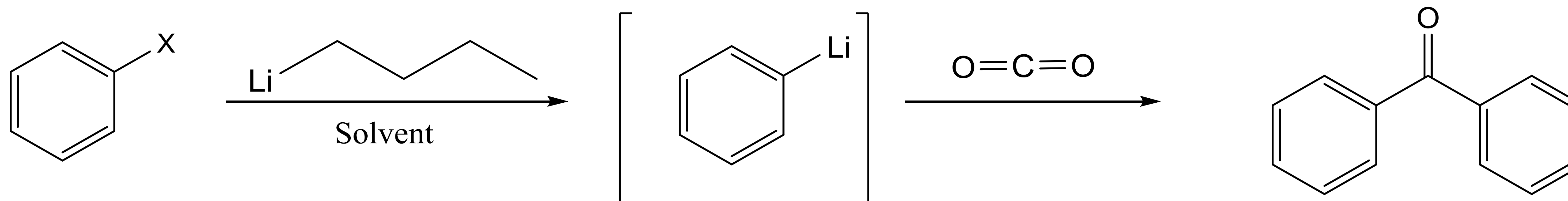


The Effect of Solvent on Lithium Halogen Exchange and Subsequent Preparation of Ketones



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Introduction

Isotopes of carbon are a desirable material that can be used in stable isotopic labelling. Unfortunately, purchasing rare isotopic carbons is expensive, so the ability to use them in high yield reactions with inexpensive materials is desirable. The objective of this project was to optimize the reaction to increase the yield of isotopic labeled ketones while minimizing the amount and type of byproduct produced. This was accomplished by changing the ratio and type of solvent and co-solvent.

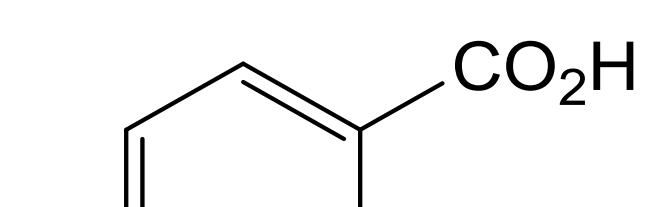
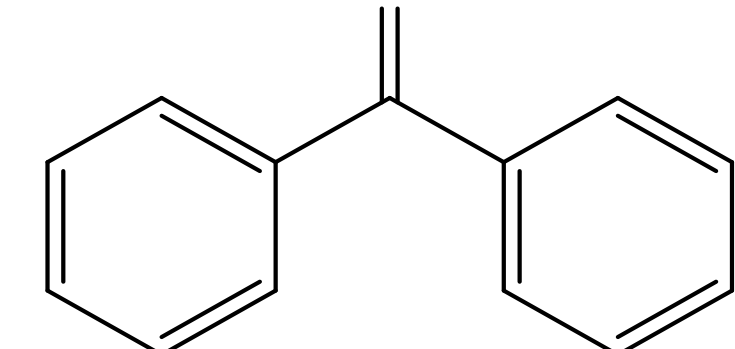


Reaction Setup

Methods

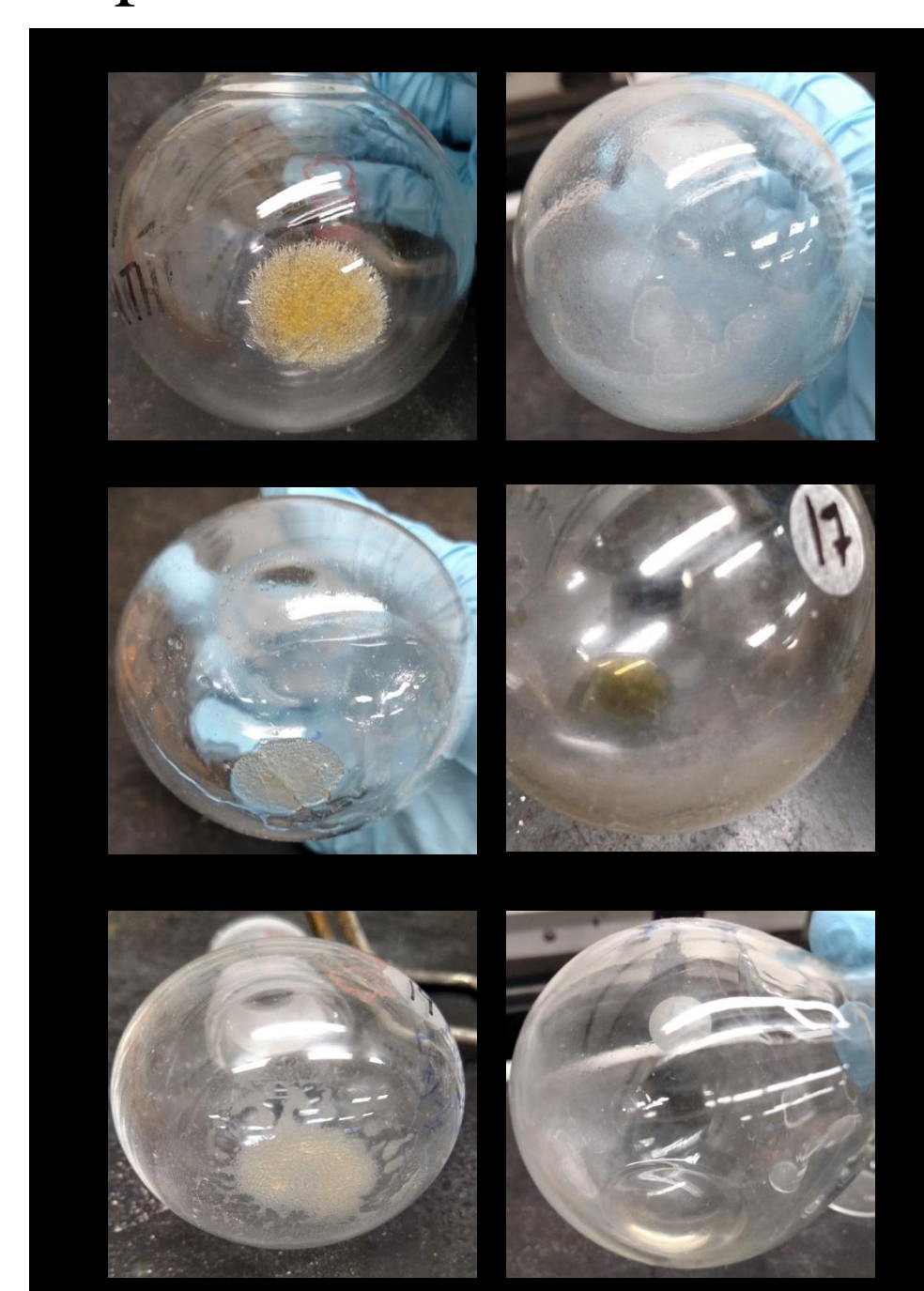
Reactants were added to sealed oven dried flasks. The reactions were kept under a nitrogen atmosphere and regulated to stay at 40°C. The bromobenzene was added first, then the solvents. Butyl lithium was then added, and finally the carbon dioxide. After an acid wash, the bottom layer was removed and the top was dried using magnesium sulfate. This was then filtered using cyclohexane and rotovaped, leaving the product behind. This was then analyzed using a GC.

Symmetrical Ketone



Carboxylic Acid

Formation of Byproducts



Final Product Appearances

Reaction Scheme

Results

Nineteen solvent mixtures were tested. Once analyzed using the GC, the data was graphed so there was a visual comparison of byproducts to present, as well as amounts of product produced. Benzophenone was the desired product. Byproducts include trityl alcohol, valerophenone, butyl benzene, and benzoic acid. Also present is unreacted bromobenzene. This is due to having an excess of bromobenzene in order to have the other reactants fully react.

Unless otherwise stated, the solvent mixtures were combined with toluene in a 1:1 ratio. If toluene was not present, then heptane was used in its stead. Other ratios of toluene and its co-solvent include a 1:9 ratio, of co-solvent to toluene, and 9:1, or toluene to co-solvent.

Discussion

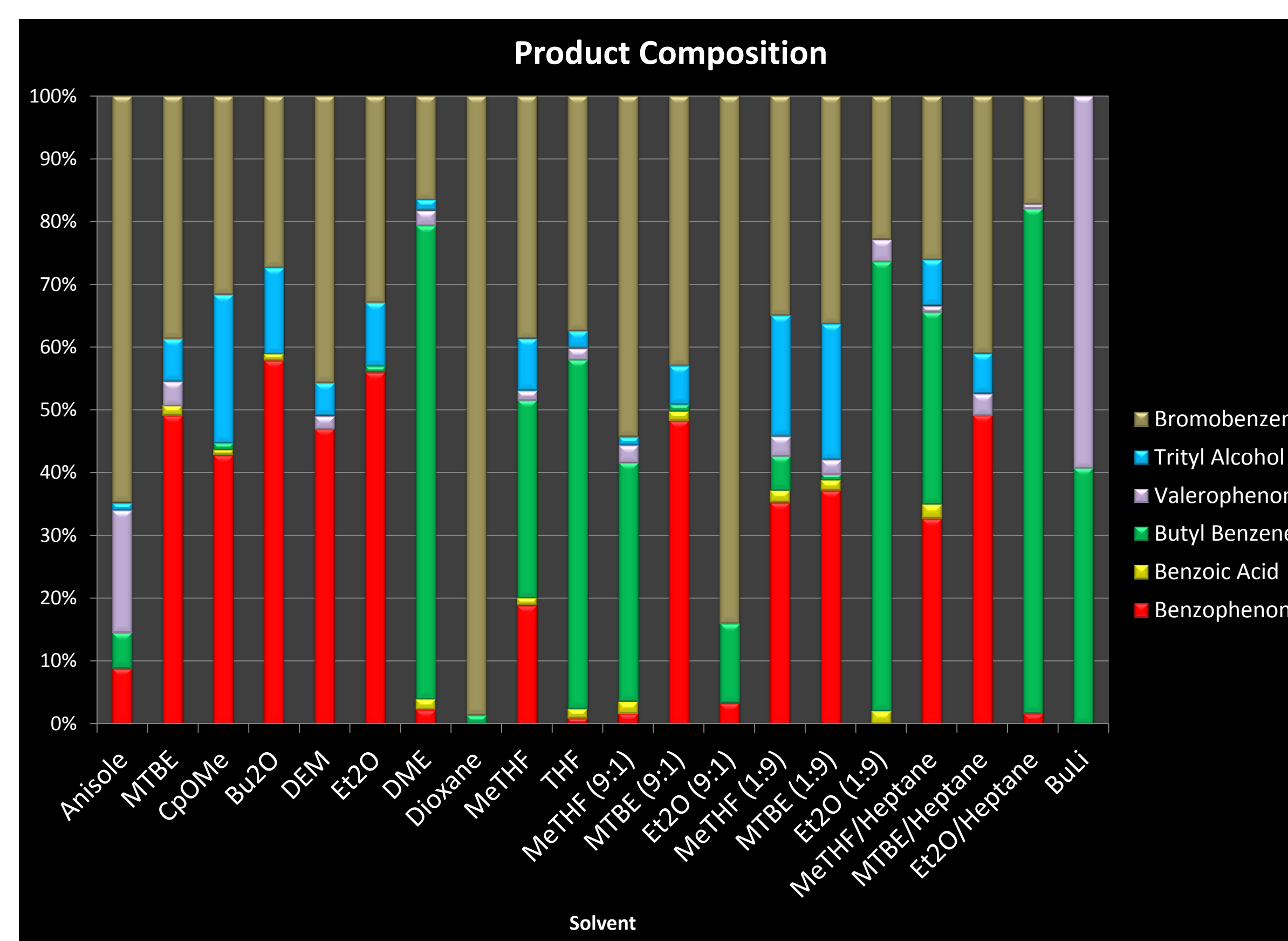
The results that were especially interesting were the reactions that occurred in the green solvents, such as methyl tetrahydrofuran (MeTHF) and Cyclopentyl methyl ether (CpOMe). Reactions that contained the highest yield of product were important, but the research also highlighted alternative solvents that formed products containing the least amount and type of byproducts. A few reactions need to be repeated, such as the Dioxane, which was composed of mostly bromobenzene, indicating a reaction did not take place. Based on previous research, diethoxymethane (DEM) and tert-butyl methyl ether (MTBE) were also explored.

Acknowledgments

Thank you to the SURF program and all of their supporting staff, the donors, Dr. Luzik, Michele Berman, and to the Chemistry and Chemical Engineering Department.

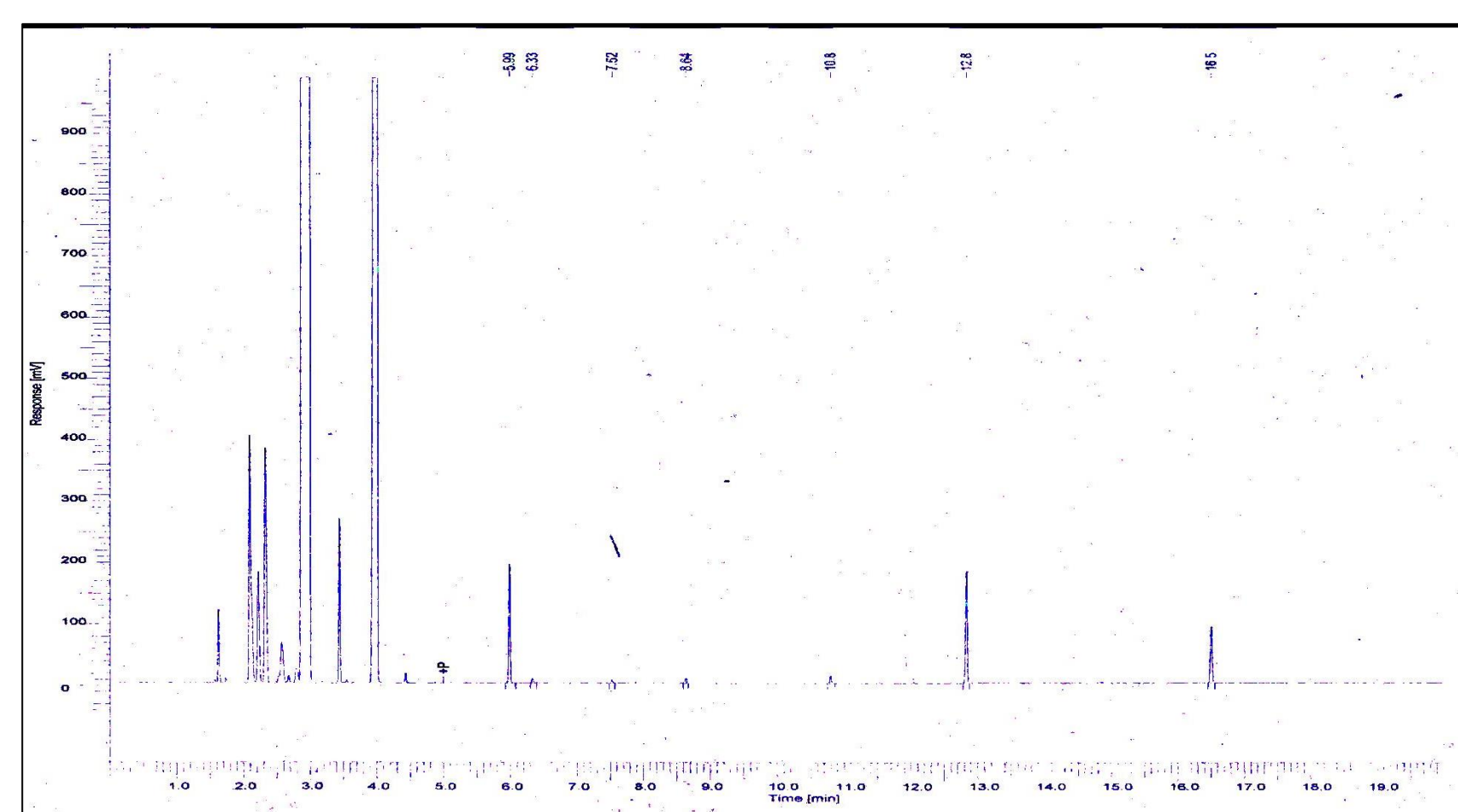
References

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Product before Filtration

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	5.987	289901.47	193688.85	35.77	35.77	BB	1.4967
2	6.329	11610.91	7900.43	1.43	1.43	BB	1.4697
3	7.522	8134.27	5522.67	1.00	1.00	BB	1.4729
4	8.635	12984.55	8955.63	1.60	1.60	BB	1.4499
5	10.797	18860.78	12494.59	2.33	2.33	BB	1.5095
6	12.834	297125.98	181661.94	36.66	36.66	BB	1.6356
7	16.509	171802.12	91486.11	21.20	21.20	BB	1.8779
		810420.07	501710.21	100.00	100.00		



Raw GC Data