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CHAPTER 1

INTRODUCTION

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Fluoroorganic chemistry, the study of organic compounds containing fluorine, emerged in the early 20th century with significant advancements during the 1930s when scientists discovered the unique properties of fluorinated compounds. Its origins trace back to the synthesis of chlorofluorocarbons (CFCs) by Thomas Midgley Jr., initially developed as refrigerants [1]. The CFCs were later developed as a wonderful fire extinguishing agent used in total flooding applications. The field expanded rapidly due to fluorine's exceptional characteristics, such as its high electronegativity and small atomic size, which impart remarkable stability, reactivity, and hydrophobicity to organic molecules [2]. These properties make fluoroorganic chemistry critical in modern science and industry. Fluorinated compounds are integral to pharmaceuticals, where approximately 20-30% of drugs, including anti-depressants and anti-cancer agents, contain fluorine to enhance metabolic stability and bioavailability [3]. In agrochemicals, fluorine improves the efficacy and environmental persistence of pesticides [3]. The field also revolutionized materials science, with fluoropolymers like polytetrafluoroethylene (PTFE), offering unmatched chemical resistance and low friction for applications in cookware, electronics, and aerospace [4]. Additionally, fluoroorganic compounds are vital in medical imaging, where fluorinated tracers are used in positron emission tomography (PET). The importance of this field lies in its ability to tailor molecular properties for specific functions, driving innovation across disciplines. Applications of fluoroorganic compounds continued to grow, from energy storage in lithium-ion batteries to advanced coatings, underscoring fluoroorganic chemistry's transformative role in addressing global challenges in health, agriculture, and technology. Based on the sources, fluoroorganic compounds are categorized into two types: naturally occurring and synthetic.

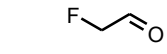
1.1 Naturally occurring Fluoroorganic compounds

Fluorine exhibits a strong affinity for certain elements, including silicon, aluminium, calcium, and magnesium. These elements are commonly present in the Earth's crust; therefore, fluorine is mostly found strongly bound within insoluble minerals. Despite the notable abundance of fluorine in the universe (24th most abundant, 4×10^{-5}%) and Earth's crust (13th most abundant, 0.054%) by weight, the existence of fluoroorganic compounds containing a covalent C-F bond is scarce in Earth's natural products. Several authors have argued that the avoidance of fluorine in natural biochemistry is attributed to the extremely low concentration of fluorine (~1.4 ppm), unlike chloride (~19,000 mg/L) and bromide (~65 mg/L), in seawater, which is due to the low solubility of the prominent CaF_2 ore in water [5,6]. Fluorine primarily

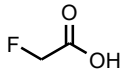
exists in insoluble fluoride minerals, Fluorite (CaF_2, solubility: 16 mg/L at 25°C) or Cryolite. The low solubility of fluoride minerals in water limits the concentration of fluoride ions in the biological system compared to other halogens. Strikingly, out of 200,000 documented naturally occurring organic compounds [7], and approximately 8400 known natural organo-halogens [8], there are only 34 known fluorinated natural products containing a single C-F bond and none with two C-F bonds (Figure 1.1). The number is much less than the natural products containing iodine (~180), which is much less abundant in the ocean than fluoride. The volcano eruption contains a few of them (tetrafluoroethylene, hexafluoropropylene, chlorodifluoromethane, chlorotrifluoroethylene, dichlorofluoromethane, trichlorofluoromethane, 1,1,2-trichloro-1,2,2-trifluoroethane), but the process of their generation is not very clear [9].

The scarcity of fluorinated organic compounds in natural products is attributed to the difficulty in the formation of the C-F bond, resulting from fluoride's high hydration energy, low bioavailability, limited enzymatic machinery, and evolutionary constraints [7]. The primary reason for this scarcity is the high electronegativity of fluorine, which presents a significant challenge for C-F bond formation in biosynthesis. The formation of natural organohalogen compounds proceeds through an enzymatic process, involving the oxidative formation of reactive species, such as halogen radicals or cations. The oxidation potential of fluoride (F^- = −2.87 eV) is above the electrode potential that can be overcome by haloperoxidase (−1.8 eV), unlike other halogens (Cl^-: −1.36 eV, Br^-: −1.07eV, I^-: −0.54 eV). Therefore, the fluoride ion cannot be oxidised by haloperoxidase to reactive species (cation or free radical) [10].

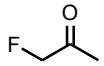
The highest electronegativity of fluorine (4.0, Pauling scale) and highly polar and strong C-F bond (C-F bond dissociation energy: ~485 kJ/mol, compared to ~327 kJ/mol for C-Cl and ~272 kJ/mol for C-Br) make it difficult for enzymes to break or manipulate C-F bonds, limiting biosynthetic pathways for incorporating fluorine into organic molecules. The small ionic radii and high charge density of fluorine lead to exceptionally high hydration energy (-506 kJ/mol). Consequently, fluoride ions are strongly hydrated in aqueous solution and are less bioavailable for enzymatic uptake. This strong hydration shell must be removed before the formation of the C-F bond. The high heat of hydration of fluoride ion (~120 kcal/mol) makes the process thermodynamically unfavourable [7]. Fluorinase (adenosyl-fluoride synthase), initially isolated from the soil bacterium *Streptomyces cattleya*, is the only known fluorination enzyme that catalyses the formation of a C-F bond in nature. This enzyme operates with a high energy barrier, due to the high hydration energy of fluoride ion, and its rarity in nature limits the fluoroorganic compounds in biosynthesis [11].



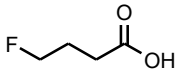
Fluoroacetaldehyde
prod. by *Streptomyces cattleya*



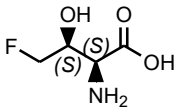
Fluoroacetic acid
prod. by *Streptomyces cattleya*
and many plant species



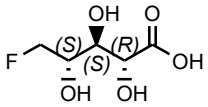
Fluoroacetone
prod. by *Acacia georginae*



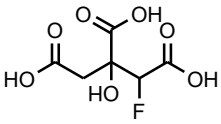
4-Fluorobutanoic acid
prod. by *Saccharomyces cerevisiae*



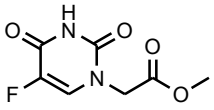
4-Fluoro-L-threonine
prod. by *Streptomyces cattleya*



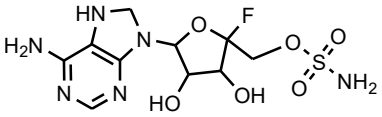
5-Fluoro-2,3,4-trihydroxypentanoic acid
prod. by *Streptomyces* sp. MA 37



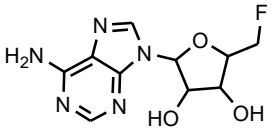
Fluorocitric acid
Found in cattle bones and in soybean leaves, alfaalfa, tea plant etc.



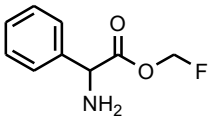
5-Fluoro-1-(methoxycarbonyl methyl)uracil
prod. by *Phakellia fusca*



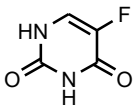
Nucleocidin
prod. by *Streptomyces calvus* T3018-Atcc13382



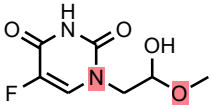
5'-Fluoro-5'-deoxyadenosine
prod. by *Streptomyces cattleya*



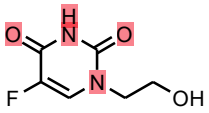
Fluoromethyl ester of 2-amino-2-phenylacetic acid
prod. by the larvae of *Chrysomya megalocephala*



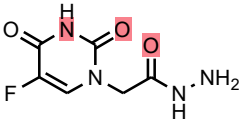
5-Fluorouracil
prod. by *Phakellia fusca*



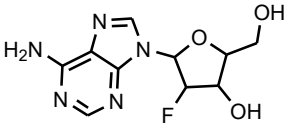
5-Fluoro-1-(2-hydroxy-2-methoxyethyl)uracil
prod. by *Phakellia fusca*



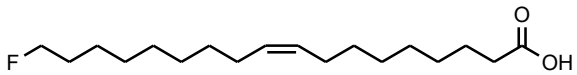
5-Fluoro-1-(2-hydroxyethyl)uracil
prod. by *Phakellia fusca*



prod. by *Phakellia fusca*



2'-Fluoro-2'-deoxyadenosine
prod. by larvae of *Chrysomya megalocephala*



w-fluorooleic acid
(Plus around 30 minor lipid metabolites drived from this in Dichapaetalum toxicarium

Figure 1.1: Naturally occurring fluoroorganic compounds [7]

1.2 Fluoroorganic chemistry – basically a synthetic field

The difficulty in the synthesis of the C-F bond can be expressed in the statement of two famous fluorine chemists, Graham Sandford (University of Durham, UK) and David O'Hagan (University of St Andrews, UK), “Even Nature finds fluorine chemistry difficult, so no wonder the element is a challenge for chemists” [12].

From the very first example of fluorine chemistry discovered in the second half of the 19th century [13], the field has grown rapidly due to its wide area of applications. The fluorinated organic compounds have widespread applications in different fields, including medicinal chemistry, pharmaceuticals, agrochemicals, diagnostics, polymers, molecular electronics, catalysis, liquid crystals, refrigeration, and lubricants [14]. The high occurrence of fluorinated molecules in these applications can be attributed to several factors. First, the C-F bond, the strongest bond, increases the thermal stability, chemical stability, and metabolic stability of the molecule. Second, the replacement of a hydrogen (H) atom by fluorine (F), does not drastically alter the parent structure of the drug molecule. Third, owing to the high electronegativity of fluorine, the introduction of fluorine induces bond polarization, which affects the lipophilicity/hydrophilicity of the material. It also changes the acidity and basicity of the molecule. Fourth, it can be used as a bioisostere of the OH group due to the weak hydrogen bond acceptor nature of fluorine. Therefore, the introduction of fluorine in the molecules enormously changes the nature of the molecule.

The study makes it clear that very few fluorinated compounds exist naturally, and most of them are mono-fluorinated. None of the difluorinated naturally occurring fluoro-organic compounds has been separated yet. Additionally, none of the natural C-F compounds have been isolated for utilization. Therefore, fluoroorganic chemistry is virtually a completely man-made branch of organic chemistry, where essentially all of the fluoro-organic compounds in the world are man-made [14]. The major surge in the field of fluorine chemistry and the study of fluorinated compounds began with the Manhattan Project in 1941, where fluorine was required on a large scale for the enrichment of ^{235}U. The use of fluorine in human life remained restricted until the discovery of the first fluorinated pharmaceutical 9-fluor 9-fluorohydrocortisone (an anti-inflammatory drug) and 5-fluorouracil (an anticancer drug) (Figure 1.2) in the 1950s.

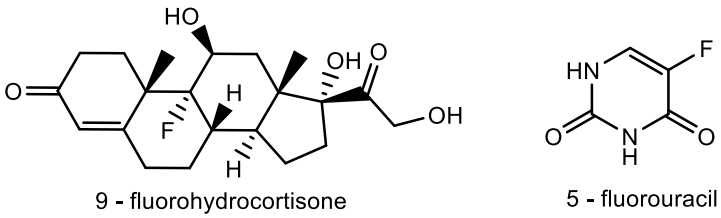


Figure 1.2: Fluorinated Drugs

1.3 Methods for the synthesis of fluoroorganic compounds

Owing to the wide utility of fluoroorganic compounds, an impressive array of reagents and several methods exist for the formation of the C-F bond in aliphatic and aromatic compounds. It can be achieved by electrophilic fluorination, nucleophilic fluorination, and radical fluorination (Figure 1.3).

1.3.1 Electrophilic fluorination

The process of electrophilic fluorination has evolved significantly since its beginning. The process involves the transfer of a fluoronium ion (F^+) to a nucleophilic substrate. Elemental fluorine (F_2) is a well-known electrophilic fluorinating reagent. However, the extreme reactivity, corrosiveness, and toxicity of fluorine gas posed a significant challenge in handling. Therefore, only qualified researchers can utilise its synthetic utility with specialised equipment. Its synthetic utility is exploited by using a low temperature, after diluting with an inert gas [15].

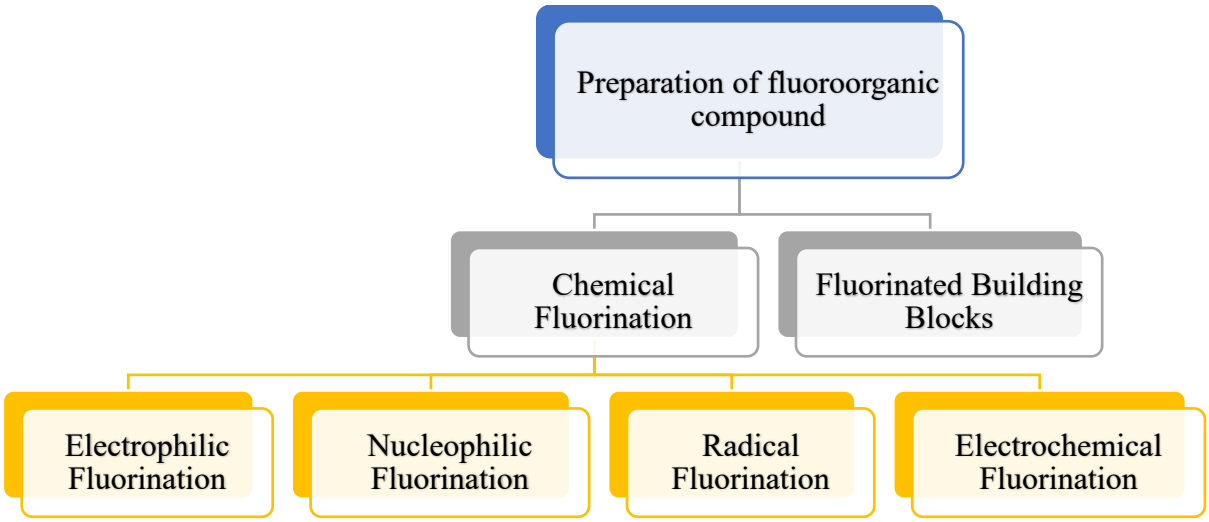
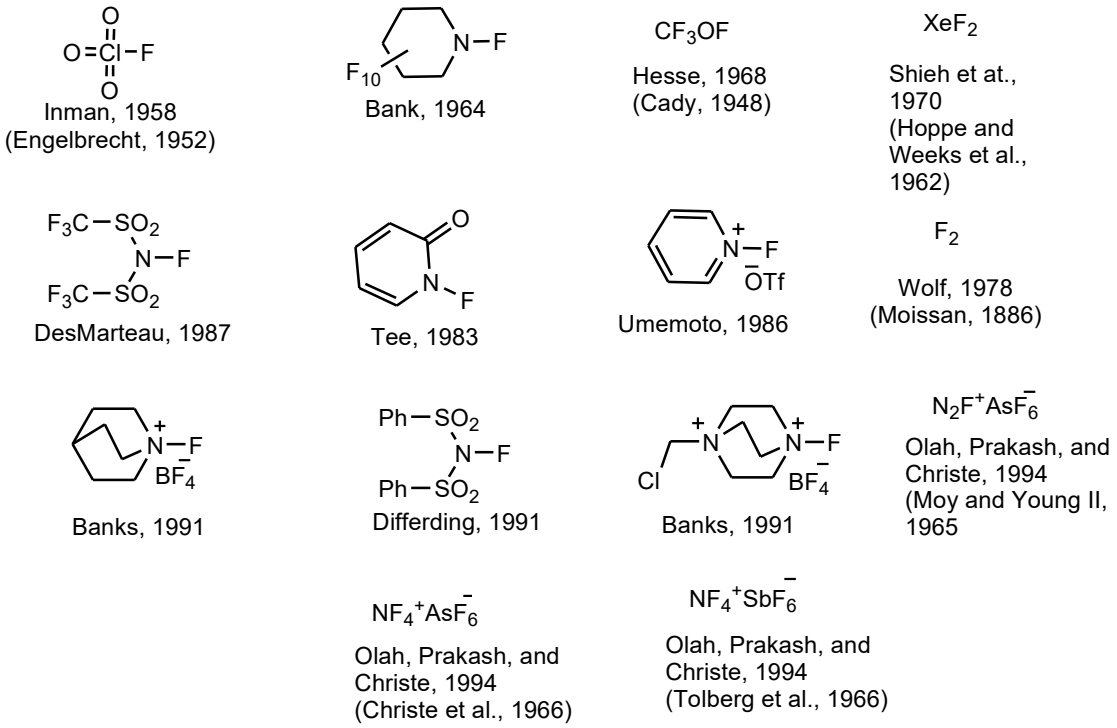


Figure 1.3: Method for preparation of organofluorine compound

Beyond its toxicity, the selectivity of elemental fluorine is also very poor. It reacts violently with most organic compounds, often leading to unselective fluorination of almost all C-H groups. Cobalt (III) fluoride (CoF_3) and xenon difluoride (XeF_2) are also powerful electrophilic fluorinating reagents (Figure 1.4) [16]. Perchloryl fluoride, $FClO_3$, employed in the synthesis of fluorinated organic compounds, has represented the real significance of an electrophilic fluorinating agent [17]. These broad categories of reagents offer a variety of chemical environments, distinct reaction mechanisms, and challenging synthetic limitations.



(The numbers in parentheses indicate the year when these reagents were first prepared)

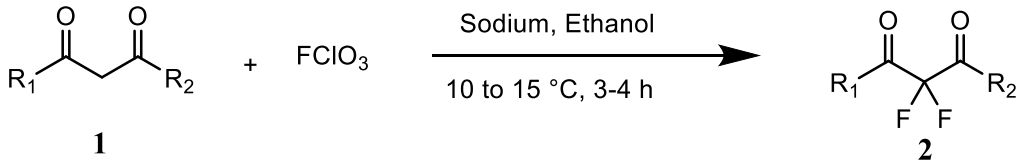
Figure 1.4: Electrophilic fluorinating agents

The high reactivity and corrosive nature of electrophilic fluorinating reagents like fluorine (F_2) gas, fluoroxysulfates, and hypo fluorites present the handling and functional group intolerance challenges [18]. This led to the development of bench-stable and easy-to-handle N-F reagents, such as Selectfluor, *N*-fluoropyridinium salts, and *N*-fluorobenzenesulfonimide (NFSI). These reagents have significantly impacted the area of electrophilic fluorination. The electron density at the N-F site plays a major role in determining the fluorinating process. Selectfluor, NFSI, and *N*-fluoropyridinium salts are the most dominant N-F reagents that serve as F^+ sources

(Figure 1.4). Electrophilic fluorinating reagents have progressed from corrosive "first generation" fluorine sources to easy to handle, more selective “Fourth Generation” reagents with increased stability and strong reactivity [19]. The preparation of these reagents, however, is costly and requires fluorine gas, which restricts their use, particularly on a laboratory scale. The following schemes will discuss some of the electrophilic fluorinating agents in detail.

1.3.1.1 Perchloryl fluoride ($FClO_3$)

Inman et al. achieved the first electrophilic fluorination of reactive methylene by using perchloryl fluoride ($FClO_3$) to provide fluorinated compounds. The reaction was carried out by passing the perchloride fluoride gas into a solution of sodium salts of active methylene compound **1** in absolute ethanol at low temperature to get a difluorinated compound **2** (Scheme 1.1). The reaction is highly exothermic, and all the methylene protons on the molecule are replaced with fluorine [20].

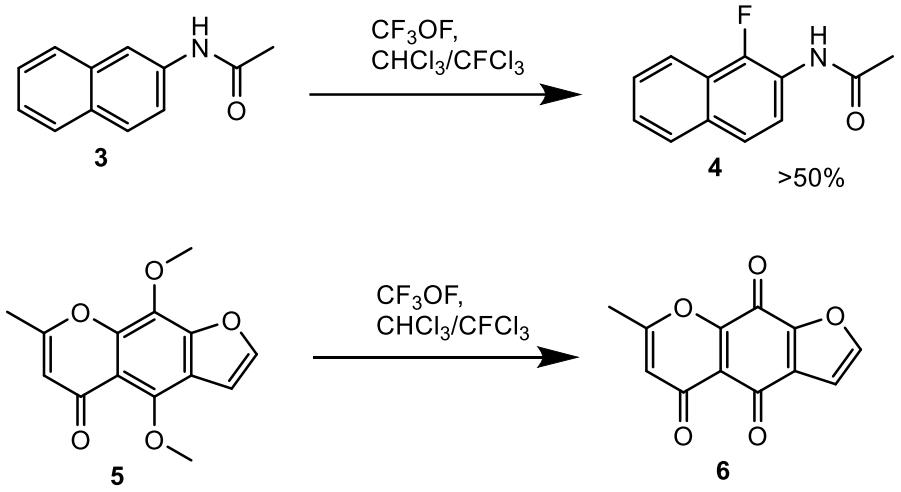


Scheme 1.1: Fluorination of the active methylene group

The use of the reagent emerged during the late 1950s to early 1960s for fluorination of electron-rich sites, but its use was restricted sharply due to safety concerns.

1.3.1.2 Electrophilic reagent containing an O-F bond

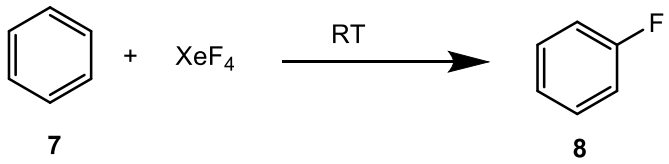
Barton and Hesse used the fluoroxytrifluoromethane (CF_3OF) as a versatile reagent for electrophilic fluorinations of activated olefinic and suitable activated aromatic rings (Scheme 1.2) [21]. Different activated olefines, aromatic **3** and heteroaromatics were fluorinated with CF_3OF to form mono-fluorinated product **4** or mono- and di-fluorinated product. However, in some cases, the oxidation product was formed; for example, the heterocyclic natural product khellin **5,** (4,9-dimethoxy-7-methylfuro[3,2-g]chromen-5-one) was oxidised to the quinone derivative **6**. Their elegant work in the field of electrophilic fluorination further led to the development of a family of O–F based electrophilic fluorinating reagents, including CF_3CO_2F, $CsSO_4F$, and HOF. Hesse and Mukhametshin reviewed work on this reagent during the late 1970s, but the use declined sharply due to the commercial availability and high cost [22].



Scheme 1.2: Electrophilic fluorinations of activated olefinic

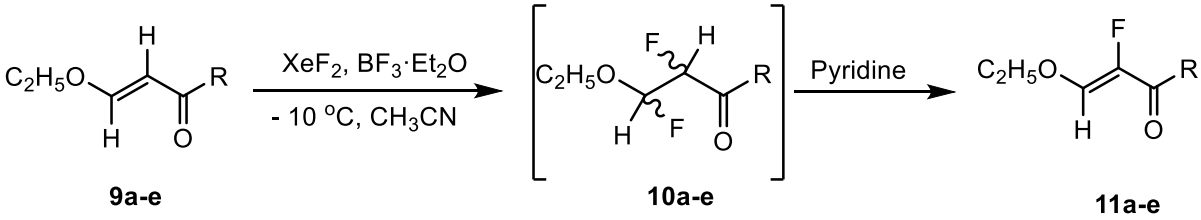
1.3.1.3 Xenon Fluorides

In 1970, Yang and co-workers reported the fluorination of alkenes and aromatics **7** by xenon fluorides (XeF_2, XeF_4, and XeF_6) [23]. The reaction proceeds smoothly at room temperature or below room temperature to give 13% of fluorobenzene (Scheme 1.3).



Scheme 1.3: Fluorination of alkenes and aromatics by xenon fluoride

The enones **9a-e,** when reacted with XeF_2 in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ in CH_3CN below – 10 ºC, give the vicinal difluoro ketone **10a-e** as the major product (Scheme 1.4) [24]. Since the difluoro ketone is not stable for isolation, it can be easily converted to β-alkoxy-α-fluoro vinyl trifluoromethyl ketone **11a-e** by elimination of HF in the presence of pyridine base. The product **11a-c** was purified and obtained in 68%, 71% and 70% yields, respectively. Other product, **11d-e,** was obtained in low yield and purity.



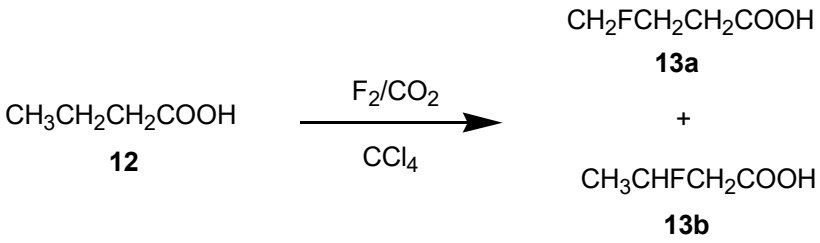
9a-e **10a-e** **11a-e**

R = CF_3 (a), CF_2H (b), CF_2Cl (c), C_2F_5 (d), C_3F_7 (e)

Scheme 1.4: Fluorination of enones with xenon difluoride

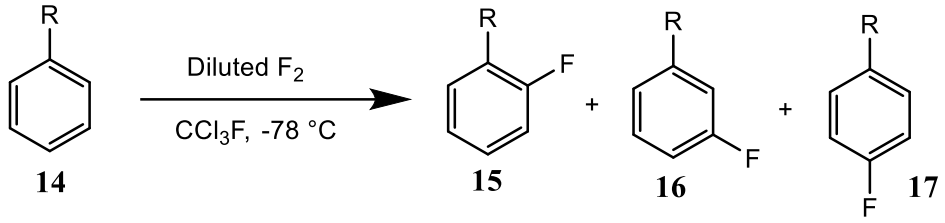
1.3.1.4 Elemental Fluorine

The elemental fluorine reacts violently with organic compounds, resulting in the burning of the substrate with an explosion. Bockmuller in 1933 observed that this problem can be solved by dissolving the substrate in an inert solvent and bubbling the mixture of fluorine gas diluted with an inert gas. He demonstrated a selective fluorination of *n*-butanoic acid **12** to prepare a mixture of 3 & 4 fluorinated *n*-butanoic acid **13a** & **13b** (Scheme 1.5) [25]. The vapour phase fluorination is another approach developed by Fredenhagen and Cadenbach to control direct fluorination of hydrocarbons by reacting the vapour of an organic compound with fluorine gas in copper meshes [26].



Scheme 1.5: Selective fluorination of n-butanoic acid by F_2 gas

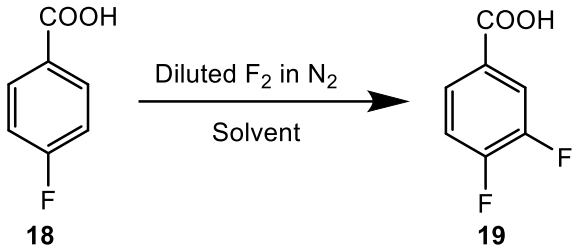
In 1978, Cacace and Wolf were able to carry out the selective electrophilic fluorination of aromatic compound **14** using highly diluted molecular fluorine (0.75 mol%) in inert gas, nitrogen or argon. Reactions were carried out in the dark at low temperature (-78 °C) using a very dilute solution of substrate (0.01-0.1 M) in inert solvents ($CC1_3F$, CH_3CN, C_6F_6, or C_7F_8) (Scheme 1.6). Activating group on aromatic ring and lower temperature favour the reaction at ortho-para **15-16,** while the deactivating group (nitro) and higher temperature favour the m-fluorination **17** in an aprotic solvent. The arenium ion formed by the electrophilic attack on the benzene ring by a polarised fluorine molecule, further attacked by fluoride ion, leading to the formation of the product [27].



R	Ortho (%) 15	Meta (%) 16	Para (%) 17
CH_3	60 ± 2	11 ± 1.5	29 ± 2
NO_2	9 ± 2	80 ± 3	11 ± 2
OCH_3	76 ± 3	0.5 ± 0.1	23.5 ± 2

Scheme 1.6: selective electrophilic fluorination of aromatic compounds

The rate of fluorination is directly impacted by the solubility of fluorine in the solvent. The effect of polar and acidic solvents on promoting the electrophilic fluorination of 4-fluorobenzoic acid **18** was studied by Chambers et al. [28]. The results show that with an increase in the acidity of the solvent, the conversion increases to form 3,4-fluorobenzoic acid **19**. This indicates the interaction between the solvent and fluorine during the reaction (Scheme 1.7) [28].

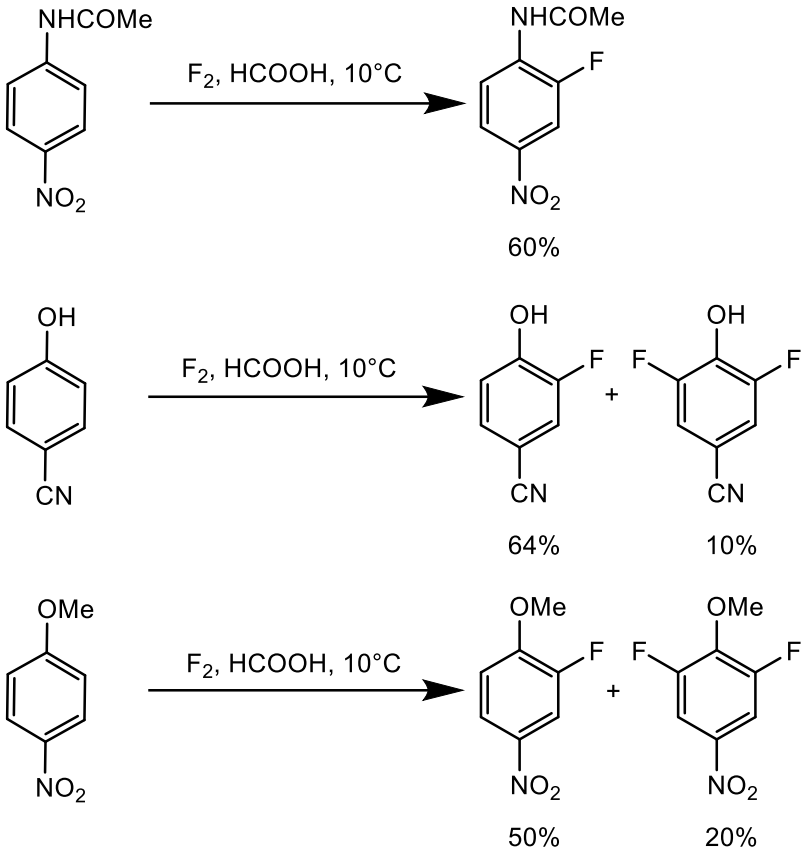


Solvent	$CF_2ClCFCl_2$	CH_3CN	CF_3COOH	HCOOH	Conc. H_2SO_4
% Conversion	0	53	56	65	84

Scheme 1.7: Effect of solubility of fluorine on the rate of fluorination

Aromatic compounds containing two or more groups activating the same carbon atom for electrophilic substitution serve as a better substrate for electrophilic fluorination for

preparing fluoroaromatic derivatives (Scheme 1.8) [29]. Although extensive studies from the late 1960s to the early 1970s on electrophilic fluorination focused on O-F moiety-based fluorinating reagents. However, difficulties associated with their synthesis, handling and commercialization significantly hindered their applications. Later in the 1980s to the early 1990s, the more stable N-F reagents were developed and significantly impacted the electrophilic fluorination process.

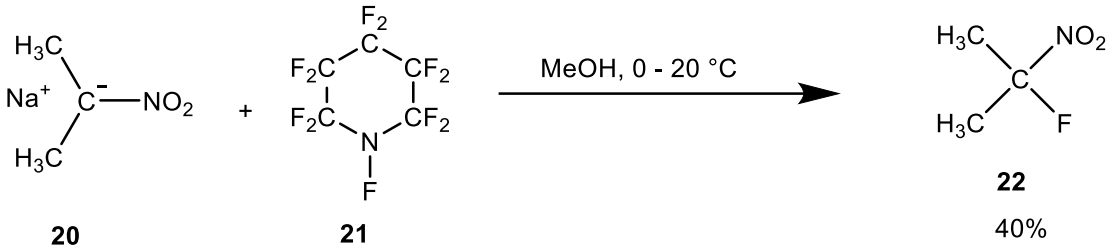


Scheme 1.8: Effect of substituents on fluorination

1.3.1.5 N-F Reagents for electrophilic fluorination

Bank and Williamson in 1964 used N-F reagent for the first time in electrophilic fluorination. They demonstrated that perfluoro-N-fluoropiperidine **21** reacts with the sodium salt of 2-nitropropane **20** to form 2-fluoro-2-nitropropane **22** [30]. However, the reagent could not be widely used due to the low yield of fluorination (Scheme 1.9). Real interest in electrophilic fluorination by N-F reagent began in the early 1980s with the discovery of several N-F reagents, including N-fluoropyridine-2-(1H)-one, N-fluoro-N-alkylsulfonamide, N-fluoropyridinium salt, and N-fluoroquinuclidinium fluoride. Triethylenediamine (TEDA) based N-F reagent of Selectfluor™ family (Figure 1.5) was introduced by Banks and coworkers

in 1992 [31]. The electrophilicity of these reagents can be simply altered by changing the electron-withdrawing nature of the R group. The fluorinating power of Selectfluor increases with the electron-withdrawing nature of the R group. The tetrafluoroborate salts are commercially available due to their cost-effectiveness [32].

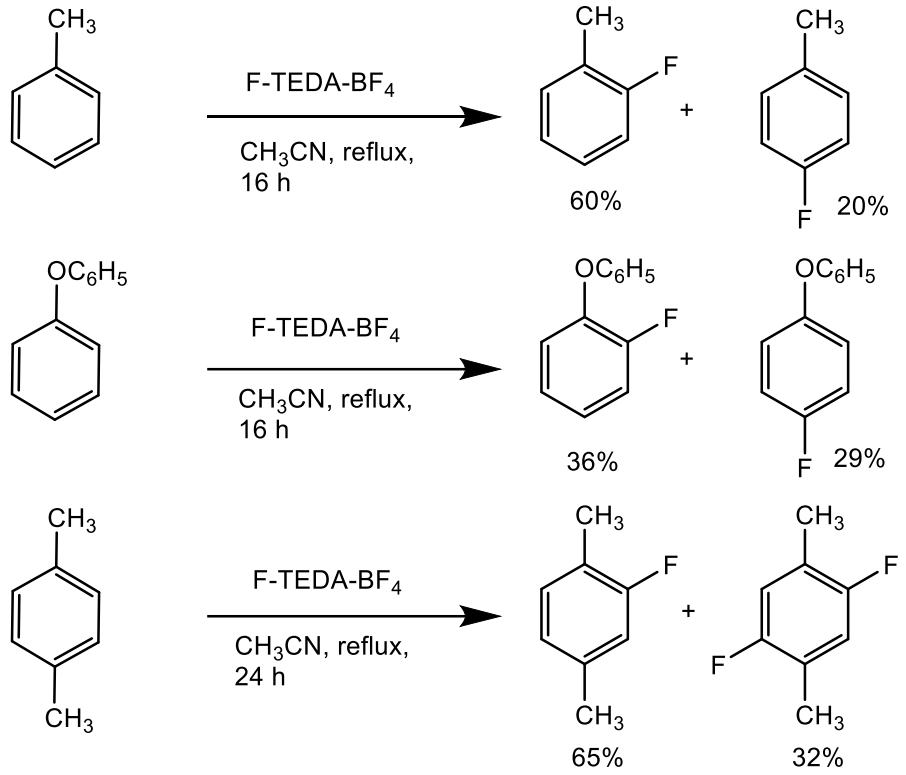


Scheme 1.9: Perfluoro-N-fluoropiperidine mediated fluorination

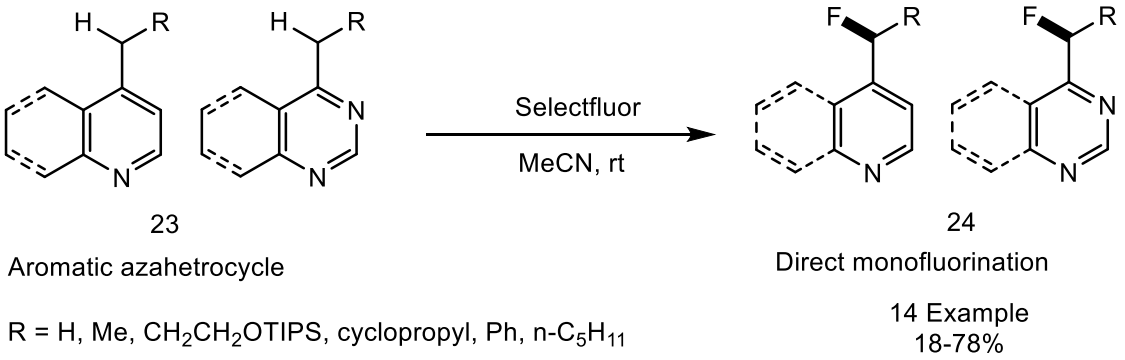
Figure 1.5: Selectfluor™

Selectfiuor™ has been widely used for electrophilic fluorination since its discovery. The aromatic compound with a donating group reacts with Selectfluor to give mono- and difluorinated derivatives under mild conditions. A few examples of fluorination of aromatics with Selectfluor are listed in Scheme 1.10. Humbeck and colleagues studied a mild and selective approach for the benzylic fluorination of aromatic azaheterocycles [33]. The azaheterocycle compound **23,** on treatment with Selectfluor in MeCN at room temperature, leads to mono-fluorination at the benzylic site **24** in good to excellent yield (Scheme 1.11). Alkyl and aryl substitutions in derivatives work well with the process. Benzylic positions connected to azaheterocycles undergo preferential fluorination, regardless of the presence of other benzylic positions [33]. Tian et al. carry out Selectfluor-mediated selective fluorination of 6-substituted 2-aminopyrazines (Scheme 1.12) [34]. In a silver carbonate catalysed reaction, substrate **25** reacts with Selectfluor in acetonitrile to produce monofluorinated product under mild conditions. The product 5-fluoropyrazin-2-amine **26** was formed in good yield, along with a small amount of 3-fluoropyrazin-2-amine **27** and 3,5-difluoropyrazin-2-amine **28**. The

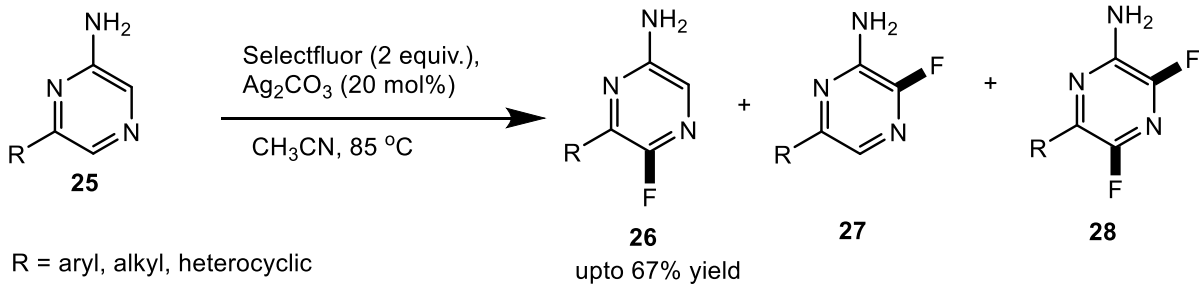
reaction produces a respectable yield of aryl-substituted pyrazine with the electron-withdrawing group and heteroaryl group.



Scheme 1.10: Electrophilic fluorination by Selectfluor™

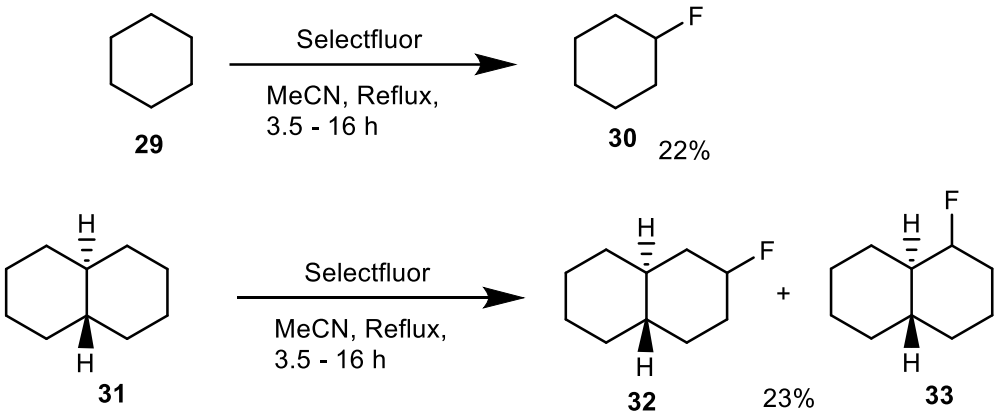


Scheme 1.11: Benzylic fluorination of azaheterocycles



Scheme 1.12: Fluorination of 6-substituted 2-aminopyrazines with Selectfluor

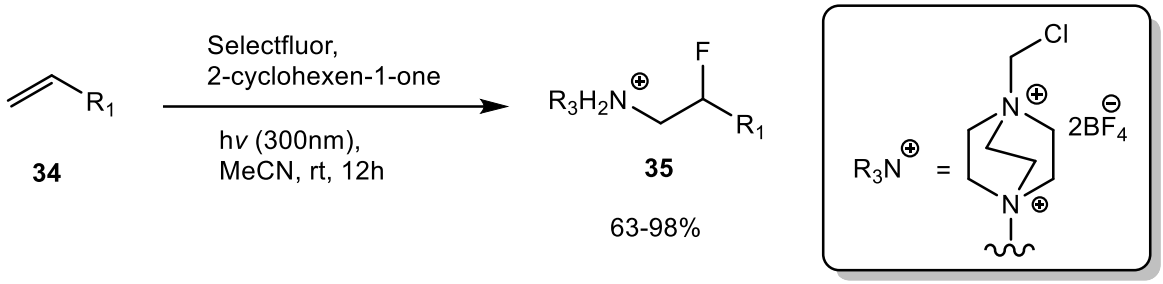
The conversion of a saturated C-H bond to a C-F bond was studied by Chambers et al. The transformation was achieved by refluxing the mixture of substrate and Selectfluor in acetonitrile [35]. The investigation revealed that the results obtained for fluorination with Selectfluor were parallel to those obtained with elemental fluorine in most of the substrates used. Like fluorination of decane **29** gives the same result, but on the other side, the fluorination of decalin **31** with Selectfluor takes place at a less hindered secondary (CH_2) site against the fluorination at the tertiary (CH) site using fluorine. This may be attributed to the greater steric requirement of Selectfluor (Scheme 1.13) [35].



Scheme 1.13: Fluorination of saturated C-H bond

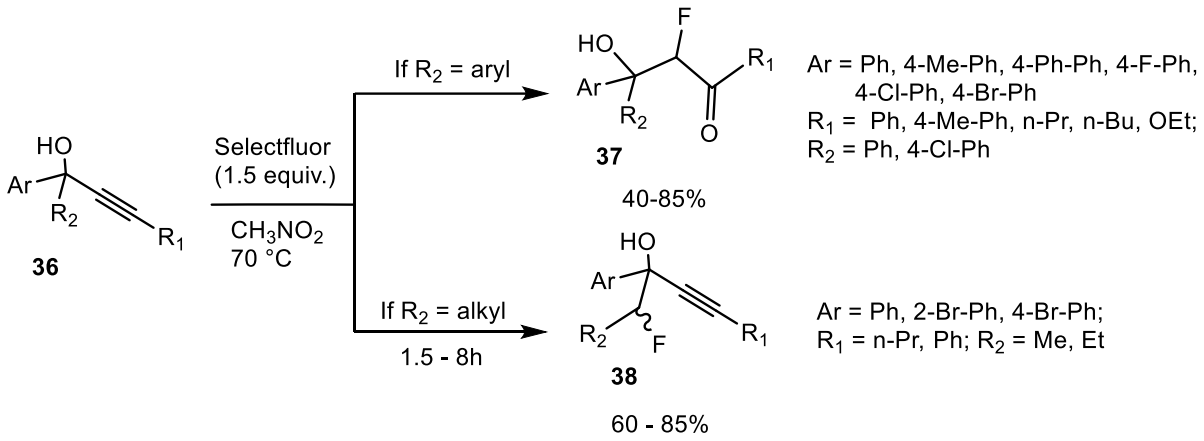
Capilato et al. disclosed regioselective fluorofunctionalization of alkenes with Selectfluor [36]. The irradiation of alkene **34** with UV (300 nm) radiation in the presence of Selectfluor and photo-sensitiser (2-cyclohexen-1-one) leads to the formation of the desired ammonio-fluoride **35** in 63 – 98% yield (Scheme 1.14) [36]. The yield was calculated based on NMR data. More substituted olefins typically lead to trace fluorination, a mixture of products, or both, whereas monosubstituted alkenes perform best. Alkenes with an alkyl or aryl substituent, oxygen-containing functional groups like carbonyl, acetoxy, benzoyloxy, and

sulfonyl, as well as nitrogen-containing functional groups like amido, phthalimido, sulfonamide, and cyano, were found to selectively provide the ammoniofluorinated products in good yields.



Scheme 1.14: Regioselectivity fluorofunctionalization of alkene

Naveen and Balamurugan reported a catalyst-free electrophilic mono-fluorination of tertiary propargyl alcohols with Selectfluor, resulting in either α-fluoro-β-hydroxy ketones or α-fluoro-ynols, depending on the alcohol substituent [37]. The anticipated α-fluoro-β-hydroxy ketones **37** were produced in good yield when aryl propargyl alcohol **36** was treated with Selectfluor in nitromethane under a nitrogen environment at 70 °C. In contrast, the reaction of alkyl propargyl alcohol produces α-fluoro-ynols **38** (Scheme 1.15).



Scheme 1.15: Preparation of α-fluoro-β-hydroxy ketones/ α-fluoro-ynols

N-Fluorobenzenesulfonimide (NFSI) (Figure 1.6) was developed by Differding and coworkers in 1991. Fluorination of benzenesulfonimide with 10% F_2/N_2 at −40 °C in acetonitrile in the presence of powdered sodium fluoride produces the reagent in good yield. It is a bench stable white crystalline solid with a melting point of 114–116 °C [38]. NFSI has been successfully used for the fluorination of various classes of organic compounds.

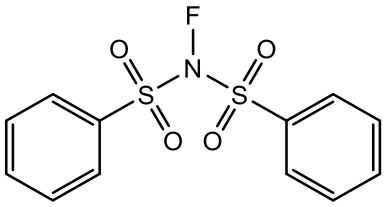
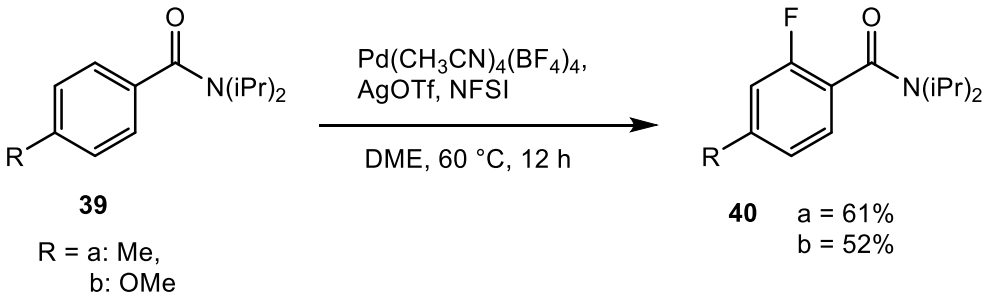


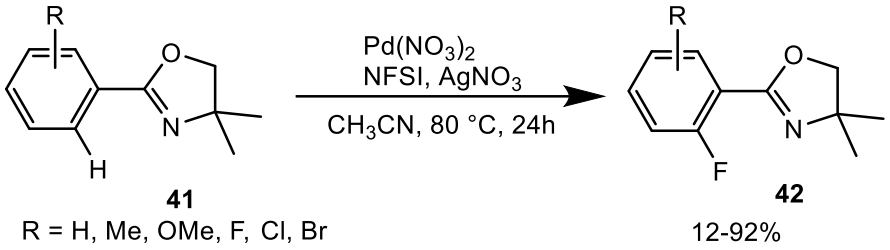
Figure 1.6: *N*-Fluorobenzenesulfonimide (NFSI)

Qiu et al. reported the *o*-fluorination of methyl or methoxy substituted N, N-diisopropylbenzamide by palladium-catalysed fluorination in the presence of NFSI [39]. The benzamide 39, on reaction with $Pd(CH_3CN)_4(BF_4)_4$ (10 mol%), AgOTf (20 mol%), NSFI (1.5 eq.), in DME at 60 °C for 12 h, gives the 2-fluorobenzamide 40 in 52 – 61% yield (Scheme 1.16) [39].

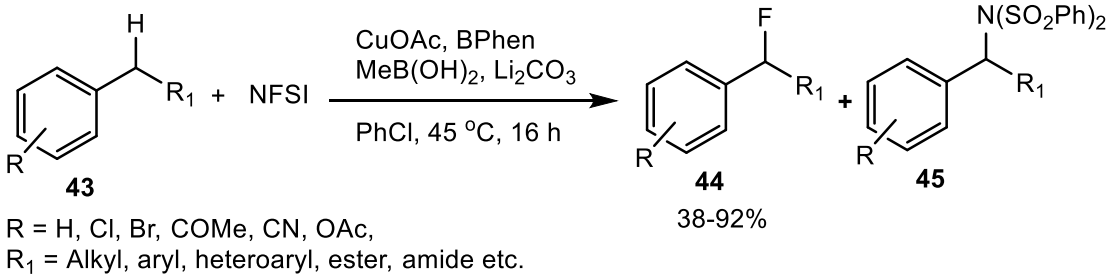


Scheme 1.16: Palladium-catalysed fluorination of benzamides

Dimethyloxazoline was investigated as an *ortho*-directing removable group for Pd-catalysed C-H fluorination of arene [40]. The oxazoline is easily converted to carboxylic acid, giving the wide synthetic application of this transformation. The oxazoline **41,** on treating with NFSI, in the presence of catalyst $Pd(NO_3)_2$ and activator $AgNO_3$ in MeCN, converts to *ortho* fluorinated product **42,** (Scheme 1.17) [40]. A copper-catalysed benzylic fluorination of substituted aromatics **43** using a redox buffer and Brønsted base was developed by the Stahl group [41]. NFSI oxidised the Cu^{I} to Cu^{II} in the reaction. $MeB(OH)_2$ acts as a "redox buffer" for the Cu catalyst and slowly reduces the Cu^{II} to Cu^{I} during the reaction. The investigation demonstrates that the reaction proceeds to the form C−N **44** over the C−F **45** bond in the absence of $MeB(OH)_2$, BPhen or base. The reaction is compatible with a different substituent, such as Br, OMe, OAc, Cl, CN, and t-Bu on the benzene ring and methyl, Cl, Br, ester, ether, cyclic rings, phenyl rings, and heterocycles on the alkyl chain (Scheme 1.18).

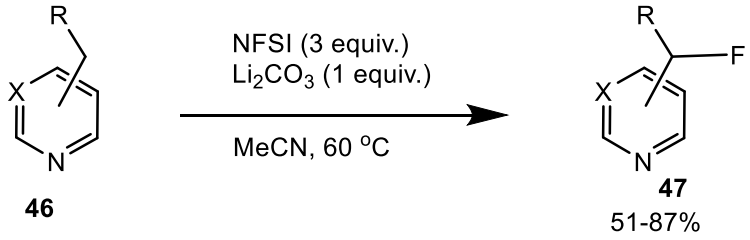


Scheme 1.17: Oxazoline-directed fluorination of arene



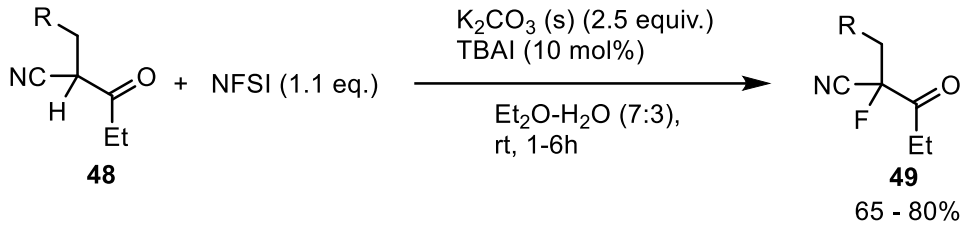
Scheme 1.18: Copper-catalysed benzylic fluorination

A selective fluorination method was given for pyridylic C-H bond, where the reaction proceeds well by simply stirring the pyridylic compound, like 4-(cyclopropylmethyl)pyridine **46,** in excess of NFSI and lithium carbonate in MeCN at 60 °C to give the pyridylic fluorinated product **47** in 77% yield (Scheme 19) [42]. The pyridilic fluorination is smooth with 2- and 4-substituted pyridines but fails with 3-substituted pyridines.



Scheme 1.19: Fluorination of 4-(cyclopropylmethyl)pyridine

Benzyl and allyl substituted α-cyanoacetates **48** were electrophilically fluorinated by Jain and Das using a phase transfer catalyst (TBAI) in diethyl ether/water (7:3) co-solvent with NFSI and K_2CO_3 at room temperature to produce the excellent yield of α-fluorinated α-cyanoacetate derivatives **49** in an aqueous and mild environment (Scheme 20) [43]. The reaction proceeds in the absence of water and PTC but takes a longer time.



R = Ph, 4-$MeOC_6H_5$, 4-$CF_3C_6H_5$, 3-BrC_6H_5, 4-$NO_2C_6H_5$, CH_2=CH_2 etc.
TBAI = Tetrabutyl ammonium iodide

Scheme 1.20: α-Fluorination of allyl and benzyl substituted α-cyanoacetates

1.3.2 Nucleophilic Fluorination

Nucleophilic fluorination is an alternative method for introducing a fluorine atom to a molecule by a polar process. This method is cheaper, has better functional group (FG) tolerance compared to electrophilic fluorination, and is more desirable for ^{18}F PET imaging. Furthermore, in contrast to electrophilic fluorinating reagents, the nucleophilic fluorinating reagent exhibits no oxidising properties, hence offering better functional group compatibility [44,45]. From the very first reported nucleophilic fluorination in 1835, the field has advanced in designing nucleophilic reagents in nearly 200 years; however, the most effective nucleophilic fluorinating reagents are limited to only those shown in Figure 1.7 [46,47].

1.3.2.1 Alkali metal fluoride

Alkali metal fluorides, like LiF, NaF, KF, and CsF, are cheap sources of nucleophilic fluorine; however, their limited solubility in organic solvents restricts their widespread applications. Phase transfer catalyst [48] has been successfully employed to increase the solubility and reactivity of metal fluoride in the organic solvent. CsF is the most reactive metal fluoride, but due to the cost benefits, the spray-dried KF is the most widely used reagent. For example, KF was used for the formation of β-fluoroamine **51** by fluorination of β-chloroamine **50** in the presence of *N*-ethylated bis-urea catalyst **52** (Hydrogen Bonding Phase-Transfer Catalysis, HB-PTC) at –15 °C in $CHCl_3$ (0.5 M) for 72 h, giving moderate to high yield (Scheme 1.21) [49].

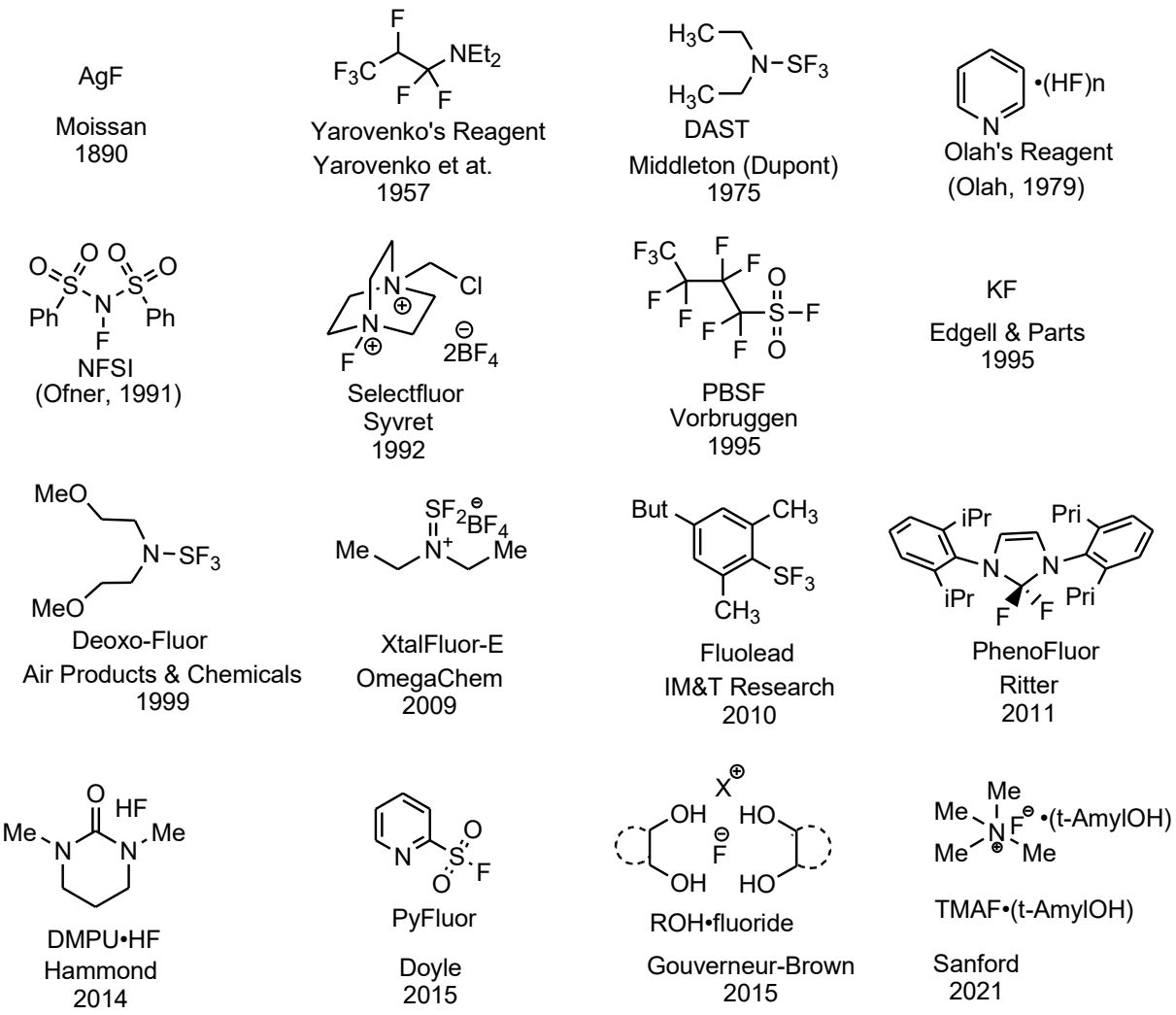
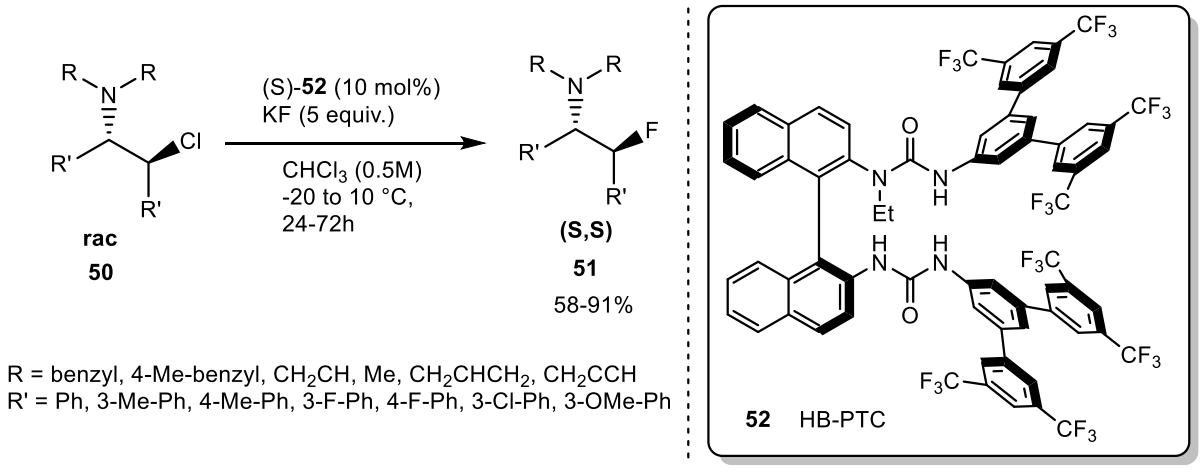
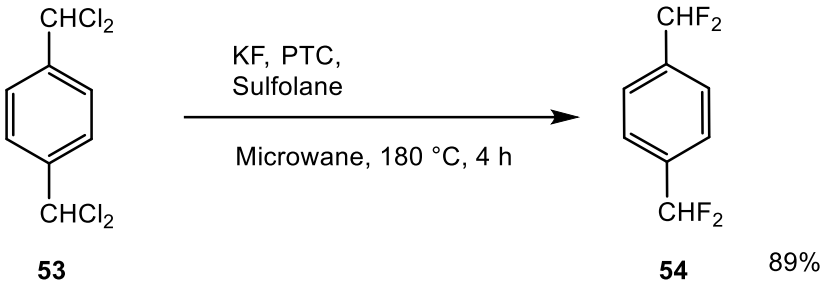


Figure 1.7: Nucleophilic fluorinating agents



Scheme 1.21: Fluorination of *rac*-β-chloroamine with KF/HB-PTC

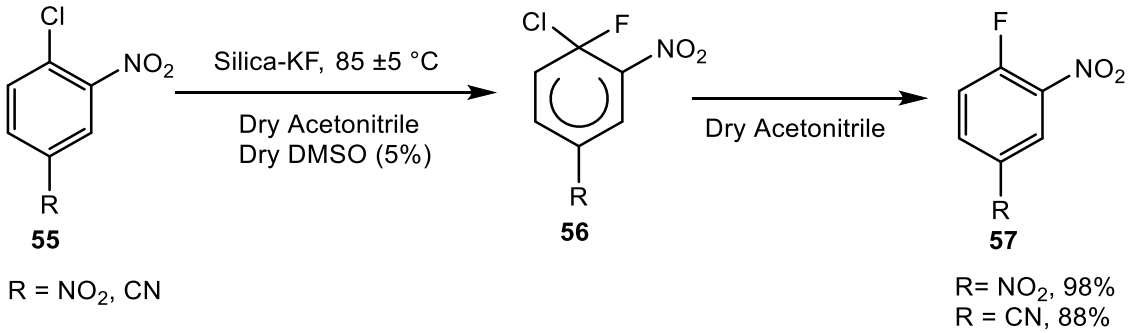
Pan et al. reported the microwave-assisted fluorination of 1,4-bis(dichloromethyl)benzene **53** to give 1,4-bis(difluoromethyl)benzene (**54**) [50]. The reaction proceeds well with KF, phase transfer catalyst (3 mol% Ph_4PCl and 1 mol% 18-crown-6) in Sulfolane at 180 °C, providing excellent yield (89%) (Scheme 1.22).



PTC = phase transfer catalyst (3 mol % Ph_4PCl and 1 mol % 18-crown-6)

Scheme 1.22: Microwave-assisted synthesis of 1,4-bis(difluoromethyl)benzene

2,4-Dinitrochlorobenzene and 4-chloro-3-nitrobenzonitrile **55** were fluorinated with a novel silica-KF reagent to form 4-fluoro-3-nitrobenzene derivative **57** [51]. Reaction was performed with silica-KF composite in dry acetonitrile and dry DMSO (5%) at 85 ±5 °C in two steps. In the first step, the carbon bearing the chlorine atom is attacked by the fluorine to form the Meisenheimer complex **56** under nitrogen atmosphere. The chlorine atom leaves the complex **56,** on further heating at 80 °C in dry CH_3CN, giving the fluorinated product **57** in the second step **(**Scheme 1.23) [52].



R = NO_2, CN

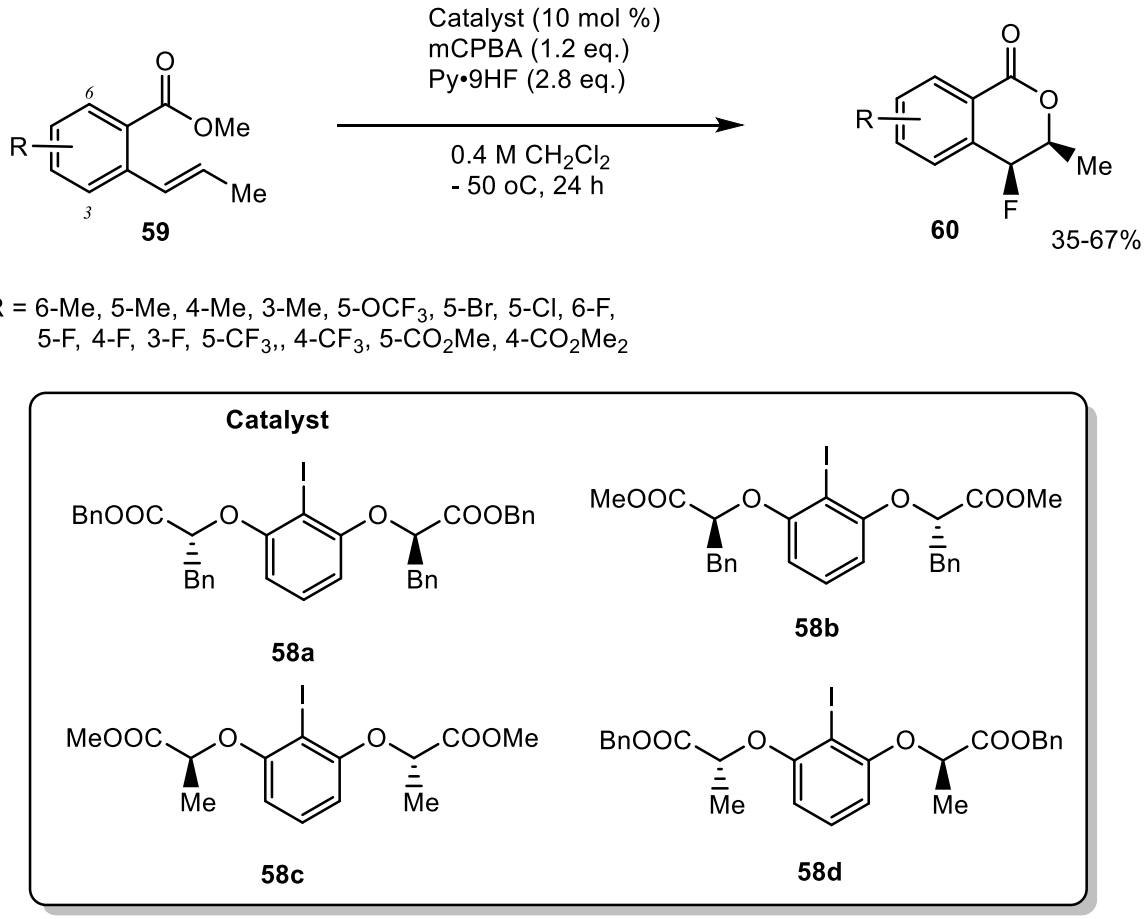
R= NO_2, 98%
R = CN, 88%

Scheme 1.23: Silica–KF reagent in fluorination

1.3.2.2 Amine-HF reagents

Hydrofluoric acid (HF) is the simplest reagent for nucleophilic fluorination, but, at the same time, it is the most hazardous reagent used in synthetic chemistry [53]. This problem has

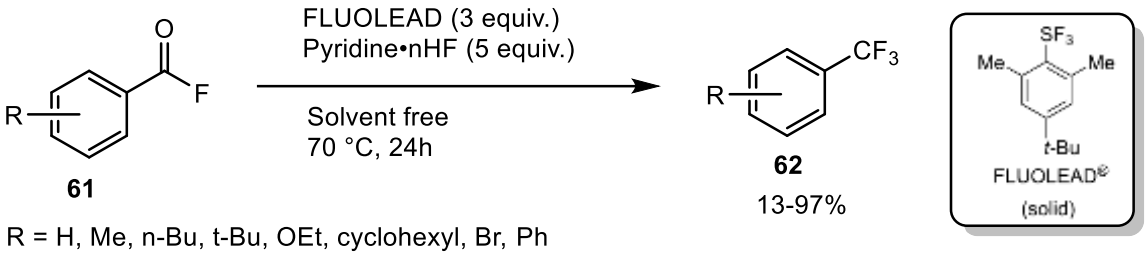
been solved to some extent by stabilising HF with the addition of a hydrogen bond acceptor, e.g., Olah's reagent Pyridine-HF(x) (Py•xHF) [54]. These poly(hydrogen fluoride) can be prepared not only with pyridine but also with picoline, triethylamine, and triethanolamine and contain up to 70 wt% hydrogen fluoride. These reagents have found applications in various fluorination reactions, including dehydroxyfluorination of alcohols, hydrofluorination of alkenes and alkynes, ring-opening fluorination of epoxides and deaminative fluorination of α-amino acids. Woerly et al. demonstrated that methyl benzoate derivatives **59,** when reacted with Py·9HF, *m*CPBA, and Resorcinol derivatives catalyst **58a-d** (10 mol%) in dichloromethane at -50 °C, undergo cyclisation to give fluoroisochromanone **60** as the exclusive product in 86% yield (Scheme 1.24) [55].



Scheme 1.24: Enantioselective synthesis of 4-fluoroisochromanones

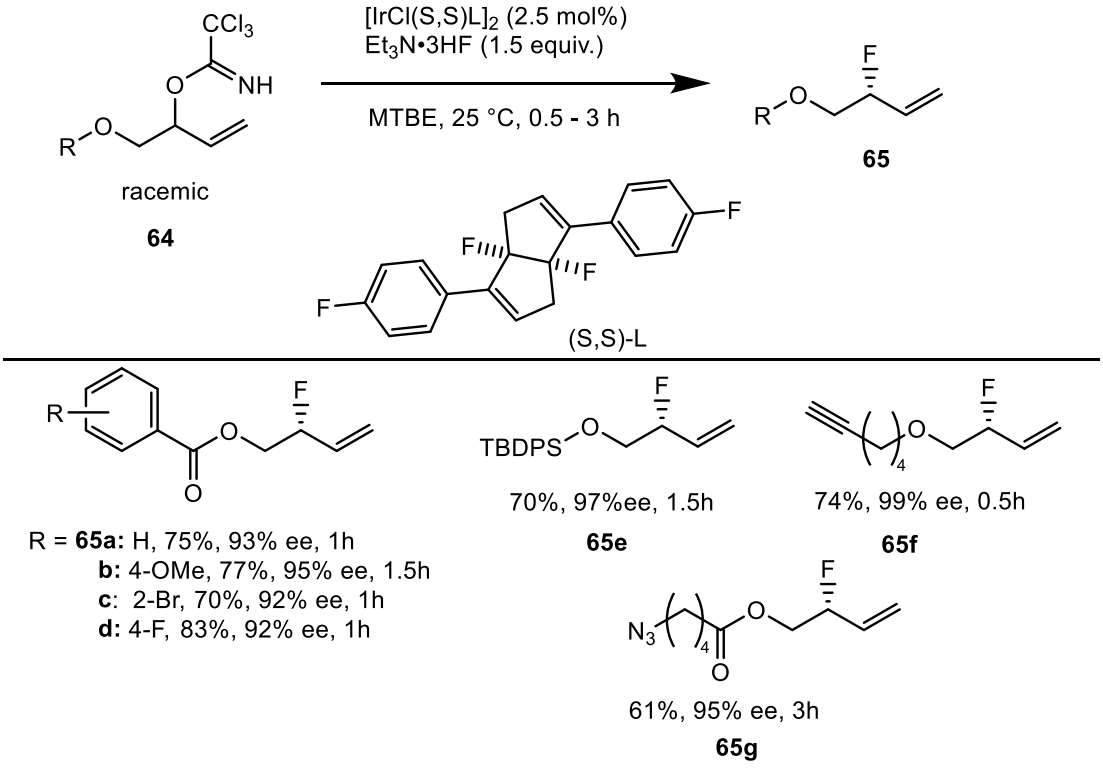
Another group used FLUOLEAD®/Olah's reagent for the deoxofluorination of acyl fluoride to a trifluoromethyl compound in a solvent-free environment [56]. Carbonyl fluoride **61,** on reaction with FLUOLEAD® and *n*HF·pyridine under solvent-free conditions at 70 °C

for 24 h, provides the trifluoromethylated product **62** in good to excellent yield (Scheme 1.25). The reaction works well with various aromatic, heteroaromatic, aliphatic, and alicyclic acyl fluorides [56].



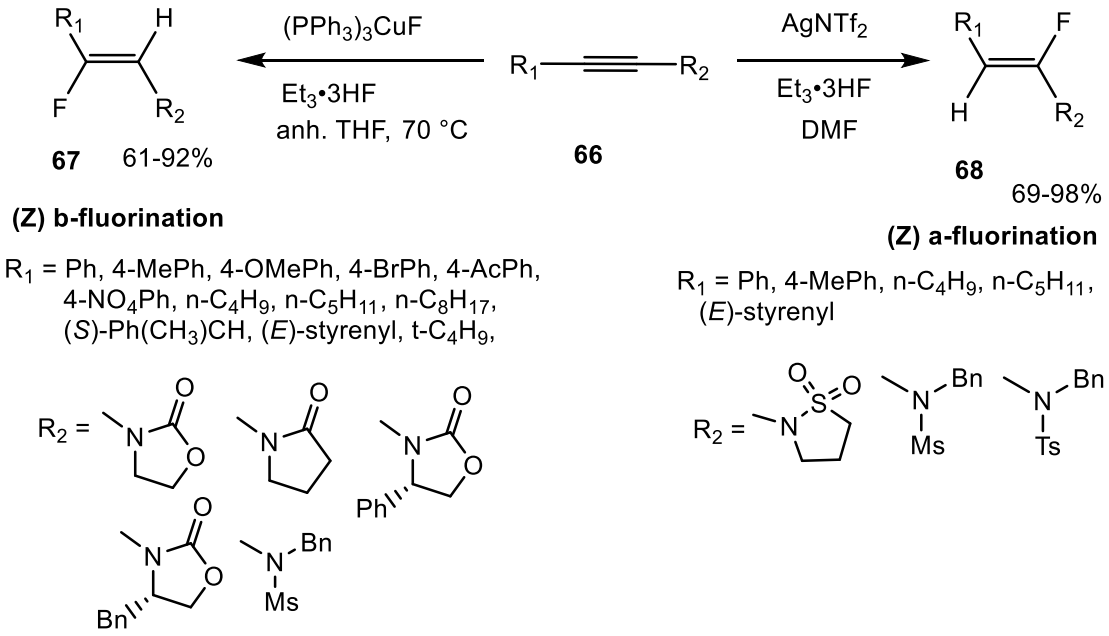
Scheme 1.25: Deoxyfluorination of acyl fluoride to trifluoromethylated compounds

In another report, racemic β-oxygen-substituted imidates were fluorinated in an enantioselective allylic fluorination with a chiral catalyst bicyclo[3.3.0]octadiene-ligated iridium complex and $Et_3N{\cdot}3HF$ [57]. β-oxygen-substituted allylic trichloroacetimidate **64** on reaction with $Et_3N{\cdot}3HF$ in presence of catalyst in MBTE gives the allylic fluoride **65a-g** in excellent yield with high enantioselectivity (Scheme 1.26) [57].



Scheme 1.26: $[IrCl(S,S)L]_2$ catalyzed allylic fluorination

Zhu et al. have developed a Cu(I)- or Ag(I)-catalysed fluorination with a relatively benign fluorine source like $Et_3N{\cdot}3HF$ gave β/α-site-regiocontrolled *trans*-hydrofluorination of alkynamides [58]. $(PPh_3)_3CuF$ catalysed hydro fluorination of alkynamides **66** with $Et_3N.3HF$ in anhydrous tetrahydrofuran, afforded the desired β-site regio-controlled fluoroenamide (Z) **67** in high yield with excellent regioselectivity (Scheme 1.27) [58]. The reaction yields are highly affected by the solvent. $(PPh_3)_3CuF$ shows better catalytic ability than CuCl. The reaction yield decreased using other fluorinating agents like pyridine/HF, LiF, CsF, and ZnF_2. The reaction is suitable for both N-aryl alkynylated and N-alkylalkynylated oxazolidinones for the β-site regioselective fluorination. Electron-donating group on arene of N-aryl alkynyl substituted oxazolidinones offer higher reactivity and regioselectivity as compared to the electron-withdrawing group. The alkenyl alkynyl-substituted substrate also undergoes the conversion; however, N-sulfonyl acyclic ynamide does not support the conversion. The reaction also occurs with a sterically hindering group like *t*-Bu bearing substrate. The silver catalyst $AgNTf_2$ leads to (Z) α-fluorination **68** with $Et_3N.3HF$ in dimethylformamide (DMF) in excellent yield (Scheme 1.27) [58].

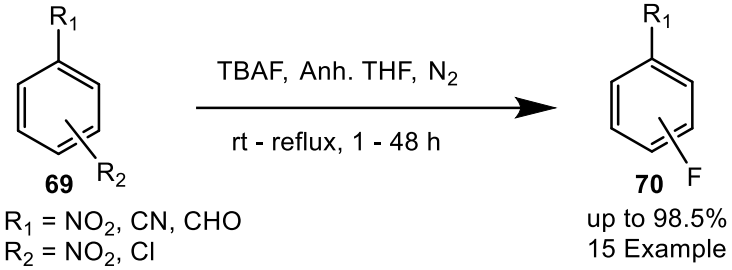


Scheme 1.27: Cu(I) and Ag(I) catalyzed *trans*-hydrofluorination of ynamides with $Et_3N{\cdot}3HF$

1.3.2.3 Tetrabutylammonium fluoride (TBAF) reagent

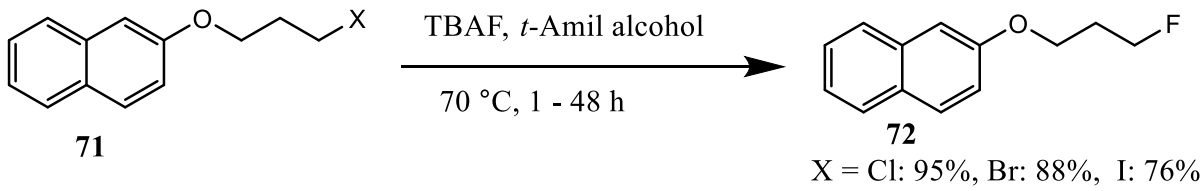
Tetrabutylammonium fluoride (TBAF) is also an interesting source of nucleophilic fluorine [59]. Obtaining this reagent in anhydrous form is a critical challenge. The *in-situ* generation of TBAF by reaction of hexafluorobenzene with tetrabutylammonium cyanide is a

useful strategy to produce this reagent in anhydrous form [60]. Yu Feng Hu and coworkers demonstrated the utility of TBAF for the fluorination of nitroaromatics and chloroaromatics under mild conditions [61]. Stirring a mixture of substrate **69** and TBAF in anhydrous THF for the required time, at room temperature or in reflux conditions under an inert environment, afforded the fluorinated product **70** in excellent yield [61]. The observation revealed that the substrate bearing electron-withdrawing groups at the 2- or 4-position requires only a few hours at room temperature. On the other hand, the substitution at the 3-position requires a longer duration of heating and a higher temperature to complete the reaction (Scheme 1.28).

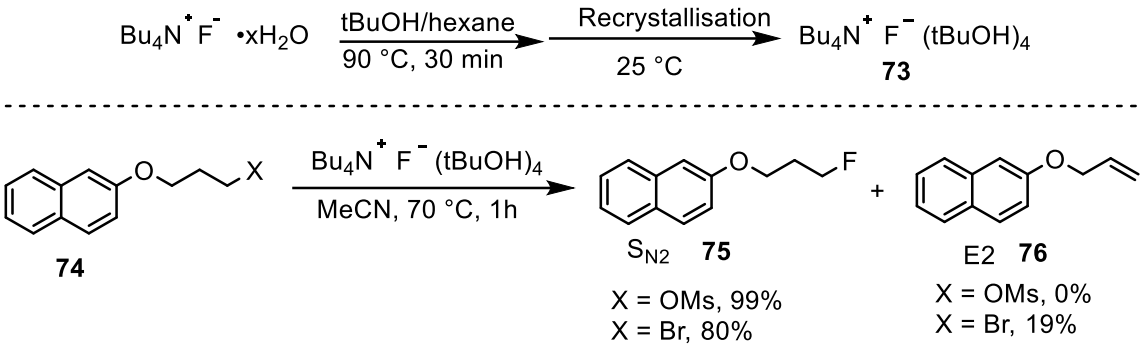


Scheme 1.28: Fluorination of nitrobenzene derivatives

Primary alkyl halides were fluorinated by Kim et al., in a TBAF mediated nucleophilic fluorination a nonpolar protic solvent. The reaction of primary alkyl halide **71** and TBAF in t-amyl alcohol at 70 ºC gives the alkyl fluoride **72** in good to excellent yield [59]. Although the rate of reaction in *t*-amyl alcohol is lower than the aprotic polar solvent (CH_3CN) but the product yield is sufficiently high, reducing the side reaction (olefins and alcohol). The *t*-amyl alcohol reduces the basicity of TBAF while maintaining the nucleophilicity of the reagent to provide a reasonable reaction rate even under mild conditions (Scheme 1.29) [62]. TBAF is a widely used nucleophilic fluorinating reagent, but its hygroscopic nature makes it difficult to get it in anhydrous form. Fluorination using hydrated reagent competes with hydroxylation to form alcohols as the side product [63]. To resolve the problem, Kim and Jeong group [64] prepared the TBAF(*t*-BuOH)$_4$ complex **73** by refluxing the hydrated TBAF with *t*-BuOH in hexane for 30 minutes at 90 °C and used as a F^- source in nucleophilic fluorination of mesylate, tosylate and bromide. The mesylate **74** on fluorination with the fluoride source (2 equiv.) in acetonitrile at 70 °C gives almost a quantitative yield of fluorinated product **75** in 1 hour (Scheme 30). The bromide demonstrated less selectivity towards fluorination (S_N2) and resulted in a mixture of fluorination (S_N2) and elimination (E2) product **76**. The other solvents, like DMF and *t*-BuOH, are also suitable solvents for this reaction.

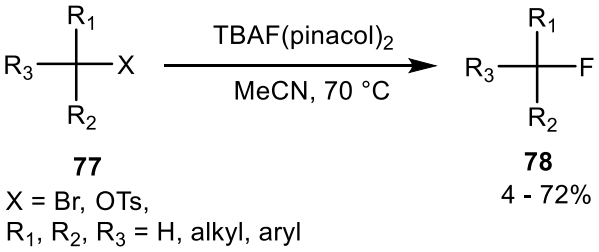


Scheme 1.29: Fluorination of alkyl halide in a non-polar protic solvent



Scheme 1.30: TBAF(t-BuOH)$_4$ complex mediated nucleophilic fluorination

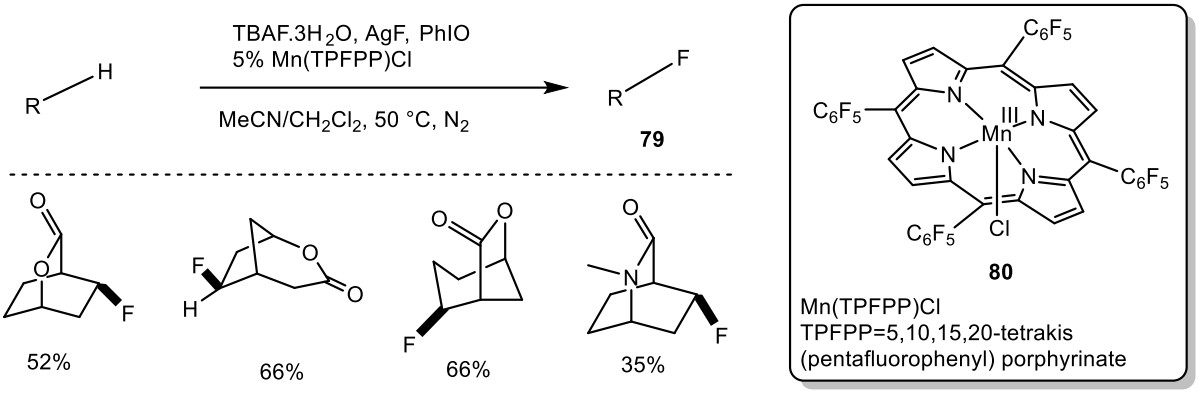
Winton et al. studied the applicability of tetra-*N*-butylammonium fluoride bis-pinacol [TBAF(pinacol)$_2$] for nucleophilic fluorination of primary, secondary, and tertiary tosylates and alkyl bromides [65]. The substrate **77,** on reaction with TBAF (pinacol)$_2$ at 70 °C in acetonitrile, gives the fluorinated product **78** (Scheme 1.31). The primary substituted substrate shows better conversion compared to the secondary or tertiary substituted substrate. Bromide shows better conversion after 18 h of reaction, while for tosylate, 2 h was sufficient reaction time.



Scheme 1.31: TBAF(pincacol)$_2$ mediated fluorination

The selective fluorination of unactivated aliphatic C-H bond of electron-deficient and sterically hindered molecules catalysed by electron-deficient manganese porphyrin Mn(TPFPP)Cl **80** was explored [66]. Fluorination of lactone and lactam derivatives in

optimised conditions gives a moderate to good yield of fluorinated products **79** (Scheme 1.32) [66].

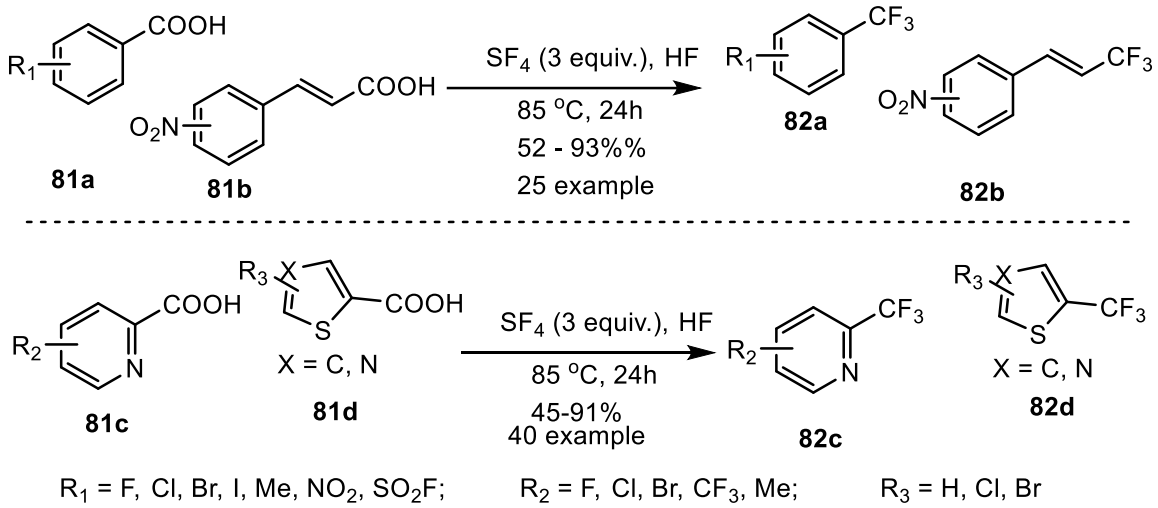


Scheme 1.32: Fluorination of lactones and a lactam

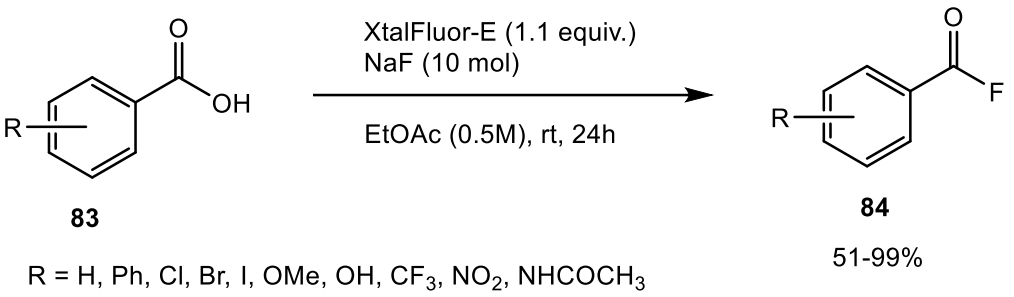
1.3.2.4 Sulphur Reagent

Diethylaminosulfur trifluoride (DAST) [67] emerged as a popular reagent for converting alcohols to the corresponding fluoride, along with several other transformations. However relative instability of the sulphur-nitrogen bond limited its use to under 50 °C (it can explode if heated over 50 °C). Morpholino Sulphur trifluoride (MOST) and Deoxofluor are some other useful reagents used in a similar activation displacement sequence. A metal-free deoxofluorination of an aromatic and heteroaromatic carboxylic acid with SF_4 was demonstrated [68]. The aromatic carboxylic acid **(81a-b)** on treatment with SF_4 at 85 – 90 °C for 24 h afforded the corresponding trifluoromethyl substituted product **(82a-b)** in 52 – 93% yield. Similarly, the five- or six-membered heterocyclic carboxylic acid **(81c-d)** bearing different substituents also converts to the corresponding trifluoromethyl-substituted product **(82c-d)** in 45-91% yield (Scheme 1.33).

Further, Paquin et al. employed diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E) for room temperature deoxofluorination of carboxylic acids [69]. XtalFluor-E plays both roles of activator as well as a fluoride source. Carboxylic acid **83** on treatment with XtalFluor-E and a catalytic amount of NaF in EtOAc (0.5 M) at room temperature (rt) offers the acyl fluoride **84** in excellent isolated yield in 24 h (Scheme 1.34) [69].

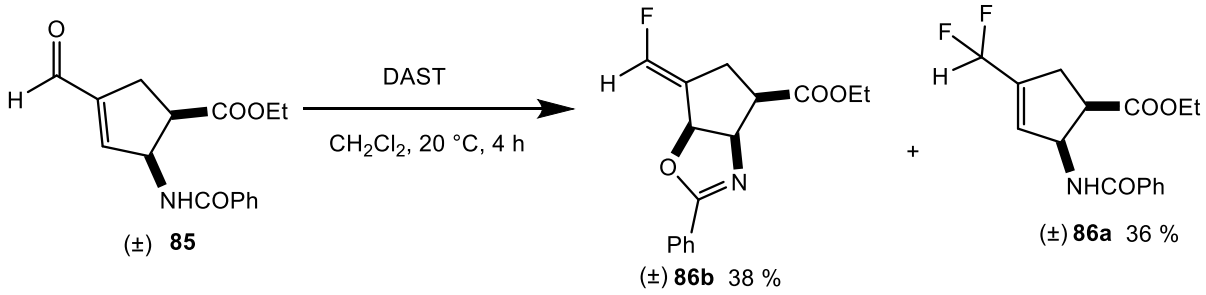


Scheme 1.33: Deoxofluorination of the aromatic and heteroaromatic carboxylic acid with SF_4



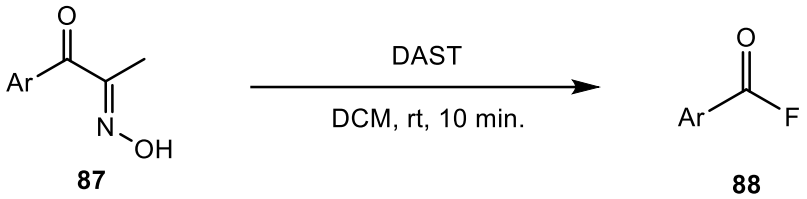
Scheme 1.34: NaF-assisted deoxofluorination of carboxylic acids with XtalFluor-E

Another group used DAST and Deoxofluor for the deoxofluorination of α,β-unsaturated aldehydes [70]. Heating the mixture of α,β-unsaturated aldehydes **85** with DAST or deoxofluor in dichloromethane at 20 °C gives the allyl difluoride (1,2-addition) **86a** and vinyl fluoride (1,4-addition) **86b** moiety containing product in 1:1 ratio (Scheme 1.35) [70].



Scheme 1.35: DAST mediated fluorination of unsaturated aldehyde

Kim and Lim reported a DAST-mediated C-C bond cleavage of α-oximes activated 1,2-diketone to form acyl fluoride [71]. Reacting α-oxime of 1,2-diketone **87** with DAST in dichloromethane at room temperature gives the benzoyl fluoride **88** within 10 minutes (Scheme 36). The other fluorinating agent, like Deoxo-Fluor (93% yield in 10 minutes), XtalFluor-E/Et_3N/HF (83% yield in 10 minutes), Fluolead (88% yield in 10 minutes), Ishikawa's reagent (79% yield in 10 minutes), and Prakash's reagent (85% yield in 60 minutes), also gives comparable conversion [71].

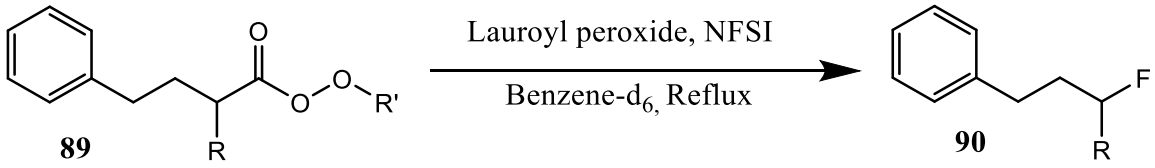


Ar = a: 4-OMe-Ph, 87%; f: 3-Br-Ph, 81%; k: 3,4-di-Cl-Ph, 73%;
b: 2-F-Ph, 80%; g: 4-CF_3-Ph, 73%; l: 3-NO_2-Ph, 83%;
c: 4-OH-Ph, 74%; h: 4-CH_2OH-Ph, 41%; m: 4-PhCO-Ph, 95%;
d: 4-CH_2Br-Ph, 87%; i: 4-CH_2OAc-Ph, 86%; n: 4-COOMe-Ph, 74%;
e: 4-$C(CH_2)CH_3$-Ph, 82%; j: 4-CHCH-Ph, 91%

Scheme 1.36: Synthesis of acyl fluoride

1.3.3 Radical Fluorination

Radical fluorination is a different approach from nucleophilic and electrophilic fluorination, but it has limited synthetic utility due to low selectivity and the hazardous nature of the first generation of reagents (F_2, hypofluorite, XeF_2) [45]. A selective radical fluorination has become possible by use of N-F reagents (NFSI, Selectfluor and N-fluoropyridinum salts). Becerril et al have demonstrated the decarboxylative fluorination of tert-butyl peresters by NFSI [72]. On refluxing a mixture of peracetate **89**, NFSI and radical initiator lauroyl peroxide in benzene-d_6 produces up to 98% yield of fluorodecarboxylated product **90** in a short reaction time (Scheme 1.37).

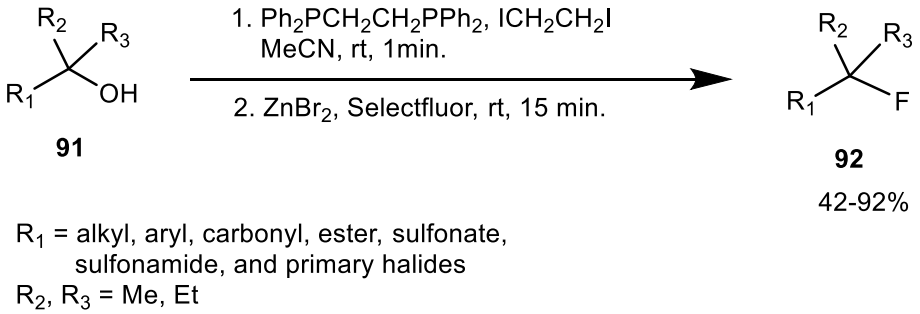


R, R' = Alkyl

up to 98%

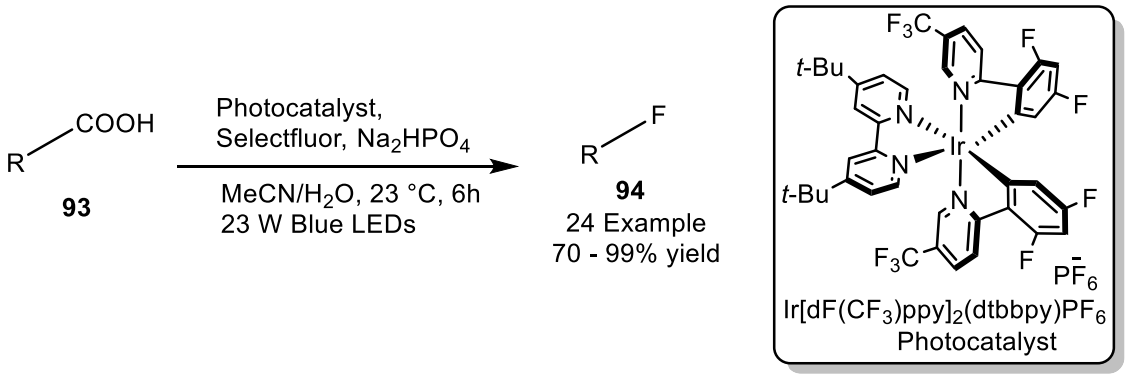
Scheme 1.37: Decarboxylative fluorination of tert-butyl peresters

The dehydroxylative fluorination of the tertiary alcohols was studied by Chen and coworkers in a $Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$-mediated activation of the tertiary hydroxyl group [73]. The tertiary alcohol **91,** on reaction with $Ph_2PCH_2CH_2PPh_2$, ICH_2CH_2I, $ZnBr_2$, and Selectfluor (3 eq.) in MeCN, provides the tertiary fluoride **92** in 15 minutes at room temperature with high yield (Scheme 1.38). The reaction proceeds in an iodination/bromination-fluorination sequence. First, $Ph_2PCH_2CH_2PPh_2$ reacts with ICH_2CH_2I to produce I^-, which is readily consumed in a redox reaction with Selectfluor. Since the $ZnBr_2$ does not completely dissociate to provide bromide ions, the redox reaction of $ZnBr_2$ with Selectfluor would not occur easily, and it will promote the bromination effectively. Therefore, $ZnBr_2$ is essential for fluorination.



Scheme 1.38: Dehydroxylative fluorination of tertiary alcohols

MacMillan reported the direct synthesis of alkyl fluorides from aliphatic carboxylic acids by using a commercial photocatalyst and a blue LED light source [74]. A range of aliphatic carboxylic acids **93** on irradiation with visible light (23 W Blue LED) at 23 °C for 6 hours, in presence of Selectfluor, heteroleptic iridium (III) photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and disodium hydrogen phosphate in $MeCN/H_2O$ leads to formation of alkyl fluoride **94** in excellent yield (Scheme 1.39). The results of the reaction demonstrated that shorter reaction durations and less quantity of electrophilic fluorinating reagent are needed for highly activated substrates. The carboxylate was subjected to photon-induced oxidation to form carboxyl radicals, which easily underwent CO_2-extrusion and F• transfer (from a fluorinating reagent) to produce the necessary fluoroalkanes.

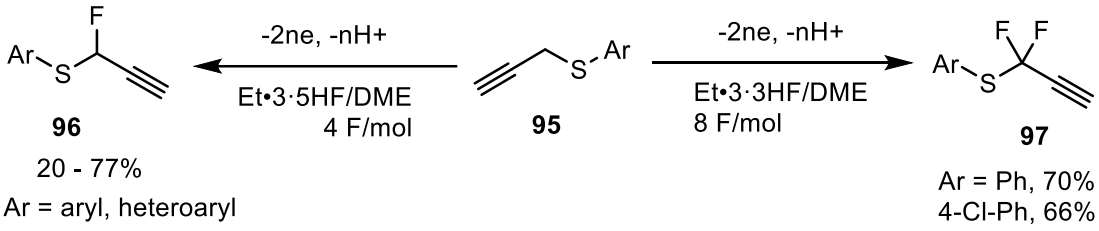


Scheme 1.39: Decarboxylative fluorination of carboxylic acid

1.3.4 Electrochemical Fluorination

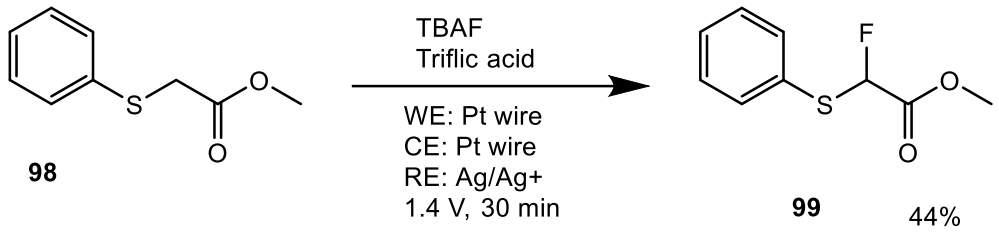
The electrochemical fluorination was performed by J.H. Simons for the first time in the 1940s using anhydrous HF [75]. Perfluorinated compounds can be obtained in a step process by electrochemical fluorination. Cleavage of the C-C bond normally occurs in this process, and selectivity is low; therefore, synthesis of partially fluorinated compounds is difficult. In recent years, HF-pyridine (Olah's reagent) has been used for the selective fluorination of both aliphatic and aromatic substrates [54]. Another reagent, $Et_3N{\cdot}3HF$, is also found to be useful for the selective electrochemical Fluorination [76]. Selective electrochemical fluorination is generally carried out in aprotic solvents containing supporting electrolytes, leading to mostly mono- and difluorinated products. However, product selectivity and durability of anodes are always a concern.

Fuchigami et al. prepared the fluorinated triazole by electrochemical fluorination of an alkyne derivative [77]. The substrate **95** selectively converts to mono-fluorinated **96** or difluorinated product **97,** depending on the supporting HF salt and the amount of electricity used. The HF source $Et_3N{\cdot}3HF$ and 8.0 F/mol electricity produce the difluorinated product, while $Et_3N{\cdot}5HF$ and 4 F/mol electricity leads to the mono-fluorinated product (Scheme 1.40).

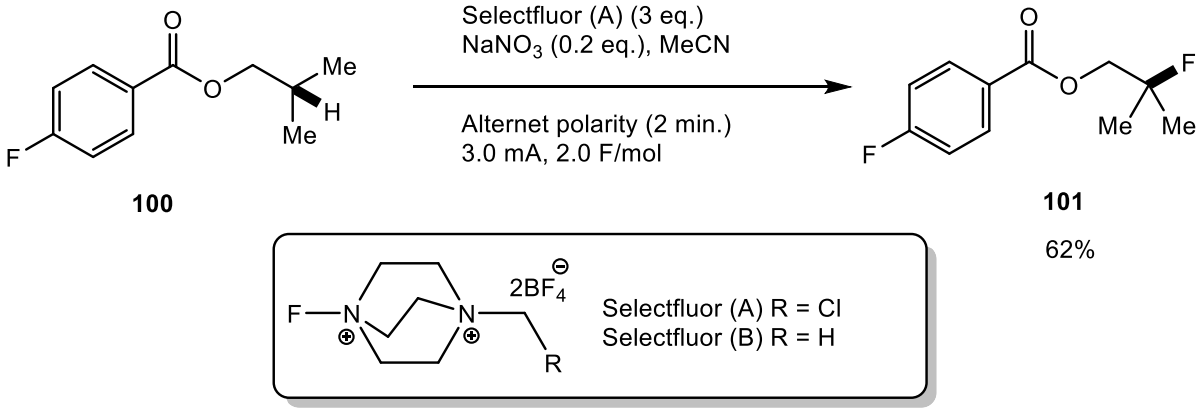


Scheme 1.40: Electrochemical fluorination of alkyne derivative

In another report, methyl-2-fluoro-2-(phenylthio)acetate was prepared by electrochemical fluorination of methyl 2-(phenylthio)acetate using TBAF [78]. The substrate **98,** on fluorination at constant potential with TBAF and triflic acid, gives the fluorinated acetate **99** in 44% yield at 60 °C (Scheme 1.41). Another group reported electrochemical fluorination of unactivated primary and secondary C(sp^3)-H bonds with Selectfluor and nitrate additives [79]. By fluorinating the substrate **100** with Selectfluor (3.0 eq.) and $NaNO_3$ (0.2 eq.) in acetonitrile at 3 mA using a pair of reticulated vitreous carbon (RVC) electrodes, the compound **101** was produced in 62% yield (Scheme 1.42) [79]. Nitrate is required to start the reaction because it is oxidised anodically to create a radical species that can abstract the hydrogen from the substrate. The reaction is oxygen-sensitive [80].



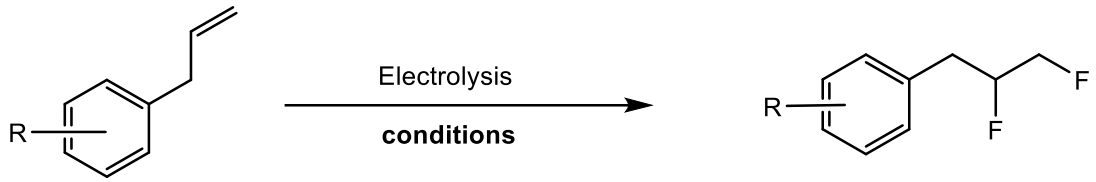
Scheme 1.41: Methyl-2-(phenylthio)acetate fluorination using TBAF



Scheme 1.42: Electrochemical fluorination of C(sp^3)-H bond

Another report describes the electrochemical vicinal difluorination of an unactivated alkene by electrochemical generation of difluoro-λ^3-tolyl iodane [81]. The substrate allyl benzene (**102**) on electrochemical fluorination using iodotoluene as a mediator, in 3-part Py·5.6HF or Et_3N·5.6HF and one part co-solvent (solvent = CH_2Cl_2:HFIP = 7:3) and passing 3.5 F/kol electricity on Pt electrode gives the vicinal difluorinated product **103** in 81% NMR

yield in 12 h (Scheme 1.43). The yield is further increased by electron-withdrawing substitution on the aromatic ring.



102 **103** 12-60 % yield

R = Me, OMe, NMe_2, etc

Conditions:
316 (1.2 mmol) (0.3M) and iodotoluene (1 equiv.) in 3 part Py.5.6HF or Et_3N.5.6HF and 1 part CH_2Cl_2:HFIP (7:3); electrolysis : 12 mA, 3.5 F/mol, Pt electrode, undivided cell then stirring for 12h.

Scheme 1.43: Electrochemical vicinal difluorination of alkene

1.4 Research gap and present requirements

The electrophilic fluorination is very effective at forming the C-F bonds. But it has some inherent drawbacks. These include poor regioselectivity and chemoselectivity, arising due to the high reactivity of the fluorine source. These drawbacks often lead to polyfluorination in electron-rich arenes like phenols. It is also ineffective for monofluorination of alkynes or enolates without significant overoxidation or side reactions caused by radical paths. The nucleophilic fluorination uses fluoride sources like metal fluoride, HF-pyridine or TBAF. The low nucleophilicity of F^- due to its high hydration energy and basicity limits nucleophilic fluorination. This results in a larger proportion of elimination (E2) than substitution (S_N2) in secondary or tertiary alkyl halides. The application of nucleophilic reagents is very limited for the fluorination of non-activated aryl or vinyl systems without using hypervalent iodine or transition-metal catalysis. The radical fluorination methods, using initiators like photocatalysts or metal mediators with F_2 or hypofluorites, are prone to non-selective fluorination, arising from non-specific hydrogen atom transfer (HAT) or single-electron transfer (SET) mechanisms. The process results in overfluorination, HF elimination, or disproportionation byproducts, alongside safety hazards from explosive reagents, and requires controlled conditions to mitigate competitive pathways. Electrochemical fluorination uses anodic oxidation for in situ generation of fluorinating species. This process faces significant limitations, including limited selectivity for monofluorination, substrate-dependent faradaic efficiency, anode passivation by polymeric coatings in protic solvents, and scalability problems. The known catalytic methods suffered from high catalyst loading, limited substrate

scope, uncontrolled selectivity, and the requirement of coordinating groups. A key challenge is the development of novel fluorinating reagents to balance their reactivity, selectivity, develop lower molecular weight reagents with predictable and functional group tolerant, and develop fluorination by using fluoride, and catalyse by a readily available, inexpensive catalyst. With known wide applications of fluorinated compounds, there is always scope for the development of facile and environmentally friendly methods.

Intending to design and develop a catalyst or reagent for the fluorination of organic molecules, the following are the three main objectives was undertaken during the tenure of the research work.

Objective 1: Directed C–H Fluorination

Objective 2: Aliphatic C–H Fluorination

Objective 3: Aromatic/ hetero-aromatic C–H Fluorination

To fulfil the above objectives, the thesis has been divided into four chapters:

Chapter 1: Introduction

Chapter 2: Materials and Methods

Chapter 3: Results and Discussion

Chapter 4: Summary, Prospects, and Social Impact

References

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials and Instruments

The commercially available starting materials were purchased from various sources and used without further purification.

2.1.1 Chemicals

The chemicals used in this research work were either purchased directly from the reputed vendors/companies or synthesized. The following chemicals were purchased from different manufacturers/vendors as given in small brackets against their names.

i. **Fluorinating reagents:** Selectfluor, *N*-fluorobenzenesulfonimide (NFSI), Tetrabutylammonium fluoride trihydrate (TBAF •3H_2O), TBAF (1M Sol in THF), and Potassium Fluoride (Make: Spectrochem).

ii. **Acetophenone derivatives:** Acetophenone, 4-Methoxy acetophenone, 4-Methylacetophenone, 4-Nitroacetophenone, 4-Chloroacetophenone, 2,4-Dichloroacetophenone, and 3-Methoxy acetophenone (Make: Sigma Aldrich); 4-Fluoro acetophenone, 4-Bromoacetophenone, 3-Bromoacetophenone, 1-Acetonaphthone (Make: Spectrochem).

iii. **Indole derivatives:** Indole acetic acid (Make: Spectrochem), 3-methyl indole, and 1*H*-Indoleacetonitrile (Make: CDH).

iv. **Alcohols:** Methanol (CH_3OH), Ethanol (CH_3CH_2OH), *n*-Propanol ($CH_3CH_2CH_2OH$), *n*-Butanol ($CH_3CH_2CH_2CH_2OH$), 2-propanol ($(CH_3)_2CHOH$), and 3,3,3-Trifluoropropanol ($CF_3CH_2CH_2OH$) (Make: Spectrochem); 2-Chlorobenzyl alcohol, 4-Methoxybenzyl alcohol, 4-Nitrobenzyl alcohol, and Phenyl ethyl alcohol (Make: Sigma Aldrich).

v. **Solvents:** Acetonitrile (CH_3CN), chlorobenzene (PhCl), dichloromethane (CH_2Cl_2), 1,2-dichloroethane (CH_2ClCH_2Cl), and diethyl ether ($C_2H_5OC_2H_5$) (Make: Spectrochem); acetone (CH_3COCH_3), ethyl acetate, and hexane, (Make: Sigma Aldrich), petroleum ether (Make: Finar), and deuterated solvents for recording the NMR ($CDCl_3$, Methanol-d_4, and DMSO-d_6), (Make: Sigma Aldrich).

vi. **Other Chemicals and reagents:** Iron (III) nitrate, $Fe(NO_3)_3 \cdot 9H_2O$ (Make: Sigma Aldrich), Potassium Bromide (KBr) (Make: Sigma Aldrich), Sodium Bromide (NaBr), (Make: Sigma Aldrich), Lithium Bromide (LiBr) (Make: Sigma Aldrich), Anhydrous Sodium Sulphate (Make: Spectrochem), Sodium Chloride, (Make: Spectrochem), Ammonium chloride, (Make: Spectrochem), Sulphuric acid, *N, N′*-

Dicyclohexylcarbodiimide (DCC), 4-Dimethylaminopyridine (DMAP), Silica gel, mesh size: 60 – 120, and Silica gel, mesh size: 100 – 200 (Make: Spectrochem). Polyurethane (Elastollen® 13 series, Make: BASF).

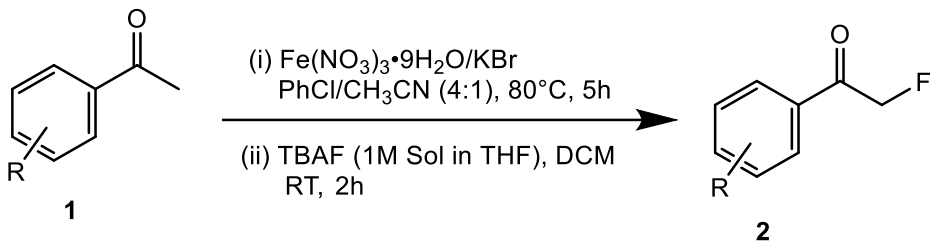
vii. **The ester derivatives of indole acetic acid** with different alcohols were synthesized in the laboratory using the literature methods: Methyl 2-(1*H*-indol-3-yl) acetate, Ethyl 2-(1*H*-indol-3-yl) acetate, n-Propyl 2-(1*H*-indol-3-yl) acetate, n-Butyl 2-(1*H*-indol-3-yl) acetate, Isopropyl 2-(1*H*-indol-3-yl) acetate, 3,3,3-trifluoropropyl 2-(1*H*-indol-3-yl) acetate, 2-Chlorobenzyl 2-(1*H*-indol-3-yl) acetate, Phenethyl 2-(1H-indol-3-yl) acetate, 4-nitrobenzyl 2-(1H-indol-3-yl) acetate, 4-Methoxybenzyl 2-(1H-indol-3-yl) acetate.

2.1.2 Instruments

A magnetic stirrer with a hot plate (Make: IKA, Model: RCT basic with external temperature control) was used for controlled heating and stirring of the reaction mixture. TLC plates, Silica gel 60 RP-18 F_{254}s (Make: Merck), were used for monitoring the reaction. The melting points of the synthesized compounds were determined by the OptiMelt Automated Melting Point System (Make: Stanford Research Systems). The NMR of the synthesized starting materials and final compounds was recorded on an NMR spectrometer (Make: JEOL, JNM-ECZL S series), operating at 400 MHz for ^{1}H NMR, 376 MHZ for ^{19}F NMR, and 100 MHz for ^{13}C NMR, in solution phase using deuterated solvents. The IR spectra were measured with an FTIR (Make: Thermo Scientific, Model: Nicolet™ iS50) Spectrometer.

2.2 General procedure for synthesis of α-fluoroacetophenone derivatives (2)

The synthesis of α-fluoroacetophenone derivatives (or 2-fluoro-1-(4-methoxyphenyl)ethenone) have been done as per Scheme 2.1.

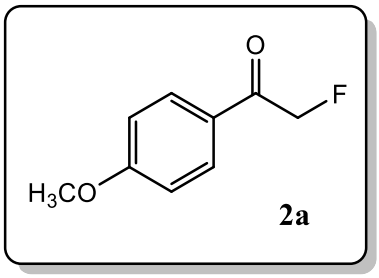


R: (a) 4-OCH_3, (b) 3-OCH_3, (c) 4-CH_3, (d) H, (e) 4-Br, (f) 3-Br, (g) 4-Cl, (h) 2,4-dichloro, (i) 4-F, (j) 4-NO_2

Scheme 2.1: Synthesis of α-fluoroacetophenone derivatives

In a two-necked round-bottom flask (50 mL) fitted with a reflux condenser and magnetic stirring bar, the acetophenone derivative (**1**) (1 mmol) and KBr (1.1 mmol) were dissolved in chlorobenzene (4 mL) and acetonitrile (1 mL). After that, Iron (III) nitrate nanohydrate (1.5 mmol) was added, and the reaction mixture was stirred at 80 °C for 5 h. The progress of the reaction was monitored by TLC. After complete consumption of acetophenone, as indicated by TLC, the reaction mixture was cooled to room temperature. TBAF (1 M solution in THF) (6 mmol) and 2 mL of dichloromethane were then added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in diethyl ether (30 mL), and a saturated solution of ammonium chloride (20 mL) was added to it. The mixture was stirred at room temperature for 10 minutes. After the solution became colorless/light-colored, it was extracted with diethyl ether (10 mL × 3). The organic layer was washed with brine (10 mL × 2), separated, and dried on anhydrous sodium sulfate overnight. The organic layer was filtered, and the solvent was removed in a rotary evaporator. The crude product was eluted by column chromatography on silica gel (100 – 200 mesh) in hexane/ethyl acetate solvent (95:5) and finally re-crystallized from petroleum ether to get the pure product. The products have been characterized using spectroscopic data such as FTIR, ^{1}H-, ^{13}C-, and ^{19}F-NMR along with comparison with literature melting point.

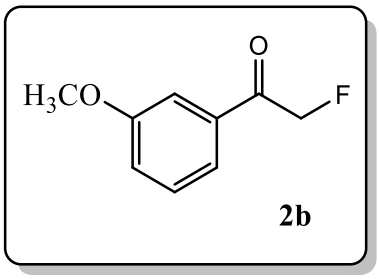
2-Fluoro-1-(4-methoxyphenyl)ethenone (2a):



2a

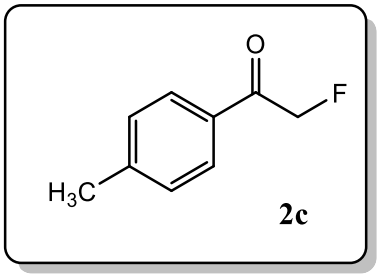
White solid, Yield: 69%, m.p.: 81 – 83 °C (lit: 80.6 – 81.7 °C [1]). FTIR (neat): 3059, 3025, 2983, 2949, 2840, 1702, 1690, 1600, 1519, 1244, 1171, 1079, 1031, 978, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3H), 5.47 (d, J = 47.2 Hz, 2H, CH_2F), 6.95 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 55.5, 83.4 (d, J_{C-F} = 180.6 Hz), 114.1, 126.6, 130.1 (d, J_{C-F} = 1.9 Hz), 164.2, 191.8 (d, J_{C-F} = 15.8 Hz, **C**O) ; ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -230.0 (t, J = 46.6 Hz).

2-Fluoro-1-(3-methoxyphenyl)ethenone (2b):



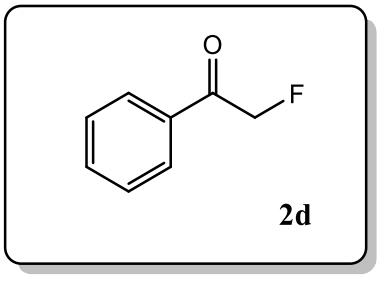
White solid, Yield: 68%, m.p.: 54 – 56 °C (lit. 53 – 54 °C [2]). FTIR (neat): 3061, 2978, 2946, 2848, 1702, 1583, 1458, 1440, 1294, 1268, 1084, 912, 770, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 5.52 (d, J = 46.9 Hz, 2H, CH_2F), 7.15-7.19 (m, 1H), 7.37-7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 83.5 (d, J = 182.5 Hz), 120.1, 120.6, 129.9, 134.9 160.0, 193.1 (d, J = 15.4 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -230.6 (J = 46.6 Hz).

2-Fluoro-1-(4-methylphenyl)ethenone (2c):



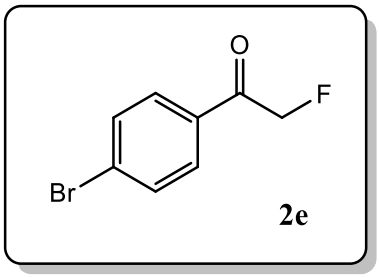
White solid, Yield: 65%, m.p.: 23 – 25 °C (lit. 22.9 – 24.3 °C [1]). FTIR (neat): 3035, 2930, 2866, 1702, 1612, 1238, 1188, 1097, 972, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 5.50 (d, J = 47 Hz, 2H, CH_2F), 7.28 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 83.4 (d, J = 182.9 Hz, **C**H_2F), 127.8, 129.5, 131.1, 145.2, 193 (d, J = 15.5 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ – 230.8 (t, J = 46.6 Hz).

2-Fluoro-1-phenylethanone (2d):



Viscous liquid, Yield: 50%, (freezes to white solid in a deep freezer at -5 °C) (lit. Clear liquid [1]). FTIR (neat): 2989, 2939, 2844, 1714, 1513, 1464, 1264, 1088, 1022, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (d, J = 47.0 Hz, 2H, CH_2F), 7.48-7.51 (m, 2H), 7.60-7.64 (m, 1H), 7.88-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.5 (d, J = 182.5 Hz), 127.8, 128.9, 133.6, 134.1, 193.4 (d, J = 15.4 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -231.0 (t, J = 46.6 Hz).

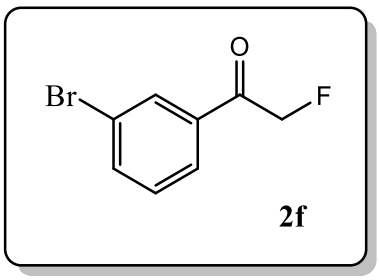
2-Fluoro-1-(4-bromophenyl)ethenone (2e):



2e

White solid, Yield: 65%, m.p.: 70 - 73 °C (lit: 71.2 – 72.6 °C [1]). FTIR (neat): 3071, 3038, 2952, 1690, 1589, 1403, 1227, 1072, 975, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 = (d, J = 46.8 Hz, 2H, CH_2F), 7.64 (J = 8.6 Hz, 2H), 7.77 (J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.5 (d, J = 184.4 Hz), 129.4, 129.4, 132.3, 132.4, 192.7 (d, J = 15.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -229.7 (t, J = 46.2 Hz).

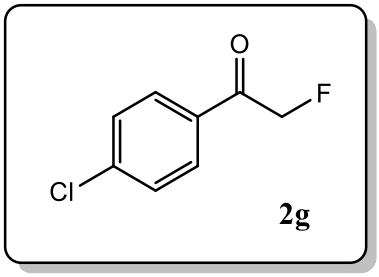
2-Fluoro-1-(3-bromophenyl)ethenone (2f):



2f

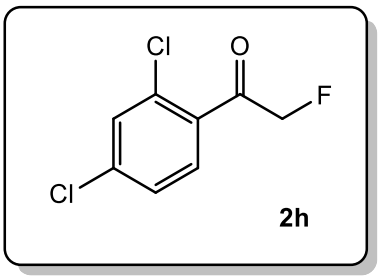
White solid, Yield: 59%, m.p.: 48 – 50 °C (lit. Clear oil [3]). FTIR (neat): 3069, 2932, 2850, 1710, 1573, 1427, 1378, 1227, 1098, 989, 903, 781, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (d, J = 46.8 Hz, 2H, CH_2F), 7.36 – 7.40 (m, 1H), 7.77 (dd, J = 17, 6.4 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.5 (d, J = 184.4 Hz), 123.2, 126.4, 130.5, 131.0, 135.3, 136.9, 192.3 (d, J = 15.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = - 229.9 (t, J = 46.6 Hz).

2-Fluoro-1-(4-chlorophenyl)ethenone (2g):



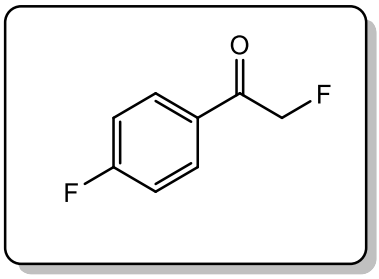
White solid, Yield: 62%, m.p.: 51-52 °C (lit: 51-52°C [3]). FTIR (neat): 3093, 2964, 2933, 2872, 1707, 1593, 1493, 1407, 1233, 1093, 1016, 977, 824, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (d, J_{HF} = 46.9 Hz, 2H, CH_2F), 7.47 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.5 (d, J = 183.5 Hz), 129.2, 129.3 (d, J = 2.9 Hz) 131.9, 140.6, 192.4 (d, J = 15.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -229.7 (t, J = 47.1 Hz).

2-Fluoro-1-(2,4-dichlorophenyl)ethenone (2h):



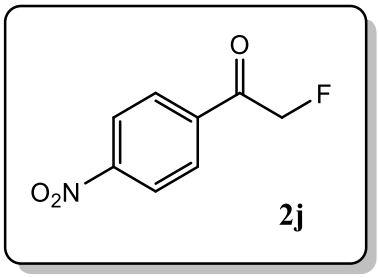
Viscous liquid, Yield: 55%, m.p.: 41 – 42 °C. FTIR (neat): 3050, 2960, 1689, 1575, 1511, 1450, 1239, 1188, 1045, 940, 803, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39 (d, J = 47.2 Hz, 2H, CH_2F), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.8 (d, J = 186.3 Hz), 127.6, 130.5, 131.3, 132.9, 133.2, 139.1, 195.2 (d, J = 18.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = - 223.9 (t, J = 47.1 Hz).

2-Fluoro-1-(4-fluorophenyl)ethenone (2i):



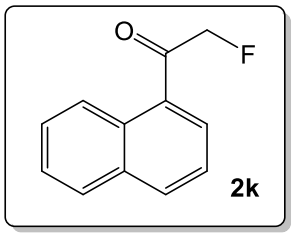
White solid, Yield: 64%, m.p.: 50 – 53 °C (lit. 49-51°C [4]). FTIR (neat): 3116, 3077, 2950, 1683, 1599, 1515, 1411, 1233, 1163, 1083, 977, 837, 600, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (d, J = 46.9 Hz, 2H, CH_2F), 7.17 (d, J = 8.2 Hz, 2H), 7.93-7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.5 (d, J = 183.0 Hz), 116.2 (d, J = 22.2 Hz), 130.2, 130.7 (dd, J_{1CF} = 9.4 Hz, J_{2CF} = 2.6 Hz), 166.2 (d, J = 256.7 Hz), 192.0 (d, J = 15.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -102.66 (m), -229.2 (t, J = 47.1 Hz).

2-Fluoro-1-(4-nitrophenyl)ethenone (2j):



White solid, Yield: 35%, m.p.: 90-92 °C (lit. 90-92°C [5]). FTIR (neat): 3059, 3035, 2930, 2866, 1710, 1608, 1599, 1528, 1348, 1227, 1092, 975, 799, 750, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (d, J = 46.8 Hz, 2H, CH_2F), 8.09 (d, J = 8.7 Hz, 2H), 8.35 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.8 (d, J = 185.0 Hz), 124.1, 129.2, 129.2, 138.1, 150.8, 192.6 (J = 16.9 Hz, **C**O); ^{19}F NMR (376 MHz, $CDCl_3$): δ -228.8 (t, J = 46.6 Hz).

2-Fluoro-1-(1-naphthyl)ethenone (2k):



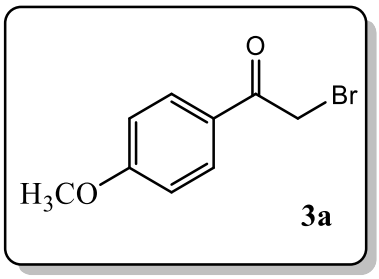
White solid, Yield: 72%, m.p.: 44 – 45 °C (lit. 44–45°C [6]). FTIR (neat): 3050, 2958, 1694, 1599, 1577, 1509, 1446, 1241, 1188, 1049, 938, 803, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (d, J = 47.2 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.6

Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.06 (d, J =8.4 Hz, 1H), 8.79 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.9 (d, J = 185.8 Hz), 124.1, 125.4, 126.8, 128.0, 128.1, 128.5, 130.2, 131.1, 133.9, 134.1, 196.9 (d, J = 16.4 Hz, CO); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -224.8 (t, J = 45.1 Hz).

2.3 General procedure for intermediates formed [2-bromo-1-(4-methoxyphenyl)ethan-1-one (3a) and 2-bromo-1-(4-bromophenyl)ethan-1-one (3e)] during side chain fluorination:

In a two-necked round-bottom flask (50 mL) fitted with a reflux condenser and magnetic stirring bar, the acetophenone derivative (1 mmol) and KBr (1.1 mmol) were dissolved in chlorobenzene (4 mL) and acetonitrile (1 mL). After that, Iron (III) nitrate nonahydrate (1.5 mmol) was added, and the reaction mixture was stirred at 80 °C for 5 h. The progress of the reaction was monitored by TLC. After complete consumption of acetophenone as indicated in TLC, the reaction mixture was cooled down to room temperature and filtered through a filter paper. The filtrate was extracted with dichloromethane; the organic layer was collected and passed through a 5 cm silica gel column. After that, the filtrate was dried under vacuum to get the pale-yellow solid. The solid was washed with a petroleum ether: water (1:1) mixture two to three times and finally re-crystallized from petroleum ether. The products have been characterized using spectroscopic data such as FTIR, ^{1}H-, and ^{13}C-NMR along with comparison with literature melting point.

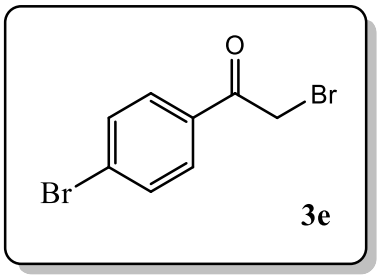
2-Bromo-1-(4-methoxyphenyl)ethenone (3a):



3a

White solid, Yields 78% m.p.: 70 – 72 ℃ (lit. 71-72 ℃ [7]); FTIR (neat): 3077, 3020, 2981, 2942, 2846, 1687, 1603, 1517, 1329, 1264, 1210, 1167, 1028, 846, 822, 756, 588, 564 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3H), 4.39 (s, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6, 55.5, 114.0, 126.9, 131.3, 164.1, 189.9.

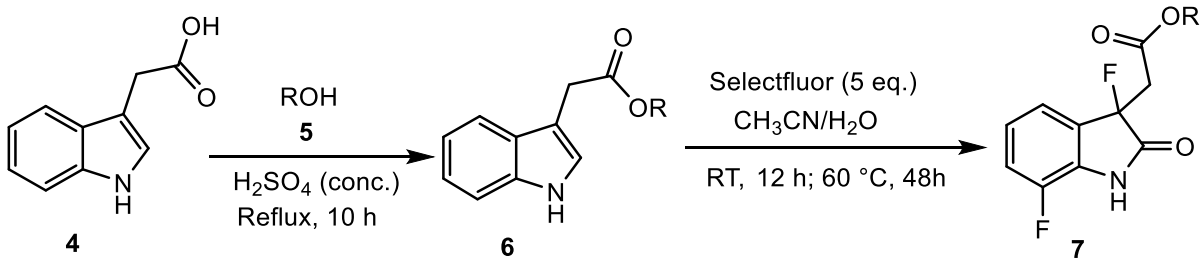
2-Bromo-1-(4-bromophenyl)ethenone (3e):



White solid, Yield 82%, m.p.: 106 – 108 °C (lit. 107-109 °C [7]); FTIR (neat): 3036, 3003, 2954, 1698, 1583, 1562, 1401, 1274, 1196, 1073, 994, 809, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.39 (s, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3, 129.3, 130.4, 131.2, 132.2, 132.7, 190.4.

2.4 General procedure for synthesis of 3,7-difluoro-oxindole derivatives (7):

The synthesis of 3,7-difluoro-oxindole derivatives (7) has been achieved in one pot two-step procedure (Scheme 2.2).



Scheme 2.2: Synthesis of esters of indole acetic acid

In the first step, the ester **6** of indole acetic acid (**4**) was synthesized with acid-catalyzed **6a-f** or DCC/DMAP-assisted **6g-j** esterification process. The fluorination of these esters was carried out in the second step to prepare the 3,7-difluorooxindole derivatives (**7**).

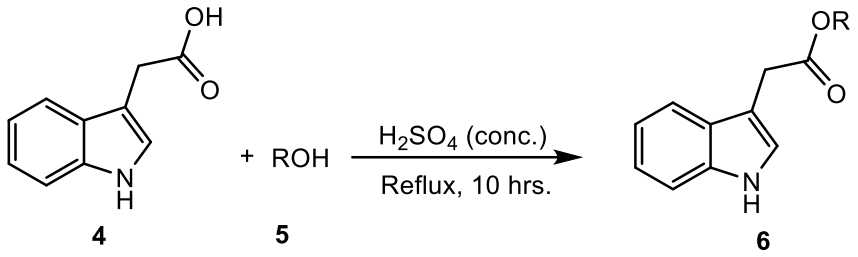
2.4.1 General procedures for synthesis of starting materials (6):

The esters of indole acetic acid **6** are not available commercially. Therefore, these were synthesized in the laboratory using an appropriate synthetic method (Schemes 2.3 & 2.4).

2.4.1.1 Synthesis of alkyl 2-(1H-indol-3-yl)acetate (6a – 6f)

The aliphatic ester of indole acetic acid was synthesized according to the method described in the literature [8]. Indole-3-acetic acid (**4**, 5.7 mmol) was dissolved in aliphatic alcohol (**5**, 20 mL), and concentrated sulfuric acid (0.2 mL) was added to it at room

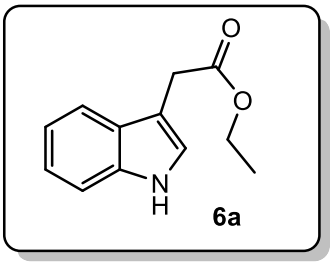
temperature. The resulting solution was refluxed for 10 h using an oil bath. The progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under vacuum to remove the excess alcohol. The residue was dissolved in 15 mL of DCM and washed with 5% aqueous sodium bicarbonate solution (2 × 6 mL). The organic layer was dried over anhydrous sodium sulfate overnight, filtered, and then concentrated under vacuum. The crude product was purified by column chromatography using hexane: ethyl acetate (9:1) to get the pure product. The products have been characterized using spectroscopic data such as FTIR, ^{1}H-, and ^{13}C-NMR along with comparison with literature melting point.



R: **6a.** -CH_2CH_3, **6b.** -CH_3, **6c.** -$CH_2CH_2CH_3$, **6d.** -$CH_2CH_2CH_2CH_3$, **6e.** -$CH_2CH_2CH_3$, **6f.** -$CH(CH_3)_2$

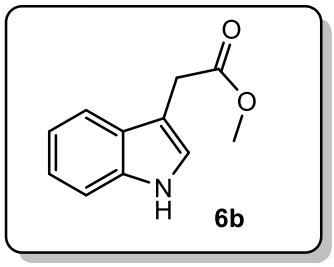
Scheme 2.3: H_2SO_4-catalysed esterification of indole acetic acid

Ethyl 2-(1*H*-Indol-3-yl)acetate (6a):



Burgundy colored oil, [9] Yield 88%, FTIR (neat): 3406, 3087, 3052, 2983, 2934, 2903, 2872, 1722, 1456, 1372, 1333, 1303, 1268, 1251, 1161, 1098, 1026, 1012, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3H), 3.79 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 7.11-7.23 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 31.4, 60.8, 108.4, 111.2, 118.9, 119.6, 122.1, 123.1, 127.2, 136.0, 172.2.

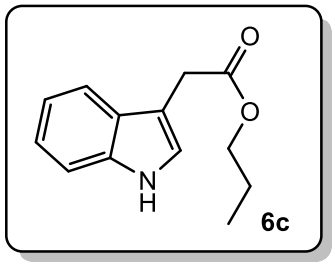
Methyl 2-(1H-Indol-3-yl)acetate (6b):



6b

Burgundy colored Solid, Yield 88%, m.p.: 51-52 °C, (lit 47-48 °C) [10], FTIR (neat): 3355, 3121, 3083, 3059, 3019, 2961, 2904, 2844, 1716, 1461, 1431, 1409, 1338, 1302, 1242, 1222, 1163, 1103, 991, 751, 741, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 3H), 3.80 (s, 2H), 7.12 -7.24 (m, 3H), 7.34 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.1, 52.0, 108.2, 111.2, 118.8, 119.6, 122.1, 123.1, 127.1, 136.0, 172.6.

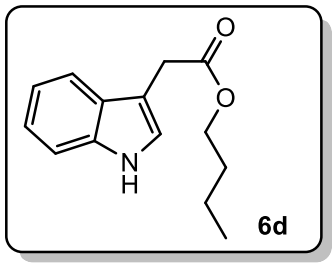
Propyl 2-(1*H*-indol-3-yl)acetate (6c):



6c

Burgundy colored oil, Yield 89%, FTIR (neat): 3412, 3080, 3060, 2974, 2909, 1728, 1622, 1457, 1431, 1389, 1350, 1298, 1260, 1151, 1133, 1099, 1071, 1013, 748, 561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3H), 1.62 – 1.71 (m, 2H), 3.80 (s, 2H), 4.09 (t, J = 6.7 Hz, 2H), 7.11-7.23 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 21.9, 31.3, 66.4, 108.4, 111.2, 118.8, 119.5, 122.1, 123.1, 127.2, 136.0, 172.3.

Butyl 2-(1H-indol-3-yl)acetate (6d):

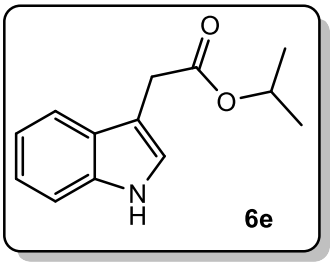


6d

Burgundy colored oil, Yield 84%, FTIR (neat): 3409, 3083, 3059, 2969, 2936, 2876, 1720, 1460, 1339, 1301, 1272, 1247, 1161, 1147, 1100, 1014, 971, 746 cm^{-1}; ^{1}H NMR (400 MHz,

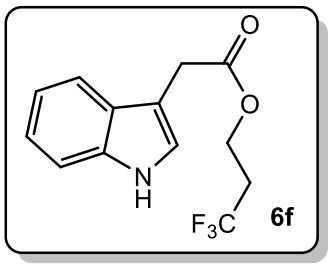
$CDCl_3$): δ = 0.91 (t, J = 7.4 Hz, 3H), 1.31-1.41 (m, 2H), 1.61 (dd, J = 14.0, 6.7 Hz, 2H), 3.78 (s, 2H), 4.12 (t, J = 6.7 Hz, 2H), 7.12-7.22 (m, 3H), 7.35 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 19.1, 30.6, 31.4, 64.7, 108.5, 111.1, 118.9, 119.6, 122.1, 123.0, 127.2, 136.0, 172.2.

Isopropyl 2-(1H-indol-3-yl)acetate (6e):



White Solid, Yield 85%, m.p.: 73 – 75 ºC, FTIR (neat): 3341, 3122, 3085, 3061, 2975, 2928, 2905, 1716, 1462, 1375, 1260, 1192, 1104, 963, 740, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, J = 6.3 Hz, 6H), 3.75 (s, 2H), 5.00-5.10 (m, 1H), 7.12-7.22 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 31.7, 68.1, 108.7, 111.1, 118.9, 119.5, 122.1, 123.0, 127.2, 136.1, 171.7.

3,3,3-Trifluoropropyl 2-(1H-indol-3-yl)acetate (6f)

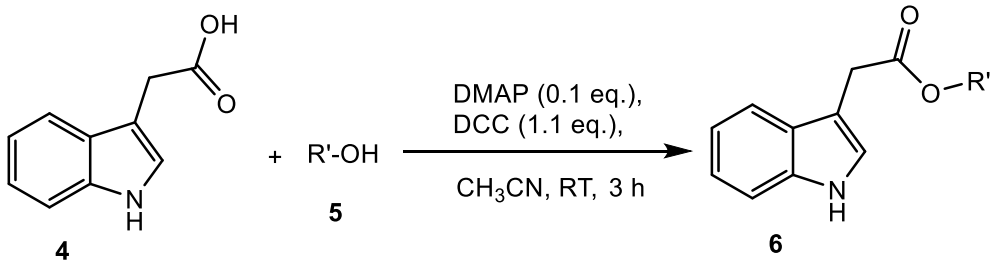


Burgundy colored oil, Yield: 82%, FTIR (neat): 3412, 3080, 3060, 2974, 2909, 1728, 1622, 1457, 1431, 1389, 1350, 1298, 1260, 1151, 1133, 1099, 1071, 1013, 748, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41-2.52 (m, 2H), 3.81 (s, 2H), 4.33 (t, J = 6.5 Hz, 2H), 7.14-7.24 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 33.3 (q, J = 29.1 Hz), 57.5 (d, J = 3.9 Hz), 107.9, 111.2, 118.7, 119.7, 122.2, 123.1, 124.3, 127.1, 136.0, 171.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -64.8 (t, J = 10.3 Hz).

2.4.1.2 Synthesis of aryl 2-(1H-indol-3-yl)acetate (6g – 6j)

The aryl ester of indoleacetic acid was synthesized according to the method described in the literature, with slight modification using acetonitrile as solvent [11]. Indole-3-acetic acid

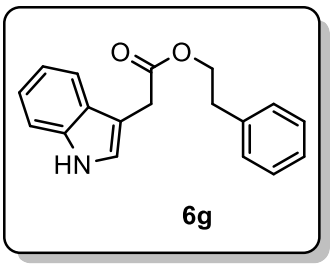
(**4,** 5.7 mmol), aryl alcohol (**5,** 11.4 mmol, 2 eq.), and DMAP (0.5 mmol, 0.1 eq.) were dissolved in acetonitrile (20 mL) to make a homogeneous solution in a 100 mL round-bottom flask. The solution was cooled down to 0 °C. Now DCC (6.2 mmol, 1.1 eq.) was added at 0 °C to the reaction mixture, and the reaction mixture was stirred at 0 °C for five minutes. After that, the reaction mixture was allowed to attain room temperature and further stirred for 3 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitate formed was filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in DCM (15 mL), and washed with 0.5N HCl and saturated aqueous sodium bicarbonate solution (2 × 6 mL). The organic layer was separated and dried over anhydrous sodium sulfate overnight. The organic layer was filtered and concentrated under vacuum to get the crude product. The crude product was purified by column chromatography on silica gel hexane: ethyl acetate (9:1) to get the pure product. The products have been characterized using spectroscopic data such as FTIR, ^{1}H-, and ^{13}C-NMR along with comparison with literature melting point.



R' = **6g.** EtPh, **6h.** 2-Cl-Bn, **6i.** 4-NO_2-Bn, **6j.** 4-OMeBn

Scheme 2.4: DCC-mediated esterification of indoleacetic acid

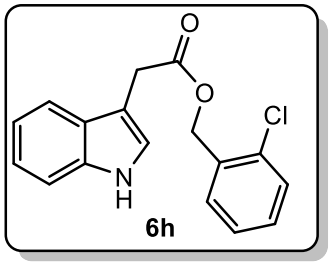
Phenethyl 2-(1*H*-indol-3-yl)acetate (6g):



White Solid, Yield 94%, m.p.: 80 – 82 °C, FTIR (neat): 3391, 3144, 3057, 3033, 2965, 2939, 2906, 2885, 2876, 1732, 1455, 1399, 1368, 1340, 1320, 1175, 1121, 1091, 976, 747, 701, 584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (t, J = 7.0 Hz, 2H), 3.76 (s, 2H), 4.31- 4.35 (m, 2H), 7.04-7.29 (m, 8H), 7.34 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 8.08 (s, 1H); ^{13}C-

NMR (100 MHz, $CDCl_3$): δ = 31.3, 35.0, 65.2, 108.3, 111.1, 118.8, 119.6, 122.1, 123.0, 126.5, 127.2, 128.4, 128.9, 136.0, 137.8, 172.0.

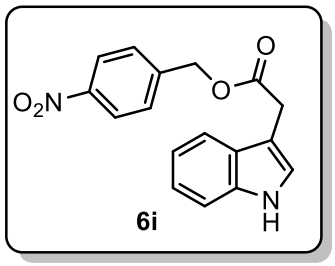
2-Chlorobenzyl 2-(1*H*-indol-3-yl)acetate (6h):



6h

White Solid, Yield 92%, m.p.: 81.7 – 83.3 ºC, FTIR (neat): 3397, 3049, 2995, 2963, 2947, 2898, 1734, 1461, 1336, 1296, 1198, 1147, 1057, 974, 749, 594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 2H), 5.27 (s, 2H), 7.11-7.28 (m, 5H), 7.33-7.40 (m, 3H), 7.62 (d, J = 7.9 Hz, 1H), 8.11 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.2, 63.9, 76.7, 108.2, 111.1, 118.8, 119.7, 122.2, 123.1, 126.8, 127.1, 129.4, 129.5, 129.7, 133.5, 136.0, 171.7.

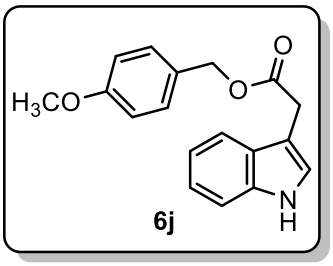
4-Nitrobenzyl 2-(1*H*-indol-3-yl)acetate (6i):



6i

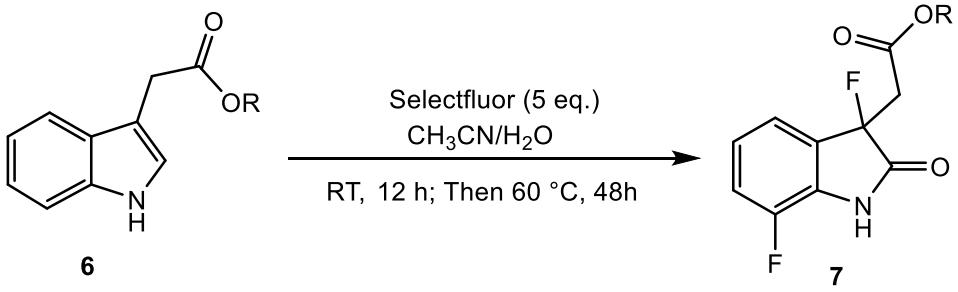
Yellow Solid, Yield 87%, m.p.: 122 – 124 ºC, FTIR (neat): 3341, 3111, 3073, 3059, 2930, 2918, 2852, 1732, 1602, 1519, 1461, 1338, 1169, 1103, 1011, 848, 734, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 2H), 5.22 (s, 2H), 7.12-7.16 (m, 2H), 7.20-7.24 (m, 1H), 7.36 (d, J = 8, 1H), 7.39 (d, J = 8.8, 2H), 7.60 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 8.8 Hz, 2H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 64.9, 107.9, 111.3, 118.7, 119.7, 122.3, 123.1, 123.6, 127.0, 128.2, 136.0, 143.2, 147.5, 171.5.

4-Methoxybenzyl 2-(1*H*-indol-3-yl)acetate (6j):



White Solid, Yield 79%, m.p.: 59 – 61 °C, FTIR (neat): 3390, 3071, 3042, 3011, 2956, 2942, 2895, 2838, 1720, 1612, 1515, 1460, 1301, 1251, 1200, 1174, 1032, 957, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 5H), 5.10 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.11-7.14 (m, 2H), 7.20 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 8.13 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.3, 55.3, 66.4, 76.7, 77.0, 77.3, 108.4, 111.1, 113.9, 118.9, 119.6, 122.2, 123.0, 127.2, 128.0, 130.1, 136.0, 159.5, 171.9.

2.4.2 General procedure for synthesis of alkyl/aryl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7)

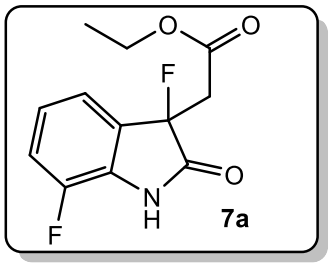


Scheme 2.5: Synthesis of alkyl/aryl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate

In a two-necked round-bottom flask (50 mL), 1.22 mmol of indoleacetic acid ester (**6**) was taken and suspended in distilled water (10 mL), then Selectfluor (3.68 mmol, 3 eq.) was added and thoroughly mixed. After mixing, acetonitrile (10 mL) was added, and the solution was stirred at room temperature for 12 h. The reaction was monitored by TLC to ascertain the complete consumption of oxindole formed in the reaction intermediate step. After that, additional Selectfluor (2.44 mmol, 2 eq.) was added to the reaction mixture, and the temperature was raised to 60 °C. The reaction mixture was stirred for 48 h at this temperature. The Selectfluor was added in a small portion to avoid decomposition by water. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was separated, kept at anhydrous sodium sulfate

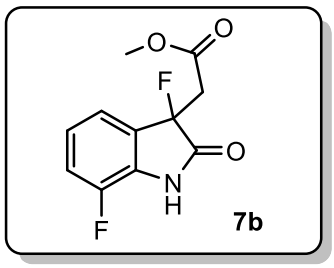
overnight, and dried under vacuum to get the crude product. The final product **7** was purified by column chromatography, silica gel (60 – 120 mesh), hexane/ethyl acetate. The products have been characterized using spectroscopic data such as FTIR, ^{1}H-, ^{13}C-, and ^{19}F-NMR.

Ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7a):



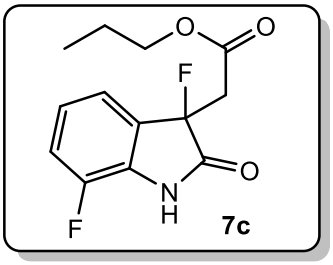
White Solid, Yield 57%, m.p.: 85 – 86 ºC, FTIR (neat): 3214, 3135, 3104, 2994, 2913, 2851, 1737, 1719, 1631, 1491, 1478, 1262, 1201, 1021, 880, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.1 Hz, 3H), 3.26-3.34 (m, 2H), 4.01-4.04 (m, 2H), 6.87 (dd, J = 8.5, 4.1 Hz, 1H), 7.05 (tt, J = 8.8, 2.3 Hz, 1H), 7.19 (dt, J = 7.4, 2.3 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 39.2 (d, J = 31.2 Hz), 61.3, 90.1 (d, J = 185.3 Hz), 111.6 (d, J = 7.3 Hz), 113.1 (d, J = 24.7 Hz), 118.2 (dd, J = 23.6, 3.3 Hz), 126.3 (q, J = 8.5 Hz), 138.1 (q, J = 2.4 Hz), 159.1 (dd, J = 242.7, 3.6 Hz), 167.5 (d, J = 16.7 Hz), 173.7 (d, J = 19.6 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = -119.1 (s, 1F), -153.8 (t, J = 9.7 Hz, 1F).

Methyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7b):



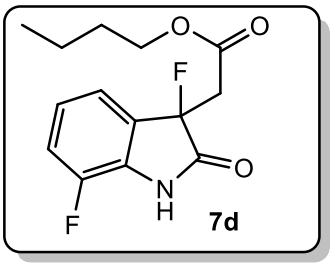
White Solid, Yield 42%, m.p.: 98 – 99 ºC, FTIR (neat): 3221, 3121, 3066, 2960, 2853, 1739, 1633, 1615, 1495, 1442, 1280, 1185, 1027, 995, 874, 846, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.28-3.43 (m, 2H), 3.60 (s, 3H), 6.87 (dd, J = 8.1, 3.6 Hz, 1H), 7.05 (m, 1H), 7.19 (m, 1H), 8.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.9 (d, J = 32.0 Hz), 52.3, 90.0 (d, J = 184.5 Hz), 111.8 (d, J = 8.0 Hz), 113.2 (d, J = 25.4 Hz), 118.3 (d, J = 20.3 Hz), 126.3 (q, J = 8.5 Hz), 138.1, 159.1 (d, J = 242.7 Hz), 168.1 (d, J = 16.7 Hz), 173.6 (d, J = 19.6 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = -119.0 (s, 1F), -154.1 (t, J = 11.1 Hz, 1F).

Propyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7c):



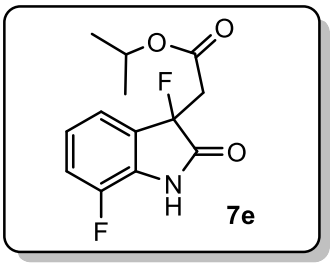
White Solid, Yield 62%, m.p.: 63 – 65 ºC, FTIR (neat): 3217, 3094, 2966, 2935, 2880, 1733, 1623, 1478, 1401, 1287, 1187, 1101, 836, 658, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.4 Hz, 3H), 1.51 (td, J = 14.3, 7.3 Hz, 2H), 3.27-3.44 (m, 2H), 3.90-3.96 (m, 2H), 6.87 (m, 1H), 7.05 (m, 1H), 7.20 (m, 1H), 8.73 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.1, 21.6, 39.1 (d, J = 31.3 Hz), 66.8 (d, J = 14.0 Hz), 90.0 (d, J = 185.4 Hz), 111.6 (d, J = 7.7 Hz), 113.1 (d, J = 25.5 Hz), 118.2 (d, J = 23.1 Hz), 126.4 (dd, J = 17.3, 7.7 Hz), 138.1 (d, J = 5.3 Hz), 159.1 (d, J = 246.1 Hz), 167.5 (d, J = 17.3 Hz), 173.6 (d, J = 19.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.9--119.0 (m, 1F), -153.5 (t, J = 9.8 Hz, 1F).

Butyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7d):



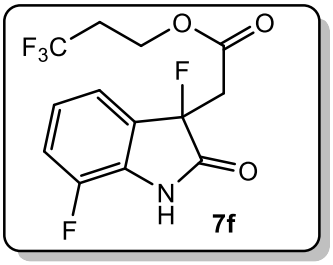
Yellowish Oil, Yield 15%, FTIR (neat): 3308, 2962, 2939, 2880, 1735, 1637, 1489, 1468, 1289, 1189, 1025, 876, 823, 779, 732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.4 Hz, 3H), 1.24 (td, J = 14.9, 7.5 Hz, 2H), 1.43-1.50 (m, 2H), 3.26-3.43 (m, 2H), 3.97 (td, J = 6.6, 2.8 Hz, 2H), 6.85-6.88 (m, 1H), 7.02-7.08 (m, 1H), 7.18-7.21 (m, 1H), 8.72 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.5, 18.9, 30.2, 39.2 (d, J = 31.3 Hz), 65.2, 90.0 (d, J = 185.4 Hz), 111.6 (d, J = 7.7 Hz), 113.1 (d, J = 25.0 Hz), 118.2 (dd, J = 23.6, 2.9 Hz), 126.4 (dd, J = 17.3, 7.7 Hz), 138.1 (d, J = 3.4 Hz), 159.1 (dd, J = 242.5, 3.1 Hz), 167.5 (d, J = 16.9 Hz), 173.6 (d, J = 19.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.9--119.0 (m, 1F), -153.4 (t, J = 10.3 Hz, 1F).

Isopropyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7e):



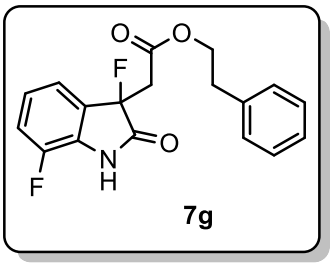
White Solid, Yield 25%, m.p.: 113 – 114 °C, FTIR (neat): 3378, 2988, 2976, 2964, 2929, 2851, 1754, 1717, 1491, 1391, 1380, 1225, 1184, 1109, 862, 827, 774, 725 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.06 (dd, J = 13.0, 6.2 Hz, 6H), 3.41-3.21 (m, 2H), 4.80-4.89 (m, 1H), 6.87 (dd, J = 8.6, 3.2 Hz, 1H), 7.02-7.08 (m, 1H), 7.20 (m, 1H), 8.78 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3 (d, J = 11.6 Hz), 39.5 (d, J = 31.3 Hz), 69.1, 90.1 (d, J = 185.4 Hz), 111.6 (d, J = 7.7 Hz), 113.1 (d, J = 25.0 Hz), 118.1 (d, J = 23.6 Hz), 126.4 (dd, J = 17.8, 8.2 Hz), 138.1, 159.1 (d, J = 242.8 Hz), 166.8 (d, J = 17.3 Hz), 173.8 (d, J = 20.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.9--119.0 (m, 1F), -153.3 (t, J = 11.9 Hz, 1F).

3,3,3-trifluoropropyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7f):



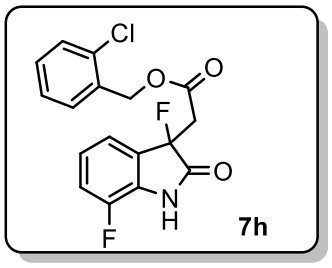
White Solid, Yield 22%, m.p.: 82 – 84 °C, FTIR (neat): 3206, 3107, 3049, 2997, 2930, 2844, 1738, 1706, 1630, 1475, 1354, 1252, 1198, 1165, 1145, 1055, 1017, 1009, 781 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.30-2.41 (m, 2H), 3.29-3.44 (m, 2H), 4.21 (t, J = 6.4 Hz, 2H), 6.88 (dd, J = 8.6, 4.0 Hz, 1H), 7.07 (t, J = 8.7 Hz, 1H), 7.20 (dt, J = 7.4, 2.2 Hz, 1H), 8.46 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 33.0 (q, J = 29.5 Hz), 38.9 (d, J = 31.8 Hz), 57.9 (d, J = 3.4 Hz), 89.8 (d, J = 185.4 Hz), 111.7 (d, J = 7.7 Hz), 113.2 (d, J = 25.0 Hz), 118.4 (dd, J = 23.6, 2.9 Hz), 125.4 (d, J = 277.7 Hz), 126.1 (dd, J = 17.3, 7.7 Hz), 137.9 (d, J = 3.4 Hz), 159.1 (d, J = 239.9 Hz), 167.1 (d, J = 16.4 Hz), 173.3 (d, J = 19.7 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -65.1 (t, J = 10.3 Hz, 3F), -118.7 (s, 1F), -153.5 (t, J = 10.7 Hz, 1F).

Phenethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7g):



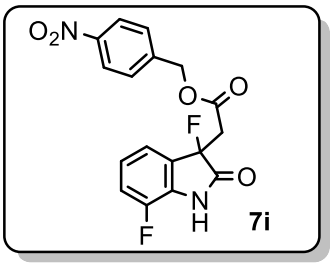
White Solid, Yield 62%, m.p.: 84 – 87 °C, FTIR (neat): 3208, 3166, 3115, 3086, 2960, 2906, 2853, 1733, 1627, 1476, 1401, 1211, 1187, 1101, 834, 727, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, J = 7.0 Hz, 2H), 3.28-3.47 (m, 2H), 4.24 (t, J = 7.3 Hz, 2H), 6.82-6.85 (m, 1H), 7.08 (tt, J = 8.8, 2.2 Hz, 1H), 7.16 -7.20 (m, 2H), 7.26-7.36 (m, 3H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6, 39.1 (d, J = 31.8 Hz), 65.6, 89.9 (d, J = 185.4 Hz), 111.5 (d, J = 7.7 Hz), 113.2 (d, J = 25.0 Hz), 118.2 (dd, J = 23.6, 2.9 Hz), 126.2 (dd, J = 17.6, 7.9 Hz), 126.7, 128.5, 128.8, 137.2, 137.9 (d, J = 3.4 Hz), 159.0 (dd, J = 242.8, 2.9 Hz), 167.4 (d, J = 17.3 Hz), 173.3 (d, J = 19.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.8 (t, J = 8.1 Hz, 1F), -153.4 (t, J = 9.8 Hz, 1F).

2-Chlorobenzyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7h):



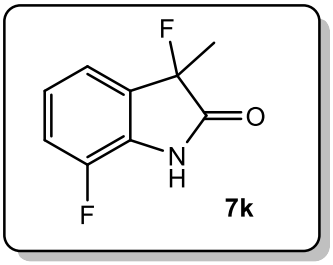
White Solid, Yield 61%, m.p.: 117 – 119 °C, FTIR (neat): 3209, 3109, 3046, 2967, 2928, 2842, 1733, 1684, 1629, 1478, 1392, 1355, 1215, 1199, 1035, 1003, 791, 758, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32-3.49 (m, 2H), 5.10 (dd, J = 19.5, 12.7 Hz, 2H), 6.73-6.76 (m, 1H), 6.99 (tt, J = 8.8, 2.3 Hz, 1H), 7.19-7.26 (m, 4H), 7.33 (d, J = 7.9 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.1 (d, J = 31.8 Hz), 64.3, 89.9 (d, J = 186.4 Hz), 111.6 (d, J = 7.2 Hz), 113.1 (d, J = 25.0 Hz), 118.2 (d, J = 20.7 Hz), 126.1 (dd, J = 17.3, 7.7 Hz), 126.9, 129.6, 129.9, 130.2, 132.4, 133.9, 137.9, 159.0 (dd, J = 242.8, 2.9 Hz), 167.0 (d, J = 17.3 Hz), 173.4 (d, J = 19.7 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -118.8 (m, 1F), -153.2 (t, J = 9.8 Hz, 1F).

4-Nitrobenzyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7i):



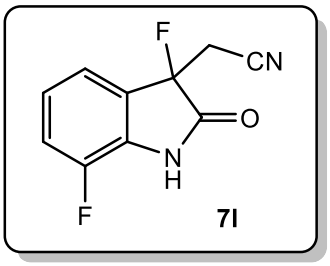
Yellow Solid, Yield 71%, m.p.: 186 – 189 °C, FTIR (neat): 3208, 3184, 3155, 3112, 3041, 2931, 2841, 1735, 1654, 1607, 1521, 1342, 1193, 1048, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-D6): δ = 3.90-3.95 (m, 2H), 5.20 (s, 2H), 5.79-5.89 (m, 1H), 5.95-5.99 (m, 1H), 6.15-6.25 (m, 2H), 6.29-6.35 (m, 1H), 6.94 (m, 2H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ = 38.6 (d, J = 12.0 Hz), 65.4 (d, J = 8.2 Hz), 90.8 (d, J = 180.1 Hz), 111.2, 112.2 (d, J = 6.7), 113.7 (d, J = 26.0 Hz), 118.7 (dd, J = 22.9, 3.1 Hz), 122.9, 123.9, 125.8, 128.9 (d, J = 17.3 Hz), 132.4, 143.6 (d, J = 5.8 Hz), 147.6 (d, J = 4.3 Hz), 167.7 (d, J = 17.8 Hz), 173.0 (d, J = 19.7 Hz); ^{19}F NMR (376 MHz, DMSO-d6): δ = -119.4 (s, 1F), -153.8 (t, J = 11.9 Hz, 1F).

3,7-Difluoro-3-methylindolin-2-one (7k):



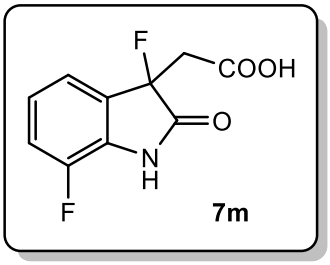
White Solid, Yield 47%, m.p.: 149 – 151 °C, FTIR (neat): 3196, 3093, 2936, 2881, 1730, 1630, 1487, 1468, 1282, 1221, 1180, 1104, 1053, 922, 836, 783, 723, 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (d, J = 22.2 Hz, 3H), 6.9 (m, 1H), 7.01-7.07 (m, 1H), 7.2 (m, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (d, J = 29.4 Hz), 91.3 (d, J = 186.4 Hz), 111.7 (d, J = 7.7 Hz), 112.5 (d, J = 24.6 Hz), 117.6 (d, J = 23.6 Hz), 129.0 (dd, J = 18.8, 7.7 Hz), 136.6, 159.4 (d, J = 245.6 Hz), 175.6 (d, J = 21.2 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -118.9 (q, J = 6.5 Hz, 1F), -153.6 (q, J = 22.0 Hz, 1F).

2-(3,7-Difluoro-2-oxoindolin-3-yl)acetonitrile (7l):



Reddish yellow Solid, Yield 47%, m.p.: 167 – 170 °C, FTIR (neat): 3226, 3174, 3121, 3089, 3063, 2947, 2860, 2269, 1740, 1624, 1498, 1467, 1294, 1190, 1161, 1095, 886, 834, 743, 647, 580 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$ + Methanol D4): δ = 3.28-2.82 (m, 2H), 6.82 (m, 1H), 7.01-7.06 (m, 1H), 7.33 (dt, J = 7.3, 2.1 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$+ Methanol D_4): δ = 24.2 (d, J = 32.8 Hz), 88.2 (d, J = 197.0 Hz), 112.0 (d, J = 7.7 Hz), 113.1 (d, J = 25.5 Hz), 113.8 (d, J = 5.8 Hz), 118.9 (d, J = 21.7 Hz), 124.5 (dd, J = 18.3, 8.2 Hz), 137.7 (d, J = 4.8 Hz), 159.0 (d, J = 243.2 Hz), 171.6 (d, J = 20.2 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$ + Methanol D_4): δ = -118.4 (dd, J = 10.3, 8.1 Hz, 1F), -156.9 (dd, J = 24.4, 9.2 Hz, 1F).

2-(3,7-Difluoro-2-oxoindolin-3-yl)acetic acid (7m):



Pale yellow Solid, Yield 42%, decomposes above 250 °C. FTIR (neat): 3335, 2923, 2860, 2605, 1703, 1633, 1615, 1489, 1423, 1293, 1195, 1048, 874, 834, 781, 738, 554 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$+Methanol D4): δ = 3.26-3.29 (m, 2H), 6.81-6.84 (m, 1H), 6.99 - 7.04 (m, 1H), 7.20 (dt, J = 7.5, 2.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$+Methanol D_4): δ = 38.6 (d, J = 30.8 Hz), 90.1 (d, J = 183.0 Hz), 111.3 (d, J = 7.2 Hz), 112.7 (d, J = 25.0 Hz), 117.6 (dd, J = 23.6, 2.4 Hz), 126.5 (dd, J = 17.6, 7.9 Hz), 138.6 (d, J = 3.9 Hz), 158.8 (dd, J = 241.5, 3.1 Hz), 169.5 (d, J = 15.9 Hz), 173.9 (d, J = 19.7 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$+Methanol D_4): δ = -116.2 (dt, J = 16.3, 4.1 Hz, 1F), -150.7 (t, J = 10.3 Hz, 1F).

2.5 General procedure for evaluation of flame-retardant property

The selected fluorinated compounds from α-fluoroacetophenones and alkyl/aryl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate were evaluated for their flame retardancy in polyurethane thin film as per the procedure mentioned in the UL-94 standard [12].

2.5.1 Preparation of film

The polyurethane was purchased from commercial sources (Elastollan® 13 series, Make: BASF). Polyurethane (1.25 g) was added to 1,3-dioxalane (10 mL), and the mixture was stirred at room temperature using an overhead stirrer for 2 h to dissolve the polyurethane completely. Now, the synthesized fluorinated compound (0.25 g) was added to the solution and mixed thoroughly to prepare a homogeneous solution. The silicone release paper was fixed on a hard horizontal surface, and the polyurethane solution was poured on the silicone release paper. The solution was spread evenly on the paper using a sharp blade to get a thin film and left to dry at room temperature for 24 h. The film dried at room temperature was further dried in an oven for 2 h at 60 °C, followed by 30 minutes at 80 °C. Caution should be taken while preparing the film; any undissolved material shall be removed from the solution before pouring on silicon release paper, and bubble formation shall be avoided. After complete drying, the thin films were removed from the silicon release paper. A thin film of blank polyurethane was also prepared in the same manner for comparative purposes. The thickness of the film was measured using a screw gauge, and it was found to be 30 – 40 microns.

2.5.2 Preparation and conditioning of the sample

The prepared films were cut into 200 ± 5 mm in length by 50 ± 1 mm in width test specimens. The test specimens were marked at 125 mm from the bottom; the longitudinal axis of the specimen was wrapped around the longitudinal axis of a 12.7 ± 0.5 mm diameter mandrel to form a lapped cylinder. The overlapping ends of the specimen were secured within the 75 mm portion above the 125 mm mark (upper tube section) by means of pressure-sensitive tape. The mandrel is removed, and the specimens were preconditioned at 23 ± 2°C and 50 ± 5% relative humidity for 48 hours as per procedure (article 11.5) in UL-94 [12].

2.5.3 The Test Setup

The setup was prepared according to the description in the UL-94 thin film test setup requirement. A draft-free vertical stainless steel test chamber equipped with an exhaust system to remove combustion byproducts was used to house the specimen. The specimen was clamped at the top and suspended freely. A calibrated burner, fueled by methane, adjusted to produce a 20 mm high clean blue flame (flow rate of 105 ml/min approx.) with a specific heat output. A stopwatch and ruler are used to measure burning time, flame height, and extent of burning. The

dry layer of surgical cotton was placed 300 mm below the specimen to detect flaming drips from the test sample.

2.5.4 The Test Method

The chamber was maintained at 23 ± 2°C and 50 ± 5% relative humidity. The burner was positioned at a 45° angle to apply the flame to the bottom edge of the specimen. Now apply the 20 mm flame to the bottom edge of the specimen for 3 seconds and immediately withdraw the burner and record the after-flame time (t_1) in seconds. Once the specimen ceases flaming, reapply the flame for an additional 3 seconds. Withdraw the burner and record: After flame time (t_2) and Afterglow time (t_3). Observations were recorded for after flame time, afterglow time, and whether drips ignite the cotton (flamed dripping or non-flamed dripping). Based on the observations, the specimen samples are classified for flame retardancy rating into VTM-0, VTM-1, or VTM-2 for burn behaviour. Proper documentation and adherence to safety protocols, including personal protective equipment and fire suppression systems, are critical for reliable and safe testing.

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CHAPTER 3

RESULTS AND DISCUSSION

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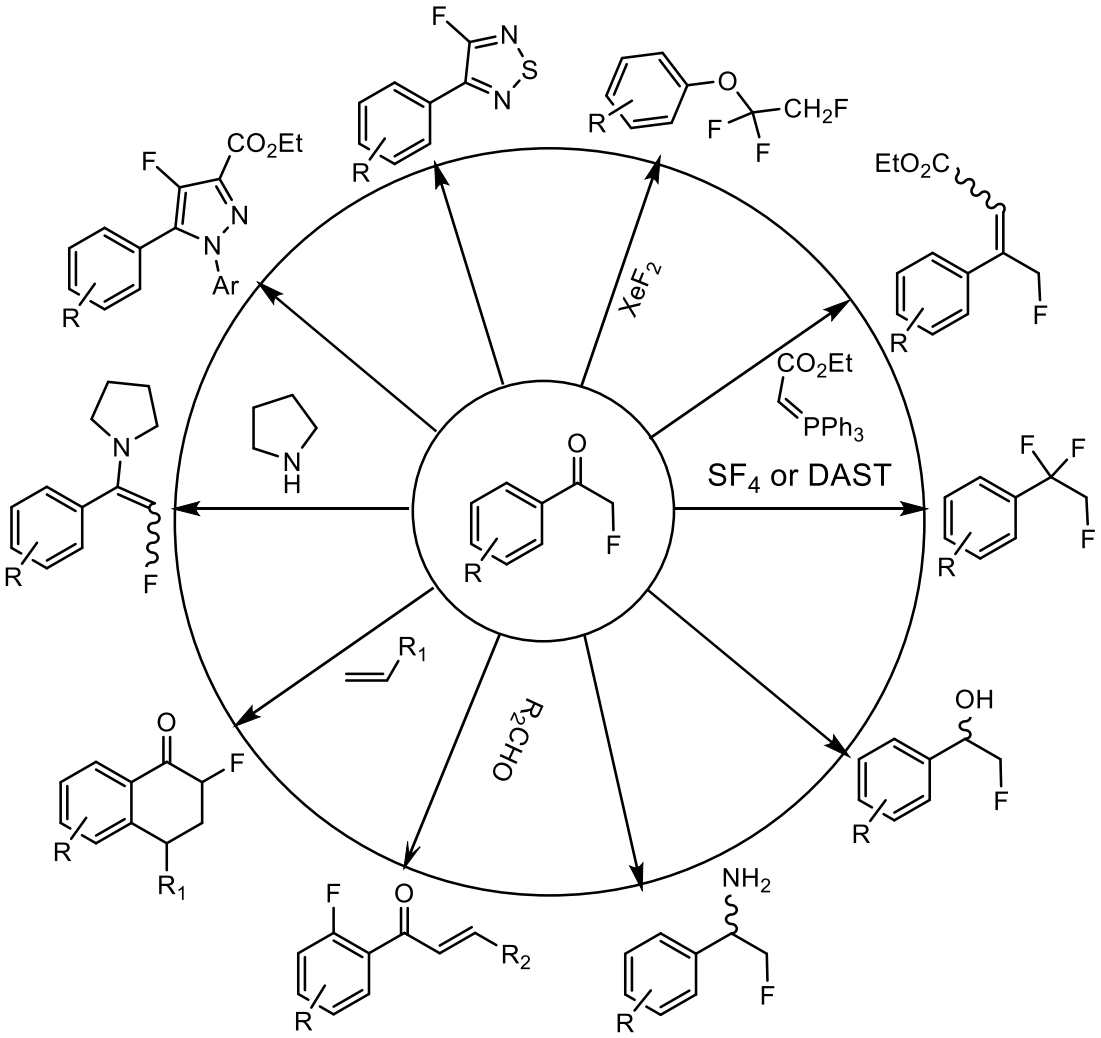
3.1 Synthesis of α-Fluoroacetophenone

Acetophenone is one of the simplest aromatic ketones in which the phenyl ring is substituted with an acyl group. α-Fluoroacetophenone (1-fluoro-1-phenylethan-2-one) derivatives are structurally simple, yet chemically significant molecules. In these compounds, a hydrogen atom of the CH_3 group in acetophenone is replaced by a fluorine atom. The high electronegativity (3.98) of fluorine and strong C-F bond (bond dissociation energy ~485 kJ/mol) significantly impact the electrophilicity and chemical stability of the compound, making them a valuable intermediate for the preparation of more sophisticated fluoroorganic molecules in organic synthesis. α-Fluoroacetophenones are important fluorinated building blocks, as several interesting molecules can be generated from them by functionalization at the α-carbon atom, keto group, and aromatic ring, including fluorinated thiadiazoles [1], pyrazoles [2], and tetralones [3], providing important fluorinated intermediates for pharmaceutical and agrochemical chemistry [4]. These are also proven suitable raw materials for the synthesis of 1,1,2-trifluoroethyl aryl ethers [5], aryl-1,1,2-fluoroethanes [6], 1-aryl-2-fluoroenamines, and allylic fluorides [2,3,6]. The synthetic utility of α-fluoroacetophenone as a building block is summarised in Scheme 3.1 [4].

Owing to the synthetic utility of the α-fluoroacetophenone, several methods for its synthesis have been developed over a period of several decades. Early methods for synthesising α-fluoroacetophenone relied on indirect fluorination approaches in which an α-haloacetpheenone (e.g., α-bromo- or α-chloroacetophenone) was treated with inorganic fluorides like KF or CsF under phase transfer conditions. These methods, while effective, often suffer from low selectivity, harsh reaction conditions, low yield, and long reaction times. The advancement of electrophilic fluorinating agents in the 1990s, notably N-fluorobenzenesulfonimide (NFSI) and Selectfluor, has revolutionised the synthesis of α-fluoroacetophenone. These reagents allowed the direct fluorination of acetophenone *via* enolate intermediates under milder, safer, and more selective conditions. The synthetic methodologies can be divided into two broad headings: (i) Nucleophilic Fluorination and (ii) Electrophilic Fluorination. On the other hand, additionally, Friedel–Crafts chemistry [7,8], coupling chemistry [9], and reactions involving diazo ketones [10], are also used for the preparation of α-fluoroacetophenones. Reagents used for the synthesis of α-fluoroacetophenone are given in Table 3.1.



Scheme 3.1: Synthetic utility of α-fluoroacetophenone

Table 3.1: Reagents and reaction conditions for the synthesis of α-fluoroacetophenone

S. No.	Substrate/Reagents, Reaction Conditions	Ref.
Nucleophilic Fluorination		
1.	α-Bromoacetophenone/ Pyridine•9HF, HgO, 50 °C, 15 h.	[11]
2.	α-Bromoacetophenone/ KF, Glycerine, 130 °C, Vacuum.	[12]
3.	α-chloroacetophenone/CH_2N_2, Ether, then Pyridine•9HF rt, 4 h.	[10]
4.	α-Bromoacetophenone/ KF, Ph_3SnF (10 mol%), Sulfolane: CH_3CH (1:2), 95 °C, 4 h.	[13]
5.	α-Bromoacetophenone/ $TBAHF_2$, THF, Reflux.	[14]
7.	α-Bromoacetophenone/ KF, PEG-400, CH_3CN, 80 °C, 18 h	[15]
8.	α-Bromoacetophenone/ TBAF•$3H_2O$, ZnF_2, and KF, CH_3CN, 80 °C, 10 h.	[15]
9.	Acetophenone/ DES (choline chloride + *p*-toluene sulfonic acid), DCDMH, CH_3CN, rt, 1 h, then ZnF_2, TBAF•$3H_2O$, 80 °C 10 h.	[15]
10	Acetophenone/ DBDMH, CH_3OH, 40 °C, 3 h, then Et_3N.HF, CH_3CN, reflux, 18 h.	[16]
11.	Bromoacetophenone/ TBAF.$3H_2O$, H_2O, 100 °C, 20 min.	[17]
Electrophilic Fluorination		
1.	Acetophenone/ Me_2SiCl, LDA, CF_3OF, $CFCl_3$, -70 °C, 3 h.	[18]
2.	Silyl enol ether of acetophenone/ $CFCl_3$, F_2/N_2, -78 °C, 3.5 h.	[19]
3.	Trifluoromethyl acetophenone/ Mg/TMSCl, THF, 0 °C, 2 h, then 5M HCl, rt, overnight.	[20]
4.	Acetophenone/ Me_2SiCl, DBU, Selectfluor, CH_3CN, rt	[14]
5.	Acetophenone/ Selectfluor, MeOH, reflux, 2-11 days, then $CF_3COOH/H_2O/CHCl_3$, reflux, 20 h.	[14]
6.	Acetophenone/ Selectfluor, MeOH, MW, 1-2 h, H_2O, MW (80W), 20 min.	[21]
7.	Acetophenone/ Selectfluor, SDS (0.1 – 0.2 M) MeOH, MW, H_2O, 80 °C.	[22]
Miscellaneous methods		
1.	Fluorinated enol tosylates/ NaOH, DMSO/water (1:1), 80 °C, 5 h.	[23]
2.	Dichlorofluoromethyl aryl ketones/ Rongalite, EtOH, Reflux, 30-45 min.	[24]
3.	Trifluoromethyl β-Diketones/ Na_2CO_3, Selectfluor, MeCN:H_2O (3:2), °C, 8 h.	[25]

α-Bromoacetophenones are widely used for the synthesis of α-fluoroacetophenones by nucleophilic fluorination. Recently, Chai *et.al*. [26] used $Fe(NO_3)_3 \cdot 9H_2O$ as an oxidant for the mild oxidative α-bromination of ketones in the presence of bromide salt. Therefore, we thought to use the strategy for the α-fluorination of acetophenone using α-bromoacetophenone intermediate without isolation.

We started our study with 4-methoxyacetophenone (**1a**) as the model substrate because the substrate is easily distinguishable in TLC from its α-bromo and α-fluoro counterparts. A total of 14 reactions were performed to optimize the reaction conditions (**Table 3.2**, Scheme 3.2). The ^{19}F NMR analysis of the crude reaction mixture was used for the confirmation of product formation in the reaction. The polar aprotic solvents do not solvate the fluoride ion and increase its nucleophilicity there they are preferred in nucleophilic fluorination. At the start, the compound **1a**, $Fe(NO_3)_3 \cdot 9H_2O$, and LiBr (taken in a 1:1:1 ratio) were dissolved in DCM, and the reaction mixture was refluxed for 12 h. The reaction mixture was cooled down to room temperature, and then TBAF·$3H_2O$ (3 eq.) was added at room temperature and further stirred for 1 h. The crude was filtered and taken for ^{19}F NMR analysis, but no signal corresponding to the product was observed in ^{19}F NMR (**Table 3.2, entry 1**). This confirmed that no fluorination took place at the required site and change in reaction condition/solvent was required. Therefore, the solvent was changed to acetonitrile, and the reaction mixture was stirred at 70 °C for 4 h, followed by stirring for 2 h at room temperature after adding the TBAF·$3H_2O$ (3 eq.), but no ^{19}F NMR peak corresponding to the product was detected (**Table 3.2, entry 2**). Therefore, we changed the solvent to 1,2-dichloroethane (DCE) and heated the reaction mixture at 70 °C for 12 h, the reaction mixture was cooled down to room temperature. The fluorinating agent, TBAF·$3H_2O$ (3 eq.) was added at room temperature and the reaction mixture was further stirred for 2 h, at this temperature. The ^{19}F NMR analysis of crude reaction mixture shows a very small peak at δ = -230.0 (t, J = 46.6 Hz) corresponding to the product, which confirmed the fluorination at required site (**Table 3.2, entry 3**). On confirmation of the product, we proceed with the optimization of reaction parameters. On increasing the molar ratio (substrate: bromide: nitrate) from 1:1:1 to 1:1.1:1.5 and using 4 equivalents of fluorinating agent (TBAF·$3H_2O$), no significant change in product quantity was observed (Table 3.2, entry 4). Further increasing the TBAF·$3H_2O$ to 5 equivalents resulted in a 10% yield of the product 2-fluoro-1-(4-methoxyphenyl)ethenone (**2a**) (**Table 3.2, entry 5**). On changing the solvent from DCE to chlorobenzene, the yield was increased to 20% (**Table 3.2, entry 6**). To reduce the time in the first step, lithium bromide was replaced with potassium bromide, and it was observed that the

time in the first step was reduced to 8 h, with a corresponding increase in product yield to 23% (**Table 3.2, entry 7**).

Scheme 3.2

To improve the yield of the fluorinated product, various solvent system such as chloroform, ethyl acetate, acetonitrile, and the higher molar ratio of fluorinating agent were explored. On changing the solvent to $CHCl_3$: EtOAc (1:1), the first step was completed in 3 h at reflux temperature, and further stirring the reaction at room temperature with 6 eq. of TBAF·$3H_2O$, the yield was increased to 30%. On changing the solvent to PhCl: CH_3CN (3:1) with 6 eq. of fluorinating agent, the yield was increased to 52%. (**Table 3.2, entries 8** & **9**). The water in the fluorinating agent may be hindering the reaction by forming the hydrogen bond with fluoride ion and reducing its nucleophilicity [27]. By virtue of strong hydrogen bonding capability of fluoride ion with water, the hydrated and anhydrous TBAF shows huge difference in fluoride ion nucleophilicity [28]. To further improve the yield, the hydrated TBAF·$3H_2O$ was replaced with anhydrous TBAF (1M sol in THF), and the yield was increased to 59%. On adding the TBAF (1M sol in THF) further diluted in dichloromethane, the yield of the product was increased to 66%. Using PhCl: CH_3CN in (4:1) and TBAF (1M sol in THF) in DCM, a 69% yield was obtained (**Table 3.2, entries 10 – 12**). We also explore the Selectfluor and NFSI in place of TBAF (1M sol in THF), but they fail to provide the required fluorination (**Table 3.2, entry 13** & **14**). The final product was obtained as a white solid [25] after general workup and purification by column chromatography separation. The formation of the product was confirmed from its spectral analysis. In the ^1H NMR spectrum of **2a** (**Figure 3.1**), a three protons singlet at δ 3.87 is corresponding to -OC**H₃** group, a two protons doublet at δ 5.47 represent the -C**H₂**F group which is further confirmed with J_{H-F} value of 47.2 Hz. Four aromatic proton appears as two separate doublets at δ 6.95 and δ 7.87 with J values of 8.8 Hz each. The ^{13}C NMR spectrum of the compound **2a** (**Figure 3.2**) shows signal at δ 55.5 for O**C**H_3 carbon, a doublet at 83.4 for **C**H_2F carbon with J_{C-F} value of 180.6 Hz, the peaks at 114.1, 126.6, 130.1, and 164.2 are due to automatic carbons.

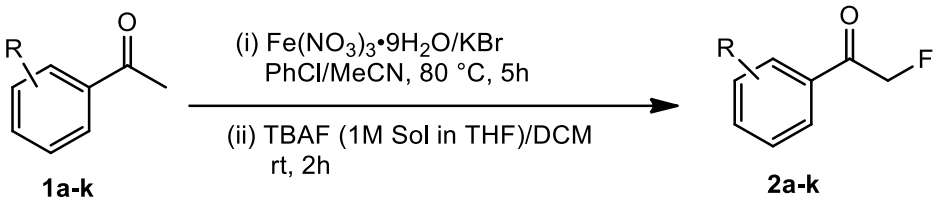
Table 3.2: Optimization of reaction parameters for α-fluoroacetophenone

Entry	Bromide Source	Solvent	Molar ratio (substrate: bromide: nitrate)	First step		Second step			Yield %
				T (°C)	Time (h)	Fluorinating agent		Time (h)	
1	LiBr	CH_2Cl_2	1:1:1	reflux	12	TBAF·3H₂O	3 eq.	1	0
2	LiBr	CH_3CN	1:1:1	70	4	TBAF·3H₂O	3 eq.	2	0
3	LiBr	DCE	1:1:1	70	12	TBAF·3H₂O	3 eq.	2	Trace
4	LiBr	DCE	1:1.1:1.5	70	12	TBAF·3H₂O	4 eq.	2	Trace
5	LiBr	DCE	1:1.1:1.5	70	12	TBAF·3H₂O	5 eq.	2	10
6	LiBr	PhCl	1:1.1:1.5	70	10	TBAF·3H₂O	5 eq.	2	20
7	KBr	PhCl	1:1.1:1.5	70	8	TBAF·3H₂O	5 eq.	2	23
8	KBr	$CHCl_3$: EtOAc	1:1.1:1.5	reflux	3	TBAF·3H₂O	6 eq.	3	30
9	KBr	PhCl: CH_3CN (3:1)	1:1.1:1.5	80	4	TBAF·3H₂O	6 eq.	2	52
10	KBr	PhCl: CH_3CN (3:1)	1:1.1:1.5	80	4	TBAF (1M in THF)	6 eq.	2	59
11	KBr	PhCl: CH_3CN (3:1)	1:1.1:1.5	80	4	TBAF (1M in THF)	6 eq.	2	66
12	**KBr**	**PhCl: CH_3CN (4:1)**	**1:1.1:1.5**	**80**	**5**	**TBAF (1M in THF) + DCM**	**6 eq.**	**2**	**69**
13	KBr	PhCl: CH_3CN (4:1)	1:1.1:1.5	80	5	Selectfluor	6 eq.	2	0
14	KBr	PhCl: CH_3CN (4:1)	1:1.1:1.5	80	5	NFSI	6 eq.	2	0

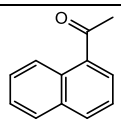
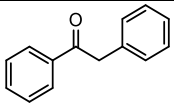
The carbon for carbonyl group (**C=O**) appears as doublet at 191.8 with J_{C-F} value of 15.8 Hz. In the ^{19}F-NMR spectrum of **2a** (**Figure 3.3**) a triplet at δ -230.0 indicate the monofluorinated -CH_2**F** group in the compound. FTIR spectrum of **2a** (**Figure 3.4**) shows **C=O** stretching at 1702 cm^{-1} in addition to other peaks. Therefore, stirring **1a**/KBr/$Fe(NO_3)_3 \cdot 9H_2O$ in a 1:1.1:1.5 molar ratio in PhCl: CH_3CN (4:1) at 80 °C for 5h, then addition of 6 equivalent TBAF (1M sol in THF) mixed with an equal volume of DCM and stirring for 2 h was selected as optimized reaction conditions (**Scheme 3.2**).

After successfully optimizing the conditions for the synthesis of 2-fluoro-1-(4-methoxyphenyl)ethenone (**2a**), we turned our attention to explored the scope of the one-pot fluorination process to synthesize the other substituted acetophenone derivatives (**Table 3.3**) to be ascertain about the applicability of the developed process to with acetophenone bearing different substituents, a brief study was carried out. First, we attamed the fluorination of acetophenone bearing electron-donating substitution. The 3-methoxy acetophenone (**1b**) was readily fluorinated under standard conditions to give 68% of the product, 2-fluoro-1-(3-methoxyphenyl)ethenone (**2b**) (**Table 3.3, entry 2**). The 4-methylacetophenone (**1c**) and acetophenone (**1d**) were also compatible with the reaction and produced 65% and 50% yield of fluorinated acetophenone 2-fluoro-1-(4-methylyphenyl)ethenone (**2c**) and 2-fluoro-1-phenylethenone (**2d**), respectively (**Table 3.3, entries 3** & **4**). The slight lower yield of the product **2d** may be attributed to the loss of the product during the removal of solvent under vacuum from the crude and final product. Then we turn our attention to the developed protocol for the fluorination of acetophenone with an electron-withdrawing substitution. Reaction was found compatible with halogen substitution on acetophenone. 4-Bromo (**1e**) and 3-bromo (**1f**) substituted acetophenone were also good substrates in this conversion to form respective products 2-fluoro-1-(4-bromophenyl)ethenone (**2e**) and 2-fluoro-1-(3-bromophenyl)ethenone (**2f**) in 65% and 59% yield (**Table 3.3, entries 5-6**). 4-Chloro (**1g**) and 2,4-dichloro (**1h**) acetophenones produced 62% and 55% of the respective fluorinated products (**Table 3.3, entries 7-8**). The lower yield of 2,4-dichloroacetophenones fluorination should be resulted due to the stearic hindrance from ortho substitution on acetophenone ring. 4-Fluoro derivative (**1i**) was also fluorinated to give 64% yield (**Table 3.3, entry 9**). The fluorination of 4-nitroacetophenone (**1j**) took a longer reaction time in the bromination step, and gave a lower yield of 35% (**Table 3.3, entry 10**). It was notable that the naphthalene ring was also compatible with fluorination process and 1-acetonaphthanone (**1k**) leads to the α-fluorinated compound (**2k**) in 72% yield using the developed protocol (**Table 3.3, entry 11**).

Table 3.3: The α-fluorination of various acetophenone/ketones



1a-k 2a-k

Entry	Substrate	(R)	Product	Isolated Yield (%)	Observed melting point	Lit. melting point (ref)
1	1a	4-OCH_3	2a	69	81 – 83 °C	80.6 –81.7 °C [25]
2	1b	3-OCH_3	2b	68	54 – 56 °C	53 – 54 °C [29]
3	1c	4-CH_3	2c	65	23 – 25 °C	22.9 –24.3 °C [25]
4	1d	H	2d	50	Viscous liquid	Clear liquid [25]
5	1e	4-Br	2e	65	70 – 73 °C	71.2 –72.6 °C [25]
6	1f	3-Br	2f	59	48 – 50 °C	Clear oil [15]
7	1g	4-Cl	2g	62	51– 52 °C	51 – 52 °C [15]
8	1h	2,4-Dichloro	2h	55	41 – 42 °C	
9	1i	4-F	2i	64	50 – 53 °C	49 – 51 °C [14]
10	1j	4-NO_2	2l	35	90 – 92 °C	90 – 92 °C [10]
11	1k		2k	72	44 – 45 °C	44–45 °C [21]
12	1l		No reaction			

1,2-Diphenylethan-1-one (**1l**) does not undergo the fluorination reaction. However, in the case of ortho and *p*-hydroxyacetophenone, a complex mixture was obtained and could not be separated in column chromatography. The acetophenone bearing electron donating group (-

OCH_3, -CH_3) and halogens (Br, Cl, & F) at para or meta position on benzene ring gives the desired mono fluorinated product in good yield, however the acetophenone with strong electron withdrawing substitution (NO_2, OH) gives the lower yield or fails to provide separable yield. The results are summarized in Table 3.3.

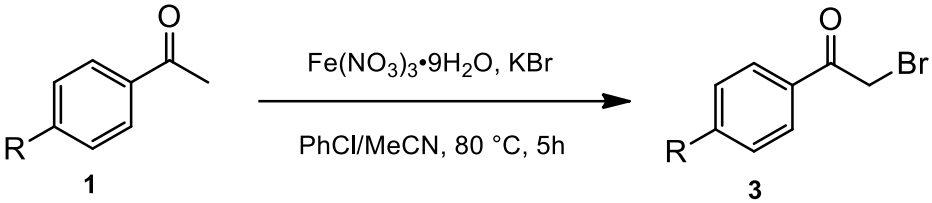
3.2 Formation of the brominated compound in the first step of fluorination

To get insight into the reaction mechanism of one-pot fluorination and confirm the identity of the intermediate formed in the first step, two intermediate compounds were isolated and characterized after completion of the first step (**Table 3.4**). In a typical reaction, 4-methoxyacetophenone (**1a**) and KBr were taken and dissolved in the solvent mixture of chlorobenzene (4 mL) and acetonitrile (1 mL). After that, Iron (III) nitrate nonahydrate was added, and the reaction mixture was heated to 80 °C. The progress was monitored by TLC. After consumption of 4-methoxy acetophenone, the reaction mixture was cooled down to room temperature and filtered through a filter paper. The fluorinating agent was not added to the reaction mixture. The filtrate was extracted with DCM; the organic layer was collected and passed through a 5 cm silica gel column. After that, the filtrate was dried under vacuum to get the pale-yellow solid. The solid was washed with a petroleum ether-water (1:1) mixture two to three times and finally re-crystallized from petroleum ether to get the 2-bromo-1-(4-methoxyphenyl)ethenone (**3a**) as a white crystalline solid in 78% yield. This product was confirmed as **3a** from its spectroscopic characterization. In ^{1}H NMR spectrum of the compound **3a** (**Figure 3.5**) the three-proton singlet for -OC**H**$_3$ appears at δ 3.87, a two-proton singlet at δ 4.39 is due to -C(O)C**H**$_2$Br, the aromatic protons appear as two doublets at δ 6.95 with *J* value of 9.0, and 7.96 with *J* value of 8.9 Hz. In ^{13}C NMR spectra of **3a** (**Figure 3.6**), the -**C**H_2Br appears at δ 30.6 and the carbonyl carbon of the **C**=O group is found at δ 189.9. In the FTIR spectrum of the compound **3a** (**Figure 3.7**), the stretching for the carbonyl (**C**=O) group appeared at 1687 cm^{-1}.

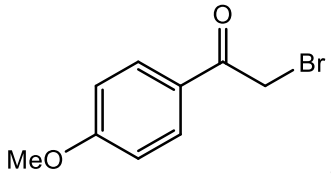
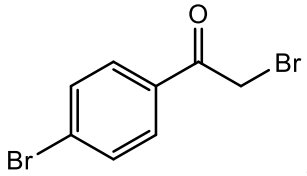
The same process was repeated with another acetophenone derivative, 4-bromoacetophenone (**1e**), to prepare the intermediate compound 2-bromo-1-(4-bromophenyl)ethenone (**3e**). On purification by column chromatography and recrystallization from petroleum ether, a white crystalline solid of **3e** was obtained in 82% yield. The structure of the compound was also confirmed by its spectroscopic characterization. In ^{1}H NMR spectrum of the compound **3e** (**Figure 3.8**) a two-proton singlet at δ 4.3 is due to -C(O)C**H**$_2$Br, the aromatic protons appear as two doublets at δ 7.60 with *J* value of 8.30, and 7.80 with *J*

value of 8.50 Hz. In ^{13}C NMR spectra of **3e** (**Figure 3.9**), the -CH_2Br appears at δ 30.3 and the carbonyl carbon of the **C**=O group is found at δ 190.4 in addition to other aromatic carbons at 129.3, 130.4, 131.2, 132.2, and 132.7. In the FTIR spectrum of the compound **3e** (**Figure 3.10**), the stretching for the carbonyl (**C**=O) group appeared at 1698 cm^{-1}. The results are summarized in Table 3.4.

Table 3.4: The α-brominated intermediate of various acetophenones

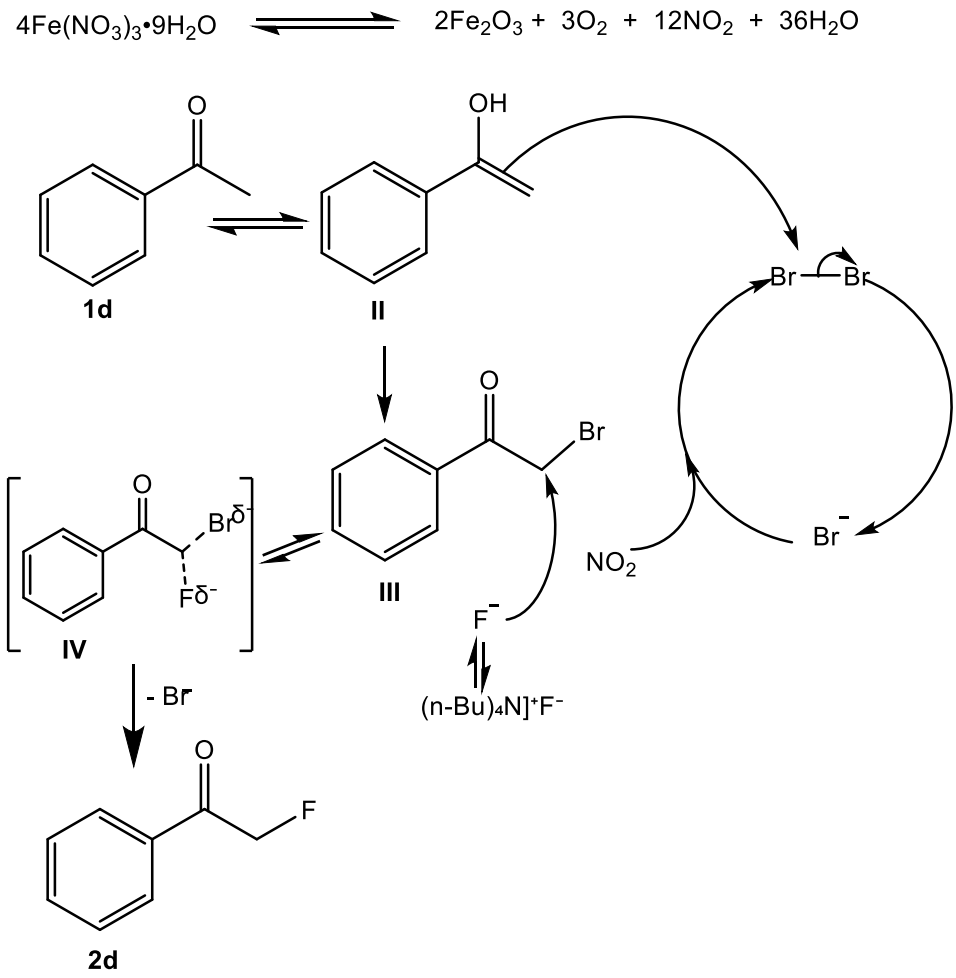


R = **1a** : 4-OMe
1e : 4-Br

Intermediate	Isolated Yield (%)	Observed melting point	Lit. melting point (ref)
 **3a**	78%	70 - 72 °C	71-72 °C [30]
 **3e**	82%	106 – 108 °C	107-109 [30]

Based on the intermediate formed and literature evidences, the plausible mechanism for one-pot fluorination has been proposed. Iron (III) nitrate nanohydrate decomposed to NO_2/N_2O_4 on heating [26]. The water produced by the decomposition of $Fe(NO_3)_3 \cdot 9H_2O$ system help in ionisation of potassium bromide. Bromide ion liberate from ionization of KBr is oxidized by NO_2 to generate intermediate Br_2. In situ generated bromine reacts with the enol form (II) of ketones to afford α-bromoketone (III) as the intermediate product, and the bromine ion is liberated back into the oxidation cycle. In the next step the fluoride ion from TBAF

attacks the carbon of α- bromoketone (III) in an S_N2 manner [28] to give α-fluoroacetophenone (**2d**) via a transition state (IV) (**Scheme 3.5**).



Scheme 3.5: Proposed mechanism of α-fluoroacetophenone synthesis.

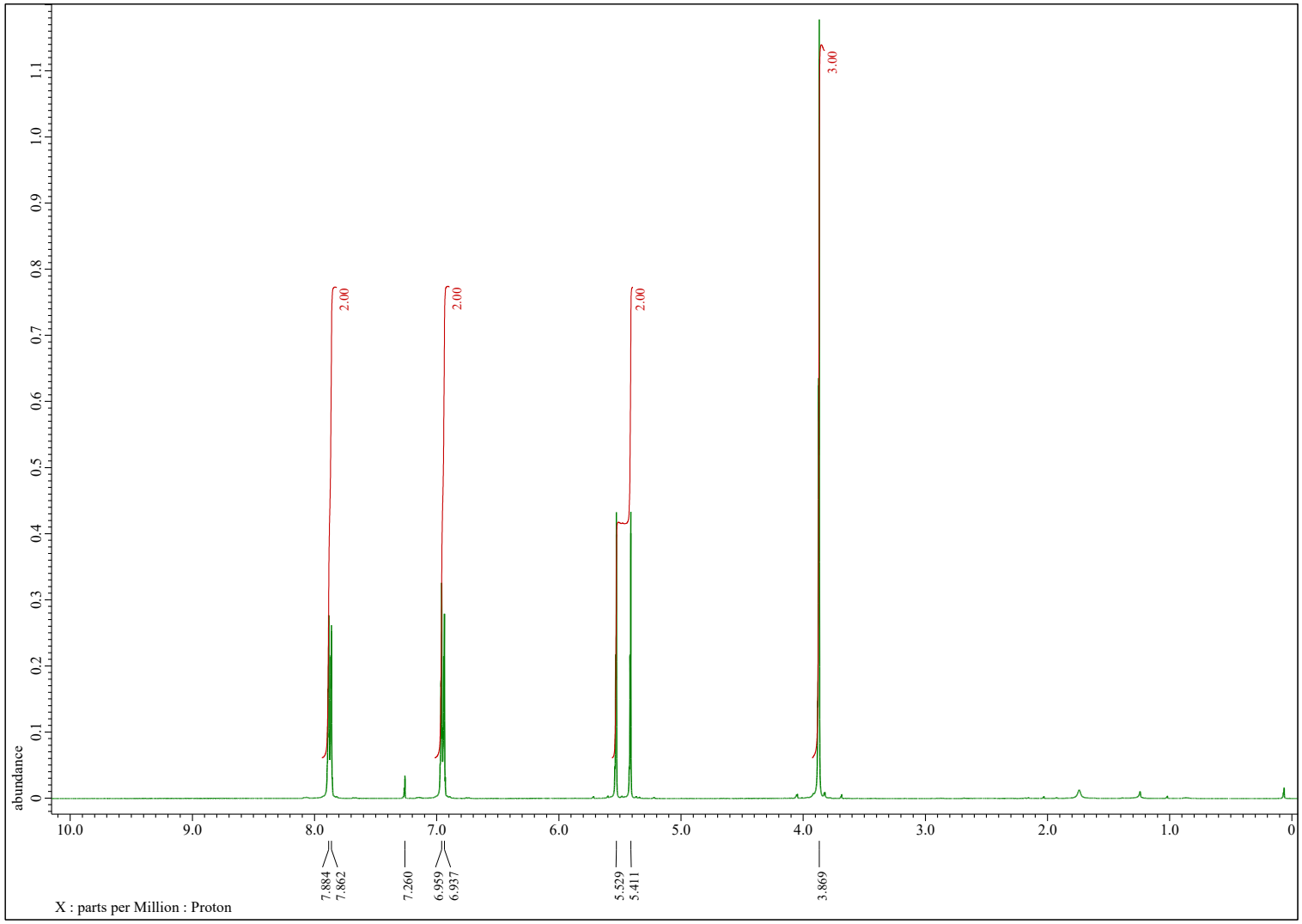


Figure 3.1: ^{1}H NMR spectrum of 2-fluoro-1-(4-methoxyphenyl)ethan-1-one (**2a**)

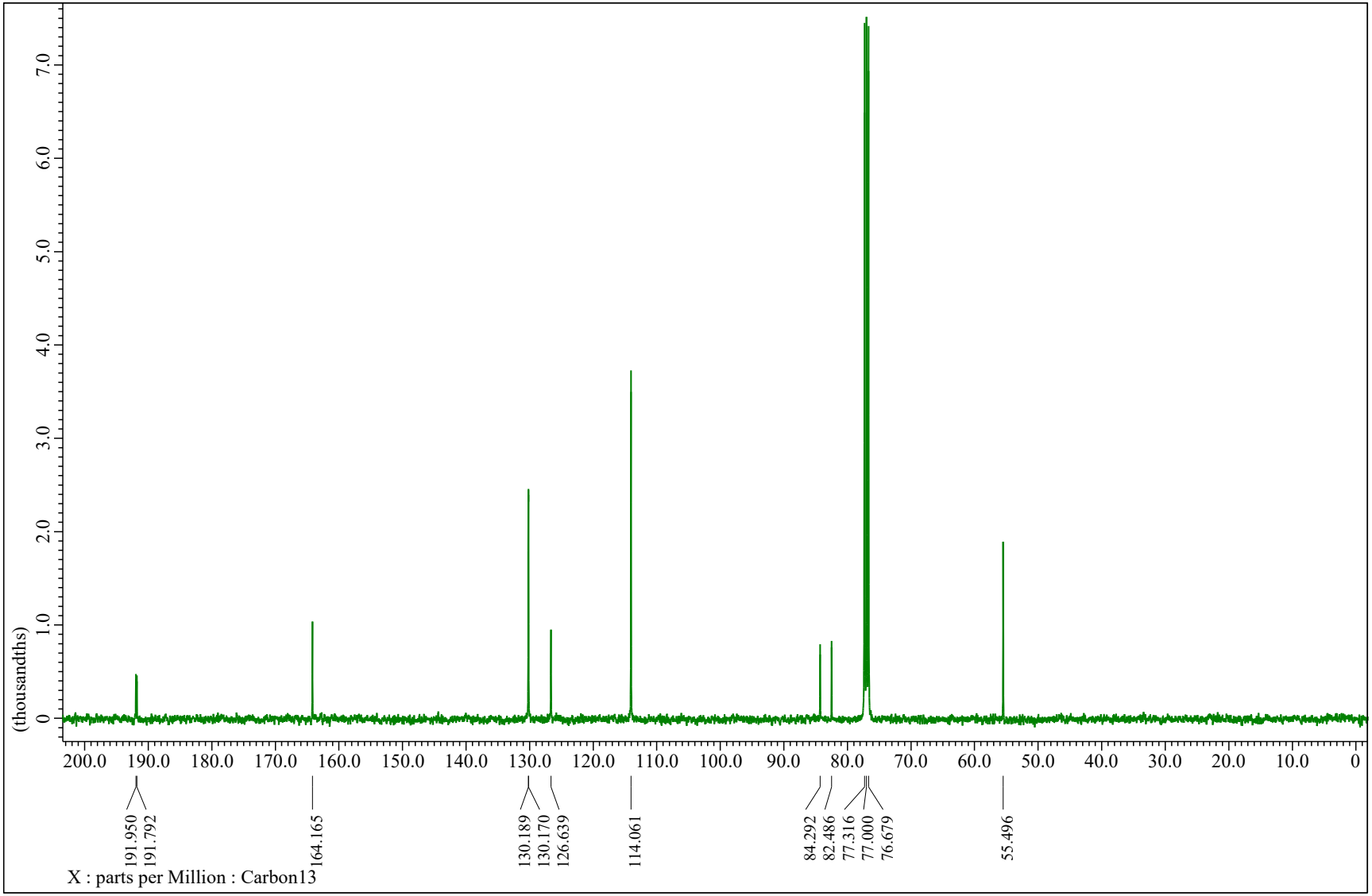


Figure 3.2: ^{13}C NMR spectrum of 2-fluoro-1-(4-methoxyphenyl)ethan-1-one (**2a**)

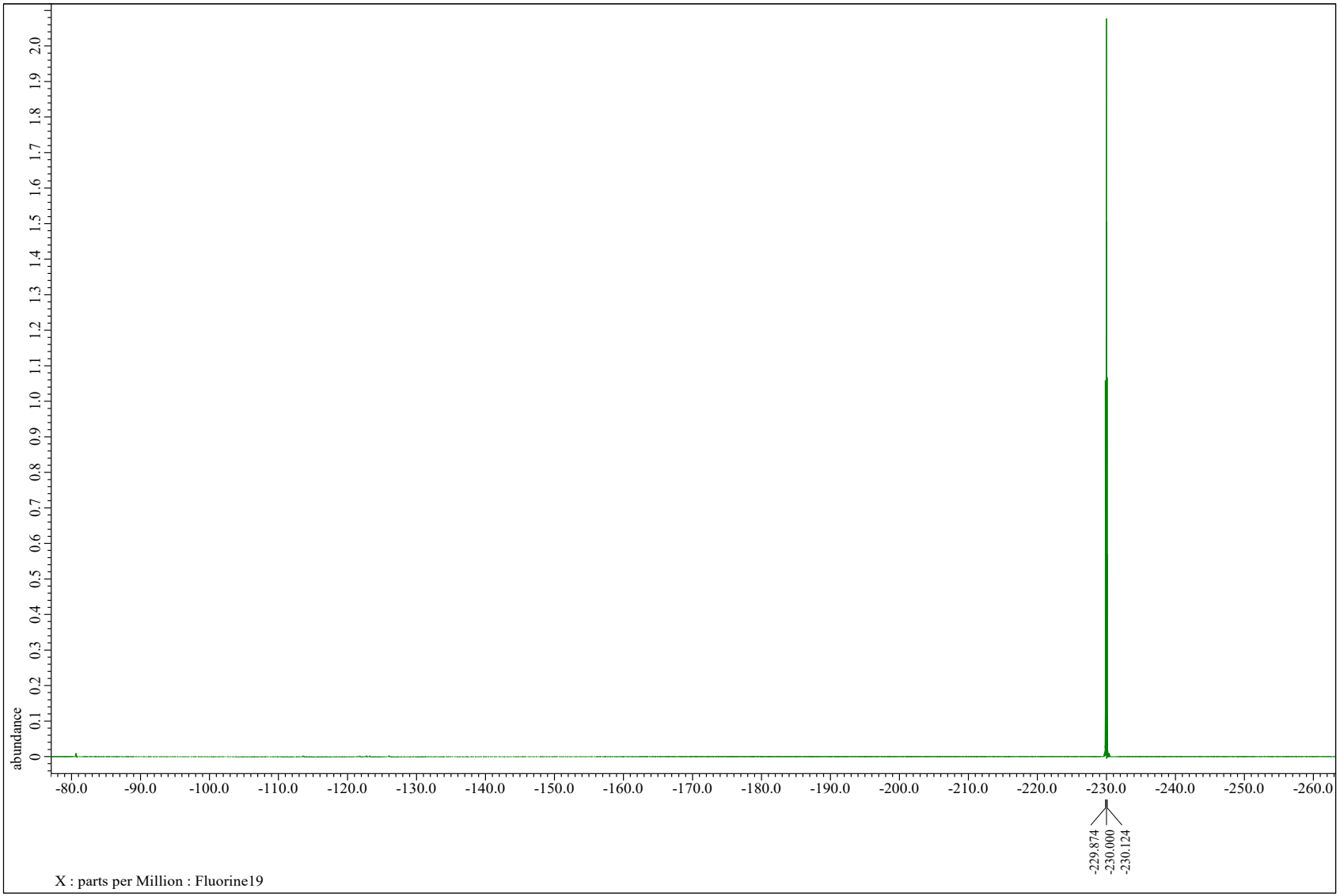


Figure 3.3: ^{19}F NMR spectrum of 2-fluoro-1-(4-methoxyphenyl)ethan-1-one (**2a**)

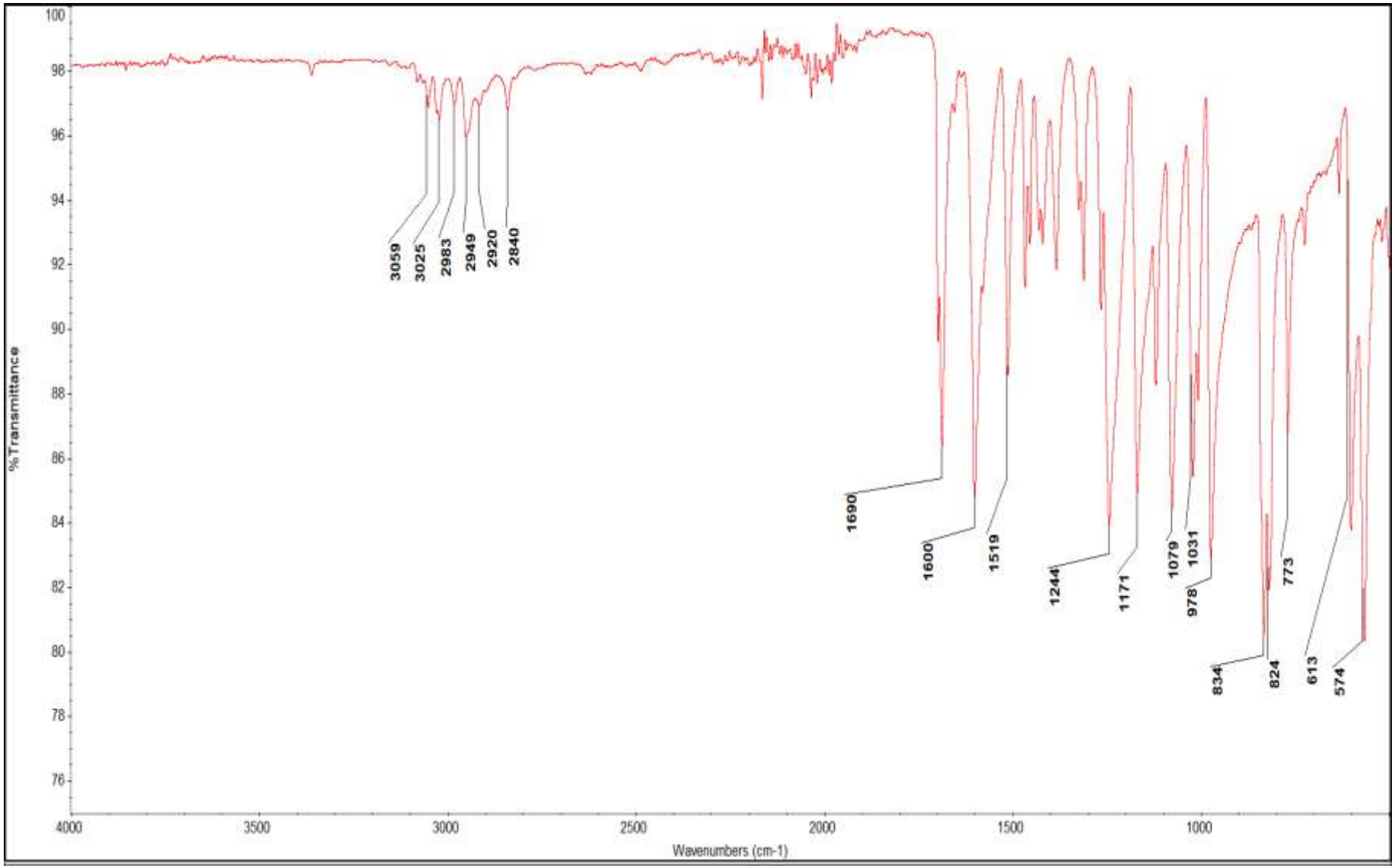


Figure 3.4: FTIR spectrum of 2-fluoro-1-(4-methoxyphenyl)ethan-1-one (**2a**)

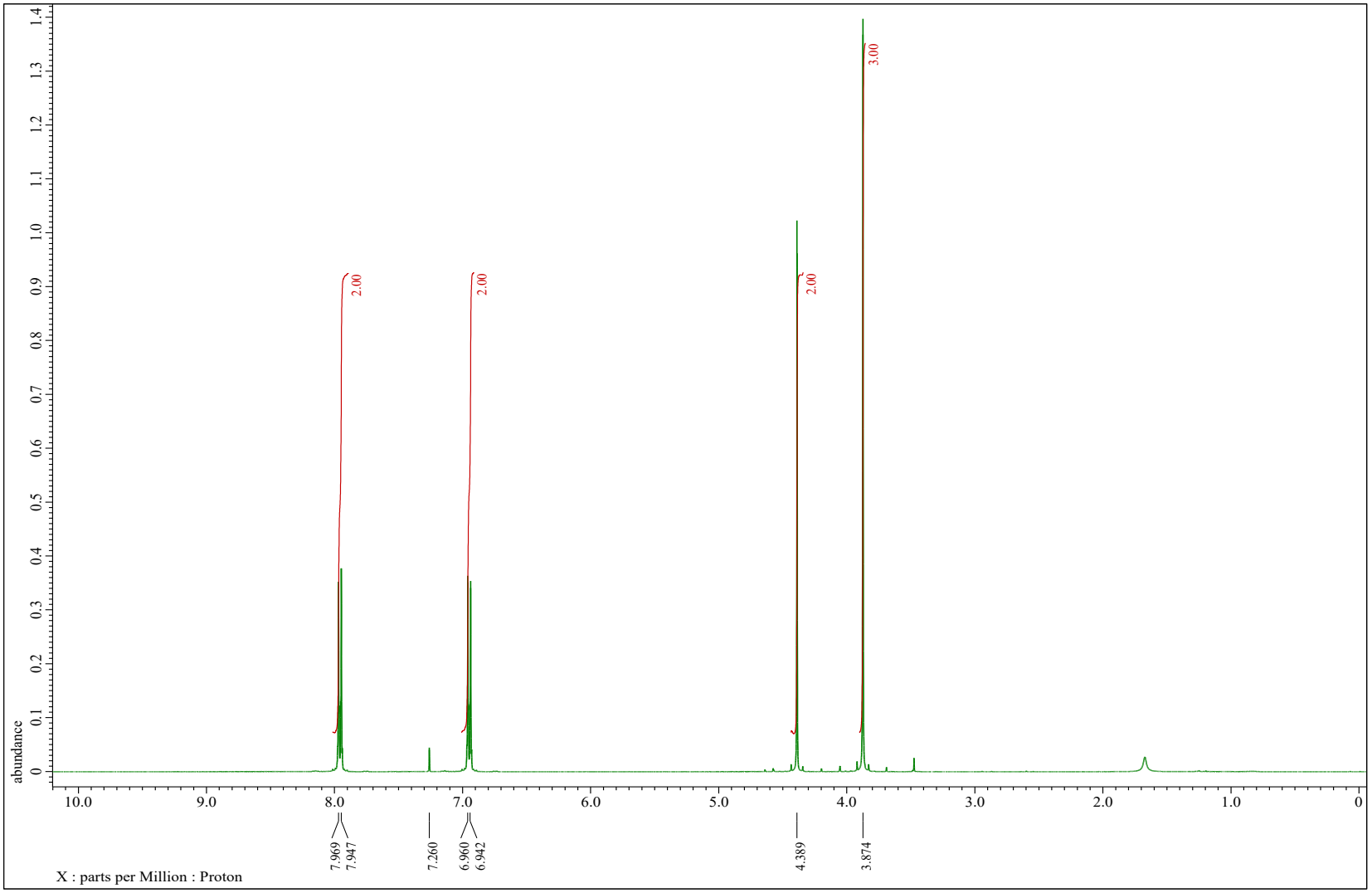


Figure 3.5: ^{1}H NMR spectrum of 2-Bromo-1-(4-methoxyphenyl)ethan-1-one (**3a**)

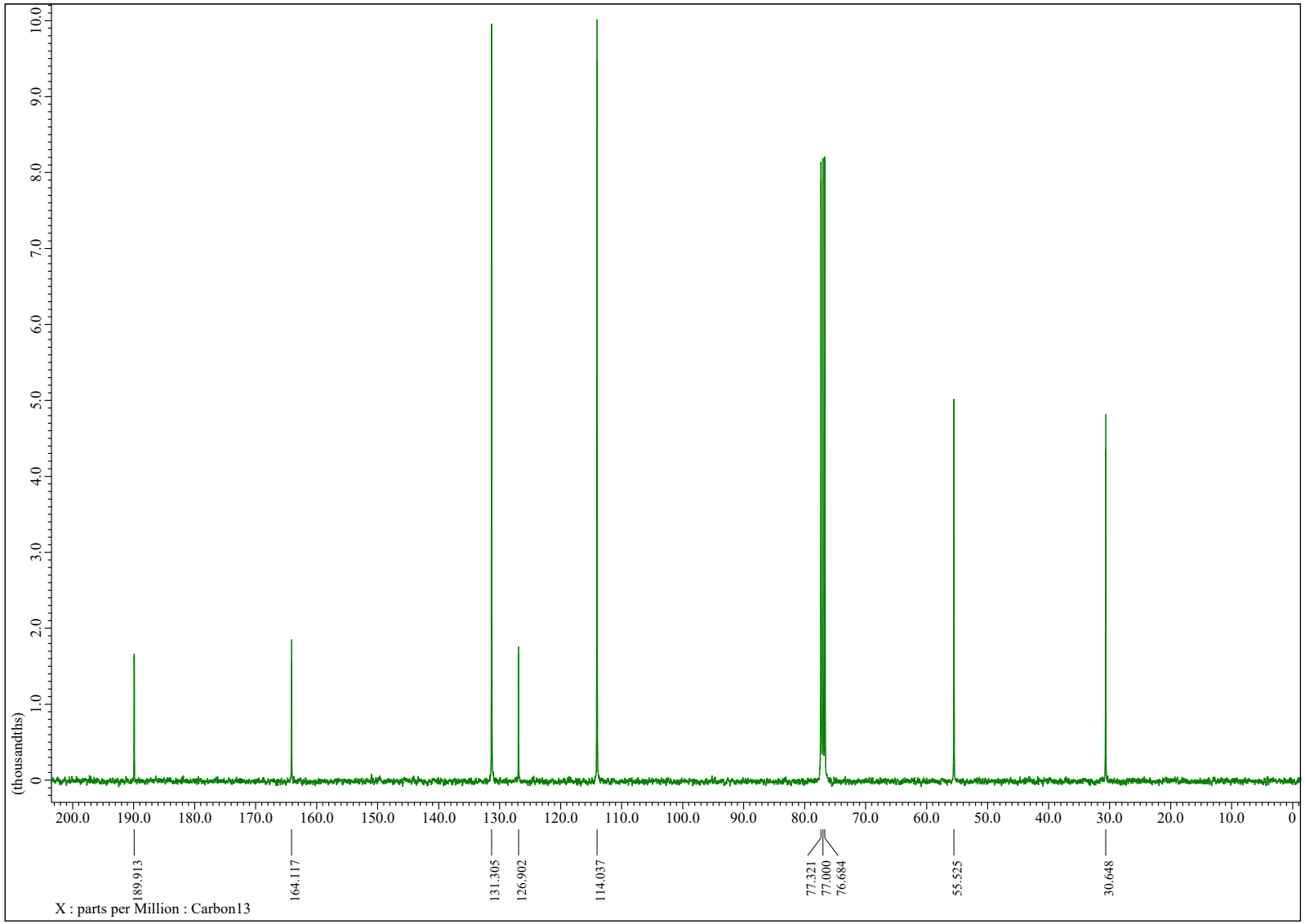


Figure 3.6: ^{13}C NMR spectrum of 2-Bromo-1-(4-methoxyphenyl)ethan-1-one (**3a**)

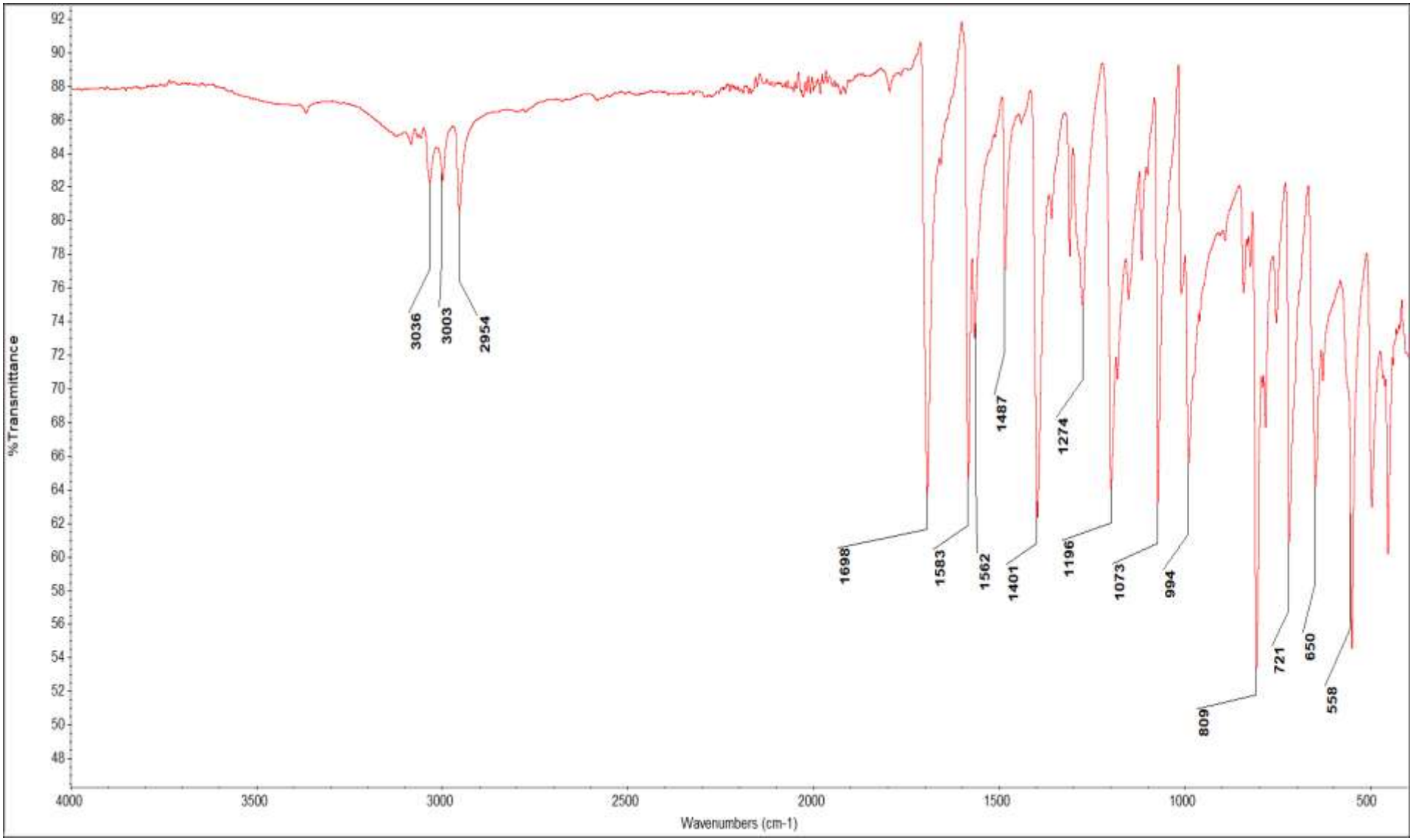


Figure 3.7: FTIR spectrum of 2-Bromo-1-(4-methoxyphenyl)ethan-1-one (**3a**)

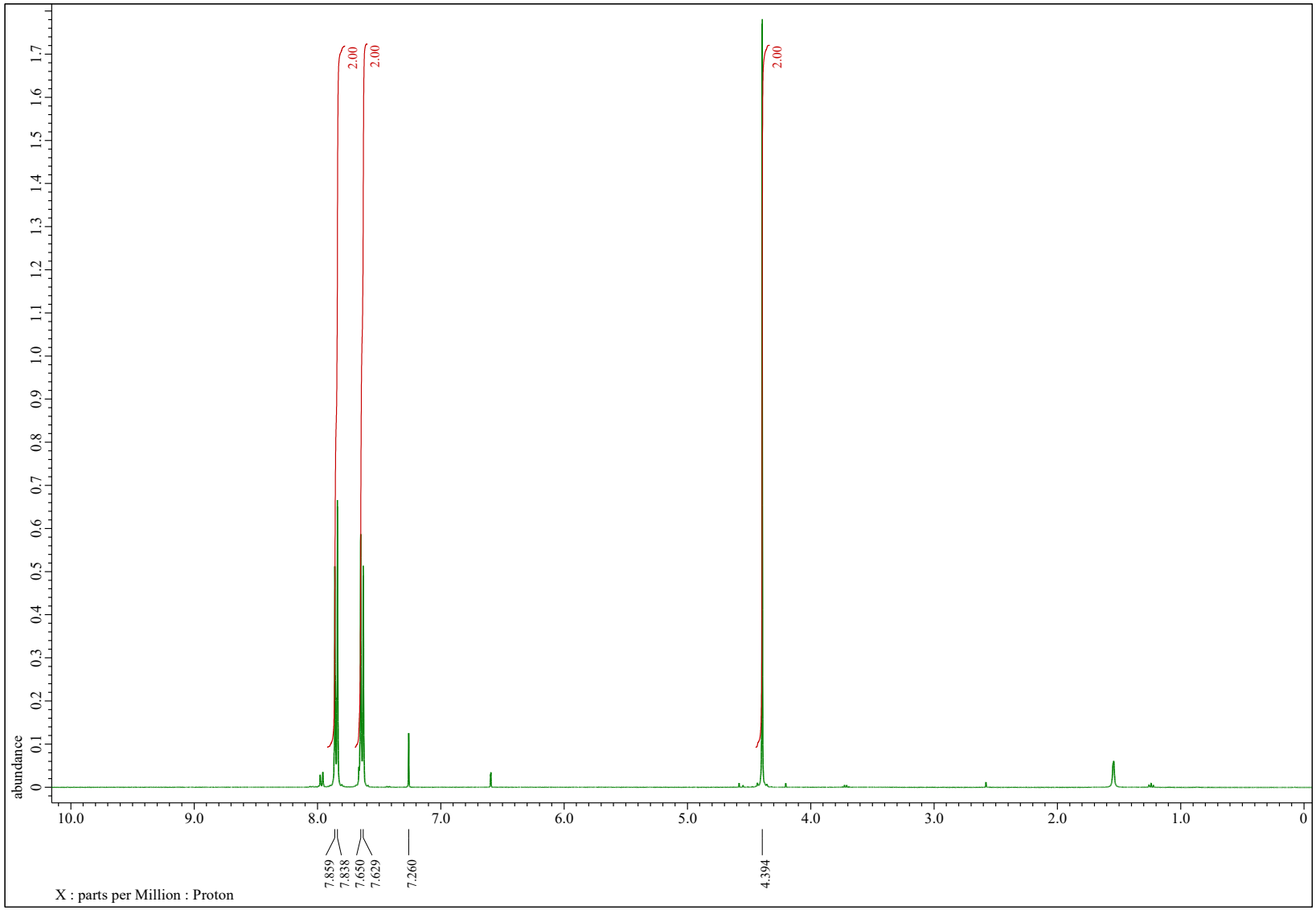


Figure 3.8: ^{1}H NMR spectrum of 2-Bromo-1-(4-bromophenyl)ethan-1-one (**3e**)

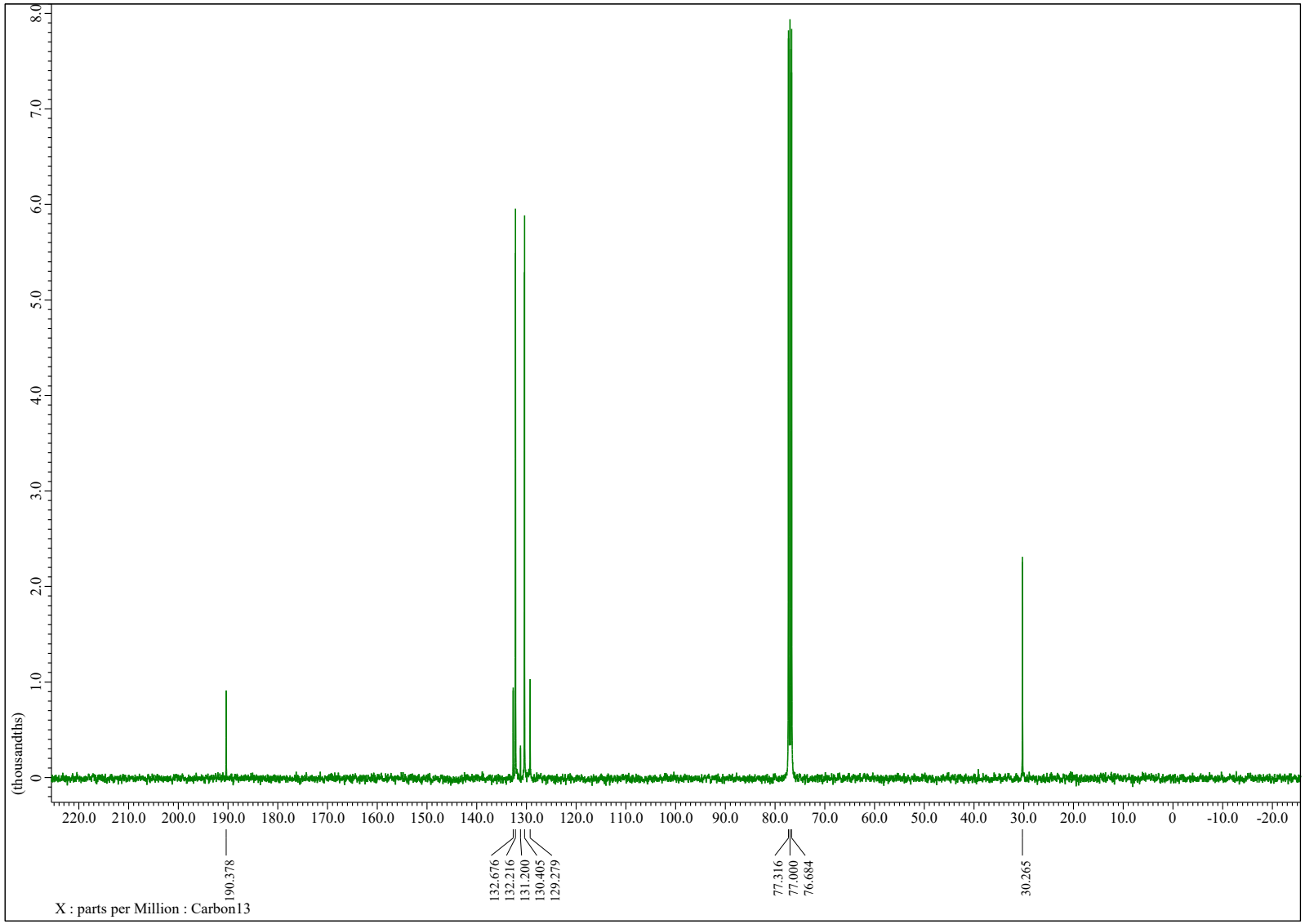


Figure 3.9: ^{13}C NMR spectrum of 2-Bromo-1-(4-bromophenyl)ethan-1-one (**3e**)

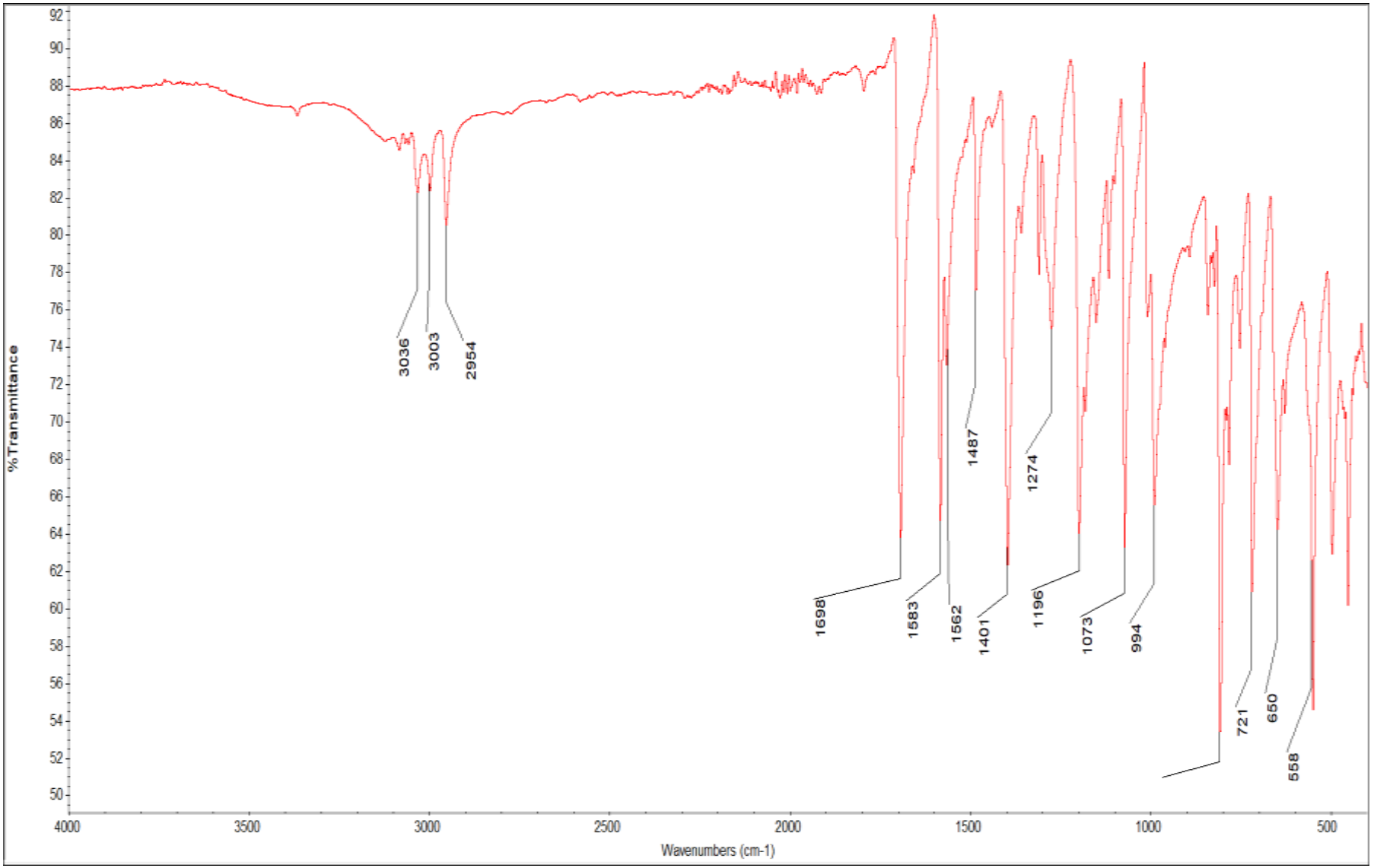


Figure 3.10: FTIR spectrum of 2-Bromo-1-(4-bromophenyl)ethan-1-one (**3e**)

3.3 Aromatic C-H Fluorination

The development of the aromatic carbon-fluorine (C-F) bond in organic compounds has great implications in modern fluoroorganic chemistry. These compounds are tremendously important in the fields of pharmaceuticals, agrochemicals, and materials science [31]. The incorporation of fluorine into aromatic systems significantly alters the chemical and physical properties of the molecule, enriching the value of fluorochemicals in different applications. The small size and high electronegativity of the fluorine atom are key factors in providing the high bond strength (bond dissociation energy ~104 kcal/mol) and polarity to the C-F bond. The enhanced chemical stability, lipophilicity, and metabolic stability of the molecule enhance the drug efficiency by improving bioavailability and therapeutic value [32]. The element's small size minimizes steric interference, and its electronegativity impacts the electron density, increasing binding affinity in enzyme inhibitors or receptor ligands. In pharmaceuticals, approximately 20-25% of drugs, including blockbusters like Lipitor and Prozac, contain C-F bonds [33]. The fluoroaromatics have great importance in advanced materials. The large portions of liquid crystals comprise the fluorinated substituents [34].

The fluorinated aromatic compounds have significantly affected the field of fire-retardant chemistry. The introduction of a fluorine atom into aromatic compounds dramatically enhances their thermal stability and oxidative degradation resistance, making them highly valuable for flame-retardant applications. For example, pentafluorobenzene derivatives and fluorinated biphenyls are being widely studied as core units in fire-retardant systems due to their high-temperature resistance, high char yield, and low flammability [35–37]. The aromatic C–F bonds contribute to flame retardancy in the gas phase as well as the condensed phase during the combustion process. For example, the fluorinated aromatic phosphate esters, viz. tris(4-fluorophenyl)phosphine and tris(2,2,2-trifluoroethyl) Phosphite are well studied as flame-retarding additives in Li-Ion Batteries due to their strong flame inhibition through thermal shielding and char formation [38]. Similarly, fluorinated bisphenol A derivatives used in epoxy resins can significantly improve the Limiting Oxygen Index (LOI), indicating better flame resistance [36]. These compounds release non-flammable fluorinated volatiles during pyrolysis in flame, which dilute combustible gases and suppress the flame. The phosphorus–nitrogen–fluorine synergistic systems, such as fluorinated flame retardant (**Figure 3.11**), have been reported to significantly improve the flame retardancy of rigid polyurethane foam with higher LOI values and lower peak heat release rates. The aromatic C–F bond enhances char yield and flame retardancy while maintaining thermal performance [35]. Therefore,

incorporating a fluorine atom in an organic compound is a powerful strategy for designing the next-generation flame-retardant materials, useful in electronics, aerospace, and advanced polymer applications.

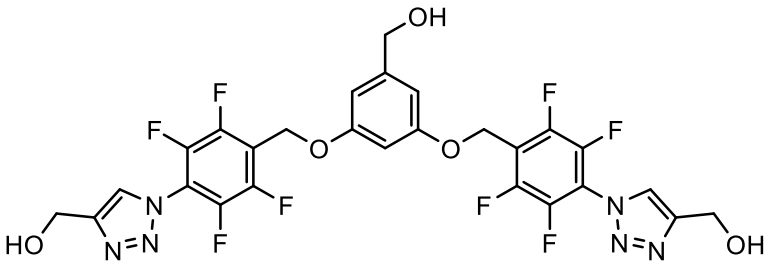


Figure 3.11: Fluorinated flame retardant

The field of aromatic fluorination has seen a remarkable change from the first successful aromatic C-F bond formation in the 1870s [39]. Later, Balz-Schiemann reaction was reported as original method for transformation of aromatic amins to aromatic fluoride *via* diazonium tetrafluoroborate intermediate [40]. The aromatic fluorination has significantly advanced from early unselective and hazardous processes to more selective and safer techniques using electrophilic and nucleophilic fluorinating reagent [40]. The development of transition metal catalysed fluorination has enabled the precise introduction of C-F bonds in aromatic compound, overcoming challenges posed by high reactivity of fluorine and the inert nature of aromatic C-H bonds [41]. These developments have streamlined the fluoro aromatics synthesis by reducing the costs, and improving yield. The fluorination of N-heterocycles has played its role in various fields, utilizing different methods of fluorination.

The synthesis of fluorinated oxindoles has been widely reported due to their important biological activities. For instance, C3-fluorinated oxindoles have been synthesized using various methods, e.g., various catalytic systems have been reported for the fluorination of oxindoles to give 3-fluorooxindoles [42–47]. Reports are also documented for the preparation of fluorinated oxindole from the fluorination of indole [48]. Several other processes are also reported for the synthesis of 3-fluorooxindole from different starting materials, such as nucleophilic fluorination of isatin with diethylaminosulfur trifluoride (DAST) [49], an intramolecular multistep approach from 2-fluoronitrobenzene [50], *N*-aryl diazoacetamides using NFSI as fluorine source [51], and electrochemical synthesis [52]. Few methods reported in the literature for the synthesis of 3-fluorooxindoles are summarized in **Table 3.5**.

Table 3.5: Reagents and reaction conditions for the synthesis of 3-fluorooxindoles

S. No.	Reagents & Reaction Conditions	Reference
Synthesis of 3-fluorooxindoles from 3-substituted indoles		
1.	Selectfluor, CH_3CN/H_2O (1:1), rt, overnight.	[53]
2.	Selectfluor, [bmim][BF_4]/MeOH (1:1), 20 °C, 3 h.	[54]
3.	Selectfluor, $NaHCO_3$, CH_3CN/H_2O (1:1), rt, 16-24 h.	[55]
4.	Quinoxalin-2(1*H*)-one, $CeCl_3$ (0.5 to 1 mol%), MeCN, Air, Blue LED, rt, 1 – 3 h, then NFSI, air, 50 °C, 3 h.	[48]
Synthesis of 3-fluorooxindoles from oxindoles		
1.	NFSI, Pd-cat, Isopropanol, rt, 5 h.	[42]
2.	Selectfluor, LiOAc, DCE, 70 – 80 °C, 15 h.	[46]
3.	Selectfluor, CH3CN, rt, 16 h.	[47]
4.	TBAF•$3H_2O$, DMF, MS 4Å, 0 °C, 2 – 3 h	[56]

3.3.1 Synthesis of starting materials: Esters of indole acetic acid

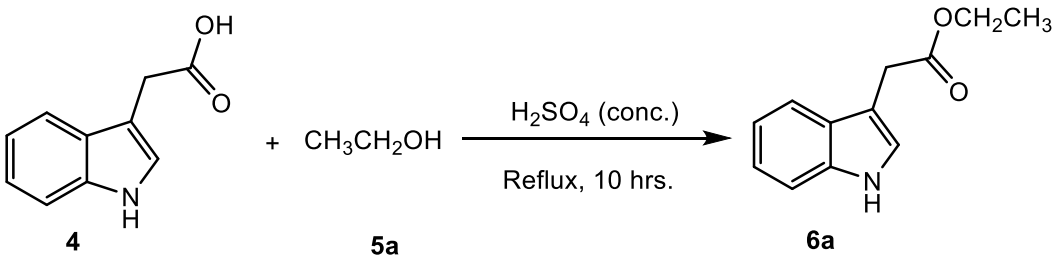
At the outset, we synthesized the esters of indole acetic acid using the reported literature method [57,58]. Based on ease of synthesis, the esters were synthesized using two methodologies. In one method (Method-A), the esterification was done using concentrated sulphuric acid as a dehydrating agent, while in the second esterification method (Method-B), DCC was used as a dehydrating agent in a DMAP-catalysed reaction.

Method-A

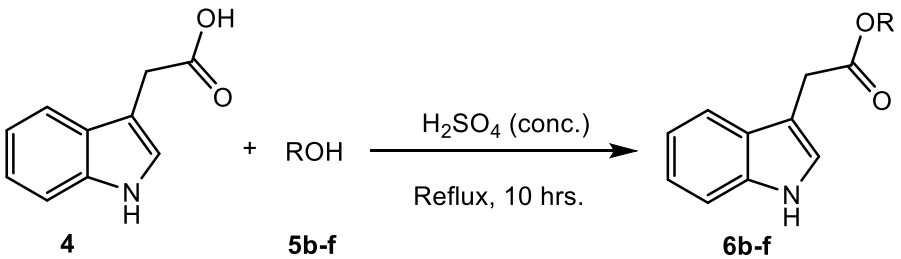
Esterification of indole-3-acetic acid (4) using concentrated sulphuric acid as a dehydrating agent

The precursor ethyl 2-(1*H*-Indol-3-yl)acetate (**6a**) was prepared by the method described by Katz et al. in US Patent 4,670,462A [57]. In this reaction indole-3-acetic acid (**4**) was dissolved ethanol (**5a**), and concentrated sulfuric acid was added to it (**Scheme 3.6**). The resulting solution was refluxed for 10 h. The progress was monitored by TLC. The completion of reaction was indicated by complete consumption of reactant **4** in the reaction mixture. After completion of the reaction, the reaction mixture was concentrated under vacuum to remove the excess remaining alcohol to get the reddish-brown viscous residue. The residue was dissolved in dichloromethane and the resulting solution was washed with sodium bicarbonate solution to

neutralize the unreacted sulphuric acid. The organic layer was separated, dried over anhydrous sodium sulphate, and filtered. The crude product was obtained from DCM after its removal under vacuum using rotary evaporator, which was further purified using column chromatography. The structure of the precursor **6a** was confirmed as ethyl 2-(1*H*-indol-3-yl) acetate by its spectral data. The ^{1}H NMR spectrum of **6a** (**Figure 3.12**) has a broad D_2O exchangeable NH peak at δ 8.16, along with the aromatic CH peak appearing in the region 7.64-7.11 ppm for five protons. In the aliphatic region, the three-proton triplet appeared at δ value 1.28 ppm confirmed to the **CH₃**CH_2- group, a two-proton quartet at 4.19 ppm is due to the CH_3**CH₂**- group, while a two-proton singlet at δ 3.79 represents the -**CH₂**C=O. A peak at δ 172.2 in the ^{13}C-NMR spectrum (**Figure 3.13**) confirms the carbonyl carbon (**C**O) along with other aliphatic and aromatic carbons. In the FTIR spectrum (**Figure 3.14**), the NH stretching peak appeared at 3406 cm^{-1} and the stretching for the ester group (C=O) appeared at 1722 cm^{-1}. Further, a series of alkyl 2-(1*H*-indol-3-yl) acetate (**6b-f**) was prepared by reaction of **4** and aliphatic alcohols (**6b-f**) (**Scheme 3.7**). The results are summarized in Table 3.6.



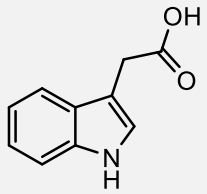
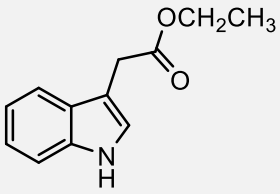
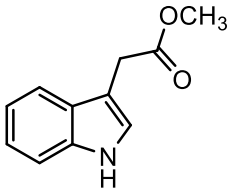
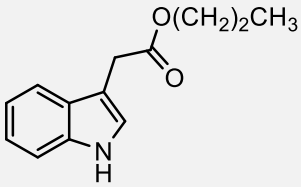
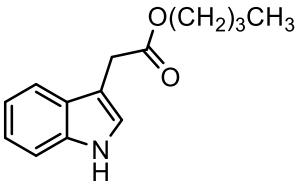
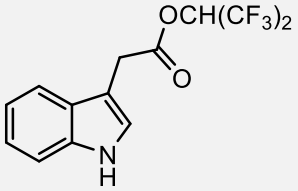
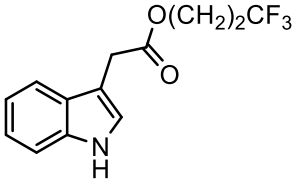
Scheme 3.6: Synthesis of ethyl 2-(1*H*-Indol-3-yl)acetate (**6a**)



R = Me, *n*-Pr, *n*-Bu, *i*Pr, $CF_3CH_2CH_2$

Scheme 3.7: Synthesis of esters of indole acetic acid (**6b-f**)

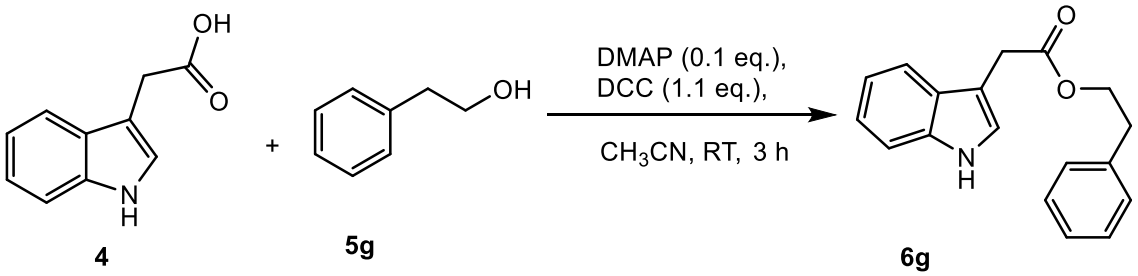
Table 3.6: Ester synthesized using concentrated sulphuric acid as a dehydrating agent

Substrate (4)	Alcohol (5)	Time (h)	Product (6)	Yield %
 **4**	CH_3CH_2OH **5a**	10	 **6a**	88%
4	CH_3OH **5b**	10	 **6b**	88%
4	$CH_3CH_2CH_2OH$ **5c**	10	 **6c**	89%
4	$CH_3(CH_2)_3OH$ **5d**	10	 **6d**	84%
4	$(CH_3)_2CHOH$ **5e**	10	 **6e**	85%
4	$CF_3CH_2CH_2OH$ **5f**	24	 **6f**	82%

Method-B

Esterification of indole-3-acetic acid (4) using DCC/DMAP

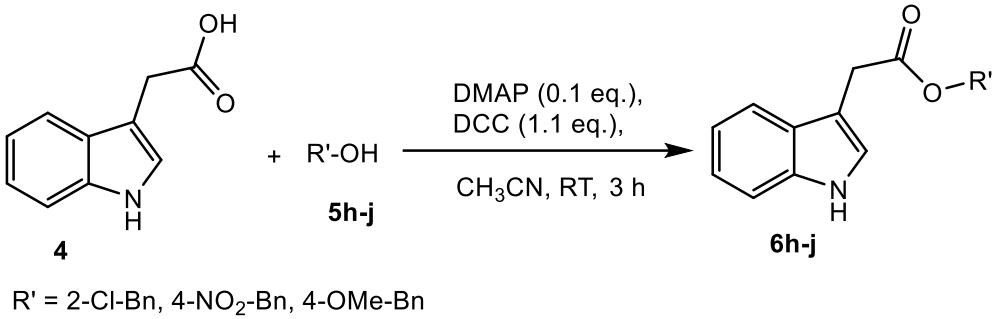
The precursor phenethyl 2-(1*H*-indol-3-yl)acetate (**6g**) was prepared by the method described in the literature using acetonitrile as solvent [58]. In this process, the indole-3-acetic acid (**4**) is reacted with 2-phenylethan-1-ol (**5g**) in the presence of DMAP using the solvent acetonitrile. The solution was cooled down to 0 °C using a cooling bath controlled with circulator. When the required temperature of reaction solution was attained, the DCC was added to it in small portion maintaining the temperature at 0 °C. After complete addition of DCC, the reaction mixture was stirred for five minutes at 0 °C and then it was allowed to attain room temperature and further stirred for 3 h at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction, as indicated by consumption of indoleacetic acid in reaction mixture by TLC, the white precipitate formed was filtered using vacuum filtration, and the filtrate was concentrated under vacuum. The residue was dissolved in of dichloromethane and the white precipitate, if formed, was again filtered. The filtrate was washed with 0.5N HCl, followed by saturated sodium bicarbonate solution. The organic layer was collected and dried over anhydrous sodium sulphate for overnight, filtered. The filtrate was concentrated under vacuum using rotary evaporator to get the crude product. The crude product was further purified by column chromatography on silica gel, using hexane:ethyl acetate, to get the final product **6g** (**Scheme 3.8**).



Scheme 3.8: Synthesis of phenethyl 2-(1*H*-indol-3-yl)acetate (**6g**)

The structure of the product **6g** was confirmed as phenethyl 2-(1*H*-indol-3-yl) acetate by its spectral data. The ^{1}H NMR spectrum of **6g** (**Figure 3.15**) shows a broad D_2O exchangeable NH peak at δ 8.08 (s, 1H), the aromatic CH peak appears as multiplet in the region 7.29-7.04 ppm for 8 protons. Two doublets appeared at 7.34 ppm with *J* value 8.1 Hz, and 7.57 ppm with *J* value 7.9 Hz. In the aliphatic region, the two-proton triplet at δ 2.93 confirms to the Ar-**CH**$_3$CH$_2$-, two-proton multiples at δ 4.35-4.31 are due to the ArCH$_3$**CH$_2$**-,

while a two-proton singlet at δ 3.76 represents the -CH_2C=O. A peak at δ 172.0 in the ^{13}C-NMR spectrum of the compound **6g** (**Figure 3.16**) confirms the carbonyl carbon (**C**O) along with other aliphatic and aromatic carbon. In the FTIR spectrum of **6g** (**Figure 3.17**), the NH stretching peak appeared at 3391 $cm^{-1,}$ and the stretching for the ester group (C=O) appeared at 1732 cm^{-1}. The above data confirmed the formation of ester **6g**. Further, a series of alkyl 2-(1*H*-indol-3-yl) acetate (**6h-j**) was prepared by reaction of indoleacetic acid (**4**) and corresponding alcohols (**5h-j**) (**Scheme 3.9**). The results are summarized in **Table 3.7**.

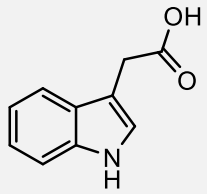
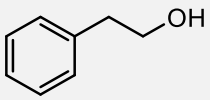
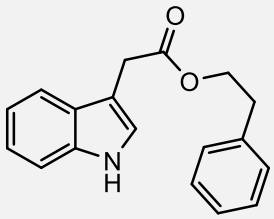
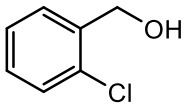
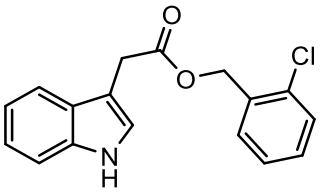
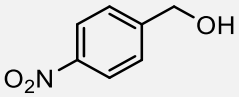
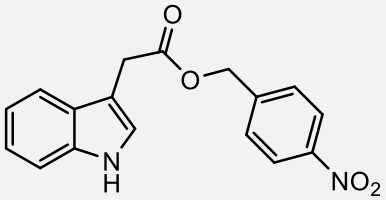
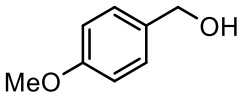
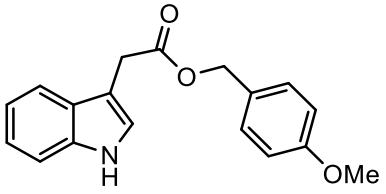


Scheme 3.9: Synthesis of esters of indole acetic acid (**6h-j**)

3.3.2 Synthesis of alkyl/aryl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (7)

We begin our study with ethyl 2-(1*H*-indol-3-yl)acetate (**6a**) as a model substrate for fluorination. The ^{19}F NMR is widely used to identify the fluorinated compounds; therefore, we used it for monitoring the reaction for the formation of the fluorinated product. Selectfluor in acetonitrile has been extensively reported for the fluorination of olefines and has been successfully applied in 3-fluorooxindole synthesis [53]. Also, oxygen present in air is reported as an oxygen source in chemical reactions [59,60]. NFSI has also been reported as a good electrophilic fluorinating agent for the fluorination of aromatic compounds [42]. Therefore, we chose NFSI as fluorinating agent (3 eq.), acetonitrile as solvent (**Table 3.8, entry 1)** and carried out the reaction in an open vessel to use air as oxygen source. The reaction mixture was stirred at room temperature for 12 h. However, the desired fluorinated product ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**) was not formed. Next, we increased the temperature to 50 °C and continued the reaction for 24 h (**Table 3.8, entry 2**), but the formation of the product **7a** was not detected.

Table 3.7: Esters synthesized using DCC/DMAP

Substrate (4)	Alcohol (5)	Time (h)	Product (5)	Yield
	 **2g**	3	 **6g**	94%
	 **2h**	3	 **6h**	92%
4	 **2i**	3	 **6i**	87%
4	 **2j**	3	 **6j**	79%

Further, we used DMSO (1.1 eq.) [61,62] as an oxygen source and conducted the reaction at room temperature for 12 h, but no fluorination was detected. Increasing the temperature to 50 °C for 12 h was also ineffective for the formation of the fluorination product (**Table 3.8**, **entries 3** and **4**). Then water was tried as an oxygen source (**Table 3.8**, **entry 5**), and the C-3 fluorinated product was detected as the main product on stirring the reaction mixture at 50 °C for 12 h, as indicated by ^{19}F NMR. Now we tried to change the solvent to get the difluorinated product. Switching the solvent from acetonitrile to acetone, methanol, and DMF only offered the C-3 monofluorinated oxindole (**Table 3.8**, **entries 6-8**). Therefore, we changed the fluorinating

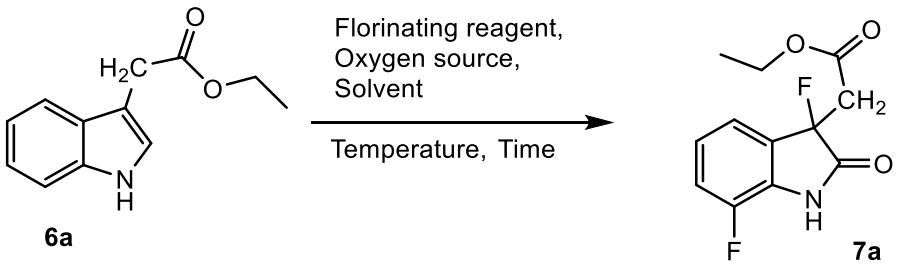
agent from NFSI to Selectfluor. Using Air or DMSO (1.1 eq.) in acetonitrile as an oxygen source is not proven fruitful with Selectfluor (**Table 3.8**, **entries 9-12**). Further we used solvent system acetone/water (1:1) with Selectfluor and stirred the reaction at room temperature for 24 hours (till the intermediate oxindole formed was consumed) followed at 60 ^{o}C for 8 h (till the C-3 fluorinated intermediate was consumed) and 27% of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**) was obtained as white solid (**Table 3.8**, **entry 13**) (**Scheme 3.10**).

Table 3.8: Experimentation for fluorination of indole derivatives

Entry	**Fluorinating reagent**	**Solvent**	**Oxygen Source**	**Temp (°C)**	**Time (hrs.)**	**Yield**	**Remarks**
1.	NFSI	CH_3CN	Air	rt	12	--	No desired product
2.	NFSI	CH_3CN	Air	50 °C	24	--	No desired product
3.	NFSI	CH_3CN	DMSO	rt	12	--	No Fluorination
4.	NFSI	CH_3CN	DMSO	50 °C	24	--	No Fluorination
5.	NFSI	CH_3CN	H_2O	50 °C	12	--	C-3 fluorination
6.	NFSI	Acetone	H_2O	50 °C	12	--	C-3 fluorination
7.	NFSI	CH_3OH	H_2O	50 °C	12	--	C-3 fluorination
8.	NFSI	DMF	H_2O	50 °C	12	--	C-3 fluorination
9.	Selectfluor	CH_3CN	Air	rt	12	--	No desired product
10.	Selectfluor	CH_3CN	Air	50 °C	24	--	No desired product
11.	Selectfluor	CH_3CN	DMSO	rt	12	--	No Fluorination
12.	Selectfluor	CH_3CN	DMSO	50 °C	24	--	No Fluorination
13.	**Selectfluor (3 eq.)**	**Acetone**	**H_2O**	**rt**	**24**	**27%**	**4a detected**
				60 °C	8		

On general workup and chromatographic purification, the product was confirmed as ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl) acetate (**7a**), and the structure of the compound was confirmed by spectral characterization. In the ^{1}H NMR spectrum of the compound **7a** (**Figure 3.18**), a D_2O exchangeable peak for NH proton appears as a singlet at δ 8.8, the aliphatic protons for CH_3 and CH_2 appear as a triplet and quartet at 1.1 and 4.01– 4.04 ppm respectively.

A multiplet peak in the region 3.26 - 3.43 ppm for two protons is due to the CH_2 proton in the -C**H**$_2$COC_2H_5 group. The remaining three aromatic protons appear in the aromatic region 6.87 - 7.19 ppm. In the ^{13}C NMR spectrum of **7a** (**Figure 3.19**), the aliphatic carbons are found at 13.8, 39.2, and 61.3 ppm. The carbon bearing the C-F bond appears at 90.1, and 159.1 ppm. The two carbonyl carbons were found at 167.5 and 173.7 ppm, the remaining carbon appears as 111.6, 113.1, 118.2, 126.3, and 138.1 ppm. All the values are in the range of literature. In the ^{19}F-NMR spectrum (**Figure 3.20**), the fluorine at the 3-position appears as a triplet at δ -153.8 with *J* value of 9.7 Hz while the fluorine at the 7th position was found at -119.1 as singlet. In the FTIR spectrum (**Figure 3.21**), the NH stretching appears at 3214 cm^{-1}, and the two-carbonyl group stretching is at 1737 and 1719 cm^{-1} in addition to other stretching and bending peaks. The above data confirmed the chemical structure of compound **7a**.

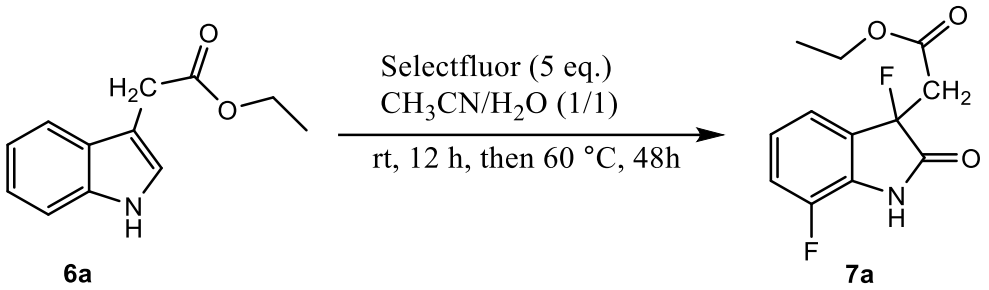


Scheme 3.10: Synthesis of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

3.3.3 Optimizations for solvent, time, and temperature

After successful product confirmation, it was decided to optimize the reaction conditions (**Table 3.9**). First, we choose to screen the solvent. In an effort to increase the yield, the use of solvent methanol (**Table 3.9, entry 1**) and DMF (**Table 3.9, entry 2**) proved ineffective in improving the reaction yield and offered 15% and 33% yield, respectively. When acetonitrile was used as solvent 22% of the desired product **7a** was obtained in reaction at rt for 12 h, followed by 24 h at 50 °C (**Table 3.9, entry 3**). It was also observed that the C-3 monofluorinated oxindole was present in the reaction. Therefore, the amount of Selectfluor was increased. Using Selectfluor in 5 equivalent quantities increased the yield of the product **7a** to 43% in 36 h at 60 °C (**Table 3.9**, **entry 4**). The yield of product **7a** was further increased to 57% by increasing the time to 48 hours (**Table 3.9, entry 5**). However, the yield decreased to 55% on further increasing the reaction time (**Table 3.9, entry 6**). A minute quantity of the 3-Fluorooxindole was also visible in TLC. Merely 10% of the intended product was obtained by directly heating the reaction mixture at 60 °C, whilst no desirable product was produced at

80°C (**Table 3.9**, **entries 7-8**). It was noticed that reactions performed with TBAF.3H_2O (3 eq.) or TBAF (1M in THF) (5 eq.) failed to generate any product (**Table 3.9**, **entries 9-10**). Therefore, Selectfluor (5 equivalent) in CH_3CN/water (1/1) at room temperature for 12 h followed by 48 h at 60 °C, was taken as the optimised condition (**Scheme 3.11**).



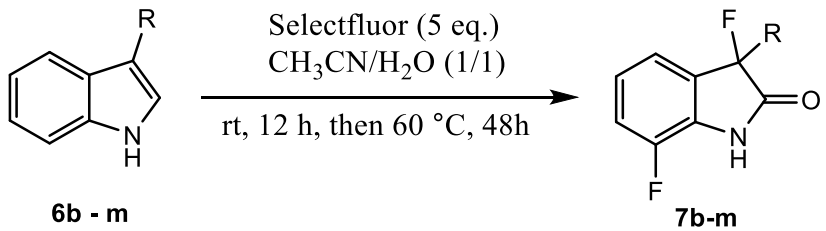
Scheme 3.11: Optimized reaction condition for the synthesis of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

First, we investigated the effect of the alkyl chain of esters obtained from aliphatic alcohol. The reaction performs well for methyl (**6b**) and propyl (**6c**) substituents, giving a good yield of the product; however, a poor yield was obtained for butyl (**6d**) and isopropyl (**6e**) substituents. The reaction also performs well for alkyl chains bearing the electron-withdrawing group (**6f),** giving a fair yield. Now we have shifted our investigation to the esters obtained from aromatic alcohol. Reaction gives a 62% yield for phenyl ethyl (**6g**) substituent. Benzyl group with electron withdrawing group, 2-chlorobenzyl (**6h**) and 4-nitrobenzyl (**6i**) are good substrates for reaction; however, 4-Methoxybenzyl 2-(1*H*-indol-3-yl)acetate (**6j**) gives a complex mixture and the reaction fails to give the product (**6j**) in a non-separable yield. Apart from esters, the reaction conditions are also compatible for the indole with 3-substituted methyl (**6k**), acetonitrile (**6l**), and carboxylic acid (**6m**) group, but require a longer reaction time of 60 h at 60 ºC and 6 eq. of Selectfluor for **6l** and **6m**. The optimized reaction conditions are well tolerated by both the alkyl and aryl esters giving fair to good yield. However, the yield is slightly higher in case of aryl esters bearing the electronegative group on benzene ring. The reaction fails with aryl ester bearing electron donating group (**6j**) and a non-separable complex mixture was obtained. The results are summarised in Table **3.10**.

Table 3.9: Optimizations for solvent, time, and temperature for **7a**

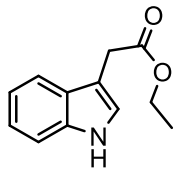
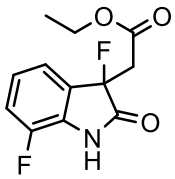
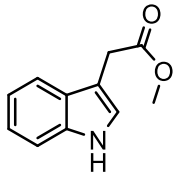
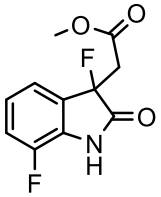
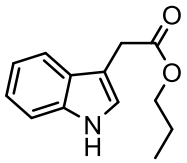
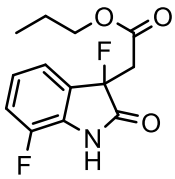
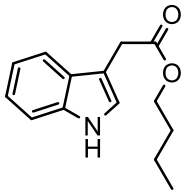
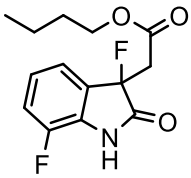
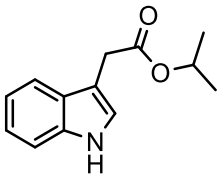
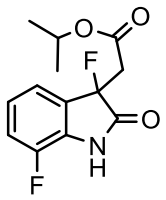
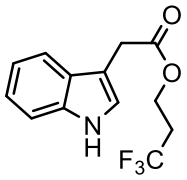
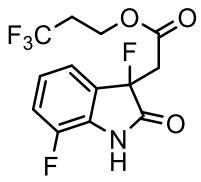
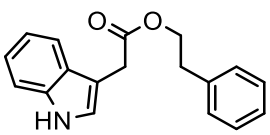
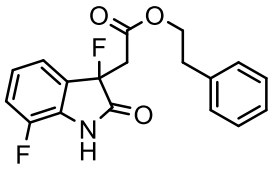
Entry	Fluorinating reagent	Solvent	Oxygen Source	Temp (°C)	Time (hrs.)	Yield	Remarks
1.	Selectfluor (3 eq.)	CH_3OH	H_2O	Rt 60 °C	10 6	15%	-
2.	Selectfluor (3 eq.)	DMF	H_2O	Rt 60 °C	12 8	33%	-
3.	Selectfluor (3 eq.)	CH_3CN	H_2O	Rt 50 °C	12 24	22%	-
4.	Selectfluor (5 eq.)	CH_3CN	H_2O	Rt 60 °C	12 36	43%	-
5.	**Selectfluor (5 eq.)**	**CH_3CN**	**H_2O**	**Rt** **60 °C**	**12** **48**	**57%**	-
6.	Selectfluor (5 eq.)	CH_3CN	H_2O	Rt 60 °C	12 60	55%	-
7.	Selectfluor (5 eq.)	CH_3CN	H_2O	60 °C	7	10%	-
8.	Selectfluor (5 eq.)	CH_3CN	H_2O	80 °C	5	--	No desired product
9.	$TBAF.3H_2O$ (5 eq.)	CH_3CN	H_2O	Rt 60 °C	12 24	--	No desired product
10.	TBAF (1M in THF) (5 eq.)	CH_3CN	H_2O	Rt 60 °C	12 24	--	No desired product

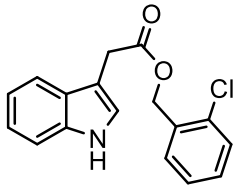
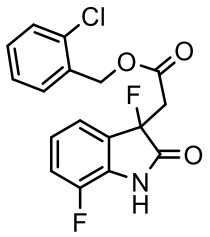
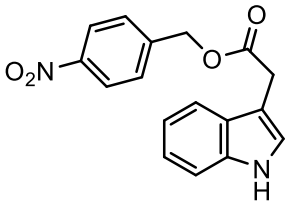
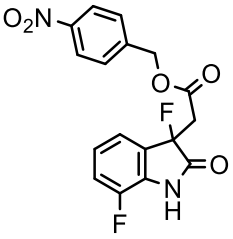
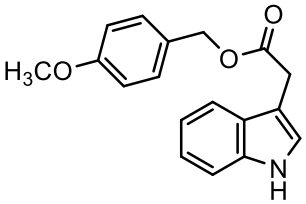
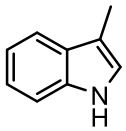
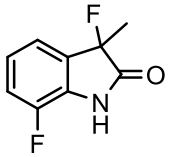
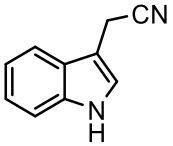
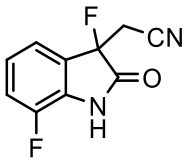
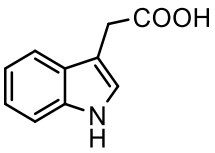
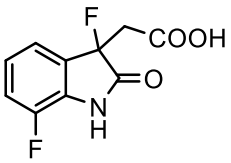
Now, with these ready optimised reaction conditions, we began investigating the scope of the reaction for the synthesis of 3,7-difluorinated oxindole (Scheme 3.12).



Scheme 3.12: Synthesis of 3,7-difluorinated oxindole derivatives **7b-m**

Table 3.10: Synthesized 3,7-difluorinated oxindoles

Entry	Substrate		Time/Temp	Product		Yield (%)
1.	**6a**		rt, 12 h, 60 °C 48 h	**7a**		57%
2.	**6b**		rt, 12 h, 60 °C 48 h	**7b**		42%
3.	**6c**		rt, 12 h, 60 °C 48 h	**7c**		62%
4.	**6d**		Rt 12 h, 60 °C 48 h	**7d**		15%
5.	**6e**		Rt 12 h, 60 °C 48 h	**7e**		25%
6.	**6f**		Rt 12 h, 60 °C 48 h	**7f**		22%
7.	**6g**		Rt 12 h, 60 °C 48 h	**7g**		62%

8.	**6h**		Rt 12 h, 60 °C 60 h	**7h**		61%
9.	**6i**		Rt 12 h, 60 °C 60 h	**7i**		71%
10.	**6j**		Rt 12 h, 60 °C 12 h	**7j**	Non-separable complex mixture formed	--
11.	**6k**		Rt 12 h, 60 °C 48 h	**7k**		47%
12.	**6l**		Rt 12 h, 60 °C 60 h	**7l**		50%
13.	**6m**		Rt 12 h, 60 °C 60 h	**7m**		42%

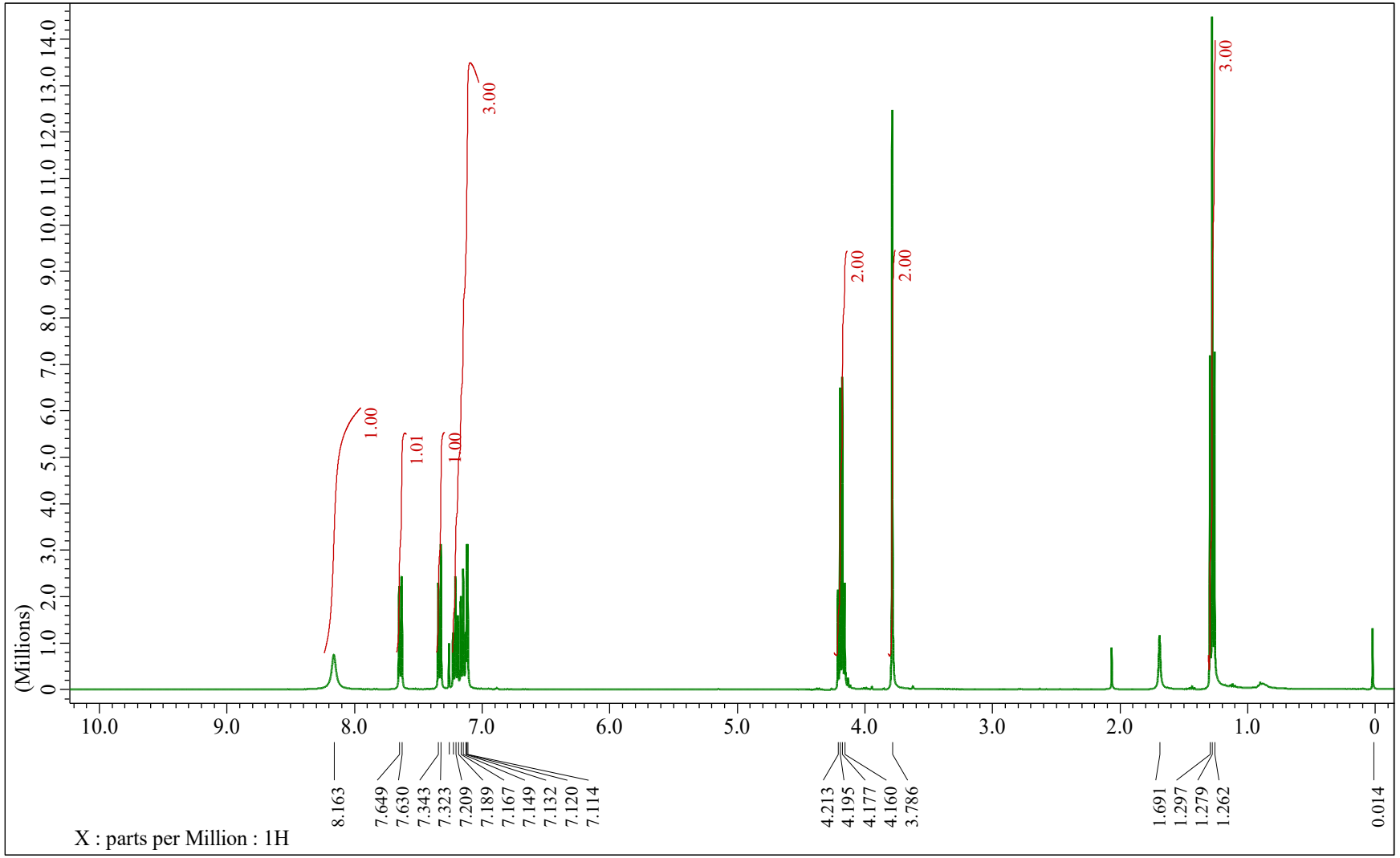


Figure 3.12: ^{1}H NMR spectrum of ethyl 2-(1*H*-indol-3-yl)acetate (**6a**)

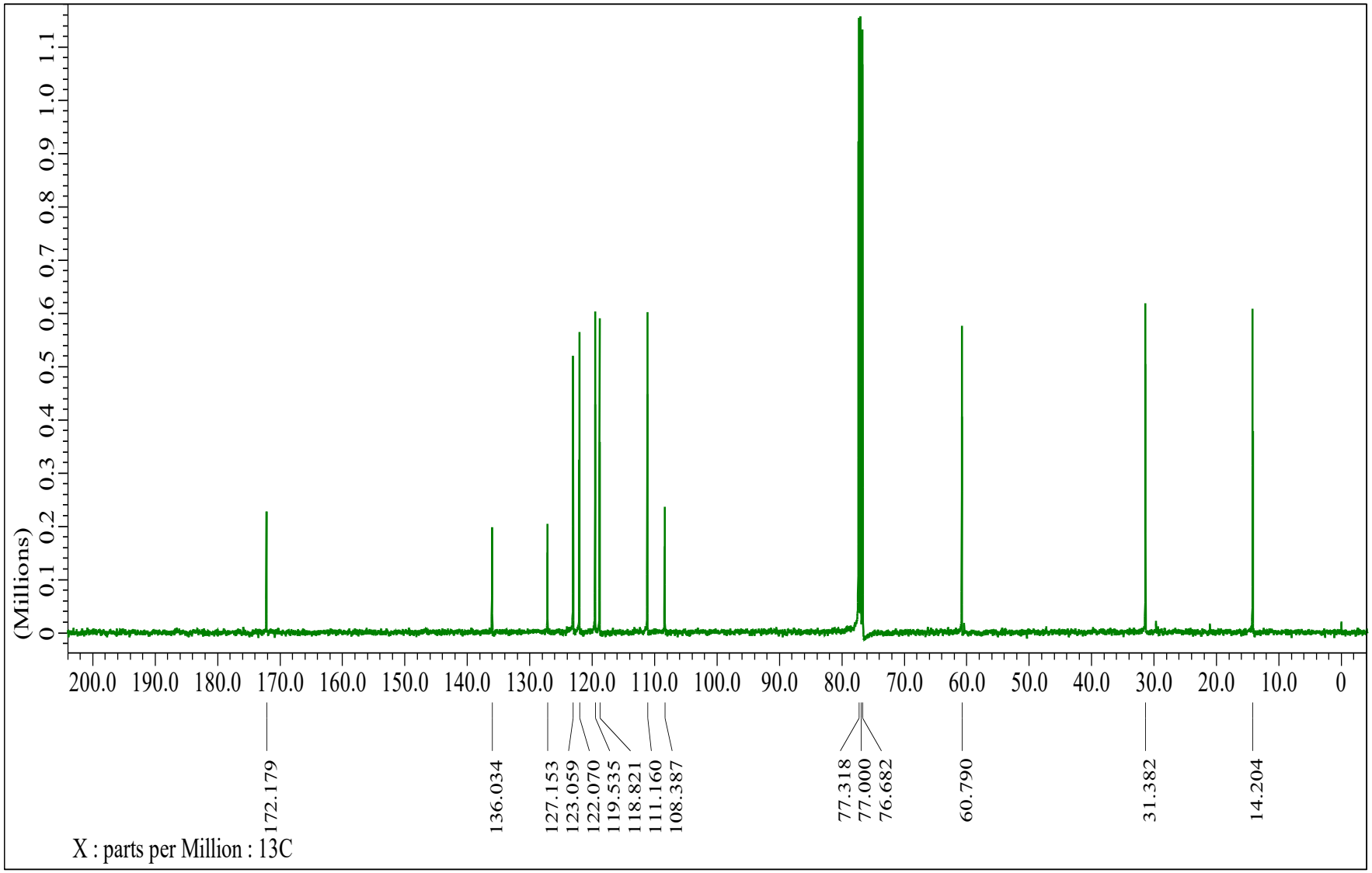


Figure 3.13: ^{13}C NMR spectrum of ethyl 2-(1*H*-indol-3-yl)acetate (**6a**)

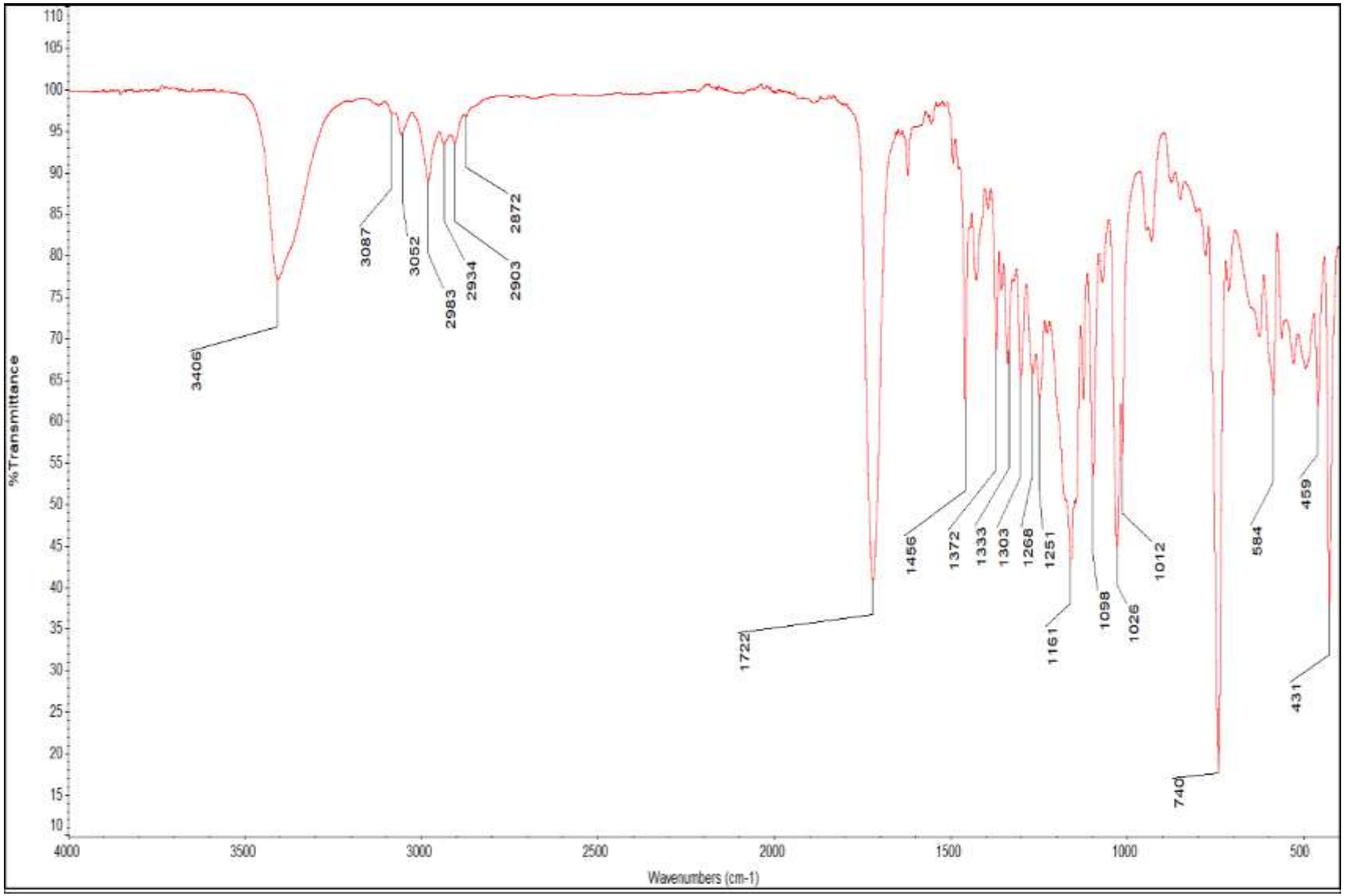


Figure 3.14: FTIR spectrum of ethyl 2-(1*H*-indol-3-yl)acetate (**6a**)

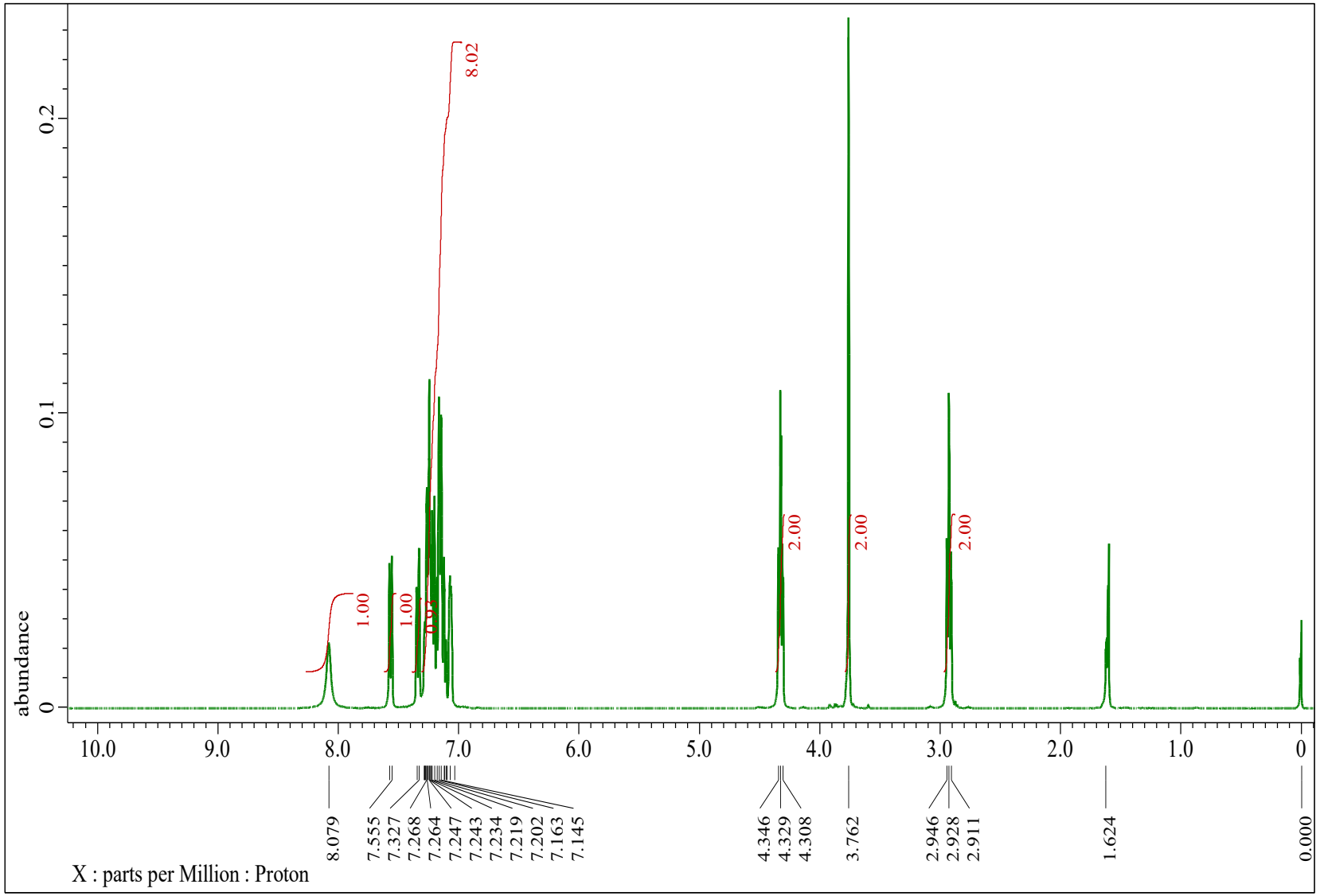


Figure 3.15: ^{1}H NMR spectrum of phenethyl 2-(1H-indol-3-yl)acetate (**6g**)

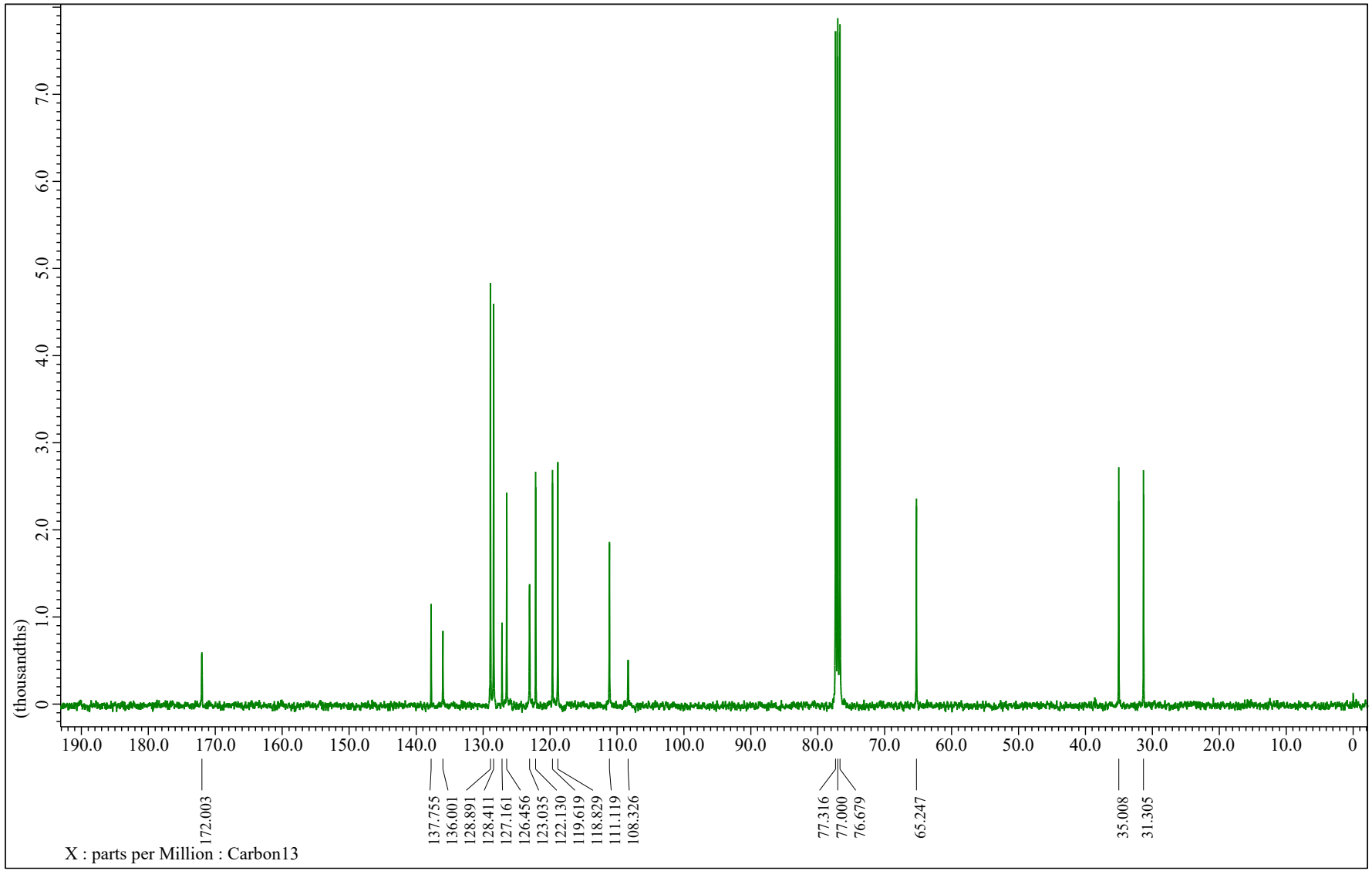


Figure 3.16: ^{13}C NMR spectrum of phenethyl 2-(1H-indol-3-yl)acetate (**6g**)

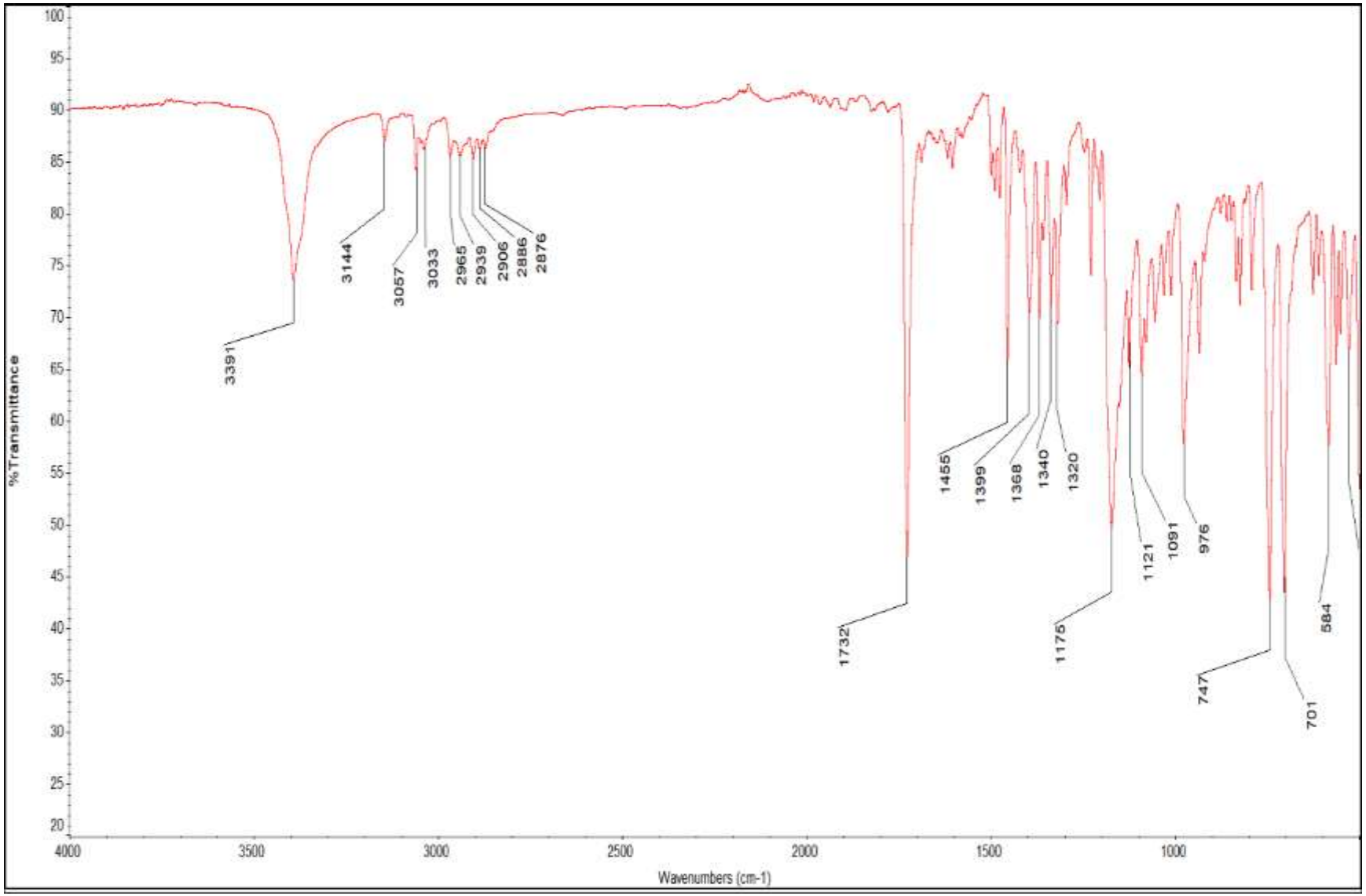


Figure 3.17: FTIR spectrum of phenethyl 2-(1H-indol-3-yl)acetate (**6g**)

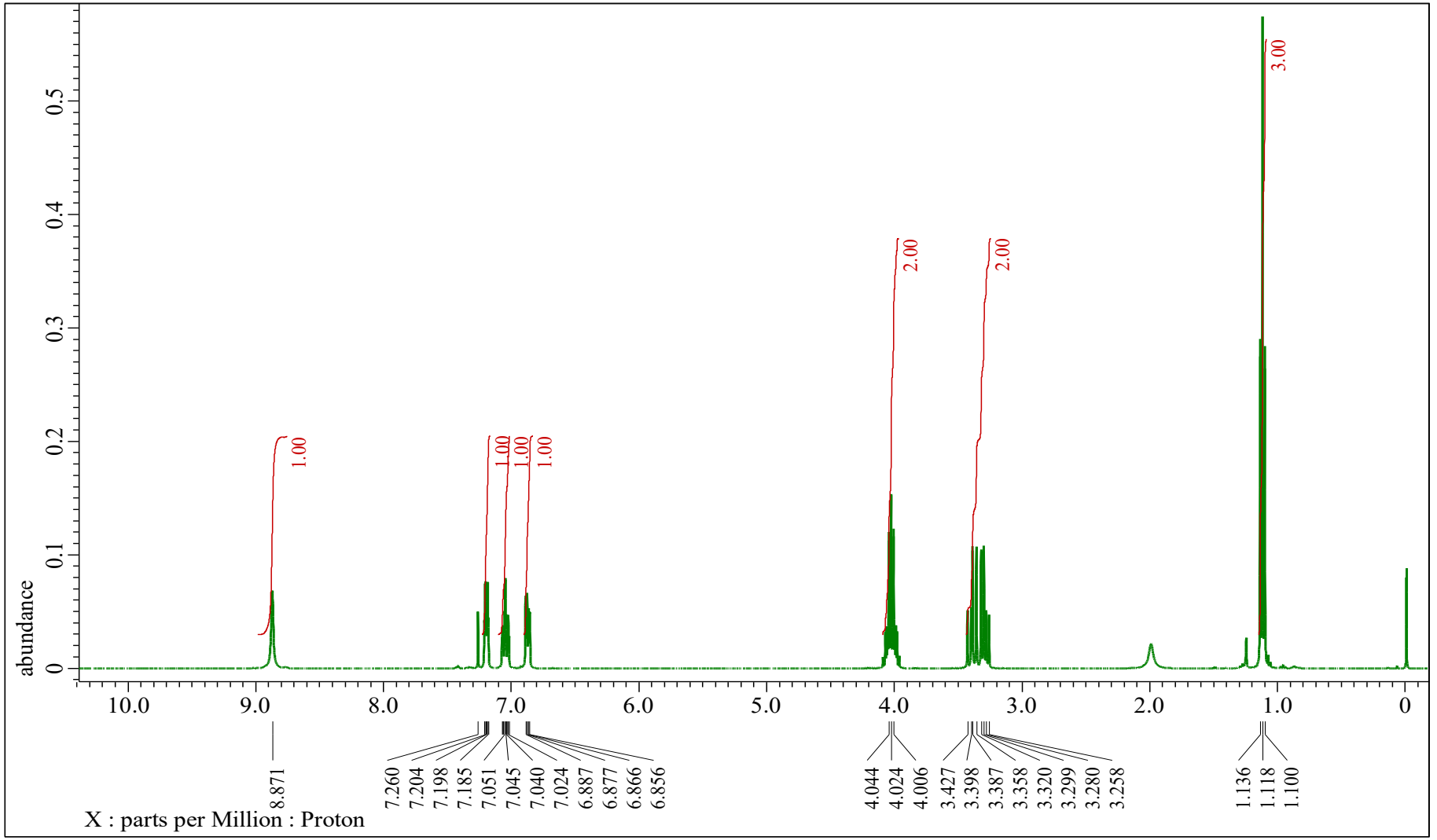


Figure 3.18: ^{1}H NMR spectrum of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

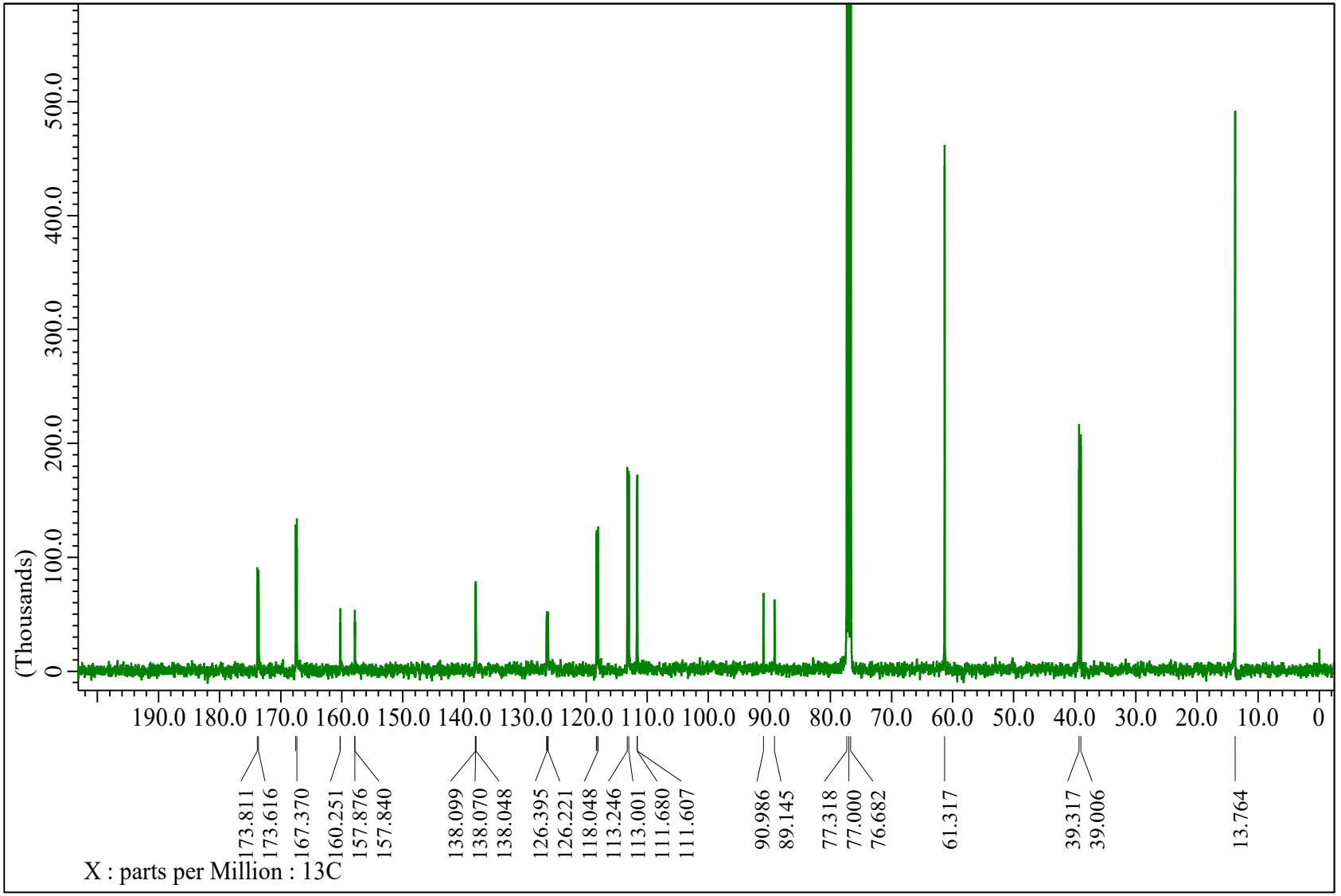


Figure 3.19: ^{13}C NMR spectrum of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

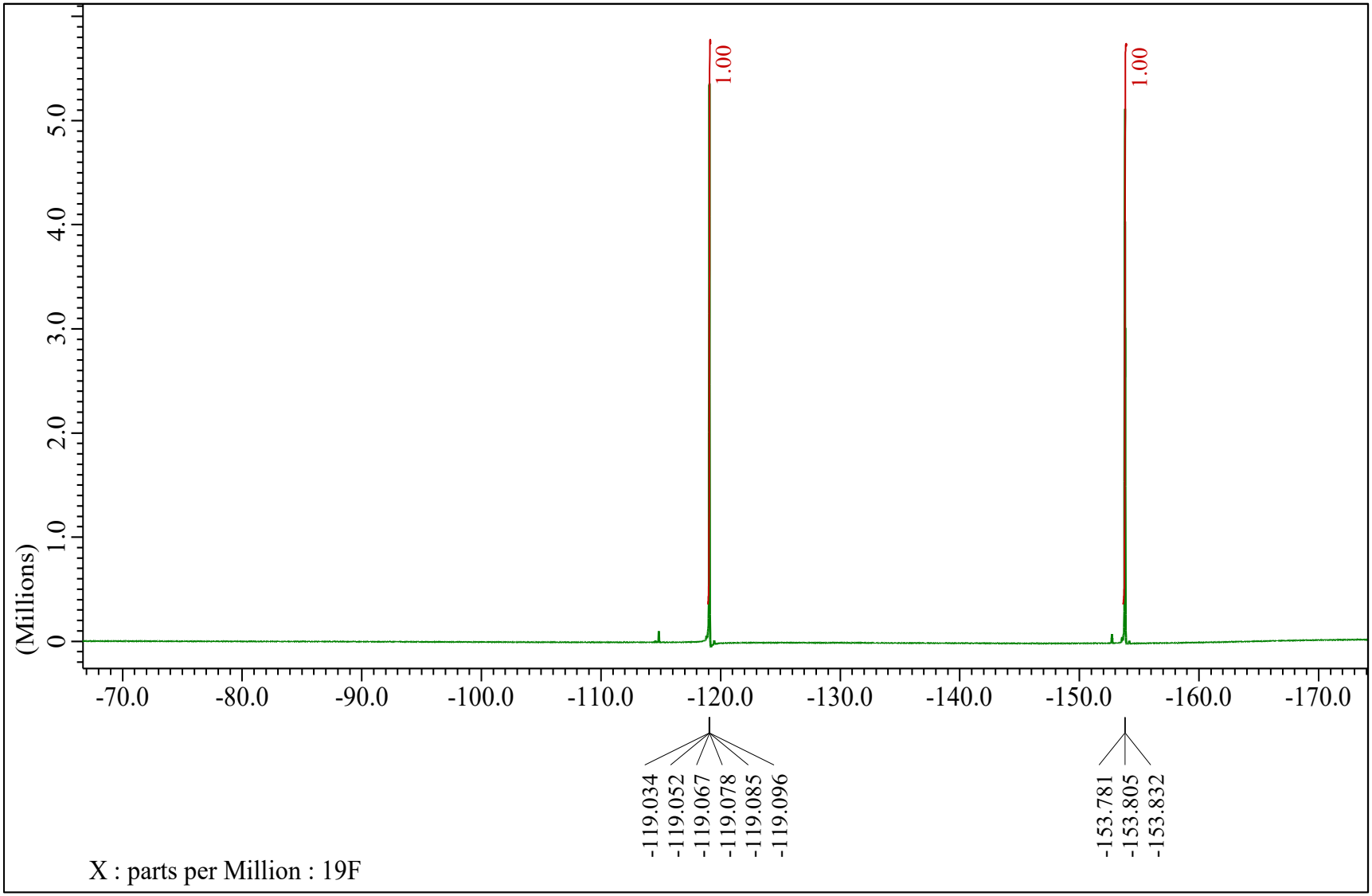


Figure 3.20: ^{19}F NMR spectrum of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

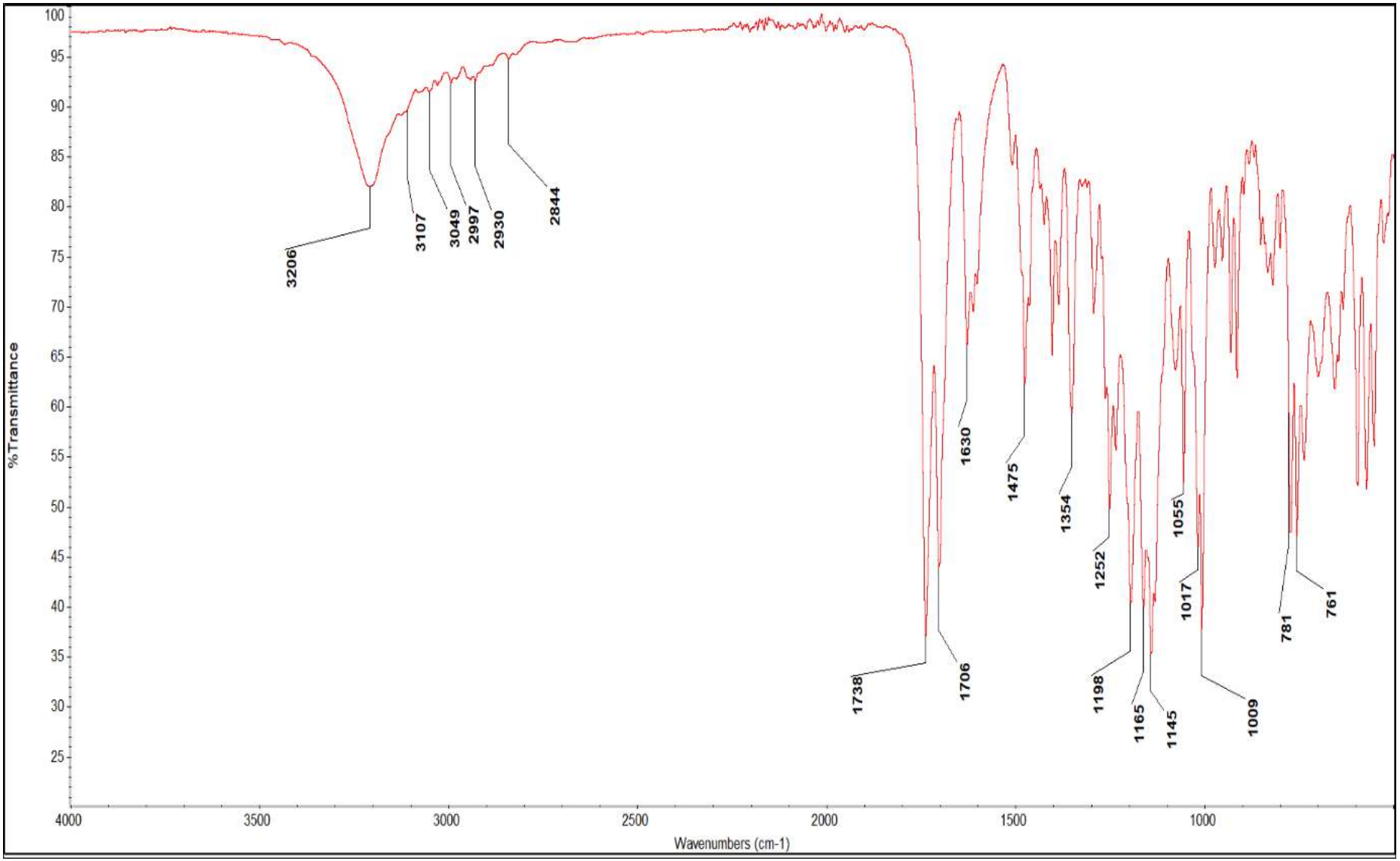


Figure 3.21: FTIR spectrum of ethyl 2-(3,7-difluoro-2-oxoindolin-3-yl)acetate (**7a**)

3.4 Evaluation for flame-retardant property

The flame retardancy in ability of a material to withstand ignition or reduce the rate of flame spread in the presence of heat or fire. It is achieved by addition of a chemical or material by physical mixing or incorporating in to the chemical structure. A chemical or additive which is used to improve the flame retardancy is called a flame retardant. These flame retardants slow down the spread of flame by interfering with the combustion process, either by releasing the non-flammable gases that restrict flames by creating an oxygen barrier, or increasing the char formation. These materials are designed to resist ignition, slow the spread of flame, and minimize the release of toxic gases, thereby providing crucial time for evacuation and fire suppression. Flame retardants can be halogen-based, phosphorus-based, or mineral-based (for example, aluminium hydroxide). Flame-retardant breathable polyurethane (PU) film is an advanced polymer designed to provide moisture vapor permeability and fire resistance, making it an ideal choice for applications needing both comfort and safety [63]. Flame-retardant breathable polyurethane films have a wide range of applications, including transportation, medical textiles, and protective gear. These films ensure comfort to the wearer during the high-stress activities. These films when used in protective clothing, such as military uniforms and firefighting gear, acts as a barrier against heat and flames, while allowing the sweat vapor to escape thereby maintaining the body temperature. Although polyurethane films are naturally flexible and durable, they are highly flammable and presents problems in high-risk applications. This problem can be addressed by adding flame-retardants in the PU matrix during manufacturing process. Phosphorus-based compounds and halogen-free intumescent materials are generally used for this purpose [63]. Incorporation of fluorine into organic compounds enhances chemical and thermal stability and allows them to withstand high temperatures. Fluorinated flame retardants are commonly used protective clothing, like firefighting gear in which they improve flame resistance as well as durability.

Fluorine and nitrogen-containing compounds have been reported for their flame-retardant properties. There are also a few reports where the indole derivatives have been studied for imparting flame retardancy in polymers [35,64,65]. The introduction of a fluorine atom into organic compounds is known to increase their thermal stability and chemical inertness. Fluorine can increase the overall stability of the molecular structure and can contribute to flame retardancy by forming a protective char layer during combustion. The nitrogen-containing flame retardants acts in both vapor phase and condensed phase. In vapor phase they act by releasing non-flammable gases (such as N_2 CO_2, H_2O) when exposed to high temperatures.

These non-flammable gases dilute the combustible gases, reduce the temperature and reduce the oxygen concentration in the flame zone. In condensed phase, nitrogen compounds can form intumescent char layers that insulate the underlying material from outer heat source and cut the oxygen supply leading to extinguishment of flame [66]. The presence of nitrogen and fluorine atoms in 3,7-difluorooxindole derivatives could theoretically enhance their flame-retardant potential. Therefore, we tested the synthesized compounds for flame retardancy in PU films. The films were tested as per the procedure in UL-94 Standard, used to determine the flammability of plastic materials. This determines the ability to extinguish or spread the flame after ignition and its dripping behavior in response to a small open flame or radiant heat source. Based on the response of the material (Table 3.11) to flame, V0, V1, or V2 ratings are assigned to the tested material.

Four compounds from the synthesized α-fluoroacetophenones (**2e**, **2g**, **2h**, and **2j**) and three compounds from 3,7-difliorinated oxindoles (**7g**, **7h**, and **7i**) were selected to study the flame-retardancy effect on the flammability of polyurethane polymer. Elastollan® 11, thermoplastic polyurethane (TPU) manufactured by BASF, was purchased from the market and used to study the effect of selected synthesized compounds on its flame retardancy. The flexible thin film of thickness around 30 – 40 microns were prepared by dissolving the polyurethane and selected compounds in 1,3-dioxolane for the study.

Table 3.11: Criteria for rating of sample as per UL-94

Criteria	VTM-0	VTM-1	VTM-2
After flame time for each individual specimen, t_1 or t_2	≤10s	≤30s	≤30s
Total after flame for any condition set (t_1+t_2 for 5 specimens)	≤50s	≤250s	≤250s
After flame plus afterglow time for each individual specimen after the second flame application (t_2+t_3)	≤30s	≤60s	≤60s
Did the after flame or afterglow of any specimen progress up to the 125 mm mark	No	No	No
Was the cotton indicator ignited by flaming particles or a drop	No	No	Yes

3.4.1 Preparation of polyurethane films

The polyurethane was purchased from commercial source and used for preparing the flexible thin film by combining with selected synthesized compounds. For preparation of films, the polymer solution casting technique was used. In this technique the polymer is dissolved in as solvent to form the homogeneous solution. This polymer solution is then coated on a carrier substrate. A solid layer is created on the carrier substrate, on drying the solvent at required temperature. This solid layer can be stripped to form a stand along film. This technique provides low temperature operation and ease of using additive at laboratory scale. For preparation of polyurethane film with synthesized compound, the 1.25 g of polyurethane was taken in a beaker and dissolved in 1,3-dioxolane (10 mL) at room temperature by stirring with overhead stirrer for 30 minutes. It is important to ensure complete dissolution of polyurethane on solvent. After that 0.25 g of the synthesized compound was added to it dissolve to prepare a homogeneous solution. A silicone release paper was fixed on a horizontally levelled hard surface. The solution was poured on a silicon release paper and spread evenly on the paper to get a thin film. The films were allowed to dry at room temperature for 24 h, followed by drying in an oven at 60 °C for 2 h and at 80 °C for 30 min (**Figure 3.22**). By following the same procedure, the films for compounds **2e**, **2g**, **2h**, and **2j** from fluorinated acetophenone and for compound **7g**, **7h**, and **7i** from 3,7-difluorinated oxindoles were prepared. A blank film containing polyurethane only, was also made for comparison purpose.

3.4.2 Preparation and conditioning of the test sample

The testing as per UL standard require a standard size of specimen sample. Therefore, after complete drying the film, these were removed from the silicon release paper to prepare the test specimen. The dried films were cut into size 200 ± 5 mm in length and 50 ± 1 mm in width test specimen and marked at 125 mm from the bottom. The longitudinal axis of the specimen was wrapped around the longitudinal axis of a 12.7 7 ±0.5 mm diameter mandrel to form a lapped cylinder. The overlapping ends of the specimen were secured within the 75 mm portion above the 125 mm mark (upper tube section) through pressure-sensitive tape. The mandrel is removed. The prepared specimens were preconditioned at 23 ± 2°C and 50 ± 5 percent relative humidity for 48 hours and tested as per procedure (article 11.5) in UL-94.

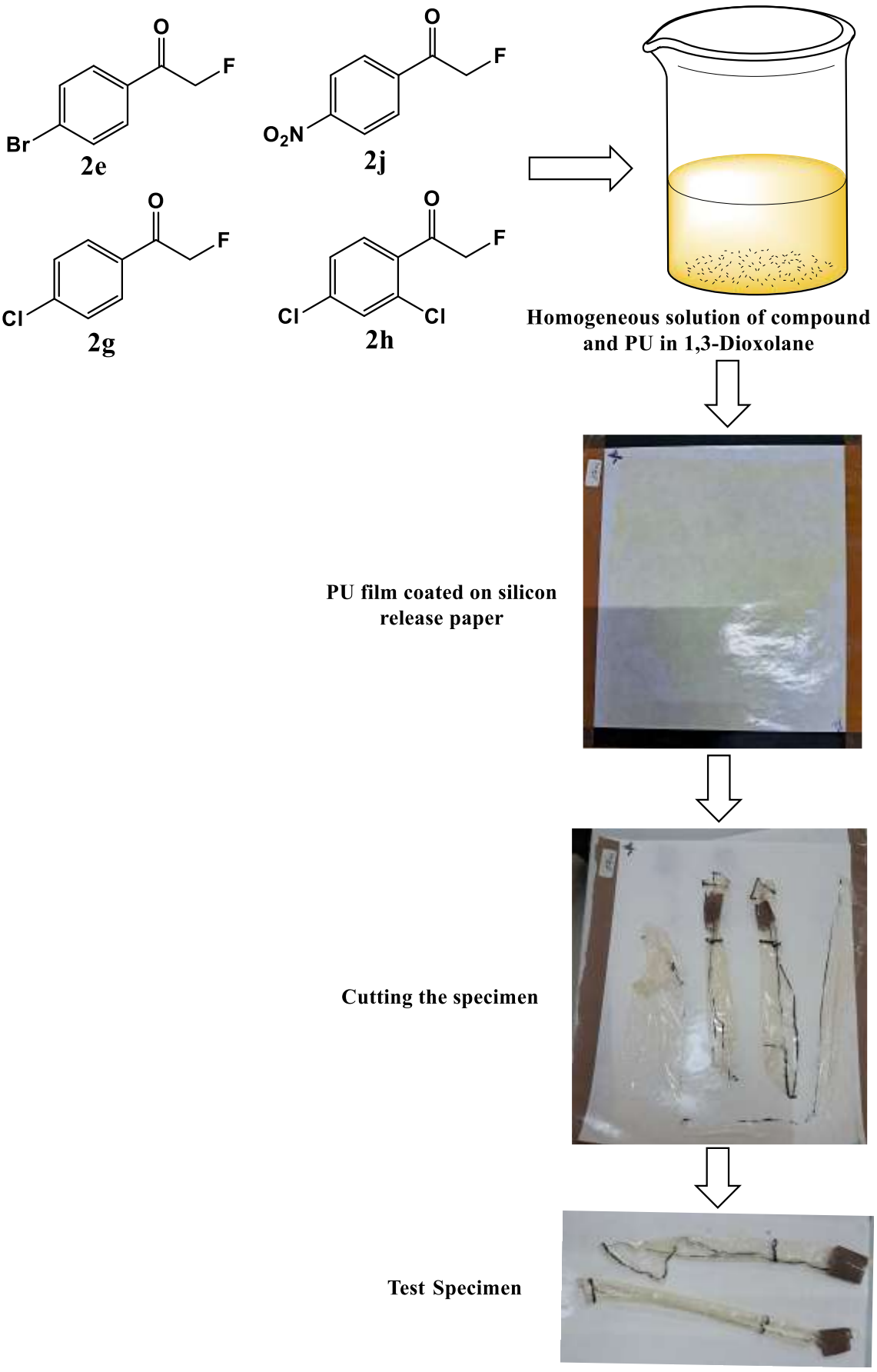


Fig 3.22: Preparation of α-fluoroacetophenone + PU film

3.4.3 Flame Retardancy Testing

The test setup was prepared as described in UL-94 for thin film testing (**Figure 3.23**), and all test samples were tested as the general procedure described in general procedure and the results were compared with the blank polyurethane film.

α-Fluoroacetophenone + PU film sample

The conditioned samples were taken out and tested as per procedure. All the samples were burned up to the clamp within three seconds of flame application. Therefore, no rating was obtained (**Table 3.12**).

Table 3.12: Effect of α-fluoroacetophenone on the flame retardancy of Polyurethane film

Sample No.	Composition		UL-94	
	PU (g)	α-Acetophenone (g)	Rating	t_1/t_2 (Sec.)
1	1.25	0.25 (2d)	No Rating	Burn to clamp
2	1.25	0.25 (2e)	No Rating	Burn to clamp
3	1.25	0.25 (2g)	No Rating	Burn to clamp
4	1.25	0.25 (2j)	No Rating	Burn to clamp
5.	1.25	--	No Rating	Burn to clamp

3,7-Difluorinated oxindole + PU Film sample

The film sample was prepared by dissolving the desired quantity of the sample (0.25 g) and polyurethane (1.25 g) in 10 mL of 1,3-dioxolane. The films were cast on silicon-released paper and dried as per the procedure described earlier (**Figure 3.24**). Test specimens were prepared and conditioned as per the general procedure (**Figure 3.25**). The test setup was prepared, and the conditioned specimens were tested as per the procedure described earlier, compared with the blank PU film (**Figure 3.26**). All the samples were burned up to the clamp within three seconds of flame application. It was observed that the time taken to burn up to the clamp was slightly higher than the blank PU film in the case of the sample containing **7g**. However, it was also burned within 3 seconds up to the clamp with flamed drips. Therefore, no rating was obtained for any sample (**Table 3.13**).

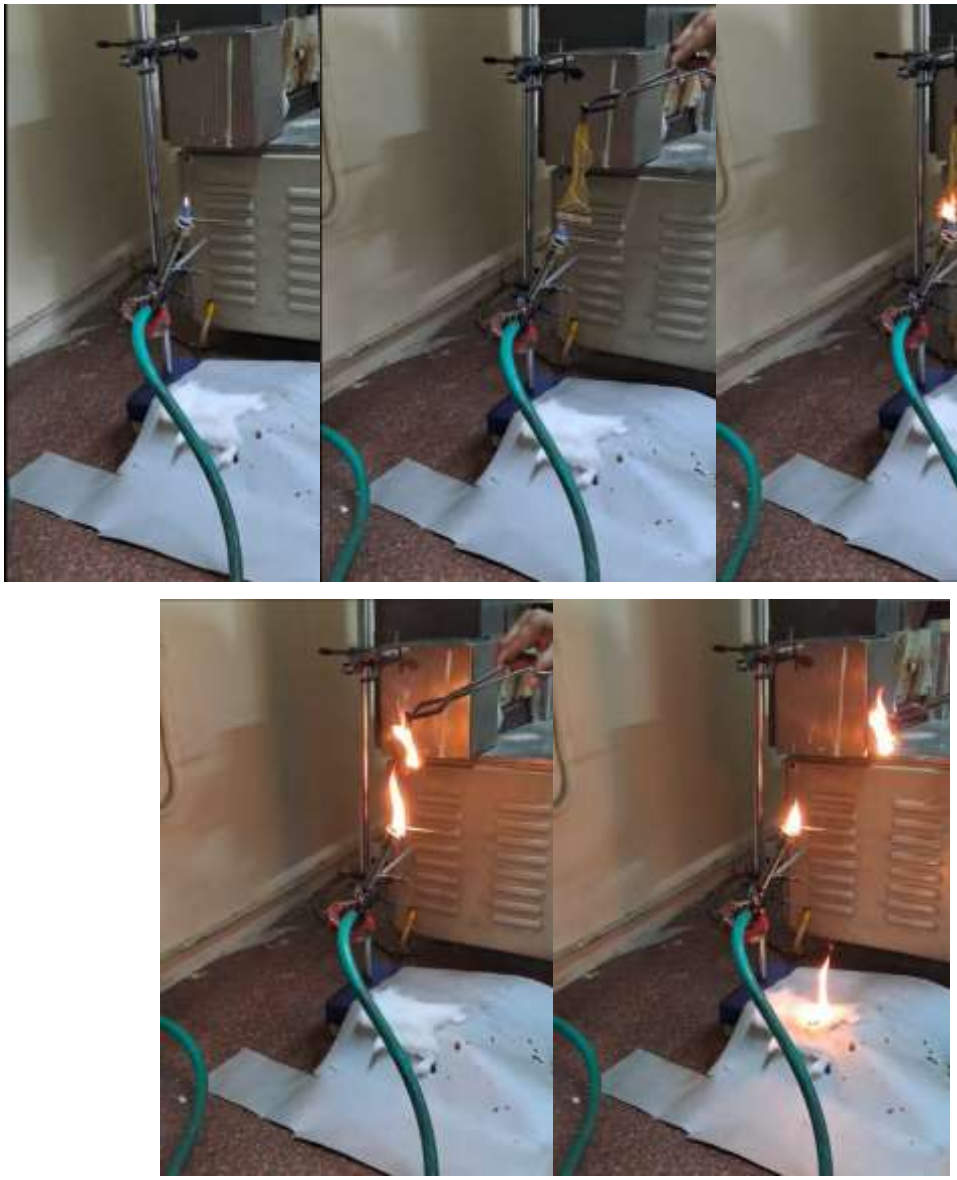


Figure 3.23: UL 94 vertical setup and testing of the specimen

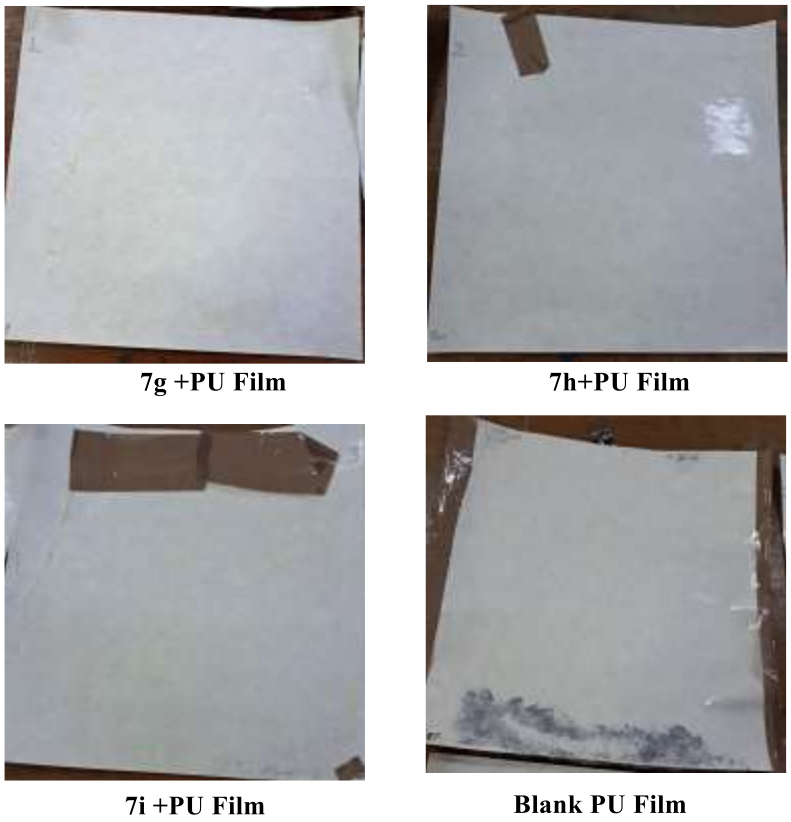


Figure 3.24: Prepared fluorinated oxindole + PU Film

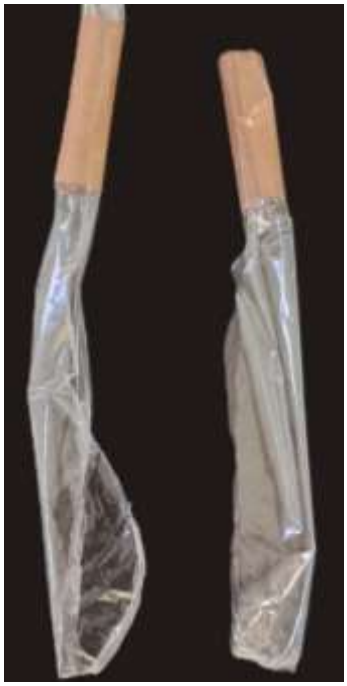


Figure 3.25: Test Specimen of fluorinated oxindole + PU Film

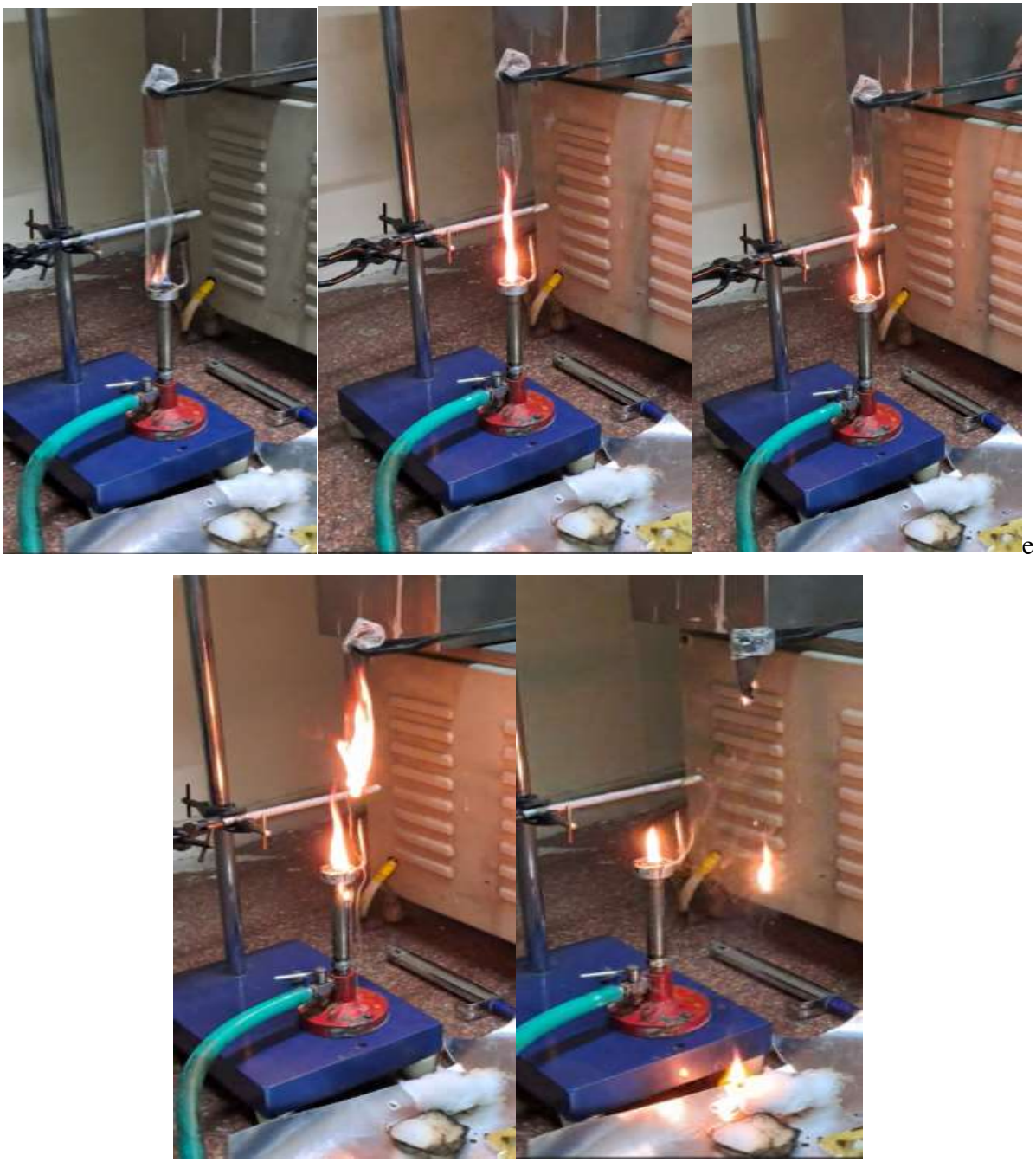


Fig.3.26: UL 94 vertical setup, and testing of the specimen

Table 3.13: Effect of 3,7-difluorooxindole on the flame retardancy of Polyurethane film.

Sample No.	Composition		UL-94	
	PU (g)	3,7-difluorooxindole (g)	Rating	t_1/t_2 (Sec.)
1	1.25	0.25 (2g)	No Rating	Burn to clamp
2	1.25	0.25 (2h)	No Rating	Burn to clamp
3	1.25	0.25 (2i)	No Rating	Burn to clamp

3.5 Conclusion

In summary, we have developed a simple method for the synthesis of α-fluorinated acetophenone directly from acetophenone. The process involves $Fe(NO_3)_3 \cdot 9H_2O$/KBr/TBAF (1 M Solution in THF) as a fluorinating mixture for a simple and efficient fluorination process. The process is useful for the one-pot fluorination of acetophenone derivatives bearing both electron-withdrawing and electron-donating groups on the aromatic ring. We have also developed an efficient and selective method for the synthesis of 3,7-difluorinated oxindole derivatives directly from 3-substituted indoles using Selectfluor as the fluorine source. This reaction exploits the inherent electronic characteristics of the indole ring to achieve selective fluorination at the C3 and C7 positions. The reaction proceeds under mild, metal-free conditions with broad substrate scope and high functional group tolerance, including electron-donating and electron-withdrawing groups, on the indole ring, delivering difluorinated products in good to high yields. The method circumvents the need for pre-functionalized substrates or directing groups and does not require the transition metal catalysts, which makes it operationally simple and amenable to scale-up. This protocol significantly expands the synthetic utility of Selectfluor in the direct and selective fluorination of complex heterocycles, establishing a valuable route for synthesizing difluorinated oxindole for pharmaceutical and agrochemical applications. We have explored the implications of synthesised compounds on the flame retardancy of polyurethane film. The selected compound out of the synthesized fluorinated acetophenones, as well as 3,7-difluorinated oxindoles, tested for flame retardancy failed to improve the flame retardancy of the polyurethane film when tested as per UL 94.

CHAPTER – 4

SUMMARY, PROSPECTS, AND SOCIAL IMPACT

4.1 Summary

Fluoroorganic chemistry, which deals with the study of fluorine-containing organic compounds. It gained significant momentum in the early 1930s with the development of chlorofluorocarbons (CFCs) by Thomas Midgley Jr. The specific properties of fluorine, such as high electronegativity and small size, which provide exceptional stability, reactivity, and hydrophobicity to organic molecules, lead to the rapid growth of this branch of chemistry. These characters make fluorinated compounds important across industries, including pharmaceuticals, agrochemicals, materials science (e.g., Teflon), medical imaging (PET tracers), and emerging technologies like energy storage and advanced coatings. The field's ability to fine-tune molecular properties continues to fuel innovation in health, agriculture, and technology.

From the very first example of fluorine chemistry discovered in the second half of the 19th century, the field has grown rapidly due to its wide range of applications. Since its discovery, fluorine chemistry has tremendously impacted not only chemistry but also human daily life. The fluorinated organic compounds have a widespread application in different fields, including medicinal chemistry, pharmaceuticals, agrochemicals, diagnostics, polymers, molecular electronics, catalysis, liquid crystals, refrigeration, and lubricants. The high occurrence of fluorinated molecules in these applications can be attributed to several factors. first, the C-F bond is the strongest bond that increases the thermal stability and metabolic stability of the molecule. Second, the replacement of the hydrogen (H) atom by the second smallest fluorine (F) atom does not drastically alter the parent structure of the drug molecule. Third, owing to the high electronegativity of fluorine, the introduction of fluorine induces bond polarization, which affects the lipophilicity/hydrophilicity of the material. It also changes the acidity and basicity of the molecule. Fourth, it can be used as a bioisostere of the OH group because of the weak hydrogen bond acceptor nature of the fluorine. Therefore, the introduction of fluorine in the molecules tremendously changes the nature of the molecule.

Very few fluorinated compounds exist naturally, and most of them are mono-fluorinated. None of the difluorinated naturally occurring fluoro-organic compounds have been separated, also none of the natural C-F compounds been isolated for utilization. Therefore, organofluorine chemistry is virtually a completely man-made branch of organic chemistry, where essentially all of the fluorine compounds in the world are man-made. Since the fluorinated compound plays a significant role in medicinal chemistry, material science, agro-chemistry, radio tracing, fire extinguishing chemicals, flame retardant materials, and

refrigeration. Synthetic routes to a wide variety of fluoro-organic molecules have been developed, and an impressive array of reagents and several methods exist for the formation of the C-F bond in aliphatic and aromatic compounds. It can be achieved by nucleophilic fluorination, electrochemical fluorination, catalytic fluorination, radical fluorination, or radical fluorination.

The present work has been carried out to design the methodology and synthesis of aliphatic and aromatic fluoroorganic compounds containing the C-F bond and overcome some of the limitations reported in the literature. The work entitled "Development of C-F Bond in Organic Molecules and Their Applications" has been divided into four chapters excluding references.

Chapter 1: Introduction

Chapter 2: Materials and Methods

Chapter 3: Results and Discussion

Chapter 4: Summary, Prospects, and Social Impact

References

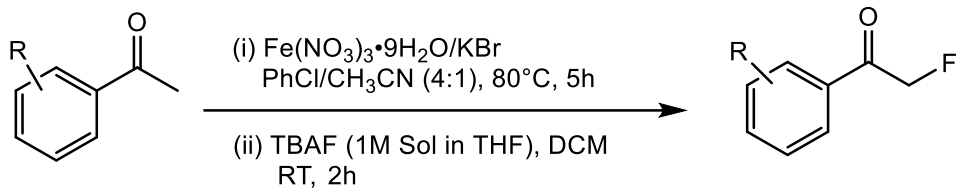
Chapter 1 provides a general description of fluoro-organic chemistry, the effect of fluorination on organic compounds, and their applications in various fields. The literature discussed in this chapter covers various fluorination mechanisms, including direct fluorination, electrochemical fluorination, nucleophilic fluorination, electrophilic fluorination, and radical fluorination, used for the synthesis of fluoroorganic compounds. This chapter also covers the different reagents used for the generation of the C-F bond in aliphatic and aromatic organic molecules.

Chapter 2 covers the materials and methods, which describe different materials and instruments used in experimentation. The section explains the procedures for the synthesis of fluoroacetophenone derivatives and the synthesis of 3,7-difluorinatedoxindole derivatives. The methods for the α-fluorination of acetophenone derivatives in a $Fe(NO_3)_3 \cdot 9H_2O$/KBr/TBAF mediated reaction and synthesis of 3,7-difluorinated oxindole derivatives, from indoles via Selectfluor mediated fluorination have been given in this chapter. This chapter also mentions the procedure for the synthesis of 3-indoleacetic acids, used as raw material. The characterisation data of the synthesized fluorinated compounds, as well as the synthesized starting materials, with different spectroscopic techniques, the determined melting points, and physical states of the synthesized compounds are also mentioned in this chapter. The general

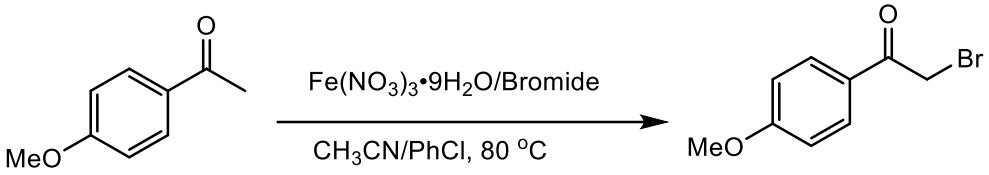
Method for the evaluation of flame retardancy of the selected synthesized compounds as per UL 94 has also been covered in this chapter.

Chapter 3 is the results and discussion, which covers a detailed explanation about the design of the methodology for fluorination, optimization of reaction conditions, and synthesis and characterization of different fluorinated molecules. It also covers the detailed procedure for the preparation of polyurethane films, their testing, and results. To synthesize the 3,7-difluorinated oxindole derivatives, the ester of indoleacetic acid was synthesized by reaction with various alcohols.

A novel, facile, one-pot, multicomponent protocol for the synthesis of α-fluoroacetophenone derivatives has been developed using $Fe(NO_3)_3 \cdot 9H_2O$/KBr/TBAF in chlorobenzene/acetonitrile solvent system. The fluorination of acetophenone derivatives gave the side-chain fluorinated acetophenone in 35–72% yield (**Scheme 4.1**). To establish the formation of α-bromoacetophenone, the intermediate product for in first step of for reaction of 4-methoxyacetophenone and 4-bromoacetophenone was isolated and characterized. (Scheme 4.2).



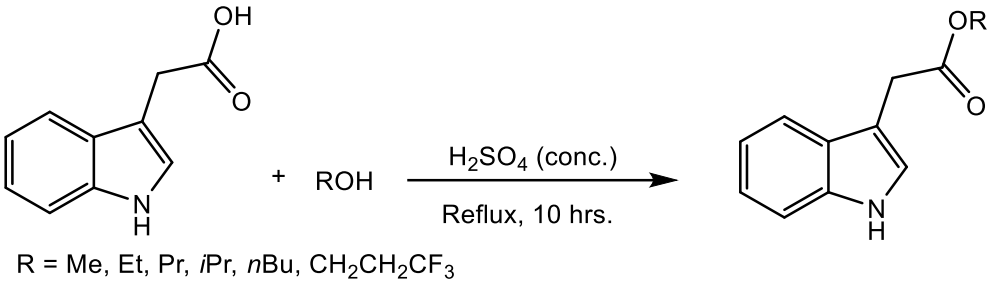
Scheme 4.1. Synthesis of α-fluorinated acetophenone



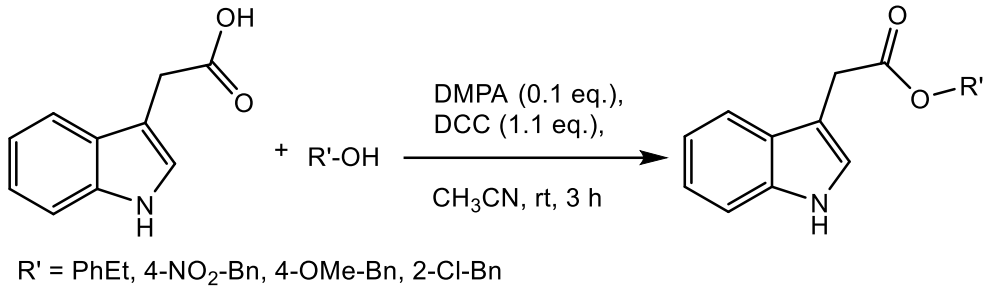
Scheme 4.2. Isolation of intermediate bromide derivatives

The ester derivatives of indoleacetic acid used for the preparation of 3,7-difluorined-oxindoles were synthesized using the literature methods. In one method, the indoleacetic acid was reacted with a large quantity of alcohol in the presence of a catalytic amount of

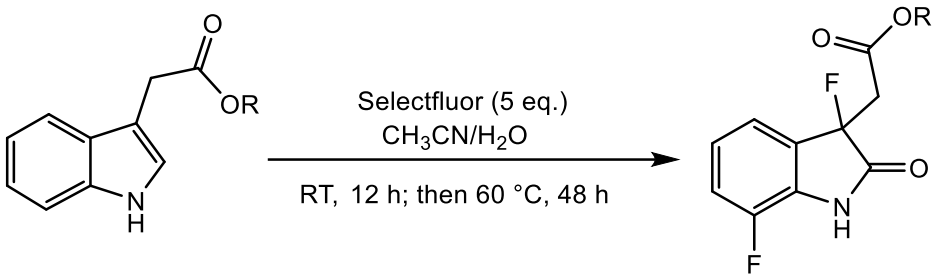
concentrated H_2SO_4. In the second method, the indole acetic acid and corresponding alcohol were reacted in the presence of DCC with a catalytic amount of DMAP in acetonitrile (Schemes **4.3** & **4.4**). The synthesized esters were characterized by ^{1}H NMR, ^{13}C NMR, and FTIR. The 3,7-difluoro oxindoles were synthesized from 3-substituted indoles in a Selectfluor-mediated fluorination protocol in acetonitrile/water cosolvent under mild conditions. A total of 12 derivatives were synthesized and characterized by spectroscopic techniques. The optimized reaction conditions give 15 – 71% yields (**Scheme 4.5**)



Scheme 4.3. Synthesis of the ester of indoleacetic acid (Method-A)



Scheme 4.4. Synthesis of the ester of indoleacetic acid (Method-B)



Scheme 4.5. Synthesis of 3,7-difluorinated oxindole

The selected synthesized derivatives of both fluorinated acetophenone and 3,7-difluorinated oxindole were evaluated for their flame retardancy as per UL 94 (Thin film) after making the thin film with polyurethane in a 5:1 w/w ratio. Unfortunately, the synthesized compounds were not able to impart flame retardancy in thin polyurethane film.

4.2 Prospects

The synthesized fluorinated acetophenone and 3,7-difluorooxindole derivatives did not provide a positive result in flame retardancy evaluation when incorporated into polyurethane (PU) films and tested as per UL-94. however, the results provide a valuable empirical baseline for future research into the structure–property relationships of fluorinated aromatics tailored for flame-retardant applications. The inability of the compounds to provide flame retardancy in PU thin film may be due to the low thermal stability of the material, poor char formation and char quality, or limited interaction with fire in the PU matrix. Therefore, future research should prioritize iterative structural optimization by higher substitution patterns (e.g., ortho/para-fluorination or polyfluorination) to increase the fluorine content in the molecule, in order to enhance the thermal stability and flame inhibition gas-phase radical scavenging. Mechanistic studies, such as thermal degradation profiling by thermogravimetric analysis coupled with Fourier-transform infrared spectroscopy (TGA-FTIR) for real-time evolved gas analysis, identifying volatile fragments using pyrolysis-GC-MS analysis, and comprehensive combustion pathway analysis through microscale combustion calorimetry, will be essential to understand the behaviour of these compounds under fire conditions. The synthesized mono-fluorinated compounds can be converted to polyfluorinated compounds to see the effect of increased fluorine content on fire retardancy. The fluorinated cores of these molecules can be coupled with phosphorus (e.g., phosphonate esters), nitrogen (e.g., triazine heterocycles), or silicon (e.g., siloxane linkages) functionalities to increase the cooperative flame-suppression mechanisms, such as intumescent char reinforcement or condensed-phase radical trapping. In summary, while the initial results were negative for flame retardancy in PU films, the unique properties of fluorinated acetophenone and oxindole derivatives emphasize on continued exploration across broader material platforms and multifunctional applications.

4.3 Social Impact

The development of new synthetic routes for fluorinated acetophenones represents a significant contribution to the development of a simple and impactful process. This process

will help reduce the time required for their synthesis because it eliminates the need for separation and purification of the intermediate. The cost-effective method will also prove energy-saving and reduce the burden on the environment. The synthesis of novel 3,7-difluorinated oxindoles represents a meaningful contribution to the library of fluorinated oxindoles. Even though these compounds did not prove impactful in imparting flame retardancy in polyurethane (PU) films. From a perspective of scientific and social responsibility, this research holds significant value in several dimensions. By defining the synthetic methodology and flame retardancy results, this work will contribute to understanding the structure-property relationship for helping in designing the functional fluorinated flame retardant. The negative flame retardancy results are themselves unacceptable for the application purpose, but they are socially valuable. These results will prevent redundant efforts and will be helpful to guide future research in the right direction, away from ineffective molecular designs, and encourage more targeted exploration of flame retardants. Reporting the unfavourable results upholds the principle of responsible scientific reporting, where transparency and reproducibility are prioritized over selective favourable reporting. Further, the methodology can be utilized for the synthesis of more novel and complex fluorinated molecules to expand the molecular toolbox available to chemists working in different fields, viz., pharmaceuticals, agrochemicals, and materials science. The utility of these compounds may be explored in different domains, like building blocks for more complex molecules.

Finally, by enriching the fluorine chemistry with novel synthetic methodologies, and rigorous testing, this work is truly significant in systematic evaluation and an interdisciplinary approach of the research. It emphasizes the collaboration between synthetic chemists, materials scientists, and environmental researchers for designing and developing the safer technologies and more effective compounds to solve the real-world problems in firefighting. In this way, the current research not only contributes to scientific progress in fluorine chemistry but also embodies a commitment towards public welfare, resource efficiency, and knowledge dissemination in society.

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