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# Azanyl carbamates: Synthesis, characterization and chemistry.

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# Azanyl carbamates: synthesis, characterization and chemistry

By

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# Tabulation of Figures

# Tabulation of Tables

# Tabulation of Schemes

# Abstract

Azanyl carbamates are an understudied, rarely reported class of compounds in the organic chemistry literature. The azanyl carbamate moiety contains both a carbamate and an amine functional group. As such, this class of compounds features a high ratio of heteroatoms (atoms that are not carbon or hydrogen) relative to carbon: a characteristic of many natural and synthetic organic catalysts.[1] Another reason we are particularly interested in azanyl carbamates is the fact that the amine is incorporated as an aminooxy group. An aminooxy group consists of an amine directly connected to an oxygen atom. The aminooxy group is of special interest to us because of its unusual electronic properties and selective reactivity toward molecules containing carbonyl groups (e.g., aldehydes and ketones).[2] For these reasons, we speculated that azanyl carbamate compounds might be used for unique and novel organic chemical transformations.

The present work on azanyl carbamates is best broken down into three categories: synthesis, application, and analysis.

The synthesis category involves the methodology and optimization we devised and employed to create two azanyl carbamate precursors, 1-(aminooxy)- *N*, *N*-dimethyl-1-oxomethanamine-Boc and *N*-((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine-Boc, and four new azanyl carabamte compounds, 1-(aminooxy)- *N*, *N*-dimethyl-1- oxomethanamine•HCl, *N*-((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine•HCl, 1-(aminooxy)- *N*, *N*-dimethyl-1-oxomethanamine•OTf, and *N*-((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine•OTf.

The application category focuses on experimental techniques and observations from reactions of 1-(aminooxy)- *N*, *N*-dimethyl-1- oxomethanamine•HCl and 1-(aminooxy)- *N*, *N*-dimethyl-1- oxomethanamine•OTf in transforming aldehydes to nitriles and in our use of *N*-

((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine•HCl and *N*-((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine•OTf to add amino-functionality to select molecules.

Lastly, the analysis category concerns our proposed explanation as to why our azanyl carbamates perform the transformations they do under certain conditions. This category has also been bolstered by collaboration with Prof. Lee Thompson and his research group at the University of Louisville, who provided a computational chemistry perspective.

Overall, the studies and analyses described below demonstrate that it is possible to synthesize new azanyl carbamates in a straightforward and efficient manner and that these compounds can be effective in facilitating, at minimum, two organic transformations that have been traditionally difficult to accomplish under mild conditions. In a broader scope, these studies and analyses further confirm the notion that heteroatom rich molecules have strong potential to act as catalysts.

## Lay Summary

Modern organic chemistry is a field that is constantly evolving in its methods and technology. From the evolution of simple substitution and elimination reactions to complex named reactions as well as the progression from simple chromatograms to more sophisticated Nuclear Magnetic Resonance (NMR) spectroscopy and tandem Gas Chromatography-Mass Spectrometry (GC-MS), organic chemists all over the world are now capable of performing analyses that past pioneers in the field could not even have fathomed. However, a few fundamental goals have remained constant through this growth and evolution: chemists continue to seek the ability to easily transform molecules into target compounds and to conduct these transformations in a way that is both time and cost effective.

Our work focused on an understudied class of compounds to help achieve this goal: azanyl carbamates. Figure 1 is a structural representation of an azanyl carbamate, which is composed of both a carbamate (dotted outline) and an amine functional group. Additionally, when an amine is directly connected to an oxygen, as in the structure below (solid outline), the functionality is termed an aminooxy group.

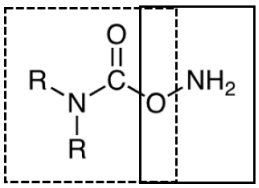



**Figure 1.** Generic depiction of an azanyl carbamate. R represents the non-reactive rest of the molecule.

This functionality is interesting as it is rare to see organic compounds with four heteroatoms (i.e., atoms that are not carbon and hydrogen), as most compounds only feature one to three. It is also rare to see compounds with such high levels of reactive potential, created by

the reactive carbamate and aminooxy groups on each end of the molecule, without being chemically unstable.

Our experiments were centered on two azanyl carbamate compounds and their ability to facilitate two traditionally difficult chemical reactions: aldehyde-to-nitrile conversions and electrophilic amination (Figure 2). Aminooxy reagents in the literature have previously been shown to facilitate these reactions; however, the known reagents required heating, additives, or radical chemistry (reactive and dangerous unpaired electrons) to work properly.[2-7]

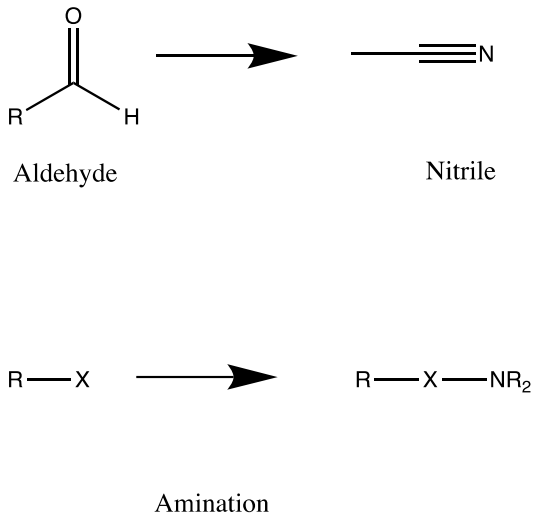



**Figure 2.** General depiction of aldehyde-to-nitrile conversion and electrophilic amination. X can represent any heteroatom.

The results from our experiments revealed that our two prototype azanyl carbamate reagents, for which we use the acronyms ADOM and EVE, successfully facilitated aldehyde to nitrile conversions and amination respectively. Additionally, these azanyl carbamates facilitated these two reactions with minimal to no additions of metal, base, acid, or radical initiators, at room or iced temperatures, and in a time efficient a relatively hands-off manner. These results

could have major implications as the formed chemical types, nitriles and aminated species, are often used in pharmaceuticals, chemical industry, and even rocket fuel.[8, 9]

Further studies on these compounds are needed to more fully assess their scope and mechanism of facilitation.

# Introduction

In the field of Organic Chemistry, many investigations have an objective of inventing or improving synthetic methods to maximize efficiency in the production of new organic materials. This is often done by devising reagents that achieve timely chemical conversions with high atom efficiency for sustainability reasons as well as to obtain good product yields under mild conditions of temperature, pressure, and concentration.

After parsing the literature, we hypothesized that azanyl carbamates might be promising candidates for performing certain nitrogen transfer reactions under milder conditions than traditional routes. Azanyl carbamates are composed of both a carbamate and an amine functional group. Figure 1 displays this outline in the unsubstituted form. Additionally, when an amine is directly connected to an oxygen, as in the structure below, the functionality is termed an aminooxy group.

Azanyl carbamates are a minimally explored functional group; however, their functionality and structure resemble other classes of compounds that have been more explored. Specifically, the heteroatom richness of these compounds (i.e., atoms that are not carbon and hydrogen) is a characteristic shared by known natural and synthetic organocatalysts. For example, a recent review of organocatalysts by Xiang *et al.* describes *N*-acetyl-L-phenylalanine, which features six heteroatoms, and its use to merge organocatalysis and photocatalysis principles for intermolecular decarboxylative cross-coupling.[1]

To explore our hypothesis on azanyl carbamates we synthesized two compounds using the methodology of Ibaraki *et al.*: 1-(aminooxy)- *N, N*-dimethyl-1- oxomethanamine, that we abbreviate as ADOM, and *N*-((aminooxy)carbonyl)-*N*-isopropylpropan-2- amine, that for

convenience we call EVE (prepared as the second azanyl carbamate example).[10] These compounds feature both electrophilic sites (the site of a molecule that accepts electrons to form a bond with its reaction partner) and nucleophilic sites (the site of a molecule that donates electrons to form a bond with its reaction partner). For example, amino-nitrogens are typically nucleophilic, but because the attached carbamoyloxy group is electron-withdrawing, which confers leaving group ability to the amine, the amino-nitrogen in this case is also electrophilic. This leads to the critical question: *in what context do these new reagents react, nucleophilically or electrophilically?* This question is of utmost importance in relation to our hypothesis as nucleophilic and electrophilic behavior are some of the most important factors in catalytic reactivity.

We have been able to explore our critical question with respect to ADOM and EVE in two major applications: transformation of aldehydes to nitriles and amination of amines. Both of these applications are traditionally time and energy inefficient nitrogen transfer reactions; however, in the first application, the amine must first behave as a nucleophile and in the latter case, the amine acts as an electrophile. We have also collaborated with a computational team to gain an understanding of how ADOM "behaves" in theoretical models to lend extra support to our experimental work. Lastly, in an effort to optimize conditions for aldehyde to nitrile conversions, we have evaluated a panel of solvents for their effects on the formation of reaction intermediates and products.

# Background

While azanyl carbamates have not been thoroughly explored and few examples are reported in organic chemistry literature, there has been in-depth reporting on the reactivity of the aminooxy functional group. The most common reaction involving aminooxy compounds is condensation with a carbonyl functional group to form what is known as an oxime ether (Figure 3).[11]

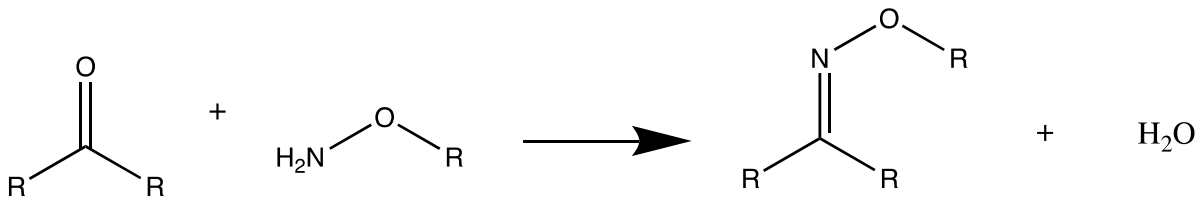
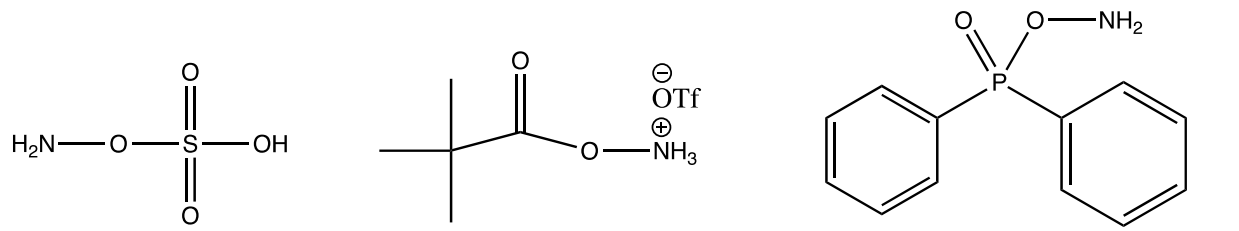



**Figure 3.** Oximation is the reaction between a carbonyl of an aldehyde or ketone with an aminooxy group to form an oxime ether and water.

However, it has been noted in the literature that different functionality around the aminooxy group can have a great impact on reactivity and behavior of the group. For example, Morales *et al*. observed that when an aminooxy group was adjacent to a pi electron system the nucleophilicity of the terminal amine was greatly reduced.[12] This is significant as nucleophilic attack is the mechanism of the traditional carbonyl-aminooxy conjugation outlined above.

The findings by Morales *et al*. opened the door to understanding and using more varied functionality around aminooxy groups to achieve novel transformations beyond oxime forming reactions. Figure 4 outlines a few more aminooxy compounds with varied surrounding functionality. These examples were compiled by Sabir *et al*. in a review article on aminooxy compounds.[2]




Hydroxylamine-O-sulfonic acid PivONH$_3$·OTF O-(diphenylphosphinyl)hydroxylamine

**Figure 4.** Examples of functionalized aminooxy compounds, as compiled by Sabir *et al*. Piv = $(CH_3)_3CCO_2$.

Aminooxy compounds have been previously used to facilitate the two transformations we were interested in: aldehyde to nitrile conversion and amination (the addition of a nitrogen functional group).

Quinn *et al*., An *et al*., Wallace *et al*., and Sabir *et al*. have all done or compiled work on the transformation of aldehydes to nitriles using aminooxy reagents as the nitrogen source. Quinn *et al*. were successfully able to form nitriles with an array of aldehydes at up to 95% yield using hydroxylamine-*O*-sulfonic acid (HOSA) as the nitrogen source for reactions in acidic water heated to 50 °C. [3]An *et al*. reported using an *O*-benzoyl hydroxylamine (BHA) as the nitrogen source to yield nitriles from various aldehydes at up to 94% in dimethoxymethane heated to 80 °C with frifluoracetic acid and frifluoromethyl radical initiator added.[4] Wallace *et al*. reported using HOSA as the nitrogen source to convert aromatic aldehydes to nitriles at 76% yield in water chilled to 5 °C with sodium bicarbonate and sodium hydroxide added.[5] Lastly, Sabir *et al.* outlined work by Laulhe *et al.* on *O*-(diphenylphosphinyl)hydroxylamine (DPPH) (Figure 5), *O*-(4-$CF_3$-benzyl)hydroxylamine, and HOSA as nitrogen sources that again converted a variety of aldehydes to nitriles at yields up to 96%, 91%, and 97% respectively.[2, 13] These reagents required heating, hydronium ($H_3O^+$), and heated acidic water respectively. While these studies provided

promising results, we noticed the trend of these existing aminooxy reagents needing heating, acid, or additives to successfully transform aldehydes to nitriles.

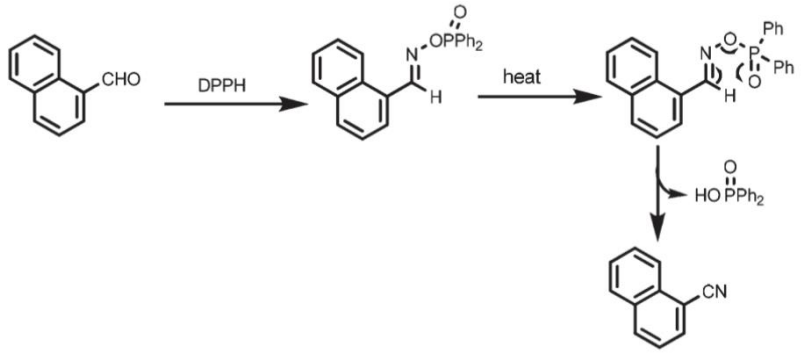



**Figure 5.** Outline by Sabir *et al*. on work by Laulhe *et al.* regarding DPPH as facilitator of aldehyde to nitrile conversion.

Minisci *et al*., Chatterjee *et al*., and Sabir *et al*. have all done or compiled work on the amination using aminooxy reagents. Minisci *et al*. described their use of HOSA to form radical $NH_3$+ that could then be added to alkenes at a 25-45% yield with a standard radical propagation mechanism (Figure 6).[6] Chatterjee *et al*. outlined their work on the amination of styrene, a common alkene, with $PivONH_3$•OTf and an iron catalyst that resulted in yields up to up to 60%.[7] Lastly, Sabir *et al*. outlined work the amination of aromatic compounds, the amination of nitrogen nucleophiles to form hydrazines, and the amination of sulfur nucleophiles to form NH-sulfoximes. The amination of aromatic compounds featured the use of *N*-methyl-O-tosylhydroxylamine and a DuBois catalyst to obtain yields of up to 89%. The amination of nitrogen nucleophiles to form hydrazines was done by using 2,4 dinitrophenylhydroxylamine (DPH) and a strong base to reach yields of up to 89%.The amination of sulfur nucleophiles to form NH-sulfoximes was facilitated again by DPH, but instead of base, the catalyst $Rh_2(esp)_2$ was added. This led to yields of up to 90%.[2] Again, despite these works showing much promise,

we noticed the trend for existing aminooxy compounds to require strong bases, radical initiation, or metal catalysis to successfully facilitate amination.

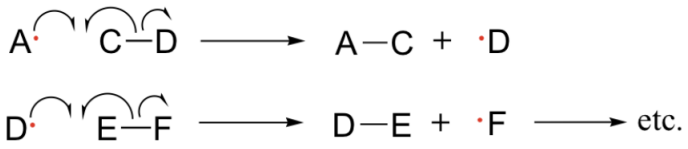



**Figure 6.** Traditional mechanism of radical propagation. Red dot signifies unpaired radical electron.

These results led us to question what other functionality could be synthetically placed around an aminooxy group to facilitate aldehyde to nitrile conversion and amination in a more time, resource, and energy efficient way. We then parsed the work of Zinner *et al*., Conway *et al*, and Ibaraki *et al*. on the synthesis of azanyl carbamates.[10, 14, 15] This was a class of compound that placed a carbamate group adjacent to the aminooxy. Carbamates were of particular note to us as Caplow *et al*. had outlined how carbamates spontaneously decarboxylate and add interesting reactivity to compounds.[16]

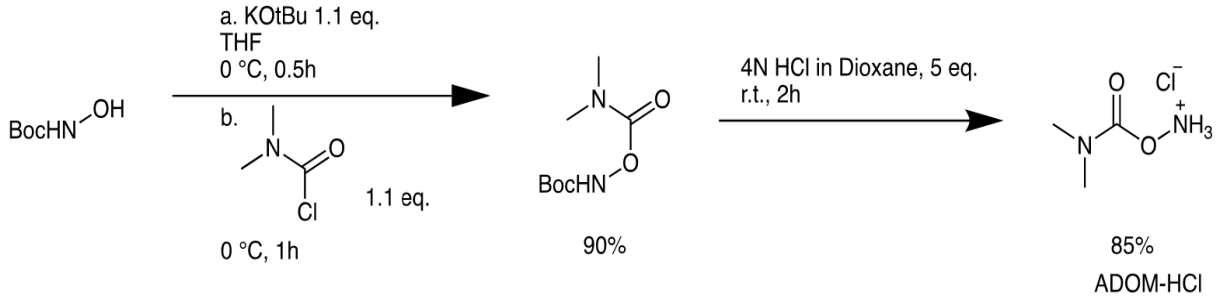
This led us to our final hypothesis: that azanyl carbamates, with an inherently reactive carbamate group adjacent to the previously studied aminooxy group, could help facilitate aldehyde to nitrile conversion and amination in a manner that was superior to previously described aminooxy reagents with other various surrounding functionality. This work would also fill the gap in organic chemistry literature regarding characterization and reactivity profiling of azanyl carbamate compounds.

# Results and Discussion

## Synthesis of ADOM-Boc and ADOM•HCl

The synthesis of ADOM-Boc featured acylation of Boc-protected hydroxylamine using carbamoyl chloride to afford ADOM-Boc as a white solid (Scheme 1). A US patent by Ibaraki *et al*. reported this step utilizing NaH and BocNHOH followed by addition of dimethyl carbamoyl chloride.[10] In an attempt to optimize this step, we changed the base from NaH to KOt-Bu. This modification proved fruitful as indicated by the $^{1}$H NMR data that showed no impurities after simple workup and an isolated yield of 90% compared to the 83% reported in the patent.

The synthesis of ADOM•HCl featured an acid-mediated Boc-deprotection that resulted in the formation of the azanyl carbamate as a salt, ADOM•HCl (Scheme 1). The reference patent achieved this by utilizing ADOM-Boc and 4N HCl in EtOAc.[10] Attempts to optimize this step were difficult due to the inherent instability of the product. An impurity, dimethyl ammonium chloride, was always detected at some level. It is formed from decomposition of ADOM•HCl via loss of $CO_2$. Although the terminal $NH_2$ group should prevent decarboxylation, the amine is susceptible to removal by other nucleophiles (possibly chloride), thus affording an intermediate carbamic acid that then readily decarboxylates




**Scheme 1.** A new synthesis of ADOM•HCl. Boc = C(O)O*t*-Bu.

Three possible routes were explored to minimize the presence of unintended side products: 1) methodically modifying the standard acid-mediated deprotection reaction to minimize decomposition; 2) finding a method for purification of ADOM•HCl to remove the impurities formed from decomposition; and 3) trying two alternative, unorthodox deprotection methods to possibly improve the process.

The first variable manipulated was reaction time. In nearly identical experimental procedures where the reaction time was varied between two and four hours, $^{1}$H NMR data indicated a 5% versus 22% resultant impurity, respectively. The yield for the two-hour versus four-hour experiment was also significantly better at 95% to 65%, respectively. The second variable manipulated was acid type. In nearly identical experimental procedures where the acid added was either HCl or trifluoroacetic acid (TFA), the $^{1}$H NMR data indicated a 5% versus 33% impurity, respectively. Product yield for the HCl versus TFA condition was also significantly better at 95% to 23%. The third variable manipulated was the purity of the reactant; although the Boc-protected intermediate appeared pure by TLC and NMR after workup, we considered that trace impurities or residual moisture might contribute to the formation of dimethyl ammonium impurity. Deprotection for a trial that utilized silica columned (for dehydration purposes) ADOM-Boc showed a 10% impurity and a yield of 91%. This suggested that the column step was not beneficial in terms of time and effort as it did not produce an improved result. Thus, we determined that the optimal conditions for this step were to deprotect ADOM-Boc using HCl over two hours. Although these conditions still led to a remnant 5% impurity, this amount of impurity seemed unavoidable given the sensitive nature of the compound.

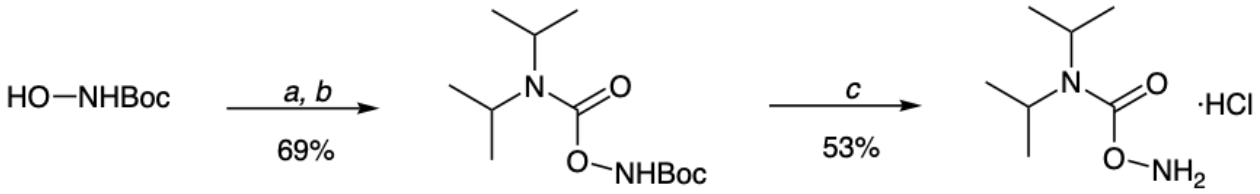
Our first attempt at purifying ADOM•HCl obtained using the conditions described above consisted of selective solvation of ADOM in acetonitrile. We speculated that ADOM•HCl would

dissolve in acetonitrile while the dimethyl ammonium impurity might not and thereby be a filterable precipitate. Unfortunately, this method resulted in an increase in the amount of impurity (up to 40% impurity) and only 74% collected mass overall.

While researching acid-mediated Boc-deprotection methods, we found a paper that outlined loading the Boc-protected compound onto silica and then microwaving in intervals to gradually induce deprotection.[17] We examined this method for deprotecting ADOM-Boc as we thought that this deprotection could yield a non-salt form under neutral conditions that would be less likely to form the dimethyl ammonium impurity. While this method appeared to work in some micro trials, silica was needed in a 500:1 w/w ratio of mg silica to mg ADOM-Boc to work properly. For this reason, this method was not scaled up. Also in our literature search, another alternate method that involved a Boc-protected compound loaded on silica was found. This method involved placing the silica loaded compound under vacuum and letting it react over the course of many hours.[18] While TLC analysis of this method indicated that it was working at the beginning of the process, the deprotection ended up stalling and never completing the process. For this reason, this method also was disregarded and no longer pursued.

**Synthesis of EVE-Boc and EVE•HCl**

EVE-Boc was synthesized in a similar method to ADOM-Boc using the modified reference patent method outlined above. First, acylation of Boc-protected hydroxylamine using diisopropylcarbamoyl chloride afforded a Boc-protected intermediate in 69% yield (Scheme 2). $^{1}$H NMR data showed no impurities after simple workup. Next, acid-mediated Boc-deprotection using hydrochloric acid (Scheme 2) generated the azanyl carbamate EVE•HCl as a salt with an isolated yield of 53%. The decomposition product, in this case diisopropyl ammonium chloride, was also present in the isolated crude solid as a 10% impurity.




**Scheme 2.** Synthesis of EVE•HCl.

EVE (Figure 7) has the potential to exist in tautomeric forms, either as an amide or iminol. We were unable to conclusively determine the preferred conformation from our NMR and IR studies. The IR spectrum of EVE•HCl did not show clear -OH or C=N stretches. A strong IR signal at 1741 $cm^{-1}$ suggests either C=N or C=O, which supports both the amide/iminol tautomers. The $^{1}H$ NMR of EVE•HCl in DMSO-$d_6$ showed the expected signals as well as an interesting triplet at δ 7.47 ppm integrating to one with a large splitting ($J$ = 50 Hz) suggestive of a proton experiencing splitting by 14N (a spin 1 nucleus). This could result from a strong intramolecular hydrogen bond, as shown in Figure 7. H-N 1J triplets with coupling around 50 Hz are noted in the literature for protons directly bound to nitrogen.[19] A similar triplet was also reported for a carboxylic acid proton hydrogen bonded to a nitrogen.[20] It is also worth noting that the $^{1}H$ spectrum of $NH_4Cl$ is reported to appear as a triplet at 7.1 ppm. Analysis of the $^{13}C$NMR also supported the presence of both tautomeric forms without indicating which is dominant. The peaks at 20.3 ppm and 46.6 ppm represent EVE•HCl's isopropyl groups. These beaks are broad which is unusual for $^{13}C$NMR; however, this can suggest the presence of two forms of a molecule that are not completely discrete or forms that are transitioning (such as the transition of two tautomeric forms).

Computational results in collaboration with the Thompson research group also examined EVE's possible tautomeric forms particularly with regard to the presumed hydrogen bond

depicted in Figure 7 by pink dashed lines. They found that, "[a]lthough the amide tautomer appears to be energetically more stable than the iminol tautomer, it is the iminol tautomer that has the more favorable geometry for a strong hydrogen bond." In the iminol form, "the distance between the hydrogen bond donor and acceptor is between 1.7 to 2.0 Å, which is within the optimized range for a strong hydrogen bond."

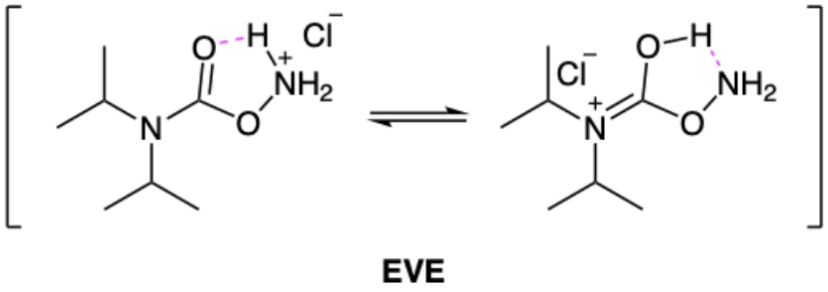
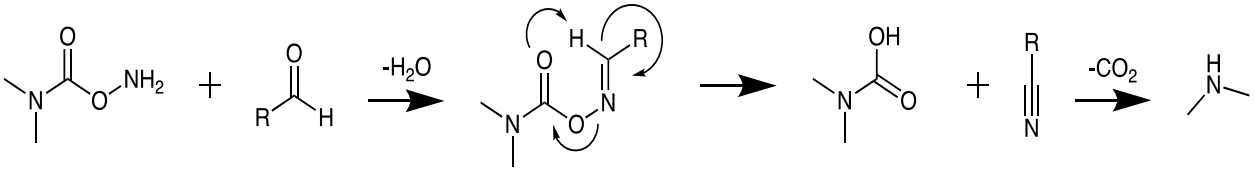



**Figure 7**. Tautomeric forms of EVE•HCl.

**ADOM•HCl mediated conversion of aldehydes to nitriles**

We speculated that ADOM•HCl could help facilitate a functional group conversion of an aldehyde to a nitrile in two steps through a condensation reaction followed by a speculated intramolecular elimination step (Scheme 3). The true mechanism of the elimination step requires further analysis to be confirmed.



**Scheme 3.** Speculated mechanism of ADOM•HCl mediated conversion of aldehydes to nitriles.

This functional group interconversion would be of major significance as the traditional route of converting aldehydes to nitriles involves acidic and/or harsh conditions for many hours.[21] For our initial trials we chose benzaldehyde and *p*-anisaldehyde as model aldehydes due to the UV absorbance properties of these compounds that would allow for easy monitoring with TLC. Our first test was a room temperature, simple-stirring reaction for 10 min, which resulted in 40% conversion of benzaldehyde to benzonitrile and 71% conversion of PAA to 4-methoxybenzonitrile (Table 1). The GC peak of benzonitrile was identified based on a parent ion of m/z 103 ($C_7H_5N$ calculated mass: 103.0422). The GC peak of 4-methoxybenzonitrile was identified based on a parent ion of m/z 133 ($C_8H_7NO$ calculated mass: 133.0527). The GC data of this reaction showed only two peaks corresponding to the aldehyde and nitrile for both the benzaldehyde and p-anisaldehyde. This led us to conclude that the elimination step of this reaction was very fast, producing dimethyl ammonium that could deactivate the remaining reagent. The species formed from this self-quenching, if unstable or highly volatile, could be indetectable in the GC chromatograph due to the solvent delay. We then speculated that chilling the reaction could slow the second step enough to let the first step go to completion. The cooled reaction was conducted for 45 min over an ice/brine bath and resulted in 85% conversion of benzaldehyde to benzonitrile and 9% conversion of PAA to 4-methoxybenzonitrile (Table 1). The reduction of yield in the chilled PAA trial was attributed to the electron donating nature of the methoxy group that decreased the electrophilicity of the carbonyl group. Understandably, the reaction could be pushed to completion by adding more than 1.1 equivalents of ADOM•HCl; however, this would take away from the elegance of the reaction and perhaps create even more volatile byproducts.

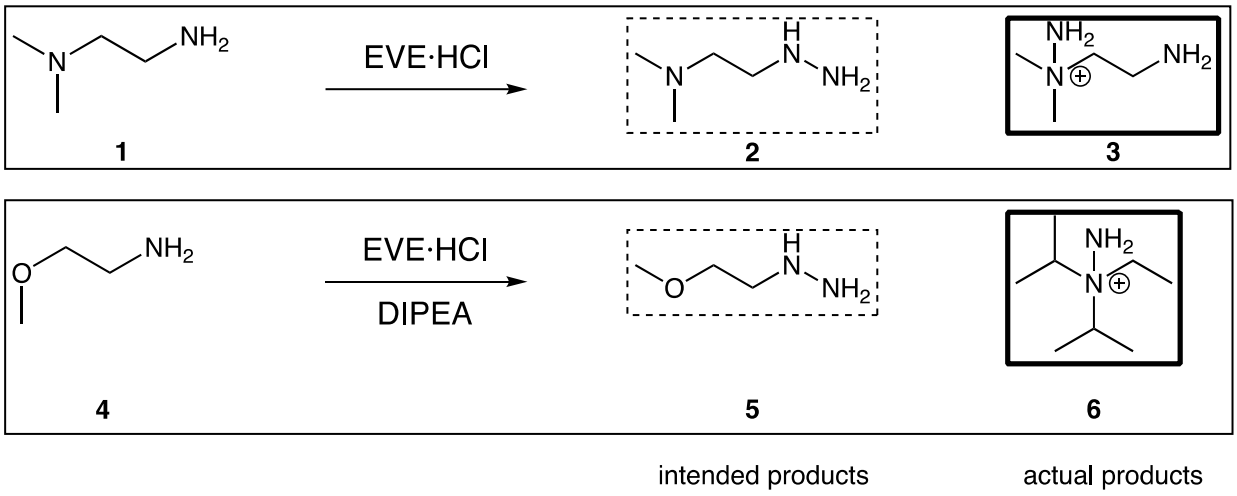
**Table 1.** GC data for Aldehyde to Nitrile Conversion.

| Starting Aldehyde | Conditions | Conversion to nitrile |
|---|---|---|
| Benzaldehyde | Room Temperature, 10 Mins | 40% |
| | 0 °C, 45 mins | **84%** |
| Para-Anisaldehyde | Room Temperature, 10 Mins | **71%** |
| | 0 °C, 45 mins | 9% |

**EVE•HCl mediated amination**

To test the potential of EVE•HCl to serve as a reagent for hydrazine synthesis via electrophilic amination of an amine, we chose dimethylethylenediamine (**1**) and 2-methoxyethylamine (**4**) (Scheme 4) as model amines because they have unhindered primary amines and for the possibility of using GC-MS to monitor the reaction. Scheme 4 depicts our expectation for these reactions as well as the surprising results. While monitoring reaction progress by GCMS, we observed no apparent conversion for either reaction after several hours of stirring at room temperature. Left to stir for several days, however, GC-MS showed that EVE was consumed, yet no new chromatographic peaks were observed to indicate that the desired hydrazine formations had occurred. Since GC-MS is limited to the detection of volatile species, we performed high resolution MS (direct liquid injection) to detect formation of non-volatile ionizable species in our test reactions. The expected mass for hydrazine **2** was present (Scheme 4); however, after column chromatography and further analysis, we deemed the product to be hydrazinium ion **3**, which shares the same mass as **2** but is a quaternary ammonium salt, hence its absence from the gas chromatogram. The characterization of **3** by NMR was based on

observations of distinct downfield shifts for the carbons that indicated connection to a quaternary nitrogen (Figure 8).




**Scheme 4.** Attempted hydrazine syntheses by reaction of EVE with two primary amines.

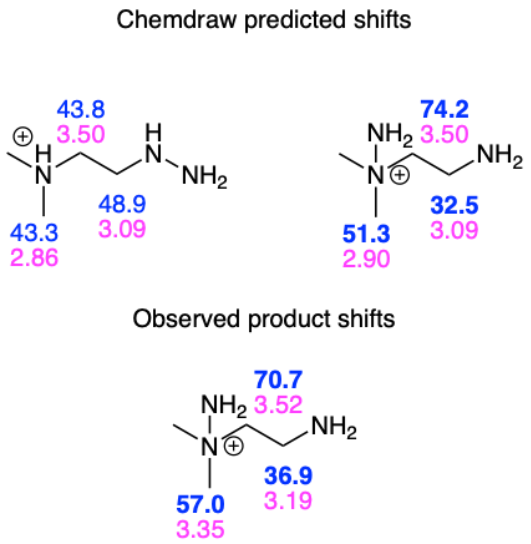



**Figure 8**. Predicted and observed $^{1}H$ (pink) and $^{13}C$ (blue) shifts for compounds **2** and **3** of Scheme 4.

For the reaction with model amine **4** (Scheme 4) a non-nucleophilic bulky base, diisopropylethylamine (DIPEA) was added to maintain neutral amine species in solution. To our

surprise, HRMS revealed that desired hydrazine **5** was not formed, rather, DIPEA had been aminated, forming quaternary hydrazinium **6** as evidenced by an observed mass of 145.1695 places (calculated m/z for $[C_8H_{21}N_2]^+$ = 145.1699). This was not in line with our expectations, as the steric bulk of DIPEA generally prevents its reaction with electrophiles. These interesting results suggest that the nucleophilicity of the amine is a critical determinant for the regiochemical preference observed.

**Transition to the use of a triflate counterion instead of chloride**

As outlined above, we were able to determine that the hydrochloride salt of ADOM was able to facilitate room temperature aldehyde-to-nitrile conversions and that the hydrochloride salt of EVE was useful in creating hydrazinium salts through electrophilic amination. However, we saw that these hydrochloride salts were difficult to purify and overly reactive, yielding side products and deteriorating during storage to form corresponding ammonium chlorides. For this reason, we shifted our efforts to synthesizing triflate salt versions of both ADOM and EVE. We hypothesized that the non-nucleophilic, highly delocalized nature of the triflate counterion ($CF_3SO_3^-$), in contrast to the somewhat nucleophilic nature of the chloride counterion, would serve to temper the reactivity of ADOM and EVE in a way that minimized unwanted side reactions but still allowed for unique and novel transformations.

**ADOM•OTf and EVE•OTf synthesis**

The synthesis of ADOM•OTf and EVE•OTf (Figure 9) followed the same fundamental synthetic method as ADOM•HCl and EVE•HCl outlined in Schemes 1 and 2 above. ADOM-Boc and EVE-Boc were both used as starting materials that were then acid deprotected by trifluoromethanesulfonic acid (triflic acid). There were slight conditional changes in temperature

and pace of addition due to the fuming and exothermic nature of triflic acid, but the overall time and resource efficiency of this deprotection was comparable to that of the HCl deprotection.

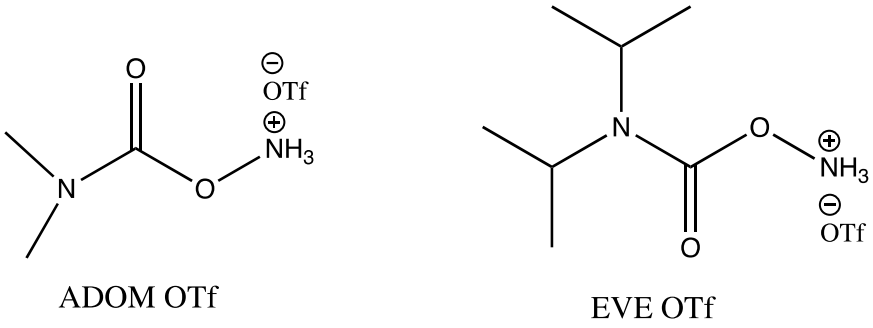



**Figure 9.** Depictions of ADOM•OTf and EVE•OTf.

In both cases, the triflic acid-mediated Boc-deprotections gave final yields that were comparable or slightly lower than the final yield of the corresponding HCl-mediated Boc-deprotections, 56% for ADOM•OTf and 60.4% EVE•OTf. However, the amounts of both the dimethyl- and diisopropyl ammonium side products were decreased when triflic acid was used. We speculate that this is principally due to the non-nucleophilic nature of the triflate counterion.

**EVE•OTf mediated oxime formation solvent test**

We performed small scale reactions of oxime carbamate formation with EVE•OTf and 2,2-dimethyl-cyclopentanone (Figure 10) for GC-MS detection and larger scale reactions of the same type for product isolation and characterization. This experiment was important in regard to the previous aldehyde to nitrile conversions as if the oxime forming step in Scheme 3 was indeed slow compared to the nitrile forming step, then it was important to determine what conditions could promote the formation of the key oxime intermediate. Table 2 below displays our analysis of the GC-MS data for seventeen trials with our model ketone. Representative structures and proposed mechanisms of formation for the interesting side products we observed are given; these

include a pair of unsaturated nitriles (Figure 10) and a methanolysis product (Figure 11). Data for unknown side products are also shown for each trial.

The characterizations of the oxime carbamate formed are included in the experimental section. The yield of this formation in DMF was approximately 76% (conditions as in entry 6 of Table 2).

**Table 2.** GC-MS data for seventeen trials of EVE•OTf with 2,2-dimethylcyclopentanone. Values indicate the product distribution as a percentage: (ion count of peak/ sum of ion count of reaction products)*100. Data for unknown side products are included for various retention times (R.T.) when their ion counts represented >10% of formed products.

| Entry | Solvent | Ketone Eq. | Base | Oxime | Nitriles | Methanolysis | R.T. 9.55 | R.T. 13.19 |
|---|---|---|---|---|---|---|---|---|
| 1 | MeCN | 2 | - | 15 | 6 | | | |
| 2 | MeCN | 1.1 | - | 15 | 6 | | | |
| 3 | MeCN | 2 | NaHCO3 (0.5 mg) | 62 | 0 | | | |
| 4 | MeCN | 1.1 | Pyridine (1 eq.) | 45 | 25 | | | |
| 5 | DMF | 2 | - | 100 | 0 | | | |
| 6 | DMF | 1.1 | - | 86 | 0 | | | |
| 7 | DMF | 2 | NaHCO3 (0.5 mg) | 97 | 0 | | | |
| 8 | DMF | 1.1 | Pyridine (1 eq.) | 23 | 8 | | | |
| 9 | DMSO | 2 | - | 100 | 0 | | | |
| 10 | THF | 2 | - | 38 | 21 | | | |
| 11 | THF | 1.1 | - | 0 | 76 | | | |
| 12 | THF | 2 | NaHCO3 (0.5 mg) | 71 | 0 | | | 15 |
| 13 | THF | 1.1 | Pyridine (1 eq.) | 35 | 20 | | | |
| 14 | CHCl3 | 1.1 | - | 0 | 51 | | 32 | |
| 15 | CHCl3 | 1.1 | Pyridine (1 eq.) | 0 | 0 | | | |
| 16 | MeOH | 1.1 | - | 0 | 36 | 31 | | |
| 17 | MeOH | 1.1 | Pyridine (1 eq.) | 1 | 31 | 20 | | |

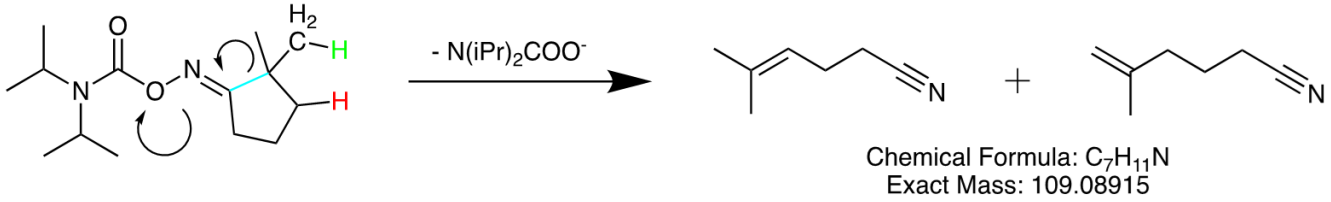



**Figure 10.** Proposed mechanism of nitrile formation. First product is from loss of red Hydrogen. Seconds product is from loss of green Hydrogen.

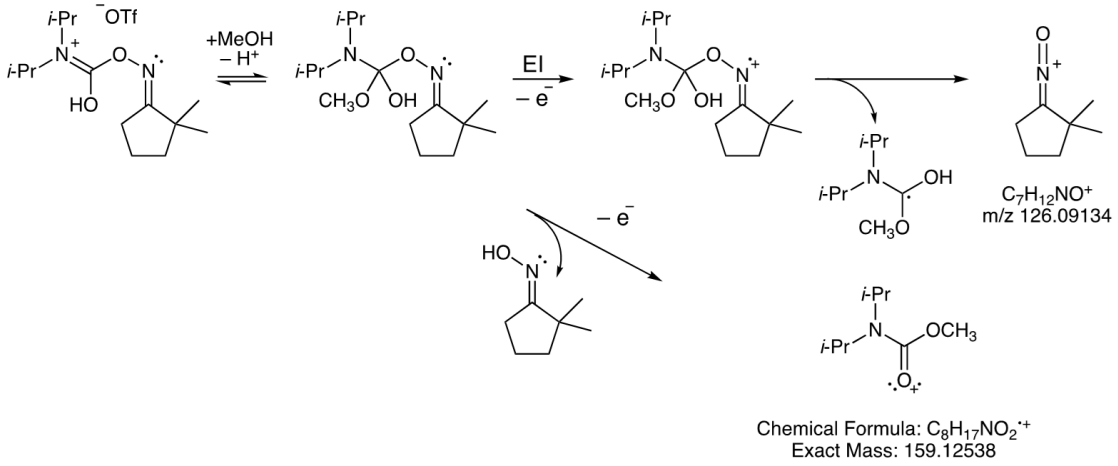



**Figure 11.** Representative structures and proposed mechanism of methanolysis product formation.

With these results we were able to determine that an excess of ketone in DMF and DMSO was optimal for EVE•OTf to facilitate oxime carbamate formation. This is interesting as DMF and DMSO both act as good Lewis-bases.[22] The superiority of these solvents compared to others, even with added base, leads us to suspect that 1) inherent Lewis-basicity of the environment is likely one factor in the activation via deprotonation of the amine, and 2) these basic and polar aprotic solvents may also provide stabilization of the transition-state that leads to oxime carbamate formation.

Overall, the inclusion of a base produced mixed results. The addition of sodium hydrogen carbonate slowed the reaction, as noted by a reduction in the overall conversion of starting material (data not shown), but had the positive effect of inhibiting side product formation, (e.g. table entry 11 versus 12). The addition of pyridine, on the other hand, did not have a positive impact on the turnover or cleanness of the reaction.

We identified the formation of nitrile products by a GC-MS result of m/z 109 (Figure 10). Nitrile formation in this experiment was both surprising and informative to us. The model ketone, 2,2 dimethyl cyclopentanone, was chosen for its steric properties in order to encourage formation of a single (E) isomer of the oxime carbamate. However, the presence of the dimethyl group on the alpha carbon and the presence of beta hydrogens (indicated with green and red in Figure 10) inadvertently made 2,2 dimethyl cyclopentanone a good substrate for nitrile formation via H+ elimination. The substituted ring position alpha to the oxime would provide stabilization for the positive charge generated by cleavage of the bond highlighted in blue in Figure 10. The presence of beta hydrogens also allows for proton abstraction to satisfy the lost electron pair. Nitrile formation also produces three stable species (accounting for $CO_2$ loss from the carbamic acid), which would be preferred thermodynamically to the oxime carbamate based on entropy. It is also worth noting that when the reaction was scaled up for product isolation and characterization, the nitriles were able to be isolated indicating that nitrile formation was not a GC-MS heat-induced phenomenon.

We also observed methanolysis of the oxime occurring (Table 2) by GC-MS. Two chromatographic peaks were seen with positively charged mass fragments of m/z 126 and 159 respectively (Figure 11). These masses occurred solely in the MeOH spectra and represent an addition of methanol at the amide carbonyl (159) with elimination of the companion fragment (126). After parsing the literature, we were able to find a source that describes a methanolysis mechanism similar to the one depicted in Figure 11.[23] This observed methanolysis is noteworthy as it shows that our oxime carbamate product is unusually vulnerable to nucleophilic attack at its amide carbonyl rather than at the oxime carbon, the typical site of hydrolysis for oxime ether

species. As these products were not isolated, it is not known whether this was a GC-MS induced methanolysis or a true reaction product.

**ADOM•OTf mediated aldehyde to nitrile solvent test**

Having evaluated the effect of different solvents on oxime formation with ADOM•OTf and a ketone, we then replicated our solvent study with an aldehyde as the reaction partner. We were interested to confirm that the optimal solvent conditions of oxime formation with a ketone also facilitated aldehyde to nitrile conversion. Six small scale reactions were performed in DMF, DMSO, THF, MeCN, $CHCl_3$, and MeOH. All conditions featured a slight excess of ADOM•OTf that reacted with heptanal for 30 minutes at room temperature. Heptanal was chosen as the model aldehyde as it was well suited to GCMS analysis. A standard, a MEM ether protected tetraflurobenzyl alcohol, was also added for normalization/quantification purposes.

After 30 minutes, the reactions were diluted with $CHCl_3$ for GCMS analysis. The GCMS data showed four major peaks: one known and three unknown. The starting heptanal was absent from all six conditions. The GC peak of heptanenitrile was identified based on a parent ion of m/z 96.1 and had a retention time of 6.9 minutes. Three GC peaks at retention times 8, 15, and 18 minutes had parent ion m/z of 115, 221.1, and 140 and were not identifiable. Table 3 below displays the results of each solvent.

**Table 3.** GC-MS data for six trials of ADOM•OTf with heptanal. Values indicate the quantitative value of heptanenitrile formed measured by GCMS integration or product distribution as a percentage: (ion count of peak/ sum of ion count of reaction products)*100. Data for unknown side products are included for various retention times (R.T.).

| Solvent | Integration Value for Heptanonitrile | Heptanonitrile Percentage | R.T. 8 Minutes Percentage | R.T. 15 Minutes Percentage | R.T. 18 Minutes Percentage |
|---|---|---|---|---|---|
| DMF | 3131361 | 62.1 | | | 37.9 |
| DMSO | 1673668 | 100 | | | |
| CHCl3 | 4345914 | 58.1 | | | 41.9 |
| MeCN | 8118236 | 48.9 | | | 51.1 |
| MeOH | 18237859 | 48.3 | 21.8 | | 29.9 |
| THF | 9965643 | 49.3 | | 3.2 | 47.5 |

From the data above we were able to see that MeOH yielded the most heptanenitrile by quantity, but DMSO yielded the cleanest heptanenitrile product. This was significant as DMSO was also a preferred solvent for EVE•OTf mediated oxime formation providing further support that the mechanism of azanyl carbamate-mediated aldehyde to nitrile conversion involves an oxime intermediate as outlined in Scheme 3. This result is also corroborated by Fukui index data from the Thompson research group that highlighted DMF and DMSO as particularly fitting solvents for reactions in which the amine of ADOM would need to act as a nucleophile. Fukui indices are measures for reactivity; they provide information about which atoms in a molecule have a larger tendency to lose or accept an electron. This can then be interpreted as susceptibility for nucleophilic or electrophilic attack respectively.[24]

An important control experiment was also performed to eliminate the possibility that aldehyde to nitrile conversions were taking place during GC-MS analysis rather than in the reaction solution. The inlet of the GC-MS, typically around 200 °C, could potentially provide thermal activation of the elimination reaction that leads to nitrile formation. To address this concern, we used a head space sampling called solid phase microextraction (SPME). This method features a sensitive organic-absorbing microfiber that is placed in the headspace of a reaction vessel for qualitative analysis of what is being formed over the course of a reaction. With this method, we conducted a non-quantitative follow up trial at room temperature where a small amount of ADOM•OTf, drop of DMSO, and drop of heptanal were mixed and allowed to react. This trial was analyzed via mass spectroscopy and revealed the sole presence of heptanenitrile at a retention time of 6.8 minutes and parent ion of m/z 96. By doing SPME in this case we were able to verify that ADOM•OTf mediated formation of heptanenitrile was not catalyzed or dependent on heat from the GCMS instrument.

**EVE•OTf mediated amination**

Analogous to EVE•HCl, we believed EVE•OTf could facilitate hydrazine synthesis via electrophilic amination. To test this, we chose *N*-methylpiperazine as a model amine. *N*-methylpiperazine was chosen as it features both a secondary and tertiary amine that are easy to distinguish with CNMR. Ease of distinguishability was especially of interest to us after the results of EVE•HCl aminating tertiary amines in an unexpected manner.

The methodology for this reaction was very simple: make a 0.2M solution of EVE•OTf in MeCN, add *N*-methylpiperazine in 1:1 equivalence, and then react for 120 hours with magnetic stirring. Due the results of the EVE•HCl amination experiment that took over one week, the

reaction was not monitored and just left to react. After 120 hours an orange-yellow oil, typical of hydrazines, had formed. The crude product was then dried and subjected to $C^{13}$ NMR analysis.

Figure 12 below displays the predicted chemical shift for the unreacted *N*-methylpiperazine, *N*-methylpiperazine aminated in the tertiary position (less sterically preferred), and *N*-methylpiperazine aminated in the secondary position (more sterically preferred). The CNMR of the crude reaction product revealed a peak at 65 ppm which is very close to the predicted shift of 62 ppm for adjacent carbons in the *N*-methylpiperazine aminated in the secondary position. The shift of 65 ppm was also well clear of the predicted shift of 72 ppm for the *N*-methylpiperazine aminated in the tertiary position.

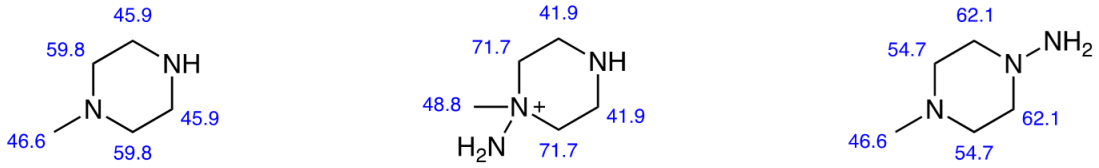



**Figure 12.** Predicted CNMR shifts of unreacted *N*-methylpiperazine, *N*-methylpiperazine aminated in the tertiary position, and *N*-methylpiperazine aminated in the secondary position.

This led us to conclude that EVE•OTf had successfully aminated *N*-methylpiperazine to form a hydrazine at the secondary amine. In conjunction with the results of EVE•HCl's amination experiments, we were able to more broadly conclude that the nucleophilic nature of the counterion of azanyl carbamtes partially determines which factor, being electronics or sterics, is more important in directing the site of amination.

# Conclusions

We have described an efficient synthetic route to three novel azanyl carbamates, isolated stable crystalline forms, characterized them spectrally, investigated their reactivity in two different applications. We have demonstrated that azanyl carbamates have functional use in fast, room temperature aldehyde to nitrile conversions at mild pH. Furthermore, we showed that under equally mild conditions, azanyl carbamates can electrophilically aminate secondary and tertiary amines, producing hydrazines and hydrazinium ions. The above studies have also shown that azanyl carbamates' ability to act as a nucleophile or an electrophile can be modulated based on reaction conditions such as solvent. These findings open the door for more azanyl carbamate compounds to be synthesized and studied in facilitation of other traditionally difficult organic transformations. Future studies regarding specifically aldehyde to nitrile conversions and amination reactions could provide more clarity on the scope and limitations of these transformations. Additionally, more in-depth studies on the mechanisms of aldehyde to nitrile conversions and the electrophilic amination would give further insight into how the arrangement of heteroatoms in azanyl carbamates contributes to their unique reactivity. Work has already been outlined in the Nantz Lab and in the Thompson lab to help bridge these gaps in our knowledge.

# Experimental

## ADOM-Boc synthesis

KOt-Bu (45 mL of 1 M solution in THF, 0.045 mol) was added via syringe to a round-bottom flask containing BocNHOH (2.12 g, 0.016 mol). The mixture was stirred for 30 mins at 0 °C over an ice/brine bath. Freshly distilled dimethyl carbamoyl chloride (1.71 g, 0.016 mol) in THF (15 mL) was then added to the basified hydroxylamine solution. The reaction was then stirred for 1 hour at 0 °C. Next, the reaction was worked up by washing with water (1x 100 mL) and was extracted with EtOAc (4x 100mL), washed with brine (1x 50 mL), and dried with sodium sulfate. In a later synthesis, this product was columned on silica gel (isocratic 30% EtOAc in Hexanes, 87.4%). $^{1}$H NMR (CDCl3, 400 MHz): δ 1.47 (s, 9H), 2.97 (s, 3H), 3.00 (s, 3H), 7.85 (D, 1H, J=18 Hz). $^{13}$C NMR (CDCl3, 100 MHz): (6 signals) δ 28.2, 35.8, 37.3, 82.8, 156.3, 156.6.

## EVE-Boc Synthesis

KOt-Bu (6.7 mL of 1 M solution in THF, 0.0067 mol) was added via syringe to a round-bottom flask containing BocNHOH (0.814 g, 0.006 mol). The mixture was stirred for 30 mins at 0 °C over an ice/brine bath. Fresh diisopropyl carbamoyl chloride (1.00 g, 0.006 mol) in THF (15 mL) was then added to the basified hydroxylamine solution. The reaction was then stirred for 1 hour at 0 °C. Next, water was added (20 mL) and the aqueous solution was extracted with EtOAc (3x 25mL), the combined organic layers were washed with brine (1x 15 mL), and dried with sodium sulfate, yielding 0.9917 g (69 % yield) of a yellow oil. Rf 0.65 $^{1}$H NMR (CDCl3, 400 MHz): δ 1.269 (d,12H), 1.488 (s,9H), 3.952 (sept., 2H), 8.80 (s,1H);$^{13}$C NMR (CDCl3, 100 MHz): δ 20.7, 28.0,47.0, 82.5,156.

**ADOM•HCl synthesis**

ADOM-Boc (1.03g, 0.005 mol) from Synthesis Step 1 was added to a clean reaction flask with enough dioxane to dilute the solution to 0.2M. Then, 6.3 mL of 4N HCl in dioxane was added and the reaction was stirred for 4.5 hours. The reaction flask was then placed in an ice bath for 10 mins and a small amount of diethyl ether was added to crash out crystals. The resulting crystals were isolated via filtration and dried under vacuum. In a later synthesis, this method was identically repeated but with a 2 hour reaction time instead of 4.5h. $^{1}$H NMR (CD3OD, 400 MHz): δ 2.99 (s,3H), 3.01(s, 3H) (dimethyl ammonium impurity δ 2.703 (s)); $^{13}$C NMR (CDCl3, 100 MHz): (3 signals) δ 36.0, 37.7, 153.7 (dimethyl ammonium impurity δ 35.4).

**EVE•HCl synthesis**

EVE-Boc (2.005g, 0.0076mol) was added to a clean reaction flask with dioxane (28.4 mL). Then, 9.6 mL of 4N HCl in dioxane was added and the reaction was stirred for 2 hours. The reaction flask was then placed in an ice bath for 10 mins and a small amount of diethyl ether was added to crash out crystals. The resulting crystals were isolated via filtration and dried under vacuum, 0.791 g (53% yield) containing an additional 10% diisopropyl ammonium chloride as an impurity. $^{1}$H NMR (DMSO, 400 MHz): δ1.185(d, 12H), 3.850-3.930 (multiplet,2H), 7.466 (t,1H), 10.978 (s,2H); $^{13}$C NMR (CDCl3, 100 MHz)δ 18.5, 20.3, 39.4, 46.0, 46.7, 151.7.

**ADOM•HCl mediated aldehyde to nitrile**

ADOM•HCl (0.006g, 0.000043 mol) was diluted to 0.2M by dissolving in MeCN. This was then combined with either Benzaldehyde (0.0041g, 0.000039mmol) or p-anisaldehyde (0.0053g, 0.000039 mol) in a small, sealed vial. The mixture was then left to react for 10 minutes at room

temperature. In a later synthesis, this method was identically repeated but for 45 mins at 0 °C over an ice/brine bath.

**EVE•HCl mediated amination solvent test**

Four measures of EVE•HCl (0.010g, 0.0005 mol) were added to four reaction flasks containing either MeCN, THF, DMF, or EtOH (0.5 mL). Dimethylethylenediamine (0.01 mL, 0.0000929 mol) was added to each tube and the reaction was stirred at room temperature for 24. The reactions were then sampled and analyzed via TLC (1:1 EtOAc:Hexanes). The THF and MeCN reactions alone revealed a new spot (Rf: 0.6). On this basis, the polar aprotic solvent MeCN was selected for the hydrazine transfer reactions.

**EVE•HCl mediated amination of Dimethylethylenediamine**

EVE•HCl (0.0815g, 0.000415 mol) was added to a clean reaction flask with MeCN (2.1 mL). Dimethylethylenediamine (0.044 mL, 0.00041 mol) was added and the reaction was stirred for about one week at room temperature. After removal of the solvent in vacuo, a portion of the crude product was columned using propylamine-modified silica yielding a yellow oil, 0.008 g. $^{1}$H NMR (CDCl3, 400 MHz): δ 1.287(s, 2H), 3.195(t, 2H), 3.32-3.37 (multiplet,8H), 3.524 (t, 2H), 4.837 (s, 2H).$^{13}$C NMR (CDCl3, 100 MHz): δ 37.0, 57.0, 70.77.

**EVE•HCl mediated amination of 2-methoxyethylamine**

EVE•HCl (0.1g, 0.000509 mol) was added to a clean reaction flask with MeCN (2.54 mL) and Diisopropylethylamine (0.1974g, 0.001527 mol). 2-methoxyethylamine (0.038g, 0.000509mol) was added and the reaction was stirred for about one week at room temperature. Direct injection HRMS was performed on the crude mixture. The product was not purified.

**ADOM•OTf synthesis**

ADOM-Boc (0.206 g, 1 mmol) was added to a reaction flask along with 5 mL of diethyl ether to create a 0.2M solution. This solution was then stirred for 20 mins before being chilled to 0 °C via an ice/brine bath. Triflic acid (0.15 g, 1 mmol) was then added dropwise over 30 mins. After the addition was complete, the reaction was left to stir at 0 °C for an additional 30 mins. After this, the ice/brine bath was removed, and the solution was allowed to stir at room temperature for 30 minutes. A white solid had formed, so the mixture was filtered, and the resulting powder was left to dry for 30 mins under vacuum. TLC of the solid in 1:1 Hex:EtOAc indicated a pure product with an Rf of 0.37. In total after drying, 0.142g (56% yield) of white solid was collected. $^{1}$H NMR (CDCl3, 400 MHz): δ 3.01 (s, 3H), 3.03 (s, 3H).

**EVE•OTf synthesis**

EVE-Boc (0.278 g, 1.07 mmol) was added to a reaction flask along with 5.35 mL of diethyl ether to create a 0.2M solution. This solution was then stirred for 20 mins before being chilled to 0 °C via an ice/brine bath. Triflic acid (0.16 g, 1.07 mmol) was then added dropwise over 30 mins. After the addition was complete, the reaction was left to stir at 0 °C for an additional 30 mins. After this, the ice/brine bath was removed, and the solution was allowed to stir at room temperature for 30 minutes. A white solid had formed, so the mixture was filtered, and the resulting powder was left to dry for 30 mins under vacuum. TLC of the solid in 1:1 Hex:EtOAc indicated a pure product with an Rf of 0.4. In total after drying, 0.198g (60.4% yield) of white solid was collected. $^{1}$H NMR (CDCl3, 400 MHz): δ 1.3 (multiplet, 12H), 3.966(t, 2H).

**EVE•OTf mediated oxime formation solvent test**

EVE•OTf (2 mg, 0.0064 mmol) was added to multiple microcentrifuge tubes with 32 µL of various solvents (MeCN, DMF, DMSO, THF, CHCl3, and MeOH) to create a 0.2M solution. Then 2,2 dimethyl cyclopentanone (either 2 or 1.1 equivalents) was added to each tube. Some tubes then had base (either 0.5 mg NaHCO3 or 1 equivalent of pyridine) added. These tubes were then left to react on a shaker overnight. After this, the solutions were sampled and diluted with EtOAc for Gas Chromatography Mass Spectrometry (GC-MS) analysis. $^{1}$H NMR (CDCl3, 400 MHz): δ 0.83-0.99(multiplet, 1H), 1.2-1.3(multiplet, 20H), 1.66 (t, 2H), 1.7-1.8 (multiplet, 2H), 2.6 (t, 2H), 3.9 (s, 2H).

**ADOM•OTf mediated aldehyde to nitrile solvent test**

ADOM•OTf (6 mg, 0.024 mmol) was added to six microcentrifuge tubes. To this, 100µL of 0.2M heptanal in various solvents(MeCN, DMF, DMSO, THF, CHCl3, and MeOH) was added. 2.7 mg of MEM ether protected tetraflurobenzyl alcohol was also added as a standard. These tubes were then left to react for 30 mins before 4.4µL aliquots of each were taken and quenched with 216 µL of CHCl3 in Gas Chromatography Mass Spectrometry (GC-MS) vials to yield six GCMS samples for analysis.

**EVE•OTf mediated amination**

EVE•OTf (50 mg, 0.161 mmol) was dissolved by 0.8 mL of MeCN to yield a 0.2M solution. To this, 17.75 µL of 1-methylpiperazine (0.161mmol) was added. The resulting solution was then left under magnetic stirring at room temperature for 120 hours. The solvent was then removed in vacuo to yield a yellow oil. A portion of the oil was then diluted with deuterated methanol for NMR analysis. $^{13}$C NMR (CD3OD, 100 MHz) δ 46.0, 49.0, 53.3, 65.6.

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# References


(1) Xiang, S.-H.; Tan, B. Advances in asymmetric organocatalysis over the last 10 years. *Nature Communications* **2020**, *11* (1), 3786. DOI: 10.1038/s41467-020-17580-z.

(2) Sabir, S.; Kumar, G.; Jat, J. L. O-Substituted hydroxyl amine reagents: an overview of recent synthetic advances. *Organic & Biomolecular Chemistry* **2018**, *16* (18), 3314-3327, 10.1039/C8OB00146D. DOI: 10.1039/C8OB00146D.

(3) Quinn, D. J.; Haun, G. J.; Moura-Letts, G. Direct synthesis of nitriles from aldehydes with hydroxylamine-O-sulfonic acid in acidic water. *Tetrahedron Letters* **2016**, *57* (34), 3844-3847. DOI: https://doi.org/10.1016/j.tetlet.2016.07.047.

(4) An, X. D.; Yu, S. Direct Synthesis of Nitriles from Aldehydes Using an O-Benzoyl Hydroxylamine (BHA) as the Nitrogen Source. *Org Lett* **2015**, *17* (20), 5064-5067. DOI: 10.1021/acs.orglett.5b02547 From NLM PubMed-not-MEDLINE.

(5) Wallace, R. G. Hydroxylamine-O-sulfonicacid - a versatile synthetic reagent. *Aldrichimica Acta* **1980**, *13*, 3-11. (acccessed Feb 20, 2023).

(6) Minisci, F. New types of amination of olefinic, acetylenic and aromatic compounds by hydroxylamine-o-sulfonic acid and hydroxylamines/metal salts redox systems. *Tetrahedron Letters* **1965**, *22*, 1679-1684.

(7) Chatterjee, S.; Harden, I.; Bistoni, G.; Castillo, R. G.; Chabbra, S.; van Gastel, M.; Schnegg, A.; Bill, E.; Birrell, J. A.; Morandi, B.; et al. A Combined Spectroscopic and Computational Study on the Mechanism of Iron-Catalyzed Aminofunctionalization of Olefins Using Hydroxylamine Derived N–O Reagent as the "Amino" Source and "Oxidant". *Journal of the American Chemical Society* **2022**, *144* (6), 2637-2656. DOI: 10.1021/jacs.1c11083.

(8) Administrator, B. *Nitriles Structure and Properties Reactions and Uses of nitriles: Chemistry*. https://byjus.com/chemistry/nitriles/ (accessed Feb 20, 2023).

(9) Adlard, E. R. Michael D. Larrañaga, Richard J. Lewis and Robert A. Lewis (Eds.): Hawley's Condensed Chemical Dictionary. 16th Edn. *Chromatographia* **2017**, *80* (6), 997-997. DOI: 10.1007/s10337-017-3313-3.

(10) Yoshida, I.; Suzuki, S. Heterocyclic compound having oxime group. 2005.

(11) Barbosa, M.; Martins, M. C.; Gomes, P. Grafting Techniques towards Production of Peptide-Tethered Hydrogels, a Novel Class of Materials with Biomedical Interest. *Gels* **2015**, *1*, 194-218. DOI: 10.3390/gels1020194.

(12) Morales, S.; Aceña, J. L.; García Ruano, J. L.; Cid, M. B. Sustainable Synthesis of Oximes, Hydrazones, and Thiosemicarbazones under Mild Organocatalyzed Reaction Conditions. *The Journal of Organic Chemistry* **2016**, *81* (20), 10016-10022. DOI: 10.1021/acs.joc.6b01912.

(13) Laulhé, S. Aminooxy reagents for synthesis and analysis : expanding the role of oximation. 2013.

(14) Zinner, G.; Nebel, G.; Hitze, M. [N-unsubstituted O-acyl-hydroxylamines. 41. Hydroxylamine derivatives]. *Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft* **1970**, *303 4*, 317-320.

(15) Conway, T. T.; DeMaster, E. G.; Goon, D. J.; Shirota, F. N.; Nagasawa, H. T. Diethylcarbamoylating/nitroxylating agents as dual action inhibitors of aldehyde dehydrogenase: a disulfiram-cyanamide merger. *J Med Chem* **1999**, *42* (20), 4016-4020. DOI: 10.1021/jm990235p PubMed.

(16) Caplow, M. Kinetics of carbamate formation and breakdown. *Journal of the American Chemical Society* **1968**, *90*, 6795-6803.

(17) Siro, J. G.; Martín, J.; García-Navío, J. L.; Remuiñan, M. J.; Vaquero, J. J. Easy Microwave Assisted Deprotection of N-Boc Derivatives. *Synlett* **1998**, *1998* (02), 147-148. DOI: 10.1055/s-1998-1604.

(18) apelqvist, T.; Wensbo, D. Selective removal of the N-BOC protective group using silica gel at low pressure. *Tetrahedron Letters* **1996**, *37* (9), 1471-1472. DOI: https://doi.org/10.1016/0040-4039(95)02398-4.

(19) Kupai, J.; Razali, M.; Buyuktiryaki, S.; Kecili, R.; Szekely, G. Long-term stability and reusability of molecularly imprinted polymers. *Polymer Chemistry* **2017**, *8* (4), 666-673, 10.1039/C6PY01853J. DOI: 10.1039/C6PY01853J.

(20) Alam, K. M.; Kumar, P.; Gusarov, S.; Kobryn, A. E.; Kalra, A. P.; Zeng, S.; Goswami, A.; Thundat, T.; Shankar, K. Synthesis and Characterization of Zinc Phthalocyanine-Cellulose Nanocrystal (CNC) Conjugates: Toward Highly Functional CNCs. *ACS Applied Materials & Interfaces* **2020**, *12* (39), 43992-44006. DOI: 10.1021/acsami.0c07179.

(21) Leggio, A.; Belsito, E. L.; Gallo, S.; Liguori, A. One-pot conversion of aldehydes to nitriles mediated by TiCl4. *Tetrahedron Letters* **2017**, *58* (15), 1512-1514. DOI: https://doi.org/10.1016/j.tetlet.2017.03.007.

(22) Fawcett, W. R.; Fedurco, M. Medium effects in the electroreduction of benzophenone in aprotic solvents. *The Journal of Physical Chemistry* **1993**, *97* (27), 7075-7080. DOI: 10.1021/j100129a025.

(23) Annibaletto, J.; Martzel, T.; Levacher, V.; Oudeyer, S.; Brière, J.-F. Multicomponent Catalytic Enantioselective Synthesis of Isoxazolidin-5-Ones. *Advanced Synthesis & Catalysis* **2021**, *363* (18), 4447-4451. DOI: https://doi.org/10.1002/adsc.202100719.

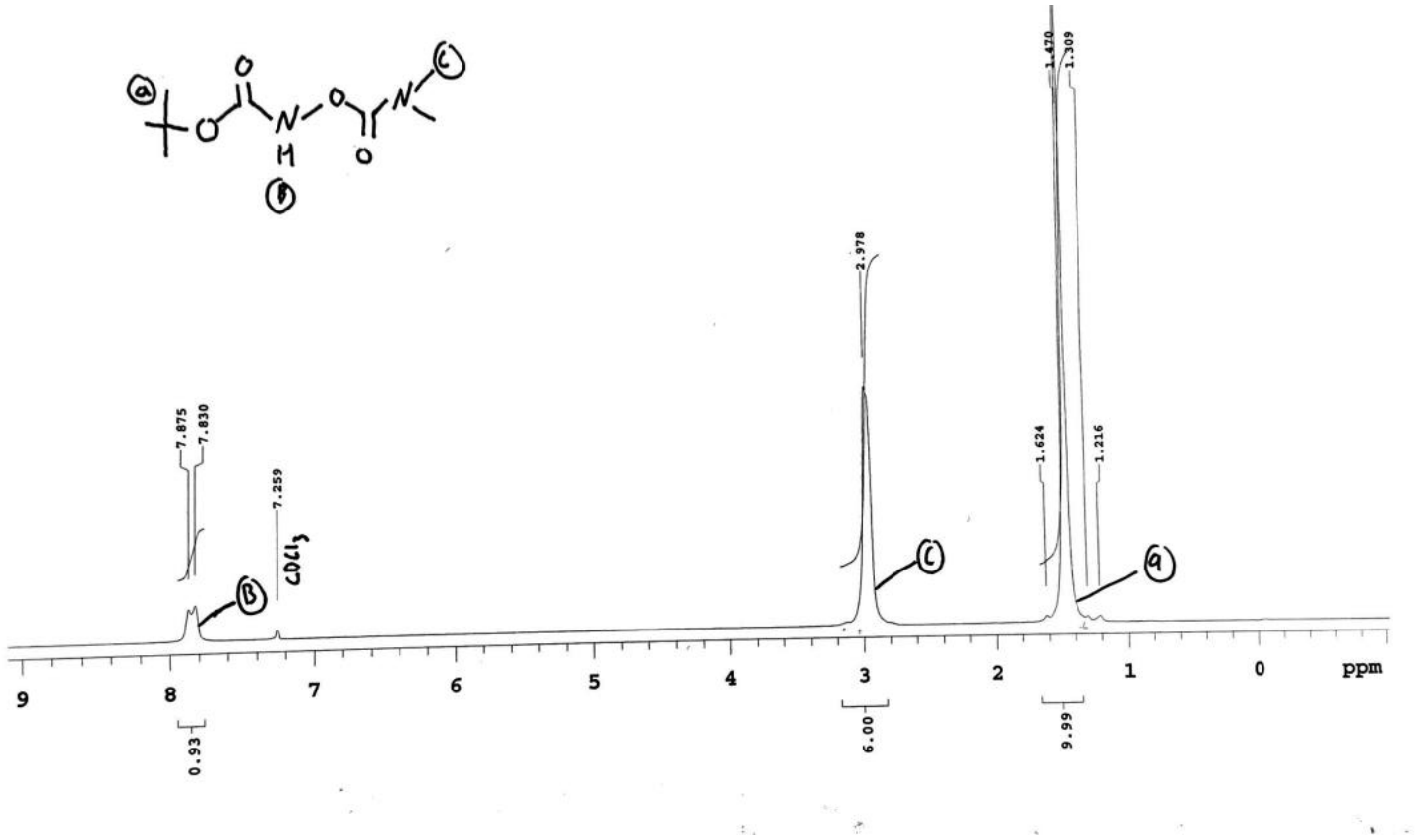
(24) Zamora, P. P.; Bieger, K.; Cuchillo, A.; Tello, A.; Muena, J. P. Theoretical determination of a reaction intermediate: Fukui function analysis, dual reactivity descriptor and activation energy. *Journal of Molecular Structure* **2021**, *1227*, 129369. DOI: https://doi.org/10.1016/j.molstruc.2020.129369.

# Appendix

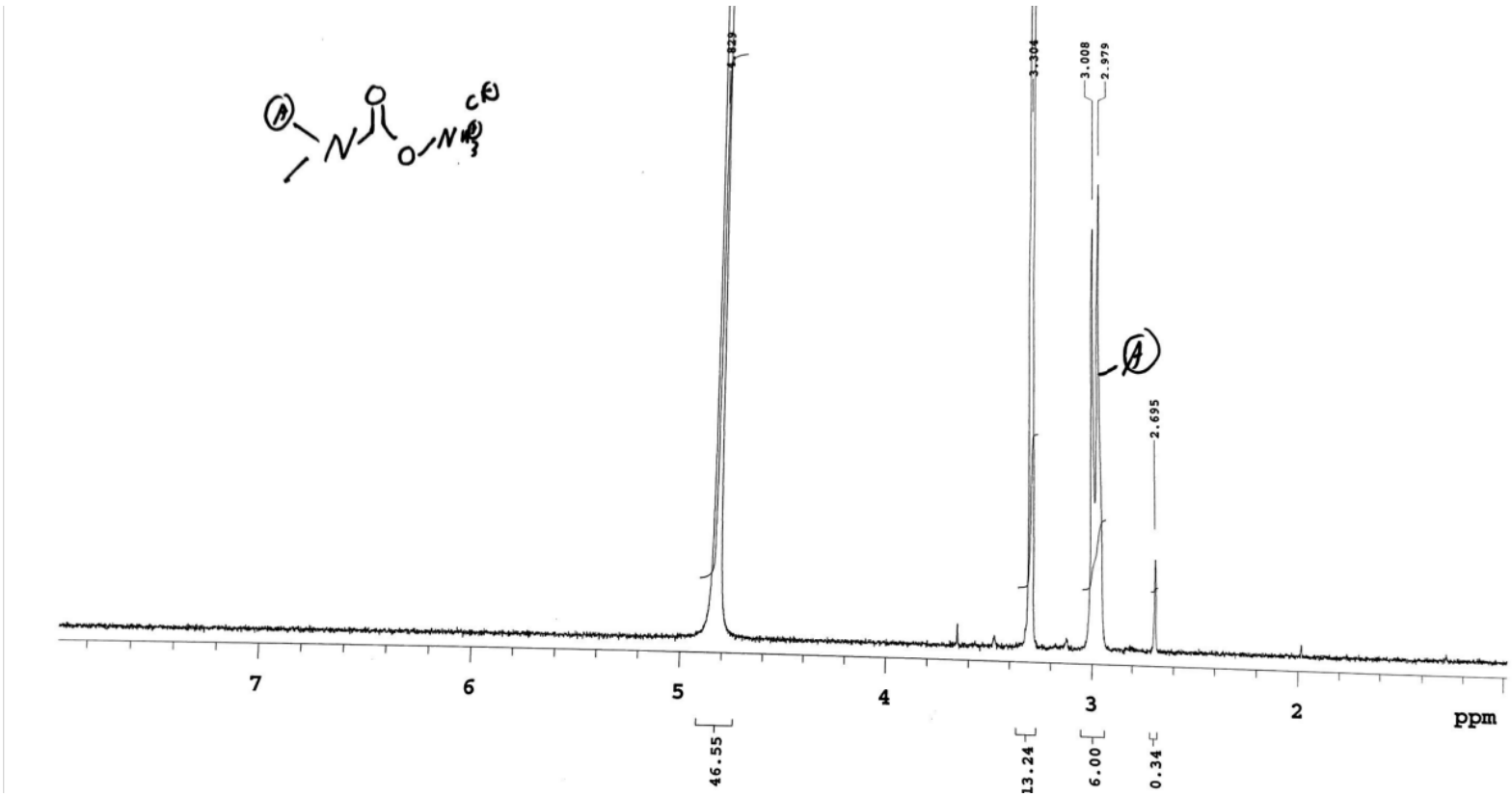
Below are presented various $^{1}H$ and $^{13}C$ nuclear magnetic resonance spectra obtained in deuterated solvents using department instrumentation. The vertical axis represents the intensity of atoms (e.g., the number of hydrogen atoms contributing to the signal). The horizontal axis is termed the "chemical shift" given in δ units. The scale is commonly expressed in parts per million (ppm) which is independent of the spectrometer frequency. The position of horizontal axis was set based on the peak of the solvent being used.

$$\delta = \frac{\text{frequency of signal} - \text{frequency of standard}}{\text{spectrometerfrequency}} \times 10^{6}$$

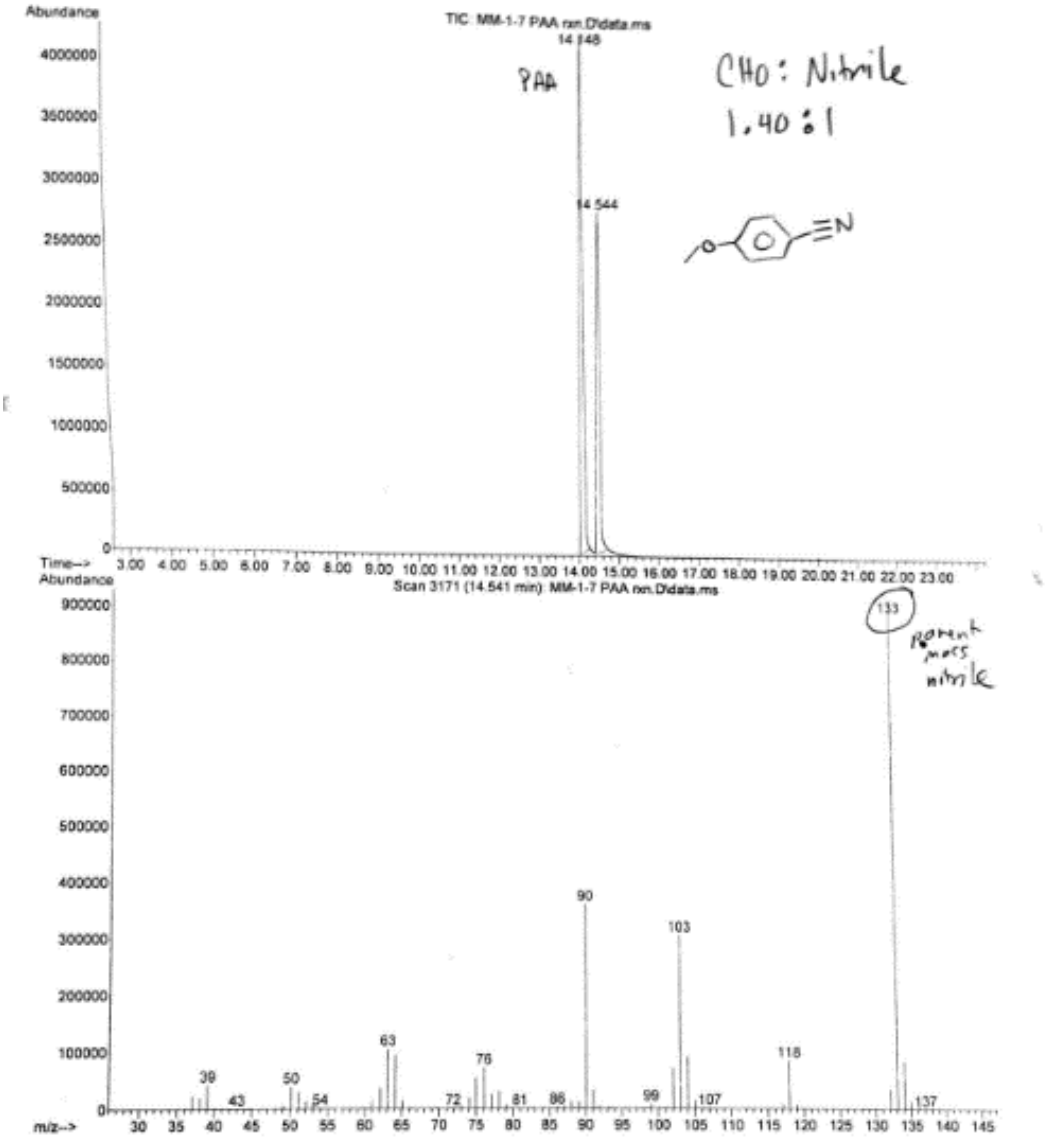
A: $^{1}H$ NMR Spectra of ADOM-Boc.



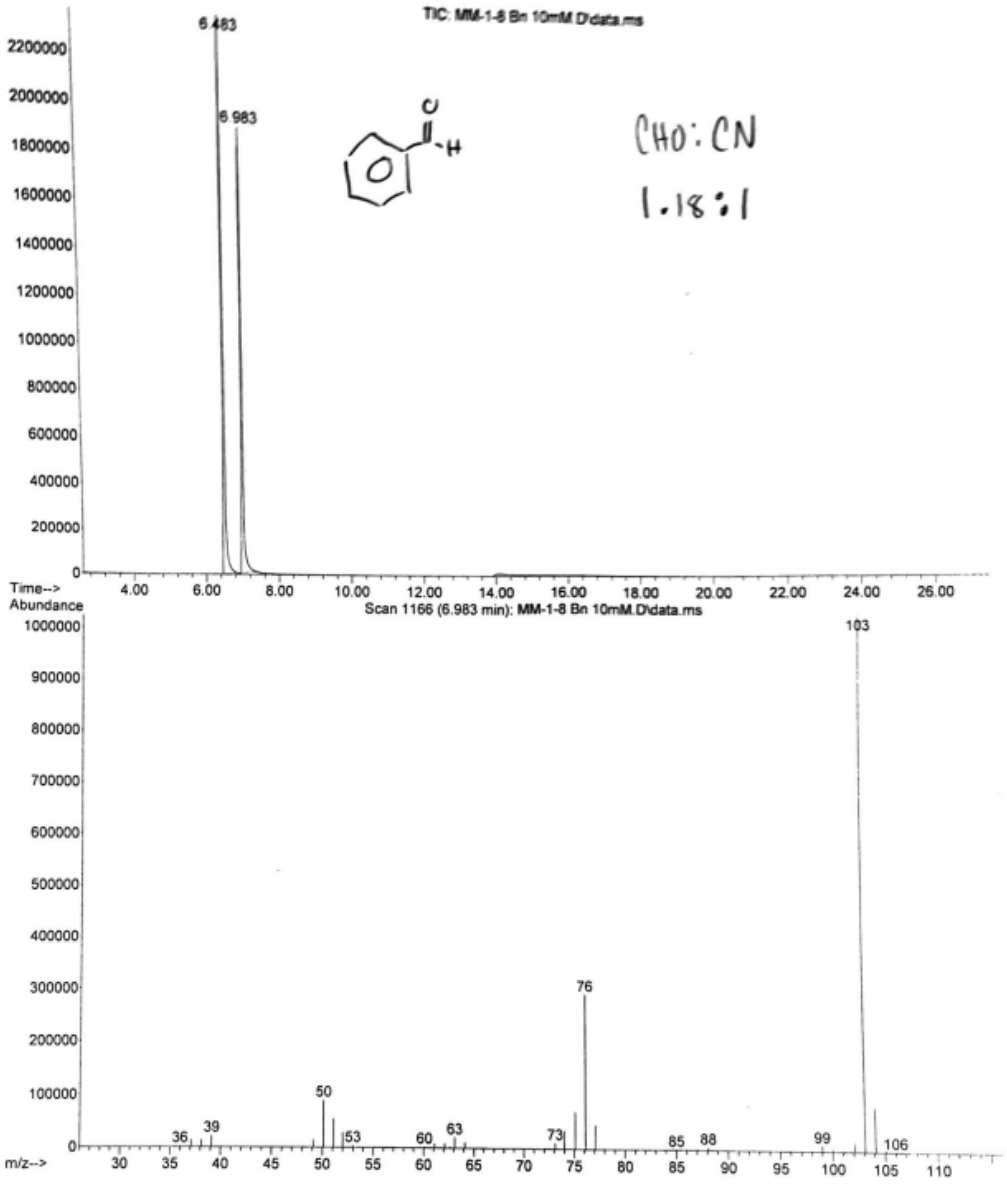
B: $^{1}H$ NMR of ADOM•HCl.



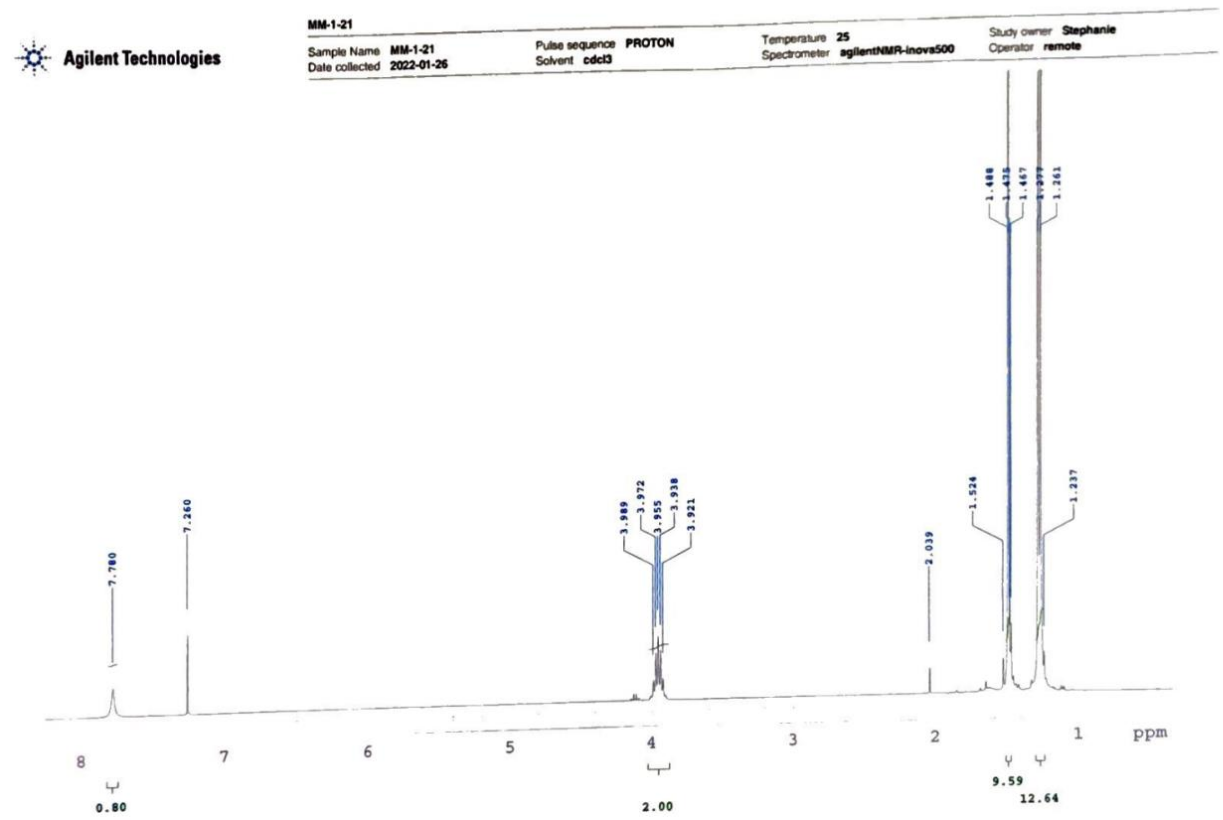
C: GC Spectra of Para-anisaldehyde conversion to 4-methoxy-benzonotrile



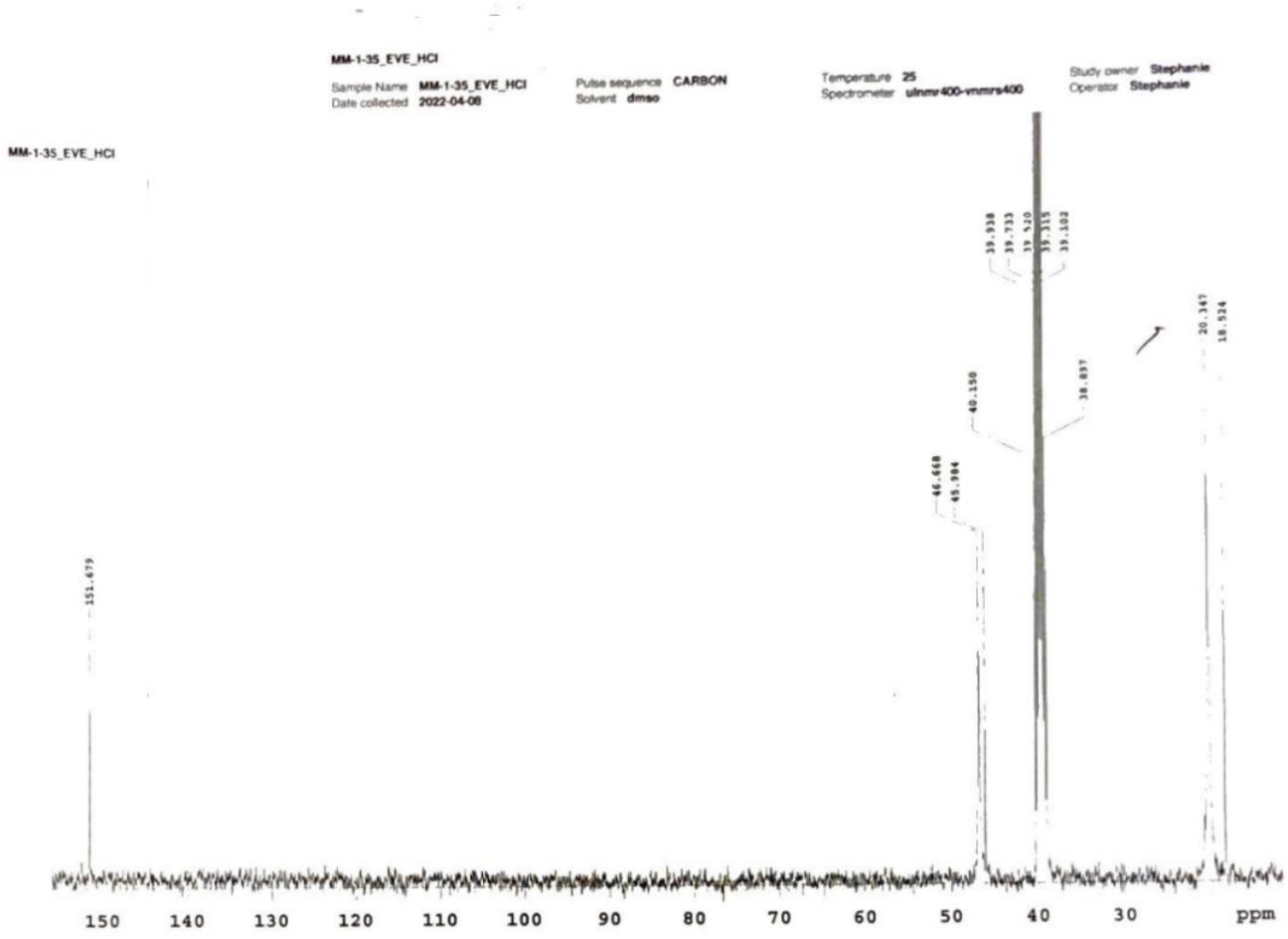
D: GC Spectra of Benzaldehyde conversion to Benzonitrile



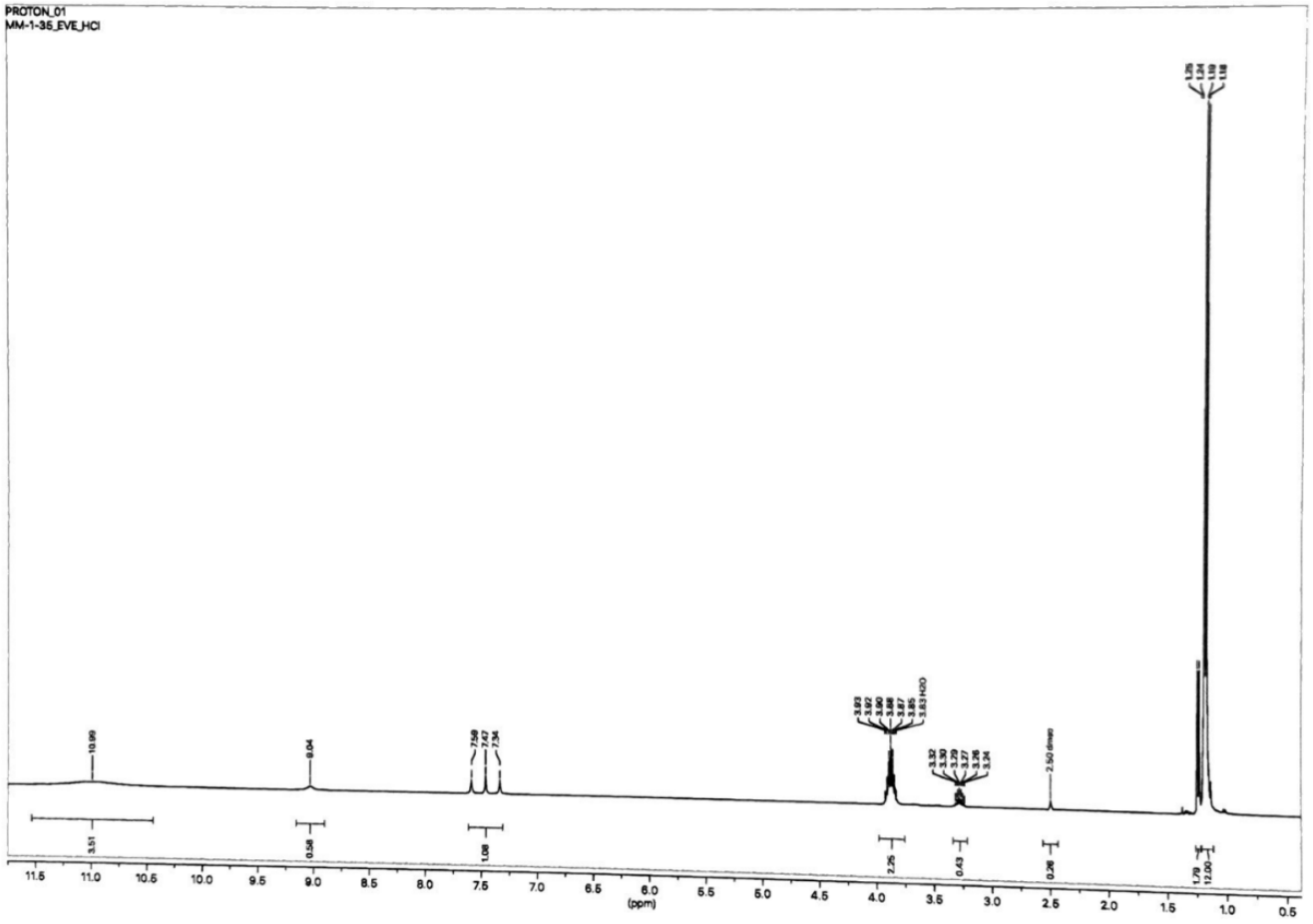
E: $^{1}H$ NMR spectrum of EVE-Boc.



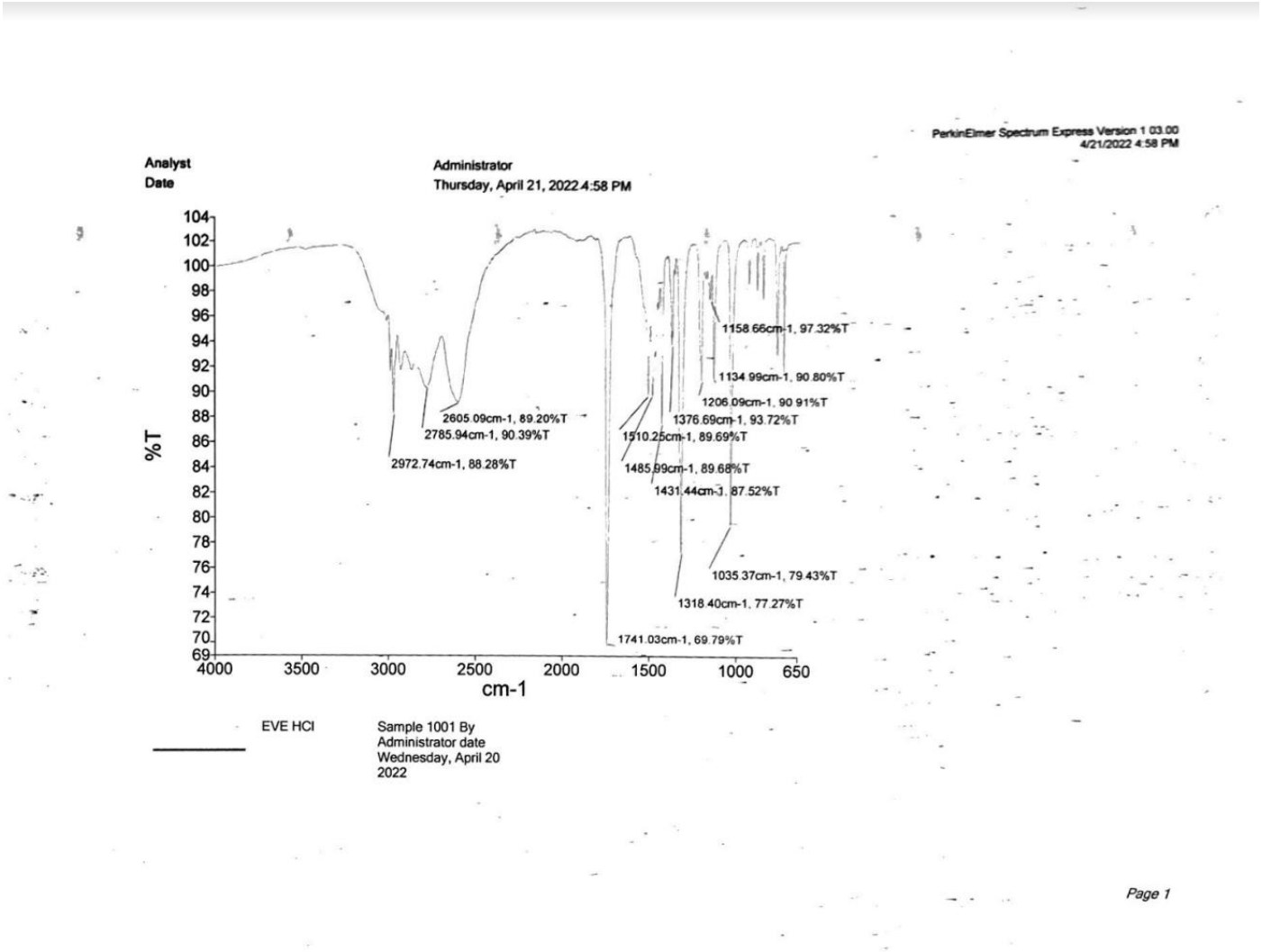
F: $^{13}C$ NMR spectrum of EVE•HCl.



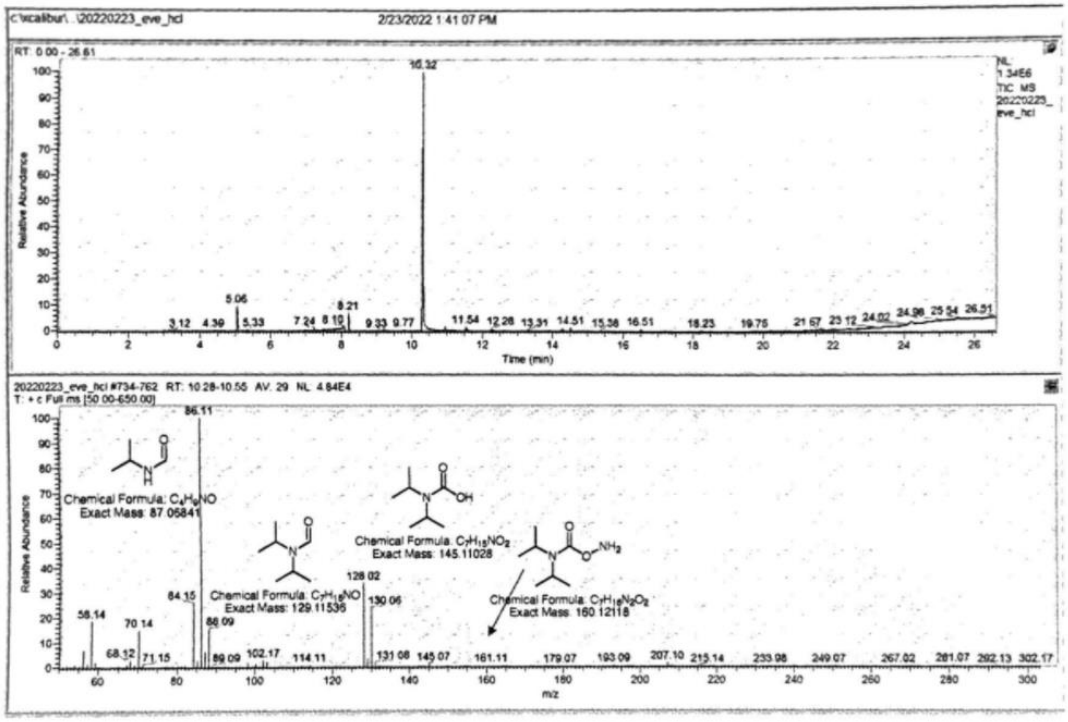
G: $^{1}$H NMR spectrumof EVE•HCl.



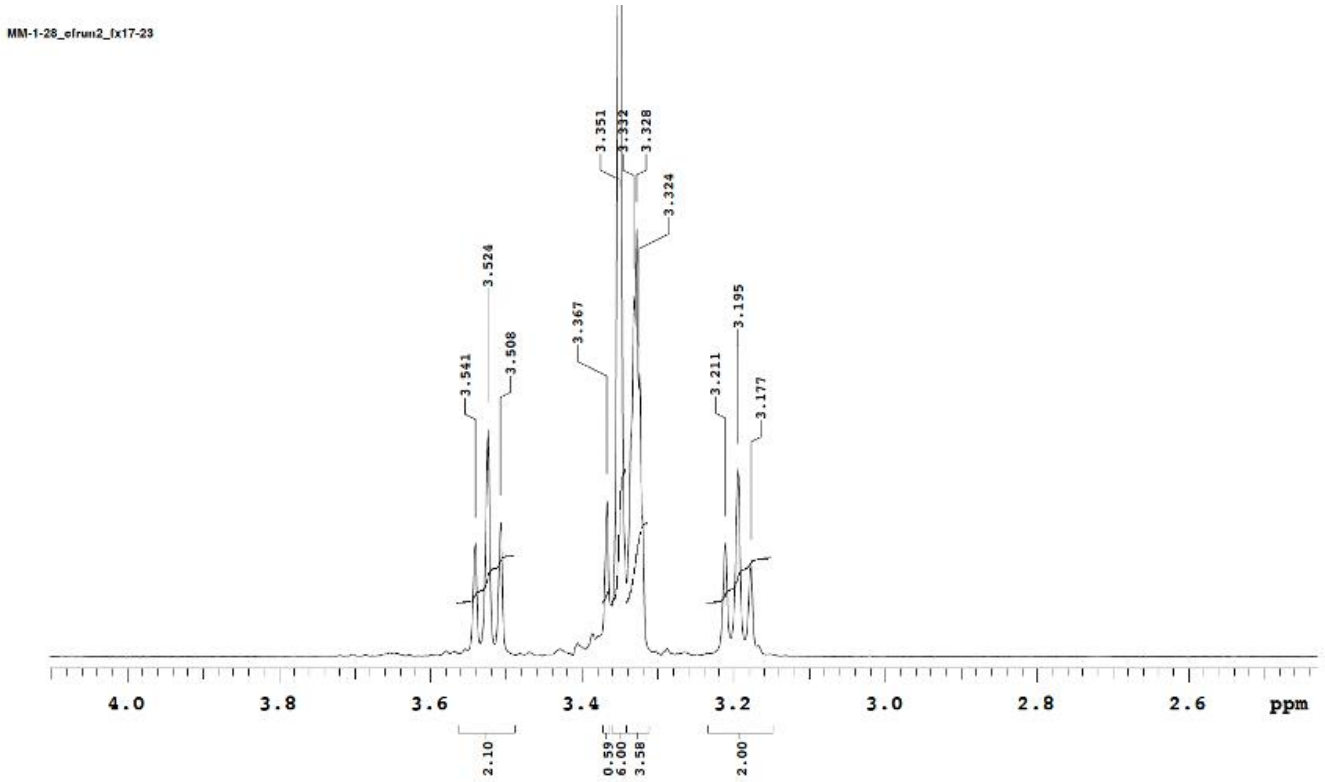
H: IR spectrum (neat) of EVE•HCl.



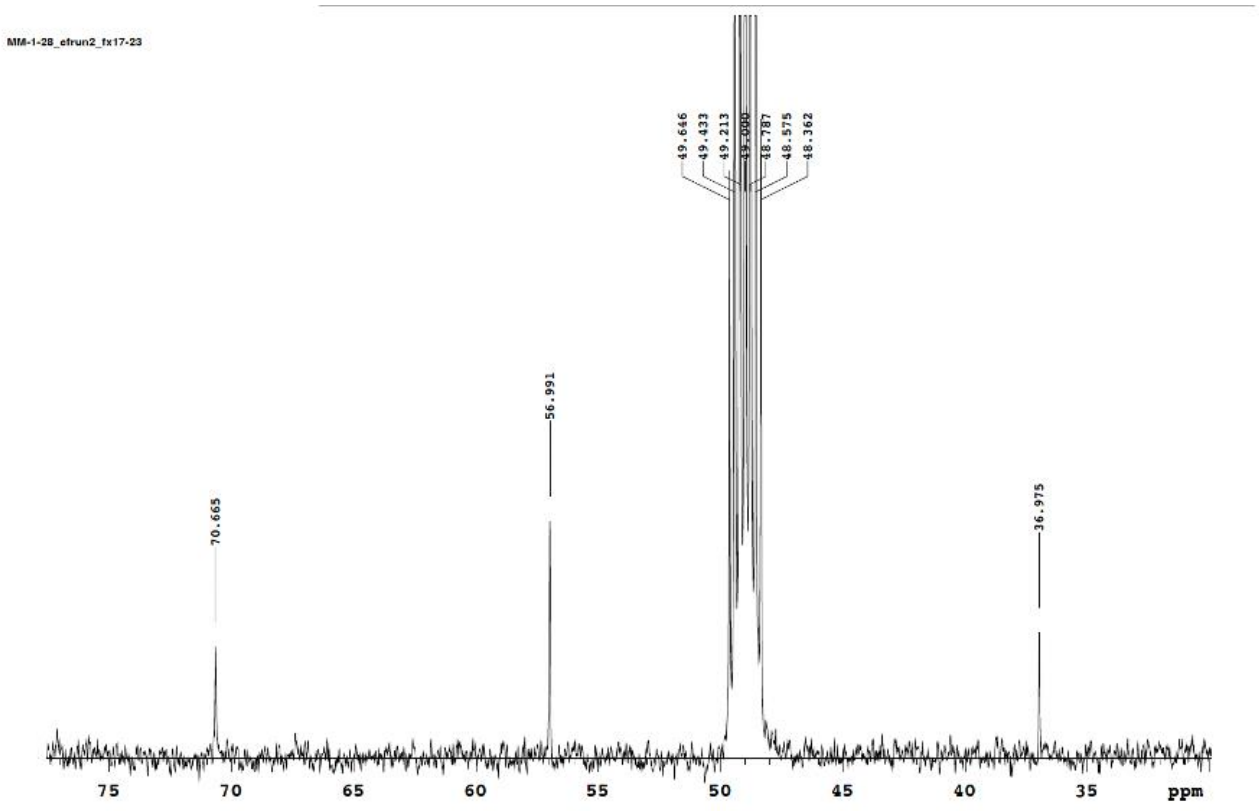
I: GCMS results of EVE•HCl in MeCN.



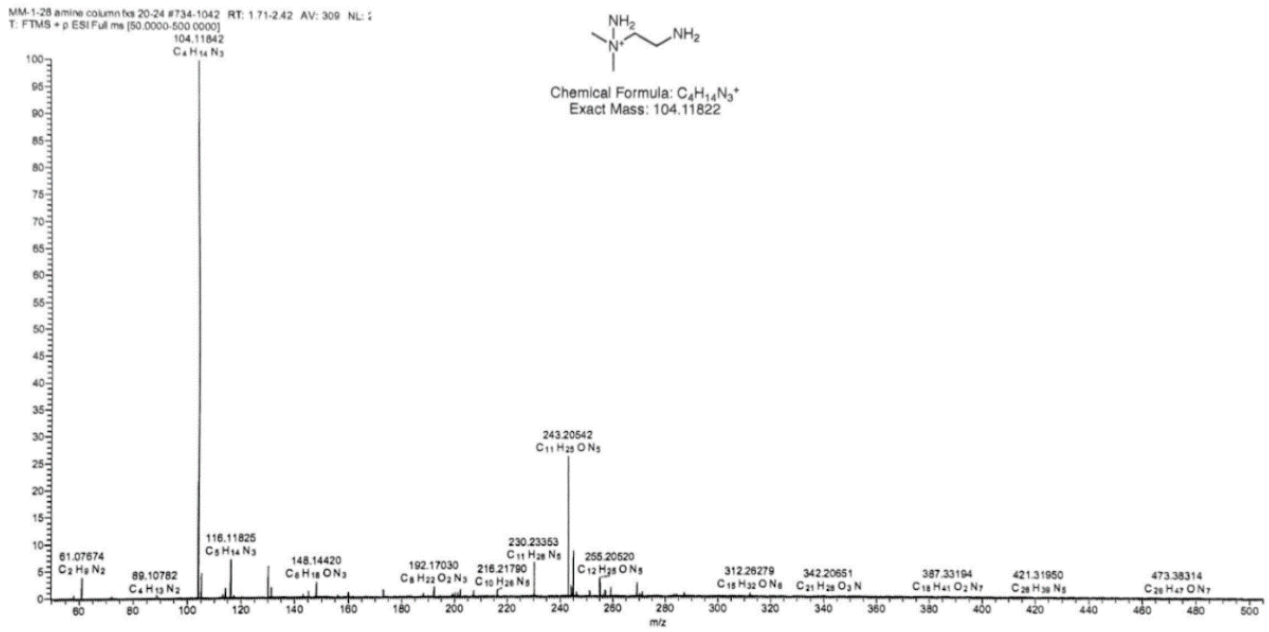
J: $^{1}$H NMR spectrum of hydrazinium salt **3**.



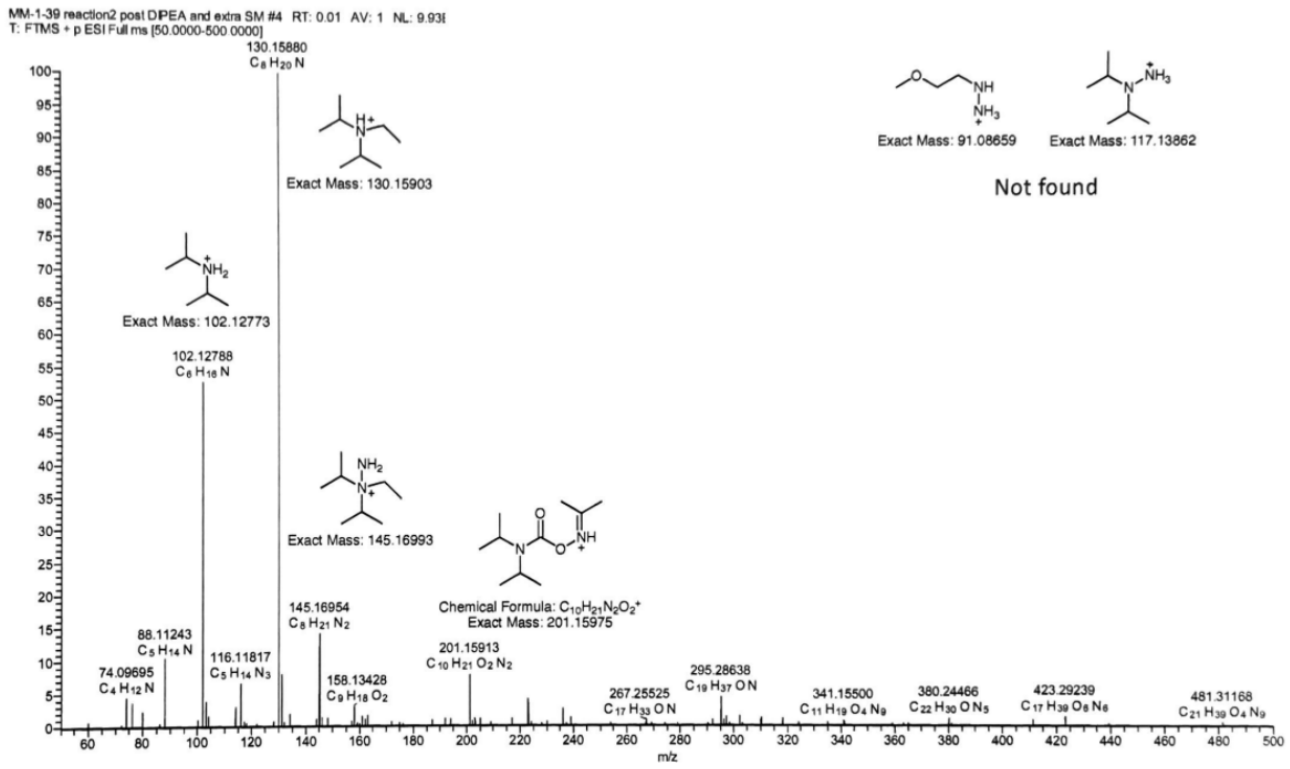
K: $^{13}C$ NMR spectrum ($CDCl_3$, 100 MHz) of hydrazinium salt **3**.



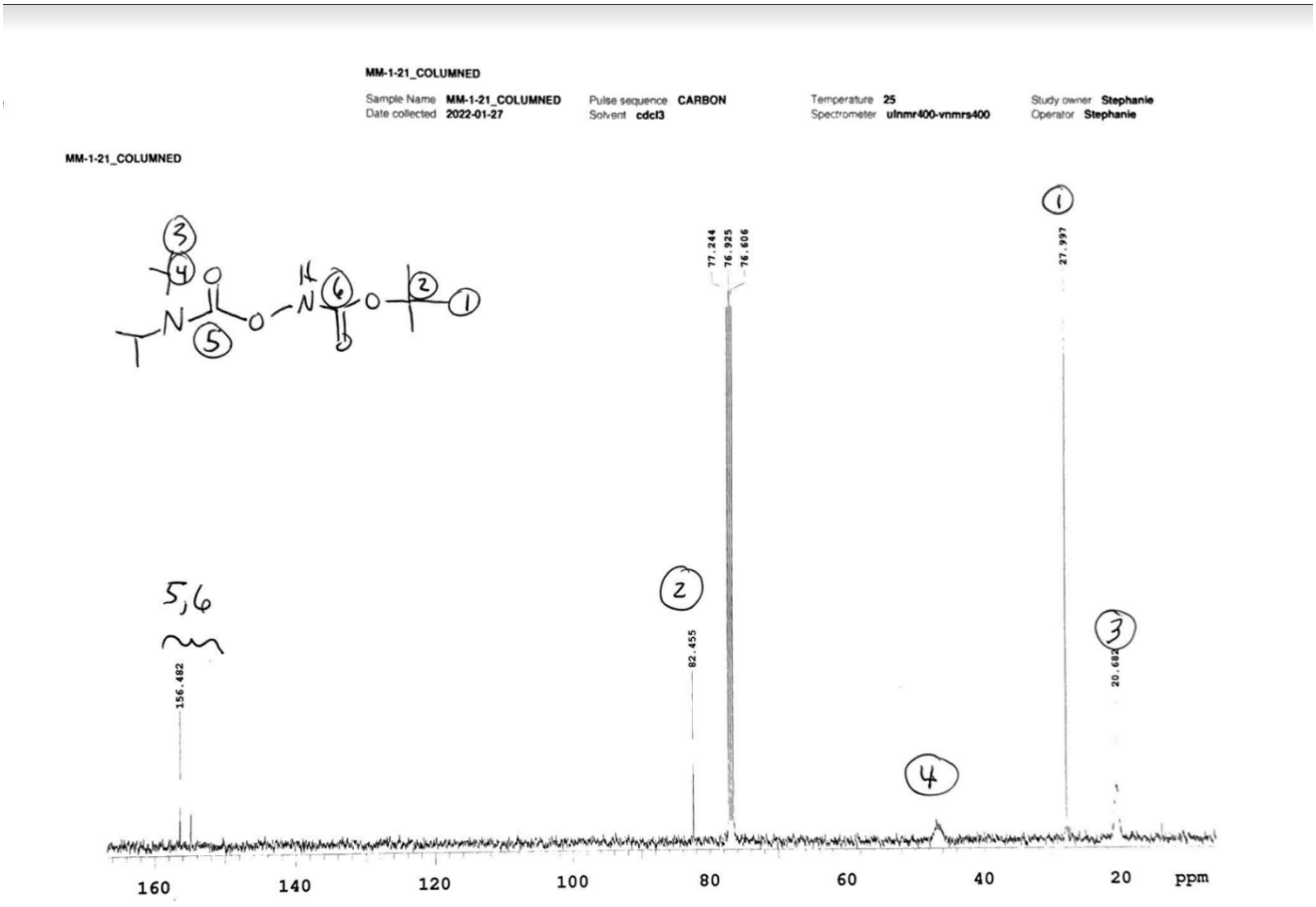
L: GCMS results of Hydrazinium salt **3** in MeCN**.**



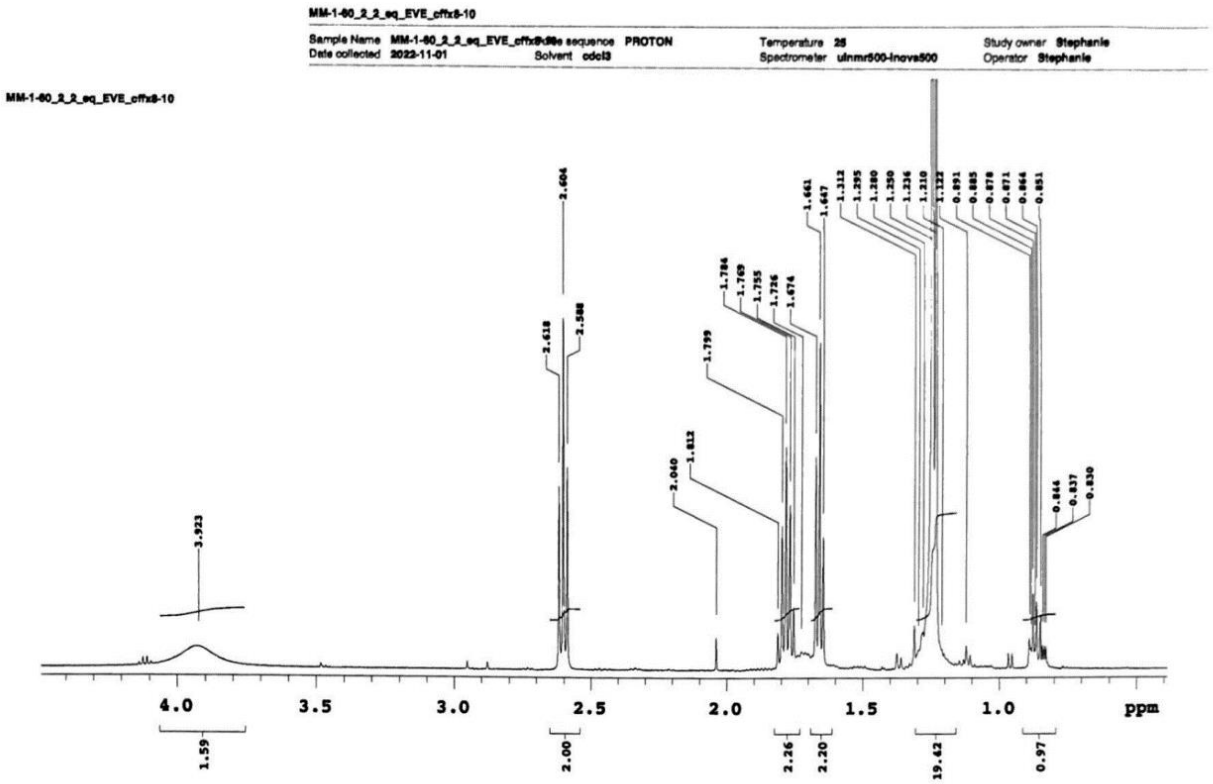
M: GCMS results of Hydrazinium salt **6** in MeCN**.**



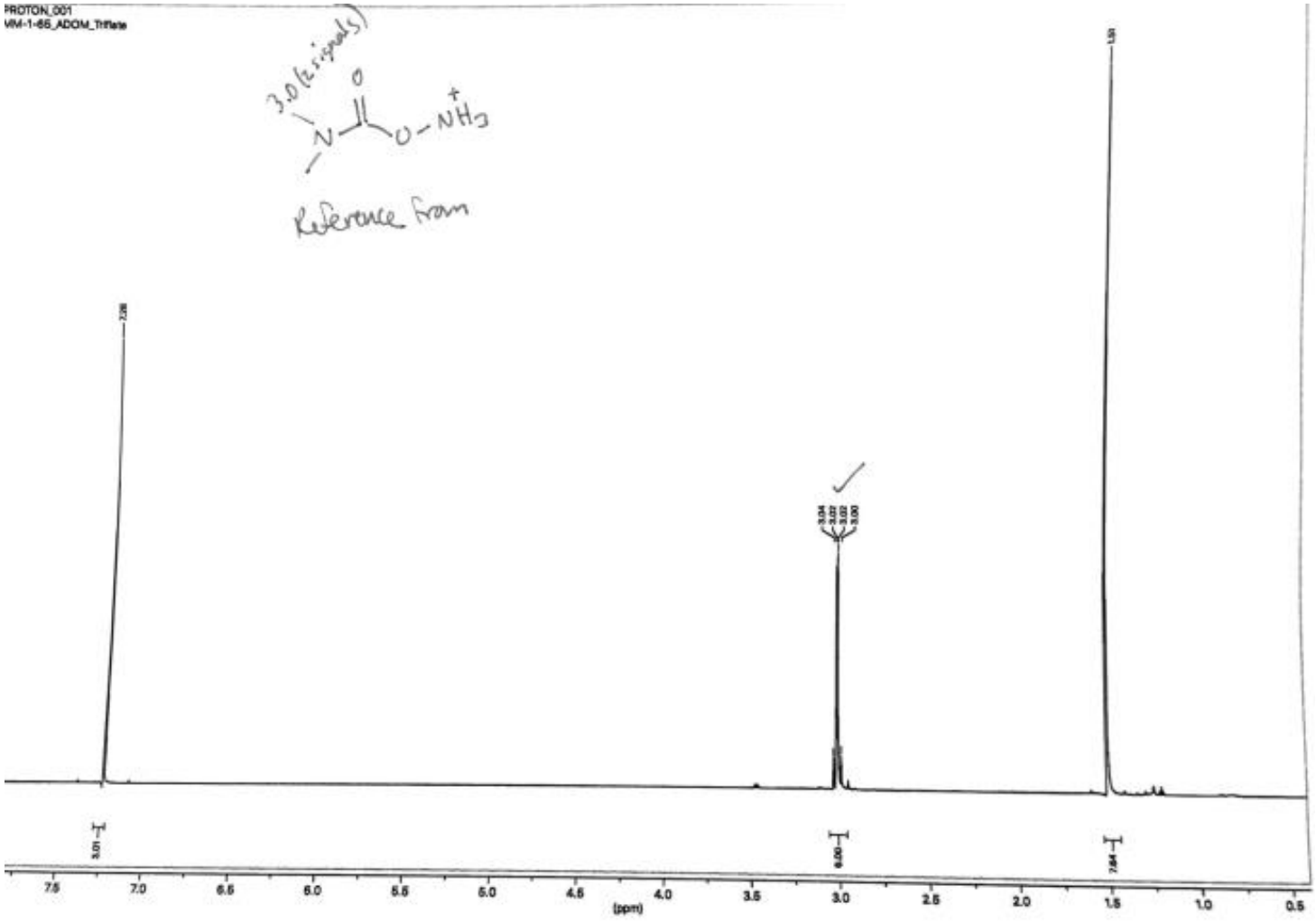
N: $^{13}C$ NMR spectrum of EVE-Boc.



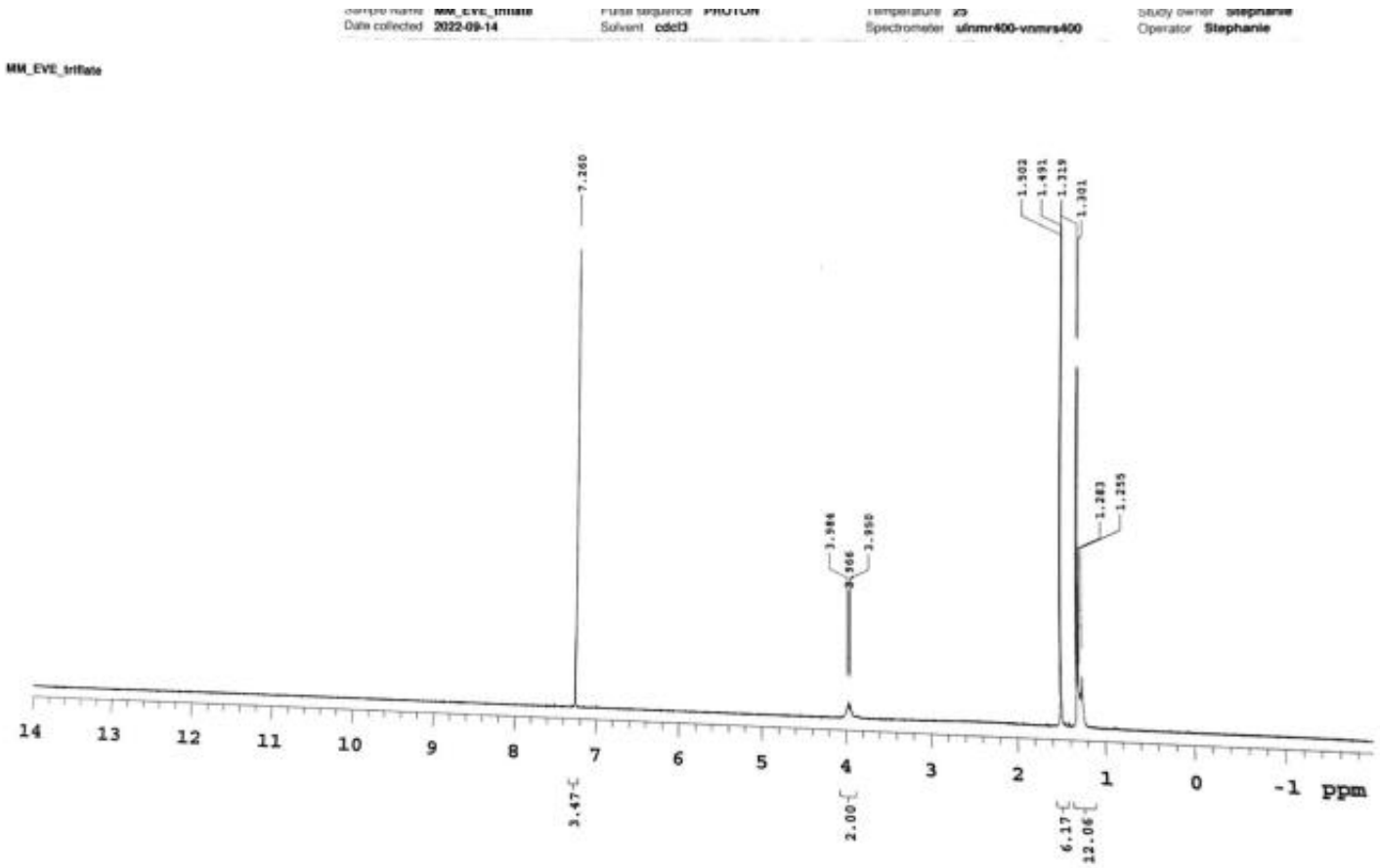
O: $^{1}H$ NMR spectrum of Oxime Carbamate Product.



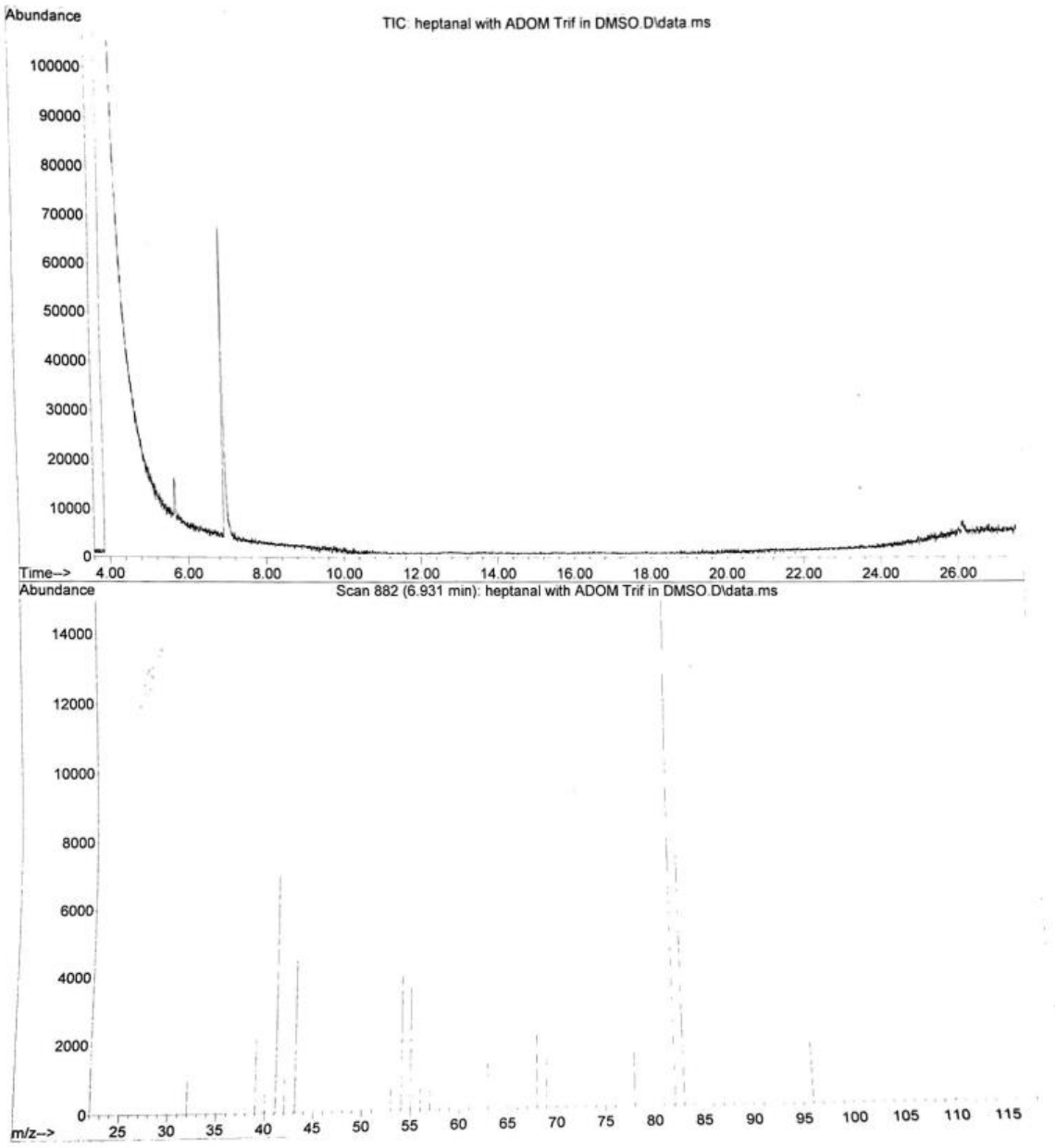
P: $^{1}H$ NMR spectrum of ADOM•OTf.



Q: $^{1}$H NMR spectrum of EVE•OTf.



R: GC-MS Spectrum of ADOM•OTf facilitated formation of heptanenitrile in DMSO.



S:[13]CNMR Spectrum of EVE•OTf facilitated amination of *N*-methylpiperazine.