratios of CF_3I, small amounts of a bis(trifluoromethyl)derivative, probably **6a**, were also obtained. The material was identified by mass spectrum (M^+ 263) and yields are based on GC analysis; however, no effort was made to isolate **6b**.

*1-Methyl-2-methylthio-5-(trifluoromethyl)pyrrole (**5b**)*

colorless oil, bp 80 - 81 °C/30 Torr; ^1H NMR δ (acetone-d_6)=2.32 (s, 3H, SCH_3), 3.77 (q, 3H, J=0.7 Hz, NCH_3), 6.31 (AB, 1H, J=4.0 Hz, H-3), 6.57 (AB-q, 1H, J=4.0 Hz and 0.9 Hz, H-4); ^{19}F NMR δ_F (acetone-d_6)=17.9 (s); MS (EI, 20 eV) m/z 195 (100, M^+), 180 (61). Found: C, 43.02; H, 4.17; N, 7.09; S, 16.36%. Calcd for $C_7H_9NF_3S$: C, 43.07; H, 4.13; N, 7.18; S, 16.42%.

*UV-Induced Trifluoromethylation of 1-Methyl-2,5-bis(methylthio)pyrrole (**3b**)*

Following the procedure used with **2a**, **3b** gave **7b** (3.9%), **5b** (10.2%) and unreacted **3b** (38.1%). The mixture of pyrroles was separated by silica gel chromatography with 100% hexane; the pure products were obtained following removal of solvent in a glass tube oven. The results of additional runs are given in Table 2.5.

*1-Methyl-2,5-bis(methylthio)-3-trifluoromethylpyrrole (**7b**)*

colorless oil, bp 164 - 168 °C; ^1H NMR δ (acetone-d_6)=2.29 (s, 3H, SCH_3), 2.36 (s, 3H, SCH_3), 3.83 (br s, 3H, NCH_3), 6.56 (br s, 1H, H-4); ^{19}F NMR δ_F (acetone-d_6)=20.9 (s); MS (EI, 20 eV) m/z 241 (100, M^+), 226 (73) 185 (74). Found: C, 39.88; H, 4.21; N, 5.72%. Calcd for $C_7H_9N_2F_3S_2$: C, 39.82; H, 4.18; N, 5.80%.

Hydrogenolysis of Methylthio Groups of Imidazoles

To an ethanol solution (30 mL) of 1-methyl-2-methylthio-5-(trifluoromethyl)imidazole (**5a**) (1.34 g, 6.81 mmol) was added Raney nickel dampened with ethanol (*ca.* 10 g), and the reaction mixture was vigorously stirred under reflux for 5 h. The nickel was removed by filtration, the filtrate was poured into water (100 mL), and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was vacuum distilled in a glass tube oven to give **9a** in 57.3% yield.

*1-Methyl-5-(trifluoromethyl)imidazole (**7a**)*

white needles, mp 38 - 41 °C; ^1H NMR δ (acetone-d_6)=3.83 (s, 3H, NCH_3), 7.41 (br s, 1H, H-4), 7.76 (br s, 1H, H-2) (Lit., δ=3.83, 7.40, 7.75 [17]); ^{19}F NMR δ_F (acetone-d_6)=17.8 (s); MS (EI, 20 eV) m/z 150 (M^+).

Hydrogenolysis of methylthio groups in other imidazoles was carried out by a similar procedure.

*1-Methyl-4-(trifluoromethyl)imidazole (**8a**)*

54.5% yield from **4a**, 86.6% yield from **7a**; colorless oil, bp 222 - 225 °C; ^1H NMR δ (acetone-d_6)=3.82 (br s, 3H, NCH_3), 7.58 (br s, 1H, H-2), 7.66 (br s, 1H, H-5) (Lit., δ=3.88, 7.58, 7.64 [17]); ^{19}F NMR δ_F (acetone-d_6)=15.3 (s); MS (EI, 20 eV) m/z 150 (M^+).

Hydrogenolysis of Methylthio Groups in Pyrroles

To an ethanol solution (25 mL) of 1-methyl-2-methylthio-5-(trifluoromethyl)pyrrole (**5b**) (1.68 g, 8.60 mmol), was added Raney nickel dampened with ethanol (*ca.* 15 g), and the reaction mixture was vigorously stirred under reflux for 1 h. The nickel was removed by filtration, the filtrate was poured into water (100 mL), and the mixture was extracted with dichloromethane (2 × 100 mL). The organic layers were combined, washed with water and dried (Na_2SO_4). The solvent was removed and the estimated yield of **9b** was 60%, determined by GC analysis. Properties of **9b** were determined using a sample (90% purity) obtained in a microdistillation apparatus.

*1-Methyl-2-(trifluoromethyl)pyrrole (**9b**)*

colorless oil, bp 114 °C; ^1H NMR δ (acetone-d_6)=3.75 (br s, 3H, NCH_3), 6.08 (m, 1H, ring), 6.55 (m, 1H, ring), 6.91 (m, 1H, ring) (Lit., δ($CDCl_3$)= 3.60, 5.90, 6.36, 6.48 [4]); ^{19}F NMR δ_F (acetone-d_6)=18.8 (s); MS (EI, 20 eV) m/z 149 (M^+).

Hydrogenolysis of the methylthio groups of **7b** was carried out by a similar procedure, and the estimated yield of **8b** was 41% determined by GC analysis. A sample of **8b** could not be obtained by preparative GC and microdistillation led to a dark tarry product; properties of **8b** were determined using a dichloromethane solution.

*1-Methyl-3-(trifluoromethyl)pyrrole (**8b**)*

^{19}F NMR δ_F (acetone-d_6)=21.0 (s); MS (EI, 20 eV) m/z 149 (M^+).

Facile Perfluoroalkylation of Uracils and Uridines at the C-5 Position with Bis(perfluoroalkanoyl) Peroxides

Method A. Preparation of 5-Perfluoroalkyl Derivatives of Uracil

To a solution of 1.28 g (5 mmol) of 2,4-bis(trimethylsilyloxy)pyrimidine (**13**) [48] in 20 mL of Freon 113 (ClF_2CCCl_2F) was added, over 1 min at

ambient temperature, 21.6 g of a 5.0% solution of bis(heptafluorobutyryl) peroxide in Freon 113 (2.5 mmol). The reaction mixture was stirred at 30 °C for 3 h and heated at reflux (48 °C) for 2 h. The mixture was cooled to ambient temperature; 100 mL of water was added, and the two-phase system was stirred for 2 h. The mixture was extracted with three portions of ethyl acetate (150, 100, and 100 mL); the combined extracts were washed with saturated $NaHCO_3$ solution and with water, dried (Na_2SO_4) and evaporated. Silica gel chromatography of the colorless residue (eluent: ethyl acetate) gave 0.40 g (56.5%) of 5-(heptafluoropropyl)uracil (**15b**). Yields in several runs are given in Table 2.6.

*2,4-Dimethoxy-5-(heptafluoropropyl)pyrimidine (**12**)*

bp 214 - 215 °C; IR ν(cm^{-1}) 1340 (CF_3), 1235 (CF_2); ^1H NMR δ(DMSO-d_6)=4.05 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.99 (s, 1H, H-6); ^{19}F NMR δ_F (DMSO-d_6)=-3.31 (t, 3F, J=9.93 Hz, γ-CF_3), -32.64 (q, 2F, J=9.92 Hz, α-CF_2), -48.93 (s, 2F, β-CF_2) [54]; MS (EI, 70 eV) m/z 308 (8.1, M^+), 278 (5.7), 189 (100).

*5-(Heptafluoropropyl)uracil (**15b**)*

mp 258 - 259 °C dec (EtOAc); IR ν(cm^{-1}) 3160 (NH), 1680, 1750 (C=O), 1360 (CF_3), 1230 (CF_2); ^1H NMR δ(DMSO-d_6)=7.99 (s, H-6); ^{19}F NMR δ_F (DMSO-d_6)=-1.52 (t, 3F, J=8.68 Hz, γ-CF_3), -30.67 (q, 2F, J=9.93 Hz, α-CF_2), -46.87 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 280 (5.0, M^+), 261 (1.3), 161 (100).

*5-(Tridecafluorohexyl)uracil (**15c**)*

eluent, EtOAc; mp 277 - 278 °C dec (EtOAc) (Lit., 250 °C dec [39]); IR ν(cm^{-1}) 3240 (NH), 1670, 1760 (C=O), 1325 (CF_3), 1255 (CF_2); ^1H NMR δ=7.98 (s, H-6); ^{19}F NMR δ=-2.08 (t, 3F, J=8.7 Hz, ζ-CF_3), -29.94 (t, 2F, J=13.7 Hz, α-CF_2), -42.60 (br s, 2F, β-CF_2), -43.39 (br s, 2F, γ-CF_2), -44.21 (br s, 2F, δ-CF_2), -47.53 (br s, 2F, J=7.4 Hz, ε-CF_2); MS (EI, 70 eV) m/z 430 (4.6, M^+), 411 (2.7), 161 (100).

The low solubility of **14c** in both ethyl acetate and water retarded complete hydrolysis; product **15c** was contaminated with trace amounts of impurities which were apparently generated during chromatography.

*Preparation of 5-(Trifluoromethyl)uracil (**15a**)*

In a large ampoule was placed a solution of 1.55 g (6 mmol) of **13** in 30 mL of Freon 113. While an argon atmosphere was maintained, 113.5 g of a solution (0.6%) of bis(trifluoroacetyl) peroxide in Freon 113 (3 mmol) was added dropwise. The ampoule was sealed under vacuum and maintained at 70 °C for 5 h, since bis(trifluoroacetyl) peroxide is more stable than its

higher homologs and requires a higher reaction temperature for fragmentation. The contents of the ampoule were evaporated, 100 mL of water was added to the residue and the mixture was heated at reflux for 1 h. The mixture was concentrated to dryness and the residue was extracted with ethyl acetate (4 × 100 mL). The combined extracts were evaporated and the residual material was subjected to silica gel chromatography. The product obtained by elution with ethyl acetate / 2-propanol / water, 75 : 16 : 9, was impure. A cleaner product (0.069 g, 12.7%) was obtained by elution with ethyl acetate alone, but the low solubility of **15a** in ethyl acetate required the use of relatively large volumes of the eluting solvent.

*5-(Trifluoromethyl)uracil (**15a**)*

mp 236 - 237 °C dec (EtOAc) (Lit., 247 °C [42]; 238 - 241 °C [43]); IR ν(cm^{-1}) 3240 (NH), 1680, 1715, 1750 (C=O), 1350 (CF_3); ^1H NMR δ(DMSO-d_6)=8.01 (s, H-6); ^{19}F NMR δ_F (DMSO-d_6)=16.90 (s); MS (EI, 70 eV) m/z 180 (100, M^+), 137 (44).

Method B. 5-Perfluoroalkyl Derivatives of 6-Substituted Uracils and Uracil Analogs

A stirred suspension of 6-methyluracil (**22a**, 0.76 g, 6.03 mmol) in 30 mL of dry dioxane, containing 1.83 g (18.1 mmol) of triethylamine, was maintained under argon at ambient temperature while 1.96 g (18.0 mmol) of chlorotrimethylsilane was added dropwise. The immediate formation of a white precipitate was accompanied by a slight rise in temperature. The reaction mixture was stirred for 15 h, the precipitate was removed by filtration and volatile materials were removed by evaporation under vacuum. To the residual pale yellow oil was added 30 mL of Freon 113 to give a white suspension. To the mixture was added 51.37 g of a 5.0% solution of bis(heptafluorobutyryl) peroxide in Freon 113 (6.03 mmol). The reaction mixture was stirred for 2 h at 30 °C and then heated at reflux for 1.5 h. Following removal of the solvent under reduced pressure, the residual dark yellow oil was hydrolyzed by addition of water (100 mL) and ethyl acetate (100 mL) and stirring for 2 h. The aqueous layer was neutralized with saturated $NaHCO_3$ solution and was extracted with ethyl acetate (4 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give a light yellow powder. Silica gel chromatography with ethyl acetate gave **22b** (0.64 g, 36.1%). Yields are given in Table 2.6.

*5-(Heptafluoropropyl)-6-methyluracil (**22b**)*

eluent, EtOAc; mp 274 - 277 °C dec (EtOAc); IR ν(cm^{-1}) 3150 (NH), 1690, 1760 (C=O), 1360 (CF_3), 1230 (CF_2); ^{1}H NMR δ(DMSO-d_6)=2.23 (t, J=3.5 Hz, CH_3), 11.46 (br s, NH); ^{19}F NMR δ_F (DMSO-d_6)=-1.41 (t, 3F, J=8.7 Hz, γ-CF_3), -24.90 (m, 2F, α-CF_2), -46.90 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 294 (24, M$^+$), 275 (9), 175 (100).

*5-(Heptafluoropropyl)-6-(trifluoromethyl)uracil (**23b**)*

eluent, EtOAc followed by MeOH / EtOAc 1 : 9; mp 162 - 165 °C dec (EtOAc); IR ν(cm^{-1}) 3160 (NH), 1650 (C=O), 1350, 1370 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=10.40 (br s, NH); ^{19}F NMR δ_F (DMSO-d_6)=14.88 (m, 3F, 6-CF_3), -1.55 (t, 3F, J=9.9 Hz, γ-CF_3), -22.50 (m, 2F, α-CF_2), -43.68 (q, 2F, J=9.9 Hz, β-CF_2); MS (EI, 70 eV) m/z 348 (16, M$^+$), 329 (12), 286 (25), 236 (55), 229 (100), 186 (100).

*5-(Heptafluoropropyl)-2-thiouracil (**24b**)*

eluent, EtOAc; mp 249 - 251 °C dec (EtOAc); IR ν(cm^{-1}) 3090 (NH), 1690 (C=O), 1360 (CF_3), 1240 (CF_2), 1210 (C=S); ^{1}H NMR δ(DMSO-d_6)=7.88 (s, H-6); ^{19}F NMR δ_F (DMSO-d_6)=-1.38 (t, 3F, J=9.9 Hz, γ-CF_3), -31.55 (q, 2F, J=9.9 Hz, α-CF_2), -46.76 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 296 (100, M$^+$), 238 (10), 191 (19), 177 (45).

*5-(Heptafluoropropyl)-6-azauracil (**25b**)*

eluent, ethyl ether followed by EtOAc; mp 158 - 161 °C dec (EtOAc); IR ν(cm^{-1}) 3250 (NH), 1710, 1750 (C=O), 1360 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=12.4 (br s, NH), 13.2 (br s, NH); ^{19}F NMR δ_F (DMSO-d_6)=-1.26 (t, 3F, J=8.7 Hz, γ-CF_3), -34.16 (q, 2F, J=8.7 Hz, α-CF_2), -46.67 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 281 (29, M$^+$), 262 (13), 210 (44), 162 (100).

Method C. Perfluoroalkylation of Pyrimidine Nucleosides

Method B was followed, except that 5 equiv of chlorotrimethylsilane and of triethylamine were used to prepare the persilylated intermediate. The perfluoroalkylation mixture, containing 1.2 equiv of the bis(perfluoroalkanoyl) peroxide, was kept at 30 °C for 20 h. Yields are given in Table 2.7.

*5-(Heptafluoropropyl)uridine (**20b**)*

eluent, EtOAc; mp 207 - 209 °C dec (EtOAc); IR ν(cm^{-1}) 3340 (OH), 1680, 1710 (C=O), 1360 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=3.67 (br s, 2H, CH_2), 3.80 - 4.20 (3H, OH's), 5.00 - 5.60 (3H, H-2', 3', 4'), 5.76 (d, 1H, H-1'), 8.85 (s, 1H, H-6), 11.81 (br s, 1H, NH); ^{19}F NMR δ_F (DMSO-d_6)=-1.35 (t, 3F, J= 8.7 Hz, γ-CF_3), -30.34 (q, 2F, J= 8.7 Hz, α-CF_2), -46.87 (s, 2F, β-CF_2); MS

(EI, 20 eV) m/z 394 (8.5, M$^+$-H_2O), 339 (7.1), 281 (25); MS (CI, isobutane, 20 eV) m/z 413 (M$^+$+1).

*5-(Tridecafluorohexyl)uridine (**20c**)*

eluent, EtOAc; mp 214 - 216 °C dec (EtOAc) (Lit., 220 - 223 °C [39]); IR ν(cm^{-1}) 3400 (OH), 1695, 1740 (C=O), 1370 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=3.68 (br s, 2H, CH_2), 3.80 - 4.20 (3H, OH's), 5.00 - 5.65 (3H, H-2', 3', 4'), 5.77 (d, 1H, H-1'), 8.68 (s, 1H, H-6), 11.81 (br s, 1H, NH); ^{19}F NMR δ_F (DMSO-d_6)=-1.93 (t, 3F, J=8.7 Hz, ζ-CF_3), -29.56 (t, 2F, J=8.7 Hz, α-CF_2), -42.54 (br s, 2F, β-CF_2), -43.27 (br s, 2F, γ-CF_2), -44.07 (br s, 2F, δ-CF_2), -47.37 (br s, 2F, ε-CF_2); MS (EI, 20 eV) m/z 544 (6.3, M$^+$-H_2O), 489 (5.5), 431 (21); MS (CI, isobutane, 20 eV) m/z 563 (M$^+$+1).

*5-(Heptafluoropropyl)-2'-deoxyuridine (**21b**)*

eluent, EtOAc; mp 158 - 159 °C dec (EtOAc); IR ν(cm^{-1}) 3450 (OH), 1690, 1740 (C=O), 1350 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=1.95 - 2.60 (m, 2H, H-2'), 3.40 - 3.60 (br s, 2H, H-5'), 3.60 - 4.00 (br s, 1H, H-4'), 4.70 - 5.00 (m, 1H, H-3'), 4.50 - 5.60 (m, 2H, OH's), 6.12 (t, 1H, J=6.05 Hz, H-1'), 8.85 (s, 1H, H-6), 11.81 (br s, 1H, NH); ^{19}F NMR δ_F (DMSO-d_6)=-1.38 (t, 3F, J=8.7 Hz, γ-CF_3), -30.47 (q, 2F, J=9.9 Hz, α-CF_2), -46.93 (s, 2F, β-CF_2); MS (EI, 20 eV) m/z 336 (10), 307 (19), 304 (20); MS (CI, isobutane, 20 eV) m/z 397 (M$^+$+1).

*5-(Tridecafluorohexyl)-2'-deoxyuridine (**21c**)*

eluent, EtOAc; mp 183 - 185 °C dec (EtOAc); IR ν(cm^{-1}) 3450 (OH), 1680, 1740 (C=O), 1370 (CF_3), 1240 (CF_2); ^{1}H NMR δ(DMSO-d_6)=1.95 - 2.60 (m, 2H, H-2'), 3.50 - 3.80 (br s, 2H, H-5'), 3.80 - 4.00 (br s, 1H, H-4'), 4.20 - 4.45 (m, 1H, H-3'), 5.00 - 5.50 (m, 2H, OH's), 6.13 (t, 1H, J=5.93 Hz, H-1'), 8.85 (s, 1H, H-6); ^{19}F NMR δ_F (DMSO-d_6)=-1.82 (br s, 3F, ζ-CF_3), -29.65 (t, 2F, J=12.4 Hz, α-CF_2), -42.53 (br s, 2F, β-CF_2), -43.18 (br s, 2F, γ-CF_2), -44.00 (br s, 2F, δ-CF_2), -47.31 (br s, 2F, ε-CF_2); MS (EI, 20 eV) m/z 457 (6.7), 454 (6.1), 431 (17); MS (CI, isobutane, 20 eV) m/z 547 (M$^+$+1).

Elemental analyses for perfluoroalkylated uracils and uridines are summarized in Table 2.9.

Direct Heptafluoropropylation of Purines with Bis(heptafluorobutyryl) Peroxide

General Procedure for Heptafluoropropylation of Purines with Bis(heptafluorobutyryl) Peroxide

To adenine (**26a**, 0.81 g, 5.99 mmol) in a 100 mL flask were added BSTFA (5 mL, 18.8 mmol), pyridine (0.5 mL) and chlorotrimethylsilane (3 drops), in the order given. The reaction mixture was stirred under argon at 100 °C for 1 h, at which time the solution was clear. Unreacted BSTFA, trifluoroacetamide and low-boiling materials were removed at 60 °C and 10 - 20 mm Hg. The residual light yellow oil was dissolved in 30 mL of Freon 113 and this solution was added to a 5.1% solution (60.09 g, 7.19 mmol) of bis(heptafluorobutyryl) peroxide in Freon 113. The reaction mixture was stirred at 30 °C for 2 h and was then heated at reflux for 1 h to form an orange suspension. The reaction mixture was evaporated *in vacuo* and the residual yellow orange oil was hydrolyzed by addition of water (100 mL) and ethyl acetate (100 mL). The aqueous layer was neutralized with $NaHCO_3$ and was extracted with ethyl acetate (4 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residual brown amorphous solid was subjected to silica gel chromatography (eluent: ethyl acetate); appropriate fractions were combined, evaporated to dryness and the residual solids were washed with ether and hexane.

*8-(Heptafluoropropyl)adenine (**28a**)*

eluent, EtOAc; colorless needles (EtOAc); mp 290 - 295 °C dec; IR ν(cm^{-1}) 3140, 3330, 3480 (NH), 1350 (CF_3), 1220 (CF_2); ^{1}H NMR δ(acetone-d_6)=7.6 (br s, NH_2), 8.40 (s, H-2); ^{19}F NMR δ_F (acetone-d_6)=-3.19 (t, 3F, J=9.9 Hz, γ-CF_3), -34.29 (q, 2F, J=9.9 Hz, α-CF_2), -49.16 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 303 (77, M$^+$), 284 (12), 184 (100). Found: C, 31.57; H, 1.37; N, 23.50%. Calcd for $C_8H_4F_7N_5$: C, 31.70; H, 1.33; N, 23.10%.

*2-(Heptafluoropropyl)adenine (**29a**)*

eluent, EtOAc; IR ν(cm^{-1}) 3190, 3330, 3490 (NH), 1345 (CF_3), 1235 (CF_2); ^{1}H NMR δ (acetone-d_6)=7.4 (br s, NH_2), 8.29 (s, H-8); ^{19}F NMR δ_F (acetone-d_6)=-3.40 (t, 3F, J=9.9 Hz, γ-CF_3), -36.42 (q, 2F, J=9.9 Hz, α-CF_2), -48.69 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 303 (100, M$^+$), 284 (16), 184 (81).

*N^6-Acetyl-8-(heptafluoropropyl)adenine (**28b**)*

eluent, EtOAc; colorless needles (EtOAc); mp 237 - 238 °C; IR ν(cm^{-1}) 2950, 3290 (NH), 1720 (C=O), 1340 (CF_3), 1220 (CF_2); ^{1}H NMR δ(acetone-d_6)=2.43 (s, CH_3CO), 8.63 (s, H-2), 10.8 (br s, NH); ^{19}F NMR δ_F (acetone-d_6)=-3.43 (t, 3F, J=7.4 Hz, γ-CF_3), -36.27 (m, 2F, α-CF_2), -48.72 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 345 (41, M$^+$), 303 (92), 284 (14), 184 (100). Found: C, 35.09; H, 1.75; N, 20.05%. Calcd for $C_{10}H_6F_7N_5O$: C, 34.79; H, 1.75; N, 20.29%.

*N^6-Acetyl-2,8-bis(heptafluoropropyl)adenine (**30b**)*

MS (EI, 70 eV) m/z 513 (32, M$^+$), 471 (69), 452 (29), 352 (100).

*6-Dimethylamino-8-(heptafluoropropyl)purine (**28c**)*:

eluent, EtOAc-ether (1 : 1); colorless needles (EtOAc); mp 198 - 199 °C; IR ν(cm^{-1}) 1350 (CF_3), 1220 (CF_2); ^{1}H NMR δ(acetone-d_6)=3.39 (s, CH_3), 8.37 (s, H-2); ^{19}F NMR δ_F (acetone-d_6)=-3.16 (t, 3F, J=8.7 Hz, γ-CF_3), -33.79 (q, 2F, J=7.5 Hz, α-CF_2), -49.10 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 331 (99, M$^+$), 316 (64), 312 (16), 302 (100). Found: C, 36.34; H, 2.43; N, 21.10%. Calcd for $C_{10}H_8F_7N_5$: C, 36.26; H, 2.43; N, 21.15%.

*8-Heptafluoropropyl-6-methoxypurine (**28d**)*

eluent, ether; colorless needles (EtOAc); mp 163 - 164 °C; IR ν(cm^{-1}) 1325 (CF_3), 1220 (CF_2); ^{1}H NMR δ(acetone-d_6)=4.19 (s, CH_3O), 8.61 (s, H-2); ^{19}F NMR δ_F (acetone-d_6)=-3.16 (t, 3F, J=8.7 Hz, γ-CF_3), -35.03 (q, 2F, J=9.9 Hz, α-CF_2), -49.19 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 318 (100, M$^+$), 317 (49), 298 (18), 288 (35), 287 (30), 260 (43). Found: C, 34.04; H, 1.58; N, 17.53%. Calcd for $C_9H_5F_7N_4O$: C, 33.97; H, 1.58; N, 17.61%.

*2-Heptafluoropropyl-6-methoxypurine (**29d**)*

eluent, EtOAc-ether (1 : 4); colorless plates (EtOAc); mp 227 - 228 °C; IR ν(cm^{-1}) 1340 (CF_3), 1225 (CF_2); ^{1}H NMR δ(acetone-d_6)=8.54 (s, H-2), 4.23 (s, CH_3O); ^{19}F NMR δ_F (acetone-d_6)=-3.31 (t, 3F, J=8.7 Hz, γ-CF_3), -36.24 (q, 2F, J=9.9 Hz, α-CF_2), -48.78 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 318 (100, M$^+$), 317 (46), 298 (23), 288 (33), 287 (26). Found: C, 34.08; H, 1.57; N, 17.54%. Calcd for $C_9H_5F_7N_4O$: C, 33.97; H, 1.58; N, 17.61%.

*8-(Heptafluoropropyl)guanine (**32g**)*

eluent, 5% MeOH/ 95% EtOAc; colorless needles (MeOH); mp 229 - 234 °C dec; IR ν(cm^{-1}) 3330, 3160 (NH), 1700 (C=O), 1345 (CF_3), 1240 (CF_2) ; ^{19}F NMR δ_F (methanol-d_4)=-3.72 (t, 3F, J=8.7 Hz, γ-CF_3), -35.68 (q, 2F, J=9.9 Hz, α-CF_2), -49.83 (s, 2F, β-CF_2); MS (EI, 70 eV) m/z 319 (100, M$^+$), 300 (18), 269 (18), 200 (100); HRMS m/z Found: 319.0344; Calcd for $C_8H_4F_7N_5O$: 319.0303.

General Method for the Thermal Condensation of Poly(amino)pyrimidines and Heptafluoropropylbutyramide

In a glass ampoule was placed a mixture of 4,5,6-triaminopyrimidine sulfate (1.116 g, 5.00 mmol) and heptafluorobutyramide (6.39 g, 0.030 mol). The ampoule was sealed under vacuum and maintained at 200 - 210 °C for 5 h. The contents of the ampoule were dissolved in ethyl acetate with some material remaining in suspension. Silica gel chromatography (eluent: ethyl acetate) of the total reaction product afforded **28a** (0.11 g, 7.3%) and 4.70 g of heptafluorobutyramide was recovered.

Condensation of 6-hydroxy-2,4,5-triaminopyrimidine sulfate and 6-hydroxy-4,5-diaminopyrimidine sulfate with heptafluoropropylbutyramide were also attempted in the same way, but no fluoroalkylated purines were obtained.

Table 2.9
Analytical Data for Perfluoroalkyluracils and Uridines.

Compound	Empirical Formula	Molecular Weight	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2	$C_9H_7F_7N_2O_2$	308.17	35.08	2.29	9.09	34.94	2.29	9.04
5b	$C_7H_3F_7N_2O_2$	280.11	30.02	1.08	10.00	30.09	1.10	10.01
5c	$C_{10}H_3F_{13}N_2O_2$	430.15	27.92	0.70	6.51	27.87	0.73	6.51
10b	$C_{12}H_{11}F_7N_2O_6$	412.23	34.96	2.69	6.80	35.00	2.73	6.74
10c	$C_{15}H_{11}F_{13}N_2O_6$	562.26	32.04	1.97	4.98	32.13	1.99	4.96
11b	$C_{12}H_{11}F_7N_2O_5$ [a]	418.26	37.33	3.13	6.70	37.35	3.14	6.49
11c	$C_{15}H_{11}F_{13}N_2O_5$	546.26	32.98	2.03	5.13	33.08	2.04	5.08
12b	$C_8H_5F_7N_2O_2$	294.14	32.67	1.71	9.53	32.74	1.75	9.49
13b	$C_8H_2F_{10}N_2O_2.H_2O$	366.13	26.25	1.10	7.65	26.20	1.10	7.75
14b	$C_7H_3F_7N_2OS$ [a]	318.20	30.20	1.58	8.80	30.13	1.53	8.81
15b	$C_6H_2F_7N_3O_2$	281.10	25.64	0.72	14.95	25.79	0.76	15.02

[a] Calculated percentage values include 0.25 EtOAc; the solvent was not lost at 80 °C in vacuo (24 h).

CHAPTER 3

SYNTHESIS OF TRIFLUOROMETHYLATED HETEROCYCLES BY γ-RAY INDUCED ADDITION REACTION TO HEXAFLUORO-2-BUTYNE

Introduction to Chapter 3

Ring formation reaction, that is the construction of cyclic compound from open-chain precursors, is a useful method for synthesis of a wide range of heterocyclic compounds. Several polyfluorinated olefins and acetylenes are readily available starting materials for synthesis of fluorinated heterocycles. These fluorinated precursors can be converted to new fluorinated heterocycles by cyclization or cycloaddition reaction. The ring formation reaction has an advantage in handling the reagents and in regio and stereo selectivities, compared with direct fluorination and perfluoroalkylation of heterocyclic compounds.

Hexafluoro-2-butyne is a stable and commercially available compound, while other haloacetylenes easily polymerize at ambient temperature and often decompose explosively. Hexafluoro-2-butyne shows unique reactivities, which are applicable to the synthesis of fluorinated heterocycles: Diels-Alder reaction, radical reaction, cycloaddition with organic and inorganic reagents, and so on. This chapter describes synthesis of heterocyclic compounds using reactions of hexafluoro-2-butyne and its adduct. With utilizing hexafluoro-2-butyne as a fluorinated precursor, were synthesized heterocyclic compounds having more than two trifluoromethyl groups, which were difficult to obtain by direct perfluoroalkylation. Further, reactivities of such electron deficient heterocycles, due to electronegativity of the trifluoromethyl group, were examined.

3.1 Synthesis of 3,4-Bis(trifluoromethyl)furan Derivatives by γ-Ray Induced Addition Reaction to Hexafluoro-2-butyne

Summary

While γ-ray induced addition reaction of alcohols to hexafluoro-2-butyne provided (*E*) and (*Z*) isomers of 1 : 1 addition products, bis(trifluoromethyl)-allyl alcohols (**3**), a similar addition reaction of aldehydes afforded (*E*) isomer of 1 : 1 addition products, bis(trifluoromethyl)vinylketones (**8**), and 1 : 2 addition products, bis(trifluoromethyl)diketone (**9**). The latter compound **9** was treated with sulfuric acid to give 2,5-dialkyl-3,4-bis(trifluoromethyl)-furan (**13**). Several reactions, such as bromination, dehydrobromination and oxidation, were carried out to prepare derivatives of **13**.

Introduction

The polyfluorinated olefins and acetylenes easily react with nucleophilic radicals because of the inductive and conjugated effects of fluorine [55, 56]. It has been reported that fluorinated olefins participated in a wide range of γ-ray induced addition reactions with ethers, alcohols, aldehydes, *etc.* [57 - 64], but little is known about the reaction of polyfluorinated acetylenes. In this section, γ-ray induced addition reaction of alcohols and aldehydes to hexafluoro-2-butyne is described.

On the other hand, heterocyclic compounds containing trifluoromethyl groups have attracted much attention and various synthetic methods have been proposed [65]. Though several papers have been reported on the syntheses of trifluoromethyl substituted furans [45, 66 - 70], only a few 2,5-disubstituted 3,4-bis(trifluoromethyl)furans have been synthesized [71]. This section also describes the synthesis of 2,5-dialkyl-3,4-bis(trifluoromethyl)furan starting from the 1:2 addition products of aldehydes to hexafluoro-2-butyne and several reactions of 3,4-bis(trifluoromethyl)furan derivatives.

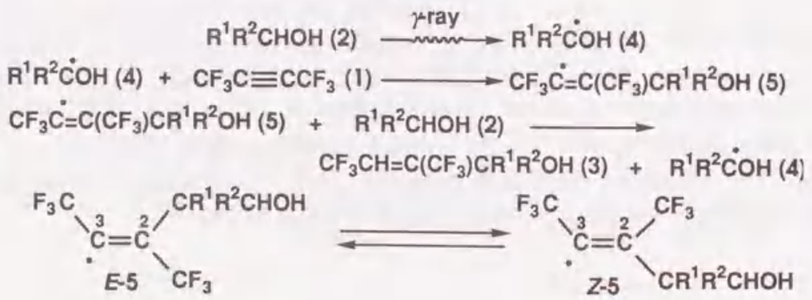
Results and Discussion

γ-Ray Induced Addition to Hexafluoro-2-butyne

Irradiation of hexafluoro-2-butyne (**1**) with alcohols (**2**) in Freon 113 afforded (*E*)- and (*Z*)-2,3-bis(trifluoromethyl)allyl alcohol **3** (Table 3.1). The stereoisomers were identified based on the ^{19}F NMR spectroscopy (*E*: J=1 Hz, *Z*: J=12 Hz) [72].

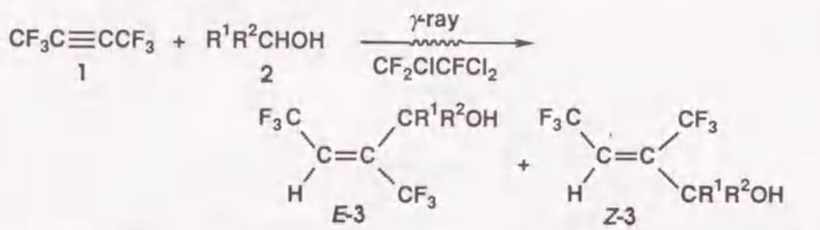
A reasonable reaction path for the formation of **3** is shown in Scheme 3.1.

Scheme 3.1



More stable 1-hydroxyalkyl radical **4** can give the products **3** in good yields (stability, primary < secondary < tertiary). Radical intermediate **5** is in equilibrium between *E*-**5** and *Z*-**5**. Steric hindrance between the CF_3 group at the 3-position and an alkyl group at the 2-position can control the product distribution, i.e., the bulky alkyl group at the 2-position may shift the equilibrium to *Z*-**5** to increase the yield of *Z*-**3**.

Table 3.1
Synthesis of 2,3-Bis(trifluoromethyl)allyl Alcohols



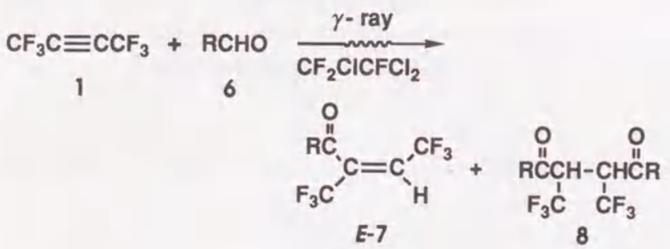
Compd	R^1	R^2	Total irradiation Mrad	Yield of **3** %	E/Z Ratio
a	H	H	197	29	100 / 0
b	H	CH_3	98	67	55 / 45
c	H	C_2H_5	98	26	47 / 53
d	CH_3	CH_3	98	88	9 / 91

γ-Ray irradiation of a mixture hexafluoro-2-butyne (**1**) and propionaldehyde (**6b**) in Freon 113 afforded ethyl 6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-one (**7b**) and 4,5-bis(trifluoromethyl)octa-3,6-dione (**8b**) in 21% and 76% yields, respectively (Scheme 3.2). The bis(trifluoromethyl)octadione **8b**, having two asymmetric carbons, consisted of two diastereomers, *meso* and *dl* in a ratio of about 3 : 2. The *dl* diastereomer gradually changed to the *meso* upon standing.

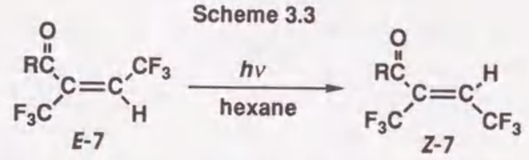
To determine the geometrical structure of **7b**, it was irradiated with a high pressure mercury lamp to give a mixture of (*E*) and (*Z*) isomers in the ratio of 4:1 (Scheme 3.3). The isomers were isolated using a preparative gas chromatograph and their structures were identified from ^1H and ^{19}F NMR spectra. Their chemical shifts of hydrogens in the vinyl groups (*E*: 6.28 ppm, *Z*: 6.58 ppm) and, in a similar to **3**, coupling constants of fluorines on

adjacent CF_3 groups (*E*: 1.7 Hz, *Z*: 10.5 Hz) indicated that the 1:1 addition product **7b** was the (*E*) form.

Scheme 3.2



Scheme 3.3



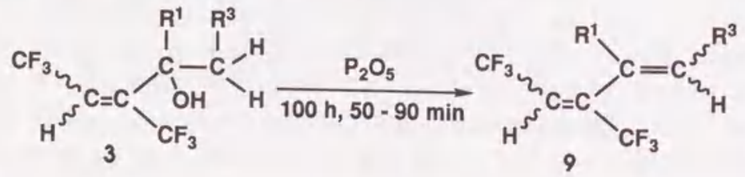
A similar reaction of acetaldehyde (**6a**) provided the 1:1 addition product, 5,5,5-trifluoro-3-trifluoromethyl-3-penten-2-one (**7a**), and the 1:2 addition product, 3,4-bis(trifluoromethyl)-2,4-hexanedione (**8a**), in 13% and 7.3% yield, respectively.

Reactions of (Trifluoromethyl)allyl Alcohols

Dehydration of a mixture of *E*- and *Z*-**3** gave a mixture of *E*- and *Z*-**9** in 60 - 95% yields (Table 3.2). In the case of **3b** and **3d**, the *E*/*Z* ratio of the products **9** concerning with the double bond with two CF_3 groups was the same as that of starting materials, suggesting that *E*- and *Z*-**3** afforded the corresponding *E*- and *Z*-**9**, respectively. In the case of **3c**, the formation of four isomers was confirmed by gas chromatography.

Table 3.2

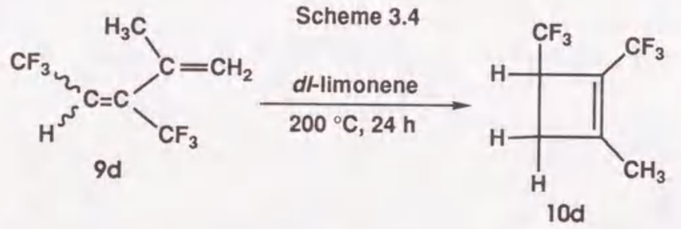
Dehydration of 2,3-Bis(trifluoromethyl)allyl Alcohols



Compd	R^1	R^3	Reaction time	Yield of **9**
			min	%
b	H	H	90	79
c	H	CH_3	50	60
d	CH_3	H	90	95

Thermal cyclization of **9d** gave 1-methyl-2,3-bis(trifluoromethyl)cyclobutene (**10d**) in 25% yield (Scheme 3.4). The structure of **10d** was confirmed by its ^1H NMR spectrum, i.e., δ values of methylene (5.01 - 5.23 ppm) and methine (5.95 - 6.14 ppm) protons of **9d** shifted to 2.57 and 3.90 ppm in **10d**, respectively. The same reaction of **9b** gave an amorphous polymer.

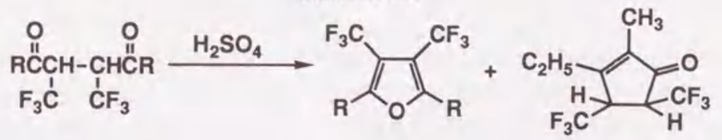
Scheme 3.4



Synthesis of 3,4-Bis(trifluoromethyl)furan Derivatives

Treatment of **8b** with sulfuric acid gave 2,5-diethyl-3,4-bis(trifluoromethyl)furan (**11b**) in 94% yield, together with a small amount of 3-ethyl-2-methyl-4,5-bis(trifluoromethyl)-2-cyclopenten-1-one (**12**). In a similar to **11b**, 2,5-dimethyl-3,4-bis(trifluoromethyl)furan (**11a**) was obtained in 68% yield from **8a** (Scheme 3.5).

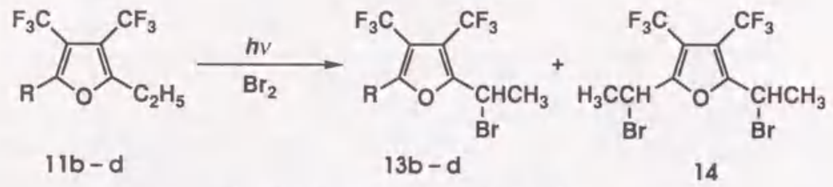
Scheme 3.5



When a molar equivalent of bromine was added to **11b** in carbon tetrachloride, 2-(1-bromoethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**13b**) and

2,5-bis(1-bromoethyl)-3,4-bis(trifluoromethyl)furan (**14**) were obtained in 59% and 13% yields, respectively (Scheme 3.6). While excess amounts of bromine was added to **11b**, only **14** was obtained in 93% yield.

Scheme 3.6

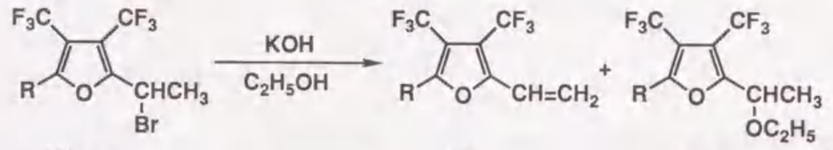


11b – d 13b – d 14

b; R = C_2H_5, c; R = H, d; R = CF_3

Dehydrobromination of **13b** with potassium hydroxide in ethanol afforded 5-ethyl-3,4-bis(trifluoromethyl)-2-vinylfuran (**15b**) in 23% yield, which easily polymerized upon standing, together with 2-(1-ethoxyethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**16b**) in 18% yield (Scheme 3.7).

Scheme 3.7

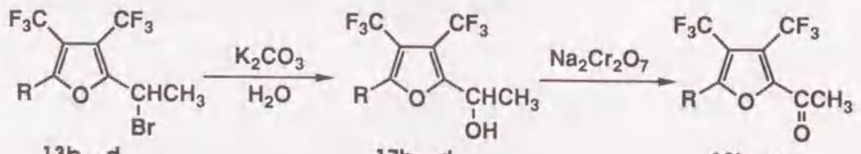


13b – d 15b 16b

b; R = C_2H_5, c; R = H, d; R = CF_3

Hydrolysis of **13b** with aqueous potassium carbonate solution afforded 5-ethyl-2-(1-hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17b**) in 60% yield, which was then oxidized with sodium bichromate to give 2-acetyl-5-ethyl-3,4-bis(trifluoromethyl)furan (**18b**) in 29% yield (Scheme 3.8).

Scheme 3.8

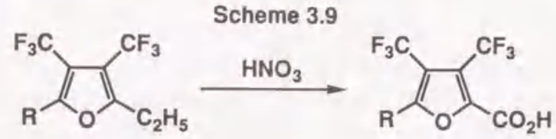


13b – d 17b – d 18b, c

b; R = C_2H_5, c; R = H, d; R = CF_3

Oxidation of **11b** with nitric acid in acetic acid at 135 - 140 °C gave 45% yield of 5-ethyl-3,4-bis(trifluoromethyl)-2-furancarboxylic acid (**20b**) along with a small amount of 5-ethyl-2-formyl-3,4-bis(trifluoromethyl)furan (**19b**, 1%) (Scheme 3.9).

Scheme 3.9

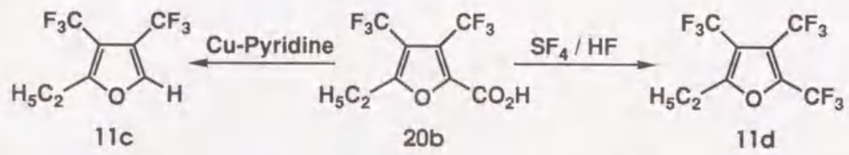


11b, c 20b, c

b; R = C_2H_5, c; R = H

2-Ethyl-3,4-bis(trifluoromethyl)furan (**11c**) was obtained in 69% yield by decarboxylation of **20b** upon treatment with copper in pyridine at 100 °C (Scheme 3.10).

Scheme 3.10



11c 20b 11d

Bromination of **11c** gave 2-(1-bromoethyl)-3,4-bis(trifluoromethyl)furan (**13c**) in 79% yield (Scheme 3.6), whose hydrolysis with potassium carbonate afforded 2-(1-hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17c**) in 76% yield. The oxidation of **17c** with sodium bichromate yielded 2-acetyl-3,4-bis(trifluoromethyl)furan (**18c**) in 50% yield (Scheme 3.8). Oxidation of **11c** with nitric acid gave only 2% yield of the corresponding furancarboxylic acid **20c**, showing **11c** less reactive than **11b** (Scheme 3.9).

In order to introduce an additional trifluoromethyl group, **20b** was treated with sulfur tetrafluoride in the presence of anhydrous hydrogen fluoride in an autoclave to give 2-ethyl-3,4,5-tris(trifluoromethyl)furan (**11d**) in 76% yield (Scheme 3.10) [69]. Though the bromination of **11d** produced 78% yield of 2-(1-bromoethyl)-3,4,5-tris(trifluoromethyl)furan (**13d**) together with 4% yield of 2-(1,2-dibromoethyl)-3,4,5-tris(trifluoromethyl)furan (**21d**) (Scheme 3.6), the hydrolysis of **13d** gave only 6% yield of 2-(1-hydroxyethyl)-3,4,5-tris(trifluoromethyl)furan (**17d**) with starting material recovered (Scheme 3.8). An attempt to oxidize **11d** with nitric acid to prepare the tris(trifluoromethyl)furancarboxylic acid was unsuccessful.

3.2 Synthesis and Photochemical Reaction of 1,4-Dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene

Summary

Diels-Alder reaction of 2,5-dialkyl-3,4-(trifluoromethyl)furan with hexafluoro-2-butyne gave 1,4-dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)-bicyclohepta-2,5-diene. Irradiation (UV) of 1,4-diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene afforded 1-ethyl-2,3,4,5-tetrakis-(trifluoromethyl)-1,4-cyclopentadiene, ethyl 3-[1-ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadienyl] ketone, and 2,7-diethyl-3,4,5,6-tetrakis-(trifluoromethyl)oxepin.

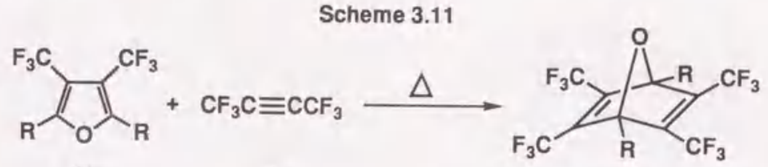
Introduction

Much attention has been focused on the synthesis of heterocycles containing trifluoromethyl groups, because they can be used as medicinal and agricultural chemicals, *etc.* The Diels-Alder reaction is one of the most useful methods to synthesize heterocyclic compounds [73 - 75]. In the preceding section, the author has described the γ-ray induced addition reaction of aldehydes with hexafluoro-2-butyne to give 2,5-dialkyl-3,4-bis(trifluoromethyl)furan. The synthesis and photochemical reaction of 1,4-diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene are represented in this section.

Results and Discussion

The Diels-Alder reaction of 2,5-diethyl-3,4-bis(trifluoromethyl)furan (**11b**) with hexafluoro-2-butyne (**1**) gave 1,4-diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-dione (**23b**) (Scheme 3.11). The best yield (*ca.* 35%) of **23b** was obtained in the molar ratio of **11b** to **1** = 1 : 1 at 160 °C. The same reaction of 2,5-dimethyl-3,4-bis(trifluoromethyl)furan (**11a**) with **1** gave 1,4-dimethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23a**) in 38% yield.

Scheme 3.11



11 1 23

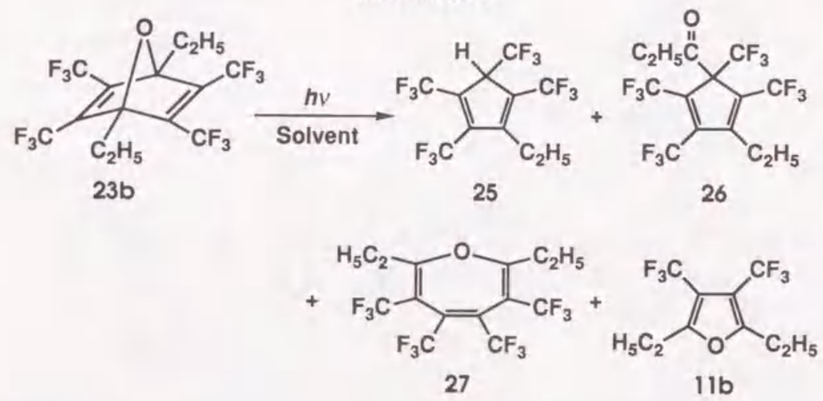
a; R = CH_3, b; R = C_2H_5

The UV irradiation of **23b** afforded 1-ethyl-2,3,5,6-tetrakis(trifluoromethyl)-1,4-cyclopentadiene (**25**), ethyl 3-[1-ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadienyl] ketone (**26**), and 2,7-diethyl-3,4,5,6-tetrakis(trifluoromethyl)oxepin (**27**) (Scheme 3.12). The products were isolated by using a preparative gas chromatograph and identified on the basis of their spectral data. The cyclopentadiene **25** showed four CF_3, one C_2H_5, one CH, and two C=C groups and molecular ion peak at m/z 336. The ketone **26** showed four CF_3, two C_2H_5, two C=C, and one C=O groups and molecular ion peak at m/z 422. The oxepin **27** had a highly symmetrical structure

and showed two sets of two CF_3 and one C_2H_5 groups and molecular ion peak at m/z 422.

The results of UV irradiation of **23b** are summarized in Table 3.3. The reaction in ether gave **26** as the main product accompanied by **25** and **27**. The longer was the irradiation time, the greater the yield of **26**. Addition of a small amount of water to the solution decreased the yield of **26**. While the reaction in carbon tetrachloride gave **27** as the main product accompanied by **11b**.

Scheme 3.12



25 26 27 11b

Table 3.3
UV Irradiation of 7-Oxabicycloheptadiene **23b**

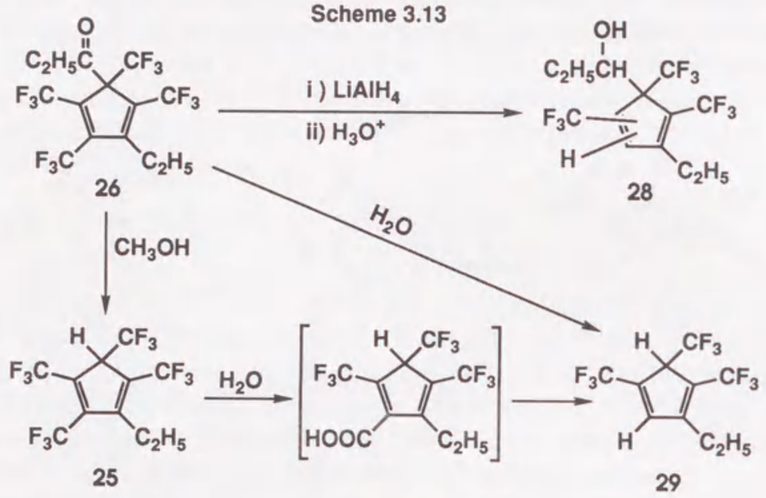
Solvent	Reaction Time (h)	Yield [a] (%)				
		11b	**23b**	**25**	**26**	**27**
ether [b]	173	0	75	14	3	8
ether	184	0	59	14	23	4
ether	337	0	32	9	57	2
carbon tetrachloride	142	10	64	0	8	16

[a] Determined by GC analysis. [b] A small amount of water was added.

In order to confirm the structure of the products, a few reactions of **25** and **26** were conducted (Scheme 3.13). The UV irradiation of **26** gave **25** in 20% yield. Since the ketone **26** had high reactivity for necleophiles, it was converted easily into **25** in methanol. The hydrolysis of **25** provided 1-ethyl-

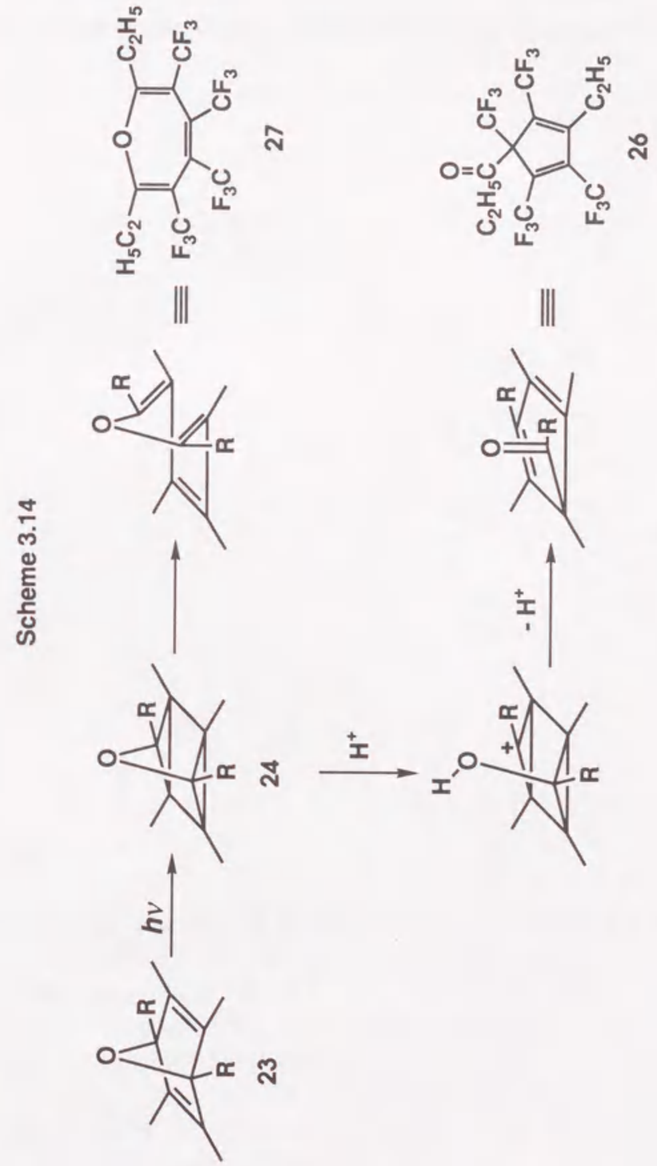
2,3,4-tris(trifluoromethyl)-1,4-cyclopentadiene (**29**), which may be formed *via* the corresponding carboxylic acid. The hydrolysis of **26** also gave **29**. The reduction of **26** with lithium aluminum hydride afforded two regioisomers of 3-[1-ethyl-tris(trifluoromethyl)-1,4-cyclopentadienyl]-1-propanol (**28**).

Scheme 3.13



A plausible mechanism for the formation of ketone **26** and oxepin **27** is shown in Scheme 3.14. The UV irradiation of **23b** can give the corresponding oxaquadricyclane **24**. Though several oxaquadricyclanes have been isolated in the literature [73, 75 - 78], the oxaquadricyclane **24** could not be isolated. Rearrangement of two σ-bonds of **24** into π-bonds gives oxepin **27** [73, 79]. Cleavage of the C-O bond of **24** gives **26** [80]. In carbon tetrachloride, the reverse Diels-Alder reaction of **23b** afforded **11b**.

Scheme 3.14



3.3 Synthesis and Stereoselective Decomposition of Pyrazolines Containing Trifluoromethyl Groups

Summary

The reaction of (*Z*)- and (*E*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-ones (**7**) with diazomethane afforded the corresponding *r*-3,*c*-4- and *r*-3,*t*-4-pyrazolines (**30**), respectively. Photochemical and thermal decompositions of the *r*-3,*t*-4-bis(trifluoromethyl)pyrazoline gave selectively *r*-1,*t*-2-bis(trifluoromethyl)-1-propionylcyclopropane (**31**) and 3,4-bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**32**). On the other hand, those transformations of the *r*-3,*c*-4-isomer of the pyrazoline gave a mixture of the *r*-1,*c*-2-isomer of **31**, **32**, and 4,5-bis(trifluoromethyl)-5-hexen-3-one (**33**).

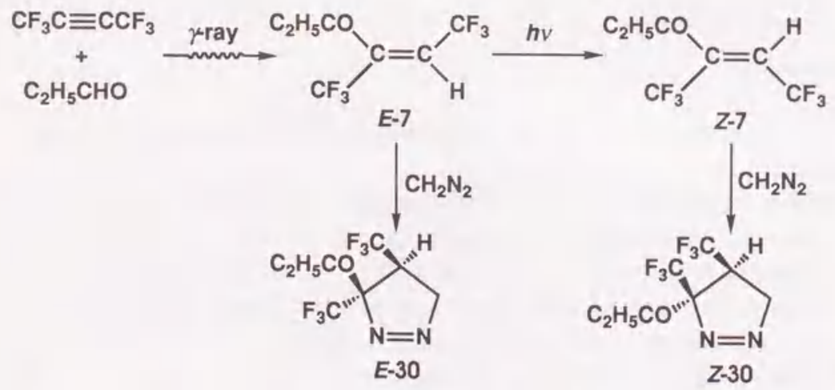
Introduction

Since cyclopropanes are one of the most important intermediates for the synthesis of medicines, due to their highly strained structure, the introduction of a trifluoromethyl group into such molecules is of interest. Several methods, such as reactions of olefins with carbenes [81 - 83], and organomercury compounds [84], as well as the decomposition of pyrazolines [85, 86] have been reported for the synthesis of (trifluoromethyl)cyclopropanes. This section describes the synthesis of pyrazolines obtained from (*E*)- and (*Z*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-ones (*E*-**7** and *Z*-**7**) (Chapter 3.1), as well as their decomposition reactions to give cyclopropanes containing two trifluoromethyl groups.

Results and Discussion

The reaction of **7** with diazomethane at ambient temperature induced a 1,3-dipolar addition reaction to give 3,4-bis(trifluoromethyl)-3-propionylpyrazoline (**30**) quantitatively (Scheme 3.15). The stereoselectivity of this reaction concerning two trifluoromethyl groups was determined on the basis of the ^{19}F NMR spectra (the coupling constant of the fluorine atom between trifluoromethyl groups at the 3- and 4-positions: *r*-3,*c*-4, J=11.7 Hz; *r*-3,*t*-4, J=1.3 Hz).

Scheme 3.15



Though both *r*-3,*c*-4-pyrazoline (*Z*-**30**) and *r*-3,*t*-4-pyrazoline (*E*-**30**) were stable in the dark at room temperature, they easily decomposed at higher

temperature or under UV irradiation. The results of the decompositions of **30** are summarized in Table 3.4. Both photochemical and thermal decompositions of *E*-**30** gave stereoselectively *r*-1,*t*-2-bis(trifluoromethyl)-1-propionylcyclopropane (*E*-**31**) and 3,4-bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**32**). Those of *Z*-**30** afforded mainly a mixture of *Z*-**31**, **32**, and 4,5-bis(trifluoromethyl)-1-hexen-3-one (**33**).

Scheme 3.16

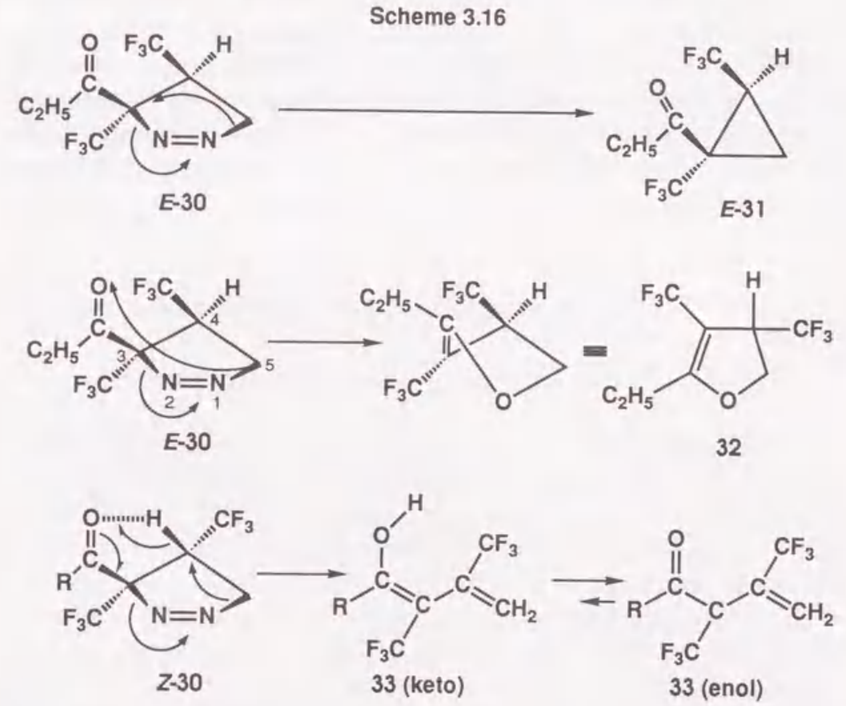


Table 3.4
Decomposition of 3,4-Bis(trifluoromethyl)-3-propionylpyrazolines (**30**)

Pyrazoline	Method	Total time (min)	Yield (%)			
			E-**31**	*Z*-**31**	**32**	**33**
E-**30**	Pyrolysis	90	47	0.9	52	0
E-**30**	Photolysis	100	80	2.2	18	0
Z-**30**	Pyrolysis	90	4.4	54	11	31
Z-**30**	Photolysis	100	0.3	94	1.3	4.3

Concerning the mechanism of decomposition of 1-pyrazolines, three processes (such as a 1,3-diradical, a zwitterionic intermediate, and an electrocyclic process) were proposed; the decomposition of pyrazoline bearing α-electron withdrawing groups is not yet completely understood [87].

Although a plausible reaction mechanism for the stereoselective formation of **31**, **32**, and **33** is shown in Scheme 3.16, a diradical or zwitterionic mechanism can not be excluded, since the formation of **32** can also be explained by the ionic intermediate process. Regarding the formation of **33** from the *Z*-**30** isomer, an intramolecular hydrogen bond between the hydrogen on the C-4 carbon and the carbonyl oxygen seems to assist to give an enol form of **33**, which then tautomerizes to the keto form of **33**, as shown in Scheme 3.16.

EXPERIMENTAL

Analytical Methods and Instrumentation

All boiling and melting points are uncorrected. IR spectra were recorded on Hitachi EPI-2 and 285H infrared spectrophotometers. ^{1}H NMR spectra were measured in carbon tetrachloride with a Hitachi R-22 (90 MHz) spectrometer. ^{19}F NMR spectra were measured in carbon tetrachloride with a Hitachi R-20B (56.45 MHz) and positive δ value are downfield from trifluoroacetic acid as an external reference. Preparative gas chromatograph was performed on a Varian model 700 instrument, using aluminum column (5 mm x 300 cm) packed with 10% OV-17 on Chromosorb WAW DMCS (60 - 80 mesh). Mass spectra were measured with a Hitachi RMU-7 spectrometer.

γ-Ray Induced Addition Reaction to Hexafluoro-2-butyne

*General Procedure for Addition Reaction of Alcohols (**2**) to Hexafluoro-2-butyne (**1**)*

Hexafluoro-2-butyne (**1**) (16.28 g, 0.10 mol), ethanol (**2b**) (5.57g, 0.12 mol), and 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113) (20.15 g, 0.11 mol) were placed in a glass ampoule (100 mL). The ampoule was degassed by a freeze-thaw cycle and was sealed under reduced pressure. The γ-ray irradiation was carried out at 6.2 x 10^4 Rh^{-1} by ^{60}Co for 158 h at ambient temperature (total irradiation, 98.2 Mrad). After the reaction, were evaporated the starting material, ethanol, and Freon 113. The residual liquid was distilled to give a mixture (14 g) of (*E*)- and (*Z*)-3,4-bis(trifluoromethyl)-3-buten-2-ol (*E*-**3b** and *Z*-**3b**), which were separated using a preparative gas chromatograph. The physical and spectral data are shown below.

*(E)-2,3-Bis(trifluoromethyl)-2-propen-1-ol (E-**3a**)*

bp 110 °C; n^{20}_D 1.3368; d^{20}_4 1.501; IR ν(cm^{-1}) 1690 (C=C); ^{1}H NMR δ=3.58 (br s, 1H, OH), 4.42 (br s, 2H, CH_2), 6.35 (qq, J=7.8 and 1.8 Hz, 1H, C=CH); ^{19}F NMR δ_F=11.1 (dq, J=2 and 1 Hz, 2-CF_3), 20.8 (dq, J=8 and 1 Hz, 3-CF_3). Found: C, 31.06; H, 2.06 %. Calcd for $C_5H_4F_6O$: C, 30.95; H, 2.08%.

*(E)-3,4-Bis(trifluoromethyl)-3-buten-2-ol (E-**3b**)*

bp 115 °C; n^{20}_D 1.3484; d^{20}_4 1.408; IR ν(cm^{-1}) 1682 (C=C); ^1H NMR δ=1.49 (d, J=6.0 Hz, 3H, CH_3), 3.79 (br s, 1H, OH), 5.02 (q, J=6.0 Hz, 1H, 1-CH), 6.22 (qq, J=8.4 and 1.2 Hz, 1H, 3-CH); ^{19}F NMR δ_F=15.6 (dq, 1 and 1 Hz, 2-CF_3), 21.6 (dq, 8 and 1 Hz, 3-CF_3). Found: C, 34.57; H, 3.04%. Calcd for $C_6H_6F_6O$: C, 34.63; H, 2.91%.

*(Z)-3,4-Bis(trifluoromethyl)-3-buten-2-ol (Z-**3b**)*

bp 128 °C; n^{20}_D 1.3500; d^{20}_4 1.427; IR ν(cm^{-1}) 1691 (C=C); ^1H NMR δ=1.45 (d, J=6.0 Hz, 3H, CH_3), 3.23 (br s, 1H, OH), 4.58 (q, J=6.0 Hz, 1H, 1-CH), 6.37 (q, J=8.4 Hz, 1H, 3-CH); ^{19}F NMR δ_F=18.0 (q, J=12 Hz, 2-CF_3), 21.6 (dq, J=8 and 12 Hz, 3-CF_3). Found: C, 34.63; H, 2.66%. Calcd for $C_6H_6F_6O$: C, 34.63; H, 2.91%.

*(E)-1,2-Bis(trifluoromethyl)-1-penten-3-ol (E-**3c**)*

bp 126 °C; n^{20}_D 1.3579; d^{20}_4 1.343; IR ν(cm^{-1}) 1678 (C=C); ^1H NMR δ=1.02 (t, J=6.6 Hz, 3H, CH_3), 1.67 (dq, J=6.6 and 6.0 Hz, 2H, CH_2), 3.63 (br s, 1H, OH), 4.74 (d, J=6.0 Hz, 1H, 1-CH), 6.37 (q, J=7.8 Hz, 1H, 3-CH); ^{19}F NMR δ_F=16.8 (q, J=1 Hz, 2-CF_3), 22.8 (dq, J= 8 and 1 Hz, 3-CF_3). Found: C, 37.56; H, 3.80%. Calcd for $C_7H_8F_6O$: C, 37.70; H, 3.62%.

*(Z)-1,2-Bis(trifluoromethyl)-1-penten-3-ol (Z-**3c**)*

bp 139 °C; n^{20}_D 1.3589; d^{20}_4 1.360; IR ν(cm^{-1}) 1687 (C=C); ^1H NMR δ=1.00 (t, J=6.6 Hz, 3H, CH_3), 1.62 (br, 2H, CH_2), 2.83 (br s, 1H, OH), 4.37 (br, 1H, 1-CH), 6.34 (q, J=9.0 Hz, 1H, 3-CH); ^{19}F NMR δ_F=17.6 (q, J=12 Hz, 2-CF_3), 20.4 (dq, J=9 and 12 Hz, 3-CF_3). Found: C, 37.85; H, 3.67 %. Calcd for $C_7H_8F_6O$: C, 37.70; H, 3.62%.

*(E)-3,4-Bis(trifluoromethyl)-2-methyl-3-buten-2-ol (E-**3d**)*

bp 119 °C; n^{20}_D 1.3604; d^{20}_4 1.360; IR ν(cm^{-1}) 1673 (C=C); ^1H NMR δ=1.58 (br s, 6H, CH_3), 2.86 (br s, 1H, OH), 6.27 (qq, J=9.6 and 1.8 Hz, 1H, CH); ^{19}F NMR δ_F=14.8 (dq, J=2 and 2 Hz, 2-CF_3), 24.8 (dq, J=10 and 2 Hz, 3-CF_3). Found: C, 37.73; H, 3.58%. Calcd for $C_7H_8F_6O$: C, 37.70; H, 3.62%.

*(Z)-3,4-Bis(trifluoromethyl)-2-methyl-3-buten-2-ol (Z-**3d**)*

bp 134 °C; n^{20}_D 1.3596; d^{20}_4 1.356; IR ν(cm^{-1}) 1679 (C=C); ^1H NMR δ=1.52 (br s, 6H, CH_3), 2.61 (br s, 1H, OH), 6.56 (q, J=8.4 Hz, 1H, CH); ^{19}F NMR δ_F=21.0 (s, 2-CF_3), 21.0 (d, J=10 Hz, 3-CF_3). Found: C, 37.63; H, 3.62%. Calcd for $C_7H_8F_6O$: C, 37.70; H, 3.62%.

*General Procedure of Addition Reaction of Aldehydes (**6**) to Hexafluoro-2-butyne (**1**)*

Freshly distilled propionaldehyde (**6b**) (197 g, 3.39 mol) was dissolved in Freon 113 (259 g) in an ampoule. Hexafluoro-2-butyne (**1**) (259 g, 1.8 mol) was then introduced into the ampoule using a vacuum line. The mixture was degassed by a freeze-thaw cycle and sealed in an ampoule. The γ-ray irradiation was carried out at 2.0 x 10^5 rh^{-1} by ^{60}Co for 101 h at ambient temperature (total irradiation 20 Mrad). After the reaction, precipitates which formed were separated by filtration to give *meso*-4,5-bis(trifluoromethyl)octa-3,6-dione (**8b**, 211 g, 46%). The distillation of the filtrate gave (*E*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-one (*E*-**7b**, 74.5 g, 21%) and *dl*-4,5-bis(trifluoromethyl)octa-3,6-dione (**8b**, 126 g, 30%). The physical and spectral data are shown below.

*(E)-5,5,5-Trifluoro-3-trifluoromethyl-3-penten-2-one (E-**7a**)*

bp 90 - 90.5 °C; n^{20}_D 1.3259; d^{20}_4 1.391; ^1H NMR δ=2.42 (s, CH_3), 6.38 (qq, J=7.7 and 1.5 Hz, CH); ^{19}F NMR δ_F=11.5 (t, J=1.5 Hz), 15.7 (dd, J=7.7 and 1.5 Hz). Found: C, 34.79; H, 2.02%. Calcd for $C_6H_4OF_4$: C, 35.00; H, 2.00%

*meso-3,4-Bis(trifluoromethyl)-2,4-hexanedione (meso-**8a**)*

mp 125 °C; ^1H NMR δ=2.35 (s, CH_3), 3.96 (m, CH); ^{19}F NMR δ_F=14.8 (m). Found: C, 38.45; H, 3.18%. Calcd for $C_8H_8O_2F_6$: C, 38.41; H, 3.22%.

*dl-3,4-Bis(trifluoromethyl)-2,4-hexanedione (dl-**8a**)*

bp 85 - 88 °C/ 81 mmHg; n^{20}_D 1.3608; d^{20}_4 1.388; ^1H NMR δ=1.15 (s, CH_3), 1.9 - 2.1 (m, CH); ^{19}F NMR δ_F=14.8 (m).

*(E)-6,6,6-Trifluoro-4-trifluoromethyl-4-hexen-3-one (E-**7b**)*

bp 106 °C; n^{20}_D 1.3382; d^{20}_4 1.318; ^1H NMR δ=1.13 (t, J=7.4 Hz, CH_3), 2.68 (q, J=7.4 Hz, CH_2), 6.28 (qq, J=7.5 and 1.5 Hz, CH); ^{19}F NMR δ_F=12.9 (quintet, J=1.7 and 1.5 Hz), 17.2 (dq, J=1.7 and 7.5 Hz); Found: C, 38.14; H, 2.80%. Calcd for $C_7H_6OF_6$: C, 38.19; H, 2.75%

*meso-4,5-Bis(trifluoromethyl)octa-3,6-dione (meso-**8b**)*

mp 123 °C; ^1H NMR δ=1.05 (t, J=7.2 Hz, CH_3), 2.82 (dq, J=7.2 and 3.3 Hz, CH_2), 4.13 (m, CH); ^{19}F NMR δ_F=13.9 (m). Found: C, 43.47; H, 4.55%. Calcd for $C_{10}H_{12}O_2F_6$: C, 43.17; H, 4.35%.

*dl-4,5-Bis(trifluoromethyl)octa-3,6-dione(dl-**8b**)*

bp 121 °C/ 75 mmHg; n^{20}_D 1.3678; d^{20}_4 1.281; ^1H NMR δ=1.01 (t, J=6.5 Hz, CH_3), 2.4 - 2.8 (m, CH_2), 4.12 (m, CH); ^{19}F NMR δ_F=14.7 (m). Found: C, 42.91; H, 4.49%. Calcd for $C_{10}H_{12}O_2F_6$: C, 43.17; H, 4.35%.

*Isomerization of (E)-6,6,6-Trifluoro-4-trifluoromethyl-4-hexen-3-one (E-**7**) under UV Irradiation*

In an ampoule made of quartz and equipped with a Dimroth condenser was placed a hexane solution of *E*-**7** (23.4 g, 0.106 mol), which was irradiated with a 1 kW high-pressure mercury lamp for 8 h. After the reaction, the products were distilled to afford (*E*)- and (*Z*)- mixture of **7** in a ratio of 3:1. The (*Z*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-one (*Z*-**7**) was isolated using a preparative gas chromatograph.

*(Z)-6,6,6-Trifluoro-4-trifluoromethyl-4-hexen-3-one (Z-**7**)*

bp 121°C; ^{1}H NMR δ=1.13 (t, J=7.4 Hz, CH_3), 2.71 (q, J=7.4 Hz, CH_2), 6.58 (q, J=8.3 Hz, CH); ^{19}F NMR δ_F=18.4 (q, J=10.5 Hz), 19.7 (dq, J=10.5 and 8.3 Hz). Found: C, 38.31; H, 2.87%. Calcd for $C_7H_6OF_6$: C, 38.19; H, 2.75%.

Reaction of (Trifluoromethyl)allyl Alcohols

*Dehydration of 2,3-Bis(trifluoromethyl)allyl Alcohols (**3**)*

In a flask (100 mL) equipped with a distillation apparatus, were placed a mixture of (*E*)- and (*Z*)-3,4-bis(trifluoromethyl)-3-buten-2-ol (**3b**) (12.3 g, 0.06 mol) and phosphorus pentaoxide (24 g, 0.17 mol). The mixture was heated at 100 °C. As the reaction proceeded, was distilled out a mixture of (*E*)- and (*Z*)-1,2-bis(trifluoromethyl)-1,3-butadiene (**9b**, 8.9 g), which were separated using a preparative gas chromatograph. The physical and spectral data are shown below.

*(E)-1,2-Bis(trifluoromethyl)-1,3-butadiene (E-**9b**)*

bp 53 °C; n^{20}_D 1.3321; d^{20}_4 1.302; IR ν(cm^{-1}) 1613, 1668 (C=C); ^{1}H NMR δ=5.4 - 6.7 (m, 3H, $CH=CH_2$), 6.15 (q, J=9.0 Hz, 1H, CF_3CH); ^{19}F NMR δ_F=12.6 (d, J=1 Hz, 2-CF_3), 19.4 (dq, J=9 and 1 Hz, 1-CF_3). Found: C, 37.86; H, 2.07%. Calcd for $C_6H_4F_6$: C, 37.91; H, 2.12%.

*(Z)-Bis(trifluoromethyl)-1,3-butadiene (Z-**9b**)*

n^{20}_D 1.3410; d^{20}_4 1.350; IR ν(cm^{-1}) 1691 (C=C); ^{1}H NMR δ=5.3 - 6.7 (m, 3H, $CH=CH_2$), 6.00 (q, J=7.8 Hz, 1H, CF_3CH); ^{19}F NMR δ_F=15.2 (q, J=11 Hz, 2-CF_3), 19.7 (dq, J=8 and 11 Hz, 1-CF_3). Found: C, 37.49; H, 2.16%. Calcd for $C_6H_4F_6$: C, 37.91; H, 2.12%.

*(E)-1,2-Bis(trifluoromethyl)-3-methyl-1,3-butadiene (E-**9d**)*

bp 67 °C; n^{20}_D 1.3277; d^{20}_4 1.221; IR ν(cm^{-1}) 1641, 1681 (C=C); ^{1}H NMR δ=1.94 (br s, 3H, CH_3), 5.01 (br s, 1H, CH_2), 5.23 (q, J=1.2 Hz, 1H, CH_2), 6.14 (qq, J=7.2 and 1.8 Hz, 1H, CH); ^{19}F NMR δ_F=9.7 (br s, 2-CF_3), 18.3 (br d, 1-CF_3). Found: C, 40.67; H, 2.87%. Calcd for $C_7H_6F_6$: C, 41.19; H, 2.96%.

*(Z)-1,2-Bis(trifluoromethyl)-3-methyl-1,3-butadiene (Z-**9d**)*

bp 89 °C; n^{20}_D 1.3441; d^{20}_4 1.280; IR ν(cm^{-1}) 1648, 1669 (C=C); ^{1}H NMR δ=1.96 (q, J=8.2 Hz, 3H, CH_3), 5.21 (br s, 2H, CH_2), 5.95 (q, J=8.4 Hz, 1H, CH); ^{19}F NMR δ_F=17.0 (q, J=13 Hz, 2-CF_3), 19.8 (dq, J=8 and 13 Hz, 1-CF_3). Found: C, 40.90; H, 2.92%. Calcd for $C_7H_6F_6$: C, 41.19; H, 2.96%.

*Cyclization of 1,2-Bis(trifluoromethyl)-1,3-butadiene (**9d**)*

In a stainless steel autoclave (100 mL) was placed a mixture of (*E*)- and (*Z*)-1,2-bis(trifluoromethyl)-3-methyl-1,3-butadiene (**10d**, 5.9 g, 28.9 mmol) and *dl*-limonene (1.0 g, a polymerization inhibitor). After heating the reaction mixture at 200 °C for 24 h, the product was distilled and purified using a preparative gas chromatograph to afford 1-methyl-2,3-bis(trifluoromethyl)-cyclobutene (**10d**, 1.5 g) in 25% yield.

*1-Methyl-2,3-bis(trifluoromethyl)cyclobutene (**10d**)*

bp 107°C; n^{20}_D 1.3362; d^{20}_4 1.305; IR ν(cm^{-1}) 1694 (C=C); ^{1}H NMR δ=1.90 (br s, 3H, CH_3), 2.57 (br s, 2H, CH_2), 3.90 (br s, H, CH); ^{19}F NMR δ_F=5.7 (dq, J=8 and 2 Hz, CCF_3), 13.8 (br, $CHCF_3$). Found: C, 40.90; H, 2.88%. Calcd for $C_7H_6F_6$: C, 41.19; H, 2.96%.

Synthesis of 3,4-Bis(trifluoromethyl)furan Derivatives

*General Procedure of Synthesis of 2,5-Dialkyl-3,4-trifluoromethylfurans (**11**)*

To 4,5-bis(trifluoromethyl)octa-3,6-dione (**8b**) (79.9 g, 0.287 mol) was added dropwise sulfuric acid (80 mL) with moderate stirring for 30 min. The resultant yellow oil was poured into a mixture of ice and ether. The ether layer was separated, washed with water, and dried over sodium sulfate. After evaporation of ether, the residual liquid was distilled to give 2,5-diethyl-3,4-bis(trifluoromethyl)furan (**11b**, 70.1 g, 94%). From the residue, 3-ethyl-2-methyl-4,5-bis(trifluoromethyl)-2-cyclopenten-1-one (**12**) was isolated in 1% yield using a preparative gas chromatograph.

*2,5-Dimethyl-3,4-bis(trifluoromethyl)furan (**11a**)*

bp 77 - 78 °C/88 mmHg ; n^{20}_D 1.3686; d^{20}_4 1.384; ^{1}H NMR δ=2.35 (s, CH_3); ^{19}F NMR δ_F=20.5 (s). Found: C,41.22; H,2.65%. Calcd for $C_8H_6F_6O$: C,41.39; H,2.61%.

*2,5-Diethyl-3,4-bis(trifluoromethyl)furan (**11b**)*

bp 86 - 87 °C/ 90 mmHg; n^{20}_D 1.3820; d^{20}_4 1.276; ^{1}H NMR δ=1.25 (t, J=7.5 Hz, CH_3), 2.80 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ_F=20.8 (s). Found: C, 46.21; H, 3.76%. Calcd for $C_{10}H_{10}OF_6$: C, 46.16; H, 3.87%.

*3-Ethyl-2-methyl-4,5-bis(trifluoromethyl)-2-cyclopenten-1-one (**12**)*

bp 184 °C; n^{20}_D 1.3994; d^{20}_4 1.276; ^{1}H NMR δ=1.22 (t, J=7.5 Hz, CH_3), 1.82 (s, CH_3), 2.68 (q, J=7.5 Hz, CH_2), 3.20 (m, H), 3.70 (m, H); ^{19}F NMR δ_F=9.34 (m), 9.50 (m). Found: C, 46.33; H, 4.07%. Calcd for $C_{10}H_{10}OF_6$: C, 46.16; H, 3.87%.

*Bromination of (Trifluoromethyl)furans **11***

To a carbon tetrachloride solution of **11b** (38.0 g, 0.15 mol), was added carbon tetrachloride solution of bromine (24.3 g, 0.15 mol) under UV irradiation with stirring. After the irradiation (30 min), the reaction mixture poured into dichloromethane. The organic layer was washed with water, 10% aqueous sodium hydroxide solution, and dried over sodium sulfate. Distillation of the organic layer gave 2-(1-bromoethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**13b**, 32.3 g, 59%) and 2,5-bis(1-bromoethyl)-3,4-bis(trifluoromethyl)furan (**14**, 7.6 g, 13%) respectively, together with starting material (**11b**, 7.0 g). When excess amounts of bromine (3.14 equiv) was added to **11b**, followed by UV irradiation for 16.5 h, **14** was obtained in 93% yield along with a small amounts of **13b** (0.7%).

In a similar procedure, the bromination of **11c** and **11d** gave 2-(1-bromoethyl)-3,4-bis(trifluoromethyl)furan (**13c**) and 2-(1-bromoethyl)-3,4,5-tris(trifluoromethyl)furan (**13d**) in 79% and 78% yields, respectively. In the case of **11d**, 2-(1,2-dibromoethyl)-3,4,5-tris(trifluoromethyl)furan (**21d**) was also detected in 4% yield and identified by GC-MS analysis.

*2-(1-Bromoethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**13b**)*

bp 98 - 99 °C/ 20 mmHg; n^{20}_D 1.4248; d^{20}_4 1.547; ^{1}H NMR δ=1.33 (t, J=7.5 Hz, CH_3), 2.03 (d, J=7.2 Hz, CH_3), 2.88 (q, J=7.5 Hz, CH_2), 5.33 (q, J=7.2 Hz, CH); ^{19}F NMR δ_F=21.8 (m). Found: C, 35.20; H, 2.68%. Calcd for $C_{10}H_9OF_6Br$: C, 35.42; H, 2.68%.

*2,5-Bis(1-bromoethyl)-3,4-bis(trifluoromethyl)furan (**14**) (diastereomer)*

bp 84 - 85 °C/ 3.5 mmHg; n^{20}_D 1.4619; d^{20}_4 1.779; ^{1}H NMR δ=2.07 (d, J=7.2 Hz, CH_3), 2.14 (d, J=7.2 Hz, CH_3), 5.38 (q, J=7.2 Hz, CH), 5.42 (q, J=7.2 Hz, CH); ^{19}F NMR δ_F=21.8 (s), 22.0 (s). Found: C, 28.76; H, 2.01%. Calcd for $C_{10}H_8OF_6Br_2$: C, 28.74; H, 1.93%.

*2-(1-Bromoethyl)-3,4-bis(trifluoromethyl)furan (**13c**)*

bp 97 - 99 °C/ 61 mmHg; n^{20}_D 1.4140; d^{20}_4 1.667; ^{1}H NMR δ=2.04 (d, J=7.0 Hz, CH_3), 5.30 (q, J=7.0 Hz, CH_2), 7.77 (q, J=1.2 Hz, CH); ^{19}F NMR δ_F=19.2 (dq, J=6.1 and 1.2 Hz), 21.7 (q, J=6.1 Hz). Found: C, 30.87; H, 1.69%. Calcd for $C_8H_5OF_6Br$: C, 30.89; H, 1.62%.

*2-(1-Bromoethyl)-3,4,5-tris(trifluoromethyl)furan (**13d**)*

bp 65 - 66 °C/ 18 mmHg; n^{20}_D 1.3887; d^{20}_4 1.730; ^{1}H NMR δ=2.08 (d, J=7.2 Hz, CH_3), 5.35 (q, J=7.2 Hz, CH); ^{19}F NMR δ_F=16.7 (m), 21.3 (m). Found: C, 28.53; H, 0.99%. Calcd for $C_9H_4OF_9Br$: C, 28.52; H, 1.06%.

*2-(1,2-Dibromoethyl)-3,4,5-tris(trifluoromethyl)furan (**21d**)*

n^{20}_D 1.4209; IR ν(cm^{-1}) 1598, 1622, 1642 (C=C); ^{19}F NMR δ_F=17.0 (m), 21.6 (m); MS *m/z* 379, 377 (72, M^+-Br), 359, 357 (17, M^+-H-F-Br), 298 (100, M^+-H-2Br), 279 (34, M^+-H-F-2Br).

*Dehydrobromination of 2-(1-Bromoethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**13b**)*

To an ethanol solution (10 mL) of 8.97 g (26 mmol) of monobromide **13b** containing a small amount of hydroquinone as a polymerization inhibitor, was added dropwise an ethanol solution (30 mL) of 2.26 g (40 mmol) of potassium hydroxide. The reaction mixture was heated to reflux for 1 h and poured into water, then extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and distilled to provide 1.59 g (23%) of 5-ethyl-3,4-bis(trifluoromethyl)-2-vinylfuran (**15b**) and 1.44 g (18%) of 2-(1-ethoxyethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**16b**). The vinyl compounds **15b** polymerized easily at ambient temperature without addition of an inhibitor.

*5-Ethyl-3,4-bis(trifluoromethyl)-2-vinylfuran (**15b**)*

bp 140 - 142 °C (with hydroquinone); IR ν(cm^{-1}) 1560, 1612 (C=C); ^{1}H NMR δ=1.31 (t, J=7.5 Hz, CH_3), 2.82 (q, J=7.5 Hz, CH_2), 5.38 - 6.98 (m, $CH=CH_2$); ^{19}F NMR δ_F=21.6 (q, J=7.0 Hz), 22.4 (q, J=7.0 Hz); MS *m/z* 258 (34, M^+), 243 (100, M^+-CH_3), 239 (16, M^+-F).

*2-(1-Ethoxyethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**16b**)*

bp 191 - 192 °C; n^{20}_D 1.3933; d^{20}_4 1.308; ^{1}H NMR δ=1.17 (t, J=7.5 Hz, CH_3), 1.28 (t, J=7.4 Hz, CH_3), 1.50 (d, J=6.8 Hz, CH_3), 2.86 (q, J=7.5 Hz, CH_2), 3.40 (q, J=7.4 Hz, OCH_2), 4.72 (q, J=6.8 Hz, CH); ^{19}F NMR δ_F=21.4 (q, J=7.3 Hz), 22.2 (q, J=7.3 Hz). Found: C, 47.23; H, 4.25%. Calcd for $C_{12}H_{14}O_2F_6$: C, 47.37; H, 4.64%.

*Hydrolysis of (Bromoethyl)furans **13** with Potassium Carbonate*

2-(1-Bromoethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**13b**) (17.3 g, 51.0 mmol) was refluxed in 10% aqueous potassium carbonate solution (100 mL) for 7 h. After cooling, the mixture was acidified with dilute sulfuric acid and extracted with ether, which was dried over sodium sulfate. The distillation of the ethereal solution gave 5-ethyl-2-(1-hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17b**, 8.43 g, 60%).

In a similar procedure, the hydrolyses of **13c** and **13d** gave 2-(1-hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17c**) and 2-(1-hydroxyethyl)-3,4,5-tris(trifluoromethyl)furan (**17d**) in 76% and 6% yields, respectively.

*5-Ethyl-2-(1-hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17b**)*

bp 105 - 106°C/ 17 mmHg; n^{20}_D 1.4010; d^{20}_4 1.361; ^{1}H NMR δ=1.25 (q, J=7.6 Hz, CH_3), 1.46 (d, J=6.6 Hz, CH_3), 2.84 (q, J=7.6 Hz, CH_2), 3.67 (s, OH), 5.02 (q, J=6.6 Hz, CH); ^{19}F NMR δ_F=21.6 (q, J=7.3 Hz), 22.2 (q, J=7.3 Hz). Found: C, 43.47; H, 3.60%. Calcd for $C_{10}H_{10}O_2F_6$: C, 43.49; H, 3.65%.

*2-(1-Hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17c**)*

bp 92 - 93°C/ 14 mmHg; n^{20}_D 1.3863; d^{20}_4 1.474; ^{1}H NMR δ=1.48 (q, J=6.7 Hz, CH_3), 3.72 (s, CH), 5.05 (q, J=6.7 Hz, CH), 7.73 (s, OH); ^{19}F NMR δ_F=19.1 (dq, J=6.2 and 1.4 Hz), 22.3 (q, J=6.2 Hz). Found: C, 38.57; H, 2.58%. Calcd for $C_8H_6O_2F_6$: C, 38.72; H, 2.44%.

*2-(1-Hydroxyethyl)-3,4,5-tris(trifluoromethyl)furan (**17d**)*

mp 34 - 36 °C; IR ν(cm^{-1}) 3620, 3350 (OH), 1641, 1621, 1597 (C=C); ^{1}H NMR δ=1.61 (d, J=6.3 Hz, CH_3), 2.11 (s, OH), 5.20 (q, J=6.3 Hz, CH); ^{19}F NMR δ_F=17.0 (q, J=8.2 Hz), 21.6 (heptet, J=8.2 and 7.4 Hz), 22.5 (q, J=7.4 Hz); MS *m/z* 316 (3, M^+), 301 (28, M^+-CH_3), 281 (100, M^+-H-F-CH_3), 253 (27, M^+-4H-F-2C-O).

*Oxidation of (Hydroxyethyl)furans **17** with Sodium Dichromate*

To a dilute sulfuric acid solution of sodium dichromate (2.81 g, 9.41 mmol) was added 2-(1-hydroxyethyl)-5-ethyl-3,4-bis(trifluoromethyl)furan (**17b**) (3.70 g, 13.4 mmol). The reaction mixture was heated at *ca.* 60 °C for 2 h and poured into water. The products were extracted with ether and washed with 5% aqueous potassium hydroxide solution. The distillation of ethereal solution gave 2-acetyl-5-ethyl-3,4-bis(trifluoromethyl)furan (**18b**) together with unchanged **17b**. The acetylfuran **17b** (0.70 g, 29%) was isolated using a preparative gas chromatograph.

In a similar procedure, 2-acetyl-3,4-bis(trifluoromethyl)furan (**18c**) was obtained in 40% yield from **17c** by sodium dichromate oxidation.

*2-Acetyl-5-ethyl-3,4-bis(trifluoromethyl)furan (**18b**)*

bp 215 °C; n^{20}_D 1.4109; d^{20}_4 1.383; ^{1}H NMR δ=1.35 (t, J=7.5 Hz, CH_3), 2.50 (s, $COCH_3$), 2.96 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ_F=21.9 (s). Found: C, 43.76; H, 2.90%. Calcd for $C_{10}H_8O_2F_6$: C, 43.81; H, 2.94%.

*2-Acetyl-3,4-bis(trifluoromethyl)furan (**18c**)*

bp 57 - 58 °C/ 2 mmHg; n^{20}_D 1.3930; d^{20}_4 1.508; ^{1}H NMR δ=2.54 (s, $COCH_3$), 7.88 (s, CH); ^{19}F NMR δ_F=19.3 (q, J=7.6 Hz), 21.7 (q, J=7.6 Hz). Found: C, 38.92; H, 1.63%. Calcd for $C_8H_4O_2F_6$: C, 39.04; H, 1.64%.

*Nitric Acid Oxidation of Ethyl-3,4-bis(trifluoromethyl)furans **11***

A mixture of 2,5-diethyl-3,4-bis(trifluoromethyl)furan (**11b**) (47.8 g, 0.18 mol) and nitric acid (d 1.38, 140 mL) in acetic acid (400 mL) was refluxed for 50 h. The reaction mixture was poured into water and extracted with dichloromethane (200 mL). The organic layer was dried over sodium sulfate. Evaporation of dichloromethane yielded white precipitates, which were separated by filtration and recrystallized from hexane to give 5-ethyl-3,4-bis(trifluoromethyl)-2-furancarboxylic acid (**20b**, 23 g, 45%). The filtrate was washed with 5% aqueous sodium bicarbonate solution, extracted with dichloromethane and dried. Distillation of the extract gave 5-ethyl-2-formyl-3,4-bis(trifluoromethyl)furan (**19b**, 0.57 g, 1%).

*5-Ethyl-2-formyl-3,4-bis(trifluoromethyl)furan (**19b**)*

bp 186 °C; n^{20}_D 1.4110; d^{20}_4 1.433; ^{1}H NMR δ=1.38 (t, J=7.6 Hz, CH_3), 2.98 (qq, J=7.6 and 1.3 Hz, CH_2), 9.72 (s, CHO); ^{19}F NMR δ_F=21.5 (tq, J=7.4 and 1.3 Hz), 22.8 (q, J=7.4 Hz). Found: C, 41.49; H, 2.63%. Calcd for $C_9H_6O_2F_6$: C, 41.55; H, 2.33%.

*3,4-Bis(trifluoromethyl)-2-furancarboxylic acid (**20b**)*

mp 93 °C; ^{1}H NMR δ=1.36 (t, J=7.5 Hz, CH_3), 2.09 (q, J=7.5 Hz, CH_2), 11.64 (s, COOH); ^{19}F NMR δ_F=22.1 (m). Found: C, 38.99; H, 2.27%. Calcd for $C_9H_6O_3F_6$: C, 39.14; H, 2.19%.

In a similar procedure, a mixture of 2-ethyl-3,4-bis(trifluoromethyl)furan (**11c**) (11.9 g, 51.4 mmol) and nitric acid (d 1.38, 30 mL) was poured into water (700 mL) and extracted with dichloromethane (150 mL). The organic layer was washed with water and dried over sodium sulfate. After the distillation of the solvent, the products were isolated using a preparative gas chromatograph. 2-(1-Hydroxyethyl)-3,4-bis(trifluoromethyl)furan (**17c**, 0.53 g, 4%), 3,4-bis(trifluoromethyl)-2-furancarboxylic acid (**20c**, 0.27 g, 2%),

and 2-(1-acetoxyethyl)-3,4-bis(trifluoromethyl)furan (**22c**, 0.77 g, 5%) were isolated.

*3,4-Bis(trifluoromethyl)-2-furancarboxylic acid (**20c**)*

mp 126 - 127 °C; ^{1}H NMR δ=8.19 (s, CH), 10.38 (s, COOH); ^{19}F NMR δ_F=19.2 (dq, J=7.8 and 1.2 Hz), 22.1 (q, J=7.8 Hz). Found: C, 33.84; H, 1.13%. Calcd for $C_7H_2O_3F_6$: C, 33.89; H, 0.81%.

*2-(1-Acetoxyethyl)-3,4-bis(trifluoromethyl)furan (**22c**)*

bp 186 °C; n^{20}_D 1.3922; ^{1}H NMR δ=1.59 (d, J=6.6 Hz, CH_3), 2.04 (s, $COCH_3$), 6.03 (q, J=6.6 Hz, CH), 7.79 (s, CH); ^{19}F NMR δ_F=22.2 (m). Found: C, 41.01; H, 2.79%. Calcd for $C_{10}H_8O_3F_6$: C, 41.39; H, 2.78%.

*Decarboxylation of 5-Ethyl-3,4-bis(trifluoromethyl)-2-furancarboxylic Acid (**20b**)*

5-Ethyl-3,4-bis(trifluoromethyl)-2-furancarboxylic acid (**20b**) (48.8 g, 0.148 mol) and copper powder (22.0 g) were heated in pyridine (170 mL) at 100 °C for 4 h. After the reaction, the solution was acidified with 50% sulfuric acid and extracted with ether. The distillation of the extract gave 2-ethyl-3,4-bis(trifluoromethyl)furan (**13c**, 23.7 g, 69%).

*2-Ethyl-3,4-bis(trifluoromethyl)furan (**13c**)*

bp 129 °C; n^{20}_D 1.3625; d^{20}_4 1.353; ^{1}H NMR δ=1.29 (t, J=6.7 Hz, CH_3), 2.87 (qq, J=6.7 and 1.3 Hz, CH_2), 7.63 (q, J=1.3 Hz, CH); ^{19}F NMR δ_F=19.1 (dq, J=6.2 and 1.3 Hz), 22.3 (tq, J=6.2 and 1.3 Hz). Found: C, 41.22; H, 2.60%. Calcd for $C_8H_6OF_6$: C, 41.39; H, 2.61%.

*Fluorination of 5-Ethyl-3,4-bis(trifluoromethyl)-2-furancarboxylic Acid (**20b**) with Sulfur Tetrafluoride*

In an autoclave (100 mL) made of Hastelloy was placed **20b** (5.03 g, 18.2 mmol) and anhydrous hydrogen fluoride (5.64 g), then cooled with liquid nitrogen. Sulfur tetrafluoride (13.7 g, 126 mmol) was introduced into the autoclave using a vacuum line. The autoclave was heated at 100 °C for 2 h and then at 130 °C for 10 h. After cooling, gaseous products were removed. The product was poured into a mixture of ice and 10% aqueous potassium hydroxide solution, and extracted with dichloromethane, and dried over sodium sulfate. Distillation of the extract gave 2-ethyl-3,4,5-tris(trifluoromethyl)furan (**13d**, 4.15 g, 76%).

*2-Ethyl-3,4,5-tris(trifluoromethyl)furan (**13d**)*

bp 110 °C; n^{20}_D 1.3470; d^{20}_4 1.477; ^{1}H NMR δ=1.35 (t, J=7.5 Hz, CH_3), 2.92 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ_F=16.8 (q, J=7.6 Hz), 21.2 (m), 21.5 (m). Found: C, 35.89; H, 1.53%. Calcd for $C_9H_5OF_9$: C, 36.01; H, 1.68%.

Synthesis and Photochemical Reaction of 1,4-Dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene

*Diels-Alder Reaction of 2,5-Dialkyl-3,4-bis(trifluoromethyl)furans (**11**) with Hexafluoro-2-butyne (**1**)*

In a stainless steel cylinder (200 mL) equipped with a magnetic stirrer was placed **11b** (57.02 g, 0.219 mol). Into the cylinder cooled by liquid nitrogen was introduced **1** (38.5 g, 0.238 mol) under reduced pressure. The cylinder was heated at 140 °C for 80 h and then cooled to room temperature. After unreacted **1** was recovered, a mixture of 1,4-diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23b**, 32% GC yield) and **11b** was obtained. The oxabicycloheptadiene **11b** was isolated by using a gas chromatograph (24.66 g, 27% yield).

*1,4-Diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23b**)*

bp 153 - 157 °C; n^{20}_D 1.3603; d^{20}_4 1.463; IR ν(cm^{-1}) 1664 (C=C); ^{1}H NMR δ=1.06 (t, J=7.2 Hz, CH_3), 2.57 (q, J=7.2 Hz, CH_2); ^{19}F NMR δ_F=17.9 (s); MS m/z 422 (M^+). Found: C, 39.35; H, 2.33%. Calcd for $C_{14}H_{10}F_{12}O$: C, 39.83; H, 2.39%.

In a procedure similar to **23b**, the Diels-Alder reaction of **11a** with **1** provided 1,4-dimethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23a**) (10.36 g, 23% yield).

*1,4-Dimethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23a**)*

bp 143 - 146 °C; n^{20}_D 1.3437; d^{20}_4 1.526; IR ν(cm^{-1}) 1677 (C=C); ^{1}H NMR δ=1.92 (s); ^{19}F NMR δ_F=18.2 (s). Found: C, 36.93; H, 1.77%. Calcd for $C_{12}H_6F_{12}O$: C, 36.57; H, 1.57%.

*UV Irradiation of 1,4-Diethyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene (**23b**)*

An anhydrous ether solution of **23b** (13.23 g, 31.35 mmol) sealed under an argon atmosphere in a quartz ampoule (50 mL) was irradiated with a 1 kW high pressure mercury lamp at a distance of about 10 - 15 cm for 184 h

at room temperature. Products were analyzed by a gas chromatograph. Three products, 1-ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadiene (**25**, 14% GC yield), ethyl 3-[1-ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadienyl] ketone (**26**, 23% GC yield), and 2,7-diethyl-3,4,5,6-tetrakis(trifluoromethyl)oxepin (**27**, 4% GC yield) were isolated by using a preparative gas chromatograph.

*1-Ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadiene (**25**)*

bp 152 - 153 °C; n^{20}_D 1.3542; d^{20}_4 1.551; IR ν(cm^{-1}) 1601, 1660 (C=C); ^{1}H NMR δ=1.19 (t, J=7.5 Hz, CH_3), 2.52 (q, J=7.5 Hz, CH_2), 4.32 (q, J=6.0 Hz, CH); ^{19}F NMR d_F=21.0 (br s), 20.3 (br s), 17.4 (br s), 14.7 (br s); MS *m/z* 336 (M^+). Found: C, 36.37; H, 1.93%. Calcd for $C_{11}H_6F_{12}$: C, 36.08; H, 1.65%.

*Ethyl 3-[1-ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadienyl] ketone (**26**)*

bp 81 - 82 °C/12 mmHg; n^{20}_D 1.3822; d^{20}_4 1.496; IR ν(cm^{-1}) 1754 (C=O), 1592, 1648 (C=C); ^{1}H NMR δ=1.05 (t, CH_3), 1.21 (t, CH_3), 2.17 (q, CH_2), 2.68 (q, CH_2); ^{19}F NMR d_F=22.9 (br s), 21.9 (br s), 17.9 (br s), 14.1 (br s); MS *m/z* 422 (M^+). Found: C, 39.74; H, 2.53%. Calcd for $C_{14}H_{10}F_{12}O$: C, 39.83; H, 2.39%.

*2,7-Diethyl-3,4,5,6-tetrakis(trifluoromethyl)oxepin (**27**)*

n^{20}_D 1.3841; d^{20}_4 1.482; IR ν(cm^{-1}) 1607, 1653 (C=C); ^{1}H NMR δ=1.23 (t, J=7.5 Hz, CH_3), 2.50 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ_F=22.5 (br s), 20.6 (br s); MS *m/z* 422 (M^+). Found: C, 40.49; H, 2.70%. Calcd for $C_{14}H_{10}F_{12}O$: C, 39.83; H, 2.39%.

*Reaction of Ethyl 3-[1-Ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadienyl] Ketone (**26**)*

1) UV Irradiation

An anhydrous ether solution (180 mL) of the ketone **26** (3.83 g) sealed under argon atmosphere in a quartz ampoule (200 mL) was irradiated using a 1 kW high pressure mercury lamp in the distance of about 12 cm for 256 h at room temperature. After evaporation of the solvent, residual crude **25** was purified by a preparative gas chromatograph (20% yield).

2) With Methanol

A methanol solution (0.513 g, 16.0 mol) of the ketone **26** (5.64 g, 13.4 mmol) was stirred for 4.5 h at room temperature. The dark yellow reaction mixture was distilled under reduced pressure to give **25** (3.19 g, 65% yield).

3) With Water

To an ether solution (2 mL) of ketone **26** (0.188 g) was added 2 drops of water. The reaction mixture was stirred for 2.5 h and allowed to stand overnight. The reaction afforded a mixture of **25** and 1-ethyl-2,3,4-tris(trifluoromethyl)-1,4-cyclopentadiene (**29**).

4) With Lithium Aluminum Hydride

To an ether solution (80 mL) of the ketone **6** (5.58 g, 13.2 mmol) was added lithium aluminum hydride (1.50 g, 39.6 mmol). After refluxing the solution for 90 min, the solution was poured into dilute sulfuric acid solution. The product was extracted, distilled, and purified by a preparative gas chromatograph to give 3-[1-ethyl-tris(trifluoromethyl)-1,4-cyclopentadienyl]-1-propanol (**28**, 0.44 g, 9.4%).

*3-[1-Ethyl-tris(trifluoromethyl)-1,4-cyclopentadienyl]-1-propanol (**28**) (regioisomer)*

IR ν(cm^{-1}) 3475, 3640 (OH), 1644, 1693 (C=C); ^{1}H NMR δ=0.9 - 1.4 (CH_3), 2.0 - 3.2 (CH_2), 3.9 - 4.3 (CH), 6.35 (s, =CH-), 7.70 (s, =CH-); ^{19}F NMR δ_F=23.1 (br s), 13.7 (br s), 11.5 (br s), 22.0 (br s), 14.1 (br s), 12.5 (br s). Found: C, 43.91; H, 3.95%. Calcd for $C_{13}H_{13}F_9O$: C, 43.83; H, 3.68%.

*Hydrolysis of 1-Ethyl-2,3,4,5-tetrakis(trifluoromethyl)-1,4-cyclopentadiene (**25**)*

To an ether solution (5 mL) of cyclopentadiene **25** (3.61 g, 9.86 mmol) was added water (0.45 g, 25.1 mmol) with stirring. After stirring the solution for 5 h, the product was distilled and purified by using a preparative gas chromatograph to give 1-ethyl-2,3,4-tris(trifluoromethyl)-1,4-cyclopentadiene (**29**, 1.11 g, 38%).

*1-Ethyl-2,3,4-tris(trifluoromethyl)-1,4-cyclopentadiene (**29**)*

IR ν(cm^{-1}) 1597, 1649 (C=C); ^{1}H NMR δ=1.16 (t, J=7.5 Hz, CH_3), 2.54 (q, J=7.5 Hz, CH_2), 4.18 (q, J=7.5 Hz, CH), 6.80 (s, =CH-); ^{19}F NMR δ_F=20.1 (br s), 16.2 (br s), 12.8 (br s); MS *m/z* 298 (M^+). Found: C, 40.43; H, 2.32%. Calcd for $C_{10}H_7F_9$: C, 40.29; H, 2.37%.

Synthesis and Stereoselective Decomposition of Pyrazolines Containing Trifluoromethyl Groups

*Synthesis of 3,4-Bis(trifluoromethyl)-3-propionyl-4,5-dihydro-3H-pyrazole (**30**)*

To an ether solution (30 mL) of *E*-**7b** (2.50 g, 11.4 mmol), was added an ether solution of diazomethane cooled with ice, which was allowed to stand

at ambient temperature for 30 min. After evaporating the solvent, pure *r*-3,*t*-4-bis(trifluoromethyl)-3-propionylpyrazoline (*E*-**30**) was obtained in 98% yield (2.91 g).

*r-3,t-4-Bis(trifluoromethyl)-3-propionylpyrazoline (E-**30**)*

n^{20}_D 1.3860; IR $\nu(cm^{-1})$ 1741 (C=O), 1572 (N=N); ^1H NMR δ=1.01 (t, J=7.2 Hz, CH_3), 2.56 (q, J=7.2 Hz, CH_2), 3.0 - 3.6 (m, $CHCF_3$), 4.90 (br s, CH_2N=N), 4.98 (br s, CH_2N=N); ^{19}F NMR δ_F=7.2 (q, J=1.3 Hz), 14.5 (dq, J=9.0 and 1.3 Hz).

r-3,*c*-4-Bis(trifluoromethyl)-3-propionylpyrazoline (*Z*-**30**) was obtained quantitatively using a similar procedure.

*r-3,c-4-Bis(trifluoromethyl)-3-propionylpyrazoline (Z-**30**)*

n^{20}_D 1.3879; IR $\nu(cm^{-1})$ 1739 (C=O), 1565 (N=N); ^1H NMR δ=1.07 (t, J=7.0 Hz, CH_3), 2.83 (q, J=7.0 Hz, CH_2), 3.1 - 3.7 (m, $CHCF_3$), 4.72 (br s, CH_2N=N); ^{19}F NMR δ_F=12.6 (q, J=11.7 Hz), 13.8 (q, J=11.7 Hz).

*Decomposition of Pyrazolines **30***

1) Pyrolysis

In a flask equipped with a Dimroth condenser was placed *E*-**30** (13.23 g, 31.35 mmol), which was heated at 140 °C. After a reaction, volatile products were evaporated. The resulting products were isolated using a preparative gas chromatograph.

2) Photolysis

Into a quartz ampoule (diameter: 10 mm) was placed *E*-**30** (13.23 g, 31.35 mmol), which was irradiated at room temperature using a high-pressure mercury lamp (distance: 6 - 10 cm) under a nitrogen atmosphere. After a reaction was complete, volatile products were evaporated. The resulting products were isolated using a preparative gas chromatograph.

*r-1,t-2-Bis(trifluoromethyl)-1-propionylcyclopropane (E-**31**)*

bp 127 °C; n^{20}_D 1.3522; d^{20}_4 1.322; IR $\nu(cm^{-1})$ 1735 (C=O); ^1H NMR δ=1.10 (t, J=7.4 Hz, CH_3), 1.4 - 1.7 (m, $CHCF_3$), 1.9 - 2.4 (m, ring CH_2), 2.73 (q, J=7.4 Hz, CH_2); ^{19}F NMR δ_F=11.8 (s), 16.3 (d, J=6.0 Hz); MS *m/z* 234 (M^+). Found: C, 40.99; H, 3.47%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

*r-1,c-2-Bis(trifluoromethyl)-1-propionylcyclopropane (Z-**31**)*

bp 135 °C; n^{20}_D 1.3590; d^{20}_4 1.357; IR $\nu(cm^{-1})$ 1723 (C=O); ^1H NMR δ=1.09 (t, J=7.5 Hz, CH_3), 1.3 - 2.5 (m, $CHCF_3$), 1.86 (br s, ring CH_2), 2.87 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ_F=18.7 (d, J=4.6 Hz), 18.7 (s); MS *m/z* 234 (M^+). Found: C, 40.95; H, 3.53%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

*3,4-Bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**32**)*

bp 137 °C; n^{20}_D 1.3628; d^{20}_4 1.338; IR $\nu(cm^{-1})$ 1674 (C=C); ^1H NMR δ=1.14 (t, J=7.0 Hz, CH_3), 2.40 (q, J=7.0 Hz, CH_2), 3.5 - 3.9 (m, $CHCF_3$), 4.39 (br s, ring CH_2), 4.54 (br s, ring CH_2); ^{19}F NMR δ_F=5.1 (dq, J=7.3 and 4.8 Hz), 21.8 (q, J=4.8 Hz). Found: C, 40.52; H, 3.34%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

*4,5-Bis(trifluoromethyl)-1-hexen-3-one (**33**)*

bp 130 °C; n^{20}_D 1.3525; IR $\nu(cm^{-1})$ 1743 (C=O), 1662 (C=C); ^1H NMR δ=1.10 (t, J=7.2 Hz, CH_3), 2.56 (q, J=7.2 Hz, CH_2), 4.05 (q, J=8.2 Hz, $CHCF_3$), 6.03 (s, CH), 6.13 (s, CH); ^{19}F NMR δ_F=9.0 (s), 12.2 (d, J=8.2 Hz).

CHAPTER 4

SYNTHESIS AND POLYMERIZATION OF TRIFLUOROMETHYLATED ETHYNYLAROMATIC COMPOUNDS

Introduction to Chapter 4

Polyacetylenes have unique properties caused by alternating double bonds along the main chain. Highly conjugated π-electron system with a polyene structure is responsible to electrical conductivity, paramagnetism, and colors. These compounds are practicable for electronic materials: some compounds display the properties of semiconductors or of 'organic metals' by doping with iodine or alkali metals. The polyene structure also has chain stiffness and geometrical isomerism because of obstructing free rotation of the main chain. This specific structure contributes to the high solubility of substituted polyacetylenes: these functions of substituted polyacetylenes might be applied to oxygen enrichment of air, separation of ethanol-water mixtures, and so on. Accordingly, synthesis and properties of polyacetylenes have been investigated intensively.

Polyacetylenes are sensitive to various reagents, such as oxygen, because of high π-electron density of the main chain. Introduction of trifluoromethylated heteroaromatic and aromatic rings into side chain is expected to improve the stability and/or properties of polyacetylenes, owing to the electronegativity of fluorine atom and the bulkiness of substituents. This chapter describes substituted polyacetylenes containing trifluoromethylated heteroaromatic and aromatic ring, and the substituent effects on synthesis and polymerization of the trifluoromethylated ethynylaromatic compounds and on properties of polymers obtained were examined.

4.1 Synthesis and Polymerization of Trifluoromethylated Ethynylthiophenes and Ethynylfurans

Summary

Fluorination of thiophenedicarboxylic acid with sulfur tetrafluoride in the presence of anhydrous hydrogen fluoride provided mono and bis(trifluoromethyl)thiophenes in moderate yields. Ethynylthiophenes and ethynylfurans containing trifluoromethyl groups were prepared *via* 2,2-dichloro-1-fluorovinyl compounds. In polymerizations using transition metal catalysts, 3-ethynylthiophenes gave polymers in high yields, which were soluble in THF and/or fluorocompounds, while 2-ethynylthiophenes polymerized in low yields. In γ-ray induced polymerization, only 2,5-bis(trifluoromethyl)-3-ethynylthiophene afforded the corresponding polymers. Thermal decomposition temperatures of polymers obtained increased by introduction of the trifluoromethyl groups as well as the methyl groups.

Introduction

Polymers containing highly conjugated systems, such as polyacetylenes and poly(thiophenediyl)s, are of interest as potential organic conductors and chromatic materials. Recently both poly(2-ethynylthiophene) and poly(3-ethynylthiophene) proved to work as semiconductors by I_2-doping [88, 89]. Although introduction of trifluoromethyl groups into phenylacetylenes improved the polymerizability and properties of polymers obtained [90, 91], some 2-ethynyl(trifluoromethyl)furans only produced insoluble polymers by thermal polymerization and low molecular weight oligomers by γ-ray induced polymerization [71]. In this section, several ethynylthiophenes and ethynylfurans having trifluoromethyl groups were synthesized, and substituent effects on polymerization and polymer properties were examined.

Results and Discussion

Introduction of Trifluoromethyl Groups into Thiophene

Fluorination of a carboxylic group with sulfur tetrafluoride is a useful method for introduction of the trifluoromethyl group into aromatic rings [92]. The fluorination of 2,5-furandicaboxylic acid (**2b**) with sulfur tetrafluoride provides 2,5-bis(trifluoromethyl)furan (**4b**), but in the presence of anhydrous HF, **4b** is readily converted into 2,5-difluoro-2,5-bis(trifluoromethyl)-2,5-dihydrofuran (**5b**) by addition of fluorine atoms to the ring [69, 93]. The author achieved the reaction of 2,5-thiophene- and -furan-dicarboxylic acid (**2**) with sulfur tetrafluoride and anhydrous HF (Scheme 4.1).

Scheme 4.1

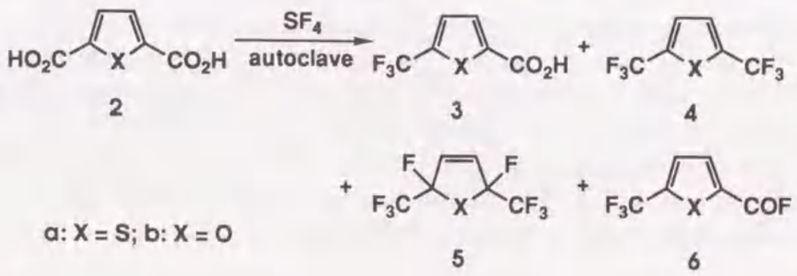


Table 4.1
Fluorination of 2,5-Thiophene- and -Furan-dicarboxylic Acid by Sulfur Tetrafluoride

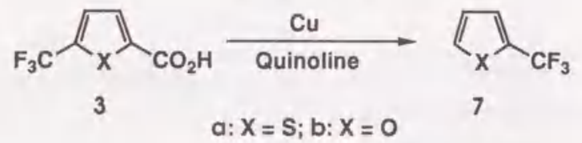
Run No.	X=	SF_4 (eq.)	HF (mL)	Temp. (°C)	Time (h)	Yield (%) 3	4	5	6
1	S	3.5	20	100	20	51.8	10.5	–	–
2	S	5.0	20	130	20	–	69.2	–	–
3	O	3.5	8	100	20	37.8	5.1 [a]	3.6 [a]	9.9 [a]
4	O	5.0	8	130	20	–	–	24.0	–
5	O	5.0	–	100	48	3.8	53.2	–	–

[a] Calculated from GLC, and others represent isolated yields.

The reaction conditions and yields are shown in Table I. Addition of fluorine atoms to the thiophene ring never occurred at 130 °C even if anhydrous HF was added, and only 2,5-bis(trifluoromethyl)thiophene (**4a**) was obtained in 69% yield (run 2). At lower temperature (100 °C) and SF_4 ratio (3.5 equivalent), 5-trifluoromethyl-2-thiophenecarboxylic acid (**3a**) was obtained in 52% yield (run 1). 2,5-Furandicarboxylic acid (**2b**) provided **5b** or **6b** as by-products regardless of the reaction temperature and SF_4 ratio (run 3). Further fluorination of the ring occurred only on **4b** to give **5b** because of the low aromaticity of the furan ring of **4b** (run 4).

Decarboxylation of **3** offered mono trifluoromethyl compounds (**7**) in 75 - 80% yields (Scheme 4.2).

Scheme 4.2



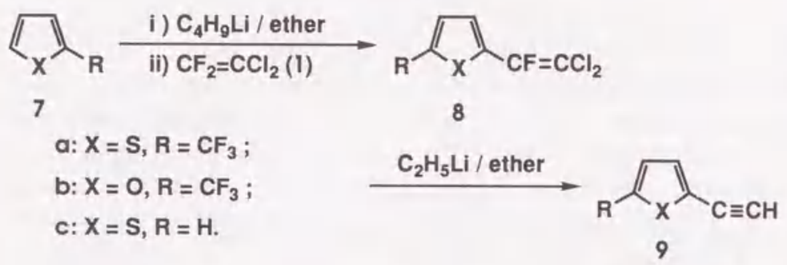
Synthesis of Ethynylthiophenes and Ethynylfurans Containing Trifluoromethyl Groups

As shown in Schemes 4.3 and 4.4, ethynylthiophenes and ethynylfurans were synthesized *via* 2,2-dichloro-1-fluorovinyl intermediates [71, 94].

Both 2-(trifluoromethyl)-thiophene and -furan (**7**) were directly converted to the corresponding lithio compounds without the need to make bromo compounds, and the lithiation occurred only at α-position (5-position).

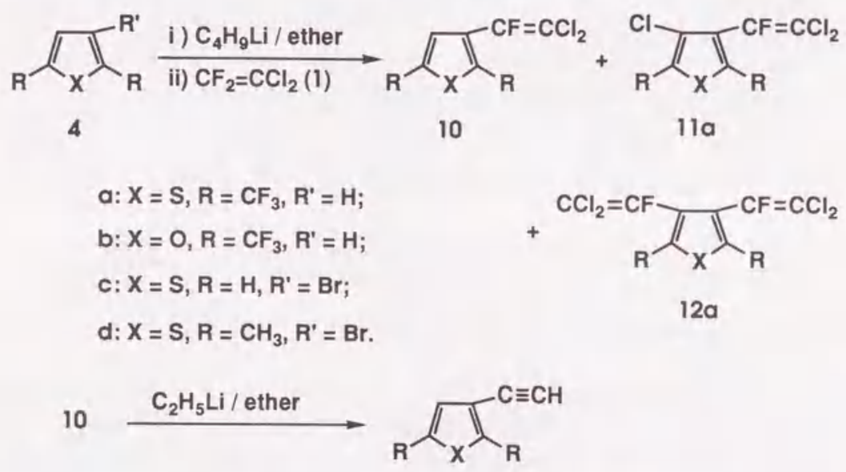
Since the reaction of 2,5-bis(trifluoromethyl)thiophene (**4a**) gave both **11a** and **12a**, an inverse addition method was used to synthesize **10a**.

Scheme 4.3



Reaction of 2,5-bis(trifluoromethyl)furan (**4b**) with *n*-butyllithium gave vinyl compound (**10b**) in quite low yield (7 - 10%) and isolation of pure **10b** was impracticable owing to formation of many by-products, which might arise from the 2,5-addition of *n*-butyllithium to the furan ring of **4b** followed by telomerization. As these side reactions happened for **4b** alone, analogously to the formation of **5b**, they could be explained by the low aromaticity of **4b**.

Scheme 4.4



Polymerization of Ethynylthiophenes and Ethynylfurans

Although polymerizations of substituted acetylenes do not always give higher molecular weight polymers, Masuda *et. al.* have reported efficient transition metal catalysts for converting mono- or disubstituted acetylenes into high molecular weight polyacetylenes [91, 95]. Recently, it was also reported that photochemically activated $W(CO)_6$ in CCl_4 was effective for polymerization of (trifluoromethyl)phenylacetylenes [90]. With reference to these results, polymerization of trifluoromethylated ethynylthiophenes and ethynylfurans was achieved in the following four ways.

A. $W(CO)_6$-CCl_4-light irradiation system
B. WCl_6-Ph_4Sn system
C. $TaCl_5$ system
D. γ-ray induced polymerization

The polymerization conditions, yields and molecular weights are shown in Table 4.2 - 4.5.

Table 4.2
Polymerization by $W(CO)_6$-CCl_4-$h\nu$ (A) [a]

Monomer	$[M]_0$ (mol / L)	$W(CO)_6$ (mol / L)	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)	Mw / Mn
9a	0.23	56.9	0	-	-	-
9b	0.25	56.8	0	-	-	-
9c	0.37	56.8	21	1.9	0.48	3.6
13a	0.16	56.8	85 [c]	1.1	0.73	1.6
13c	0.37	56.8	25	1.2	0.48	2.5
13d	0.29	56.8	90	2.1	1.1	1.9

[a] Polymerized in carbon tetrachloride at 30 °C for 24 h. [b] Weight-average molecular weight (Mw) and number-average molecular weight (Mn) determined by GPC.
[c] Partly soluble in THF.

Poly(**13a**) was totally or partly insoluble in THF, but completely soluble in fluorocompounds such as Freon 113 and *p*-bis(trifluoromethyl)benzene (BTFB). Intrinsic viscosities of the polymers were measured in BTFB (Table 4.6). The viscosities [η] in BTFB varied inversely as the solubilities in THF, and insolubility of poly(**13a**) in THF was considered to be due to high molecular weight of the polymer.

Table 4.3
Polymerization by WCl_6-Ph_4Sn (B) [a]

Monomer	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)	Mw / Mn
9a	0	-	-	-
9b	0	-	-	-
9c	5	0.45	0.21	2.1
13a	96 [c]	-	-	-
13c	89	2.56	1.02	2.5
13d	27	1.66	0.68	2.4

[a] Polymerized in toluene at 30 °C for 24 h: $[M]_0$=0.50 (mol / L); $[WCl_6]_0=[Ph_4Sn]_0$=10 (mol / L). [b] Weight-average molecular weight (Mw) and number-average molecular weight (Mn) determined by GPC. [c] Totally insoluble in THF.

Table 4.4
Polymerization by $TaCl_5$ (C) [a]

Monomer	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)	Mw / Mn
9a	0	-	-	-
9b	0	-	-	-
9c	7.2	0.48	0.21	2.3
13a	0	-	-	-
13c	0	-	-	-
13d	0	-	-	-

[a] Polymerized in toluene at 30 °C for 24 h: $[M]_0$=0.50 (mol / L); $[TaCl_5]_0$=20 (mol / L). [b] Weight-average molecular weight (Mw) and number-average molecular weight (Mn) determined by GPC.

The polymerizations by the tungsten complex (Systems A and B: Tables 4.2 and 4.3) had the same tendency in the yields and molecular weights, but the tantalum complex (System C) was inactive as a polymerization catalyst (Table 4.4). By using tungsten complexes, all 3-ethynylthiophenes synthesized (**13**) gave higher molecular weight polymers (10^4 Mw), while 2-ethynylthiophenes(**9**) except **9c**, formed no polymers. The polymerization of **13** was particularly improved by the introduction of substituents, but in

polymerization of **9**, the trifluoromethyl group reduced polymerizability of ethynylthiophenes.

This difference of polymerizabilities between **9** and **13** may be derived partly from inactivation of catalyst metals by sulfur atoms. Thus the propagating ends of poly(3-ethynylthiophene)s are apart from the sulfur atoms, therefore sulfur does not seem to react as a catalytic poison.

In γ-ray induced polymerization (System D: Table 4.5), **13a**, which has two trifluoromethyl groups, only gave high molecular weight polymer, while other acetylenes synthesized gave no polymers.

Table 4.5
γ-Ray Induced Polymerization (D) [a]

Monomer	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)	Mw / Mn
9a	0	-	-	-
9b	0	-	-	-
9c	3.0	0.14	0.10	1.4
13a	30 [c]	0.88	0.68	1.3
13c	0.9	-	-	-
13d	0.7	-	-	-

[a] Polymerized by γ-ray (Co^{60} 40 Mrad) at ambient temperature. [b] Weight-average molecular weight (Mw) and number-average molecular weight (Mn) determined by GPC. [c] Partly insoluble in THF.

Table 4.6
Intrinsic Viscosities [η] of Poly(**13a**) in BTFB [a] at 30°C

Polymer	$W(CO)_6$-CCl_4 (A)	WCl_6-Ph_4Sn (B)	γ-ray (D)
Soluble part in THF	5%	0%	62%
[η] (dl / g)	0.21	0.52	0.091

[a] All polymers were completely soluble in BTFB.
[BTFB: 1,4-bis(trifluoromethyl)benzene]

Substituent Effects of the Trifluoromethyl Group on the Thermal Stability

In order to examine the substituent effect of the trifluoromethyl group on stability of polymers obtained, thermal gravity analysis was performed. The initiation points of thermal decomposition (Td) of the polymers are indicated in Table 4.7.

Table 4.7
Thermal Decomposition Points of Polymers (°C)

Polymer	$W(CO)_6$-CCl_4 (A)	WCl_6-Ph_4Sn (B)	$TaCl_5$ (C)	γ-ray (D)
Poly(**9c**)	229	211	199	-
Poly(**13a**)	278	287	-	282
Poly(**13c**)	215	261	-	-
Poly(**13d**)	292	301	-	-

Td values of polyacetylenes from substituted 3-ethynylthiophenes increased in the following order, **13c<<13d=13a**, and the weight losses decreased, **13c<13d<13a**, independent of polymerization methods. Introduction of substituents increased Td values regardless of species of substituent. Polyacetylenes having trifluoromethyl groups decomposed more rapidly than those with methyl groups.

4.2 Synthesis and Polymerization of 2,5-Disubstituted Phenylacetylenes Containing Trifluoromethyl Groups

Summary

Four phenylacetylenes (2-R^2-5-R^5-$C_6H_3C{\equiv}CH$: **14a** $R^2{=}R^5{=}CF_3$; **14b** $R^2{=}CF_3$, $R^5{=}CH_3$; **14c** $R^2{=}CH_3$, $R^5{=}CF_3$; **14d** $R^2{=}R^5{=}CH_3$) were synthesized *via* lithio compounds or Grignard reagent. Bromo(methyl)-benzotrifluorides, the precursors for the lithio compounds, were prepared by the fluorination of the corresponding benzoic acids with sulfur tetrafluoride. Polymerization using transition metal catalysts provided polyacetylenes in high yields for all the monomers, while the yields of γ-ray induced polymerization depended on the monomers. The molecular weights of polyacetylenes have a positive correlation with the yields for all the polymerizations. The substituent effects on the molecular weights and thermal stabilities of polymers obtained were discussed.

Introduction

Polyphenylacetylenes having trifluoromethyl groups and polydiphenyldiacetylenes derived from the phenylacetylenes can be used as various functional materials such as resists, electric conductors and nonlinear optical devices [96]. These specific properties arise from the conjugated double-bonds and trifluoromethyl group of the side chain. The trifluoromethyl group causes asymmetric distortion of the conjugated system and intramolecular charge transfer. However, when a conjugated system has both electron attracting and donating groups at opposite ends, the π-electron energy levels are greatly shifted [97, 98]. Hence, it should be significant to study phenylacetylenes containing both electron attracting and donating substituents.

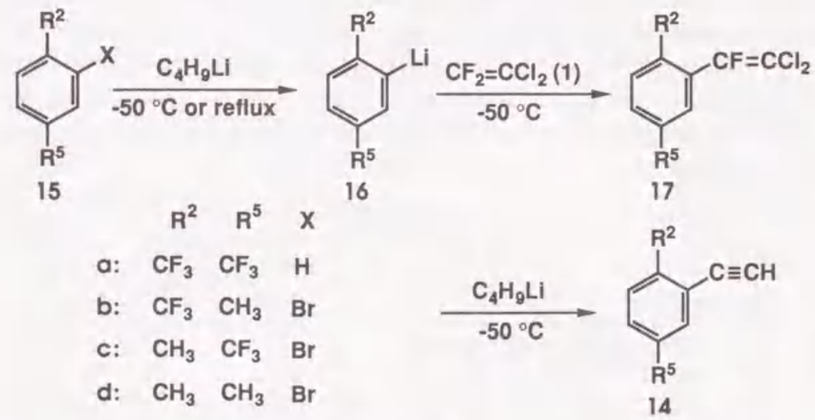
Previously, synthesis and polymerization of various substituted phenylacetylenes containing the trifluoromethyl group have been reported [90, 91], and the author has also described synthesis and polymerization of ethynylthiophenes and ethynylfurans containing trifluoromethyl groups (Chapter 4.1). In all cases of trifluoromethylated arylacetylenes, to the author's knowledge, the position of the substituents was shown to affect greatly the polymerizability and the properties of the polymer. In this section, the author examined the synthesis and polymerization of two interesting acetylenes, [methyl(trifluoromethyl)phenyl]acetylenes (**14b** and **14c**), which have electron attracting and donating substituents at opposite ends. In addition, [2,5-bis(trifluoromethyl)phenyl]acetylene (**14a**) and (2,5-dimethylphenyl)acetylene (**14d**) were also examined in order to compare the polymerizability and the properties of the polymers with those of the [methyl(trifluoromethyl)phenyl]acetylenes.

Results and Discussion

Preparation of Monomer Acetylenes

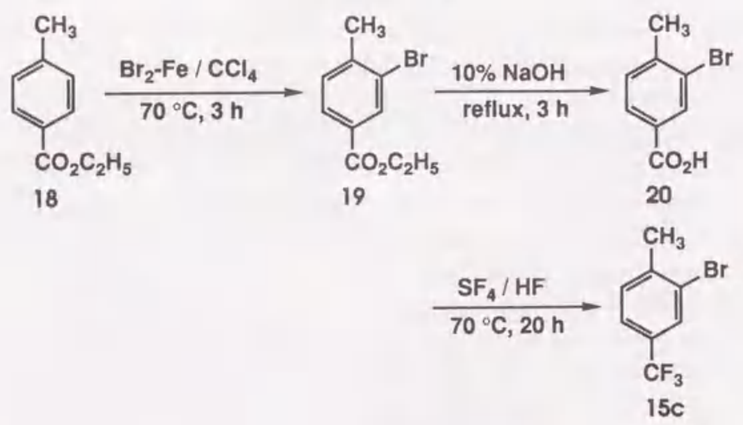
Several phenylacetylenes have been prepared by a route *via* 2,2-dichloro-1-fluorovinylbenzene intermediates [94, 99]. Preparation of [2,5-bis(trifluoromethyl)phenyl]acetylene (**14a**) was carried out according to Scheme 4.5. Other 2,5-disubstituted acetylenes (**14b - d**) were also prepared in a similar manner.

Scheme 4.5



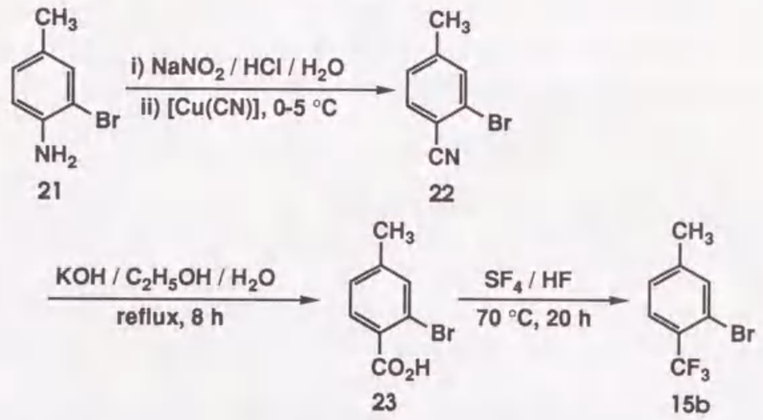
Because of the difficulty of the lithiation of 4-methylbenzotrifluoride, the lithio compound (**16c**) was obtained from 3-bromo-4-methylbenzotrifluoride (**15c**), which was then converted to [2-methyl-5-(trifluoromethyl)phenyl]-acetylene (**14c**) (43% overall yield). The bromide (**15c**) was prepared in 52% yield by the fluorination of 3-bromo-4-methylbenzoic acid (**20**) with sulfur tetrafluoride (Scheme 4.6). Reaction of 4-methylbenzotrifluoride and bromine did not give the bromide (**15c**) but a large quantity of benzoic acid derivatives as by-products due to hydrolysis of the trifluoromethyl group.

Scheme 4.6



[5-Methyl-2-(trifluoromethyl)phenyl]acetylene (**14b**) was prepared in 50% overall yield from 2-bromo-4-methylbenzotrifluoride (**15b**), and **15b** was prepared as shown in Scheme 4.7. Preparation of 2-bromo-4-methylbenzonitrile (**22**) was carried out by Sandmeyer reaction from 2-bromo-*p*-toluidine (**21**), and the carboxylic acid (**23**) was obtained by the hydrolysis of **22**. The fluorination of **23** with sulfur tetrafluoride provided the benzotrifluoride (**15b**) in 79% yield.

Scheme 4.7



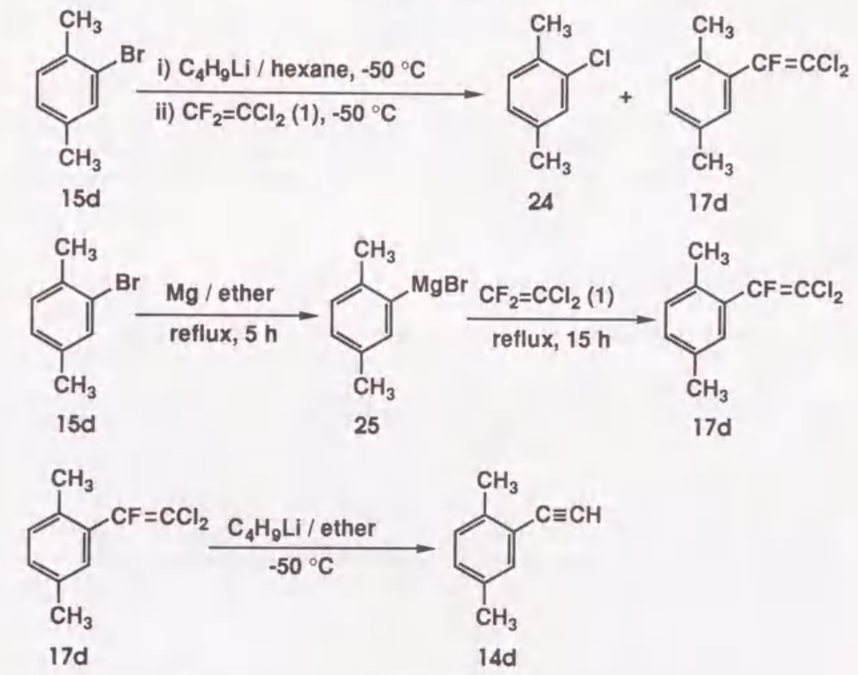
As the fluorination of *p*-toluic acid with sulfur tetrafluoride at 130 °C gave 4-methylbenzotrifluoride in high yield, the author attempted the fluorination of bromo(methyl)benzoic acids (**20** and **23**) under similar conditions, but only a tarry product resulted. By lowering the reaction temperature (70 °C), however, **15b** and **15c** were obtained in moderate yields.

The reaction between the bromides (**15b**, **c**) and butyllithium provided the lithio compounds (**16b**, **c**). The reaction of these lithio compounds (**16**) with CF_2=CCl_2 (**1**) had to be run by the inverse addition method in order to prevent the formation of chloro(methyl)benzotrifluorides caused by the Cl-Li exchange. In the case of 2-bromo-*p*-xylene (**15d**), neither method of addition could prevent the Cl-Li exchange, forming predominantly 2-chloro-*p*-xylene (**17d** : **24**=1 : 3) (Scheme 4.8).

The results are in agreement with Okuhara's proposal that the main determining factor of the proportion of the exchange is the extent of delocalization of the negative charge in the reagent [94]. Therefore, (2,5-dimethylphenyl)acetylene (**14d**) was prepared by the procedure using the

Grignard reagent (**25**) (28% overall yield) (Scheme 4.8). As shown above, the electronegativity of the substituents significantly affected the formation of the lithio compounds (**16**), but their positions hardly influenced the lithiation.

Scheme 4.8



Polymerization of 2,5-Disubstituted Phenylacetylenes

Polymerization of 2,5-disubstituted phenylacetylenes was carried out in a similar manner to trifluoromethylated ethynylthiophenes and ethynylfurans (Chapter 4.1).

A. $W(CO)_6$-CCl_4-light irradiation system
B. WCl_6-Ph_4Sn system
C. $TaCl_5$ system
D. γ-ray induced polymerization

The reaction conditions, yields and molecular weights of the formed polymers are summarized in Table 4.8 - 4.10. The attempts of polymerization using $TaCl_5$ (method C) were unsuccessful.

Table 4.8
Polymerization by $W(CO)_6$-CCl_4-*hv* (A) [a]

Monomer	$[M]_0$ mol / L	$W(CO)_6$ mmol / L	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)
14a	0.20	56.8	92	11.4	8.4
14b	0.22	56.8	92	17.3	11.9
14c	0.22	56.8	100	45.6	29.1
14d	0.30	56.8	95	6.0	2.2

[a] Polymerized in carbon tetrachloride at 30 °C for 24 h. [b] Determined by GPC.

Table 4.9
Polymerization by WCl_6-Ph_4Sn (B) [a]

Monomer	$[M]_0$ mol / L	WCl_6 mmol / L	Ph_4Sn mmol / L	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)
14a	0.68	10	10	96 [c]	-	-
14b	0.75	10	10	67	14.4	9.7
14c	0.73	10	10	100	16.7	9.3
14d	0.70	10	10	100	5.4	2.9

[a] Polymerized in toluene at 30 °C for 24 h. [b] Determined by GPC. [c] Totally insoluble in THF.

For all four monomers, the polymerization using transition metal catalysts (method A and B) offered high molecular weight polymers in high yields (above 90%), but the polymerization of **14a** by method B was considered to give cross linked polymers because it only swelled and was insoluble in organic solvents such as THF. The molecular weights of polymers obtained were found to increase by introduction of trifluoromethyl groups. However, the polymerization of the acetylenes having both trifluoromethyl and methyl groups (**14b** and **14c**), provided larger molecular weight polymers than the acetylene having only trifluoromethyl groups (**14a**) (the molecular weights decreased in the following order, poly(**14c**) > poly(**14b**) > poly(**14a**) > poly(**14d**)). The earlier papers have suggested that the polymerizability of phenylacetylene is improved when the substituent

possesses high electronegativity [90] and steric hindrance [91]. In spite of having the most electronegative and bulky substituents, the polymerization of **14a** did not always offer the highest molecular weight polymer. As the phase separation of the polymerization mixture occurred in the course of the polymerization because of low solubilities of the polymers, the propagation of the polymerization might be suppressed. This result indicates that the solubility of polymer also affects its molecular weight.

Table 4.10
γ-Ray Induced Polymerization (D) [a]

Monomer	Yield (%)	Mw [b] (x 10^4)	Mn [b] (x 10^4)
14a	87 [c]	50.1	45.2
14b	27	2.6	1.3
14c	12	1.1	0.6
14d	5	0.3	0.2

[a] Polymerized by γ-ray (Co^{60} 38 Mrad) at ambient temperature. [b] Determined by GPC. [c] Partly insoluble in THF.

The γ-ray induced polymerization (method D) demonstrated a positive correlation between the yields and molecular weights of polymers obtained. Both of them increased with increasing number of trifluoromethyl groups (poly(**14a**) > poly(**14b**) > poly(**14c**) > poly(**14d**)). The majority of the polymer from **14a** was insoluble in THF. The γ-ray induced polymerization was less effective for the polymerization of other phenylacetylene (**14b** - **d**) and unreacted monomers were mostly recovered. The tendency of polymerization is considered to be due to the efficiency of the irradiation energy of γ-rays. Probably, the electron attraction of trifluoromethyl groups shifts π-electron energy levels of ethynyl groups to lower levels.

Thermogravimetric Analyses of the Polymers

The initiation points of thermal decomposition (Td) of polymers obtained from 2,5-disubstituted phenylacetylenes are indicated in Table 4.11.

In the case of polymers obtained by method A and B, Td values were approximately equal, but slightly higher than those by method D. This is because γ-ray induced polymerization (method D) produced polymers having

more branches than those by methods A and B. Independent of polymerization methods, Td values increased with increasing number of trifluoromethyl groups. The presence of trifluoromethyl groups at the *ortho*-position to the ethynyl group especially raised Td. Hence, Td values seemed to be influenced by both the electron attraction and steric hindrance of the trifluoromethyl group.

Table 4.11
Thermal Decomposition Points of Polymers (°C)

Polymer	$W(CO)_6$-CCl_4 (A)	WCl_6-Ph_4Sn (B)	γ-ray (C)
poly(**14a**)	327	334	311
poly(**14b**)	311	308	300
poly(**14c**)	297	281	265
poly(**14d**)	260	260	224

It has been proposed that the thermal degradation of the polyacetylenes involves the process of formation of biradicals, and the twisted conformation of the main chain obstructs the production of biradicals [100]. The *ortho*-position substituent of a polyphenylacetylene should much more affect the conformation of the main chain in the polymer than substituents in other positions. Therefore, introduction of the trifluoromethyl group at the *ortho*-position relative to the ethynyl group is considered to enhance the Td value of the polymer.

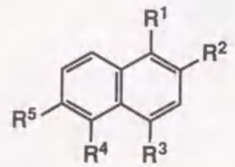
4.3 Synthesis and Polymerization of Some Trifluoromethylated Ethynylnaphthalenes

Summary

Some bromonaphthoic acids were fluorinated with SF_4 to bromo(trifluoromethyl)naphthalenes. Although a reaction of Grignard reagent of one of the bromides with $Cl_2C{=}CF_2$ gave low yield of a (dichlorofluorovinyl)-(trifluoromethyl)naphthalene, lithio derivatives gave the desired ethynyl-(trifluoromethyl)naphthalenes in improved yields after subsequent eliminations of the vinylic halogens with *n*-butyllithium. Polymerization of the acetylenes was carried out with photo-activated $W(CO)_6$ catalyst to yield high molecular weight polymers.

Introduction

The author has reported the synthesis of some trifluoromethylated ethynylaromatic compounds and their polymerizations (Chapter 4.1 and 4.2). This section describes the synthesis of some ethynyl(trifluoromethyl)naphthalenes (**26a - d**) and their polymerization. The preparation of 1-ethynylnaphthalene from Grignard reagent of 1-bromonaphthalene from Grignard reagent of 1-bromonaphthalene with $Cl_2C{=}CF_2$ (**1**) was previously reported [94]. However, some different reactivities were observed in the similar reactions of bromo(trifluoromethyl)naphthalenes (**27a - d**). Photochemically activated $W(CO)_6$ catalysts effected the polymerization of the naphthylacetylenes **26** to high molecular weight polymers.



	26a	26b	26c	26d	27a	27b	27c	27d
R^1	C≡CH	C≡CH	C≡CH	C≡CH	Br	Br	Br	Br
R^2	H	CF_3	H	H	H	CF_3	H	H
R^3	CF_3	H	H	H	CF_3	H	H	H
R^4	H	H	CF_3	H	H	H	CF_3	H
R^5	H	H	H	CF_3	H	H	H	CF_3

Results and Discussion

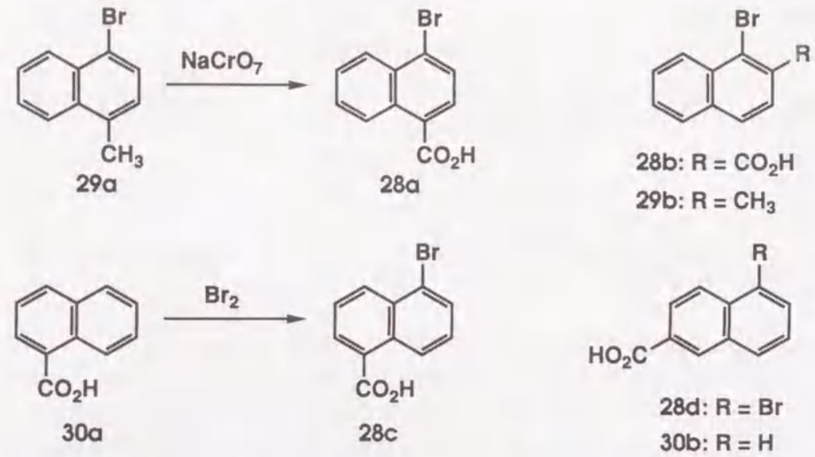
*Preparation of Bromo(trifluoromethyl)naphthalenes (**27**)*

4-Bromo-1-naphthoic acid (**28a**) was prepared from 1-bromo-4-methylnaphthalene (**29a**) [101, 102] by bichromate oxidation in 43% yield. Similarly, 1-bromo-2-naphthoic acid (**28b**) was prepared from 1-bromo-2-methylnaphthalene (**29b**) (31%) [103].

Bromination of 1-naphthoic acid (**30a**) gave only 5-bromo-1-naphthoic acid (**28c**) [104]. However, bromination of 2-naphthoic acid (**30d**) did not

give the pure 5-bromo-2-naphthoic acid (**28d**), probably because of contamination by an isomer brominated at another position, though there were reports that claimed the reaction had given only 5-brominated product [104, 105]. Thus, **28d** had to be purified by successive recrystallizations of its methyl ester followed by alkaline hydrolysis again to **28d** (Scheme 4.9).

Scheme 4.9



Fluorination of these bromonaphthoic acids **28** was carried out by sulfur tetrafluoride in anhydrous hydrogen fluoride at 70 °C for 20 h in an autoclave to afford bromo(trifluoromethyl)naphthalene (**27a - d**) in moderate yields (Scheme 4.10, Table 4.12). Addition of HF lowered the reaction temperature in comparison with the fluorination of nitronaphthoic acids [106]. At a higher reaction temperature, no expected product was isolated from the intractable tar (Table 4.12, **28b**). The methyl ester of **28d** also gave no trifluoride **27d**.

Sheme 4.10

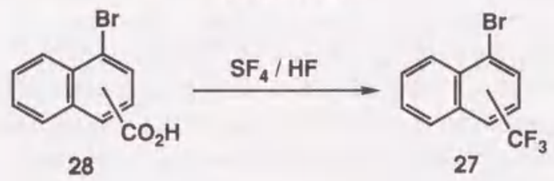


Table 4.12
Fluorination of Bromonaphthoic Acids **28** to Bromo(trifluoromethyl)naphthalenes **27**

Acid	Product	Reaction Temp.	Yield	mp (bp)
28a	**27a**	70 °C	66%	bp; 96 - 98 °C
		90 °C	77%	/ 4 mm Hg
28b	**27b**	70 °C	66%	mp; 61 - 63 °C
		130 °C	– [a]	
28c	**27c**	70 °C	62%	mp; 37 - 38.5 °C
28d	**27d**	50 °C	38%	bp; 106 - 107 °C
		70 °C	48%	/ 5 mm Hg
		80 °C [b]	– [a]	

[a] No identifiable product. [b] Methyl ester of **28d**.

Introduction of Ethynyl Group into Trifluoromethylnaphthalene

In a previous paper [94], the reaction of α-naphthyl magnesium bromide and 1,1-dichloro-2,2-difluoroethylene (**1**) was reported to give good yield of the dichlorofluorovinylated product in spite of the lower yield of the similar reaction of the olefin **1** and α-naphthyllithium. However, the Grignard reagent of trifluoromethyl derivative **27a** afforded the corresponding substitution product **31a** in low yield (15%) due to an unexpected coupling reaction to the binaphthyl **32** (26%) (Scheme 4.11). This change of the reactivity was probably caused by the introduction of an electron-withdrawing trifluoromethyl group. A more suitable reaction which gave higher yields and selectivity was lithiation with *n*-butyllithium (diethyl ether solution) in ether at -70 °C and subsequent slow addition of dichlorodifluoroethylene **1** at the same temperature. In this way, bromo(trifluoromethyl)naphthalenes **27** were converted to the acetylene precursors **31** although the by-products, (trifluoromethyl)naphthalenes **33** and chloro(trifluoromethyl)naphthalenes **34**, were not separable (**31** : **33** : **34** = 9 : 1 : 1) (Scheme 4.11). The reaction times were similar (1 h at -70 °C) in each case except for **27b** which required a longer time (2 h at -70 °C) because the reactivity was decreased by steric hindrance. Higher reaction temperature or use of *n*-butyllithium in *n*-hexane solution causes the decrease of the selectivity due to increase in

the ratio of the halogen exchange products **34** and the protonated (trifluoromethyl)naphthalenes **33**.

Conversion of these precursor olefins **31** to acetylenes **26** was performed by treatment of the resulting products mixtures with 2-molar amounts of *n*-butyllithium (*n*-hexane solution) in ether at -70 °C, the reaction mixtures being separated by preparative HPLC (SiO_2, *n*-hexane). Yields of the acetylenes **26** were 47 - 69% from the corresponding bromides **27** (Table 4.13).

Scheme 4.11

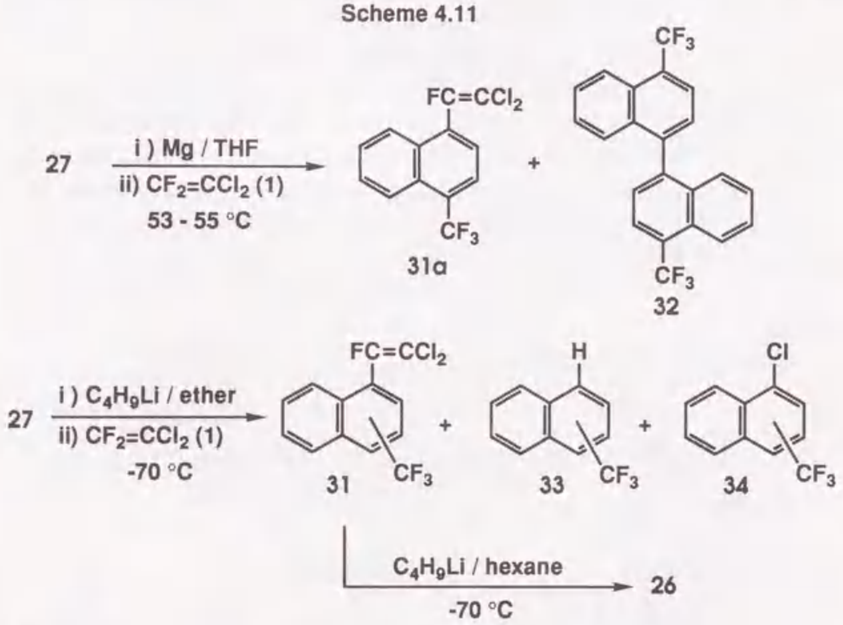


Table 4.13
Conversion of Bromo(trifluoromethyl)naphthalenes **27** to Ethynyl(trifluoromethyl)-naphthalenes **26**

Bromide	Acetylene	Yield	^{1}H NMR (CCl_4)
27a	**26a**	48%	3.49 (s, 1H), 7.4 - 8.6 (m, 6H)
27b	**26b**	47%	3.70 (s, 1H), 7.4 - 8.5 (m, 6H)
27c	**26c**	60%	3.34 (s, 1H), 7.1 - 8.6 (m, 6H)
27d	**26d**	69%	3.36 (s, 1H), 7.2 - 8.5 (m, 6H)

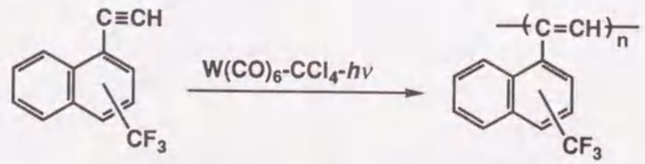
Polymerization of the Acetylenes **26**

Polymerization of the (trifluoromethyl)naphthylacetylenes **26** was carried out with $W(CO)_6$-CCl_4-*hν* system (method A). For comparison, α-naphthylacetylene was also polymerized under the same conditions. In Table 4.14, the reaction conditions, yields and molecular weights of the formed polymers are summarized.

Yields of polymerization of the naphthylacetylene monomers were more than 90% at appropriate monomer and catalyst concentration except for monomer **26b**, which gave no polymer under the given reaction conditions. The decrease of the polymerizability of **26b** was affected by the steric hindrance of the two *ortho*-position substituents. Such reduced polymerizability was also observed in the case of 2,6-bis(trifluoromethyl)phenylacetylene. It has been reported that the steric effects of the monomer acetylenes prevents their cyclotrimerization to give benzene derivatives [95]. However, there seems to be a limitation of bulkiness of the monomers which polymerize with the transition metal catalysts.

Table 4.14

Polymerization of Ethynylnaphthalene **26**



Monomer	$[M]_0$ mol / L	$W(CO)_6$ mmol / L	Yield (%)	*Mw* (x 10^4)	*Mn* (x 10^4)
1-ethynyl-naphthalene	0.67	60	96	3.94	1.21
26a	0.33	60	100	10.8	3.26
26b	0.30	60	0	-	-
26c	1.09	60	77	4.63	2.02
	0.49	60	97	3.02	1.17
	0.065	60	44	3.51	0.99
	0.49	6	12	18.1	6.69
26d	0.55	60	93	14.7	4.25

Molecular weight of the polymer is a function of the monomer as shown in Table 4.14. Especially, the naphthylacetylenes with a trifluoromethyl group tend to afford polymers which have similar or higher molecular weight than the parent naphthylacetylene. Similar results were observed in the polymerization of (trifluoromethyl)phenylacetylene and the parent phenylacetylene [90, 96]. In the polymerization of **26c**, it was observed that the molecular weight increased with increasing monomer concentration and with decreasing catalyst concentration. Similar results were obtained in the polymerization of *o*-(trifluoromethyl)phenylacetylene [90]. Thermal stabilities of the fluorinated polymers were all comparable to the parent polynaphthylacetylene (decomposition temperature; Td= 291 - 344 °C in air or N_2) and the apparent effect of introduction of trifluoromethyl group was not found; see experimental.

As described above, some novel ethynyl(trifluoromethyl)naphthalenes were prepared from the corresponding bromonaphthoic acids and polymerized with $W(CO)_6$ catalyst to high molecular weight polymers except for the sterically hindered 2-trifluoromethyl derivative **26b**.

EXPERIMENTAL

Analytical Methods and Instrumentation

All boiling and melting points are uncorrected. IR spectra were obtained on a Jasco IR-810 infrared spectrophotometer. ^{1}H NMR spectra were measured on Hitachi R-90H (90 MHz) and R-22 (90 MHz) instruments. ^{19}F NMR spectra were measured on Hitachi R-90F (84.68 MHz) and R-20B (56.45 MHz) instruments. The chemical shifts are defined as the δ values referenced to TMS (internal) or CF_3CO_2H (external), respectively. Mass spectra were obtained on a Hitachi M-80 instrument (EI 20 eV). GC-Mass spectra were obtained on a Shimadzu GC-MS 7000 instrument (EI 70 eV, column; 2 m column packed with silicone OV-17). Elemental analyses were recorded on a Perkin-Elmer 240B analyzer. The molecular weights of polymers were estimated with a Jasco Trirotar liquid chromatograph (eluent: THF; column: Shodex A80M), and the calibration curve for polystyrene was used to calculate the molecular weights. Thermal gravity analyses were performed on a Seiko I & E SSC/580 II instrument.

Materials

Ethereal solutions of an alkyllithium were prepared from corresponding alkylbromides and lithium metal in anhydrous diethyl ether. 1,1-Dichloro-2,2-difluoroethylene (**1**) was prepared by isomerization of 1,2-difluoro-1,1,2,2-tetrachloroethane (Freon 112) and subsequent dehalogenation [94]. 2,5-Thiophenedicarboxylic acid (**2a**) were prepared by oxidation of 2,5-bis(hydroxymethyl)thiophene, which was prepared from 2,5-bis(chloromethyl)thiophene [107]. 2,5-Furandicarboxylic acid (**2b**) was obtained by dehydration and cyclization of mucic acid [108]. 2-Ethynylthiophene (**9c**) [94], 3-ethynylthiophene (**13c**) [89], and bis(trifluoromethyl)phenyl]acetylene (**14a**) [99] were prepared as described in the previous papers, respectively. Other reagents were all commercially obtained, and used without further purification. The reactions using alkyllithiums, Grignard reagents, and the transition metal catalysts were carried out under an argon atmosphere.

Synthesis of Trifluoromethylated Ethynylthiophenes and Ethynylfurans

*Fluorination of 2,5-Thiophenedicarboxylic Acid (**2a**) by Sulfur Tetrafluoride in the Presence of Hydrogen Fluoride*

A mixture of 2,5-thiophenedicarboxylic acid (**2a**) (21.1 g, 0.123 mol) and anhydrous hydrogen fluoride (20 mL) was placed in a 100 mL autoclave made of Hastelloy C. Into the autoclave cooled by liquid nitrogen, sulfur tetrafluoride (45.9 g, 0.425 mol) was added under reduced pressure, and then the autoclave was heated at 100 °C for 20 h. After the autoclave was cooled to ambient temperature, gaseous products were released. The residual contents was poured into a mixture of ice and diethyl ether. The ether layer was separated and washed with 10% KOH solutions, and was dried over anhydrous Na_2SO_4. The ether solution was evaporated, and distilled to yield 2,5-bis(trifluoromethyl)thiophene (**4a**) (2.84 g, 10.5%).

In the alkaline water layer, remained 5-trifluoromethyl-2-thiophenecarboxylic acid (**3a**). The KOH aqueous solution extracts combined were heated at 70 - 80 °C with activated carbon, and then the precipitate was filtered off. As the filtrate was acidified again by conc. HCl, a white precipitate was formed, and was collected. Crude precipitate was recrystallized from hot hexane to yield **3a** (12.5 g, 51.8%).

*2,5-Bis(trifluoromethyl)thiophene (**4a**)*

bp 94 °C; ^{1}H NMR δ ($CDCl_3$)=7.49 (s, ring); ^{19}F NMR δ_F ($CDCl_3$)=22.5 (s); MS *m/z* 220 (84, M^+), 201 (100, M^+-F), 170 (43, M^+-CF_2), 151 (87, M^+-CF_3). Found: C, 33.03; H, 0.82%. Calcd for $C_6H_2SF_6$: C, 32.74; H, 0.92%.

*5-Trifluoromethyl-2-thiophenecarboxylic Acid (**3a**)*

mp 79 °C; ^{1}H NMR δ ($CDCl_3$)=7.45 (m, ring), 7.84 (m, ring), 11.23 (br s, CO_2H); ^{19}F NMR δ_F ($CDCl_3$)=22.3 (s). Found: C, 36.92; H, 1.41%. Calcd for $C_6H_3O_2SF_3$: C, 36.74; H, 1.54%.

*Fluorination of 2,5-Furandicarboxylic Acid (**2b**) by Sulfur Tetrafluoride in the Presence of Hydrogen Fluoride*

The following products were obtained from **2b** in a similar procedure as above.

*2,5-Bis(trifluoromethyl)furan (**4b**)*

bp 63 °C (Lit., 70.5 - 71 °C [69]); ^{1}H NMR δ ($CDCl_3$)=7.41 (s, ring); ^{19}F NMR δ_F ($CDCl_3$)=22.5 (s); MS *m/z* 204 (3, M^+), 172 (100, M^+-H-CF), 154 (35, M^+-CF_2).

*5-Trifluoromethyl-2-thiophenecarboxylic acid (**3b**)*

mp 115 °C (sublimed) (Lit., 118 - 119 °C [69]); Found: C, 40.29; H, 1.39%. Calcd for $C_6H_3O_3F_3$: C, 40.02; H, 1.68%.

*2,5-Difluoro-2,5-bis(trifluoromethyl)-2,5-dihydrofuran (**5b**) (cis trans mixture)*

bp 80 °C (Lit., 87.5 °C [93]); ^{1}H NMR δ ($CDCl_3$)=6.57 (s, ring); ^{19}F NMR δ_F ($CDCl_3$)=-4.22 (s, CF_3), -4.22 (s, CF_3), -34.3 (s, F), -42.5 (s, F); MS *m/z* 223 (9, M^+), 203 (5, M^+-2F-H), 195 (5, M^+-F-CO), 173 (100, M^+-CF_3).

*2-Trifluoromethylthiophene (**7a**)*

To a solution of recrystallized **3a** (12.0 g, 0.061 mol) in quinoline (25 mL), was added copper powder (1.7 g, 0.27 g-atom), and heated up to 190 - 200 °C. The reaction mixture turned black at about 120 °C, and then colorless liquid was distilled accompanying the evolution of carbon dioxide above 180 °C. The fractional distillation of the liquid product yielded **7a** (6.2 g, 67%).

bp 95 °C; ^{1}H NMR δ ($CDCl_3$)=7.02 (m, ring), 7.39 (m, ring); ^{19}F NMR δ_F ($CDCl_3$)=19.4 (s, CF_3); MS *m/z* 152 (100, M^+), 133 (97, M^+-F), 102 (50, M^+-CF_2). Found: C, 39.60; H, 1.76%. Calcd for $C_5H_3SF_3$: C, 39.47; H, 1.99%. (Lit. [109])

*2-Trifluoromethylfuran (**7b**)*

By a similar procedure to **7a**, **7b** was obtained in 78% yield from **3b**.

bp 50 °C (Lit., 58 °C [69]); ^{1}H NMR δ ($CDCl_3$)=6.44 (br s), 6.75 (br s), 7.48 (s); ^{19}F NMR δ_F ($CDCl_3$)=14.0 (s, CF_3); MS *m/z* 136 (100, M^+), 117 (45, M^+-F).

*2-(2',2'-Dichloro-1'-fluorovinyl)-5-trifluoromethylthiophene (**8a**)*

To a stirred solution of 2-trifluoromethylthiophene (**7a**) (10.0 g, 0.066 mol) in anhydrous diethyl ether (25 mL), cooled at -50 °C by a dry ice-ethanol bath, was added ethereal *n*-butyllithium (43 mL, 0.068 mmol). After the reaction mixture was stirred for 2 h at -50 °C, 1,1-dichloro-2,2-difluoroethylene (**1**) (13 g, 0.098 mol) was added dropwise into the solution, whilst maintaining the reaction temperature below -55 °C. The reaction mixture was stirred for an additional 1 h, and then was poured into a mixture of conc. HCl and crushed ice, and extracted with ether. The extract was washed with aqueous $NaHCO_3$ solution and water, and dried over anhydrous Na_2SO_4. After the ether layer was evaporated, the residual liquid was distilled to yield **8a** (10.9 g, 62%).

bp 108 °C/ 30 mmHg; ^{1}H NMR δ ($CDCl_3$)=7.41 (br s, ring); ^{19}F NMR δ_F ($CDCl_3$)=22.9 (s, CF_3), -22.3 (s, F); MS *m/z* 268, 266, 264 (100, M^+). Found: C, 31.41; H, 0.56%. Calcd for $C_7H_2SF_4Cl_2$: C, 31.72; H, 0.56%.

*2-(2',2'-Dichloro-1'-fluorovinyl)-5-trifluoromethylfuran (**8b**)*

By a similar procedure to **8a**, **8b** was obtained in 78% yield from **7b**.

bp 90 °C/ 40 mmHg; ^{1}H NMR δ ($CDCl_3$)=6.87 (br s, ring); ^{19}F NMR δ_F ($CDCl_3$)=13.9 (s, CF_3), -35.1 (s, F); MS *m/z* 250, 248 (100, M^+), 231, 229 (13, M^+-F), 153, 151 (89, M^+-CF_2). Found: C, 33.85; H, 0.64%. Calcd for $C_7H_2OF_4$: C, 33.78; H, 0.81%.

*2,5-Bis(trifluoromethyl)-3-(2',2'-dichloro-1'-fluorovinyl)thiophene (**10a**) (inverse addition method)*

To a solution of **4a** (22.9 g, 0.104 mol) in anhydrous diethyl ether (30 mL) cooled below -55 °C, was added ethereal *n*-butyllithium (95 mL, 0.149 mol). Then the reaction mixture was stirred at -30 °C for 2 h, and was dropped into **1** (84 g, 0.63 mol) in an another flask by the inverse addition method, whilst maintaining the temperature below -50 °C. The reaction mixture was poured into an aqueous HCl solution, and then the ether layer was separated, washed with aqueous $NaHCO_3$ solution and water. GC and GC-MS analyses of the ether layer showed three products (**10a** : **11a** : **12a** = 25 : 1.4 : 1). The main product **10a** was isolated by fractional distillation in 39% yield.

bp 88 °C/ 30 mmHg; ^{1}H NMR δ($CDCl_3$)=7.65 (t, J=1.1 Hz, ring); ^{19}F NMR δ_F ($CDCl_3$)=22.9 (d, J=13 Hz, CF_3), 21.9 (s, CF_3), -13.1 (q, J=11 Hz, F); MS *m/z* 336, 334, 332 (78, M^+), 317, 315, 313 (21, M^+-F), 299, 297 (100, M^+-Cl), 262 (28, M^+-2Cl). Found: C, 28.94; H, 0.26%. Calcd for $C_8HSF_7Cl_2$: C, 28.85; H, 0.30%.

2,5-Bis(trifluoromethyl)-3-chloro-4-(2',2'-dichloro-1'-fluorovinyl)thiophene (**11a**)

MS *m/z* 370, 368, 366 (100, M^+), 349, 347 (15, M^+-F), 333, 331 (30, M^+-2Cl).

*3,4-Bis(2',2'-dichloro-1'-fluorovinyl)-2,5-bis(trifluoromethyl)thiophene (**12a**)*

MS *m/z* 414, 412, 410 (34, M^+), 377, 375 (24, M^+-Cl), 342, 340 (48, M^+-2Cl), 307, 305 (100, M^+-3Cl).

*2,5-Dimethyl-3-(2',2'-dichloro-1'-fluorovinyl)thiophene (**10d**)*

To a solution of 2,5-dimethyl-3-bromothiophene (**4d**) (18.2 g, 0.095 mol) in anhydrous diethyl ether (50 mL) cooled at -30 °C, was added ethereal *n*-butyllithium (65 mL, 0.103 mol). After stirring for 1 h, **1** (21 g, 0.16 mol) was dropped into the reaction mixture below -50 °C. The reaction mixture was treated using the above mentioned procedure to give **10d** (13.5 g, 63%).

bp 100 °C/ 8 mmHg; ^{1}H NMR δ ($CDCl_3$)=2.38 (s, CH_3), 2.41 (s, CH_3), 6.71 (br s, ring); ^{19}F NMR δ_F ($CDCl_3$)=-11.9 (q, J=11 Hz, F); MS *m/z* 228, 226, 224 (82, M^+), 211, 209 (9, M^+-CH_3), 191, 189 (100, M^+-Cl), 154 (39, M^+-2Cl), 153 (30, M^+-2Cl-H). Found: C, 42.63; H, 3.05%. Calcd for $C_8H_7SFCl_2$: C, 42.68; H, 3.13%.

*2-Ethynyl-5-trifluoromethylthiophene (**9a**)*

To a solution of **8a** (12.9 g, 0.049 mol) in anhydrous diethyl ether (25 mL) cooled below -55 °C, was added ethereal ethyllithium (80 mL, 0.113 mol). The reaction mixture was stirred for 30 min, and then was poured into ice-water acidified with conc. HCl. The ether layer was separated, washed with aq. $NaHCO_3$ solution and water. The ether layer was dried over Na_2SO_4, and distilled to yield **9a** (5.5 g, 62%).

bp 70 °C/ 90 mmHg; ^{1}H NMR δ ($CDCl_3$)=3.40 (s, C≡CH), 7.23 (br s, ring), 7.25 (br s, ring); ^{19}F NMR δ_F ($CDCl_3$)=22.9 (s, CF_3); MS *m/z* 176 (100, M^+), 157 (33, M^+-F), 126 (32, M^+-CF_2). Found: C, 47.69; H, 1.63%. Calcd for $C_7H_3SF_3$: C, 47.72; H, 1.72%.

The following acetylenes were synthesized from corresponding vinyl compounds by a similar procedure to that for **9a**.

*2-Ethynyl-5-trifluoromethylfuran (**9b**)*

Yield 64%; bp 82 °C; ^{1}H NMR δ ($CDCl_3$)=3.42 (s, C≡CH), 6.63 - 6.75 (m, ring); ^{19}F NMR δ_F ($CDCl_3$)=14.3 (s, CF_3); MS *m/z* 160 (100, M^+), 141 (19, M^+-F), 110 (13, M^+-CF_2). Found: C, 52.74; H, 1.80%. Calcd for $C_7H_3OF_3$: C, 52.52; H, 1.89%.

*2,5-Bis(trifluoromethyl)-3-ethynylthiophene (**13a**)*

Yield 64%; bp 73 °C/ 100 mmHg; ^{1}H NMR δ ($CDCl_3$)=3.36 (s, C ≡CH), 7.47 (br s, ring); ^{19}F NMR δ_F ($CDCl_3$)=21.9 (s, CF_3), 21.7 (s, CF_3); MS *m/z* 244 (100, M^+), 225 (56, M^+-F), 194 (19, M^+-CF_2), 175 (80, M^+-CF_3). Found: C, 39.11; H, 0.72%. Calcd for $C_8H_2SF_6$: C, 39.35; H, 0.83%.

*2,5-Dimethyl-3-ethynylthiophene (**13d**)*

Yield 43%; bp 68 °C/ 12 mmHg; ^{1}H NMR δ ($CDCl_3$)=2.35 (s, CH_3), 2.45 (s, CH_3), 3.09 (s, C ≡CH), 6.60 (br d, ring); MS *m/z* 136 (100, M^+), 135 (75, M^+-H), 121 (36, M^+-CH_3). Found: C, 70.57; H, 5.70%. Calcd for C_8H_8S: C, 70.54; H, 5.92%.

*Reaction of 2,5-Bis(trifluoromethyl)furan (**4b**) with n-Butyllithium and 1,1-dichloro-2,2-difluoroethylene (**1**)*

To a solution of **4b** (20.0 g, 0.098 mol) in anhydrous diethyl ether (50 mL) was added ethereal *n*-butyllithium (85 mL, 0.587 mol) below -55 °C, and then the reaction mixture was dropped into **1** (78.0 g, 0.587 mol) by the inverse addition method, maintaining the reaction temperature below -50 °C. The reaction mixture was poured into an aqueous HCl solution, and then the ether layer was separated, washed with aqueous $NaHCO_3$ and water. The ether layer was dried over Na_2SO_4, distilled to remove ether. GC and GC-MS analyses of the residue showed many by-products, therefore the desired product **10b** (2.29 g, 7.36% GC calculated) could not be isolated by fractional distillation.

*2,5-Bis(trifluoromethyl)-3-(2',2'-dichloro-1',1'-fluorovinyl)furan (**10b**)*

MS *m/z* 320, 318, 316 (100, M^+), 299, 297 (24, M^+-F), 283, 281 (60, M^+-Cl).

Synthesis of 2,5-Disubstituted Phenylacetylenes Containing Trifluoromethyl Groups

*3-Bromo-4-methylbenzoic acid (**20**)*

To a mixture of ethyl 4-methylbenzoate (**18**) (61.1 g, 0.372 mol) and iron powder (1.20 g, 0.022 g-atom) in CCl_4 (100 mL), was added a solution of bromine (63.3 g, 0.408 mol) in CCl_4 (43 mL), and then stirring was continued for 3 h at 70 - 75 °C. The reaction mixture was cooled and poured into a $NaHSO_3$ solution. The organic layer was separated and evaporated. To the residue, was added an aqueous 10% NaOH solution (200 mL), which was refluxed for 3 h. After cooling, the solid material was filtered off, and the filtrate was acidified with conc. HCl. Formed precipitates were collected and recrystallized from ethanol to yield 3-bromo-4-methylbenzoic acid (**20**) (34.6 g, 43%).

mp 204 - 206 °C (Lit., 203 - 204 °C [110]); MS *m/z* 216, 214 (100, M^+), 199, 197 (33, M^+-OH), 171, 169 (29, M^+-CO_2H), 135 (25, M^+-Br).

*2-Bromo-4-methylbenzonitrile (**22**)*

To a suspension of 2-bromo-4-methylaniline (**21**) (51.4 g, 0.276 mol) in 5 N HCl (150 mL), was added with stirring an aqueous solution of $NaNO_2$ (14.2 g, 0.203 mol) at 0 - 5 °C, and stirring was continued for 2 h. The reaction mixture was neutralized with Na_2CO_3, and then was added a suspension of copper cyanide (83.3 g, 0.522 mol) in water (70 mL) and toluene (200 mL) at 0 - 5 °C. The reaction mixture was stirred for 30 min further, and then for an additional 2 h at room temperature. The toluene layer was separated, and was then steam distilled. After removal of toluene, the residual material was recrystallized from ethanol to yield 2-bromo-4-methylbenzonitrile (**22**) (26.0 g, 48%).

IR ν(cm^{-1}) 2205(C ≡N), 1600, 1490, 1270, 1200, 1050, 1040, 950, 890, 860, 810.

*2-Bromo-4-methylbenzoic acid (**23**)*

A solution of 2-bromo-4-methylbenzonitrile (**22**) (22.5 g, 0.115 mol) in 150 mL of ethanol was added to an aqueous solution (50 mL) of KOH (9.05 g, 0.115 mol), and was heated under refluxing for 8 h. The reaction mixture was evaporated, and the residual aqueous solution was acidified with conc. HCl. The resultant white precipitate was collected. 2-Bromo-4-methylbenzoic acid (**23**) (19.9 g, 81%) was obtained by recrystallization from water-ethanol (2 : 5).

mp 141 °C (Lit., 141 - 142 °C [111]); MS *m/z* 216, 214 (86, M^+), 199, 197 (100, M^+-OH), 171, 169 (20, M^+-CO_2H), 135 (3, M^+-Br).

*3-Bromo-4-methylbenzotrifluoride (**15c**)*

In a 100 mL autoclave made of Hastelloy C, was placed a mixture of 3-bromo-4-methylbenzoic acid (**20**) (20.0 g, 0.093 mol) and anhydrous hydrogen fluoride (20 mL). The autoclave was cooled with liquid nitrogen, and sulfur tetrafluoride (45.5 g, 0.421 mol) was added using a vacuum line. Then the autoclave was heated at 70 °C for 20 h. After cooling the autoclave with water, the contents were poured into ice-water and extracted with ether, and the extract was washed with an aqueous 10% KOH solution. The ether solution was dried over anhydrous Na_2SO_4, and evaporated. The residue was distilled to give 3-bromo-4-methylbenzotrifluoride (**15c**) (23.3 g, 52%).

bp 66 - 67 °C/ 20 mmHg; ^{1}H NMR δ ($CDCl_3$)=2.42 (s, CH_3), 7.22 - 7.39 (AB, 2H), 7.76 (s, 1H) (Lit., δ=2.35 (s, 3H), 7.5 (m, 3H) [112]); ^{19}F NMR, δ_F

($CDCl_3$)=16.0 (s,CF_3); MS *m/z* 240, 238 (86, M^+), 221, 219 (11, M^+-F), 171, 169 (15, M^+-CF_3), 159 (100, M^+-Br). Found: C, 39.92; H, 2.47%. Calcd for $C_8H_6F_3Br$: C, 40.20; H, 2.53%.

*2-Bromo-4-methylbenzotrifluoride (**15b**)*

By a similar procedure to **15c**, 2-bromo-4-methylbenzotrifluoride (**15b**) was obtained in 79% yield from **23**.

bp 80 °C/ 20 mmHg; ^1H NMR, δ ($CDCl_3$)=2.34 (s, CH_3), 7.10 - 7.56 (AB, 2H), 7.48 (s, 1H); ^{19}F NMR, δ_F ($CDCl_3$)=16.5 (s, CF_3); MS *m/z*, 240, 238 (100, M^+), 221, 219 (10, M^+-F), 171, 169 (40, M^+-CF_3), 159 (58, M^+-Br). Found: C, 40.26; H, 2.36%. Calcd for $C_8H_6F_3Br$: C, 40.20; H, 2.53%.

*1-Methyl-4-trifluoromethyl-2-(2',2'-dichloro-1'-fluorovinyl)benzene (**17c**)*

To a solution of 3-bromo-4-methylbenzotrifluoride (**15c**) (18.9 g, 0.079 mol) in anhydrous diethyl ether (50 mL), cooled at -50 °C, was added ethereal *n*-butyllithium (73 mL, 0.116 mol). After stirring for 30 min, the reaction mixture was dropped into a solution of CF_2=CCl_2 (**1**) (31.5 g, 0.237 mol) in anhydrous ether (30 mL) by the inverse addition method, keeping the reaction temperature below -50 °C. The reaction mixture was stirred for an additional 30 min, and then poured into a mixture of conc. HCl and crushed ice. The ether layer was separated, dried and then the solvent was evaporated. The residue was vacuum distilled to yield **17c** (13.1 g, 61%).

bp 96 °C/ 15 mmHg; ^1H NMR δ ($CDCl_3$)=2.42 (s, CH_3), 7.24 - 7.57 (AB, 2H), 7.66 (s, 1H); ^{19}F NMR δ_F ($CDCl_3$)=16.1 (s, CF_3), -10.3 (s, F); MS *m/z* 276, 274, 272 (49, M^+), 239, 237 (33, M^+-Cl), 202 (19, M^+-2Cl), 201 (100, M^+-H-2Cl), 133 (34). Found C, 44.13; H, 2.03%. Calcd for $C_{10}H_6F_4Cl_2$ C, 43.99; H, 2.21%.

*[2-Methyl-5-(trifluoromethyl)phenyl]acetylene (**14c**)*

To a solution of **17c** (10.2 g, 0.020 mol) in anhydrous diethyl ether (40 mL), ethereal *n*-butyllithium (55 mL, 0.086 mol) was added and stirred for 30 min at -50 °C. The reaction mixture was poured into a mixture of conc. HCl and crushed ice. The ether layer was separated, washed with $NaHCO_3$ solution and water. The ether layer was dried over Na_2SO_4, and was distilled to yield **14c** (4.87 g, 71%).

bp 71 °C/ 20 mmHg; ^1H NMR δ ($CDCl_3$)=2.47 (s, CH_3), 3.31 (s, C≡CH), 7.22 - 7.40 (AB, 2H), 7.69 (s, 1H); ^{19}F NMR δ_F ($CDCl_3$)=15.9 (s, CF_3); MS

m/z 184 (100, M^+), 115 (89, M^+-CF_3). Found: C, 64.98; H, 3.53%. Calcd for $C_{10}H_7F_3$: C, 65.22; H, 3.83%.

*1-Methyl-4-trifluoromethyl-3-(2',2'-dichloro-1'-fluorovinyl)benzene (**17b**)*

By a similar procedure to **17c**, **17b** was obtained in 71% yield from **15b**.

bp 107-108 °C/ 27 mmHg; ^1H NMR δ ($CDCl_3$)=2.43 (s, CH_3), 7.35 (s, 1H), 7.23 - 7.69 (AB, 2H); ^{19}F NMR δ_F ($CDCl_3$)=17.3 (d, CF_3), -6.2 (q, F); MS *m/z* 276, 274, 272 (100, M^+), 239, 237 (86, M^+-Cl), 202 (17, M^+-2Cl), 201 (17, M^+-H-2Cl). Found: C, 44.19; H, 2.13%. Calcd for $C_{10}H_6F_4Cl_2$: C, 43.99; H, 2.21%.

*[5-Methyl-2-(trifluoromethyl)phenyl]acetylene (**14b**)*

By a similar procedure to **14c**, **14b** was obtained in 70% yield from **17b**.

bp 80 °C/ 20 mmHg; ^1H NMR δ ($CDCl_3$)=2.32 (s, CH_3), 3.29 (s, C≡CH), 7.41 (s, 1H), 7.12 - 7.54 (AB, 2H); ^{19}F NMR δ_F ($CDCl_3$)=16.8 (s, CF_3); MS *m/z* 184 (52, M^+), 115 (100, M^+-CF_3). Found: C, 65.03; H, 3.64%. Calcd for $C_{10}H_7F_3$: C, 65.22; H, 3.83%.

*1,4-Dimethyl-2-(2',2'-dichloro-1'-fluorovinyl)benzene (**17d**)*
(1) via lithio compound

To a solution of 2-bromo-*p*-xylene (**5d**) (30.2 g, 0.163 mol) in anhydrous diethyl ether (180 mL), was added ethereal *n*-butyllithium (142 mL, 0.228 mol) at -40 to -50 °C. The temperature of the reaction mixture was allowed to rise to 0 °C. After stirring for 1 h, the reaction suspension was added to a solution of CF_2=CCl_2 (**1**) (65.0 g, 0.489 mol) in anhydrous ether (100 mL). After confirmation of complete consumption of the starting material by means of GC analysis, the reaction mixture was poured into an aqueous HCl solution. The ether layer was separated, washed with aqueous $NaHCO_3$ solution and water. GC-Mass analysis of the ether layer showed two products, **17d** and **24**, from which **24** was removed by fractional distillation. There was obtained 3.3 g (9% yield) of **17d**.

(2) via Grignard reagent

To magnesium ribbons (2.73 g, 0.112 g-atom), was added anhydrous diethyl ether (20 mL) with gently stirring by a mechanical stirrer. A small amount of 2-bromo-*p*-xylene diluted in anhydrous ether was added in order to initiate the reaction, and the remainder of the diluted bromide was then added dropwise to maintain refluxing (total amount of bromide: 18.9 g,

0.102 mol). After stirring for 2 h under refluxing, the reaction mixture was poured into an aqueous HCl solution, and was worked up as mentioned above to give **17d** (8.69 g, 39%).

bp 99 °C/ 10 mmHg ; ^{1}H NMR δ ($CDCl_3$)=2.18 (s, CH_3), 2.28 (s, CH_3), 7.11 (s, 2H), 7.15 (s, 1H); ^{19}F NMR δ_F ($CDCl_3$)=-8.32 (s, F); MS *m/z* 220, 218 (60, M^+), 185, 183 (49, M^+-Cl), 147 (100, M^+-H-2Cl), 133 (26, M^+-Cl-CH_3). Found: C, 55.01; H, 4.13%. Calcd for $C_{10}H_9FCl_2$: C, 54.82; H, 4.14%.

*1,4-Dimethyl-2-chlorobenzene (**24**)*

MS *m/z* 142, 140 (58, M^+), 105 (100, M^+-Cl).

*(2,5-Dimethylphenyl)acetylene (**14d**)*

By a similar procedure to **14c**, there was obtained **14d** in 71% yield from **17d**.

bp 90 °C/ 30 mmHg (Lit., 49 °C/ 2 mmHg [113]); ^{1}H NMR δ ($CDCl_3$) =2.25 (s, CH_3), 2.38 (s, CH_3), 3.19 (s, C≡CH), 7.03 (s, 2H), 7.26 (s, 1H); MS *m/z* 130 (88, M^+), 129 (44, M^+-H), 115 (100, M^+-CH_3). Found: C, 92.48; H, 7.56%. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74%.

Synthesis of Some Trifluoromethylated Ethynylnaphthalenes

*4-Bromo-1-naphthoic Acid (**28a**)*

1-Bromo-4-methylnaphthalene (**29a**) (50.0 g, 0.23 mol) was dispersed in aq. $Na_2Cr_7O_7$•$2H_2O$) solution (2.7 M, 150 mL), and the mixture was heated in an autoclave at 250 °C for 20 h (max. 18 atm). The cooled mixture was dissolved with 1000 mL of water and then the mixture was acidified with conc. HCl. The formed precipitates were filtered and dried. Free acid **28a** was recrystallized from acetic acid (24.8 g, 43%): mp 220 - 224 °C (Lit., 217 - 220 °C [101]; 212 °C [102]).

*1-Bromo-2-naphthoic Acid (**28b**)*

Reaction of 1-bromo-2-methylnaphthalene (**29b**) (50.0 g, 0.23 mol) with aq. $Na_2Cr_7O_7$•$2H_2O$ solution (2.7 M, 150 mL) as described above gave acid **28b** (17.9 g, 31%): mp 182 - 186 °C (Lit., 186 °C [103]).

*5-Bromo-1-naphthoic Acid (**28c**)*

Bromination of 1-naphthoic acid (**30a**) was carried out according to Hausmann's procedure [104].

*5-Bromo-2-naphthoic Acid (**28d**)*

Bromination of 2-naphthoic acid (**30b**) (50.0 g, 0.29 mol) did not give pure acid **28d**. The mixture of brominated acids (51.9 g) was dissolved in conc. H_2SO_4 (25 mL) and methanol (500 mL), and the mixture was refluxed for 5 h. The cooled mixture was evaporated under reduced pressure to concentrate to *ca.* 100 mL, and was poured into water (1000 mL). After extraction of the mixture with ether, evaporation of the solvent gave a solid mixture of esters. Successive recrystallizations from methanol afforded pure methyl 5-bromo-2-naphthoate (25.5 g).

mp 73 - 74 °C (Lit., 73 °C [105]); IR ν(cm^{-1}) 1725; ^{1}H NMR δ(CCl_4)=3.92 (s, 3H), 7.2 - 8.5 (m, 6H); MS *m/z* 266 (99, M^++2), 264 (100, M^+).

Methyl 5-bromo-2-naphthoate was dissolved to aq. NaOH solution (2.5 M, 250 mL), and stirred under refluxing for 3 h. The resulting clear solution was acidified with conc. HCl, yielding a precipitate which was filtered off and dried to give pure 5-bromo-2-naphthoic acid (**28d**) (24.0 g, 33% from 2-naphthoic acid **30b**): mp 250 - 255 °C (Lit., 270 °C [105]).

General Procedure for Fluorination of Bromonaphthoic Acids

To a mixture of a bromonaphthoic acid (**28**) (*ca.* 100 mmol) and anhydrous hydrogen fluoride (40 mL) in a 100 mL autoclave made of Hastelloy C under cooling with liquid N_2, SF_4 (43.2 g, 400 mmol) was added under reduced pressure. The reaction vessel was heated at 70 °C for 20 h (maximum pressure; 16 atm). The cooled mixture was poured into ice-water and extracted with ether. The combined extracts were washed with water and aq. KOH solution, dried with Na_2SO_4, and evaporated under reduced pressure to give a residue, which was distilled under reduced pressure (**27a**, **27d**) or recrystallized from ethanol (**27b**, **27c**).

*1-Bromo-4-(trifluoromethyl)naphthalene (**27a**)*

Yield 66%; IR ν(cm^{-1}) 3080, 1573, 1512, 1340, 1305, 1268, 1142, 1120, 987, 840, 765; ^{1}H NMR δ (CCl_4)=7.3 - 8.2 (m); ^{19}F NMR δ_F (CCl_4)=18.5 (d, J=2.2 Hz); MS *m/z* 276 (99, M^++2), 274 (100, M^+), 195 (92, M^+-Br), 175 (39), 126 (29). Found: C, 47.86; H, 2.01%. Calcd for $C_{11}H_6BrF_3$: C, 48.03; H, 2.20%.

*1-Bromo-2-(trifluoromethyl)naphthalene (**27b**)*

Yield 67%; IR ν(cm^{-1}) 3060, 1600, 1465, 1337, 1286, 1248, 1155, 1130, 1100, 965, 820, 758, 745; ^{1}H NMR δ (CCl_4)=7.4 - 8.4 (m); ^{19}F NMR δ_F (CCl_4)=17.2 (s); MS *m/z* 276 (98, M^++2), 274 (100, M^+), 195 (97, M^+-Br), 175

(31), 126 (27). Found: C, 47.76; H, 2.15%. Calcd for $C_{11}H_6BrF_3$: C, 48.03; H, 2.20%.

*1-Bromo-5-(trifluoromethyl)naphthalene (**27c**)*

Yield 64%; IR ν(cm^{-1}) 3070, 1573, 1503, 1310, 1232, 1202, 1155, 1140, 1115, 800, 690; ^1H NMR δ (CCl_4)=7.2 - 8.4 (m); ^{19}F NMR δ_F (CCl_4)=18.7 (d, J=2.0 Hz); MS *m/z* 276 (95, M^++2), 274 (100, M^+), 195 (96, M^+-Br), 175 (39), 145 (25), 97 (26). Found: C, 47.93; H, 2.29%. Calcd for $C_{11}H_6BrF_3$: C, 48.03; H, 2.20%.

*1-Bromo-6-(trifluoromethyl)naphthalene (**27d**)*

Yield 49%; IR ν(cm^{-1}) 3070, 1602, 1504, 1355, 1314, 1265, 1200, 1155, 1130, 1075, 892, 840, 795; ^1H NMR δ (CCl_4)=7.3 - 8.3 (m); ^{19}F NMR δ_F (CCl_4)=15.0 (s); MS *m/z* 276 (95, M^++2), 274 (100, M^+), 195 (96, M^+-Br), 175 (36), 126 (30). Found: C, 47.81; H, 2.20%. Calcd for $C_{11}H_6BrF_3$: C, 48.03; H, 2.20%.

*Reaction of 1,1-Dichloro-2,2-difluoroethylene (**1**) and the Grignard Reagent Prepared from **27a***

To a stirred mixture of magnesium turnings (4.00 g, 165 mmol) and anhydrous THF (10 mL), a mixture of **27a** (39.37 g, 143 mmol) and THF (300 mL) was added dropwise in 1 h under gentle reflux. The mixture was stirred under reflux for an additional 2 h and was then red-brown. After the bromide **27a** was completely consumed, several portions of 1,1-dichloro-2,2-difluoroethylene (**1**) (60 mL, *ca.* 680 mmol) were added to the solution, and the mixture was refluxed at 53 - 55 °C for 10 h. The cooled mixture was poured into ice-water (400 mL), acidified with conc. HCl (40 mL), and extracted with ether. The combined extract was washed with water and saturated $NaHCO_3$ solution and dried with Na_2SO_4. Removal of the solvent and chromatography on a silica gel column (*n*-hexane) gave 1-(2',2'-dichloro-1'-fluorovinyl)-4-(trifluoromethyl)naphthalene (**31a**) (6.78 g, 15%), bis-1,1-[4-(trifluoromethyl)naphthyl] (**32**) (7.25 g, 26%), and other unseparable minor fractions.

*1-(2',2'-Dichloro-1'-fluorovinyl)-4-(trifluoromethyl)naphthalene (**31a**)*

bp 102 - 106 °C/ 3 mmHg; IR ν(cm^{-1}) 3070, 1655, 1594, 1522, 1318, 969, 942, 778, 762; ^1H NMR δ (CCl_4)=7.6 - 8.4 (m); ^{19}F NMR δ_F (CCl_4)=19.6 (s, 3F), -6.7 (s, 1F); MS *m/z* 310 (17, M^++2), 308 (27, M^+), 275 (23, M^++2-Cl), 273 (65, M^+-Cl),238 (100), 204 (28). Found: C, 50.53; H, 1.80%. Calcd for $C_{13}H_6Cl_2F_4$: C, 50.52; H, 1.96%.

*Bis-1,1-[4-(trifluoromethyl)naphthyl] (**32**)*

mp 152 - 154 °C; IR ν(cm^{-1}) 3060, 2920, 1578, 1506, 1330, 1262, 1118, 765; ^1H NMR δ (CCl_4)=7.3 - 8.5 (m); ^{19}F NMR δ_F (CCl_4)=20.2 (s); MS *m/z* 391 (24, M^++1), 390 (100, M^+), 321 (60), 320 (40), 252 (48). Found: C, 67.70; H, 3.10%. Calcd for $C_{22}H_{12}F_6$: C, 67.70; H, 3.10%.

*Ethynyl(trifluoromethyl)naphthalene (**26**) from Bromo(trifluoromethyl)-naphthalene (**27**)*

To a stirred mixture of a bromo(trifluoromethyl)naphthalene (**27**) (10 g, 36 mmol) in anhydrous diethyl ether (100 mL), *n*-butyllithium in diethyl ether (1 M, 40 mL, 40 mmol) was added at -70 °C in 30 min, and the resulting mixture was stirred at -70 °C for additional 1 h. After completion of lithiation, 1,1-dichloro-2,2-difluoroethylene (**1**) (10 mL, *ca.* 110 mol) was carefully added at -70 °C in 15 min. The mixture was stirred at -70 °C for 1 h further (2 h for **27b**), and then allowed to warm to room temperature, poured into water, acidified with conc. HCl (2 mL), and extracted with ether. The combined extracts were washed with water and saturated $NaHCO_3$ solution and dried with Na_2SO_4. Removal of the solvent and Kugel-rohr distillation (110 °C/ 0.2 mmHg) of the residue gave a 9 : 1 : 1 mixture of (2',2'-dichloro-1'-fluorovinyl)(trifluoromethyl)naphthalene (**31**), (trifluoromethyl)naphthalene (**33**) (*m/z* 196) and chloro(trifluoromethyl)naphthalene (**34**) (*m/z* 230) as a pale yellow oil (*ca.* 10 g). The mixture (*ca.* 10 g) was dissolved in anhydrous ether (100 mL), and *n*-butyllithium (1.60 M *n*-hexane solution, 40 mL, 64 mmol) was added dropwise in 1 h at -70 °C to the mixture. After stirring at -70 °C for 2 h, the dark blue mixture was poured into water (100 mL), acidified with conc. HCl to pH≈3, and extracted with ether. The combined extracts were washed with water, saturated $NaHCO_3$ solution, and again with water, and dried with Na_2SO_4. Evaporation of the solvent and preparative HPLC on a silica gel packed column (Waters Prep LC/ System 500A; Prep PAK-500/ SILICA) on elution with *n*-hexane give ethynyl(trifluoromethyl)naphthalene (**26**) and a mixture of (trifluoromethyl)naphthalene (**33**) and chloro(trifluoromethyl)naphthalene (**34**).

*1-Ethynyl-4-(trifluoromethyl)naphthalene (**26a**)*

colorless oil; IR ν(cm^{-1}) 3295, 3070, 2100, 1582, 1518, 1328, 1312, 1264, 1124, 844, 764; ^{19}F NMR δ_F (CCl_4)=19.0 (s); MS *m/z* 221 (13, M^++1), 220 (100, M^+), 219 (30), 201 (26), 170 (42). Found: C, 70.79; H, 3.32%. Calcd for $C_{13}H_6F_3$: C, 70.91; H, 3.20%.

1-Ethynyl-2-(trifluoromethyl)naphthalene (**26b**)

mp 36 - 38 °C; IR ν(cm^{-1}) 3305, 3070, 2115, 1598, 1472, 1345, 1298, 1175, 1130, 825, 658; ^{19}F NMR δ_F (CCl_4)=17.1 (s); MS *m/z* 221 (17, M^++1), 220 (100, M^+), 219 (33), 201 (31), 170 (35). Found: C, 70.87; H, 3.08%. Calcd for $C_{13}H_6F_3$: C, 70.91; H, 3.20%.

1-Ethynyl-5-(trifluoromethyl)naphthalene (**26c**)

colorless oil; IR ν(cm^{-1}) 3200, 3060, 2100, 1584, 1512, 1312, 1122, 792; ^{19}F NMR δ_F (CCl_4)=19.5 (s); MS *m/z* 221 (13, M^++1), 220 (100, M^+), 219 (31), 201 (13), 170 (42). Found: C, 70.88; H, 3.23%. Calcd for $C_{13}H_6F_3$: C, 70.91; H, 3.20%.

1-Ethynyl-6-(trifluoromethyl)naphthalene (**26d**)

colorless oil; IR ν(cm^{-1}) 3300, 3055, 2100, 1596, 1470, 1308, 1122, 798; ^{19}F NMR δ_F (CCl_4)=16.7 (s); MS *m/z* 221 (15, M^++1), 220 (100, M^+), 219 (30), 201 (27), 170 (25). Found: C, 70.94; H, 3.17%. Calcd for $C_{13}H_6F_3$: C, 70.91; H, 3.20%.

Polymerization of Trifluoromethylated Ethynylaromatic Compounds

(1) $W(CO)_6$-CCl_4-light Irradiation System (Method A)

A solution of $W(CO)_6$ (0.50 g, 1.4 mmol) in carbon tetrachloride (25 mL) was activated by irradiating with a 100 W high pressure mercury lamp at 30 °C for 30 min. A monomer acetylene (1.00 g) was added to this catalytic solution, and continued to react in a dark place at 30 °C for 24 h. The polymerization was terminated with methanol, and the precipitated polymers were purified by dissolving in THF and reprecipitating with methanol. The polymers were collected by filtration, washed with methanol, and dried to constant weight.

(2) WCl_6-Ph_4Sn System (Method B)

In a three-necked flask were placed WCl_6 (21 mg) and Ph_4Sn (23 mg) dissolved in toluene (5 mL) and stirred for 30 min. The catalytic solution was added to monomer (0.7 g) in another flask. After polymerization at 30 °C for 24 h, the reaction was terminated by addition of methanol. Formed precipitates were collected, then washed with methanol and dried to constant weight.

(3) $TaCl_5$ System (Method C)

Polymerization was carried out according to a similar procedure to the WCl_6-Ph_4Sn system (method B).

(4) γ-Ray Induced Polymerization (Method D)

In an ampoule was placed the monomer (0.5 mL), and degassed by a successive freezing and melting procedure. The ampoule was sealed under vacuum, and was irradiated by the γ-ray (^{60}Co) of 3.34 x 10^5 rad/h for 114 h at ambient temperature without any solvents. The contents of the ampoule were poured into methanol, and the precipitate formed was collected by filtration, and washed by methanol and dried to constant weight.

CHAPTER 5

CONCLUSION

Organic fluorine compounds are anticipated for highly functional and valuable materials because of unique properties of fluorine atom. These practical applications appeared in various fields: engineering materials such as fluoro-polymers and chlorofluorocarbons; biologically active chemicals such as antitumor agents, anti-inflammatory drugs, and agrochemicals. This dissertation describes synthesis and reactions of perfluoroalkylated heterocyclic and ethynylaromatic compounds, which are important for industrial and medicinal chemistry.

Nitrogen-containing heteroaromatic compounds are widely distributed in nature and several nitrogen heterocycles are essential components of amino acids or nucleic acids. In Chapter 2, perfluoroalkylated analogs of these heterocycles, which have potentialities of biological activities as drugs and agrochemicals, were studied.

In Chapter 2.1, photochemical trifluoromethylation of 1-methylimidazoles and 1-methylpyrroles containing methylthio groups was studied. Although photochemical perfluoroalkylation is applicable to various heteroaromatic compounds under mild conditions, a problem for the trifluoromethylation of several heterocycles lies in poor regio selectivity. In order not only to block available reactive sites in the ring but also to increase electron density, the methylthio group was introduced before the trifluoromethylation. In both cases of 1-methylimidazole and 1-methylpyrrole, the introduction of 2-methylthio group improved the yields and selectivity in trifluoromethylation, whereas 2,5-bis(methylthio) compounds afforded trifluoromethylated derivatives in low yields. The methylthio groups were readily removed by Raney nickel. Pure trifluoromethylated 1-methylimidazoles were obtained without a tedious separation procedure.

In Chapter 2.2 and Chapter 2.3, perfluoroalkylation of nucleic acid bases with bis(perfluoroalkanoyl) peroxides was studied. Perfluoroalkylation with the peroxide was a convenient synthetic method for electron-rich aromatics, but electron-poor rings, such as uracil, did not react with the peroxide. Introduction of the trimethylsilyl groups increases solubilities and electron density of the rings. The trimethylsilyl derivatives of uracil reacted with the peroxide to provide perfluoroalkylated uracils with hydration of the silylated group. Similar perfluoroalkylation of uridines and 6-substituted uracils

gave the corresponding perfluoroalkylated derivatives only at the C-5 position. Silylated purines were synthesized with *N,O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA) and then were reacted with bis(heptafluoro-butyryl) peroxide in a similar manner to the uracils. The heptafluoro-propylation of silylated purines occurs preferentially at the C-8 position; 6-methoxypurine gave the C-2 isomer as well in isolable yield. Replacement of the 6-amino group of adenine with the dimethylamino or methoxy group improved the yields of the heptafluoropropylated derivatives.

Though direct fluorination and perfluoroalkylation are effective synthetic methods, they have some difficulties. Polyfluorinated olefins industrially manufactured as monomers at a low price are useful precursors for fluorinated compounds; new perfluoroalkylated heterocycles could be prepared by using addition and/or cyclization reaction. In Chapter 3, synthesis of trifluoromethylated heterocycles by γ-ray induced addition reaction to hexafluoro-2-butyne was studied.

In Chapter 3.1, synthesis of 3,4-bis(trifluoromethyl)furan derivatives by γ-ray induced addition reaction of alcohols and aldehydes to hexafluoro-2-butyne was studied. The polyfluorinated olefins easily react with nucleophilic radicals on account of the electron withdrawing effect of fluorine atom. By γ-ray irradiation, alcohols and aldehydes formed radicals at α-carbon and added to hexafluoro-2-butyne: alcohols afforded (*E*) and (*Z*) mixture of 1:1 adducts; aldehydes afforded 1:2 adducts and (*E*) isomer of 1:1 adducts. The 1:2 adduct of hexafluoro-2-butyne and aldehydes cyclized using sulfuric acid to afford 2,5-dialkyl-3,4-bis(trifluoromethyl)furans, of which alkyl groups readily converted to various functional groups without decomposition of the trifluoromethyl groups.

In Chapter 3.2, synthesis and UV induced decomposition of 1,4-dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene were studied. The 2,5-dialkyl-3,4-bis(trifluoromethyl)furans reacted with hexafluoro-2-butyne by heating to provide the trifluoromethylated dialkyloxabicyclo-heptadienes. By UV irradiation, the diethyloxabicycloheptadiene was converted to an unstable oxaquadricyclane intermediate, which decomposed to give three new trifluoromethylated products, the two cyclopentadienes, and the oxepin.

In Chapter 3.3, synthesis and stereoselective decomposition of trifluoro-methylated pyrazolines were studied. The 1,3-dipolar addition of diazo-methane with the 1:1 adducts of hexafluoro-2-butyne with propionaldehyde

provided trifluoromethylated pyrazolines. Thermal decomposition and photolysis of the pyrazoline gave the trifluoromethylated cyclopropanes stereoselectively. Both (*E*) and (*Z*) isomers of the pyrazoline gave 3,4-bis-(trifluoromethyl)-2-ethyl-3,4-dihydrofuran, whereas only the (*Z*) isomer of the pyrazoline gave 4,5-bis(trifluoromethyl)-5-hexen-3-one.

Polyacetylenes have unique properties caused by alternating double bonds along the main chain. Therefore, polymerization of acetylenes and their application to electronic materials and gas permeable membranes have been studied extensively. Introduction of fluorinated substituents into the polyacetylenes was expected to affect their properties due to electronegativity and bulkiness of the substituents. In Chapter 4, synthesis and polymerization of trifluoromethylated ethynylaromatic compounds were studied.

Trifluoromethylated ethynylaromatic compounds were prepared in moderate yields via 2,2-dichloro-1-fluorovinyl compounds, which were obtained by reaction of lithio intermediates or Grignard reagents with 1,1-dichloro-2,2-difluoroethylene. Trifluoromethylated thiophenes and furans were prepared by the fluorination reaction of dicarboxylic acid derivatives with sulfur tetrafluoride, monocarboxylic acids, however, formed tarry products. Fluorination of bromophenylcarboxylic acids and bromonaphthylcarboxylic acids with sulfur tetrafluoride were successful only at lower temperature to provide the corresponding trifluoromethylated compounds.

Polymerization was carried out by the following methods: (1) $W(CO)_6$-CCl_4-*hv*; (2) WCl_6-Ph_4Sn; (3) γ-ray induced polymerization. Polymerization using transition metal catalysts ((1) and (2)) showed a similar tendency: 3-ethynylthiophenes gave polymers in high yields, while 2-ethynylthiophenes afforded oligomers; both phenyl- and naphthyl-acetylenes polymerized in high yields by transition metal catalysts. In γ-ray induced polymerization, only ethynylaromatic compounds having two trifluoromethyl groups polymerized in high yields, polymers obtained, however, were insoluble in all solvents examined. Introduction of the trifluoromethyl group improved yields, molecular weights, and thermal stability of polymers obtained from ethynylaromatic compounds.

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Main Publications

[1] (*Chapter 2.1*)
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[2] (*Chapter 2.2*)
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[3] (*Chapter 2.3*)
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[5] (*Chapter 3.1*)
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[11] Synthesis of Hexanuclear Molybdenum Cluster Alkyl Complexes Coordinated with Trialkylphosphines: Crystal Structures of *trans*-$[(Mo_6Cl_8)Cl_4\{P(n\text{-}C_4H_9)_3\}_2]$ and *all-trans*-$[(Mo_6Cl_8)Cl_2(C_2H_5)_2\{P(n\text{-}C_4H_9)_3\}_2]\cdot 2C_6H_5CH_3$.
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