Discovery and Optimization of the Acylation-Insertion Reaction

Luke Henningsen
Senior Thesis, Spring 2015
Department of Chemistry
Ripon College

ABSTRACT

Phthalimides can easily be converted into primary amines, which are useful in a wide variety of laboratory and industrial applications. A new reaction has been discovered which allows for the synthesis of *N*-phthalimido-*O*-acyl-*N*,*O*-acetals from acyl phthalimides and aldehydes. These products can undergo hydrazinolysis to become useful primary amines. In addition, it is possible to combine the reaction with the synthesis of the participating acyl phthalimides, resulting in a one-pot synthesis of *N*-phthalimido-*O*-acyl-*N*,*O*-acetals from an acid chloride, phthalimide salt, and aldehyde.

Previous research showed that a metal Lewis acid and a tertiary amine were required for the reaction to take place. The optimal conditions included at least 10 mole percent $LiBF_4$ and acetonitrile as the solvent. The reaction proceeds to 99% completion in less than 1 hour. Early mechanistic experiments show that the acyl group and phthalimide group completely dissociate to facilitate the insertion of the aldehyde.

INTRODUCTION

Amines are among the most common and useful functional families in organic chemistry. They are incredibly important in biological systems; they are an important structural component of the amino acids that make up proteins, and they are found in many neurotransmitters.[1-2] They are also found in almost all pharmaceuticals and have widespread uses in agriculture, laboratory work, and even the food industry. Large, complex amines are often biologically active, and stereoselectivity commonly influences the activity of the compounds.[3] Therefore, the stereoselective synthesis of complex amines is an important type of reaction in organic chemistry.

One example of a useful family of complex amines is aryl amines. This particular family can be a precursor to compounds with uses that include myriad pharmaceutical functions (including antiviral, antibacterial, and anti-cancer properties) as well as usefulness as pesticides and laboratory reagents.[4] Currently, there are three main ways to synthesize complex aryl amines: the Ugi reaction, the Mannich reaction, and the Petasis-Modified Mannich reaction, which can be seen in Figure 1.[4-6] Unfortunately, each of these methods has the drawback of involving harsh reagents or conditions such as heat and strong

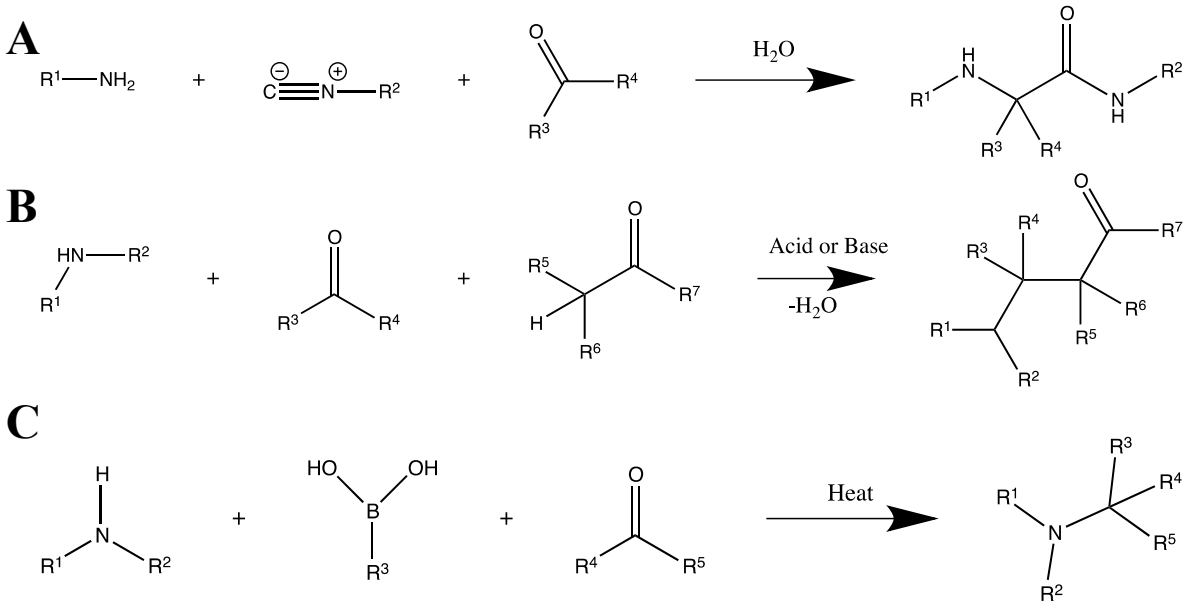


Figure 1. Current methods of complex amine synthesis: (A) The general Ugi reaction, (B) the general Mannich reaction, and (C) the general Petasis-modified Mannich reaction.

acids or bases. This can be detrimental if the target compound involves sensitive functional groups that may be damaged or destroyed by such conditions. It would thus be beneficial to develop a synthesis method that avoids this issue in order to create compounds that include sensitive functional groups.

One potential solution is to use phthalimides, the structure of which can be found in Figure 2, to synthesize these amines. Conveniently, phthalimides serve as an effective protecting group for primary

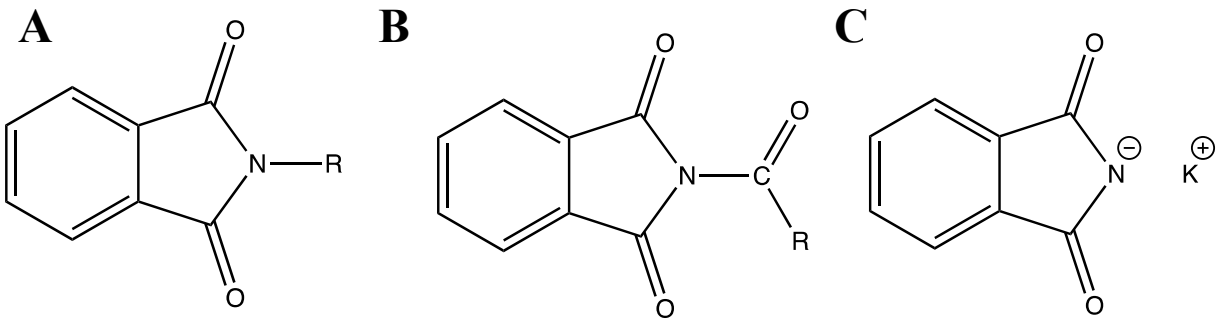


Figure 2. Examples of phthalimides: (A) general phthalimide structure, (B) acyl phthalmimide structure, and (C) potassium phthalimide, an example of a phthalimide salt.

amines.[7] Through a modified Gabriel synthesis, the rings of the phthalimide can be replaced by hydrogens. An example of this is hydrazinolysis, which can be seen in Figure 3.[8]

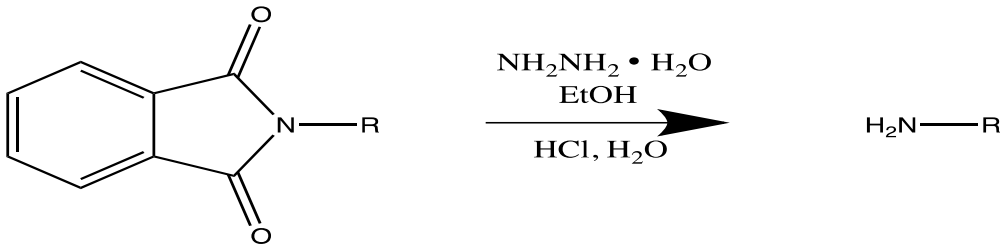


Figure 3. The general hydrazinolysis reaction, which can be used to convert acyl phthalimides into primary amines.

Phthalimides have a number of properties beyond their protective capabilities that make them appealing. Much of this stems from the chemical activity of the imide group, which is formed by the nitrogen surrounded by two carbonyl groups. Even more interesting are acyl phthalimides, which gain an additional imide group formed by the carbonyl on the acyl branch and either of the cyclic carbonyls. Research has been done which shows that the latter imide group has the ability to coordinate with Lewis

acids, as shown in Figure 4.[9] Here, the iminium ion created has a notable similarity to the enolate generated in an aldol reaction, so an aldol-like reaction was originally hypothesized.

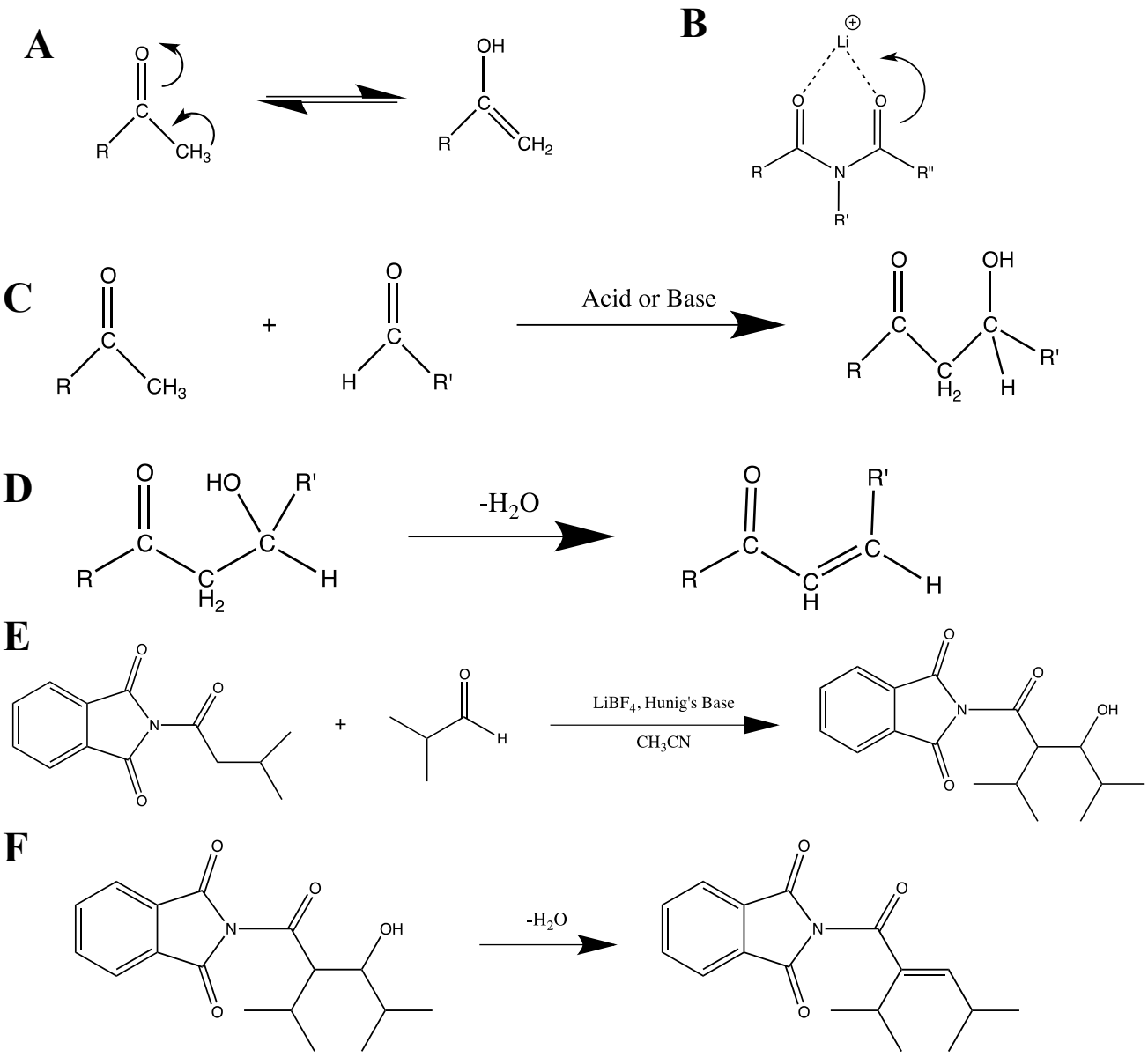


Figure 4. The formation of an enolate (A) is similar to the coordination of a metal Lewis base with an imide (B). The general aldol reaction (C) and the subsequent condensation that can result (D) were therefore hypothesized to have the same general scheme as the proposed reaction between an acyl phthalimide and aldehyde (E), which could then undergo condensation (F).

EXPERIMENTAL

Preparation of Acyl Phthalimides[10]

In a 50 mL round-bottomed flask, 1.14 g isovaleryl chloride and 1.68 g potassium phthalimide were dissolved in 10 mL dichloromethane. The starting materials and solvent were all purchased commercially. The reaction vessel was sealed with a septum, which was then pierced with a needle to allow airflow between the vessel and the environment. The reaction mixture was allowed to stir overnight at room temperature. The solid was removed via gravity filtration, and a rotary evaporator was used to remove the solvent from the remaining solution. ^{1}HNMR analysis was used to determine whether the product was isovaleryl phthalimide.

The experiment was repeated with different acid chlorides. Acetyl chloride was used for the preparation of acetyl phthalimide, and phenylacetyl chloride was used for phenylacetyl phthalimide.

Preparation of N-*phthalimido*-O-*acyl*-N,O-*acetals*

In a 2 mL storage vial, 144 mg isobuteraldehyde and 100 mg isovaleryl phthalimide from the above procedure were dissolved in enough acetonitrile to give 0.5 M with respect to the phthalimide. To this reaction mixure were added 2 equivalents *N,N*-diisopropylethylamine and 0.5 equivalents $LiBF_4$, again with respect to the phalimide. All compounds other than the isovaleryl phthalimide were purchased commercially. The reaction mixture was capped and allowed to stir overnight at room temperature, then was filtered through silica gel. The solvent from the filtrate was removed using a rotary evaporator and an ^{1}HNMR spectrum of the product was obtained. The experiment was repeated with numerous aldehydes and acyl phthalimides to determine the scope of the reaction. This reaction was also used as a template for a number of optimization experiments, with alterations to the identity and relative amounts of the reagents as follows.

Characterization of Novel N-*phthalimido*-O-*acyl*-N,O-*acetals*

Various aldehydes and acyl phthalimides were used to perform the *N*-phthalimido-*O*-acyl-*N,O*-acetal synthesis described above. Gel chromatography was performed using a silica gel flash column and 20%-50% ethanol in acetonitrile, then a rotary evaporator was used to drive off the solvent. The resulting acyl phthalimides were characterized using ^{1}HNMR, ^{13}CNMR, infrared spectroscopy, and gas chromatography/mass spectroscopy.

Optimization of N-*phthalimido*-O-*acyl*-N,O-*acetal synthesis*

The *N*-phthalimido-*O*-acyl-*N,O*-acetal synthesis described above was repeated with 50, 10, and 1 mole percent $LiBF_4$ with respect to the acyl phthalimide. It was also run with the original reagent ratios, but with dimethylsulfoxide and tetrahydrofuran as solvents. The completion time of the reaction was tested by performing the original procedure, then taking an aliquot at 15 minutes, 1 hour, and 3 hours. In each case, TLC and ^{1}HNMR data were used to determine the success and approximate yield of the reaction.

Preparation of 4-methyl-N-*isovalerylphthalimide*

In a 100 mL round-bottomed flask, 500 mg 4-methylphthalimide was dissolved with 340 mg isovaleryl chloride in enough dichloromethane to give a 1.0 M solution with respect to the isovaleryl chloride. The reaction vessel was placed in an ice bath and 1.5 equivalents of triethyl amine were added. The vessel was covered with a septum and allowed to stir for 30 minutes. The vessel was then removed from the ice bath, the septum was pierced with a needle, and the reaction mixture was allowed to stir overnight.

The next day, the mixture was diluted in about 10 mL ethyl acetate. The solution was transferred to a seperatory funnel, where 10 mL 1.0 M NH_4Cl was added. The bottom layer was discarded, and the step was repeated with a saturated solution of NaCl. After the bottom layer was again discarded, the remaining solution was dried with a spatula tip of magnesium sulfate. Once dried, the solution was

transferred to a silica gel flash column, where gel chromatography was performed using a 30-50% gradient of ethanol in acetonitrile. The solvent was removed using a rotary evaporator, and an ^{1}HNMR spectrum of the product was obtained.

Double Label Experiment

In a 2 mL storage vial, 50 mg phenylacetyl phthalimide, prepared as described above, was dissolved to 0.5 M in acetonitrile with one equivalent of the 4-methyl-*N*-isovalerylphthalimide synthesized in the last procedure and 1.5 equivalents isobuteraldehyde. To the solution were added one equivalent of $LiBF_4$ and 4.0 equivalents of diisopropylethylamine. The reaction mixture was capped and allowed to stir overnight at room temperature. A silica gel flash column was used to perform gel chromatography with a 30-50% gradient of ethanol in acetonitrile, after which the solvent was removed with a rotary evaporator. An ^{1}HNMR spectrum and LC-MS analysis were obtained and examined to identify the number and identity of resulting products.

RESULTS

N-*phthalimido*-O-*acyl*-N,O-*acetal synthesis*

The initial reaction of isobuteraldehyde and isovaleryl phthalimide yielded the ^{1}HNMR spectrum shown in Figure 5. Similar reactions with various acyl phthalimides and aldehydes yielded the results listed in Table 1**.**

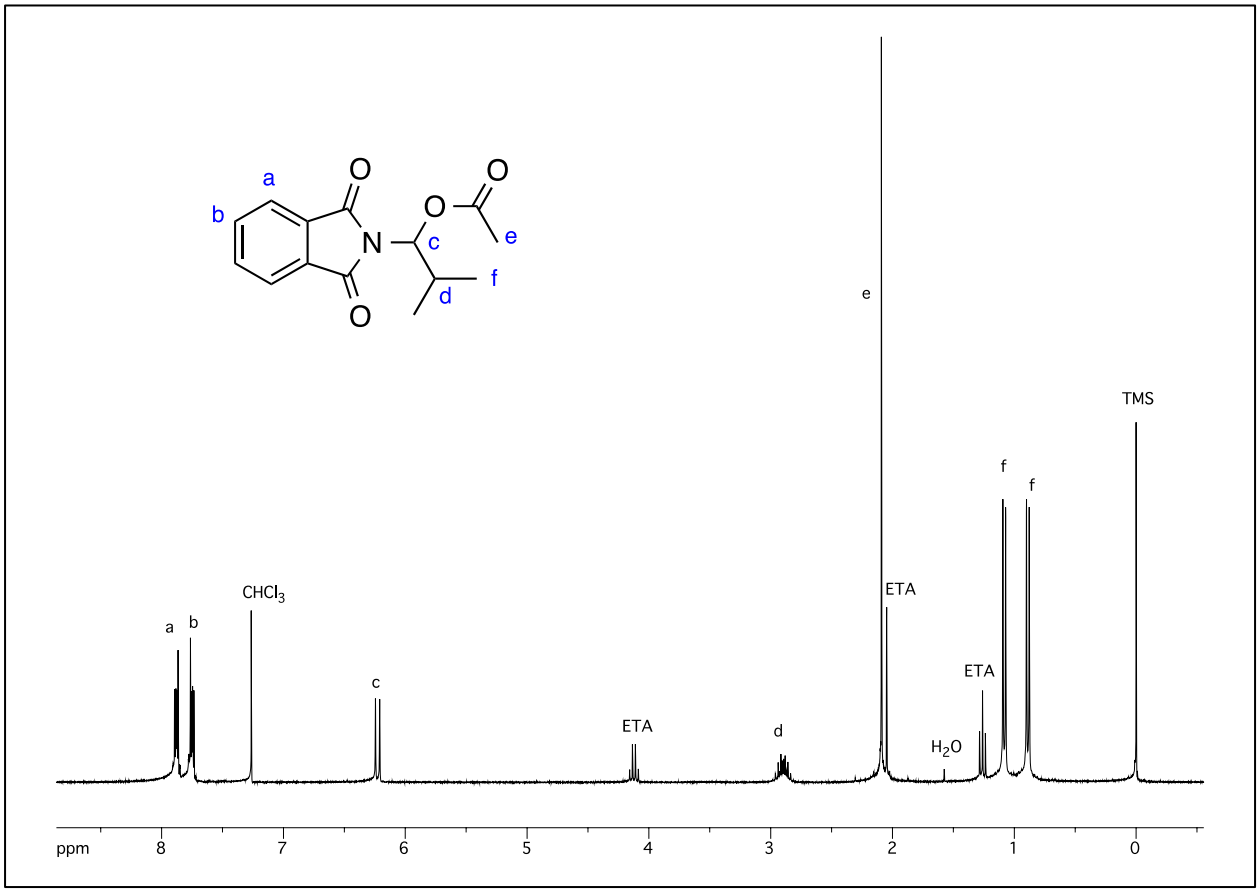


Figure 5. ^{1}HNMR spectrum of the product of isobuteraldehyde and isovaleryl phthalimide. Non-product peaks are labelled.

Table 1. Results of acyl phthalimide + aldehyde reactions. Success was determined by examining the ^{1}HNMR spectrum for evidence of starting material and product

Phthalimide	Aldehyde	Success?
Acetyl	Isobutyraldehyde	Yes
Acetyl	Isovaleraldehyde	Yes
Phenylacetyl	Isovaleraldehyde	Yes
Acetyl	Citronellal	Yes
Acetyl	Acetaldehyde	Yes
Acetyl	p-Anisaldehyde	No
Acetyl	p-Tolualdehyde	No
Acetyl	Dimethylformamide	No
Acetyl	Acetophenone	No

Optimization Results

Analysis by TLC and ^{1}HNMR showed that full conversion was obtained with 50 mole percent $LiBF_4$. Evidence of conversion was found at 10 mole percent of $LiBF_4$, but full conversion was not as obvious as with 50 percent. No evidence of conversion was found at one mole percent $LiBF_4$.

Analysis by ^{1}HNMR was also used to determine reaction completion in the time experiment. It was found that starting material was present after 15 minutes, but had been consumed by the reaction by the 1 hour point.

In the solvent experiments, acetonitrile was found to have the best conversion rate by ^{1}HNMR analysis. The reaction mixture, however, was heterogeneous upon the addition of Hunig's base. Homogeneity was achieved when the reaction mixture was heated slightly, but conversion rates were decreased. The reaction mixture was clearly heterogeneous in THF. In DMF, homogeneity was achieved, but no reaction was detected by ^{1}HNMR analysis.

Double Label Results

The double label experiment yielded the ^{1}HNMR spectrum and LC-MS data shown in Figure 6**.** The composition of each LC-MS peak can be found in Appendix A. The main m/z value of each peak has been overlaid on Figure 6 for convenience.

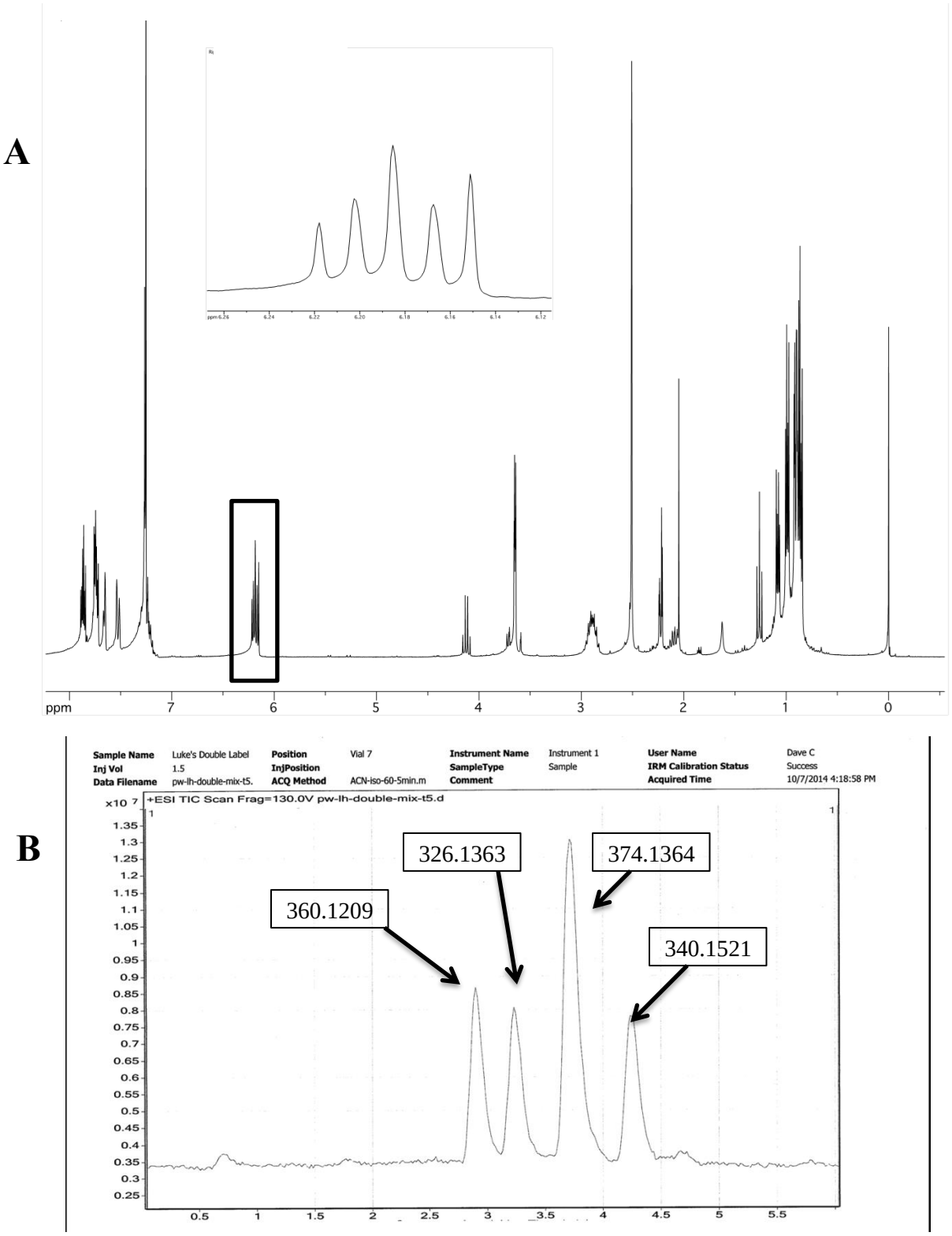


Figure 6. [1]HNMR spectrum with inset of 6.2 multiplet (A**)** and LC-MS analysis (B) of double label products with overlaid m/z values.

DISCUSSION

Scope

Though the peaks of the ^{1}HNMR shown in Figure 5 clearly match up with the hydrogens of the labelled compound overlaid on the image, it was actually very difficult to determine the identity of the compound based on the spectrum alone. In fact, spectra taken before the compound was purified were assumed to show the expected aldol condensation product. The spectrum is close to what would be expected of this compound, but the mass of the compound matched the pre-condensation aldol product. After my purification, it was clear that the minor differences between this spectrum and the expected aldol product spectrum were due to a different chemical structure as opposed to impurities, which explained the discrepancy between the expected spectrum and mass. It became apparent that the aldehyde was not being added to the end of the acyl branch, but was rather being inserted between the acyl and the phthalimide group. When the actual product was hypothesized, my results were compared to the known spectral data of this compound[9] and my compound was confirmed to be the proposed product. The reaction scheme was thus revised from the aldol-like proposed reaction to the reaction shown in Figure 7.

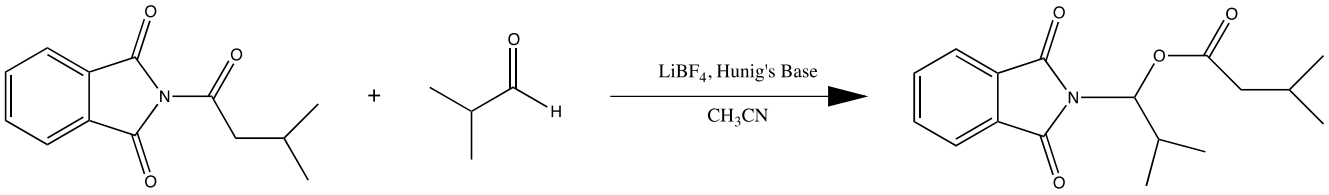


Figure 7. Experimentally determined reaction scheme of the acylation-insertion reaction.

Having recognized the existence of what was named the acylation-insertion reaction, the focus shifted to determining what compounds could participate. Since previous experimentation suggested that all three of our acyl phthalimides behaved similarly, most of my scope experiments used acetyl phthalimide and focused on examining the reactivity of the aldehydes.

As expected, aldehydes with simple, branched alkyl groups and α-hydrogens reacted very successfully. Even the long, unsaturated citronellal was able to react well with acetyl phthalimide. Aryl aldehydes had notably less success. Both of my aromatic aldehydes were unsuccessful, which suggests that α-hydrogens play an important part in this reaction. It should be noted that later research under the direction of Patrick Willoughby showed that benzaldehyde was able to participate in the reaction, so α-hydrogens are not essential; however, the benzaldehyde reaction was considerable slower, so this position does play a major part in the reaction's success.

Optimization

None of my optimization experiments prompted any major changes to the experimental setup. Acetonitrile continued to be the preferred solvent, and for the sake of maximizing yields, 50 mole percent $LiBF_4$ was used, though further experimentation revealed that the solid form of the compound worked just as well and was more efficient than the aqueous form used in my initial experiments. The most useful finding came from the time experiment. Since the reaction was proceeding to completion within an hour, it could be set up and completed the same day rather than overnight. This saved a considerable amount of time.

Mechanism

The double label experiment was perhaps the most impactful of all. The main question that the experiment sought to answer was whether the acyl branch ever completely dissociated from the phthalimide group. A visual representation of the possible products and their mechanistic implication is shown in Figure 8.

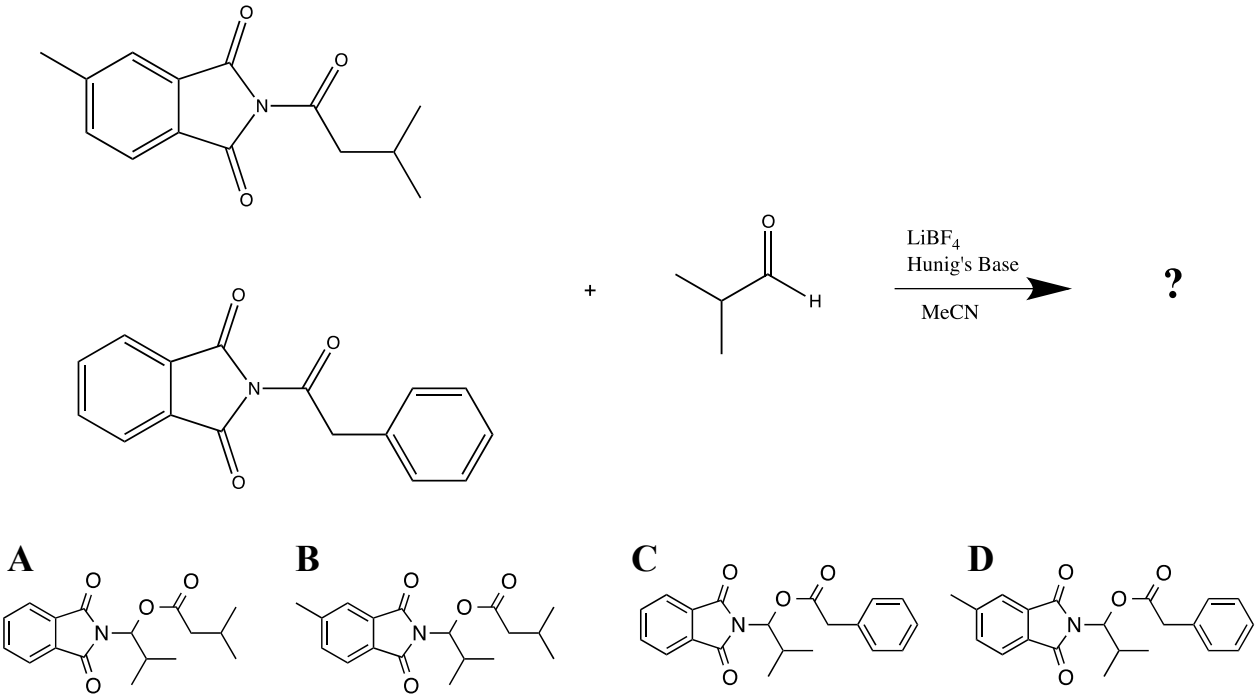


Figure 8. The double label experiment and its possible products. If the acyl branch and phthalimide do not completely dissociate, then the 4-methylphthalimide will always stay with the isovaleryl branch and the regular phthalimide will stay with the phenylacetyl branch, resulting in only products (B) and (C). If the groups completely dissociate, however, than either phthalimide could end up with either acyl branch, resulting in all four products.

The biggest challenge with this experiment was determining how to distinguish between the phthalimide groups. Being able to do so is essential to identify the individual products. At first, deuterium was used in an attempt to label one of the phthalimides. Despite multiple experimental setups, there was no indication of deuterium incorporation in any products. The next option was to attach a functional group to the phthalimide. Though this is easier since such compounds are available commercially, there was concern over whether this would change the reactivity and behavior of the compound.

Two substituated phthalimides were synthesized, and one was ultimately used for the double label experiment. The first was 3-nitrophthalimide. After a few tries, there was evidence of a successful reaction, but there was difficulty with this synthesis and with the subsequent acylation-insertion reaction. The compound was deemed unfit for this reaction. There was considerably more success with 4-methylphthalimide. Analysis by ^{1}HNMR showed evidence of conversion to the product that would be

expected from an unsubstituated phthalimide, albeit with the added aromatic methyl group, when 4-methylphthalimide was reacted with an aldehyde. More importantly, this was demonstrated with isovaleraldehyde, though the reaction occurs slightly slower than with an unsubstituated acyl phthalimide. The decision was made to proceed with the double label experiment using an acyl 4-methylphthalimide as one of our starting materials.

At first, the experiment was inconclusive. At the time, the only suitable instrument to which we had access was the ^{1}HNMR. Theoretically, a very pure sample and a very high resolution NMR could be used to determine whether two or four products were obtained, and possibly even to confirm their identity. This would be done by inspecting the peaks around 6.2 ppm. Each product should produce a doublet in this region that is slightly different than any of the others. As can be seen in the inlay of Figure 6A, however, this region was cluttered with unidentifiable peaks. It was impossible to tell the number of products, let alone confirm their identities.

Later, Ripon College obtained an LC-MS. The results from my sample, shown in Figure 6B and Appendix A, were outstanding. The graph showed four distinct peaks, immediately suggesting full dissociation of the starting materials' functional groups. The MS data confirmed well above acceptable levels that each of the peaks corresponded to one of our expected products, further confirming our hypothesis. This result was mechanistically significant and was helpful in directing further mechanistic experimentation.

Practical Application of the Acylation-Insertion Reaction

Though the discovery of a new reaction is inherently exciting, not all are particularly useful. In this case, that is a concern; acyl phthalimides are hardly in high demand as an end product. They can, however, serve as a precursor to more significant compounds, making them suddenly very useful. An example of this is given in Figure 9, where the acylation-insertion reaction synthesizes a precursor in the known reaction for the synthesis of citrazine dihydrochloride.[11]

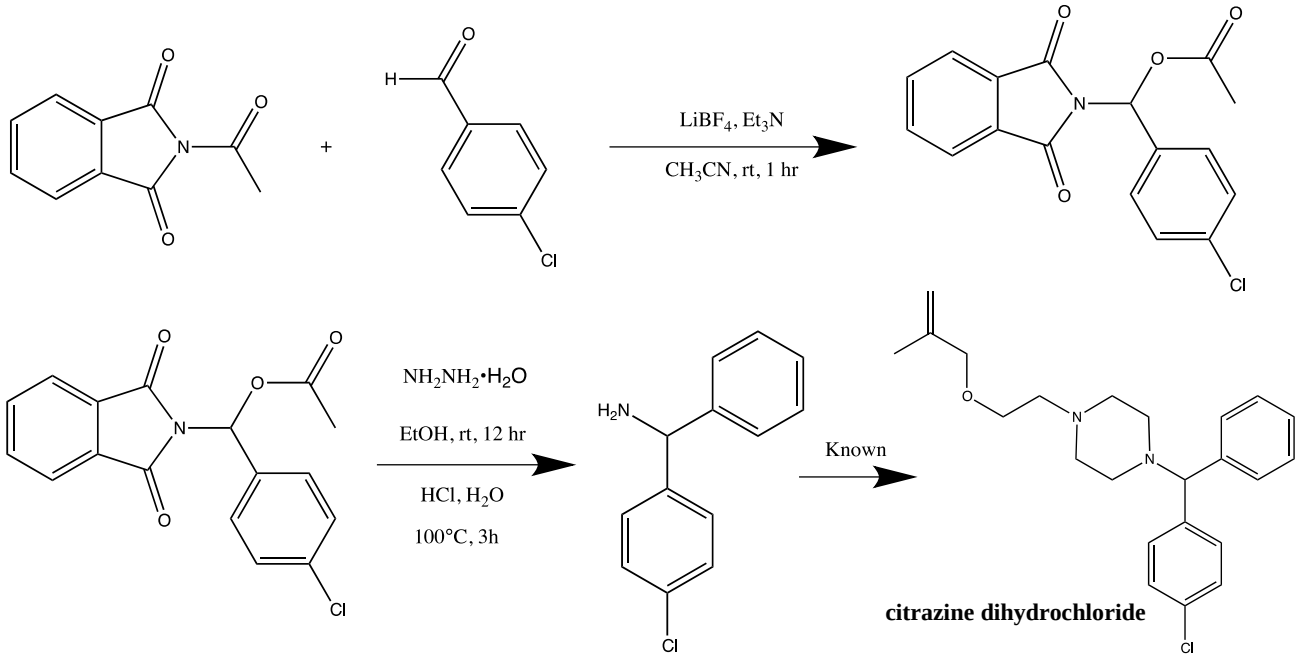


Figure 9. Synthesis of citrazine dihydrochloride, using the acylation-insertion reaction to generate the precursor. The reaction has been successfully performed up to the known synthesis reaction of the final product.

Similar reactions have been hypothesized and consequently tested in the synthesis of the β-3 adrenergic agonist BMS-196085 and the monoamine oxidase inhibitor Rasagiline, which is used to treat early onset Parkinson's disease.[12] In both cases, the precursor necessary for the known reaction has been successfully synthesized using the acylation-insertion reaction.

Future Research

Since this is an ongoing research project, much progress has been made since the end of my participation. One major discovery was that the reaction used to synthesize our acyl phthalimides could be combined with the novel reaction for a one-pot synthesis under the conditions shown in Figure 10.

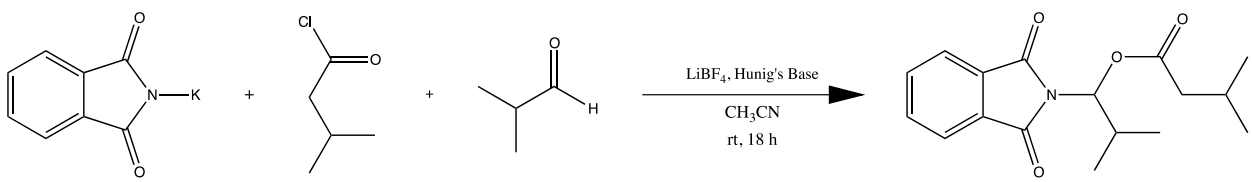


Figure 10. One-pot synthesis of acylation-insertion product from starting phthalimide salt, acid chloride, and aldehyde.

Having a one-pot homogeneous synthesis makes the reaction considerably more useful as it saves time and resources by eliminating the need to purchase or synthesize the more complicated reactants in the acylation-insertion reaction.

Other research has given far more insight into the mechanism of the reaction. Continuing to explore the mechanism and scope of the reaction will likely be the most high-yield experiments in the near future, as well as exploring other possible useful compounds that use acylation insertion products as a precursor.

CONCLUSION

The acylation-insertion reaction is a promising new reaction that can quickly and efficiently synthesize *N*-phthalimido-*O*-acyl-*N,O*-acetals. These compounds can then be converted into primary amines, which can be precursors to useful, biologically active compounds. Advances such as the one-pot synthesis of the final product continue to make the reaction more appealing, and the current optimization of conditions provides very satisfactory yields. Future experimentation should continue to expand our understanding of the mechanism and scope of the experiment.

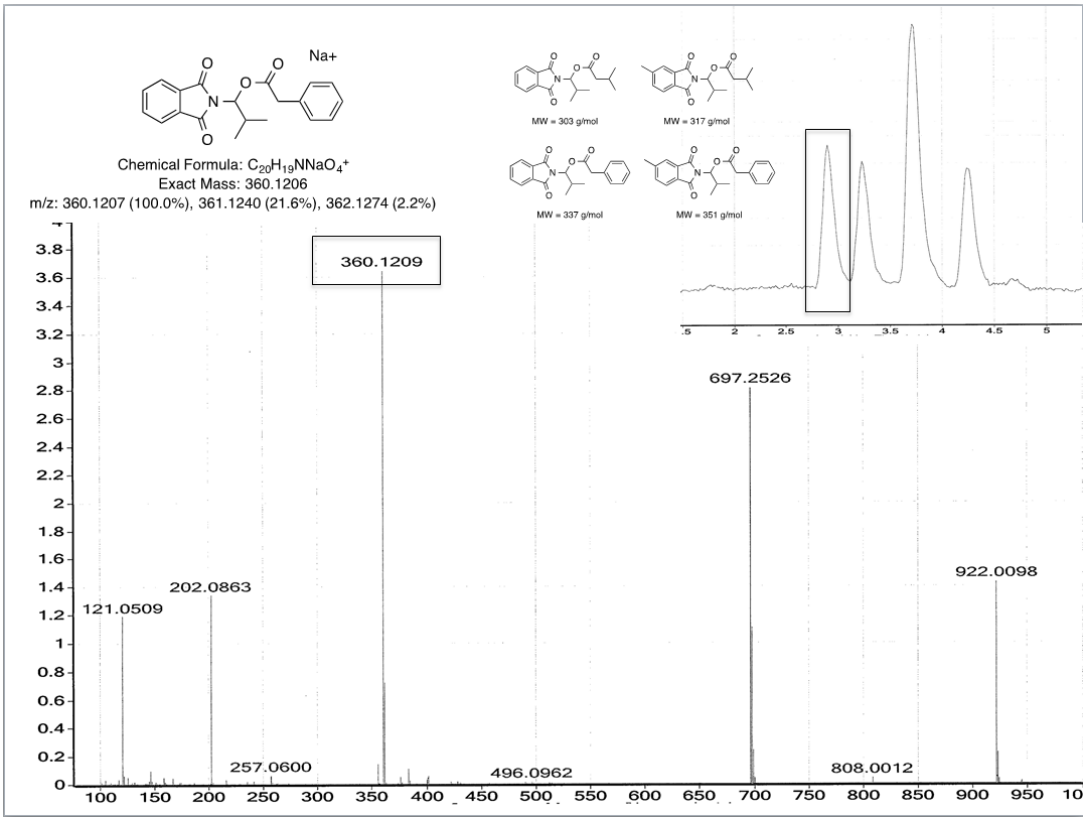
ACKNOWLEDGMENTS

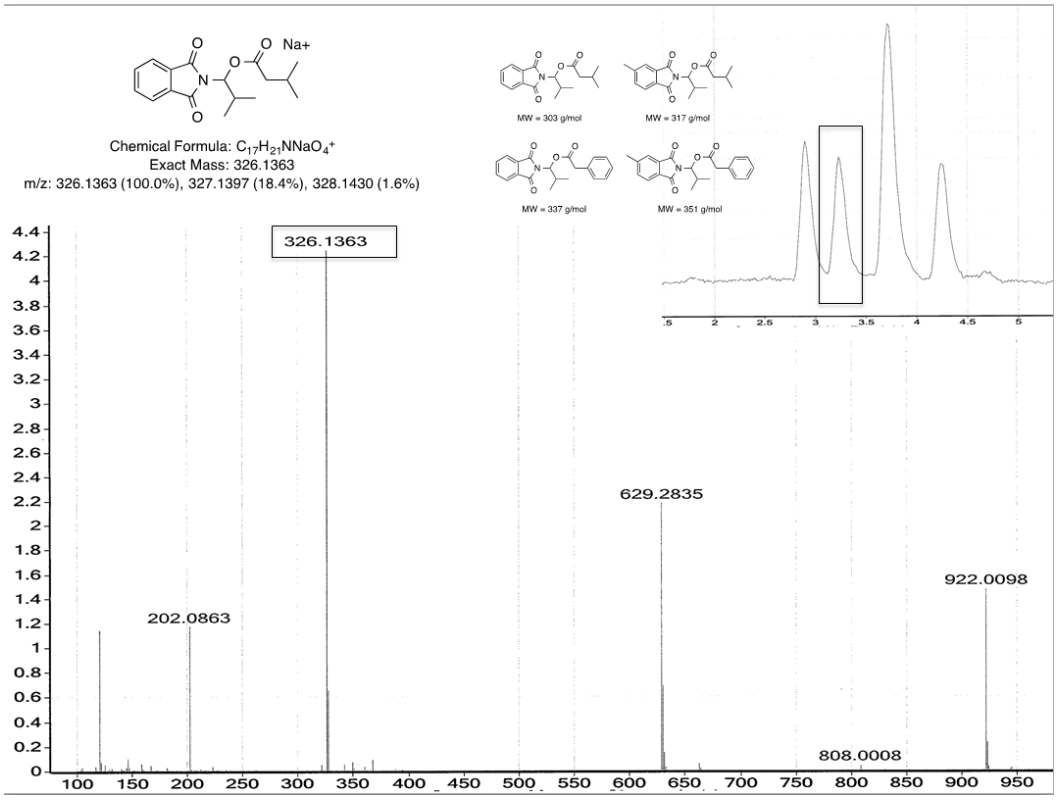
This research was performed in the laboratory of Dr. Patrick Willoughby at Ripon College during the summer of 2014. Support and guidance was provided by the entire Ripon College Chemistry Department. Funding for the project was provided by American Chemical Society Petroleum Research Foundation and National Science Foundation: Major Research Instrumentation (CHE-1429616) grants, and my participation in the project was funded by the Ripon College Knop Scholarship.

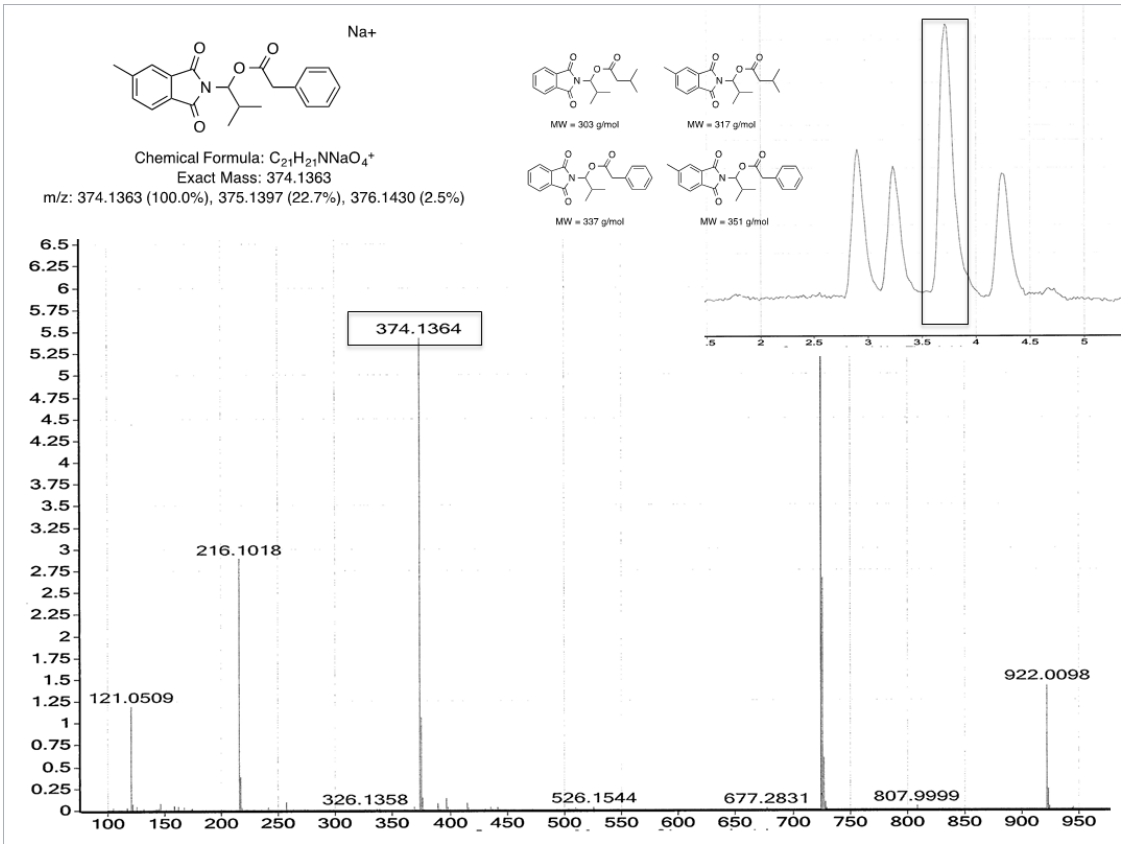
REFERENCES

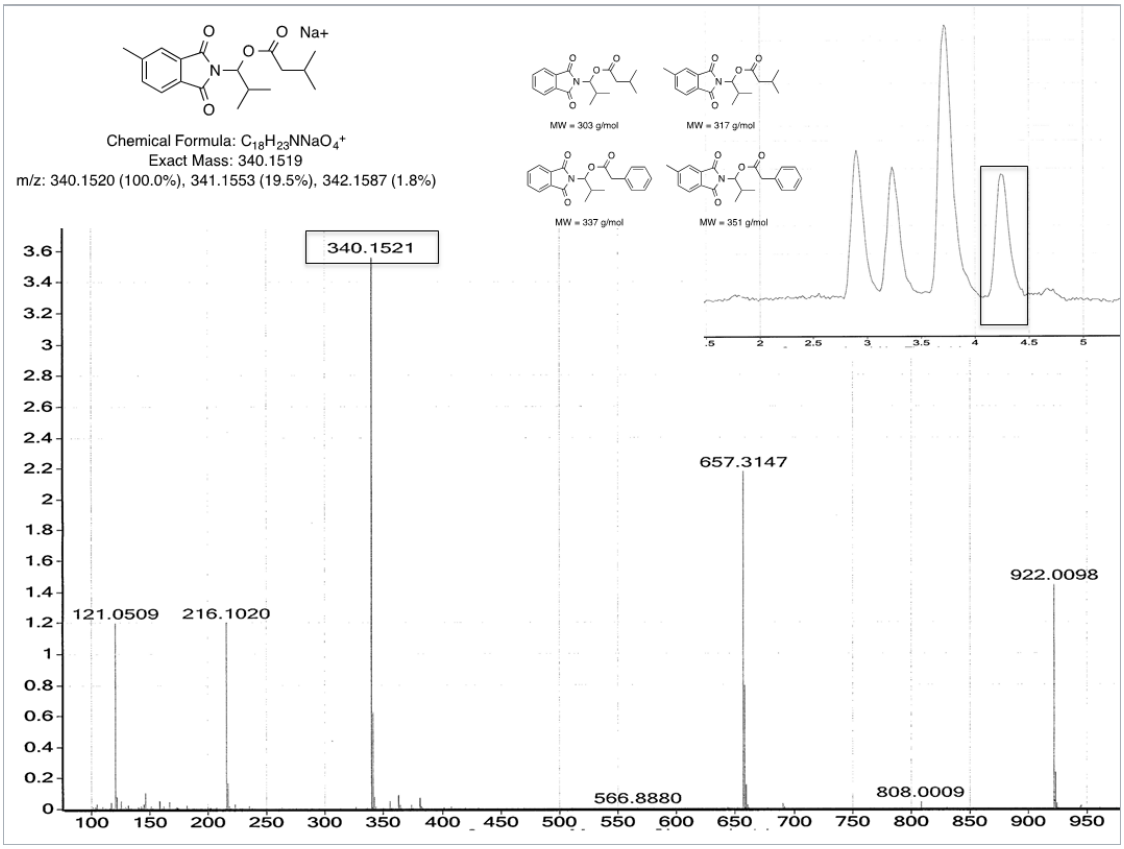
1. Dill, K. A. Dominant Forces in Protein Folding. *Biochemistry* **1990**, *29*, 7133-7155.
2. McMurry, J. Fundamentals of Organic Chemistry, Seventh Edition; Brooks/Cole Cengage Learning: Belmont, 2011; p 308.
3. Williams, R. M. *Synthesis of Optically Active α-Amino Acids*. Baldwin, J. E., Magnus, P. D., Eds.; Organic Chemistry Series; Pergamon: New York, 1989; Vol. 7, pp ix-x.
4. Bala, S.; Sharma, N.; Kajal, A.; Kamboj, S.; Saini, V. Mannich bases: an important pharmacophore in present scenario. *Int. J. Med. Chem.* **2014**, 2014, 191072.
5. Ugi, I. The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem., Int. Ed.* **1962**, *1*, 1-64.
6. Petasis, N. A.; Zavialov, I. A. A New and Practical Synthesis of α-Amino Acids from Alkenyl Boronic Acids. *J. Am. Chem. Soc.* **1997**, *119* , 445-446.
7. Greene, Theodora W. *Protective Groups in Organic Synthesis*, John Wiley & Sons: New York, 1981; p 265.
8. Weiner, B.; Baeza, A.; Jerphagnon, T.; Feringa, B. L. Aldehyde Selective Wacker Oxidations of Phthalimide Protected Allylic Amines: A New Catalytic Route to β3-Amino Acids. *J. Am. Chem. Soc.* **2009**, *131* , 9473-9474.
9. Renaud, P.; Stojanovic, A. Stereoselectivity of the reactions of N-phthaloyl iminium ions and amino-substituted radicals derived from threonine. *Tetrahedron Letters*, **1996**, *37*, 2569-2572.
10. Sheehan, J. C.; Bolhofer, W. A. An Improved Procedure for the Condensation of Potassium Phthalimide with Organic Halides. *J. Am. Chem. Soc.*, **1950**, *72*, pp 2786–2788.
11. Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. Asymmetric synthesis of cetirizine dihydrochloride. *Tetrahedron Letters* **2002**, *43*, 923-926
12. Gavai, A.V.; Sher, P. M.; Mikkilineni, A. B.; Poss, K. M.; McCann, PJ, Girotra, R. N.; Fisher, L. G.; Wu, G.; Bednarz, M. S,; Mathur, A.; Wang, T. C,; Sun, C.; Slusarchyk, D. A.; Skwish, S.; Allen, G. T.; Hillyer, D. E.; Frohlich, B. H,; Abboa-Offei, B. E.; Cap, M.; Waldron, T. L.; George, R. J.; Tesfamariam, B.; Harper, T. W.; Ciosek, C. P.Jr; Young, D. A.; Dickinson, K. E.; Seymour, A. A.; Arbeeny, C. M.; Washburn, W. N. BMS-196085: A potent and selective full agonist of the human β3 adrenergic receptor. *Bioorganic & Medical Chemistry Letters*, **2001**, 11, pp 3041–3044.

APPENDIX A


Na+
Chemical Formula: $C_{20}H_{19}NNaO_4^+$
Exact Mass: 360.1206
m/z: 360.1207 (100.0%), 361.1240 (21.6%), 362.1274 (2.2%)
MW = 303 g/mol
MW = 317 g/mol
MW = 337 g/mol
MW = 351 g/mol
360.1209
697.2526
922.0098
202.0863
121.0509
257.0600
496.0962
808.0012


Na+
Chemical Formula: $C_{17}H_{21}NNaO_4^+$
Exact Mass: 326.1363
m/z: 326.1363 (100.0%), 327.1397 (18.4%), 328.1430 (1.6%)
MW = 303 g/mol
MW = 317 g/mol
MW = 337 g/mol
MW = 351 g/mol
326.1363
629.2835
922.0098
202.0863
808.0008


Na+
Chemical Formula: $C_{21}H_{21}NNaO_4^+$
Exact Mass: 374.1363
m/z: 374.1363 (100.0%), 375.1397 (22.7%), 376.1430 (2.5%)
MW = 303 g/mol
MW = 317 g/mol
MW = 337 g/mol
MW = 351 g/mol
374.1364
216.1018
121.0509
326.1358
526.1544
677.2831
807.9999
922.0098


Na+
Chemical Formula: $C_{18}H_{23}NNaO_4^+$
Exact Mass: 340.1519
m/z: 340.1520 (100.0%), 341.1553 (19.5%), 342.1587 (1.8%)
MW = 303 g/mol
MW = 317 g/mol
MW = 337 g/mol
MW = 351 g/mol
340.1521
657.3147
922.0098
121.0509
216.1020
566.8880
808.0009