EXPLORING THE USE OF ENABLING TECHNOLOGIES FOR SYNTHETIC ORGANIC CHEMISTRY

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This thesis presented for the award of degree of Master of Philosophy (Chemistry) of Cardiff University

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Abbreviations

BPR – backpressure regulator

DCM - dichloromethane

DMAP – 4-dimethylaminopyridine

DMSO – dimethyl sulfoxide

DNA – deoxyribonucleic acid

DSC – differential scanning calorimetry

HPLC – high performance liquid chromatography

HRMS – high resolution mass spectrometry

LAG – liquid assisted grinding

NMR – nuclear magnetic resonance

PFA – perfluoroalkoxy alkane

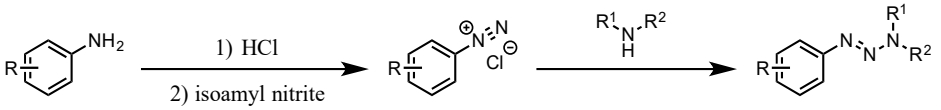
RNA – ribonucleic acid

S_NAr – nucleophilic aromatic substitution

VT NMR – variable temperature nuclear magnetic resonance

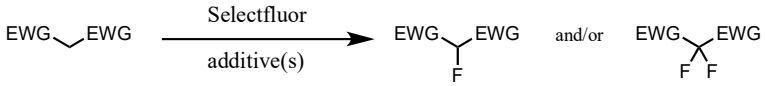
Summary

The two-step preparation of triazenes from commercially available anilines using a continuous-flow technique was demonstrated **(Scheme 1)**. Furthermore, once conditions for the production were optimised, these conditions were applied on a variety of substrates, including both anilines and secondary amines. Finally, the scalability of the procedure was demonstrated during an 18-hour operation.



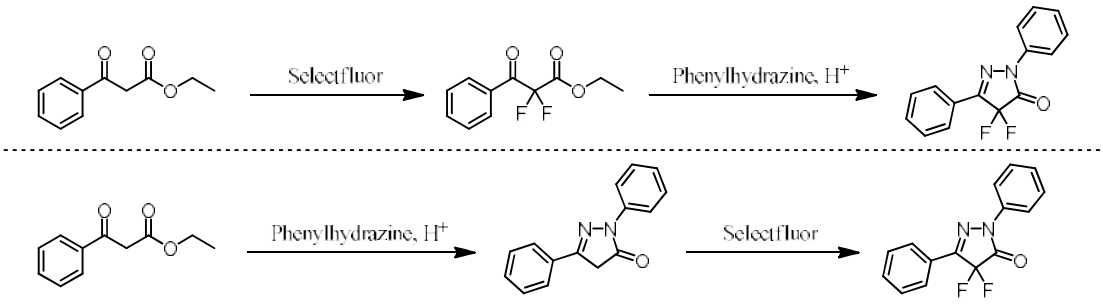
Scheme 1. The continuous-flow synthesis of triazenes

Secondly, the electrophilic fluorination of a variety of activated methylene compounds was performed mechanochemically **(Scheme 2)**. The efficiency of the mechanochemical fluorination is demonstrated by the following outcomes: the increase of the product yield for some examples, reduction of reaction time and/or more selective production of mono- versus difluorinated compounds (in the presence of a LAG or a base) compared to solution-based reactions.



Scheme 2. The mechanochemical electrophilic fluorination of activated methylene compounds

Finally, the multistep mechanochemical synthesis of a fluorinated pyrazolone was conducted. The electrophilic fluorination of a *β*-ketoester was performed followed by a cyclisation with phenylhydrazine to form a pyrazolone. Alternatively, the reaction order could be reversed, first forming the pyrazolone followed by the electrophilic fluorination **(Scheme 3)**. The optimisation of these reactions was made separately and the products were obtained in excellent yields.



Scheme 3. The multistep mechanochemical preparation of fluorinated pyrazolone

Acknowledgments

First of all, I would like to thank my supervisor, Dr Duncan Browne, for his continuous support and guidance during my studies at Cardiff University. It was difficult to adapt to a completely new environment, including scientific one, due to being a citizen of a country with a completely different mentality and education system. However, Dr Duncan Browne and his research group members have helped me with my adaptation, and because of them I have gained a lot of knowledge in organic chemistry and chemistry in general in a very friendly atmosphere.

A special mention is for my extraordinary labmates, namely Christiane, Joseph, Roderick and three crazy guys: Robert, William and Tom. They have made lab working exciting and I will really miss all of them after my return to Kazakhstan.

Finally, I express my gratitude to my sponsor, JSC "Center for International Programs", for giving me such an opportunity to gain world-class knowledge in one of the best universities in the world.

The results presented in **Scheme 10** were obtained by Christiane Schotten, a PhD student, and Martyn Shepherd, a BSc student. Triazene substrate scope presented in **Schemes 11&12** was prepared in collaboration with Christiane Schotten. Optimisation reactions presented in **Table 1** and substrate scope of fluorinated 1,3-diketones and *ß*-ketoesters presented in **Schemes 19, 20, 22&23** were performed in collaboration with Joseph Howard, a PhD student. The non-commercially available 1,3-diketones and *ß*-ketoesters used were synthesised by Joseph Howard and Christiane Schotten.

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A Continuous-Flow Synthesis of Triazenes

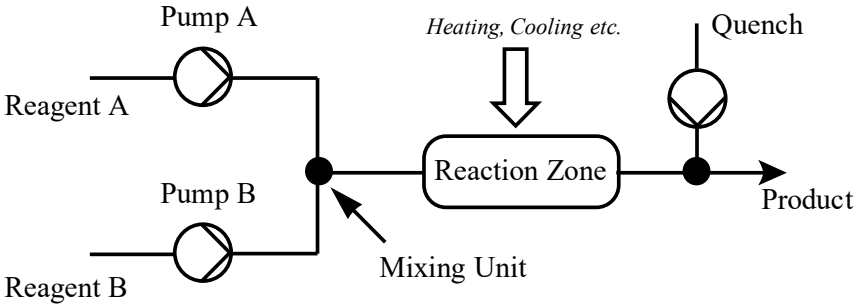
Introduction

1) Flow Chemistry

Organic reactions are usually performed using conventional solvent-based batch techniques. One example is the production of pharmaceuticals, where drugs are usually synthesized using conventional batch or semi-batch technique. That is due to the complexity of drug molecules, and their production often requires multistep synthesis. However, there are a number of challenges faced by this type of processing. Firstly, the multistep synthesis of drugs includes 6-10 steps on average, and each step is followed by purification (recrystallization, column chromatography, distillation etc.).[1] Secondly, hazardous, unstable, toxic and explosive intermediates can be produced at one or some stages of the synthesis. For instance, if an explosive compound can be produced, the large-scale production of the compound is highly undesirable, consequently the production is very rare. Thus, the investigation of safe, automatic and continuous methods for the synthesis of drugs and complex organic compounds is always in high demand and flow chemistry can offer a way to improve current and complement methods.

The continuous processing for the production of chemicals is already common in certain types of industries, such as oil and bulk chemical industries. This method possesses a number of benefits, providing safe, profitable and efficient production of compounds. Taking into account the successful experience of oil and bulk chemical industries for the production of chemicals, the interest in application of continuous-flow processing for the synthesis of drugs and complex organic compounds has been increasingly growing amongst academic researchers and pharmaceutical industries during the last few years.[2-3]

A typical continuous-flow system consists of inlets, from where starting materials, catalysts and quenching agents are pumped, tube reactors, which go through a reaction zone, where the synthesis is performed and an outlet **(Scheme 4)**. It is notable that all reactions can be conducted in solution as one continuous process.



Scheme 4. Example of a continuous-flow setup

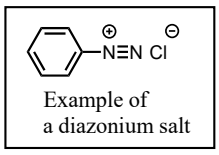
This processing type has a number of advantages. First of all, all the reaction steps, including work-up and purification of intermediate products can be conducted in one continuous-flow setup.[4] Secondly, the drug development commences from the synthesis of a target molecule in millimole scale. However, the production of kilograms of drugs using conventional batch reactors is challenging for pharmaceutical industries in terms of time, safety and space. Moreover, the scale up can result in decrease of selectivity and/or yield of a product. However, continuous-flow techniques offer improved scalability and automation. In addition, optimised conditions for the flow synthesis of compounds in laboratories in most cases can be easily performed on large scales, requiring only some minor alterations to the process.[5]

Another advantage of continuous-flow techniques over conventional batch methods is that the reaction temperature can be controlled more precisely due to high surface-area-to-volume ratio of reaction tubes. In addition, the small volumes of reactors, where reagents encounter, allow more efficient mixing.[6] Furthermore, the addition of backpressure regulator (BPR), controlling the pressure of the system, allows reactions to be conducted in continuous-flow setup at high pressures.[7] This allows solvents to be heated above their boiling points, enabling high temperatures to be used, which can decrease reaction times. In addition, it is difficult to prepare a conventional batch setup for scaling-up the reactions which have to be performed under high pressure or at high temperature. However, this problem can be overcome using continuous-flow techniques instead.

A number of syntheses of pharmaceuticals include the production of unstable and hazardous compounds, therefore it is difficult to scale up these syntheses due to safety issues. However, the use of continuous-flow methods allows the production of these compounds *in situ* as intermediates and immediate use of them in order to synthesize more stable and less hazardous products.[8] Reaction volumes in the tubes are small, therefore hazardous compounds are produced only in small quantities at a certain point along the tube.

2) Diazonium Compounds and Triazenes.

One of the main aims of synthetic chemistry is the production of useful products, such as pharmaceuticals. In addition, the preparation of reagents, which are environmentally friendly, safe and "green", is of interest, especially on large, industrial scales. In particular, methods to prepare nitrogen-containing compounds are in high demand due to their frequent appearance in drug scaffolds. For instance, the synthesis and use of diazonium compounds is of interest for chemists as they represent a method to use C-N building blocks, which can be further used for the production of complex organic compounds.

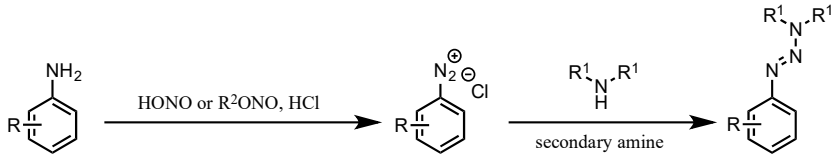


Example of a diazonium salt

Diazonium compounds (salts, ions) are a class of organic compounds with a common formula $RN_2^+X^-$, where "R" is usually an aryl group, and "X" an organic or inorganic anion (Cl^-, CH_3COO^-, NO_3^- etc.). The versatility of diazonium salts as intermediates is well known. They are used in a number of reactions, such as Sandmeyer[9], Balz-Schiemann[10] and Meerwein[11] reactions. Moreover, aryl group-containing diazonium salts are extremely important intermediates for the production of dyes.[12] Despite being extremely useful reagents for the synthesis of a variety of organic compounds, there are some challenges faced in terms of safety hazards. This is due to their limited stability and potential of being explosive as their decomposition releases nitrogen gas.[13] The isolation of diazonium compounds as dry salts can be too dangerous, therefore they are produced *in situ* and used for further reactions. In addition, the synthesis of diazonium compounds is sensitive to reaction temperature. For example, the preparation of chlorides and acetates requires temperatures below 0 °C.[14] Because of these hazards, the synthesis of diazonium salts requires caution in the laboratory, and industrial production of them is rare.[15] Consequently, a safer technique of handling diazonium salts is desirable.[16] Continuous-flow methods were devised as an alternative method for the synthesis of diazonium compounds. Firstly, these hazardous and sensitive intermediates are produced and used *in situ* in the same continuous-flow reaction without accumulating a bulk amount of diazonium compounds. Secondly, heat transfer of the reaction is controlled more accurately due to the high surface area-to-volume ratio. This is extremely important for such sensitive reactions.

The de Mello group performed the first continuous-flow synthesis where a diazonium salt was generated and consumed, in 2002.[17] Aniline and sodium nitrite were used to produce the diazonium salt, which then underwent reaction with 2-naphthol to generate Sudan I, an azo dye, in 52% yield. Another example of the use of diazonium salts in a continuous-flow reactor has been demonstrated by the Wirth group.[18] They performed Heck-Matsuda coupling, firstly producing diazonium salts from a variety of anilines and *tert*-butylnitrite, consequently adding different types of terminal alkenes. The Balz-Schiemann reaction in a continuous-flow setup has been conducted by Yu and co-workers.[19] This system included two steps, where aromatic amines underwent diazotisation, then the generated diazonium salts reacted with HBF_4. Subsequently, the diazonium tetrafluoroboronates underwent thermal decomposition, producing the corresponding aryl fluorides in good to excellent yields (72-95%). This reaction was scaled up, and more than 1 kilogram of *o*-difluorobenzene was produced using this continuous-flow technique.[20]

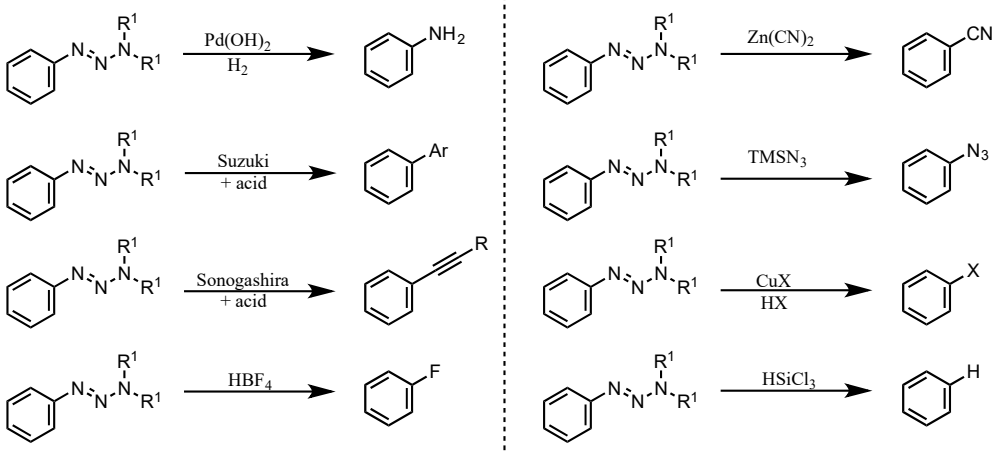
Triazenes are compounds derived from diazonium salts following treatment of the corresponding salt with a secondary amine **(Scheme 5)**.



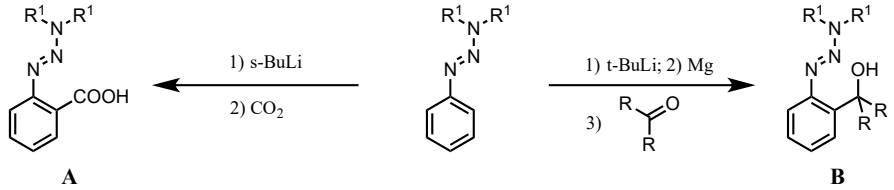
Scheme 5. Synthesis of triazenes from anilines

Triazenes are versatile reagents in organic synthesis, behaving similarly to their diazonium congeners.[21] Triazenes can be used as a source of diazonium species as under acidic conditions a triazene-diazonium equilibrium occurs. Therefore, the secondary amine protecting group can be cleaved, allowing further reactions. For instance, triazenes can be reduced to corresponding anilines using hydrogen gas with a palladium catalyst.[22] Triazenes also can undergo Suzuki[23] and Sonogashira[24] couplings. Balz-Schiemann[25] and Sandmeyer[26] reactions of triazenes allow the preparation of halogenated compounds. Furthermore, the reactions of triazenes with $TMSN_3$[27], $Zn(CN)_2$[28] and $HSiCl_3$[29] produce the corresponding azides, nitriles and benzenes respectively **(Scheme 6)**.

In addition, triazenes can be used as *ortho*-directing groups. For example, triazenes can be *ortho*-deprotonated with *sec*- or *tert*-butyllithium, consequently reacting with CO_2[30] or a ketone[31] to produce compounds **A** and **B (Scheme 7)**

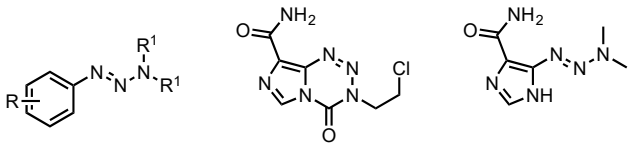


Scheme 6. Examples of the transformation of triazenes to other functional groups



Scheme 7. Examples of the use of triazenes as directing groups

As to the application of triazenes, 1-aryl-3,3-dialkyltriazenes display antitumor activity **(Scheme 8)**.[32] Moreover, triazenes Mitozolomide and Dacarbazine are representatives of antineoplastic drugs **(Scheme 8)**.[33]



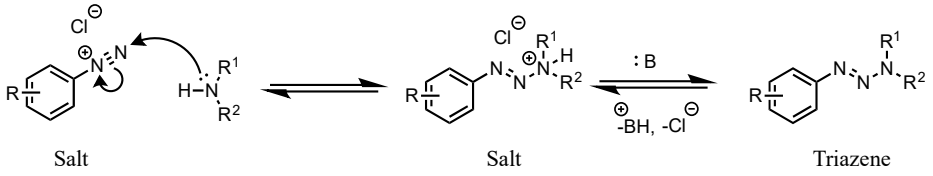
Scheme 8. Triazenes as drug compounds

Although there is no experimental literature evidence about the stability of triazenes compared to diazonium congeners, much literature states that triazenes are stable, and there is no information that triazenes are associated with the risk of explosion. Taking into account reported observations, it was decided to synthesize triazenes using continuous-flow technique.[34]

The aim of this project is to utilize a continuous-flow technique for the synthesis of triazenes. Paying particular attention to handling the formation of expected slurries & precipitates and designing the system in such a way to manage this. Consequently, optimised conditions will be applied on a substrate scope. Lastly, the preparation of triazenes will be scaled up.

Results and Discussion

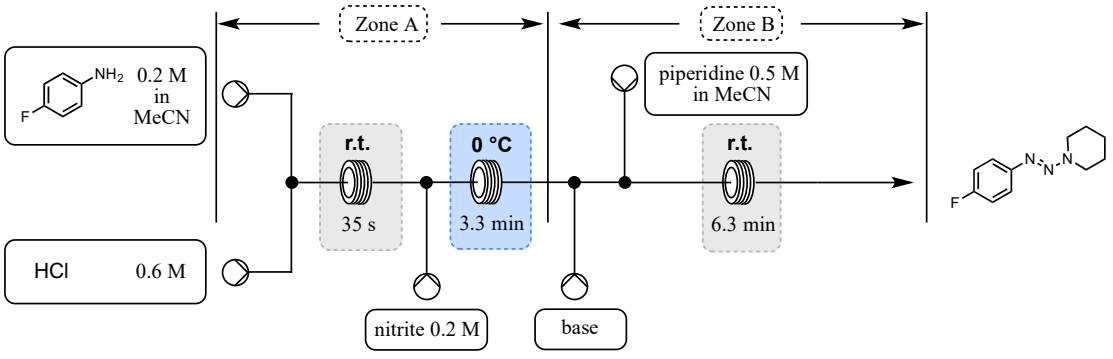
Initially, the first step towards the synthesis of triazenes was the establishment of a continuous-flow setup. Consideration of the mechanism shows that several salts will be formed. Under continuous-flow conditions this can be problematic due to their limited solubilities in common organic solvents. After the production of a diazonium salt as an intermediate, a secondary amine attacks the electrophilic diazonium ion, leading to the protonated form of the triazene. This form has to be deprotonated in order to produce the triazene **(Scheme 9)**.



Scheme 9. Mechanism of the synthesis of a triazene from diazonium salt

The determination of an optimal solvent system was crucial to avoid precipitation, which can lead to the blockage of reactor tubes. Moreover, the precipitation of diazonium salts is highly undesirable due to their nature as potential contact explosives. In addition, it is known that it is necessary to use a mineral base to neutralise the protonated triazene **(Scheme 9)**. Taking into account this information, a continuous-flow system was set up **(Scheme 10)**. It consisted of five streams to perform the two steps of the synthesis of triazenes. The model reaction was the diazotisation of *p*-fluoroaniline, conducting the reaction between the aniline, HCl and sodium nitrite **(Scheme 10, Zone A)**. *p*-Fluoroaniline was chosen so as to permit monitoring the conversion via ^{19}F NMR with an internal standard. It was observed that the use of isoamyl nitrite instead of sodium nitrite prevents precipitation in the reaction tube **(Scheme 10, Entries 1 and 2)**. In addition, acetonitrile could be used instead of water as a solvent. The investigation of conditions for the second step demonstrated that the use of an aqueous solution of a mineral base is not suitable due to its insolubility in the organic solvent, resulting in a blockage due to the formation of a precipitate in the T-piece (mixing unit) **(Scheme 10, Entry 3)**. Consequently, in order to find optimal conditions for the second reaction, conventional solvent-based syntheses of a triazene were performed **(Scheme 10, Entries 4-7)**. Using ^{19}F NMR to quickly analyze the reactions, it was found that the use of an aqueous solution of sodium hydrogen carbonate leads to the desired product. However, this reaction also led to

the formation of a precipitate, therefore it was decided not to use a mineral base for the neutralization and try a variety of organic bases. It was observed that the use of triethylamine, dimethylaminopyridine (DMAP) and piperidine did not cause the production of a precipitate. However, only the use of DMAP and piperidine yielded pure triazene, whereas the use of triethylamine led to a mixture of products. Eventually, piperidine was chosen as a base and reactant for the synthesis of the triazene, which allowed the use of a single pump instead of two, using 4.5 equivalents in total. To be more precise, 1.5 equivalents of piperidine were used for the formation of triazene (0.5 equivalents as excess amount), 2 equivalents of the amine quenched the remaining amount of HCl and 1 equivalent was used for deprotonation of produced protonated triazene. The final setup consisted of 4 inlets (10 mL each), from where starting materials were pumped. It took 20 minutes for steady state to be reached. After that the reaction solution was collected for 25 minutes and after extraction with ethyl acetate and washing with sodium hydrogen carbonate the desired triazene was obtained with an isolated yield of 48% **(7)**. Such a low yield can be explained by a competing S_NAr reaction, where piperidine behaves as a nucleophile and the produced triazene or diazonium salt behaves as a *para*-electron-withdrawing group towards the fluorine leaving group. This setup allows starting material to be processed at a rate of 2.4 mmol per hour. For the yield of 48% for compound **7**, this corresponds to 1.15 mmol of product per hour, producing 48 mL of solvent waste per hour. The concentration of starting materials was limited by the solubility of diazonium salts in the solvent system, with the concentration of 0.1 M during the diazonium salt formation identified as necessary in certain cases to avoid precipitation and blocking of the tubing in certain cases.

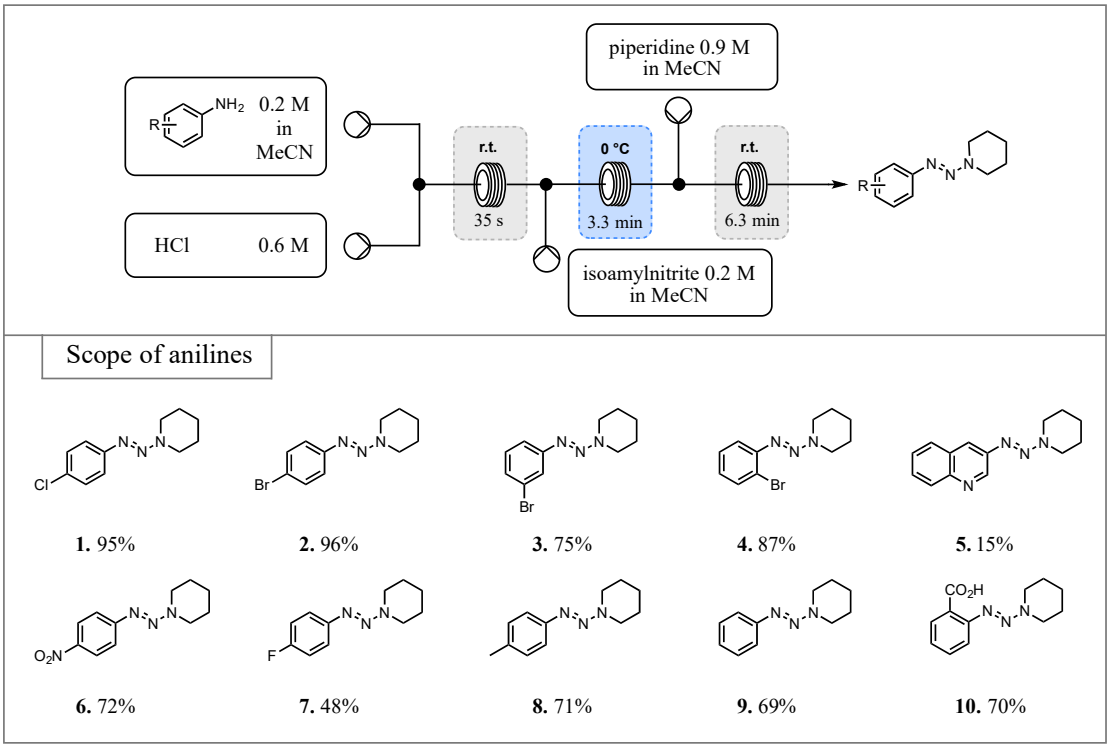


Entry	Setup	Nitrite/Solvent	Base/Solvent	Observations
1	zone A	$NaNO_2/H_2O$	-	precipitate formed
2	zone A	IAN[a]/MeCN	-	no precipitate formed
3	zones A and B	IAN/MeCN	K_2CO_3/H_2O	precipitate formed in zone B
4	BR[b]	IAN/MeCN	$NaHCO_3/H_2O$	precipitate formed – triazene formed
5	BR	IAN/MeCN	Et_3N/MeCN	no precipitate – mixture of products
6	BR	IAN/MeCN	DMAP/MeCN	no precipitate - triazene formed
7	BR	IAN/MeCN	piperidine/MeCN	no precipitate - triazene formed
8	**zones A and B**	**IAN/MeCN**	**piperidine/MeCN**	**no precipitate - triazene – 48% yield**

Scheme 10[I]. A continuous-flow setup and optimization table of synthesis of a triazene

[a] isoamylnitrite; [b] batch reaction

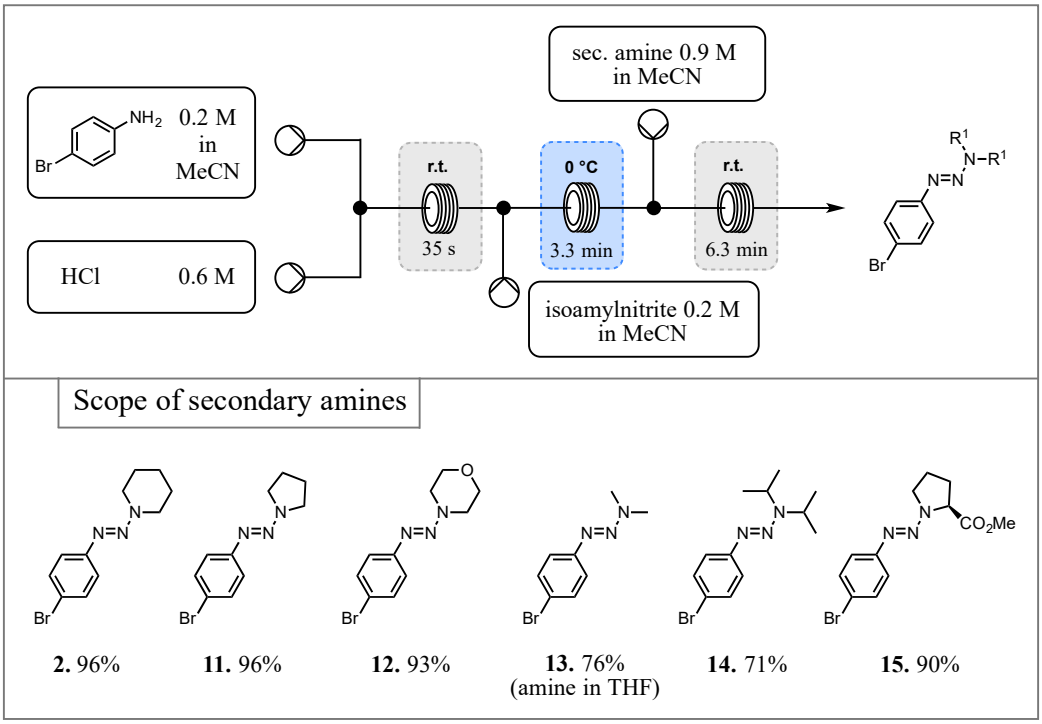
After the optimization of the reaction conditions to avoid precipitate formation with the model substrate, which are shown in **Scheme 10**, the scope of the synthesis using a variety of anilines was investigated **(Scheme 11)**.



Scheme 11[II]. Substrate scope regarding anilines

[I] Christiane Schotten and Martyn Shepherd are acknowledged for the results in this scheme
[II] Christiane Schotten is acknowledged for the results in this scheme

According to the results, the use of other halogenated anilines (ortho-, meta- and para-) led to good to excellent yields of the corresponding triazenes **(1-4)**. Encourangingly, changing to a range of anilines demonstrated that the conditions were robust against precipitate formation. With *p*-nitroaniline, the production of gas, possibly nitrogen gas, was observed, leading to slugs of liquid and gas in the reaction tube. This observation can be explained by the electron-withdrawing nature of the nitro group, which facilitates S_NAr reactivity. Despite this, the desired triazene was isolated with a yield of 72% **(6)**. Looking into the substrate scope further, a variety of secondary amines, namely pyrrolidine, morpholine**,** dimethylamine, diisopropylamine and L-prolinemethyl ester were used in order to produce triazenes **11-15 (Scheme 12)**. Furthermore, it is important to highlight that it is known from literature that triazenes exhibit restricted rotation around the triazene bridge substituents on the nitrogen.[81] This leads to the problem with temperature-dependent coalescence. For example, the signals corresponding to carbon atoms adjacent to nitrogen atom (in the secondary amine moiety) are extremely broad and this makes impossible to distinguish the signals from the baseline in ^{13}C NMR spectra. The same problem appeared to hydrogen atoms of the secondary amine moiety. The signals are broad and do not show any couplings in ^{1}H NMR spectra.

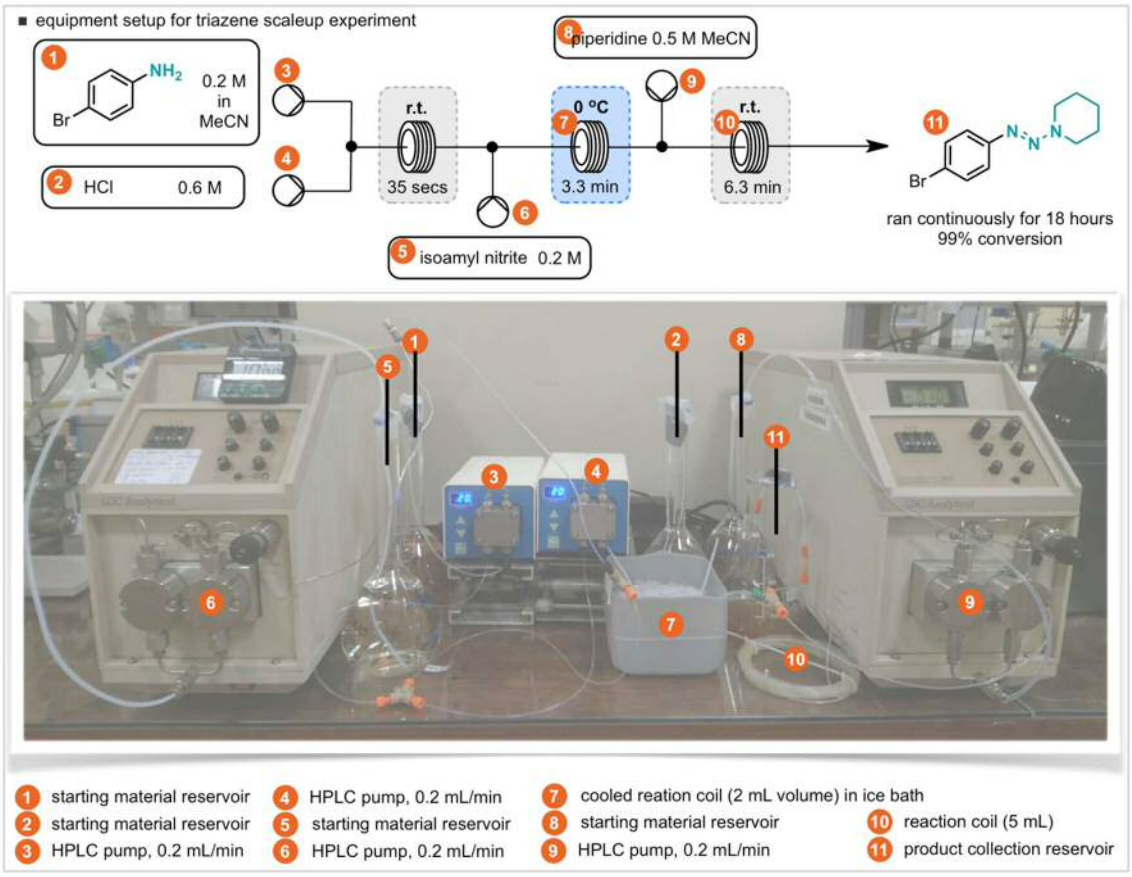


Scheme 12[III]. Substrate scope regarding secondary amines

[III] Christiane Schotten is acknowledged for the results in this scheme

As to secondary amine scope, the products were obtained in good to excellent yields for all amines including L-prolinemethyl ester.

Finally, the scalability of this process was demonstrated using high-performance liquid chromatography (HPLC) pumps **(Scheme 13)**. The flow setup consisted of four 2-piston HPLC pumps, the required reactor tubes and solvent reservoirs bottles. *p*-Bromoaniline and piperidine were chosen for this synthesis. The first sample was collected after 30 minutes, and after extraction 92% yield of product was obtained. This continuous-flow process was performed for 18 hours without problems occurring, spot checks were performed throughout the process to demonstrate reliable behaviour and operation of the system.



Scheme 13. Continuous-flow synthesis of a triazene using HPLC pumps

Conclusion and Future Work

To conclude, the synthesis of triazenes using continuous-flow techniques has been developed. Firstly, it should be noted that diazonium salts were produced in small quantities and consumed *in situ*, avoiding the isolation and decreasing the risk of explosion of these potentially explosive compounds. Secondly, the importance of starting materials and solvents for the reaction has been taken into account in order to avoid any precipitate formation. Consequently, optimised conditions have been applied for the reactions of a range of substrates, both anilines and secondary amines, mostly resulting in good to excellent yields. Finally, the scalability of the procedure has been demonstrated. The continuous-flow HPLC setup has been used for this operation for 18 hours.

According to the observed results and reported literature, it is known that triazenes exhibit restricted rotation behaviour. This feature will be studied via variable temperature (VT) NMR to understand this behaviour in depth. Additionally, although it is widely accepted that triazenes are more stable than their diazonium precursors measurement, at least there is no experimental evidence that proves it. The use of DSC to compare the temperatures of decomposition of diazonium salts and triazenes would show which is more stable and by how much. Use of triazenes to direct C-H insertion processes is also of interest to us. Therefore, it is planned to add one or two more steps to this continuous-flow setup in order to conduct C-H insertion reactions starting from a variety of anilines.

Mechanochemical Electrophilic Fluorination of Activated Methylene Compounds & Multistep Mechanochemical Synthesis of Fluorinated Heterocycles

Introduction

1) Mechanochemistry

Humans have always been interested in using processes which involve mechanical impact, starting from the first attempts to produce fire in the prehistoric period. Some time later, mechanical force was used in the experiments of the alchemists, who were trying to achieve the transformation of some metals to others using a pestle and mortar **(Figure 1a)**.

Michael Faraday conducted mechanochemical reactions with metals in 1820, reducing AgCl in the presence of various metals, such as Zn, Sn, Cu and Fe, to produce silver.[35] Later, Carey Lea demonstrated that mechanochemical reactions of mercury and silver halides lead to decomposition of these salts instead of melting or sublimation on heating.[36]

Eventually, Ostwald classified mechanochemistry as an individual branch of chemistry and defined the term ”mechanochemistry” for the first time in 1919.[37] Since then mechanochemistry has been defined as a section of chemistry that studies physical and chemical transformations (usually between solids) under mechanical impact, such as deformation, friction and shock compression. The plastic deformation of a solid body usually leads not only to changes in the shape of the solid body, but also to the accumulation of defects in it, changing the physico-chemical properties, including the reactivity. The accumulation of defects is used to accelerate chemical reactions.[38]

Although the exact mechanism how the reaction occurs is not well understood, there are a number of hypotheses exist. The first hypothesis is that hot spots with a small surface are formed with temperatures 1000 ^{0}C or above under the friction impact.[39] However, if this mechanism was the main or the only one, thermal decomposition would be observed in mechanochemical organic reactions. Considering that it is not the main, there is the second hypothesis suggesting that reactions proceed through liquid eutectic state caused by the breakage of covalent bonds under mechanical impact.[40] However, these hypotheses have not proved yet, and more research should be done in order to understand the mechanism in depth.

The first mechanochemical reactions were conducted using a pestle and mortar. However, this method has a number of disadvantages. Firstly, the reactions conducted using this method are often irreproducible as yields are highly dependant on the person and their stamina, strength etc.[41] Secondly, there is also a safety concern, because dust and/or toxic gases can be produced and released during the grinding process. In addition, manual mechanochemical reactions cannot be performed applying constant energy for the full duration of the reaction time.[42]

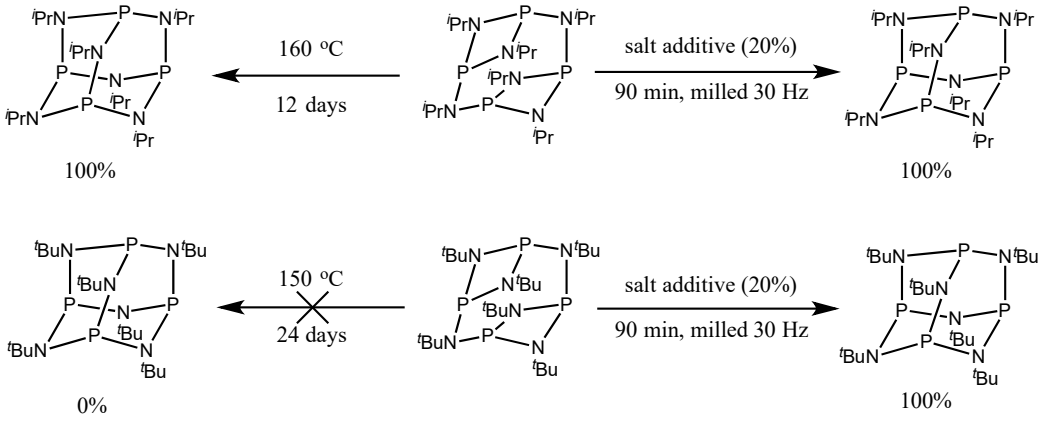
In order to overcome these problems, these methods have been continuously modified since mechanochemical reactions were discovered. Nowadays, it has become ubiquitous to use ball mills to carry out the reactions. Originally, ball mills were designed to mill solid materials to small particles.[43] However, it has been found that it is feasible to conduct solvent-free reactions, including organic reactions using ball mills.

In order to perform a reaction in a ball mill, jars and balls (usually made from stainless steel) are used.[44] The pictures of a ball mill, jars and balls are shown on **Figure 1**. Usually reagents and a ball/balls are placed in a jar, which is placed in a mill, where it is shaken at a set frequency. This causes the ball/balls to collide with starting materials, grinding them to smaller particles and leading to increased surface area, energy and structure defects. Subsequently, a reaction may occur through mechanochemical activation.[45]

Figure 1. (a) pestle and mortar; (b) The Retsch MM-400 mixer mill; (c) stainless steel balls; (d) stainless steel jars

Recently a number of organic reactions were reported in ball mills. For instance, the feasibility of C-C, C-N and C-X bond formations mechanochemically have all been demonstrated. A number of metal-catalyzed cross-coupling reactions, namely Suzuki,[46] Heck,[47] Sonogashira,[48] Michael addition[49] and the synthesis of peptides and nucleosides have also been demonstrated.[50-53] In most cases, performing these reactions mechanochemically has demonstrated some advantages over solution-based batch reactions, such as reduction of reaction time, increased yields and improved selectivity.[54]

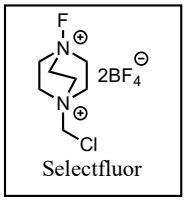
One example demonstrating of the efficiency of mechanochemical reactions over solvent-based reactions is the synthesis of adamantoid phosphazanes from the corresponding phosphorus-nitrogen (PN) heterocycles **(Scheme 14)**.[55] It can be pointed out that the synthesis of isopropyl-substituted adamantoid phosphazane required 90 min when the reaction was performed in the ball mill. However, corresponding solvent-based reaction under high temperature required 12 days. Moreover, the first synthesis of tert-butyl derivative of adamantoid phosphazane was conducted mechanochemically in 90 min, whereas it was not possible to perform a similar reaction using conventional solvent based technique. In both mechanochemical reactions 100% yield was observed.



Scheme 14. Synthesis of adamantoid phosphazanes

In addition, performing organic reactions using conventional methods usually requires a large amount of solvent, and many solvents have a harmful effect on the environment.[56] Therefore, mechanochemical synthesis, being a solvent-free process, can be described as "green chemistry". If it is feasible to perform the reactions on large scales in the future, then mechanochemical synthesis could play a significant role in the chemical industry.

2) Fluorination



Selectfluor

Approximately 40% of agrochemicals and 20% of pharmaceuticals contain fluorine.[57] The use of fluorine-labeled compounds enables the study of metabolic processes, mechanisms of enzymatic reactions and the structure of active centres of enzymes.[58] Therefore, interest in fluorination has grown in recent years.

The discovery of a significant increase in the activity of steroid hormones by the introduction of fluorine by Josef Fried and Emily F. Sabo attracted the attention of the pharmaceutical industry to fluorine-containing compounds.[59]

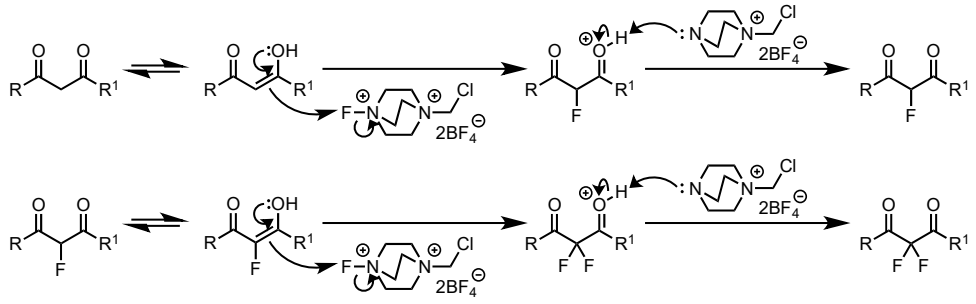
Since then, many medical uses of fluorinated compounds have been discovered, such as the use of fluorine-labeled compounds for studying mechanisms of physiological processes.[60] However, special attention is given to drugs with known mechanisms of action – drugs to which the introduction of fluorine leads to a significant increase in activity. This is due to the effect of fluorination on pKa, lipophilicity and solubility. For example, introduction of fluorine into the structure of drugs blocks the oxidative metabolism, and the amount of a particular drug, which reaches a target organ, significantly increases.[61] As a result, many fluorinating reagents and fluorination methods, including nucleophilic and electrophilic, have been developed.

Despite the fact that many nucleophilic fluorine-containing sources were discovered, there were limited sources of electrophilic fluorine for a long period of time. The first known source of F^+ is fluorine gas (F_2). However, many problems occurred when reactions were conducted with this gas due to its toxicity.[62] Subsequently, some other sources of electrophilic fluorine were discovered, such as CF_3OF[63], $FClO_3$[64] and $CsSO_4F$[65]. These fluorinating agents are safer than fluorine gas, but there was still a demand for stable and mild sources of electrophilic fluorine.

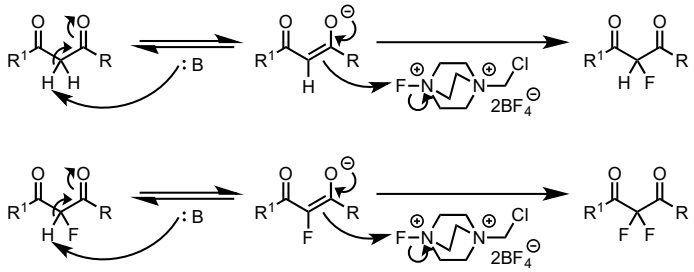
Therefore, considerable effort has been spent searching for safe, easy to store and handle fluorinating reagents. Selectfluor® was discovered, which represents a mild, effective and commercially available source of electrophilic fluorine.[66]

4) Electrophilic Fluorination of Activated Methylene Compounds

Activated methylene compounds feature two electron-withdrawing groups, which are connected via a methylene bridge. The electrophilic fluorination of activated methylene compounds can occur more than once, giving rise to monofluorinated and difluorinated compounds. For instance, for 1,3-dicarbonyls, which are enolisable compounds, fluorination can be conducted with or without addition of base. In the absence of a base **(Scheme 15)**, 1,3-dicarbonyls enolise and the enol acts as a nucleophile, which consequently attacks the electrophilic fluorine atom. However, despite the fact that the introduction of one fluorine atom should make the hydrogen atom on the methylene bridge more electron deficient, therefore more acidic, the rate of difluorination is not as fast as expected. An explanation for this is due to the position of equilibrium between keto/enol forms of the monofluorinated activated methylene compound. In the enol form there is a double bond between a carbon atom, which is attached to a fluorine atom, and a carbon atom, which is attached to an oxygen atom. A carbon-carbon double bond attached to two electron-withdrawing atoms is not preferable. Therefore, this explains that the monofluorinated activated methylene compound preferentially exists in keto form. In this keto form no further reaction can occur in the absence of a base. However, in the presence of a base **(Scheme 16)**, the monofluorinated activated methylene compound is deprotonated to form the enolate ion, which then attacks electrophilic fluorine atom, giving the difluorinated product.



Scheme 15. Electrophilic fluorination of 1,3-dicarbonyls without base, enol pathway



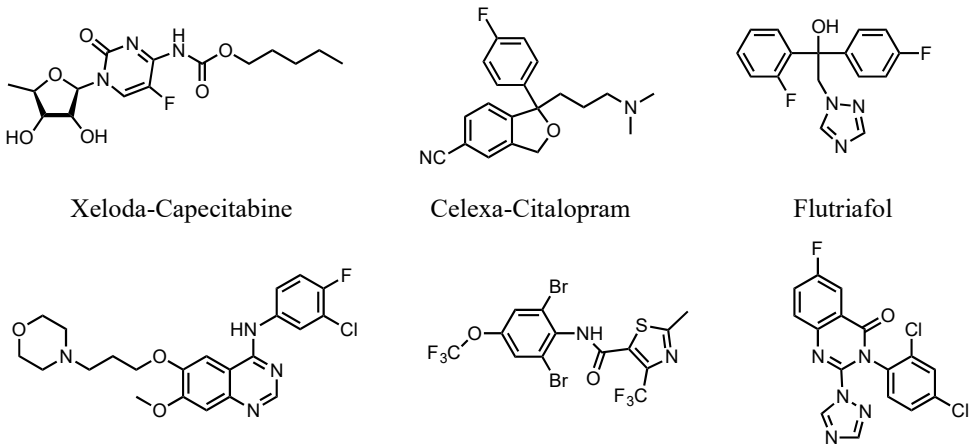
Scheme 16. Electrophilic fluorination of 1,3-dicarbonyls under basic conditions, enolate pathway

Previous work investigating the fluorination of activated methylene compounds has been reported by Banks and Shreeve. E. Banks and co-workers conducted electrophilic fluorination reactions of a variety of activated methylene compounds, namely 1,3-diketones, *ß*-ketoesters and *ß*-ketoamides using conventional batch technique in 1994.[67] Later, Shreeve and co-workers also did research on the same type of reactions under different conditions in 2003 and in microwave in 2005.[68-69]

5) Fluorinated Heterocycles

Chemistry of heterocycles is a branch of organic chemistry which studies cyclic organic compounds, where a ring consists of carbon atoms and one or more other atoms. Nitrogen, oxygen and sulfur-containing heterocycles are some examples. Many drugs, natural products, DNA and RNA include heterocyclic rings in their structure. Therefore, organic chemists and fine chemical industries are highly interested in the investigation of methods for the preparation of heterocyclic compounds.

In the "Fluorination" part of this chapter the role of fluorine-containing compounds in pharmaceutical and agrochemical market was discussed. In addition to that, it is notable that a considerable amount of drugs and agrochemicals include fluorinated heterocyclic rings in their structure. For instance, the anticancer drugs Xeloda-Capecitabine, Iressa-Gefitinib, antidepressant Celexa-Citalopram and some agrochemicals, such as Thifluzamide, Flutriafol, Fluquinconazole are representatives of fluorinated heterocycles **(Scheme 17)**.[70]



Scheme 17. Examples of drugs and agrochemicals, which include fluorinated heterocyclic moieties

The first synthesis of a fluorinated heterocycle, namely 2-fluoropyridine, was performed by Chichibabin in 1915.[71] However, the development of syntheses of fluoroheterocycles, along with the investigation of fluorinating compounds, started in 1950s. In this period the synthesis of 5-fluorouracil, a drug with anticancer properties, was discovered.[72] This breakthrough commenced the rapid development of a number of pharmaceuticals.[73] For example, ciprofloxacine, a representative of fluoroquinolone antibiotics, was a popular drug in the USA

approximately 30 years ago.[74] Eventually, it became clear that fluorinated heterocycles are of high interest to the pharmaceutical industry.

As to the preparation procedure, the synthesis of fluorinated heterocycles can be performed using two methods. The synthesis of fluorine-containing heterocycles from fluorinated precursors is the first approach, so called fluorine building block approach. Alternatively, late stage fluorination of heterocycles can also be carried out.

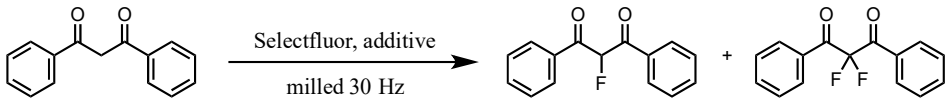
The aim of this project is to find optimal conditions for performing mechanochemical selective mono- and difluorination reactions of a variety of activated methylene compounds, using Selectfluor® and the presence of different additives. In addition, mechanochemical synthesis of a heterocycle, namely a pyrazolone, will be conducted using a *β*-ketoester and phenylhydrazine as starting materials. Consequently, produced pyrazolone will undergo mechanochemical electrophilic fluorination reaction. Finally, a multistep preparation of fluorinated pyrazolone will be explored mechanochemically.

Results and Discussion

Initially, 1 mmol of dibenzoylmethane (solid) and 1 equivalent of Selectfluor® were placed in a 10 mL stainless steel jar with a 4 g stainless steel ball and milled at 30 Hz for 1 hour. Yields of 53% of mono- and 4% of difluorinated compounds were observed **(Table 1, Entry 1)**. Subsequently, the amount of Selectfluor® was doubled and the reaction time increased to 2 hours, which resulted in 87% of mono- and 11% of difluorinated products **(Table 1, Entry 2)**.

Recently, mechanochemical cocrystallisation reactions with the use of LAG (Liquid Assisted Grinding) were reported, in which a small quantity of liquid is added. This method can accelerate mechanochemical reactions and lead to increased yields and improved selectivities.[75] Therefore, the use of LAG in the electrophilic fluorination reaction was explored.

A variety of solvents was screened to test the effect of LAG on this reaction manifold, starting from 0.25 mL of each solvent. The use of isopropanol, toluene and dichloromethane demonstrated unsatisfying results **(Table 1, Entries 8,9&10)**. Surprisingly, the addition of water entirely inhibited the fluorination, while it is known that Selectfluor® is soluble and stable in water **(Table 1, Entry 7)**.[76] Surprisingly, the use of acetonitrile afforded better selectivity for the monofluorination over difluorination, resulting in 91% of mono- and 7% of difluorinated products **(Table 1, Entry 5)**. Finally, the reduction of MeCN by 2 times (0.125 mL or 3 equivalents) achieved full conversion of dibenzoylmethane to monofluorinated product after milling for 2 hours **(Table 1, Entry 11)**. These LAG conditions significantly increased selectivity towards monofluorination compared to the reaction without presence of additives.



16 **17**

Entry	Equiv of S.f.	Time (h)	Additive	Yield **16**[a]	Yield **17**[a]
1	1	1	-	53%	4%
2	2	1	-	87%	11%
3	2	0.5	-	53%	4%
4	2	1	MeCN (0.25 mL)	79%	0%
5	2	2	MeCN (0.25 mL)	91%	7%
6	2	2	-	61%	38%
7	2	2	H_2O (0.25 mL)	0%	0%
8	2	2	*i*-PrOH (0.25 mL)	9%	3%
9	2	2	PhMe (0.25 mL)	30%	2%
10	2	2	CH_2Cl_2 (0.25 mL)	20%	0%
11	**2**	**2**	**MeCN (0.125 mL)**	**100%**	**0%**
12	**2**	**2**	**Na_2CO_3 (1 equiv)**	**6%**	**94%**
13	2	2	K_2CO_3 (1 equiv)	2%	87%
14	2	2	Cs_2CO_3 (1 equiv)	2%	68%
15	2	2	$CaCO_3$ (1 equiv)	53%	19%

Table 1[IV] Optimization of conditions for selective electrophilic mono- and difluorination of dibenzoylmethane in a ball mill;

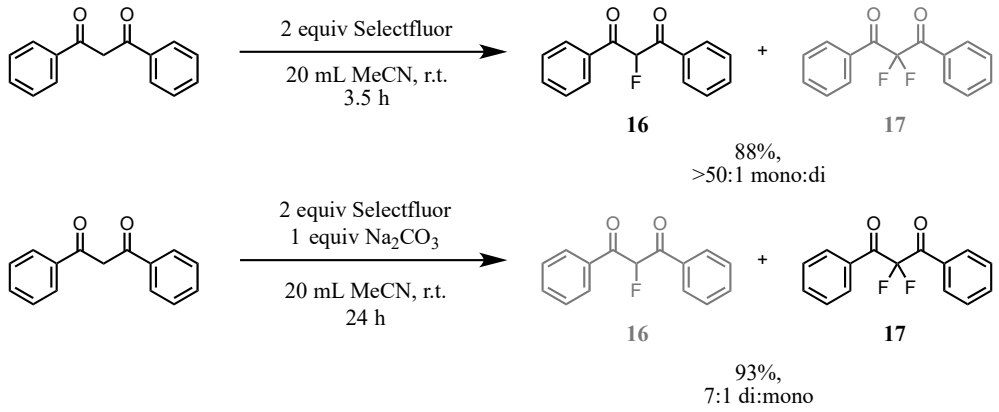
[a] determined by ^{19}F NMR with trifluorotoluene as internal standard, remaining mass balance is recovered starting material

After optimisation of the monofluorination conditions, conditions were investigated for selective difluorination. It was decided to introduce a base to facilitate the formation of difluorinated product. Different types of carbonates as bases were screened. The introduction of caesium and potassium carbonates resulted in moderate and good yields of difluorinated dibenzoylmethane, 68% and 87% respectively **(Table 1, Entries 13&14)**. However, the use of sodium carbonate as a base demonstrated the best result, giving 94% of di- and 6% of monofluorinated products after milling for 2 hours **(Table 1, Entry 12)**.

Previously the electrophilic fluorination of dicarbonyl compounds has been reported by Banks and co-workers.[77] The solution-based comparison reactions were performed analogous to their work, but using 2 equivalents of Selectfluor® for rigorous comparison **(Scheme 18)**. As a result, the monofluorination reaction in batch required 3.5 hours for completion and demonstrated 88% yield with an excellent selectivity. As for the difluorination reaction, it was found that completion of this reaction takes 24 hours. Hence, comparison of the results of difluorination reactions performed in solvent batch and mechanochemically clearly

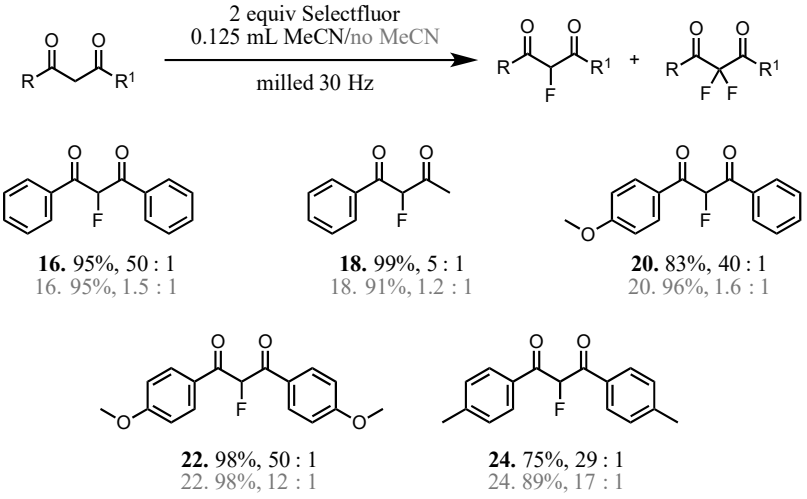
[IV] Joseph Howard is acknowledged for the results in this table

demonstrates that the reaction time significantly reduced by 12 times (from 24 hours to 2 hours).



Scheme 18. Electrophilic fluorination reactions of dibenzoylmethane in batch

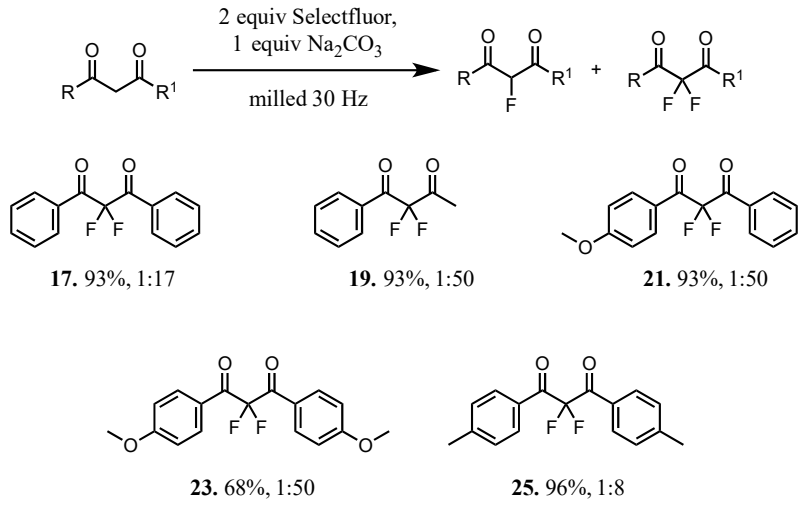
Consequently, the mechanochemical mono- and difluorinations of a variety of 1,3-diketones (solids) were performed in order to test the general applicability of these conditions. In addition, mechanochemical comparison reactions without LAG for monofluorination were also conducted. The results in **Scheme 19** clearly show that the addition of acetonitrile facilitates increased selectivity of monofluorination reactions for all examples.



Scheme 19[V]. Monofluorination of 1,3-diketones with and without LAG

[V] Joseph Howard is acknowledged for the results in this scheme

As to the mechanochemical difluorination reaction of diketones under basic conditions, all substrates were converted in good to excellent yields. Therefore, it has been demonstrated that mechanochemical difluorination of diketones requires much less time when compared to solution-based reactions **(Scheme 20)**.



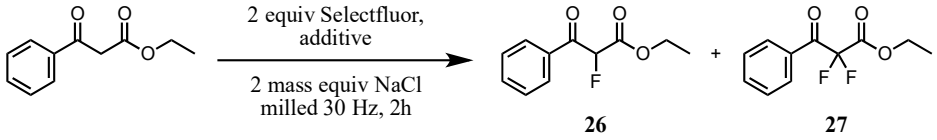
Scheme 20[VI]. Difluorination of 1,3-diketones under basic conditions

In order to probe these results further, it was decided to perform electrophilic fluorination of another class of 1,3-dicarbonyl compounds – *ß*-ketoesters. The reactions were conducted in a similar fashion as the fluorination of diketones. However, it was taken into account that *ß*-ketoesters are liquid compounds. Indeed, grinding a mixture of liquid and solid substrates can lead to "gumming" in the reactor jar and inefficient mass transfer. It is known from the literature

that the use of an inert solid additive such as a grinding agent, usually an inorganic salt, is ubiquitous in such situations to overcome the problem of "gumming".[78] Initially, the fluorination of the liquid *ß*-ketoester, ethyl benzoylacetate, was investigated using sodium chloride as a grinding agent, applying the previously optimised conditions for mono- and difluorination of 1,3-diketones. 2 mass equivalents (twice the total mass of reagents) of sodium chloride were used. As a result, 83% yield was observed with ratio 11:1 between mono- and difluorinated products (Table 2, Entry 1). After attempting to find the best conditions for monofluorination, it was discovered that doubling the amount of LAG resulted in an excellent yield with a good selectivity, 96% and 13:1 respectively (Table 2, Entry 2).

[VI] Joseph Howard is acknowledged for the results in this scheme

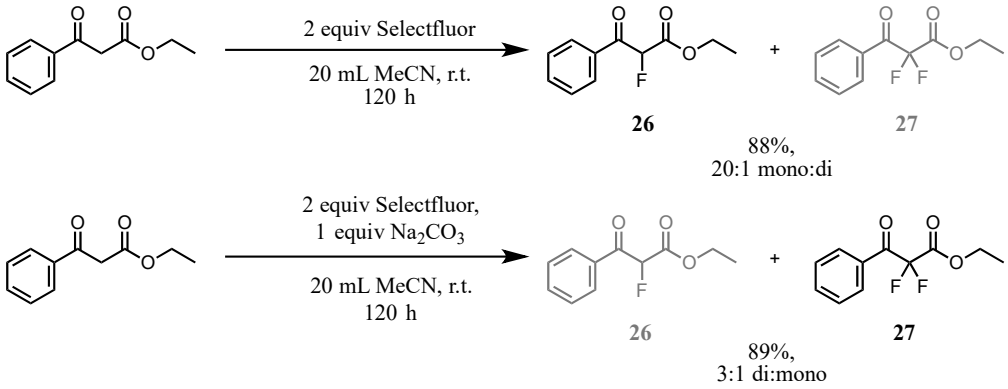
Surprisingly, after fluorination in the absence of acetonitrile (Table 2, Entry 3) only 32% of monofluorinated compound was obtained with 15:1 selectivity, also recovering 67% of starting material. This shows that the addition of acetonitrile increases the rate of monofluorination reaction for *ß*-ketoesters. As for difluorination of the *ß*-ketoester (Table 2, Entry 4) also showed a good outcome, yielding 98% of the product with ratio 7:1 between di- and monofluorinated compounds.



Entry	Additive	Yield	Ratio **26:27**
1	MeCN (0.125 mL)	83%	**11:1**
2	MeCN (0.25 mL)	96%	**13:1**
3	-	32%	**15:1**
4	Na_2CO_3 (1 equiv)	98%	**1:7**

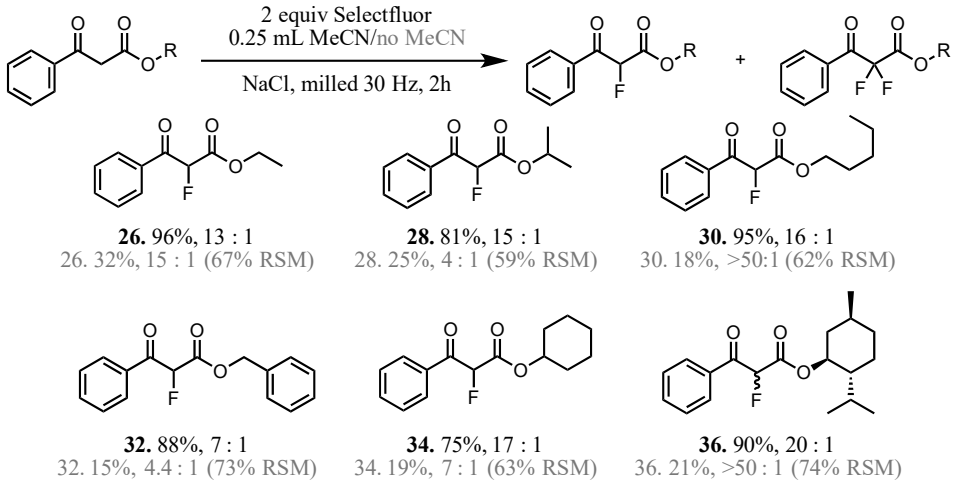
Table 2 Optimization of electrophilic fluorination of ethyl benzoylacetate

At the same time reactions were conducted in solution for comparison **(Scheme 21)**. Consequently, it can be highlighted that reaction time under neutral and basic conditions required 5 days in both cases. Hence, it is demonstrated that the reaction time is reduced significantly when these reactions are performed mechanochemically.

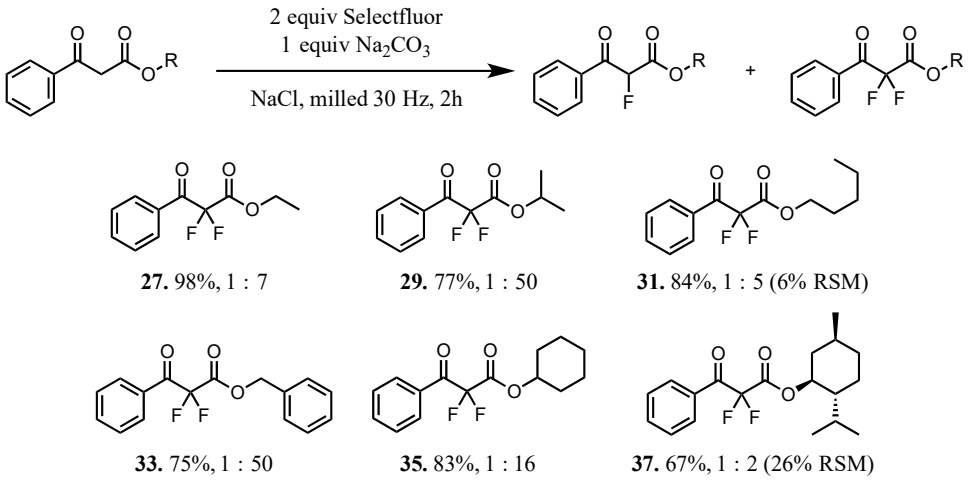


Scheme 21. Electrophilic fluorination reactions of ethyl benzoylacetate in batch

These conditions were subsequently applied to a range of *β*-ketoesters, and the results are shown in **Schemes 22 & 23**. They clearly demonstrate that acetonitrile increases the reaction rate, leading to monofluorinated products. In addition, difluorination of *β*-ketoesters was also successful, resulting in good to excellent yields. Indeed, in every case studied the reactions were faster with added LAG than without. This is shown by the return of recovered starting material in the absence of LAG.



Schemes 22[VII]. Monofluorination of *β*-ketoesters with and without LAG; RSM = recovered starting material

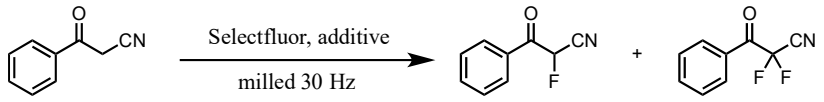


Scheme 23[VII]. Difluorination of *β*-ketoesters under basic conditions; RSM = recovered starting material

The fluorination of a third type of activated methylene compound, namely *β*-ketonitriles, was also investigated. Commercially available benzoylacetonitrile was chosen as a parent substrate. This substrate (1 mmol scale) was subjected to the previously optimised conditions for mono- and difluorination of 1,3-diketones, taking into account that this *β*-ketonitrile is a

[VII] Joseph Howard is acknowledged for the results in these schemes

solid compound. However, application of the previously optimised conditions for monofluorination resulted in 4% of mono- and 12% of difluorinated compounds **(Table 3, Entry 8)**. The use of sodium carbonate (difluorination conditions) resulted in 53% yield of difluorinated *ß*-ketonitrile **(Table 3, Entry 10)**. However, the reaction of the *ß*-ketonitrile and 2 equivalents of Selectfluor® after milling for 2 hours in the absence of any additives resulted in 59% of difluorinated *ß*-ketonitrile **(Table 3, Entry 3)**. It was potentially expected that electrophilic fluorination of *ß*-ketonitriles could be faster than the fluorination of 1,3-dicarbonyls because the pKa for *ß*-ketonitriles (10.2 in DMSO) is considerably lower than 1,3-diketones or *ß*-ketoesters (13.3 and 15 in DMSO respectively).[79] Furthermore, reactions were conducted in the absence and presence of additives (MeCN, Na_2CO_3) using different reaction time in order to investigate optimal conditions for electrophilic fluorination of benzoylacetonitrile. Finally, 65% yield of difluorinated *ß*-ketonitrile was observed when benzoylacetonitrile was milled with 2 equivalents of Selectfluor® for 3 hours without any additives **(Table 3, Entry 4)**.



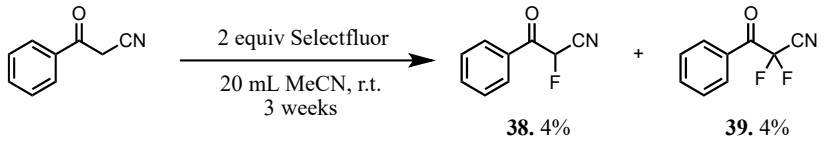
38 **39**

Entry	Equiv of S.f.	Time (h)	Additive	Yield **38**[a]	Yield **39**[a]
1	1	1	-	4%	19%
2	1	2	-	4%	21%
3	2	2	-	0%	59%
4	**2**	**3**	**-**	**0%**	**65%**
5	2	4	-	0%	61%
6	2	5	-	0%	63%
7	2	1	MeCN (0.125 mL))	5%	9%
8	2	2	MeCN (0.125 mL)	4%	12%
9	2	1	Na_2CO_3 (1 equiv)	0%	37%
10	2	2	Na_2CO_3 (1 equiv)	0%	53%
11	2	3	Na_2CO_3 (1 equiv)	0%	27%
12	2	4	Na_2CO_3 (1 equiv)	0%	27%

Table 3 Optimization of electrophilic fluorination of benzoylacetonitrile

[a] determined by ^{19}F NMR with trifluorotoluene as internal standard

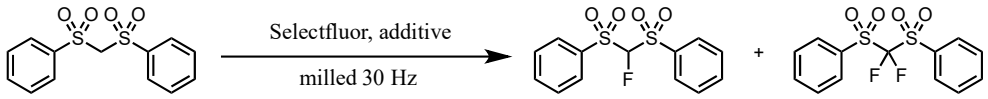
Conducting the reaction using conventional solvent-based technique **(Scheme 24)** resulted only in 4% of mono- and 4% of difluorinated compound after 3 weeks. Therefore, it can be concluded that the yield of the difluorinated *ß*-ketonitriles can be considerably improved and the reaction time dramatically decreased when reactions were performed mechanochemically compared to the conventional batch reactions.



38. 4% **39.** 4%

Scheme 24. Electrophilic fluorination reaction of benzoylacetonitrile in batch

Bissulfones were chosen as the final representative of activated methylene compounds. Bis(phenylsulfonyl)methane (solid, pKa 12.2 in DMSO)[74] was selected as a parent substrate. Before performing a fluorination reaction there was a doubt in the enolization capability of bissulfones. Milling bis(phenylsulfonyl)methane with 2 equivalents of Selectfluor® without any additives and in the presence of acetonitrile resulted in 0% yield of fluorinated products **(Table 4, Entries 1&2)**. After the addition of 1 equivalent of sodium carbonate 77% yield of mono- and 8% yield of difluorinated bissulfones (ratio 9.5:1) were observed after 2 hours of milling **(Table 4, Entry 4)**. This result demonstrates that electrophilic fluorination of bissulfones requires the presence of a base, which firstly deprotonates the substrate. The reduction of reaction time resulted in a decreased yield, whereas the increase of reaction time led to a slow conversion of monofluorinated bissulfone to difluorinated product.



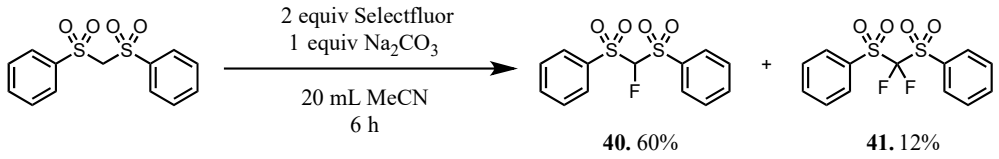
40 **41**

Entry	Equiv of S.f.	Time (h)	Additive	Yield **40**[a]	Yield **41**[a]
1	2	2	-	0%	0%
2	2	2	MeCN (0.125 mL)	0%	0%
3	2	1	Na_2CO_3 (1 equiv)	31%	0%
4	**2**	**2**	**Na_2CO_3 (1 equiv)**	**77%**	**8%**
5	2	3	Na_2CO_3 (1 equiv)	73%	14%
6	2	4	Na_2CO_3 (1 equiv)	69%	18%

Table 4 Optimization of electrophilic fluorination of bis(phenylsulfonyl)methane

[a] determined by ^{19}F NMR with trifluorotoluene as internal standard

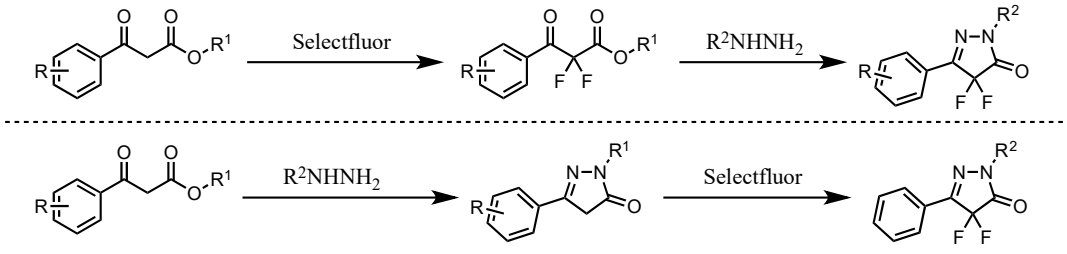
Furthermore, a conventional solvent-based reaction was conducted under basic conditions **(Scheme 25)**. This synthesis resulted in 60% of mono- and 12% of difluorinated products (ratio 5:1) after stirring the reaction mixture for 6 hours.



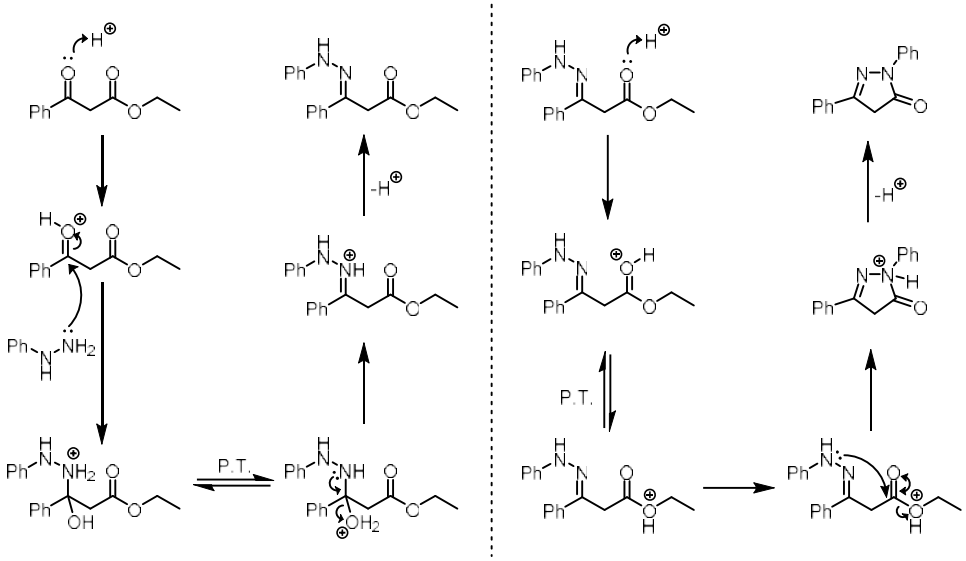
Scheme 25. Electrophilic fluorination reaction of bis(phenylsulfonyl)methane in batch

Consequently, an increased yield of monofluorinated bissulfone, improved selectivity and the reduction of reaction time were observed when fluorination reaction was conducted mechanochemically.

Following the investigation of conditions for the electrophilic fluorination of different activated methylene compounds we opted to explore the multistep synthesis of difluorinated pyrazolones. Two possible ways were considered for this procedure. The first approach would first perform electrophilic fluorination of a *ß*-ketoester, then difluorinated *ß*-ketoester reacts with a hydrazine, producing difluorinated pyrazolone. Alternatively, a pyrazolone can be prepared from a *ß*-ketoester and a hydrazine, followed by the formed pyrazolone undergoing electrophilic fluorination. This approach is summarised in **Scheme 26**. In addition, an example of the mechanism of pyrazolone formation, where ethyl benzoylacetate and phenylhydrazine are used as starting materials, is illustrated in **Scheme 27**.



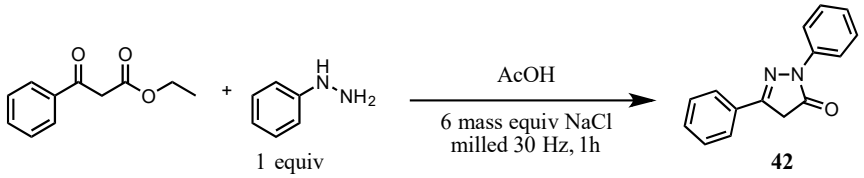
Scheme 26. Possible ways of synthesis of fluorinated pyrazolones



Scheme 27. An example of pyrazolone formation mechanism

First of all, it was crucial to investigate the conditions for the synthesis of a pyrazolone. Ethyl benzoylacetate and phenylhydrazine were chosen as parent substrates. According to the literature it is known that this reaction is performed in conventional solution–based reaction in acetic acid, which behaves as a solvent and a catalyst for this reaction.[80] Therefore, acetic acid was chosen as a catalyst for this mechanochemical reaction. In addition, sodium chloride was added as a grinding agent, because both substrates are liquids.

Initially, the first reaction was performed at 1 mmol scale with the addition of 0.25 mL of acetic acid and 6 mass equivalents of sodium chloride for 1 hour. Under these conditions 97% yield of a pyrazolone was observed **(Table 5, Entry 1)**. Furthermore, the amount of acid was decreased. Eventually, it was found that the use of 0.03 mL (0.5 equivalents) of acid led to the same yield of the pyrazolone **(Table 5, Entry 3)**.

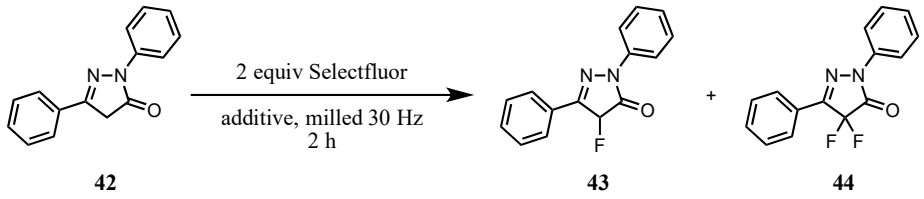


Entry	Equiv of AcOH (mL)	Yield **42**[a]
1	0.25	97%
2	0.1	97%
3	0.03	97%
4	0.005	86%

Table 5 Optimization of the synthesis of a pyrazolone

[a] determined by ^{1}H NMR with mesitylene as internal standard

Following this, the mechanochemical fluorination reaction of the pyrazolone was performed under various conditions. Firstly, it was taken into account that the pyrazolone is a solid compound, therefore the use of sodium chloride was not needed. Considering the pyrazolone as a cyclic activated methylene compound, the previously optimised conditions were applied. As a result, under basic conditions and without any additives 95% yield of difluorinated compound was produced after 2 hours **(Table 6, Entries 1&2)**.



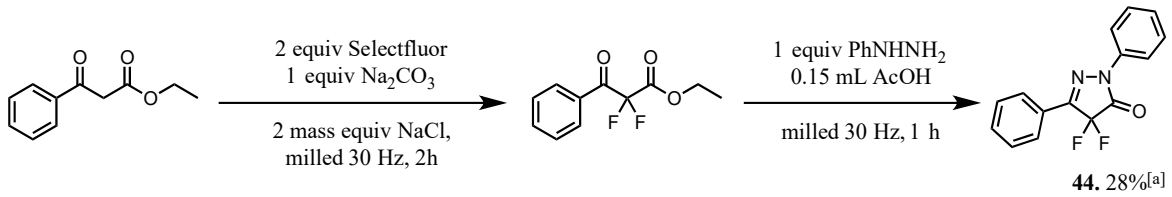
Entry	Additive	Yield **43**[a]	Yield **44**[b]
1	-	0%	95%
2	Na_2CO_3 (1 equiv)	0%	95%

Table 6 Optimization of electrophilic fluorination of a pyrazolone

[a] determined by ^{19}F NMR with trifluorotoluene as internal standard

After the separate investigations of conditions for the formation of the pyrazolone and the fluorination of the pyrazolone, it was decided to conduct the two-step one-jar preparation of difluorinated pyrazolone via first approach **(Scheme 28)**. Taking into account that the conditions for difluorination of *β*-ketoesters were optimised, the multistep mechanochemical

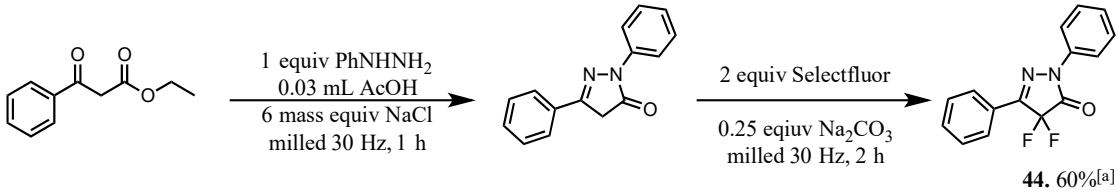
reaction was performed. Notably, the amount of the acid was increased from 0.03 mL (0.5 equivalents) to 0.15 mL (2.5 equivalents), because these extra 2 equivalents were needed to neutralise the base, namely sodium carbonate. As a result, difluorinated pyrazolone was produced in the yield of 28%.



44. 28%[a]

Scheme 28. Multistep mechanochemical synthesis of difluorinated pyrazolone. First method.

Finally, the synthesis of difluorinated pyrazolone was performed using an alternative way **(Scheme 29)**. Firstly, the optimised conditions for the synthesis of the pyrazolone were used, then without any purification, 2 equivalents of Selectfluor® and 0.25 equivalents of sodium carbonate were added to the jar and milled for 2 hours. This amount of sodium carbonate was used for neutralization of acetic acid. This process afforded 60% yield of difluorinated product.



44. 60%[a]

Scheme 29. Multistep mechanochemical synthesis of difluorinated pyrazolone. Second method.

[a] determined by ^{19}F NMR with trifluorotoluene as internal standard

Conclusion and Future Work

In conclusion, this project demonstrates the feasibility of mechanochemical C-F bond formation. In addition, despite the fact that there is no definite evidence of how LAG affects organic reactions and the influence of other factors, such as ratio between volume of starting materials, a ball and a jar, is not well understood, these reactions could become a basis for further investigations in mechanochemical organic synthesis. In addition, it has been shown that in comparison to solution-based reactions, mechanochemical fluorination achieved decreased reaction time, improved selectivity and/or increased yields. Certain reactions achieved 12-60 fold reduction of reaction time. Furthermore, the feasibility of mechanochemical synthesis of heterocycles, namely pyrazolones, has been demonstrated. as well as the multistep preparation of fluorinated pyrazolones in a single jar.

Finally, the project will be continued by the synthesis of fluorinated heterocycles using fluorinated activated methylene compounds as starting materials. Moreover, the investigation of conditions for multistep mechanochemical reactions via two possible routes will be continued. The amount & type of a grinding agent, the reaction time will be optimised. Additionally, further investigation towards understanding how LAG effects on mechanochemical reactions will be explored by performing solubility tests of starting materials and products, conducting solid state NMR experiments and studying crystal structures of reagents and products in LAG environment. This will help to understand the effect of LAG agents depending on their nature, amount added and possibly other properties. In the future, more reactions will be performed via mechanochemical technique, e.g. Negishi and Chan-Lam couplings. Increased yields, decreased reaction time can be achieved and other reactivities and mechanisms of reactions can be discovered.

Experimental procedures for the synthesis of triazenes

Note: only those compounds synthesized by me have been included in this experimental section

General methods

All reagents and solvents were commercially available and were used without further purification unless stated otherwise. Petroleum ether refers to the 40-60 °C fraction.

For the measurement of ^{1}H, ^{13}C and ^{19}F NMR spectra a Bruker Fourier 300 (300 MHz), 400 UltraShield™ (400 MHz) or Ascend™500 (500 MHz) was used. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal or to the standard trifluorotoluene (-63.72 ppm) in the case of ^{19}F NMR. Spin-spin coupling constants *J* are given in Hz. ^{13}C spectra are reported as obtained at default temperature (room temperature approximately 18 °C) and reported to the nearest 0.5 ppm.

The flow setup consisted of PFA (perfluoroalkoxy alkane) tubing of 0.8 mm I.D. and two dual syringe pumps or four HPLC piston pumps. The residence coils were made from the tubing by taking the appropriate length for the desired volume.

Column chromatography was performed using 60 Å (40-64 micron) silica and solvent mixtures of petroleum ether and ethyl acetate or dichloromethane.

High resolution mass spectroscopy (HRMS) data were obtained on a Waters MALDI-TOF mx at Cardiff University or on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University.

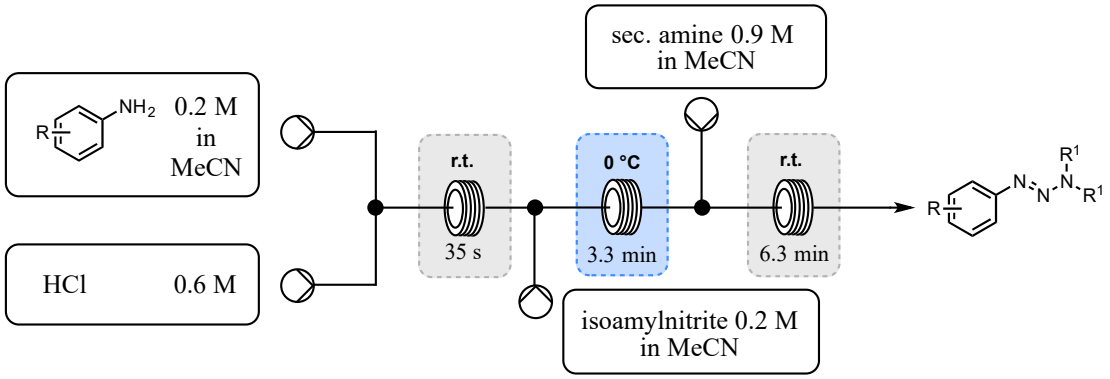
IR spectra were obtained from a Shimadzu IR-Affinity-1S FTIR and melting points using a Gallenkamp apparatus and are reported uncorrected.

References to spectroscopic data are given for known compounds.

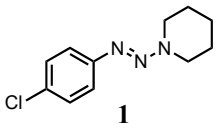
Synthesis of triazenes in flow (Aniline Scope)

General procedure 1 (GP1)

Solutions of the aniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile) and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system **(Scheme 30)** at a flow rate of 0.2 mLmin^{-1}. Once steady state was reached (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction solution was washed with aqueous $NaHCO_3$, extracted with EtOAc (3 x 20 mL), washed with brine and dried over $MgSO_4$. After removing the solvent under reduced pressure the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If the purity of the product did not exceed 90% the crude product was further purified by column chromatography. ***During the course of our studies, we noted that triazenes exhibit restricted rotation behaviour. Indeed, this has been previously documented albeit for a relatively small set of substrates.[81] Owing to this only ^{1}H and ^{13}C/mass spectra are reported as they appear at room temperature.***



Scheme 30. General setup for the preparation of triazenes using continuous flow conditions



1

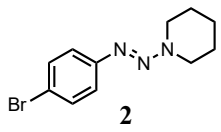
1-((4-chlorophenyl)diazenyl)piperidine[82]

Prepared according to **GP1**, 213 mg, 0.95 mmol, 95%, pale yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.9 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 3.77 – 3.63 (m, 4H), 1.71 – 1.54 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 131.0, 129.0, 122.0, 25.5, 24.5.[a]

[a] ^{13}C peaks corresponding to the CH_2 groups adjacent to the nitrogen were not observed in ^{13}C NMR spectra due to line broadening



2

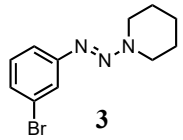
1-((4-bromophenyl)diazenyl)piperidine[84]

Prepared according to **GP1**, 257 mg, 0.96 mmol, 96%, orange solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 3.77 (d, *J* = 5.6 Hz, 4H), 1.70 (d, *J* = 1.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.5, 25.5, 24.5.[a]

[a] ^{13}C peaks corresponding to the CH_2 groups adjacent to the nitrogen were not observed in ^{13}C NMR spectra due to line broadening



3

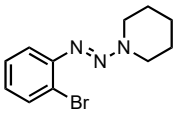
1-((3-bromophenyl)diazenyl)piperidine[82]

Prepared according to **GP1**, 201 mg, 0.75 mmol, 75%, pale orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 1.9 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 – 7.25 (m, 1H), 7.24 – 7.18 (m, 1H), 3.86 – 3.76 (m, 4H), 1.83 – 1.65 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 130.0, 128.0, 123.0, 123.0, 120.0, 25.5, 24.5.[a]

[a] ^{13}C peaks corresponding to the CH_2 groups adjacent to the nitrogen were not observed in ^{13}C NMR spectra due to line broadening



4

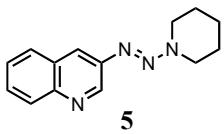
1-((2-bromophenyl)diazenyl)piperidine[82]

Prepared according to **GP1**, 233 mg, 0.87 mmol, 87%, pale orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 1.9 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.02 – 6.94 (m, 1H), 3.98 – 3.70 (m, 4H), 1.81 – 1.64 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 133.0, 128.0, 126.5, 120.0, 118.5, 25.0, 24.5.[a]

[a] ^{13}C peaks corresponding to the CH_2 groups adjacent to the nitrogen were not observed in ^{13}C NMR spectra due to line broadening



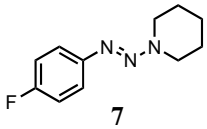
5

3-(piperidin-1-yldiazenyl)quinoline

Prepared according to **GP1**, 36 mg, 0.15 mmol, 15%, obtained as a mixture with another quinoline derivative.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 – 9.07 (m, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 1H), 7.51 – 7.45 (m, 1H), 3.94 – 3.78 (m, 4H), 1.80 – 1.66 (m, 6H).

HRMS (EI+): [$C_{14}H_{16}N_4$] calc. 240.1375, found 240.1373.



7

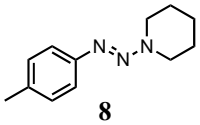
1-((4-fluorophenyl)diazenyl)piperidine[83]

Prepared according to **GP1**, 99 mg, 0.48 mmol, 48%, yellow oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.05 – 6.98 (m, 1H), 3.81 – 3.69 (m, 4H), 1.77 – 1.64 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0 (d, J = 244.4 Hz), 147.5 (d, J = 2.9 Hz), 122.0 (d, J = 8.1 Hz), 115.5 (d, J = 22.4 Hz), 48.5, 25.5, 24.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -119.01 (s).



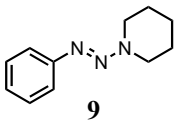
8

1-((4-methylphenyl)diazenyl)piperidine[82]

Prepared according to **GP1**, 145 mg, 0.71 mmol, 71%, orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 3.81 – 3.67 (m, 4H), 2.34 (s, 3H), 1.79 – 1.61 (m, 6H).

HRMS (EI+): [$C_{12}H_{17}N_3$] calc. 203.1422, found 203.1423.



9

1-(phenyldiazenyl)piperidine[82]

Prepared according to **GP1**, 130 mg, 0.69 mmol, 69%, orange oil

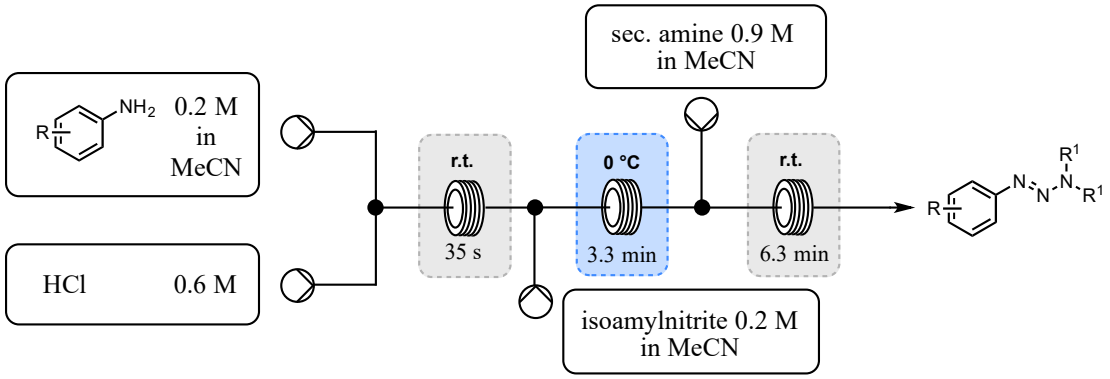
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.37 – 7.30 (m, 2H), 7.15 (t, J = 8.4 Hz, 1H), 3.84 – 3.71 (m, 4H), 1.77 – 1.64 (m, 6H).

HRMS (EI+): [$C_{11}H_{15}N_3$] calc. 189.1266, found 189.1263.

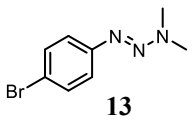
Synthesis of triazenes in flow (Secondary Amine Scope)

General procedure 2 (GP2)

Solutions of the *p*-bromoaniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile) and a secondary amine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system **(Scheme 30)** at a flow rate of 0.2 mLmin^{-1}. Once steady state was reached (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction mixture was washed with aqueous $NaHCO_3$, extracted with EtOAc (3 x 20 mL), washed with brine and dried over $MgSO_4$. After removing the solvent under reduced pressure the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If the purity of the product did not exceed 90% the crude product was further purified by column chromatography.



Scheme 30. General setup for the preparation of triazenes using continuous flow conditions



13

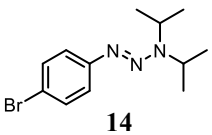
1-(4-bromophenyl)-3,3-dimethyltriaz-1-ene

Prepared according to **GP2** (but using dimethylamine in THF), 173 mg, 0.76 mmol, 76%, red oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H), 3.34 (bs, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.50.[b]

[b] ^{13}C peaks corresponding to the CH_3 groups adjacent to the nitrogen were not observed in ^{13}C NMR spectra due to line broadening



14

1-(4-bromophenyl)-3,3-diisopropyltriaz-1-ene[85]

Prepared according to **GP2**, 201 mg, 0.71 mmol, 71%, orange oil

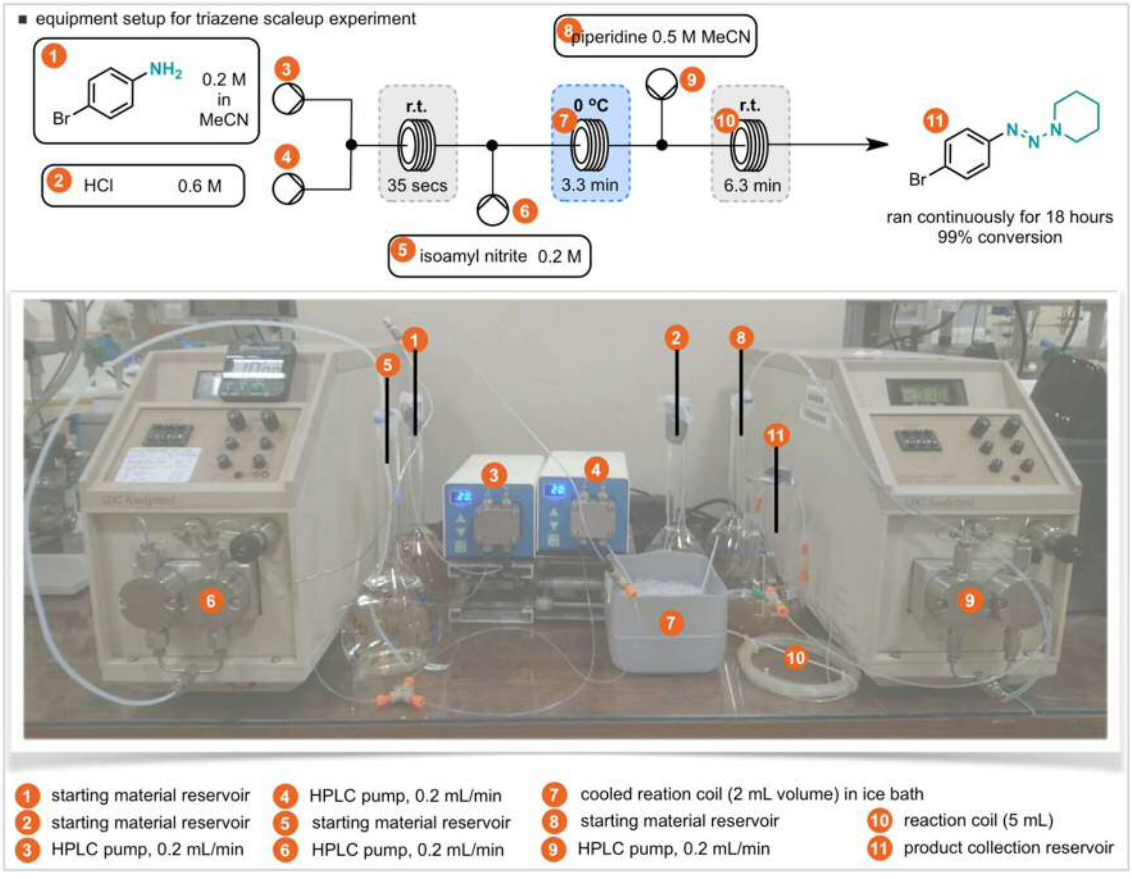
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 5.27 (bs, 1H), 3.99 (bs, 1H), 1.30 (bs, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 132.0, 122.0, 117.5, 49.0, 46.0, 24.0, 19.5.[c]

[c] ^{13}C peaks corresponding to the CH and CH_3 from secondary amine moiety were observed as 4 separate peaks (instead of 2) in ^{13}C NMR spectra due to the restricted rotation around the triazene bridge steric substituents on the nitrogen, therefore these carbon atoms become chemically inequivalent

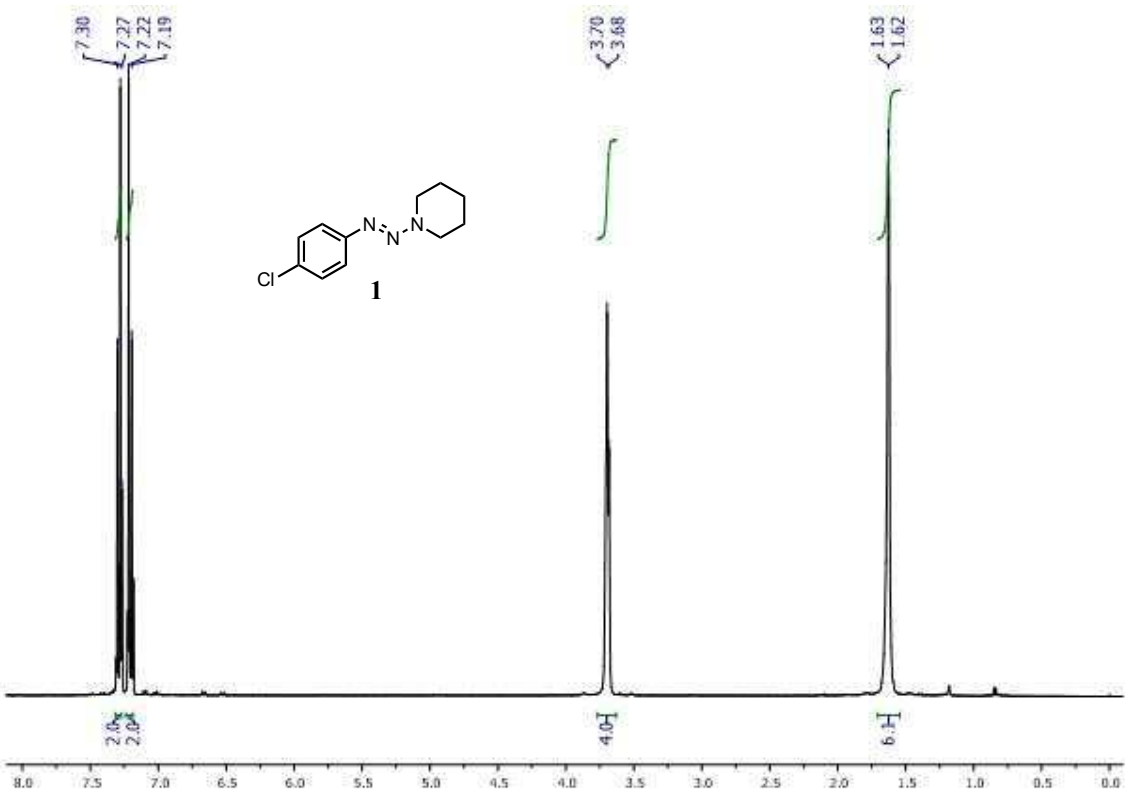
Large scale experiment

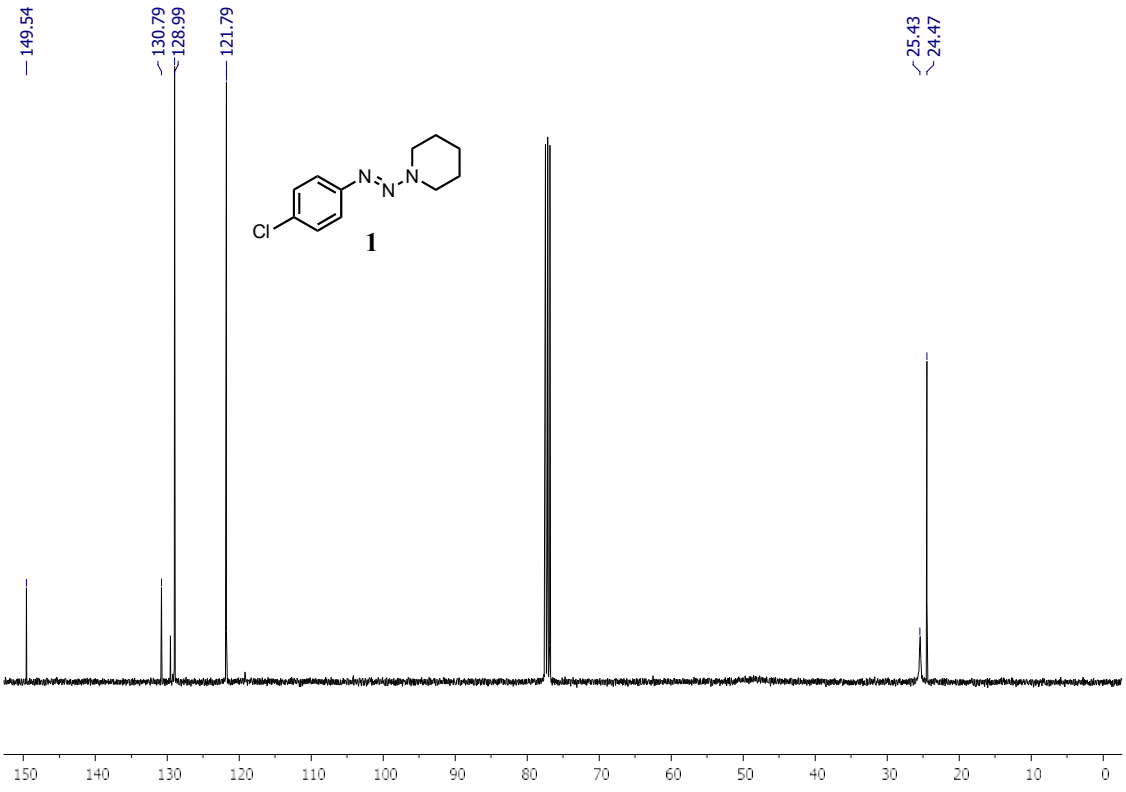
Solutions of *p*-bromoaniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile) and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system **(Scheme 31)** at a flow rate of 0.2 $mLmin^{-1}$. After reaching steady state (20 min) the reaction was run for 18 h. The first 50 mL (2.5 mmol, 62.5 min) were collected. The reaction solution was neutralised with aqueous $NaHCO_3$, extracted with EtOAc (3 x 50 mL), washed with brine and dried over $MgSO_4$. After removing the solvent under reduced pressure the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica to yield the clean compound **2** (92%, 0.587 g, 2.3 mmol).

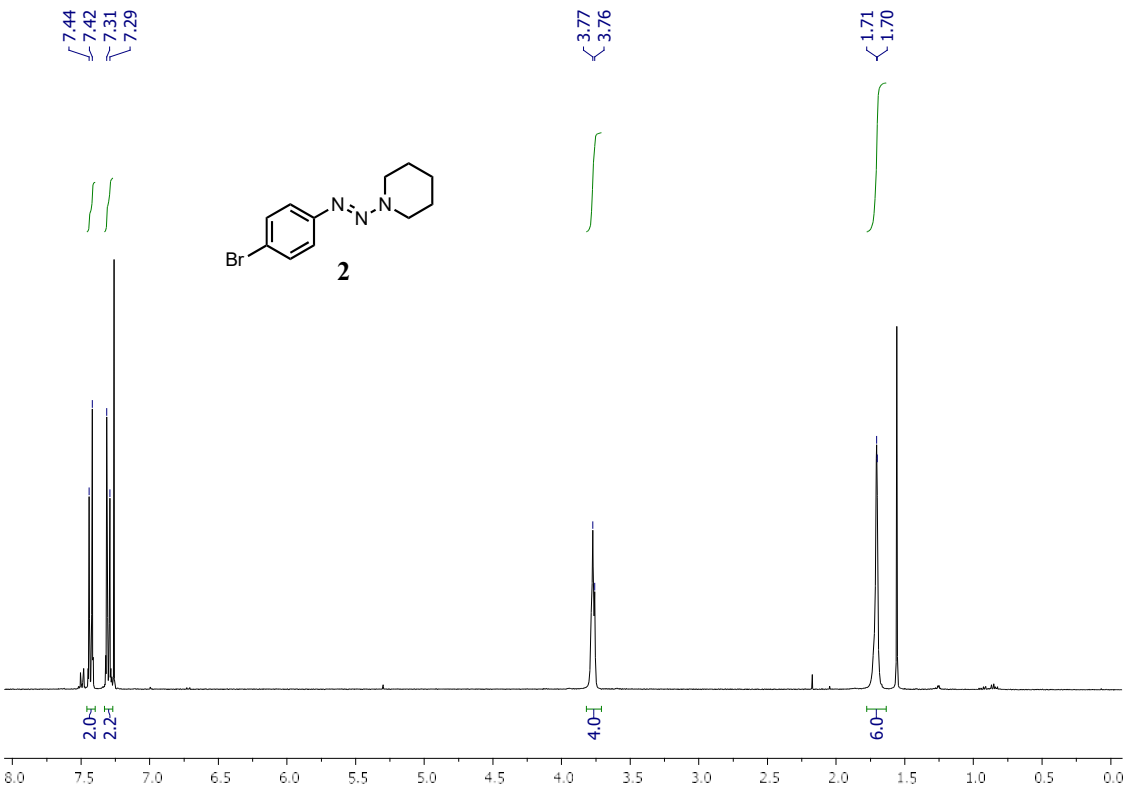


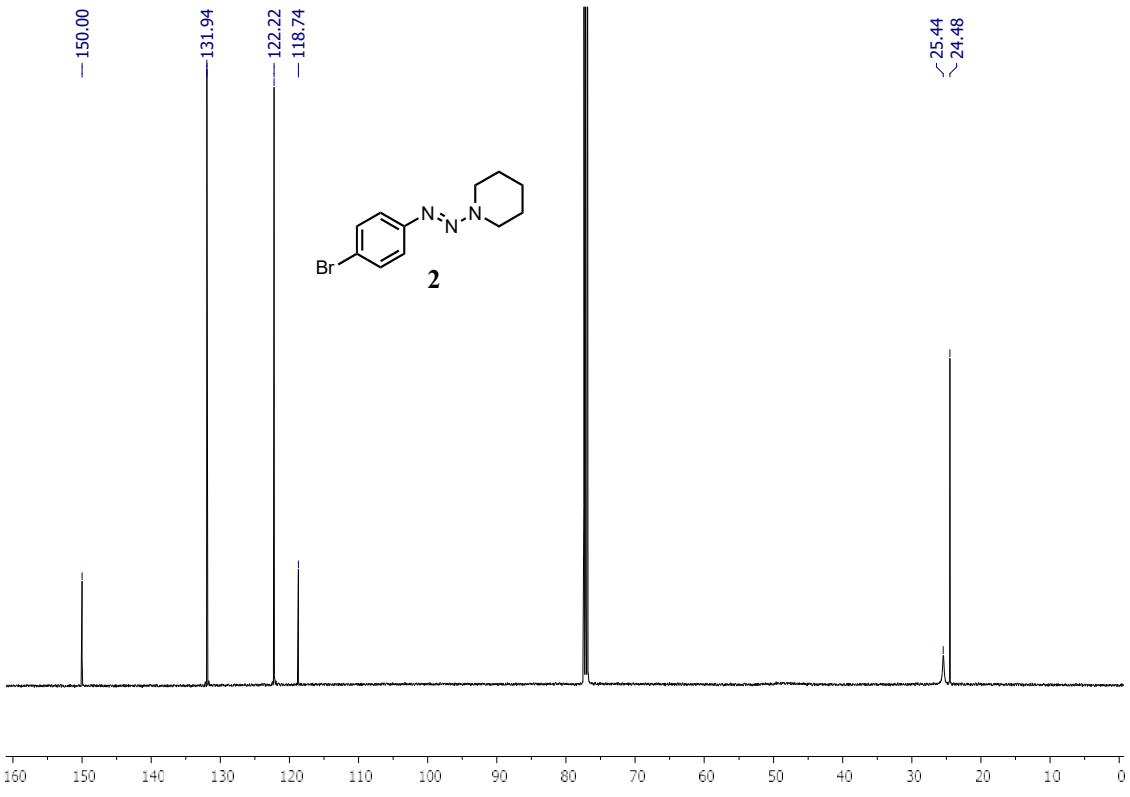
Scheme 31. Continuous-flow synthesis of a triazene using HPLC pumps

Spectroscopic Data






7.44
7.42
7.31
7.29
3.77
3.76
1.71
1.70
Br
2
2.0
2.2
4.0
6.0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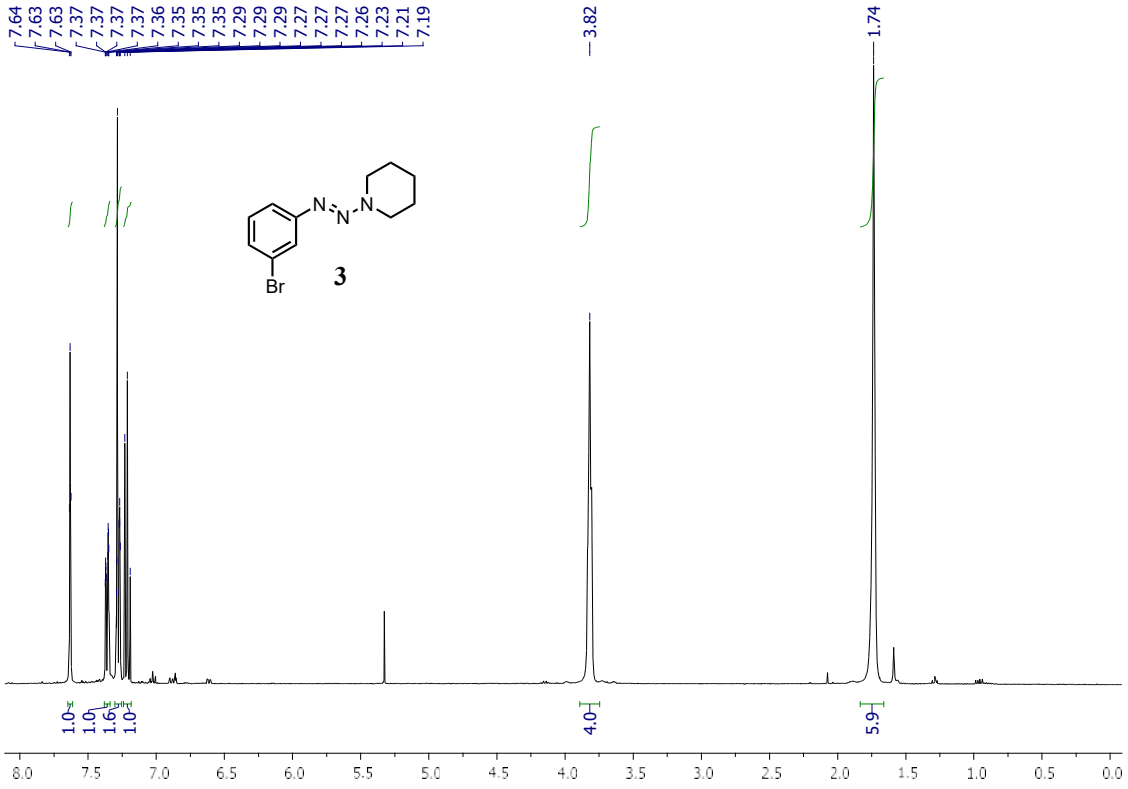
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7.29
7.27
7.27
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7.23
7.21
7.19
3.82
1.74
Br
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1.0
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6.0
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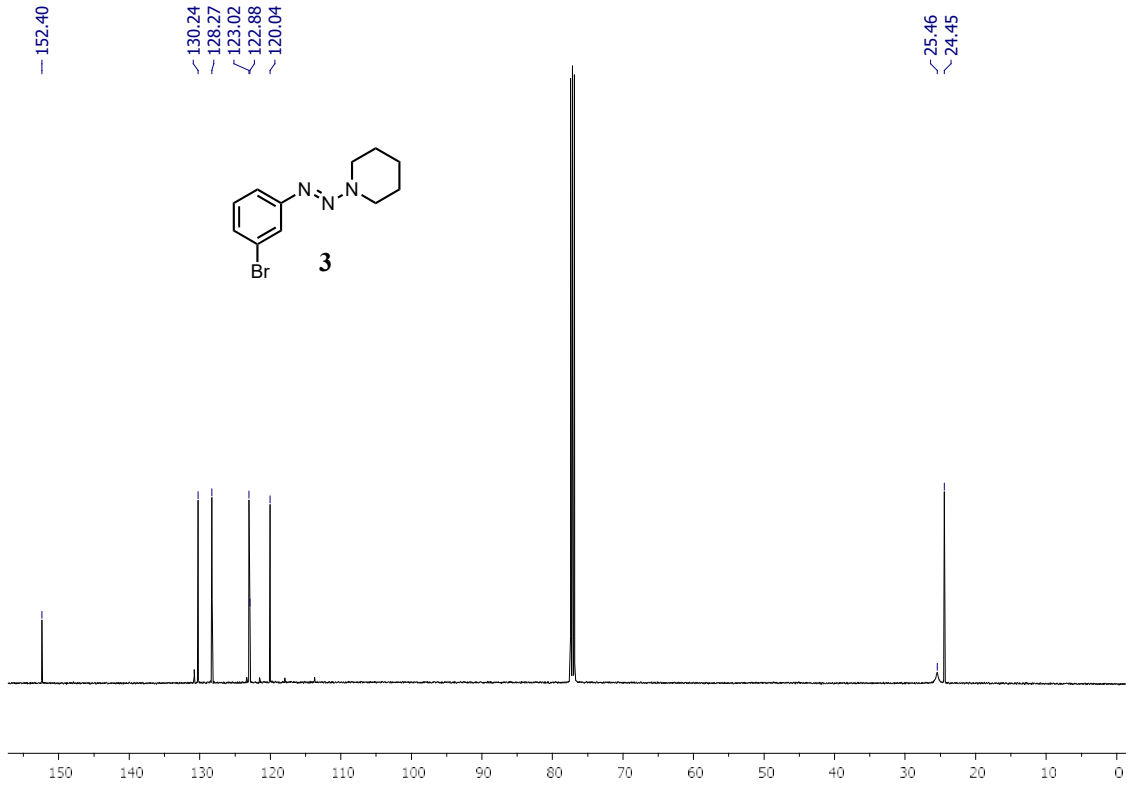
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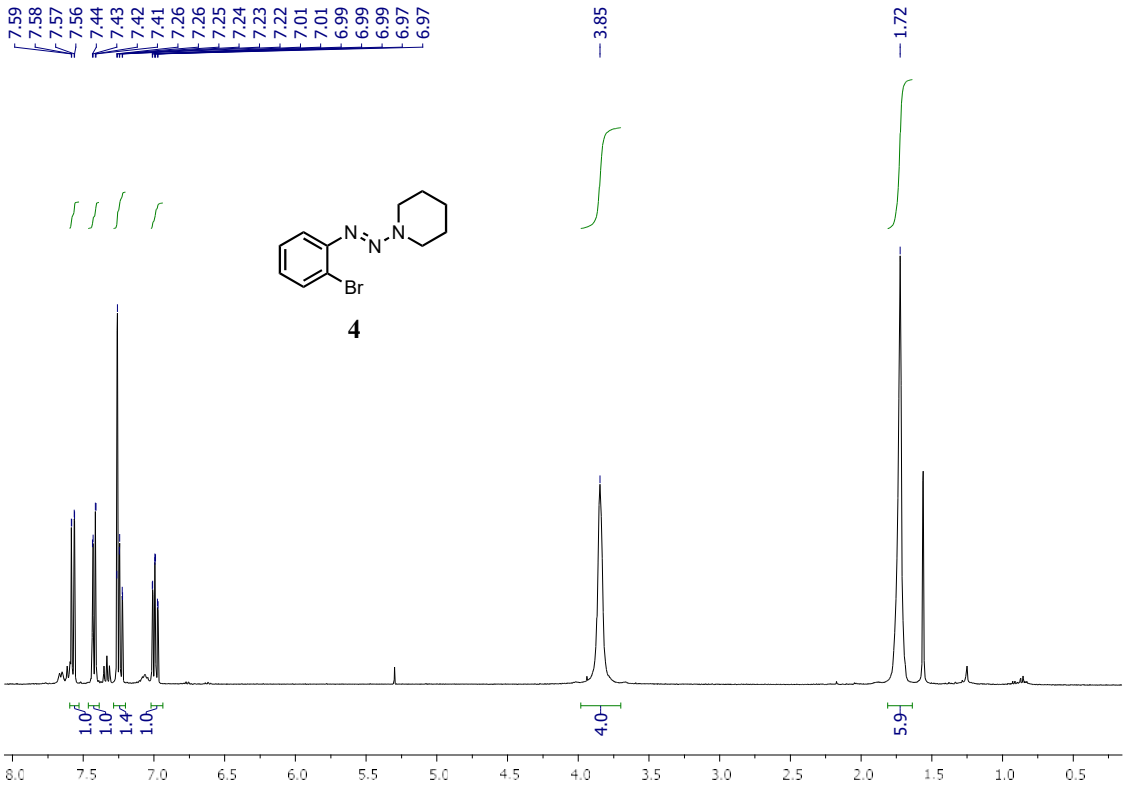
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7.22
7.01
7.01
6.99
6.99
6.99
6.97
6.97
3.85
1.72
1.0
1.0
1.4
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4.0
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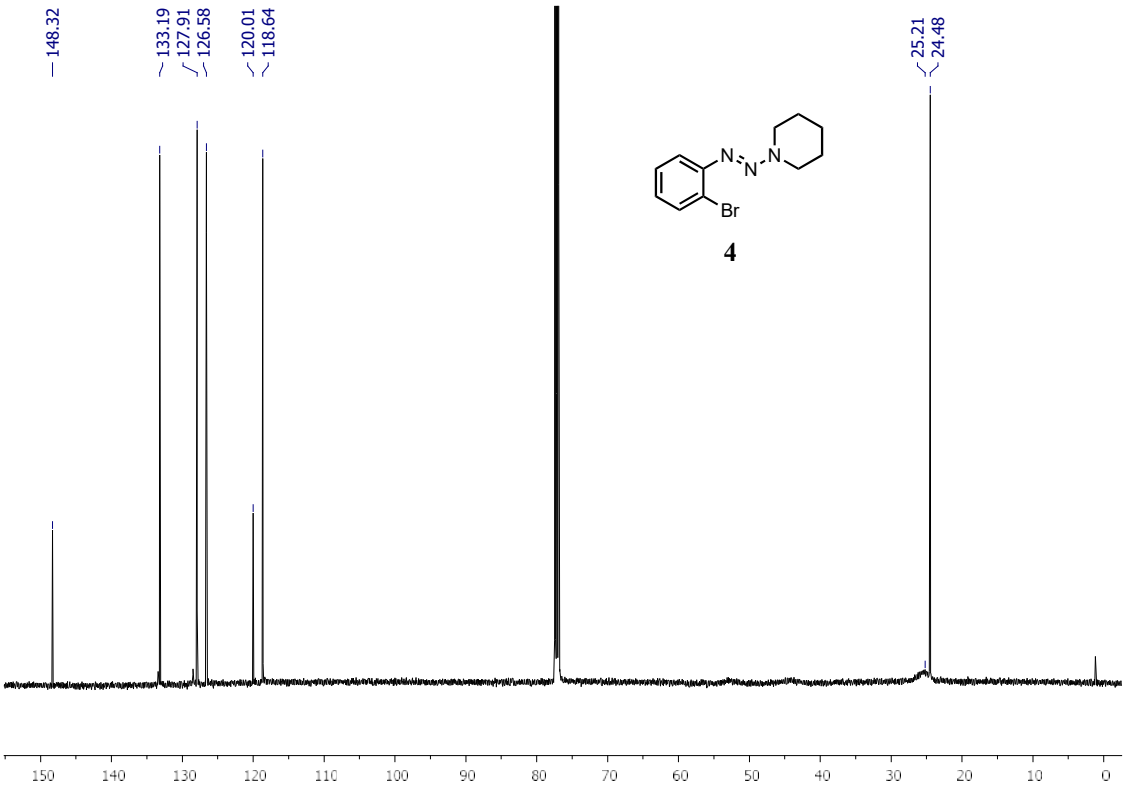
4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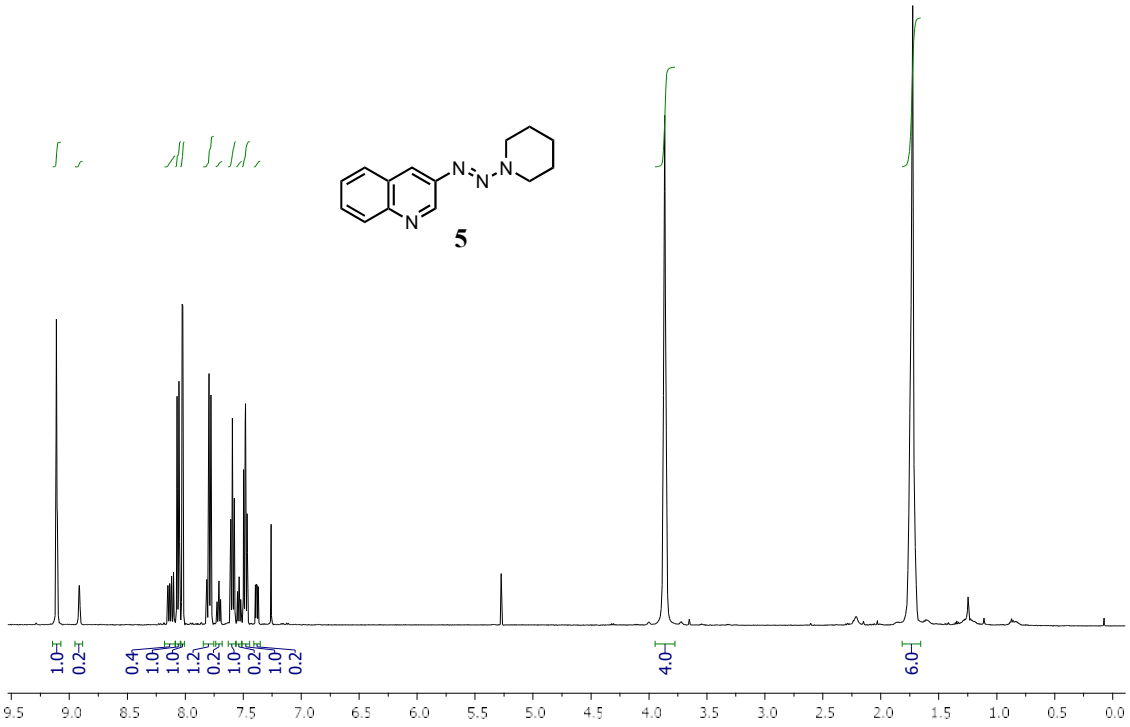
4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4.0
6.0


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7.40
7.40
7.39
7.38
7.03
7.02
7.00
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3.75
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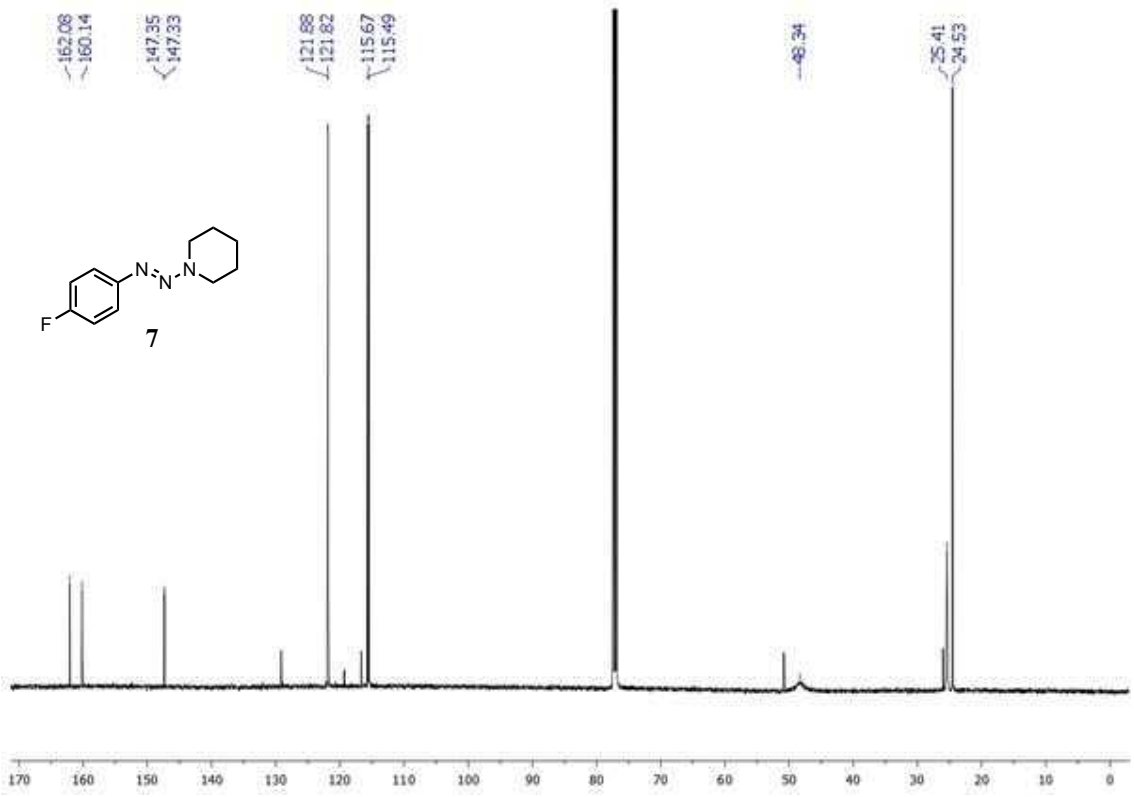
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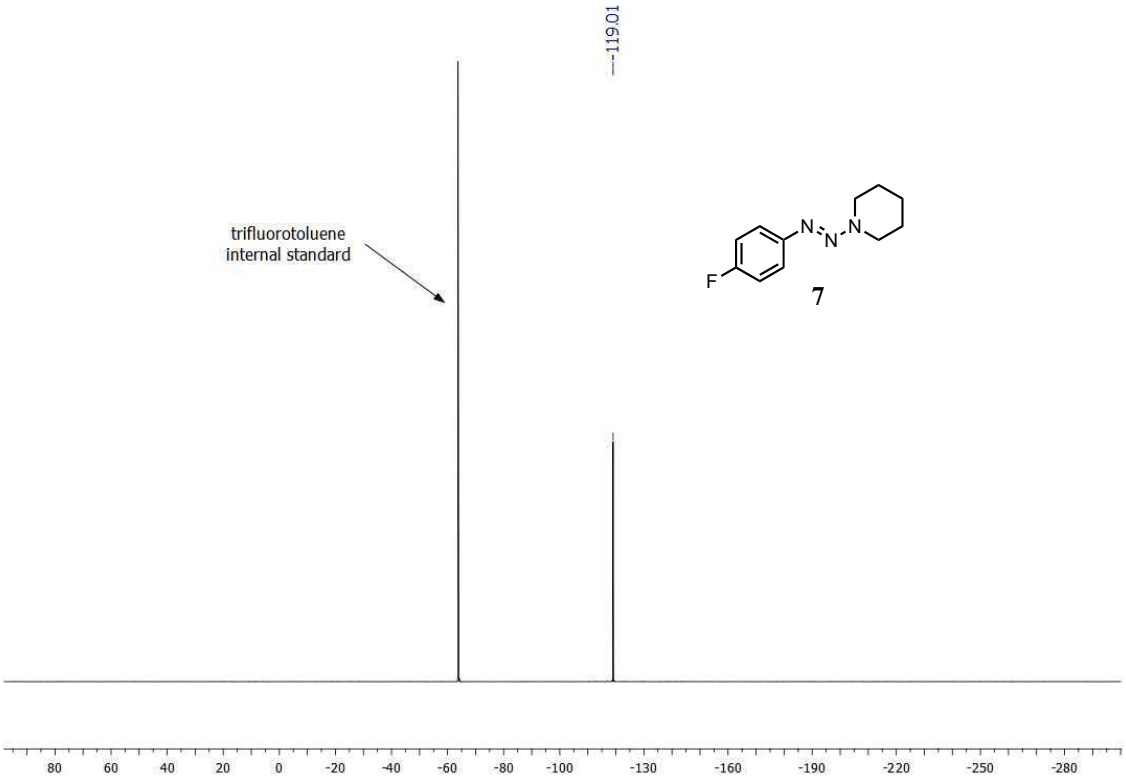
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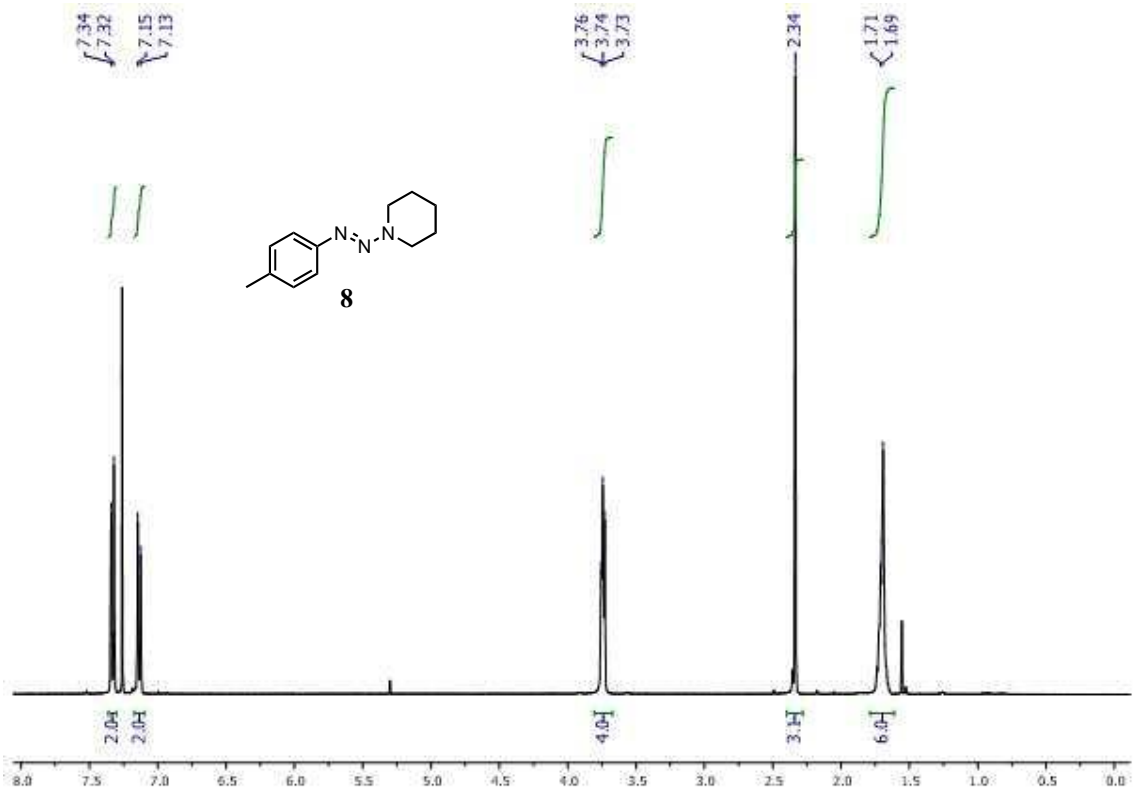
trifluorotoluene
internal standard
7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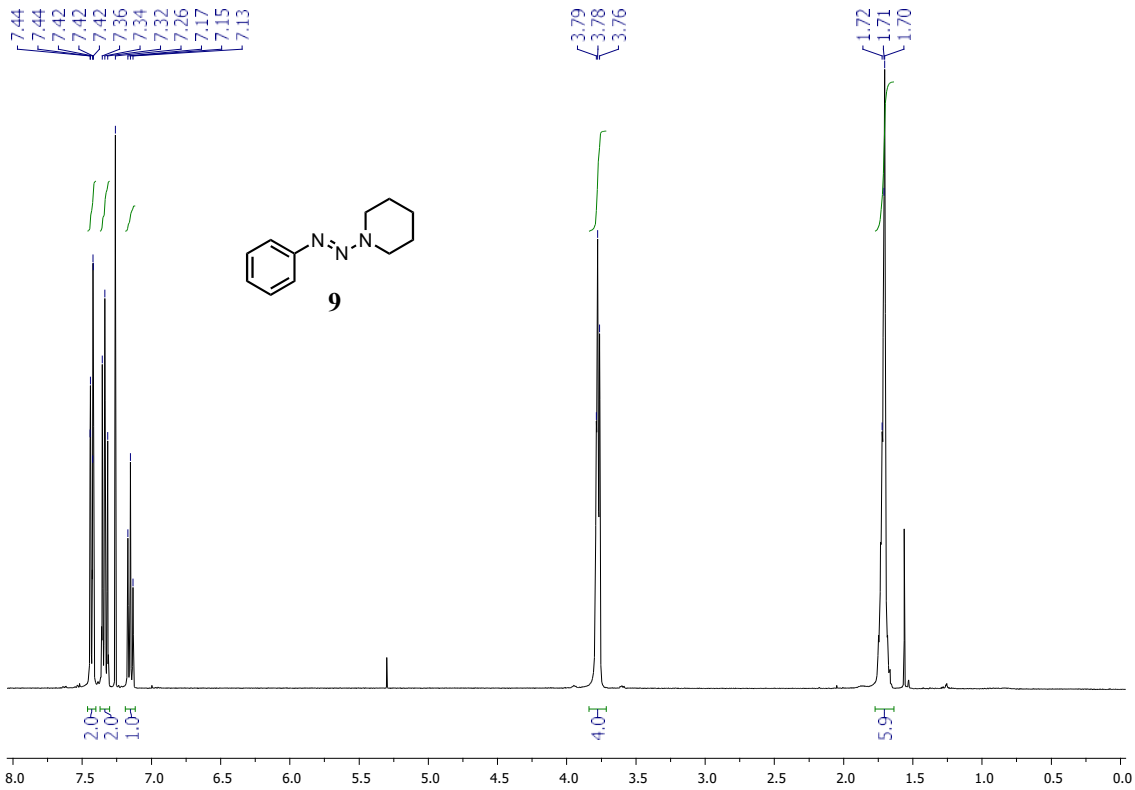
3.1H
6.0H

8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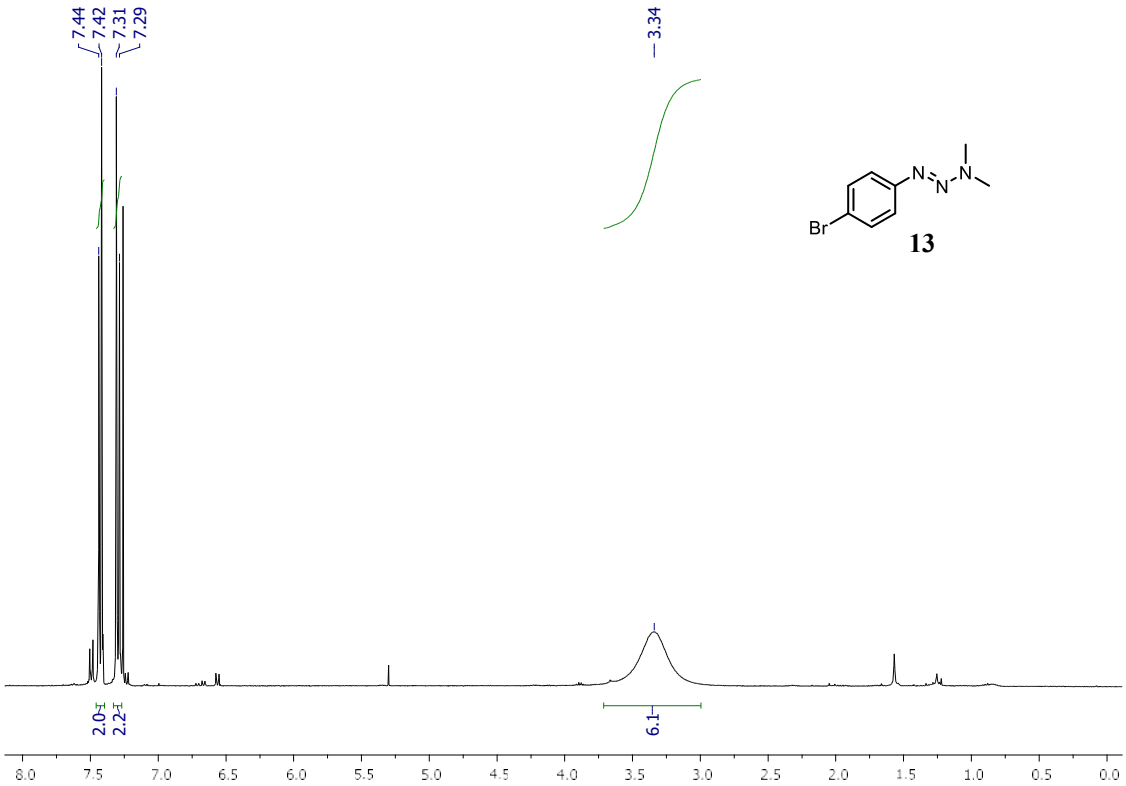
1.0H
4.0H
5.9H

9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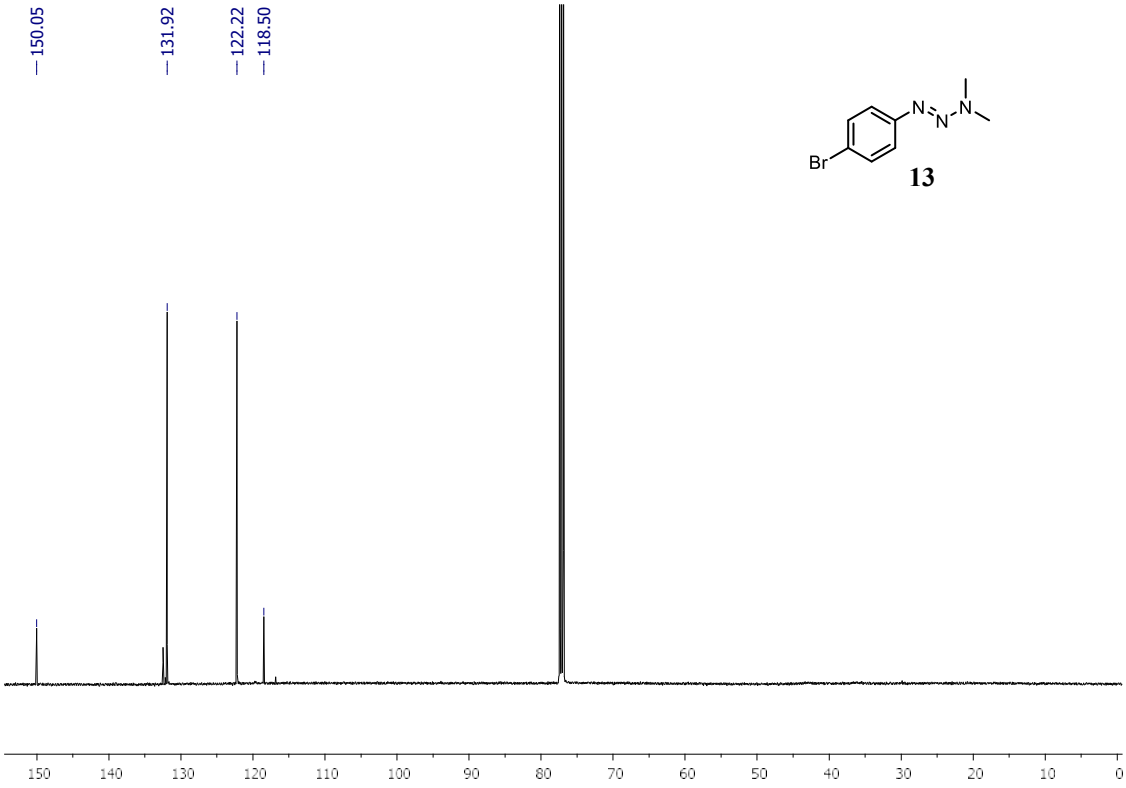
0.0

N
N
N
Br

13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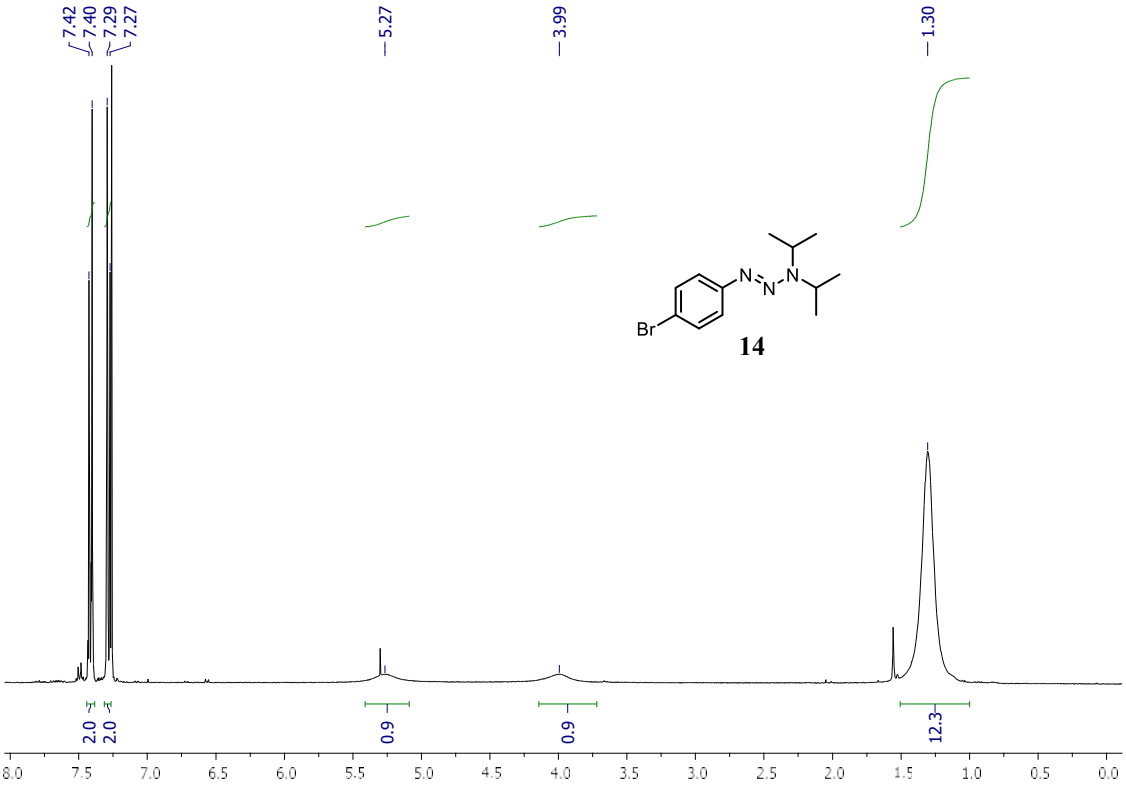
N
Br

13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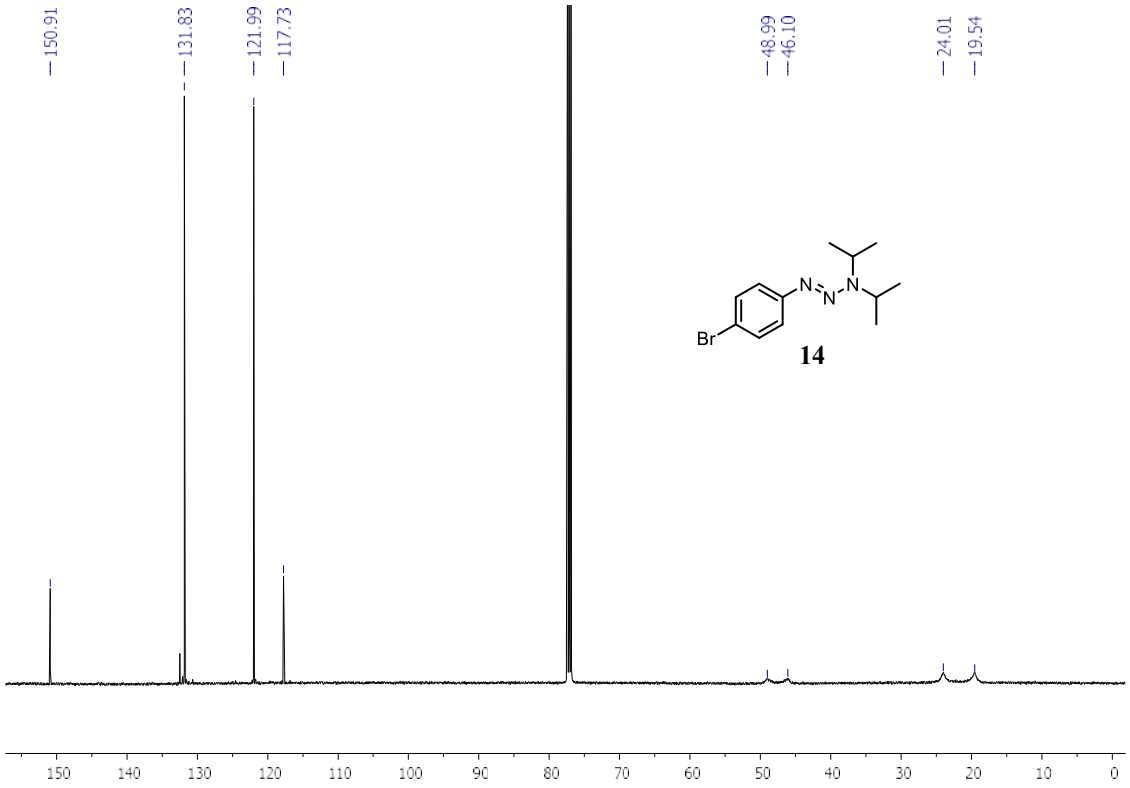
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50
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10
0

Experimental procedures for the synthesis of fluorinated activated methylene compounds and a fluorinated pyrazolone

Note: only those compounds synthesized by me have been included in this experimental section

General methods

All chemicals were obtained from commercial sources and used without further purification unless stated otherwise.

^{1}H, ^{19}F and ^{13}C NMR spectra were obtained on Bruker 300 Ultrashield™, Bruker 400 MHz and Bruker 500 MHz spectrometers with chloroform-d as deuterated solvent. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal (7.26 and 77.16 ppm for ^{1}H and ^{13}C respectively). Spin-spin coupling constants *J* are given in Hz and refer to apparent multiplicities rather than true coupling constants. Data are reported as: chemical shift, multiplicity and integration.

High resolution mass spectral (HRMS) data were obtained on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University or on a Waters MALDI-TOF mx in Cardiff University. Spectra were obtained using electron impact ionization (EI), chemical ionization (CI), positive electrospray (ES), pneumatically-assisted electrospray (pNSI) or atmospheric solids analysis probe (ASAP+).

Infrared spectra were recorded on a Shimadzu IR-Affinity-1S FTIR spectrometer.

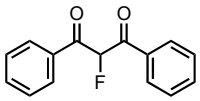
Melting points were measured using a Gallenkamp apparatus and are reported uncorrected.

The ball mill used was a Retsch MM 400 mixer mill. Unless otherwise stated, mechanochemical reactions were performed in 10 mL stainless steel jars with one stainless steel ball of mass 4 g. The longest time that this mill can be programmed to run is 99 minutes. In order to run longer reaction times the mill was started, then additional time added to the timer in order to ensure that the mill was running continuously for the desired reaction time.

Mechanochemical monofluorination of 1,3-diketones

General procedure 3 (GP3)

To a 10 mL stainless steel milling jar was added the 1,3-diketone (1 mmol), Selectfluor® (708 mg, 2 mmol) and acetonitrile (0.125 mL). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as an NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



16

2-fluoro-1,3-diphenylpropane-1,3-dione[6]

Prepared according to **GP3**, 236 mg, 0.98 mmol, 98%, 50:1 mono:di, yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 4H), 7.65 – 7.59 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 4H), 6.54 (d, *J* = 49.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.3 (d, *J* = 20.2 Hz), 134.7, 133.7 (d, *J* = 2.0 Hz), 130.0 (d, *J* = 3.5 Hz), 128.9, 96.7 (d, *J* = 199.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -186.88 (d, *J* = 48.9 Hz).

IR: 1697, 1672, 1593, 1448, 1282, 1097, 1022, 1001, 966, 867, 779, 705, 680, 553, 457 cm^{-1}

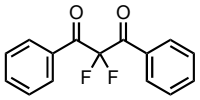
HRMS (EI+): [$C_{15}H_{11}O_2F + NH_4$] calc. 260.1081, found 260.1083

mp 74-76 °C (chloroform)

Mechanochemical difluorination of 1,3-diketones

General Procedure 4 (GP4)

To a 10 mL stainless steel milling jar was added the 1,3-diketone (1 mmol), Selectfluor® (708 mg, 2 mmol) and sodium carbonate (106 mg, 1 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



17

2,2-difluoro-1,3-diphenylpropane-1,3-dione[8]

Prepared according to **GP4**, 242 mg, 0.93 mmol, 93%, 17:1 di:mono, brown crystals

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 4H), 7.66 (t, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 187.5 (t, *J* = 26.8 Hz), 135.2 (t, *J* = 62.7 Hz), 131.8, 130.4 (t, *J* = 2.6 Hz), 129.1, 112.8 (t, *J* = 265.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.66 (s).

IR: 1697, 1672, 1595, 1448, 1284, 1097, 968, 939, 867, 707, 680, 553, 457 cm^{-1}

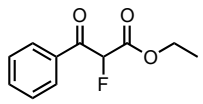
HRMS (EI+): [M+NH_4^+] [$C_{15}H_{14}O_2F_2$] calc. 278.0987, found 278.0988

mp 58-60 °C (chloroform)

Mechanochemical monofluorination of *β*-ketoesters

General Procedure 5 (GP5)

To a 10 mL stainless steel milling jar was added *β*-ketoester (1 mmol), Selectfluor® (708 mg, 2 mmol), sodium chloride (twice the total mass of substrate and Selectfluor®) and acetonitrile (0.25 mL). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



26

ethyl 2-fluoro-3-oxo-3-phenylpropanoate[6]

Prepared according to **GP5**, 201 mg, 0.96 mmol, 96%, 12.5:1 mono:di, dark red liquid

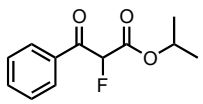
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 5.86 (d, *J* = 48.9 Hz, 1H), 4.30 (q, *J* = 6.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7 (d, *J* = 20.2 Hz), 165.1 (d, *J* = 24.2 Hz), 134.7, 133.5, 129.7 (d, *J* = 3.4 Hz), 129.0, 90.2 (d, *J* = 197.7 Hz), 62.7, 14.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.29 (d, *J* = 48.8 Hz).

IR: 2983, 1759, 1693, 1597, 1448, 1371, 1242, 1095, 686 cm^{-1}

HRMS (ASAP+) [$C_{11}H_{11}O_3F$ + H] calc. 211.0770, found 211.0773



28

isopropyl 2-fluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP5**, 182 mg, 0.81 mmol, 81%, 15:1 mono:di, light brown liquid

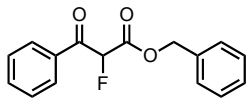
^{1}H NMR (400 MHz,) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 5.83 (d, *J* = 48.9 Hz, 1H), 5.20 – 5.10 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (d, *J* = 20.1 Hz), 164.6 (d, *J* = 24.1 Hz), 134.6, 129.6 (d, *J* = 3.3 Hz), 128.9, 128.6 (d, *J* = 26.3 Hz), 90.3 (d, *J* = 197.4 Hz), 71.1, 21.7, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.28 (d, *J* = 48.9 Hz).

IR: 2984, 1755, 1692, 1597, 1449, 1098, 689 cm^{-1}

HRMS (ASAP+) [$C_{12}H_{13}O_3F$ + H] calc. 225.0927, found 225.0922



32

benzyl 2-fluoro-3-oxo-3-phenylpropanoate[5]

Prepared according to **GP5**, 239 mg, 0.88 mmol, 88%, 7:1 mono:di, dark yellow liquid

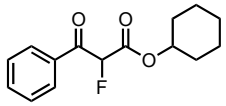
^{1}H NMR (400 MHz, $CDCLl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 3H), 7.31 (s, 4H), 5.92 (d, *J* = 48.7 Hz, 1H), 5.31 – 5.21 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5 (d, *J* = 20.2 Hz), 164.9 (d, *J* = 24.3 Hz), 134.7, 134.5, 129.7 (d, *J* = 3.4 Hz), 129.1 (d, *J* = 4.9 Hz), 129.0, 128.8, 128.8, 128.5, 90.1 (d, *J* = 198.1 Hz), 68.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.39 (d, *J* = 48.6 Hz).

IR: 1761, 1688, 1597, 1449, 1101, 955, 743, 687, 586 cm^{-1}

HRMS (EI+): [$C_{16}H_{13}O_3F$] calc. 272.0849, found 272.0850



34

cyclohexyl 2-fluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP5**, 199 mg, 0.75 mmol, 75%, 17:1 mono:di, yellow liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 5.85 (d, *J* = 48.9 Hz, 1H), 4.96 – 4.90 (m, 1H), 1.91 – 1.15 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (d, *J* = 20.0 Hz), 164.5 (d, *J* = 24.2 Hz), 134.6, 133.6 (d, *J* = 1.9 Hz), 129.6 (d, *J* = 3.3 Hz), 128.9, 90.2 (d, *J* = 197.1 Hz), 75.6, 31.3, 31.1, 25.2, 23.4, 23.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.44 (d, *J* = 49.0 Hz).

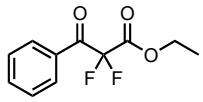
IR: 2936, 2860, 1755, 1690, 1597, 1449, 1236, 1007, 689 cm^{-1}

HRMS (EI+): [$C_{15}H_{17}O_3F$] calc. 264.1162, found 264.1161

Mechanochemical difluorination of *β*-ketoesters

General Procedure 6 (GP6)

To a 10 mL stainless steel milling jar was added *β*-ketoester (1 mmol), Selectfluor® (708 mg, 2 mmol), sodium carbonate (106 mg, 1 mmol) and sodium chloride (twice the total mass of substrate and Selectfluor®). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



27

ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP6**, 227 mg, 1 mmol, 100%, 7:1 di:mono, yellow-green liquid

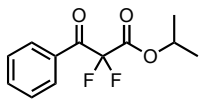
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6 (t, *J* = 30.3 Hz), 162.0 (t, *J* = 30.6 Hz), 135.2, 131.2, 130.1 (t, *J* = 2.7 Hz), 129.1, 109.9 (t, *J* = 264.6 Hz), 63.9, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.61 (s).

IR: 1770, 1697, 1597, 1450, 1371, 1307, 1255, 1155, 1097, 1001, 921, 684, 582 cm^{-1}

HRMS (ASAP+) [$C_{11}H_{10}O_3F_2$ + H] calc. 229.0676, found 229.0680



29

isopropyl 2,2-difluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP6**, 187 mg, 0.77 mmol, 77%, >50:1 di:mono, light yellow liquid

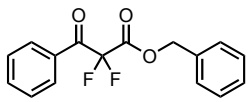
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 5.29 – 5.14 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7 (t, *J* = 27.5 Hz), 161.5 (t, *J* = 30.3 Hz), 135.2, 131.3 (t, *J* = 1.9 Hz), 130.0 (t, *J* = 2.7 Hz), 129.1, 109.7 (t, *J* = 264.5 Hz), 72.5, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.93 (s).

IR: 2988, 1769, 1599, 1450, 1307, 1260, 1159, 1092, 922, 831, 685, 584 cm^{-1}

HRMS (EI+): [$C_{12}H_{12}O_3F_2$] calc. 242.0755, found 242.0753



33

benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP6**, 218 mg, 0.75 mmol, 75%, >50:1 di:mono, light yellow liquid

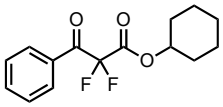
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.9 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.28 (m, *J* = 5.7 Hz, 5H), 5.34 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (t, *J* = 27.4 Hz), 161.8 (t, *J* = 30.7 Hz), 135.2, 133.9, 131.1 (t, *J* = 1.9 Hz), 130.0 (t, *J* = 2.7 Hz), 129.1, 129.1, 128.8, 128.6, 109.9 (t, *J* = 265.1 Hz), 69.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.40 (s).

IR: 1773, 1697, 1597, 1450, 1304, 1263, 1155, 1099, 920, 793, 745, 685 cm^{-1}

HRMS (EI+): [$C_{16}H_{12}O_3F_2$] calc. 290.0755, found 290.0752



35

cyclohexyl 2,2-difluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP6**, 234 mg, 0.83 mmol, 83%, 16:1 di:mono, light yellow liquid

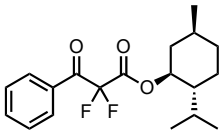
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 5.04 – 4.95 (m, 1H), 1.90 – 1.18 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6 (t, *J* = 27.4 Hz), 161.4 (t, *J* = 30.4 Hz), 135.1, 131.3 (t, *J* = 1.7 Hz), 130.0 (t, *J* = 2.7 Hz), 129.1, 109.7 (t, *J* = 264.2 Hz), 77.0, 31.0, 25.2, 23.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.90 (s).

IR: 2940, 2862, 1769, 1697, 1597, 1450, 1306, 1258, 1161, 1101, 1003, 930, 826, 685, 407 cm^{-1}

HRMS (EI+): [$C_{15}H_{16}O_3F_2$] calc. 282.1068, found 282.1067



37

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2,2-difluoro-3-oxo-3-phenylpropanoate

Prepared according to **GP6**, 263 mg, 0.78 mmol, 78%, 2.25:1 di:mono, orange liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.90 (m, 2H), 7.72 – 7.55 (m, 1H), 7.55 – 7.37 (m, 2H), 4.91 – 4.65 (m, 1H), 2.10 – 0.38 (m, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3 (t, *J* = 27.3 Hz), 161.5 (t, *J* = 30.0 Hz), 135.0, 129.8 (t, *J* = 2.6 Hz), 129.5 (dd, *J* = 8.9, 3.3 Hz), 129.0, 90.3 (dd, *J* = 197.4, 21.9 Hz), 78.7, 46.6, 40.0, 33.9, 31.4, 25.9, 23.1, 21.9, 20.6, 15.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.37 (d, *J* = 284.5 Hz), -108.58 (d, *J* = 284.5 Hz).

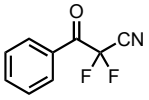
IR: 2957, 1765, 1695, 1599, 1450, 1369, 1308, 908, 687 cm^{-1}

HRMS (EI+): [$C_{19}H_{24}O_3F_2$] calc. 338.1694, found 338.1696

Mechanochemical difluorination of a *β*-ketonitrile

General Procedure 7 (GP7)

To a 10 mL stainless steel milling jar was added a *β*-ketonitrile (1 mmol) and Selectfluor® (708 mg, 2 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



39

2,2-difluoro-3-oxo-3-phenylpropanenitrile

Prepared according to **GP7**, 118 mg, 0.65 mmol, 65%, 50:1 di:mono, yellow liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.0 (t, *J* = 27.6 Hz), 136.3 (s), 130.4 (t, *J* = 2.5 Hz), 129.5 (s), 129.2 (t, *J* = 2.6 Hz), 110.3 (t, *J* = 42.4 Hz), 106.1 (t, *J* = 260.7 Hz).

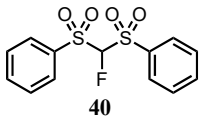
^{19}F NMR (376 MHz, $CDCl_3$) δ -92.02 (s).

IR: 2345, 2261,1701, 1597, 1450, 1292, 1175, 1094, 887, 716 cm^{-1}

Mechanochemical monofluorination of a bissulfone

General Procedure 8 (GP8)

To a 10 mL stainless steel milling jar was added a bissulfone (1 mmol), Selectfluor® (708 mg, 2 mmol) and sodium carbonate (106 mg, 1 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



40

α-fluorobis(phenylsulfonyl)methane

Prepared according to **GP8**, 267 mg, 0.85 mmol, 85%, 9.5:1 mono:di, white solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.93 (m, 4H), 7.86 – 7.74 (m, 2H), 7.69 – 7.58 (m, 4H), 5.71 (d, *J* = 45.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9 (s), 135.5 (s), 130.3 (s), 129.6 (s), 105.9 (d, *J* = 266.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -168.21 (d, *J* = 45.8 Hz).

IR: 2365, 1582, 1449, 1356, 1167, 1096, 1076, 791, 681, 550, 517 cm^{-1}

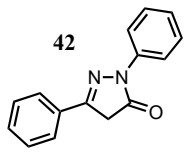
HRMS (ES+): [$C_{13}H_{11}O_4F$ + H] calc. 315.0161, found 315.0172

mp 104-106 °C (chloroform)

Mechanochemical preparation of a pyrazolone

General Procedure 9 (GP9)

To a 10 mL stainless steel milling jar was added ethyl benzoylacetate (192 mg, 1 mmol), phenylhydrazine (108 mg, 1 mmol), glacial acetic acid (0.03 mL, 0.5 mmol) and sodium chloride (six the total mass of substrate and Selectfluor®). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 1 hour. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to yield the product. Mesitylene (0.068 mL, 0.5 mmol) was added as a NMR standard (δ = 6.78 (s, 3H), 2.26 (s, 9H)), then the mixture was dissolved in $CDCl_3$. ^1H NMR taken of the mixture to determine the product conversion. Consequently, crude product was purified by column chromatography.



2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one

Prepared according to **GP9**, 229 mg, 0.97 mmol, 97%, yellow solid

^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.82 – 7.76 (m, 2H), 7.52 – 7.39 (m, 5H), 7.23 (t, *J* = 7.4 Hz, 1H), 3.87 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.38 (s), 154.79 (s), 138.27 (s), 131.02 (s), 130.88 (s), 129.09 (s), 129.03 (s), 126.14 (s), 125.48 (s), 119.25 (s), 39.82 (s).

IR: 2957, 2365, 1655, 1582, 1491, 1396, 1358, 1119, 1076, 895, 752, 683 cm^{-1}

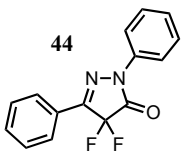
HRMS (AP+): [$C_{15}H_{12}N_2O$ + H] calc. 237.1028, found 237.1024

mp 135-137 °C (chloroform)

Mechanochemical difluorination of a pyrazolone

General Procedure 10 (GP10)

To a 10 mL stainless steel milling jar was added a pyrazolone (1 mmol) and Selectfluor® (708 mg, 2 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63.72 ppm) and ^{19}F NMR taken of the crude mixture to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR was measured again to confirm that the ratio of products had not changed after evaporation of the solvent.



4,4-Difluoro-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one

Prepared according to **GP10**, 258 mg, 0.95 mmol, 95%, 50:1 di:mono, yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 4H), 7.64 – 7.44 (m, 5H), 7.30 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 (t, *J* = 29.7 Hz), 149.9 (t, *J* = 21.2 Hz), 136.9 (s), 132.4 (s), 129.4 (s), 129.3 (s), 126.9 (s), 126.6 (s), 126.5 (s), 118.9 (s), 109.2 (t, *J* = 258.4 Hz).

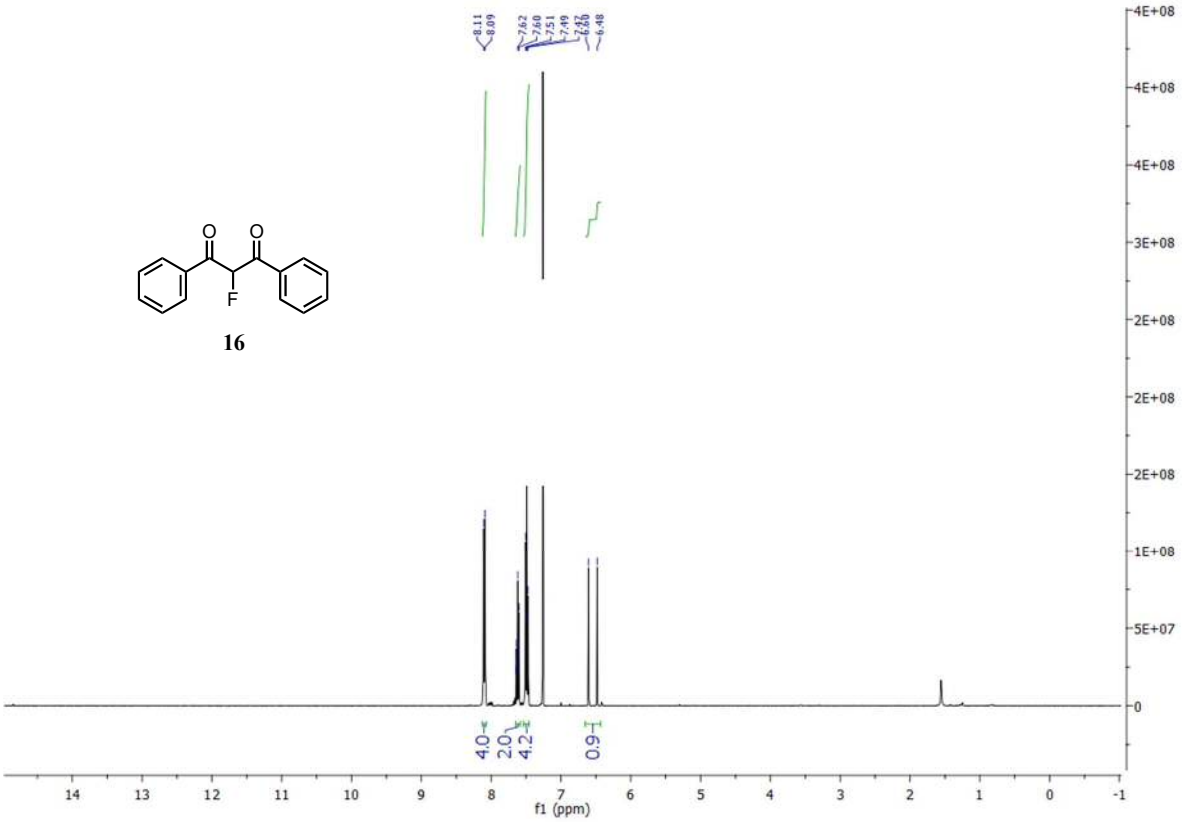
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.64 (s).

IR: 2982, 2361, 1728, 1593, 1508, 1149, 1292, 1265, 1165, 1099, 934, 756, 685 cm^{-1}

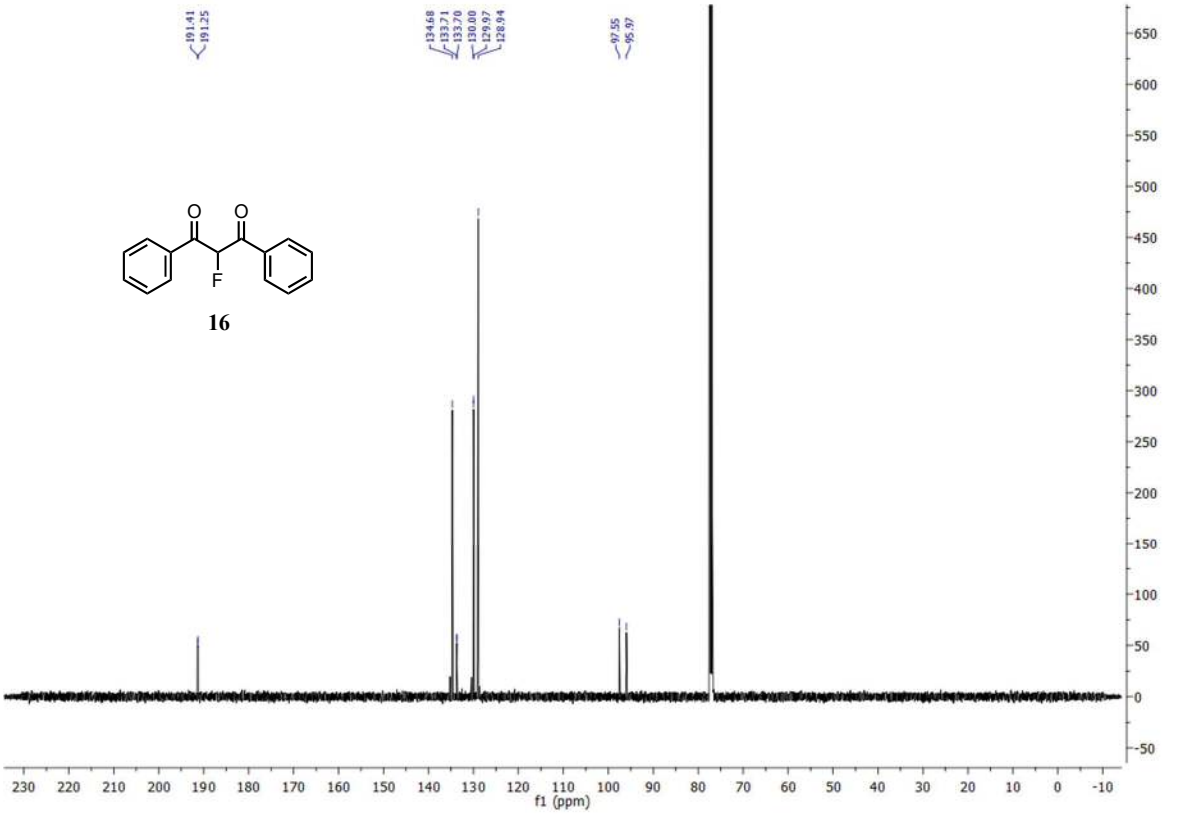
HRMS (ES+): [$C_{15}H_{10}N_2OF_2$ + H] calc. 273.0839, found 273.0841

mp 81-83 °C (chloroform)

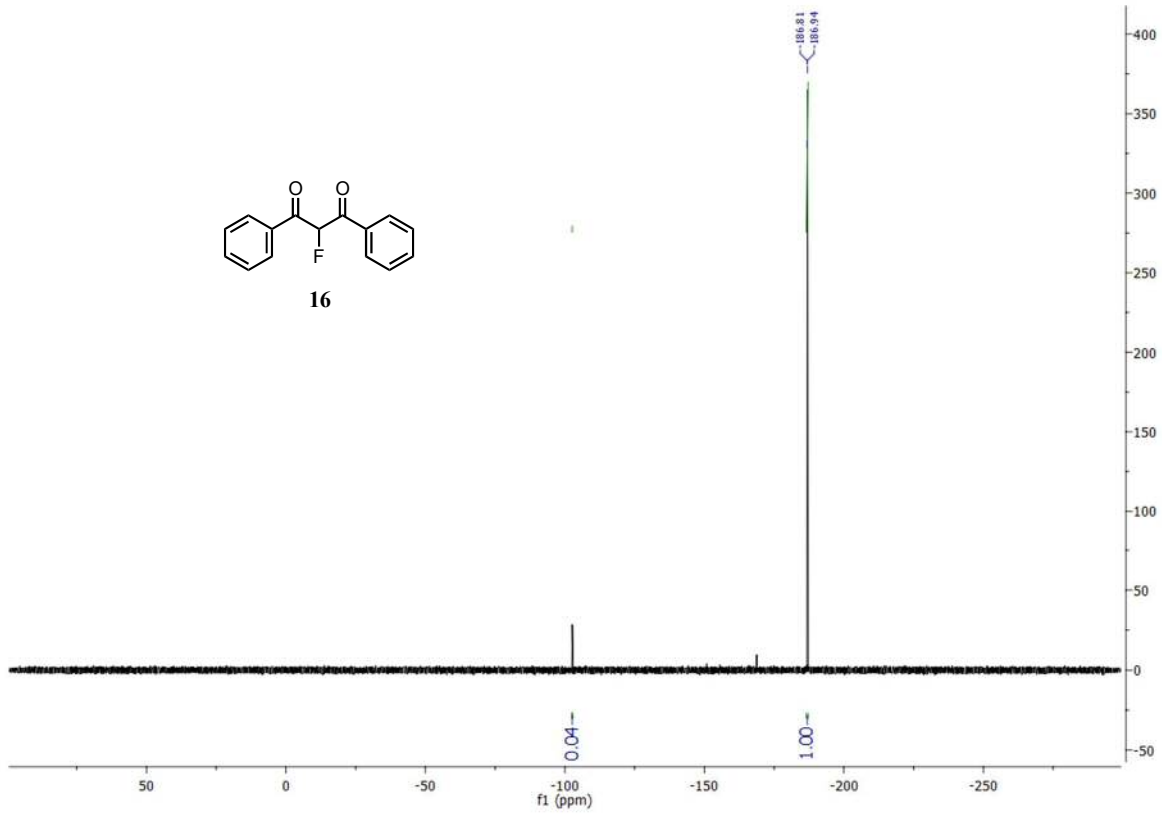
Spectroscopic Data



16



16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O
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-186.94
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350
300
250
200
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100
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0
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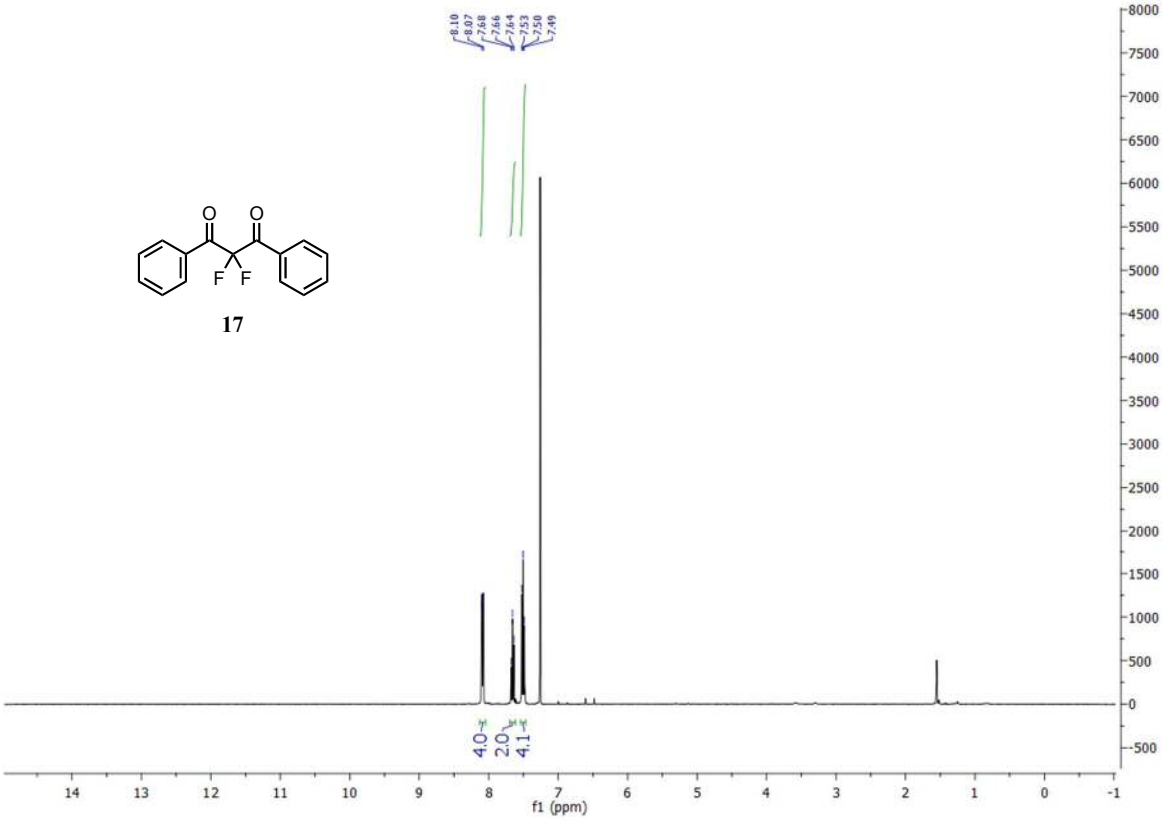
1.00
50
0
-50
-100
-150
-200
-250
f1 (ppm)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8.07
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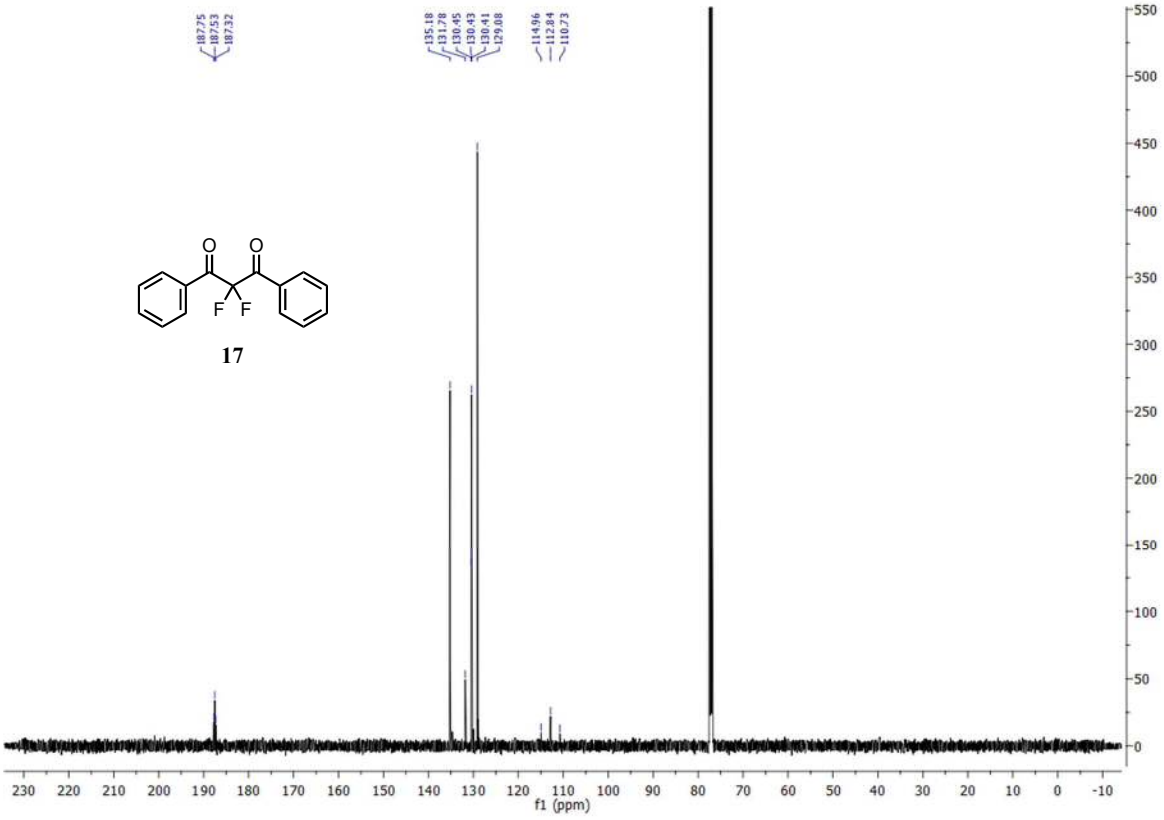
7.53
7.50
7.49
4.0
2.0
4.1
f1 (ppm)

17


187.75
187.53
187.32
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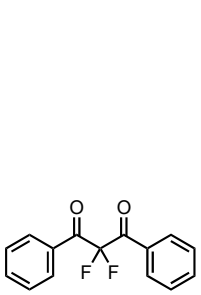
130.41
129.08
114.96
112.84
110.73
f1 (ppm)

17


O
O
F
F

17

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900
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700
600
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50
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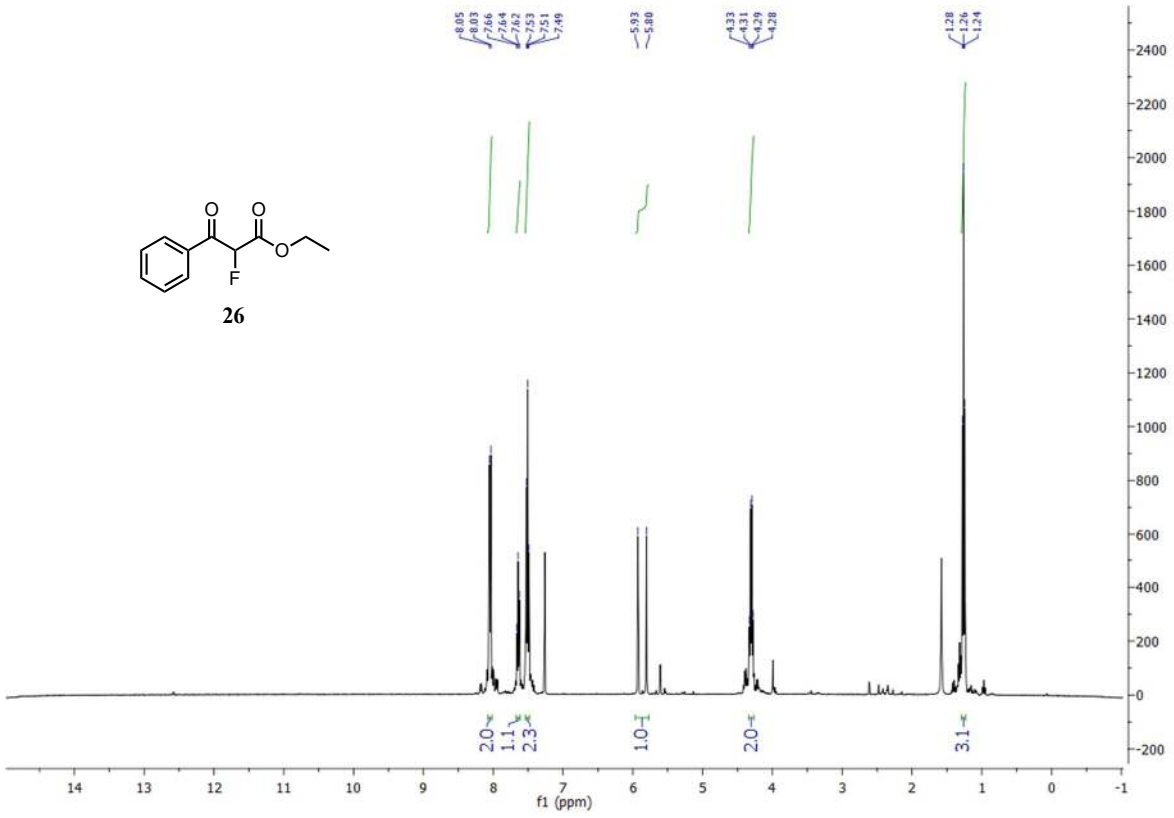
-50
-100
-150
-200
-250
f1 (ppm)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7.64
7.62
7.53
7.51
7.49
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5.80
4.33
4.31
4.29
4.28
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1.26
1.24
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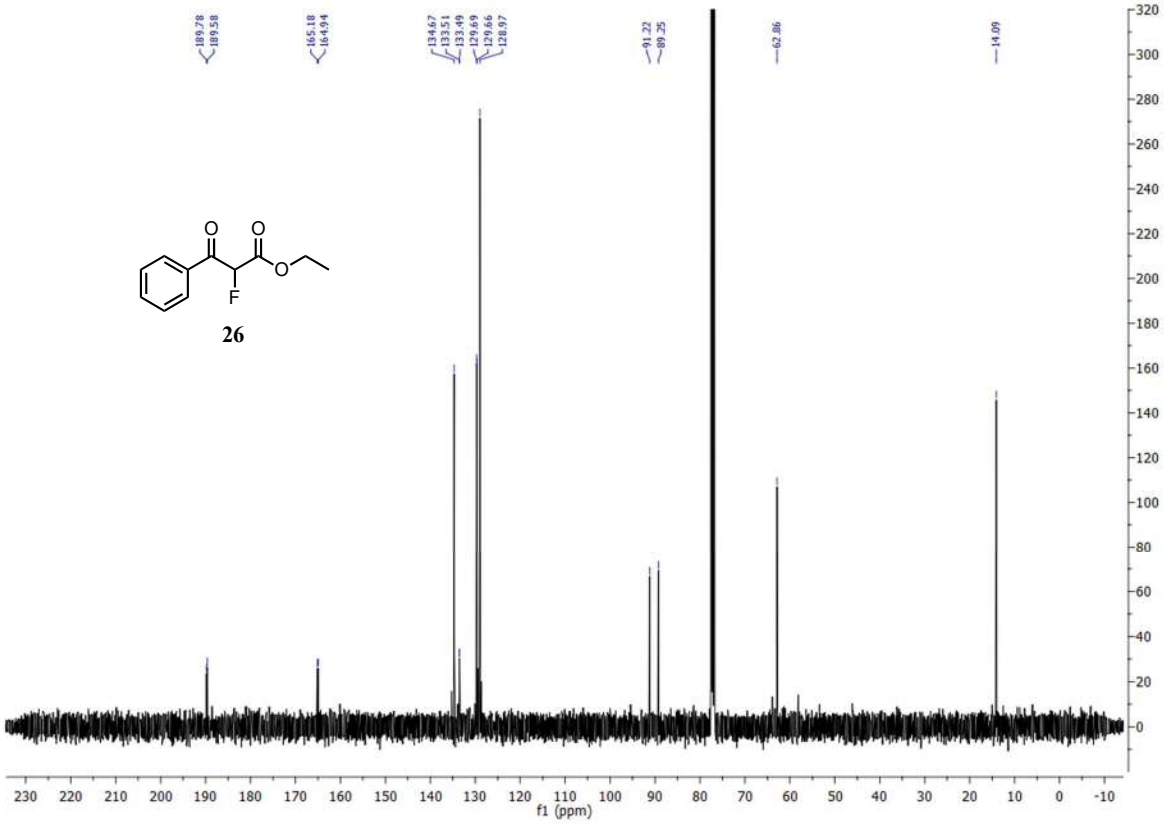
2.3
1.0
2.0
3.1
f1 (ppm)

26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129.66
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91.22
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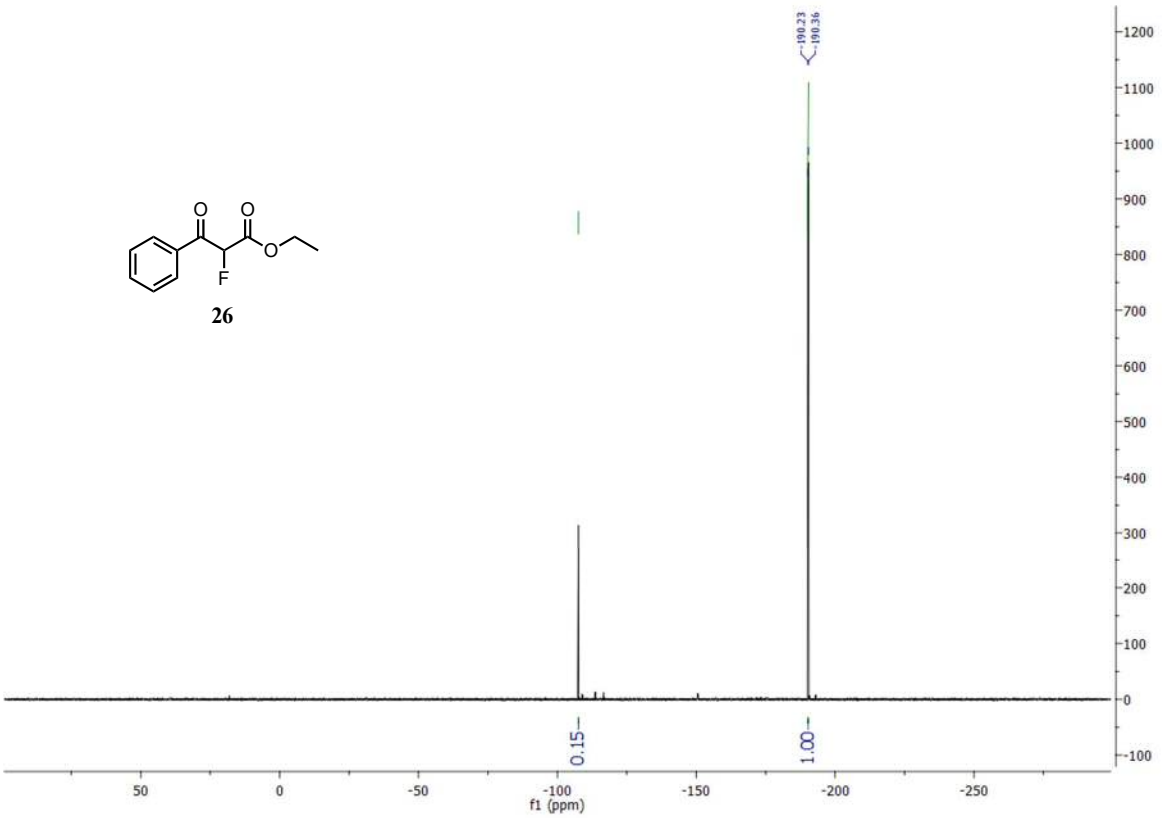
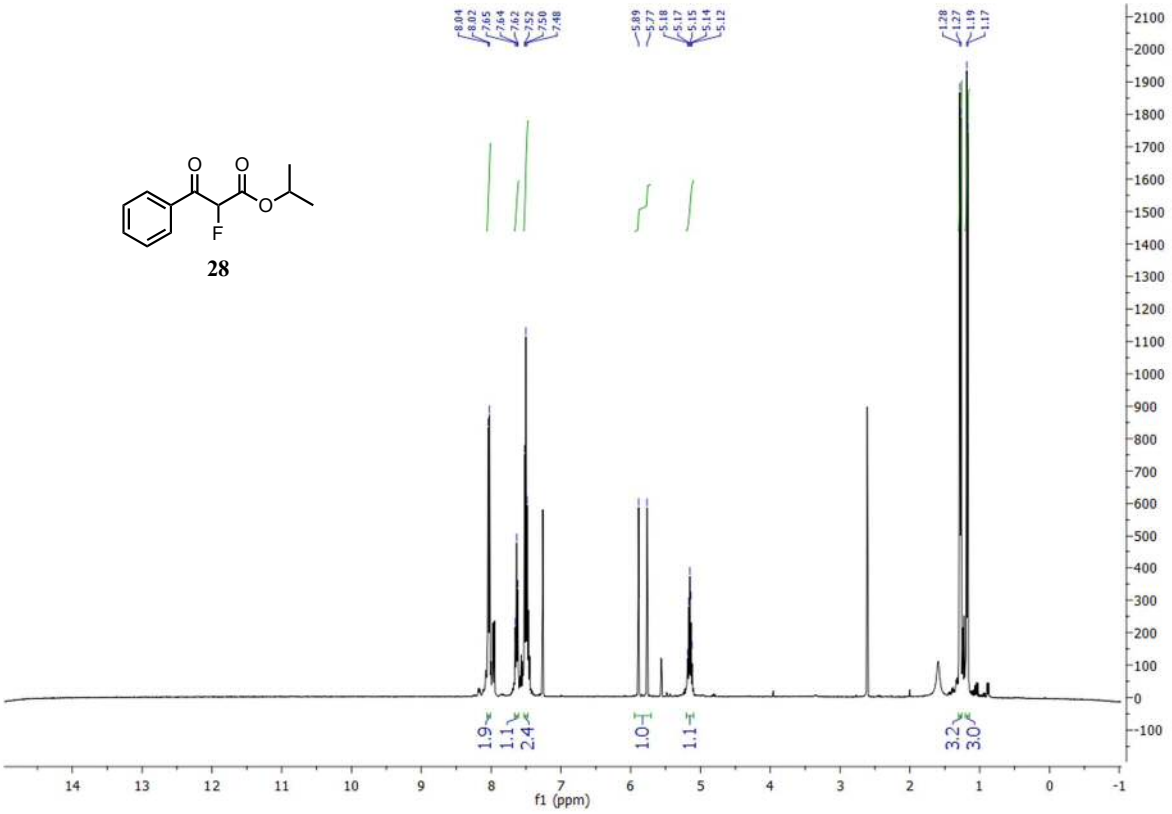
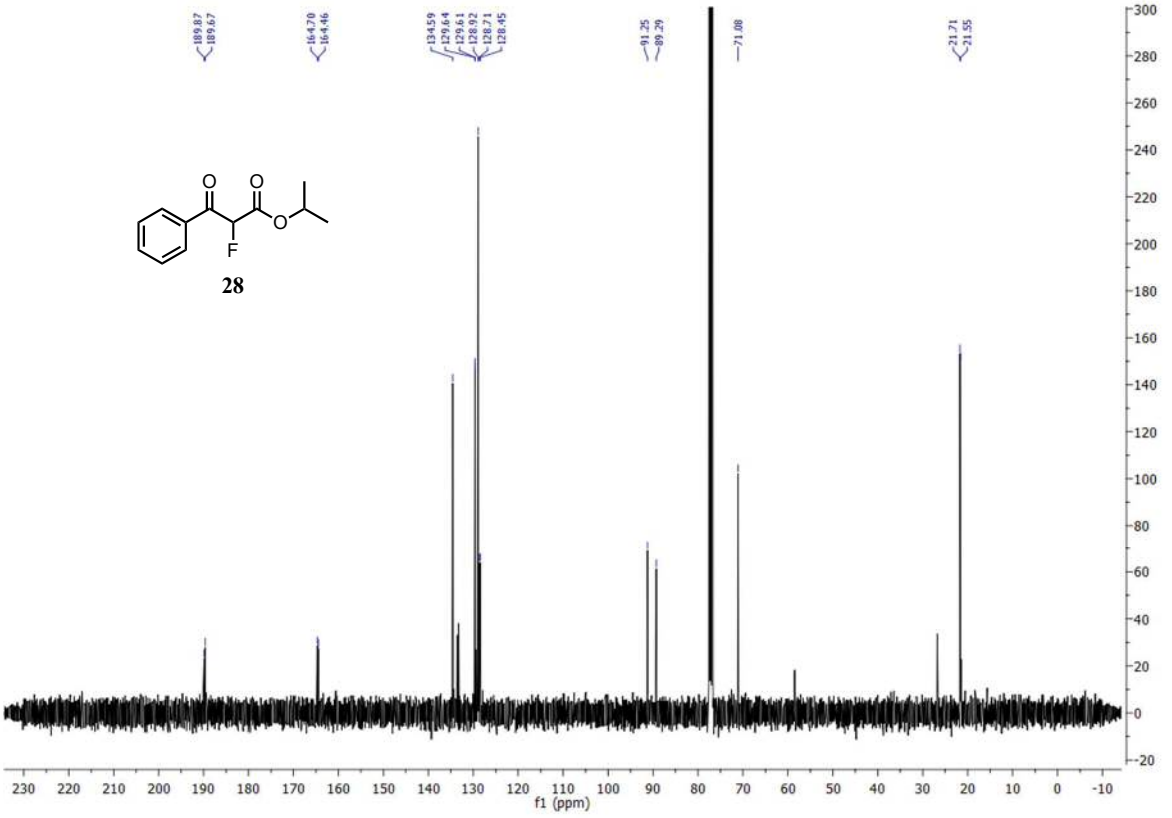
14.09
f1 (ppm)

26



26


28
f1 (ppm)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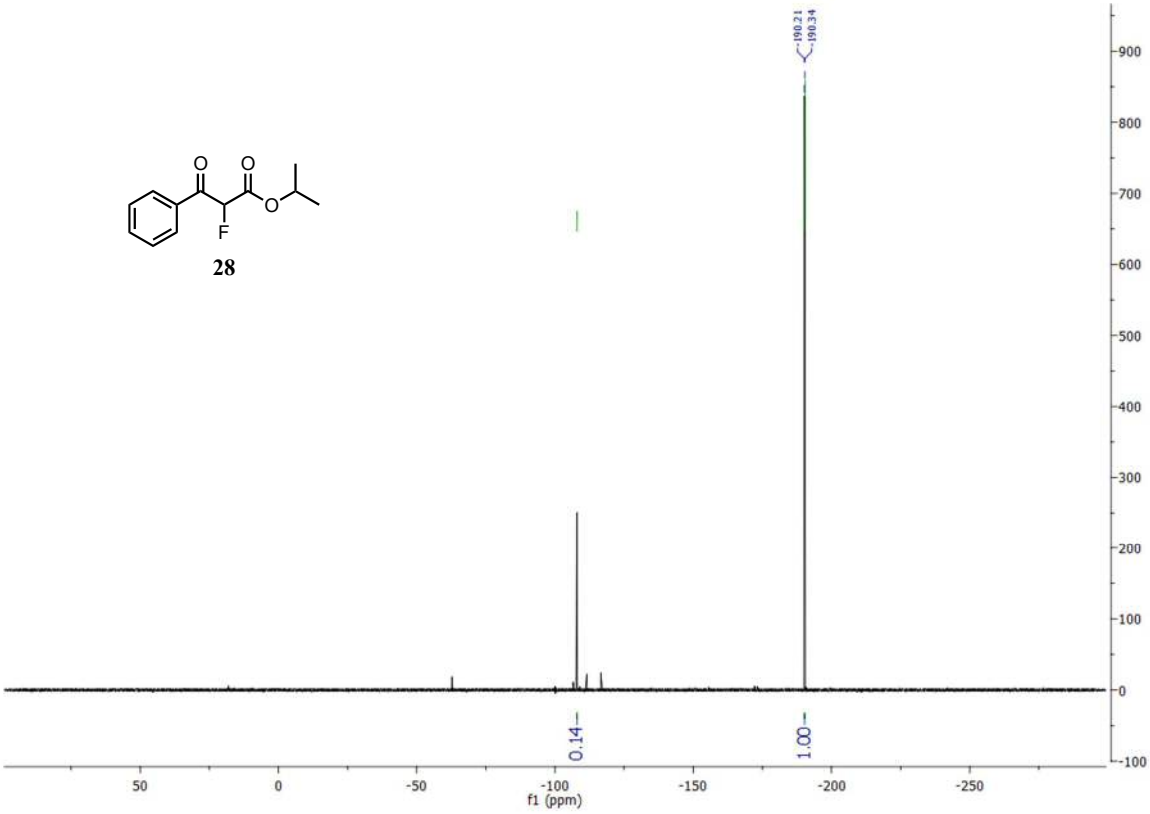
f1 (ppm)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O
O
F
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-190.34
900
800
700
600
500
400
300
200
100
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-100
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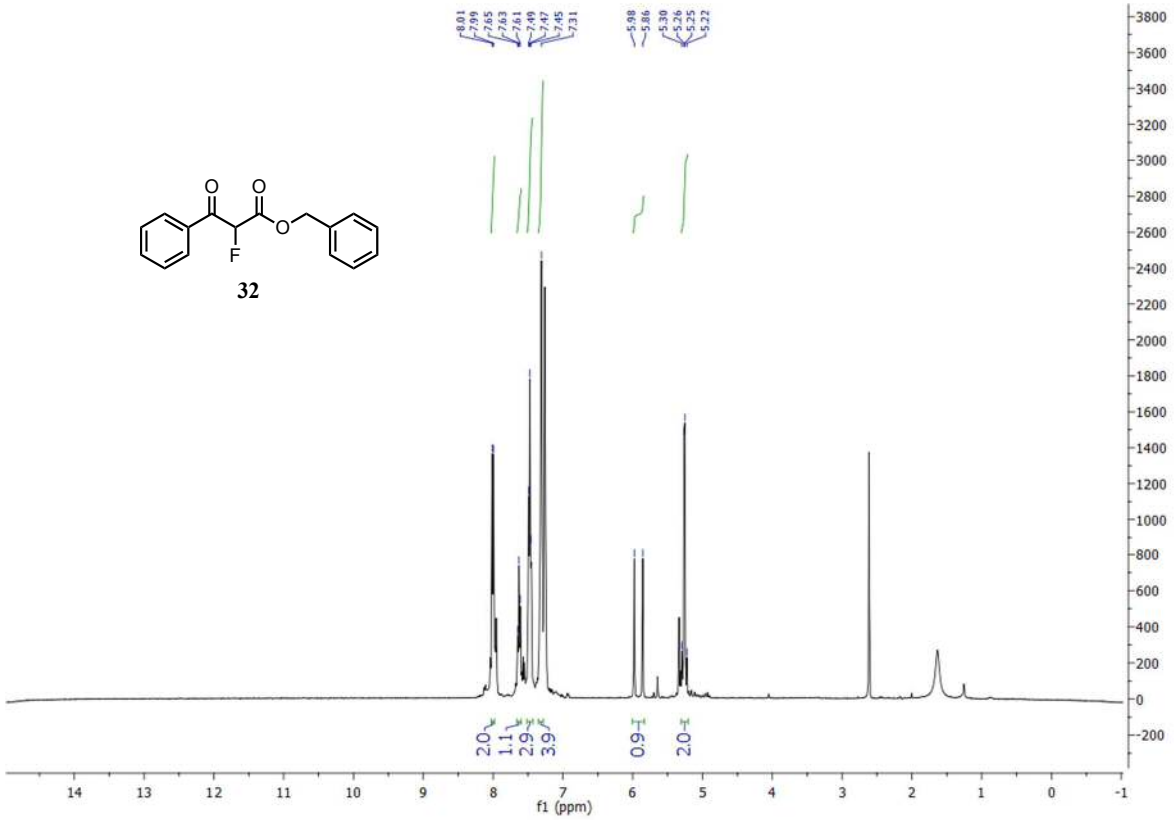
1.00
50
0
-50
-100
-150
-200
-250
f1 (ppm)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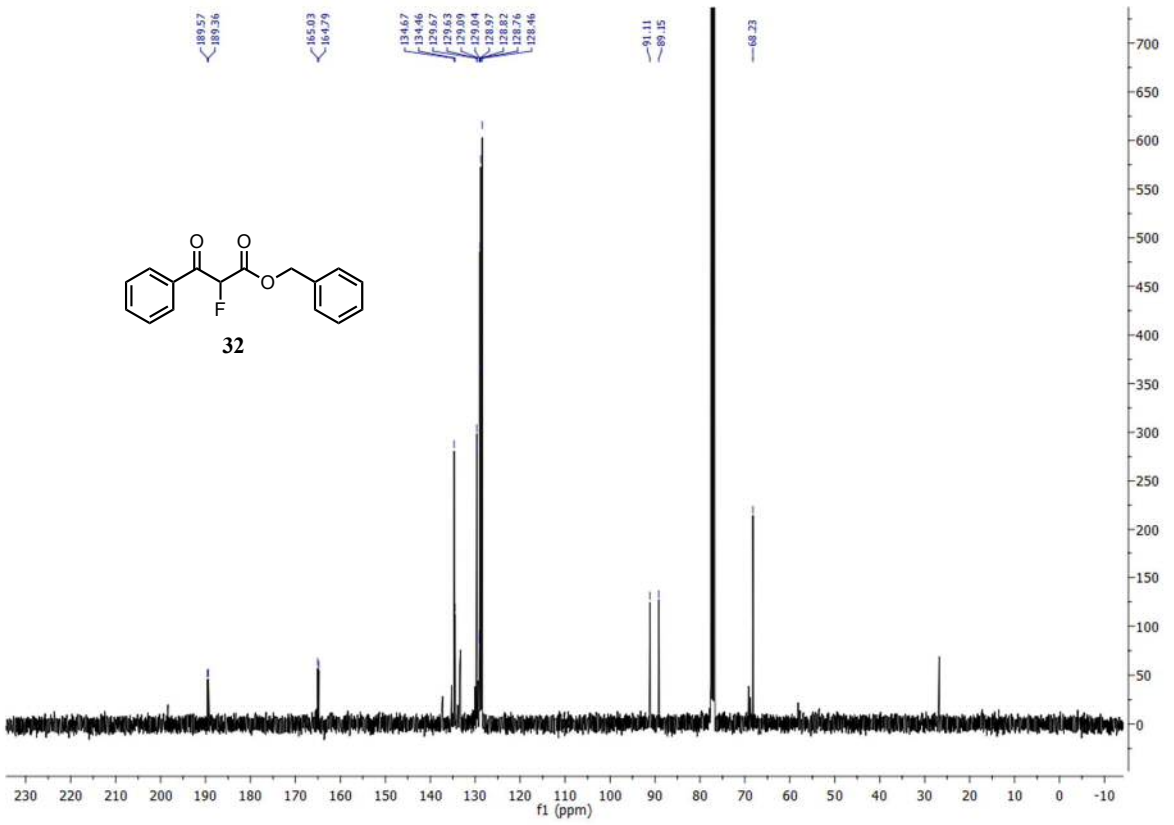
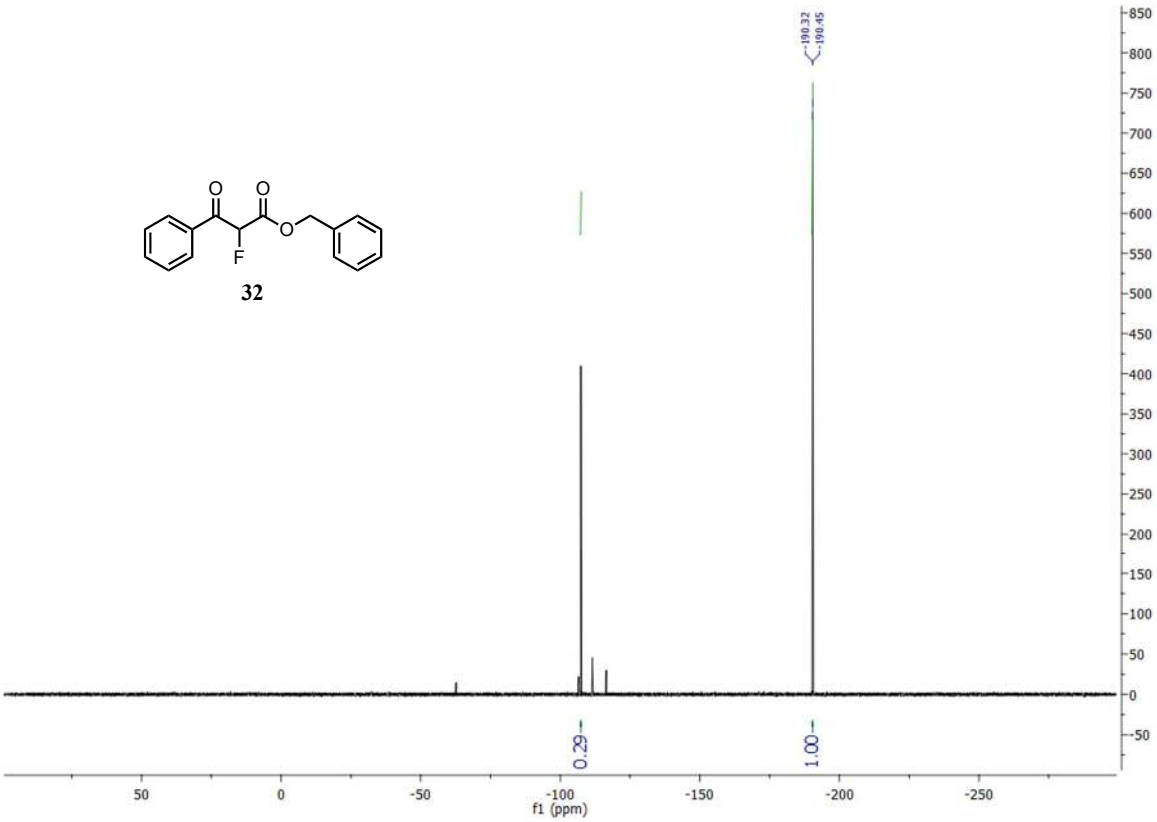
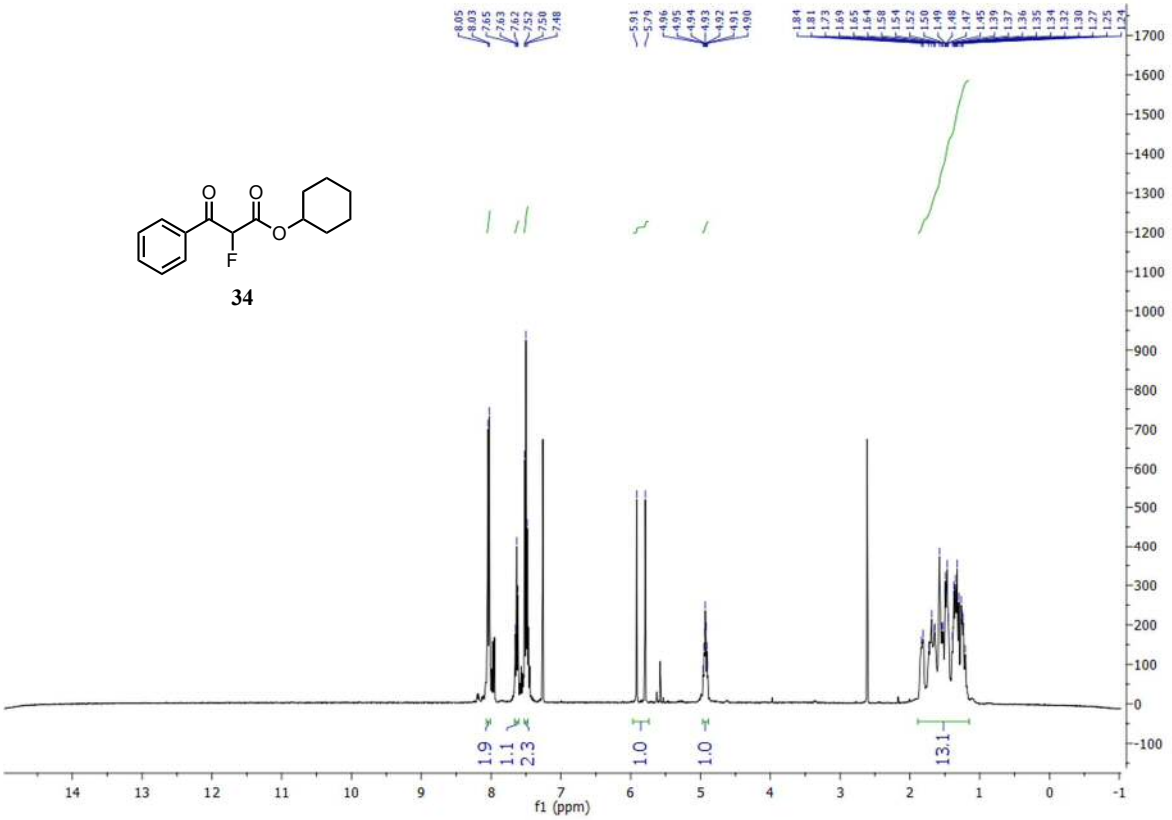
7.61
7.49
7.47
7.45
7.31
5.98
5.86
5.30
5.26
5.25
5.22
2.0
1.1
2.9
3.9
0.9
2.0
f1 (ppm)

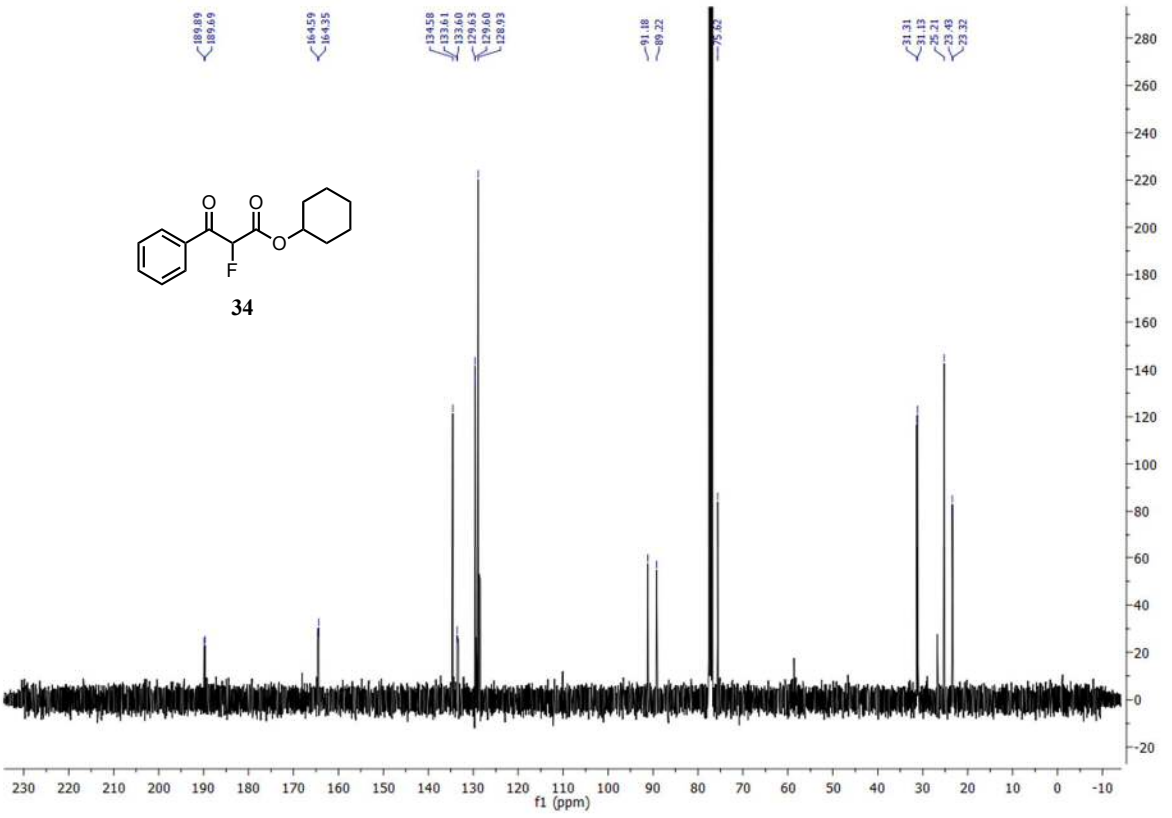
32

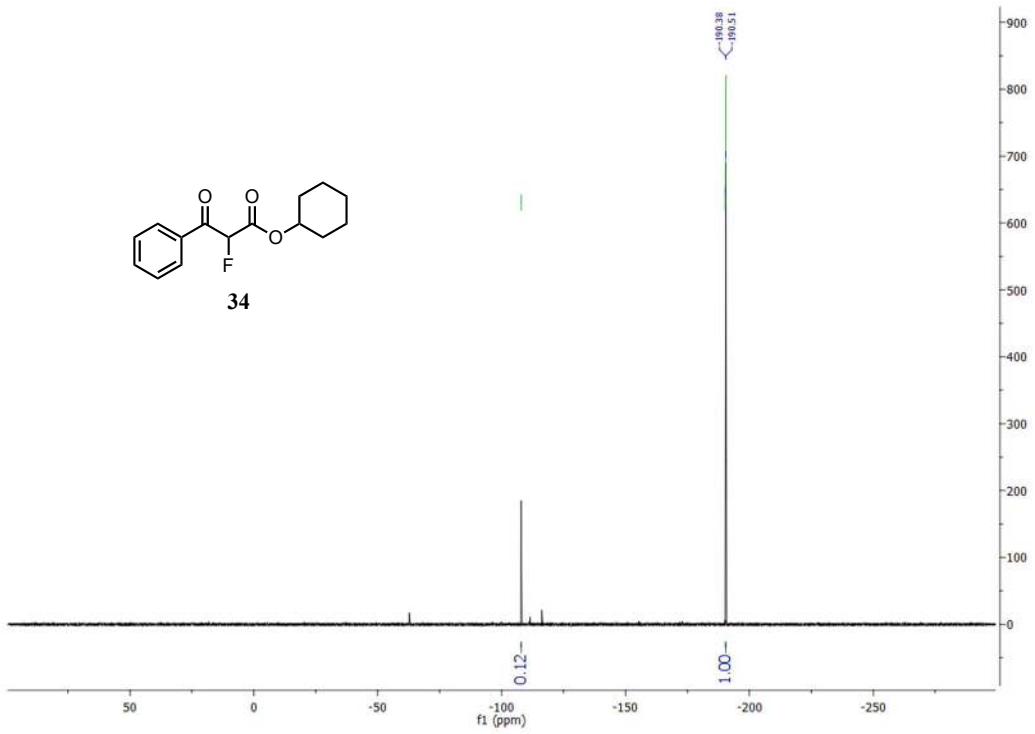

189.57
189.36
165.03
164.79
134.67
134.46
129.67
129.63
129.09
129.04
128.97
128.82
128.76
128.46
91.11
89.15
68.23
f1 (ppm)

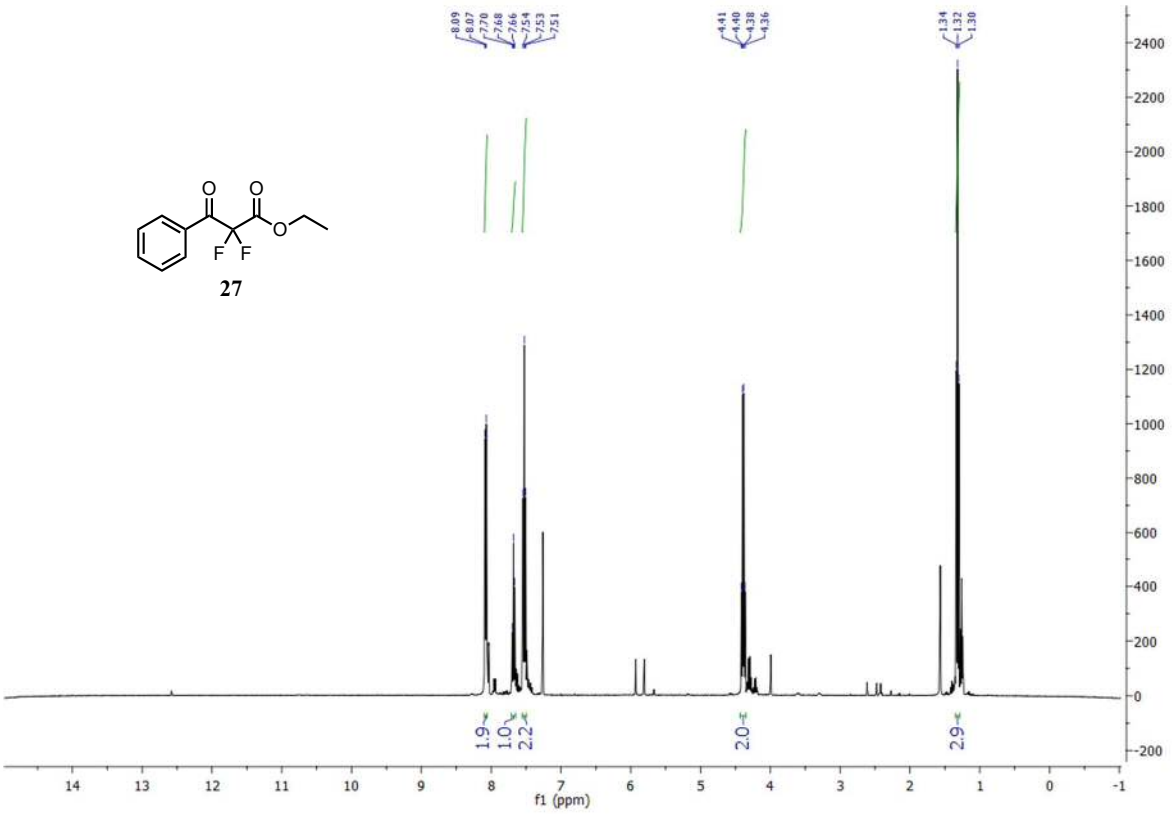
32


O
O
O
F
32
-190.32
-190.45
0.29
1.00
50
0
-50
-100
-150
-200
-250
f1 (ppm)

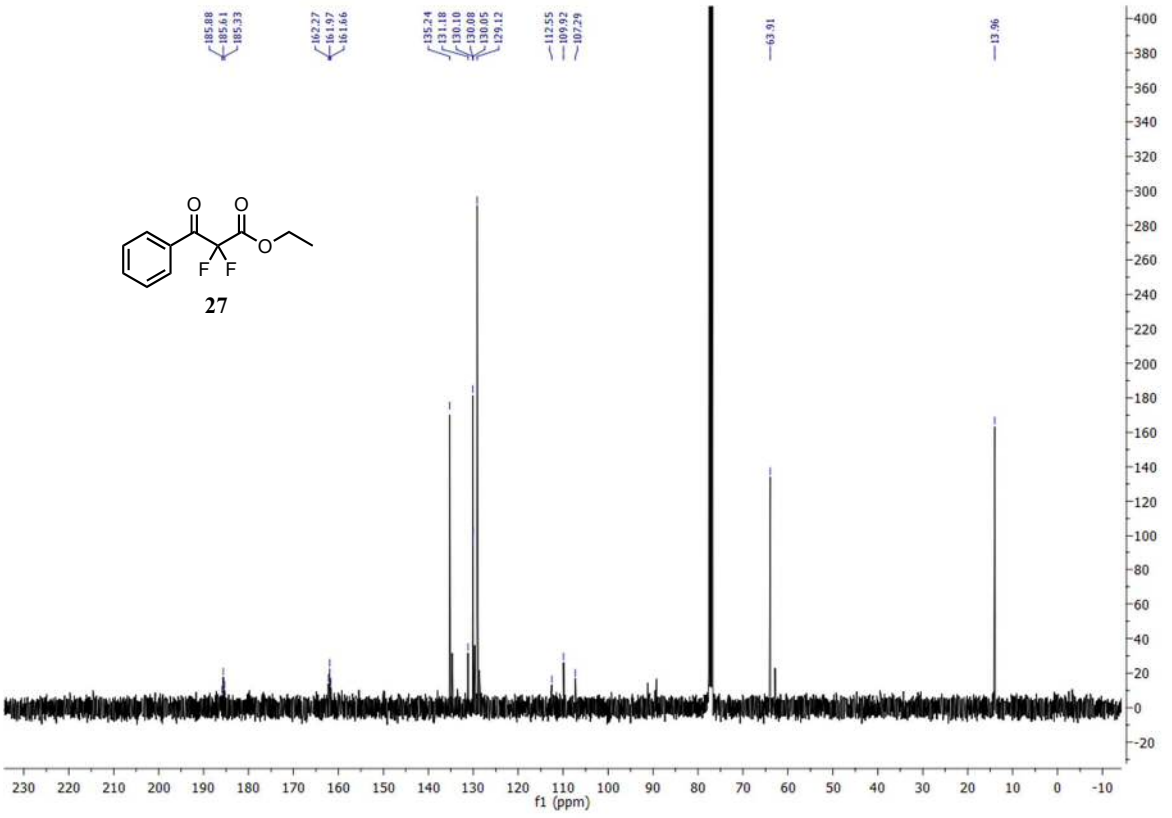

34
f1 (ppm)


34
f1 (ppm)

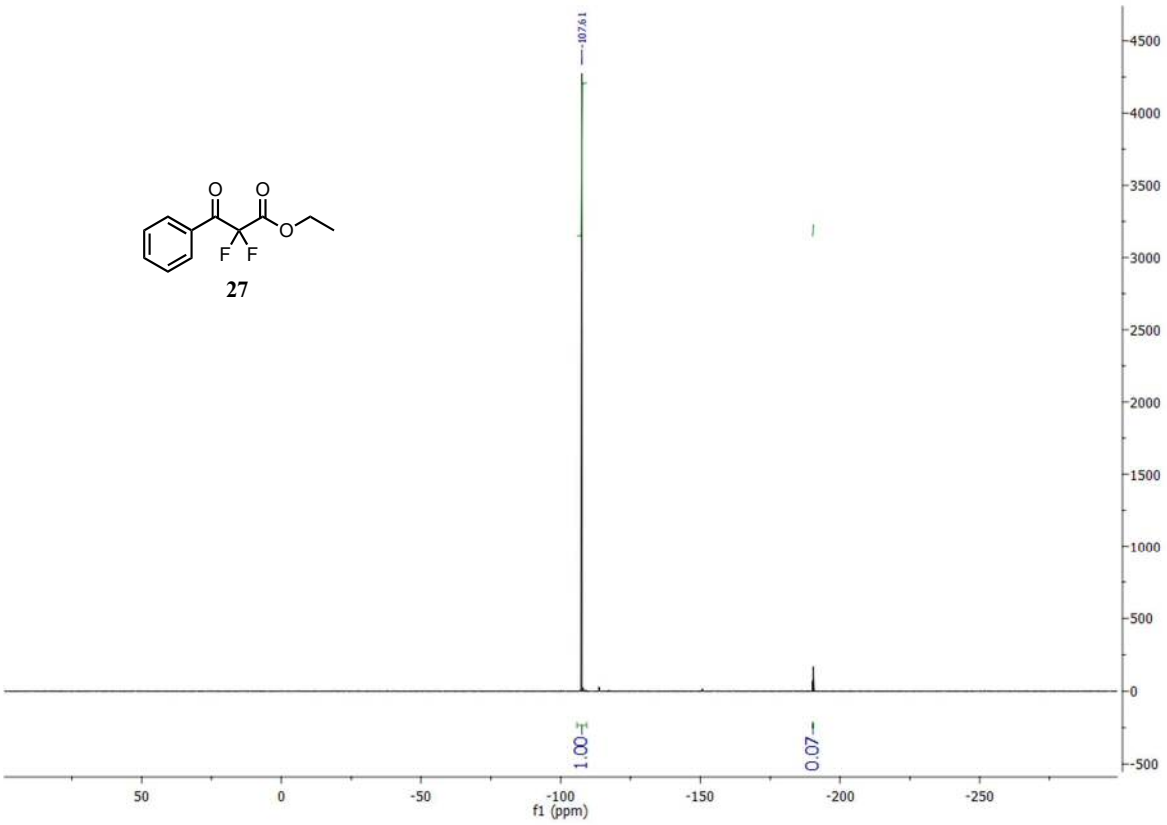

O
O
O
F
34
-190.38
-190.51
0.12
1.00
50
0
-50
-100
-150
-200
-250
f1 (ppm)
900
800
700
600
500
400
300
200
100
0


8.09
8.07
7.70
7.68
7.66
7.54
7.53
7.51
4.41
4.40
4.38
4.36
1.34
1.32
1.30
1.9
1.0
2.2
2.0
2.9
f1 (ppm)

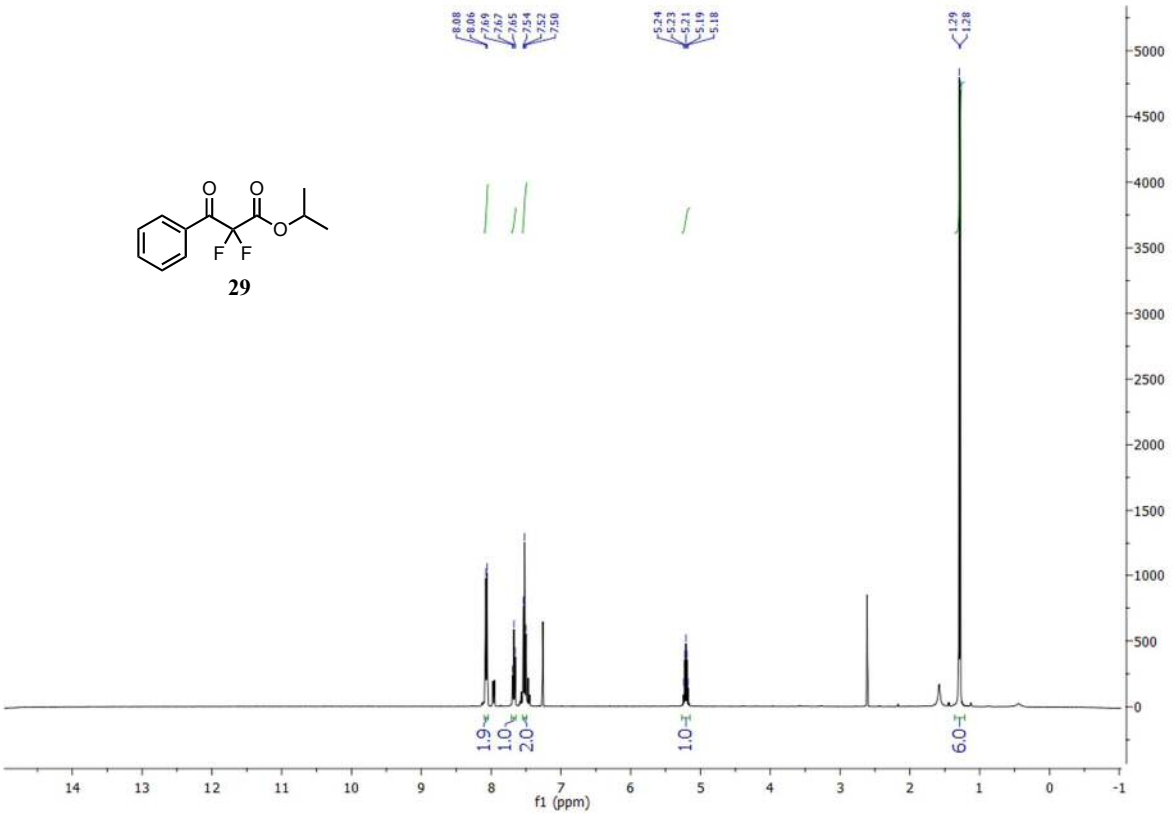
27


185.88
185.61
185.33
162.27
161.97
161.66
135.24
131.18
130.10
130.08
130.05
129.12
112.55
109.92
107.29
63.91
13.96
f1 (ppm)

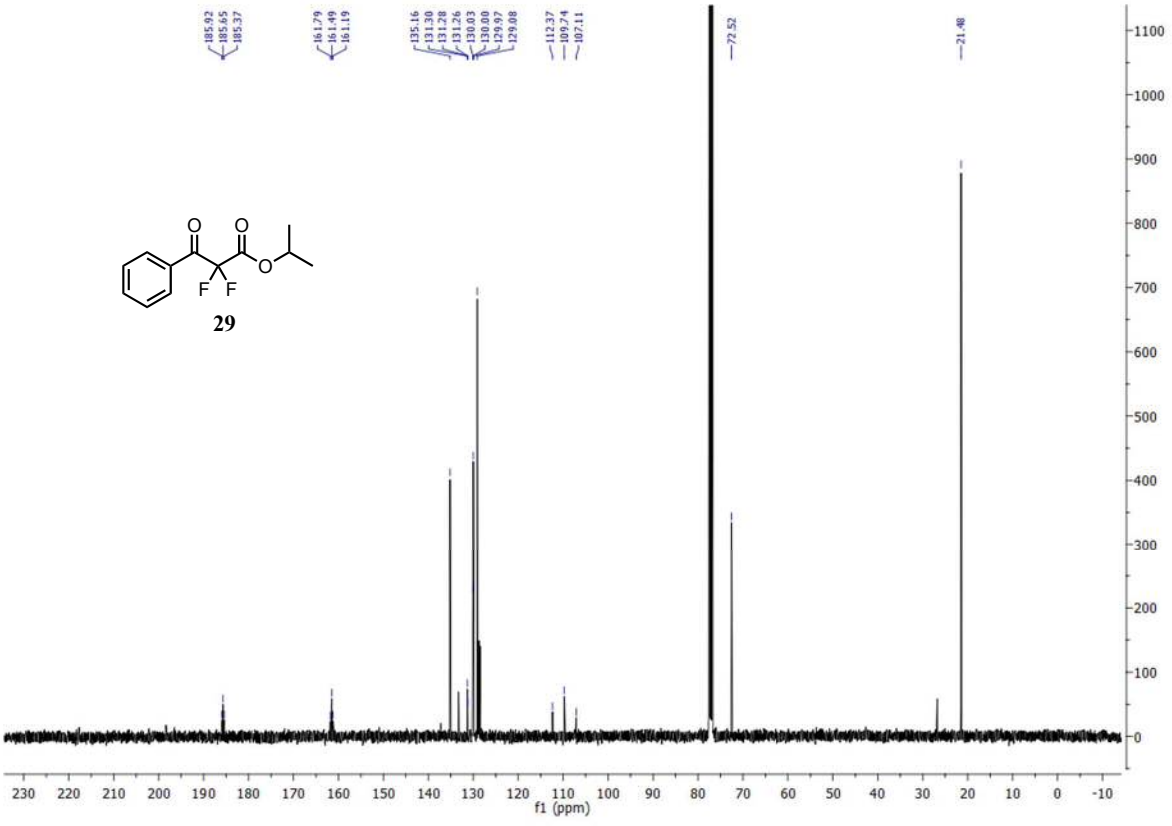
27


-10761
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
0.07
50
0
-50
-100
-150
-200
-250
f1 (ppm)

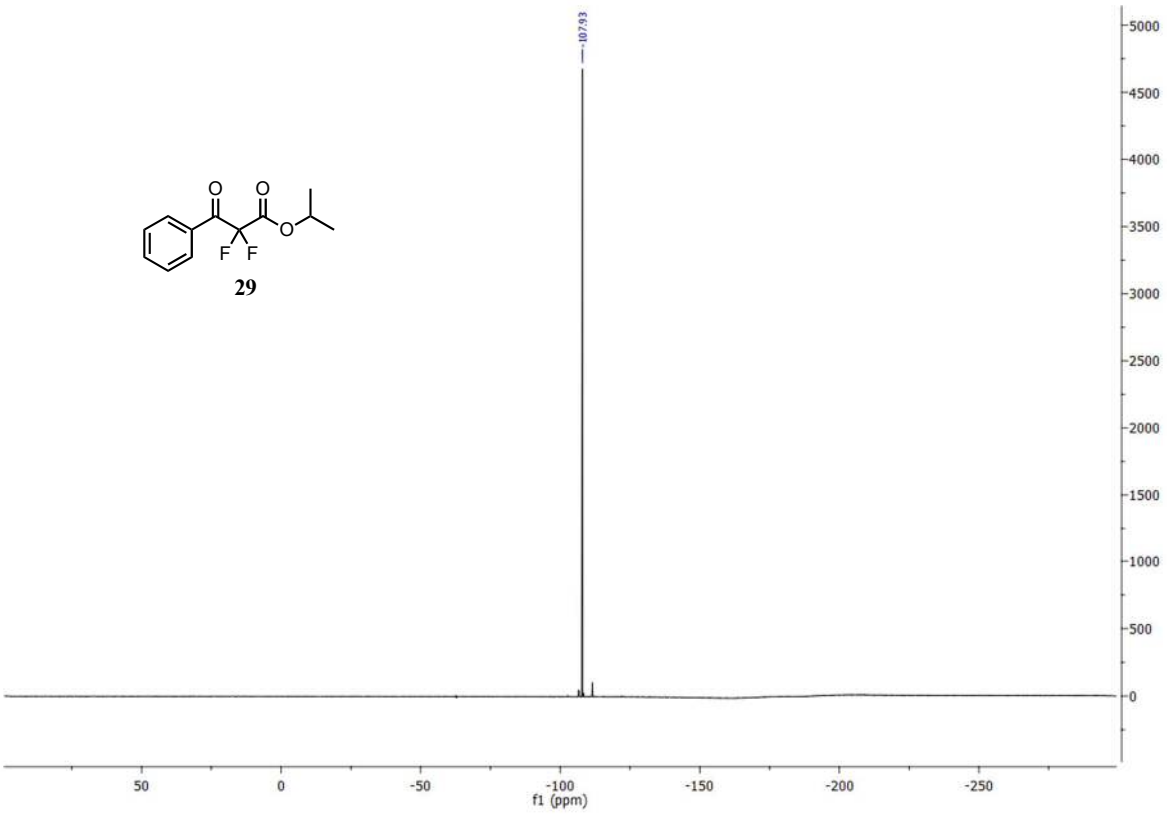
27


8.08
8.06
7.69
7.67
7.65
7.54
7.52
7.50
5.24
5.23
5.21
5.19
5.18
1.29
1.28
1.9
1.0
2.0
1.0
6.0
f1 (ppm)

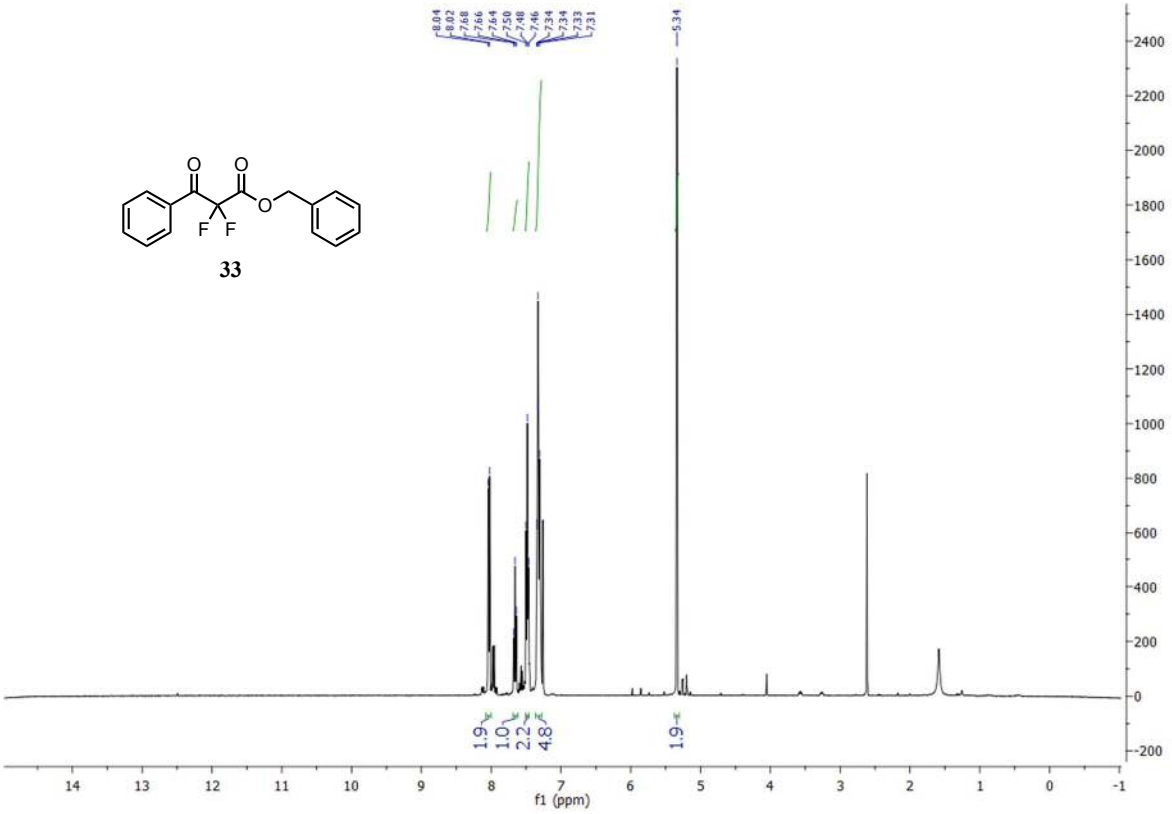
29


185.92
185.65
185.37
161.79
161.49
161.19
135.16
131.30
131.28
131.26
130.03
130.00
129.97
129.08
112.37
109.74
107.11
72.52
21.48
f1 (ppm)

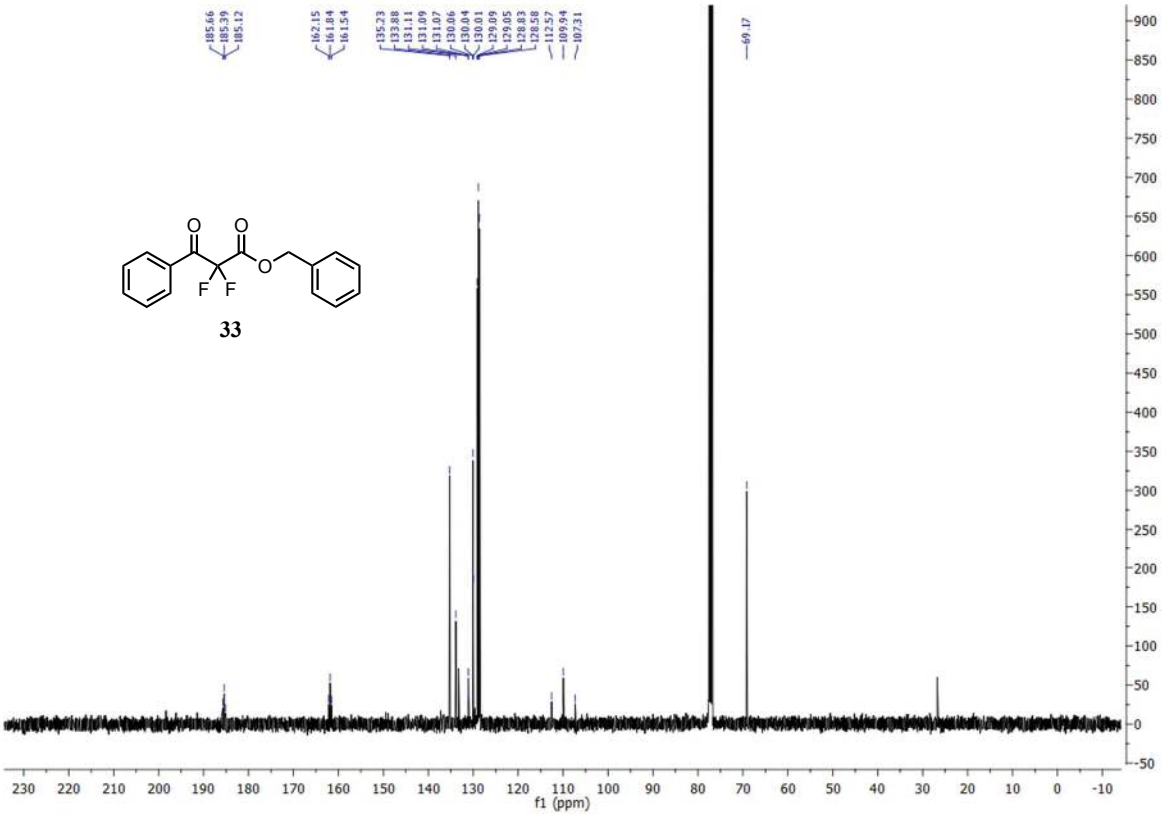
29


-10793
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
50
0
-50
-100
-150
-200
-250
f1 (ppm)

29


8.04
8.02
7.68
7.66
7.64
7.50
7.48
7.46
7.34
7.34
7.33
7.31
5.34
1.9
1.0
2.2
4.8
1.9
f1 (ppm)

33


185.66
185.39
185.12
162.15
161.84
161.54
135.23
133.88
131.11
131.09
131.07
130.06
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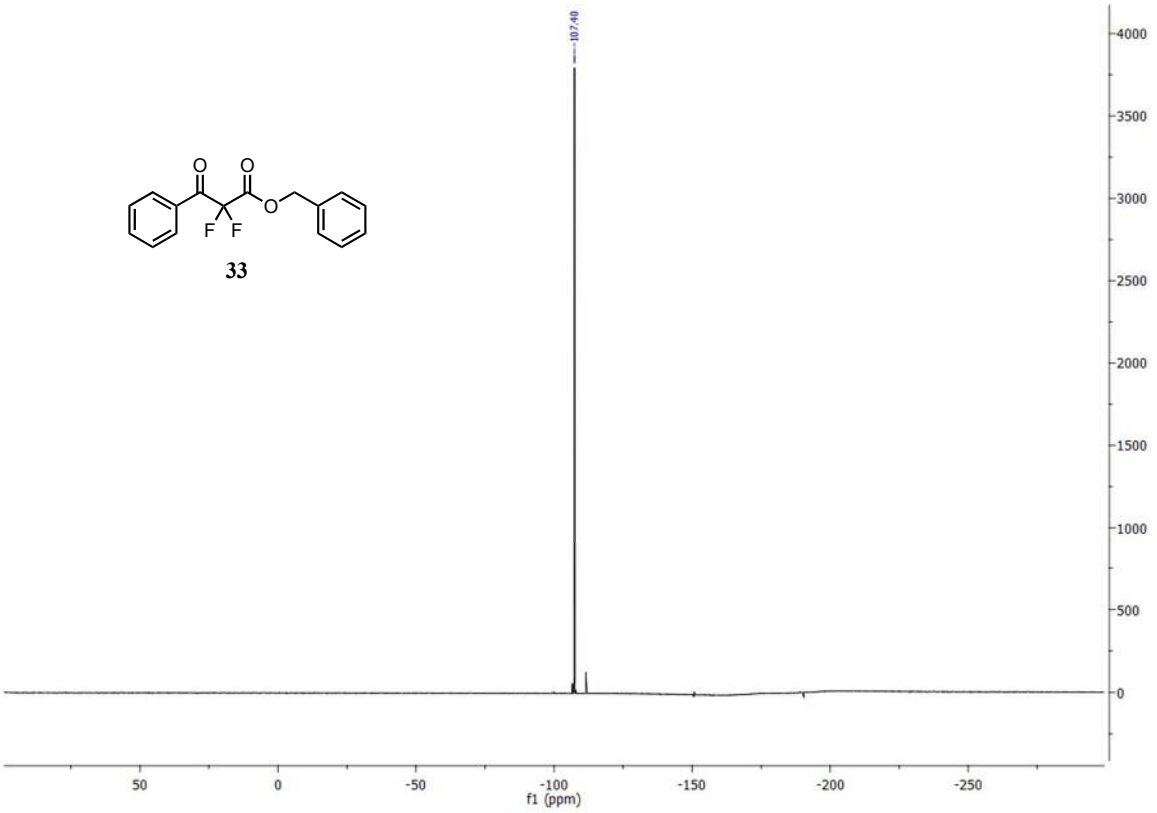
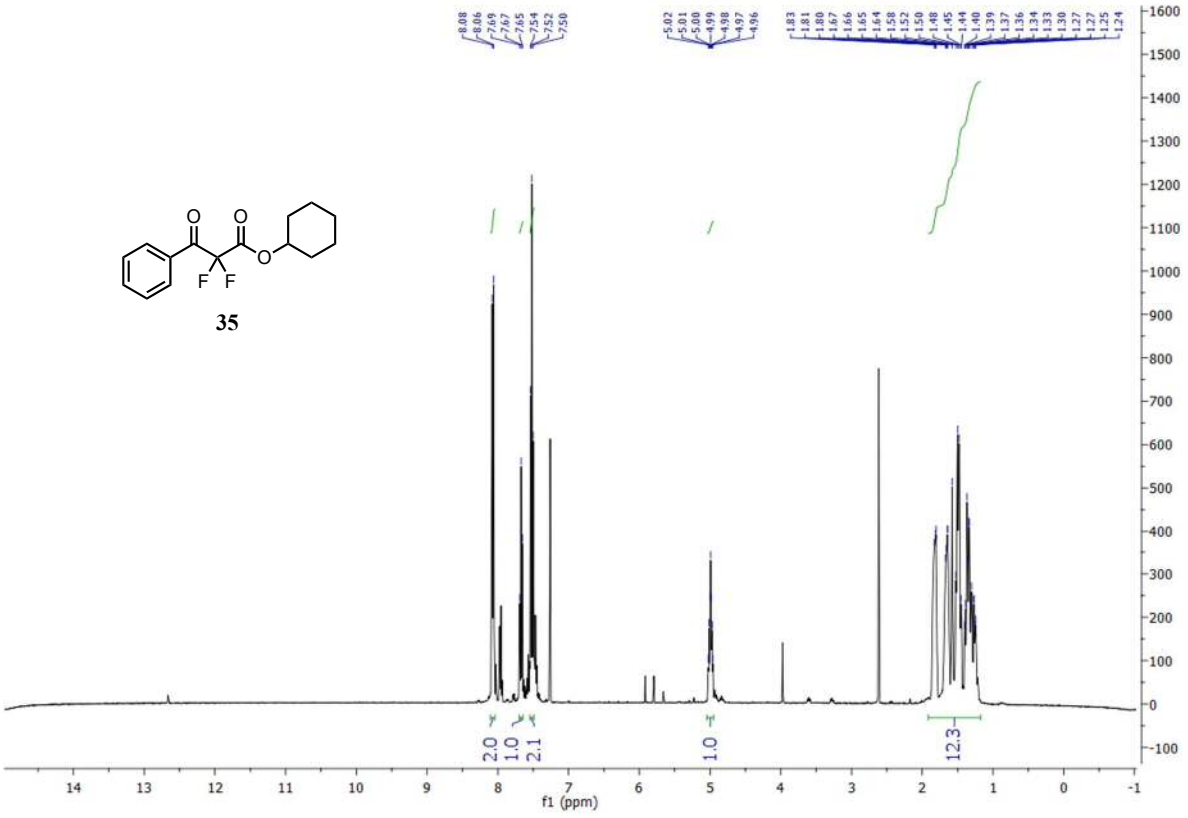
112.57
109.94
107.31
69.17
f1 (ppm)

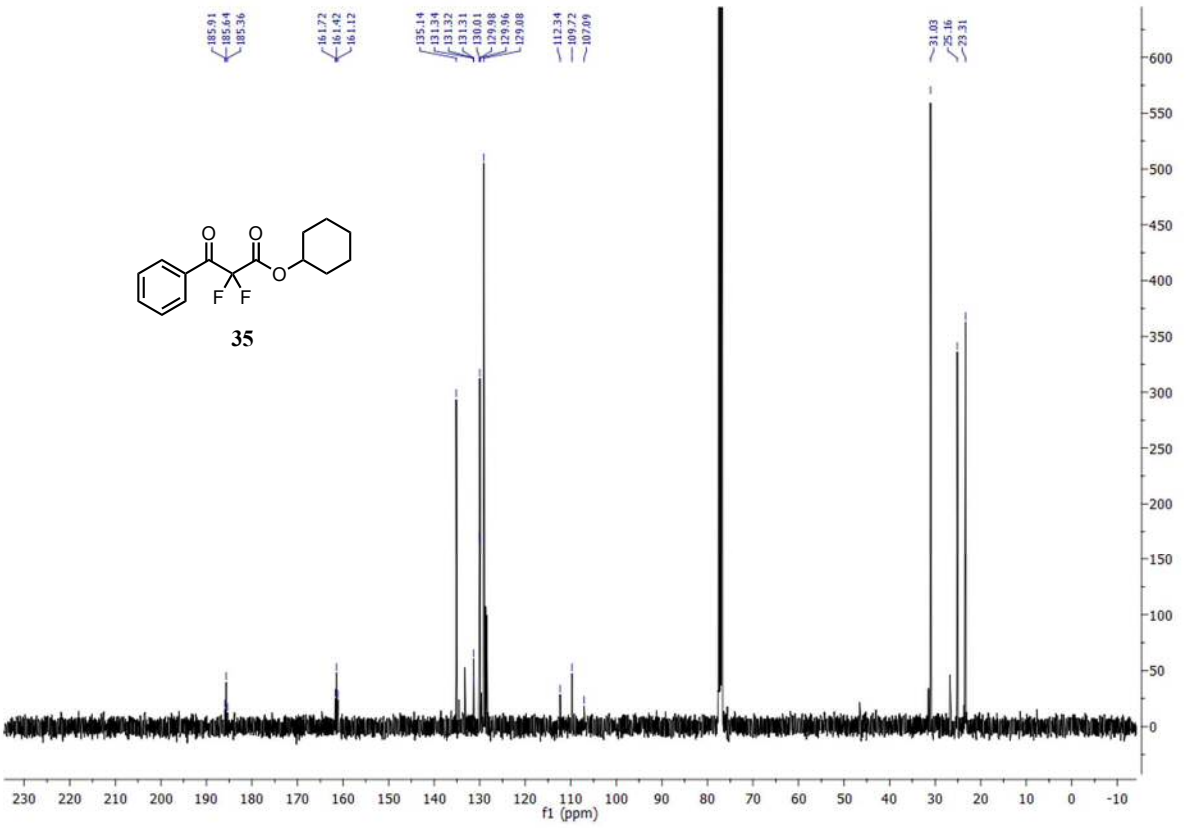
33


-107.40
4000
3500
3000
2500
2000
1500
1000
500
0
50
0
-50
-100
-150
-200
-250
f1 (ppm)

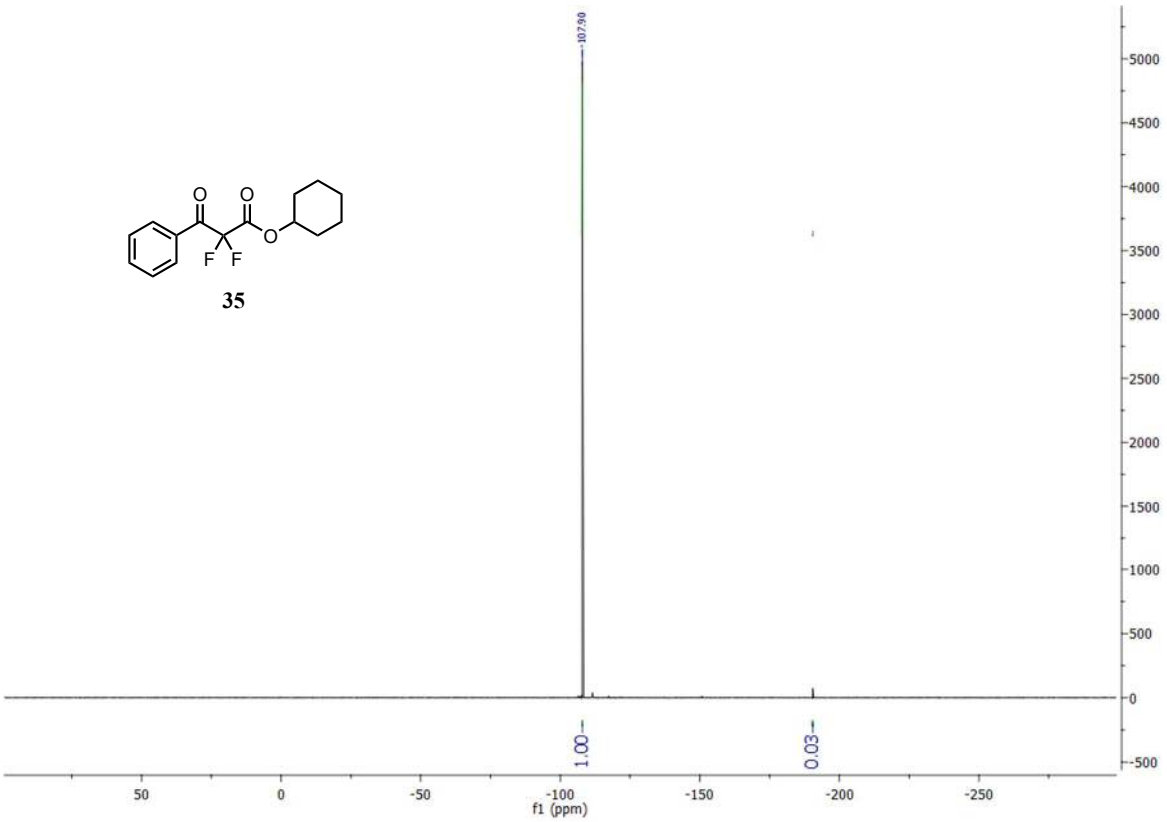
33


8.08
8.06
7.769
7.767
7.765
7.754
7.752
7.750
5.02
5.01
5.00
4.99
4.98
4.97
4.96
2.0
1.0
2.1
1.0
12.3
f1 (ppm)

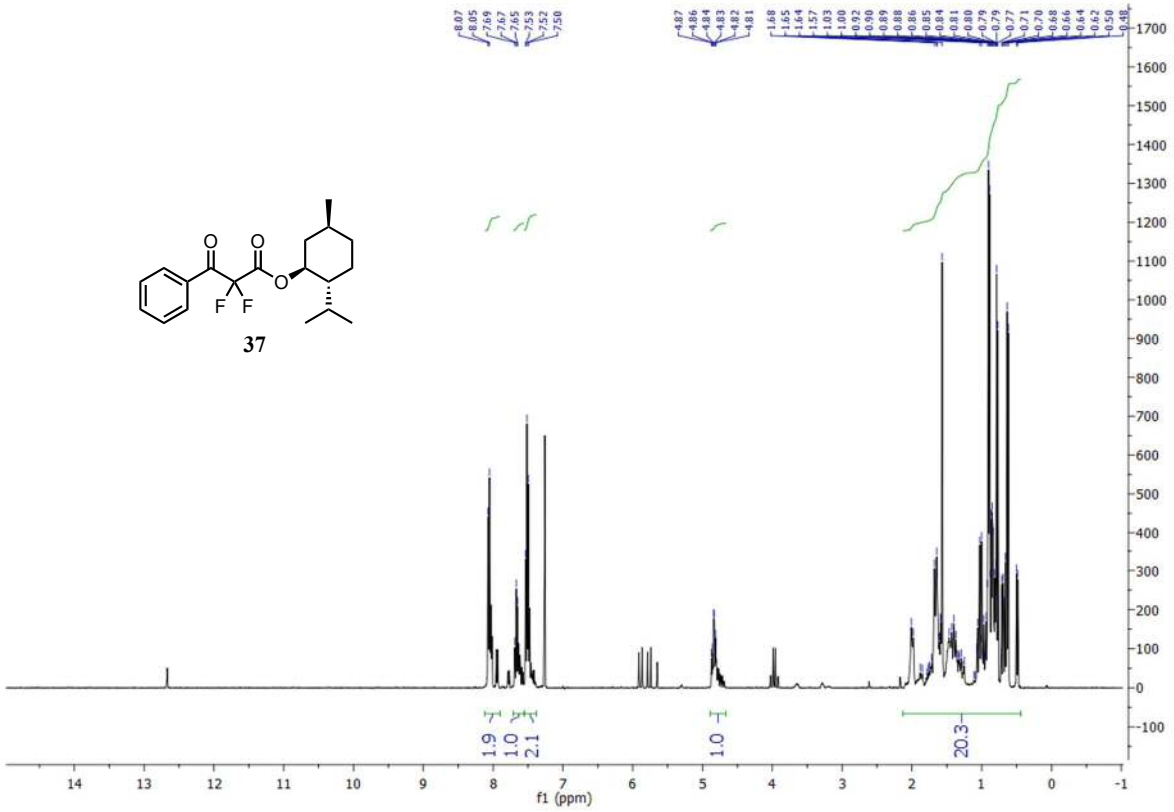
35

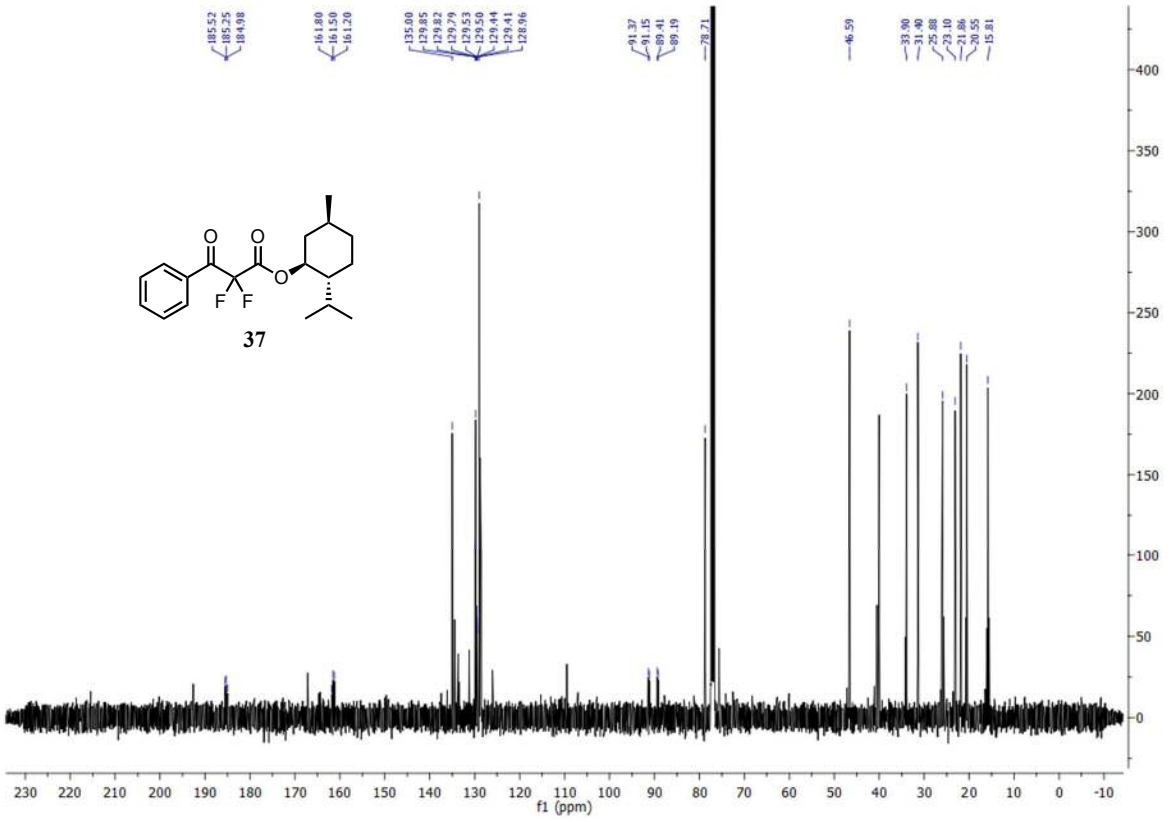

185.91
185.64
185.36
161.72
161.42
161.12
135.14
131.34
131.32
131.31
130.01
129.98
129.96
129.08
112.34
109.72
107.09
31.03
25.16
23.31
f1 (ppm)

35


10790
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
0.03
50
0
-50
-100
-150
-200
-250
f1 (ppm)

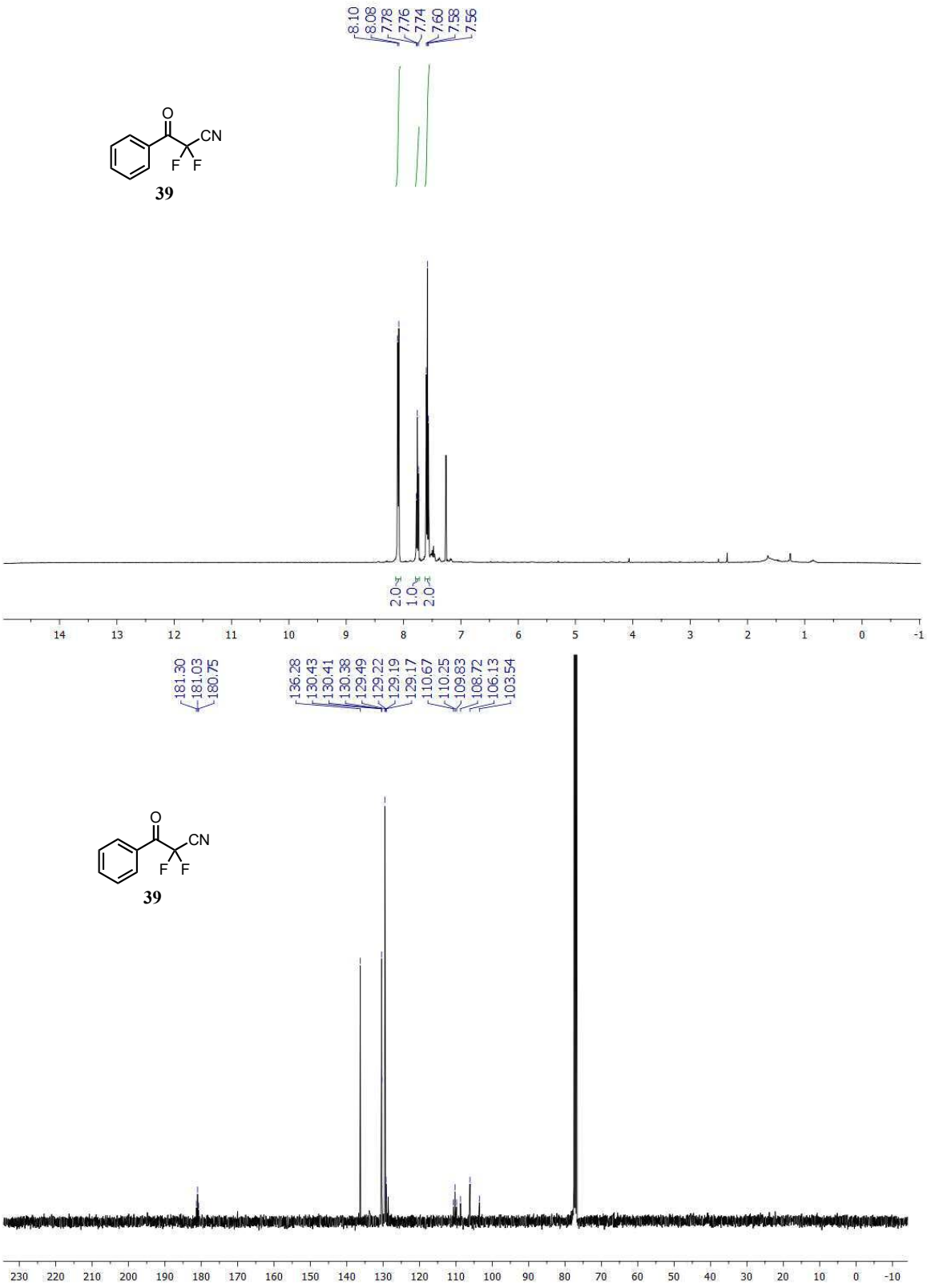
35

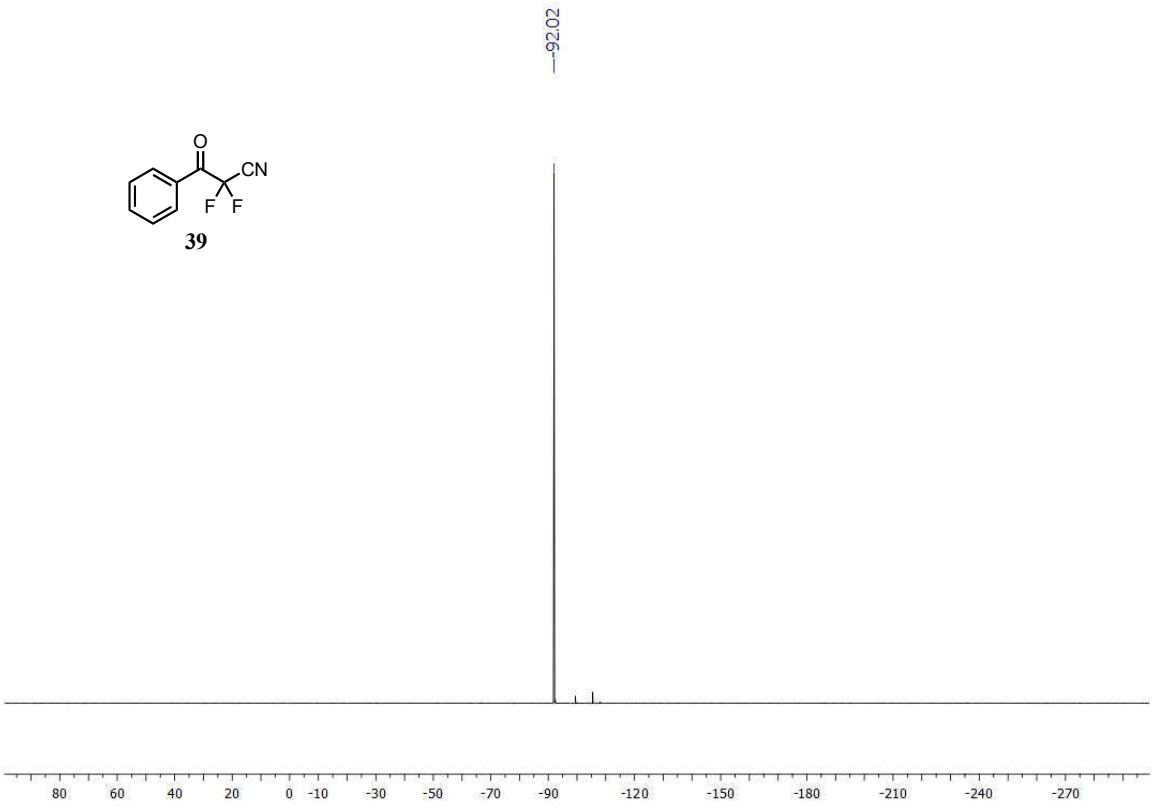

37
1.9
1.0
2.1
1.0
20.3
f1 (ppm)


37
f1 (ppm)

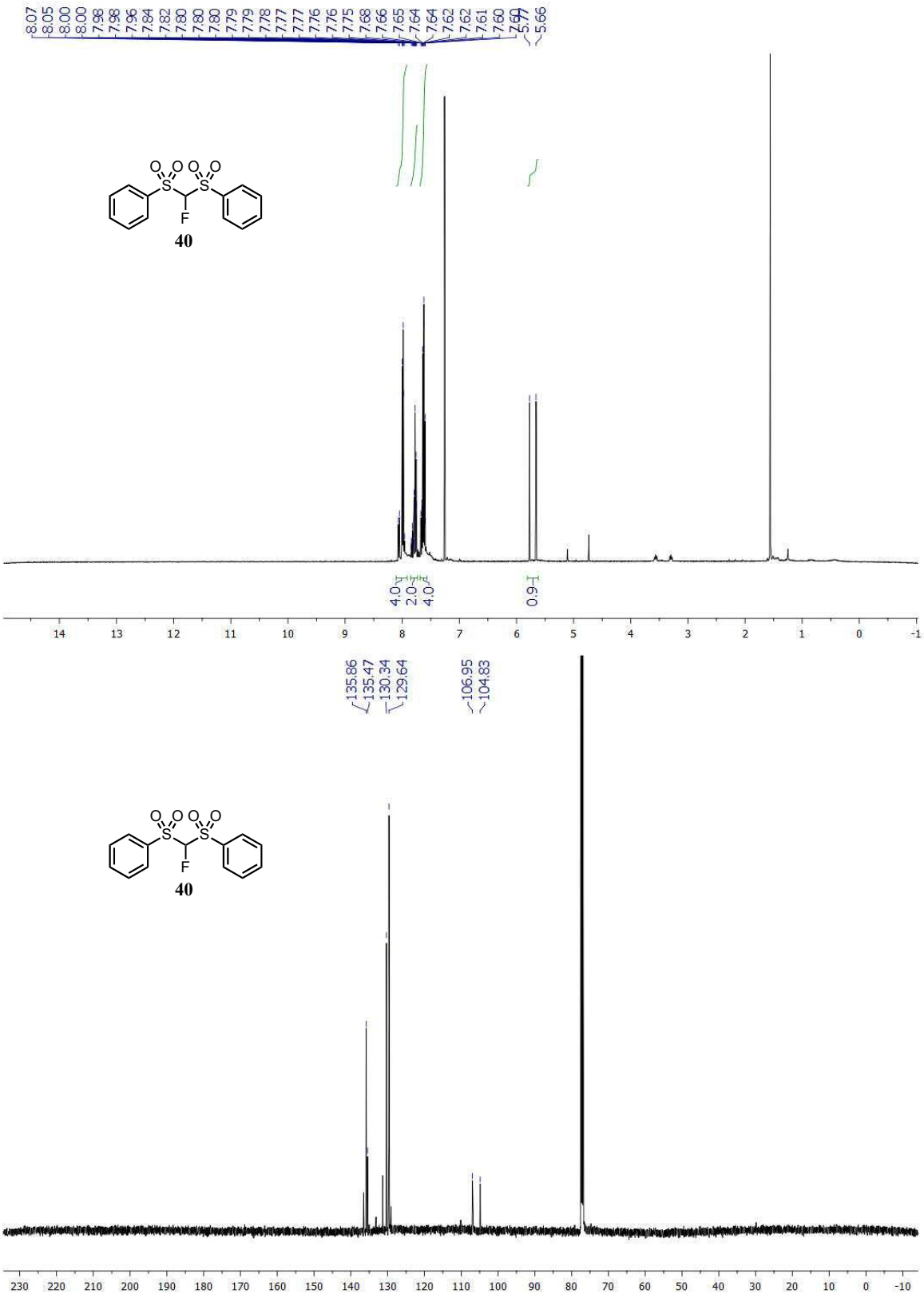

106.99
107.75
108.20
108.95
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.00
0.22
50
0
-50
-100
-150
-200
-250
f1 (ppm)

37


8.10
8.08
7.78
7.76
7.74
7.60
7.58
7.56
O
CN
F F
39
2.0
1.0
2.0
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
181.30
181.03
180.75
136.28
130.43
130.41
130.38
129.49
129.22
129.19
129.17
110.67
110.25
109.83
108.72
106.13
103.54
O
CN
F F
39
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

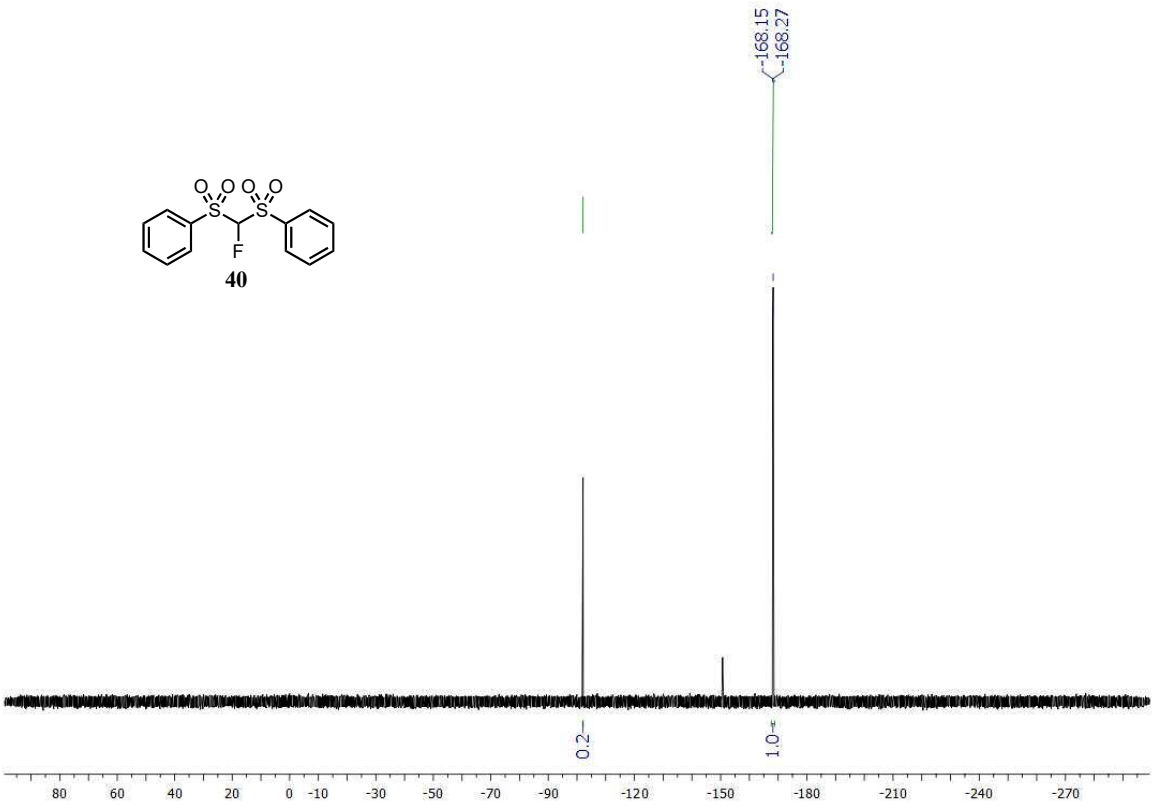


39

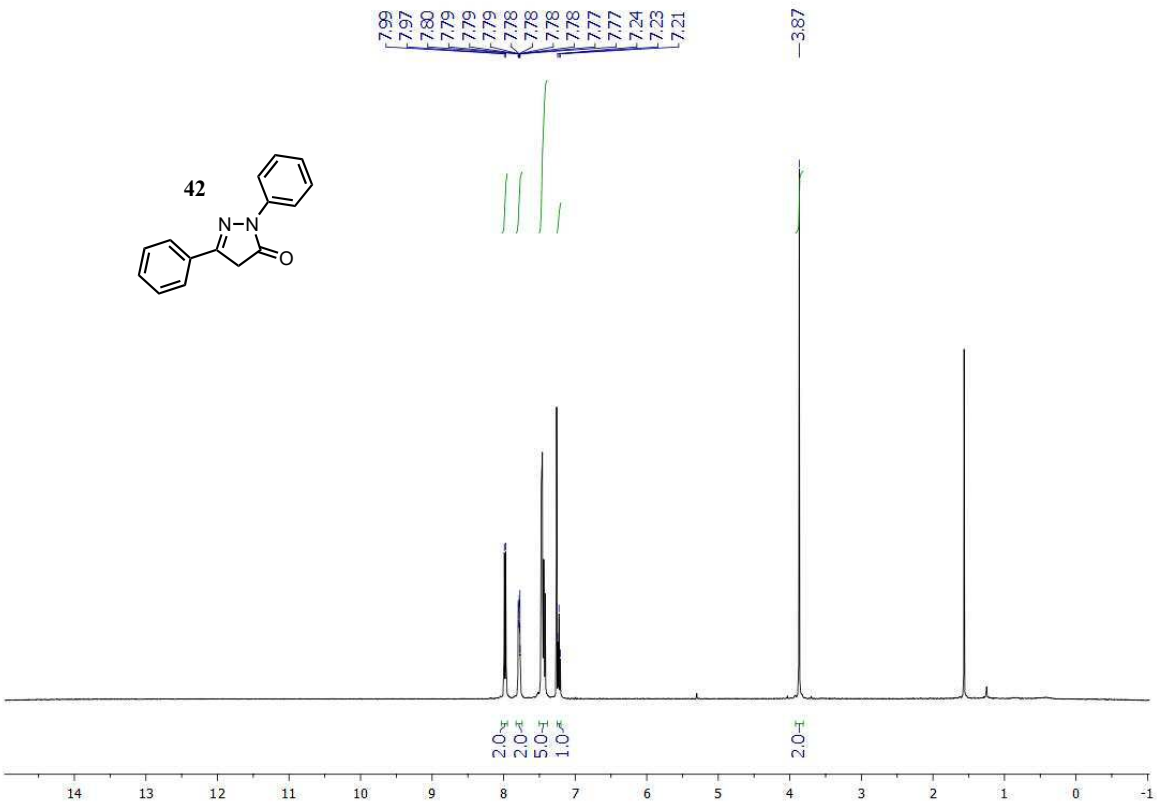

8.07
8.05
8.00
8.00
7.98
7.98
7.96
7.84
7.82
7.80
7.80
7.80
7.79
7.79
7.78
7.77
7.77
7.76
7.76
7.75
7.68
7.66
7.65
7.64
7.64
7.62
7.62
7.61
7.60
5.77
5.66
4.07
2.07
4.00
0.97
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
135.86
135.47
130.34
129.64
106.95
104.83
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

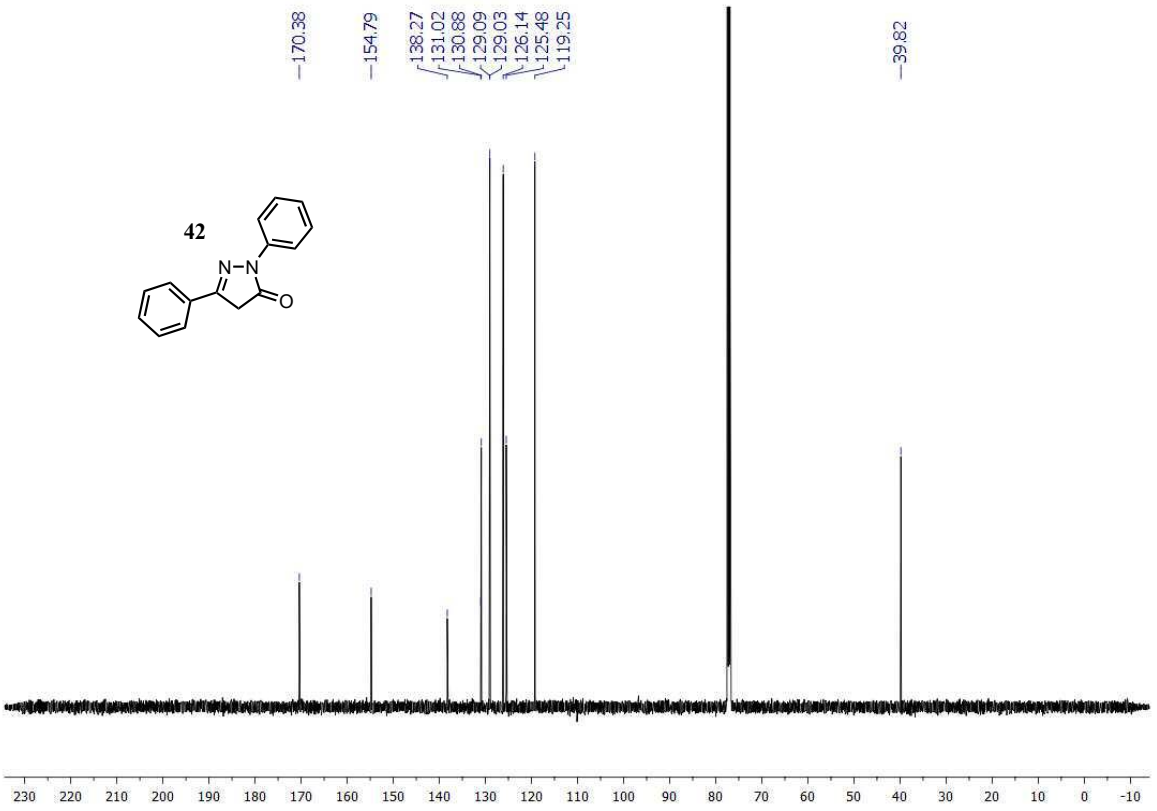
40

40


-168.15
-168.27
0.2
1.0
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

40


42
7.99
7.97
7.80
7.79
7.79
7.79
7.79
7.78
7.78
7.78
7.78
7.77
7.77
7.24
7.23
7.21
3.87
2.0
2.0
5.0
1.0
2.0


42
170.38
154.79
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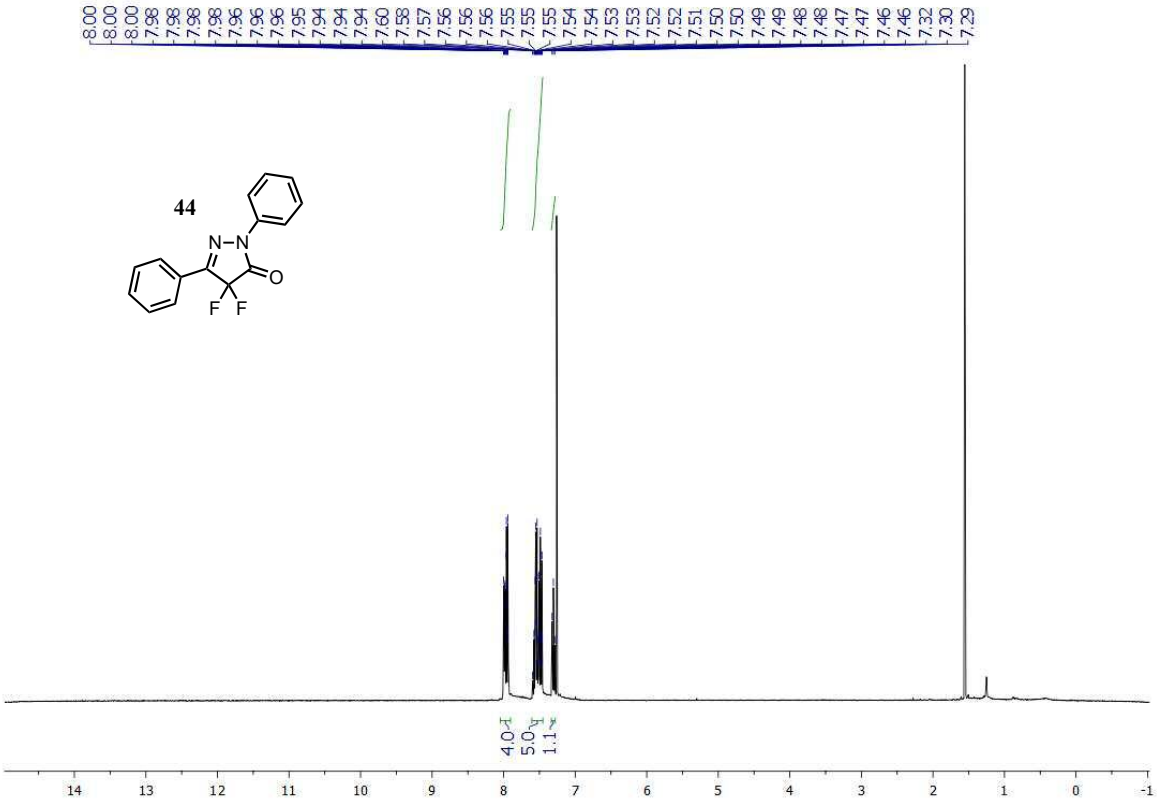
130.88
129.09
129.03
126.14
125.48
119.25
39.82


8.00
8.00
8.00
7.98
7.98
7.98
7.98
7.96
7.96
7.96
7.95
7.94
7.94
7.94
7.60
7.58
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7.56
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7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.32
7.30
7.29
44
N
N
O
F
F
4.0
5.0
1.1
14
13
12
11
10
9
8
7
6
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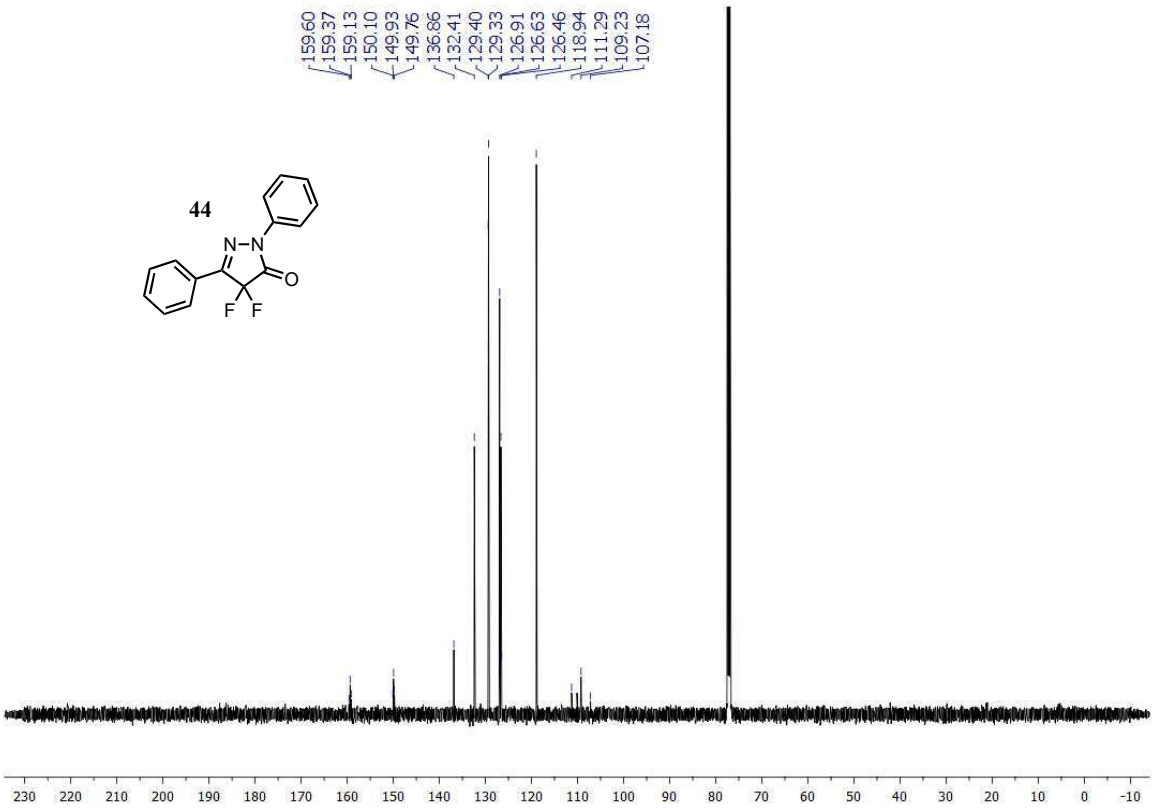
2
1
0
-1


159.60
159.37
159.13
150.10
149.93
149.76
136.86
132.41
129.40
129.33
126.91
126.63
126.46
118.94
111.29
109.23
107.18
44
N
N
O
F
F
230
220
210
200
190
180
170
160
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140
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120
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100
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80
70
60
50
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30
20
10
0
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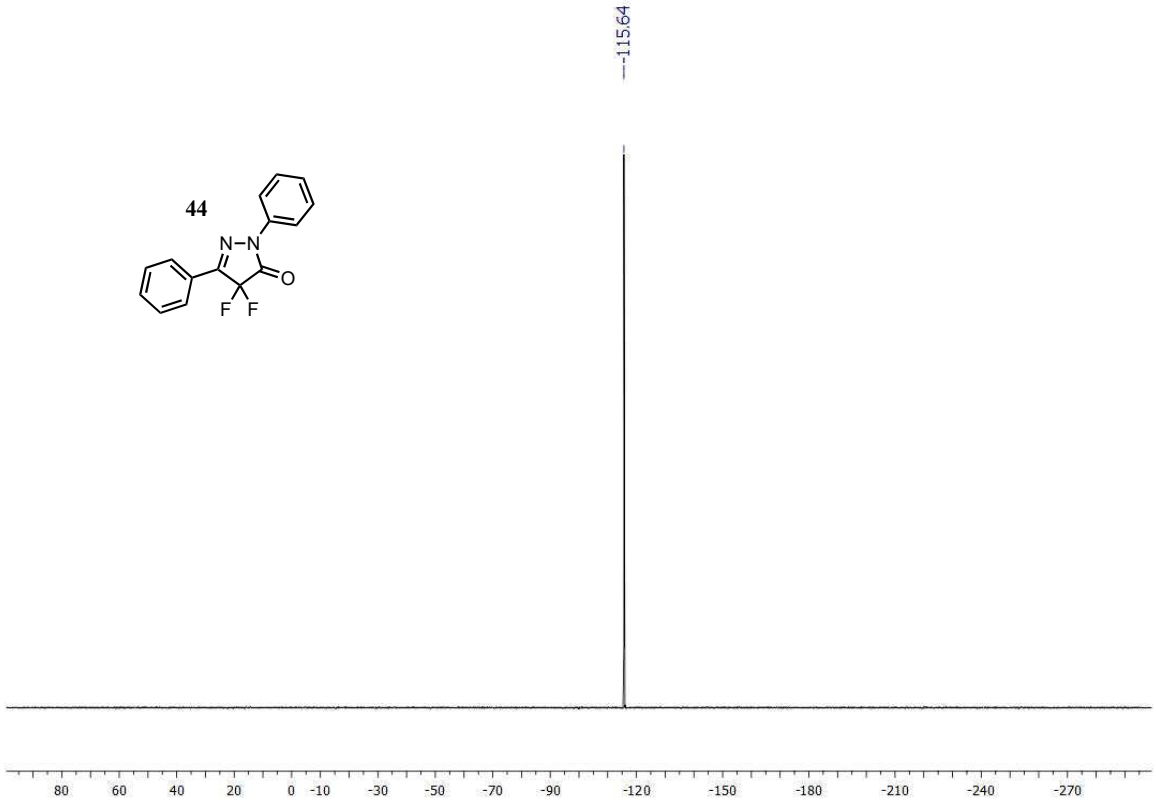
-115.64
44
N
N
O
F
F
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

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Published Papers

Full Paper

Protected Diazonium Salts: A Continuous-Flow Preparation of Triazenes Including the Anticancer Compounds Dacarbazine and Mitozolomide

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Herein, we report a continuous-flow process for the preparation of triazenes, whereby diazonium salts are generated and converted into their masked or protected triazene derivatives. Key to realizing the process, which is applicable to a wide range of substrates, is the identification of solvent and reagent parameters that avoid fouling and clogging in the tubing used in these studies. The process has also been applied to prepare the antineoplastic agents mitozolomide and dacarbazine. We also report isolation and differential scanning calorimetry (DSC) analysis of an anthranilic acid-derived triazene whose related diazonium salt is a contact explosive. The data highlights improved stability but also suggests that an exothermic process does occur with an onset temperature of 118 °C. Finally, an 18-hour continuous operation of the reaction procedure using high-performance liquid chromatography (HPLC) pumps is reported.

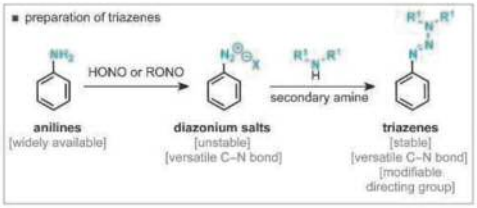
Keywords: triazenes, diazonium, salts, anti-cancer, compounds

1. Introduction

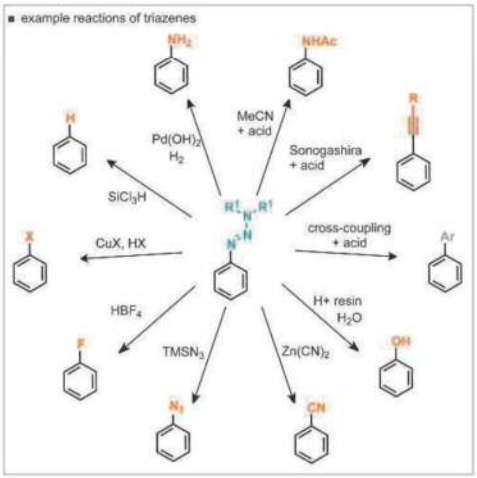
AQ4 AQ3 Chemical functional groups containing nitrogen are ubiquitous across the physical and biological sciences. Indeed, nitrogen and the amine functional group in particular are present in a large number of products from commercial suppliers of fine chemicals. However, it is notable that there are still very few methods for the activation and use of a C–N bond as a tool for the construction of more complex molecules, with the formation and use of diazo- and diazonium compounds being the most widely adopted process to achieve this goal [1]. However, there are several drawbacks to the use of diazonium compounds, not the least of which include the associated safety hazards that are well documented particularly with isolating these intermediates [2]. Unsurprisingly then, the formation and use of diazo- and diazonium compounds have been well explored under continuous-flow conditions, and indeed, this research continues to produce exciting results and is clearly a rich seam which will be further explored [3, 4]. An alternative method for the safe handling of diazonium compounds is to trap them as their more stable and protected triazene forms by reaction S1 with a secondary amine (Scheme 1) [5].

AQ5 Triazenes themselves are an exciting class of compounds displaying much of the reactivity of diazonium salts, but in recent years, they are also being demonstrated to direct catalytic or stoichiometric metalation reactions [6, 7]. Under acidic conditions, triazenes exist in equilibrium with their diazonium congeners; thus, their use as a protecting group is reversible to unveil the latent reactivity of a diazonium compound. Thus, triazenes can be converted to the corresponding azides by treatment with a Lewis S2 acid and $TMSN_3$ (Scheme 2) [6a]. Alternatively, the diazonium can be unveiled and then participate in palladium coupling chemistries such as Sonogashira, Suzuki, and amino-carbonylation reactions — with all of these processes occurring in one-pot operations from the triazene material [6b–e]. Traditional Sandmeyer chemistry can be conducted using the appropriate copper salt with addition of acid[6f]. The Balz–Schiemann fluorination reaction is also applicable where treatment with HBF_4 provides the desired transformation [6g]. With regards to directing metalation reactions, triazenes have been successfully used to guide S3 *ortho*-deprotonation using *sec*- or *tert*-butyllithium (Scheme 3). In the former case, carbon dioxide was used as a quench, leading indirectly to anthranilic acid-derived triazenes, whereas, in the latter case, the lithium was transmetalated to magnesium and then added to a cyclobutanone intermediate on the way towards the synthesis of welwitindolinone A isonitrile [7a]. More recently, AQ6 Hafner and Bräse demonstrated that a silver-mediated trifluoromethylation reaction was directed to the *ortho* position by the triazene handle [7b], while Huang showed that Rh (III) can be

Scheme 1. Preparation of triazenes from diazonium compounds



Scheme 2. Examples of the conversion of triazenes to other functional groups



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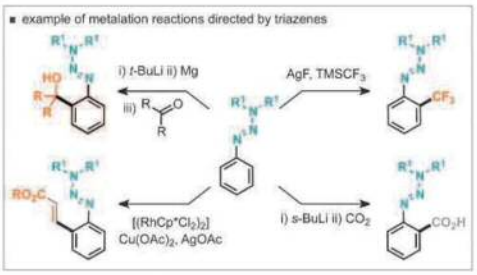
Scheme 3. Examples of the use of triazenes to direct metalation reactions



used to catalyze C–H olefination reactions *ortho* to a triazene directing group [7c].

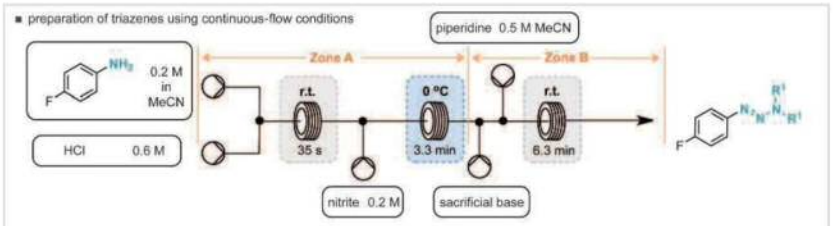
Therefore, the most exciting facet of the triazene functional group is the combination of these properties, whereby they can be installed starting from a wide variety of commercially available anilines and then used to direct controlled and selective catalytic C–H functionalization processes before being removed under acidic conditions to participate in diazonium type reactivity. Owing to this, they have been classified as a "functionalizable or modifiable directing group" [8].

Continuous-flow processing is suited for the preparation of hazardous intermediates such as diazonium compounds because they can be made and consumed within the same reactor series [9]. Thus, the total of hazardous material at any one point in time is very small. It is equal to the volume of the "hot-section" ("hot" being used to describe the section of tubing between the formation and consumption of the hazardous material) multiplied by the concentration. If the reactor is operating under segmented flow conditions where the segment volume is less than that of the "hot volume," the volume of hazardous material is just determined by the volume of the segment. In any case, the total volume of hazardous material is small. In batch mode, however, the quantity of hazardous material per unit time is directly related to the bulk reaction volume. At scale, therefore, the bulk preparation of a hazardous and potential explosive intermediate is a huge risk that could be mitigated by conducting the reaction under continuous conditions. While triazenes are protected forms of diazonium salts, they are most commonly accessed through a batch-wise preparation of the diazonium followed by quenching with a secondary amine; thus, the hazard still exists and has the opportunity to present itself during the process. We were therefore interested in establishing a multistep flow process [10] for the in situ diazotization of amines and subsequent trapping as a triazene functionality that could then be further manipulated or stored.

2. Results and Discussion

2.1. Initial Setup. From the outset, we were mindful that one of the key challenges for establishing a flow process for this chemistry would be identifying optimal solvent combination ratios to avoid precipitation and fouling of the tubular reactors [11]. This was especially true as there are some reports that highlight the possibility for diazonium salts to precipitate and behave as contact explosives [2a]. Specifically, a survey of the literature methods for the batch preparation of triazenes highlighted a common factor of the use of a mineral base in combination with the basic secondary amine of interest [6, 7]. The mineral base (such as K_2CO_3) is typically added to neutralize the acidic conditions necessary for the diazonium forming reaction with the amine and then present solely as a reactant to feature in the product. The mineral base is therefore sacrificial in nature. As shown in Scheme 4, our initial setup consequently S4 consisted of the merging of five streams to a common flow line to effect two reactions: first, the diazotization of the aniline by combining with an acid and a nitrite followed by passage through a small cooled reaction coil (Scheme 4, zone A) and, second, neutralizing this with a sacrificial base and merging with the required amine and passing through another reaction coil (Scheme 4, zone B) to form a triazene. It was found that the use of isoamyl nitrite rather than sodium nitrite meant that acetonitrile instead of water could be incorporated as a solvent within our reactor and keep materials in solution (Scheme 4 cf. entries 1 and 2). We then explored the behavior in zone B and found that the addition of an aqueous solution of a mineral base (K_2CO_3) leads to rapid precipitation at the T-piece due to insolubility in the diluted organic solvent. We conducted some observational batch experiments to identify conditions that would lead to homogenous mixtures yet still afford good conversion (using ^{19}F nuclear magnetic resonance (NMR) as a conversion guide). It was found that the use of Et_3N as base avoided precipitate formation but also resulted in complex

Scheme 4. Initial reactor setup and optimization of conditions



Entry	Setup	Nitrite Source/Solvent	Sacrificial Base/Solvent	Observations
1	zone A only	$NaNO_2$ in H_2O	–	precipitate formed
2	zone A only	isoamyl nitrite in MeCN	–	no precipitate formed
3	zone A + B	isoamyl nitrite in MeCN	K_2CO_3 in H_2O	precipitate formed in zone B
4	batch flask	isoamyl nitrite in MeCN	$NaHCO_3$ in H_2O	precipitate formed - triazene formed
5	batch flask	isoamyl nitrite in MeCN	Et_3N in MeCN	no precipitate formed - complex mixture
6	batch flask	isoamyl nitrite in MeCN	DMAP in MeCN	no precipitate formed - triazene formed
7	batch flask	isoamyl nitrite in MeCN	piperidine in MeCN	no precipitate formed - triazene formed
8	**zone A + B**	**isoamyl nitrite in MeCN**	**piperidine in MeCN**	**no precipitate formed - triazene formed - 48% yield**

mixtures as observed by ^{19}F NMR of the crude reaction material. Conversely, both dimethylaminopurine (DMAP) and piperidine provided positive results in both homogeneity and NMR analysis. Therefore, piperidine was chosen as both the sacrificial base and the amine nucleophile and, thus, delivered via a single pump in a total of 4.5 equivalents. Under continuous conditions, this afforded a 48% isolated yield of the triazene product without any solids formation (**2**). The sub-optimal yield in this particular case is due to a competing nucleophilic aromatic substitution reaction where the triazene is acting as a *para*-electron-withdrawing group to the fluorine leaving group with a piperidine nucleophile.

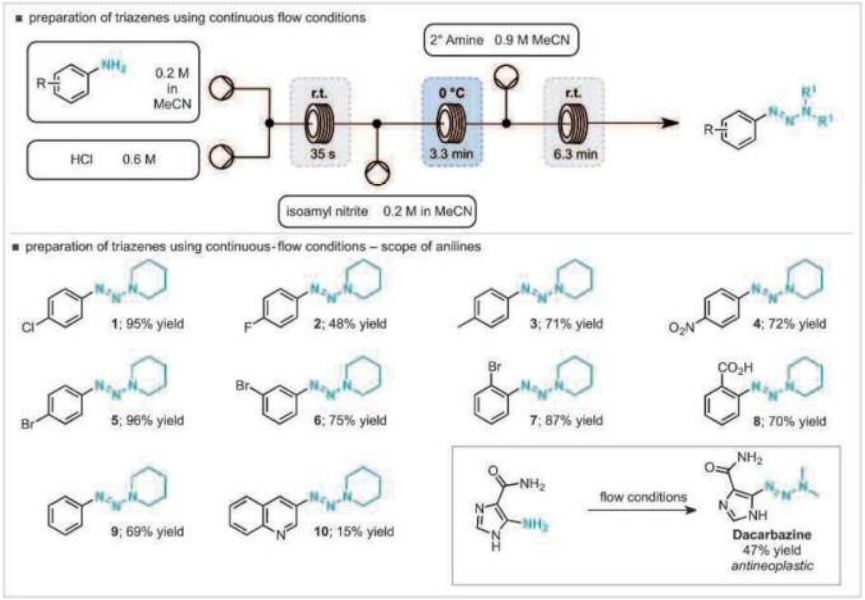
2.2. Aniline Scope. With these conditions in hand, the setup was used next to investigate the scope of the process with respect to aniline — paying particular attention to problems associated with fouling or clogging arising from covering a S5 cross-section of substrates (Scheme 5). Initially, it was found that the *para*-chloroaniline underwent the continuous process without incident, and indeed, in this case, an improved yield of 95% (**1**) was isolated, supporting the notion of a competing S_NAr process for the fluoro derivative. It was found that a range of halogen bearing anilines all proceeded in good isolated yield without incident in the reactor, including *ortho*-, *meta*-, and *para*-bromo-anilines (**5**, **6**, and **7**). Notably, the workup of the products is very straightforward with a simple liquid–liquid extraction affording products that were typically greater than 90% purity. *para*-Nitro aniline did not proceed as straightforwardly as other examples, also likely arising from S_NAr type reactivity but, this time, with N_2 gas as the leaving group of the diazonium intermediate. Indeed, outgassing, leading to segments of gas and liquid, was visible in this example. However, an isolated yield of 72% of the desired triazene (**4**) could be achieved following column chromatography.

Most notably, the triazene of anthranilic acid (**8**) was directly made using flow conditions. The diazonium salt of which is known to lose nitrogen and carbon dioxide gas to generate benzyne in situ which can react exothermically if adequate temperature control is not provided. During the course of this work, we have been unable to find experimental literature evidence as to the stability of triazenes compared to diazonium counterparts. Much literature cites that these materials are stable, and we have not found reports of them being explosive. While a lack of data suggests that they are inherently more stable (literature is available on this topic for diazonium salts), it does not afford hard evidence. We therefore decided to run differential scanning calorimetry (DSC) of the anthranilic acid-derived triazene (**8**). This material was found to be readily isolated with a workup procedure following that of the other triazene examples prepared. The DSC data (Scheme 6) show S6 that this triazene has an endothermic phase transition (melting) with an onset temperature of 84 °C; this is followed by a strongly exothermic process that is 10 times bigger than the melting phase change with an onset temperature of 118 °C. Notably, this exotherm is broad in shape and heating does not accelerate which signifies that this is not a runaway or sudden energy release.

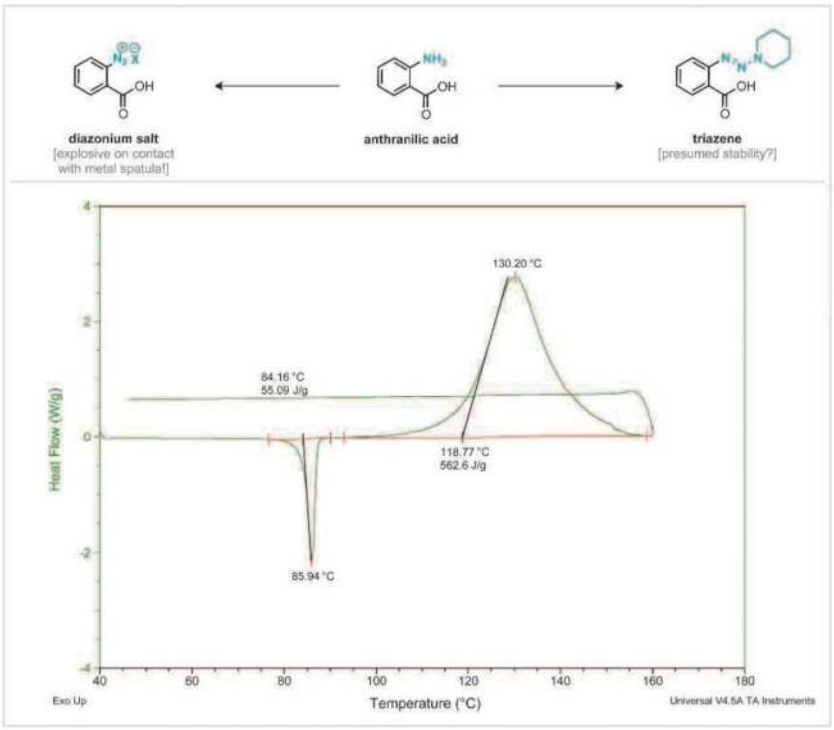
This data fully supports the notion that triazenes are more stable than diazonium salts, but one should demonstrate caution if heating the neat solid materials.

We also used our reactor system to prepare the antineoplastic compound dacarbazine, which features on the World Health Organization (WHO) model list of essential medicines [12]. Dacarbazine is active against metastatic melanoma by a DNA alkylating mode of action [13]. Here, it was prepared starting from the requisite amino imidazole and using a solution of dimethylamine in THF as the secondary amine nucleophile (Scheme 5). By delivering the amine in a changed solvent system, this may have had a knock-on effect on the isolation of the product which is also more aqueous soluble than the other materials prepared; nonetheless, dacarbazine was isolated in 47% yield.

Scheme 5. Reaction scope with respect to aniline component

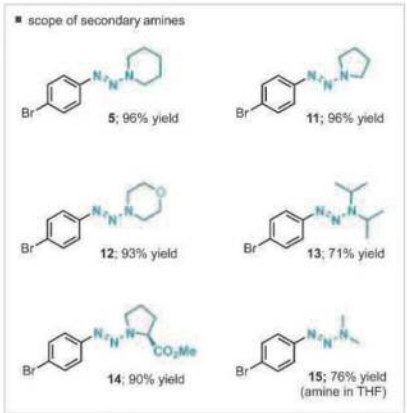


Scheme 6. Differential scanning calorimetry plot of the anthranilic acid-derived triazene



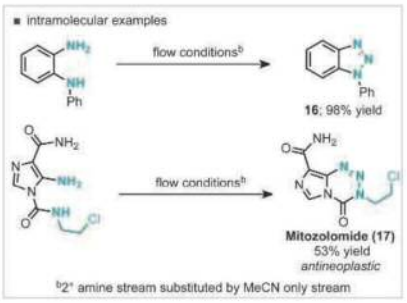
2.3. Secondary Amine Scope. Next, the scope with respect to secondary amine was explored, again, paying attention to any precipitate or fouling of the tubes across a variety of substrates. In addition to piperidine, it was also found that pyrrolidine (**11**), morpholine (**12**), diisopropylamine (**13**), and dimethylamine (**15**) were functional in the flow process without precipitate formation (Scheme 7). The resulting products were all formed in good to excellent yields. In addition, we have prepared the *S*-proline-methylester-derived triazene (**14**) in 90% isolated yield (Scheme 7). It is noteworthy that all triazenes reported here exhibit restricted rotation type behavior. This leads to temperature-dependent coalescence. Importantly, for the default room temperature ^{13}C NMR spectra of these compounds, the signals corresponding to the alpha carbons to nitrogen (of the amine component) are extremely broad and not readily discernible from the baseline. This appears to be congruent with supporting data files in other literature that concerns the preparation of triazenes but is not mentioned or noted as a general observation or phenomena [14]. We are actively exploring the rotation barriers and variable temperature NMR behavior of these materials. In addition to this, the signals of the attached protons also appear unexpectedly broad and do not show the expected (any) coupling patterns in the ^{1}H NMR spectra (see electronic Supporting Information for a brief account of this). X-ray crystallography has been used to verify and confirm the prepared material as a triazene, and variable temperature studies of the same molecule show a coalescence effect.

Scheme 7. Reaction scope with respect to secondary amine component



In addition to intermolecular examples, we also briefly explored intramolecular triazene formation where the amine component is tethered to the formed diazonium (Scheme 8). Indeed, treatment of *N*-phenyl-*o*-phenylenediamine to the flow reactor system furnished the benzotriazole product (**16**) in excellent isolated yield [15]. It was at this juncture that we were also able to prepare the antineoplastic agent mitozolomide (**17**) [16]. Treatment of the previously used dacarbazine aminoimidazole with the appropriate alkylisocyanate furnished the starting material for the flow reactor process. Application of this

Scheme 8. Intramolecular triazene examples including mitozolomide



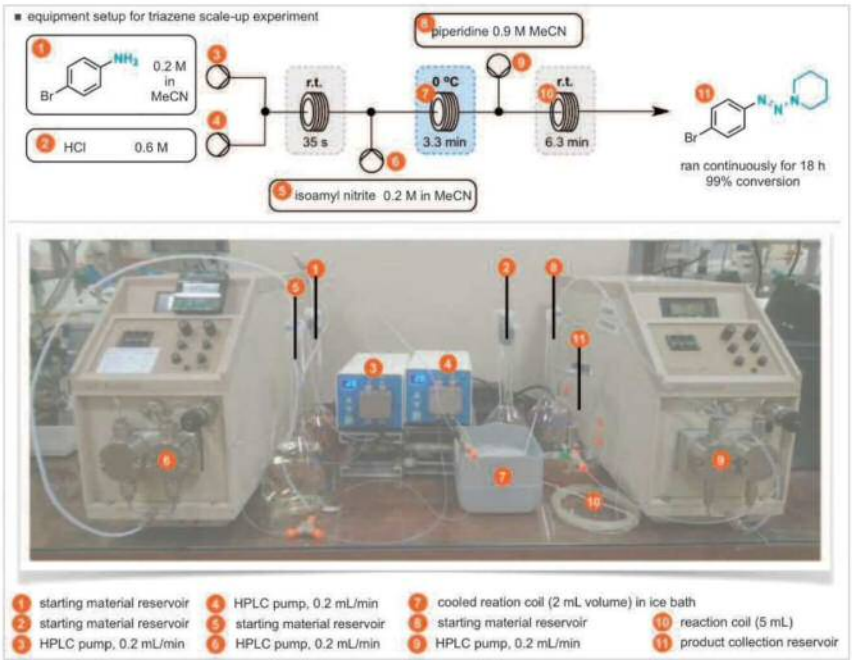
material to the flow conditions provided mitozolomide in 53% isolated yield. Again, in this instance, we suspect that the isolated yield is relatively low due to partition coefficients during the workup phase.

2.4. Large-Scale Experiment. Finally, we were mindful that, until now, the triazene materials had been prepared on relatively small scales (1–2 mmol) due to the use of single-shot syringe pumps delivering the reagents to the reactor in relatively low concentrations (these were necessary to avoid precipitation). We therefore switched our reactor setup to incorporate the use of high-performance liquid chromatography (HPLC) pumps that could continually process directly from solvent reservoir bottles. S9 Our setup is shown in Scheme 9 and comprises of four 2-piston HPLC pumps, the reactor coils, and solvent reservoirs. We chose 4-bromoaniline and piperidine as the substrates for this process demonstration. In the event, the material was processed continuously for 18 h without fouling or clogging of the reactor. In the normal fashion, low dilution leads then to a bottleneck in the downstream processing of the product solution which becomes laborious, unless an inline workup method is incorporated [17]. For the first hour of processing, the sample was collected and extracted in the usual batch-way to afford 92% isolated yield of the desired product (**5**). We proceeded to "spot-check" at time points beyond this and analyzed material by NMR spectroscopy. This highlighted that the pump flow rates deviated from the desired set point and, thus, led to less pure samples and drew our attention to the issues such as low reagent levels, pump priming, and back-washing of the pumps to get the process back on track and within the defined specification.

3. Conclusion

In summary, we have reported a continuous-flow process for the preparation of triazenes with the in situ generation and consumption of diazonium salts. Key to realizing a process was the identification of solvent and reagent parameters that would avoid fouling and clogging in the 0.8-mm ID tubing used in these studies. The process has also been applied to a wide range of substrates and the preparation of intramolecular examples including the antineoplastic mitozolomide and the dimethylamine intermolecular adduct dacarbazine. We also report isolation and DSC analysis of an anthranilic acid-derived triazene whose related diazonium salt is a contact explosive highlighting improved stability. Finally, we demonstrated an 18-hour continuous operation of the reaction procedure using HPLC pumps to deliver the material.

Scheme 9. Setup for continuous experiment using HPLC pumps in place of single-shot syringe systems



4. Experimental

4.1. General Methods. All reagents and solvents were commercially available and were used without further purification if not stated otherwise. Petroleum ether refers to the 40–60 °C fraction.

For the measurement of ^{1}H, ^{13}C, and ^{19}F NMR spectra, a Bruker Fourier^{300} (300 MHz), 400 UltraShield™ (400 MHz), or Ascend™ 500 (500 MHz) was used. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal or to the standard trifluorotoluene (−63.72 ppm) in ^{19}F NMR. Spin–spin coupling constants J are given in Hz. ^{13}C spectra are reported as obtained at default temperature (room temperature about 18 °C).

The flow setup consisted of perfluoroalkoxy (PFA) tubing of 0.8 mm ID and two pumps. The residence coils were made from the tubing by taking the appropriate length for the desired volume.

Column chromatography was performed using 60 A (40–64 μm) silica and solvent mixtures of petroleum ether and ethyl acetate or dichloromethane.

High resolution mass spectral (HRMS) data were obtained on a Waters MALDI-TOF mx at Cardiff University or on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Infrared (IR) spectra were obtained from a Shimadzu IR-Affinity-1S FTIR and melting points using a Gallenkamp apparatus and are reported uncorrected.

DSC measurements were performed using a TA instruments Q100. The sample was heated to 160 °C from 40 °C using a 5 °C/min gradient.

References to spectroscopic data are given for known compounds.

4.2. General Method for the Preparation of Triazenes 1–10 in Flow (Scheme 5). Solutions of the aniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3 × 20 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If the purity of the product did not exceed 90%, the crude product was further purified by column chromatography.

AQ7

- 1-((4-Chlorophenyl)diazenyl)piperidine (**1**) [6 h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.24–7.19 (m, 2H), 3.77–3.63 (m, 4H), 1.71–1.54 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 131.0, 129.0, 122.0, 25.5, 24.5.
- 1-((4-Fluorophenyl)diazenyl)piperidine (**2**) [18]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.37 (m, 1H), 7.05–6.98 (m, 1H), 3.81–3.69 (m, 2H), 1.77–1.64 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 160.0, 147.5 (d, J = 2.9 Hz), 129.0, 122.0 (d, J = 8.1 Hz), 116.5, 115.5 (d, J = 22.4 Hz), 48.5, 25.5, 24.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.01 (s, 1F).
- 1-((4-Methylphenyl)diazenyl)piperidine (**3**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.17–7.10 (m, 2H), 3.81–3.67 (m, 4H), 2.34 (s, 4H), 1.79–1.61 (m, 6H). HRMS (EI+): [$C_{12}H_{17}N_3$] calc. 203.1422, found 203.1423.
- 1-((4-Nitrophenyl)diazenyl)piperidine (**4**) [6h]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.14 (m, 1H), 7.54–7.46 (m, 1H), 4.03–3.73 (m, 2H), 1.93–1.58 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 145.0, 125.0, 120.5, 53.5, 44.0, 26.5, 24.5, 24.5.
- 1-((4-Bromophenyl)diazenyl)piperidine (**5**) [14]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 3.77 (d, J = 5.6 Hz, 2H), 1.70 (d, J = 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.5, 25.5, 24.5.
- 1-((3-Bromophenyl)diazenyl)piperidine (**6**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 1H), 7.38–7.33 (m, 1H), 7.31–7.25 (m, 1H), 7.24–7.18 (m, 1H), 3.86–3.76 (m, 4H), 1.83–1.65 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 130.0, 128.0, 123.0, 123.0, 120.0, 25.5, 24.5.
- 1-((2-Bromophenyl)diazenyl)piperidine (**7**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 1H), 7.–7.39 (m, 1H), 7.29–7.20 (m, 1H), 7.02–6.94 (m, 1H), 3.98–3.70 (m, 4H), 1.81–1.64 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 133.0, 128.0, 126.5, 120.0, 118.5, 25.0, 24.5.
- 2-(Piperidin-1-yldiazenyl)benzoic acid (**8**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.99 (s, 1H), 8.28–8.22 (m, 1H), 7.72–7.68 (m, 1H), 7.53–7.47 (m, 1H), 7.31–7.25 (m, 1H), 3.98–3.90 (m, 2H), 3.88–3.78 (m, 2H), 1.91–1.74 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 148.5, 133.5, 132.5, 126.5, 122.0, 116.0, 54.0, 45.5, 26.0, 24.0, 23.5. HRMS (EI+): [$C_{12}H_{15}O_2N_3$] calc. 233.1164, found 233.1162. m. p. (acetone): 88–89 °C. IR: 2945, 1703, 1704, 1593, 1410, 1109, 766, 692, 608 cm^{-1}.
- 1-(Phenyldiazenyl)piperidine (**9**) [6h]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.37–7.30 (m, 2H), 7.19–7.12 (m, 1H), 3.84–3.71 (m, 4H), 1.77–1.64 (m, 6H). HRMS (EI+): [$C_{11}H_{15}N_3$] calc. 189.1266, found 189.1263.
- 3-(Piperidin-1-yldiazenyl)quinoline (**10**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14–9.07 (m, J = 2.2 Hz, 1H), 8.09–8.04 (m, J = 8.8 Hz, 1H), 8.04–7.99 (m, J = 2.2 Hz, 1H), 7.80–7.75 (m, J = 8.5 Hz, 1H), 7.62–7.56 (m, J = 11.3, 4.0 Hz, 1H), 7.51–7.45 (m, J = 7.5 Hz, 1H), 3.94–3.78 (m, J = 5.5 Hz, 4H), 1.80–1.66 (m, 6H). HRMS (EI+): [$C_{14}H_{16}N_4$] calc. 240.1375, found 240.1373.

4.3. General Method for the Preparation of Triazenes 11–15 in Flow (Scheme 6). Solutions of the *p*-bromoaniline (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and a secondary amine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3 × 20 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica. If the purity of the product did not exceed 90%, the crude product was further purified by column chromatography.

- 1-((4-Bromophenyl)diazenyl)pyrrolidine (**11**) [19]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.31–7.26 (m, 2H), 3.77 (bs, 4H), 2.14–1.88 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 132.0, 122.0, 118.0, 51.0, 46.5, 24.0.
- 4-((4-Bromophenyl)diazenyl)morpholine (**12**) [20]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.42 (m, 2H), 7.37–7.28 (m, 2H), 3.89–3.82 (m, 4H), 3.82–3.75 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 132.0, 122.5, 120.0, 66.5.
- 1-(4-Bromophenyl)-3,3-diisopropyltriaz-1-ene (**13**) [21]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.31–7.26 (m, 2H), 5.27 (bs, 1H), 3.99 (bs, 1H), 1.30 (bs, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 132.0, 122.0, 117.5, 49.0, 46.0, 24.0, 19.5.

- Methyl(4-bromophenyl)diazenyl)-L-prolinate (**14**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.31–7.25 (m, 2H), 4.66 (bs, 1H), 4.22–3.55 (m, 5H), 2.41–2.28 (m, 1H), 2.25–1.97 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 140.5, 131.5, 122.5, 119.0, 63.5, 59.5, 52.5, 51.0, 47.0, 29.0, 23.0. HRMS (EI+): $[C_{12}H_{14}N_3O_2Br+H]^+$ calc. 312.0348, found 312.0351. IR: 2951, 2876, 1740, 1479, 1427, 1392, 1323, 1148, 1067, 827 cm^{-1}.
- 1-(4-Bromophenyl)-3,3-dimethyltriaz-1-ene (**15**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 1H), 7.33–7.27 (m, 1H), 3.34 (bs, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 132.0, 122.0, 118.50.

4.4. Preparation of Internal Triazenes 16 and 17 in Flow (Scheme 8)

4.4.1. 1-Phenyl-1H-benzo[d][1,2,3]triazole (16) [22]. Solutions of the *N*-phenyl-*o*-phenylenediamine (0.2 M in acetonitrile), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3×20 mL), washed with brine, and dried over $MgSO_4$. After column chromatography (petroleum ether–DCM), the title compound (**16**) was obtained as a colorless solid in 98% yield (0.192 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.12 (m, 1H), 7.83–7.72 (m, 3H), 7.65–7.58 (m, 2H), 7.58–7.47 (m, 2H), 7.47–7.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 137.0, 132.5, 130.0, 129.0, 128.5, 124.5, 123.0, 120.5, 110.5.

4.4.2. 3-(2-Chloroethyl)-4-oxo-3,4-dihydroimidazo[5,1 d][1,2,3,5] tetrazine-8-carboxamide (17, Mitozolomide) [23]. To a solution of 5-aminoimidazole-4-carboxamide (0.631 g, 5.0 mmol) in dry acetonitrile (50 mL) at −7 °C, 2-chloroethyl isocyanate (0.530 g, 1.1 equiv.) in dry acetonitrile (10 mL) was AQ8 added dropwise over 1 h. The mixture was stirred overnight at 25 °C and quenched with water (10 mL), and the product was collected and washed successively with water (10 mL) and ethyl acetate (3×10 mL) to yield 5-amino-N^1-(2-chloroethyl)-1*H*-imidazole-1,4-dicarboxamide as a white solid (72%, 0.838 g) [24].

^{1}H NMR (400 MHz, DMSO) δ 8.78 (t, J = 5.2 Hz, 1H), 7.65 (s, 1H), 7.03–6.66 (m, J = 36.2 Hz, 2H), 6.39 (s, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.60–3.50 (m, J = 5.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 150.5, 143.5, 126.0, 111.5, 43.0, 42.0.

Solutions of 5-amino-N^1-(2-chloroethyl)-1*H*-imidazole-1,4-dicarboxamide (0.2 M) in a mixture of DMSO and acetonitrile (1:4, *v*/*v*), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. The product was extracted with $CHCl_3$ (3×50 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was washed with petroleum ether–diethyl ether (50:50, *v*/*v*, 3×10 mL) and dried under reduced pressure to yield the product as a pale pink solid in 53% yield (0.128 g, **17**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.24 (s, 1H), 6.03 (s, 1H), 4.77 (t, J = 6.0 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 139.0, 134.0, 132.0, 128.5, 50.5, 41.0.

4.5. Method for the Preparation of 5-(3,3-Dimethyltriaz-1-en-1-yl)-1*H*-imidazole-4-carboxamide (Decarbazine)

AQ9 **[25].** Solutions of 5-amino-1*H*-imidazole-4-carboxamide (0.2 M) in a mixture of aqueous HCl (0.6 M) and acetonitrile (3.5:6.5, *v*/*v*), HCl (0.6 M in water), and isoamylnitrite (0.2 M in acetonitrile) were prepared. Together with a fourth stream of acetonitrile, these were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), 20 mL (1 mmol, 25 min) was collected. The product was extracted with $CHCl_3$ (3 × 50 mL), washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was washed with petroleum ether–diethyl ether (50:50, *v*/*v*, 3×10 mL) and dried under reduced pressure to yield the product as a pale yellow solid in 47% yield (0.855 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.91 (bs, 1H), 5.58 (bs, 1H), 2.17 (s, 6H). IR: 3279, 2193, 1709, 1524, 1449, 1371, 1343, 1261 cm^{-1}. HRMS (AP+): $C_6H_{10}N_6O+Na]^+$ calc. 205.0814, found 205.0796.

4.6. Large-Scale Experiment. Solutions of 4-bromoaniline AQ10 (0.2 M in acetonitrile), HCl (0.6 M in water), isoamylnitrite (0.2 M in acetonitrile), and piperidine (0.9 M in acetonitrile) were prepared. These were then pumped through the flow system (see Scheme 9) at a flow rate of 0.2 mL/min. After reaching steady state (20 min), the reaction was run for 18 h. The first 50 mL (2.5 mmol, 62.5 min) was collected. The reaction solution was neutralized with aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude product was taken up in CH_2Cl_2 and filtered through a plug of silica to yield the clean compound **5** (92%, 0.587 g, 2.3 mmol).

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Supporting Information

Electronic Supplementary Material (ESM), including compound characterization and copies of NMR spectra, is available in the online version at doi: 10.1556/1846.2016.00025.

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Controlling reactivity through liquid assisted grinding: the curious case of mechanochemical fluorination†

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We have identified an example of a mechanochemically milled organic reaction where liquid-assisted grinding controls the selectivity, such a phenomenon has not been reported/observed before. It was found that upon milling dibenzoylmethane with Selectfluor in the absence of any solvent, a 3 : 1 ratio of monofluorinated : difluorinated product was observed. Whereas, addition of 0.125 mL of acetonitrile (~10% of the total volume of materials present) to the ground reaction mixture afforded 50 : 1 selectivity. Furthermore, this phenomenon is applicable to a small range of diketone substrates thus far explored. Additionally, we have demonstrated that difluorination can be achieved by simply switching from adding acetonitrile to addition of sodium carbonate. Most notable, in the latter case, is the reduced reaction time compared to a conventional solvent approach, 2 hours in the mill and 24 hours in the flask.

Mechanochemical milling methods represent an attractive process for the preparation of chemical products from a sustainability perspective.[1] The concept of running reactions in the neat phase without solvent waste is irrefutably an important pursuit for a more sustainable future.[2] Indeed, recent advances in the area of metal organic frameworks have demonstrated that such processes can be scaled to the manufacture level using a twin screw extrusion apparatus.[3] Such equipment is already present in many industrial manufacturing plants for formulation, where reliable processing of powdered materials is necessary to meet regulatory demands. Most notably, this chemical processing tool has been found to vastly increase space time yields for MOF preparation. Still, solid-state milling, as applied to synthetic organic chemistry, is a relatively underexplored area given the potential gains that could be made against the economy and environment. In large part, we believe that the slow uptake of this technology is attributable to both a lack of understanding of the potential enabling attributes for organic synthesis and a poor understanding of how to optimize reactions (with respect to yield) through control of the operating parameters.[1c,4] Liquid assisted grinding (LAG) represents one such phenomenon whereby the addition of small amounts of liquid can have a profound effect on the outcome of a milled reaction. Recently it was reported

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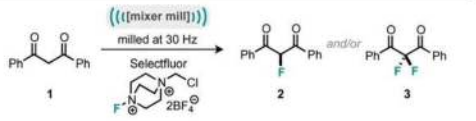
Table 1 Optimization of conditions for the selective mono or difluorination of dibenzoylmethane under mechanochemical conditions[a]



Entry	Selectfluor (equiv.)	Time (h)	Additive	2[b] [%]	3[b] [%]
1	1	1	—	53%	4%
2	2	1	—	87%	11%
3	2	0.5	—	53%	4%
4	2	1	MeCN (0.25 mL)	79%	0%
5	2	2	MeCN (0.25 mL)	91%	7%
6	2	2	—	61%	38%
7	2	2	H_2O (0.25 mL)	0%	0%
8	2	2	i-PrOH (0.25 mL)	9%	3%
9	2	2	PhMe (0.25 mL)	30%	2%
10	2	2	CH_2Cl_2 (0.25 mL)	20%	0%
11	**2**	**2**	**MeCN (0.125 mL)**	**100%**	**0%**
12	**2**	**2**	**Na_2CO_3 (1 equiv.)**	**6%**	**94%**
13	2	2	K_2CO_3 (1 equiv.)	2%	87%
14	2	2	Cs_2CO_3 (1 equiv.)	2%	68%
15	2	2	$CaCO_3$ (1 equiv.)	53%	19%

[a] Dibenzoylmethane (1 mmol), Retsch MM400, 10 mL stainless steel milling jars with one 10 mm (4 gram) stainless steel ball. [b] Determined by ^{19}F NMR with trifluorotoluene as internal standard, remaining mass balance is recovered starting material.

that both the quantity and nature of added liquid can result in the switching between polymorphs.[5] Herein we describe a related observation concerning LAG for a synthetic fluorination reaction. Fluorinated molecules are in ever increasing demand due to their ability to dramatically enhance the properties of materials.[6,7]

Given the prevalence of the carbon–fluorine bond in a range of important chemicals we were keen to investigate whether such a bond can be formed using solid-state milling techniques. Initial investigations commenced by treating solid dibenzoylmethane (**1**) with one equivalent of Selectfluor under mechanochemical mixer mill conditions. The reactions were performed on a 1 mmol scale in 10 mL stainless steel jars with one stainless steel ball (10 mm, 4.0 g) and with a frequency of 30 Hz applied. Temperature is a difficult variable to control under milling conditions, but in all cases described here the jars were cool enough to handle immediately following the end of the grinding period, thus suggesting that the jar itself did not exceed 50 °C.

Pleasingly, after milling for 1 hour with equal reagent stoichiometries, a 53% yield of the monofluorinated product (**2**) was obtained (Table 1, entry 1) with 4% of the difluorinated material (**3**) also present. The remaining mass balance was confirmed to be starting material (**1**). Initially increasing the equivalents of Selectfluor resulted in 87% of mono- and 11% difluorinated product (Table 1, entry 2). Addition of a liquid, so called liquid assisted grinding or LAG, appeared to slow down the reaction, but most importantly, increased the selectivity towards the monofluorinated product (Table 1, entry 4).[8] Pushing the LAG reaction conditions further by increasing the time to two hours resulted in complete consumption of starting material with a 91 : 7 ratio of mono- to difluorinated products (Table 1, entry 5).

Neat milling under the same conditions resulted in inferior selectivity of 3 : 2, indicating that LAG is enabling improved selectivity. The nature of the liquid used for liquid assisted grinding was also explored, with isopropanol, toluene and dichloromethane all providing vastly inferior results (Table 1, entries 8–10). Interestingly, added water seemingly resulted in a complete inhibition of the reaction, although notably Selectfluor is known to not be degraded by water (Table 1, entry 7).[9] Reducing the amount of added acetonitrile from 0.250 mL to 0.125 mL (~10% of the total volume of all materials in the milling jar) resulted in further improvements to 100 : 0 (*i.e.* no difluorination). To put these results into perspective the solvent based reaction was also performed (in a similar fashion to Banks and co-workers), but with two equivalents of Selectfluor to make for a more accurate comparison.[10] It was found that this method requires 3.5 hours to reach completion and afforded excellent selectivity (Fig. 1). Also explored was the opportunity of proceeding directly to the difluorinated compound by simply adding base to the milled reaction. Addition of one equivalent of sodium carbonate provided an isolated yield of 90% of a 9 : 1 mixture of di- to monofluorinated products, again within 2 hours (Table 1, entry 12). Other carbonate bases proved less effective to mediate this transformation.

When compared to the analogous solvent based reaction, the most notable observation was the reduced reaction time afforded by the mechanochemical technique, 24 hours against 2 hours (Fig. 1).

In order to further probe these observations and see if they are more generally applicable, the monofluorination conditions with and without LAG for a small range of other 1,3-diketones were assessed (Fig. 2). It was found, in all cases examined, that addition of 0.125 mL of acetonitrile to the solid reagents provided superior selectivity ratios to those without added acetonitrile, with all other variables remaining constant. In a similar manner, the generality of the observation that mechanochemical milling results in a reduced reaction time for the difluorination was also explored across the same range of substrates (Fig. 3). Indeed, this was found to be true: milling this reaction results in significantly faster conversion to the desired product for all cases explored. Having assessed the reactivity of 1,3-diketones with Selectfluor under mechanochemical conditions we turned to β-ketoesters which

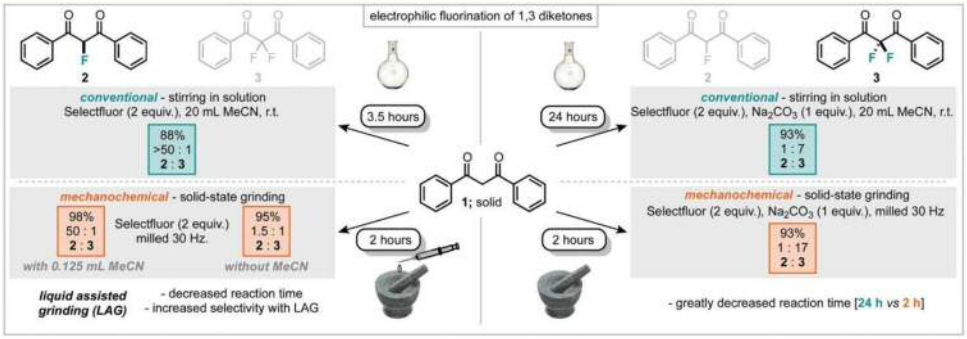


Fig. 1 Summary of key mechanochemical observations and comparison to solvent based method. Isolated yields reported.

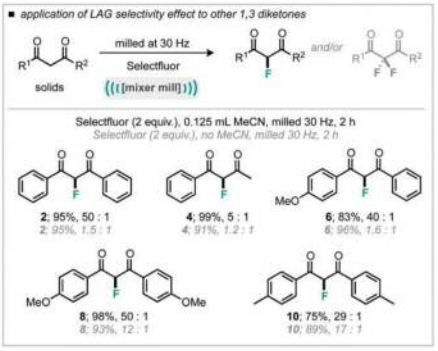


Fig. 2 Scope of the enhanced selectivity effect afforded by liquid assisted grinding of mechanochemical monofluorination reactions of 1,3-diketones.

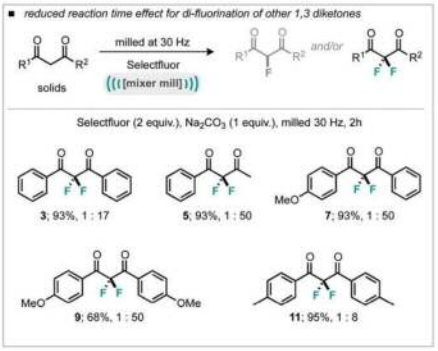


Fig. 3 Scope of the reduced reaction time effect afforded by solid-state grinding of mechanochemical difluorination reactions of 1,3-diketones.

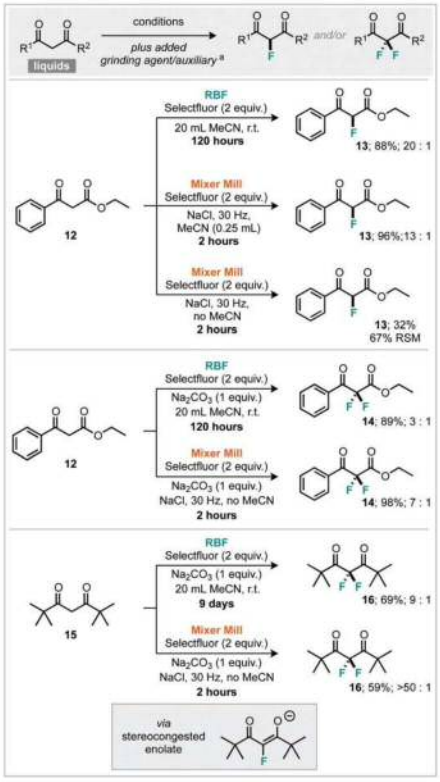


Fig. 4 Summary of key mechanochemical observations and comparison to solvent based method for liquid substrates. Isolated yields reported. [a] NaCl used as a grinding agent/auxiliary/adsorbent for liquid reactants. The amount used is equal to twice that of the total of all other reactants.

are both less reactive and liquid substrates.[10] Milling of liquid/solid mixtures can result in the gumming of the reactor vessel and therefore poor mass transfer. Additionally, low boiling liquids can vaporize and release from the milling jars if appropriate care is not taken. To account for this, it is common to use an auxiliary material such as silica, alumina, talc or inorganic salts as a milling agent/auxiliary or adsorbent.[11] In synthetic organic reactions some such materials could be considered far from innocent (such as the base used in Fig. 3!). In pharmaceutical formulation science these materials are termed 'glidants' or 'lubricants' and assist in the uniform passage of powdered materials through screw extruders.[12] On exploring the mechanochemical electrophilic fluorination of ethyl benzoylacetate, it was found that sodium chloride was a suitable material to permit adequate mass transfer and satisfactory results. Milling of the liquid ethyl benzoylacetate with Selectfluor and NaCl was explored in the presence and absence of LAG and compared to the traditional solvent based round bottom flask reaction (Fig. 4). Most striking is the reduction in reaction time that is afforded by the solid-state milling approach (Fig. 4). In this example the solvent based reaction occurs over 120 hours (5 days) whereas the milled reaction, with added acetonitrile, requires only two hours to run to completion! In the absence of (added) LAG the reaction mixture returned 67% recovered starting material and 32% yield of the monofluorination product. Difluorination of the liquid ethyl benzoylacetate was also possible within the same timeframe by adding sodium carbonate to the milled reaction mixture (in the absence of LAG), contrasting against the 5 day solvent-based reaction (Fig. 4). With this newly found capability we finally explored the difluorination of 2,2,6,6-tetramethyl-3,5-heptanedione, a liquid substrate whose intermediate monofluorinated compound features a highly stereocongested enolate.

In this instance the solvent based reaction conditions were found to require 9 days to proceed to 69% conversion (as measured by ^{19}F NMR spectroscopy with an internal standard), whereas the mechanochemically milled reaction provided 59% conversion in just two hours (Fig. 4).

In conclusion, carbon–fluorine bond formation is possible under solid-state mechanochemical milling conditions. However, more significant is the observation that liquid assisted grinding can be used to favor the formation of one reaction product over another and can give rise to improved selectivity. The precise effects of LAG on organic reactions are poorly characterized[8,13] and the exact rationale for the observed selectivity in this reaction remains unclear.[14] Our current hypothesis is that it derives from changes in the crystalline form of the mono-fluorinated product, with such forms only accessible in the presence of added acetonitrile. These forms may be meta-stable nano-crystals as described by Belenguer, Hunter, Sanders and co-workers.[5a] Indeed, Jones and co-workers have described how different quantities of added LAG can lead to different polymorphs to that of a neat reaction.[5b] The latter point is a significant one as it implies that to understand such a phenomenon will require expertise in solid-state chemistry, organic reaction mechanism and mechano- or tribo-chemical methods. We believe the reaction manifold described herein is an ideal tool for such a study as the reaction is clean, can be monitored by ^{19}F NMR and ceases to continue as soon as the product mixture is triturated away from the insoluble Selectfluor material. In addition, we have also demonstrated that mechanochemical milling can vastly reduce reaction times with little effect on yield and selectivity. This has been achieved with comparisons run in our laboratories with very closely related reaction conditions. This effect is applicable across both solid and liquid reagents, as long as the appropriate grinding agent is used.

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Notes and references

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