The Synthesis and Reactivity of Carbamoyl Fluorides

By

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To all those that I have thanked, I hope that I may tell an enjoyable story.

Abstract

Chapter 1

Herein we report a protocol for the synthesis of carbamoyl fluorides from secondary amines using inexpensive, and commercially available starting materials. This method employs the use of a difluorocarbene generated from the thermolysis of (triphenylphosphonio)difluoroacetate. This becomes oxidized by 4-methylpyridine *N*-oxide, generating difluorophosgene, which serves as the key intermediate to make the carbamoyl fluorides from secondary amine starting materials. This method allows access to carbamoyl fluorides with a vast functional group tolerance, including Lewis-basic heterocycles, alkenes, and alkynes.

Chapter 2

We report a base-free, facile cross-coupling reaction of carbamoyl fluorides to silylated nucleophiles. This reaction utilizes an affordable and Earth-abundant nickel transition metal catalyst, with a common phenanthroline ligand (both of which see an exceptionally low loading), to synthesize ureas, carbamates, and alkynamides in moderate to excellent yields. The transmetallation step of the purported catalytic cycle generates a fluorosilane, providing the thermodynamic driving force for the reaction to progress, and circumventing the requirement of base.

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List of Abbreviations and Symbols

$CF_3SO_2OCF_3$	Trifluoromethyl trifluoromethanesulfonate
$AgOCF_3$	Silver trifluoromethoxide
DAST	(Diethylaminosulfur) trifluoride
DFC	Difluorocarbene
PDFA	(Triphenylphosphonio) difluoroacetate
NMR	Nuclear Magnetic Resonance
MeCN	Acetonitrile
THF	Tetrahydrofuran
DMF	Dimethylformamide
1,2-DCE	1,2-dichloroethane
PhMe	Toluene
CO_2	Carbon dioxide
PPh_3	Triphenylphosphine
$CDCl_3$	Deuterated chloroform
δ	Chemical shift
g	Grams
mL	Milliliters
mmol	Millimoles
BTAF	Benzyltrimethylammonium fluoride
Ni	Nickel
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
TES	Triethylsilyl protecting group
TBS	*Tert*-butyldimethylsilyl protecting group
DME	Dimethoxyethane

acac	Acetylacetonate
COD	1,5-cyclooctadiene
TMEDA	Tetramethylethylenediamine
DQ	Duroquinone
CsF	Cesium fluoride
NaF	Sodium fluoride
KF	Potassium fluoride
TBAF	Tetrabutylammonium fluoride
DMSO-d_6	Deuterated dimethylsulfoxide
PET	Positron Emission Tomography

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Chapter 1
Synthesis of Carbamoyl Fluorides via the *in situ* Oxidation of Difluorocarbene

1.1 Contributions

This project was conceptualized by Dr. Christine M. Le, and Dusty Cadwallader. Optimization of reaction conditions was performed by Dusty Cadwallader. Substrate scope was conducted by Dusty Cadwallader, Tristan R. Tiburcio, and George A. Cieszynski. Mechanistic studies and kinetics experiments were done by Dusty Cadwallader and Tristan R. Tiburcio. Dr. Christine M. Le and Dusty Cadwallader wrote the manuscript. The research was guided by Dr. Christine M. Le.

1.2 Introduction and Background

Fluorine-containing molecules have importance across both pharmaceutical and agricultural industries because fluorination is an effective way to improve the metabolic stability, and effectiveness of small molecule drugs.[1,2,3] Although fluorine-containing molecules are exemplified as both synthetically useful[4,5] and biologically relevant, some classes remain underexplored. For example, carbamoyl fluorides, unlike their chlorinated analogues,[6] have witnessed slow development in terms of their synthesis, and use as reagents.[7,8] This is unfortunate, as they are benchtop stable reagents with an untapped potential in organic synthesis. Thus, we were prompted to develop a new method for the synthesis of carbamoyl fluorides that provides practical advantages from previous protocols (e.g., using cheap, commercially available, and bench-top stable starting materials) while permitting access to diverse carbamoyl fluoride products.

1.2.1 History and Importance of Carbamoyl Fluorides

Initial reports on the synthesis of carbamoyl fluorides are dated as far back as the 1940s.[9] Despite the general knowledge of their existence, they remained underutilized in organic synthesis until recently. Carbamoyl fluorides are recognized as important bioisosteres for carbamate moieties, and have been employed as intermediates in the synthesis of carbamate insecticides,[10] and can even act themselves as acetylcholinesterase and protease inhibitors.[11,12,13] Carbamoyl fluorides have potential applications in radiochemistry, as they can be radiolabelled with ^{18}F for use in positron emission tomography (PET) imaging.[14] More recently, carbamoyl fluorides have also been shown to be competent electrophiles in cross-coupling reactions, and they may display unique reactivity compared to the analogous carbamoyl chlorides.[15,16]

1.2.2 Synthetic Pathways for Carbamoyl Fluorides

One of the earliest methods of carbamoyl fluoride synthesis **(Figure 1**) involved making a carbamoyl chloride and using potassium fluoride to facilitate halogen exchange.[17] While the carbamoyl fluorides are typically generated in good yields using this method, it requires two synthetic steps from the amine starting material and long reaction times. Moreover, the use of toxic phosgene-releasing agents is required to access the carbamoyl chlorides.[18] To circumvent the necessity of a second step, difluorophosgene could be used to synthesize the carbamoyl fluorides directly from secondary amines by simple nucleophilic acyl substitution (**Figure 2**). However, difluorophosgene, like its chlorinated analogue, is highly toxic, reducing any advantage for health concerns, and it is not commercially available.

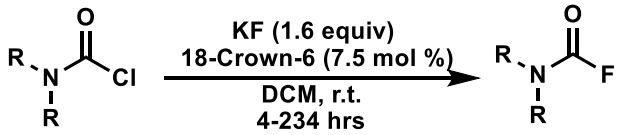


Figure 1. Olofson and Cuomo's synthesis of carbamoyl fluorides from their respective chlorides.

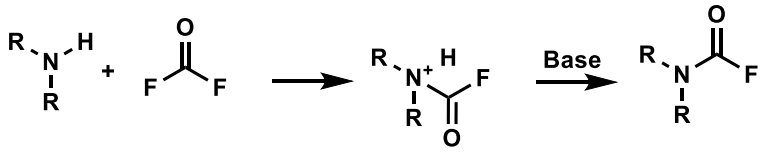


Figure 2. Synthesis of carbamoyl fluorides via nucleophilic acyl substitution of difluorophosgene by secondary amines.

Despite its toxicity, difluorophosgene has been used rather extensively in carbamoyl fluoride synthesis via *in situ* generation. Zhang's work in 2019[19] used trifluoromethyl trifluoromethanesulfonate ($CF_3SO_2OCF_3$) as a source of difluorophosgene, allowing the generation of carbamoyl fluorides directly from secondary amines (**Figure 3**). This method provided good to excellent yields of the carbamoyl fluorides with very fast reaction times, (2 minutes). Unfortunately, $CF_3SO_2OCF_3$ boils at 19° C, and is moisture sensitive[20] thus it must be stored in the freezer under P_2O_5 and used at low temperatures to avoid reagent loss.

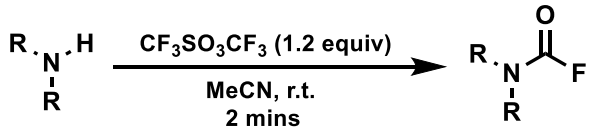


Figure 3. Zhang's synthesis of carbamoyl fluorides from secondary amines using $CF_3SO_2OCF_3$.

Schoenebeck, similar to Zhang, generated difluorophosgene *in situ* with the use of silver trifluoromethoxide ($AgOCF_3$).[21] This method allowed the generation of *N*-CF_3 carbamoyl fluorides from isothiocyanates (**Figure 4a**), as well as alkyl/aryl carbamoyl fluorides from secondary amines in good to excellent yields (**Figure 4b**). Though efficient, this method faces several issues; $AgOCF_3$ is both light and temperature sensitive, and it is not commercially available. To make

$AgOCF_3$, both triphosgene and silver fluoride (in a large excess) are required; the former being extremely toxic and the latter being very costly to use stoichiometrically.

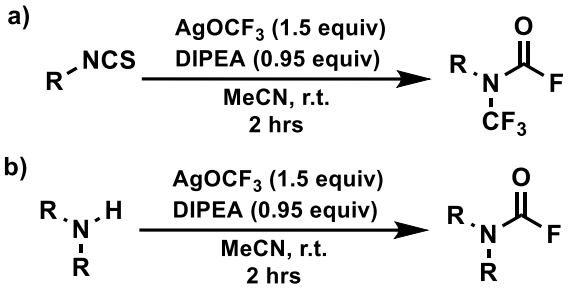


Figure 4. a) Schoenebeck's synthesis of *N*-CF_3 carbamoyl fluorides from isothiocynanates using $AgOCF_3$. b) Schoenebeck's synthesis of alkyl/aryl carbamoyl fluorides from secondary amines using $AgOCF_3$.

Recently, there has been a surge of carbamoyl fluoride syntheses that have forgone the use of difluorophosgene, and instead rely on other fluorinating reagents. Both Tlili (**Figure 5a**) and Lim (**Figure 5b**) reported that a deoxyfluorinating reagent (diethylaminosulfur) trifluoride (DAST), can be applied in a *de novo* approach to generate the desired products.[22,23] Tlili synthesized the carbamoyl fluorides using secondary amines and carbon dioxide as a C1 synthon, and Lim synthesized carbamoyl fluorides from a Beckmann fragmentation of α-oximinoamides. Despite being commercially available, DAST is both expensive and shock sensitive. Moreover, Lim's work has the added disadvantage of requiring pre-functionalization of the starting substrates. Recently, Tlili has reported a DAST-free method of carbamoyl fluoride synthesis with a novel SF_5-based reagent (**Figure 5c**).[24]

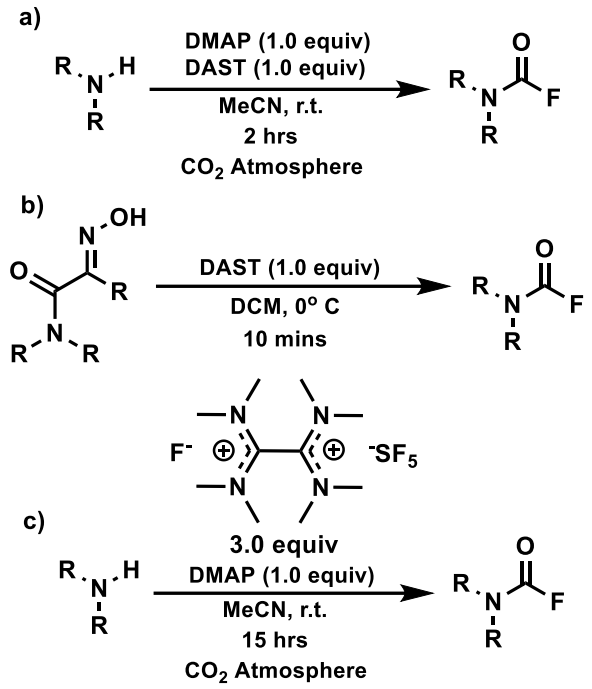


Figure 5. a) Tlili's synthesis of carbamoyl fluorides from secondary amines using DAST and a CO_2 synthon. b) Lim's synthesis of carbamoyl fluorides from α-oximinoamides using DAST. c) Tlili's synthesis of carbamoyl fluorides from secondary amines using an SF_5-based reagent and a CO_2 synthon.

An alternative method for synthesizing fluorinated compounds employs a difluorocarbene (DFC) synthon.[23] Bolm uniquely employed DFC as a C1 source in their synthesis of carbamoyl fluorides (**Figure 6**).[25] The generation of the DFC intermediate came from the thermolysis of sodium 2-bromo-2,2-difluoroacetate, and the reaction proceeded as an indirect oxidation of the DFC with hydroxylamine starting materials. Sodium 2-bromo-2,2-difluoroacetate is easy to synthesize from the cheap and commercially available ethyl 2-bromo-2,2-difluoroacetate; however, this method has several issues. Hydroxylamines are limited in their commercial availability, meaning that similar to Lim's carbamoyl fluoride synthesis, pre-functionalization of the substrates is required to facilitate this chemistry. The oxidizing conditions for the synthesis of the hydroxylamines may also pose an issue, as this may become incompatible with certain functional groups. It should be noted that only moderate yields ranging from 31-67% are obtained for the final products.

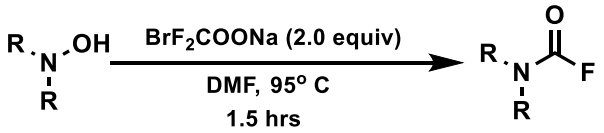


Figure 6. Bolm's synthesis of carbamoyl fluorides from hydroxylamines and a difluorocarbene source.

1.2.3 Our Proposed Method for Carbamoyl Fluoride Synthesis

With Bolm's seminal work serving as our inspiration, we proposed a method of synthesizing carbamoyl fluorides using a DFC source (**Figure 7**). To avoid the use of pre-functionalized substrates, we sought the use of an external oxidant to enable the direct oxidation of DFC to difluorophosgene. This would allow us to use commercially available secondary amines as starting materials as opposed to hydroxylamines. Xiao has recently reported that diphenylsulfoxide can oxidize DFC to difluorophosgene using (triphenylphosphonio) difluoroacetate (PDFA) as the DFC source, which is a non-hygroscopic analogue of the reagent Bolm used in their carbamoyl fluoride synthesis.[26] We explored several classes of oxidants and found that pyridine *N*-oxides are effective for this chemistry. This method provides the carbamoyl fluorides in good to excellent yields with low reaction times. In addition to using cheap and commercially available starting materials, this method also grants access to carbamoyl fluorides bearing a wide array of functional groups, including those containing Lewis-basic heterocycles, alkenes, and alkynes.

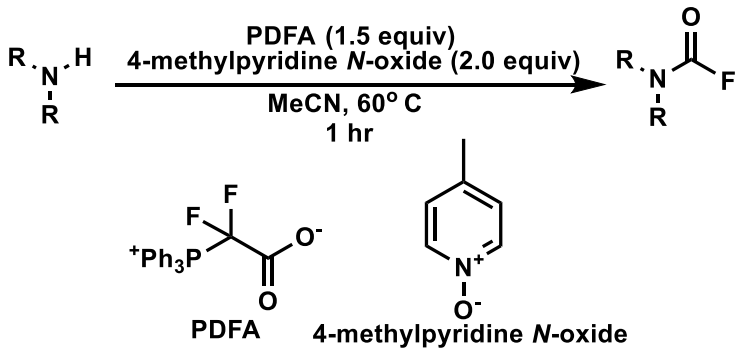


Figure 7. Our method for the synthesis of carbamoyl fluorides from secondary amines and a difluorocarbene source.

1.3 Results and Discussion

1.3.1 Optimization of Reaction Conditions

For the optimization of this reaction, four screenings were conducted: difluorocarbene source, oxidant, solvent, and temperature. All optimization screens were done with *N*-phenylbenzylamine, as the benzyl protons were anticipated to undergo a change in chemical shift after fluorocarbonylation. This would allow simple analysis by ^{1}H NMR spectroscopy to ascertain conversion and yield.

1.3.2 Difluorocarbene Source Screen

A variety of DFC generating sources were screened to determine if others were equally as effective as PDFA (**Figure 8**). Most of the DFC sources tested were analogues of PDFA, including ethyl 2-bromo-2,2-difluoroacetate (**1**), potassium 2-bromo-2,2-difluoroacetate (**2**), and sodium 2-chloro-2,2-difluoroacetate (**3**). Both **1** and **3** performed poorly, with **1** resulting in no conversion or yield of product, and **3** generating trace product with a 2% yield. Reagent **2** performed quite well, with an 89% conversion and a 79% yield. Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**7**) provided carbamoyl fluoride in a 92% yield with a 98% conversion, but required a catalytic amount of sodium fluoride (NaF) in order to form DFC *in situ*. Other miscellaneous DFC sources were screened, including diethyl(bromodifluoromethyl)phosphonate (**5**), and the Ruppert-Prakash reagent (**6**); neither of which performed well. Reagent **5** generated product in 4% yield with a 5% conversion, and **6** generated no yield and there was no conversion of starting material. Ultimately, PDFA (**4**) proved to be the optimal DFC source, garnering a 99% yield with full conversion of starting material, and thus taken forward as the optimized DFC source.

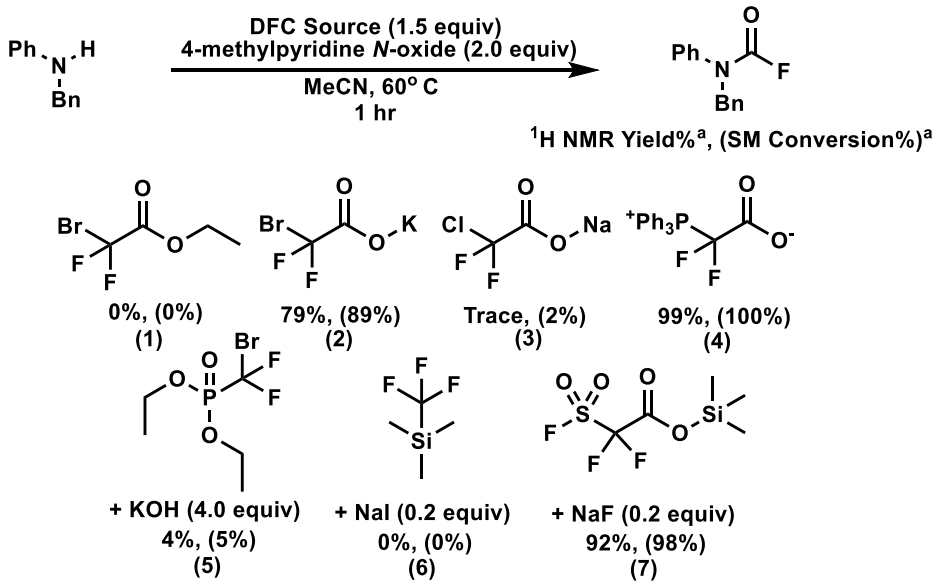


Figure 8. DFC source screen (conducted by Dusty Cadwallader). [a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

1.3.3 Oxidant Screen

For the oxidant screen, three classes of oxidants were tested: sulfoxides (inspired by previous work by Xiao[25]), trialkylamine *N*-oxides, and pyridine *N*-oxides (**Figure 9**). Three sulfoxides were tested, which were diphenyl sulfoxide (**8**), phenyl methyl sulfoxide (**9**), and dimethyl sulfoxide (**10**). It was found that both **8** and **9** performed poorly, generating product in 20% and 29% yield respectively, with conversions of 39% and 41% respectively. When **10** was used, it formed product in 63% yield with a conversion of 69%. With the success of 4-methylpyridine *N*-oxide (**13**) as an oxidant, other *N*-oxides were screened in depth with varying functional groups altering the electronic and steric components of the oxidant. A trend emerged with the pyridine *N*-oxides, in that substitution was disfavored at the 2-position (**17, 18**) due to increased steric congestion. Moreover, lower yields were also observed with both strong π-donating and withdrawing functional groups at the 4-position (**11, 14**). Trialkylamine *N*-oxides were tested and proved to be

ineffective oxidants in this chemistry (**15, 16**). With a yield of 99% and full conversion, **13** proved to be the optimal oxidant, and it was thus taken forward in the next optimization step.

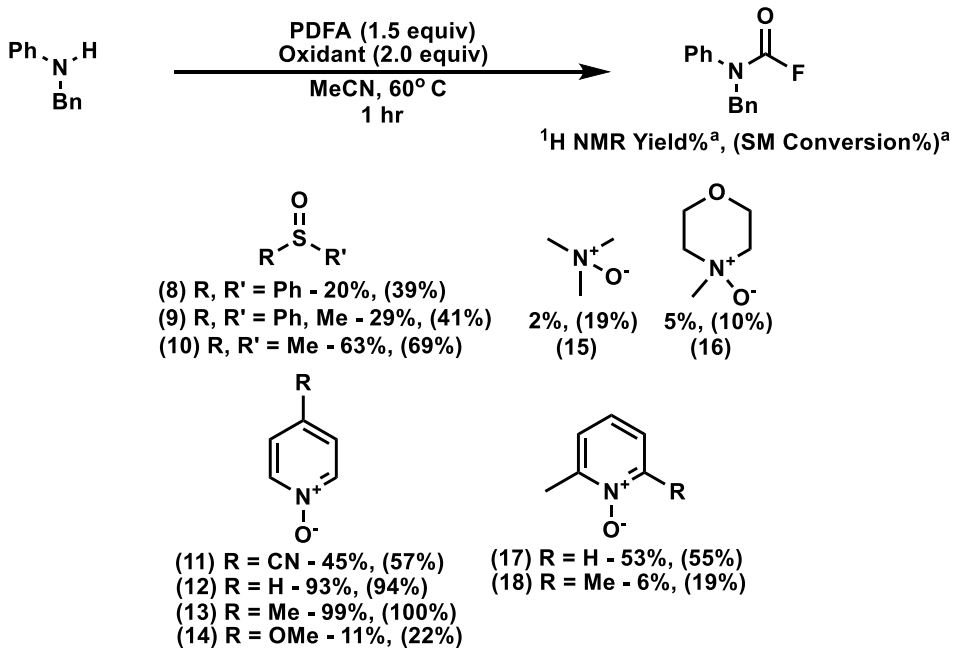
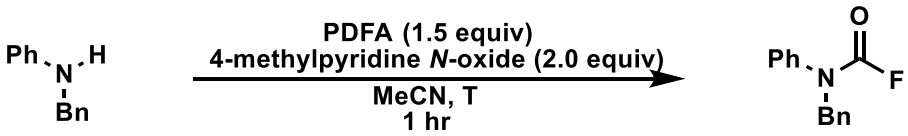


Figure 9. Oxidant screen (conducted by Dusty Cadwallader). [a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

1.3.4 Temperature Screen

As thermolysis of PDFA is required to form the DFC, other temperatures were screened to determine if a temperature lower or higher than 60 °C would perform more optimally (**Table 1**). At 70 °C, the conversion and yield were the same as when we conducted the reaction at 60 °C (**Entries 3, 4**). Since the conversion and yield were the same between these two temperatures, we opted for the milder temperature of 60 °C. At 50 °C, conversion and yield were both 99% (**Entry 2**), and at 40 °C, conversion and yield dropped to 41% and 37% respectively (**Entry 1**). With 60 °C being the mildest temperature, which maximized both conversion and yield, we took that forward as the optimized temperature.

Table 1. Temperature Screen (conducted by Dusty Cadwallader). [a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

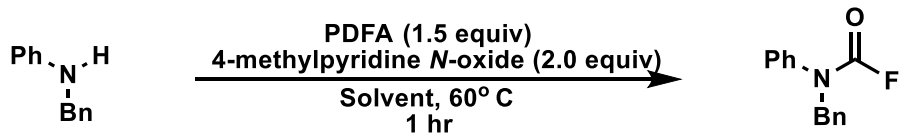


Entry	Temperature (°C)	Yield (%)[a]	Conversion (%)[a]
1	40	37	41
2	50	99	99
3	60	99	100
4	70	99	100

1.3.5 Solvent Screen

A variety of solvents were chosen for the solvent screen with differing degrees of polarity. The chemistry appeared to be quite robust, working well in all solvents tested irrespective of polarity (**Table 2, entries 1, 3-7**). The only instance where a drop in yield and conversion were observed, was with the use of solvents that were not appropriately dried, indicating the moisture sensitive nature of this chemistry (**Entry 2**). Toluene provided nearly the same yield as MeCN (**Entry 7**), however, acetonitrile was taken forward as the optimized solvent as it has a lower boiling point and is thus easier to remove (**Entry 1**).

Table 2. Solvent screen. [a]Conversions and yields were determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Wet MeCN was obtained directly from a 4-litre bottle of HPLC grade MeCN and used without treatment.



Entry	Solvent	Yield (%)[a]	Conversion (%)[a]
1	MeCN	99	100
2	MeCN (wet)[b]	57	63
3	THF	92	93
4	DMF	75	94
5	1,2-DCE	94	100
6	1,4-Dioxane	78	83
7	PhMe	100	100

1.4 Substrate Scope

With reaction conditions now optimized, a substrate scope was conducted to evaluate the functional group tolerance of this method (**Figure 10**). For substrates containing an aniline backbone substituted with an electron donating group or a halogen, in the *para* or *meta* positions (**B, C, D, F, G,**), the reaction performed optimally, with the exception of bromine-containing anilines **E** and **H** which performed moderately. Upon substitution of the ortho position with electron donating groups, the reaction was well tolerated with a methoxy group (**I**), but a drop in yield was observed, with a methyl group (**J**) likely due to increased steric bulk to the nitrogen centre. This steric effect was also observed with a naphthylamine derivative (**K**), generating only a modest yield. Substitution of the benzyl backbone with either a methyl (**L**) or a phenyl group (**M**) did not negatively impact the yield. An anthracenyl derivative (**N**) also reacted similarly. Simpler amines such as **O, P, Q,** and **R** were generated the product in good to excellent yields. Substrates **S** and **T** include a furan and thiophene moiety, which did not detriment the yield.

Compounds **U, V,** and **W** were made from pyridine and indole containing secondary amines, and provided lower yield, likely owing to the basicity of the pyridine/indole nitrogen. Substrates **X, Y, Z, AA** and **AB** provide carbamoyl fluorides in good to excellent yields containing various heterocycles, strained cyclopropane rings, and stereocentres. Both alkenes and alkynes can undergo *gem*-difluorocyclopropanation or -cyclopropenation[27,28] in the presence of DFC. This cycloaddition reaction, however, was not observed in the synthesis of substrates **AC**-**AG**.

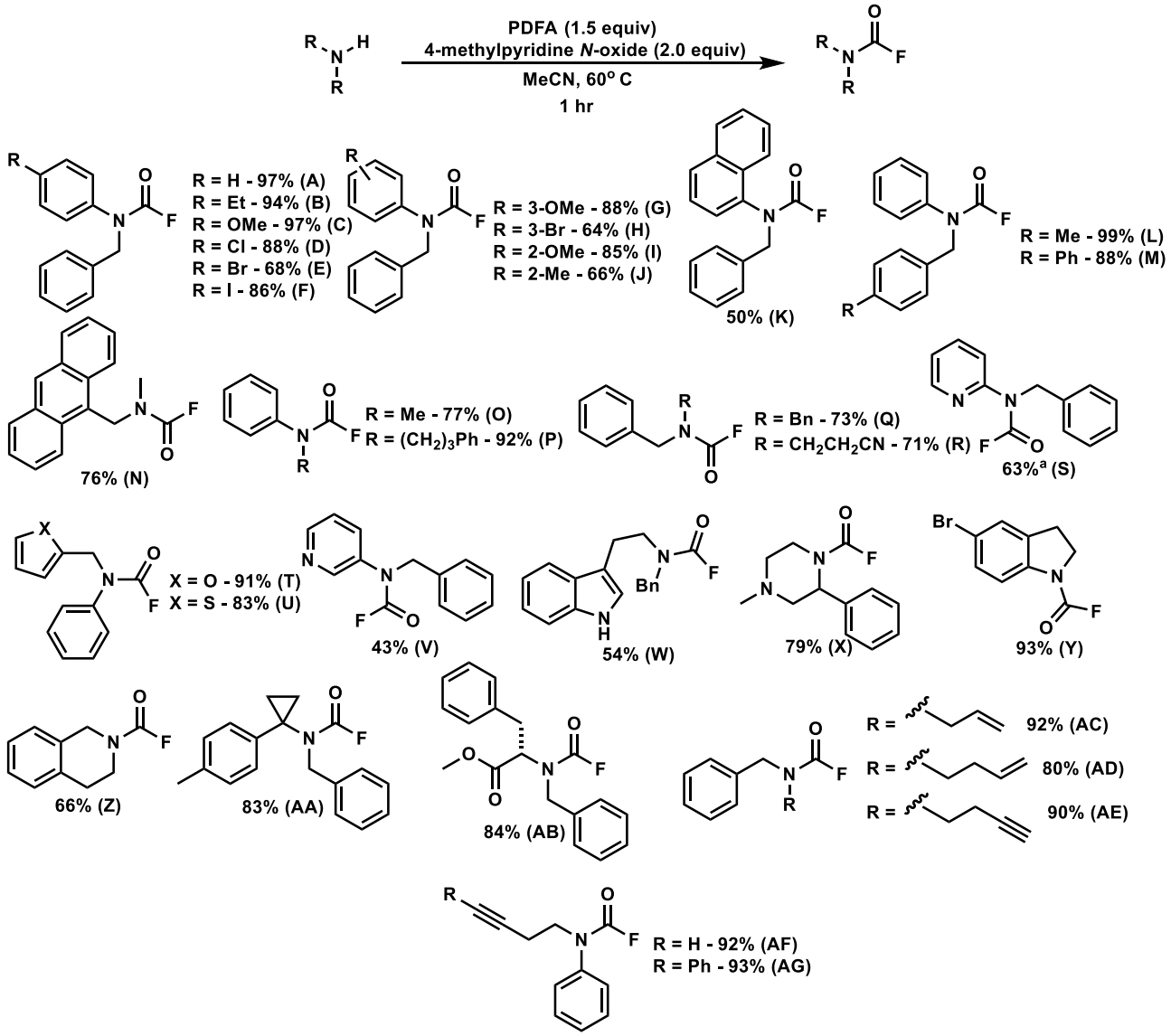


Figure 10. Substrate Scope.[29] All yields are reported as isolated yields. [a]Reaction run for 3 hours.

1.5 Mechanistic Insights and Final Mechanism Proposal

Our proposed reaction mechanism starts with the thermolysis of PDFA resulting in the formation of DFC with loss of CO_2 and PPh_3 (**Figure 12**). Upon its formation, the nucleophilic oxygen on the 4-methylpyridine *N*-oxide can intercept it, which can eliminate the pyridinium leaving group to form difluorophosgene and 4-methylpyridine. To prove the presence of difluorophosgene in their chemistry, Schoenebeck used a ReactIR probe;[21] however, as we lacked the necessary equipment to monitor via ReactIR, we sought a different approach. Zhang[30] demonstrated that difluorophosgene in the presence of carboxylic acids will form acyl fluorides; meaning if our key intermediate is difluorophosgene, we too should see acyl fluoride formation. In order to test this, two reactions were set up: a control reaction containing 4-methoxybenzoic acid and only PDFA (**Figure 11a**), and the other containing 4-methoxybenzoic acid, PDFA, and 4-methylpyridine *N*-oxide (**Figure 11b**). For the control reaction without oxidant, difluorophosgene should not form, and the only expected product would be that resulting from a CF_2 insertion into the O-H bond of the carboxylic acid. As expected, after 1 hour, there was a 50% conversion of starting material, and a 44% yield of CF_2 insertion product. For the reaction with the oxidant present, a 53% conversion of starting material was observed after an hour, but the CF_2 insertion product was not formed; instead, a 48% yield of the acyl fluoride was observed. This experiment provides indirect evidence for the *in situ* generation of difluorophosgene under our reaction conditions.

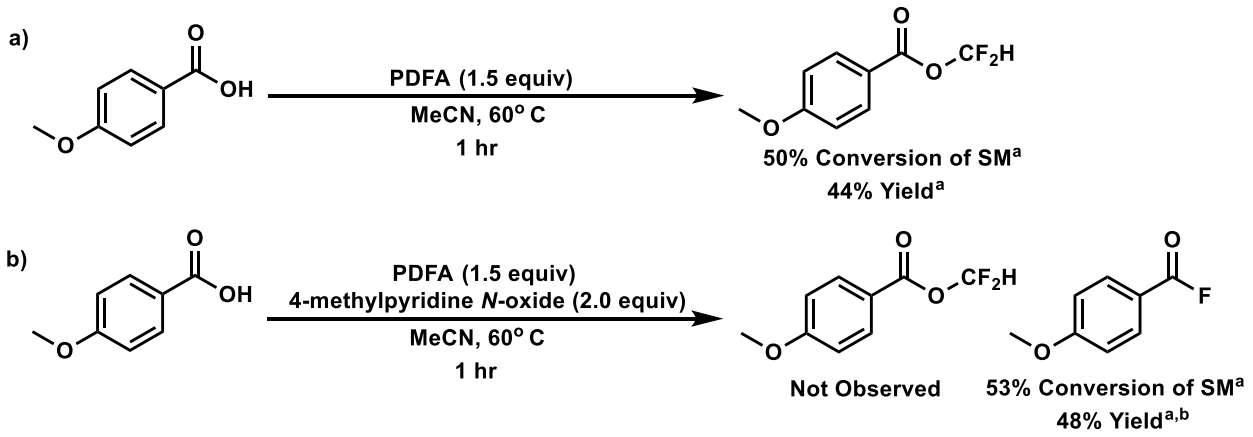


Figure 11. a) Control reaction of 4-methoxybenzoic acid with just PDFA. b) Reaction of 4-methoxybenzoic acid with PDFA and oxidant. [a]Conversions and yields were determined by quantitative ^{1}H NMR using 1,4-dinitrobenzene as an internal standard. [b]Product presence confirmed by ^{1}H NMR, ^{19}F NMR, and GC/MS.

The difluorophosgene is a potent electrophile and it reacts with the amine starting material via a nucleophilic acyl substitution. The 4-methylpyridine by-product undergoes a proton transfer with the intermediate, generating the carbamoyl fluoride product and the pyridinium hydrofluoride salt (**Figure 12**).

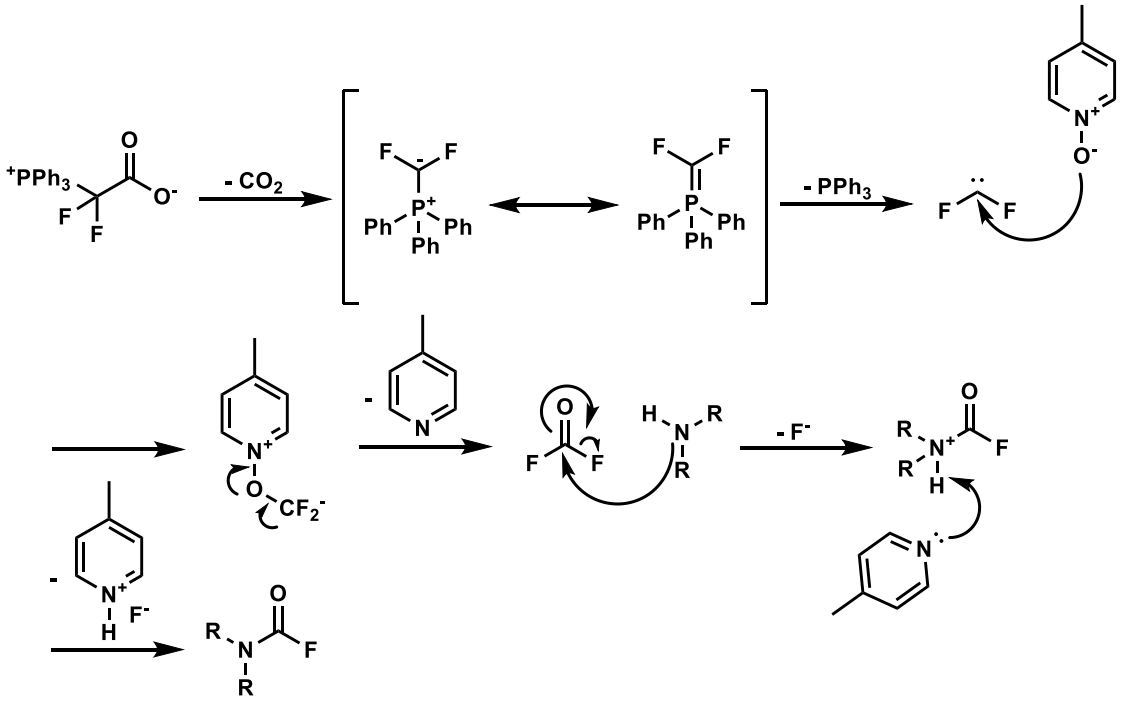


Figure 12. The proposed mechanism of our fluorocarbonylation reaction.

1.6 Conclusions and Future Work

In summary, we have developed a new method for the synthesis of carbamoyl fluorides, starting from cheap, and commercially available secondary amines. Our method utilizes a DFC source in the form of non-hygroscopic PDFA. DFC is oxidized in the presence of 4-methylpyridine *N*-oxide to form difluorophosgene, which is the key intermediate. This method allows the synthesis of carbamoyl fluorides with a vast functional group tolerance, in good to excellent yields. With the more widespread awareness of this facile carbamoyl fluoride synthesis, we anticipate that exploration into their reactivity will increase, thus providing a platform for these important fluorinated motifs.

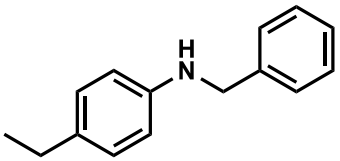
With the development of this new method for the synthesis of carbamoyl fluorides, we began to explore the use of carbamoyl fluorides as cross-coupling partners in transition metal catalyzed chemistry – the results of which will be detailed in Chapter 2.

1.7 Experimental

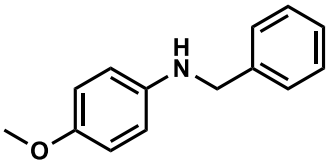
1.7.1 Synthesis and Characterization of Starting Materials

General Procedure

To a round-bottom flask equipped with a stir bar, was added the primary amine (1.1 equiv) and aldehyde (1.0 equiv). 1,2-dichloroethane was then added to achieve a concentration of 0.5 M with respect to the amine. Sodium triacetoxyborohydride (1.2 equiv) was added to the reaction in portions and was allowed to stir at room temperature until completion, as determined by thin-layer chromatography, and was quenched by addition of saturated sodium bicarbonate solution. The reaction mixture was poured into a separatory funnel and extracted 3x with EtOAc. The organic layers were collected, washed with brine, and then dried over $MgSO_4$. The $MgSO_4$ was removed by filtration, and the filtrate was concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography.

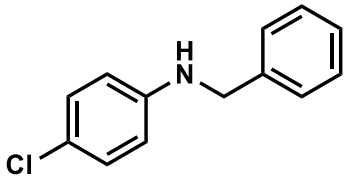


N-benzyl-4-ethylaniline. The title compound was synthesized with the general procedure using 4-ethylaniline (0.100 g, 0.83 mmol) and benzaldehyde (0.080 g, 0.75 mmol), and was isolated as an orange oil (0.114 g, 0.54 mmol, 65%) after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[31]

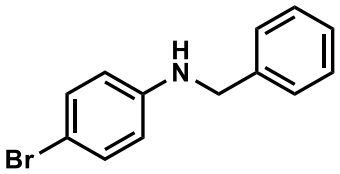


N-benzyl-4-methoxyaniline. The title compound was synthesized with the general procedure using 4-methoxyaniline (0.100 g, 0.81 mmol) and benzaldehyde (0.078 g, 0.74 mmol), and was isolated as a yellow oil (0.110 g, 0.51 mmol, 63%) after purification by flash column

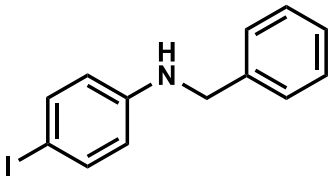
chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[32]



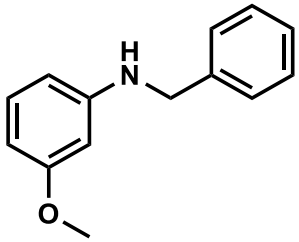
N-benzyl-4-chloroaniline. The title compound was synthesized with the general procedure using 4-chloroaniline (0.100 g, 0.78 mmol) and benzaldehyde (0.075 g, 0.71 mmol), and was isolated as a yellow oil (0.106 g, 0.49 mmol, 62%), after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[33]



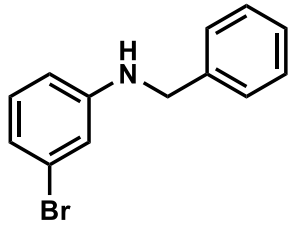
N-benzyl-4-bromoaniline. The title compound was synthesized with the general procedure using 4-bromoaniline (0.100 g, 0.58 mmol) and benzaldehyde (0.056 g, 0.53 mmol), and was isolated as a yellow solid (0.107 g, 0.41 mmol, 71%) after purification by flash column chromatography: 2% EtOAc, 1% Et_3N, in hexanes. The spectral data are consistent with literature values.[34]



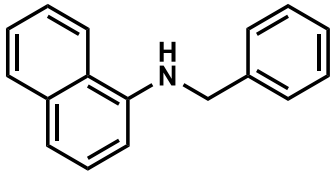
N-benzyl-4-iodoaniline. The title compound was synthesized with the general procedure using 4-iodoaniline (0.100 g, 0.46 mmol) and benzaldehyde (0.045 g, 0.42 mmol), and was isolated as a white solid (0.090 g, 0.29 mmol, 63%), after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[35]



N-benzyl-3-methoxyaniline. The title compound was synthesized with the general procedure using 3-methoxyaniline (0.100 g, 0.81 mmol) and benzaldehyde (0.078 g, 0.74 mmol), and was isolated as a yellow oil (0.131 g, 0.62 mmol, 76%) after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[36]



N-benzyl-3-bromoaniline. The title compound was synthesized with the general procedure using 3-bromoaniline (0.100 g, 0.58 mmol) and benzaldehyde (0.056 g, 0.53 mmol), and was isolated as a pale-yellow oil (0.101 g, 0.38 mmol, 66%) after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[33]



N-(1-naphthyl)benzylamine. The title compound was synthesized with the general procedure using 1-naphthylamine (0.100 g, 0.81 mmol) and benzaldehyde (0.079 g, 0.74 mmol), and was isolated as a purple solid (0.110 g, 0.51 mmol, 63%) after purification by flash column chromatography: 2% EtOAc, 1% Et_3N in hexanes. The spectral data are consistent with literature values.[34]

1.7.2 Synthesis and Characterization of Products

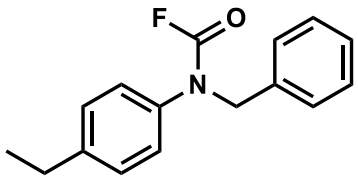
General Procedure for Secondary Amines that are Solids

To 1-dram vial was added a stir bar, amine 1 (0.20 mmol, 1.0 equiv), PDFA (0.107 g, 0.30 mmol, 1.5 equiv) and 4-methylpyridine *N*-oxide (2h) (0.044 g, 0.40 mmol, 2.0 equiv). The vial was fitted with a septum cap then evacuated and backfilled 3x with nitrogen. To the vial was added MeCN (2.0 mL) and the septum cap was rapidly removed and replaced with a Teflon-lined screwcap before submerging the vial in a pre-heated 60 ˚C oil bath. The reaction was stirred at this temperature for 1 hour. After completion of the reaction, the vial was removed from the oil bath

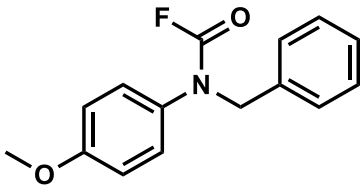
and the reaction transferred directly to a round-bottomed flask. The crude material was dry loaded on silica gel and was purified by column chromatography to yield the carbamoyl fluoride.

General Procedure for Secondary Amines that are Liquids/Oils

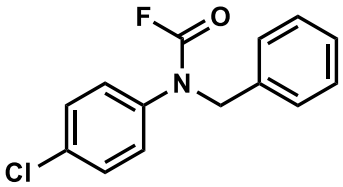
To screw-cap vial was added a stir bar, PDFA (0.107 g, 0.30 mmol, 1.5 equiv) and 4-methylpyridine *N*-oxide (2h) (0.044 g, 0.40 mmol, 2.0 equiv). The vial was fitted with a septum cap then evacuated and backfilled 3x with nitrogen. To the vial was added 1 mL of a 0.1 M solution of amine 1 in MeCN, and the septum cap was rapidly removed and replaced with a Teflon-lined screwcap before submerging the vial in a pre-heated 60 ˚C oil bath. The reaction was stirred at this temperature for 1 hour. After completion of the reaction, the vial was removed from the oil bath and the reaction transferred directly to a round-bottomed flask. The crude material was dry loaded on silica gel and was purified by column chromatography to yield the carbamoyl fluoride.



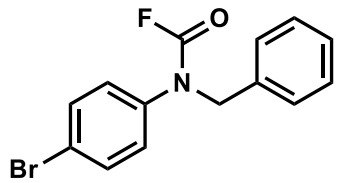
N-benzyl-N-(4-ethylphenyl)carbamoyl fluoride (B). The title compound was synthesized using ***N*-benzyl-4-ethylaniline** (0.085 g, 0.40 mmol) and isolated as an orange oil (0.072 g, 0.28 mmol, 70%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36-7.28 (m, 3H), 7.25-7.19 (m, 2.3H), 7.18-7.11 (m, 2.3H), 6.96 (d, *J* = 8.0 Hz, 1.4H), 4.81 ppm (s, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.22 ppm (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 147.0 (d, *J* = 287.5 Hz), 146.8 (d, *J* = 291.5 Hz), 144.2, 143.7, 138.1, 136.8, 136.0, 135.8, 128.7 (2C), 128.64, 128.56, 128.5, 128.13, 128.09, 127.5, 126.6, 125.8, 55.6, 55.1, 28.3 (2C), 15.23, 15.17. ^{19}F NMR (282 MHz, $CDCl_3$) δ -15.85 (s, 1F), -18.32 (s, 0.31F). HRMS (DART) calc'd for $[M+NH_4]^+$ 275.1560 found 275.1554. IR (ATR, $CDCl_3$, cm^{-1}) 3034, 2966, 2933, 2874, 1779, 1513, 1391, 1265, 1028, 839, 748, 702, 632, 570.



N-benzyl-N-(4-methoxyphenyl)carbamoyl fluoride (C). The title compound was synthesized using ***N*-benzyl-4-methoxyaniline** (0.085 g, 0.40 mmol) and isolated as a pale orange-yellow oil (0.101 g, 0.39 mmol, 97%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35-7.28 (m, 3H), 7.24-7.22 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 0.5H), 6.94 (d, *J* = 8.8 Hz, 1.5H), 6.85 (d, *J* = 8.9 Hz, 0.5H), 6.82 (d, *J* = 8.9 Hz, 1.5H), 4.77 (s, 2H), 3.78 (s, 3H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 159.1, 158.8, 147.2 (d, *J* = 287.0 Hz), 147.1 (d, *J* = 291.2 Hz), 136.0, 135.8, 133.2, 132.0, 128.9, 128.8, 128.7, 128.23, 128.18, 128.16, 127.9, 127.6, 114.6, 114.5, 55.9 (2C), 55.5 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ -15.93 (s, 1F), -19.22 (s, 0.30F). HRMS (DART) calc'd for $[M+H]^+$ 260.1087 found 260.1078. IR (ATR, $CDCl_3$, cm^{-1}) 1786, 1513, 1250, 1034, 836, 696, 631, 628, 592, 571.

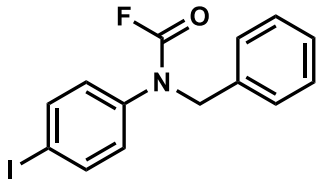


N-benzyl-N-(4-chlorophenyl)carbamoyl fluoride (D). The title compound was synthesized by using ***N*-benzyl-4-chloroaniline** (0.087 g, 0.40 mmol) and isolated as a colorless oil (0.092 g, 0.35 mmol, 88%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 7.25-7.16 (m, 2.5H), 6.99 (d, *J* = 8.4 Hz, 1.5H), 4.81 (s, 2H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 146.6 (d, *J* = 288.4 Hz, 2C), 139.0, 137.7, 135.6, 135.4, 134.1, 133.4, 129.7 , 129.1, 128.9, 128.7 (2C), 128.4 (2C), 127.6, 127.5, 55.7, 55.1 (1C overlapping with another peak in the region from 129.7–128.4). ^{19}F NMR (282 MHz, $CDCl_3$) δ -14.25 (s, 1F), -16.99 (s, 0.35F). HRMS (ESI) calc'd for $[M+Na]^+$ 286.0411 found 286.0404. IR (ATR, $CDCl_3$, cm^{-1}) 3090, 3065, 3034, 2927, 2853, 1781, 1492, 1386, 1261, 1091, 1011, 834, 746, 718, 698, 627, 569, 506.

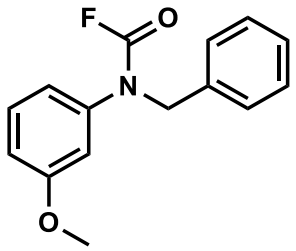


N-benzyl-N-(4-bromophenyl)carbamoyl fluoride (E). The title compound was synthesized by using ***N*-benzyl-4-bromoaniline** (0.105 g, 0.40 mmol) and isolated as a pale-yellow oil (0.084 g, 0.27 mmol, 68%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.35-7.32 (m, 3H), 7.26-7.20 (m, 2H), 7.13 (d, *J* =

8.1 Hz, 0.5H), 6.92 (d, *J* = 8.1 Hz, 1.5H), 4.81 (s, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 146.5 (d, *J* = 288.3 Hz, 2C), 139.5, 138.2, 135.6, 135.4, 132.7 (2C), 129.0, 128.9, 128.7, 128.6, 128.41, 128.36, 127.7, 127.6, 122.1, 121.4, 55.6, 55.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -15.16 (s, 1 F), -17.80 (s, 0.35 F). HRMS (ESI) calc'd for $[M+H]^+$ 308.0086 found 308.0079. IR (ATR, $CDCl_3$, cm^{-1}) 1786, 1491, 1264, 832, 697, 627, 570.

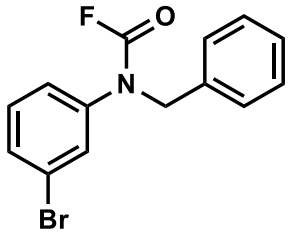


N-benzyl-N-(4-iodophenyl)carbamoyl fluoride (F). The title compound was synthesized using ***N*-benzyl-4-iodophenylaniline** (0.124 g, 0.40 mmol) and isolated as a colorless oil (0.122 g, 0.34 mmol, 86%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 7.3 Hz, 2H), 7.31 (m, 3H), 7.25-7.17 (m, 2H), 7.00 (d, 7.9 Hz, 0.5H), 6.80 (d, 8.1 Hz, 1.5H), 4.81 (s, 2H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 146.5 (d, *J* = 288.5 Hz, 2C), 140.3, 139.0, 138.7 (2C), 135.7, 135.4, 129.1, 128.9 (2C), 128.7, 128.43, 128.39, 127.9, 127.6, 93.5, 92.7, 55.6, 55.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -15.09 (s, 1F), -17.50 (s, 0.36F). HRMS (ESI) calc'd for $[M+H]^+$ 355.9948 found 355.9939. IR (ATR, $CDCl_3$, cm^{-1}) 3063, 3006, 2924, 2852, 1783, 1486, 1452, 1284, 1220, 1008, 734, 570.

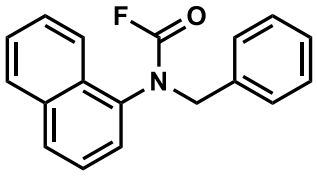


N-benzyl-N-(3-methoxyphenyl)carbamoyl fluoride (G). The title compound was synthesized by using ***N*-benzyl-3-methoxyaniline** (0.085 g, 0.40 mmol) and isolated as a pale orange-yellow oil (0.091 g, 0.35 mmol, 88%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37-7.24 (m, 6H), 6.92-6.80 (m, 1.5H), 6.71 ppm (d, *J* = 7.8 Hz, 0.75H), 6.63 ppm (s, 0.75H), 4.87 ppm (s, 2H), 3.77 (s, 3H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 160.23, 160.17, 146.9 (d, *J* = 288.0 Hz), 146.7 (d, *J* = 291.0 Hz), 141.6, 140.3, 136.1, 135.8, 130.14, 130.08, 128.9, 128.75, 128.67, 128.21, 128.17, 127.7, 119.2, 118.2, 113.8, 113.4, 112.9, 112.1, 55.6, 55.4 (2C), 55.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -15.40 (s, 1F), -17.59 (s, 0.32F).

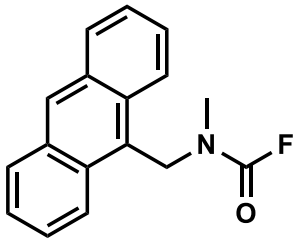
HRMS (ESI) calc'd for $[M+NH_4]^+$ 260.1087 found 260.1082. IR (ATR, $CDCl_3$, cm^{-1}) 1781, 1604, 1493, 1394, 696.



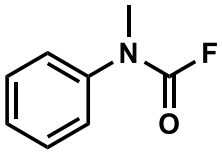
N-benzyl-N-(3-bromophenyl)carbamoyl fluoride (H). The title compound was synthesized by using ***N*-benzyl-3-bromoaniline** (0.105 g, 0.40 mmol) and isolated as a pale-yellow oil (0.080 g, 0.26 mmol, 64%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.7 Hz, 1.25H), 7.39-7.29 (m, 3H), 7.28-7.14 (m, 4H), 6.98 ppm (d, *J* = 7.7 Hz, 0.75H), 4.82 (s, 2H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 146.5 (d, *J* = 290.0 Hz, 2C), 141.7, 140.5, 135.6, 135.3, 131.4, 130.9, 130.7, 130.2, 129.2, 129.1, 128.9, 128.8, 128.6, 128.4, 127.5, 127.4, 125.9, 124.8 , 122.7 (2C), 55.7, 55.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ -14.83 (s, 1F), -17.30 (s, 0.35F). HRMS (ESI) calc'd for $[M+H]^+$ 308.0086 found 308.0081. IR (ATR, $CDCl_3$, cm^{-1}) 1784, 1574, 1478, 1389, 785, 693.



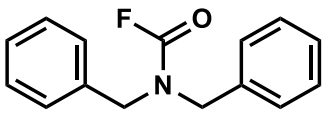
N-benzyl-N-(1-naphthyl)carbamoyl fluoride (K). The title compound was synthesized by using ***N*-(1-naphthyl)benzylamine** (0.093 g, 0.40 mmol) and isolated as a colorless oil (0.056 g, 0.20 mmol, 50%) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.77 (m, 3H), 7.63-7.54 (m, 2H), 7.45-7.20 (m, 6H), 7.17 (d, *J* = 7.3 Hz, 0.15H), 7.04 (d, *J* = 7.3 Hz, 0.85H), 5.33 (d, *J* = 14.3 Hz, 0.85H), 5.24 (d, *J* = 14.9 Hz, 0.15H), 4.53 (d, *J* = 14.9 Hz, 0.15H), 4.52 (d, *J* = 14.3 Hz, 0.85H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 147.6 (d, *J* = 287.6 Hz), 146.9 (d, *J* = 292.4 Hz), 136.1, 135.88, 135.85, 135.1, 134.8, 134.6, 129.7, 129.4 (2C), 129.3, 129.2, 128.9, 128.8, 128.73, 128.71 (2C), 128.43, 128.40, 127.5, 127.4, 126.75, 126.70, 126.3, 126.2, 125.5, 125.3, 121.9 (2C), 55.67, 55.65. ^{19}F NMR (282 MHz, $CDCl_3$) δ -14.73 (s, 1F), -19.50 (s, 0.2F). HRMS (ESI) calc'd for $[M+Na]^+$ 302.0957 found 302.0950. IR (ATR, $CDCl_3$, cm^{-1}) 3063, 3034, 2929, 2854, 1778, 1597, 1404, 1383, 1272, 1250, 1040, 901, 803, 775, 749, 701, 632, 538, 429.



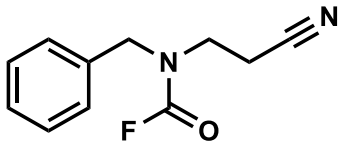
N-(9-anthrylmethyl)-N-methyl-carbamoyl fluoride (N). The title compound was synthesized by using **9-(methylaminomethyl)anthracene** (0.089 g, 0.40 mmol) and isolated as a yellow solid (0.082 g, 0.31 mmol, 76%, mp = 141-143 ˚C) after purification by flash column chromatography: 2% EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.31 (d, *J* = 8.8 Hz, 1.5H), 8.23 (d, *J* = 8.8 Hz, 0.5H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.4 Hz), 5.57 (s, 1.5H), 5.53 (s, 0.5H), 2.59 (s, 2.25H), 2.57 (s, 0.75H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ 148.1 (d, *J* = 287.8 Hz), 147.5 (d, *J* = 286.2 Hz), 131.4 (2C), 131.3, 131.2, 129.6, 129.5, 129.4, 129.2, 127.3, 127.2, 125.4, 125.3 (2C), 124.5, 123.6, 123.1, 44.3 (d, *J* = 1.4 Hz), 43.8 (d, *J* = 4.8 Hz), 32.9 (d, *J* = 1.5 Hz), 32.1 (d, *J* = 4.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -22.16 (s, 1F), -22.40 (s, 0.3F). HRMS (ESI) calc'd for $[M+H]^+$ 268.1138 found 268.1135. IR (ATR, $CDCl_3$, cm^{-1}) 3050, 2952, 2922, 2852, 1772, 1446, 1394, 1246, 1105, 990, 894, 845, 792, 772, 730, 701, 592, 583, 516



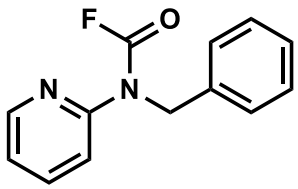
N-methyl-N-phenyl-carbamoyl fluoride (O). The title compound was synthesized by using ***N*-methylaniline** (0.021 g, 0.20 mmol) and isolated as a colorless oil (0.024 g, 0.16 mmol, 77%) after purification by flash column chromatography: 5% EtOAc in hexanes. The spectral data are consistent with literature values.[21]



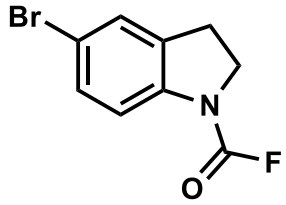
N,N-dibenzylcarbamoyl fluoride (Q). The title compound was synthesized by using **dibenzylamine** (0.079 g, 0.40 mmol) and isolated as a colorless oil (0.071 g, 0.29 mmol, 73%) after purification by flash column chromatography: 2% EtOAc in hexanes. The spectral data are consistent with literature values.[24]



N-benzyl-N-(2-cyanoethyl)carbamoyl fluoride (R). The title compound was synthesized by **using 3-(benzylamino)propionitrile** (0.064 g, 0.40 mmol) and isolated as an orange oil (0.046 g, 0.28 mmol, 71%) after purification by flash column chromatography: 20% EtOAc in hexanes. The spectral data are consistent with literature values.[24]



N-benzyl-N-(2-pyridyl)carbamoyl fluoride (S). The title compound was synthesized by using **2-benzylaminopyridine** (0.074 g, 0.40 mmol) and isolated as a yellow oil (0.041 g, 0.18 mmol, 45%) after purification by flash column chromatography: 10% EtOAc in Hexanes. When reaction time was increased to 3 hours, the yield was found to increase significantly (0.058 g, 0.25 mmol, 63%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 1H), 7.74-7.64 (m, 1.2H), 7.61-7.37 (m, 0.5H), 7.35-7.19 (m, 5.3H), 7.14 (dd, *J* = 8.1 Hz, 4.9 Hz, 1H), 5.22 (s, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.9, 148.3, 146.1 (d, *J* = 292.6 Hz), 138.1, 136.6, 128.6 (2C), 127.7, 121.6, 119.1, 51.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -7.71 (bs, 1F), -15.21 (bs, 0.81F). HRMS (DART) calc'd for $[M+H]^+$ 231.0934 found 231.0928. IR (ATR, $CDCl_3$, cm^{-1}) 1789, 1590, 1472, 1435, 1392, 1305, 1274, 1223, 779, 697.



5-bromoindoline-1-carbonyl fluoride (Y). The title compound was synthesized by using **5-bromoindoline** (0.079 g, 0.40 mmol) and isolated as a white solid (0.091 g, 0.37 mmol, 93%, mp = 115-117 ˚C) after purification by flash column chromatography: 5% EtOAc in hexanes. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.4, 1.4 Hz, 0.75H), 7.38-7.29 (m, 2H), 7.16 (dd, *J* = 9.2, 4.1 Hz, 0.25H), 4.16-4.05 (m, 2H), 3.19 (t, *J* = 8.60 Hz, 2H). ^{13}C {^{1}H} NMR (176 MHz, $CDCl_3$) δ

143.7 (d, J = 294.8 Hz), 143.0 (d, J = 289.8 Hz), 139.6, 138.9 (d, J = 5.1 Hz), 133.9, 133.5 (d, J = 4.5 Hz), 130.9 (d, J = 2.3 Hz), 130.8, 128.6, 128.1, 117.2, 117.1, 116.42, 116.35, 48.5, 47.9, 27.2, 27.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ -5.74 (s, 1F), -13.48 (s, 0.3F). HRMS (ESI) calc'd for $[M]^+$ 242.9695 found 242.9684. IR (ATR, $CDCl_3$, cm^{-1}) 2924, 2861, 1780, 1513, 1426, 1396, 1338, 953.

Chapter 2
Development of a Nickel-Catalyzed Cross-Coupling of Carbamoyl Fluorides with Silylated Nucleophiles

2.1 Contributions

This project was conceptualized by Dr. Christine M. Le and Tristan R. Tiburcio. Reaction optimization was done by Tristan R. Tiburcio. The research was guided by Dr. Christine M. Le.

2.2 Stoichiometric Reactions of Carbamoyl Fluorides

Some of the earliest reports of carbamoyl fluoride usage in organic chemistry date back to the early 1980s, mainly by Olofson and Cuomo.[37] They demonstrated that carbamoyl fluorides can couple to silyl enol ethers in a regioselective manner to form enol carbamates (**Figure 13**). This reaction occurs without a transition metal catalyst, solely requiring a catalytic amount of benzyltrimethylammonium fluoride (BTAF) as a fluoride source. We speculate that the formation of a fluorosilane by-product provides a thermodynamic driving force for the reaction, enabling the C-F bond cleavage under mild conditions. Although moderate to excellent yields of the products were obtained, the substrate scope was limited, and thus the functional group tolerance of this method remains in question.

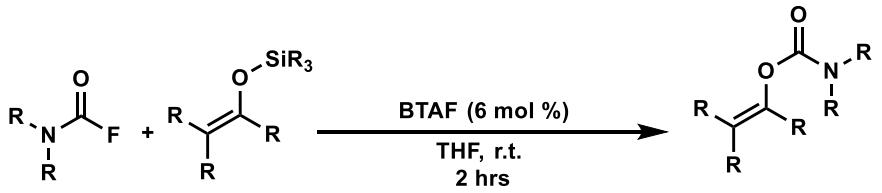


Figure 13. Olofson and Cuomo's synthesis of enol carbamates from carbamoyl fluorides and silyl enol ethers with a catalytic fluoride source.

The Schoenebeck group has reported a number of methods using carbamoyl fluorides as reagents.[38,39] More specifically, they have applied *N*-CF_3 carbamoyl fluorides in various transformations to make a plethora of amidated products (**Figure 14**). The electron-withdrawing trifluoromethyl substituent greatly increases the electrophilicity of the carbonyl carbon, allowing access to these products with simple nucleophiles. It should be noted that strong anionic nucleophiles (i.e., Grignard reagents, azides, thiolates, or selenoates) are required for these reactions to proceed.

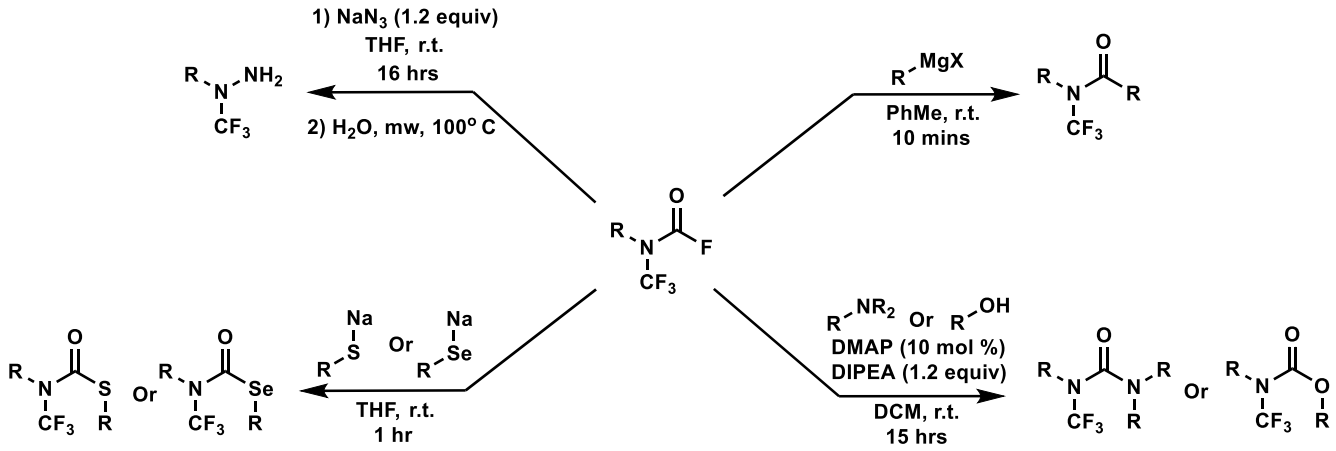


Figure 14. The numerous synthetic applications of *N*-CF_3 carbamoyl fluorides developed by Schoenebeck.

2.3 Catalytic Reactions of Carbamoyl Fluorides

In recent years, carbamoyl fluorides have gained traction as viable cross-coupling partners in transition-metal catalyzed chemistry. Ye and co-workers showed that carbamoyl fluorides containing unactivated alkenes in the presence of a nickel catalyst can undergo cyclization to form *N*-substituted pyrrolidones in moderate to excellent yields with a moderate to high degree of

enantioselectivity (**Figure 15**).[40] Interestingly, when the same optimized conditions were applied to the analogous carbamoyl chloride, both the yield of the reaction and enantioselectivity diminished significantly.

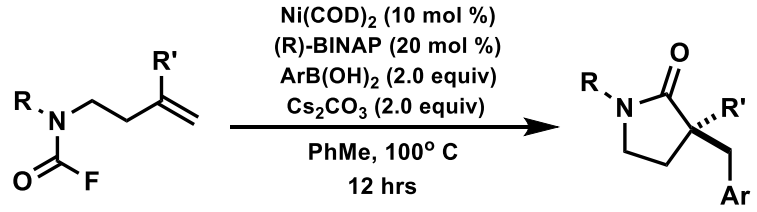


Figure 15. Ye's synthesis of *N*-substituted pyrrolidones from carbamoyl fluorides containing unactivated alkenes, employing a nickel-catalyst.

Schoenebeck and co-workers applied *N*-CF_3 carbamoyl fluorides, and silylated alkynes to synthesize *N*-CF_3 alkynamides with the use of a nickel catalyst (**Figure 16**).[41] This method of alkynamide synthesis relies on the formation of a fluorosilane, which provides a thermodynamic driving force for the reaction. Presumably, the formation of a Ni-F complex allows the transmetallation event to proceed without the addition of exogenous base. These *N*-CF_3 alkynamides are especially important as they serve as important scaffolds in drug design.

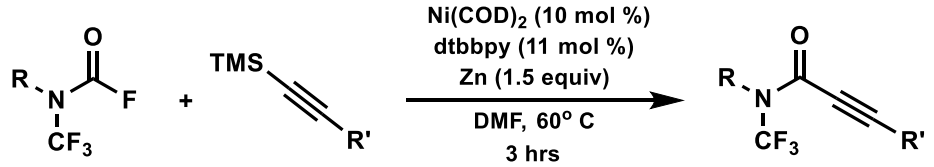


Figure 16. Schoenebeck's synthesis of *N*-CF_3 alkynamides from *N*-CF_3 carbamoyl fluorides using a nickel catalyst.

2.4 Our Cross-Coupling Proposal for Carbamoyl Fluorides with Silylated Nucleophiles

With such little contributed in the way of reactions with carbamoyl fluorides, we took it upon ourselves to add to this burgeoning field. Similar to Schoenebeck's aforementioned work, we drew inspiration from the use of a transition metal catalyst to facilitate a cross-coupling of a carbamoyl fluoride to a silylated nucleophile. Moreover, we wondered if this chemistry could be applied to more diverse substrates aside from *N*-CF_3 carbamoyl fluorides and silylated alkynes. We started our investigation employing nickel-based catalysts because they have demonstrated the ability to undergo oxidative addition into the carbamoyl fluoride C-F bond. With different silylated nucleophiles, this cross-coupling can allow us to access products such as ureas, carbamates, and alkynamides, each of which are relevant to an important field of research. Ureas and their derivatives are currently being investigated as potential drug candidates, due to their abilities to hinder enzymes responsible for diseases such as HIV/AIDS and atherosclerosis.[42,43] Carbamates are highly prevalent in agricultural chemistry, as many pesticides and insecticides contain this moiety. Alkynamides are more reputable for their use in synthesis as scaffolds to generate other drug candidates such as benzazepines.[44] Herein, we propose a nickel-catalyzed cross-coupling of bench stable carbamoyl fluorides with silylated nucleophiles to generate useful products in good to excellent yields.

2.5 Results and Discussion

2.5.1 Optimization of Reaction Conditions

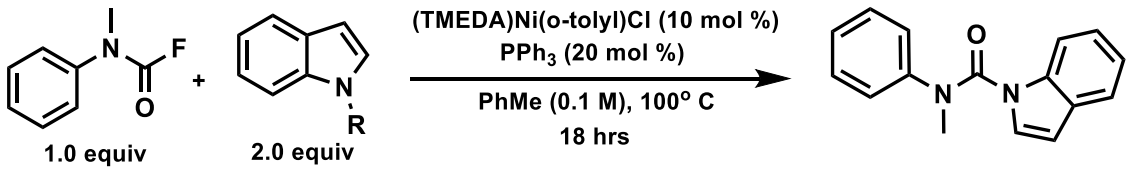
For the optimization of this reaction, the following parameters were evaluated: ligand, temperature, catalyst loading, ligand loading, concentration, metal precatalyst, and solvent. The model substrate was chosen to be *N*-methyl-*N*-phenyl carbamoyl fluoride, as we anticipate the methyl protons of

the starting material and products to have different chemical shifts in the ^{1}H NMR spectrum. This would allow simple analysis of the reaction mixture by quantitative NMR spectroscopy. The silylated coupling partner for optimization was chosen to be a silylated indole (specifically triethylsilyl/TES indole) due to its stability in storage, its ease of synthesis, and unique products upon coupling.

2.5.2 First Hits

The first hit was obtained with (TMEDA)Ni(o-tolyl)Cl (Doyle's catalyst),[45] using triphenylphosphine as the ancillary ligand. Doyle's catalyst was chosen as the precatalyst due to its air stability and affordability compared to other nickel catalysts. The amount of nickel catalyst and ligand used in the cross-coupling was 10 mol % and 20 mol % respectively, with 2.0 equivalents of TES-indole coupling partner, and the reaction only provided product in a 56% isolated yield. When these same conditions were repeated a second time to get a quantitative NMR yield using 1,3,5-trimethoxybenzene as an internal standard, product was generated at 69% yield. To test if a bulkier silyl group would affect the yield, TBS-indole was used in the reaction, which generated product in 67% yield by NMR. Without the *N*-silyl group, the cross-coupling reaction does not proceed, as subjecting simple indole to these conditions generated the product in only 1% yield. We moved forward with TES-indole as the model coupling partner, although TBS-indole provided comparable yields as well.

Table 3. Initial reaction screening.



Entry	R	Conversion (%)[a]	Yield %[a]
1	TES	97	69 (56)[b]
2	TBS	91	67
3	H	29	1

[a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.

2.5.3 Ligand Screen

Immediately following the initial hit, a ligand screen was undertaken. Three different types of ligands were screened, which included monodentate trialkyl and triarylphosphines (**1, 2**), bidentate phosphines (**3, 4**), and bidentate nitrogenous ligands (**5-15**). Both triphenylphosphine (**1**) and tri(*tert*-butyl)phosphine (**2**) had excellent conversions at 97% and 100% respectively, but both had yields of 69% and 73% respectively. The bidentate phosphine ligands performed moderately, with *rac*-BINAP (**3**) exhibiting 91% conversion and 45% yield and dppf (**4**) exhibiting 97% conversion and 67% yield. When the ligand loading for **3** and **4** was dropped to 10%, conversions remained nearly equivalent, but the yield dropped to 33% and 35% respectively. Ultimately, it was the bidentate nitrogenous ligands (specifically 1,10-phenanthroline, 2,2'-bipyridine and their derivatives) that proved to be the most effective in the cross-couplings (**6, 8-15**). This observation can be explained by the nature of *N,N* donor ligands: they are rigid, strongly chelating ligands, which form extraordinarily stable coordination complexes. *N,N* donor ligands also show

preference for hard acids,[46] and since nickel (particularly Ni^{2+}) is bordering between hard and soft (closer to hard), it further solidifies the idea that this family of ligands would be the optimal. Other *N*,*N*-donor ligands aside from 1,10-phenanthroline and 2,2'-bipyridine derivatives were tested, including 2-(2-pyridyl)benzimidazole (**7**) and 4,5-diaza-9-fluorenone (**5**), but neither performed optimally. The best result was observed with 4,7-dimethyl-1,10-phenanthroline (**14**), providing full conversion of carbamoyl fluoride, and 99% yield of the urea by NMR. When 3,4,7,8-tetramethyl-1,10-phenanthroline (**12**) was used, a drop in yield was observed to 88% with full conversion of starting material, indicating there may be a negative correlation between electron donation into the ligand and yield of the reaction. The same drop in yield was observed with 4,7-dimethoxy-1,10-phenanthroline (**15**), further lending credence to this conjecture. When 2,9-dimethyl-1,10-phenanthroline (**13**) was used, a significant drop in both yield and conversion to 20% and 46% respectively was observed, likely due to the steric bulk around the nitrogen centres. Although 4,7-dimethyl-1,10-phenanthroline (**14**) slightly outperformed 1,10-phenanthroline (**10**), we continued our initial optimization with 1,10-phenanthroline due to its lower costs.

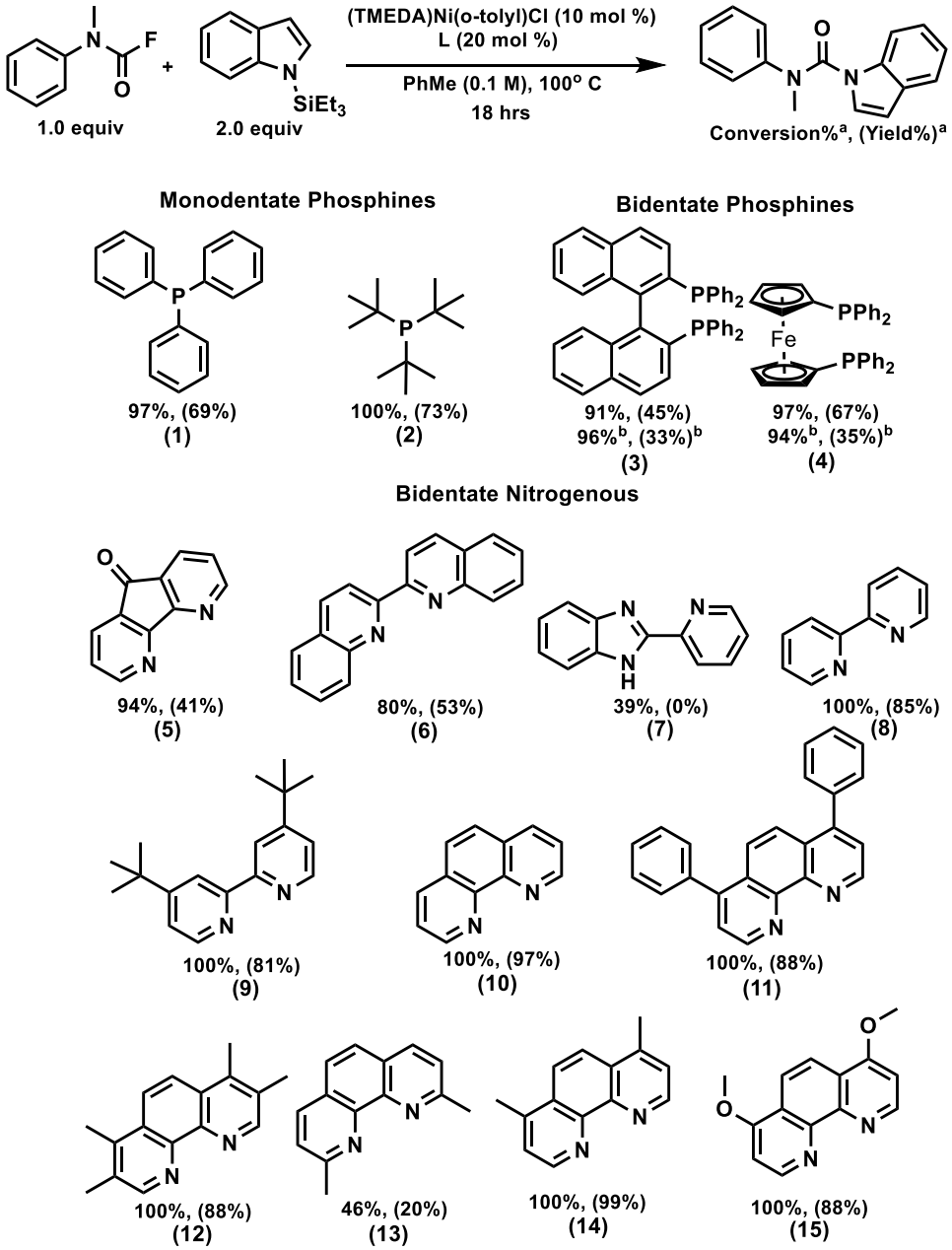


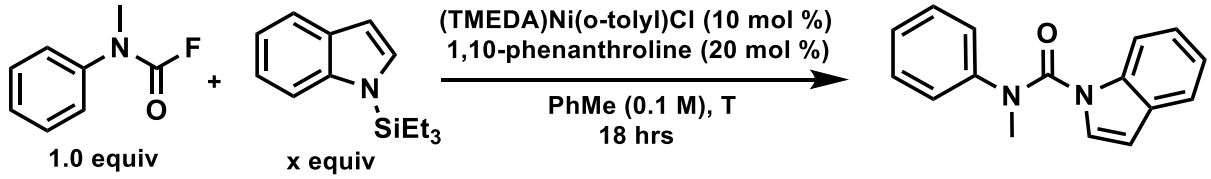
Figure 17. Ligand screen. [a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Ligand loading at 10 mol % instead of 20 mol %.

2.5.4 Temperature Screen

Following the ligand screen, we wanted to determine if the reaction could be run at a lower temperature (**Table 4**). We found that the reaction proceeded efficiently at 70 °C (**Entry 2**),

whereas lower temperatures 50 °C, and room temperature (**Entries 3,4**), resulted in reduced conversions and yields. It was also found concurrently with the temperature screen, that the equivalents of the silylated nucleophile could be lowered from 2.0 to 1.5 without any detrimental impact on the yield (**Entry 5**). However, when the equivalents were lowered to 1.1, the yield dropped to 81% (**Entry 6**).

Table 4. Temperature screen.



Entry	x	T (°C)	Conversion (%)[a]	Yield (%)[a]
1	2.0	100	100	97
2	2.0	70	100	94
3	2.0	50	88	30
4	2.0	r.t.	77	19
5	1.5	70	100	95
6	1.1	70	100	81

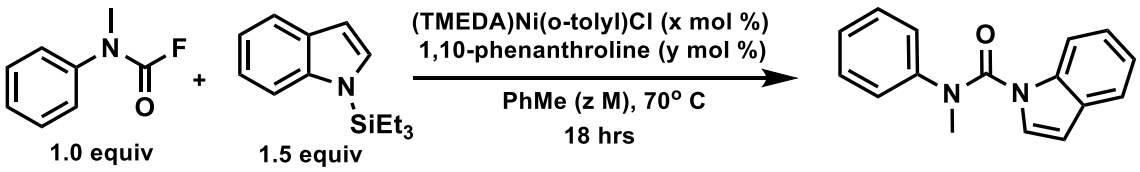
[a]Conversions and yields were determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

2.5.5 Catalyst Loading, Ligand Loading, and Concentration Screen

Initial screenings for this cross-coupling reaction were done with a catalyst loading of 10 mol % and a ligand loading of 20 mol % (**Entry 1**). A control run was conducted which contained no

catalyst or ligand, and poor conversion of 18% and no yield was observed, indicating the requirement of the transition metal for this cross-coupling (**Entry 2**). When the catalyst and ligand loading was halved to 5 mol % and 10 mol %, a drop in yield was observed (**Entry 3**). However, the yield was restored by simply doubling the concentration (**Entry 4**). The same pattern was observed when the catalyst and ligand loading were halved to 2.5 mol % and 5 mol % respectively (**Entries 5, 6**). The catalyst and ligand loading were then lowered to 1 mol % and 2 mol % respectively, and this still resulted in full conversion of carbamoyl fluoride and 92% yield of product (**Entry 7**). The ratio of catalyst to ligand was then altered from 1:2 to 1:1.5 (**Entry 8**) resulting in full conversion, but a drop in yield to 89% was observed, indicating the importance of keeping the metal:ligand ratio as 1:2.

Table 5. Catalyst loading, ligand loading, and concentration screen.



Entry	x	y	Z[b]	Conversion (%)[a]	Yield (%)[a]
1	10	20	0.1	100	97
2	0	0	0.1	18	0
3	5	10	0.1	100	90
4	5	10	0.2	100	96
5	2.5	5	0.2	100	92
6	2.5	5	0.4	100	96
7	1	2	1.0	100	92

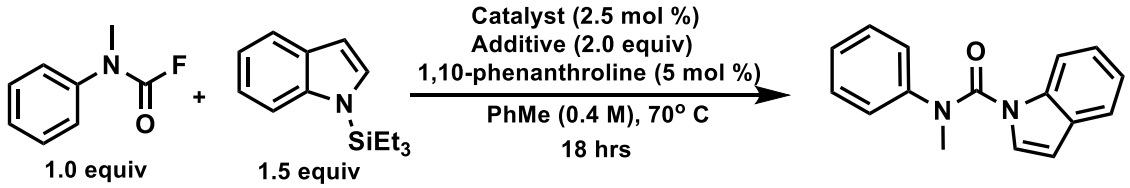
8	1	1.5	1.0	100	89

[a]Conversions and yields were determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Concentration is measured in respect to carbamoyl fluoride.

2.5.6 Metal Precatalyst Screen

We then tested other nickel(0) and nickel(II) pre-catalysts in the reaction (**Table 6**). The nickel(II) catalysts all required an external reductant in the reaction mixture to form Ni(0) as the active catalyst (**Entries 2-5**). Ni(II) species are incapable of undergoing oxidative addition into the C-F bond of carbamoyl fluorides as Ni(IV) species are not energetically accessible under these conditions. In the end, it was observed that Ni(0) catalysts such as Ni(COD)(DQ)[47] (**Entry 7**) and $Ni(COD)_2$ (**Entry 9**) performed similarly to (TMEDA)Ni(o-tolyl)Cl. Though they worked quite well, $Ni(COD)_2$ is extremely air sensitive, thus requiring the use of a glovebox. Ni(COD)(DQ) is an air-stable Ni(0) precatalyst that can be weighed out on the benchtop, but it is more expensive to use in the long run. Thus, we chose to optimize with Doyle's catalyst for the solvent screen (**Entry 1**).

Table 6. Metal Precatalyst Screen.



Entry	Catalyst	Additive	Conversion (%)[a]	Yield (%)[a]
1	(TMEDA)Ni(o-tolyl)Cl	None	100	96
2	$NiCl_2$•(DME)	None	20	1
3	$NiCl_2$•(DME)	$Mn_{(s)}$	100	88

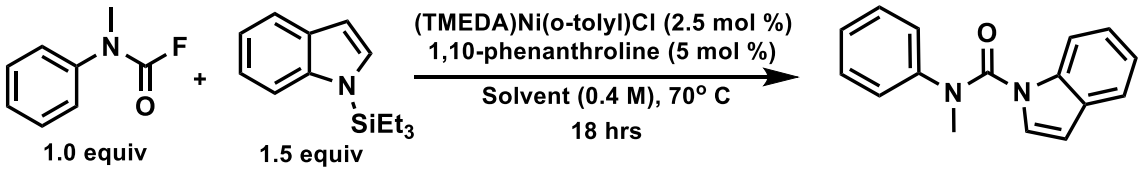
4	$Ni(acac)_2$	$Mn_{(s)}$	100	85
5	NiI_2	$Mn_{(s)}$	20	0
6	Ni(COD)(DQ)	None	100	93
7	Ni(COD)(DQ)[b]	None	100	100 (92)[c]
8	$NiBr_2$•(DME)	$Mn_{(s)}$	65	44
9	$Ni(COD)_2$[b]	None	84	70

[a]Conversions and yields were determined by quantitative ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]4,7-dimethyl-1,10-phenanthroline used as the ligand instead of 1,10-phenanthroline. [c]Isolated yield.

2.5.7 Solvent Screen

The final step of the optimization was the solvent screen (**Table 7**). The reaction worked relatively well in THF, MeCN, DMF, and 1,4-dioxane (**Entries 2, 3, 5, 6**). However, reduced reactivity was observed in 1,2-DCE (**Entry 4**). Ultimately, toluene proved to be the best solvent (**Entry 1**).

Table 7. Solvent screen.



Entry	Solvent[a]	Conversion (%)[b]	Yield (%)[b]
1	PhMe[c]	100	96
2	THF	100	87
3	MeCN	100	89

4	1,2-DCE	51	33
5	DMF	100	86
6	1,4-dioxane	100	93

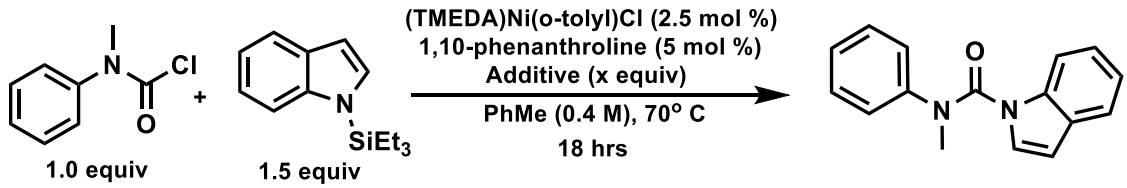
[a]All solvents were obtained from Sure/Seal™ bottles of anhydrous solvent, and used without further treatment. [b]Conversions and yields were determined by quantitative 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]Dried and degassed toluene used.

2.6 Comparison of Carbamoyl Fluoride to Chloride Analogue

The optimized conditions were then tested against the carbamoyl chloride analogue, to ascertain if the presence of a fluoride is important to the reaction (**Table 8**). Given that the halide leaving group is not present in the final cross-coupling product, it is important to determine if the use of carbamoyl fluorides provides any advantages over the analogous chlorides. Using the optimized reaction conditions, it was found that the carbamoyl chlorides reacted poorly with the silylated nucleophile (**Entry 1**). The yield only increased with the addition of cesium fluoride as a soluble fluoride source in the reaction vessel (**Entry 2**). When sodium fluoride was used as the fluoride source, poor conversion and no yield was observed, likely owing to its low solubility in toluene (**Entry 3**). Potassium fluoride was used in addition to 18-crown-6 ether (**Entry 4**), and saw full conversion and 90% yield of product, as the 18-crown-6 ether allows a greater solubility of inorganic salts in organic solvents.[48] However, it was later discovered that the fluoride simply removed the silyl protecting group and allowed the resulting anion to act as a nucleophile in the absence of the Ni catalyst. This was shown to be the prevalent mechanism with the results of two reactions set up: a control reaction with the carbamoyl chloride and TBAF only, and a test reaction with the carbamoyl chloride, TBAF, and silylated indole. In the control reaction, the carbamoyl

fluoride was not observed. In the test reaction, the urea product was generated in 100% yield. These results further reinforce the idea that the fluoride plays a special role in the reaction with the Ni catalyst.

Table 8. Carbamoyl chloride with optimized conditions.



Entry	Additive	X (equiv)	Conversion (%)[a]	Yield (%)[a]
1	None	**None**	10	0
2	CsF	**1.5**	52	29
3	NaF	**3.0**	13	0
4	KF	**3.0**	100	90
	18-Crown-6-Ether	**10 mol %**		
5	TBAF	**3.0**	100	78

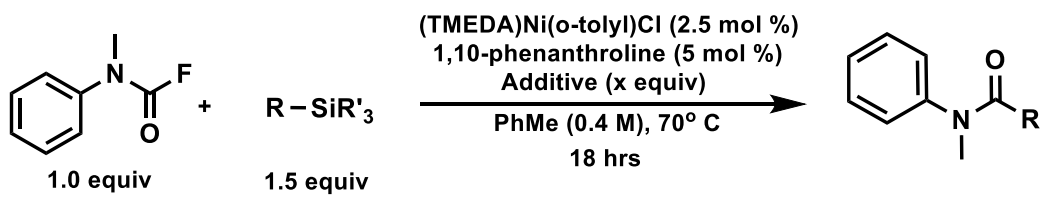
[a]Conversions and yields were determined by quantitative 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

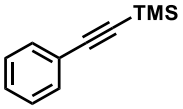
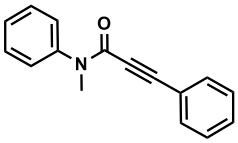
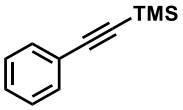
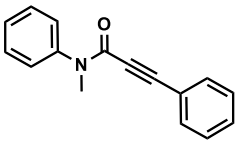
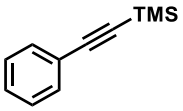
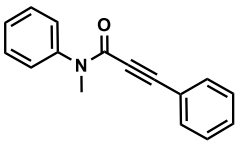
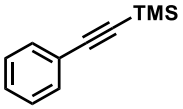
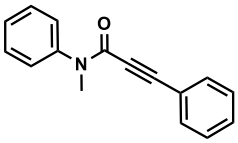
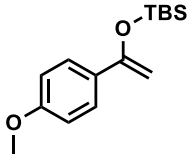
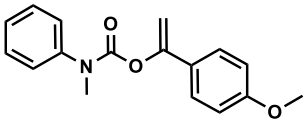
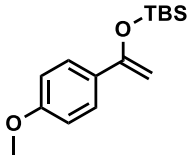
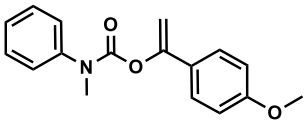
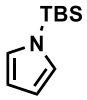
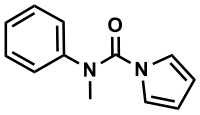
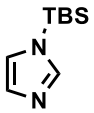
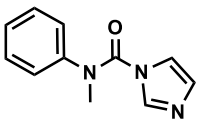
2.7 Variation in Silylated Nucleophile

Other silylated nucleophiles were tested following the optimized conditions for the silylated indole (**Table 9**). A variety of silylated functional groups were tested including alkynes, enol ethers, ketene acetals, pyridines, pyrroles, and imidazoles. When these conditions were tested with the TMS phenylacetylene (**Entry 1**), a conversion of 40% was found, with no yield of alkynamide. When 1 equivalent of TBAF (**Entry 2**) and DBU (**Entry 3**) was added into the reaction, the

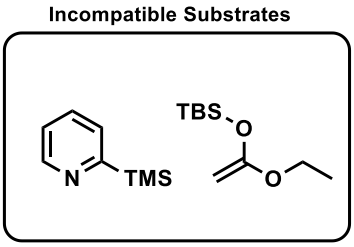
conversion of carbamoyl fluoride was 100% in both instances, but neither reaction generated product. Instead, it was observed that the carbamoyl fluoride had converted to *N*-methylaniline in a 20% and 22% yield respectively. When TMS phenylacetylene was used with TBAF in catalytic amounts (**Entry 4**), nearly full conversion of the carbamoyl fluoride was observed, but only a moderate yield of the alkynamide was obtained. Both the imidazole (**Entry 7**) and the pyrrole (**Entry 8**) underwent cross-couplings without any modifications to the optimized conditions. The silylated pyrrole and imidazole cross-coupled to make urea products like the silylated indole, however the pyrrole only generated product in moderate yield and proved challenging to purify by column chromatography, as evidenced by the low isolated yield. The reaction with the imidazole had a significantly higher conversion than the pyrrole, and had a far more impressive, isolated yield, although optimization is still required for this substrate. The silyl enol ether (**Entry 5**) similar to the TMS phenylacetylene, had poor conversion and no yield of final product under the standard optimized conditions. With the use of catalytic amounts of TBAF (**Entry 6**), it provided the O-alkylated product generating a β-methylene carbamate in low yield, but this reaction was found to also occur in the presence of just TBAF (without Ni) and was not explored further. Two other substrates were tested (*vide infra*) which were a silylated pyridine, and a silyl ketene acetal. Under no conditions was cross-coupling observed, likely owing to the lack of stability of these substrates in the reaction mixture, and their decomposition even under the best of storage conditions.

Table 9. Screen of other silylated nucleophiles.



Entry	R-SiR'$_3$	Final Product	Additive (equiv)	Conversion (%)[a]	Yield (%)[a]
1			None	40	0
2			TBAF (1.0)	100	0
3			DBU (1.0)	100	0
4			TBAF (10 mol %)	99	52 (51)[b]
5			None	27	0
6			TBAF (10 mol %)	100	28[b]
7			None	83	62 (31)[b]
8			None	100	84 (81)[b]

[a]Conversions and yields were determined by quantitative NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.



2.8 Proposed Catalytic Cycle

We believe that a Ni(0) species is the active catalyst for this cross-coupling reaction (**Figure 18**). The catalytic cycle starts with the oxidative addition into the C-F bond of the carbamoyl fluoride. A transmetallation step then occurs with the silylated nucleophile, while generating a fluorosilane by-product. C-N bond reductive elimination furnishes the final product, while regenerating the active nickel catalyst.

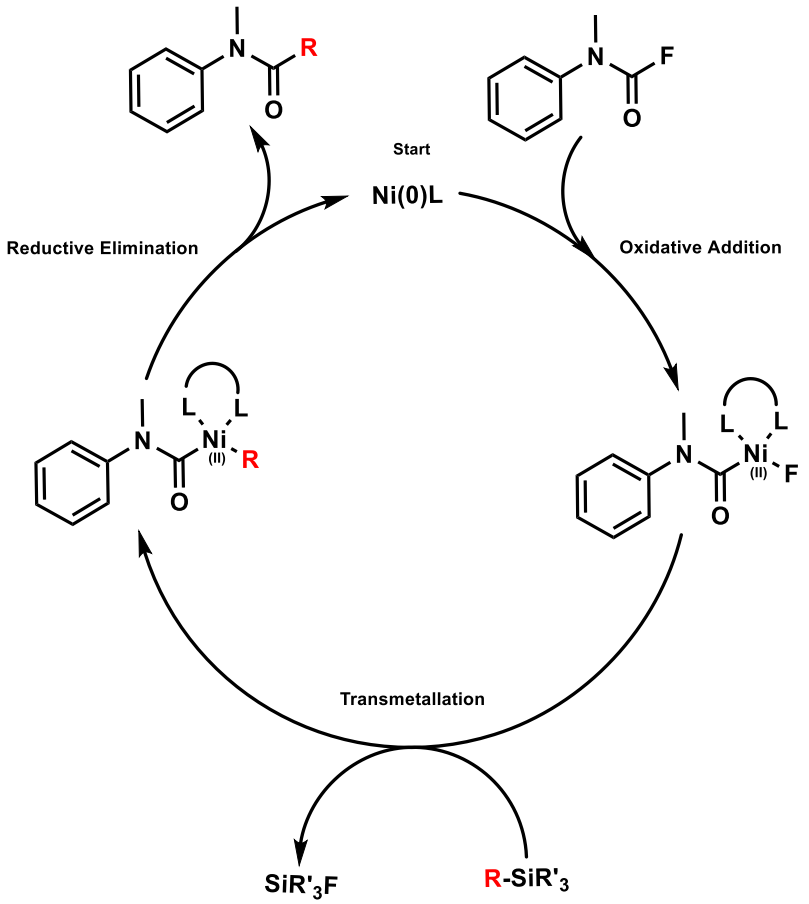


Figure 18. The proposed catalytic cycle of the cross-coupling reaction.

2.9 Conclusions and Future Work

Herein, we have developed a cross-coupling procedure of carbamoyl fluorides with silylated nucleophiles to generate new and interesting products, and thereby contributing to the limited usage of carbamoyl fluorides as reagents. The reaction applies a low catalyst loading of an Earth-abundant transition metal, in the form of a reasonably priced, air stable, and commercially available nickel catalyst; resulting in good to excellent yields for indole-based ureas and moderate to good yields for other silylated nucleophiles. With these findings, we hope to bring more attention to the use of carbamoyl fluorides as reagents in chemical syntheses.

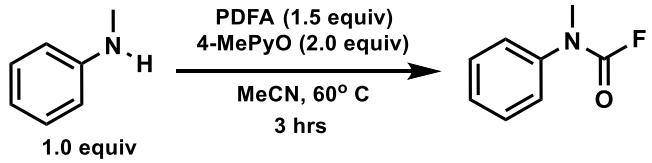
Now that conditions have been optimized for the reaction with the silylated indole, the next step is to conduct a substrate scope to determine the functional group tolerance of this method. A variety of functional groups will be tested, such as indoles that contain electron-withdrawing and donating moieties, as well as other halides; the latter of which being interesting, as they pose an oxidative addition competition point with the carbamoyl fluoride. Variations to the indole core will also be conducted to probe both steric and electronic effects of the nucleophilic coupling partner.

Once the substrate scope is completed for the silylated indole, optimization for the other silylated nucleophiles will be carried out.

2.10 Experimental Data

2.10.1 Synthesis and Characterization of Starting Materials

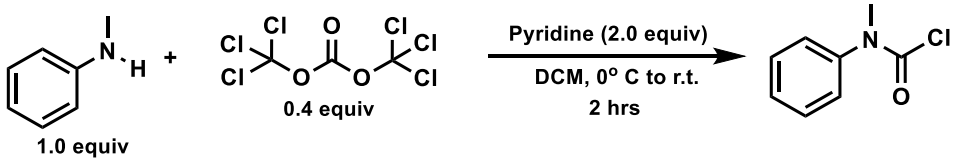
Synthesis of *N*-phenyl-*N*-methylcarbamoyl fluoride



To a flame-dried 250 mL Schlenk flask equipped with a stir bar is added PDFA (1.5 equiv, 7.1 mmol, 2.5353 g) and 4-methylpyridine *N*-oxide (2.0 equiv, 9.4 mmol, 1.0258 g). To a separate oven-dried 20 mL scintillation vial is added *N*-methylaniline (1.0 equiv, 4.7 mmol, 0.5000 g), before capping with an inverted septum and attaching to the vacuum manifold. Both the Schlenk flask and the scintillation vial are cycled between vacuum and nitrogen atmosphere 3 times. After the third cycle, the amine is taken up in MeCN and transferred into the reaction vessel via syringe. A total volume of 47 mL of MeCN is used, which results in a final reaction concentration of 0.1 M with respect to the amine. Upon complete transfer of the amine into the reaction vessel, the stopcock to the flask is closed and it is disconnected from the vacuum manifold. The flask is then lowered into a pre-heated 60 °C oil bath and allowed to stir for 3 hours, opening the stopcock every 20-30 minutes to vent the generated CO_2. After 3 hours, the flask is removed from the oil bath and

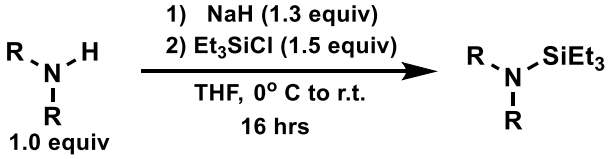
allowed to cool to room temperature. Once cooled, the contents of the reaction vessel are transferred to a sufficiently sized round bottom flask, and the Schlenk flask is rinsed out 3 times with EtOAc. The reaction mixture is then concentrated *in vacuo* before purification via column chromatography (1-5% EtOAc in hexanes). This generated the carbamoyl fluoride in an 83% yield. The spectral data are consistent with literature values.[21]

Synthesis of *N*-phenyl-*N*-methylcarbamoyl chloride



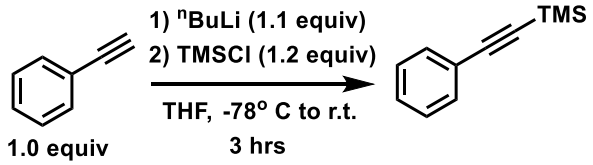
A flame-dried 50 mL round bottom flask equipped with a stir bar is cycled 3 times between vacuum and nitrogen atmosphere. At the same time, an oven-dried 20 mL scintillation vial containing *N*-methylaniline (1.0 equiv, 4.7 mmol, 0.5000 g), is also cycled 3 times between vacuum and nitrogen atmosphere. DCM is added to the scintillation vial (22 mL in 3 portions) and added to the reaction vessel via syringe. The reaction vessel is cooled to 0 °C with an ice bath, before the addition of neat anhydrous pyridine (2.0 equiv, 9.4 mmol, 0.76 mL) dropwise. To a separate oven-dried scintillation vial is added triphosgene (0.4 equiv, 1.9 mmol, 0.5638 g) under a nitrogen blanket. To the triphosgene is added DCM (25 mL in 3 portions), which is transferred into the reaction vessel via syringe, dropwise; making the concentration of the reaction 0.1 M with respect to the amine. The reaction is allowed to stir for 15 minutes at 0 °C before removing the ice bath and stirring at room temperature for 2 hours. After 2 hours, with the septum still on, the reaction is quenched with 1.0 M HCl (25 mL) and transferred into a separatory funnel. The reaction vessel is rinsed into the separatory funnel twice with DCM. The aqueous layer is extracted 3 times with DCM. The combined organic layers are added back to the separatory funnel and washed with brine. The organics are collected and dried over Na_2SO_4, and then filtered through a fritted funnel. The frit is washed with DCM, the filtrate is concentrated *in vacuo* and the crude material is purified via column chromatography (2.5% EtOAc in hexanes). This generated the carbamoyl chloride in an 84% yield. The spectral data are consistent with literature values.[49]

General Synthesis of *N*-silylated Nucleophiles



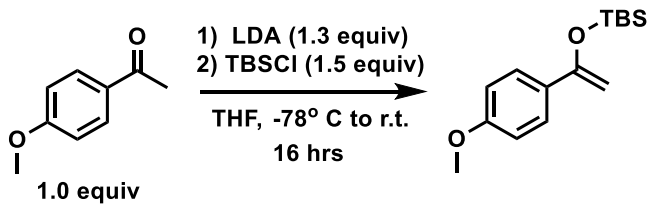
A flame-dried 100 mL round bottom flask equipped with a stir bar was brought into a glove box and charged with NaH (1.3 equiv, 22.2 mmol, 0.5328g), before being capped with a septum, brought out of the glovebox, and attached to a vacuum manifold. The flask is cycled between vacuum and nitrogen atmosphere 3 times before the addition of anhydrous THF (17 mL), followed by turning stirring on, and cooling to 0 °C with an ice bath. To a separate oven-dried 20 mL scintillation vial is added the heterocycle (indole, 1.0 equiv, 17.1 mmol, 2.0000 g) before being capped with an inverted septum and attached to the vacuum manifold. This is cycled 3 times between vacuum and nitrogen atmosphere. THF is added (17 mL in 3 portions), which is transferred over to the NaH-THF suspension dropwise over the course of 5 minutes; making the concentration of the final solution 0.5 M with respect to the heterocycle. Upon 15 minutes of stirring at 0^o C, the ice bath is removed, and the reaction is stirred for an additional 2 hours at room temperature. After 2 hours, the reaction is once again cooled to 0 °C, before adding neat chlorotriethylsilane (1.5 equiv, 25.7 mmol, 4.3 mL) dropwise. Upon 15 minutes stirring at 0^o C, the ice bath is removed, and reaction is stirred at room temperature overnight. The next day, the reaction mixture is quenched with water, diluted with Et_2O and added to a separatory funnel. The aqueous layer is extracted 3 times with Et_2O, before the combined organic layers are washed with brine, and dried over Na_2SO_4. The suspension is filtered through a fritted funnel, and washed 3 times with Et_2O. The filtrate is then concentrated *in vacuo* and purified by filtration through a small silica plug (100% hexanes). This generated the TES-indole in a 91% yield. The spectral data are consistent with literature values.[21] **Note:** The same procedure is used for the *N*-silylation of imidazole and pyrrole with the exception that tert-butyldimethylsilyl chloride (1.5 equiv, 25.7 mmol, 3.8735 g) is used instead of chlorotriethylsilane, which is added as a solution in THF (10 mL in 3 portions). The pyrrole and imidazole are generated in 93% and 91% yield respectively. The spectral data are consistent with literature values.[50,51]

Synthesis of trimethyl(phenylethynyl)silane



To a flame-dried round bottom flask equipped with a stir bar is added phenylacetylene (1.0 equiv, 4.9 mmol, 0.5000 g) in THF (10 mL) and cooled to -78° C. Upon cooling, 2.2 mL of a 2.5 M in hexanes solution of ^{n}BuLi (1.1 equiv, 5.4 mmol) is added to the reaction mixture dropwise over the course of 5 minutes. The reaction is allowed to stir for 30 minutes at -78° C before the addition of neat TMSCl (1.2 equiv, 5.9 mmol, 0.75 mL) dropwise. This is stirred at -78 °C for 1 hour, before removing the cooling bath and allowing to stir at room temperature. After 2 hours, the reaction is quenched with NH_4Cl before transferring to a separatory funnel and extracting the aqueous layer 3 times with DCM. The combined organic layers are washed with brine, and dried over Na_2SO_4. The Na_2SO_4 is filtered off using a fritted funnel, rinsing with DCM 3 times. The filtrate is collected, concentrated *in vacuo* and purified by filtration through a small silica plug (100% hexanes). This generated the silylated alkyne in a 46% yield. The spectral data are consistent with literature values.[52]

Synthesis of *tert*-butyl((1-(4-methoxyphenyl)vinyl)oxy)dimethylsilane



To a flame-dried round bottom flask equipped with a stir bar is added diisopropylamine (1.4 equiv, 9.3 mmol, 1.31 mL) in THF (10 mL) and cooled to -78 °C. Upon cooling, 3.5 mL of a 2.5 M in hexanes solution of ^{n}BuLi (1.3 equiv, 8.7 mmol) is added dropwise. The solution is allowed to stir at -78 °C. After 30 minutes, a solution of 4-methoxyacetophenone (1.0 equiv, 6.7 mmol, 1.0000 g) in THF (6 mL in 3 portions) is added to the LDA mixture dropwise, and then allowed to stir at -78 °C. After 45 minutes, a solution of TBSCl (1.5 equiv, 10.0 mmol, 1.5072 g) in THF (6 mL in 3 portions) is added dropwise to the reaction mixture. This is allowed to stir overnight still in the

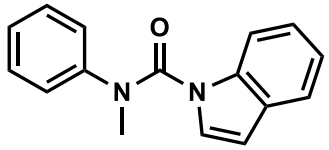
bath, allowing the reaction mixture to slowly come up to room temperature. The next day, the reaction is quenched with water, transferred to a separatory funnel, and the aqueous layer is extracted 3 times with DCM. The combined organic layers are washed with brine and dried over Na_2SO_4. The Na_2SO_4 is filtered off via fritted funnel, rinsing down with DCM 3 times. The filtrate is collected, concentrated *in vacuo* and purified by filtration through a small silica plug (100% hexanes). This generated the silyl enol ether in a 58% yield. The spectral data are consistent with literature values.[53]

2.10.2 Synthesis and Characterization of Products

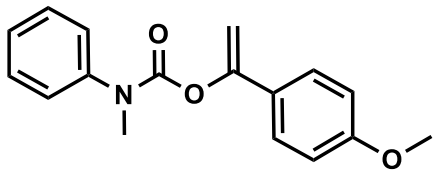
General Cross-Coupling Procedure

To an oven-dried 2 dram vial equipped with a stir bar is added (TMEDA)Ni(o-tolyl)Cl (2.5 mol %, 0.005 mmol, 0.0015 g) and 4,7-dimethyl-1,10-phenanthroline (5 mol %, 0.01 mmol, 0.0021 g), before capping with a septum and attaching to a vacuum manifold. The reaction vessel is cycled between vacuum and nitrogen atmosphere 3 times before adding dried and degassed PhMe (0.25 mL) which is allowed to stir at room temperature for 15 minutes. Two separate 2 dram vials are charged with the carbamoyl fluoride (1.0 equiv, 0.2 mmol, 0.0306 g) and silylated nucleophile (indole, 1.5 equiv, 0.3 mmol, 0.0694 g), both of which are capped with septa, evacuated and refilled with nitrogen 3 times. After the third cycle, dried and degassed PhMe is added to the vial containing the carbamoyl fluoride (0.125 mL in two portions), which is transferred into the reaction vessel via syringe. Dried and degassed PhMe is added to the vial containing the silylated nucleophile (0.125 mL in two portions), which is transferred to the reaction vessel via syringe; this results in a final reaction concentration of 0.4 M with respect to the carbamoyl fluoride. The reaction vessel septum is removed and quickly replaced with a screw cap, before being lowered into a pre-heated 70 °C oil bath. After stirring for 18 hours, the vial is removed from the oil bath and allowed to cool to room temperature. Upon cooling, the reaction mixture is diluted with EtOAc and filtered through a Monstr pipette plugged with cotton and celite. The reaction vessel is rinsed 3 times with EtOAc, and this is filtered through the Monstr pipette. The filtrate is concentrated *in vacuo* and is purified via column chromatography (10-25% Et_2O in hexanes). **For reactions with NMR yields only:** Upon concentration *in vacuo*, a measured amount of 1,3,5-trimethoxybenzene (16-20 mg) is added to the crude material, which is taken up in $CDCl_3$ (~0.4 mL) and transferred into an NMR tube. The flask holding the crude material is rinsed with minimal $CDCl_3$ (~0.2 mL)

and this is transferred into the NMR tube. A ^{1}H NMR is taken on a 300 MHz NMR spectrometer (8 scans with a relaxation delay of 10 seconds), and yield is calculated from the integration ratio of aromatic protons of 1,3,5-trimethoxybenzene compared to methyl protons in product. Conversion is calculated from the integration ratio of aromatic protons of 1,3,5-trimethoxybenzene compared to methyl protons in starting material. **Note:** The same procedure is used for the cross-coupling of silylated imidazole, pyrrole, alkyne, and enol ether; as well as cross-coupling reactions with carbamoyl chloride. **Products:** The urea products generated from silylated pyrrole and imidazole, as well as the alkynamide are known in literature, and the spectral data for these are consistent.[54,55,56]



N-*methyl*-N-*phenyl*-*1*H-*indole*-*1*-*carboxamide.* The title compound was synthesized using the general cross-coupling procedure, and isolated as a viscous yellow oil after purification by flash column chromatography (20-25% Et_2O in hexanes). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (dd, J = 8.26 Hz, 0.57 Hz, 1H), 7.49 (d, J = 7.75 Hz, 1H), 7.31-7.22 (m, 3H), 7.19-711 (m, 4H), 6.99 (d, J = 3.60 Hz, 1H), 6.37 (dd, J = 3.56 Hz, 0.36 Hz, 1 H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.3, 144.6, 135.7, 130.0, 129.2, 127.4, 126.8, 125.6, 123.8, 122.3, 121.0, 114.4, 105.8, 39.7. FTIR (Neat) cm^{-1} 1791, 1677, 1594, 1494, 1450, 1351, 743, 694, 613. HRMS (ESI) calc'd for $[M+H]^+$ 251.1179 found 251.1164.



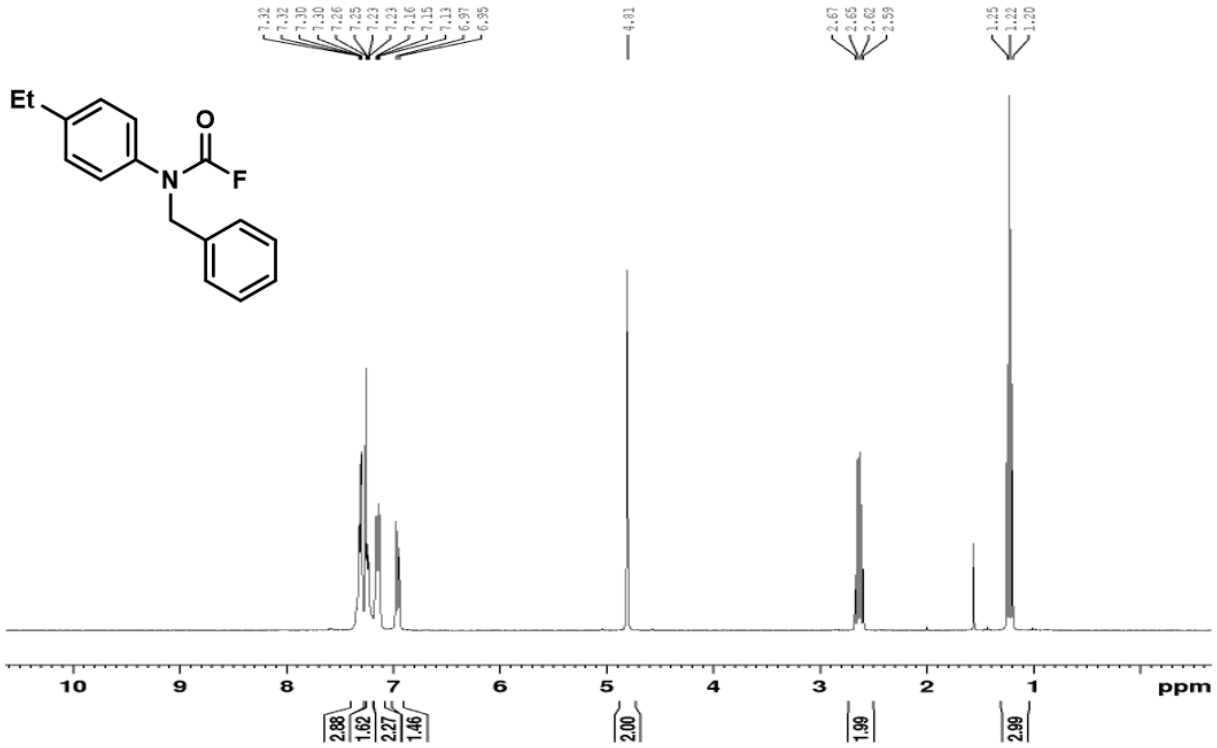
1*-*(4*-*methoxyphenyl)vinyl methyl(phenyl)carbamate. The title compound was synthesized using the general-cross coupling procedure, and isolated as a pale yellow solid after purification by flash column chromatography (10-15% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 7H), 6.84 (d, J = 8.80 Hz, 2H), 5.28 (d, J = 1.60 Hz, 1H), 4.97 (d, J = 1.64 Hz, 1H), 3.80 (s,

3H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 153.6, 153.1, 143.0, 129.1, 127.5, 126.3, 113.8, 98.7, 77.2, 55.3, 38.2. FTIR (Neat) cm^{-1} 1717, 1642, 1510, 1244, 1135, 836, 759, 695. HRMS (ESI) calc'd for $[M+H]^+$ 284.1281 found 284.1269.

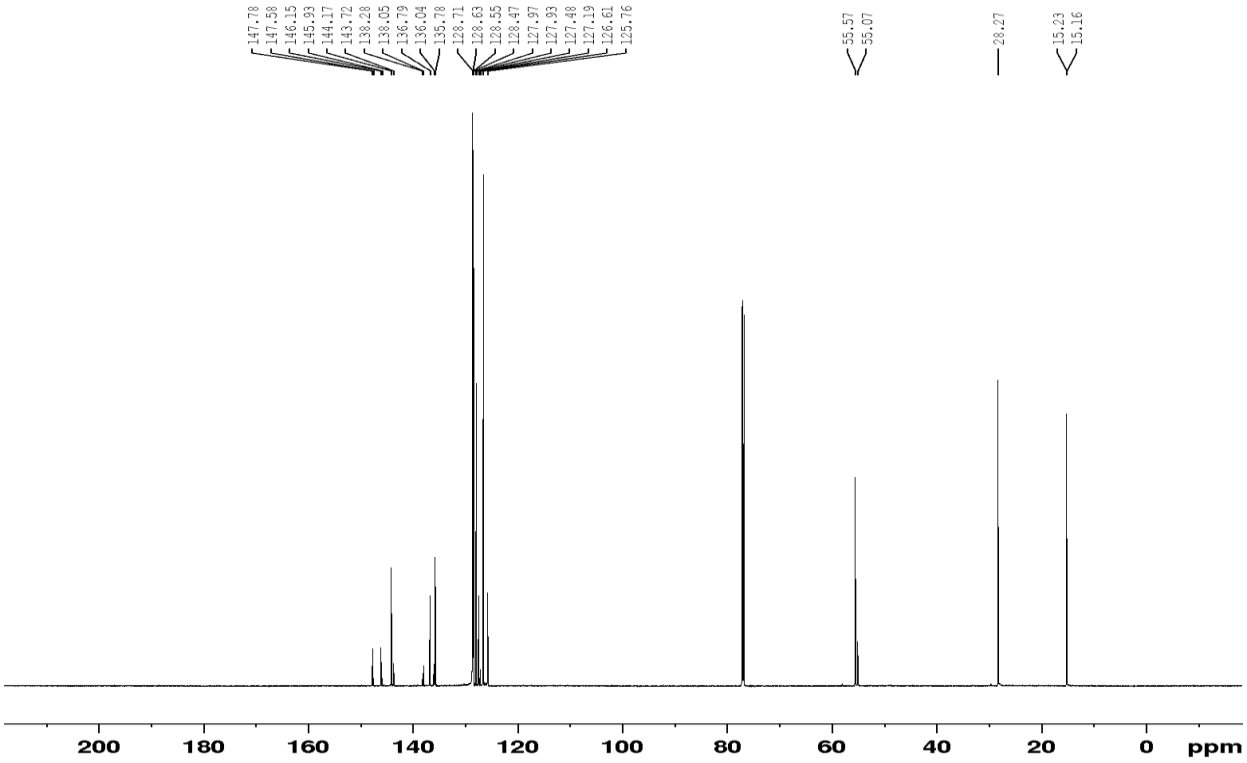
Appendix

N-benzyl-*N*-(4-ethylphenyl)carbamoyl fluoride (B)

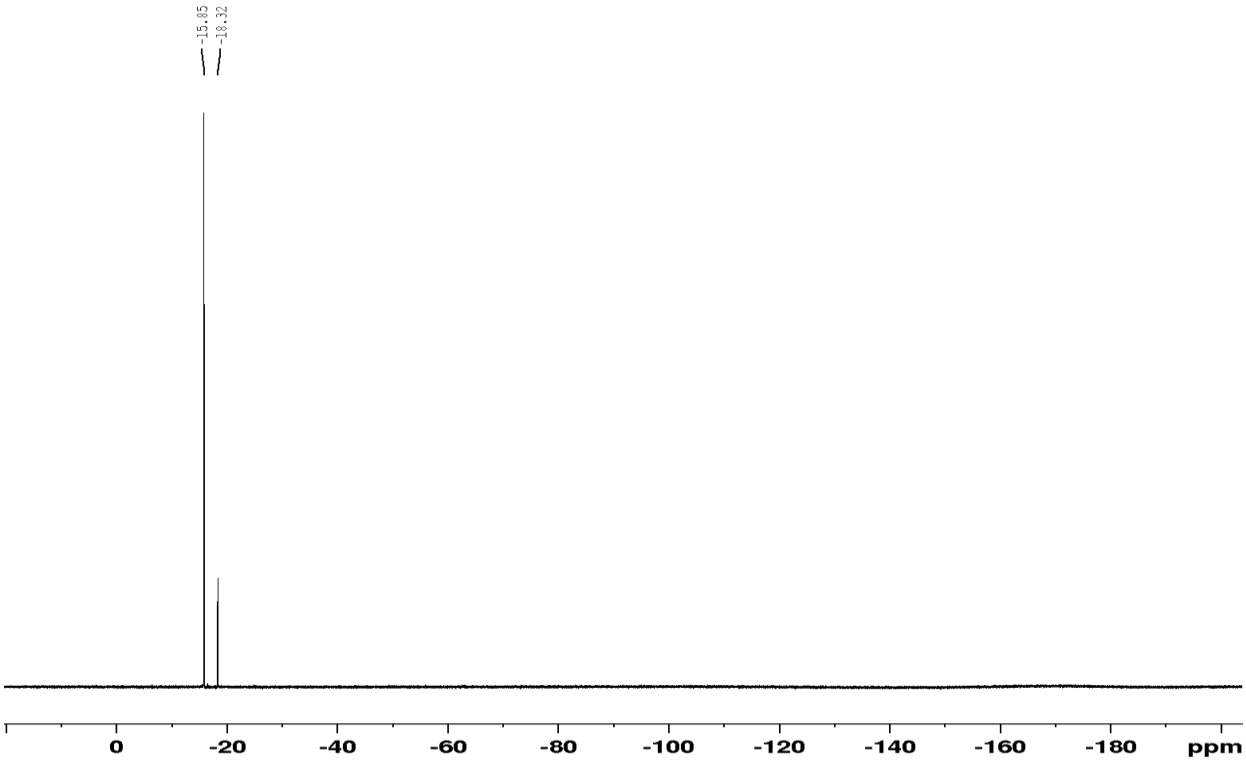
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

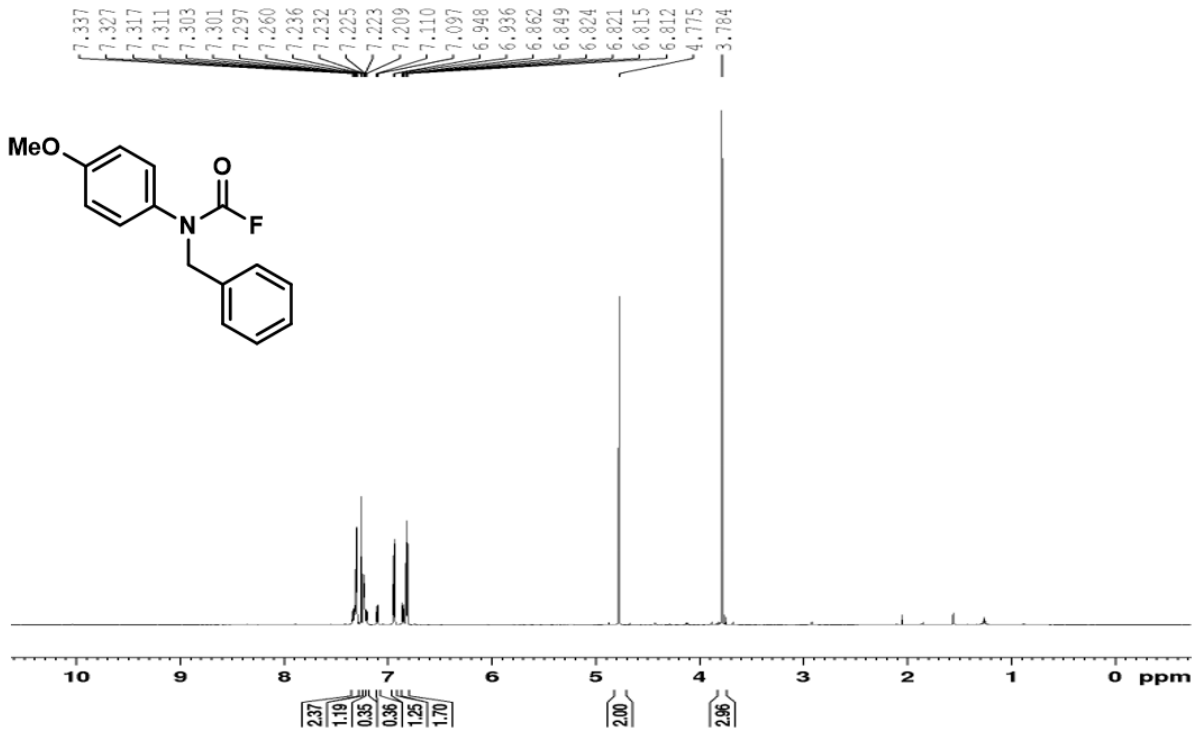


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

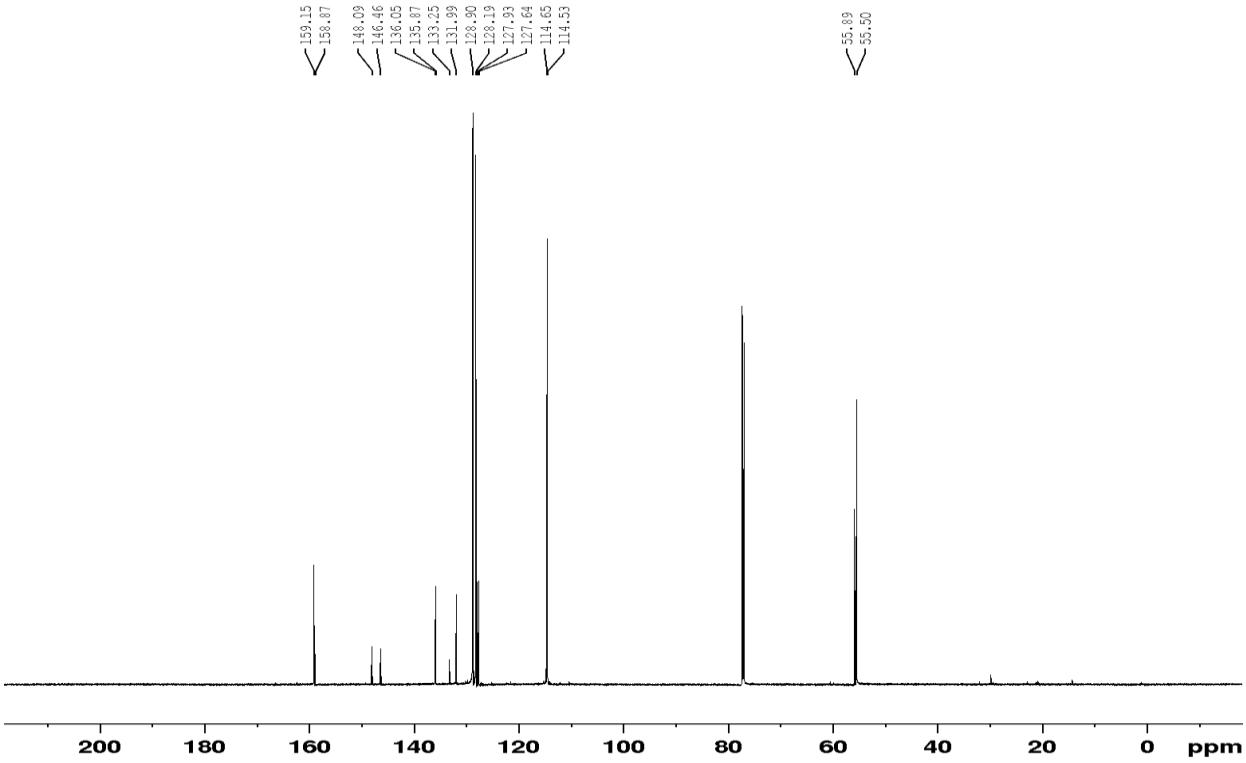


N-benzyl-*N*-(4-methoxyphenyl)carbamoyl fluoride (C)

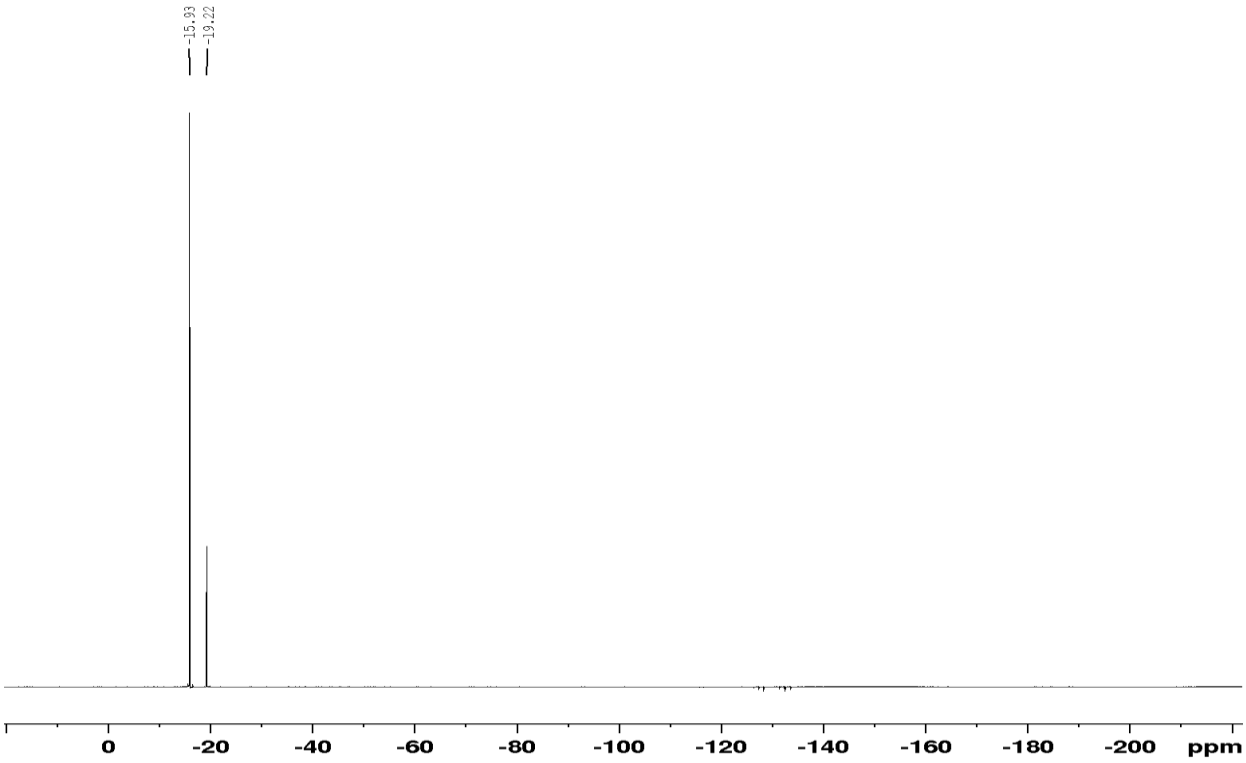
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

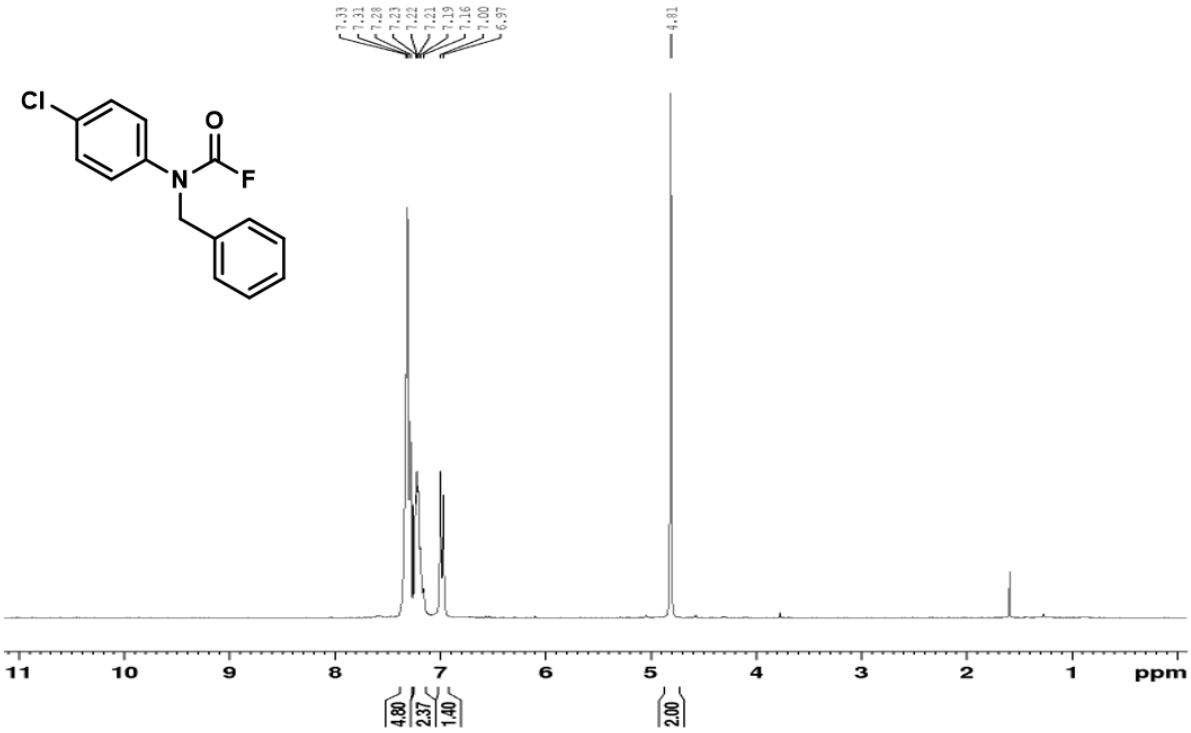


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

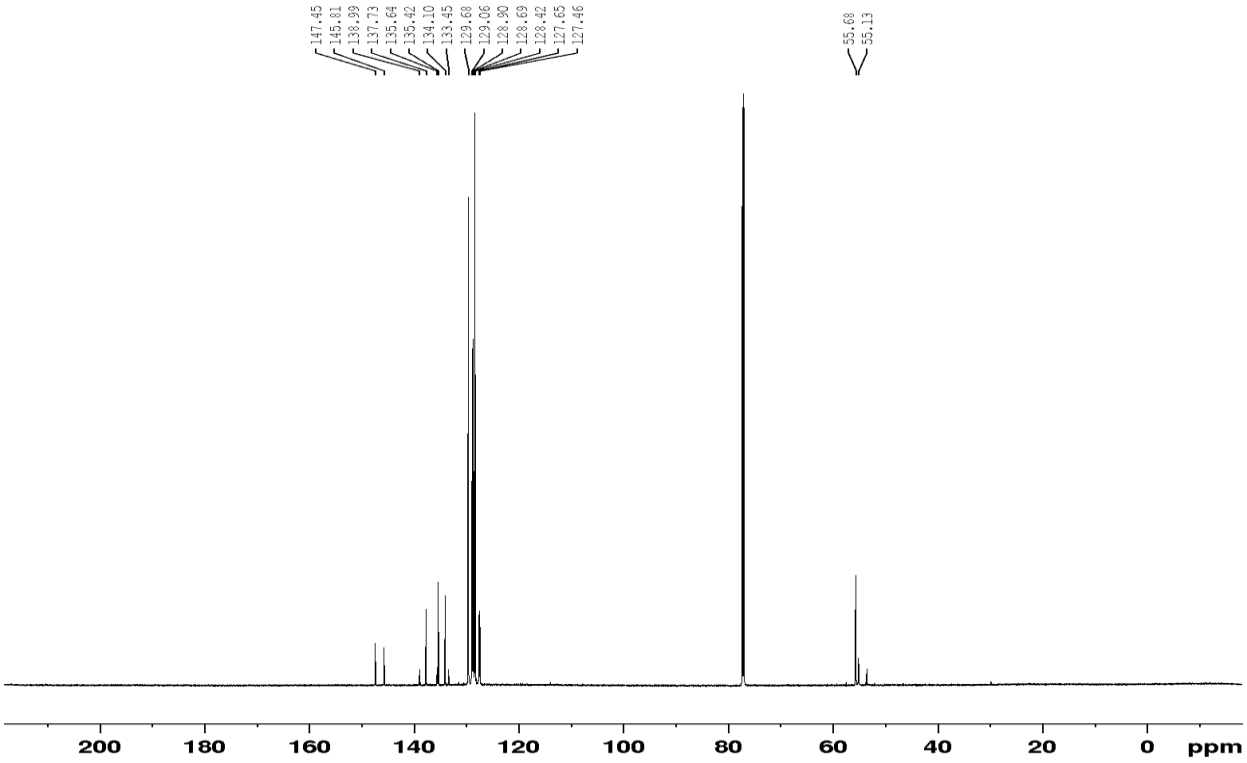


N-benzyl-*N*-(4-chlorophenyl)carbamoyl fluoride (D)

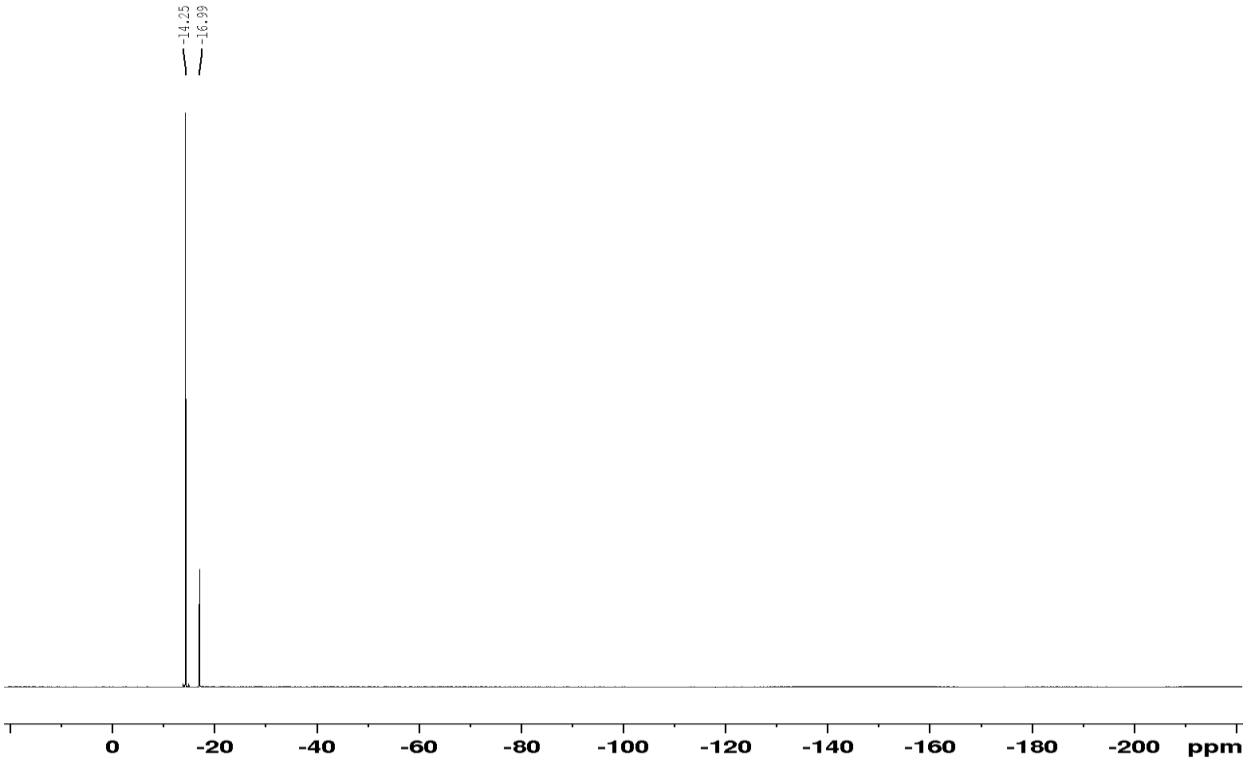
^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

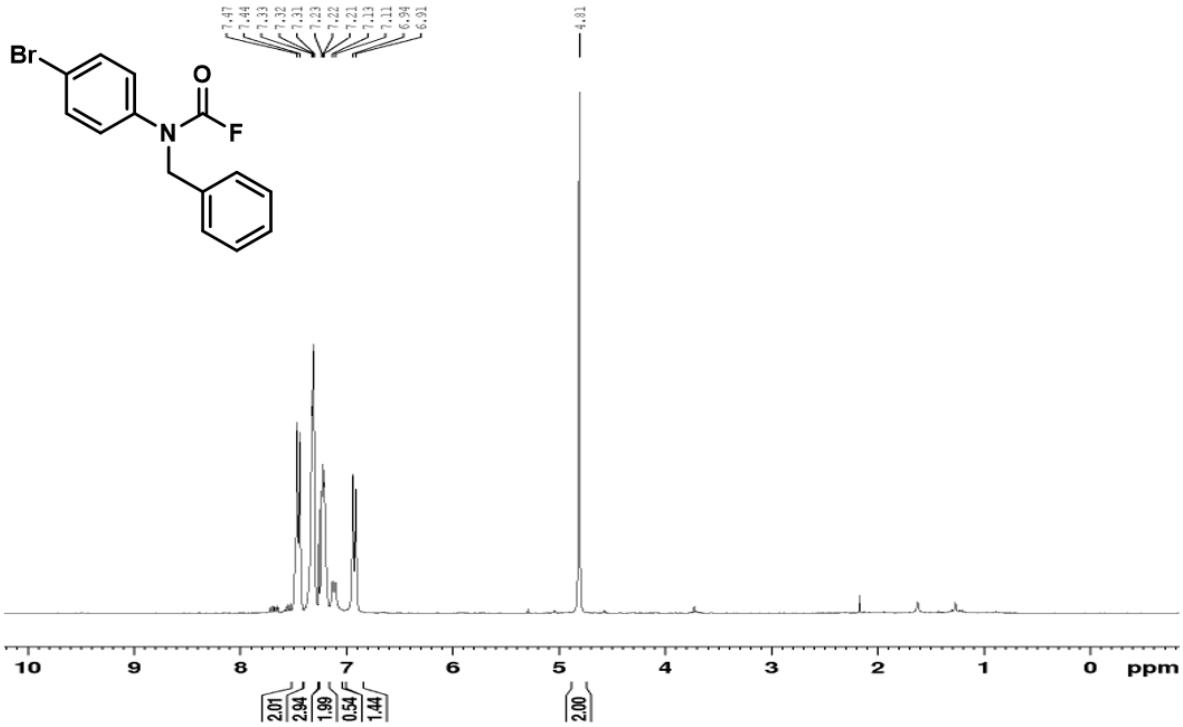


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

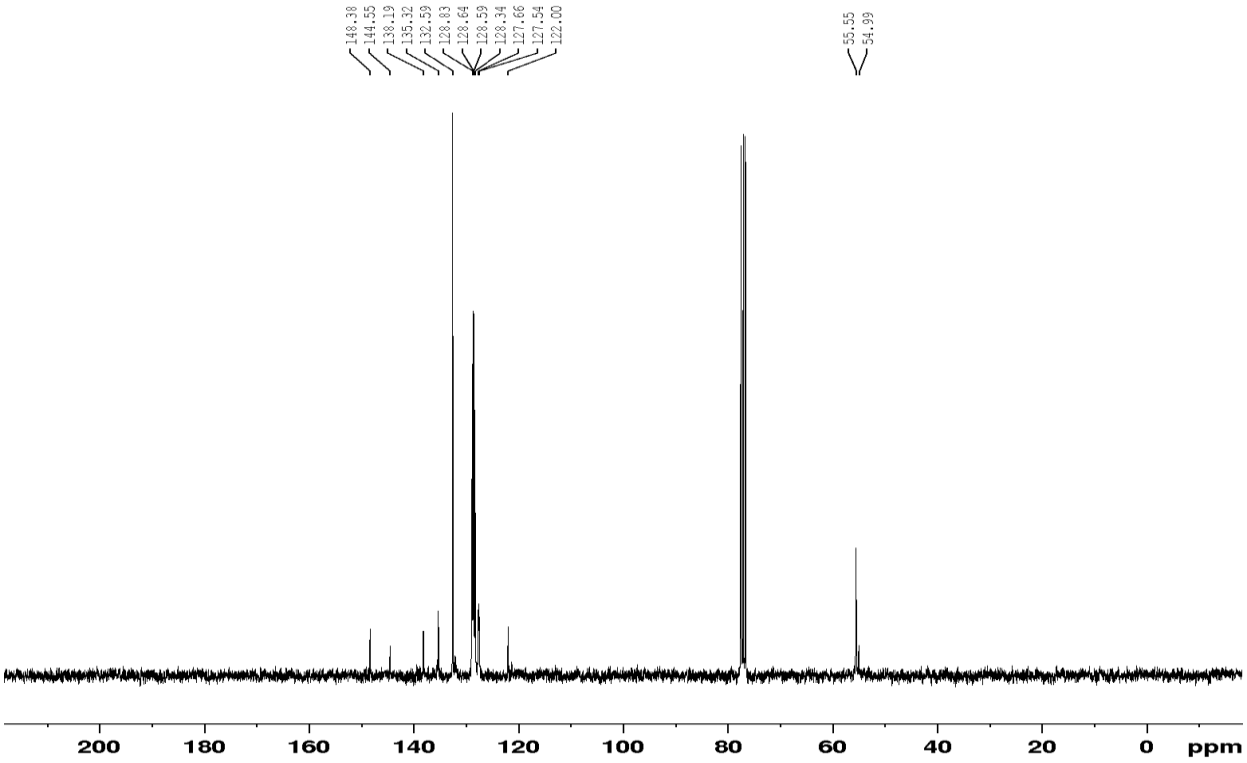


N-benzyl-*N*-(4-bromophenyl)carbamoyl fluoride (E)

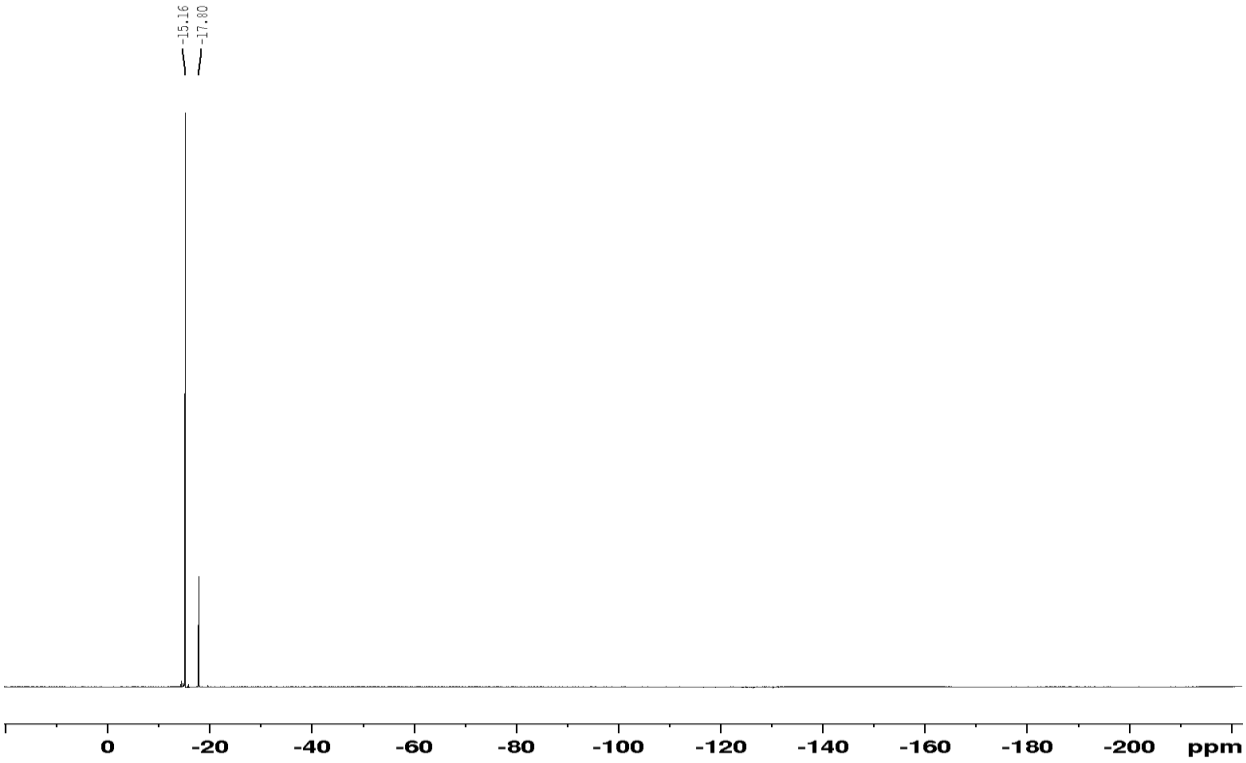
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

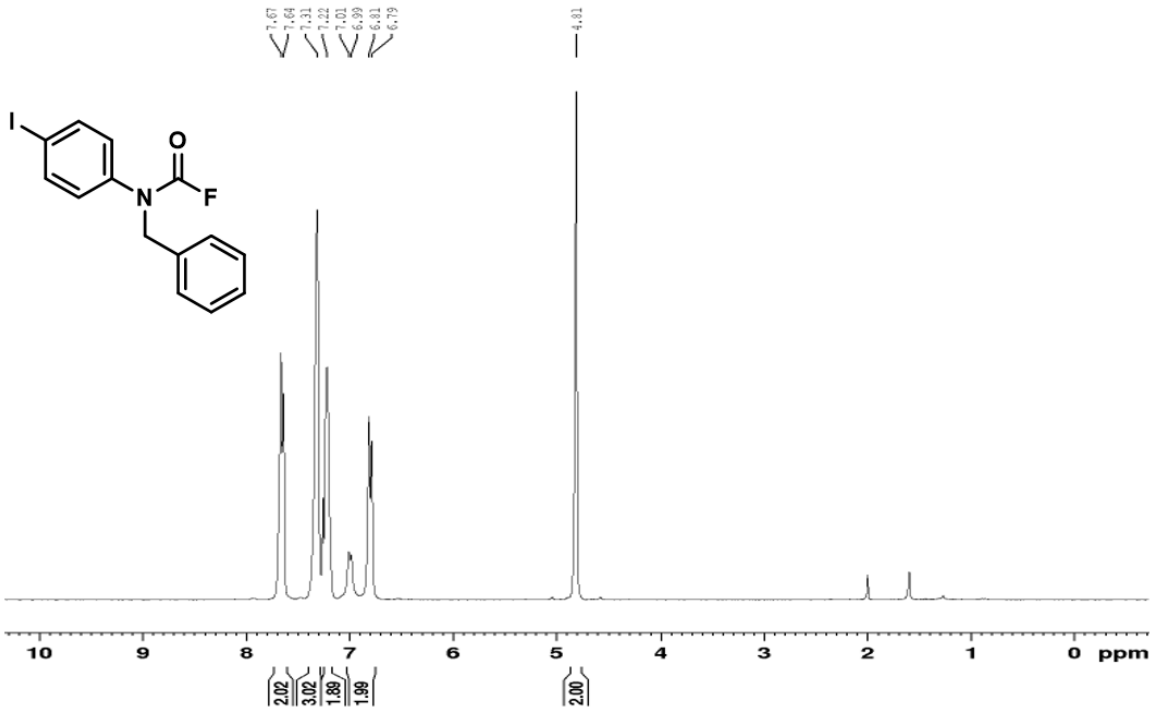


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

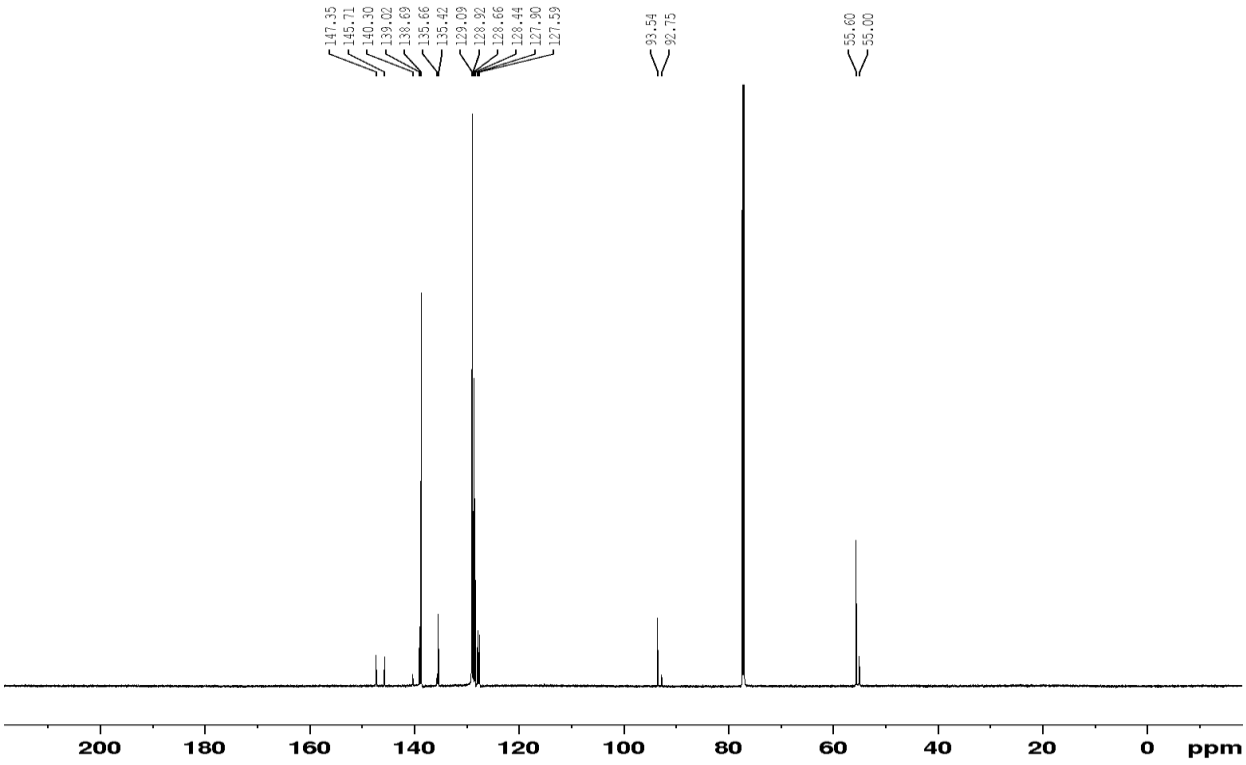


N-benzyl-*N*-(4-iodophenyl)carbamoyl fluoride (F)

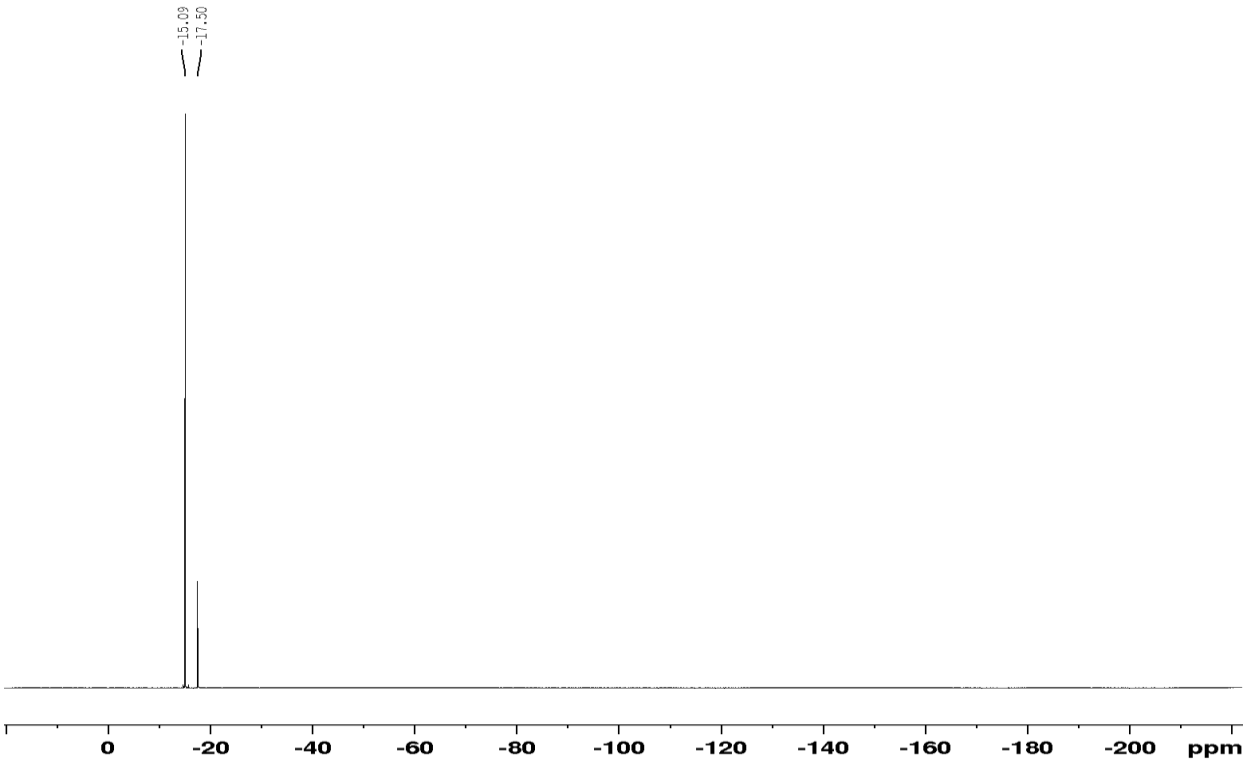
^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

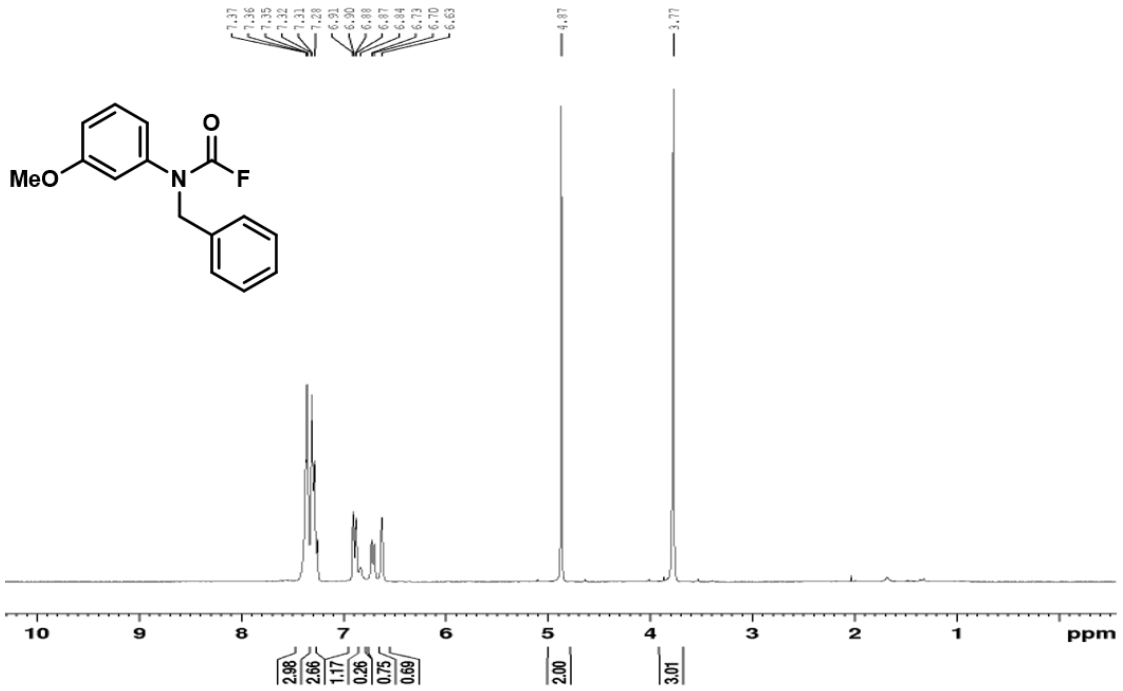


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

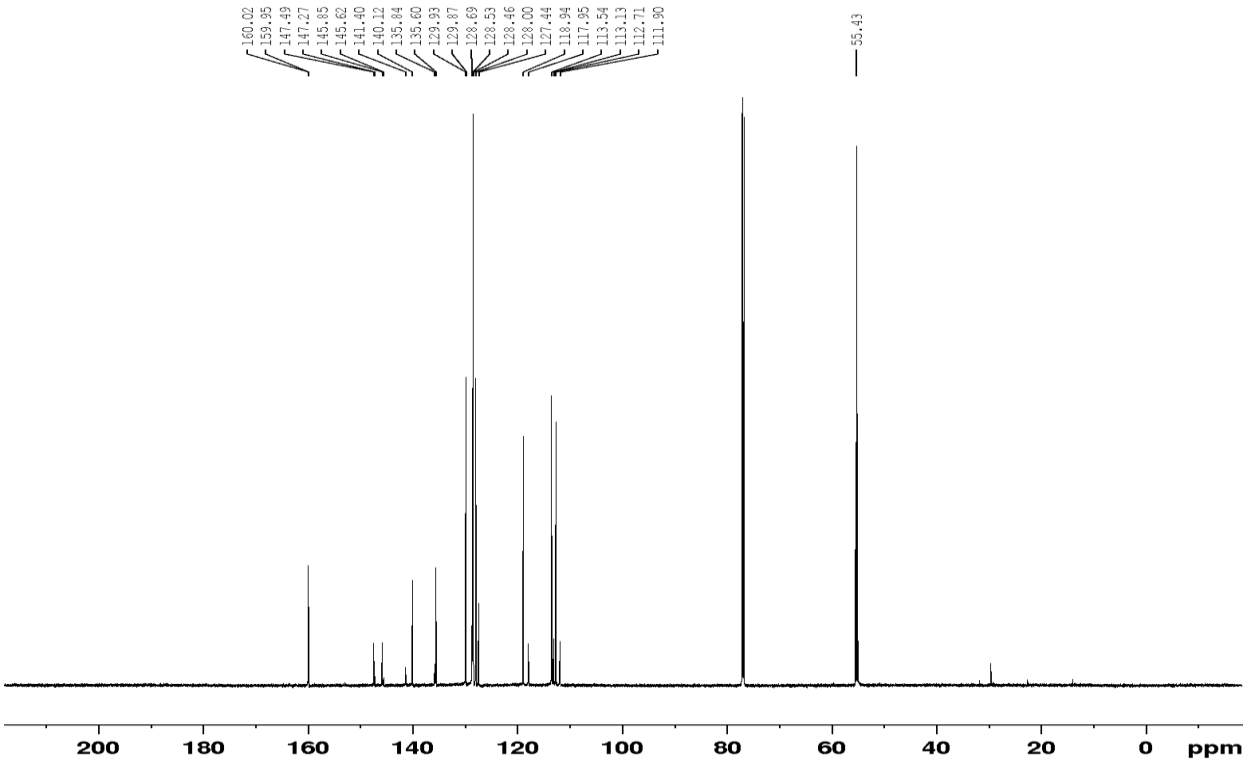


N-benzyl-*N*-(3-methoxyphenyl)carbamoyl fluoride (G)

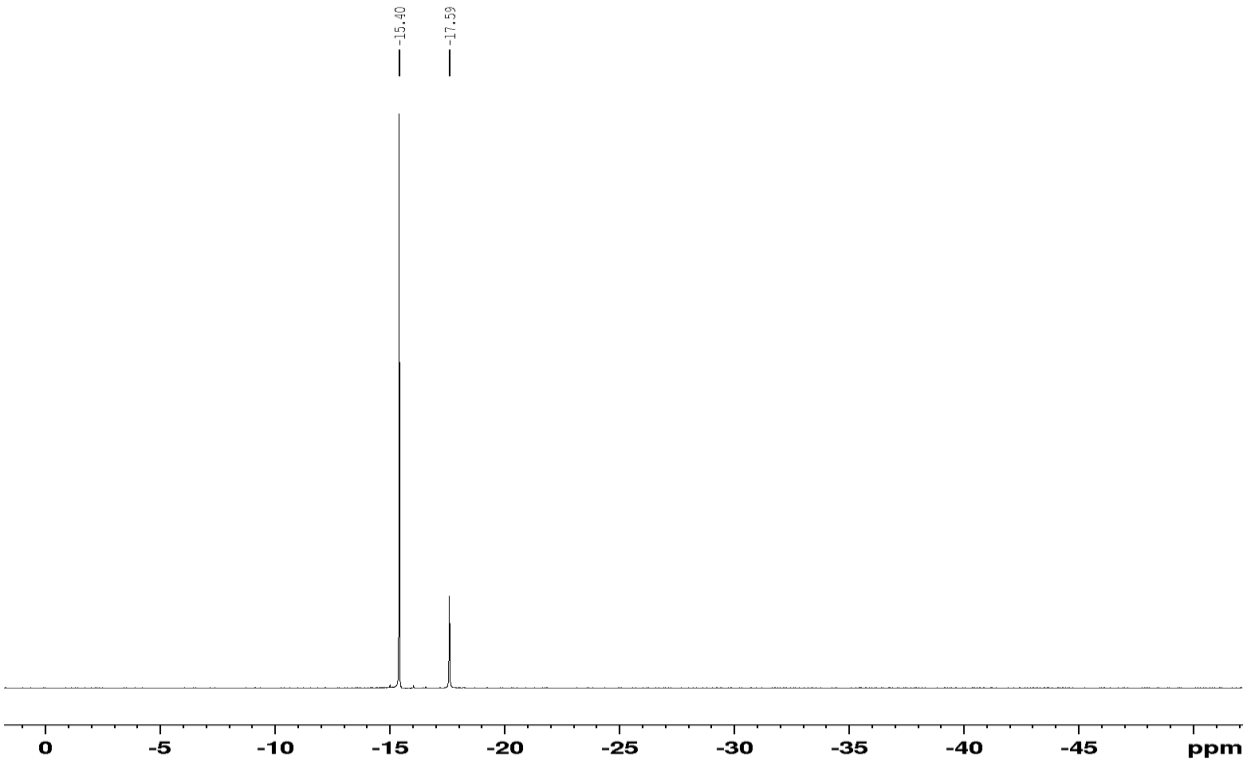
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

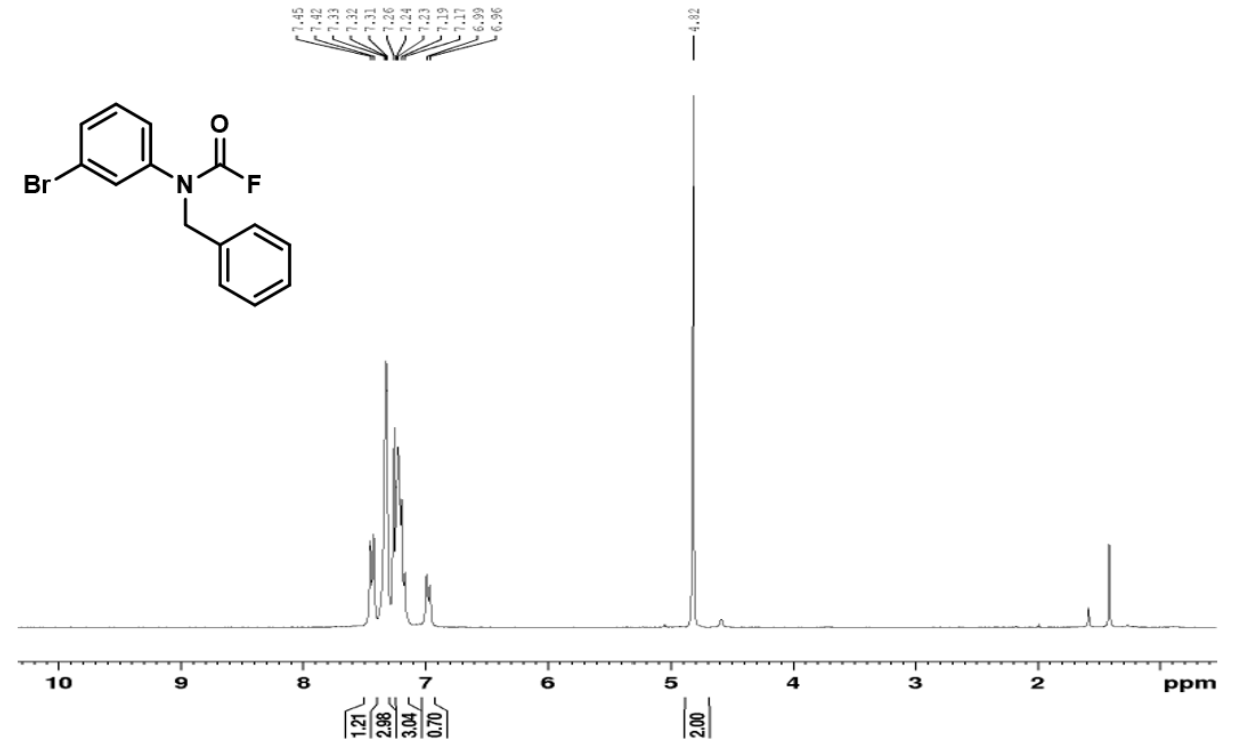


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

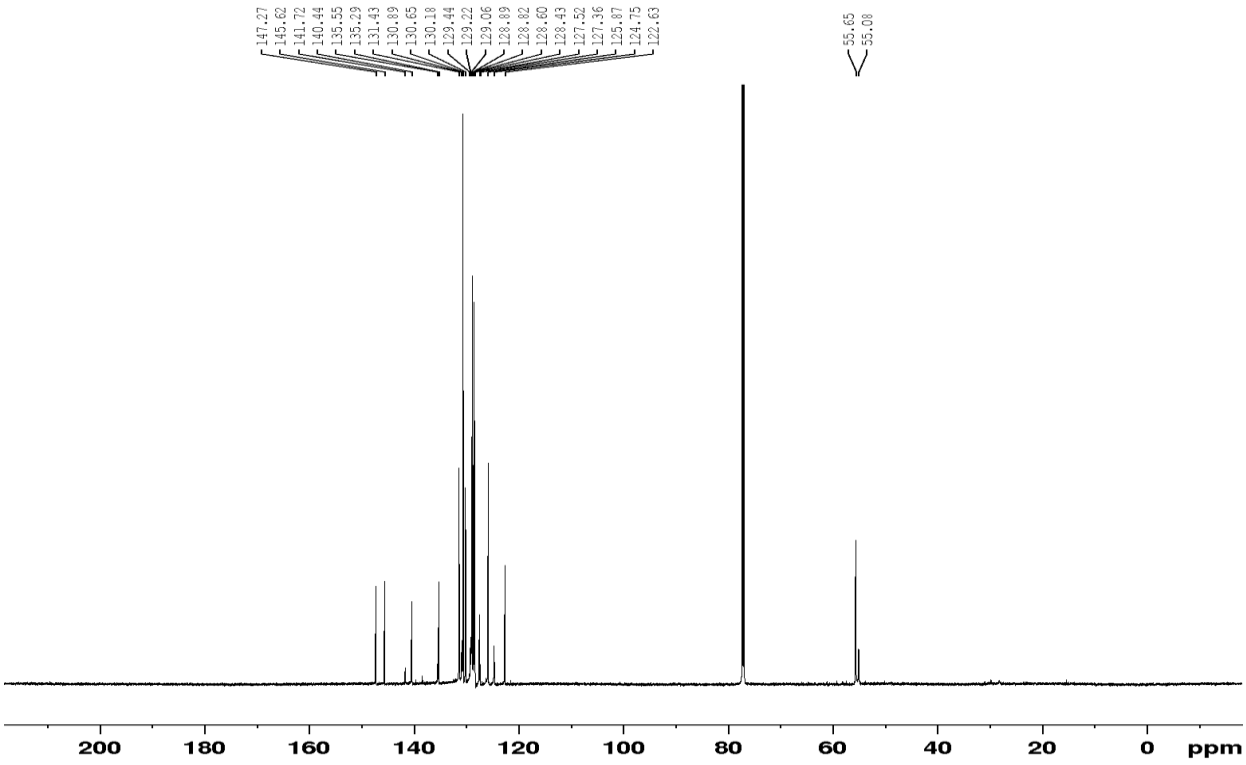


N-benzyl-*N*-(3-bromophenyl)carbamoyl fluoride (H)

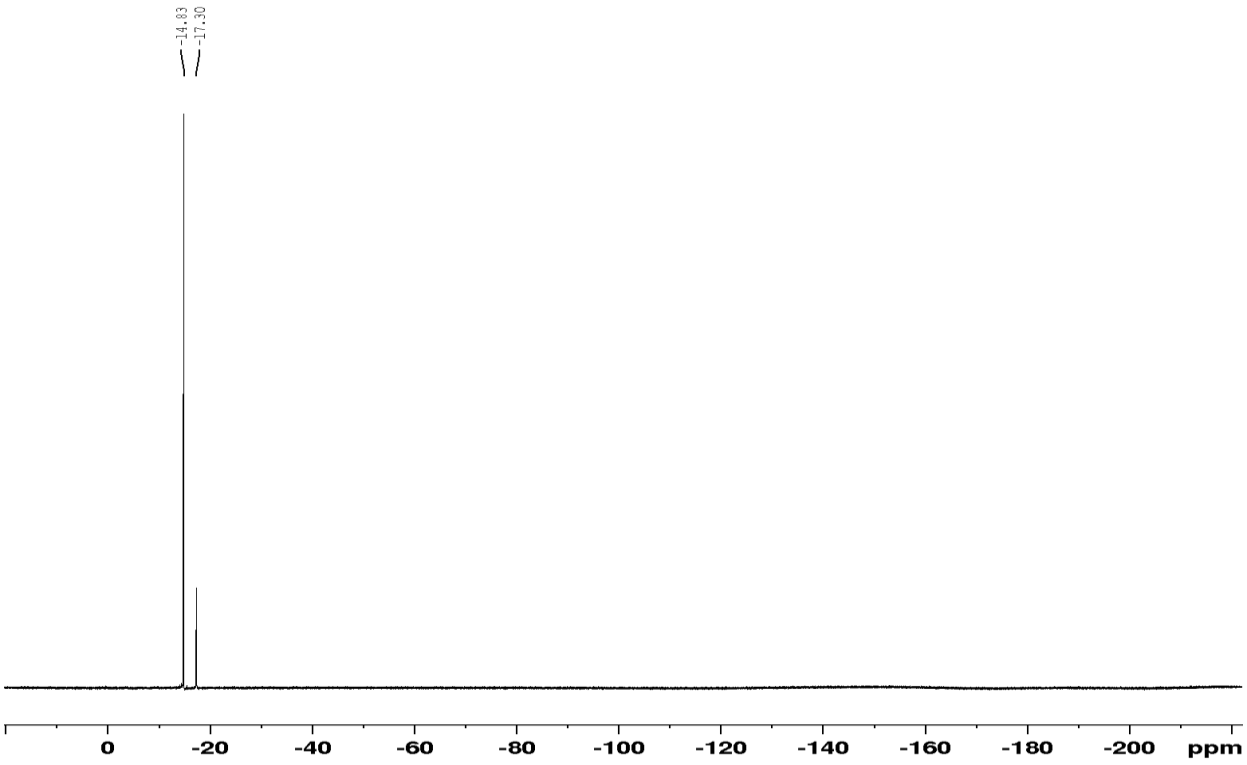
^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

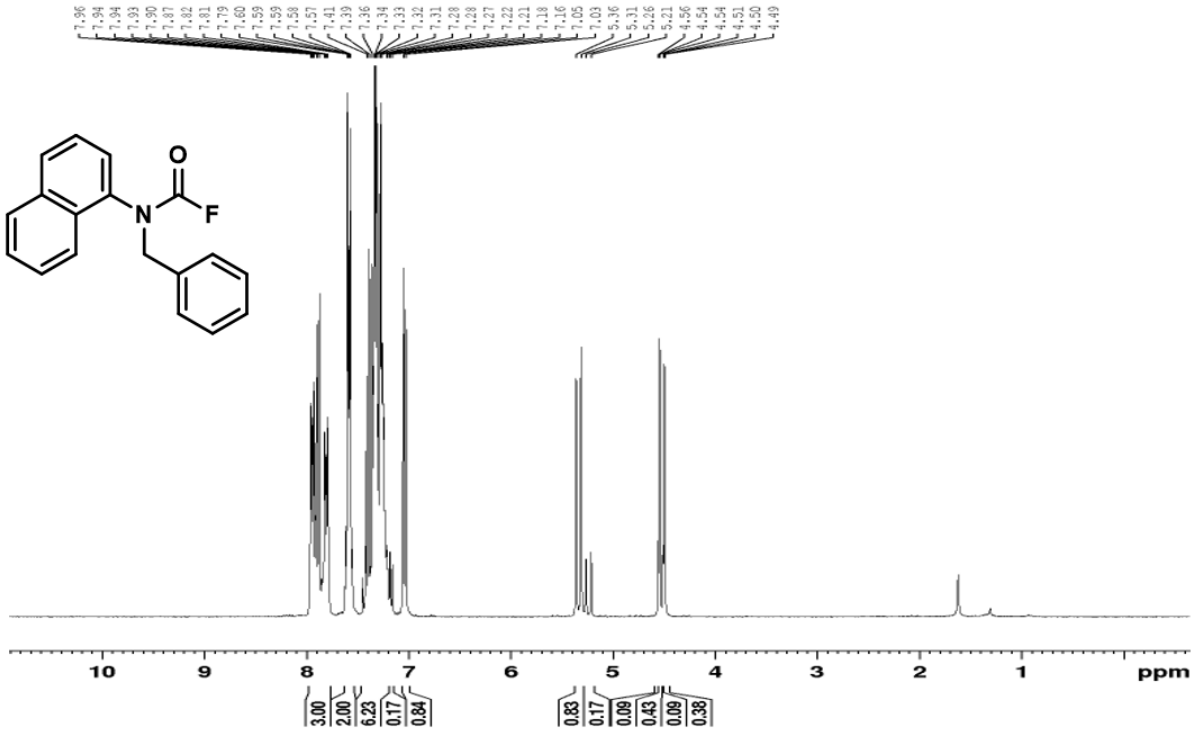


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

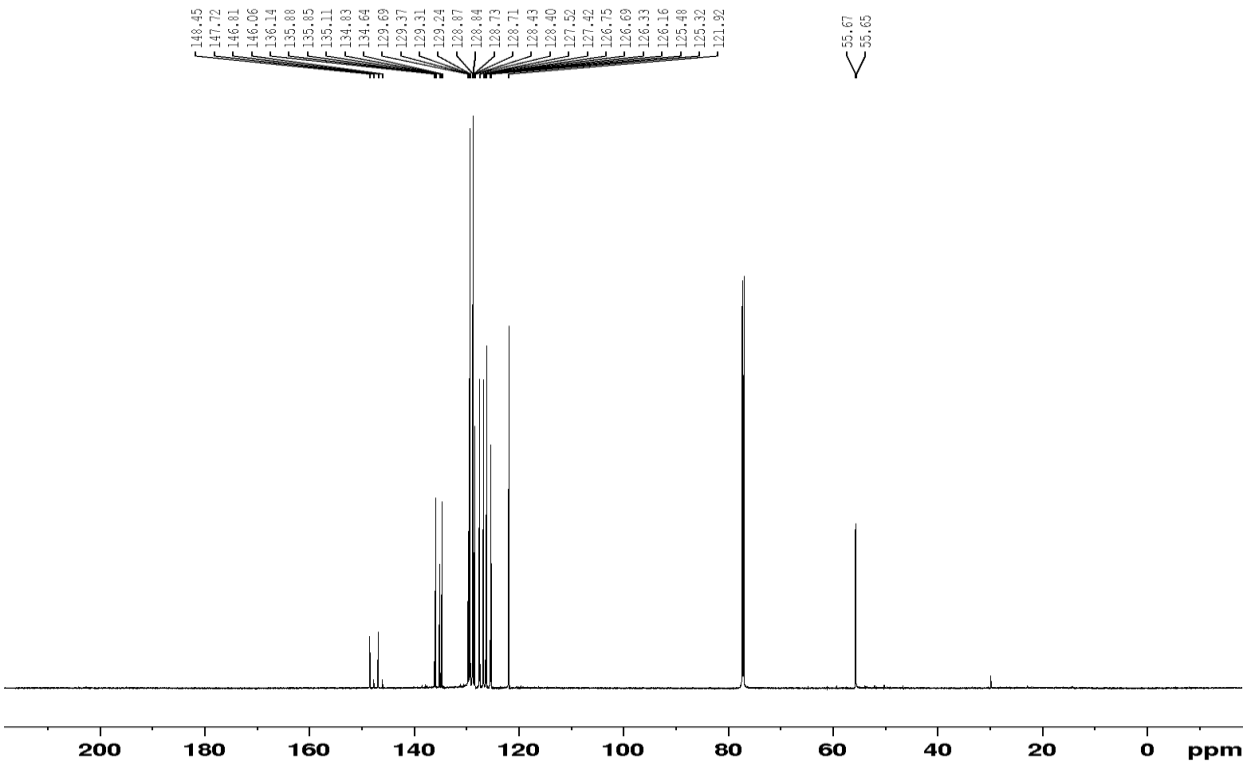


N-benzyl-*N*-(1-naphthyl)carbamoyl fluoride (K)

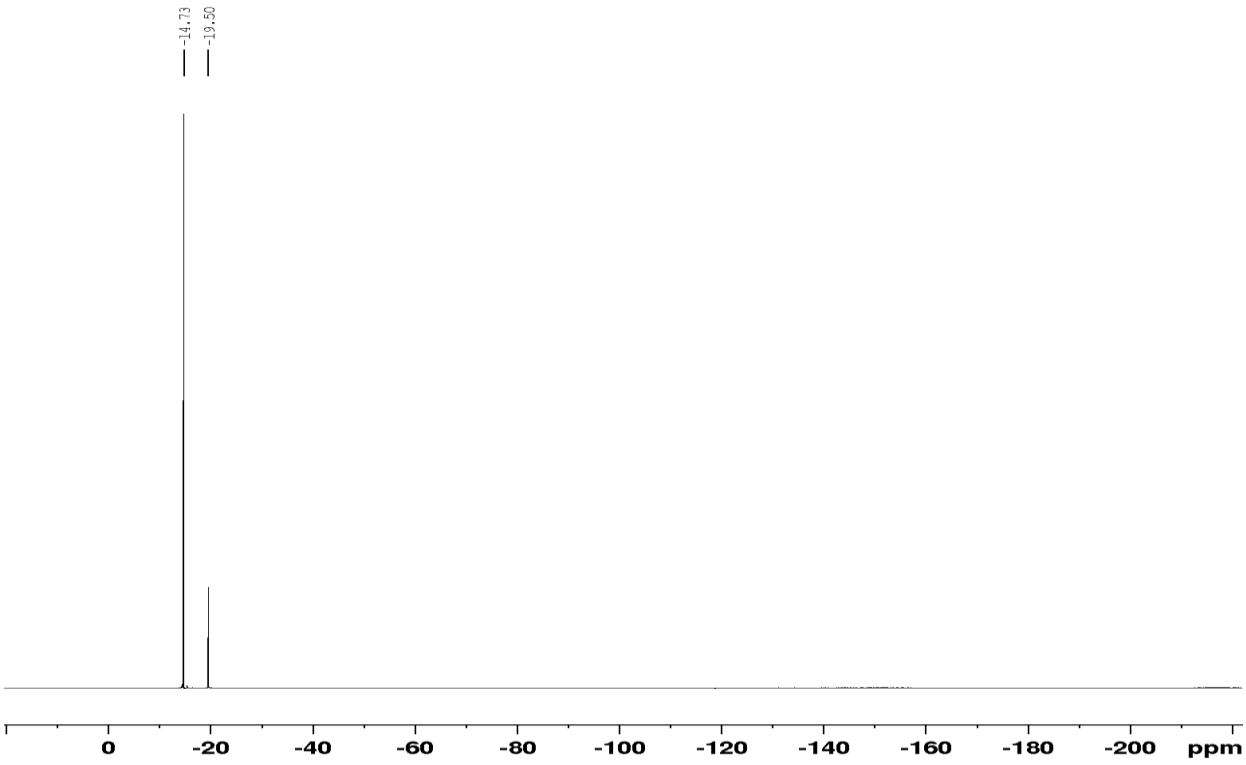
^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

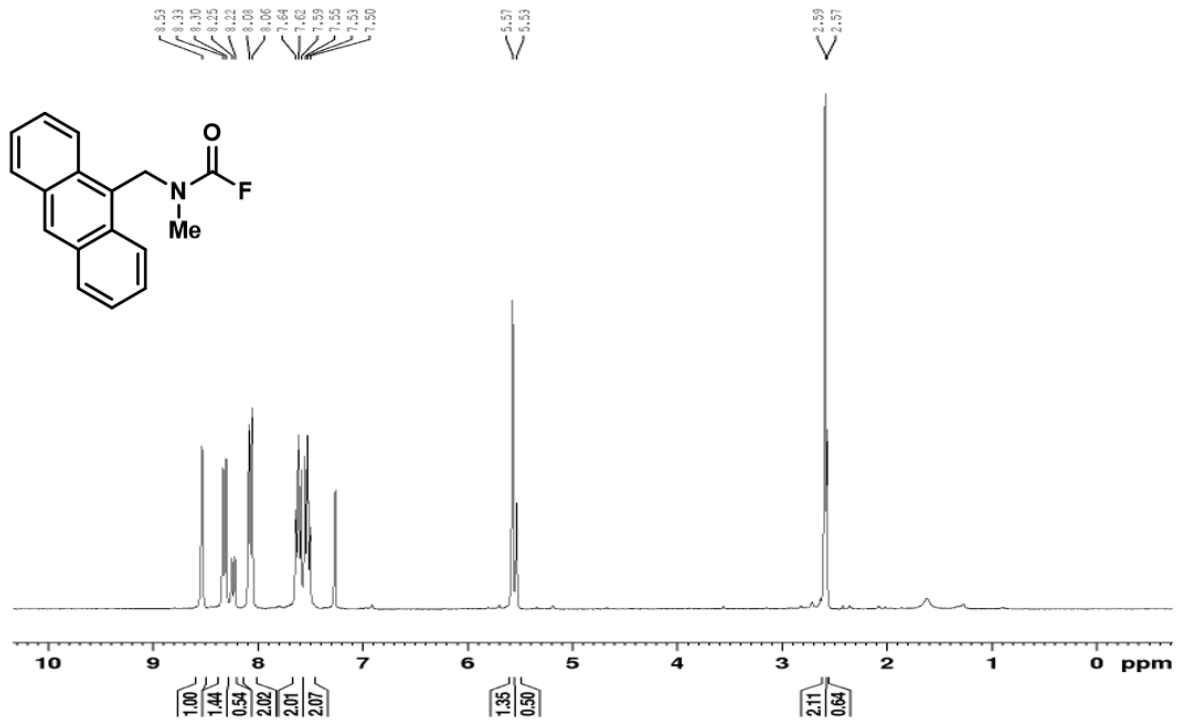


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

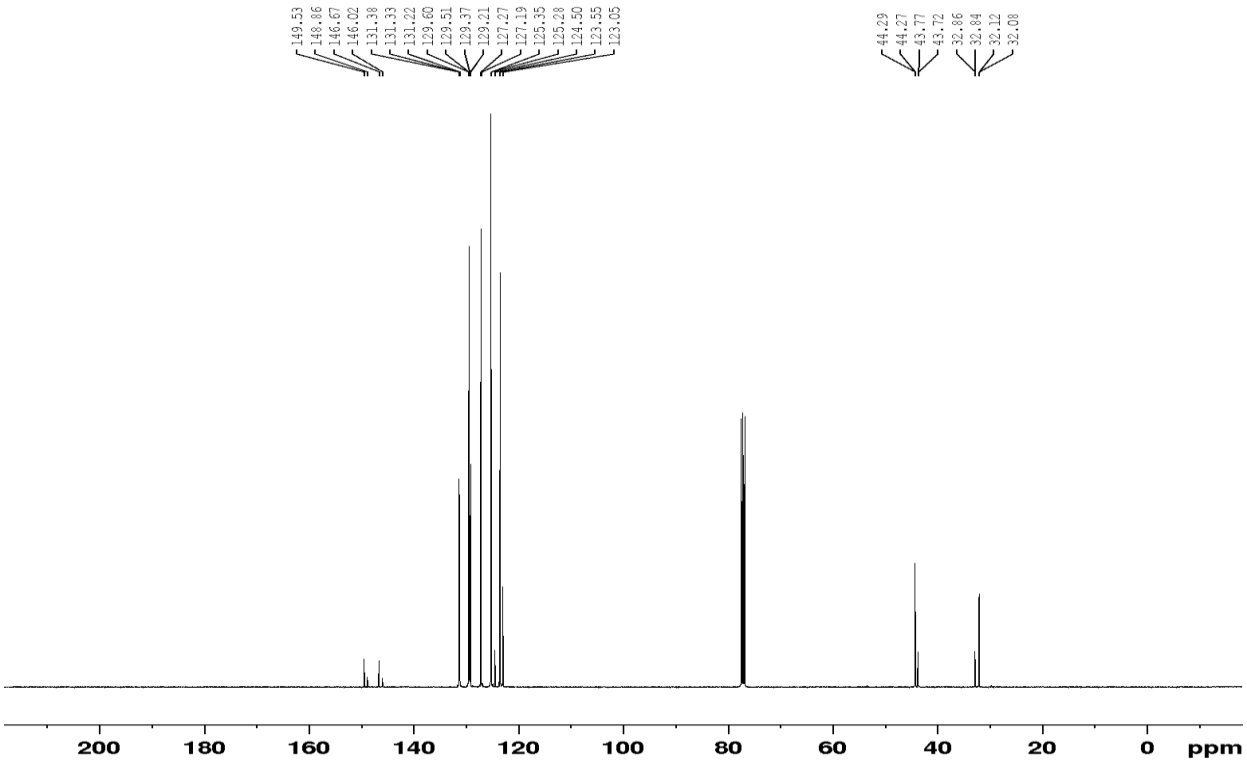


N-(9-anthrylmethyl)-*N*-methylcarbamoyl fluoride (N)

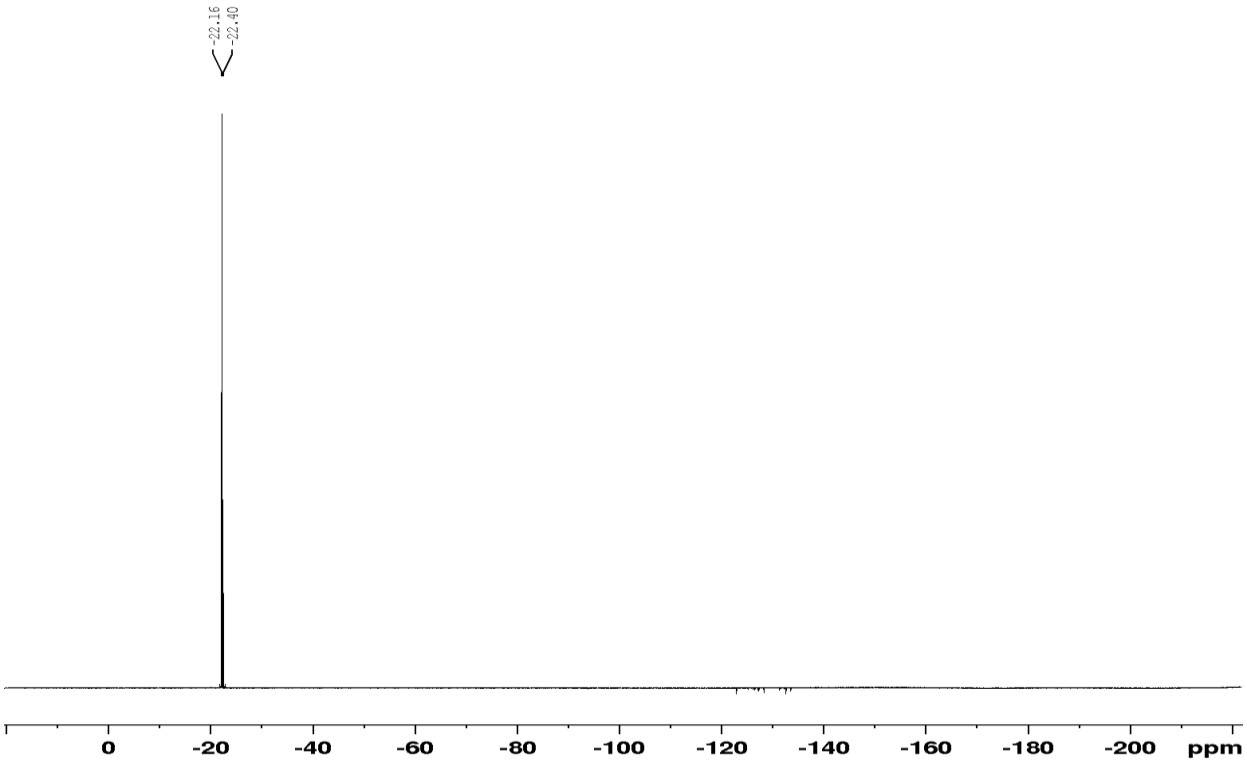
^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

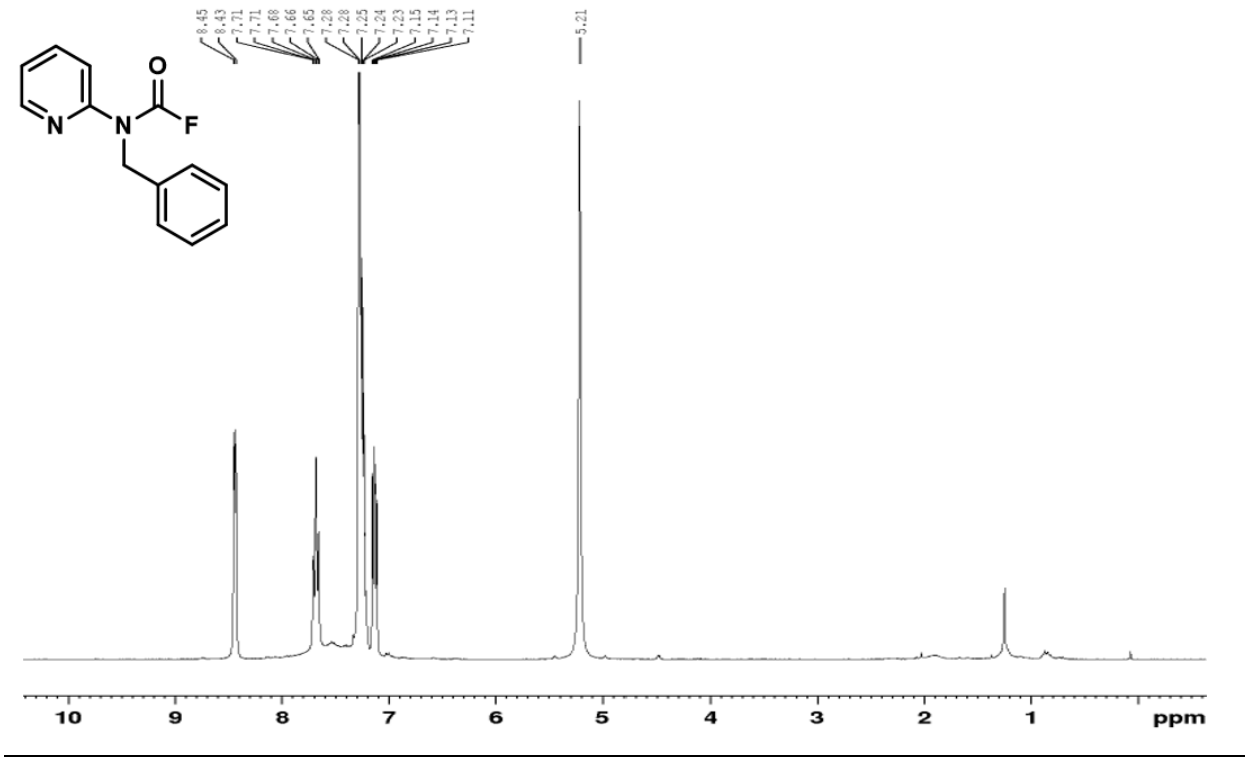


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

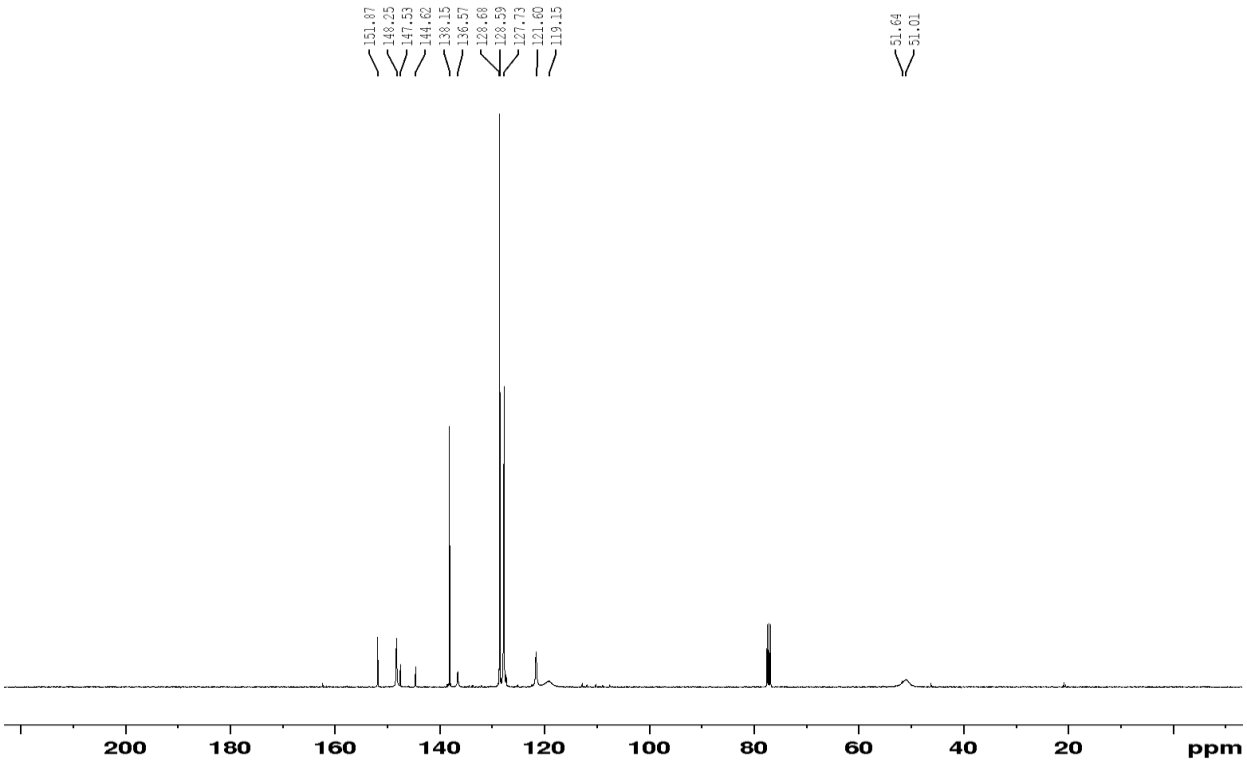


N-benzyl-*N*-(2-pyridyl)carbamoyl fluoride (S)

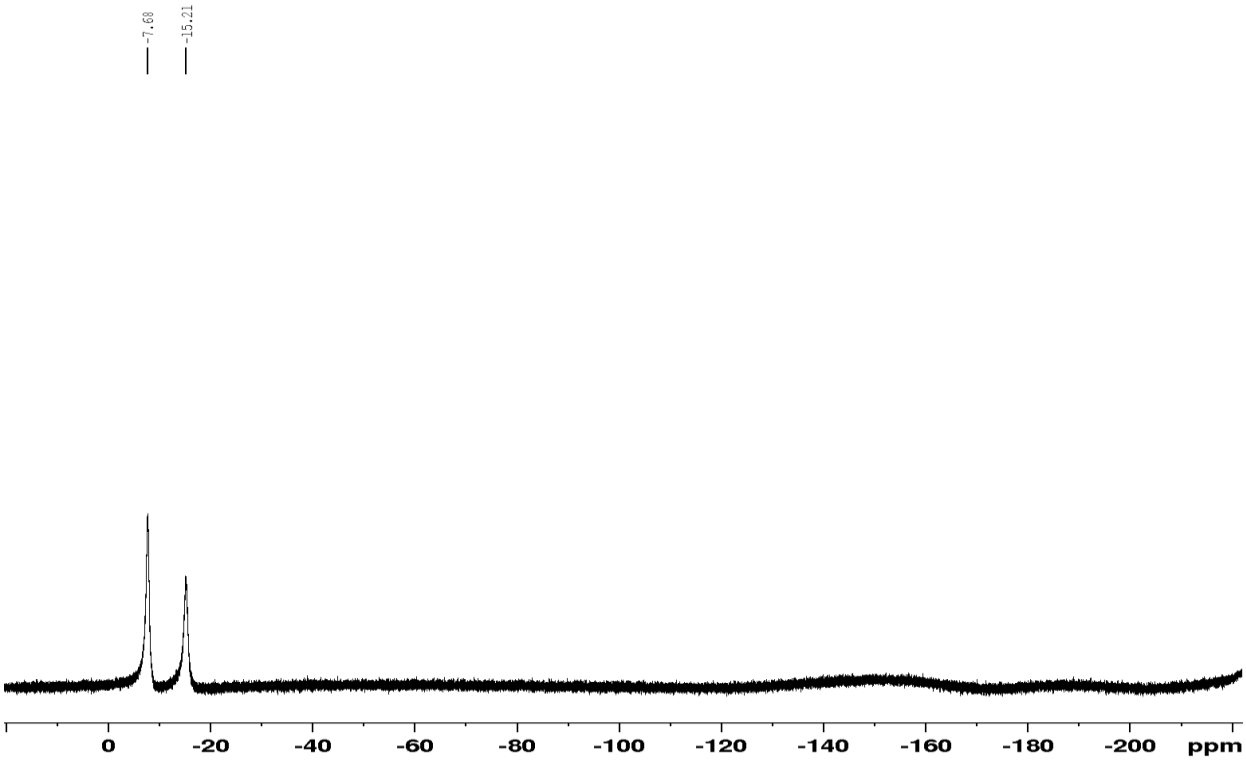
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

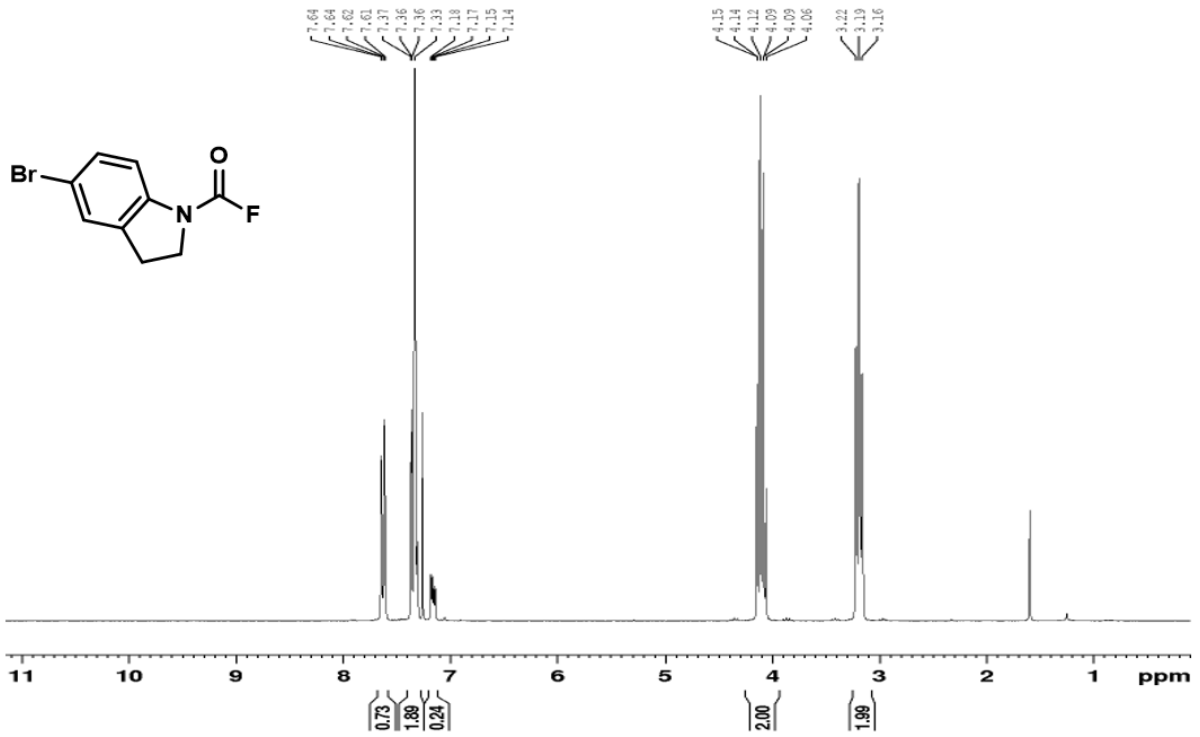


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

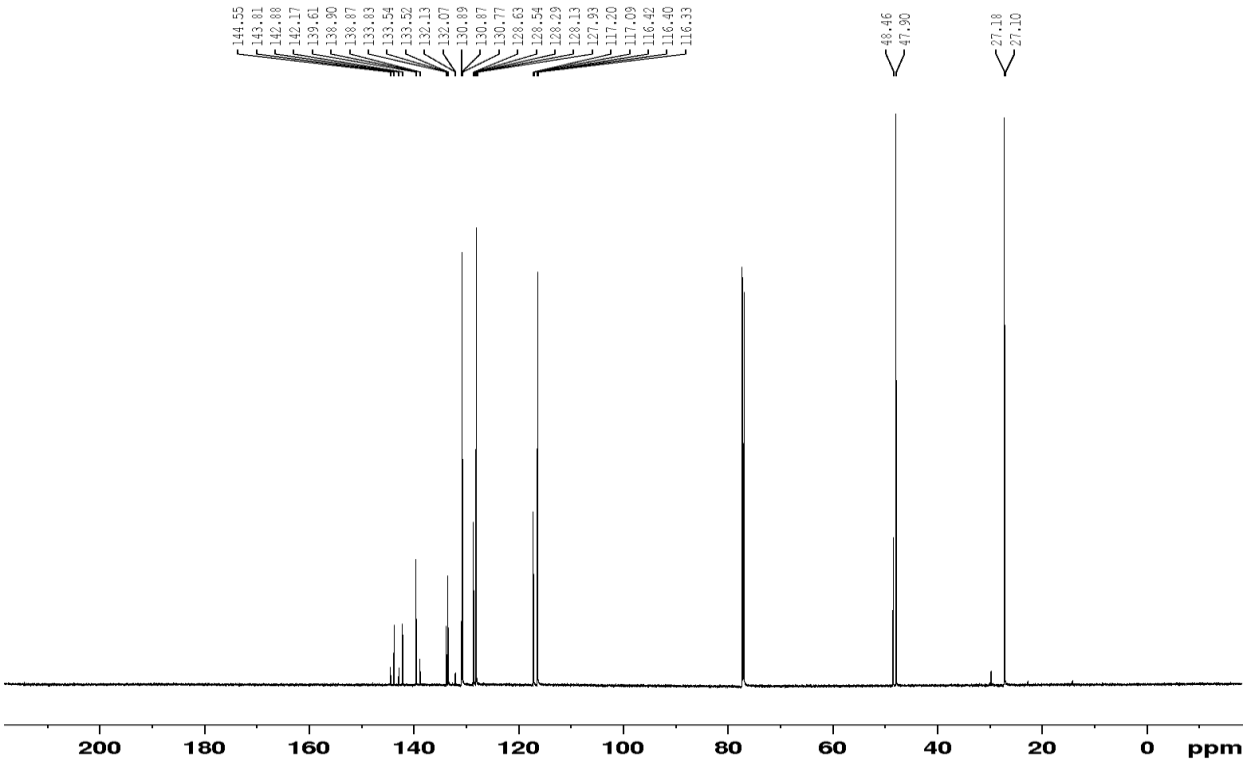


5-bromoindoline-1-carbonyl fluoride (Y)

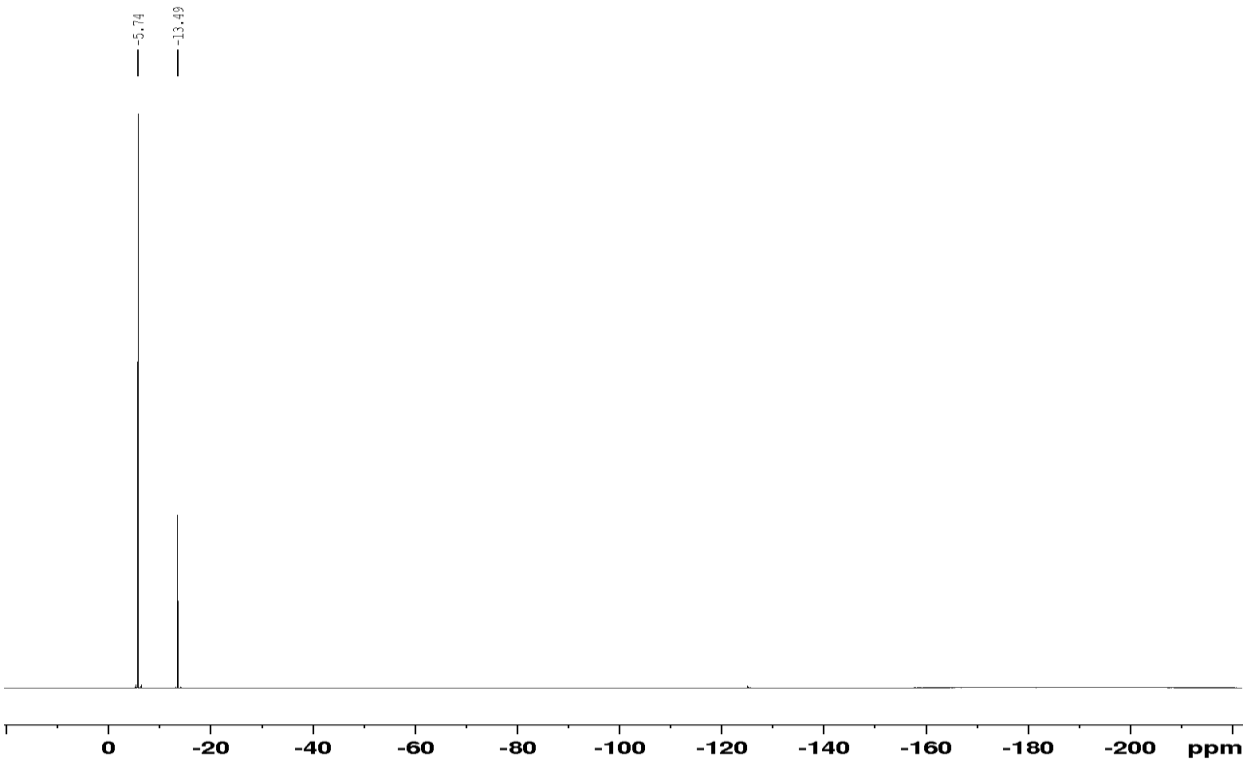
^{1}H NMR Spectrum (700 MHz, $CDCl_3$)



^{13}C NMR Spectrum (176 MHz, $CDCl_3$)

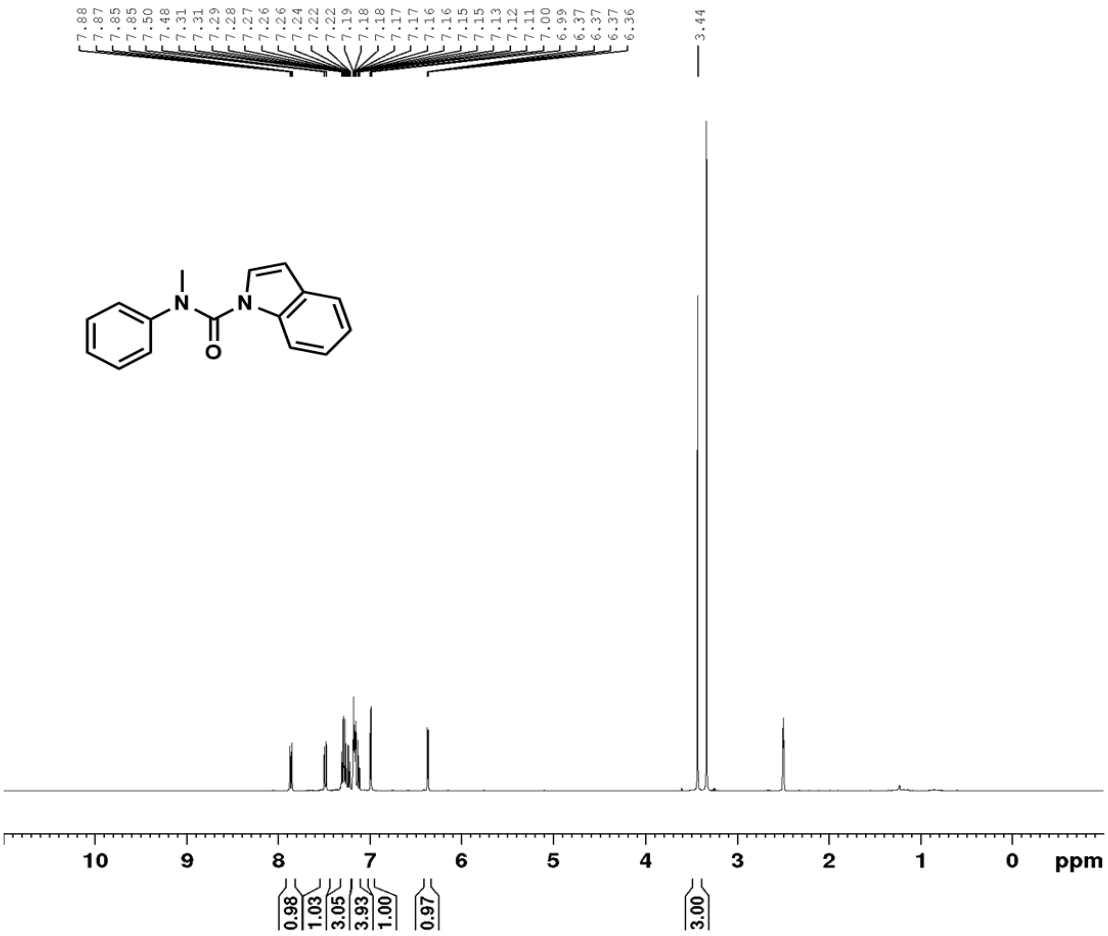


^{19}F NMR Spectrum (282 MHz, $CDCl_3$)

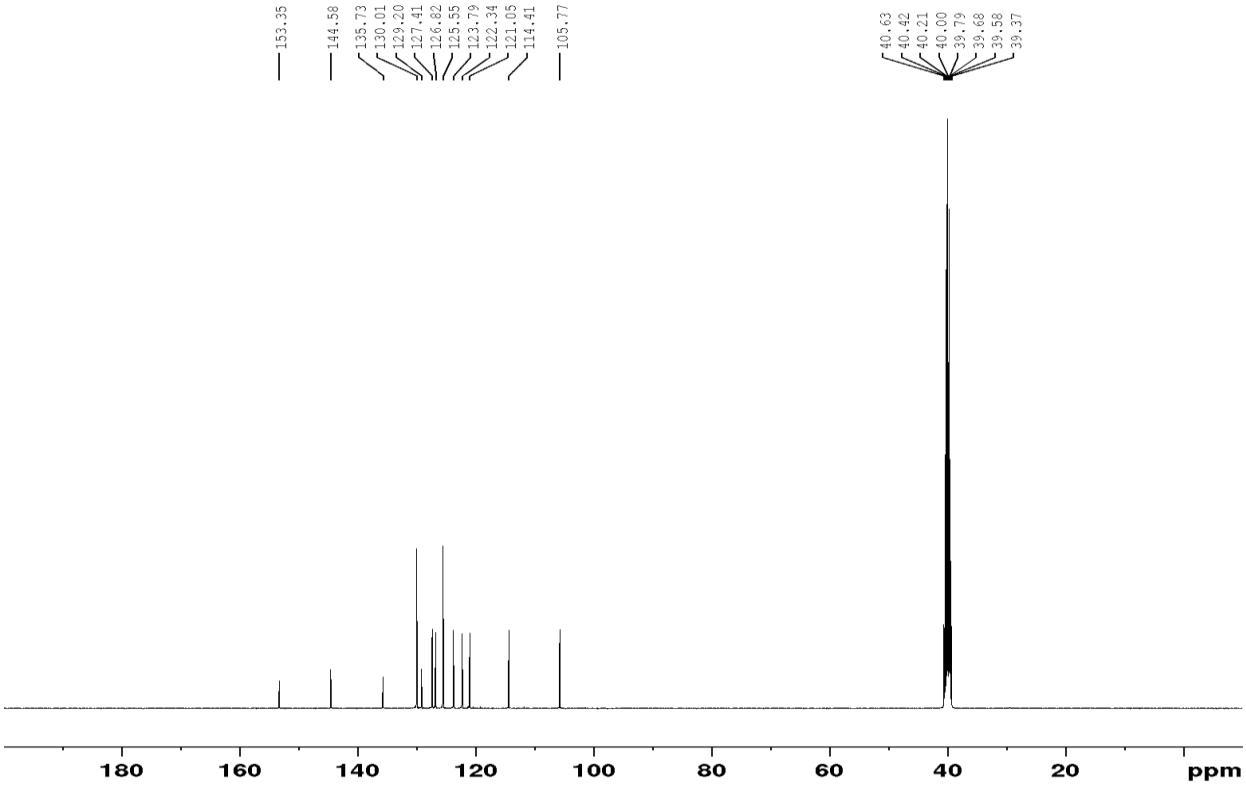


N-methyl-*N*-phenyl-1*H*-indole-1-carboxamide

^{1}H NMR Spectrum (400 MHz, DMSO-d_6)

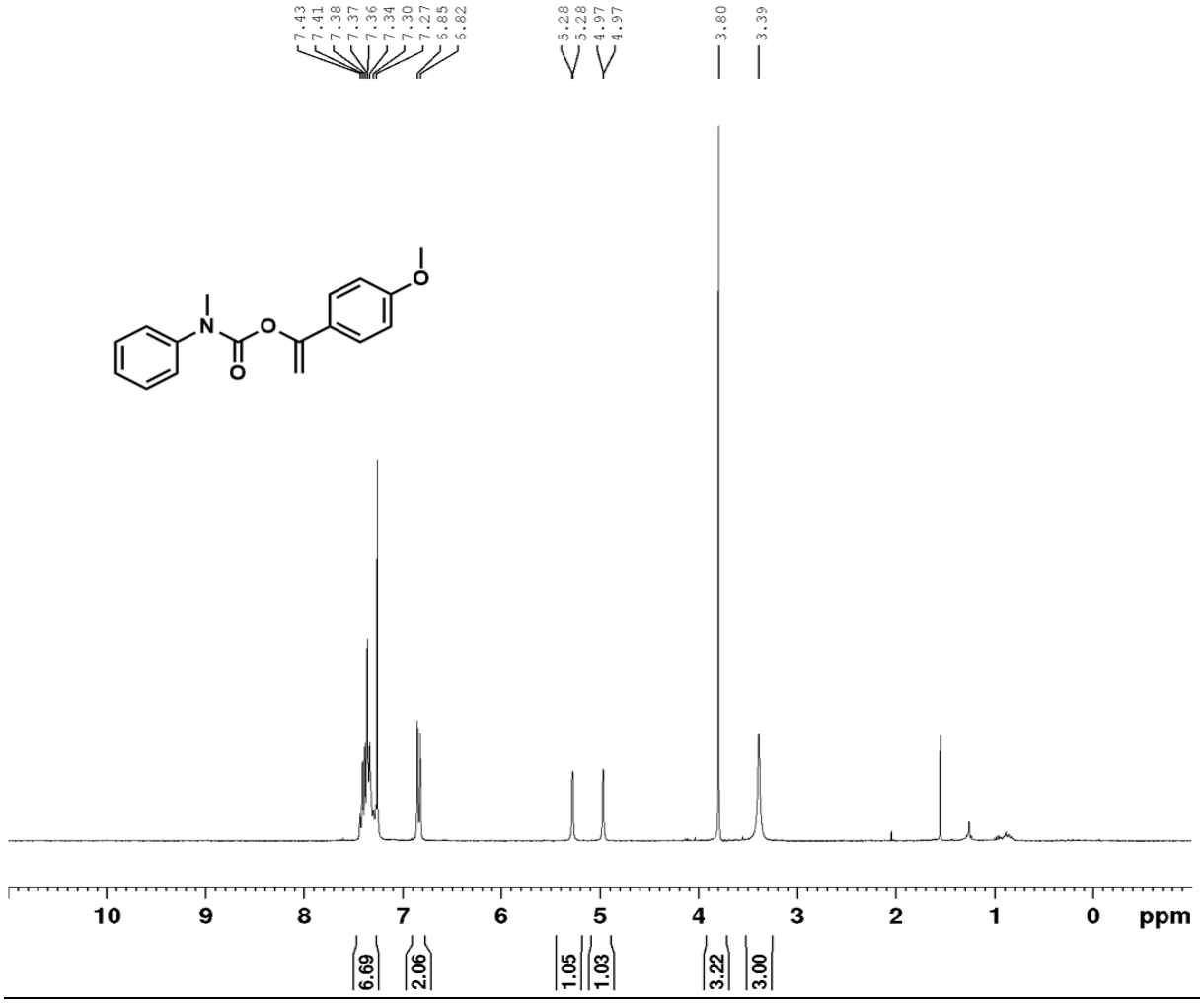


^{13}C NMR Spectrum (101 MHz, DMSO-d_6)

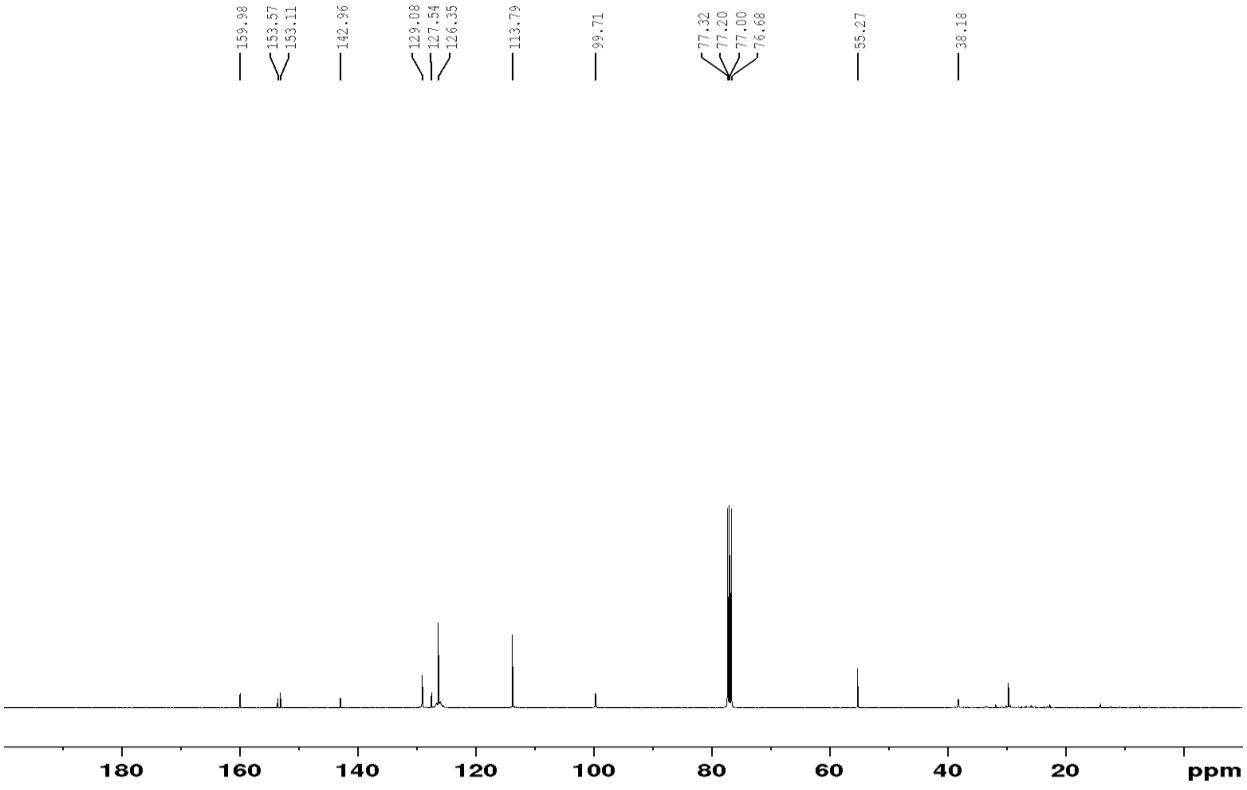


1-(4-methoxyphenyl)vinyl methyl(phenyl)carbamate

^{1}H NMR Spectrum (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum (101 MHz, $CDCl_3$)



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