

Pd-Catalyzed Unprecedented Cross-Coupling of Mixed Phenols and Halides for the Synthesis of Aromatic Ethers

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Abstract

Phenolic compounds present in medicinal and edible plants such as flavonoids, chalcones, coumarins, quinones, and phenolic acids. The antioxidant potential of phenolic compounds shows potent activities for cancer prevention and its treatment. From a green chemistry point of view, cascade (tandem) reactions are ideal techniques in organic synthesis for building complex structures. Cascade techniques are sometimes observed in coupling reactions under mild conditions with a tolerance of multifunctional groups. It will be interesting to find a cascade type reaction to synthesize polyphenolic ethers. This research project achieves a new cross-coupling method for establishing polyphenolic ethers from mixed phenols and halides in the presence of palladium catalyst in moderate to good yields.

Keywords

Microwave, Ethers from Mixed Phenols, Cross-Coupling, Cascade Type Reaction

1. Introduction

Cross-coupling becomes a common term in organic chemistry in number of different reactions namely, two different fragments are joined together with the support of a metal catalyst. Carbon-oxygen is one of the most effective bond formation reactions like C-C bond formation in organic chemistry. Cross coupling process is essentially equally applied to explore C-O bond formation reactions [1]-[10].

In 2020, after a series of tests that conducted by Al-Masum group found palladium complex, PdCl₂(dppf)CH₂Cl₂, an effective catalyst for C-O bond forma-

tion for cascade type multiple phenolic ether synthesis in one step [11]. Therefore, this project aims to extend the earlier findings of phenolic ether synthesis in investigating the possibility of making aromatic ethers from mixed phenols and halides in the presence of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ under microwave irradiation.

2. Results and Discussion

The diaryl ethers are found in a great number of natural products and synthetic pharmaceuticals [12] [13] [14]. They are found in many pesticides, polymers, and ligands. In 1905, Ullmann's reaction of phenols with aryl bromides in presence of KOH to form biaryl ethers. However, the procedure for biaryl ether formation requires stoichiometric amount of copper reagents and high temperatures (typically $> 160^\circ\text{C}$).

After a series of attempts of reactions using different ratios of starting materials, reaction times, and temperature levels, optimized reaction conditions were established that were used to synthesize variety of phenolic ethers (Figure 1).

In order to investigate further application of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$, in cross-coupling reactions of mixed phenols with bromo iodomethane **2a**, chloro iodomethane **2b**, 1,2,4-tribromobenzene **2c** were attempted. After running several reactions with different temperature levels and duration times, the cross-coupling of chloro iodomethane **2b** showed good results when interacting with mixed phenols **1b** and **1c** in the presences of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (Figure 4, product **3c**). In this reaction, we used 0.5 mmol of phenols **1b** and **1c** with 0.5 mmol of chloro iodomethane **2b**. The reaction vial was in the microwave oven for 5 hours at 100°C . The phenolic ether, **3c** was obtained in 65% yields.

The formation of ether **3c** by cross-coupling reaction involved 0.5 mmol (81 mg) of phenol **1b** and 0.5 mmol (48 mg) of phenol **1c** and 0.5 mmol (36 μL) of chloro iodomethane **2b**. The reactants were loaded in dry clean microwave vial and 2.00 mmol (195 mg) of NaO ^tBu, 5 mol% of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (20.0 mg) were added to the mixture, then it was capped with septum and flushed with argon followed by the addition of 2 mL 1,4 Dioxane as solvent. The resulting mixture was irradiated at 100°C for 5 h. For purification, the crude mixture was passed through alumina column chromatography using hexane/ethyl acetate (92%/8%) as eluents. The essentially pure product **3c** was collected.

The cross coupling of bromo iodomethane **2a** gave the desired products when reacted with phenols in the presence of 1,4-dioxane as a solvent. To furnish this

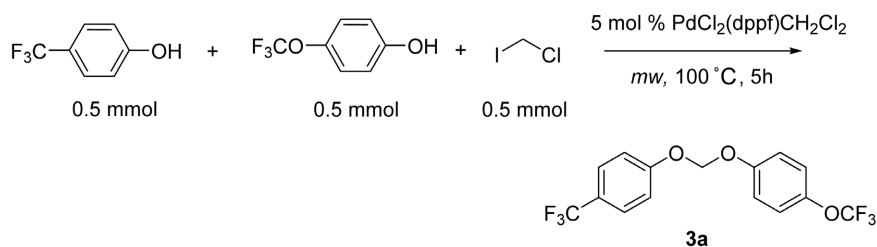


Figure 1. Phenolic ether from chloro iodomethane.

phenolic ether product, 0.5 mmol (66 μ L) of phenol **1a** and 0.5 mmol of phenol **1c** (48 mg), 0.5 mmol of bromo iodomethane, 5 mol% of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$, and 2 mmol of NaO^tBu were used. The reaction vial was in the microwave oven for 1 h at 125°C (Figure 2). In Figure 4, it is shown as a product **3b** in 72% yields.

The formation of ether **3d** by cross-coupling reaction involved 1.00 mmol (138 mg) of 1,4-benzenedimethanol **1d**, 0.5 mmol (66 μ L) 4-trifluoromethoxy phenol **1a** and 0.5 mmol (40 μ L) of bromo iodomethane **2a**. The reactants were loaded in dry clean microwave vial and 2.00 mmol (195 mg) of NaO^tBu , 5 mol% of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (20.0 mg) were added to the mixture, then it was capped with septum and flushed with argon followed by the addition of 2 mL of 1,4 Dioxane as solvent. The resulting mixture in vial was irradiated at 80°C for 5 h. The crude reaction product in reaction vial diluted with ethyl acetate was transferred into a separatory funnel. Water was then added to the funnel and after standard extraction, excess alcohol was miscible with aqueous layer and drained. The remaining organic layer in the separating funnel was collected in a small Erlenmeyer flask over anhydrous Na_2SO_4 . The ethyl acetate layer was filtered through sintered funnel and collected filtrate in a round bottom flask was completely dried by rotary evaporator in vacuo. The column chromatography technique was used to separate the product. The desired mixed phenolic ether product **3d** (Figure 4) was confirmed by ^1H NMR, ^{13}C NMR, and ^{19}F NMR (Figure 3).

NMR data of products from Figure 4, product **3a**, **3b**, **3c**, **3d**, **3e**, and **3f** are given below.

Compound **3a**, ^{13}C NMR (CDCl_3 , 100 MHz) δ 158.3, 155.5, 130.7, 129.5, 128.2, 122.2, 120.5, 116.4, 115.2, 93.5; ^{19}F NMR (CDCl_3 , 400 MHz) δ -58.3 (OCF_3), -62.0 (CF_3); LRMS: Calc'd for $\text{C}_{15}\text{H}_{10}\text{O}_3\text{F}_6(\text{M}^+)$: 352. Found: 351.95.

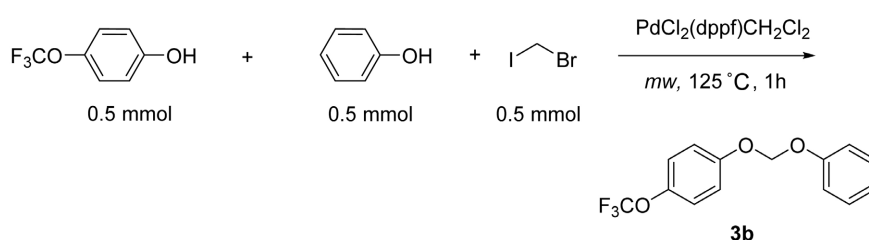


Figure 2. Cross-coupling of bromo iodomethane and phenols.

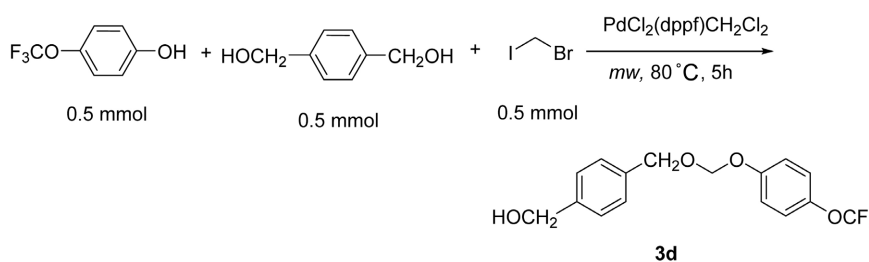


Figure 3. Phenolic ether from mixed phenol.

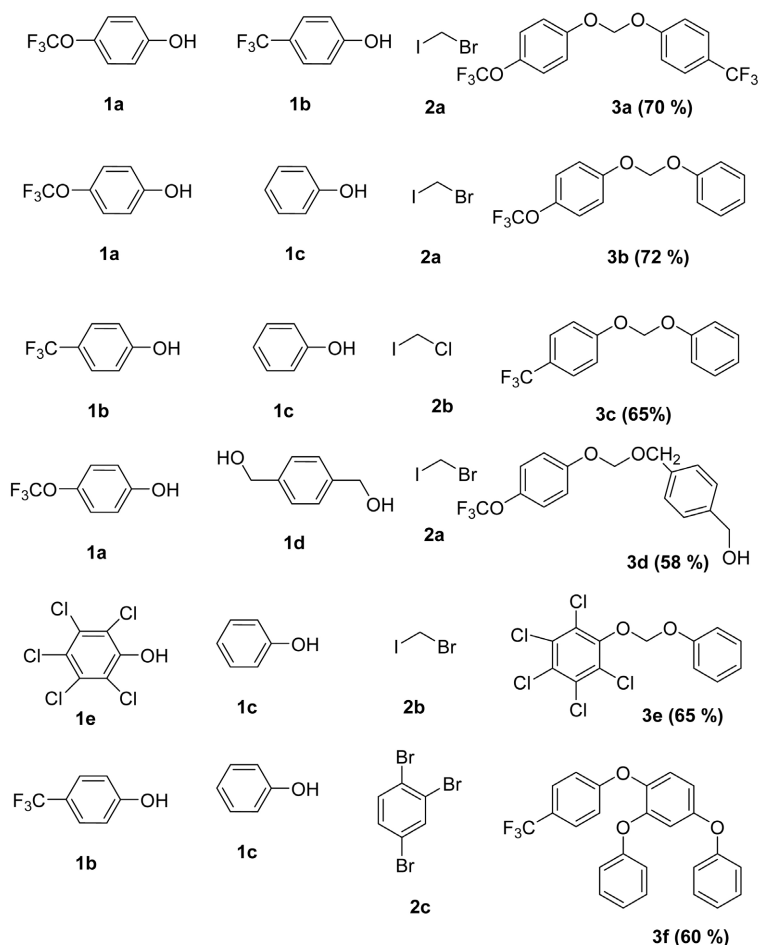


Figure 4. Phenolic ethers from mixed phenols and halides. All products are collected by passing the crude reactions products through alumina column using the eluents, hexane 92%/ethyl acetate 8%. Yields of the products are ranges from 70% to 60%.

Compound **3b**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.25 - 6.97 (m, 9H), 5.63 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 155.2, 144.1, 129.6, 122.5, 122.4, 117.4, 117.3, 116.4, 91.3; $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -58.3 (OCF₃); LRMS: Calc'd for C₁₄H₁₁O₃F₃(M⁺): 284. Found: 283.99.

Compound **3c**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.04 - 6.78 (m, 9H), 6.74 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 165.1, 160.4, 155.5, 151.0, 132.6, 129.5, 125.8, 121.8, 121.7, 115.2, 93.3; $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -61.5.

Compound **3d**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.20 - 6.72 (m, 8H), 5.01 (m, 2H), 4.4.99 (m, 2H), 4.57(m, 2H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 155.2, 141.8, 139.9, 135.7, 128.5, 126.9, 122.2, 115.9, 66.0, 64.5; $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -58.4.

Compound **3e**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.37 - 6.69 (m, 5H, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 155, 130.2, 129.5, 121.5, 120.5, 116.4, 115.293.5.

Compound **3f**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.69 - 7.20 (m, 17H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 136.0, 134.6, 131.6, 125.8, 123.7, 121.3; $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -61.9.

3. Conclusion

In conclusion, this project extends the earlier findings of phenolic ether synthesis in investigating the possibility of making aromatic ethers from mixed phenols and halides in the presence of $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ under microwave irradiation. The research paves a continuing pathway to achieve a new method for establishing polyphenolic ethers from phenols and halides. As this project obtained some success and builds upon previous studies, hopefully, it reaches new boundaries for creating novel series of polyphenolic ethers important bioactive sources for scientists interested to explore human health benefits and prevent diseases. Each step of this project was challenging because of the adjustments per small reaction scale. The separation techniques didn't perform well in some reactions which affected the final amount of the product yields.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

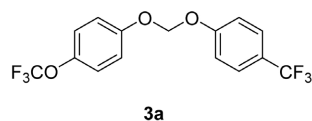
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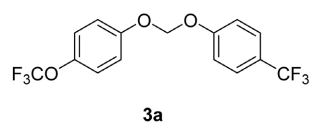
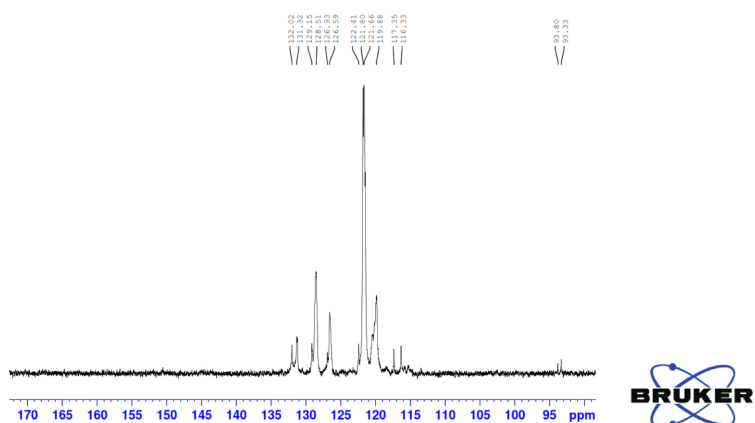
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Supporting Information

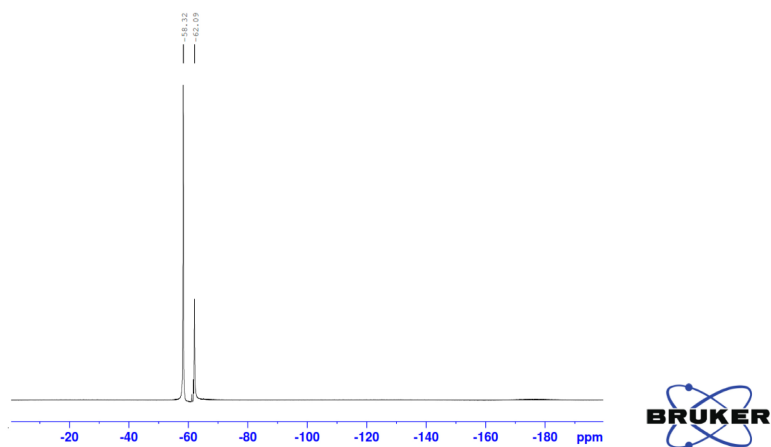
The experiments used a CEM microwave system. Also, a Varian 3900 model used to analyze GC-MS. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded by Bruker 400 MHz NMR. All the data of GC-MS and NMR spectra are shown in the appendix. All the solvents that used in the experiments were purchased through Fischer Scientific, Sigma-Aldrich with dry condition, and in Sure-sealed bottled. Also, the palladium catalysts used were purchased through Alfa Aesar. All the reagents used were purchased from Sigma-Aldrich.

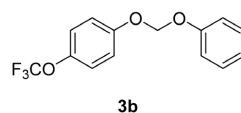
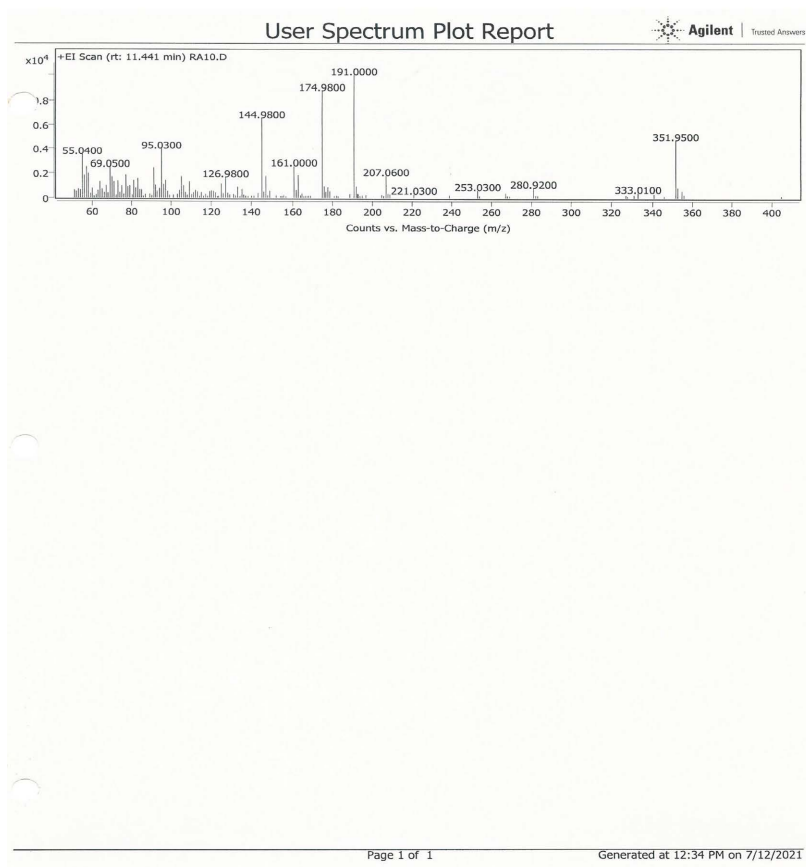
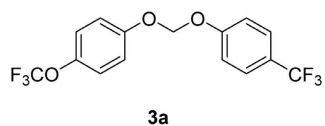


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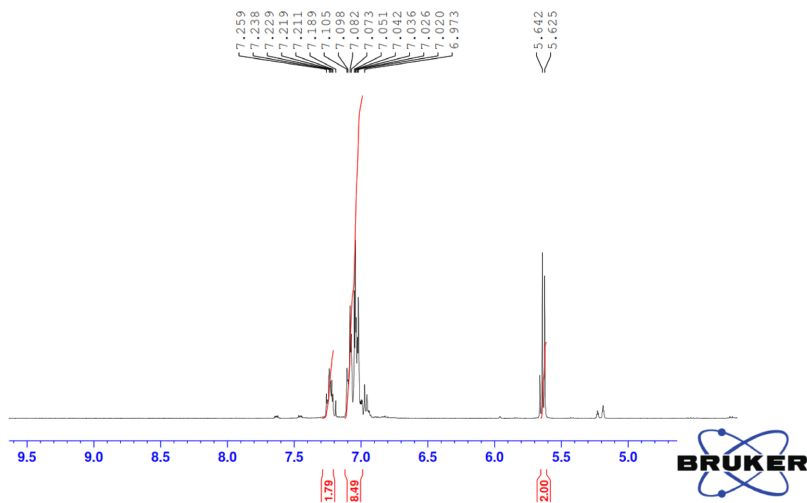


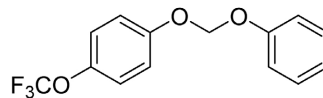
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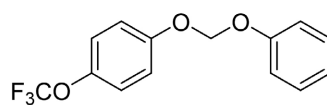
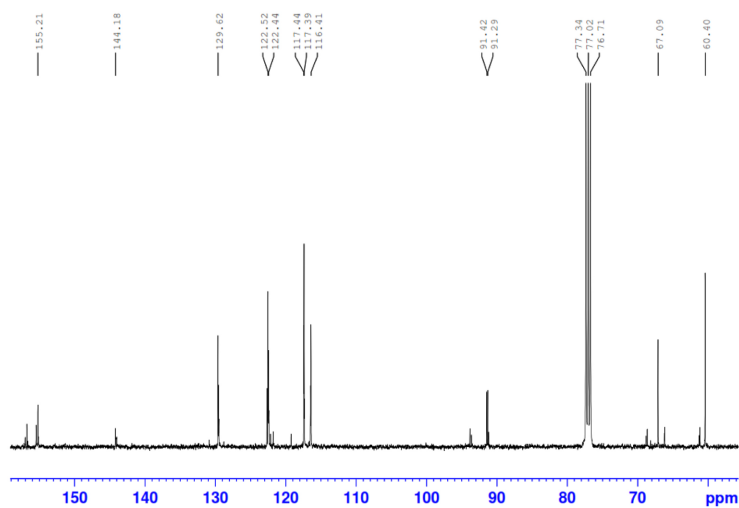


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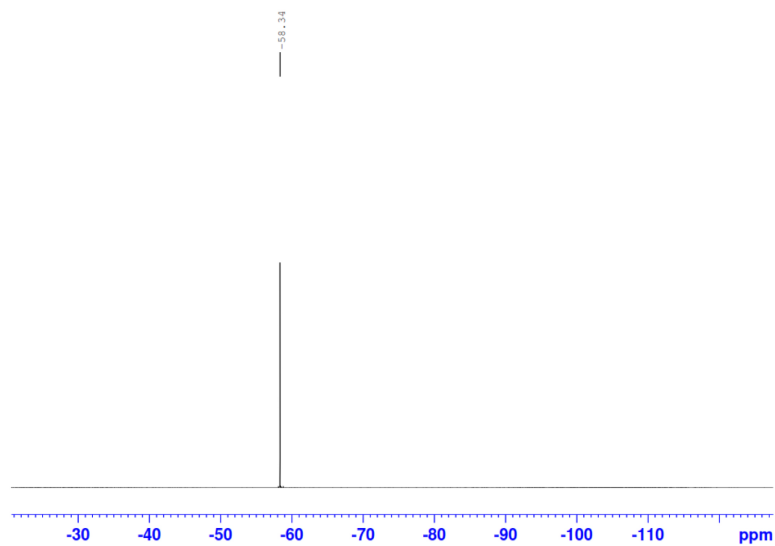


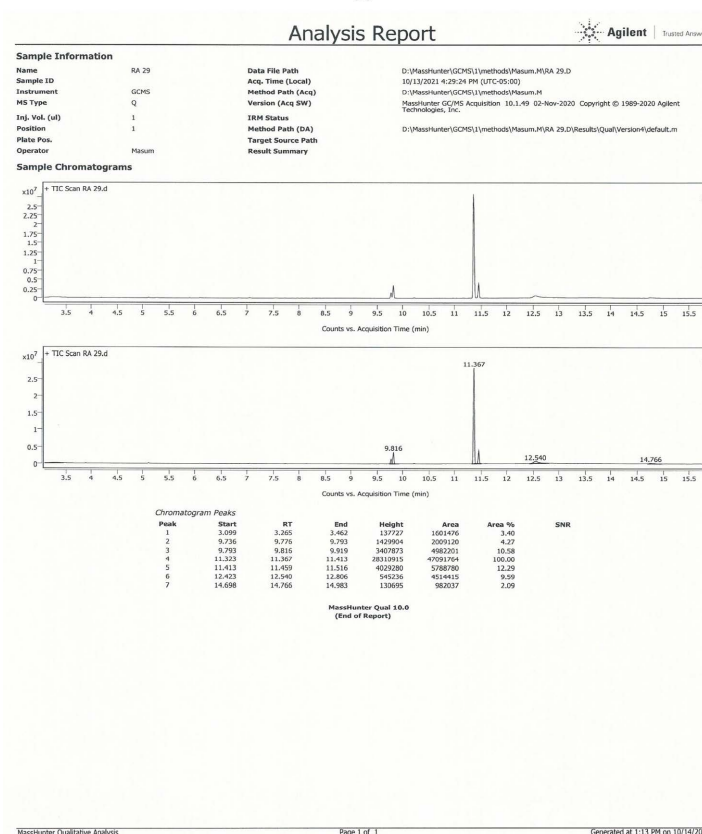
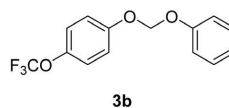
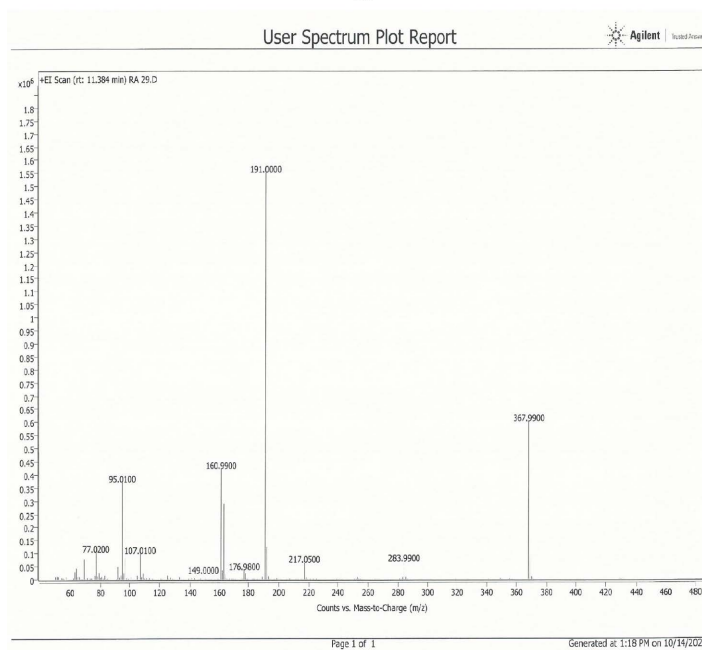
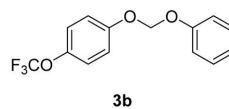
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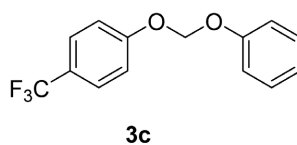
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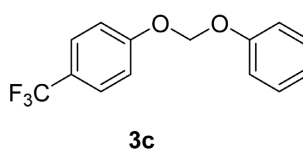
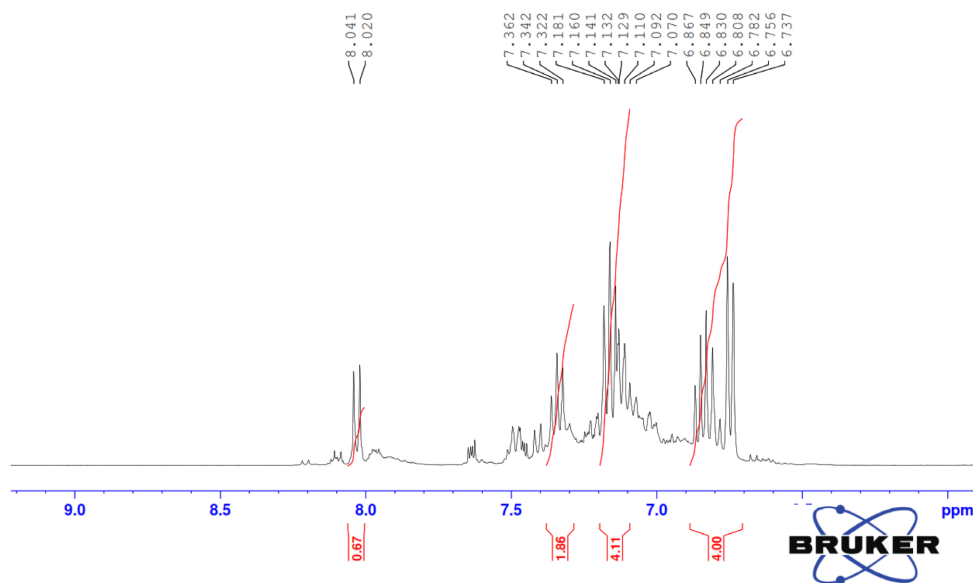
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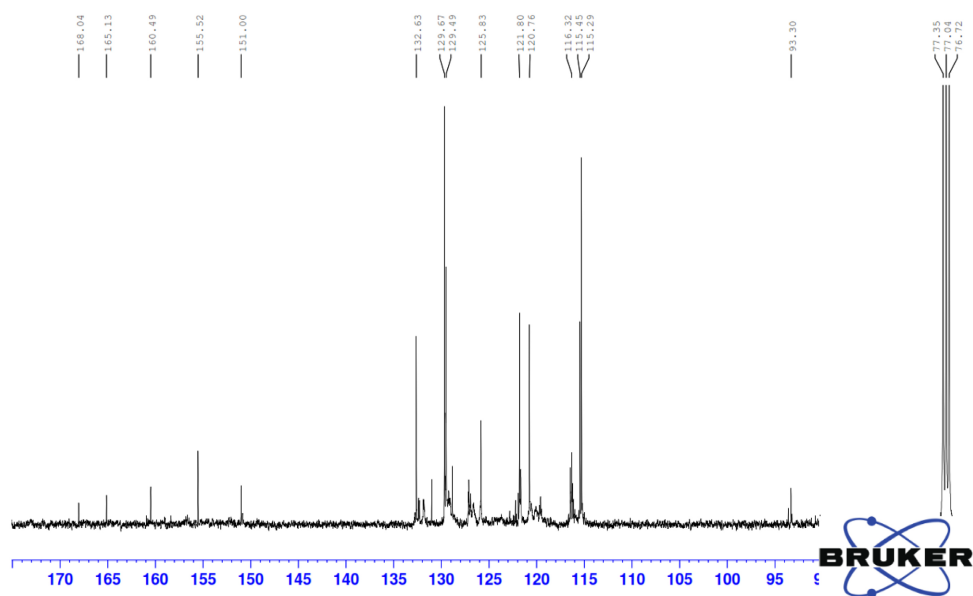


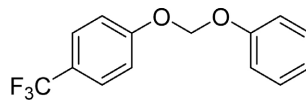


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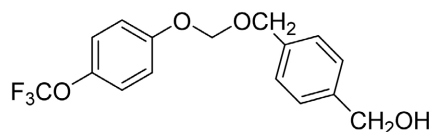
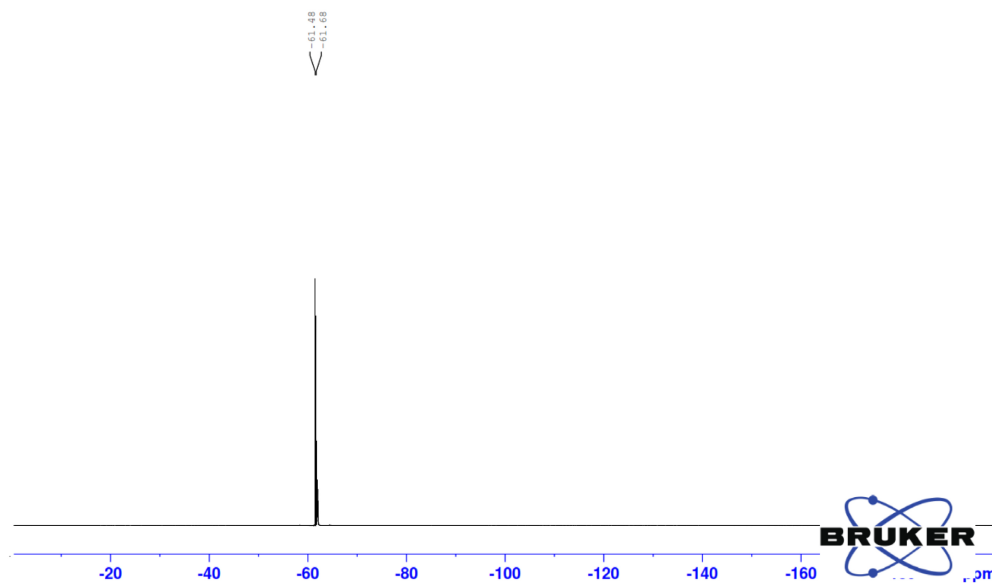
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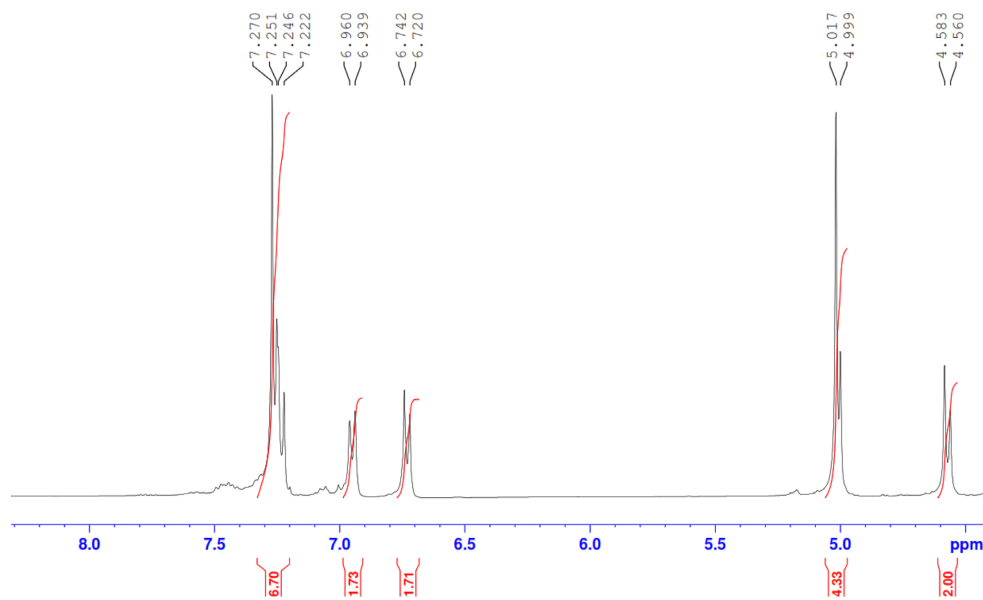
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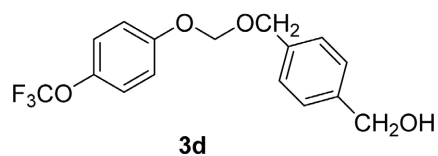
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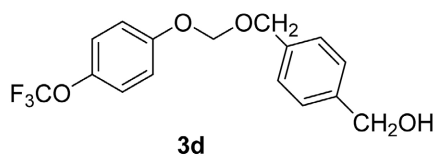
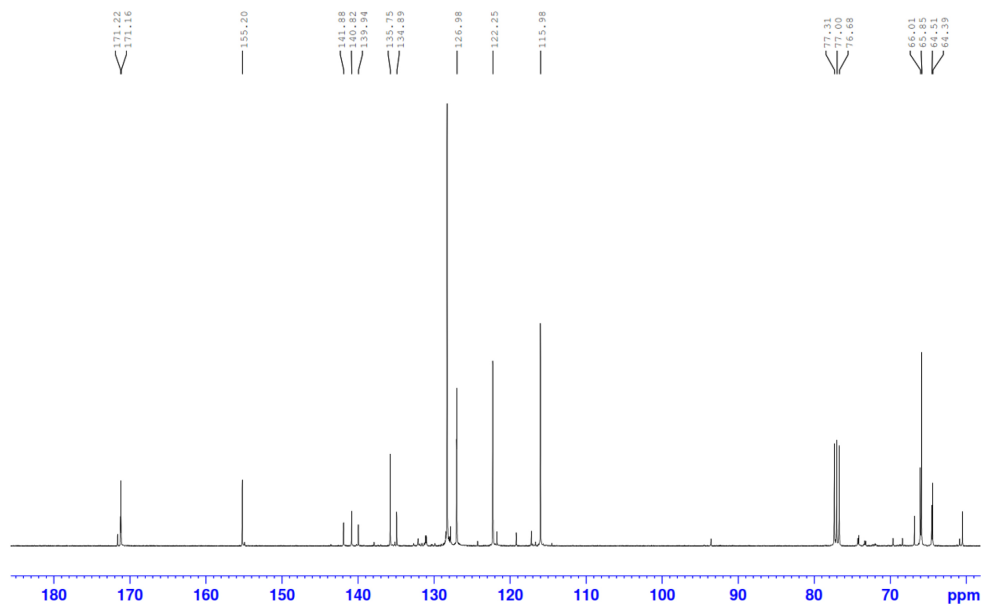
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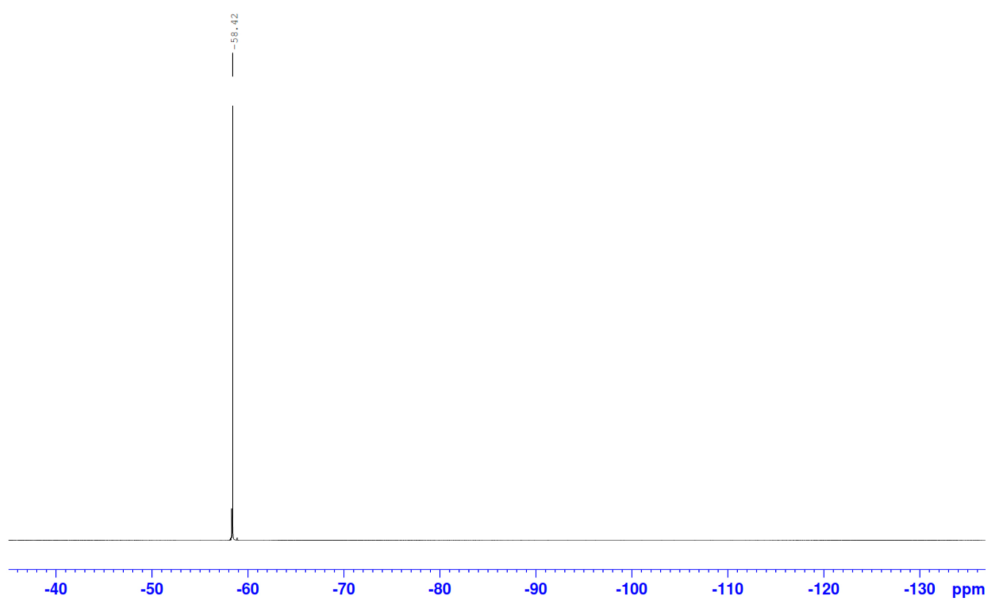


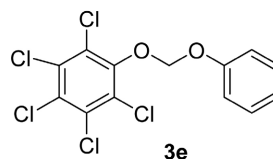
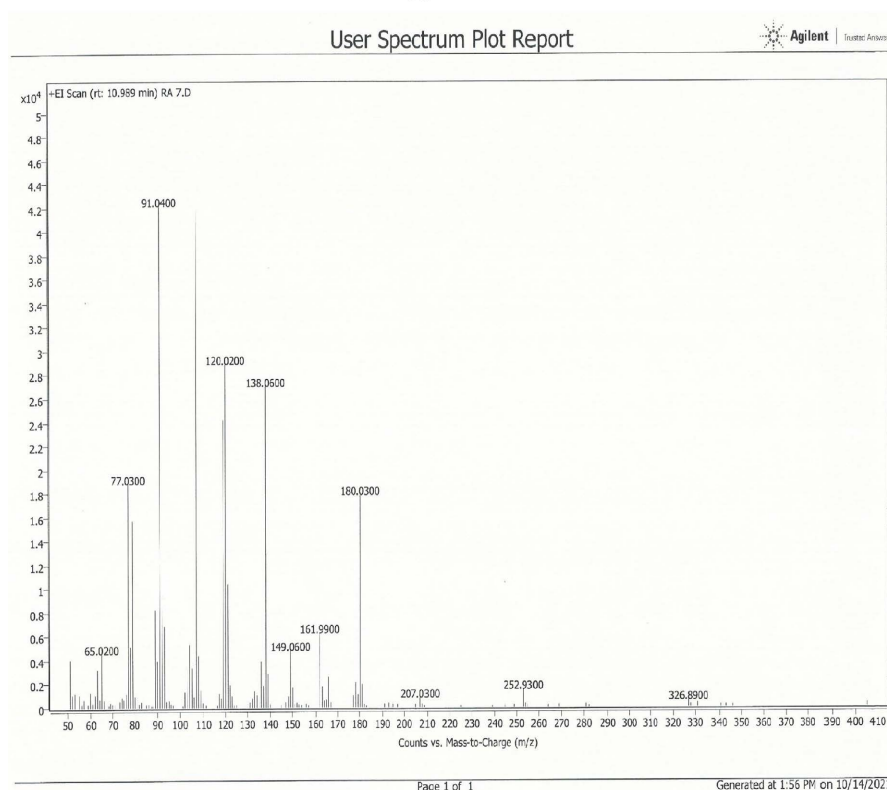
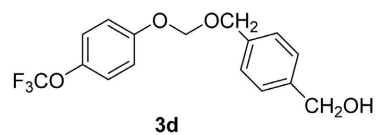


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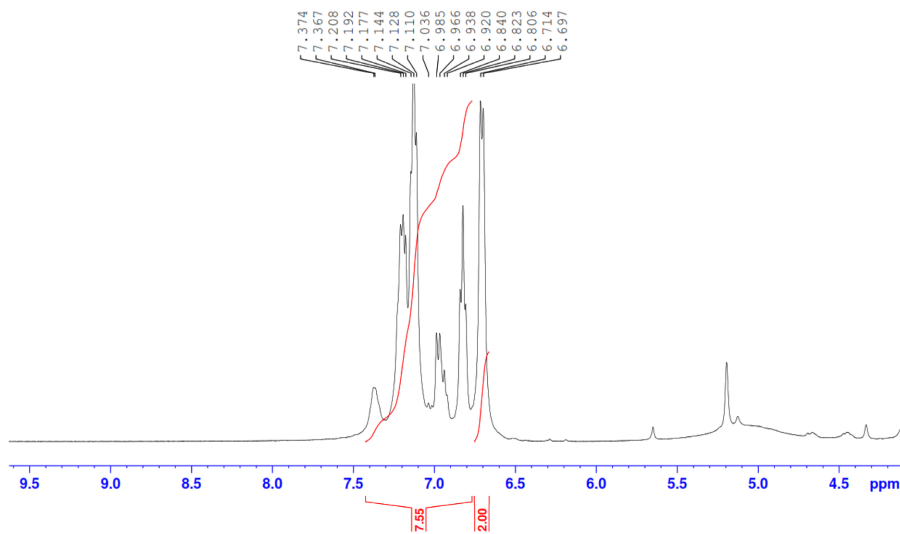


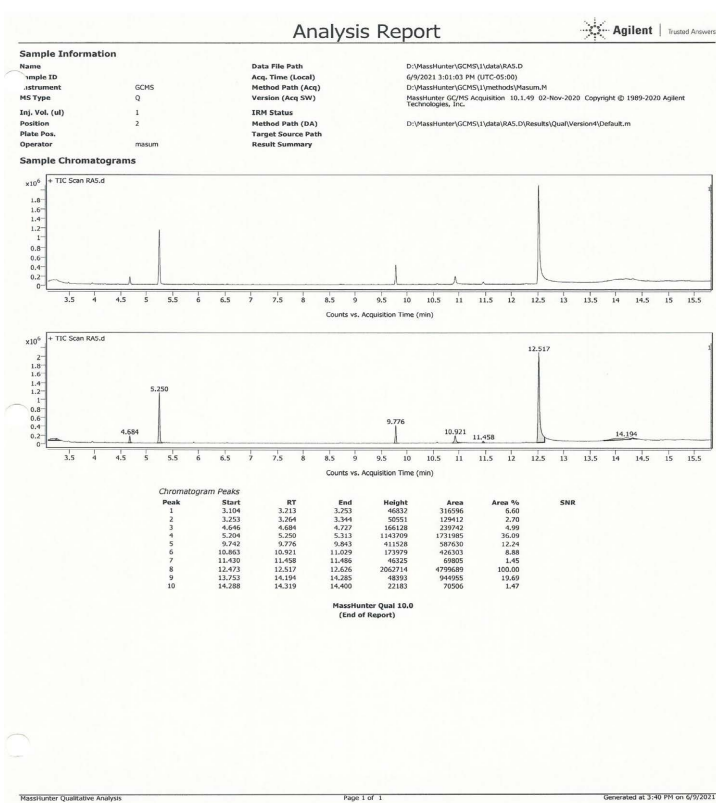
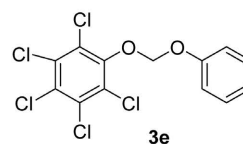
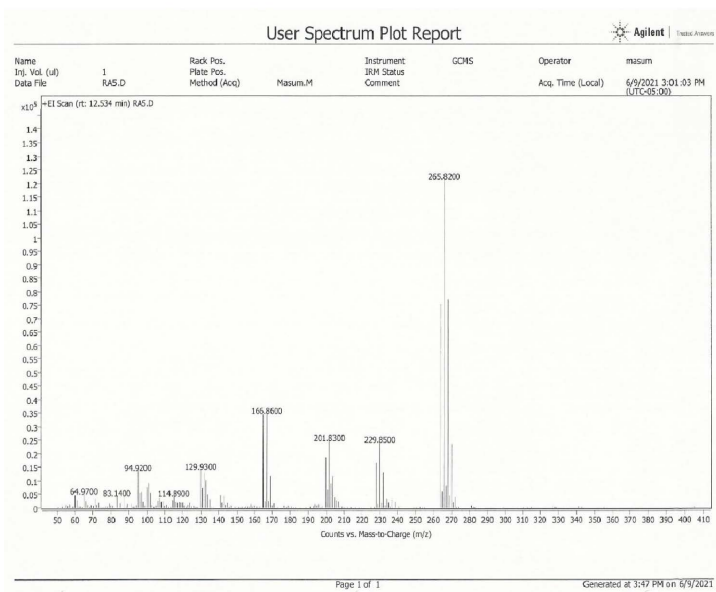
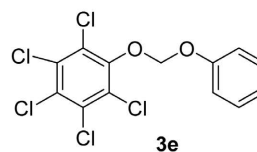
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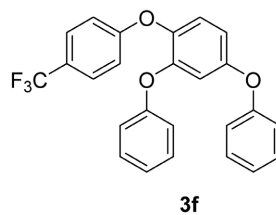




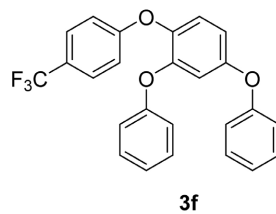
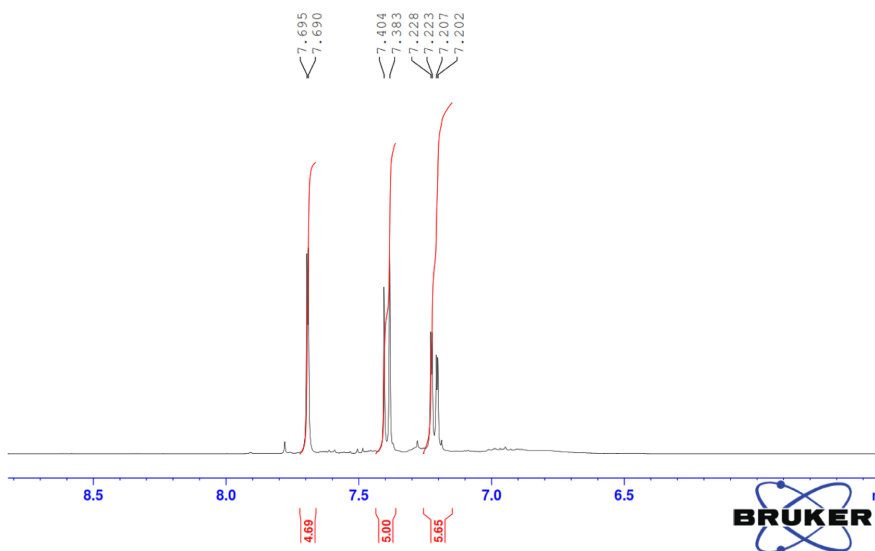
RA5_1H NMR
A_PROTON.TSU CDCl3 (C:\Bruker\TopSpin3.0\NMR_data\Almasum_group\malmasum) almasum 5



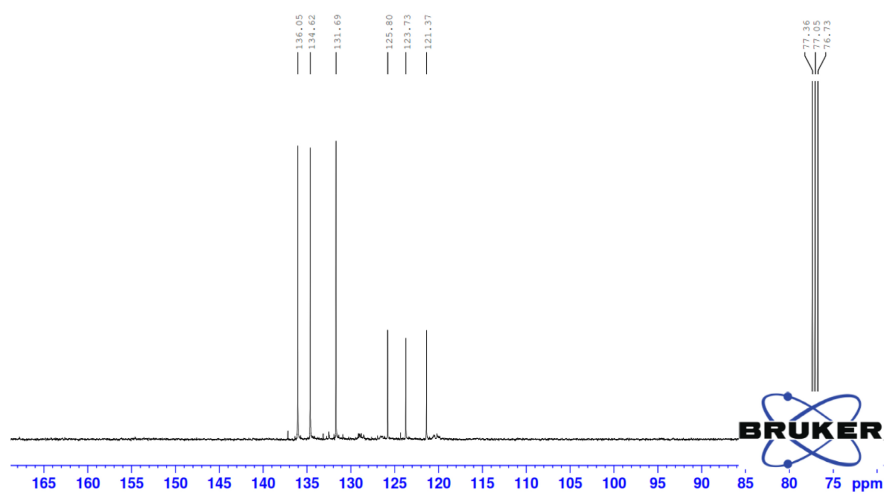


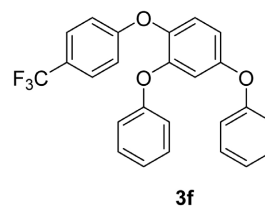


RA20-1H NMR
A_PROTON.TSU CDCl3 (C:\Bruker\TopSpin3.0\NMR_data\Almasum_group\malmasum) almasum 1



RA20-13C NMR
AA_C13CPD.TSU CDCl3 (C:\Bruker\TopSpin3.0\NMR_data\Almasum_group\malmasum) almasum 1





RA20-19F NMR
AA_F19.TSU CDCl3 (C:\Bruker\TopSpin3.0\NMR_data\Almasum_group\almasum) almasum 1

