4-14-2022

Optimizing the Alkylation of Carboxylic Acid Derivatives for Use in the Synthesis of the Oxidative Metabolites of DEHP

Hannah Harris

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Hannah G. Harris; E. Davis Oldham, Ph.D.
Department of Chemistry and Physics
University of Mary Washington, Fredericksburg, VA

University of Mary Washington

Background

Di(2-ethylhexyl) phthalate (DEHP) is a plasticizer found in polyvinylchloride (PVC), dialysis and catheter tubing, toys, food packaging, and hydraulic fluid, among other sources [1]. Like other phthalate esters, DEHP is classified as both a peroxisome proliferator chemical (PCC) [2] and an endocrine disrupting chemical (EDC) [1]. It has been seen to increase the occurrence of liver tumors as well as cause developmental changes to the male reproductive tract in mice [1]. Studies have suggested DEHP and its metabolites are able to induce these changes in gene expression through multiple nuclear receptors including PPARα and CAR [2]. Given that biological response often varies greatly between different isomers of the same compounds, it is likely the toxicity of DEHP and its metabolites could vary between the enantiomeric forms.

Methods

The first step in the synthesis of the oxidative metabolites, alkylation of a starting carboxylic acid or ester, was optimized. Various bases, starting carboxylic acid derivatives, alkyl halides, and reaction conditions were explored. The success of each reaction was evaluated using GC-MS and the final product was verified with ^{1}H NMR.

Discussion

Goals of this Research

This research aims to find the most efficient route for synthesis of the oxidative metabolites of DEHP, beginning with the alkyl side chains.

Accomplishments

It was seen that using LDA as a base, a t-Butyl ester as the starting material, and an alkyl iodide under Ar atmospheric conditions at -78°C gave the highest percent alkylation of the starting ester without byproducts. Here, t-Butyl 2-ethyl hex-5-enoate **(1)** was obtained (92% conversion from starting ester, 45% pure yield).

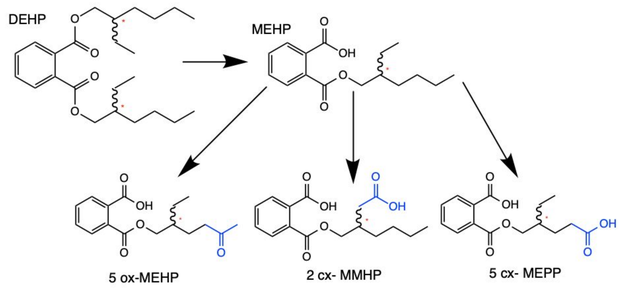
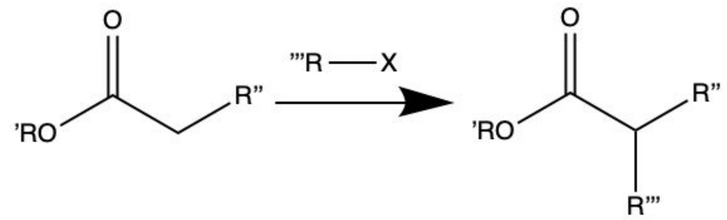
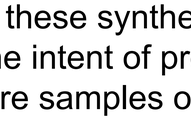
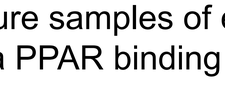
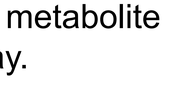
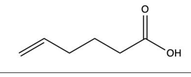
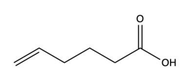
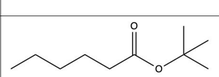
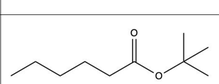
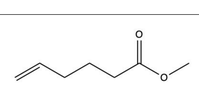
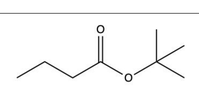
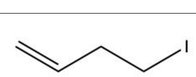


Figure 1: The primary and secondary metabolites of DEHP.

General Reaction Scheme



Results

Base	Starting Material	Alkyl Halide	Product: Unreacted Starting Material	Byproducts
NaH/LDA			0.1621: 1	Ethyl ester
LDA			0.1856: 1	Claisen
LDA/DMPU			0.7984: 1	Ethyl ester
LDA			0.9568: 1	None
LDA			1.143: 1	None
*LDA			6.994: 1	None
NaHMDS			7.264:1	Claisen
*LDA			12.38:1	None

* decreasing the time for deprotonation from 45 to 10 minutes after adding the ester produced markedly better results [3]

Future Work

(1) will be reduced to a primary alcohol, esterified with phthalic anhydride, and oxidized via Wacker oxidation to yield 5-oxo MEHP. Subsequently, the alkylation conditions found to be most efficient will be applied to synthesizing 2-cx MMHP and 5-cx MEPP. Finally, these syntheses will be re-evaluated with the intent of producing enantiomerically pure samples of each metabolite for comparison in a PPAR binding assay.

Acknowledgements

- The University of Mary Washington Undergraduate Research Program
- The Irene Piscopo Rodgers '59 and James Rodgers Research Endowment
- Dr. E. Davis Oldham

References

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3. Joosten, A.; Lambert, É.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2010**, *12* (22), 5128–5131.