11-11-2022

# Synthesis of Trifluoromethyl Ketones by (Diethylamino) Sulfur Trifluoride (DAST)-Mediated Nucleophilic Trifluoromethylation of Benzoic Acids

Michael A. Vescio
*Georgia Southern University*

**Synthesis of Trifluoromethyl Ketones by (Diethylamino) Sulfur Trifluoride (DAST)-Mediated Nucleophilic Trifluoromethylation of Benzoic Acids**

An Honors Thesis submitted in partial fulfillment of the requirements for Honors in the *Department of Chemistry & Biochemistry*

By
*Michael Angelo Vescio*

Under the mentorship of *Dr. Mohammed Abid Shaikh*

ABSTRACT

Within the past few decades, the presence of fluorine containing organic molecules has increased significantly. Many of the current industrial production methods are not cost-effective, practical, or inherently safe. This work describes a new methodology for the synthesis of trifluoromethyl ketones. Our new method involves the use of benzoic acid and trifluoromethyl trimethylsilane ($TMSCF_3$) as starting materials along with diethylamino sulfur trifluoride (DAST) as a reagent to obtain moderate to good yields of expected products in a short reaction times.

Thesis Mentor: *Dr. Mohammed Abid Shaikh*

Honors Dean: Dr. Steven Engel

December 2023
*Department of Chemistry & Biochemistry*
Honors College
**Georgia Southern University**

# ACKNOWLEDGEMENTS

The wise, patient, and unforgettable Dr. Mohammed Abid Shaikh

The Honors College

Department of Chemistry & Biochemistry

TABLE OF CONTENTS

## INTRODUCTION

Over the past few decades, organofluorine compounds have emerged as potential therapeutics to treat a wide range of diseases.[1] Fluorine incorporation to organic molecules contributes to enhance biologically important properties such as an increase in lipophilicity of the overall molecule to facilitate drug delivery.[2] Also a relatively small van der Waals radius (1.47 Å) makes it a suitable candidate for the replacement of one or more hydrogen atoms in a molecule resulting in a significant improvement in the overall molecular properties, which include, hydrogen bonding, acidity and lipid solubility.[3] The introduction of fluorine into biologically active natural cortisone was first pursued in 1953 by Fried and Sabo.[4] The anti-inflammatory activity of fluorinated cortisone was found to be 10 times greater than that of cortisone. This study fueled the idea that fluorine plays an important role in the development of biologically active compounds. Recent studies have demonstrated that the replacement of a methyl with a trifluoromethyl group significantly alters the chemical reactivity as well as biological properties of the overall molecule.[5] In 1970, only a small number of fluorine-containing drugs were available in the market, however their interesting pharmacological properties led to a tremendous development in fluorine-based drug design over the past two decades.[6,7] Currently, more than 150 commercially available drugs contain one or more fluorine atoms in their structure.[8] Some of the most well-known organofluorine drugs are Fluoxetine (anti-depressant), Ciprofloxacin (antibacterial), Celecoxib (NSAID), Atorvastatin (treatment of high triglycerides and cholesterol) and fluticasone propionate (anti-inflammatory) (Figure 1).

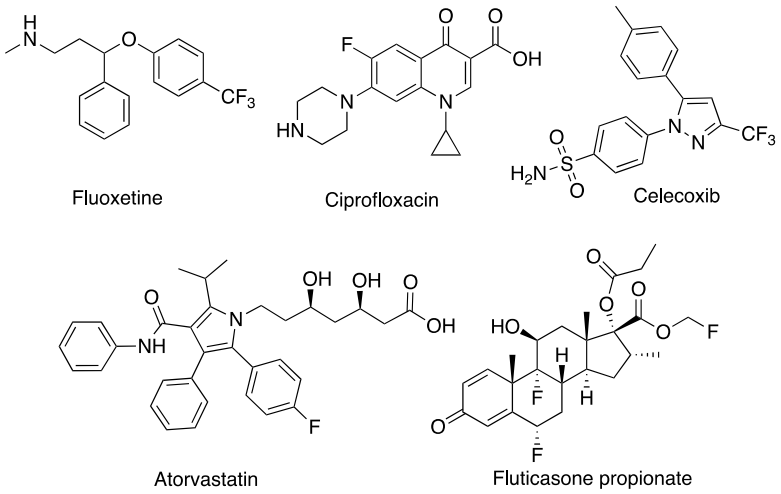


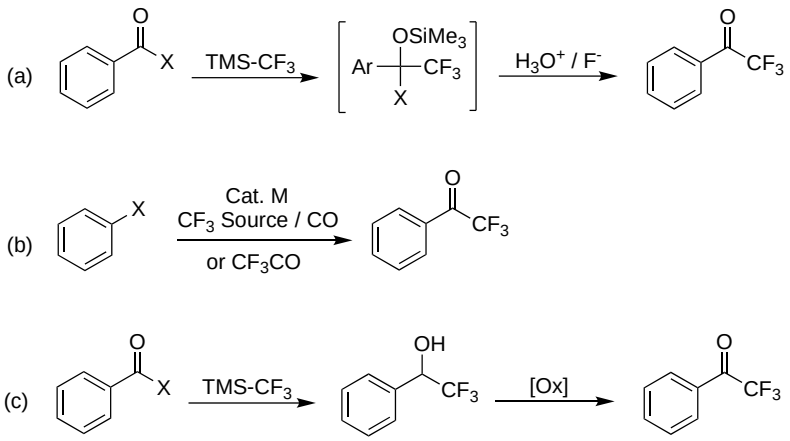

**Figure 1**. Structures of some well-known fluorine-containing drugs.

In this work, we developed a new method for the synthesis of a specific group of fluorine-containing molecules, namely, trifluoromethyl ketones. Trifluoromethyl ketones have a very high miscibility in fats, affinity for electrons, and ability to form stable hydrates provides organic chemists with reason to study them and their constituents. [9]

**Literature Overview**

Several methods exist for preparing trifluoromethyl ketones, such as the direct trifluoromethylation of esters by the Ruppert–Prakash reagent ($Me_3SiCF_3$), but the use of $HCF_3$ for this transformation reaction is still limited (Scheme 1a). The Friedel−Crafts acylation of electron-rich arenes is also used despite the narrow substrate but they did not examine the scope of the reaction (Scheme 1b). Direct nucleophilic attack of Ruppert–Prakash reagent ($Me_3SiCF_3$) to aldehydes was recently achieved. This process involves the formation of

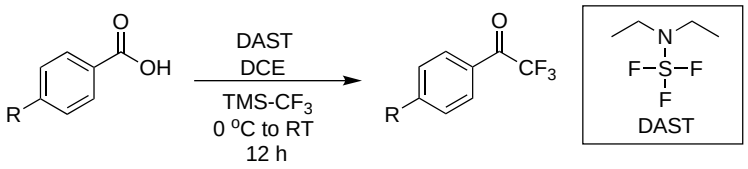
trifluoromethyl alcohols which is then further oxidized to trifluoromethyl ketones. This method is efficient but requires stoichiometric amount of toxic oxidizing agents (Scheme 1c).




**Scheme 1**. Literature methods for the synthesis of trifluoromethyl ketones.

## RESEARCH HYPOTHESIS & OBJECTIVE

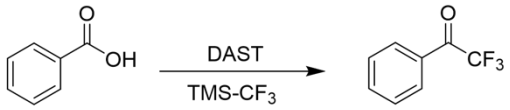
The method described in this paper highlights the use of benzoic acids as substrates for trifluoromethylation for the direct access of trifluoromethylated ketones. Diethylaminosulfur trifluoride (DAST) was used as a mediator, dichloroethane (DCE) as a solvent and trifluoromethyl trimethylsilane ($TMSCF_3$) was used as a source of nucleophilic -$CF_3$ group. In comparison with the traditionally used aryl metals, carboxylic acids are cheaper and more environmentally friendly than their counterparts. The method highlighted in this paper was performed at room temperature, safely on a common benchtop (Scheme 2).




**Scheme 2**. Newly developed method for the synthesis of trifluoromethyl ketones.

## DATA, RESULTS AND DISCUSSION

We started our study by choosing the reaction of benzoic acid with trifluoromethyl trimethylsilane ($TMSCF_3$) as the model substrates and diethylamino sulfur trifluoride (DAST) as reagent under various solvent conditions. After screening a series of common organic solvents, we obtained the highest products yield using dichloroethane. Results are summarized in Table 1.

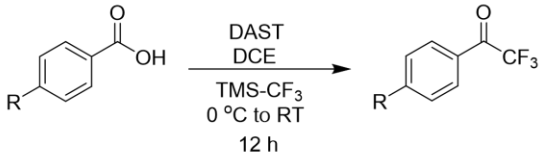


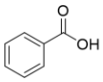
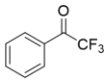
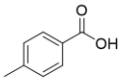
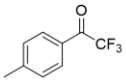
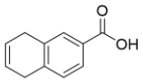
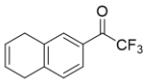
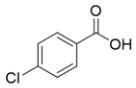
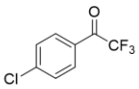
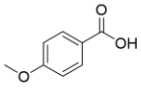
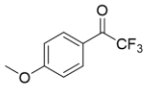
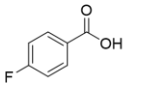
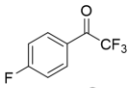
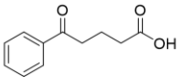
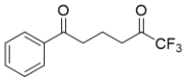

| Entry | Solvent | TLC Results |
|---|---|---|
| 1 | DMF | Low |
| 2 | THF | Medium |
| 3 | DMSO | No Product |
| 4 | Toluene | Low |
| 5 | 1,4-dioxane | No Product |
| 6 | Acetonitrile | Low |
| 7 | Dichloromethane | Medium |
| 8 | Dichloroethane | High |

**Table 1**. Solvent optimization for the synthesis of trifluoromethyl ketones.

Having the optimized conditions in hand, we further investigated the compatibility of our new method with various benzoic acids keeping $TMSCF_3$ as a common substrate. The results

showed that electron donating substituents on the aromatic ring of benzoic acid delivered the desired products in 71-74% isolated yields (Table 2, entries 2, 5). Gratifyingly, the reaction yields were consistent with electron withdrawing groups such as Cl, F, $NO_2$ (Table 2, entries 4, 6, 7). Other substrates such as, 2-naphthaoic acid (Table 2, entries 3) also provided good yield.

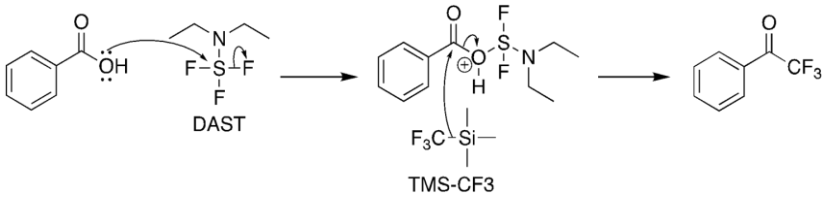



| Entry | Benzoic Acids (Reagent) | Trifluoromethyl Ketones (Product) | (%) Yield |
|---|---|---|---|
| 1 |  |  | 62 |
| 2 |  |  | 74 |
| 3 |  |  | 67 |
| 4 |  |  | 80 |
| 5 | | | 79 |
| 6 |  |  | 71 |
| 7 |  |  | 66 |
| 8 |  |  | 74 |

Isolated Yields

**Table 2**. Substrate scope with different types of benzoic acids.

Based to the above results, a plausible mechanism is depicted in Scheme 3. Benzoic acid when treated with DAST coverts the hydroxy group into a bulky leaving group. In step 2, the leaving group is replaced by the nucleophilic $CF_3$ group from $TMSCF_3$ to form the corresponding trifluoromethyl ketone.




**Scheme 3**. Plausible reaction mechanism for the synthesis of trifluoromethyl ketones.

## CONCLUSION

In summary, we have demonstrated that the trifluoromethyl ketones can be prepared in good yields starting from benzoic acids at room temperature under mild conditions. The protocol has been shown to be useful for accessing a wide range of trifluoromethyl ketones. Compared with the existing procedures, this protocol has several advantages including, the simple operation and performed under an air atmosphere. Also, our method does not make use of toxic metal-based catalysts and costly coupling reagents.

## EXPERIMENTAL METHODOLOGY

One hundred milligrams of benzoic acid sample (benzoic acid form dependent upon reaction) were placed in a screw cap vial along with a magnetic stir bar. Two milliliters of dichloroethane were added to the vial. An approximate 70-90 µL of TMS-CF3 was dispensed into the reaction mixture. The reaction was cooled to 0 ℃ with an ice-water bath. An approximate 80-90 µL of DAST was added to the solution. The reaction mixture was warmed

to room temperature and stirred for 12 hours. Product formation was monitored using TLC. After initial identification of product, the excess solvents were evaporated with rotary evaporation and vacuum filtration. The product analysis and characterization were carried out using 1H and $^{13}C$ NMR.

**BIBLIOGRAPHY**

(1) Wang, J.; Sanchez-Rosello, M.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in pharmaceutical industry: Fluorine-containing drugs introduced to the market in the last decade (2001−2011). *Chem. Rev*. **2014**, *114*, 2432-2506.

(2) Silverman, R. B. *The organic chemistry of drug design and drug action*, Elsevier Academic Press: London, **2004**, pp. 617-630.

(3) Hagmann, W. K. The many roles for fluorine in medicinal chemistry. *J. Med. Chem*. **2008**, *51*, 4359-4369.

(4) Fried, J.; Sabo, E. F. Synthesis of 17 α-hydroxycorticosterone and its 9 α-halo derivatives from 11-epi-17 α-hydrocorticosterone. *J. Am. Chem. Soc*. **1953**, *75*, 2273-2274.

(5) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature*, **2011**, *473*, 470-477.

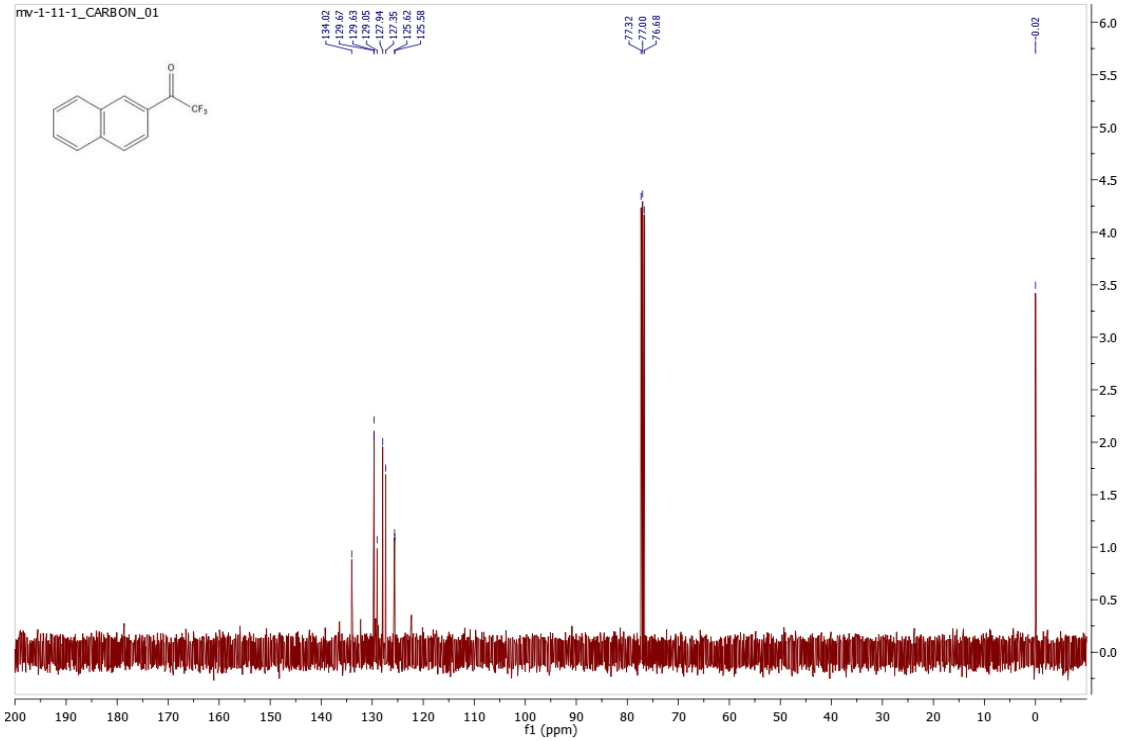
(6) Ojima, I. *Fluorine in medicinal chemistry and chemical biology*, Wiley-Blackwell, Chichester, **2009**.

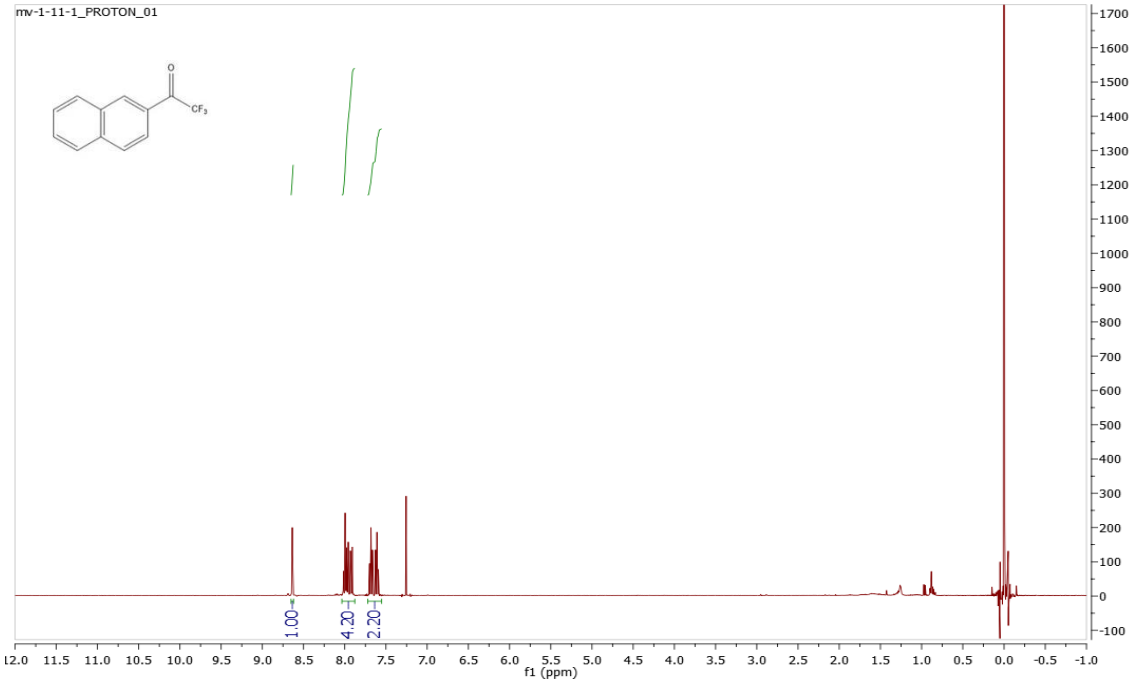
(7) Ojima, I. Exploration of fluorine chemistry at the multidisciplinary interface of chemistry and biology. *J. Org. Chem*. **2013**, *78*, 6358-6383.

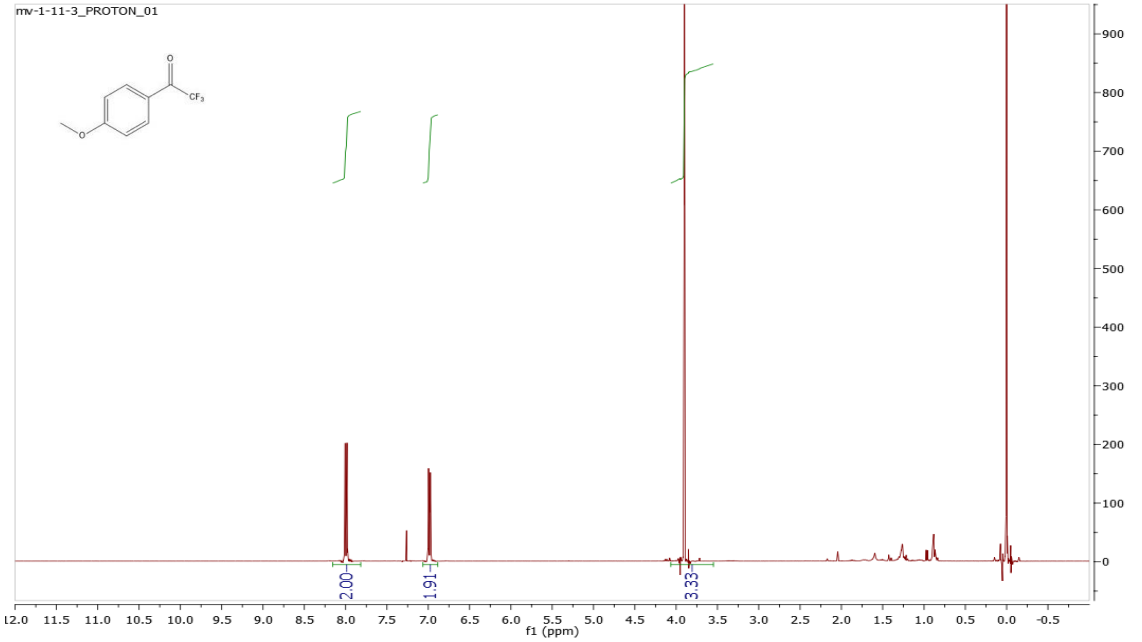
(8) Mei, H.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. Fluorine-containing drugs approved by the FDA in 2018. *Chem. Eur. J.* **2019**, *25*, 11797-11819.

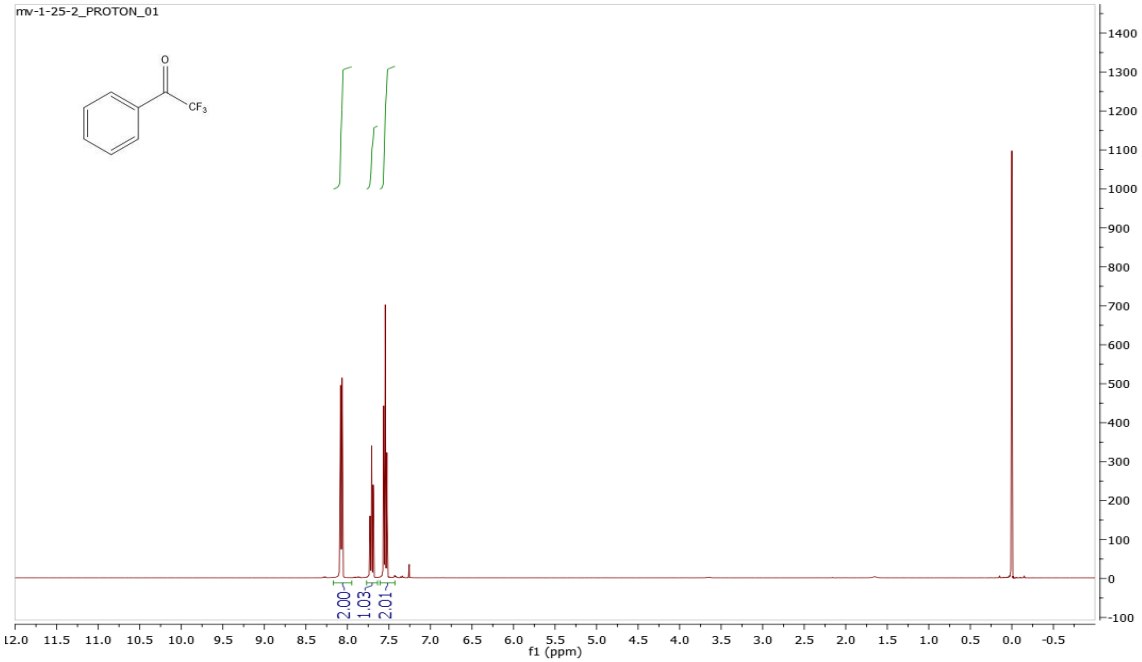
(9) Liu, X.; Liu L.; Huang T.; Zhang J.; Tang Z.; Li C.; Chen T. Trifluoromethylation of benzoic acids: An access to aryl trifluoromethyl ketones. *Org. Lett.*, **2021**, *23* (12), 4930-4934.

# APPENDIX


mv-1-11-1_CARBON_01
134.02
129.67
129.63
129.05
127.94
127.35
125.62
125.58
77.32
77.00
76.68
-0.02
f1 (ppm)


mv-1-11-1_PROTON_01
1.00
4.20
2.20
f1 (ppm)


mv-1-11-3_PROTON_01
O
CF3
O
2.00
1.91
3.33
f1 (ppm)


mv-1-25-2_PROTON_01
O
CF3
2.00
1.03
2.01
f1 (ppm)