**Olivia Miller, Chem 213**

**Synthetic #2 FFR**

# Exploring the Usefulness of Carboxylic Acid Derivatives in Nucleophilic Acyl Substitution Reactions

## Introduction

Carboxylic acid derivatives are the most widely occurring of all molecules, both in laboratory chemistry and in biological pathways. Specifically, acid derivatives are compounds in which the hydroxyl group of the carboxylic acid has been replaced by another acyl substituent that can act as a leaving group in nucleophilic acyl substitutions. These compounds can be acid halides, acid anhydrides, esters, thioesters, and amides. Some examples of carboxylic acid derivatives can be seen below in Figure 1.

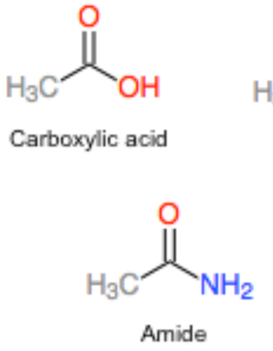


**Figure 1.** Examples of carboxylic acid derivatives.

These compounds are extremely valuable in organic chemistry synthesis as result of their primary nucleophilic acyl substitution reactions. When a nucleophile adds to a carboxylic acid derivative, the initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net nucleophilic acyl substitution reaction. This result is a consequence of the structure of acid derivatives. As soon as the tetrahedral intermediate is formed, the leaving group on the carbonyl carbon of the acid derivative is expelled to generate a new carbonyl compound. The net effect of this addition/elimination sequence is a substitution of the nucleophile for the leaving group originally bonded to the acyl carbon.[1] An example of a nucleophilic acyl substitution can be seen below in Figure 2.

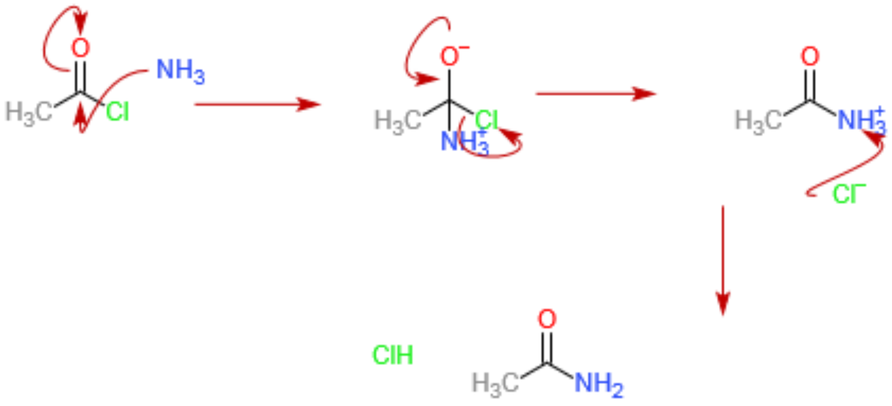
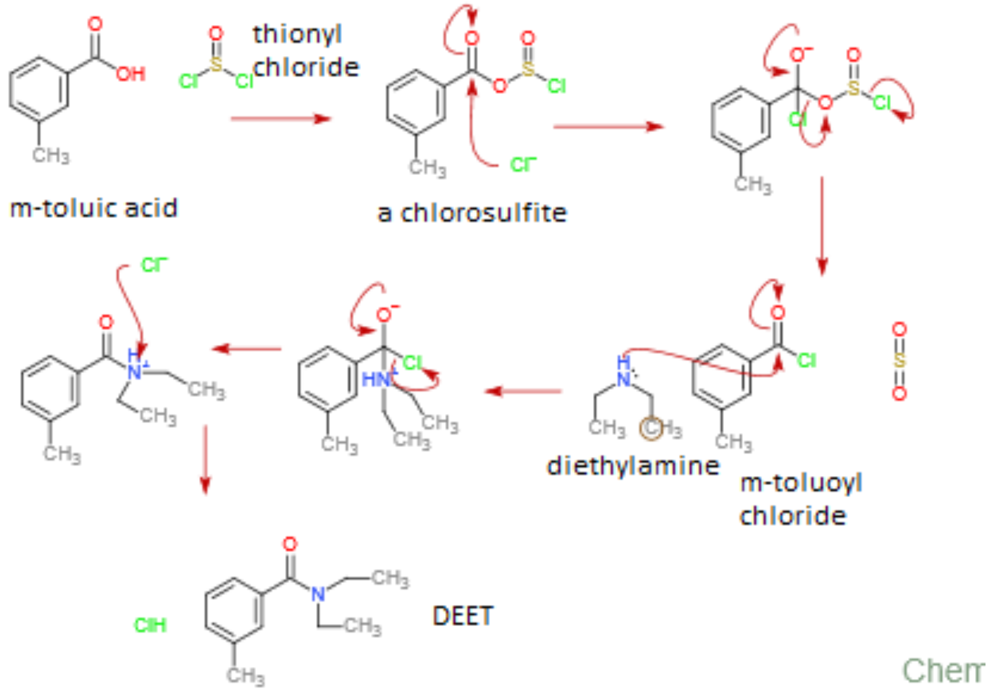


**Figure 2.** An example of a nucleophilic acyl substitution reaction with a carboxylic acid derivative.

The chemistry of carboxylic acid derivatives is dominated by the nucleophilic acyl substitution reaction. In fact, acid derivatives use this reaction in hydrolysis, alcoholysis, aminolysis, reduction and Grignard reactions. In hydrolysis, a carboxylic acid derivative is substituted with water to yield a carboxylic acid. Alcoholysis of an acid derivative yields an ester from a substitution reaction with an alcohol while aminolysis produces an amide from substitution with ammonia or an amine. Additionally, the reduction of an acid derivative affords aldehydes or alcohols from a substitution reaction with a hydride reducing agent, while substitution reactions with organometallic Grignard reagents yield ketones or alcohols.[1] Overall, carboxylic acid derivatives and their nucleophilic acyl substitution reactions allow for the production of a variety of useful products that can be used in further organic synthesis reactions.

The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the acyl substituent. Electronically, strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon thus producing a largely polarized acyl compound. As a consequence of these reactivity differences, it is usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides[1]. For example, in this experiment an acid chloride underwent aminolysis or a substitution reaction with an amine to yield an amide. This important characteristic of the acid chloride makes it useful in synthesizing other carboxylic acid derivatives.

In this experiment, m-toluic acid, a carboxylic acid, is used to synthesis N,N-Diethyl-m-Toluamide (DEET) through an acid chloride intermediate as seen below is Scheme 1.



**Scheme 1.** Mechanism for the synthesis of DEET.

This is the common method for preparation of DEET, which is carried out by first reacting thionyl chloride with the carboxylic acid to produce an acid chloride.[2] The reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate thereby replacing the hydroxyl of the acid with a much better leaving group. The chlorosulfite then reacts with a chloride nucleophile to expel the leaving group via backside nucleophilic substitution to yield the acid chloride, m-toluoyl chloride. Once m-toluoyl chloride is synthesized, diethylamine can then be added to the reaction mixture to yield DEET. Most amides like DEET are commonly synthesized via this nucleophilic acyl substitution reaction of an acid chloride with an amine. The reaction proceeds with nucleophilic attack on the fairly electropositive carbon atom of the acid chloride by the lone pair on the nitrogen atom of the amine to yield an unstable tetrahedral intermediate. The carbon-oxygen bond can then reform and expel the good chlorine leaving group. The desired amide can then be achieved by deprotonation of the nitrogen with the expelled chlorine, which produces hydrochloric acid gas.[1] Overall, the nucleophilic acyl substitution reactions used in this experiment allow for an efficient synthesis of DEET.

One of the most notable characteristics of the reaction product DEET (N,N-dimethyl m-toluamide) is its effectiveness in repelling mosquitoes and ticks[2]. In fact, DEET is the active component in most commercial insect repellents worldwide. Although there is a lot of concern about its adverse effect on human health, DEET is actually acutely toxic and safe to use on skin to repel insects with proper application. DEET is also a suitable molecular marker. Molecular markers are useful in tracing the input of wastewaters from a specific source to aquatic systems and in determining the subsequent spatial contamination. This application is of great value for tracing such inputs in tropical coastal habitats like coral reefs, which are sensitive to changing water quality. Good molecular markers, like DEET, must have widespread and massive usage, source specificity and environmental persistence.[3] At large, the amide product synthesized from m-toluic acid via an acid chloride intermediate, has many practical and commercial applications.

Carboxylic acid derivatives are interesting compounds useful in nucleophilic acyl substitution reactions. In this experiment, the practicality of carboxylic acid derivatives and their nucleophilic acyl substitution reactions is demonstrated by the reaction of an acid chloride with an amine to yield an amide. The purpose of this experiment is to synthesize DEET (N,N-Diethyl-m-Toluamide), an active ingredient in insect repellant, from m-toluic acid via aminolysis of an acid chloride by diethylamine. The product of the reaction can be quantified and analyzed via 60Hz $^1$H NMR, IR, and GC/GC-MS.

## Experimental

***N,N-Diethyl-m-Toluamide (DEET).*** m-toulic acid (200mg, 1.47mmol), and thionyl chloride (0.20 mL, 2.76 mmol) were added to a simple gas trap, which consisted of a septum, Teflon tubing, oven dried reaction tubes, and a damp cotton plug for catching emitting HCl vapors, and allowed to gently reflux for 15 minutes. Upon completion of the reaction, anhydrous ether (1.5 mL) was added to the stirring reaction mixture at room temperature until a homogenous solution was obtained. A mixture of diethylamine/anhydrous ether solution (1:2, 1.5 mL) was then added dropwise through the septum to the stirring reaction mixture to form a thick, white precipitate of diethylamine hydrochloride. The reaction was allowed to continue for 30 minutes at room temperature with periodic agitation. Once the reaction was complete, the reaction mixture was extracted with NaOH (5%, 2 x 1 mL), HCl (5%, 1mL) and saturated NaCl (1mL), respectively. After each extraction the reaction tube solution was mixed vigorously, the mixture was allowed to separate, and the lower aqueous layer was drawn off and discarded. The extractions afforded the separated ether layer containing the product, which was then dried with sodium sulfate. After drying, isolation via pipet filtration and evaporation of remaining solvent afforded the crude mixture of N,N-Diethy-m-Toluamide (DEET). TLC (ether/hexane solvent

50:50) was utilized to determine the number of components in the crude mixture. Flash Chromatography (ether/hexane solvent 50:50 and silica) was then utilized to separate and purify the product. Combining like fractions and evaporating remaining solvent thus afforded the purified product DEET (40.4 mg, 14.4%); $^1$H NMR (60MHz, $CDCl_3$) $\delta$ (ppm) 1.26 (t, 6H), 2.35 (s, 2.80H), 3.45 (s, 3.03H), 7.20 (m, 4.38); IR (ATR) $\gamma_{max}$ ($cm^{-1}$) 2971.58, 2931.42, 1715.72, 1628.95; GC (phenyl methylpolysiloxane, 40°C to 250°C at 10°C per min) RT 18.86 min; GC-MS (phenyl methylpolysiloxane, 40°C to 250°C at 10°C per min) RT 19.11 min, m/z 119.

## Results and Discussion

In this experiment N,N-Diethyl-m-Toluamide (DEET) was synthesized from m-toluic acid through two nucleophilic acyl substitution reactions. The first reaction of the experiment dealt with the synthesis of the acid chloride, m-toluoyl chloride. The direct nucleophilic acyl substitution of a carboxylic acid is difficult because hydroxyl is a poor leaving group; however, under the right circumstances acid chlorides can be prepared from carboxylic acids by nucleophilic acyl substitution reactions. In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride.[1] The reaction occurs by a nucleophilic acyl substitution pathway which can be seen in Scheme 1. Therefore, in order to convert the carboxylic acid into an acid chloride that can be used in a subsequent organic synthesis step, thionyl chloride was allowed to react with m-toluic acid. This reaction afforded m-toluoyl chloride, the acid chloride. Due to the nature of the chlorine substituent, m-toluoyl chloride is a very reactive carboxylic acid derivative. As mentioned before, it is possible to convert more reactive acid derivatives, like acid chlorides, into less reactive derivatives, like amides.[1] Therefore, in order to synthesize DEET, an amide, the acid chloride from the previous reaction was allowed to react with diethylamine via aminolysis in the second nucleophilic acyl substitution reaction. This mechanistic step, which is the common pathway for synthesizing amides like DEET, can be seen in Scheme 1. This second reaction also produced HCl vapors. The use of a simple gas trap made of a septum, Teflon tubling, oven-dried reaction tubes and a damp cotton plug was useful in catching the emitting vapors during the reaction. Once DEET was synthesized, it was extracted to remove any unreacted m-toluic acid remaining in solution. The product could then be dried to remove any water remaining from the work-up and then isolated from the drying agent via pipet filtration. Evaporation of remaining solvent afforded the crude product mixture, which contained DEET.

After the synthesis and work-up, the crude product was contaminated with relatively small amounts of impurities. Purification by flash chromatography was utilized to cleanly separate the product from remaining impurities. TLC analysis with 50:50 ether/hexanes solvent of the crude product allowed for the determination of the number of components in the mixture. The TLC analysis of the crude product showed four different spots indicating four different components in the mixture, one of them being the product of interest DEET. Therefore, four different components of the crude product mixture were separated and collected during flash chromatography. The column was run with 50:50 ether/hexanes solvent and silica to effectively separate the components of the crude mixture. Like fractions and thus components were combined and the solvent was evaporated from each. A pure DEET product was then achieved as oil left behind from one separated mixture component. Overall, the experiment synthesized N,N-Diethyl-m-Toluamide with a 14.4% yield. The reported yield for this reaction was 97%; however, organic chemistry students typically achieve yields from 30-50%.[4] The obtained yield, when compared to the reported yields, does not indicate a very efficient synthesis and purification of DEET.

The purified product was analyzed by IR spectral data in order to confirm its identity and determine the success of the experiment. The most notable change that occurs during the nucleophilic acyl substitution reactions of this experiment is the transformation of the hydroxyl group on the carboxylic acid into a diethyl amine. The hydroxyl group of a carboxylic acid characteristically has a broad peak with an absorbance from 2500-3500 $cm^{-1}$. As seen from the spectral data (Figure 2, Supplemental Information), the IR spectrum of the purified product does not show evidence of this peak. The absence of this peak indicates the absence of starting material in the purified product and confirms the success of flash chromatography in cleanly separating mixture components. The IR spectrum also confirms the identity of DEET as the purified product. The IR spectrum of DEET shows two peaks, one at 2971.58 cm$^{-1}$ and one at 2931.42 cm$^{-1}$, which corresponds to the C-H stretch of the product. The peak at 2971.58 cm$^{-1}$ corresponds to the C-H stretch of an aromatic, which characteristically has an absorbance, around 3000 cm$^{-1}$, while the peak at 2931.42 cm$^{-1}$ corresponds to the C-H stretch of the alkyl substituents on the compound, which characteristically has an absorbance from 2850-2960 cm$^{-1}$. The peak at 1715.72 cm$^{-1}$ confirms the carbon-oxygen double bond of the carbonyl compound DEET, which has a characteristic absorbance around 1700 cm$^{-1}$. Lastly, the peak at 1628.95 cm$^{-1}$ corresponds to the carbon-carbon double bonds of the aromatic, which have characteristic absorbance's around 1600 cm$^{-1}$. The presences of these characteristic peaks are strong evidence that the desired amide product was attained from the synthesis and purification cleanly.

NMR spectral data was also useful in determining the identity of the purified DEET product. Specifically, when analyzing the 60MHz $^{1}$H NMR spectrum of the product (Figure 1, Supplemental Information), several key features are visible that characterize the product as DEET. The methyl group on the aromatic ring of the product characteristically has a peak on the NMR spectral data with a shift from 2.3-2.7 ppm and an integration value of 3. The spectrum of the product showed a singlet at 2.35 ppm with an integration value of 2.80, which confirms the presence of the methyl on the aromatic ring of the product. This singlet was also consistent with the splitting of a methyl on an aromatic ring. Hydrogens on an aromatic characteristically have chemical shifts from 6.5-8 ppm. The spectrum of the purified product showed a multiplet in the aromatic region that had an integral value of 4.38. This value is close to the number of hydrogens on the aromatic ring of the product, which in DEET is four. As a result, the multiplet in the aromatic region confirms the four aromatic hydrogens of the DEET product.

Hydrogens on methyl groups characteristically have shifts from 0.7-1.3 ppm. The NMR spectrum of the product shows a triplet at 1.26, which corresponds to the methyl groups of the ethyl substituents on the amide nitrogen. Since each methyl is part of an ethyl substituent, splitting of the methyl by the two adjacent hydrogens will occur and result in a triplet. This triplet has an integration value of 6, which is consistent with the number of hydrogens present in two methyl groups. As a result, this triplet confirms the methyl groups of the ethyl substituents on the amide. The two hydrogens adjacent to the methyl groups on the ethyl substituents of the amide showed a broad peak at 3.45 ppm on the NMR spectrum. Hydrogens of alkyl substituents on amines characteristically have shifts from 2.2-2.9 ppm and appear as broad peaks. This peak is slightly off from the expected shift, which is due to the electron withdrawing effect of the carbonyl bond adjacent to the nitrogen atom. This peak had an integration value of 3.03. This value is close to the actual integration value of 4 hydrogens, and thus the NMR spectrum confirms the presence of the ethyl substituents on the nitrogen of the amide. Overall, the NMR spectrum confirms the success of the synthesis and workup by identification of the product as DEET. As mentioned before, the notable feature of the nucleophilic acyl substitution reactions is the transformation of the hydroxyl group of the carboxylic acid into a diethyl amine to produce an amide carboxylic acid derivative. The spectrum of the purified DEET product lacks peaks characteristic of a carboxylic acid. The hydrogen of the hydroxyl group of a carboxylic acid characteristically has a shift from 11-12 ppm. As seen, the spectrum of the product lacks this peak; therefore, the carboxylic acid starting material of this reaction is absent in the purified product. This characteristic of the product spectrum confirms the success of flash chromatography in cleanly separating mixture components and removing impurities from DEET. Meanwhile, the spectrum obtained from the purified product (Figure 1, Supplement Information) is similar upon comparison, to the reported $^1$H NMR spectrum for DEET, as seen in Figure 3 below, which only further identifies the product as the desired amide.

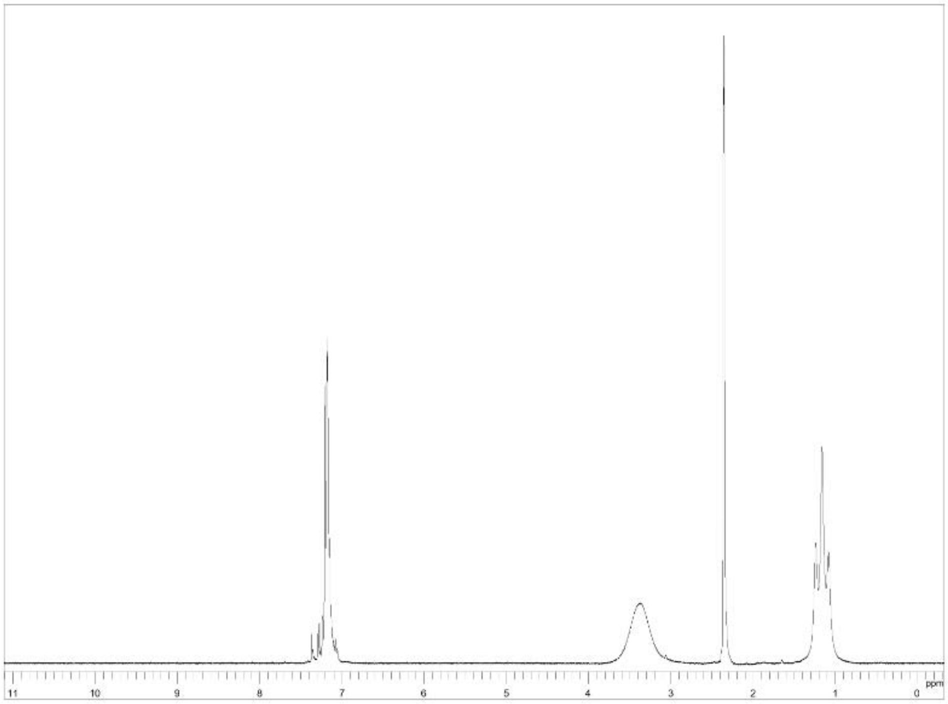


**Figure 3.** 90MHz $^1$H NMR of DEET.[5]

GC/GC-MS spectral data was also useful in ascertaining the success of the synthesis of DEET. When the purified product was run on the GC (Figure 3, Supplemental Information), some m-toulic acid starting material produced a peak at 14.82. However, this peak was much smaller in comparison to the size of the DEET peak at 18.86. Therefore, DEET was present in the final product in a much larger concentration than m-toulic acid. In fact, the concentration of m-toulic acid was so small that it did not appear on either the IR or NMR spectra. When the purified product was run on the GC-MS (Figure 4, Supplemental Information), the spectra of the product was found to match that of the reported spectra for N,N-Diethyl-m-Toluamide. Therefore, the purified product can be accurately identified as DEET and the success of the synthesis and purification can ultimately be confirmed.

Carboxylic acid derivatives are the most widely occurring of all molecules and the chemistry of these compounds is dominated by the nucleophilic acyl substitution reaction. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group. The acid chloride is the most reactive of the acid derivatives that can undergo direct nucleophilic acyl substitution to yield other carboxylic acid derivatives like, esters or amides, as seen in this experiment. Two nucleophilic acyl substitution reactions were utilized in this experiment to yield DEET (N,N-Diethyl-m-Toluamide), an active ingredient in commercial insect repellants. The first reaction synthesized an acid chloride, m-toluoyl chloride, from m-toluic acid and thionyl chloride. The acid chloride was then utilized in a subsequent nucleophilic acyl substitution reaction with diethylamine to yield the amide DEET. The crude product mixture was purified by flash chromatography with a 14.4% yield. This is a poor percent yield; however, analysis by IR, NMR, and GC/GC-MS all determine the identity of the purified product as DEET which confirms a clean reaction of starting material to product. Overall, carboxylic acid derivatives and their nucleophilic acyl substitution reactions have very useful applications in organic chemistry synthesis.

## References

1. McMurry, J; *Organic Chemistry*, 8th Ed; Brooks/Cole: Belmont CA, 2012: 814-855
2. Habeck, Jean C., Lamine Diop, and Michael Dickman. "Synthesis of N,N-Diethyl-3-methylbenzamide (DEET): Two Ways to the Same Goal." *Journal of Chemical Education* 87.5 (2010): 528-29. Web. 22 Apr. 2014.
3. Dsikosizky, L, Dwiyitno, E Heruwati, F Ariyani, and H E. Irianto. "Exceptionally high concentrations of the insect repellent N,N-diethyl-m-toluamide (DEET) in surface waters from Jakarta, Indonesia." *Environmetal Chemistry Letter* (2014): 18 pars. Web. 24 Apr. 2014.
4. Knoess, Peter, and Edward G. Neeland. "A Modified Synthesis of the Insect Repellant DEET." *Journal of Chemical Education* 75.10 (1998): 1267. Web. 24 Apr. 2014.
5. *N,N-diethyl-3-methyl-Benzamide*. AIST: Integrated Spectral Database System of Organic Compounds, Japan. Web. 24 Apr. 2014.