SUSTAINABLE SYNTHESIS OF 4-ACYLPYRIDINES THROUGH AIR OXIDATION OF DEAROMATIZED 4-ALKYLPYRIDINES

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Abstract

Nitrogen containing heterocycles such as pyridines are a frequently encountered motif found in small molecule drugs approved by the FDA. Due to their prevalence in the pharmaceutical industry, green and effective synthetic routes towards these molecules are appealing. Herein, we detail a novel synthetic route towards 4-acypyridines via the ambient oxidation of alkylidene dihydropyridines (ADHPs). We then establish the robust and chemoselective nature of this oxidation by exploring substrates with various functional groups and multiple pyridylic sites. Moreover, we detail a series of time-course NMR studies that reveal how to manipulate the stability of ADHPs by varying the nature of the chloroformate used to make these conjugated intermediates.

Acknowledgements

First and foremost, I would like to thank my family. My greatest supporters in everything I do. Mom, dad, Anna, grandma Agnessa, grandma Olga, and my grandpa. Thank you for believing in me, encouraging me, and being the foundation upon which I stand in everything I do. I am eternally thankful for your sacrifices and unwavering faith in my abilities.

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With heartfelt thanks,

Matthew Puzhitsky

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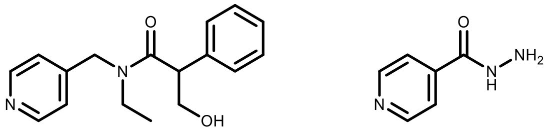
AcOH	acetic acid
ADHP	alkylidene dihydropyridines
Alloc-Cl	allyl chloroformate
API	active pharmaceutical ingredients
CH_3CN	Acetonitrile
CH_3CN	Acetonitrile
$ClCO_2R'$	R' functionalized chloroformate
$ClCH_2CO_2Et$	ethylchloro acetate
Dba	dibenzylidene acetone
DNA	deoxyribonucleic acid
DMSO	dimethylsulfoxide
Equiv	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FDA	Food and Drug Administration
HOMO	highest occupied molecular orbital
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared

L_n	ligand(s) (n = number of ligands)
M	molar
Me	methyl
MHMDS	(M=Li, Na or K) hexamethyldisilazide
Min	minute(s)
NaOH	sodium hydroxide
n-BuLi	n-Butyllithium
NEt_3	triethyl amine
NH_4HCO_2	Ammonium formate
NMR	nuclear magnetic resonance
ppm	parts per million
Pd/C	palladium on carbon
PhF	fluorobenzene
Ph	phenyl
qNMR	quantitative nuclear magnetic resonance
Rf	retention factor
r.t.	room temperature
tert	tertiary
TESOTf	triethylsilyl trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
V	volts
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthen

Chapter 1: Introduction

1.1 Importance of nitrogen-containing heterocycles

Heterocycles comprise more than 85% of all biologically active molecules, the majority of which contain nitrogen.[1] Given nitrogen's stability and its importance in biological processes such as hydrogen bonding with DNA base pairs, this comes as no surprise. A review of the FDA database shows that structures such as pyridines and pyrimidines are extremely common features in approved small molecule drugs.[2] Reactions incorporating nitrogen containing heterocycles into drug-like molecules allow for the investigation of pharmacological properties (i.e. solubility, target selectivity, drug metabolism) leading to the development of APIs present in many categories of consumer drugs (Figure 1).[2] In addition, nitrogen containing heterocycles are found in subunits of many natural products like vitamins, hormones, and antibiotics.[1,2] Due to their vast applications in medicinal chemistry, nitrogen containing heterocycles are an important target in organic synthesis, and a major effort has been made in our group to explore their chemistry.



Tropicamide (Anticholinergic) Isoniazid (Antibiotic against tuberculosis)

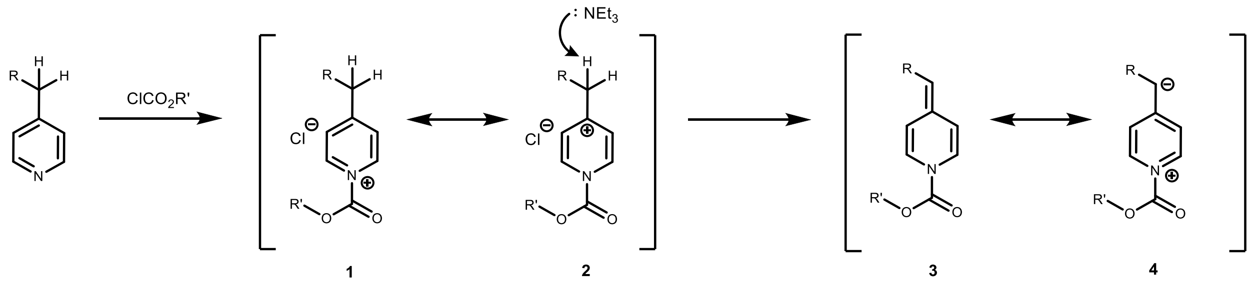
Figure 1. Nitrogen containing heterocyclic APIs

1.2 Exploring the soft enolization of pyridines

Given the utility of pyridines in drug discovery, much work has been done to explore their reactivity. The activation of the pyridylic position by the addition of chloroformates to pyridines allows for deprotonation at the pyridylic position in a process we refer to as ‘soft dearomatization’.[3] This strategy captured our groups attention due to the versatile nature of the resulting semi-stable intermediates called ADHPs. Our group and others have put much effort into the application of these molecules as nucleophiles in many useful transformations.

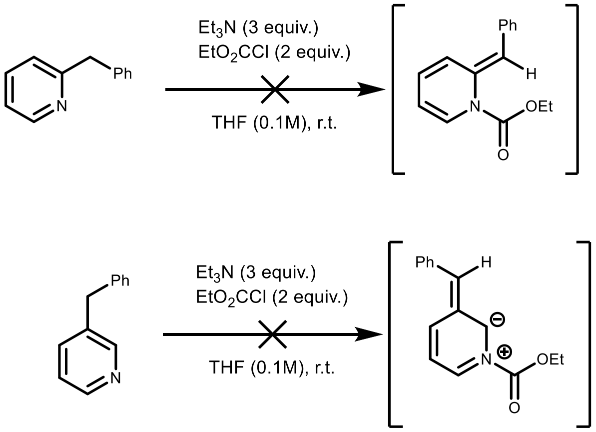
1.3 Formation of alkylidene dihydropyridines (ADHPs)

ADHPs are readily prepared through a soft dearomatization approach involving treatment of 4-alkylpyridines with chloroformates and a mild base (Scheme 1).[3] The addition of a chloroformate to 4-alkylpyridine leads to the formation of an acyl pyridinium ion (1, Scheme 1). This in turn reduces the pKa of the pyridylic protons due to the electron withdrawing nature of the chloroformate to the extent that a mild base such as triethylamine can deprotonate the acyl pyridinium, forming the ADHP under mild conditions. Resonance structures indicate the nucleophilic nature of the alkylidene carbon (Scheme 1, 4), suggesting ADHPs’ potential reactivity as an electron rich partner in many useful transformations.



Scheme 1. ADHP formation via soft-enolization

We also found that ADHPs form exclusively with 4-alkyl substituted pyridines. Previously, we established that although 2- and 3-alkylpyridines can form pyridinium salts upon the addition of a chloroformate, deprotonation of the resulting pyridinium ion does not occur, hence ADHPs do not form. Steric clash between the 2-alkyl substituent and the chloroformate's alkoxy carbonyl prevents ADHP formation with 2-alkylpyridines. This might be due to the resulting orthogonal relationship between the heterocycle and the carbonyl group which prevents deprotonation of the pyridinium salt. On the other hand, deprotonation of pyridinium salts derived from 3-alkylpyridines do not occur simply because they are not resonance-stabilized by the pyridylic nitrogen (Scheme 2).[4,5,6] This further highlights the chemoselectivity the ADHPs.

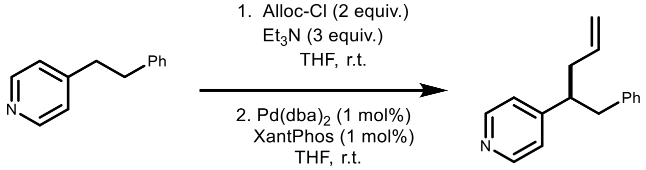


Scheme 2. Unsuccessful oxidation of 2' and 3' alkylpyridines

1.4 Mild formation of ADHPs as intermediates for useful transformations

1.4.1 Allylation of 4-alkylpyridines

Recently, our group has developed a method for the mild allylation of 4-alkyl-pyridines.[4] We showed that allyl chloroformate can be used to activate the pyridylic position via soft-enolization. Subsequent treatment of the resulting ADHP with a palladium catalyst would result in decarboxylative allylation at the pyridylic position to afford C-C bond formation (Scheme 3).

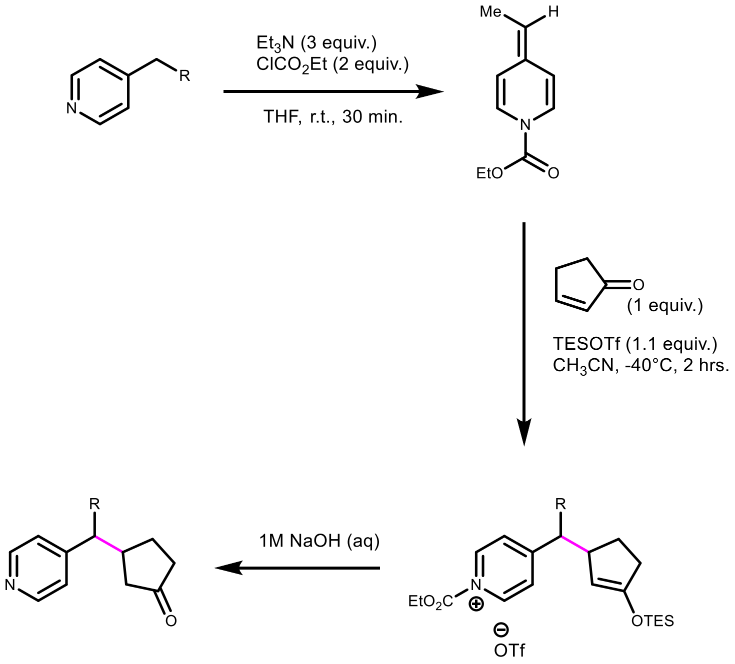


Scheme 3. Mild palladium-catalyzed selective allylation of 4-alkylpyridines

This method allows us to form a stereogenic carbon at the pyridylic position, a valuable transformation since stereogenicity is often desired to increase the target selectivity of a drug candidate. However, due to the high pKa of alkylpyridines, the usual methods to perform the same transformation involve prior activation of the pyridylic position and the use of superstoichiometric amounts of strong bases like *n*-BuLi and/or MHMDS (M=Li, Na or K). [8,9,10,11] On the other hand, the unique chemistry of ADHPs allow us to functionalise the pyridylic C(sp^3)-H position under mild conditions.[29]

1.4.2 Addition of 4-alkylpyridines to α,β-unsaturated ketones

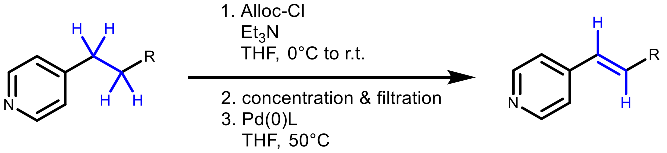
In addition to the allylation work, our group has used ADHP intermediates as soft nucleophiles towards Lewis acid activated α,β-unsaturated ketone electrophiles in conjugate addition reactions (Scheme 4).[5] Once again, this method demonstrates that ADHPs are a useful synthetic tool that allow for milder alternatives to transformations which would normally require strong bases or metal catalysts.[8,9,10,11]



Scheme 4. Lewis acid-mediated addition of ADHPs to α,β-unsaturated ketones

1.4.3 Dehydrogenation of 4-alkylpyridines

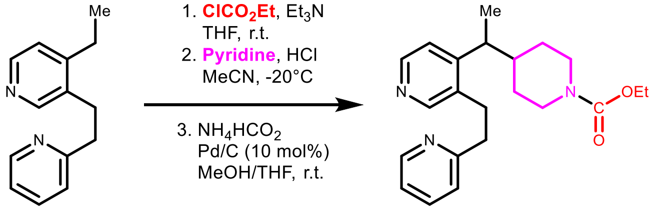
Another application of ADHP chemistry that our group has developed is the palladium-catalyzed selective dehydrogenation of 4-alkylpyridines.[6] Treatment of ADHPs with an allyl chloroformate and a palladium catalyst releases a pyridylic anion which combines with an allylpalladium (II) complex. The resulting intermediate undergoes β-hydride elimination to install a double bond at the pyridylic position (Scheme 5). Alkenylpyridines are typically prepared using strongly basic reagents, such as Grignard reagents, phosphonium ylides, or pyridylic anions, however the use of ADHP allows for the generation of the same product under softer conditions.[30,31,32]



Scheme 5. ADHP mediated synthesis of 4-alkenyl pyridines

1.4.4 Installation of piperidines on 4-alkylpyridines

Our most recent application of ADHPs was the mild synthesis of molecules consisting of 4-pyridine and 4-piperidine moieties joined by a substituted methylene group.[21] This is achieved by activation of the already inherently electrophilic 4-position of pyridine by a Brønsted acid such as HCl and the subsequent addition of the nucleophilic ADHP intermediate. Acyl migration from the resulting acylpyridinium ion to the dihydropyridine results in an adduct bearing a pyridine moiety along with a protected dihydropyridine fragment. Finally, transfer hydrogenation yields the desired product bearing pyridine and piperidine fragments. This method allows us to directly combine useful molecules such as pyridines and piperidines, both with proven utility in medicinal chemistry.



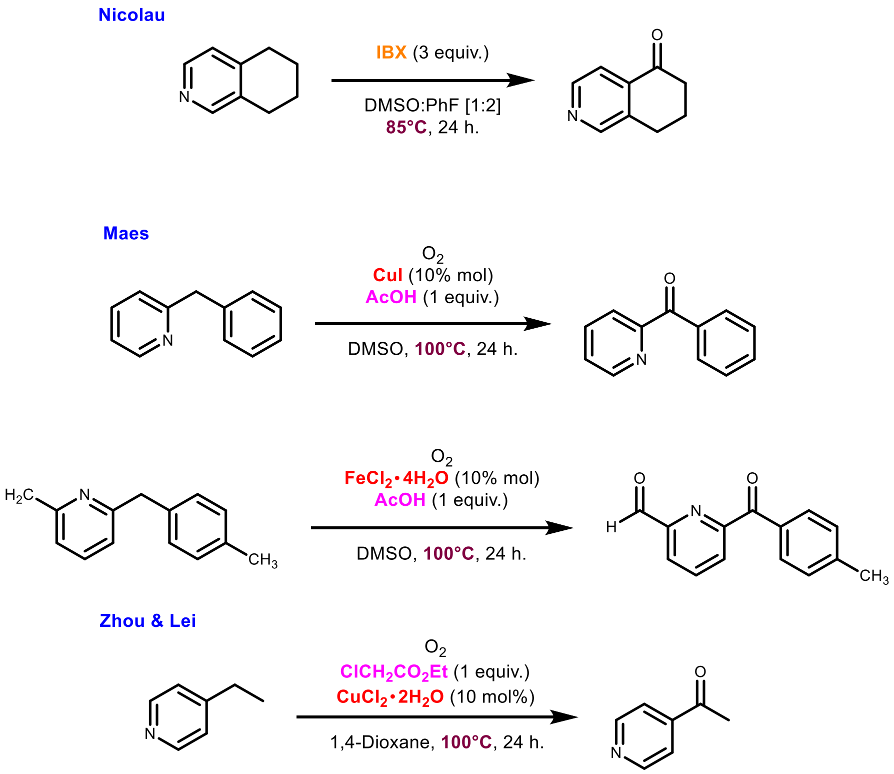
Scheme 6. ADHP mediated synthesis of "lead-like" molecules incorporating 4-pyridine and 4-piperidine

This is yet another example of our use of ADHPs to circumvent a pitfall in a conventional process. In this case, proposing a method which allows one to begin drug discovery from “lead-like” molecules instead of the conventional process which requires the initial generation of bulky molecules with increased molecular weight and lipophilicity.

Overall, the previous work done in our group shows that the nucleophilic nature of ADHP intermediates and their remarkably mild formation via soft-enolization can be leveraged to achieve valuable products using comparatively green procedures compared to the current methods used to make the same molecules.

1.5 Current syntheses of acyl pyridines

In recent years much progress has been made in the preparation of acylpyridines via oxidation of alkylpyridines with an emphasis on sustainability, mainly by using oxygen as the terminal oxidant. Despite this, some current methods still rely on the use of superstoichiometric amounts of external oxidants like 2-iodoxybenzoic acid (IBX).[8] When oxygen is employed as the terminal oxidant, it is often paired with the use of transition metals such as Cu and Fe for catalysis, prior activation of the pyridine ring via stoichiometric amounts of AcOH or $ClCH_2CO_2Et$, and harsh conditions (namely, elevated temperatures), all while also exhibiting poor chemoselectivity.[8,9,11,12,13]

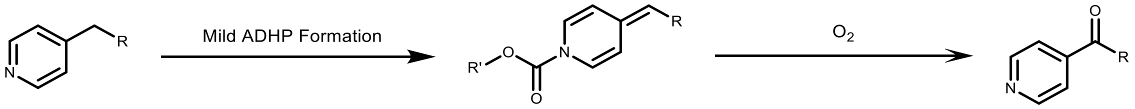


Scheme 7. Recent syntheses of acylpyridines from alkylpyridines

1.6 A Green alternative to current syntheses of pyridylic ketones

The importance of 4-acylpyridines as intermediates of in drug synthesis campaigns led us to explore the development of a more sustainable and inexpensive pathway towards this product. Despite advancements in the sustainability of alkylpyridine oxidation protocols, a completely metal-free and site-selective oxidation method that proceeds under mild conditions still does not exist. Although the above reports use relatively sustainable transition metal catalysts, metals such as Cu and Fe can be difficult to remove from heterocyclic products, thus interfering with certain biological assays and causing issues further along in the drug discovery process.[14]

While studying the unique nature of ADHPs we made the serendipitous discovery that they undergo oxidation to acylpyridines after exposure to ambient oxygen under mild conditions without the use of transition metal catalysts or any external oxidants (Scheme 8). We quickly realized that this reactivity could represent a novel strategy to access acylpyridines at large scales where management of waste streams is critical. Our newly discovered oxidation method seemed to circumvent the pitfalls of current alkylpyridine oxidations while being highly selective for 4-alkylpyridines.



Scheme 8. ADHP oxidation as a method of 4-acylpyridine formation from 4-alkylpyridines

1.7 Synthesis of 4-acylpyridines via ADHP oxidation: method optimization

Upon the discovery that the oxidation of ADHPs yields a mixture mainly consisting of acylpyridines, we first sought to optimize reaction conditions. ^{1}H-NMR spectra revealed that although the desired acylpyridine was the main component of the resulting reaction mixture, several side products were also observed (Scheme 9). Our reaction optimization process was centered around screening factors such as solvent, concentration, base additives, and temperature led us to optimized conditions which limited the amount of side products produced (Table 1, see

SI for detailed screen). The best result was found to be acetone at a concentration of 0.1M (Table 1, entry 4), as it led to conversion of the ADHP to ketone at the highest yield, with minimal byproducts (pyridylic alcohol **A**, its carbonate **B**, pyridone **C** from Scheme 9) [1].

Next, we sought to optimize a one-pot ADHP formation and oxidation process. To design a green and efficient oxidation method, designing a process in which the ADHP is both generated and oxidized *in-situ* would minimize the amount of unit operations by greatly reducing the waste produced. We first wanted to see if we can make the ADHP in acetone (our optimal solvent for oxidation) instead of THF. Once we found that this is possible, we tried to form the ADHP in acetone under an O_2 atmosphere (O_2 balloon) to allow it to oxidise *in-situ* without having to isolate the semi-stable intermediate. Once we proved the concept was possible, we sought to optimize substrate loading conditions and found that 1.2 equivalents of Et_3N and 1.05 equivalents of chloroformate gave the best result (table 4, entries 5 and 6). This led us to our final optimized one-pot ADHP oxidation conditions (scheme 7).

Entry	-R	Solvent [mol/L]	Et_3N (equiv.)	EtO_2CCl (equiv.)	ADHP **Yield** (%)	Ketone **Yield** (%)
1	-Ph	THF [0.1]	3	2	42	24
2	-Me	THF [0.1]	3	2	0	56
3	-Me	Acetone [0.1]	3	2	43	26
4	-Me	Acetone [0.1]	3	1.05	17	43
5	-Me	Acetone [0.1]	1.2	1.05	0	54
6	-Ph	Acetone [0.1]	1.2	1.05	0	78

Table 1. One-pot ADHP oxidation procedure optimization[2]

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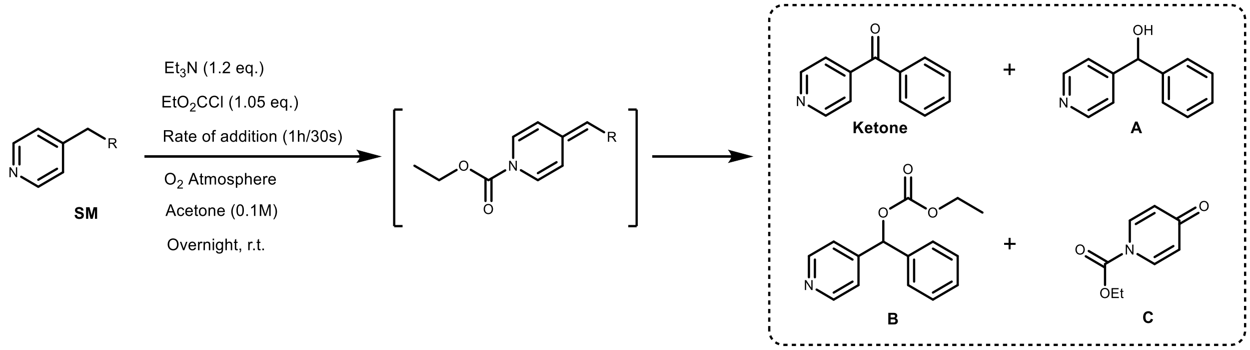
[1] Byproducts confirmed via NMR analysis.

[2] Yields reported obtained via quantitative NMR analysis.



Scheme 9. Side products formed during ADHP oxidation

1.8 Research plan

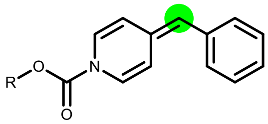
Given the limitations of existing methods for acylpyridine synthesis, my research project will aim to exploit the propensity of ADHPs to undergo ambient oxidation in hopes of developing a highly selective, yet green synthetic route towards these valuable products. To do this, I will first explore the effect of the chloroformate used to dearomatize ADHP intermediates on their resulting stability. Once a stability trend is established, I will use cyclic voltammetry (CV) to measure the oxidation potentials of the ADHPs and see whether these values corelate with our previously observed trends. Finally, we will explore the substrate scope of this reaction using a variety of pyridines bearing differing functional groups.

Chapter 2: Results and Discussion

2.1 ADHP decomposition trends

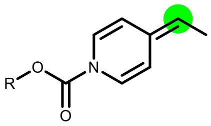
2.1.1 Electron density and decomposition of ADHPs

When first exploring the oxidation of ADHPs as a synthetic route towards 4-acylpyridines, we made the qualitative observation that the use of different chloroformates influenced stability of the resulting ADHP. Our first step in further investigating this discovery was to establish the effect of chloroformate structure on the stability of ADHPs derived from alkylpyridines. ^{1}H- and ^{13}C-NMR spectra of the ADHPs clearly demonstrate the effect that a given chloroformate has on the resulting electron density of the dearomatized intermediate. In ADHPs derived from both 4-benzylpyridine and 4-ethylpyridine, the resonance values of the alkylidene protons and the alkylidene carbons shift further downfield as the electron withdrawing capability of the chloroformate alkyl group increases (Table 2 and Table 3)



ADHP formed using "X" Chloroformate	**^{1}H NMR Shift (ppm)**	**^{13}C NMR Shift (ppm)**
Ethyl Chloroformate	5.80	114.9
Allyl Chloroformate	5.81	115.3
Benzyl Chloroformate	5.81	115.4
Phenyl Chloroformate	5.90	116.5
Trichloroethyl Chloroformate	5.9	117.1
Nitrophenyl Chloroformate	5.96	118

Table 2. ^{1}H and ^{13}C Chemical shifts of methine group: ADHPs derived from 4-benzylpyridine



ADHP formed using “X” Chloroformate	**^{1}H NMR Shift (ppm)**	**^{13}C NMR Shift (ppm)**
Ethyl Chloroformate	4.83	110.1
Allyl Chloroformate	4.85	110.4
Benzyl Chloroformate	4.86	110.6
Phenyl Chloroformate	4.94	111.8
Trichloroethyl Chloroformate	4.94	112.4
Nitrophenyl Chloroformate	5.00	113.5

Table 3. ^{1}H and ^{13}C Chemical shifts of methine group: ADHPs derived from 4-ethylpyridine

It must be noted that ADHPs derived from phenyl and 4-nitrophenyl chloroformate both proved to be considerably stable to oxidation but were prone to hydrolysis, reverting to chloroformate and the respective 4-alkylpyridine starting material. Since signals from the starting material interfered with the time-course NMR experiments due to their proximity to the signals from the desired pyridylic ketone product, we did not include these ADHPs in the above experiments.

2.1.2 Effect of chloroformate’s alkyl group on the decomposition of ADHPs

A systematic study was then conducted to study the effect of various chloroformates on the stability of the resulting ADHP. First, ADHPs were prepared using 4-benzylpyridine and commercially available chloroformates with varying alkoxy groups. The stability of the resulting ADHP was tested by monitoring its disappearance coinciding with the appearance of the acylpyridine in an NMR sample made with $CDCl_3$ and sealed under an oxygen enriched atmosphere achieved via purging with an O_2 filled balloon. The oxidation was monitored over a period of approximately seven hours, with spectra recorded every hour. Integration values of well-defined and isolated peaks corresponding to the ADHP, and ketone were compared to track the progression of the reaction (Figure 2 and Figure 3).

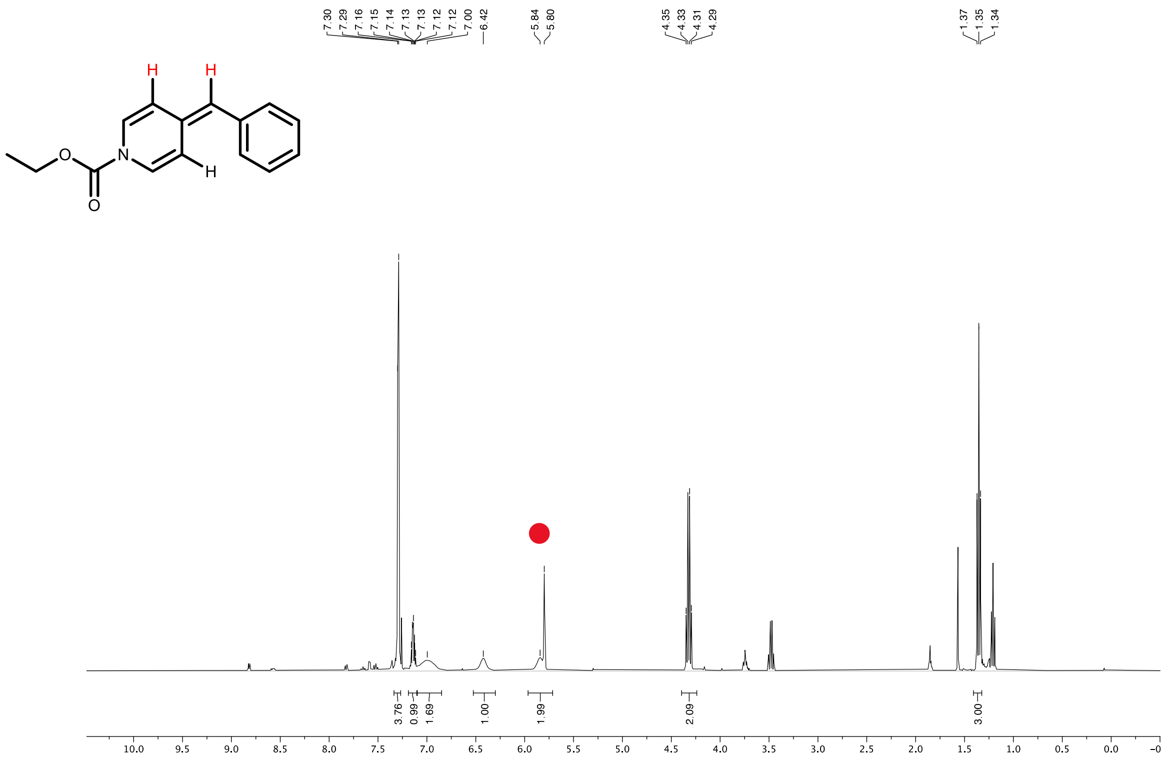


Figure 2. Signal used to monitor the disappearance of the ADHP (red)[3]

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[3] Note that the sharp signal at 5.8ppm (alkylidene proton) overlaps with the broad doublet at 5.84ppm (dearomatized pyridine C-Hs). Since both peaks result from the ADHP, both were tracked as they disappeared at the same rate as the ADHP decomposed.

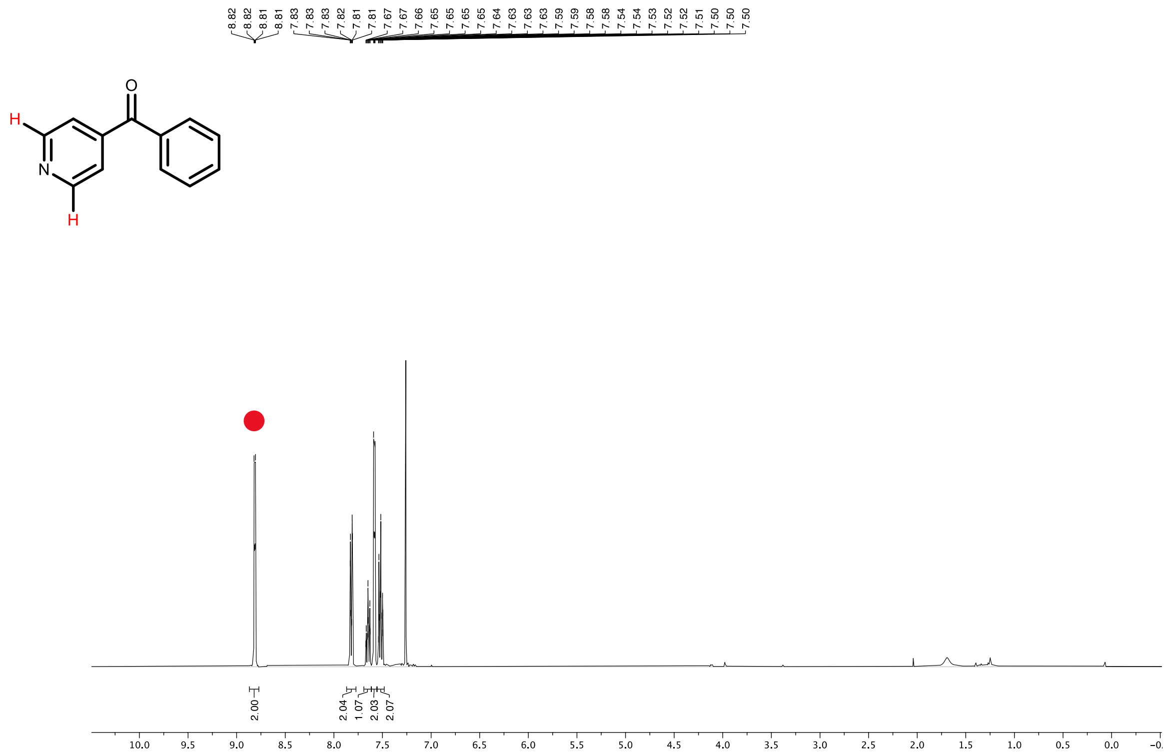


Figure 3. Signal used to monitor the formation of ketone (red)

A clear trend emerges from the compiled NMR data: more electron withdrawing R groups (e.g. Benzyl) result in more stable ADHPs, while alkyl substituted intermediates made with ethyl and allyl chloroformates are the most readily oxidized (allyl being more stable than ethyl due to higher s character from sp^2 bonds). This trend suggests that chloroformates bearing more electronegative R groups will draw electron density from alkylidene position of ADHP, making it less prone to the oxidation process in question.

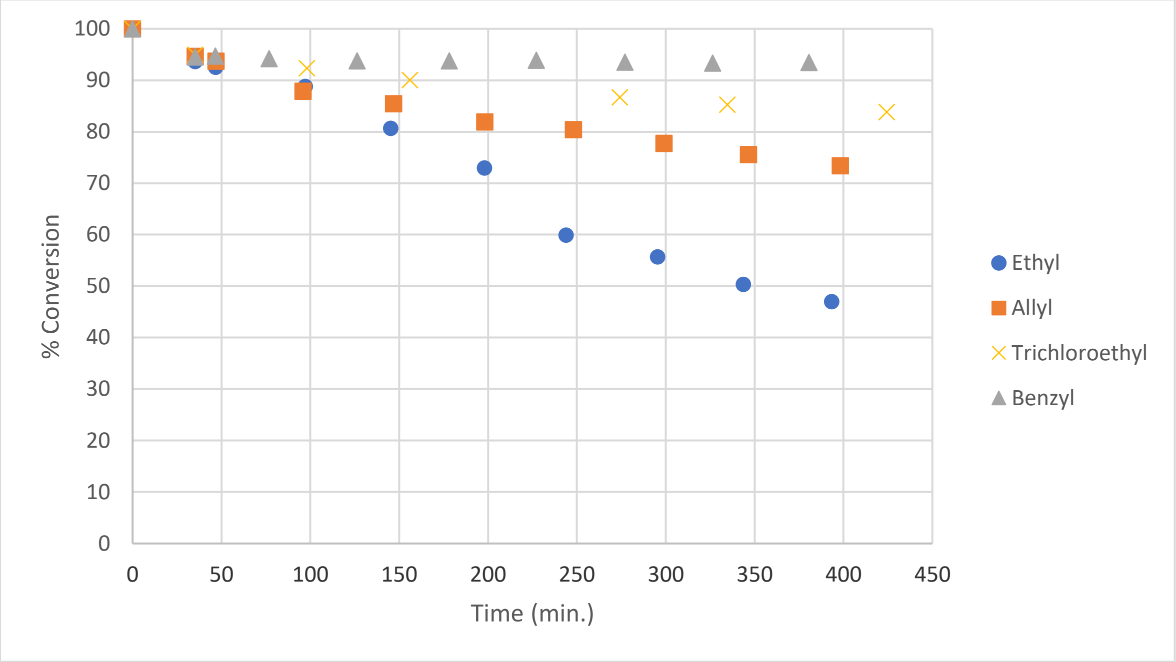


Figure 4. Effect of chloroformate alkyl group on ADHP Decomposition

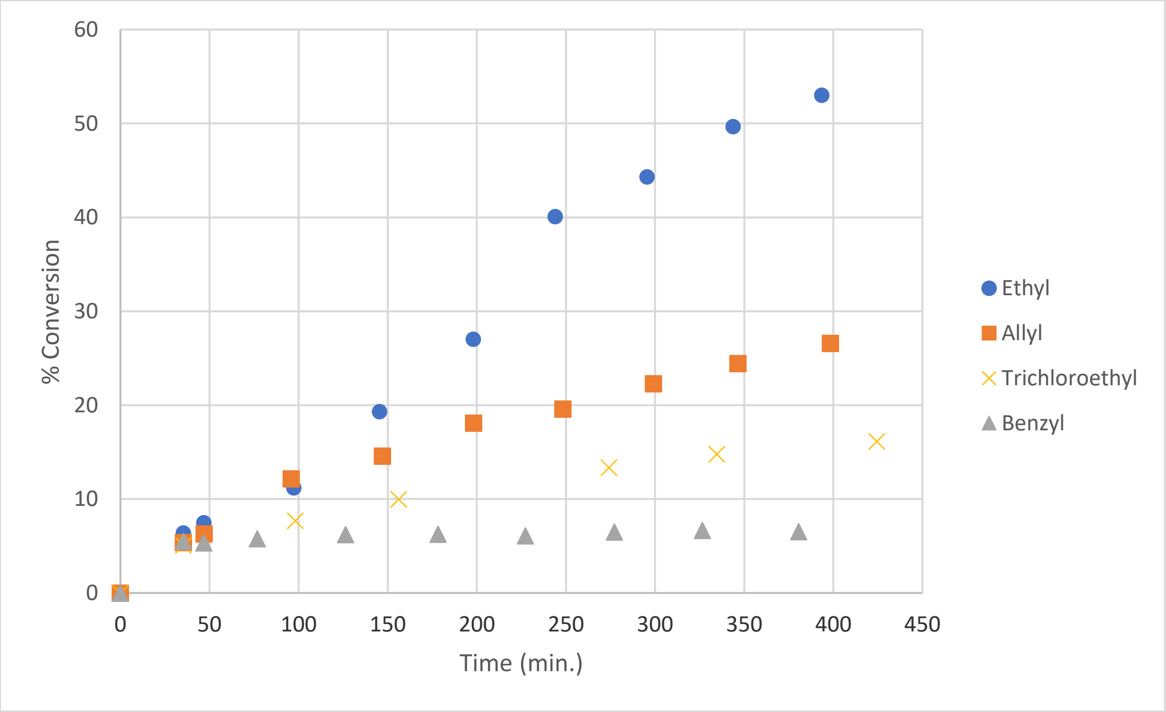


Figure 5. Effect of chloroformate alkyl group on acylpyridine formation

2.1.3 Effect of pyridine structure on the decomposition of ADHPs

In a second series of NMR experiments, using the same methodology detailed above, we sought to observe the effect of pyridine structure on the stability of ADHPs while keeping the chloroformate constant (Figure 6). We found that the ADHPs derived from 4-benzylpyridine and 4-ethylpyridine decompose more quickly than that derived from 3-bromo-4-ethylpyridine. In a discovery analogous to the previous experiment, in which, more electronegative chloroformates were found to increase the stability of the resulting ADHP, we can see that the most electron withdrawing alkylpyridine, 3-bromo-4-ethylpyridine, provided an ADHP that was completely stable (no trace of decomposition observed). While those made with benzyl and ethylpyridine decomposed at an appreciably higher rate.

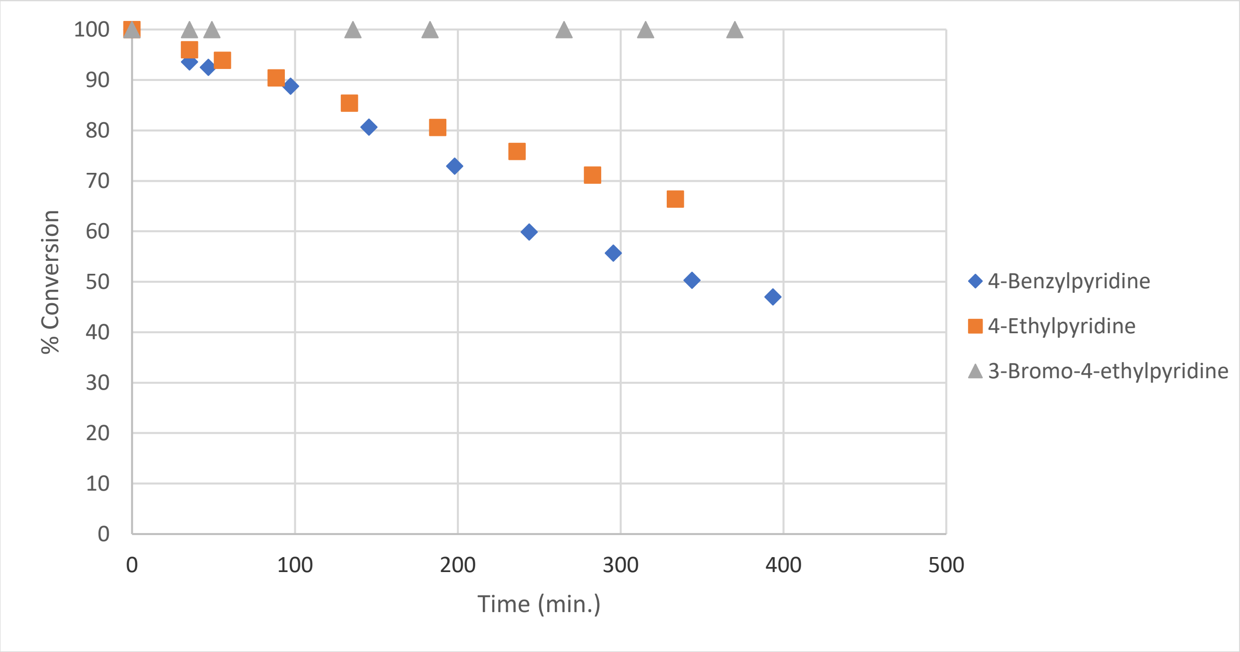


Figure 6. Effect of electron withdrawing capacity of pyridine substituent on ADHP decomposition

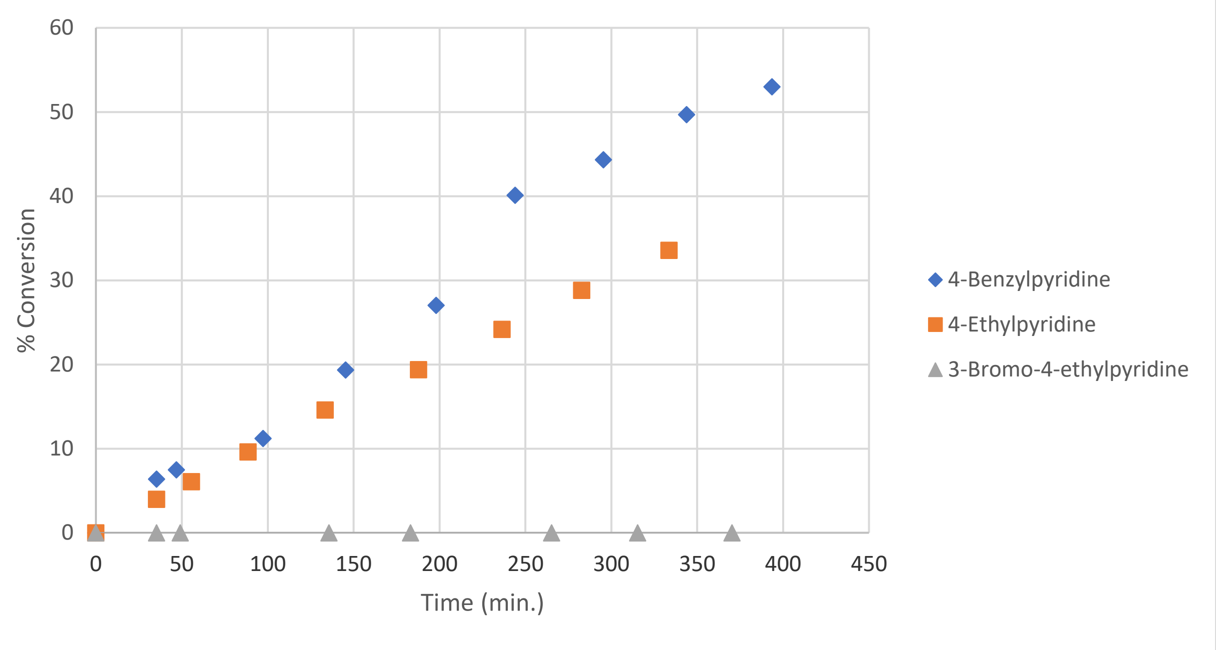
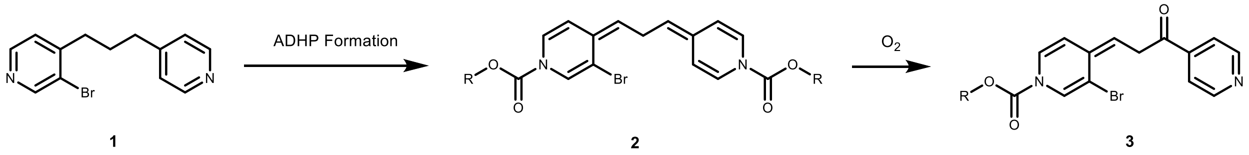


Figure 7. Effect of electron withdrawing capacity of pyridine substituent on acylpyridine formation

We have established that ADHP stability is influenced by the pyridylic substituent, as well as the chloroformate alkyl group, but to a lesser yet predictable extent. Using this information, we can deduce that incorporating electron-withdrawing functional groups into an ADHP will increase its stability and allow its manipulation for longer periods without oxidation. These findings helped us shed light on the potential utility of the unique chemistry of the ADHP intermediates in question. Given the established trends, ADHPs can be seen as a versatile intermediate which can be deliberately manipulated by purposefully choosing its building blocks to tune the resulting electron-density and control the rate at which the ADHP intermediate oxidizes to the resulting acylpyridine.

Such versatility can be leveraged in many ways. For example, ADHP chemistry can be used to selectively protect pyridine groups during a synthesis involving an intermediate molecule such as the one shown in (Scheme 10. ADHP formation as a selective pyridine protecting group. Considering the results of our time-course experiments, we can predict that although both pyridine moieties of this molecule will form ADHPs, only the pyridine lacking bromine at the 3' position will oxidize (Scheme 10, 3). Furthermore, the rate of this oxidation can also be controlled by selecting an appropriate chloroformate.



Scheme 10. ADHP formation as a selective pyridine protecting group

2.2 Determining ADHP oxidation potentials via cyclic voltammetry

Electrochemistry can be employed to study the oxidation of alkylpyridines since it is a reaction involving the transfer of electrons and, using CV, we are able to directly relate the flow of electrons to the oxidation of ADHPs.[15] This is because CV allows us to control the driving force of the oxidation process being studied electrochemically and thusly measure the potential (voltage) at which the oxidation event occurs for each ADHP.

To further investigate the effect of chloroformate alkyl groups on the electronic nature of the ADHPs formed from 4-benzylpyridine we measured their oxidation potentials using cyclic voltammetry (results found in Table 4). It must be noted that ADHPs formed using 4-ethylpyridine were too unstable for cyclic voltammetry measurements. Otherwise, the trends discovered through the previously outlines kinetic NMR studies were confirmed by CV experiments. We found that more stable ADHPs (i.e. made with benzyl chloroformate) have higher oxidation potentials, whereas ADHPs shown to be more prone to decomposition (i.e. made with ethyl chloroformate) have comparatively lower oxidation potentials (Table 4). In other words, more stable ADHPs required a higher voltage to be applied to remove an electron (oxidize) from their highest occupied molecular orbital (HOMO).

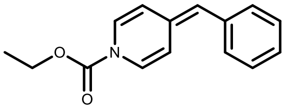
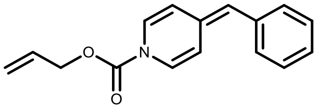
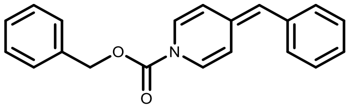
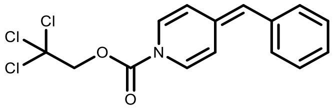
ADHP	**Oxidation Potential (V)**
4-Benzylpyridine + Ethyl Chloroformate  	0.57
4-Benzylpyridine + Allyl Chloroformate  	0.59
4-Benzylpyridine + Benzyl Chloroformate  	0.62
4-Benzylpyridine + 2,2,2-Trichloroethyl Chloroformate  	0.73

Table 4. ADHP oxidation potentials as determined by CV

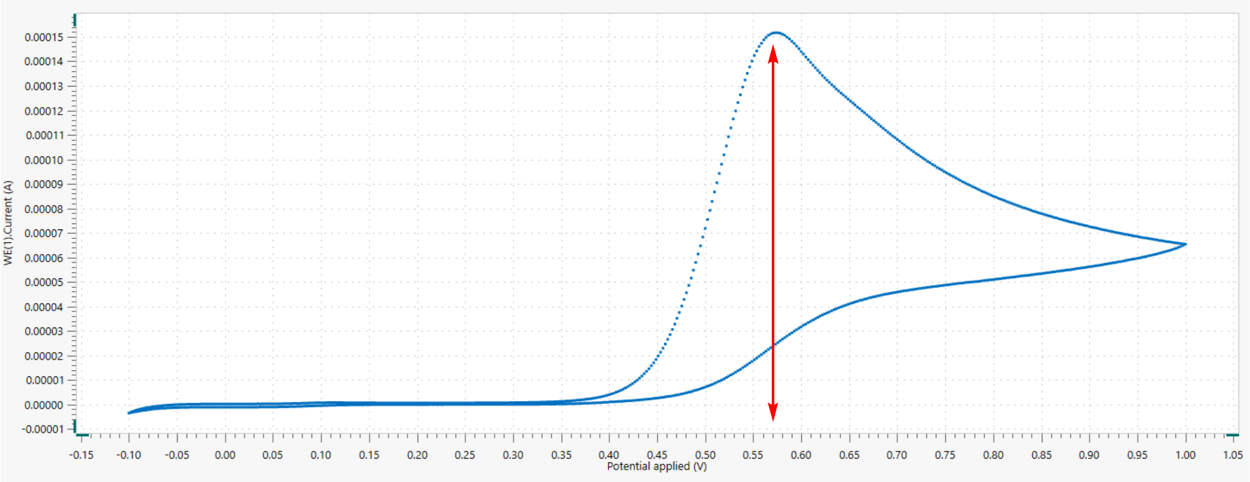


Figure 8. Sample CV plot for ADHP made from 4-benzylpyridine and ethyl chloroformate

2.3 Versatility of ADHP oxidation: determining reaction scope

The scope of this reaction was established by subjecting a selection of uniquely functionalized pyridine substrates to the optimized one-pot oxidation conditions. The versatility of our method was highlighted as it was able to selectively oxidize pyridines functionalized at the 4' position in good yields (58-99%) allowing the incorporation of various functional groups, substrate sizes, and electron withdrawing abilities (Figure 9).

It must be noted that in all cases the acylpyridine products were isolated with trace amounts of the corresponding carbonate ester byproduct. Due to this byproduct's similarity to the desired ketone in terms of R_f value, it was difficult to separate the two via column chromatography without diminishing the yield. Once the mechanistic details regarding the oxidation process in question are clearer, steps can be taken to limit byproduct formation. To temporarily address this issue, we opted to report qNMR yields (Figure 9).

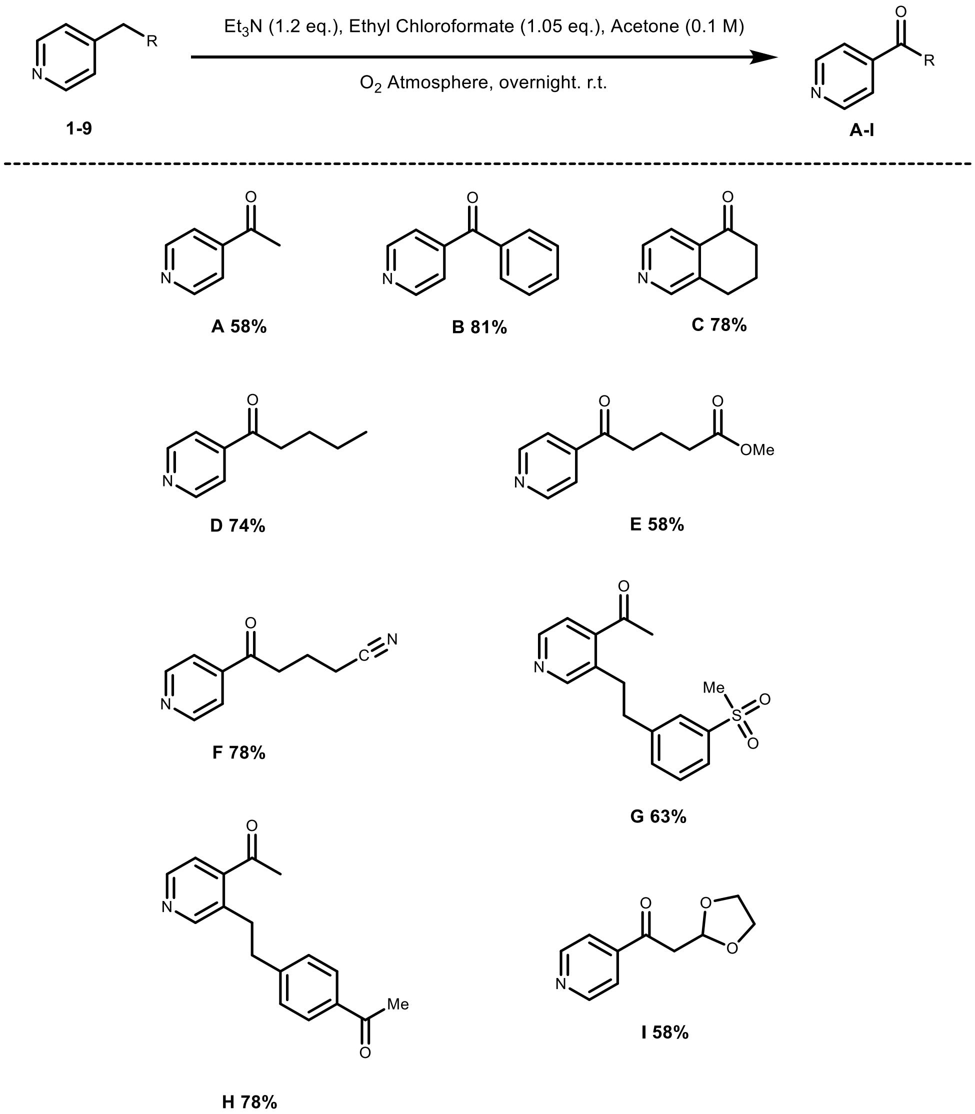


Figure 9. Substrate scope summary for 4-acylpyridine formation via ADHP oxidation

Starting with the two pyridines that were most frequently used to conduct the previously outlined experiments, 4-ethyl pyridine (**A**) and 4-benzylpyridine (**B**), we found that they provide yields of 58% and 81% respectively. In comparison, entry (**D**, 4-pentylpyridine), a substrate very similar in structure to 4-ethylpyridine provided a ketone in good yield at 74%.

Entry (**C**), tetrahydroisoquinoline, demonstrated that the method is highly selective for oxidation at the 4’ pyridylic position as it provided the ketone in 78% yield without any oxidation at the 3’ pyridylic position. To further showcase this method’s selectivity, we demonstrated that oxidation of the 4’ pyridylic position occurs even in the presence of benzylic and other 3’ pyridylic positions as seen in substrates (**G**) and (**H**), which provide yields of 63% and 78% respectively.

Bringing our attention to substrates bearing acidic protons and electrophilic functional groups such as ketones (**H**), esters (**E**), sulfones (**G**), and nitriles (**F**) (in order of lower to higher pKa, respectively), these entries were oxidized exclusively at the 4-pyridylic site with yields of 78%, 58%, 63%, and 78%, respectively.

Finally, the chemoselectivity of our method is further highlighted by showing that an acetal group (**I**) is unaffected by the reaction conditions yielding the desired ketone in 58% which, in turn, does not undergo elimination by deprotonation, demonstrating the mild nature of this reaction.

Chapter 3: Conclusion

Throughout this project, we developed a green and versatile method for the synthesis of pyridylic ketones that avoids the pitfalls of current methods. We did this by exploiting the propensity of ADHPs to undergo ambient oxidation without the necessity for any additional metal catalysts or external oxidants. A kinetic NMR study confirmed that the rate of this process can be selectively tuned by varying the alkoxy group of the chloroformate used in ADHP synthesis. Results indicate that ADHPs bearing more electron withdrawing functionality such as benzyl groups are expected to be stable and more easily manipulated in comparison to ADHPs made using less electron withdrawing groups such as ethyl and allyl. The trends discovered during time-course studies were then confirmed via cyclic voltammetry (CV) experiments as more stable ADHPs resulted in higher measured oxidation potentials. Finally, using the previously optimized one-pot ADHP formation and oxidation procedure, a wide variety of substrates were found to be compatible with this method emphasizing its versatility. Considering the drawbacks of current synthetic routes towards pyridylic ketones, the green, versatile, and highly selective nature of our 4-alkylpyridine oxidation strategy makes it an attractive option for the synthesis of pharmacologically valuable 4-acylpyridines on an industrial scale.

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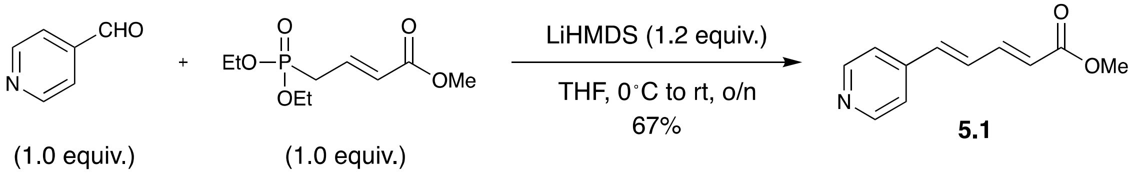
Chapter 4: Supporting Information

General experimental

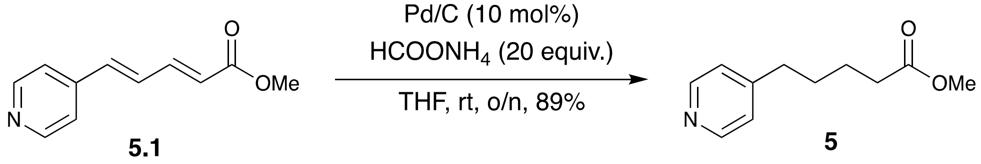
All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon using anhydrous solvents unless specified otherwise. Oxygen atmosphere conditions obtained using a balloon–needle through a rubber septum. Tetrahydrofuran (THF), diethylether (Et_2O), dichloromethane (DCM), acetonitrile (MeCN) and toluene (PhMe) were dried using an INERT® PureSolv solvent purification system. Commercial alkyl-pyridines and chloroformates were used as received. Triethyl amine (Et_3N) and di-isopropyl amine ($^iPr_2NH$) was distilled over CaH_2 under an argon atmosphere prior to use. Thin-layer chromatography was performed on SiliCycle® silica gel 60 F254 plates. Visualization was carried out using UV light (254 nm) and/or KMnO4, iodine stains. Flash column chromatography was carried out using SiliCycle® SiliaFlash® silica gel (230-400 mesh, 40- 63 μ, 60 Å pore size). Hexanes (ACS grade), acetone (ACS grade), isopropanol (ACS grade) and ethyl acetate (ACS grade) were used as received. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 AV, Bruker DRX 600, or Bruker 300 AV spectrometer in chloroform-d (99.8 % deuterated). Spectra recorded using chloroform were calibrated to 7.26 ppm ^{1}H and 77.16 ppm ^{13}C. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), sext (sextet), td (triplet of doublets), tt (triplet of triplets), dd (doublet of doublets), dddd (doublet of doublet of doublet of doublets), m (multiplet), and br (broad). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) using Alpha Platinum ATR, Bruker, diamond crystal FT-IR instrument. Any substrates not listed in the “starting material synthesis” section were purchased commercially and used as received.

Starting material synthesis

Methyl 5-(pyridin-4-yl) pentanoate (**5**)



To a 50 mL round-bottomed flask containing methyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (1.1 g, 4.6 mmol, 1.0 equiv.) in THF at 0 °C was added LiHMDS (1M in THF) (5.2 mL, 5.13 mmol) and stirred for 45 min. To this solution, isonicotinaldehyde (500 mg, 4.6 mmol) was added, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with distilled water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography using EtOAc/hexanes to afford compound **5.1** as a brown oil (591 mg, 67% yield).



A flame-dried round-bottomed flask equipped with a stir bar was charged with **5.1** (900 mg, 4.76 mmol) as a solution in THF (0.1M) at room temperature. To this solution ammonium formate (10.0 g, 95.2 mmol) was added, followed by 10% w/w Pd/C (504 mg, 0.47 mmol, 10 mol%) and stirred overnight at the same temperature. The mixture was filtered through a pad of celite® and washed with EtOAc and MeOH. The filtrate was concentrated and purified by flash column chromatography using EtOAc/hexane to give **5** (820 mg, 89%) as a yellow oil. Chromatography: 100% EtOAc (Rf. = 0.36).[22]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.53-8.41 (m, 2H) 7.14-7.00 (m, 2H), 3.66 (s, 3H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.34 (t, J = 6.8 Hz, 2H), 1.72-1.61 (m, 4H)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ 173.8, 151.5, 149.3, 124.0, 51.6, 34.9, 33.8, 29.7, 24.5.

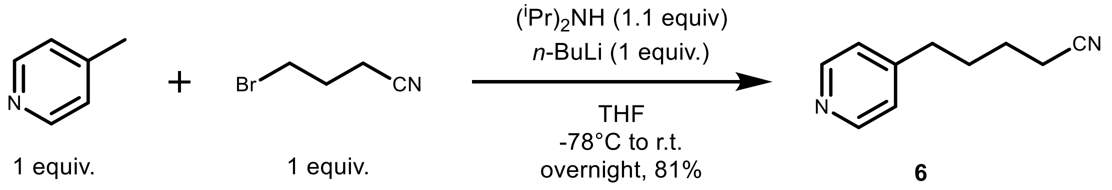
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2948, 1732, 1601, 1436, 1415, 1197, 803 (cm^{-1})

HRMS ESI

Calculated mass for $(M+H)^+$ of $C_{11}H_{16}NO_2$ is 194.1176 found 194.1173

5-(pyridin-4-yl)pentanenitrile (6):



Compound **6** was synthesized using the procedure used to make 3-bromo-4-methylpyridine (**7.1**) using diisopropylamine (0.82 mL, 5.36 mmol, 1.1 equiv.), *n*-BuLi (1.6M in THF) (3.35 mL, 5.36 mmol, 1.0 equiv.), 4-methylpyridine (0.52 g, 5.36 mmol, 1.0 equiv.) and 4-bromobutanenitrile (1.8 mL, 29.0 mmol, 1.0 equiv.). The compound **6** was obtained as a yellow oil with a 696 mg (81%). Chromatography: 100% EtOAc ($R_{f.}$ = 0.36).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.54-8.24 (m, 2H), 7.11-6.85 (m, 2H), 2.54 (t, J = 7.4 Hz, 2H); 2.26 (td, J = 7.1 Hz, 0.7 Hz, 2H), 1.77-1.63 (m, 2H), 1.63-1.48 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ 149.9, 149.6, 123.6, 119.2, 34.0, 28.9, 24.5, 16.8.

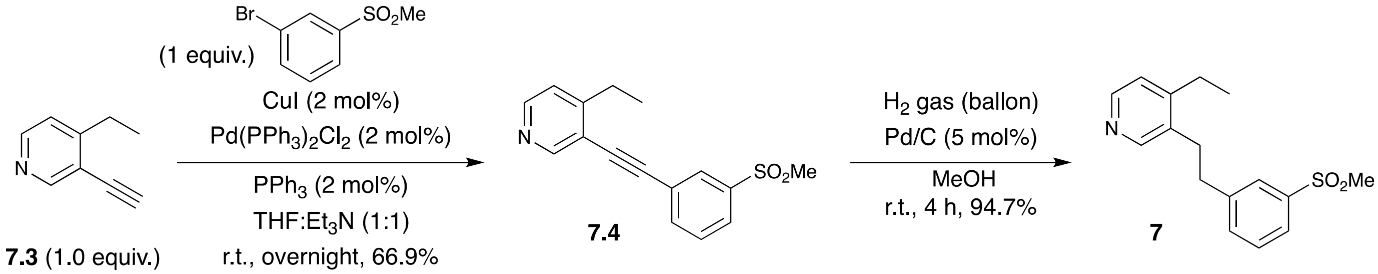
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2956, 2982, 2853, 1680, 1461, 1301, 1146 (cm^{-1})

HRMS ESI

Calculated mass for (M+H)+ of C10H13N2 is 161.1073 found 161.1072.

Synthesis of 4-ethyl-3-(3-(methylsulfonyl)phenethyl)pyridine (7):



Following Sonogoshira cross-coupling conditions to prepare **7**, 1-bromo-3-(methylsulfonyl)benzene (200 mg, 1.52 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol), CuI (5.7 mg, 0.01 mmol), triphenylphosphine (7.8 mg, 0.03 mmol) and 4-ethyl-3-ethynylpyridine (**7.3**) (200 mg, 1.52 mmol). The compound **7.4** was obtained as a colorless oil with a 66.9% yield.

To a solution of **7.4** (350 mg, 1.22 mmol) in MeOH (5 mL) was added 10% w/w Pd/C (65 mg, 0.06 mmol, 5 mol%) and the mixture was stirred under H_2 (balloon) gas at room temperature for 4 h (monitored by TLC). The mixture was filtered through a pad of celite® and washed with EtOAc and MeOH. The filtrate was concentrated and purified by flash column chromatography (EtOAc/hexane) to give **7** (334 mg, 94.7%) as a viscous liquid. Chromatography: 100% EtOAc (Rf. = 0.15).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.37-8.33 (m, 1H), 8.18 (s, 1H), 7.78 (dt, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.64 (t, *J* = 1.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.43 (dt, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 3.00 (s, 3H), 2.99-2.91 (m, 4H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 150.8, 150.4, 148.2, 142.8, 140.7, 134.0, 133.8, 129.7, 127.3, 125.4, 123.2, 44.6, 36.8, 31.6, 24.7, 14.2.

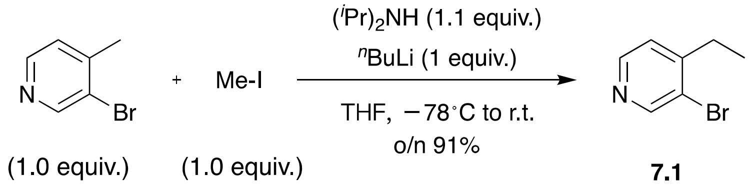
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2959, 2924, 2853, 1680, 1461, 1301, 1146 (cm^{-1})

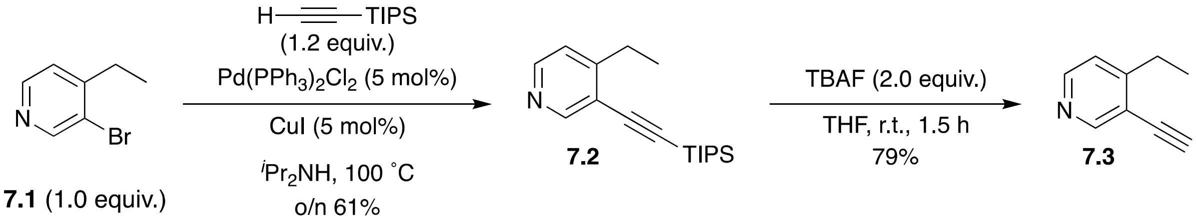
HRMS ESI

Calculated mass for $(M+H)^+$ of $C_{16}H_{20}NO_2S$ is 290.1209 found 290.1204.

4-ethyl-3-ethynylpyridine (7.3)



A flame-dried round-bottomed flask equipped with a stir bar was charged with freshly distilled di-isopropyl amine (4.47 mL, 31.9 mmol) in THF and cooled to -78 °C. To this solution, ^{n}BuLi (18.16 mL, 29.0 mmol, 1.6 M in hexanes) was added dropwise, and the mixture was stirred for 15 min. A solution of 3-bromo-4-methylpyridine (5 g, 29.0 mmol) in THF was introduced at the same temperature. The deprotonated picoline was transferred dropwise via cannula to a round-bottomed flask containing the Iodomethane (4.09 g, 29.06 mmol) in THF. The reaction was kept at −78 ˚C for one hour and then allowed to warm slowly to room temperature overnight. The reaction mixture was quenched with distilled water and the crude reaction mixture was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography using EtOAc/hexane to give **7.1** (4.89 g, 91%) as a yellow oil.[23]



To a 50 mL round-bottomed flask containing 24 mL of ^{i}Pr$_2$NH [0.1M], 3-bromo-4-ethylpyridine (**7.1**) (500 mg, 2.71 mmol) and triisopropylacetylene (729 mL, 3.26 mmol) were added copper (I) iodide (28 mg, 0.13 mmol) and bis(triphenylphosphine)-palladium (II) dichloride (94 mg, 0.13 mmol). The resulting mixture was heated at reflux overnight and then cooled to room temperature.

The reaction mixture was diluted with 100 mL of EtOAc and the resulting suspension was filtered through celite®. The filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography using EtOAC/hexanes to afford compound **7.2** as a colorless oil (475 mg, 61% yield).

A flame-dried round-bottomed flask equipped with a stir bar was charged with **7.2** (450 mg, 1.56 mmol) as a solution in THF at room temperature. To this solution tetrabutylammonium fluoride (3.13 mL, 3.13 mmol) was added and stirred for 1.5 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using EtOAc/hexane to give **7.3** (162 mg, 79%) as a yellow oil. Chromatography: 10% EtOAc in hexane (Rf. = 0.4).[21]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.63 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 7.14 (d, *J* = 5.1 Hz, 1H), 3.36 (s, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ 155.1, 153.2, 149.2, 122.6, 118.9, 83.8, 79.2, 27.0, 13.7.

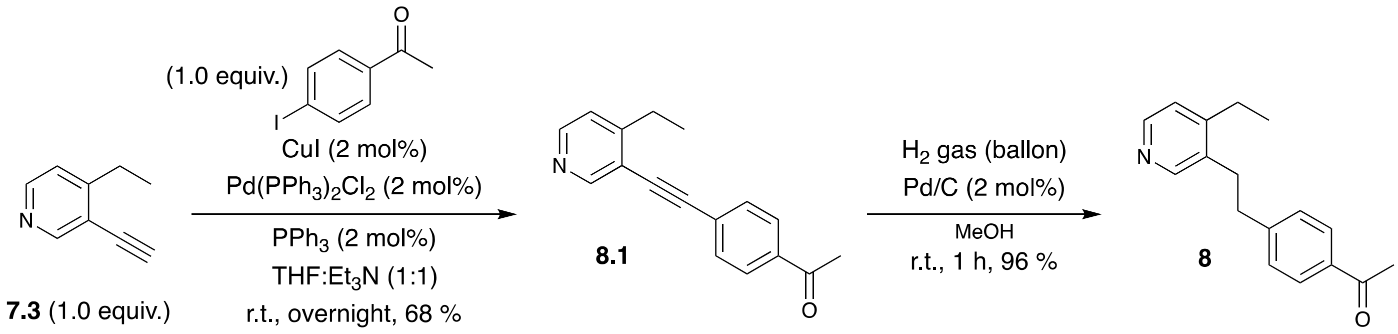
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2970, 2932, 2875, 1584, 1460, 837 (cm^{-1})

HRMS ESI

Calculated mass for $(M+H)^+$ of $C_9H_{10}N$ is 132.0808 found 132.0810.

1-(4-(2-(4-ethylpyridin-3-yl)ethyl)phenyl)ethan-1-one (8)



To a round-bottomed flask equipped with a stir bar were added 1-(4-iodophenyl)ethan-1-one (206 mg, 0.8 mmol), $Pd(PPh_3)_2Cl_2$ (11.7 mg, 0.01 mmol), CuI (3.1 mg, 0.01 mmol), triphenylphosphine (4.3 mg, 0.01 mmol) and 4-ethyl-3-ethynylpyridine (**7.3**) (110 mg, 0.8 mmol) under N_2 atmosphere at room temperature and followed by THF (3 mL) and Et_3N (3 mL) were added. The reaction mixture was stirred overnight at the same temperature. Then, the reaction mixture was quenched with water and the crude reaction mixture was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography using EtOAc/hexane to give **8.1** (142 mg, 68%) as a colorless oil.

To a solution of **8.1** (1.00 g, 4.01 mmol) in MeOH (15 mL) was added 10% w/w Pd/C (85 mg, 0.08 mmol, 2 mol%), and the mixture was stirred under H_2 (balloon) at room temperature for 1 h (monitored by TLC). The mixture was filtered through a pad of celite® and washed with EtOAc and MeOH. The filtrate was concentrated and purified by flash column chromatography (EtOAc/hexane) to give **8** (975 mg, 96%) as a white solid. Chromatography: 100% EtOAc (Rf. = 0.28).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.37 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 7.97-7.79 (m, 2H), 7.25-7.21 (m, 2H), 7.09 (d, *J* = 5.0 Hz, 1H), 2.94 (s, 4H), 2.66-2.52 (m, 5H), 1.22 (t, *J* = 7.6 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$)

δ 197.8, 150.7, 150.4, 148.1, 146.8, 135.5, 134.3, 128.8, 123.1, 37.2, 31.6, 26.7, 24.8, 14.2.

IR Alpha-Platinum ATR, Bruker, diamond crystal

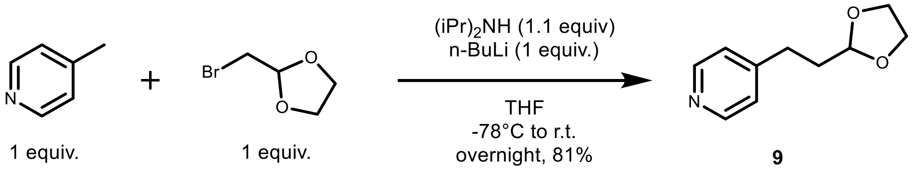
ν = 2969, 2935, 1680, 1606, 1411, 1358, 1267, 831 (cm^{-1}).

HRMS ESI

Calculated mass for $(M+H)^+$ of $C_{17}H_{20}NO$ is 254.1539 found 254.1537.

MP 61.2 – 63.1 °C

4-(2-(1,3-dioxolan-2-yl)ethyl)pyridine (9):



The compound **9** was synthesized using the same procedure used to make 3-bromo-4-methylpyridine to **(7.1)** using diisopropylamine (1.65 mL, 11.81 mmol, 1.1 equiv.), *n*-BuLi (1.6M in THF) (6.71 mL, 10.73 mmol, 1.0 equiv.), 4-methylpyridine (1.04 mL, 10.73 mmol, 1.0 equiv.) and 2-(bromomethyl)-1,3-dioxolane (1.11 mL, 10.73 mmol, 1.0 equiv.). The compound **9** was obtained as a yellow oil with a 1.576 g (82%). Chromatography: 100% EtOAc (R_f. = 0.23).[24]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.54-8.38 (m, 2H), 7.17-7.03 (m, 2H), 4.90-4.83 (m, 1H), 4.03-3.91 (m, 2H), 3.91-3.77 (m, 2H), 2.82-2.62 (m, 2H), 2.04-1.88 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ 150.7, 149.8, 123.9, 103.4, 65.1, 34.3, 29.3.

IR Alpha-Platinum ATR, Bruker, diamond crystal

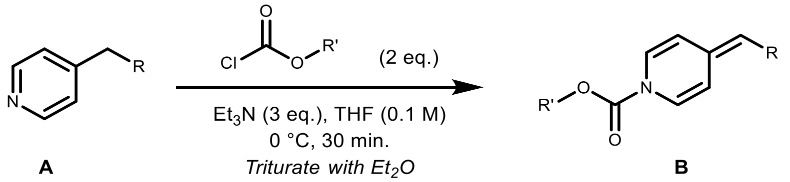
ν = 2956, 2882, 1601, 1680, 1415, 1133, 1028, 899 (cm^{-1}).

HRMS ESI

Calculated mass for (M+H)+ of C10H14NO2 is 180.1019.

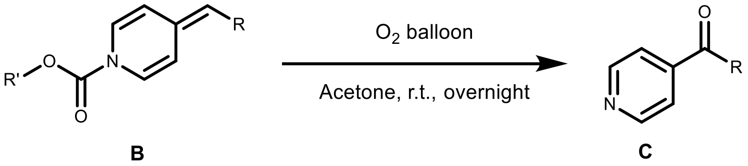
Alkylidene dihydropyridines (ADHPs): general synthesis.

General procedure 1: ADHP formation



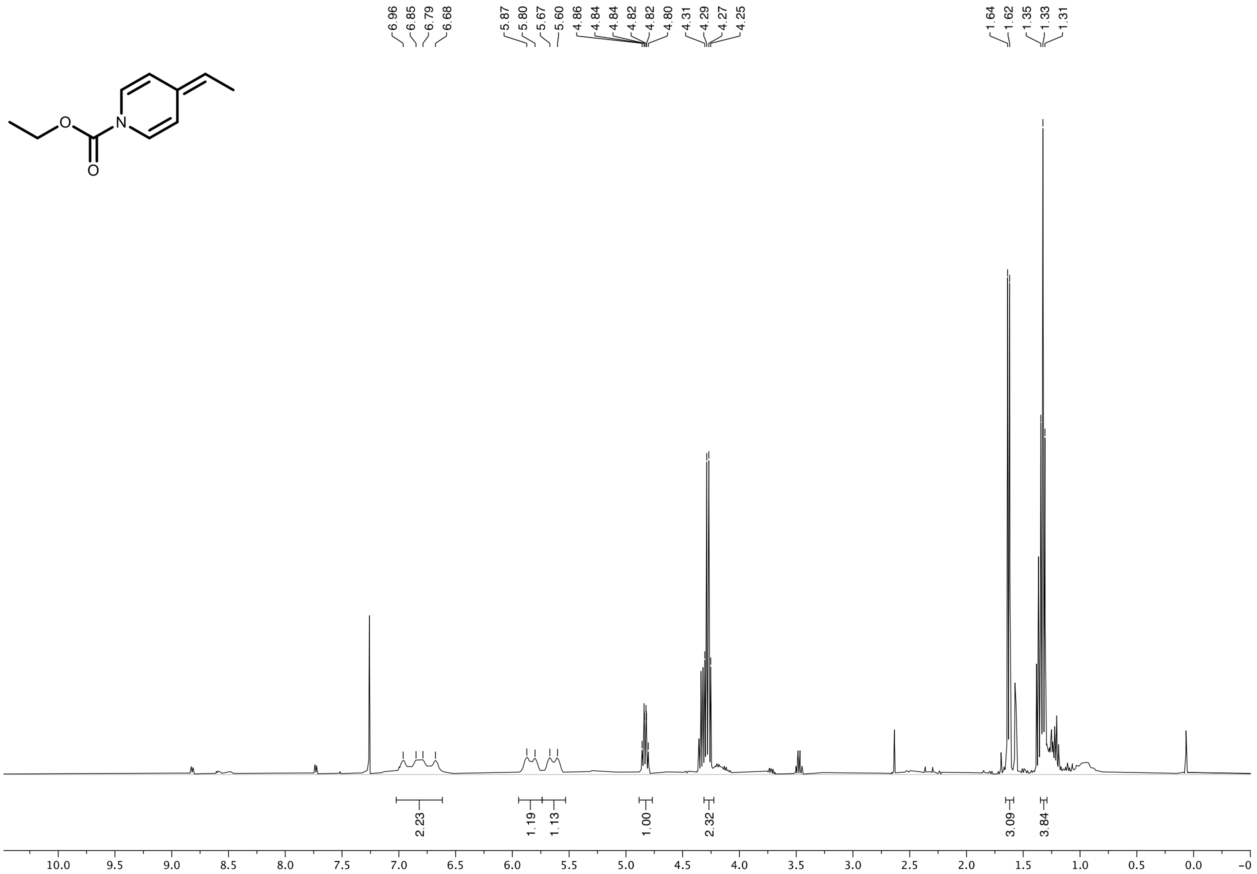
Procedure: To a flame dried round bottom flask equipped with a stir bar, 4-alkyl pyridine **A** (100 mg, 1.0 equiv.) is dissolved in anhydrous THF (0.1M) under an argon atmosphere. The flask is charged with freshly distilled Et_3N (3.0 equiv.), stirred vigorously while cooled in an ice bath. After 5 minutes of stirring, commercially provided chloroformate $ClCO_2R'$ (2.0 equiv.) is added neat dropwise and left to stir at the same temperature for 30 minutes. The resulting bright yellow cloudy mixture is concentrated *in vacuo* and the crude is suspended in anhydrous Et_2O (20 mL). The suspension is filtered through a cotton plug and concentrated *in vacuo* to give the crude ADHP as clear yellow oil. The crude ADHP is used without further purification.

General procedure 2: one-pot ADHP oxidation



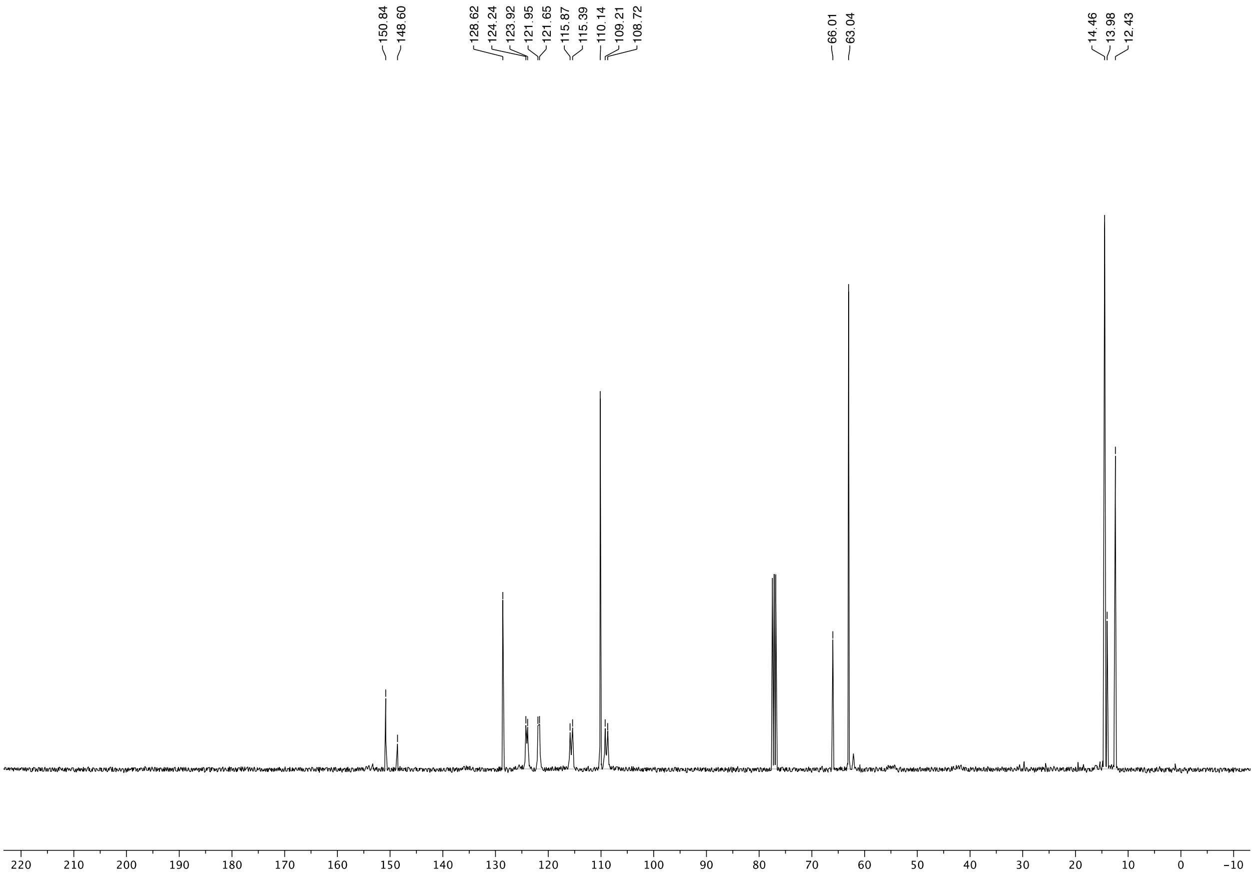
Procedure: To a flame dried round bottom flask previously purged with oxygen (10 min.) and equipped with a stir bar, 4-alkylpyridine (1 eq.) is dissolved in Acetone (0.1M). The flask is charged with distilled Et3N (1.2 eq.) and stirred vigorously at room temperature. After ~5 minutes of stirring, ClCO2R' (1.05 eq.) is added dropwise and left stir under oxygen overnight. The resulting bright yellow mixture is concentrated and anhydrous Et2O (20 mL) is added to the flask. The reaction mixture is filtered, and the collected filtrate is concentrated in vacuo to give the crude pyridilic ketone. The ketone is purified by silica gel column chromatography (EtOAc/Hexanes, 3:2) to give the purified product.

ADHP spectral data



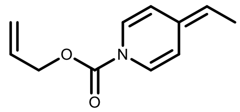
^{1}H-NMR (400 MHz, CDCl$_3$)

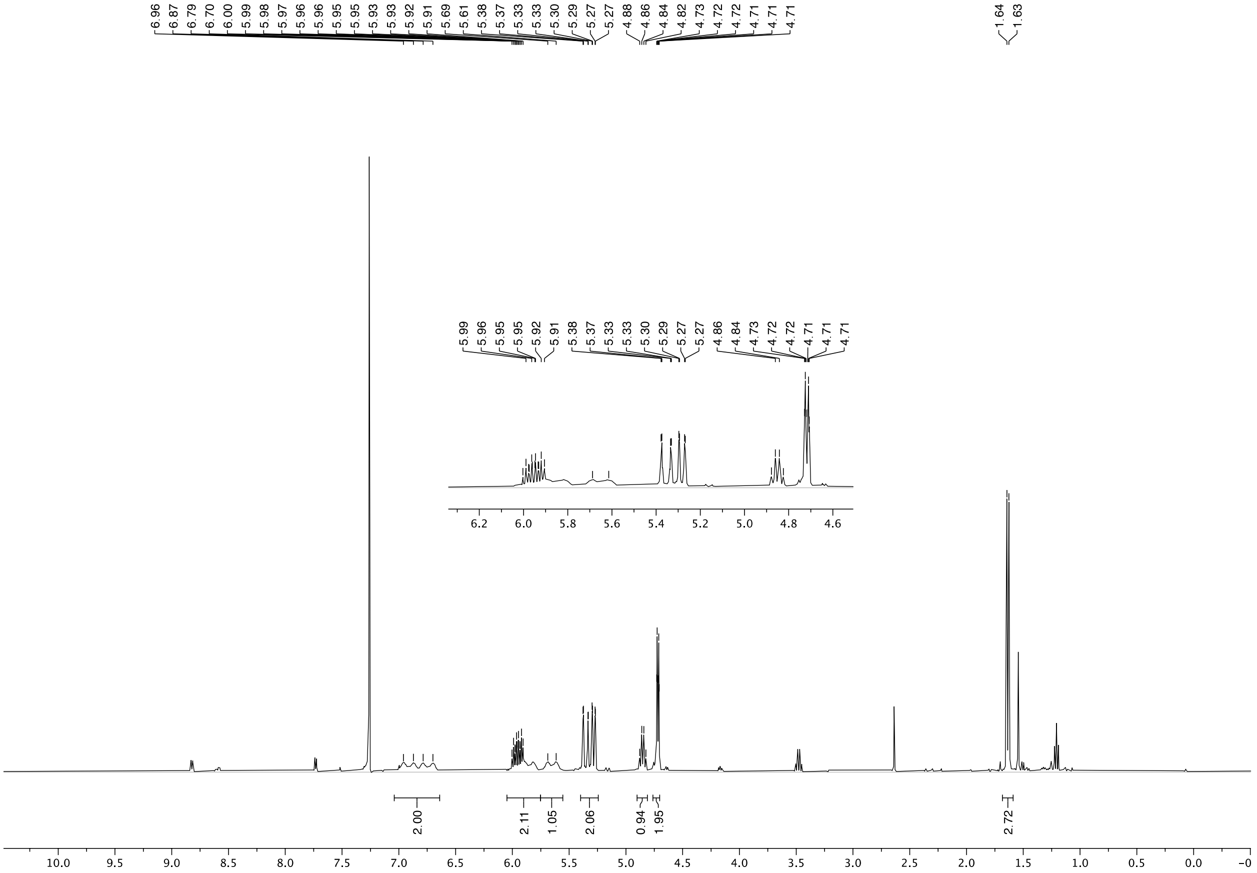
δ = 6.9 (overlapping bd, 2H), 6.7 (bd, 1H), 5.84 (bd, 1H), 5.64 (bd, 1H), 4.83 (q, 1H, *J* = 7.25 Hz), 4.28 (q, 2H, *J* = 7.14 Hz), 1.63 (d, 3H, *J* = 7.3 Hz), 1.33 (t, 3H, *J* = 7.1 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

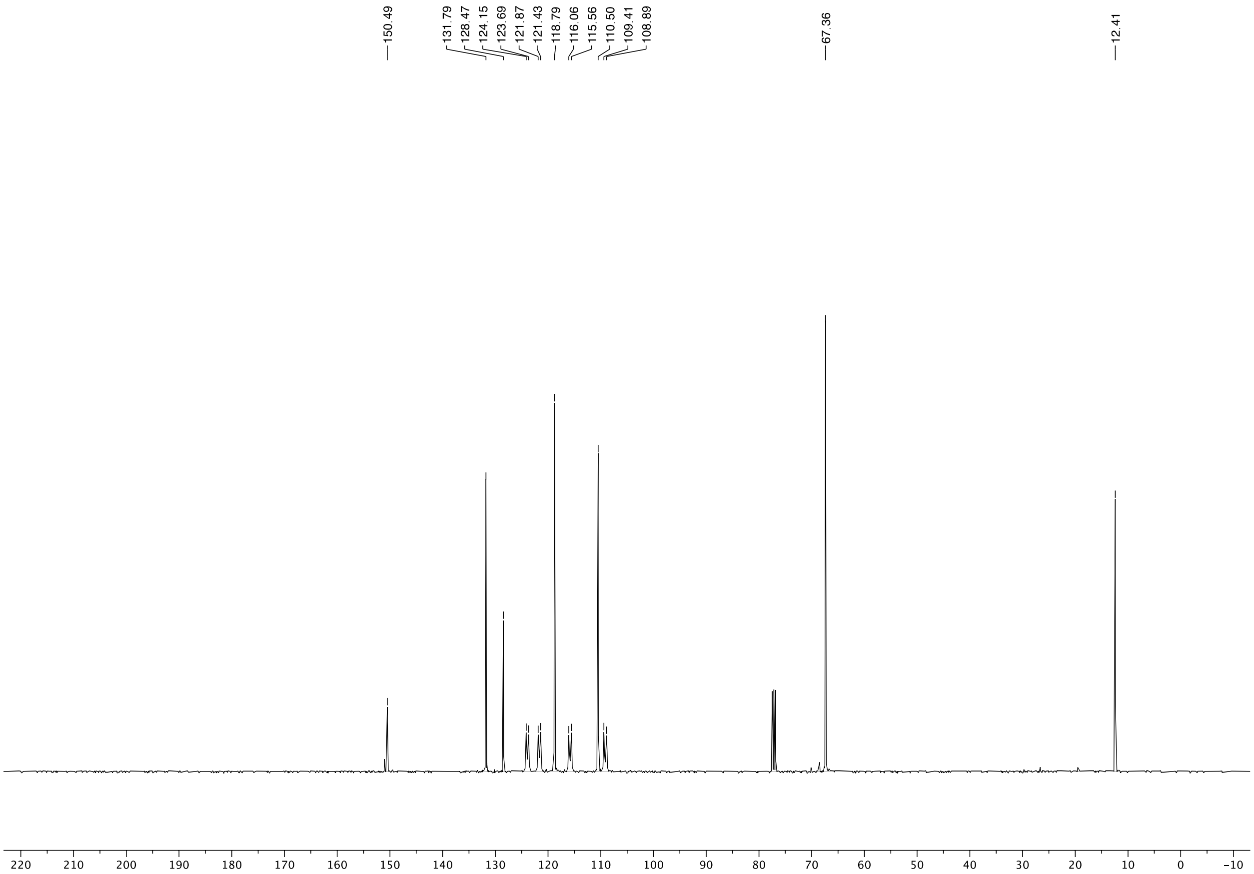
δ = 150.8, 148.6, 128.6, 124, 121.8, 115.6, 110, 109, 66, 63, 14.46, 13.98,12.43.





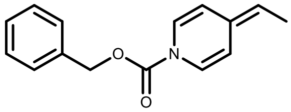
^{1}H-NMR (400 MHz, $CDCl_3$)

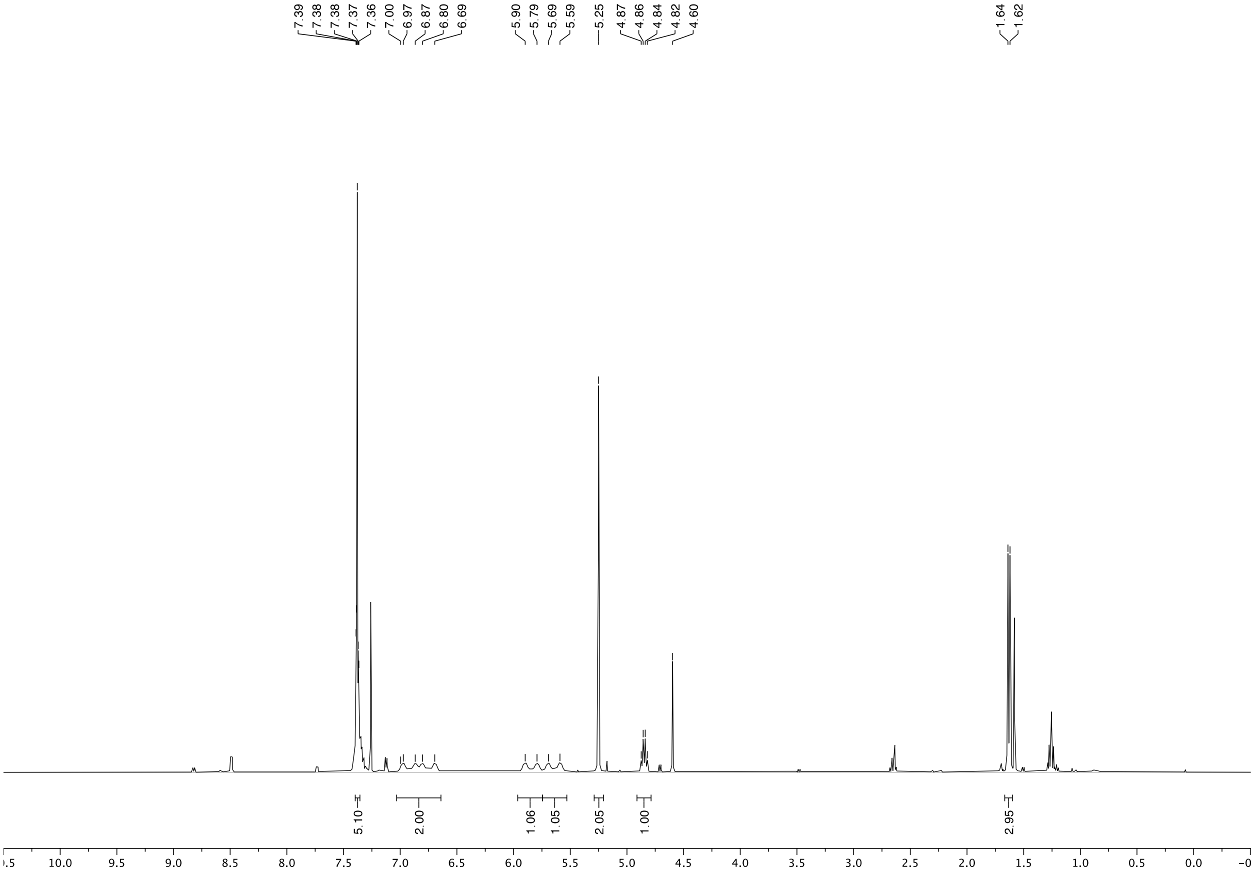
δ = 6.91 (bd, 1H), 6.74 (bd, 1H), 5.95 (m, 1H), 5.85 (bd, 1H), 5.65 (bd, 1H), 5.35 (dd, 1H, *J* = 17.2, 1.4 Hz), 5.28 (dd, 1H, *J* = 10.4, 1.3 Hz), 4.85 (q, 1H, *J* = 7.2 Hz), 4.7 (dt, 2H, *J* = 5.7, 1.3 Hz), 1.635 (d, 3H, *J* = 7.3 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

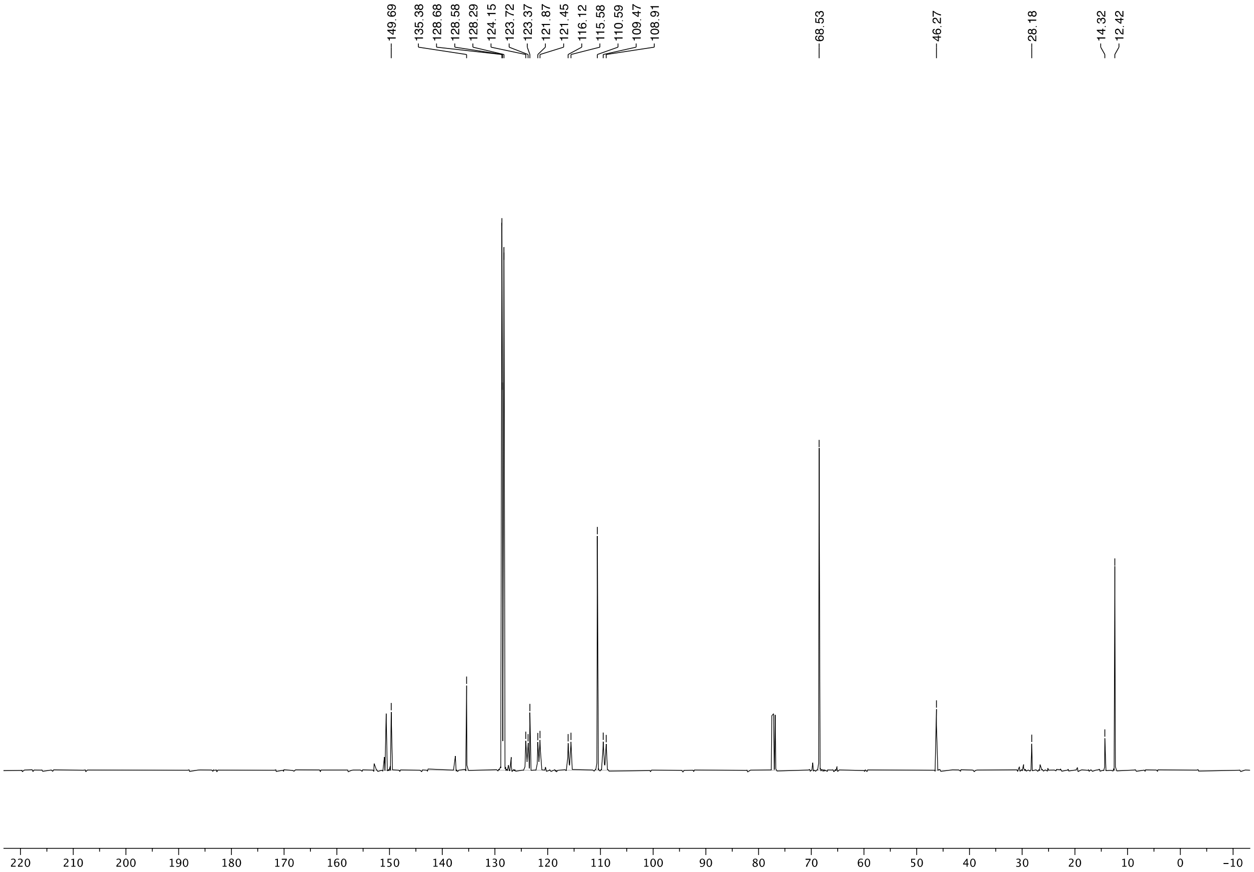
δ 151, 150.4, 131.8, 128.4, 123.9, 121.6, 118.8, 115.8, 110.4, 109, 67.3, 12.4.





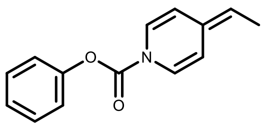
^{1}H-NMR (400 MHz, CDCl$_3$)

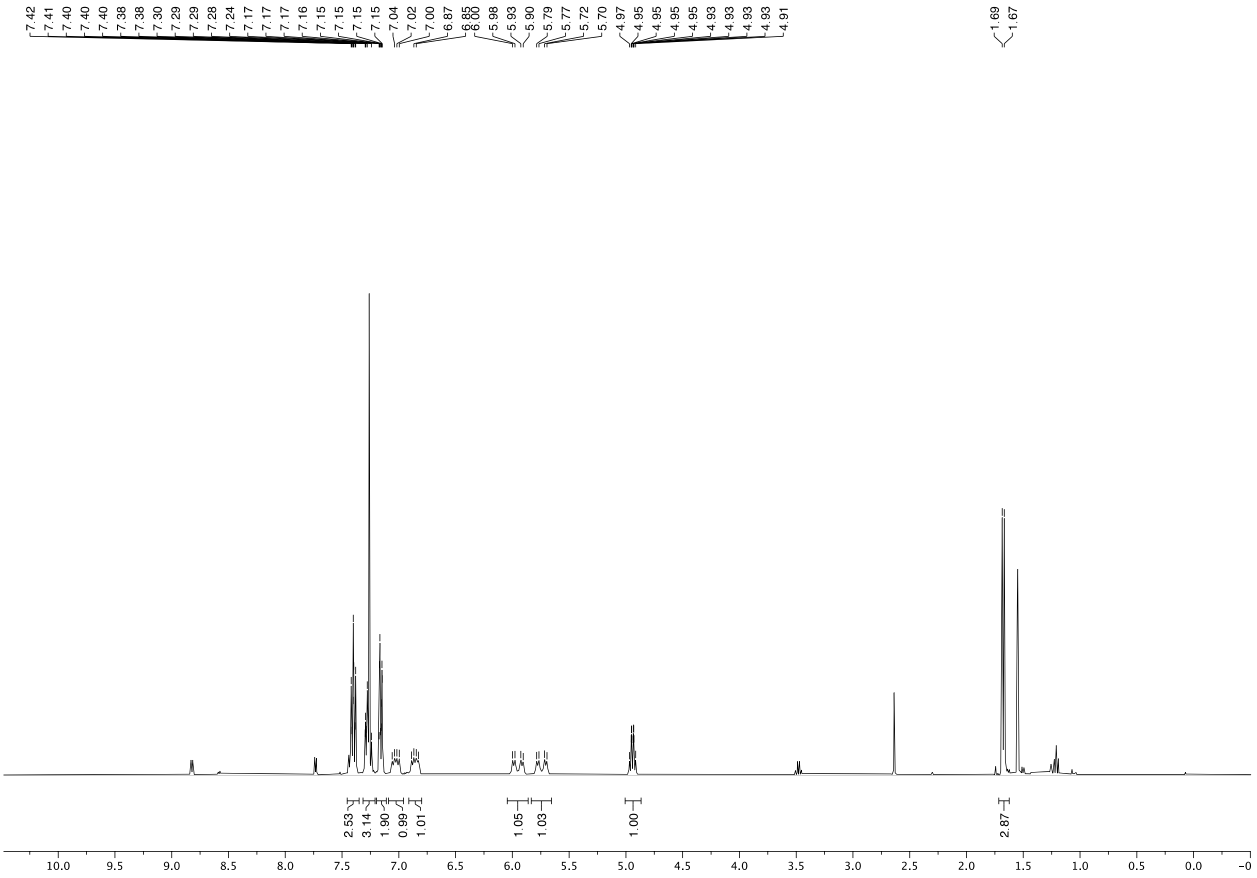
δ = 7.38 (m, 5H), 6.75 (bd, 1H), 5.85 (bd, 1H), 5.65 (bd, 1H), 5.25 (s, 2H), 4.86 (q, 1H, J = 7.4 Hz), 4.6 (s, 2H), 2.7 (q, 3H, J = 7.7), 1.63 (d, 3H, J = 7.2 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

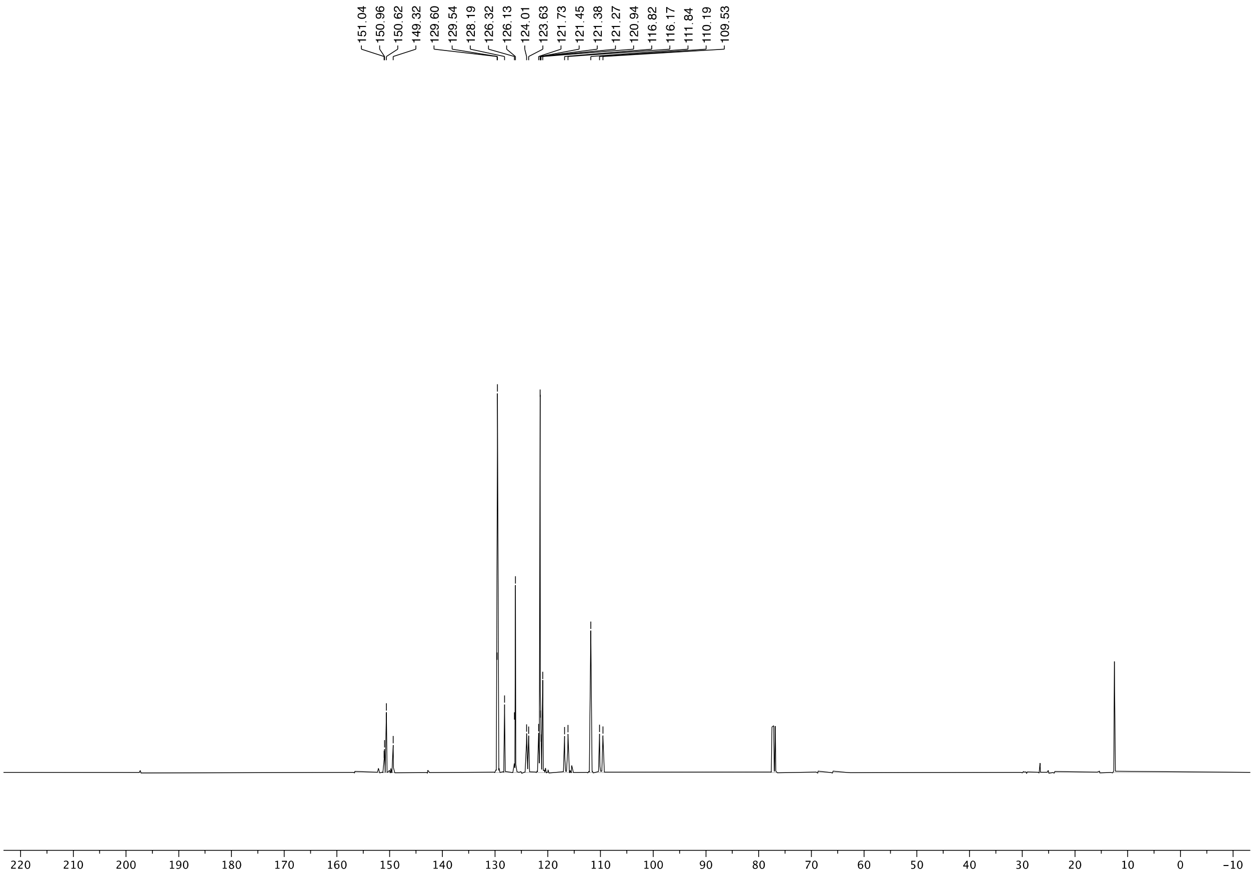
δ = 150.6, 149.7, 135.4, 128.7, 128.6, 128.3, 123.9, 121.6, 115.8, 110.6, 109.2, 68.5, 12.4.





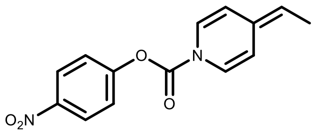
<u>^{1}H-NMR</u> **(400 MHz, $CDCl_3$)**

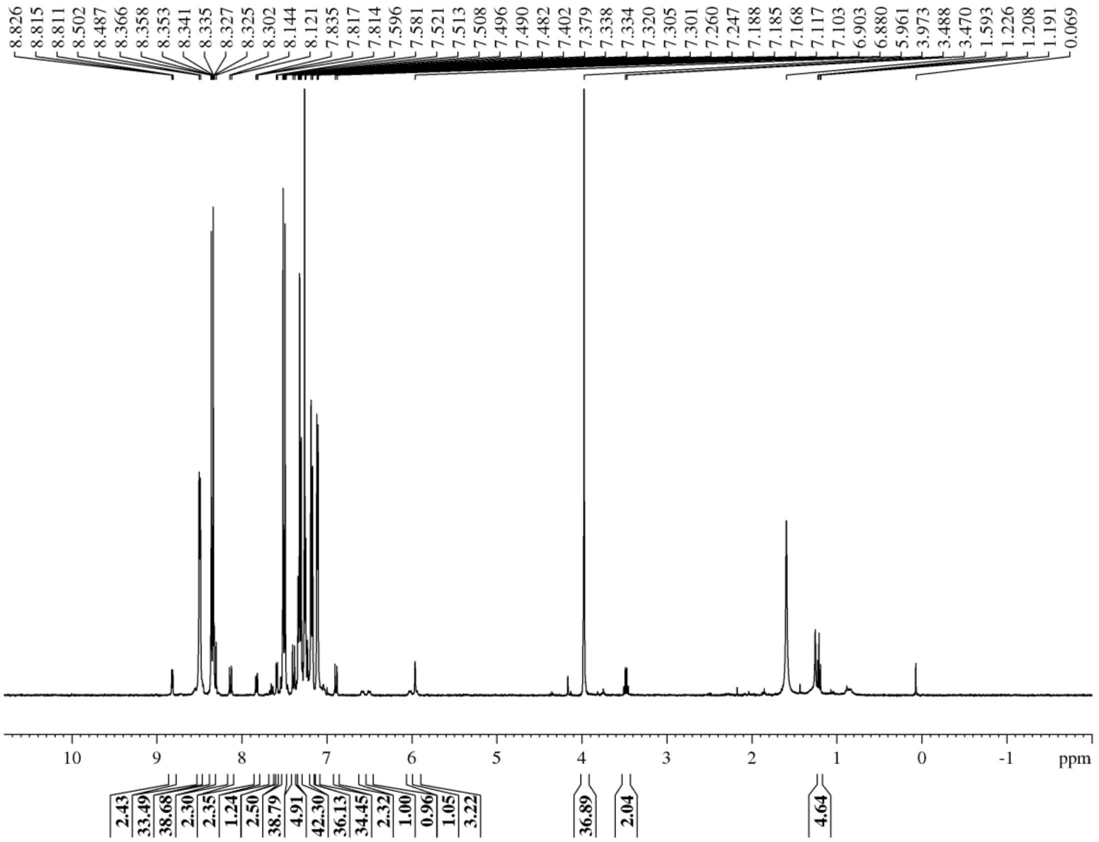
δ = 7.28 (m, 1H), 7.4 (t, 2H, *J* = 7.5 Hz), 7.16 (m, 2H), 7.03 (m, 1H), 6.86 (m, 1H), 5.95 (m, 2H), 5.74 (m, 2H), 4.94 (q, 1H, J = 7.0 Hz), 1.67 (d, 3H, J = 7.5 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

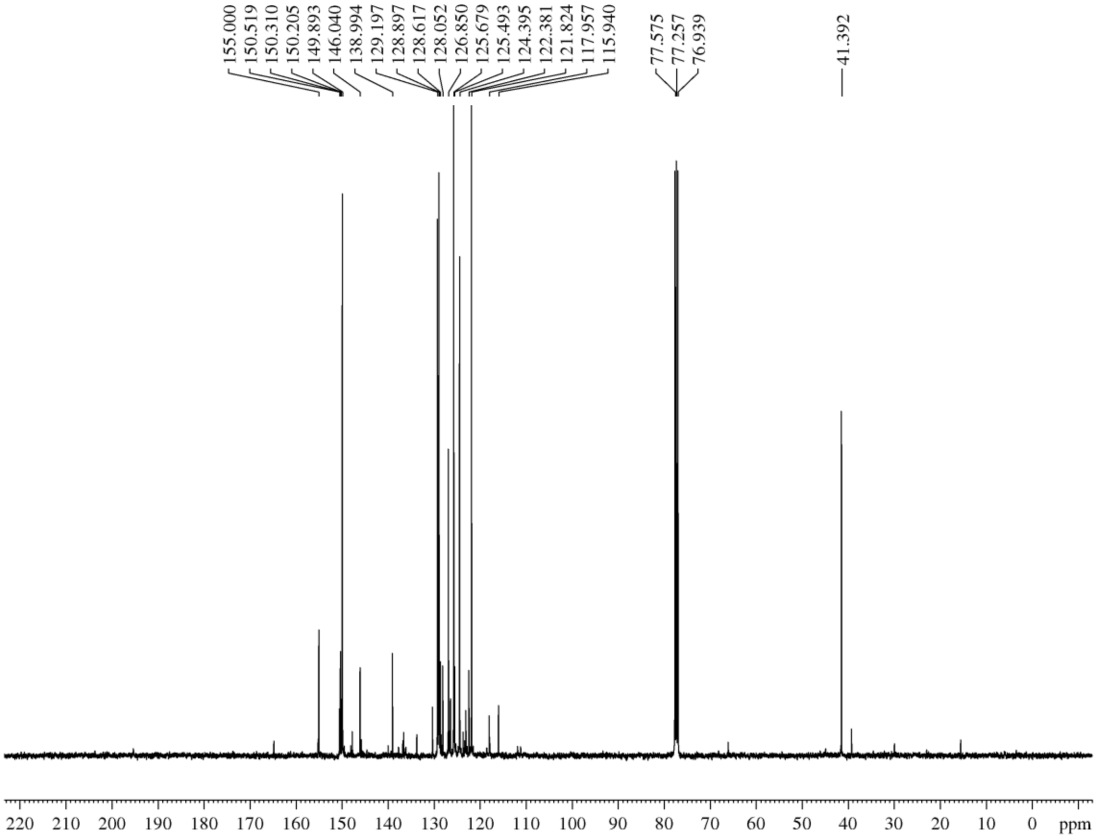
δ 151.0, 150.6, 149.3, 129.5, 128.2, 123.7, 121.3, 120.9, 111.8, 110, 12.5.





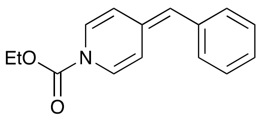
^{1}H NMR **(400 MHz, CDCL$_3$):**

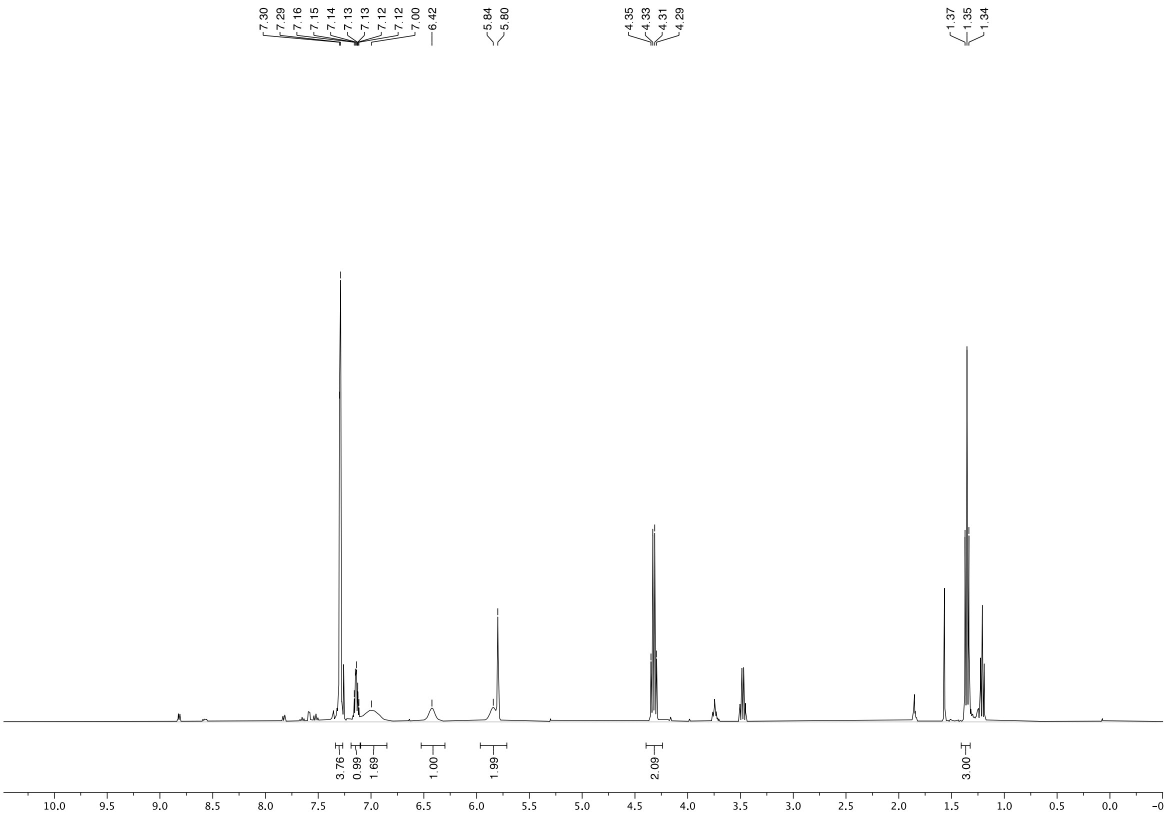
δ = 8.49 (d, 2H, *J* = 6 Hz), 8.35 (d, 4H, *J* = 9.4 Hz), 8.3 (d, 2H, *J* = 9.2 Hz), 7.73 (d, 2H, *J* = 6 Hz), 7.5 (d, 4H, *J* = 9.2 Hz), 7.37 (d, 2H, *J* = 9.2 Hz), 7.13 (d, 2H, J = 5.9 Hz), 6.98 (t, 1H, *J* = 9 Hz), 6.8 (t, 1H, *J* = 9 Hz), 6 (dd, 1H, *J* = 33.7, 8.5 Hz), 5.78 (dd, 1H, *J* = 32, 8 Hz), 5 (q, 1H, *J* = 7.4 Hz), 2.66 (q, 2H, J = 7.36 Hz), 1.69 (d, 3H, *J* = 7.54), 1.26 (t, 3H, *J* = 7.7 Hz).



<u>^{13}C NMR</u> **(400 MHz, CDCL$_3$):**

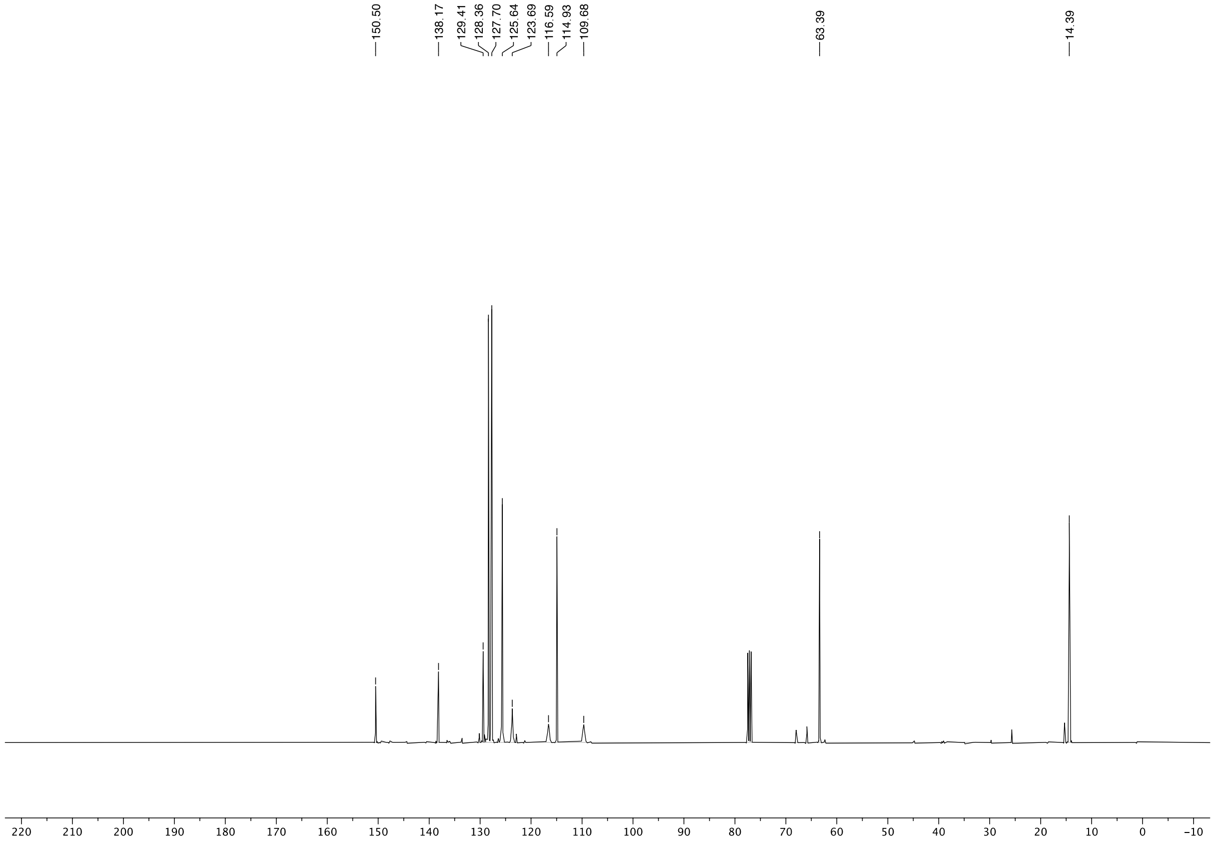
δ = 155, 153.2, 150.1, 149.5, 148, 145.5, 127.7, 126.3, 125.5, 123, 122.3, 121.2, 120.7, 117, 115.8, 113.5, 110.5, 28.2, 14.3, 12.6.





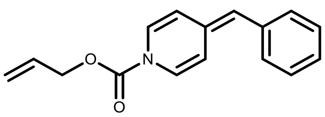
^{1}H-NMR (400 MHz, CDCl$_3$)

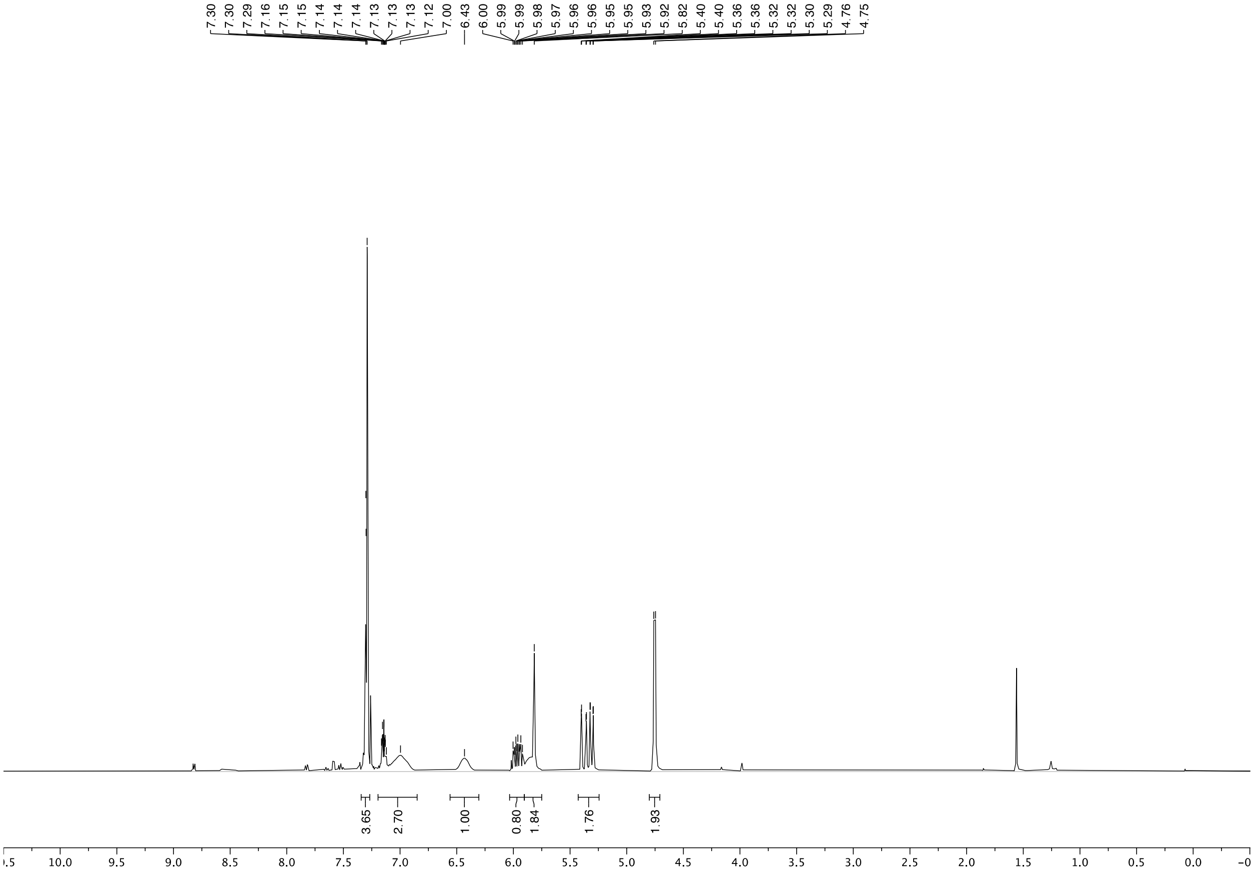
δ = 7.3-7.29 (m, 4H), 7.14 (q, 1H, *J* = 4.30), 7.00 (bs, 2H), 6.42 (bs, 1H), 5.84 (bs, 1H), 5.80 (bs, 1H), 4.32 (q, 2H, *J* = 7.14), 1.35 (t, 3H, *J* = 7.1 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

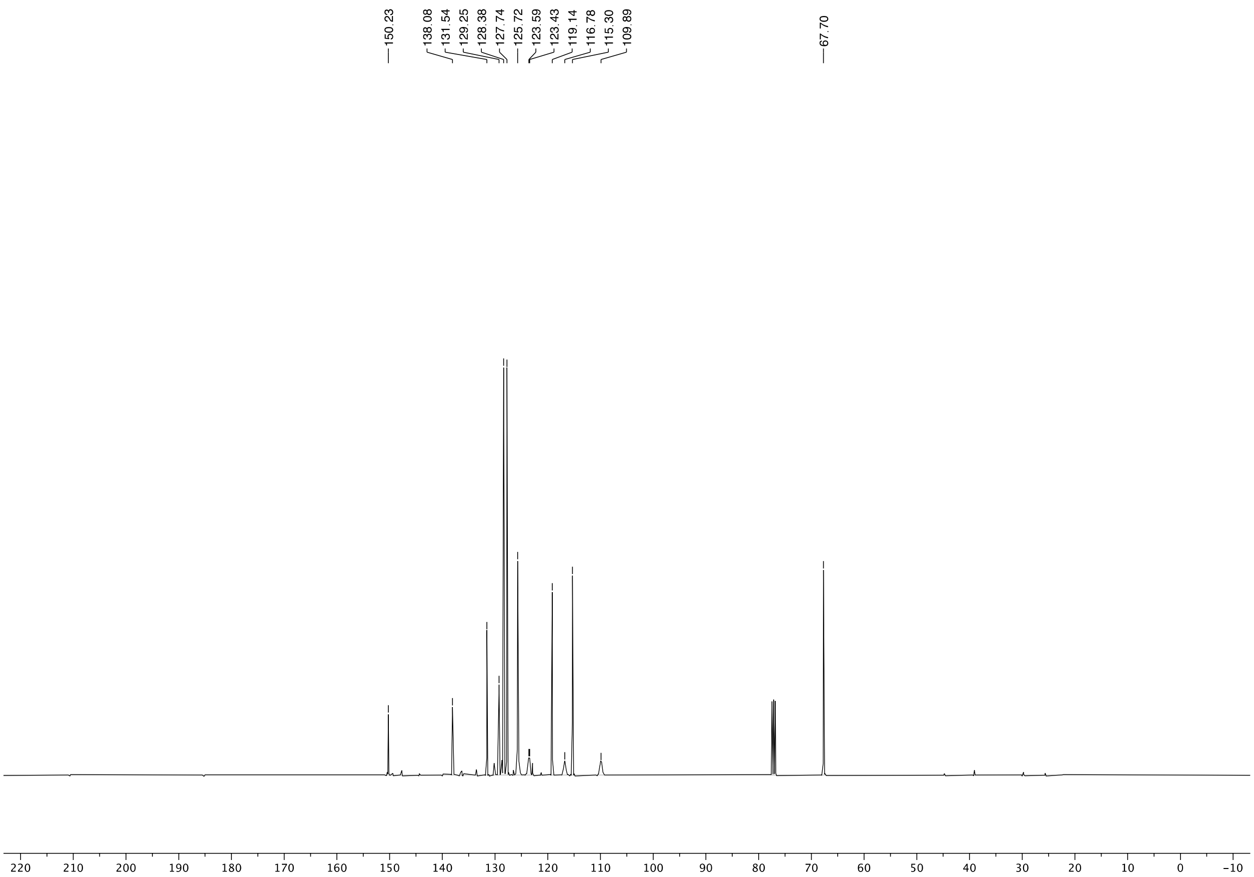
δ = 150.5, 138.2, 129.4, 128.4, 127.7, 125.6, 123.7, 116.6, 114.9, 109.6, 63.4, 14.4.





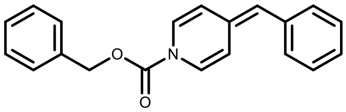
<u>^{1}H NMR</u> (400 MHz, $CDCL_3$):

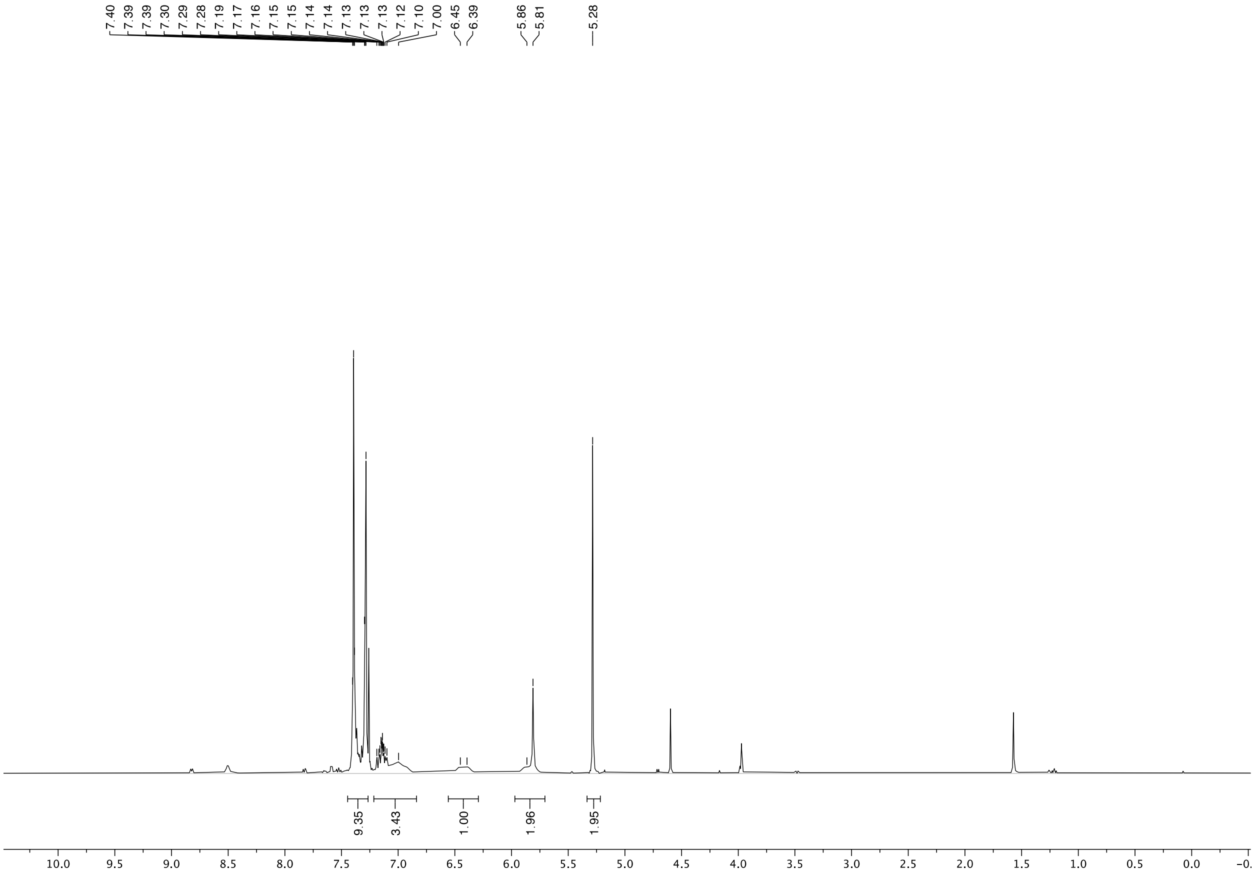
δ = 7.3-7.29 (m, 4H), 7.12-7.17 (m, 1H), 7.00 (bs, 2H), 6.43 (bs, 1H), 5.92-6.02 (m, 1H), 5.85 (bs, 1H), 5.81 (s, 1H), 5.29-5.4 (m, 2H), 4.75 (dt, 2H, *J* = 5.8, 1.36 Hz).



^{13}C NMR (400 MHz, CDCL$_3$):

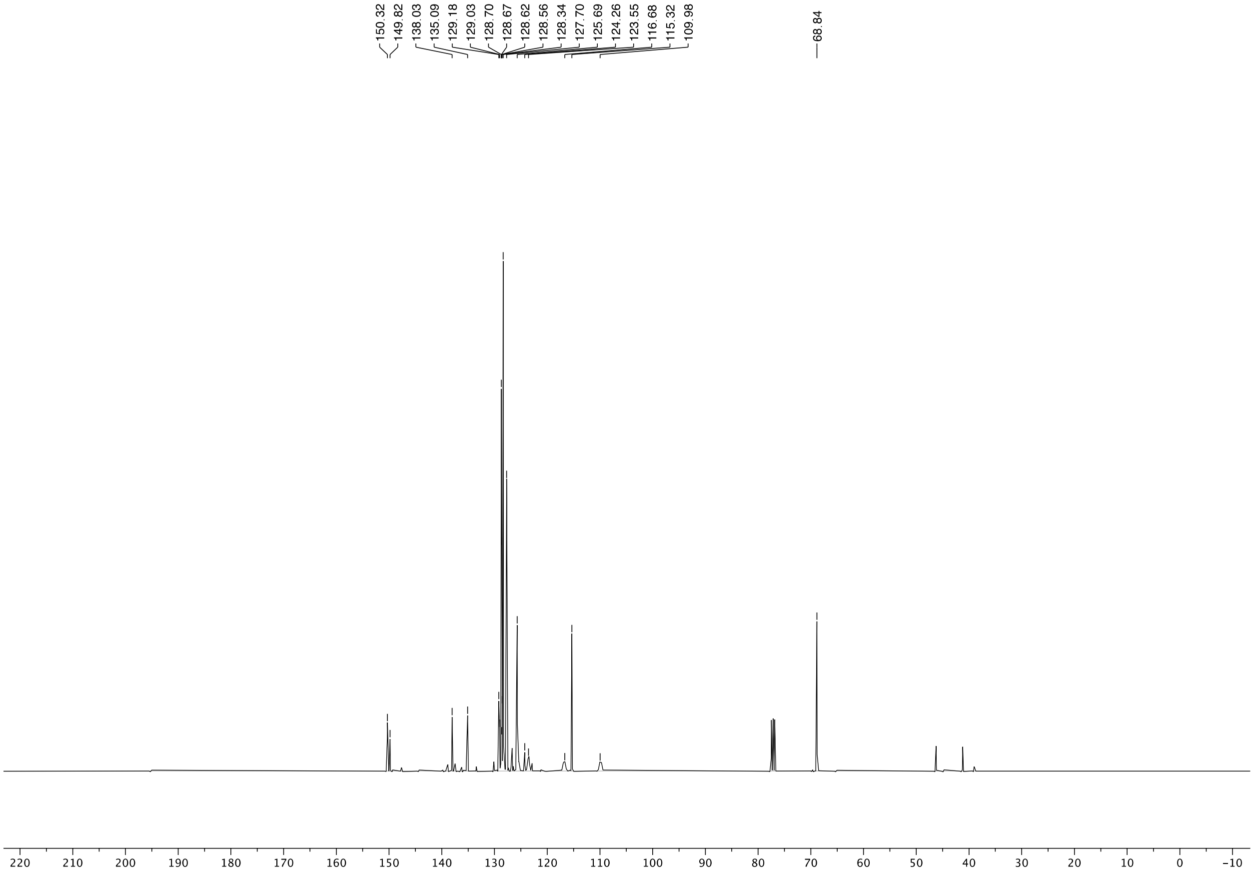
δ = 150.2, 138.1, 131.5, 129.2, 128.4, 127.7, 125.7, 125.6, 123.6, 119.1, 116.8, 115.3, 109.9, 67.7.





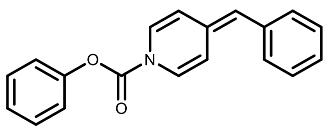
^{1}H NMR (400 MHz, CDCL$_3$):

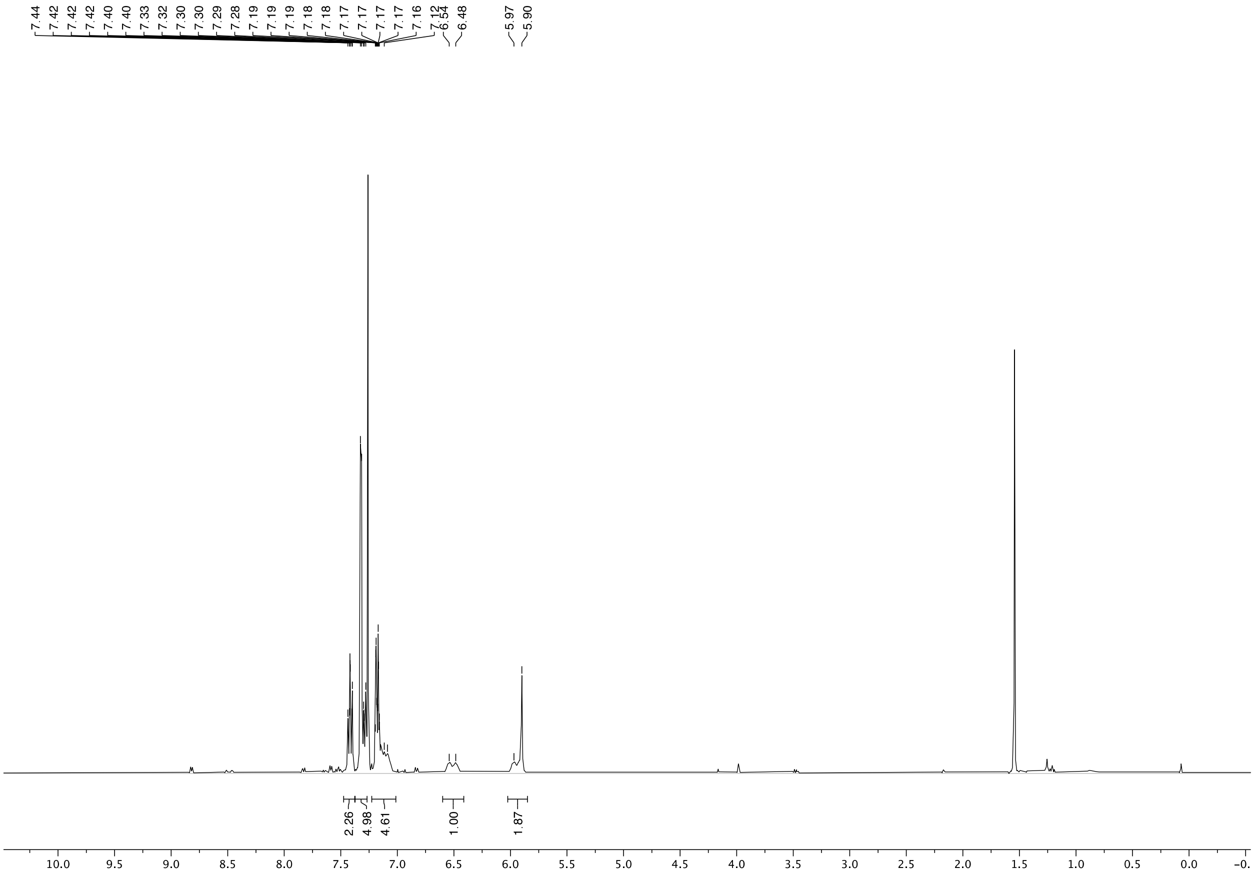
δ = 7.39-7.40 (m, 4H), 7.28-7.30 (m, 4H), 7.14 (m, 2H), 7.00 (bm, 2H), 6.42 (bd, 1H, *J* = 17.60 Hz), 5.87 (bs, 1H), 5.81 (s, 1H), 5.28 (s, 2H).



^{13}C NMR (400 MHz, CDCL$_3$):

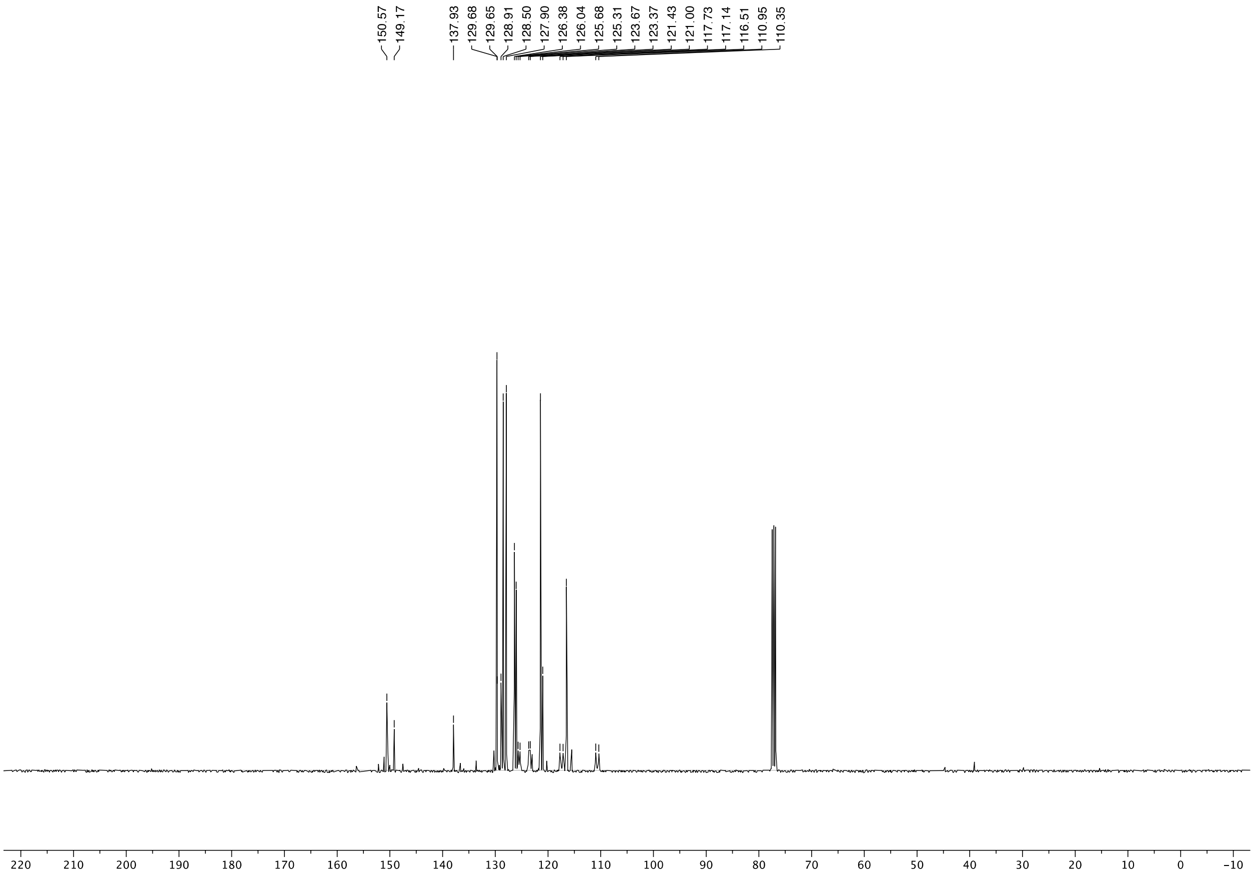
δ = 138.1, 135.2, 129.3, 129.1, 128.8, 128.6, 128.4, 127.8, 125.8, 125.6, 123.7, 116.9, 115.4, 110.0, 68.9.





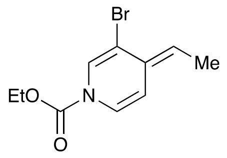
^{1}H NMR (400 MHz, $CDCL_3$):

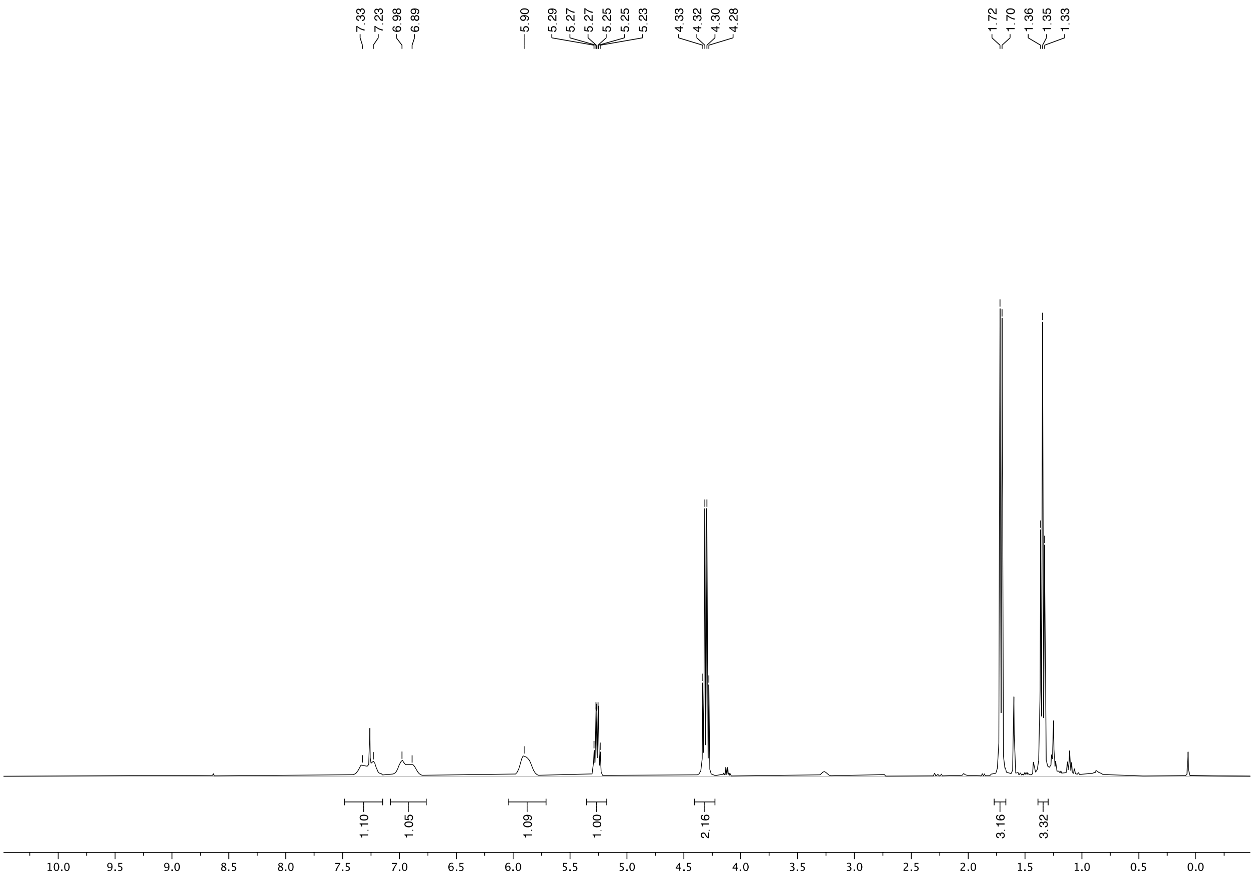
δ = 7.45-7.39 (m, 2H), 7.35-7.27 (m, 5H), 7.21-7.15 (m, 3H), 7.14-7.02 (bm, 2H), 6.51 (bd, 1H), 4.91-6.02 (bm, 1H), 5.90 (s, 1H).



^{13}C NMR (400 MHz, CDCL$_3$):

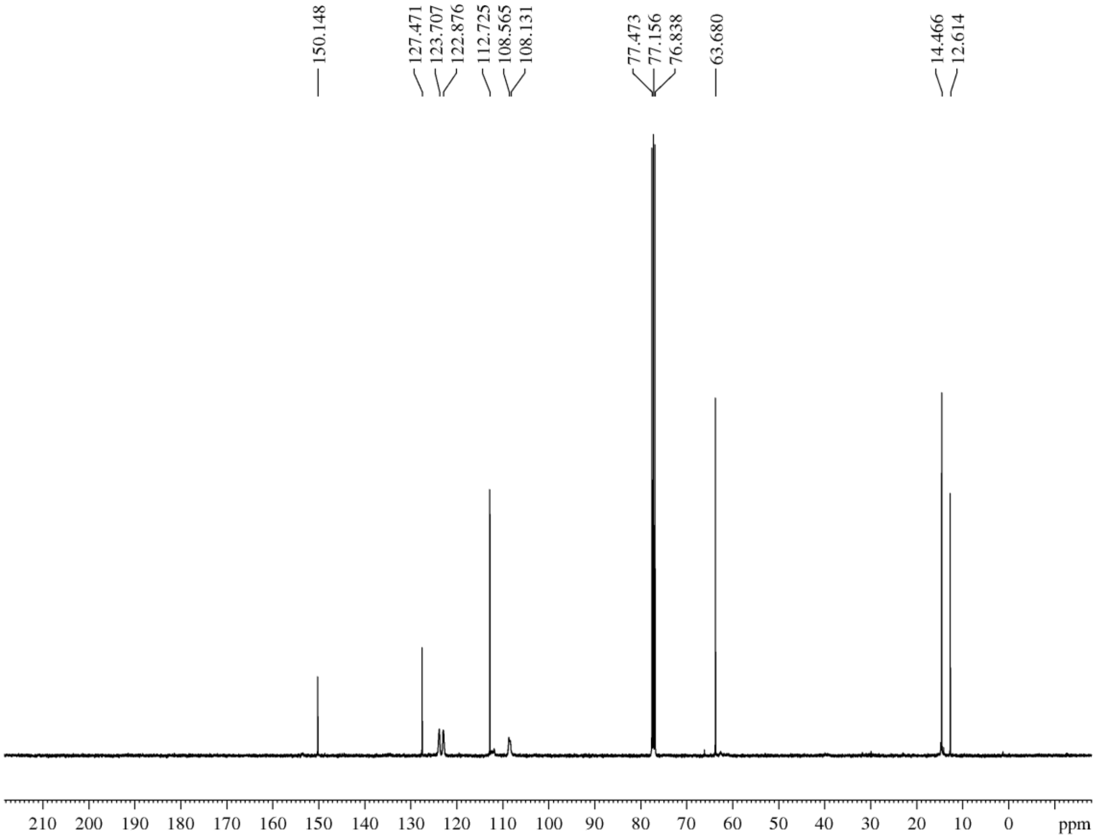
δ = 150.6, 149.2, 137.9, 129.7, 128.9, 128.5, 127.9, 126.4, 126.0, 125.7, 125.3, 123.6, 123.4, 121.4, 121.0, 117.7, 117.1, 116.5, 110.9, 110.4.





^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 7.29 (br d, 1H), 6.93 (br d, 1H), 5.90 (br s, 1H), 5.26 (q, 1H, *J* = 7.28 Hz), 4.31 (q, 2H, *J* = 7.11 Hz), 1.71 (d, 1H, *J* = 7.4 Hz), 1.35 (t, 3H, *J* = 7.1 Hz).



^{13}C-NMR (400 MHz, $CDCl_3$)

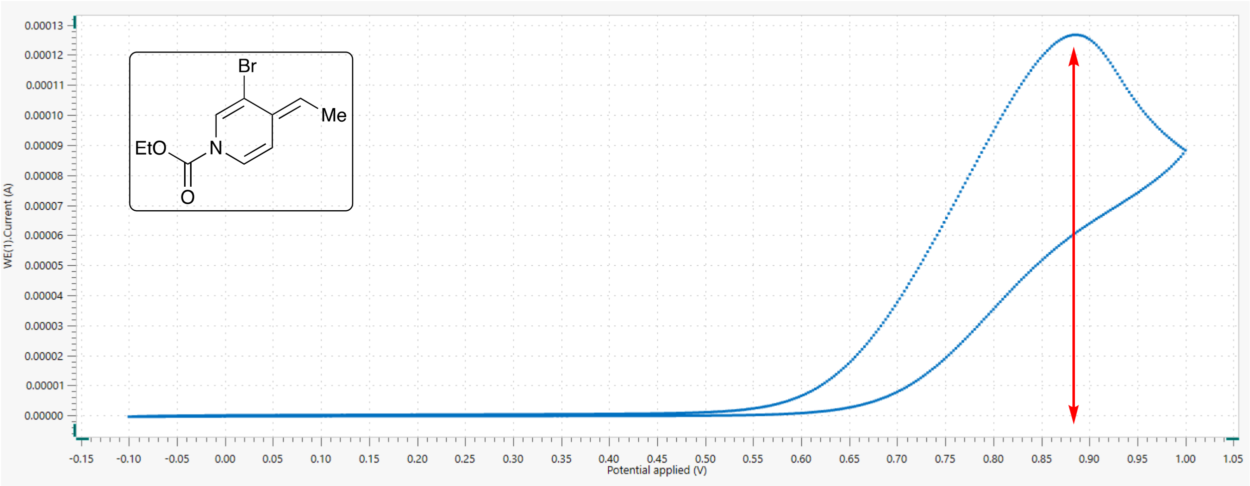
δ = 150.1, 127.5, 123.7, 122. 9, 112.7, 108.6, 108.1, 63.7, 14.5, 12.6.

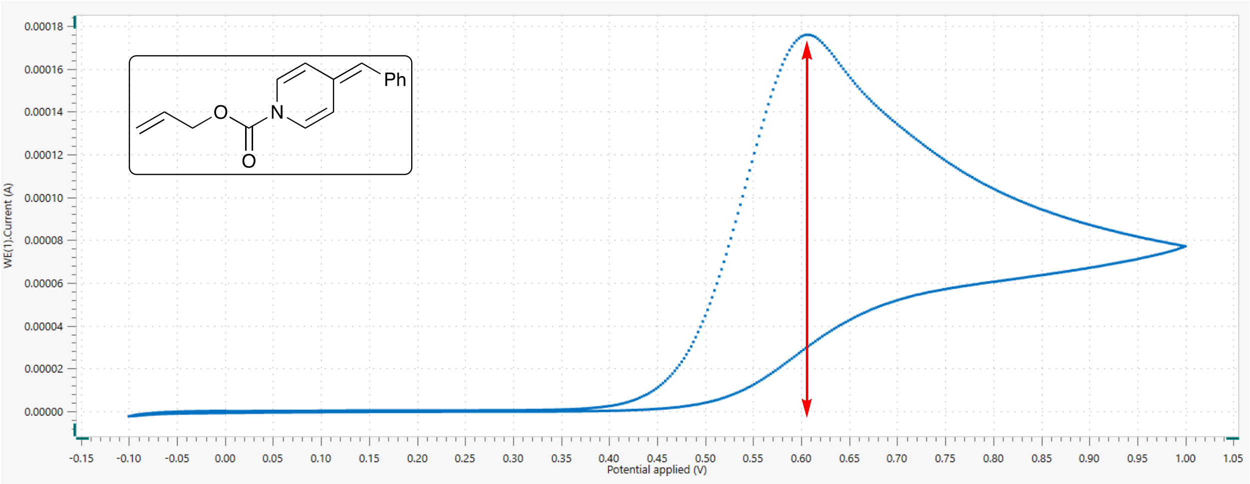
ADHP oxidation potentials: cyclic voltammetry procedure and raw data

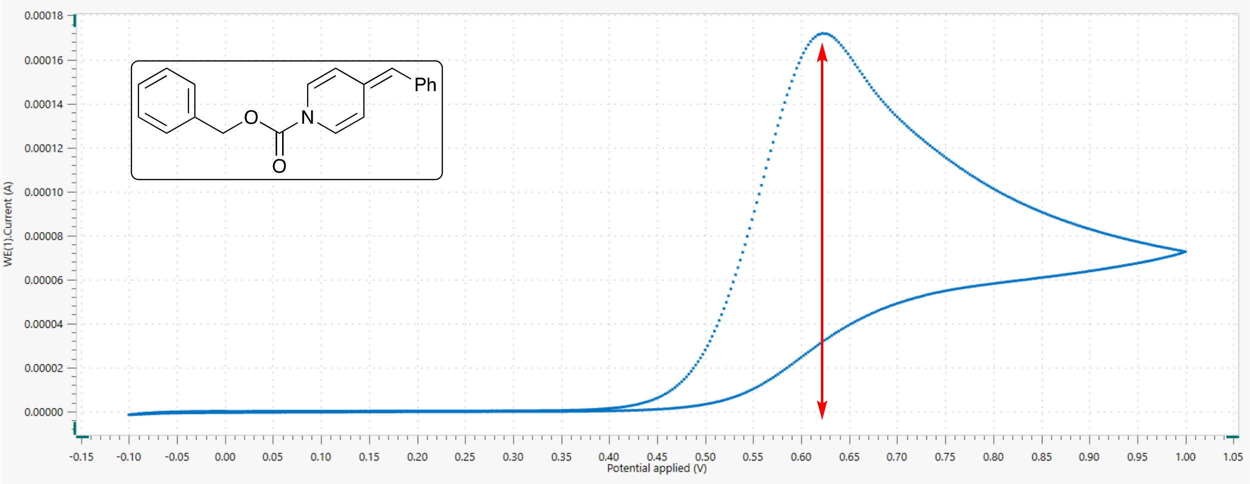
General cyclic voltammetry procedure

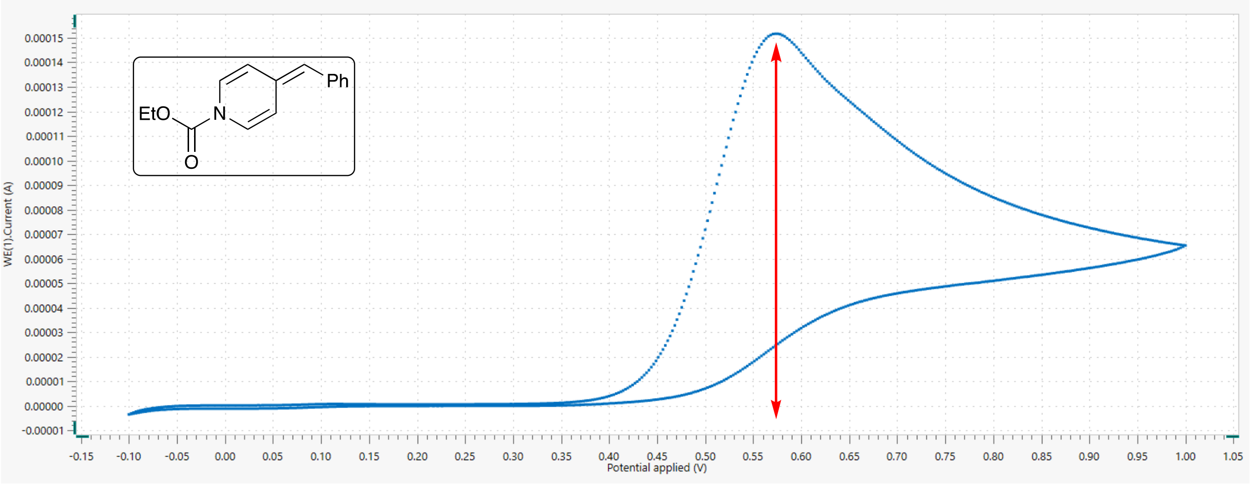
Cyclic Voltammetry was performed with an Auto lab PGSTAT204 Potentiostat operating at a 100 mV/second scan speed. The ADHP was preparade using general procedure 1, the resulting analyte was dissolved in dry acetonitrile (0.1M) containing 0.0065M tetrabutylammonium hexafluorophosphate (TABPF6). Before the measurement was taken, this solution was purged with nitrogen gas for 5 minutes then sealed in a CV compatible chamber. A typical three-electrode cell was used with a Pt wire counter electrode, an Ag/AgCl reference electrode, and a glassy carbon working electrode were used to take oxidation potential measurements.

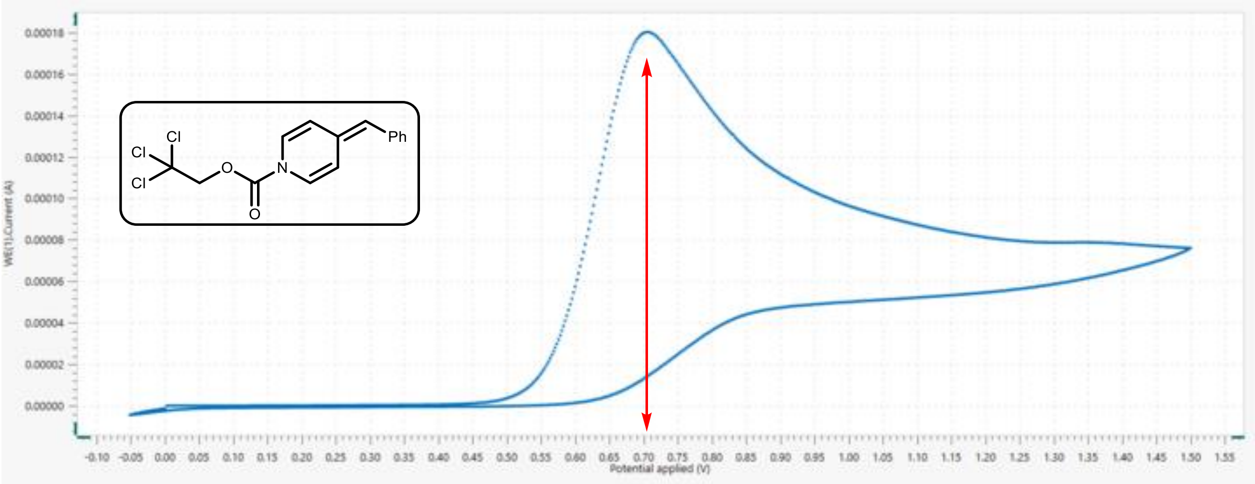
Raw cyclic voltammetry plots





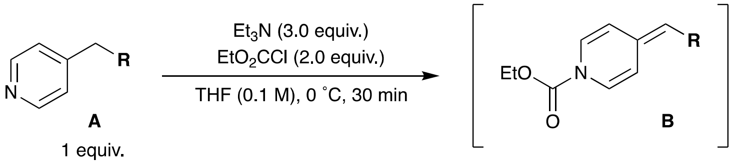

Ph
O
N
O
WE(1).Current (A)
0.00018
0.00016
0.00014
0.00012
0.00010
0.00008
0.00006
0.00004
0.00002
0.00000
-0.15 -0.10 -0.05 0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00 1.05
Potential applied (V)


Ph
EtO
N
O
WE(1).Current (A)
0.00015
0.00014
0.00013
0.00012
0.00011
0.00010
0.00009
0.00008
0.00007
0.00006
0.00005
0.00004
0.00003
0.00002
0.00001
0.00000
-0.00001
-0.15 -0.10 -0.05 0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00 1.05
Potential applied (V)


Cl
Cl
Cl
O
N
O
Ph
WE(1).Current (A)
0.00018
0.00016
0.00014
0.00012
0.00010
0.00008
0.00006
0.00004
0.00002
0.00000
-0.10 -0.05 0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00 1.05 1.10 1.15 1.20 1.25 1.30 1.35 1.40 1.45 1.50 1.55
Potential applied (V)

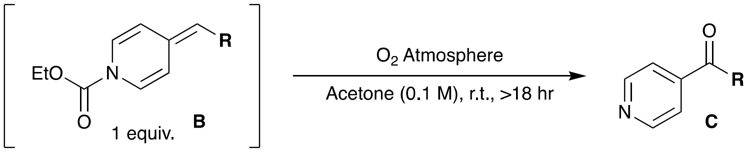
Oxidation of ADHPs: ADHP synthesis and oxidation

General procedure A: alkylidene dihydropyridine synthesis from 4-alkyl pyridines



Following our modified procedure,[8] under argon atmosphere, a 25 mL round-bottom flask equipped with a 1 cm stir-bar was charged with 4-Alkyl Pyridine **A** (1 eq), triethyl amine (3.0 eq), and anhydrous THF ([0.1 M] **A**). After stirring at 0 ˚C for 5 minutes, neat ethyl chloroformate (2.0 eq) was added dropwise, and the solution was stirred at temperature for 30 minutes. The heterogeneous yellow mixture was warmed to room temperature and concentrated *in vacuo* to remove solvent and excess reagents. The concentrate was diluted with ACS grade hexanes and filtered through a cotton plug into a 100 mL round-bottom flask. Concentration of the filtrate *in vacuo* furnished crude alkylidene dihydropyridine **B** which was used immediately without further purification.

General procedure B: Mild ADHP Oxidation to Pyridylic Ketones



A 25 mL round-bottom flask equipped with a 1 cm stir-bar was purged with an oxygen balloon for 5 minutes, followed by addition of crude alkylidene dihydropyridine **B** in ACS grade acetone ([0.1 M] **A**). The solution was stirred at room temperature overnight (>18 hr) under oxygen atmosphere. After overnight stirring, the mixture was concentrated *in vacuo* to give crude pyridylic ketone **C**. The crude ketone was dry loaded on to silica (500 mg) and purified by auto-flash chromatography (12g FlashPure EcoFlex, EtOAc/Hexanes, 0 – 100% over 12 column volumes) to give pyridylic ketone **C**.

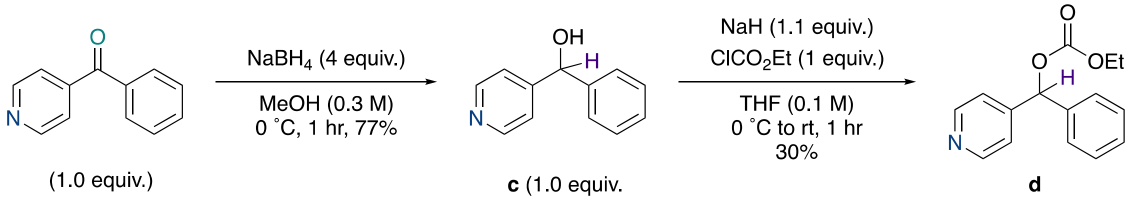
General procedure C: tracking ADHP decomposition via NMR

ADHP 1’ formation – Using procedure 1, pyridine 1 (50 mg, 1.0 equiv.) was reacted with triethylamine (3 equiv.) and allyl chloroformate (2 equiv.) to provide alkylidene dihydropyridine 1’ which is concentrated to provide a bright yellow oil. To this, anhydrous Et2O (20 mL) is added and the reaction mixture is filtered, and concentrated in vacuo to give the ADHP as clear yellow oil.

NMR reaction progress experiment – An oven-dried NMR tube was charged with AHDP 1’ (0.05 mmol) and p-Anisaldehyde (1 eq., 0.05 mmol) in CDCl3 (0.79 mL). The NMR tube containing the mixture was purged with oxygen for 1 minute prior to capping and sealing the tube with parafilm. The reaction was monitored for approximately 6.5 hours, recording a scan every hour on a Bruker 400 AV spectrometer with the relaxation delay set to 35 seconds. The reaction mixture was thoroughly vortexed for 2 minutes prior to each scan to ensure proper homogeneity of the sample throughout the experiment. The collected scans were then analyzed using Bruker Dynamics Center 2.5.5 to obtain the decay of the ADHP intermediate and formation of pyridilic ketone product.

4-Acylpyridine formation via ADHP oxidation: optimization studies

Synthesis of observed by-products (c, d, e)



Diphenylmethanol (c, CAS #: 91-01-0)

Under an open atmosphere, a 100 mL round-bottom flask equipped with a 3 cm stir-bar was charged with 4-benzoyl pyridine (1 eq, 500 mg, 2.73 mmol) and drum methanol (9 mL, [0.3 M] 4-benzoyl pyridine). After cooling the solution to 0 ˚C with an ice bath, sodium borohydride (4 eq, 413 mg, 10.9 mmol) was added completely in small portions over 3 minutes and stirred at temperature for 1 hour. The reaction was quenched with 10 mL of saturated $NH_4Cl_{(aq)}$. The ice bath was removed, and the reaction was stirred for 15 minutes. The heterogeneous mixture was diluted with EtOAc (15 mL), and the aqueous phase was extracted with EtOAc (x2 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude alcohol was dry loaded on to silica (1 g) and purified by auto-flash chromatography (12g FlashPure EcoFlex, MeOH/EtOAc, 0 – 100% over 6 column volumes) to give **c** as a white solid (386 mg, 77%) found to be consistent with reported literature.[42]

Data for **c**

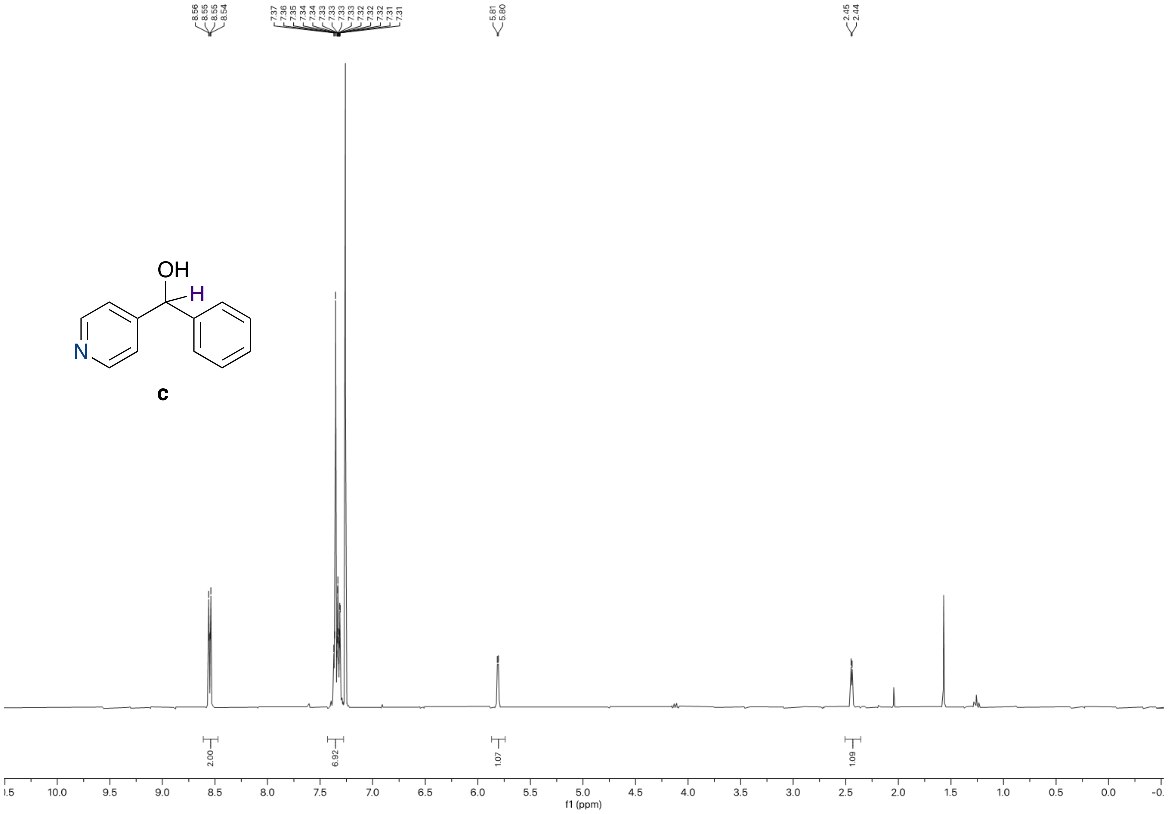
^{1}H-NMR (300 MHz, CDCl3)

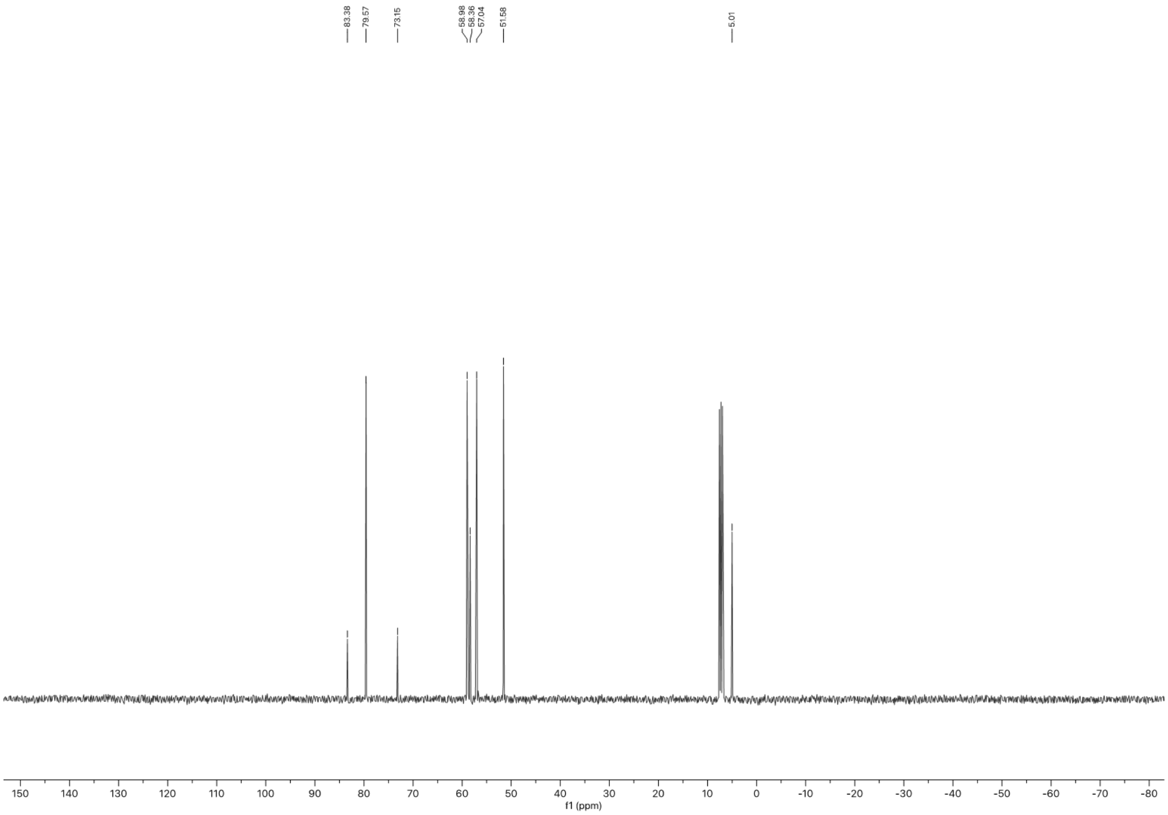
δ 8.62 – 8.47 (m, 2H), 7.45 – 7.28 (m, 7H), 5.81 (d, *J* = 3.2 Hz, 1H), 2.44 (d, *J* = 3.2 Hz, 1H).

^{13}C-NMR (101 MHz, CDCl3)

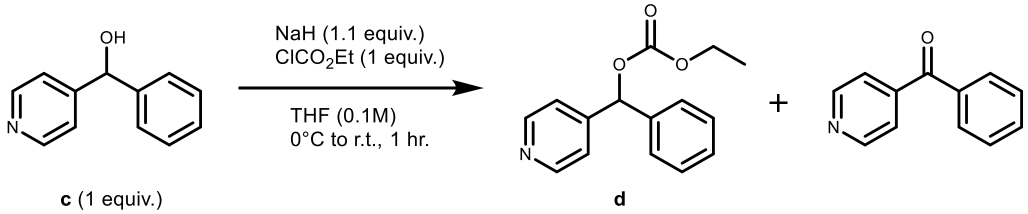
δ 153.3, 149.57, 143.1, 128.9, 128.3, 127.0, 121.5, 74.9.

^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (101 MHz, CDCl3) of **c**

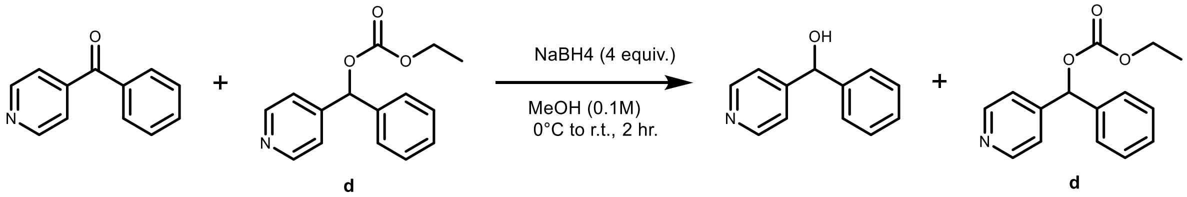




Benzhydryl ethyl carbanoate (d)



In an atmosphere-controlled glove box, a 20 mL vial equipped with a 1 cm stir-bar was charged with NaH (1.1 eq, 11 mg, 0.439 mmol) and sealed with a septum. The vial was removed from the glove box and purged with argon. A solution of **c** (74 mg, 1 eq, 0.399 mmol) in anhydrous THF (4 mL, [0.1 M] **c**) was added to the vial slowly at room temperature and stirred for 30 minutes. The solution was cooled to 0 ˚C, after which, neat ethyl chloroformate (1 eq, 0.04 mL, 0.4 mmol) was added dropwise. The solution was warmed to room temperature and stirred for an additional 30 minutes before being quenched with distilled water (10 mL). The mixture was diluted with EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (x2 5 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude carbonate ester was obtained as an inseparable mixture of **d** and 4-benzoyl pyridine (30% w/w).



This mixture was then diluted in MeOH (0.1M) and $NaBH_4$ (4 eq.) was added and stirred at 0 ˚C for 2 hours to give a mixture of **d** and 4-benzylalcohol which was purified via column chromatography (30% iPrOH in Hexanes).

Data for **d**

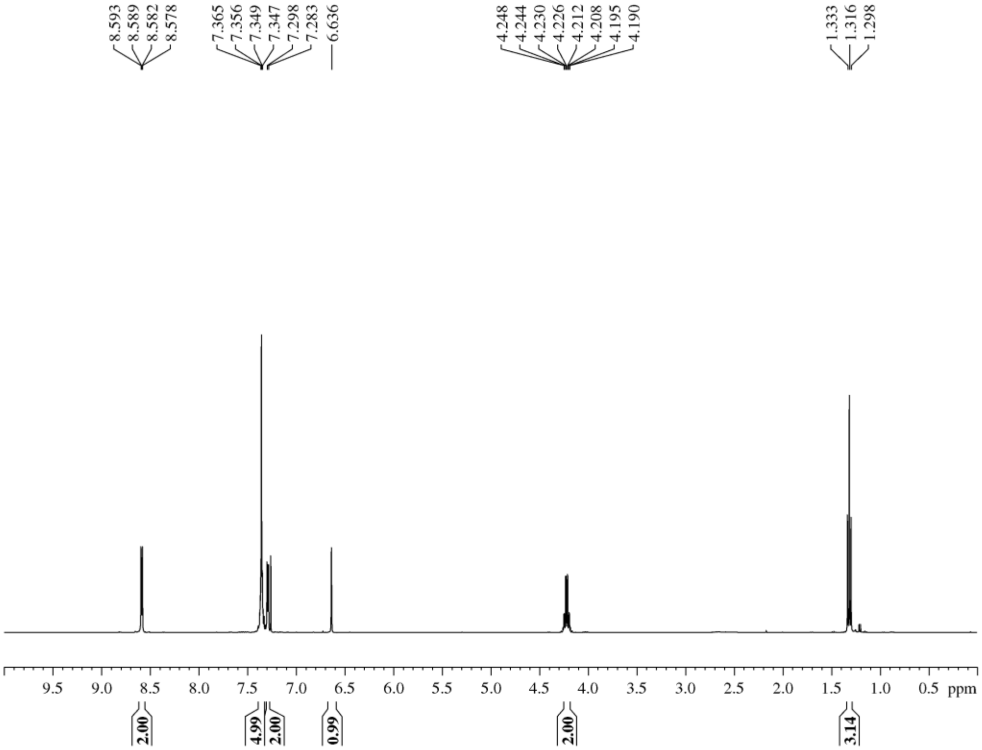
^{1}H-NMR (300 MHz, CDCl3)

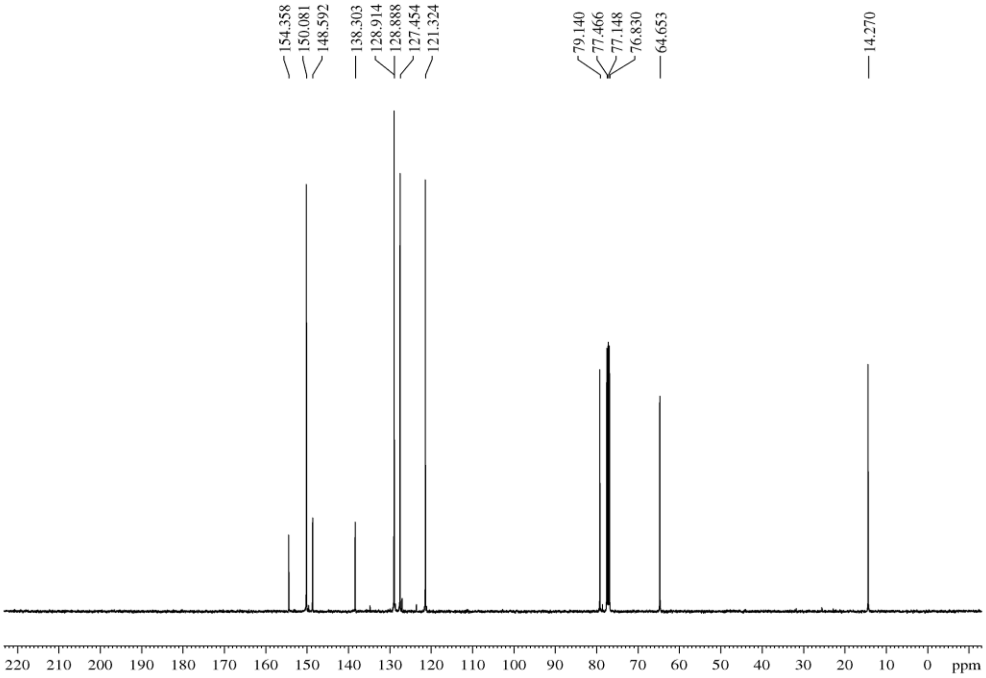
δ 8.66 – 8.45 (m, 2H), 7.40 – 7.31 (m, 5H), 7.31 – 7.26 (m, 2H), 6.63 (s, 1H), 4.22 (d, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (400 MHz, CDCl$_3$)

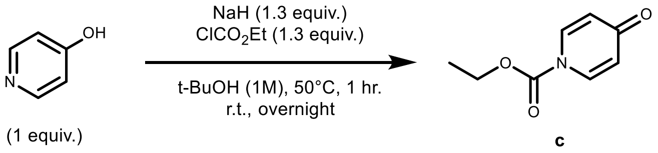
δ = 154.4, 150.1, 148.6, 138.3, 128.9, 127.5, 121.3, 79.1, 64.7, 14.3.

^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (101 MHz, CDCl3) of **d**





Ethyl 4-oxo-1(4H)-pyridinecarboxylate (e):



In an atmosphere-controlled glove box, a 20 mL vial equipped with a 1 cm stir-bar was charged with NaH (1.3 eq, 93 mg, 3.88 mmol) and sealed with a septum. The vial was removed from the glove box and purged with argon. A solution of 4-hydroxy pyridine (284 mg, 1.0 eq, 2.99 mmol) in *t*-butanol (3 mL, [1 M] 4-hydroxy pyridine) was added to the vial slowly at room temperature and stirred for 10 minutes. The solution was warmed to 50 ˚C and stirred for 15 minutes, after which, neat ethyl chloroformate (1.3 eq, 0.37 mL, 3.8 mmol) was added dropwise. The solution was stirred at temperature for 1 hour and left to cool to room temperature overnight. The mixture was quenched with distilled water (5 mL) and diluted with EtOAc (15 mL). The aqueous phase was extracted with EtOAc (x2 10 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude carbamate was dry loaded on silica (1 g) and purified by auto-flash chromatography (12g FlashPure EcoFlex, MeOH/EtOAc, 0 – 100% over 6 column volumes) to give **e** as an off-white hygroscopic solid (56%, 280 mg), found to be spectroscopically consistent with reported literature.[43]

Data for **e**

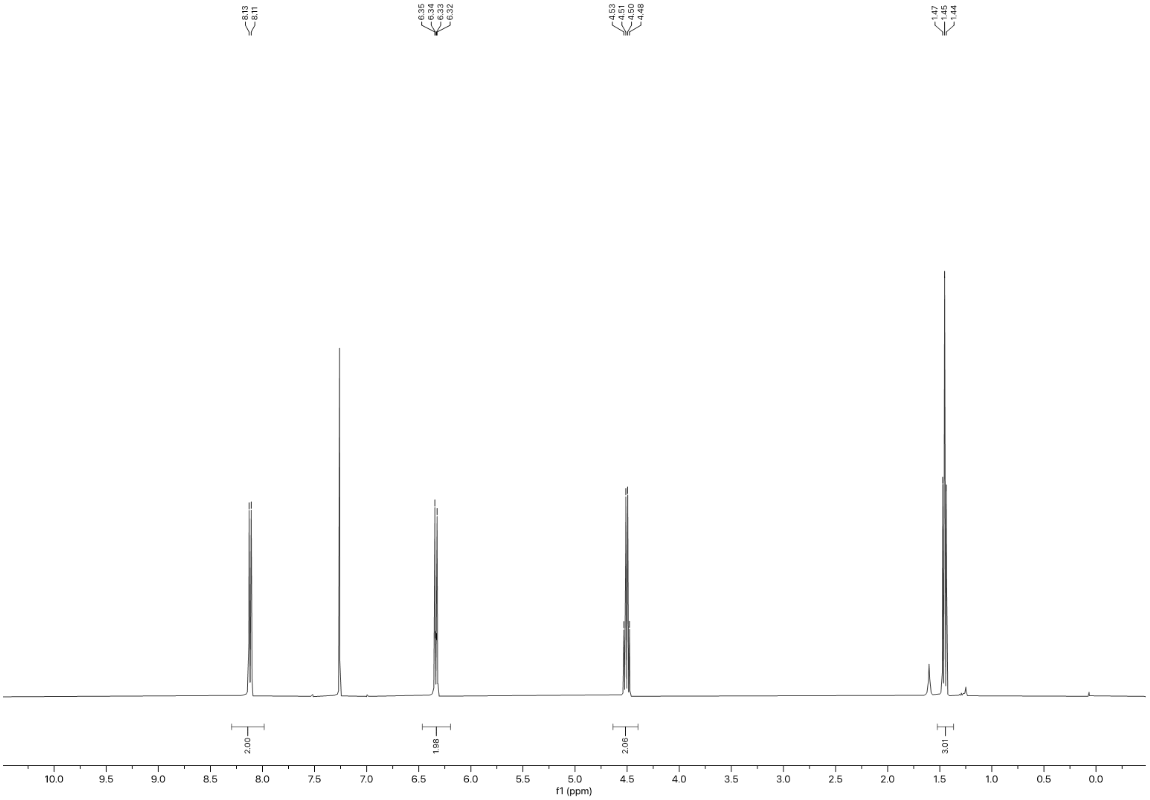
^{1}H-NMR (400 MHz, $CDCl_3$)

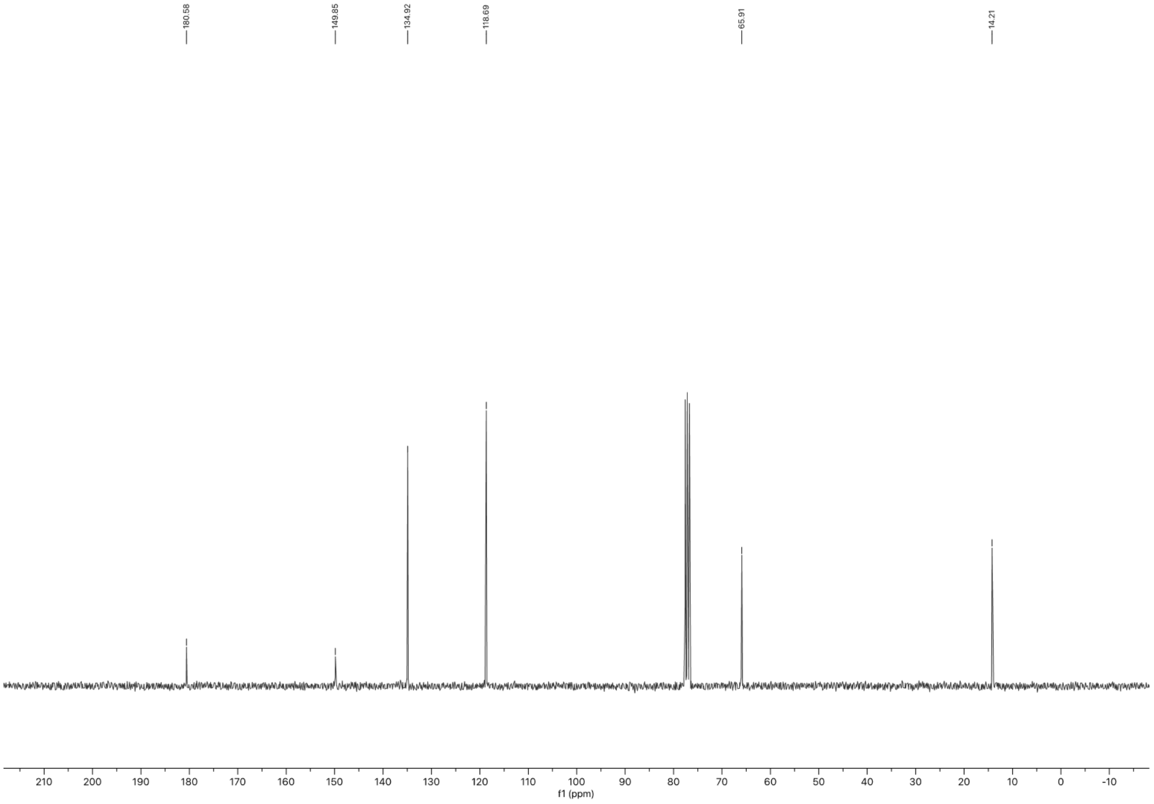
δ 8.16 – 8.08 (m, 2H), 6.38 – 6.29 (m, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$)

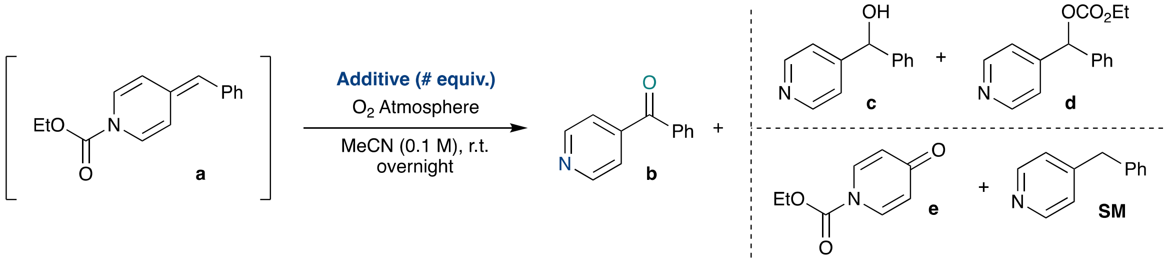
δ 180.6, 149.9, 134.9, 118.7, 65.9, 14.2.

^{1}H-NMR (400 MHz, CDCl3) and ^{13}C-NMR (75 MHz, CDCl3) for **e**





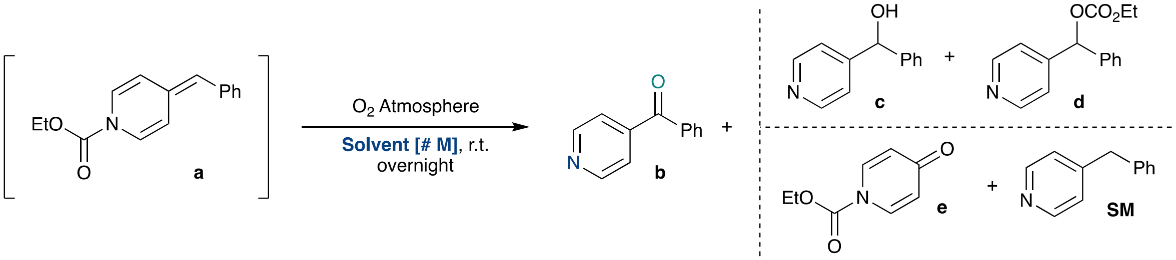
Screening basic additives



Entry	Additive	Equiv.	**a** Conv (%)	**b** (%)	**c** (%)	**d** (%)	**e** (%)	**SM** (%)
1	None	-	100	56	9	0	2	*cnd*
2	Et_3N	1	94	58	*cnd*	*cnd*	*cnd*	*cnd*
3	P-Sponge	1	51	19	0	0	0	*cnd*
4	K_2CO_3	1	100	55	*cnd*	*cnd*	3	*cnd*
5	K_2CO_3	3	100	60	*cnd*	*cnd*	3	*cnd*
6	K_2CO_3	5	100	57	*cnd*	*cnd*	1	*cnd*
7	K_2CO_3	10	100	61	*cnd*	*cnd*	4	*cnd*
8	Na_2CO_3	1	100	60	*cnd*	*cnd*	2	*cnd*
9	$NaHCO_3$	1	100	59	*cnd*	*cnd*	2	*cnd*
10	Na_2SO_4	1	100	58	*cnd*	*cnd*	2	*cnd*
11	$MgSO_4$	1	100	59	*cnd*	*cnd*	2	*cnd*
12	Cs_2CO_3	1	100	53	3	5	*cnd*	*cnd*
13	Cs_2CO_3	3	100	54	2	10	*cnd*	*cnd*
14	Cs_2CO_3	5	93	23	*cnd*	*cnd*	*cnd*	*cnd*
15	Cs_2CO_3	10	86	32	*cnd*	14	*cnd*	*cnd*

Conditions: Following general procedures **A+B**, ADHP **a** is prepared from 4-benzyl pyridine **SM** (50 mg, 0.3 mmol). Additives were weighed into the reaction vessel prior to ADHP addition. Percentages based on ^{1}H-NMR calibrated qNMR analysis with purified *p*-anisaldehyde internal standard. *Cnd* = (Could not determine).

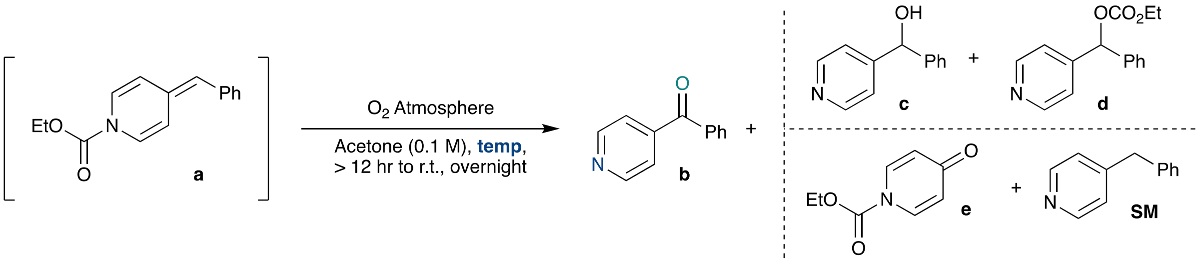
Screening solvents and reaction concentration



Entry	Solvent	Conc. [mol/L]	**a** Conv. (%)	**b** (%)	**c** (%)	**d** (%)	**e** (%)	**SM** (%)
1	MeCN	0.1	100	56	9	0	2	*cnd*
2	EtOAc	0.1	100	55	3	10	3	*cnd*
3	EtOAc	0.01	100	54	2	10	4	*cnd*
4	Acetone	0.1	100	**78**	3	0	*trace*	*cnd*
5	Acetone	0.01	100	74	0	0	*trace*	0
6	THF	0.1	100	44	4	3	4	0
7	1,2-DME	0.1	100	46	8	8	1	0
8	DCM	0.1	100	54	*cnd*	4	2	0

Conditions: Following general procedures **A+B**, ADHP **a** is prepared from 4-benzyl pyridine **SM** (50 mg, 0.3 mmol). Percentages based on ^{1}H-NMR calibrated qNMR analysis with purified *p*-anisaldehyde internal standard. *Cnd* = (Could not determine).

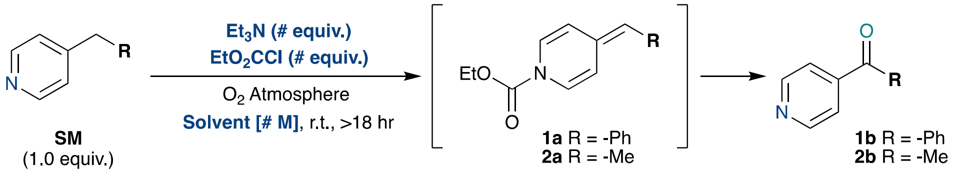
Screening temperature



Entry	Temp (˚C)	**a** Conv. (%)	**b** (%)	**c** (%)	**d** (%)	**e** (%)	**SM** (%)
1	23	100	**78**	3	0	*trace*	cnd
2	Reflux	24	12	0	0	0	0
3	0 ˚C	78	46	11	cnd	2	11

Conditions: Following general procedures **A+B**, ADHP **a** is prepared from 4-benzyl pyridine **SM** (50 mg, 0.3 mmol). Percentages based on ^{1}H-NMR calibrated qNMR analysis with purified *p*-anisaldehyde internal standard. *Cnd* = (Could not determine).

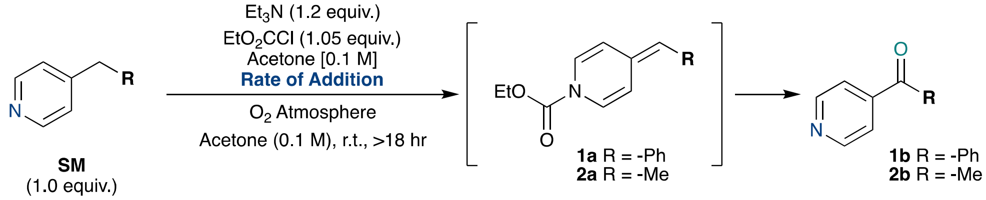
Optimizing one-pot oxidation conditions



Entry	**SM** Conv. **-R**, (%)	Solvent [mol/L]	Et_3N (equiv.)	EtO_2CCl (equiv.)	ADHP (%)	Ketone (%)
1	-Ph (96)	THF [0.1]	3	2	**1a** (42)	**1b** (24)
2	-Me (100)	THF [0.1]	3	2	**2a** (0)	**2b** (56)
3	-Me (98)	Acetone [0.1]	3	2	**2a** (43)	**2b** (26)
4	-Me (96)	Acetone [0.1]	3	1.05	**2a** (17)	**2b** (43)
5	-Me (92)	Acetone [0.1]	1.2	1.05	**2a** (0)	**2b** (54)
6	-Ph (100)	Acetone [0.1]	1.2	1.05	**1a** (0)	**1b** (78)
7	-Me (89)	Acetone [0.01]	1.2	1.05	**2a** (0)	**2b** (69)

Conditions: 1-Pot oxidation via ADHPs **1a** is prepared from 4-benzyl pyridine (50 mg, 0.3 mmol) and ADHP **2a** from 4-ethyl pyridine (50 mg, 0.47 mmol). Percentages based on ^{1}H-NMR calibrated qNMR analysis with purified *p*-anisaldehyde internal standard. *Cnd* = (Could not determine). Standardized reaction conditions are finalized prior to substrate scope (*vide infra*).

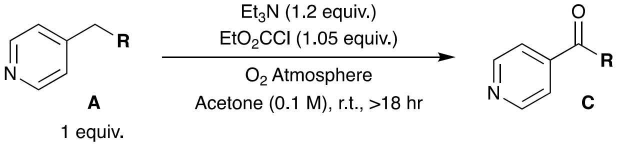
Screening rates of ethyl chloroformate addition



Entry	**SM** Conv. (%)	EtO_2CCl Addition Rate	ADHP (%)	Ketone (%)
1	-Me (92)	~30 s	**2a** (0)	**2b** (54)
2	-Me (92)	0.5 hr	**2a** (0)	**2b** (66)
3	-Me (100)	1 hr	**2a** (0)	**2b** (74)
4	-Ph (100)	~30 s	**1a** (0)	**1b** (77)
5	-Ph (100)	1 hr	**1a** (8)	**1b** (62)

Conditions: 1-Pot oxidation via ADHPs **1a** is prepared from 4-benzyl pyridine (50 mg, 0.3 mmol) and ADHP **2a** from 4-ethyl pyridine (50 mg, 0.47 mmol). Percentages based on ^{1}H-NMR calibrated qNMR analysis with purified *p*-anisaldehyde internal standard. *Cnd* = (Could not determine). Standardized reaction conditions are finalized prior to substrate scope (*vide infra*).

One-pot oxidation of 4-alkylpyridines: general procedures

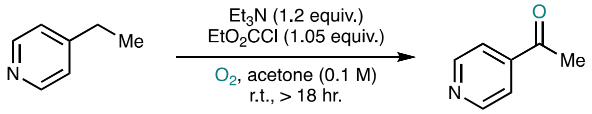


A) Slow chloroformate addition: Under oxygen atmosphere, a 25 mL round-bottom flask equipped with a 1 cm stir-bar was charged with 4-Alkyl Pyridine **A** (1 eq), triethyl amine (1.2 eq) and ACS grade acetone ([0.1 M] **A**). Concurrently, ethyl chloroformate (1.05 eq) was weighed into a 20 mL vial and diluted with ACS grade acetone ([0.1 M] **A**). To the room temperature alkyl pyridine mixture, the dilute chloroformate solution was added dropwise over 60 minutes using a syringe pump or addition funnel. After the addition was complete, the heterogenous solution was stirred at room temperature overnight (> 18 hr). After overnight stirring, the mixture is diluted with ethyl acetate and filtered through a cotton plug into a 100 mL round-bottom flask. The filtrate was concentrated *in vacuo* to give crude pyridylic ketone **C**.

B) Fast chloroformate addition: Under oxygen atmosphere, a 25 mL round-bottom flask equipped with a 1 cm stir-bar was charged with 4-Alkyl Pyridine **A** (1 eq), triethyl amine (1.2 eq) and ACS grade acetone ([0.1 M] **A**). Ethyl chloroformate (1.05 eq) was added to the room temperature alkyl pyridine mixture dropwise via syringe, rinsing the barrel with ACS grade acetone ([0.3 M] **A**). After the addition was complete, the heterogenous solution was stirred at room temperature overnight (> 18 hr). After overnight stirring, the mixture is diluted with ethyl acetate and filtered through a cotton plug into a 100 mL round-bottom flask. The filtrate was concentrated *in vacuo* to give crude pyridylic ketone **C**.

Spectral data for substrate scope study

1-(4-Pyridinyl)ethanon (1B, CAS #: 1122-54-9)



1 (1.0 equiv.) **1B** 58%

Using 1-pot oxidation procedure **A**, pyridine **1** (1.0 equiv.) provided product **1B** in 64% qNMR yield. **1B** isolated by flash chromatography was spectroscopically consistent with reported literature.[25]

Chromatography (same conditions used for all substrates):

First Column: 65-70% EtOAc in Hexanes

Second Column: 25-30% i-PrOH in Hexanes

Data for **1B**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.95 – 8.67 (m, 2H), 7.80 – 7.59 (m, 2H), 2.63 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 197.4, 151.0, 142.9, 121.4, 26.8.

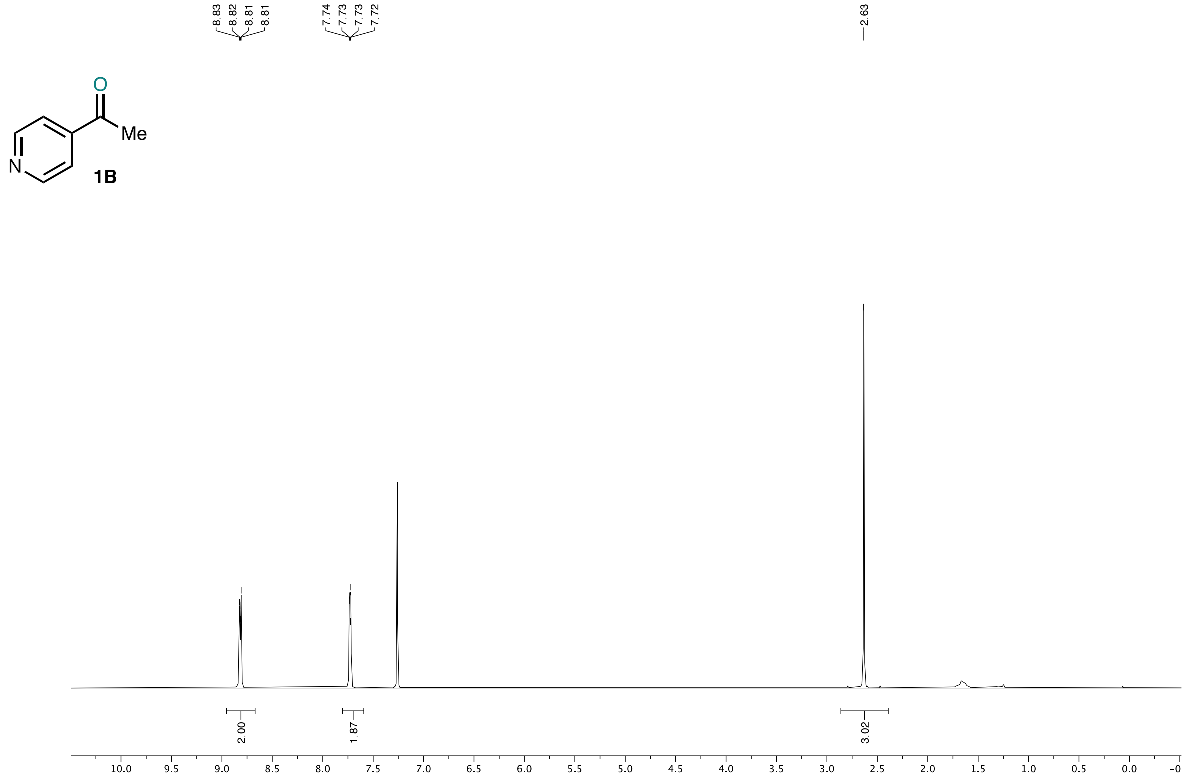
IR Alpha-Platinum ATR, Bruker, diamond crystal

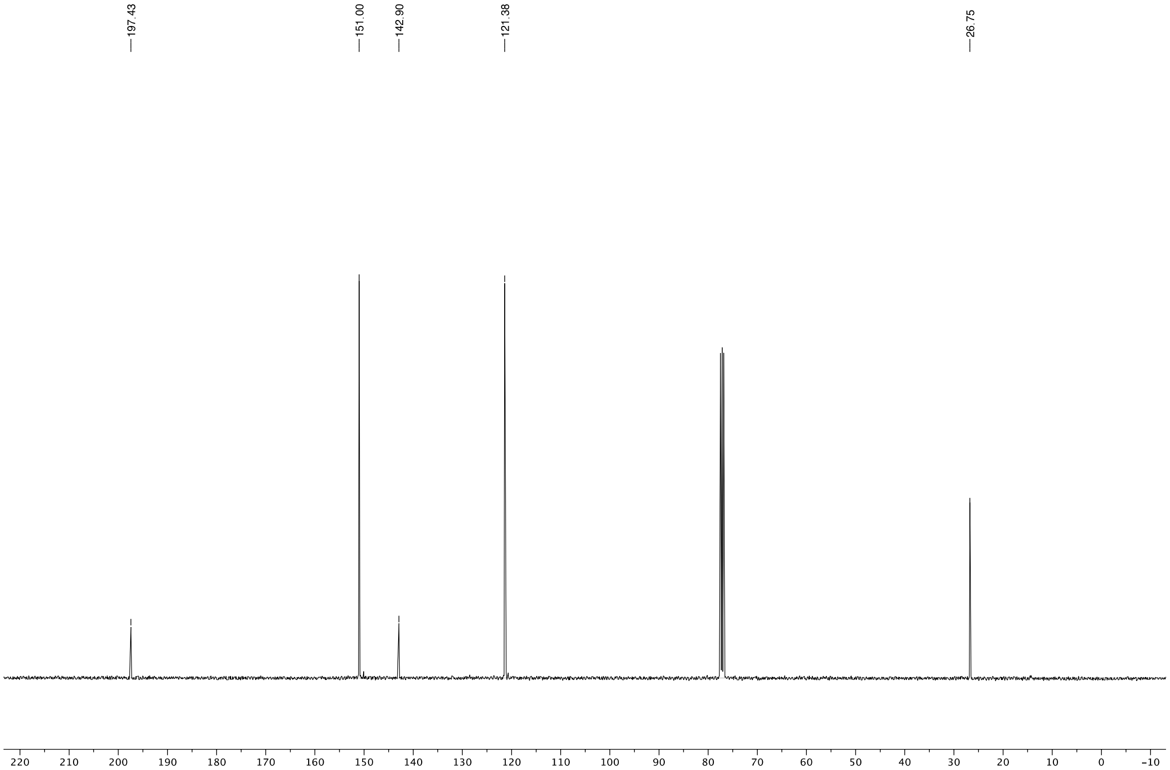
ν = 2986, 1692, 1556, 1380, 1262 (cm^{-1})

HRMS ESI

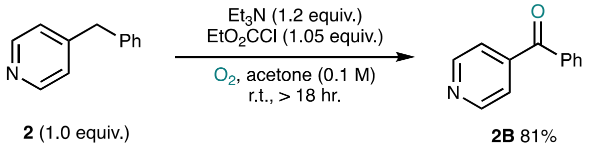
Calculated mass for $(M+H)^+$ of $C_9H_{10}NO^+$ is 122.0601, found 122.0600.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **1B**





Phenyl(4-pyridinyl)methanon (2B, CAS #: 14548-46-0)



Using 1-pot oxidation procedure **B**, pyridine **2** (1.0 equiv.) provided product **2B** in 81% qNMR yield. **2B** isolated by flash chromatography was spectroscopically consistent with reported literature.[26]

Data for **2B**

^{1}H-NMR (400 MHz, CDCl3)

δ 8.87 – 8.77 (m, 2H), 7.87 – 7.77 (m, 2H), 7.65 (ddt, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.55 – 7.48 (m, 2H).

^{13}C-NMR (101 MHz, CDCl3)

δ 195.2, 150.4, 144.4, 136.0, 133.6, 130.2, 128.7, 122.9.

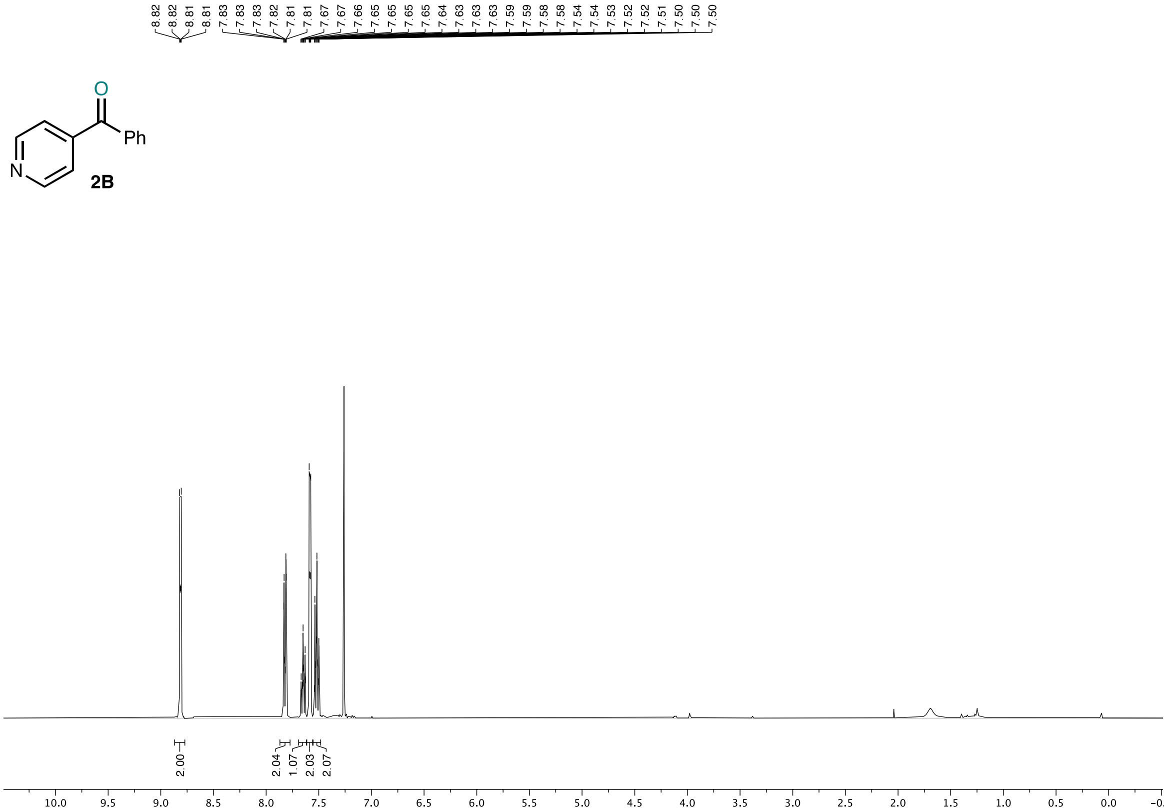
IR Alpha-Platinum ATR, Bruker, diamond crystal

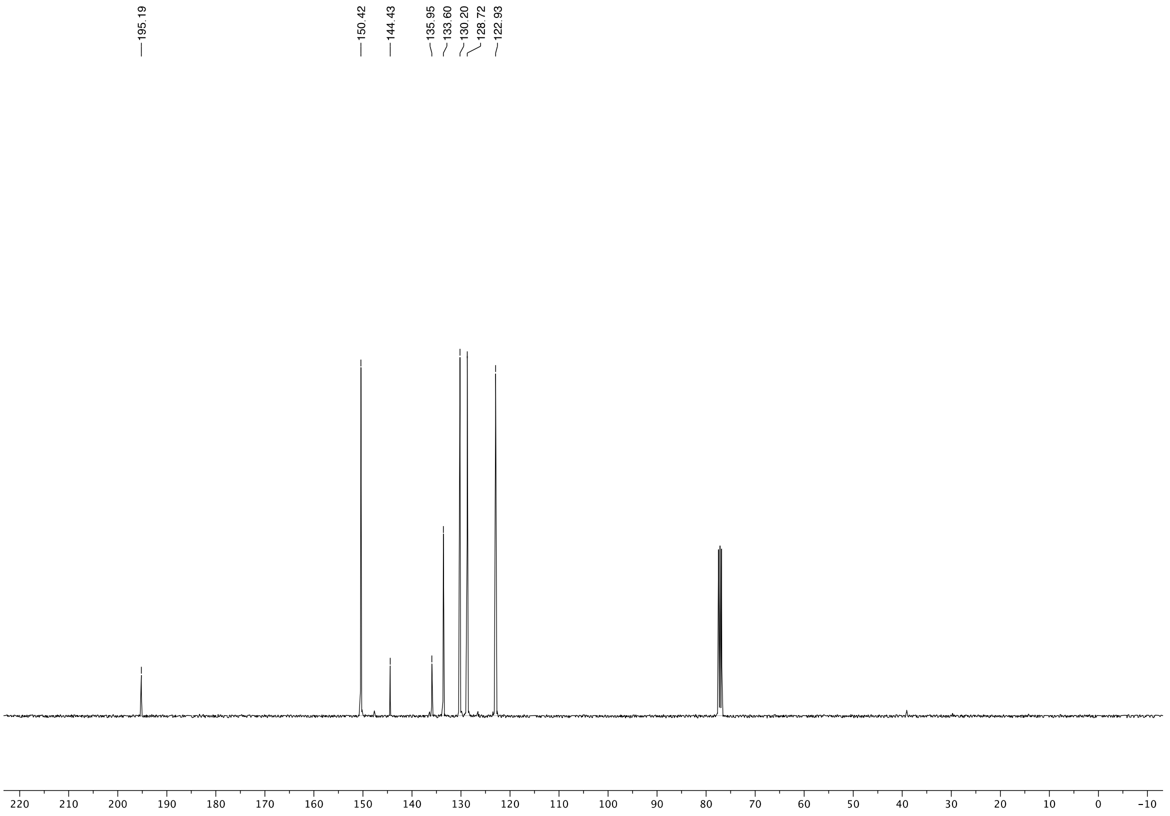
ν = 3060, 1663, 1550, 1425, 1275 (cm^{-1})

HRMS ESI

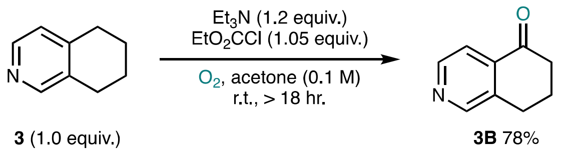
Calculated mass for $(M+H)^+$ of $C_9H_{10}NO^+$ is 184.0757, found 184.0757.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **2B**





7,8-Dihydro-5(6H)-isoquinolinone (3B, CAS #: 21917-86-2)



Using 1-pot oxidation procedure **A**, pyridine **3** (1.0 equiv.) provided product **3B** in 78% qNMR yield. **3B** isolated by flash chromatography was spectroscopically consistent with reported literature.[27]

Data for **3B**

^{1}H-NMR (400 MHz, CDCl3)

δ 8.67 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 7.76 (dd, J = 5.1, 0.8 Hz, 1H), 2.98 (t, *J* = 6.1 Hz, 2H), 2.76 – 2.67 (m, 2H), 2.20 (tt, *J* = 6.6, 5.5 Hz, 2H).

^{13}C-NMR (101 MHz, CDCl3)

δ 197.8, 151.4, 148.6, 137.7, 137.6, 119.2, 39.2, 26.4, 23.0.

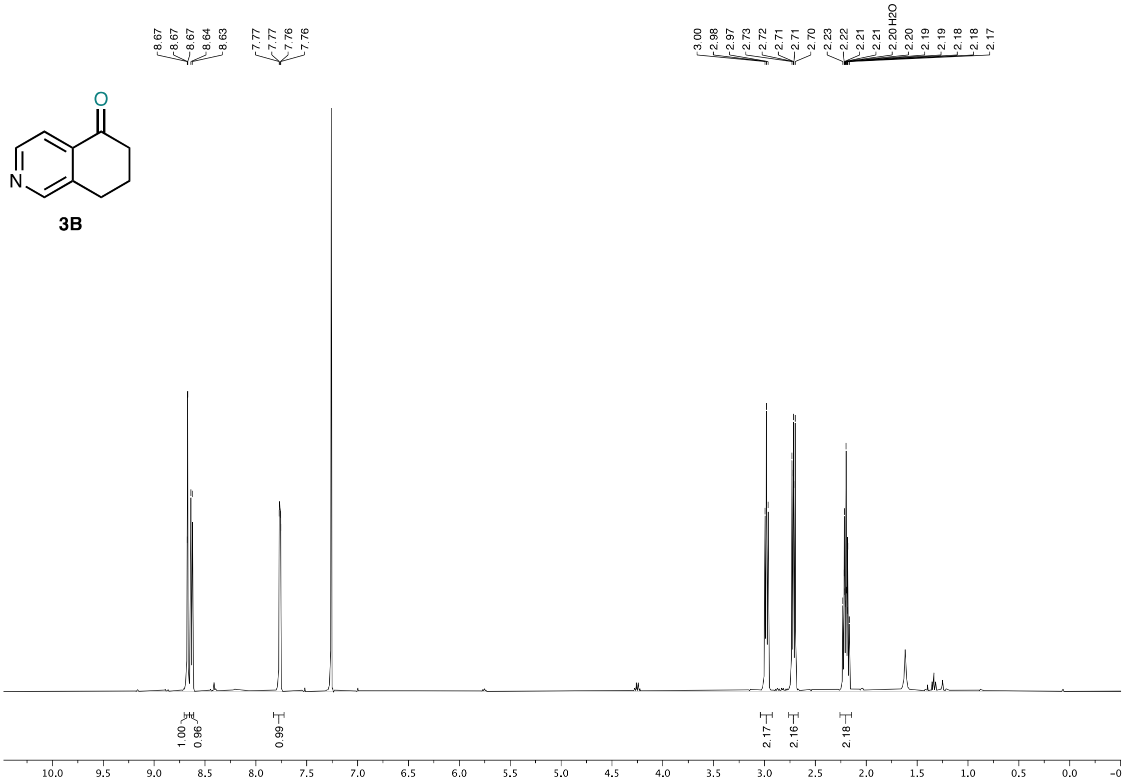
IR Alpha-Platinum ATR, Bruker, diamond crystal

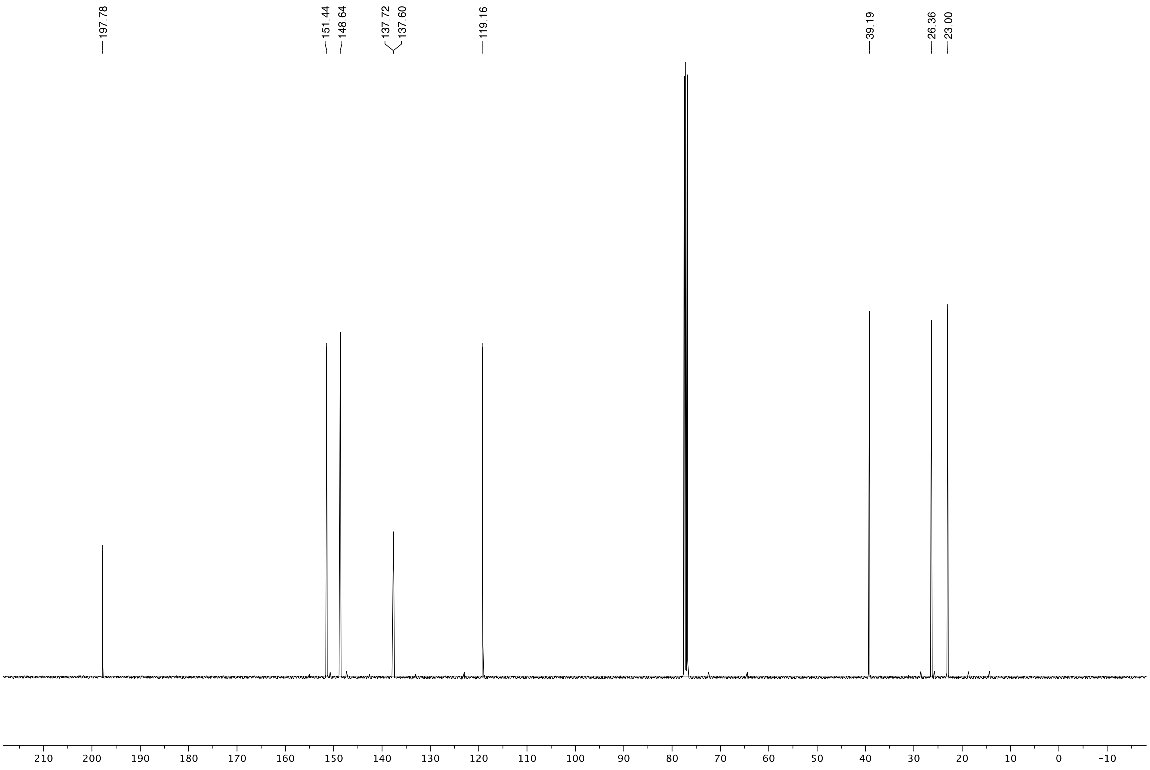
ν = 2946, 1690, 1561, 1407, 1292 (cm^{-1})

HRMS ESI

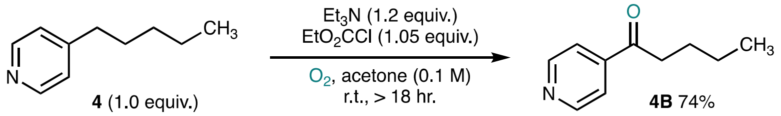
Calculated mass for $(M+H)^+$ of $C_9H_{10}NO^+$ is 148.0757, found 148.0757.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **3B**





1-(4-Pyridinyl)-1-pentanone (4B, CAS #: 1701-73-1)



Using 1-pot oxidation procedure **A**, pyridine **4** (1.0 equiv.) provided product **4B** in 74% qNMR yield. **4B** isolated by flash chromatography was spectroscopically consistent with reported literature.[28]

Data for **4B**

^{1}H-NMR (400 MHz, CDCl3)

δ 8.86 – 8.74 (m, 2H), 7.78 – 7.68 (m, 2H), 3.02 – 2.91 (m, 2H), 1.80 – 1.67 (m, 2H), 1.48 – 1.34 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 197.8, 151.4, 148.6, 137.7, 137.6, 119.2, 39.2, 26.4, 23.

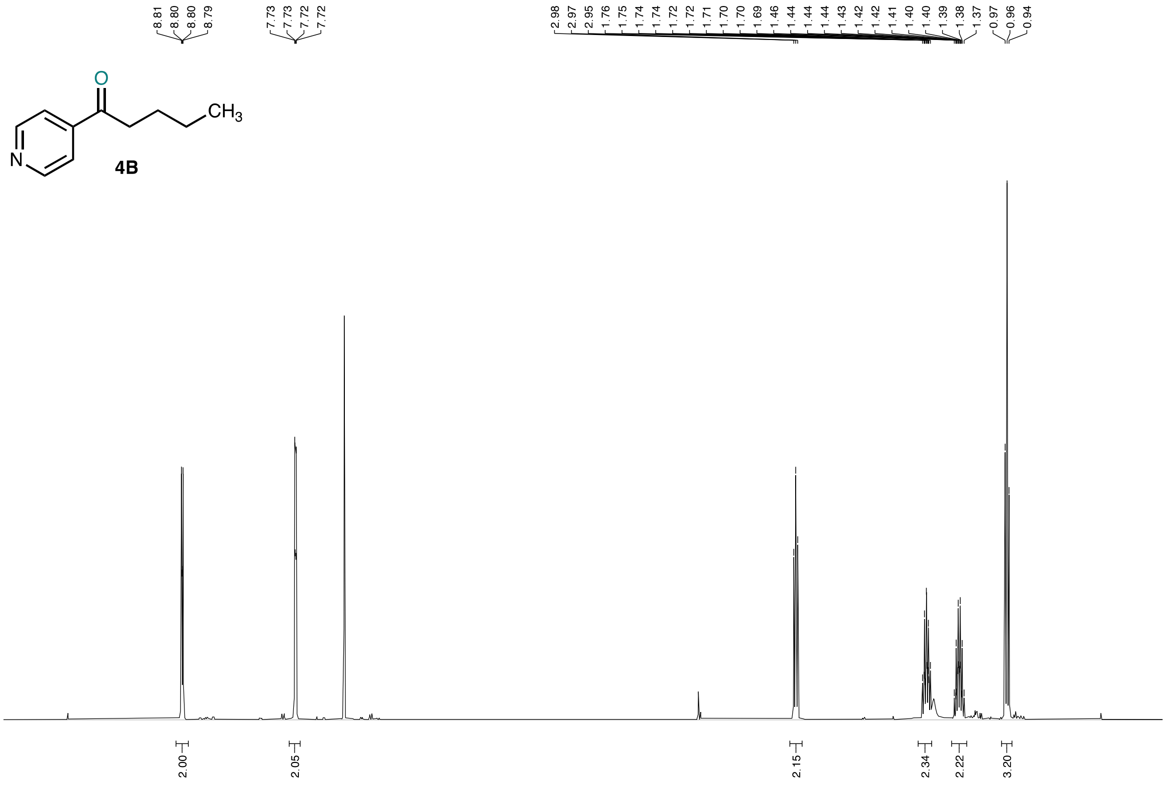
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2958, 1694, 1555, 1406, 1261, 1206 (cm^{-1})

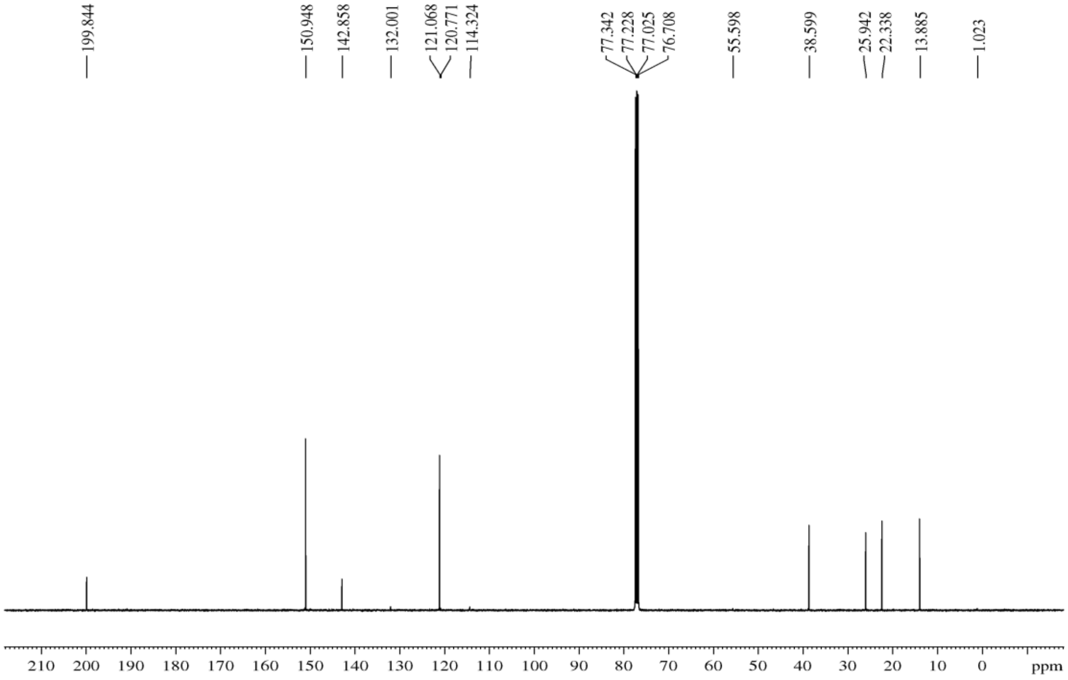
HRMS ESI

Calculated mass for $(M+H)^+$ of $C_{10}H_{14}NO^+$ is 164.1070, found 164.1071.

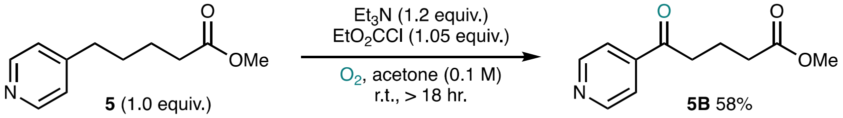
^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **4B**



4B



Methyl 5-oxo-5-(4-pyridinyl)pentanoate (5B)



Using 1-pot oxidation procedure **A**, pyridine **5** (1.0 equiv.) provided product **5B** in 58% qNMR yield. **5B** was isolated by flash chromatography.

Data for **5B**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.87 – 8.74 (m, 2H), 7.79 – 7.68 (m, 2H), 3.69 (s, 3H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.08 (p, *J* = 7.1 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 198.9, 173.6, 151.1, 142.6, 121.1, 51.8, 37.9, 32.9, 19.0.

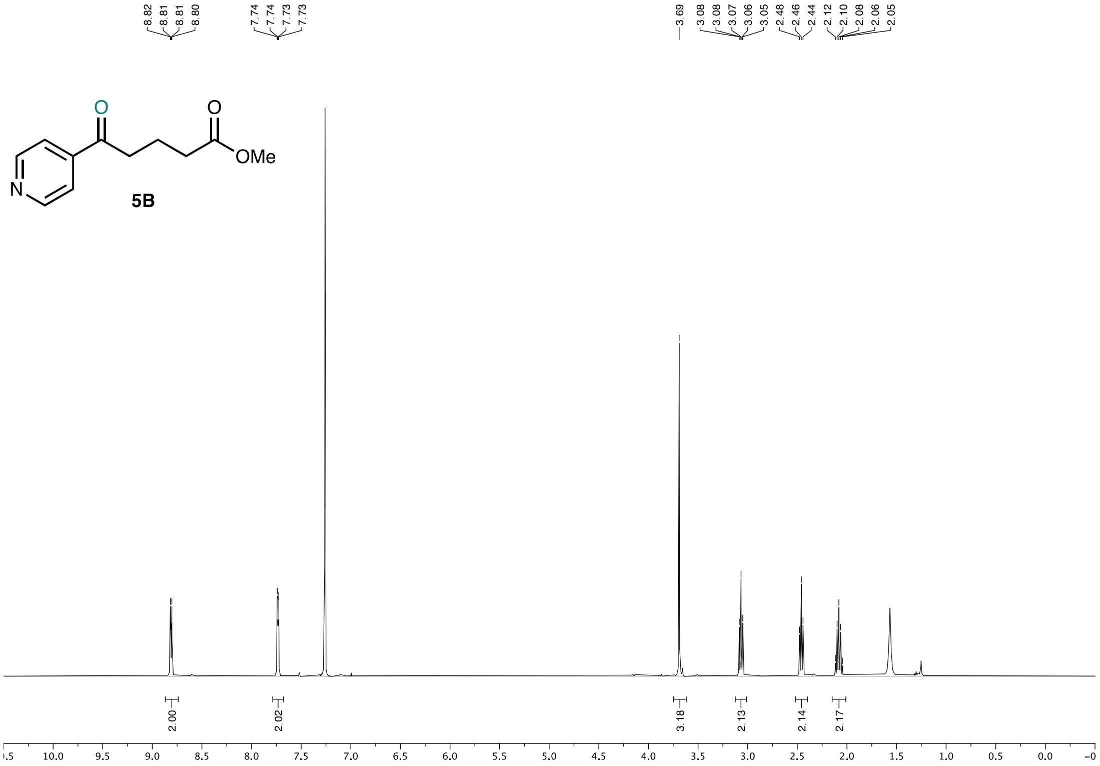
IR Alpha-Platinum ATR, Bruker, diamond crystal

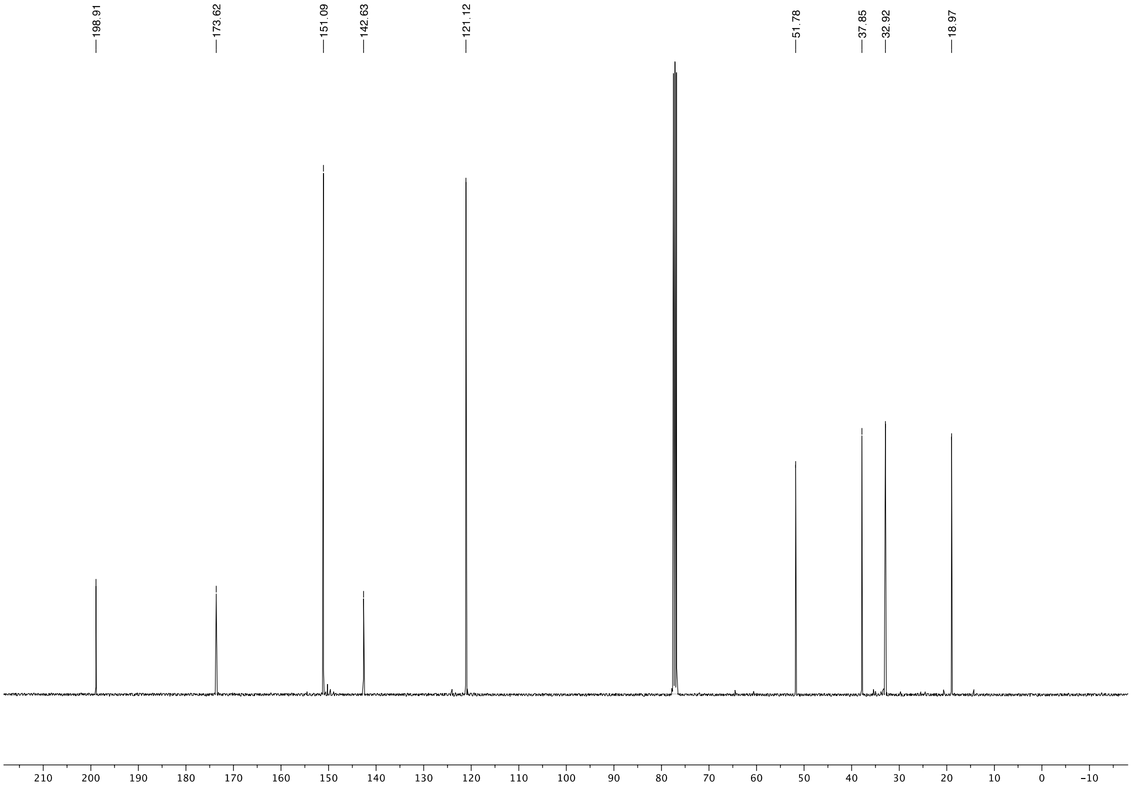
ν = 2951, 1731, 1695, 1407, 1206 (cm^{-1})

HRMS ESI

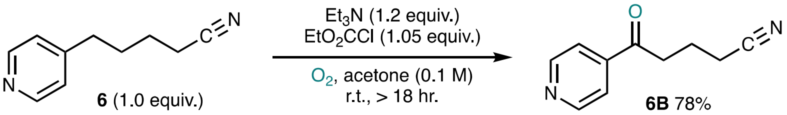
Calculated mass for $(M+H)^+$ of $C_{11}H_{14}NO_3^+$ is 208.0968, found 208.0968.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **5B**





5-Oxo-5-(4-pyridinyl)pentanenitrile (6B)



Using 1-pot oxidation procedure **A**, pyridine **6** (1.0 equiv.) provided product **6B** in 78% qNMR yield. **6B** was isolated by flash chromatography.

Data for **6B**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.89 – 8.76 (m, 2H), 7.83 – 7.66 (m, 2H), 3.19 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.14 (p, *J* = 6.8 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 197.8, 151.1, 142.2, 121.0, 119.2, 36.8, 19.4, 16.6.

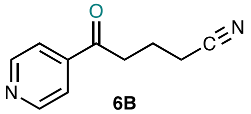
IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2974, 2246, 1695, 1557, 1407, 1232 (cm^{-1})

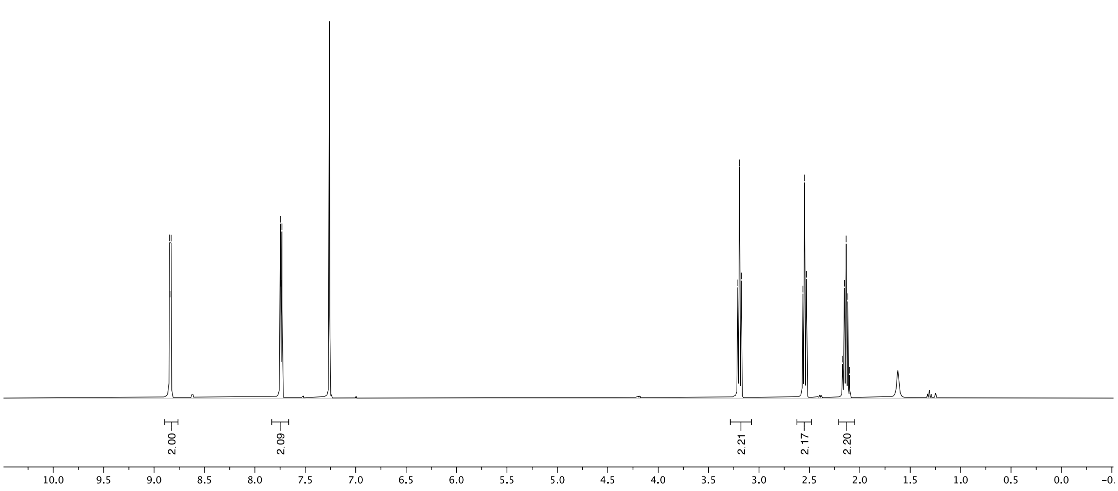
HRMS ESI

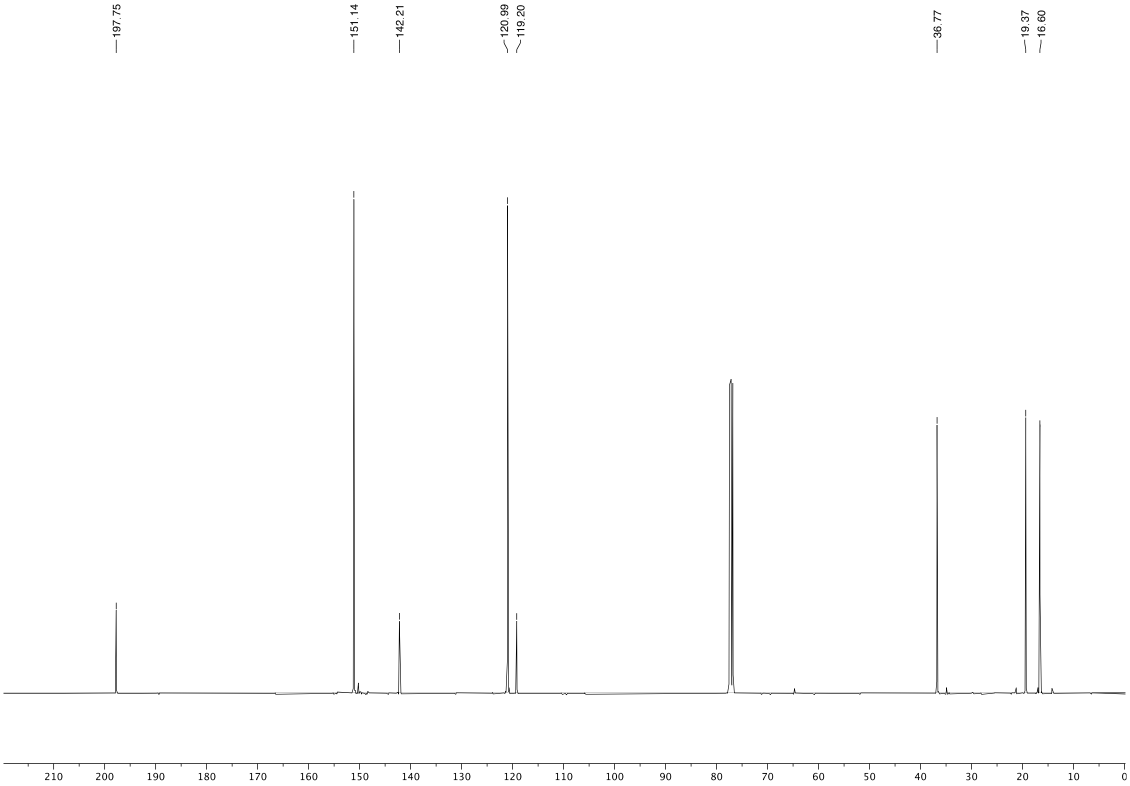
Calculated mass for $(M+H)^+$ of $C_{10}H_{11}N_2O^+$ is 175.0866, found 175.0867.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **6B**

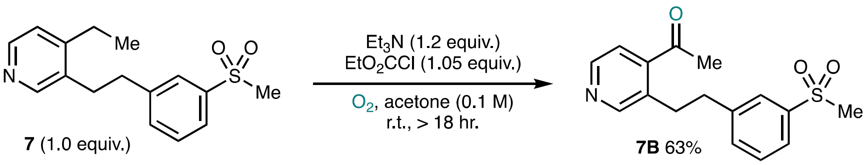


6B





1-(3-(3-(methylsulfonyl)phenethyl)pyridin-4-yl)ethan-1-one (7B)



Using 1-pot oxidation procedure **A**, pyridine **7** (1.0 equiv.) provided product **7B** in 63% qNMR yield. **7B** was isolated by flash chromatography.

Data for **7B**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.63 (d, *J* = 5.07 Hz, 1H), 8.46 (s, 1H), 7.85 – 7.75 (m, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.46 (m, 3H), 3.14 (dd, *J* = 9.5, 6.2 Hz, 2H), 3.09 – 2.92 (m, 6H), 2.58 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 200.9, 153.2, 148.8, 143.5, 143.0, 140.7, 134.2, 134.1, 129.6, 127.4, 125.3, 122.1, 44.6, 37.5, 33.1, 29.6.

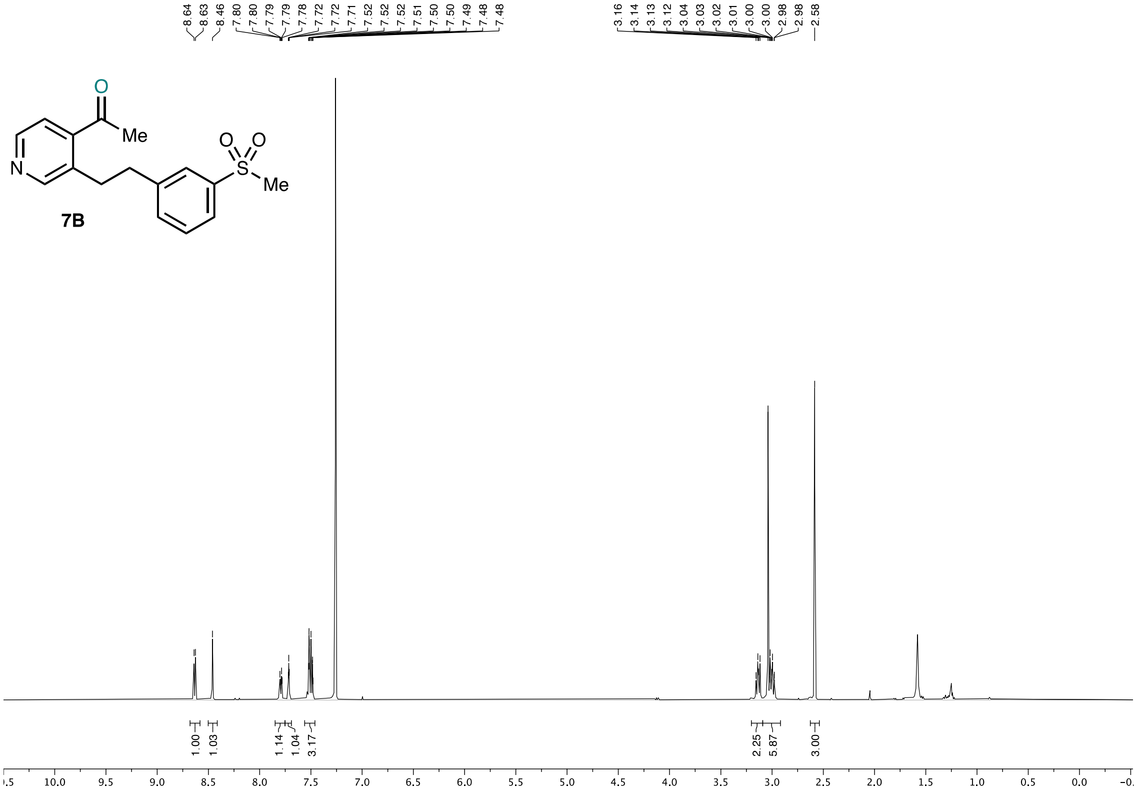
IR Alpha-Platinum ATR, Bruker, diamond crystal

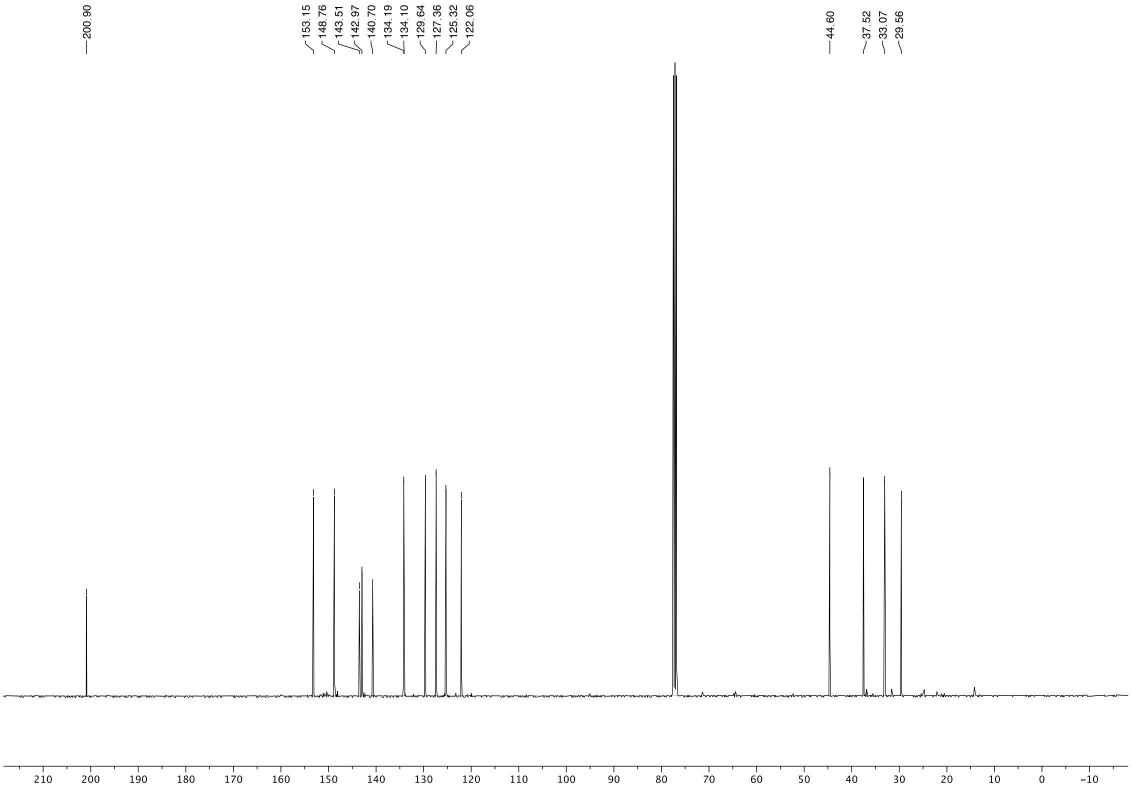
ν = 2920, 1692, 1297, 1257, 1143 (cm^{-1})

HRMS ESI

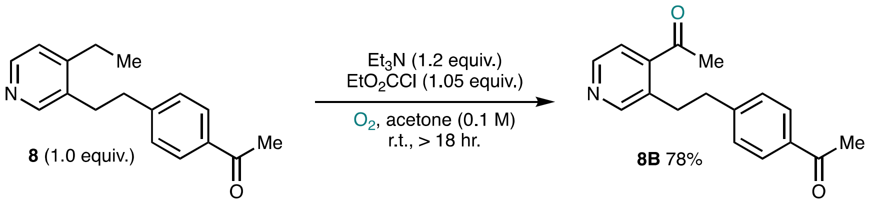
Calculated mass for $(M+H)^+$ of $C_{16}H_{18}NO_3S^+$ is 304.1002, found 304.1002.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **7B**





1-(3-(4-acetylphenethyl)pyridin-4-yl)ethan-1-one (8B)



Using 1-pot oxidation procedure **A**, pyridine **8** (1.0 equiv.) provided product **8B** in 78% qNMR yield. **8B** was isolated by flash chromatography.

Data for **8B**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.62 (d, *J* = 5.1 Hz, 1H), 8.50 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 4H), 3.13 (dd, *J* = 9.4, 6.4 Hz, 2H), 2.95 (dd, *J* = 9.4, 6.4 Hz, 2H), 2.59 (s, 3H), 2.54 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$)

δ 201.0, 197.9, 153.1, 148.5, 146.8, 143.7, 135.4, 134.3, 128.9, 128.7, 121.8, 37.8, 32.8, 29.6, 26.7.

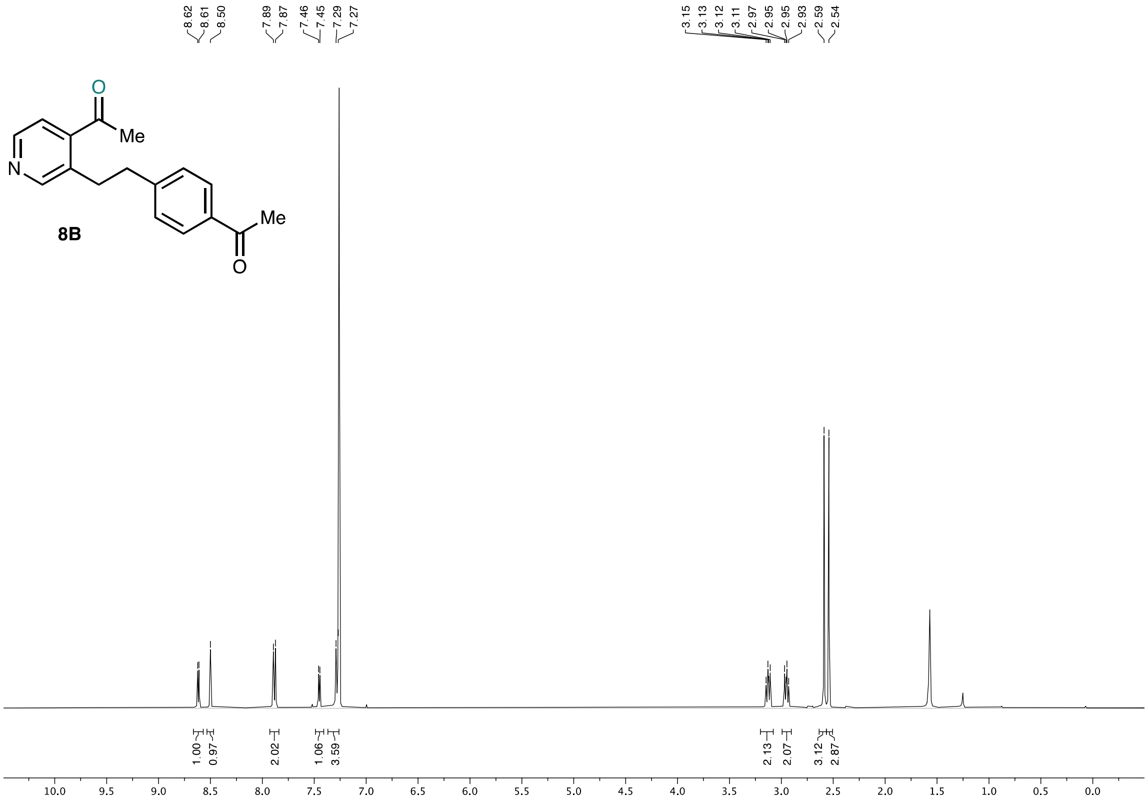
IR Alpha-Platinum ATR, Bruker, diamond crystal

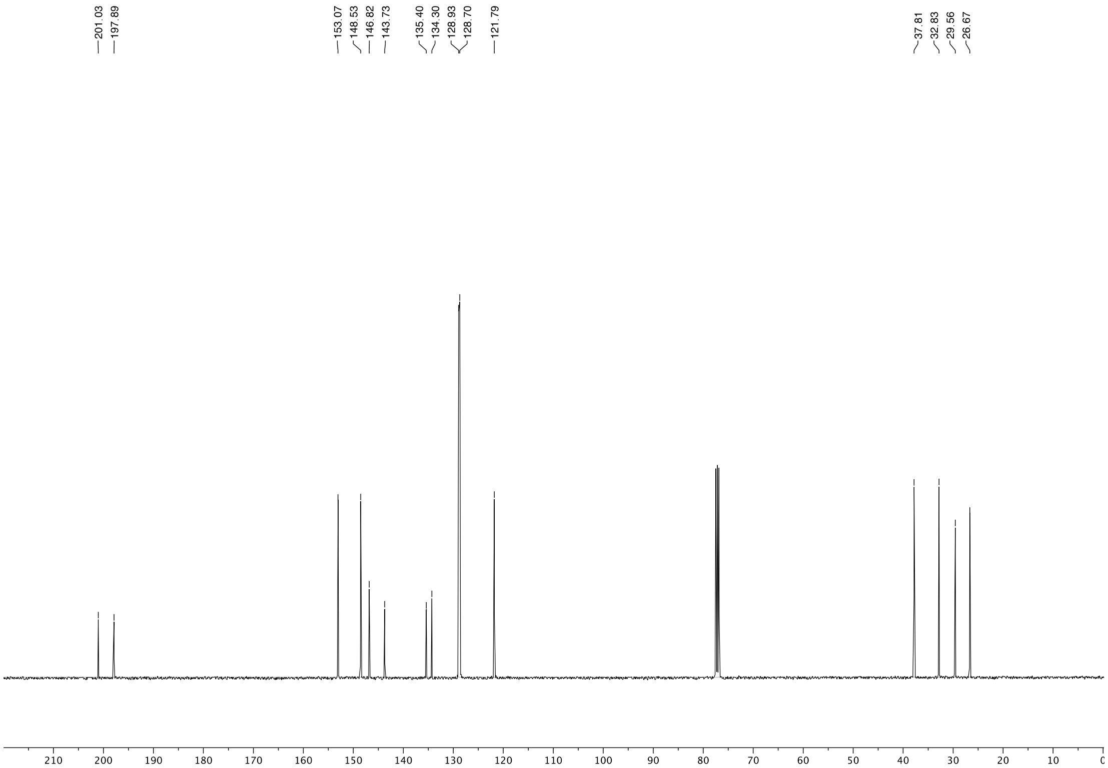
ν = 2923, 1676, 1604, 1356, 1256 (cm^{-1})

HRMS ESI

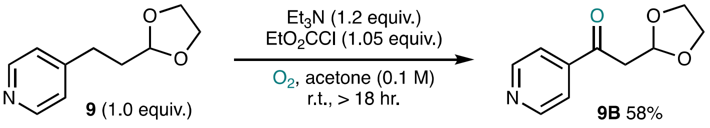
Calculated mass for $(M+H)^+$ of $C_{17}H_{18}NO_2^+$ is 268.1332, found 268.1332.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **8B**





2-(1,3-dioxolan-2-yl)-1-(pyridin-4-yl)ethan-1-one (9B)



Using 1-pot oxidation procedure **A**, pyridine **9** (1.0 equiv.) provided product **9B** in 58% qNMR yield. **9B** was isolated by flash chromatography.

Data for **9B**

^{1}H-NMR (400 MHz, CDCl$_3$)

δ 8.85 – 8.79 (m, 2H), 7.77 – 7.71 (m, 2H), 5.42 (d, J = 4.9 Hz, 1H), 4.05 – 3.87 (m, 4H), 3.34 (d, J = 4.9 Hz, 2H).

^{13}C-NMR (101 MHz, CDCl$_3$)

δ 196.3, 151.1, 142.8, 121.4, 101.1, 65.2, 43.8.

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2987, 2900, 1697, 1409, 1142 (cm^{-1})

HRMS ESI

Calculated mass for (M+H)$^+$ of $C_{10}H_{12}NO_3^+$ is 194.0812, found 194.0812.

^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$) – NMR Spectra of **9B**