Rare Earth Triflate/Alanine Catalysed Diels-Alder and Michael Reactions in Water and an Alternative Pyrrole Synthesis

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Contents

Abstract

Large amounts of organic solvents are used within the field of chemistry and nearly everything is being discarded and is not reused. A way to reduce the environmental impact that this leads to is to use a safe and natural solvent that is easy to access, like water. In this project, Diels-Alder and Michael reactions were carried out in an aqueous medium with rare earth triflates and alanine as catalytic system. Most of the Diels-Alder reactions were slow, and a good reaction rate was only reached in one of the reactions. The Michael reactions with methyl 2-nitroacetate as Michael donor were much faster, and all the performed reactions worked with high to moderate reaction rates. The Michael adducts were then used to demonstrate a short and convenient pyrrole synthesis route that with some optimisations of work up and purification could be a good alternative to the more conventional pyrrole synthesis methods used in industry and science today.

1. Introduction

1.1. Green Organic Solvents

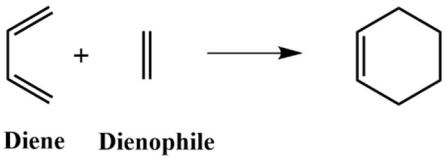
The fact that organic solvents are used in large amounts in chemistry, both for research and manufacturing, should come as no surprise to most people in the field of science. With large amounts of solvent comes large amounts of chemical waste and in a world striving for more and more renewable and sustainable technical solutions in all kinds of fields, the science of green chemistry has evolved. The basics of green chemistry is mainly to use less hazardous substances in chemical processes but also to make the processes more energy efficient and sustainable by using renewable sources. Both the production and the waste disposal of many organic solvents have high impact on pollution and carbon footprint and a big challenge within green chemistry is to find a way to reduce this impact [1].

Various solvents are used in large amounts during chemical processes, for synthesis, work up, and purification and it would be beneficial for the climate to reduce these amounts or to replace the solvents with greener alternatives. Some solvents can be produced from natural renewable resources and one way of making the chemical process greener is to just try one of those. The greenest approach possible is of course to use a solvent from the nature that does not have to be industrially produced, like water. Water is the cheapest, least hazardous, and most sustainable solvent in the world but the number of common synthetic industrial processes using water as the main solvent is surprisingly low. The chemical reactions carried out in biological systems like plants or the human body proof the possibility and diversity of synthesis in aqueous media and the fast reaction rates that can be reached if the right catalytic system is used. In organic synthesis, smaller organic and/or inorganic molecules are more commonly used as catalysts than large enzymes. Such catalysts could for example be Lewis acids like $AlCl_3$ or $ZnCl_2$. When doing synthesis in water though, these Lewis acids hydrolyse and loses their effect. Therefore, when using water as solvent, water-tolerant Lewis acids like $Yb(OTf)_3$, $Sc(OTf)_3$ or $La(OTf)_3$ could be used instead [2].

The aim of this project was to use water as reaction medium and extend the knowledge gained by earlier studies of Michael reactions in water done by Wennerberg et.al. [3], where great success was shown when catalysing the reactions with rare earth triflates (mainly $Yb(OTf)_3$) together with various amino acids as ligands. Initially, this project aimed to extend the earlier work with a study of Diels-Alder reactions, but focus was later shifted back to Michael reactions when the results from the Diels-Alder reactions did not show up as good as expected.

1.2. The Diels-Alder Reaction

The Diels-Alder reaction is a pericyclic reaction between a conjugated diene and a dienophile. The diene contributes with four π-electrons to the reaction and the dienophile contributes with two, the reaction is thus seen as a [4+2] cycloaddition [4].



Scheme 1. Reaction scheme for a general Diels-Alder reaction.

A general Diels-Alder reaction is shown in Scheme 1. One special characteristic with a cycloaddition like this is that there are two σ-bonds that are formed at the same time (concerted mechanism) without any clear nucleophile attacking an electrophile as in most of the other well-known organic reactions. The reactivity of this reaction can be explained by using orbital theory as can be seen in Figure 1 and 2, where the reaction is either HOMO-diene controlled (with normal electron-demand, Figure 1), or LUMO-diene controlled (with inverse electron-demand, Figure 2). In both cases, the concept is to facilitate a reaction by decreasing the energy difference of the HOMO:s and LUMO:s of the two reagents by using EWG:s and EDG:s. It can also be seen in Figure 1 and 2 that the Diels-Alder reaction in many cases leads to two different regioisomers, where one (major product) is favoured over the other (minor product) [4][5]. The catalysis of a Diels-Alder reaction can also be explained with orbital theory. Since the EWG in the dienophile can be coordinated by a catalytic metal ion (like Al, Yb, Sc or La), resulting in an increased electron withdrawing effect of the EWG that adds on to the energy reduction of the dienophile's LUMO (with normal electron demand). A catalytic system can also affect the stereochemical outcome of the reaction in those cases where a stereocenter is present in the product [4][6], stereochemistry was never investigated in this project though.

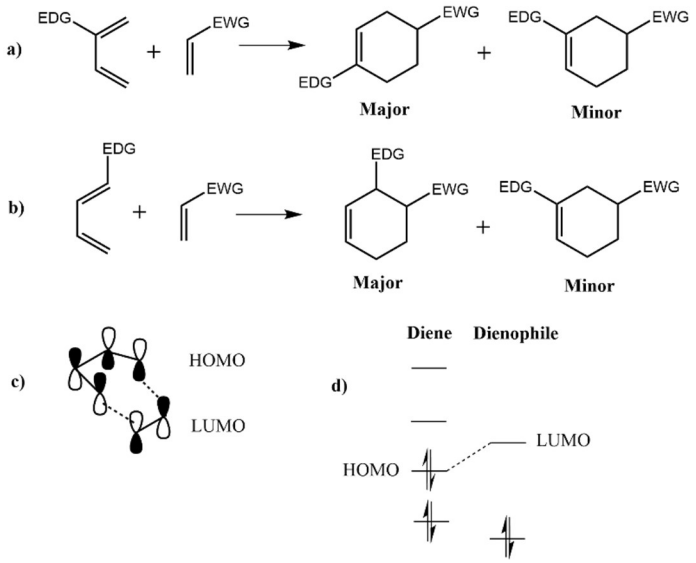


Figure 1. Normal electron-demand, HOMO-diene controlled Diels-Alder reaction. **a)** Reaction scheme with the EDG on C-2 in the diene. **b)** Reaction scheme with the EDG on C-1 in the diene. **c)** Orbital representation of the Diels-Alder reaction's mechanism, the HOMO of the diene interacts with the LUMO of the dienophile. **d)** Energy levels of the orbitals, the dotted line indicates the energy gap between the HOMO of the diene and the LUMO of the dienophile, the smaller the gap, the easier reaction.

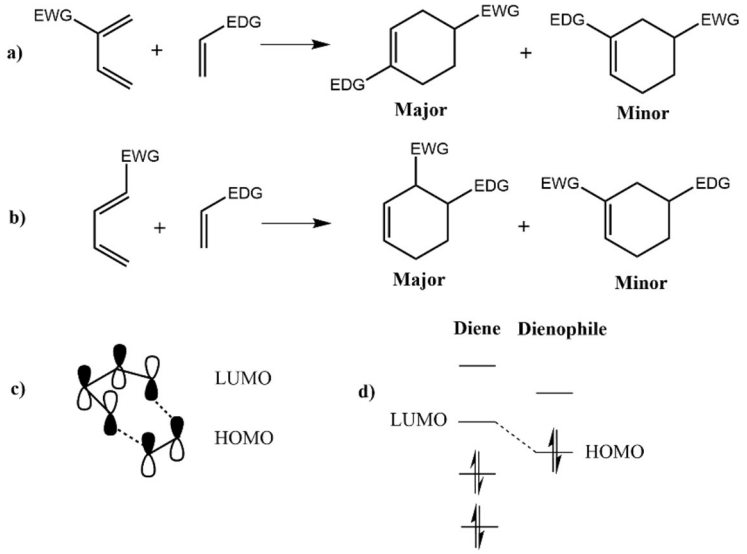
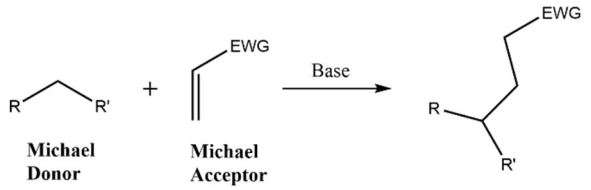


Figure 2. Inverse electron-demand, LUMO-diene controlled Diels-Alder reaction. **a)** Reaction scheme with the EWG on C-2 in the diene. **b)** Reaction scheme with the EWG on C-1 in the diene. **c)** Orbital representation of the Diels-Alder reaction's mechanism, the HOMO of the dienophile interacts with the LUMO of the diene. **d)** Energy levels of the orbitals, the dotted line indicates the energy gap between the HOMO of the dienophile and the LUMO of the diene, the smaller the gap, the easier reaction.

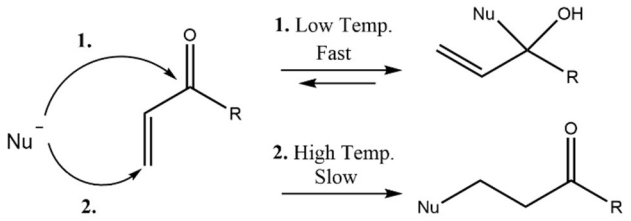
1.3. The Michael Reaction

The Michael reaction is an important reaction type when forming carbon-carbon bonds and it takes place between an electrophilic Michael acceptor and a nucleophilic Michael donor. The characteristics of a good Michael acceptor are basically the same as for the dienophile in the Diels-Alder reaction with the normal electron demand. That is an unsaturated compound with an electron withdrawing group making the unsaturated bond more electrophilic and accessible to nucleophilic attack, these compounds are mainly α,β-unsaturated carbonyl compounds. A general Michael reaction can be seen in Scheme 2. R and R' in the Michael donor are preferably EWG:s to facilitate the reaction. In most cases the donors are resonance-stabilized compounds such as a nitroalkanes and malonates that after deprotonation creates stabilized carbanions that can attack the Michael acceptor, but they could also be simpler, small non-conjugated compounds like alcohols or amines [7].



Scheme 2. Reaction scheme for a general Michael reaction.

In the cases where the Michael acceptor is a carbonyl compound, one could argue that there will be a regioselectivity problem since there will also be direct addition by the nucleophile to the electrophilic carbonyl carbon (Route 1 in Scheme 3). That is true, but the Michael acceptor has the largest coefficient of the LUMO on the outermost carbon and that favours a conjugate addition (Route 2 in Scheme 3) over a carbonyl addition. With small nucleophiles like cyanide, the direct addition to the carbonyl is the fastest (kinetically controlled) reaction whereas the conjugation addition is the thermodynamically controlled reaction, giving the more stable product. Thus, the direct addition is favoured in case of low temperatures, but it is often reversible, something that the conjugation reaction is not. Therefore, the thermodynamic product will be favoured with long reaction times even if the temperature is low. Structural and electronic differences of the nucleophiles and the Michael acceptors are, of course, also important for the regioselectivity. Some nucleophiles are dominated by electronic effects (hard nucleophiles), favouring direct addition and some are dominated by orbital effects (soft nucleophiles), favouring conjugate addition. Furthermore, some α,β-unsaturated carbonyl compounds, like enals, are much more prone to direct addition than for example α,β-unsaturated amides or esters [7].



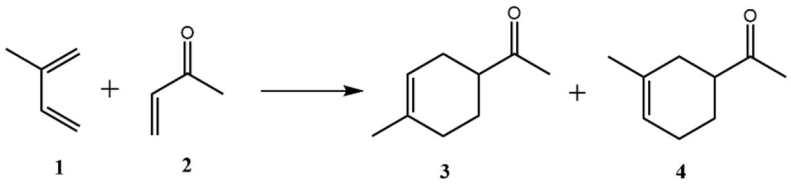
Scheme 3. Regioselectivity for nucleophilic attack on α,β-unsaturated carbonyl compounds. Direct addition to carbonyl (Route 1) and conjugate addition (Route 2).

2. Results and Discussions

2.1. Diels-Alder Reactions

To be able to investigate the effect of the catalytic systems regarding reaction rates and regioselectivity the reaction shown in Table 1 was chosen. This reaction between isoprene (**1**) and methyl vinyl ketone (MVK, **2**) gave the products **3** and **4** that are regioisomers. The reaction was carried out under some different conditions shown in Table 1. None of the catalytic systems seemed to have any effect on the regioselectivity since the ratio between the two products (**3:4**) was unchanged compared to the non-catalysed thermic reaction in toluene. The rare earth triflates seemed to influence the reaction rates during the first one or two days but the effect was not as obvious as expected considering the results gained from earlier studies with the Michael reaction [3] where full conversion was seen within 24 h. No significant differences could be seen between the various rare earth triflates used regarding catalytic effect.

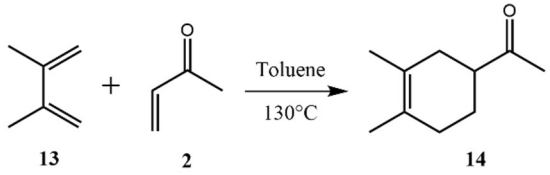
Table 1. Results from the reaction between isoprene (**1**) and MVK (**2**). The ratio between the regioisomers (**3:4**) and conversion were checked at different times with ^{1}H NMR-spectroscopy. 12 mol% of the alanine and 5 mol% of the triflate salts and the $AlCl_3$ was used. The empty spaces in the conversion column indicates that the NMR-data was unreliable.



1 **2** **3** **4**

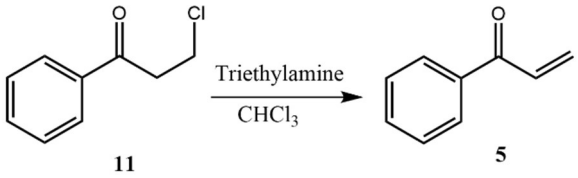
Entry	Diene:Dienophile	Conditions	Time (days)	Conversion (%)	3:4
1	2:1	Toluene, 130°C (day 1-3), 60°C (day 4-7)	1 2 3 4 7	10 38 63 65 75	70:30
2	1:1	$AlCl_3$ + 2·THF, 30°C	1 3 5	12 30 38	70:30
3	2:1	$Yb(OTf)_3$, H_2O, 60°C	1 2 3 4 7 9	19 - 29 48 49 64	70:30
4	2:1	$Yb(OTf)_3$, H_2O, 30°C	1 2 3 4 7 9 14	31 46 61 - 76 78 81	70:30
5	2:1	$Yb(OTf)_3$, DL-alanine, H_2O, 30°C	1 4 5 6 7 12	22 40 47 50 67 73	70:30
6	2:1	$Sc(OTf)_3$, H_2O, 30°C	1 2 5 7 13	26 46 66 68 78	70:30
7	2:1	$Sc(OTf)_3$, DL-alanine, H_2O, 30°C	1 2 3 4 7	18 33 62 62 67	70:30
8	2:1	$La(OTf)_3$, H_2O, 30°C	1 2 5 6 7	19 45 - 47 -	70:30
9	2:1	$La(OTf)_3$, L-alanine, H_2O, 30°C	1 2 5 6 7	23 54 69 - 70	70:30
10	3:1	$Sc(OTf)_3$, L-alanine, H_2O, 30°C	1 2 3 4 7	24 51 54 - 74	70:30

A similar Diels-Alder reaction with 2,3-dimethylbuta-1,3-diene (**13**) and MVK was also performed to get a product (**14**) without regioselectivity for comparisons. This reaction can be seen in Scheme 4 and the obtained yield was 74%.



Scheme 4. Non-regioselective Diels-Alder reaction between 2,3-dimethylbuta-1,3-diene (**13**) and MVK (**2**).

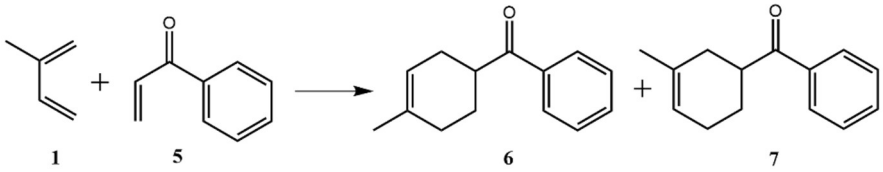
A new dienophile, phenyl vinyl ketone (PVK, **5**), was synthesized to get a product containing a phenyl group that also enabled UV-detection with LCMS and TLC. The elimination reaction from 3-chloropropiophenone (**11**) to PVK is shown in Scheme 5. This synthesis [8] was done three times, yielding 79% at best.



Scheme 5. Synthesis of phenyl vinyl ketone (PVK, **5**) from 3-chloropropiophenone (**11**).

The Diels-Alder reactions carried out with the new dienophile are shown in Table 2. This reaction seemed to have both higher rates and regioselectivity compared to the one with MVK. The PVK became on the other hand very viscous after a few days, indicating polymerisation. That made it hard to handle and dissolve and it did not dissolve in water at all, leading to no reaction. By the end of the project, new PVK was synthesised that was used in further synthesis the same day without storage [9]. This helped to bypass the problems with polymerisation and bad solubility and resulted in successful reactions with full conversion of PVK overnight and an isolated yield of 46%. The reaction was also done in water without catalyst and showed full conversion of PVK after 48 h according to ^{1}H NMR. As expected, compound **6** was the favoured product, right in line with the theory [3] [10]. No clear difference between the reactions done with and without L-alanine could be seen regarding conversion of PVK or regioselectivity but it seemed to be polymerisation when L-alanine was used, according to ^{1}H NMR. That may indicate that the PVK is sensitive to lower pH. All the reactions carried out with alanine in this project were supposed to be neutralised with 0.2 M NaOH but in some cases the pH-value could have been closer to 6 than 7 and that may have had an impact in this case.

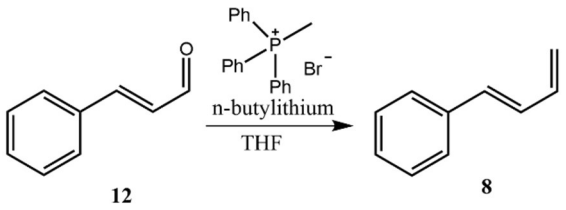
Table 2. Results from the reaction between isoprene (**1**) and PVK (**5**). The ratio between the regioisomers (**6:7**) and conversions (of PVK) were checked with ^{1}H NMR-spectroscopy. 12 mol% of the L-alanine and 5 mol% of the $Yb(OTf)_3$ and the $AlCl_3$ was used.



1 5 6 7

Entry	Diene:Dienophile	Conditions	Time (h)	Conversion of PVK (%)	6:7
1	2:1	Toluene, 130°C	26	54	80:20
2	1:1	$AlCl_3$ + 2·THF, 30°C	29	100	100:0
3	2:1	H_2O, 60°C	48	100	100:0
4	2:1	$Yb(OTf)_3$, H_2O, 60°C	20	100	100:0
5	2:1	$Yb(OTf)_3$ + L-alanine, H_2O, 60°C	24	100	100:0

The boiling temperature of isoprene is around 34°C and that became a problem since reaction temperatures of 60°C was planned. This fact, together with the mentioned practical difficulties with the PVK, led to a change of diene instead. The chosen diene was (E)-Buta-1,3-dien-1-ylbenzene (**8**) that could be synthesized from cinnamaldehyde (**12**) with a Wittig reaction shown in Scheme 6. This synthesis was carried out with two different bases, potassium tert-butoxide and n-butyllithium. The experiment done with potassium tert-butoxide resulted in a gummy residue that was problematic to extract the product from, yielding nearly no crude product at all. The experiment done with n-butyllithium went much better and yielded 52% isolated final product (**8**).

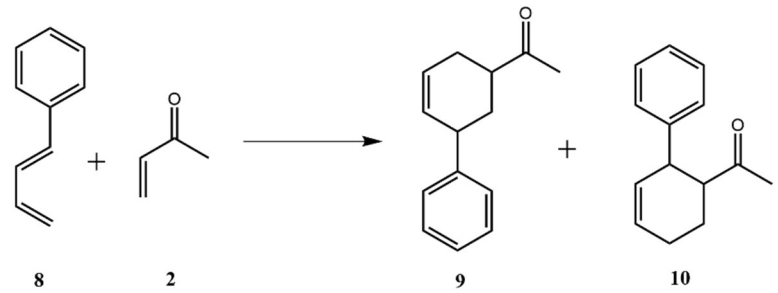


12 8

Scheme 6. Synthesis of (E)-Buta-1,3-dien-1-ylbenzene (**8**).

The Diels-Alder reactions carried out with the new diene are shown in Table 3. According to ^{1}H NMR, these reactions went a little bit faster and reached a little bit higher conversions compared to the experiments with isoprene as diene and MVK as dienophile but still not close to as good as expected. The effect of higher amounts of catalyst was also tested (Entry 3 and 4 in Table 3) and as can be seen, reaction rates, conversions and regioselectivities did not increase.

Table 3. Results from the reaction between (E)-Buta-1,3-dien-1-ylbenzene (**8**) and MVK (**2**). Conversion and the ratio between the regioisomers (**10:9**) were checked with ^{1}H NMR-spectroscopy. The empty spaces in the conversion column indicates that the NMR-data was unreliable.



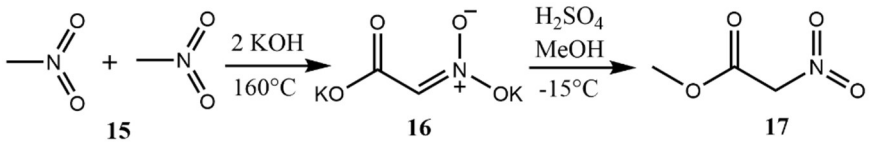
8 **2** **9** **10**

Entry	Diene:Dienophile	Conditions	Time (d)	Conversion (%)	10:9
1	1:1	$Sc(OTf)_3$ (5 mol%), DL-alanine (12 mol%), H_2O, 60°C	1 2 3 4 7	54 55 69 72 74	75:25
2	1:1	$La(OTf)_3$ (5 mol%), L-alanine (12 mol%), H_2O, 60°C	1 2 5 6 7	32 68 72 83 100	75:25
3	1:1	$Sc(OTf)_3$ (10 mol%), DL-alanine (24 mol%), H_2O, 60°C	1 2 5 6 7	50 63 71 71 83	75:25
4	1:1	$Sc(OTf)_3$ (20 mol%), DL-alanine (48 mol%), H_2O, 60°C	1 2 5 6 7	- - 65 69 -	75:25

2.2. Methyl 2-Nitroacetate as Michael Donor

Since no good results were seen with the Diels-Alder reactions during the first weeks of the project, focus was shifted towards Michael reactions with methyl 2-nitroacetate. As mentioned, earlier studies [3] have shown great success with catalysing various Michael reactions like the one between MVK and ethyl acetoacetate with help of rare earth triflates (mainly $Yb(OTf)_3$) and amino acids as ligands. Because of that success, the goal was now to investigate the catalysis of the Michael reactions between methyl 2-nitroacetate (**17**) and various Michael acceptors. Methyl 2-nitroacetate was synthesized via the route shown in Scheme 7, with nitromethane (**15**) as starting material via a dipotassium salt of 2-nitroacetate (**16**). This reaction was done with two different methods, one conventional [11] and one alternative that minimised contact with explosive compounds and hazardous solvents [12]. The conventional method contained drying of **16** in a vacuum desiccator instead of direct further synthesis to **17** as in the alternative. The alternative also contained a neutralisation

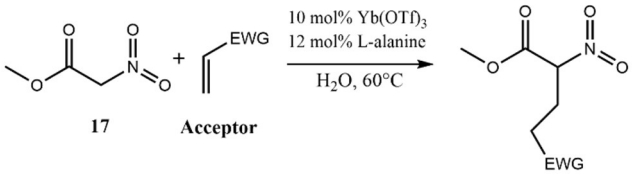
step before the product extraction that required large amounts of $NaHCO_3$ that made the extraction complicated. Both normal extraction with separation funnel and continuous extraction was used without great success. The conventional method worked thus much better since it contained an easier and more convenient extraction that also resulted in much higher amounts of crude product that after distillation yielded 51% of the final methyl 2-nitroacetate. The solvent used for the extraction was conventionally benzene but to get a safer method, toluene was used here instead.



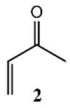
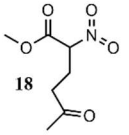
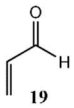
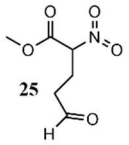
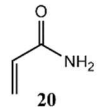
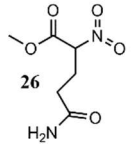
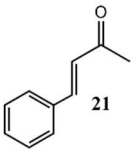
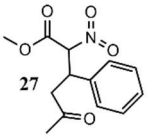
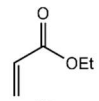
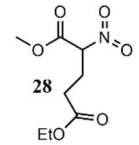
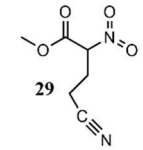
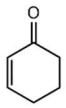
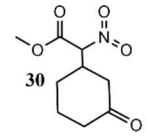
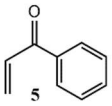
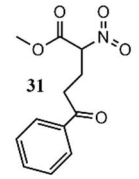
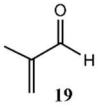
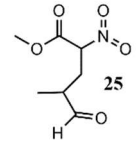
Scheme 7. Synthesis of methyl 2-nitroacetate (**17**) from nitromethane (**15**) via a dipotassium salt of 2-nitroacetate (**16**).

The Michael reactions that were performed between methyl 2-nitroacetate and various Michael acceptors are shown in Table 4 below.

Table 4. Results from Michael reaction between methyl 2-nitroacetate (**17**) and various acceptors catalysed with $Yb(OTf)_3$ and L-alanine. All reaction were carried out on a 0.5 mmol scale. Conversion (of acceptor) was checked with ^1H NMR-spectroscopy.



17 **Acceptor**

Entry	Acceptor	Time (h)	Conversion (%)	Product
1	 **2**	2	100	 **18**
2[a]	 **19**	24	-	 **25**
3	 **20**	3	100	 **26**
4	 **21**	96	16	 **27**
5	 **22**	7	80	 **28**
6	 **23**	7	80	 **29**
7	 **24**	48	65	 **30**
8	 **5**	2	100	 **31**
9[b]	 **19**	44	90	 **25**

[a] Product seemed to form but polymerisation of acrolein made the ^1H NMR hard to read.

[b] Reaction was performed on larger scale (3.6 mmol).

The results shown that the fastest and most effective reaction was the one with MVK as acceptor (Entry 1 in Table 4). When this reaction was scaled up to a 2.5 g-scale (13.4 mmol), **18** was obtained in a 75% yield. When MVK was used in excess, two molecules of MVK were added to the methyl 2-nitroacetate, giving a bis-alkylated product. Therefore, equimolar amounts of the donor and acceptor had to be used. On the other hand, in most cases (according to NMR) the methyl 2-nitroacetate was more prolonged than the acceptors in the reaction mixture and therefore a small excess of extra acceptor (0.1-0.3 eq.) could be added over time to get full conversion.

Surprisingly, the reaction with MVK worked well in water even without catalyst, where full conversion was seen after just 3-4 hours! This was not expected since earlier studies done by Keller and Feringa [2] showed that this was not possible. The difference between the experiment done here and their experiment was that the reaction was performed at 60°C instead of room temperature.

The reaction with acrolein (**19**) as acceptor (Entry 2) showed broad peaks on ^{1}H NMR already after one hour and gummy residues appeared in the reaction mixture, making it logical to suspect polymerisation of the acrolein. The correct product was probably forming to some extent, but it was hard to tell. To evade the problem with polymerisation, the reaction was tried at room temperature and with dropwise addition of acrolein instead. Even though this method gave better results than at 60°C, it still gave high amounts of impurities and clear evidence of polymerisation, and no final product (**25**) was isolated.

The experiment with acrylamide (**20**) as acceptor (Entry 3) showed full conversion after 3 h. After upscaling to a 4 mmol-scale stirred overnight, the conversion dropped to 81%. The product had high polarity and was hard to extract from the water phase, giving low yield (25%) of the crystalline product (**26**).

With (E)-benzalacetone as acceptor, the reaction rate was low and, according to ^{1}H NMR, neither the methyl 2-nitroacetate nor the (E)-benzalacetone had disappeared after 96 hours, giving only 15% conversion to the desired product (**27**). The same reaction was also carried out with a higher reaction temperature at 80°C, resulting in full disappearance of methyl 2-nitroacetate but still a low conversion (20%) to the desired product after 96 h. The experiment was therefore tried two more times, once on a 1 g-scale and once on a 5 g-scale at 80°C with a carefully pulverized (E)-benzalacetone. The conversions on these scales were higher, around 70%, but it still took long time (4-6 days). Even though the conversion seemed high, only 11% (1 g-scale) and 36% (5 g-scale) isolated yields were reached.

Ethyl acrylate (**22**) and acrylonitrile (**23**) as acceptors gave results similar to each other with no full conversion but with moderate reaction rates, no further work up and purification of compounds **28** and **29** was done.

Moderate conversion but slow reaction rate was seen when 2-cyclohexen-1-one (**24**) was used as acceptor, giving around 65% conversion after 68 h. When the same reaction was tried on 1 g-scale (4.6 mmol), both the conversion and the reaction rate increased to 84% in 22 h, yielding 39% of the final product (**30**).

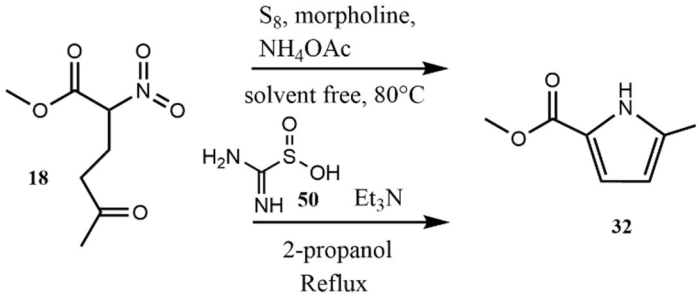
As in the case of the Diels-Alder reactions, PVK (**5**) in water showed no success when the old compound (that was synthesised in the beginning of the project) was used. Even when the gum-like PVK was nicely pulverized before addition it developed a new gum-like structure

once wetted and heated in the reaction mixture. Therefore, this reaction showed no conversion at all. As discussed earlier, a solution to the problem was to use the PVK directly after its synthesis when it was still easy to handle and had not yet polymerized [9], this resulted in full conversion after just 2 h. When this reaction was scaled up to a 3 mmol-scale, 52% isolated yield of compound **31** was obtained.

2.3. Pyrroles

To further investigate the utility of the obtained derivatives of methyl 2-nitroacetate (Michael adducts), some of the isolated products were converted to pyrroles. Pyrroles are interesting mainly since they are common structures in natural compounds and drugs. There are several possible laboratory routes to synthesise pyrroles through, including reagents as amines and ammonia together with alcohols or dicarbonyls amongst others [13]. Herein, a less conventional route is discussed. With the earlier discussed Michael adducts as starting materials, diverse pyrroles could be synthesised (Shown in Table 5).

Compound **18** was initially used to test out two different pyrrole synthesis methods (shown in Scheme 8). The first experiments done with the two methods resulted in fast conversion and the same yield (19%). The solvent free method with S_8, morpholine and NH_4OAc resulted in a dark mixture, and it was hard to tell the difference between the aqueous and organic phases during the extraction. Therefore, the method with formamidinesulfonic acid (**50**) and triethylamine was chosen as the best due to an easier work up procedure. That procedure was also tried with water as solvent instead of 2-propanol and the desired pyrrole was obtained, but in yields of just a few percent and with a handful of biproducts that made the desired product hard to isolate. Because of that, water could be concluded as an inappropriate solvent for this reaction. 2-propanol is a simple alcohol and one of the better alternatives regarding green solvents anyway, thus it could be seen as an okay solvent for this project.

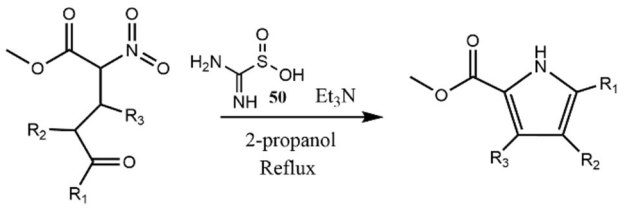


Scheme 8. The two methods tested for synthesis of pyrroles from compound **18**. The one with formidinesulfonic acid (**50**) and triethylamine in 2-propanol was chosen as the best due to easier work up procedure.

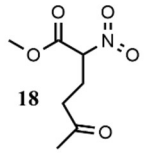
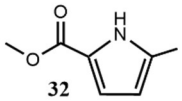
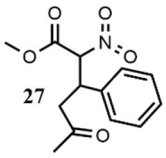
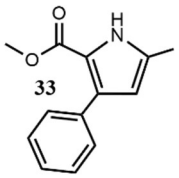
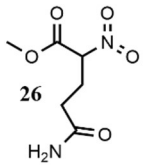
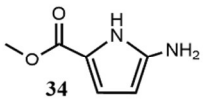
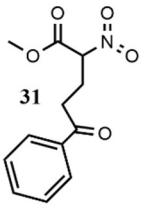
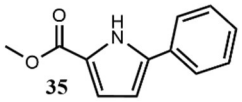
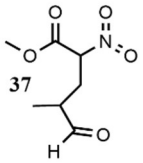
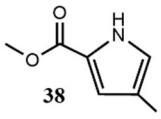
By using some of the earlier prepared Michael adducts, a number of pyrroles could be obtained. The pyrroles that were synthesised are presented in Table 5. According to analyses done with TLC and LCMS, these reactions showed full conversion after a few hours but as can be seen on the resulting yields, the work up and purification processes could need further development. The reaction with Michael adduct **26** did not show any conversion to the

pyrrole **34** at all though, this was somewhat expected due to the low reactivity of amides in general.

Table 5. Diverse pyrroles that were converted from the isolated Michael adducts.

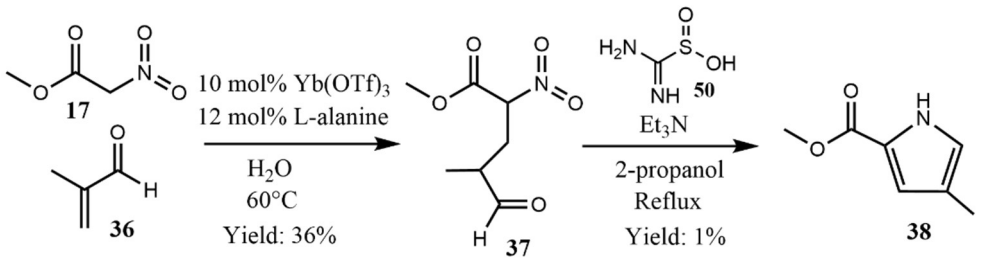


Michael Adduct Pyrrole

Entry	Michael Adduct	Pyrroles	Yield (%)
1			19
2			11
3			0
4			24
5			1

An interesting pyrrole to discuss here is compound **38**, naturally occurring as a trail pheromone from ants. It was synthesised via the same route as the rest of the pyrroles with methacrolein (**36**) as Michael acceptor (Entry 9, Table 4) and compound **37** as Michael adduct (Entry 5, Table 5). The full synthesis is shown in Scheme 9. A trail pheromone is a compound with a specific odour used by insects (in this case ants) to communicate and mark the path to food. This helps the other individuals in the nest to access the food and just a

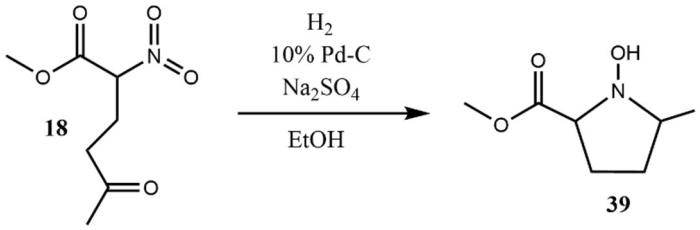
small amount (80 fg/cm) is needed to create a trail [14]. So, even if only a small amount (~2 mg) was successfully isolated in this project, it would be enough to create a leading path of 250 000 km for ants to follow! That is slightly more than 6 laps around the equator. These numbers were never validated though, since this project was focused on organic chemistry and not zoology. The main interest in this case was to produce a natural compound in a laboratory. Historically, natural compounds have been used as medication for a broad variety of diseases, but some compounds are rare and only exist in small amounts on specific places on earth. Therefore, the ability to synthesise natural compounds in larger amounts in a laboratory environment is sometimes a drift in the field of medicinal chemistry.



Scheme 9. Synthesis route for the ant trail pheromone pyrrole (**38**) with methacrolein (**36**) as Michael acceptor and compound **37** as Michael adduct.

2.4. Hydroxyl Pyrrolidines

The pyrroles are not the only ring structures that the methyl 2-nitroacetate could bring, to show an extra alternative, a hydrogenation of compound **18** was done. This hydrogenation reduced the nitro group to an amine and the resulting compound could then perform a spontaneous cyclisation to the hydroxyl pyrrolidine **39** as shown in Scheme 10. Due to problems with the crystallisation during the purification, no pure product of compound **39** was obtained but an ^{1}H NMR of the crude product (shown in Figure A32 in Appendix) indicates formation of the correct compound. The product should be a mixture of diastereomers, but the composition was not further investigated here.



Scheme 10. Hydrogenation of compound **18** giving the hydroxyl pyrrolidine **39**.

3. Future Work

If there were more time to continue this thesis or if the work would be continued by someone else in the future, there are some experiments that would be extra interesting to perform that did not fit into this project. First, more Diels-Alder reaction could be investigated, with other dienes and dienophiles than those used here. As mentioned, it was not until the end of the project that the Diels-Alder reaction with PVK (Table 2) showed fast conversion and good regioselectivity and stood out remarkably compared to the other tried Diels-Alder reactions (with MVK as dienophile). Unfortunately, it was too late to return to the investigation of the cycloadditions by then.

It would also be interesting to investigate the optimal amount of catalyst that should be used and to try everything with a variety of rare earth triflates and amino acids, not only $Yb(OTf)_3$ and alanine. Some of the Diels-Alder reactions were tried with higher amounts of catalyst (Table 3) and some were tried with a variety of rare earth triflates (Table 1) without improved results. Anyhow, that investigation could be done with even more variety and on more of the reactions, including the Michael reactions. In that way the optimal catalytic system could be found. This, together with a careful investigation of optimal reaction temperatures, atmospheres and pH could help to get the highest conversions and rates possible.

When doing these kinds of catalysed reactions in water on a large scale, the water containing the catalytic system could be reused several times before being discarded, something that is environmentally beneficial. The Michael reaction giving compound **18** was done a large scale once in this project and instead of using the regular work up procedure with extractions and chromatography or distillation, the product was separated from the reaction water in a separating funnel (Figure 3). By this procedure, no unnecessary solvents were used, and the experiment was carried out as green as possible. The number of times that the water phase containing the catalytic system could be reused for new synthesis without losing its activity was never investigated here but that is something that is left for the future.

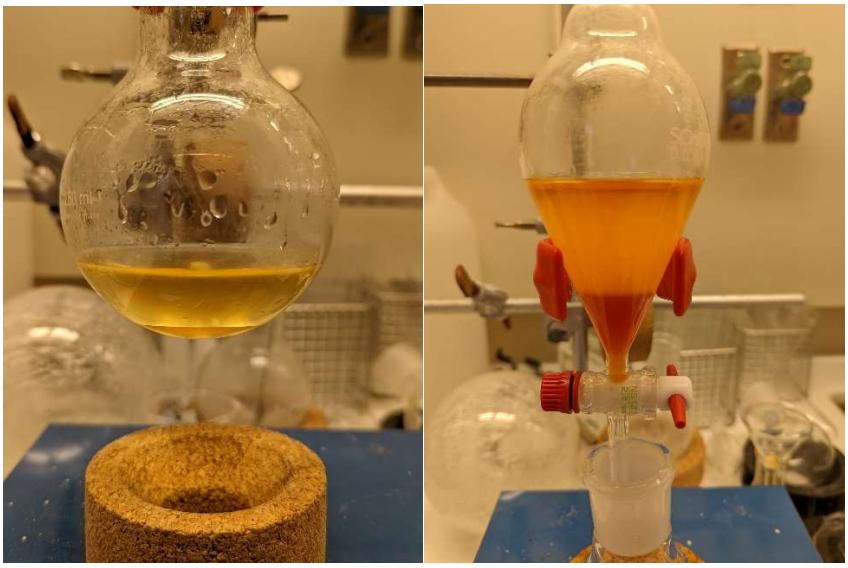
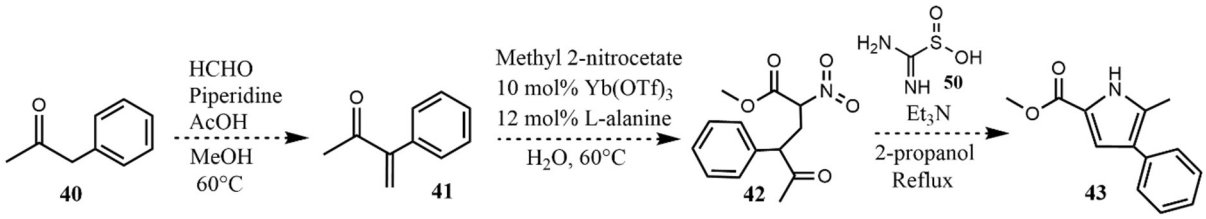


Figure 3. The oil product (bottom phase) separating from the water reaction mixture (top phase). To the left in the round bottomed flask and to the right in the separating funnel, allowing easy access to the product without work up and further purification.

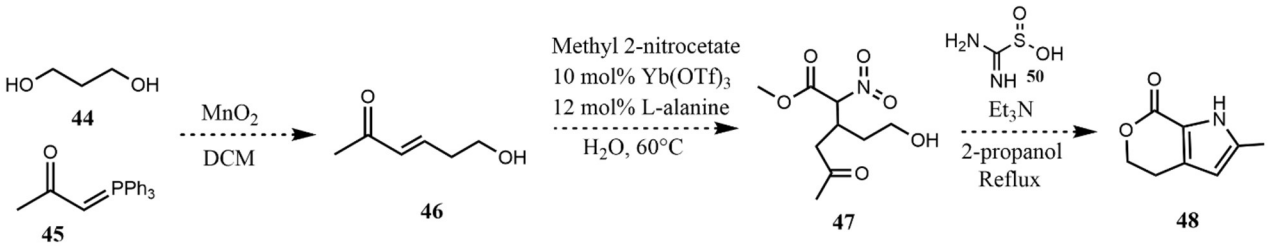
The amount of product obtained by this procedure was 6 g (55%) and 1.65 g extra product could be obtained from the water phase by extraction with EtOAc so there is obviously room for improvements in this separation technique as well. In fact, the work up methods and optimal extraction solvents could be investigated and optimised for all the Diels-Alder, Michael, pyrrole, and pyrrolidine reactions in this project to improve the yields. Most of the reactions showed full conversions, but the yields were in most cases not that high.

Regarding the pyrrole synthesis, there was two planned syntheses that could not be carried out this time. The plan was to use phenyl acetone (**40**) to create a Michael acceptor (**41**) [15] that upon reaction with methyl 2-nitroacetate and the following pyrrole synthesis could give a pyrrole with a phenyl ring in position 4 (**43**) as a nice complement to the two pyrroles created with a phenyl ring in position 3 and 5, respectively (Entry 2 and 4 in Table 5). The planned synthesis route for this pyrrole can be seen in Scheme 11. This was never performed due to a delayed application to the Swedish Medical Products Agency and the reason that an application had to be sent was that phenyl acetone is a common compound for synthesis of amphetamine and methamphetamine (something that was not planned in this project though).



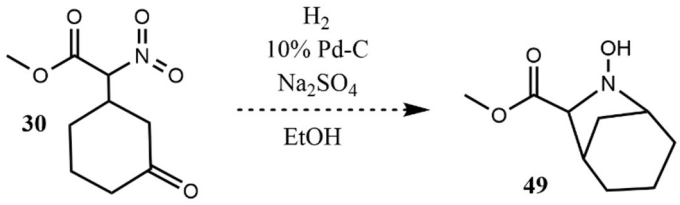
Scheme 11. Synthesis route for creation of a pyrrole with a phenyl ring in position 4 (**43**).

The second interesting pyrrole that was planned but never performed was the lactonopyrrole **48.** The planned synthetic route is shown in Scheme 12 where a Michael acceptor (**46**) is created from 1,3-propanediol (**44**) and acetylmethylene triphenylphosphorane (**45**) in a Wittig reaction. Compound **46** could then, with the same method as earlier, be converted to a pyrrole. The first step in this synthesis was tried twice without success but it could be tested again with some extra steps to protect one of the hydroxyl groups of the 1,3-propanediol before the oxidation and Wittig reaction is done [16].



Scheme 12. Multistep synthesis of the lactonopyrrole **48** with 1,3-propanediol (**44**) and acethylmethylene triphenylphosphorane (**45**) as starting materials.

There are also some additional hydrogenations that would be interesting to perform. Compound **39** was the only compound that was created by hydrogenation in this project but the creation of compound **49** (shown in Scheme 13) was also planned to be tested by a hydrogenation of Michael adduct **30**.



Scheme 13. Hydrogenation of compound **30** giving the interesting compound **49**.

There were no stereochemical investigations in this project even though many of the products (especially the Michael adducts) contained at least one stereocenter. An interesting task for the future would be to reveal the effect of the asymmetric catalysis by determination of the stereochemistry of the products using conventional methods like optical rotation and chiral HPLC or gas chromatography (GC).

4. Conclusions

The Diels-Alder reactions that were carried out with MVK (**2**) as dienophile did not show as fast conversions as expected when performed in water together with rare earth triflates and alanine as catalytic system. The expected result was instead found when performing the Diels-Alder reaction with PVK (**5**) as dienophile instead, with full conversion after just one day.

The Michael reactions with methyl 2-nitroacetate (**17**) as Michael donor showed fast to moderate conversions where most of the reactions were finished in just a few hours. The final yields were a bit lower than expected in most cases and some further work with work up and purification could be needed. It was also shown that when performing these reactions on larger scales, the product could be separated directly from the reaction water without further work up or purification. This adds on to the green approach of the project since no unnecessary solvents are used in that case.

Most of the isolated Michael adducts could be converted to pyrroles with fast conversions. The Michael reactions, followed by a conversion to pyrroles, demonstrate a short and convenient pyrrole synthesis route that with some optimisations of work up and purification could be a good alternative to the more conventional methods used in industry and science today.

5. Experimental Section

General Experimental Details: All commercial reagents and solvents were used without further purification. NMR spectra were obtained using a Varian 400 MHz instrument. Chemical shifts are reported in parts per million relative to the internal standards (tetramethylsilane (0.00 ppm) for ^{1}H; $CHCl_3$ (7.26 ppm) and MeOH (3.31 ppm). MS were obtained from HPLC Marrifield equipped with ESI source and reported as m/z. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV-light as visualizing agent and anisaldehyde or $KMnO_4$ as developing agents. Flash column chromatography on silica gel was carried out using a Biotage Isolera One chromatograph with Sphere cartridges (silica gel, 25µm) and a gradient of petroleum ether and ethyl acetate as eluent. IR-experiments were done with Agilent Cary 630 FTIR – Diamond ATR.

General Procedure 1, Thermal Diels-Alder Reaction: The diene (1 mmol) and the dienophile (1 mmol) were added to a pressure container and dissolved in toluene (5 ml). The reaction was stirred overnight at 130°C (on the aluminium plate). The solvent was removed under reduced pressure to obtain the product.

1-acetyl-3,4-dimethylcyclohex-3-ene (14): General procedure 1 was followed with methyl vinyl ketone as dienophile and 2,3-dimethylbuta-1,3-diene as diene. 117 mg (74%) of the product was obtained as a colourless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 2.61 – 2.51 (m, 1H), 2.17 (s, 3H), 2.16 – 1.88 (m, 6H), 1.63 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 211.97, 125.40, 123.95, 48.28, 33.07, 31.22, 27.97, 25.31, 19.03, 18.82.

General Procedure 2, $AlCl_3$-catalyzed Diels-Alder Reaction: $AlCl_3$ (6.6 mg, 0.05 mmol) and THF (4.1 µl, 0.10 mmol) was stirred in a screw-capped vial. After 15 minutes the dienophile was added (1 mmol). After additional 15 minutes, the diene was added (1 mmol) at 30°C. The resulting mixture was left under magnetic stirring and the conversion was followed with ^{1}H NMR-spectroscopy [10].

General procedure 3, $Yb(OTf)_3$- / $Sc(OTf)_3$- / $La(OTf)_3$-catalyzed Diels-Alder Reaction: $Yb(OTf)_3$ (0.031 g, 0.05 mmol), $Sc(OTf)_3$ (15 mg, 0.05 mmol) or $La(OTf)_3$ (29 mg, 0.05 mmol) was dissolved in deionized water (1 ml) in a screw capped vial. The dienophile (1 mmol) and the diene (2 mmol) were then added. The vial was capped, and the reaction was stirred vigorously at 30°C or 60°C (according to Table 1, 2 and 3). The conversion was followed by ^{1}H NMR-spectroscopy [3].

General Procedure 4, $Yb(OTf)_3$- / $Sc(OTf)_3$- / $La(OTf)_3$-catalyzed Diels-Alder Reaction with Alanine as Ligands: $Yb(OTf)_3$ (0.031 g, 0.05 mmol), $Sc(OTf)_3$ (15 mg, 0.05 mmol) or $La(OTf)_3$ (29 mg, 0.05 mmol) was dissolved in deionized water (0.5-1 ml) together with DL or L-alanine (0.012 mmol) in a screw capped vial. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). The dienophile (1 mmol) and the diene (2 mmol) were then added. The vial was capped, and the reaction was stirred vigorously at 30°C or 60°C (according to Table 1, 2 and 3) [3]. The conversion was followed by ^{1}H NMR-spectroscopy.

1-acetyl-4-methylcyclohex-3-ene (3) / 1-acetyl-3-methylcyclohex-3-ene (4): General procedure 1, 2, 3 and 4 were followed with methyl vinyl ketone as dienophile and isoprene as diene. Conditions can be seen in Table 1. General procedure 1 gave 93 mg (59%) of the

product after 7 days. General procedure 4 (Entry 5 in Table 1) gave 42 mg (30%) of the product after 7 days. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.40 (s, 1H), 2.68 – 2.45 (m, 1H), 2.19 (s, 3H), 2.17 – 1.79 (m, 6H), 1.69 (s, 1H), 1.66 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 212.33, 134.17, 132.75, 120.94, 119.56, 48.17, 47.55, 31.72, 29.80, 28.33, 28.32, 27.35, 25.21, 25.12, 24.79, 23.91, 23.73.

1-acetyl-2-phenylcyclohex-3-ene (10) / 1-acetyl-4-phenylcyclohex-3-ene (9): General procedure 3 and 4 was followed with methyl vinyl ketone (32 µl, 0.38 mmol) as dienophile and (E)-Buta-1,3-dien-1-ylbenzene (**8**) (54 µl, 0.38 mmol) as diene. With General Procedure 3 the best conversion was 89% after 7 days (Entry 1 in Table 3). The reaction mixture was then diluted with water (5 ml) and extracted with ethyl acetate (3 × 5 ml). The organic phases were dried with Na_2SO_4, filtered, and purified with flash chromatography. Product was lost during purification. NMR-analysis was done on the crude product. LCMS (m/z): calcd. for $C_{14}H_{16}O$ [M+H]+, 201.28; [M+NH_4]+, 218.28; found, [M+H]+, 200.9, 201.9; [M+NH_4]+, 218.0, 217.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.13 (m, 5H), 6.00 – 5.82 (m, 1H), 5.81 – 5.62 (m, 1H), 2.96 – 2.69 (m, 1H), 2.37 – 1.68 (m, 8H).

Phenyl vinyl ketone (5): 3-Chloropropiophenone (1.5 g, 8.9 mmol, 1 eq.) was stirred in chloroform (20 ml) and triethylamine (3.00 ml, 21.4 mmol, 2.4 eq.) was added dropwise for 10 minutes under atmosphere of N_2. The reaction mixture was stirred for 22 h followed by washing with 0.1 M HCl (2 × 20 ml), distilled water (2 × 20 ml), saturated $NaHCO_3$ (2 × 20 ml), and brine (1 × 20 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 925 mg (79%) of the product as a light-yellow oil [8]. LCMS (m/z): calcd. for C_9H_8O [M+H]+, 133.16 found, [M+H]+, 132.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (d, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.18 (dd, *J* = 17.1, 10.6 Hz, 1H), 6.46 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.95 (dd, *J* = 10.6, 1.6 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 191.40, 137.55, 133.31, 132.66, 130.56, 129.01, 128.93.

4-Methyl-cyclohex-3-enyl-phenyl-keton (6): $Yb(OTf)_3$ (16 mg, 0.025 mmol was dissolved in deionized water (0.5 ml) in a screw capped vial. PVK (0.5 mmol) and isoprene (1 mmol) were then added. The vial was capped, and the reaction was stirred vigorously for 22 h at 60**°**C on the aluminium plate. The reaction tube was capped, and the reaction was stirred vigorously for 20 h at 60**°**C. The reaction mixture was then diluted with water (1 ml) and extracted with ethyl acetate (3 × 2 ml). The organic phases were washed with brine (2 ml), dried with Na_2SO_4, filtered and concentrated. After purification with flash chromatography, 46 mg (46%) of the product was obtained as a yellow oil. LCMS (m/z): calcd. for $C_{14}H_{16}O$ [M+H]+, 201.28; found, 200.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.56 (t, 1H), 7.48 (t, 2H), 5.47 (s, 1H), 3.60 – 3.43 (m, 1H), 2.38 – 1.76 (m, 6H), 1.71 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 204.07, 133.15, 128.99 (d, *J* = 13.1 Hz), 128.59, 128.36, 120.02, 41.84, 38.98, 30.02, 28.56, 26.32, 23.77.

(E)-Buta-1,3-dien-1-ylbenzene (8): n-Butyllithium (1.6 M in hexane, 6.25 ml, 10 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (3.57 g, 10 mmol) in THF (50 mL) at 0**°**C. The reaction mixture was stirred for 15 min and cinnamaldehyde (1.0 ml, 8 mmol) was then added as solution in THF (10 ml). After 1 h the solution was warmed to room temperature and stirred for additional 16 hours. A saturated NH_4Cl-solution (50 ml) was added, and the mixture was extracted with Et_2O (3 × 100 ml).

The organic layers were washed with brine (100 ml), dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was applied to a plug of silica, eluted with n-heptane (3 × 40 ml), and the solvent was removed carefully under reduced pressure to obtain 540 mg (52%) of the desired compound as a colourless oil [17]. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 (s, 1H), 7.23 – 7.05 (m, 3H), 6.66 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.48 – 6.32 (m, 2H), 5.21 (d, *J* = 16.9 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 137.15, 137.08, 132.82, 129.59, 128.59, 127.61, 126.41, 117.63.

Methyl 2-nitroacetate (17): Water (56 ml) and KOH (112g, 2.00 mol) was added to a three-necked 1 l round-bottom flask under mechanical overhead stirring. Nitromethane (27 ml, 0.5 mol) was added dropwise over 30 min with a dropping funnel. When the addition was done, the reaction was heated at 160 °C (on the aluminium plate) for 1 h. The reaction was then cooled to room temperature and the crude salt was collected by filtration. The salt was rinsed with MeOH until the filtrate was colourless. The remaining salt (**16**) was dried overnight in a vacuum desiccator. The dry powder was then transferred to a new 1 l round bottom-flask together with MeOH (233 ml) with mechanical overhead stirring. The suspension was cooled to −15 °C with a bath of acetone and dry ice, the temperature was checked with a thermometer. Once cooled, H_2SO_4 (32 ml, 0.58 mol) was added dropwise over 1 h via a dropping funnel to avoid increasing temperatures. The reaction was then allowed to stir at room temperature overnight. The solution was then filtrated to remove the resulting precipitate. The MeOH was removed from the filtrate under reduced pressure [11]. The resulting material was then diluted in 100 ml of water and the organic product was extracted with toluene (3 × 60 ml). The combined organic phases were washed with brine (60 ml) and concentrated under reduced pressure to yield an orange liquid. Distillation under reduced pressure yielded 12.2 g (51%) of the desired product as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.19 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 162.22, 76.09, 53.68.

General Procedure 5, Michael Reaction with Methyl 2-Nitroacetate as Donor: $Yb(OTf)_3$ (31 mg, 0.05 mmol) was dissolved in deionized water (0.5 ml) together with L-alanine (0.53 mg, 0.06 mol) in a screw capped vial. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Methyl 2-nitroacetate (46 µl, 0.5 mmol) and the Michael acceptor (0.5 mmol) were then added. The vial was capped, and the reaction was stirred vigorously at 60°C on the aluminium plate [3]. The conversion was followed by ^{1}H NMR-spectroscopy and LCMS. All compounds in Table 4 were synthesised with this procedure at least once.

Methyl 5-oxo-2-nitropentanoate (25): General procedure 5 was followed with acrolein (33 µl, 0.5 mmol) as Michael acceptor. 100% conversion of acrolein was reached after 4 h but a lot of it was polymerising. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (s, 1H), 5.15 – 5.06 (dd, 1H), 3.86 (s, 3H), 2.74 – 2.38 (m, 4H).

Ethyl 4-methoxycarbonyl-4-nitrobutanoate (28): General procedure 5 was followed with ethyl acrylate (55 µl, 0.5 mmol) as Michael acceptor. 80% conversion of ethyl acrylate was reached after 7 h. No further purification was done. LCMS (m/z): calcd. for $C_8H_{13}NO_6$ [M+0]+, 219.19; [M+H+CH_3CN]+, 261.19 found, [M+0]+, 218.7; [M+ H+CH_3CN]+, 260.8. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.23 – 5.17 (m, 1H), 4.27 (p, *J* = 7.1 Hz, 2H), 3.92 (d, *J* = 2.9 Hz, 3H), 3.54 – 3.48 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.30 – 1.22 (m, 2H).

Methyl 4-cyano-2-nitrobutanoate (29): General procedure 5 was followed with acrylonitrile (33 µl, 0.5 mmol) as Michael acceptor. 80% conversion of acrylonitrile was reached after 7 h. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.41 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.95 (s, 3H), 3.76 – 3.53 (m, 4H). LCMS (m/z): calcd. for $C_6H_8N_2O_4$ [M+H]+, 173.14; [M+Na]+, 195.14; [M+Li]+, 179.14; [M+NH_4]+, 190.14 found, [M+H]+, 172.7; [M+Na]+, 194.8; [M+Li]+, 178.7; [M+NH_4]+, 189.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.41 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.95 (s, 3H), 3.76 – 3.47 (m, 4H).

Methyl 2-nitro-5-oxohexanoate (18): $Yb(OTf)_3$ (831 mg, 1.34 mmol, 0.10 eq.) was dissolved in deionized water (7 ml) together with L-alanine (0.143 g, 1.61 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Methyl vinyl ketone (1.22 ml, 14.7 mmol, 1.1 eq.) and methyl 2-nitroacetate (1.22 ml, 13.4 mmol, 1 eq.) were then added. The flask was capped, and the reaction was stirred vigorously at 60°C (on the aluminium plate) [3]. After 2.5 and 3.5 h, 0.1 eq. of extra MVK was added to convert the prolonged methyl 2-nitroacetate. The mixture was allowed to stir for 3 days and was then diluted with water (10 ml) and extracted with ethyl acetate (3 × 10 ml). The organic phases were washed with brine (10 ml) and dried with Na_2SO_4, filtered, and purified with Kugelrohr distillation to give 1.91 g (75%) of the product as a yellow oil. LCMS (m/z): calcd. for $C_7H_{11}NO_5$ [M+NH_4]+, 207.17; [M+Na]+, 212.17; [M+Cl]+, 224.17 found, [M+NH_4]+, 206.8; [M+Na]+, 211.9; [M+Cl]+, 223.6. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.28 (dd, *J* = 8.5, 5.9 Hz, 1H), 3.85 (s, 3H), 2.67 – 2.56 (m, 2H), 2.52 – 2.42 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 206.27, 165.04, 86.82, 53.94, 38.56, 30.26, 24.34.

Methyl 2-carbamoyl-4-nitrobutanoate (26): $Yb(OTf)_3$ (248 mg, 0.4 mmol, 0.10 eq.) was dissolved in deionized water (3 ml) together with L-alanine (42.8 mg, 0.48 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Acrylamide (284 mg, 4 mmol, 1 eq.) and methyl 2-nitroacetate (366 µl, 4 mmol, 1 eq.) were then added. The flask was capped, and the reaction was stirred vigorously at 60°C (on the aluminium plate) [3]. The mixture was allowed to stir overnight (17 h) and was then diluted with water (3 ml) and extracted with ethyl acetate (3 × 5 ml). The organic phases were washed with brine (5 ml) and dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The work up process was then repeated three more times to extract as much product as possible. The crude product was purified with flash chromatography to yield 190 mg (25%) of the final product as light-yellow crystals. LCMS (m/z): calcd. for $C_6H_{10}N_2O_5$ [M+Li]+, 197.16; [M+Na]+, 213.16 found, [M+Li]+, 196.9; [M+Na]+, 213.8. 1H NMR (400 MHz, Chloroform-d) δ 6.55 (s, 1H), 5.49 (s, 1H), 5.20 (dd, *J* = 11.2, 7.3 Hz, 1H), 3.92 (s, 3H), 3.80 – 3.31 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.76, 159.94, 151.97, 80.45, 53.15, 38.15.

Methyl 2-nitro-5-oxo-3-phenylhexanoate (27): $Yb(OTf)_3$ (1.17 g, 1.89 mmol, 0.10 eq.) was dissolved in deionized water (5 ml) together with L-alanine (0.202 g, 2.26 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). (E)-benzalacetone (2.76 g, 18.85 mmol, 1 eq.) and methyl 2-nitroacetate (2.59 ml, 28.3 mmol, 1.5 eq.) were then added. The flask was capped, and the reaction was stirred vigorously at 80°C (on the aluminium plate) [3]. After 90 h, 0.3 eq. of extra methyl 2-nitroacetate was added to convert the prolonged (E)-benzalacetone. The mixture was allowed to stir for 3 more days and was then diluted with water (10 ml) and

extracted with ethyl acetate (3 × 10 ml). The organic phases were washed with brine (10 ml) and dried with Na_2SO_4, filtered, and concentrated with flash chromatography to give 1.80 g (36%) of the product as yellow and brown crystals and clay. LCMS (m/z): calcd. for $C_{12}H_{15}NO_5$ [M+Na]+, 288.27 [M+NH_4]+, 283.27; [M+Cl]+, 310.27 found [M+Na]+, 287.8; [M+NH4]+, 282.8; [M+Cl]+, 310.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.21 (m, 5H), 5.47 (dd, *J* = 23.8, 9.0 Hz, 1H), 3.82 (s, 2H), 3.64 (s, 1H), 3.21 – 2.88 (m, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 204.63, 163.76, 128.85, 128.67, 127.85 (d, *J* = 5.8 Hz), 127.63, 90.69, 53.37, 45.14, 40.86, 29.94.

Methyl 2-[3-oxocyclohexyl]-2-nitroacetate (30): $Yb(OTf)_3$ (285 mg, 0.46 mmol, 0.10 eq.) was dissolved in deionized water (5 ml) together with L-alanine (49 mg, 0.55 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Cyclohex-2-en-1-one (453 µl, 4.6 mmol, 1 eq.) and methyl 2-nitroacetate (426 µl, 4.6 mmol, 1 eq.) were then added. The flask was capped, and the reaction was stirred vigorously at 60°C (on the aluminium plate) [3]. After 22 h, 0.1 eq. of extra cyclohex-2-en-1-one was added to convert the prolonged methyl 2-nitroacetate. The mixture was allowed to stir for 3 days and was then diluted with water (10 ml) and extracted with ethyl acetate (3 × 10 ml). The organic phases were washed with brine (10 ml) and dried with Na_2SO_4, filtered, and concentrated with flash chromatography to give 386 mg (39%) of the product as a yellow oil. LCMS (m/z): calcd. for $C_9H_{13}NO_5$ [M+NH_4]+, 233.21; [M+Na]+, 238.21 found, [M+NH_4]+, 232.9; [M+Na]+, 237.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.07 (dd, *J* = 18.7, 7.4 Hz, 1H), 3.87 (d, *J* = 3.8 Hz, 3H), 2.82 (dtq, *J* = 14.7, 7.2, 3.8 Hz, 1H), 2.56 – 1.92 (m, 8H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.58, 163.44, 90.95 (d, *J* = 13.6 Hz), 53.70 (d, *J* = 1.5 Hz), 43.12, 40.74, 38.97, 27.19 (d, *J* = 11.8 Hz), 24.07 (d, *J* = 15.8 Hz).

Methyl-2-nitro-4-benzoylbutanoate (31): Yb(OTf)3 (186 mg, 0.3 mmol, 0.10 eq.) was dissolved in deionized water (3 ml) together with L-alanine (32 mg, 0.36 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Phenyl vinyl ketone (398 µl, 3 mmol, 1 eq.) and methyl 2-nitroacetate (275 µl, 3 mmol, 1 eq.) were then added. The flask was capped, and the reaction was stirred vigorously at 60°C (on the aluminium plate). The mixture was allowed to stir for 20 h and was then diluted with water (3 ml) and extracted with ethyl acetate (3 × 5 ml). The organic phases were washed with brine (5 ml) and dried with Na_2SO_4, filtered, and concentrated with flash chromatography to give 389 mg (52%) of the product as a yellow oil [3]. LCMS (m/z): calcd. for $C_{12}H_{13}NO_5$ [M+H]+, 251.24; [M+Li]+, 258.24; [M+Na]+, 274.24 found, [M+H]+, 252.4; [M+Li]+, 257.8; [M+Na]+, 273.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.41 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.87 (s, 3H), 3.17 (dt, *J* = 13.8, 6.8 Hz, 2H), 2.71 – 2.65 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 197.72, 165.17, 133.96, 129.07, 128.28, 87.09, 53.98, 33.88, 24.80.

Methyl 5-oxo-4-methyl-2-nitropentanoate (37): Yb(OTf)3 (223 mg, 0.36 mmol, 0.10 eq.) was dissolved in deionized water (3 ml) together with L-alanine (38 mg, 0.43 mmol, 0.12 eq.) in a 50 ml round-bottom flask. NaOH (0.2 M) was then added dropwise until the pH reached 7 (checked with pH-sticks). Methyl 2-nitroacetate (330 µl, 3.6 mmol, 1 eq.) were then added and methylacrolein (300 µl, 3.6 mmol, 1 eq.) were added dropwise during 2 h as the reaction was stirred vigorously at room temperature. The mixture was allowed to stir for 43 additional hours and was then diluted with water (3 ml) and extracted with ethyl acetate (3 × 5 ml). The

organic phases were washed with brine (5 ml) and dried with Na_2SO_4, filtered, and concentrated with flash chromatography to give 243 mg (36%) of the product as a colourless oil [3]. LCMS (m/z): calcd. for $C_7H_{11}NO_5$ [M+H]+, 190.17; [M+Na]+, 212.17 found, [M+H]+, 189.6; [M+Na]+, 211.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.64 (s, 1H), 5.30 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.85 (s, 3H), 2.29 (t, *J* = 10.8 Hz, 2H), 2.20 – 2.15 (m, 1H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 202.13, 164.67, 85.99, 53.74, 42.38, 30.55, 14.14.

General Procedure 6, Pyrrole Synthesis: The Michael adduct (1 eq.) was dissolved in 2-propanol together with formamidinesulfonic acid (4 eq.) and triethylamine (1 eq.) in a 50 ml round bottom-flask. The reaction mixture was heated to reflux (ca. 90**°**C on the aluminium plate) under inert gas (argon). The solvent was then evaporated, and the residue was dissolved in water (5 ml) and extracted with ether (3 × 5 ml). The combined organic layers were dried with Na_2SO_4, filtered, and purified with flash chromatography [19] or by recrystallisation.

Methyl 5-methyl-1H-pyrrole-2-carboxylate (32): Compound **18** (189 mg, 1 mmol) was added to a 5 ml round bottom-flask together with sulphur (770 mg, 3 mmol), morpholine (262 µl, 3 mmol) and NH_4OAc (395 µl, 6 mmol). The mixture was stirred at 80**°**C for 30 minutes and conversion was followed with TLC. The reaction mixture was then diluted with water (15 ml) and extracted with DCM (2 × 10 ml). The combined organic layers were dried with Na_2SO_4, filtered [18] and purified with flash chromatography, yielding 27 mg (19%) of the desired pyrrole. General procedure 6 was also used on the same scale, giving the same yield. LCMS (m/z): calcd. for $C_7H_9NO_2$ [M+NH4]+, 157.15 found, [M+NH4]+, 156.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.76 (s, 1H), 6.82 (s, 1H), 5.96 (s, 1H), 3.84 (s, 3H), 2.32 (s, 3H).

Methyl 5-methyl-3-phenyl-1H-pyrrole-2-carboxylate (33): General procedure 6 was used with compound **27** (266 mg, 1 mmol) as Michael adduct. A large part of the crude product was lost during column loading before the chromatography due to overpressure. Some of the product was saved though and 24 mg (11%) of the crystalline pyrrole was obtained. LCMS (m/z): calcd. for $C_{13}H_{13}NO_2$ [M+H]+, 215.25 found, [M+H]+, 215.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.84 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H), 3.76 (s, 3H), 2.34 (s, 3H).

Methyl 5-phenyl-1H-pyrrole-2-carboxylate (35): General procedure 6 was used with compound **31** (251 mg, 1 mmol) as Michael adduct. 49 mg (24%) of the brown crystalline pyrrole was obtained. LCMS (m/z): calcd. for $C_{12}H_{11}NO_2$ [M+H]+, 202.23; [M+H+CH_3CN]+, 243.23 found, [M+H]+, 201.8; [M+H+CH_3CN]+, 242.9. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.29 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.97 (dd, *J* = 3.8, 2.5 Hz, 1H), 6.56 (dd, *J* = 3.8, 2.8 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.57, 136.72, 131.23, 129.05, 127.80, 124.68, 122.92, 116.80, 108.00, 51.56.

Methyl 4-methyl-1H-pyrrole-2-carboxylate (38): General Procedure 6 was used with compound **37** (189 mg, 1 mmol) as Michael adduct. 2 mg (1%) of the brown crystalline pyrrole was obtained. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 6.74 (s, 1H), 3.84 (s, 3H), 2.12 (s, 3H).

Methyl Hydroxyl pyrrolidine-2-carboxylate (39): Compound **18** (2 mmol) was added to a 50 ml round bottom-flask together with 0.2 g Na_2SO_4 and 0.1 g 10% palladium on carbon in 10 ml EtOH. The mixture was stirred for 72 h under an atmosphere of H_2. The mixture was then filtrated over a celite plug, and the plug was rinsed with EtOAc. The solvents were then removed under reduced pressure. The obtained oil was dissolved in 25 ml 2-propanol and 1 M HCl in 2-propanol (4 ml) was added dropwise during a few minutes, giving pyrrolidine crystals (HCl-salts) [2]. 197 mg of the impure hydroxyl pyrrolidine crystals were obtained.

Acetylmethylene triphenylphosphorane (45): Acetonyltriphenylphosphonium chloride (4.26 g, 12 mmol) was dissolved in DCM (180 ml) together with an aqueous solution of 2 M NaOH (120 ml). The resulting solution was stirred at 30°C for 3 h and was then extracted with EtOAc (2 × 60 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the product as a white salt in 100% yield [20]. LCMS (m/z): calcd. for $C_{21}H_{19}OP$ [M+H]+, 319.36 found, [M+H]+, 318.8.

6. References

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Appendix

A1. NMR-spectra

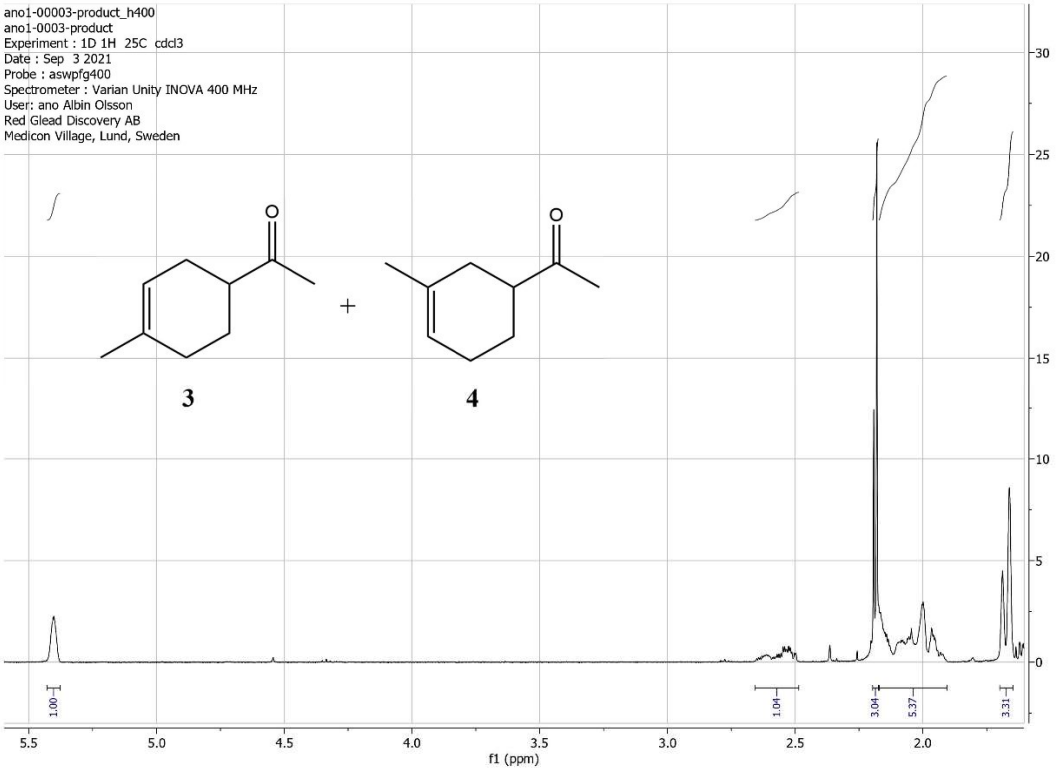


Figure A1. [1]H NMR-spectrum for compound **3** and **4**.

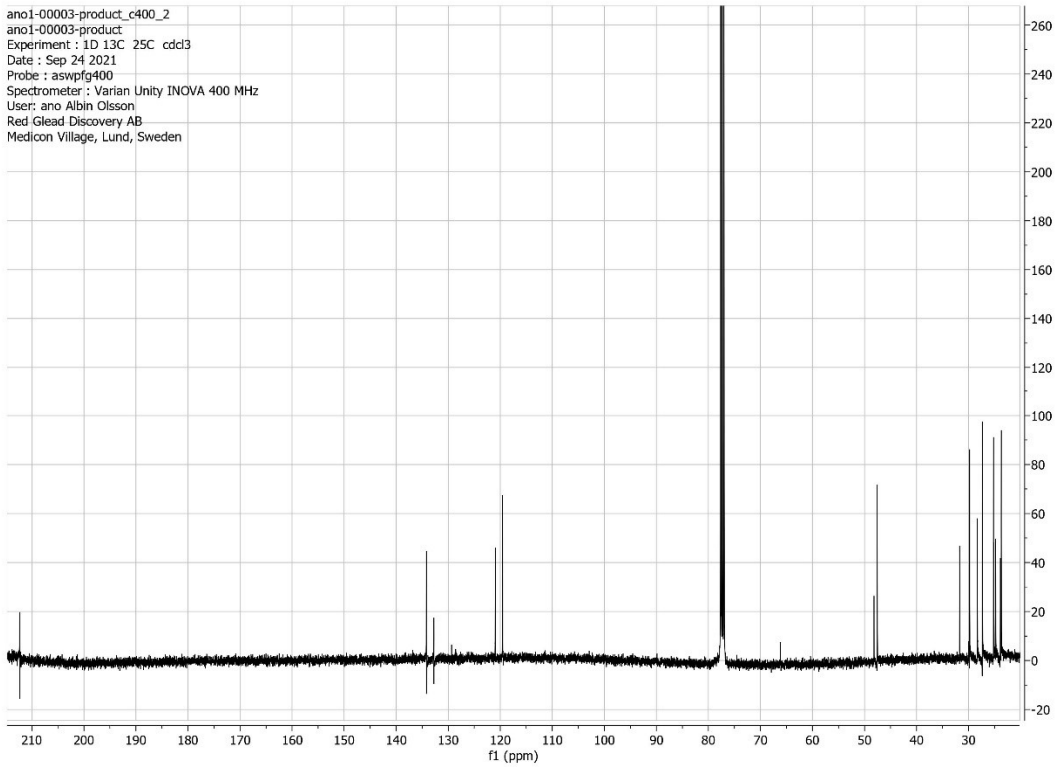


Figure A2. [13]C NMR-spectrum for compound **3** and **4**.

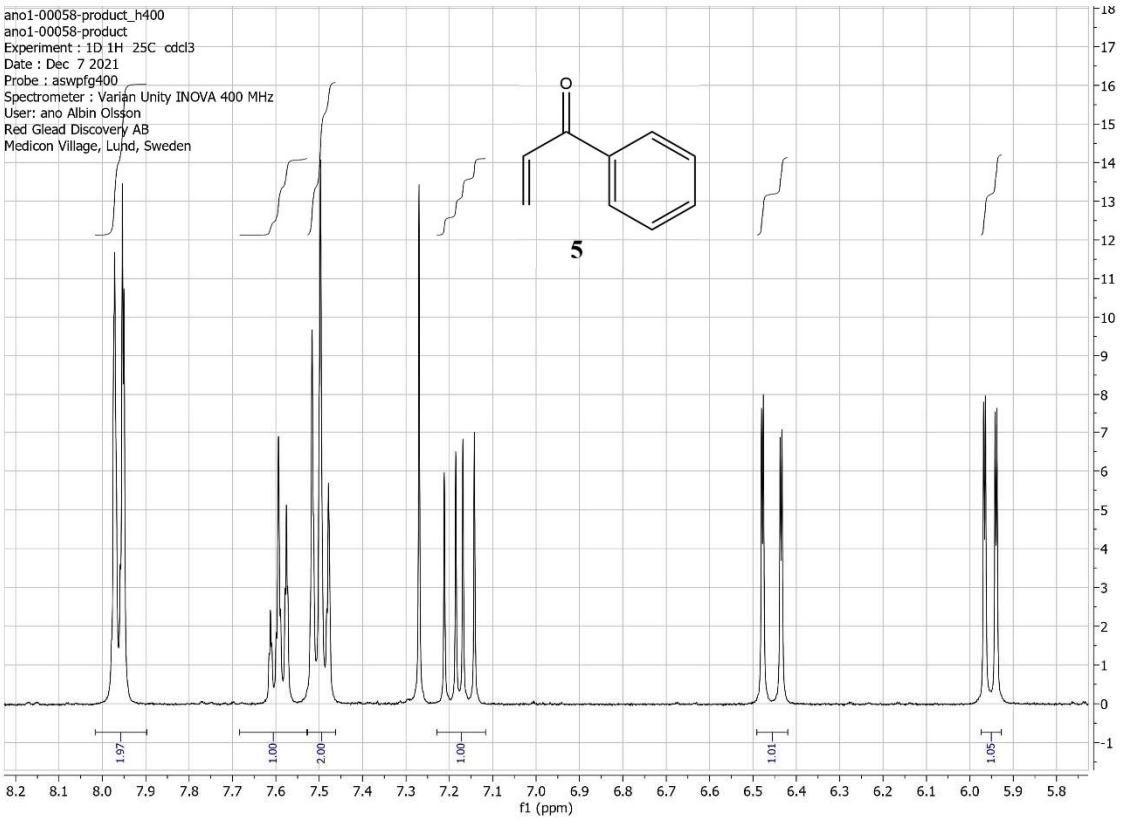


Figure A3. ^{1}H NMR-spectrum for compound **5**.

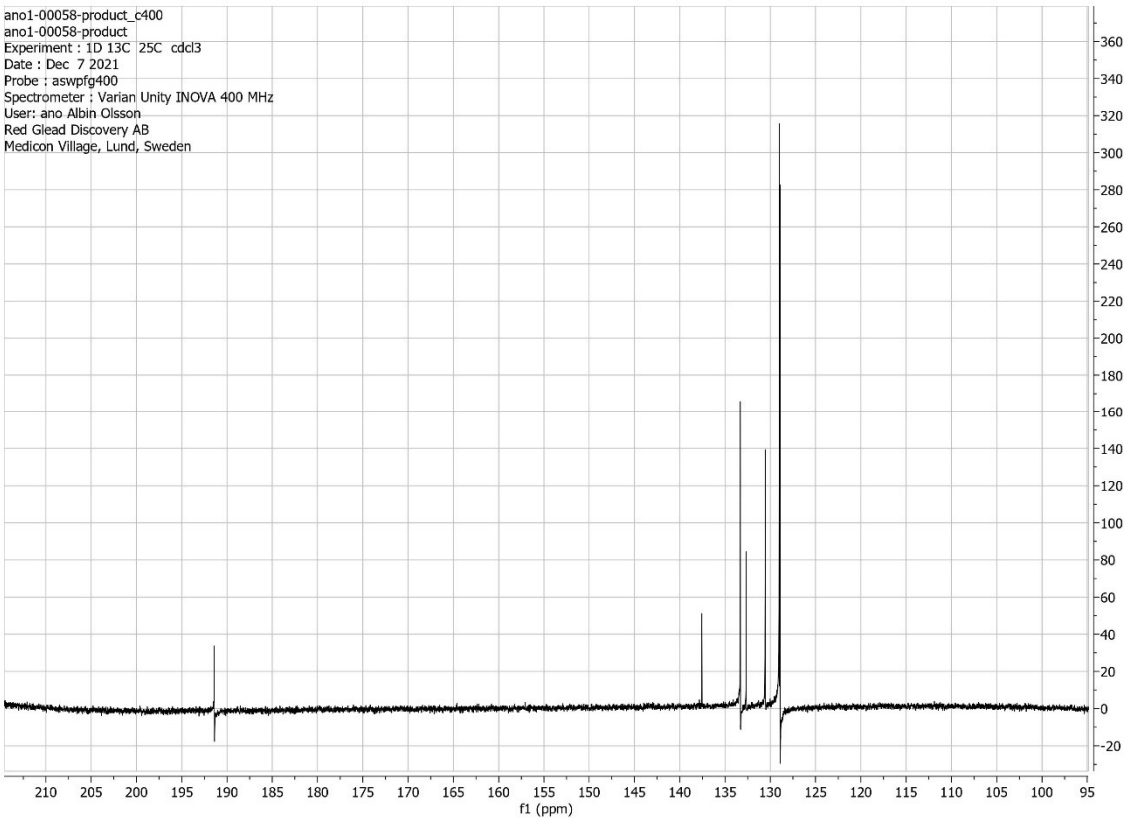


Figure A4. ^{13}C NMR-spectrum for compound **5**.

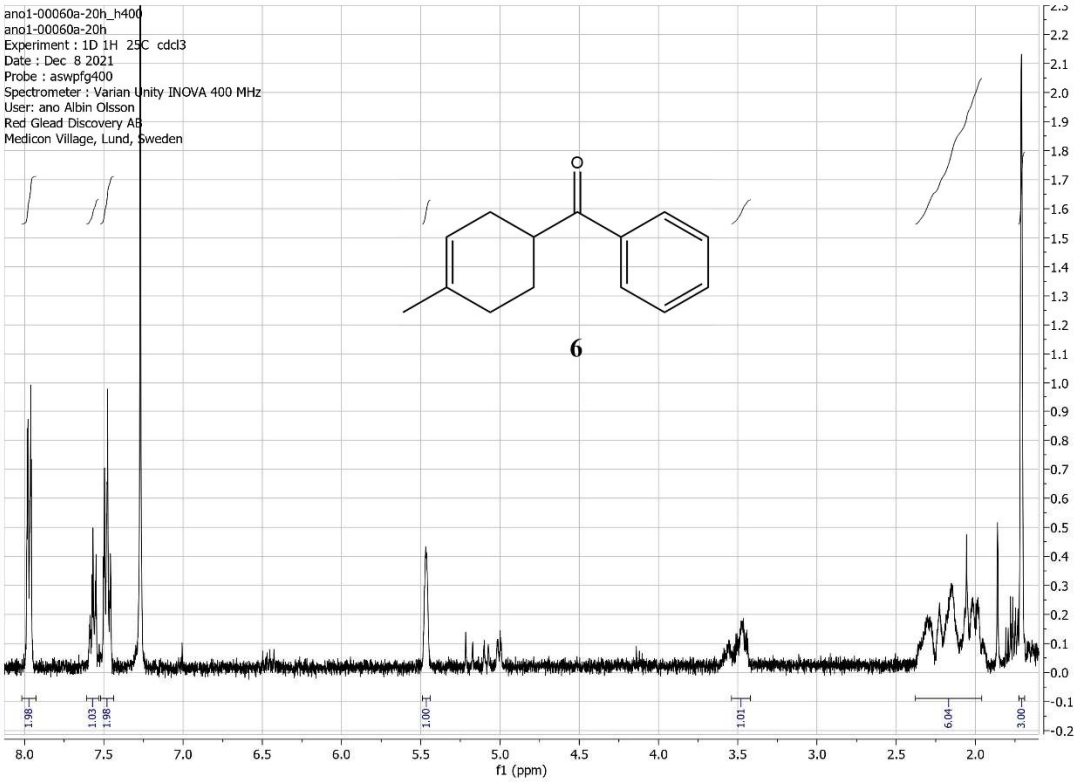


Figure A5. ^{1}H NMR-spectrum for compound **6**.

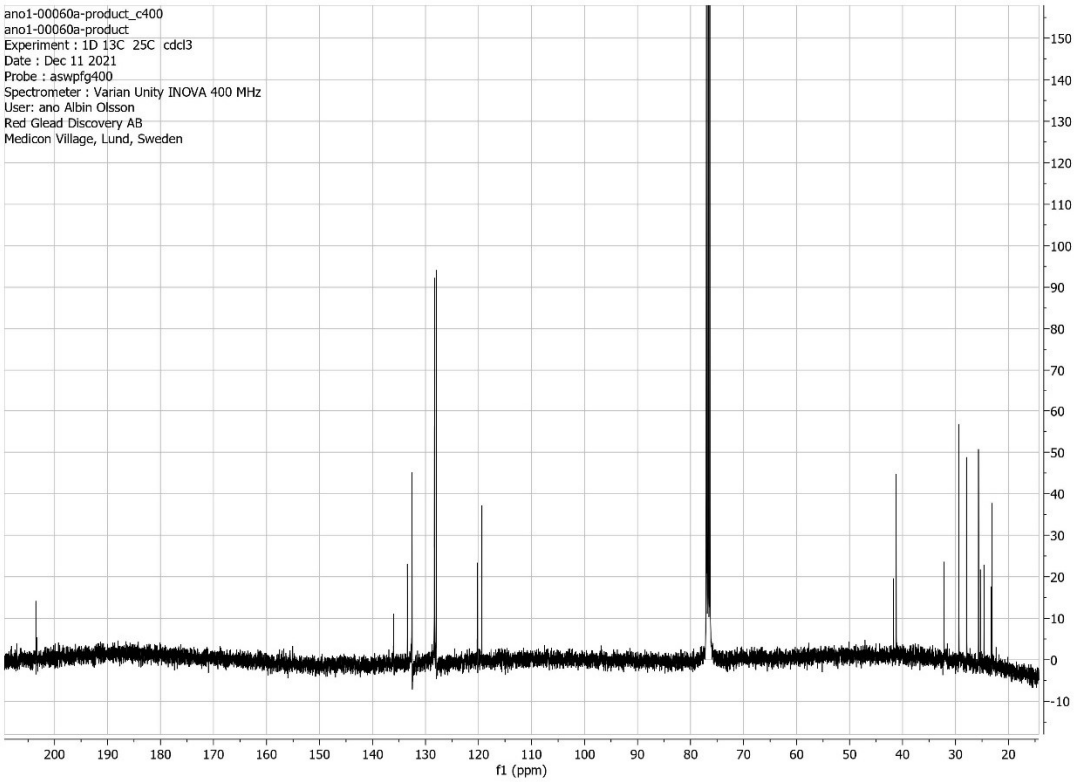


Figure A6. ^{13}C NMR-spectrum for compound **6**.

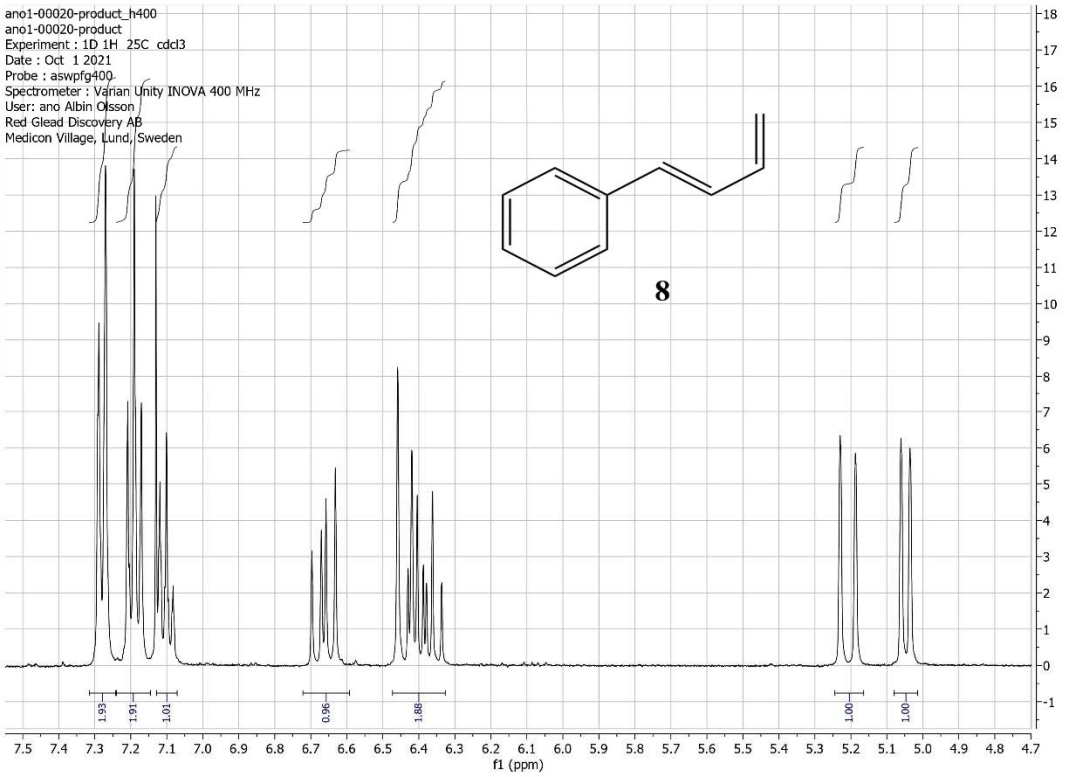


Figure A7. ^{1}H NMR-spectrum for compound **8**.

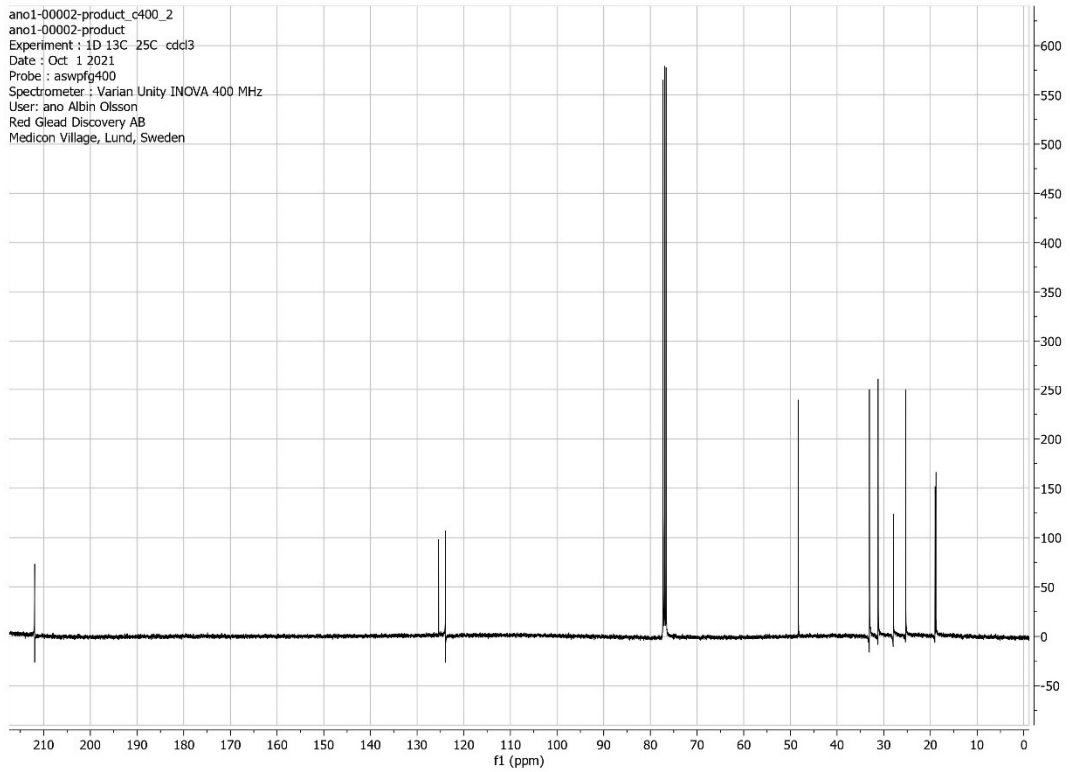


Figure A8. ^{13}C NMR-spectrum for compound **8**.

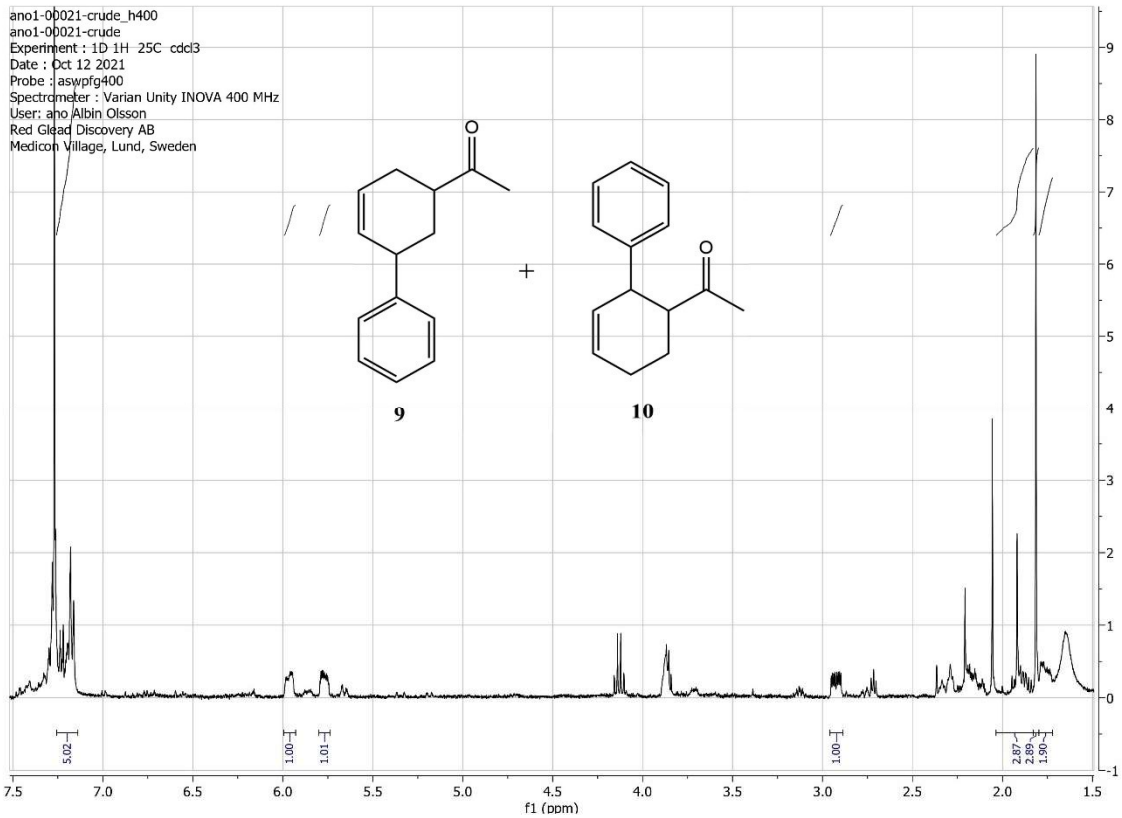


Figure A9. ^{1}H NMR-spectrum for compound **9** and **10**. Spectrum is measured on crude product.

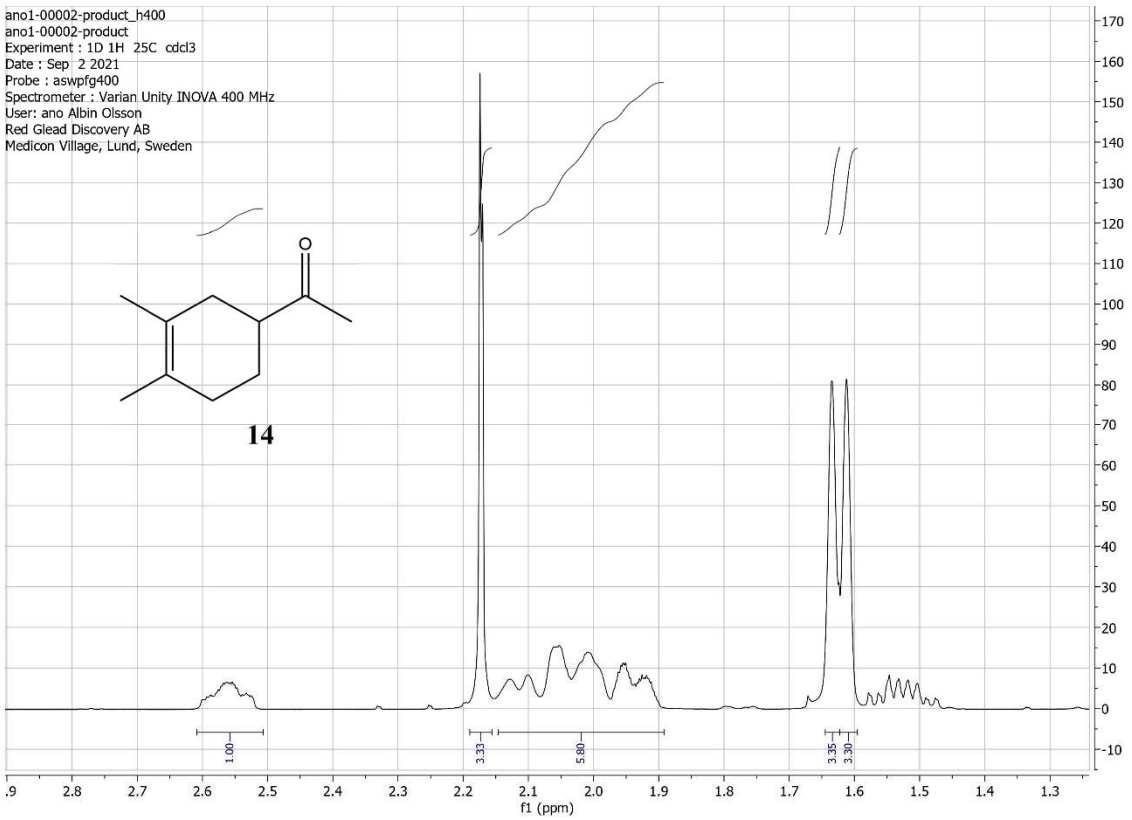


Figure A10. [1]H NMR-spectrum for compound **14**.

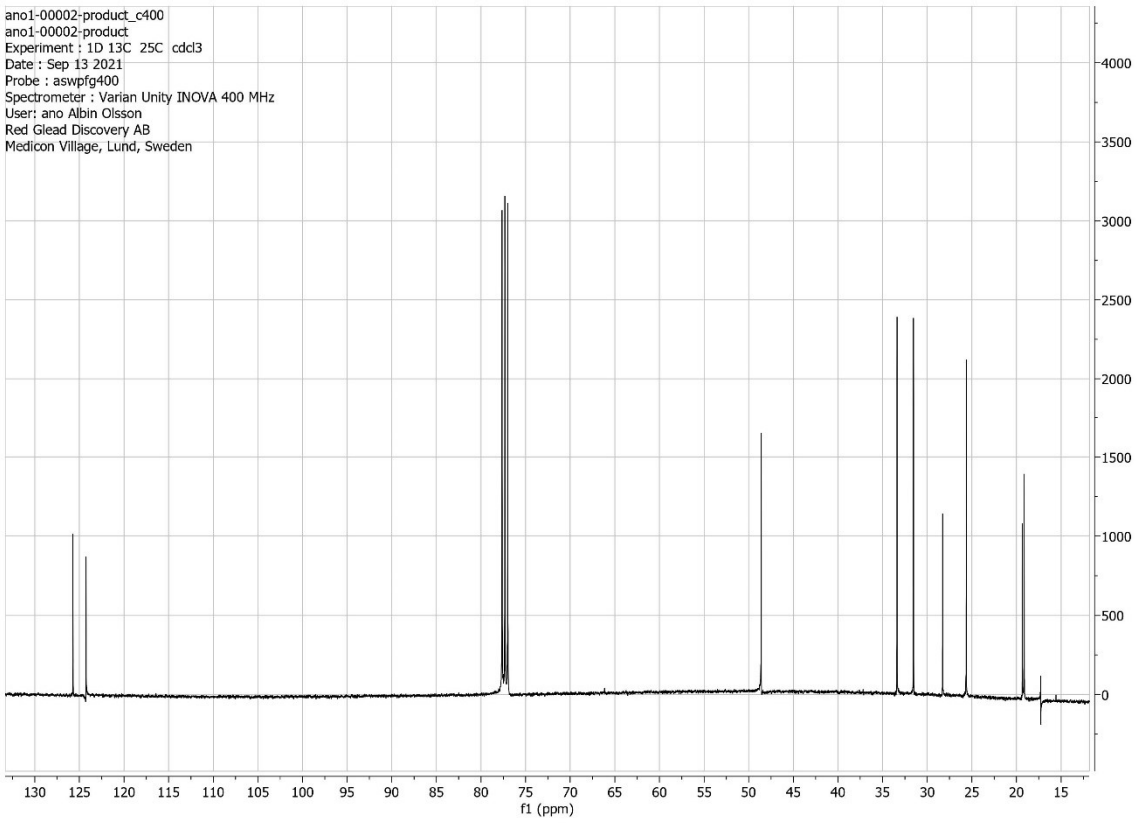


Figure A11. [13]C NMR-spectrum for compound **14**.

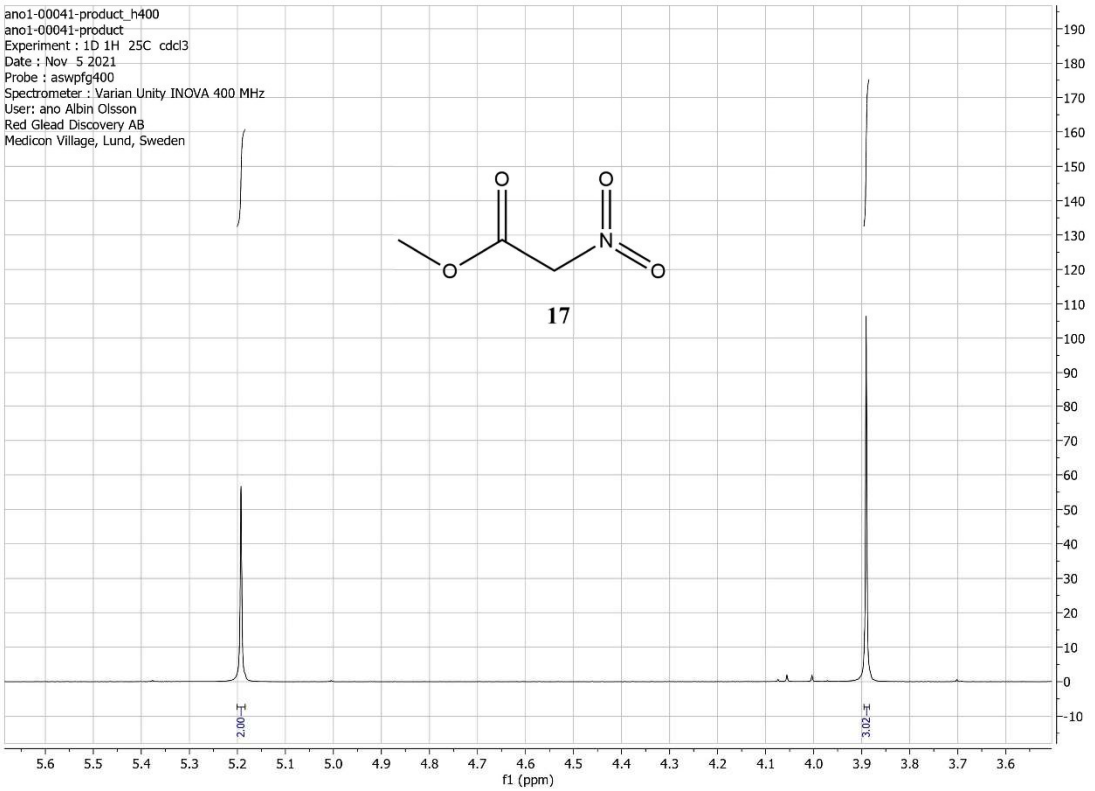
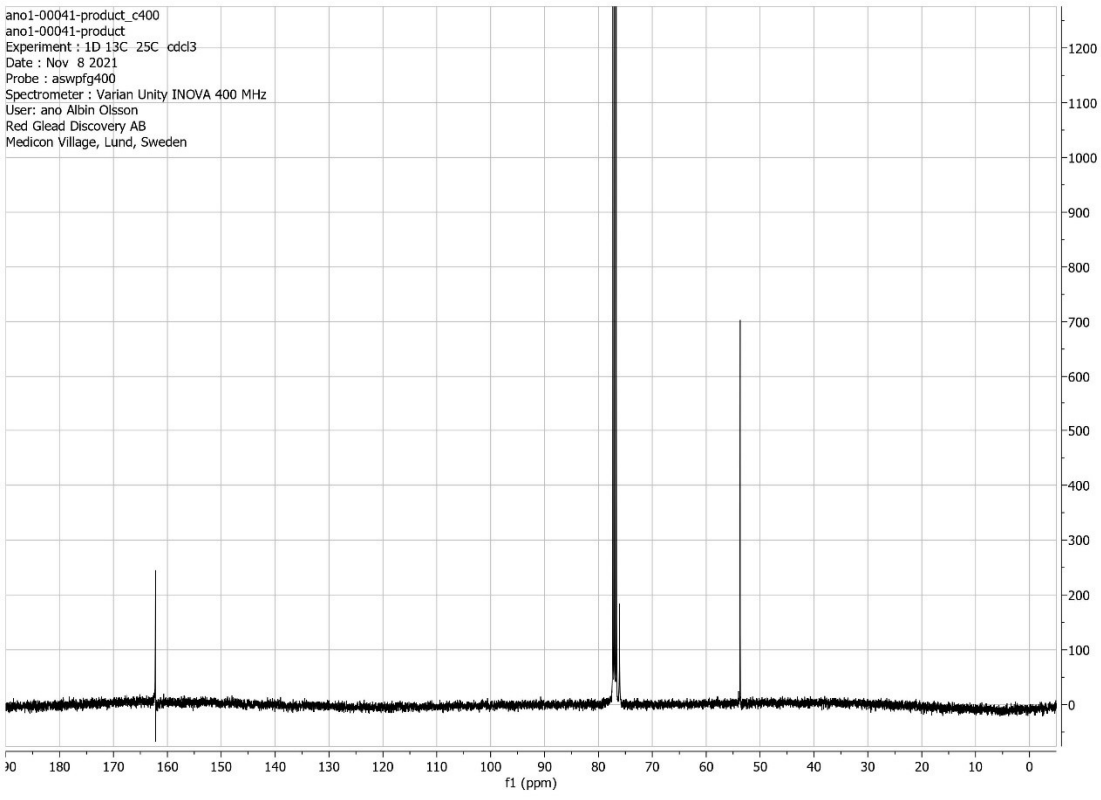


Figure A12. [1]H NMR-spectrum for compound **17**.



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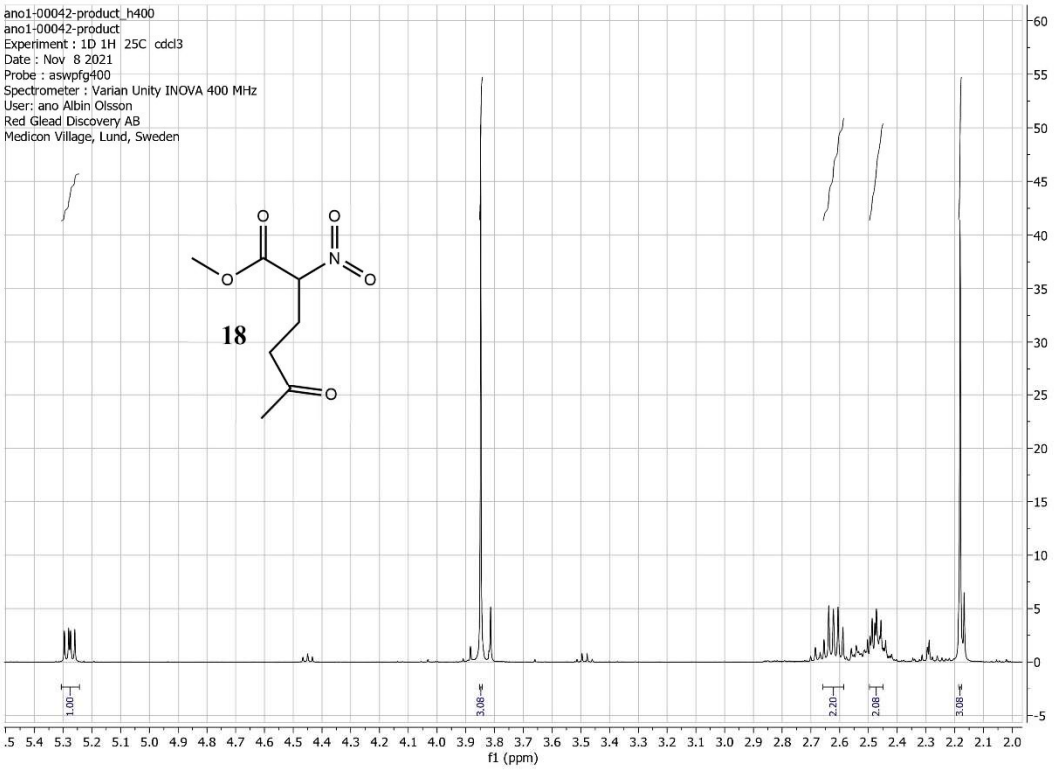

Figure A14. ^{1}H NMR-spectrum for compound **18**.

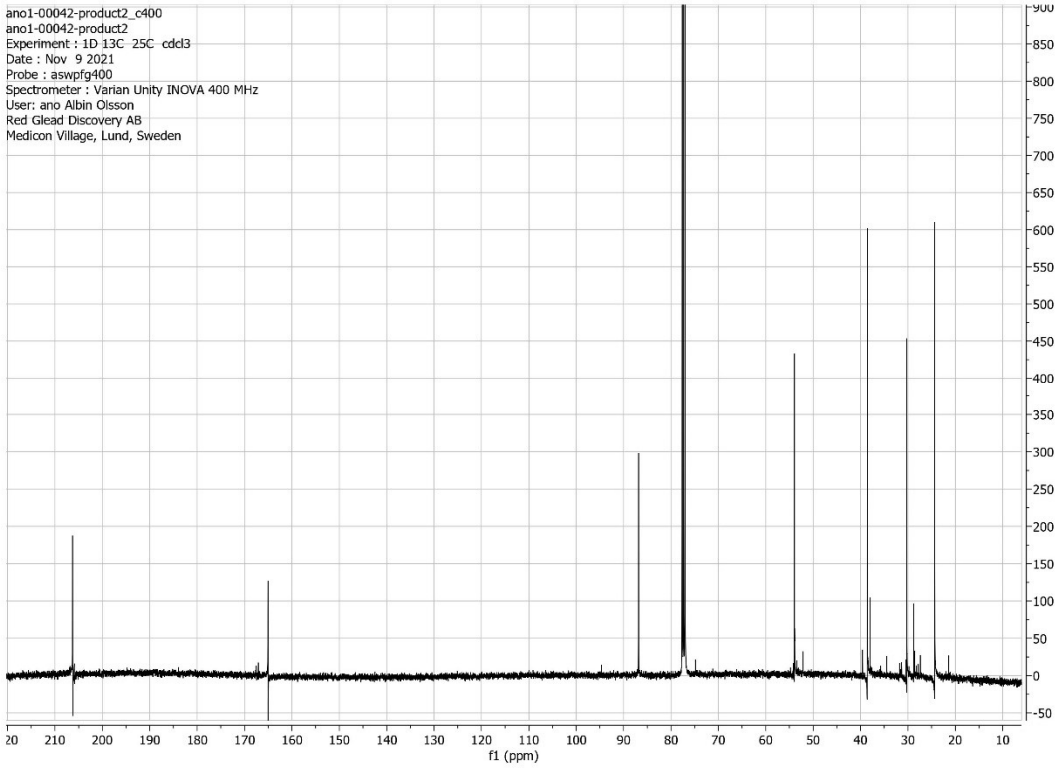

Figure A15. ^{13}C NMR-spectrum for compound **18**.

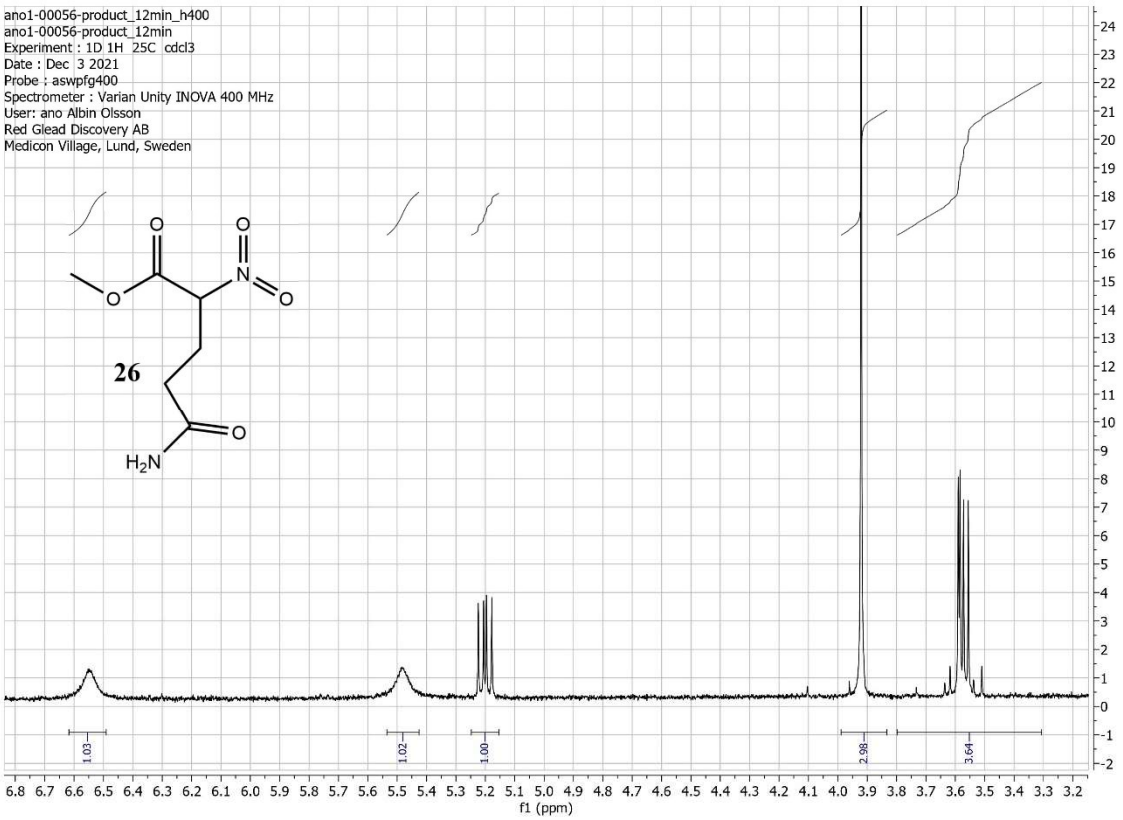

Figure A16. [1]H NMR-spectrum for compound **26**.

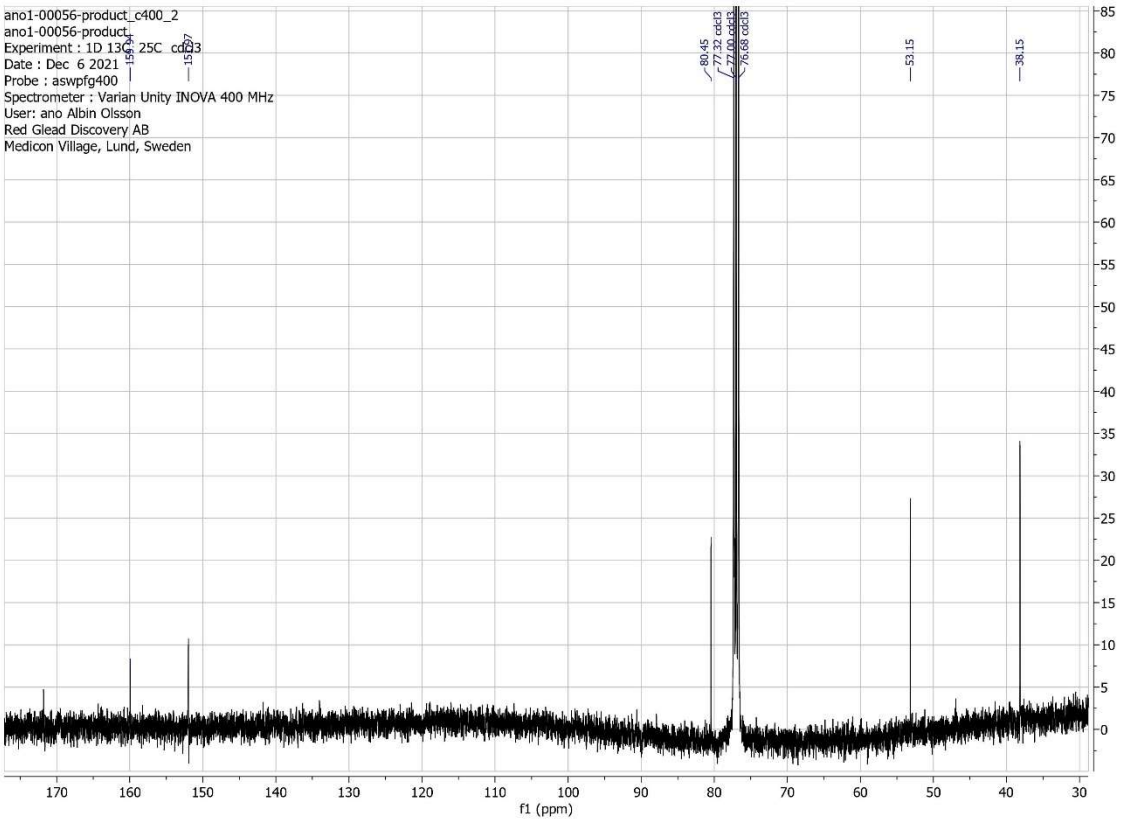

Figure A17. [13]C NMR-spectrum for compound **26**.

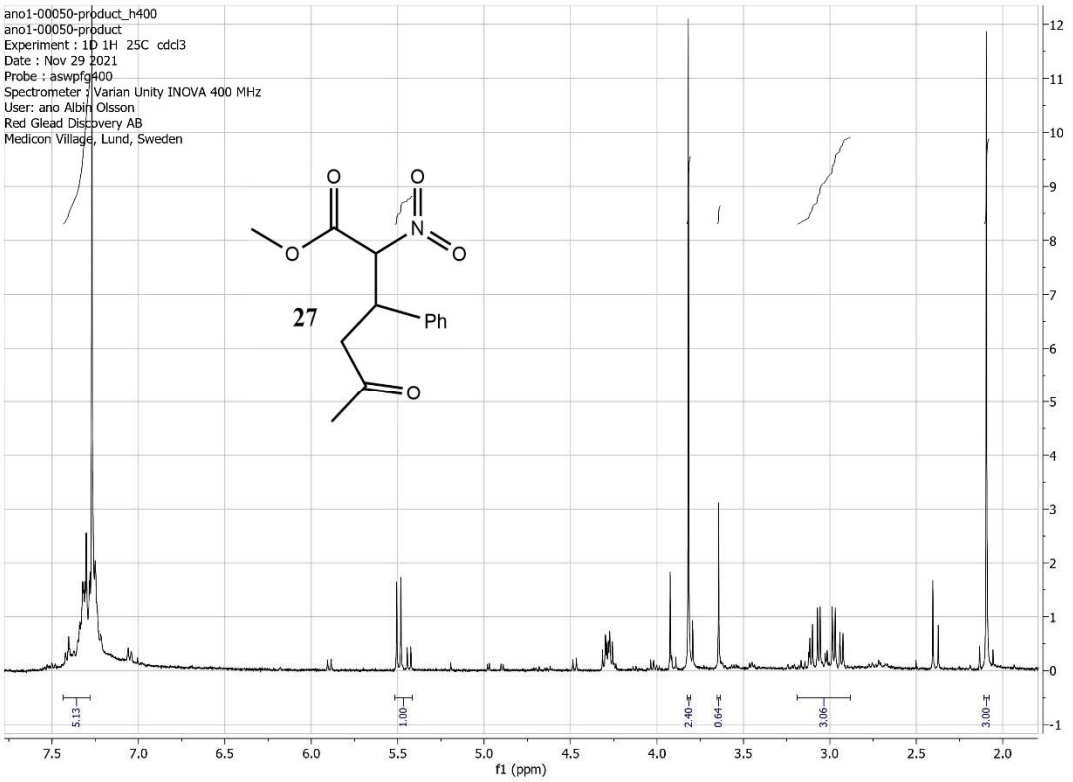

Figure A18. [1]H NMR-spectrum for compound **27**.

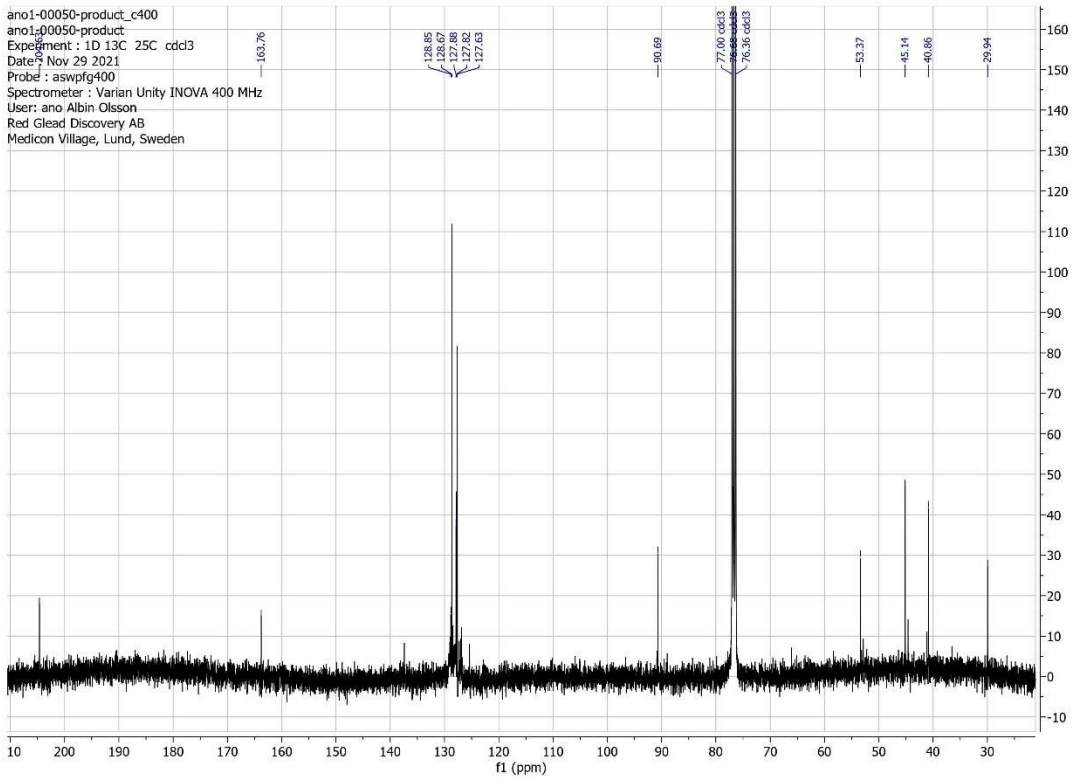

Figure A19. [13]C NMR-spectrum for compound **27**.

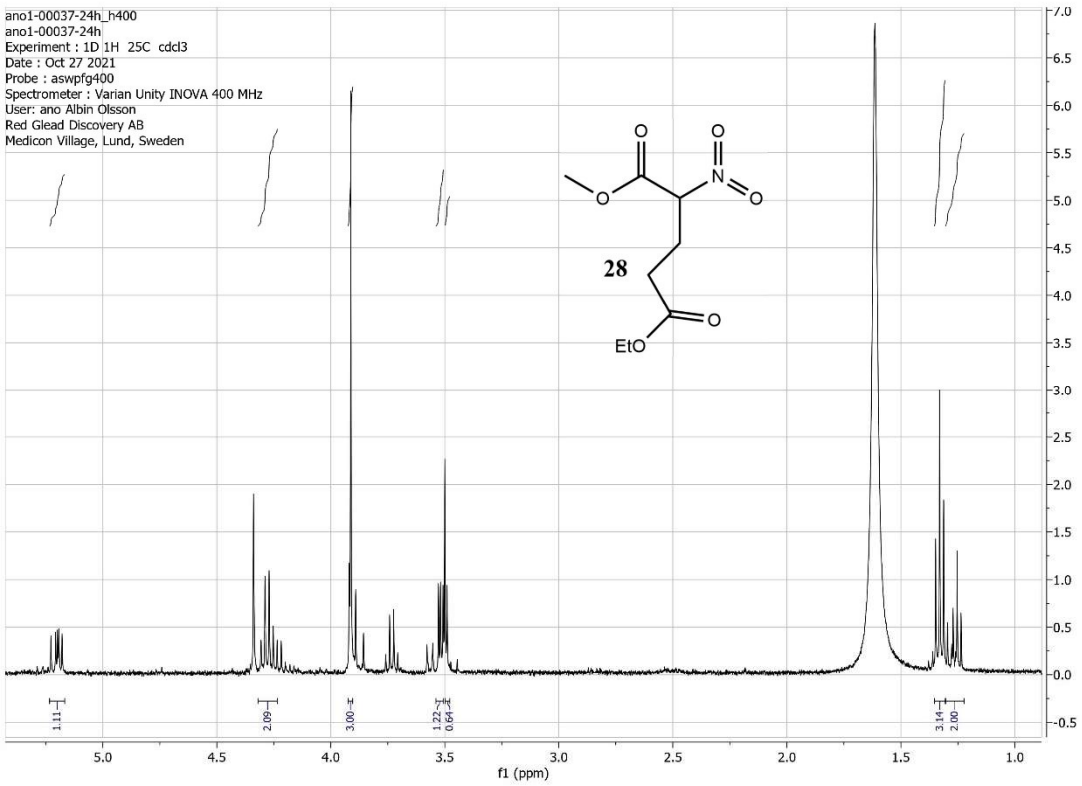

Figure A20. ^{1}H NMR-spectrum for compound **28**. Spectrum is measured on reaction mixture after 24 h.

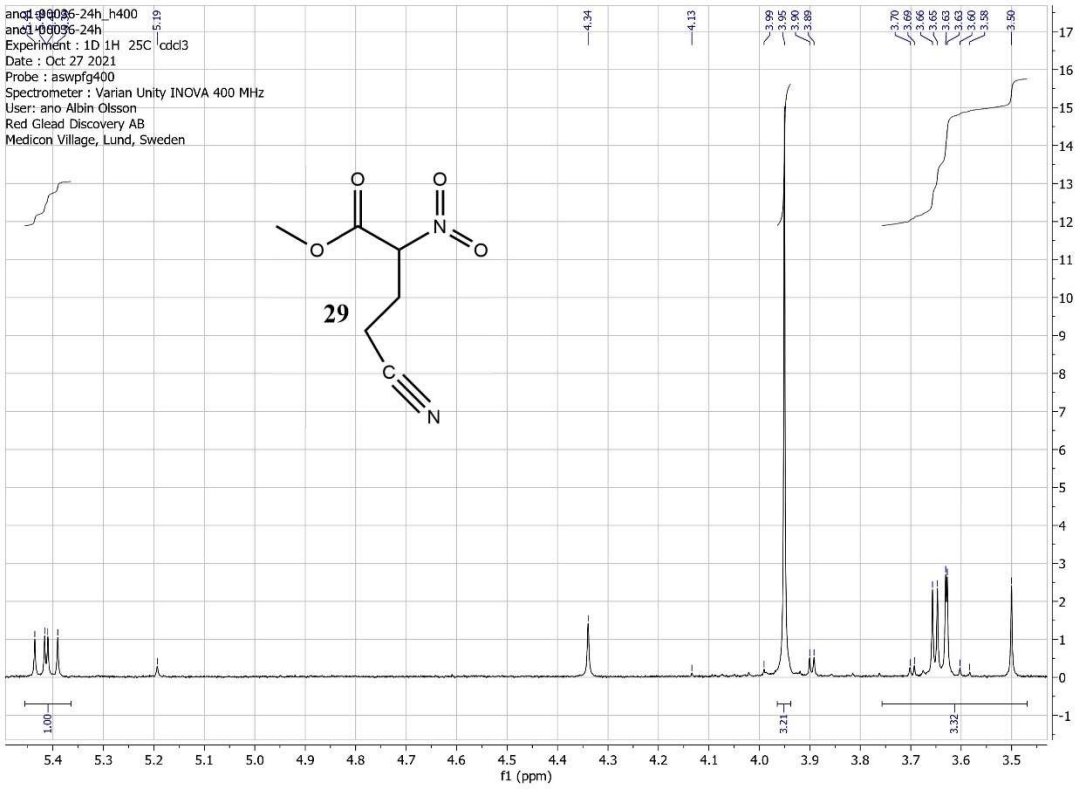

Figure A21. [1]H NMR-spectrum for compound **29**. Spectrum is measured on reaction mixture after 24 h.

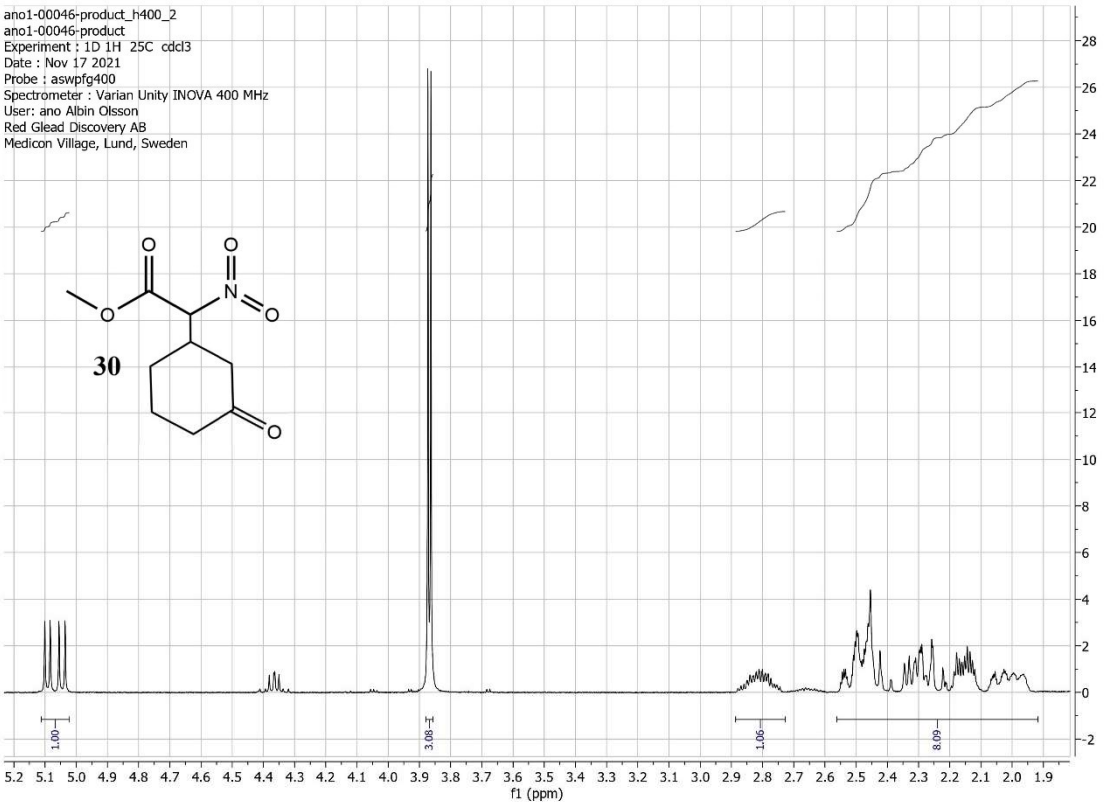

Figure A22. ^{1}H NMR-spectrum for compound **30**.

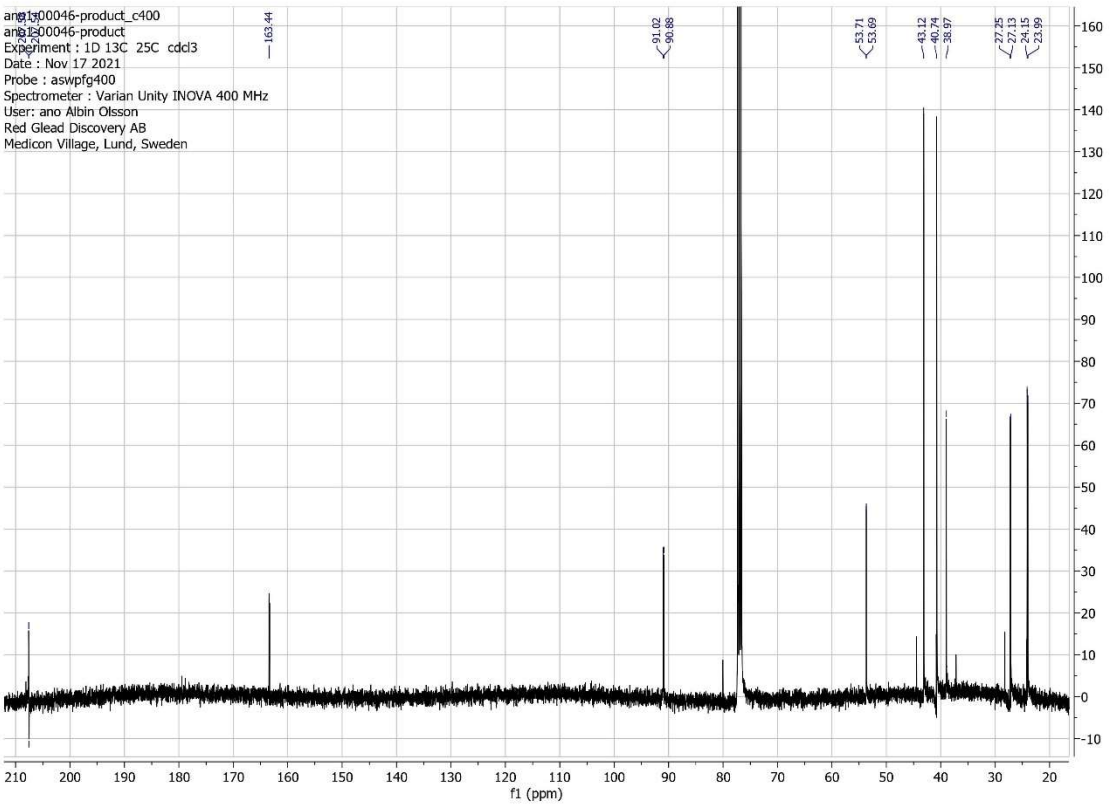

Figure A23. ^{13}C NMR-spectrum for compound **30**.

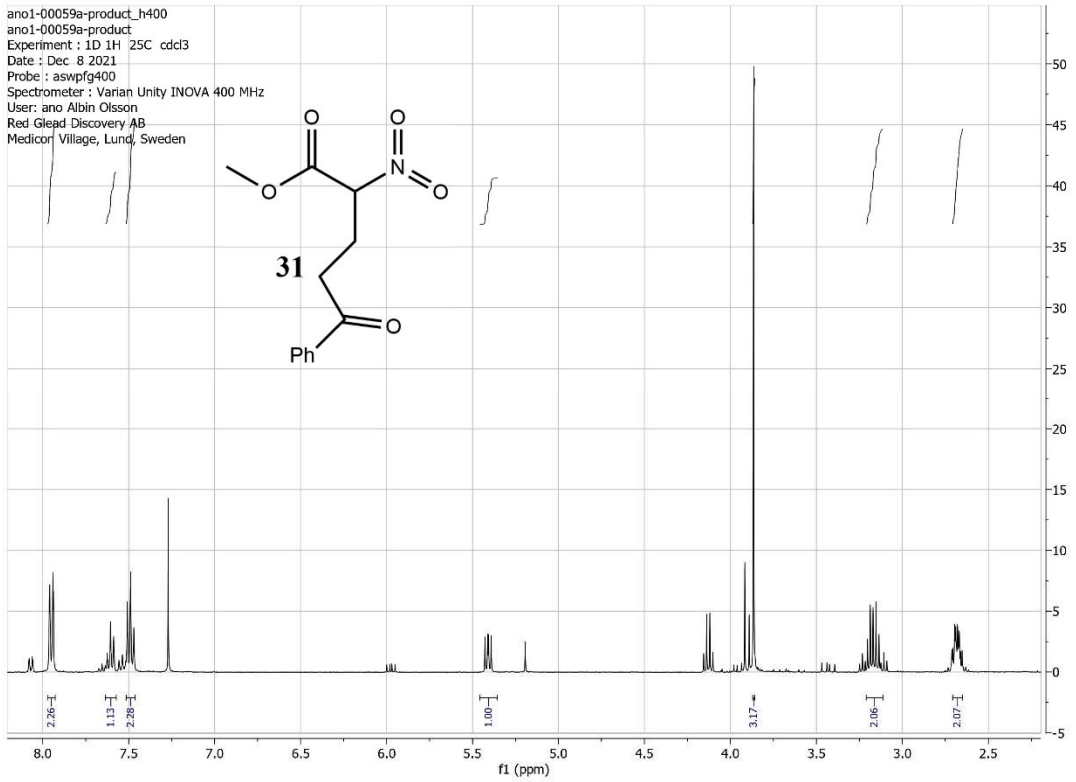

Figure A24. [1]H NMR-spectrum for compound **31**.

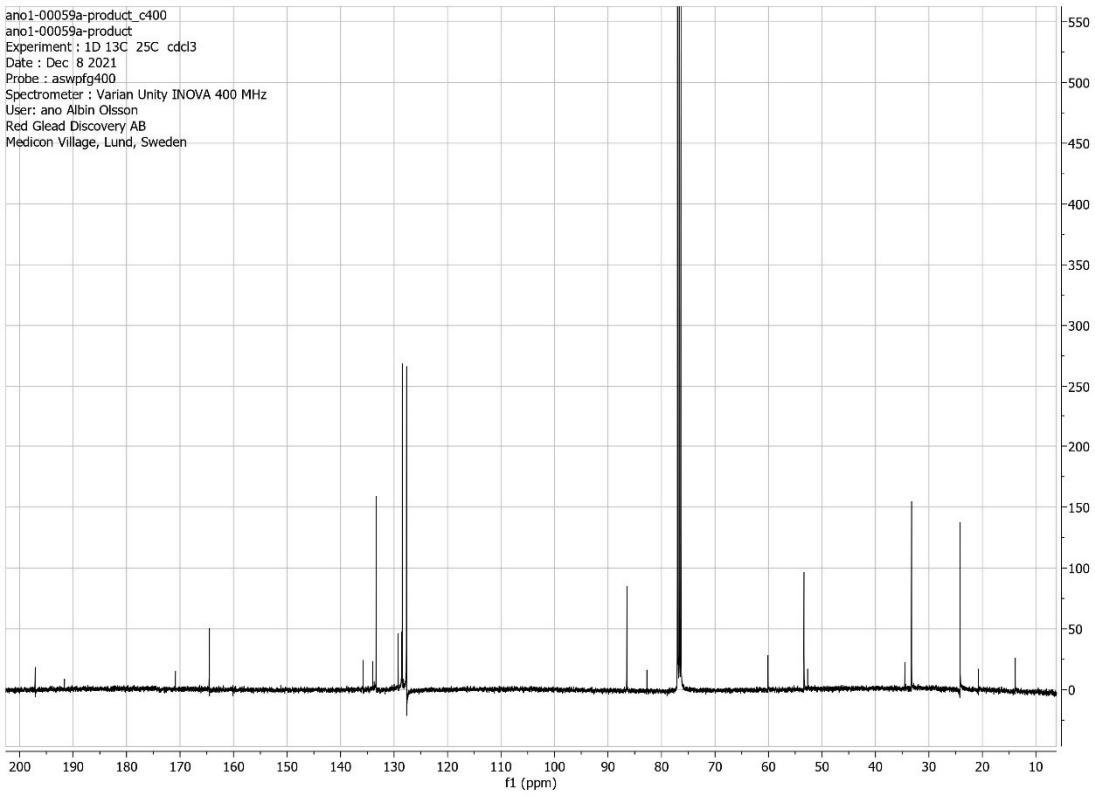

Figure A25. [13]C NMR-spectrum for compound **31**.

Figure A26. [1]H NMR-spectrum for compound **32**.

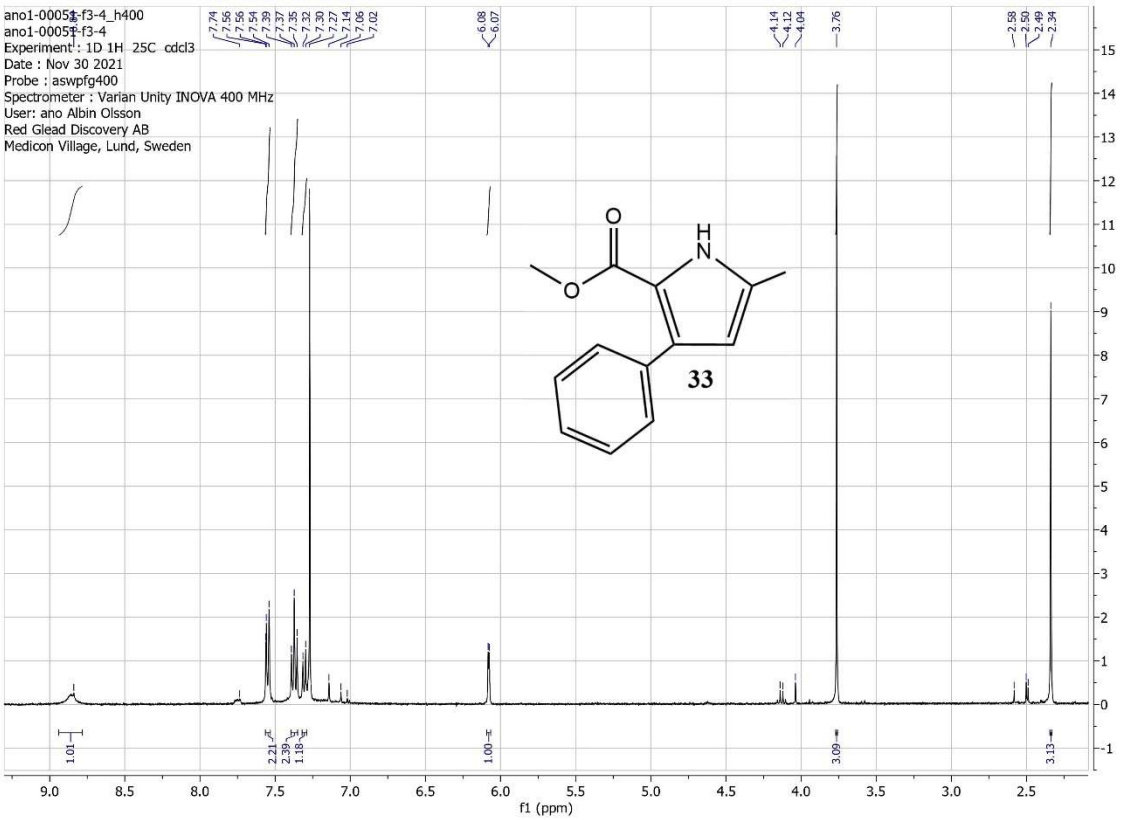

Figure A27. ^{1}H NMR-spectrum for compound **33**.

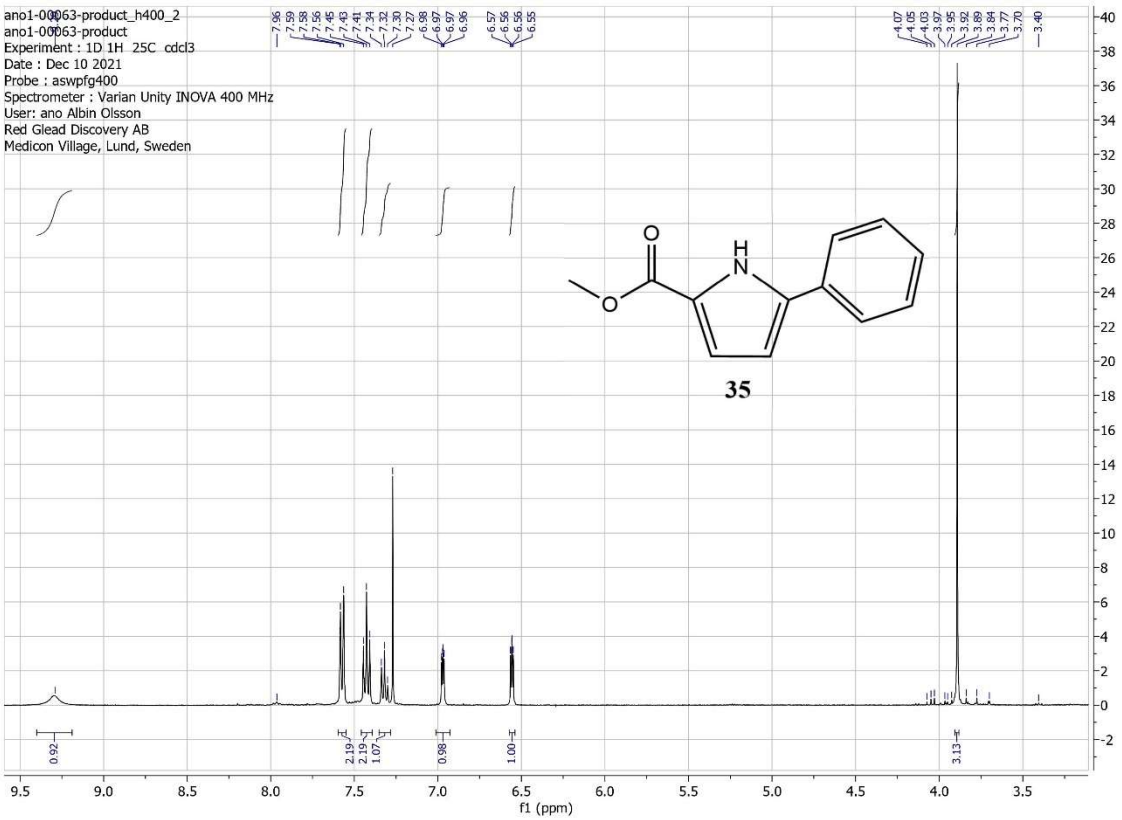

Figure A28. ^{1}H NMR-spectrum for compound **35**.

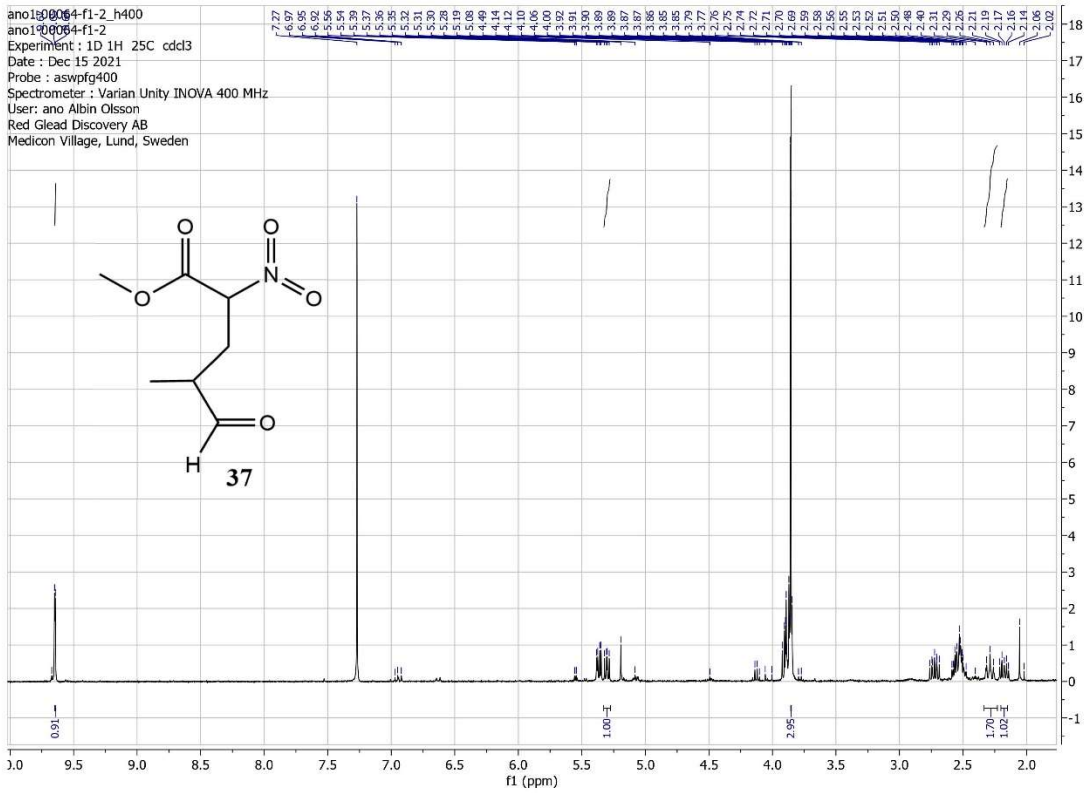

Figure A29. [1]H NMR-spectrum for compound **37**.

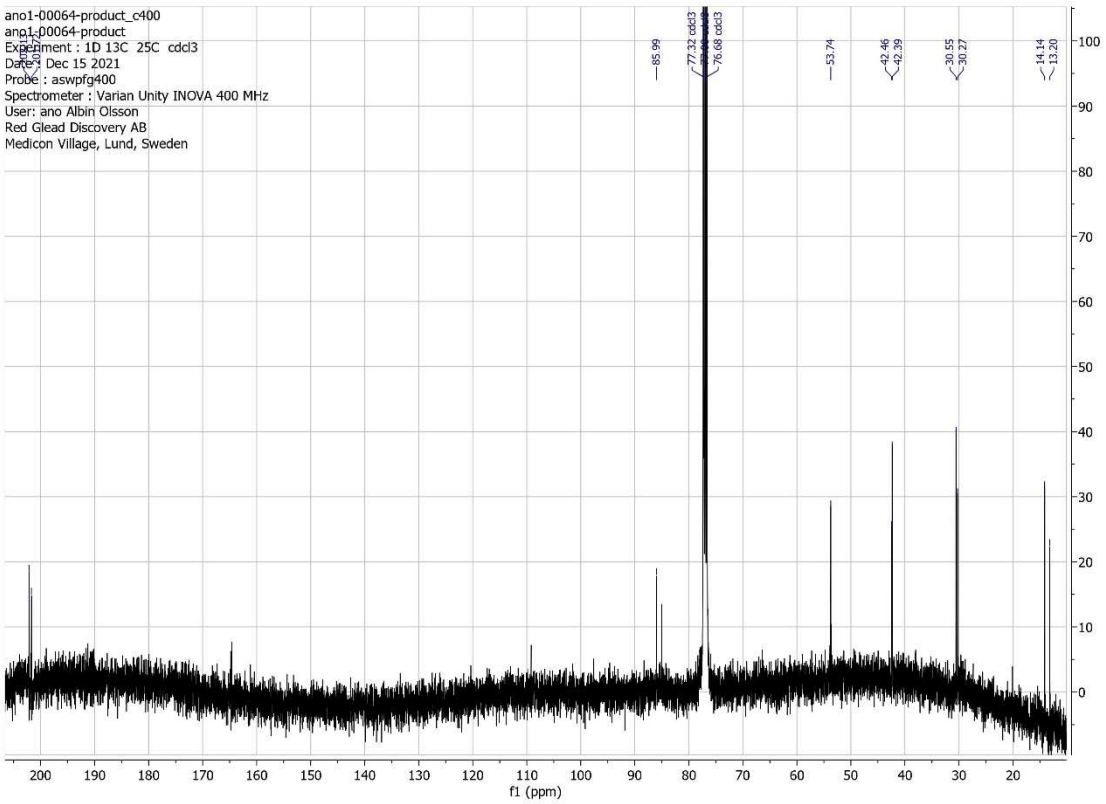

Figure A30. [13]C NMR-spectrum for compound **37**.

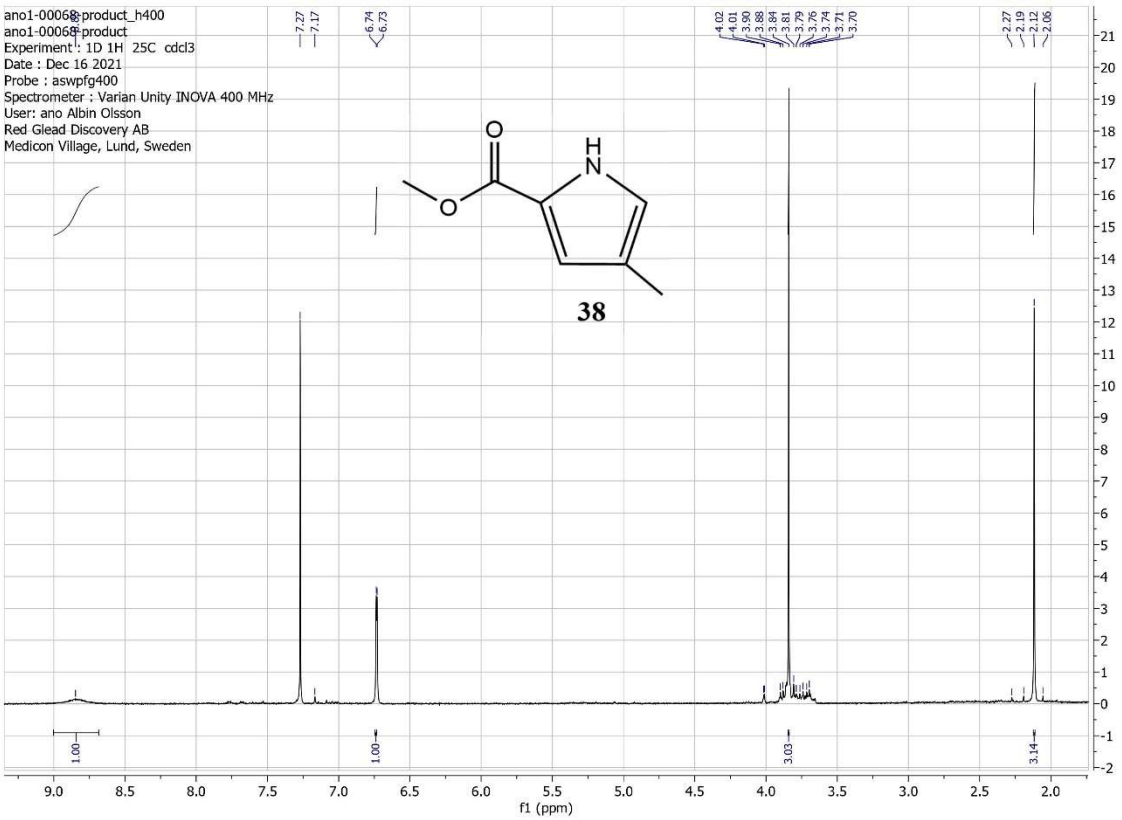

Figure A31. [1]H NMR-spectrum for compound **38**.

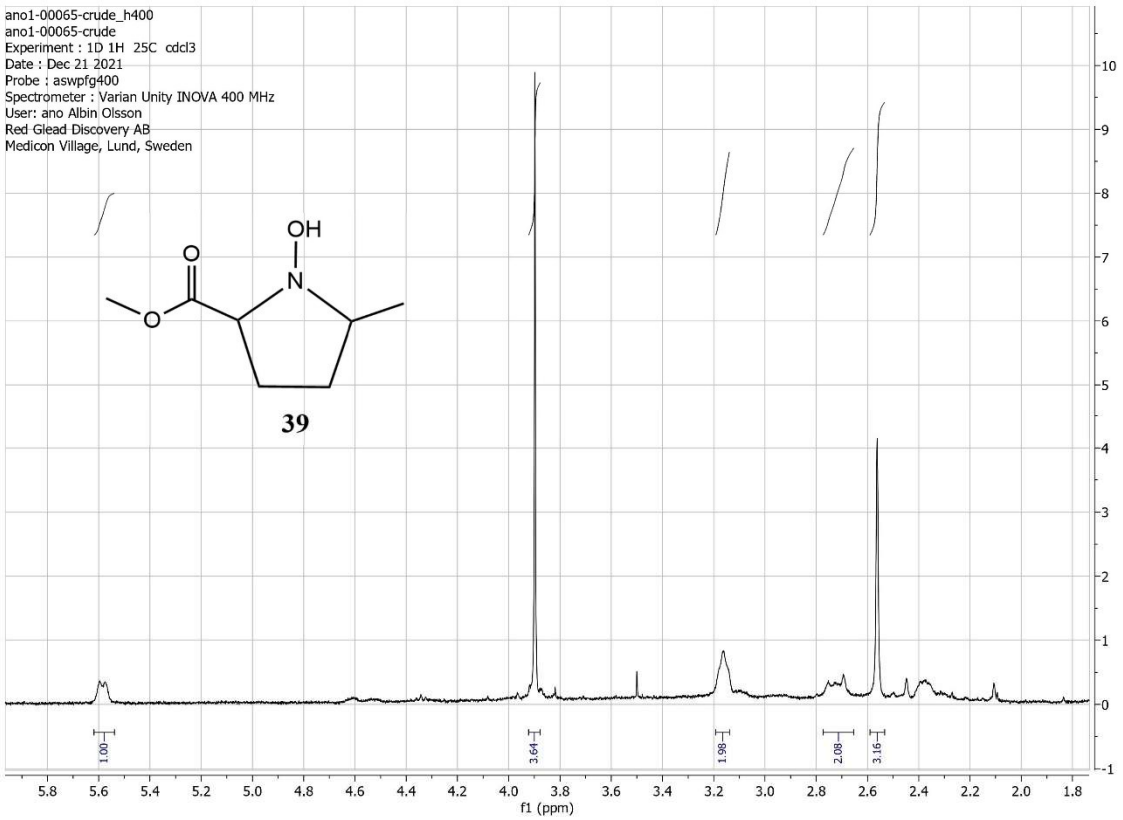

Figure A32. ^{1}H NMR-spectrum for compound **39**. Spectrum is measured on crude product.

A2. IR-spectra

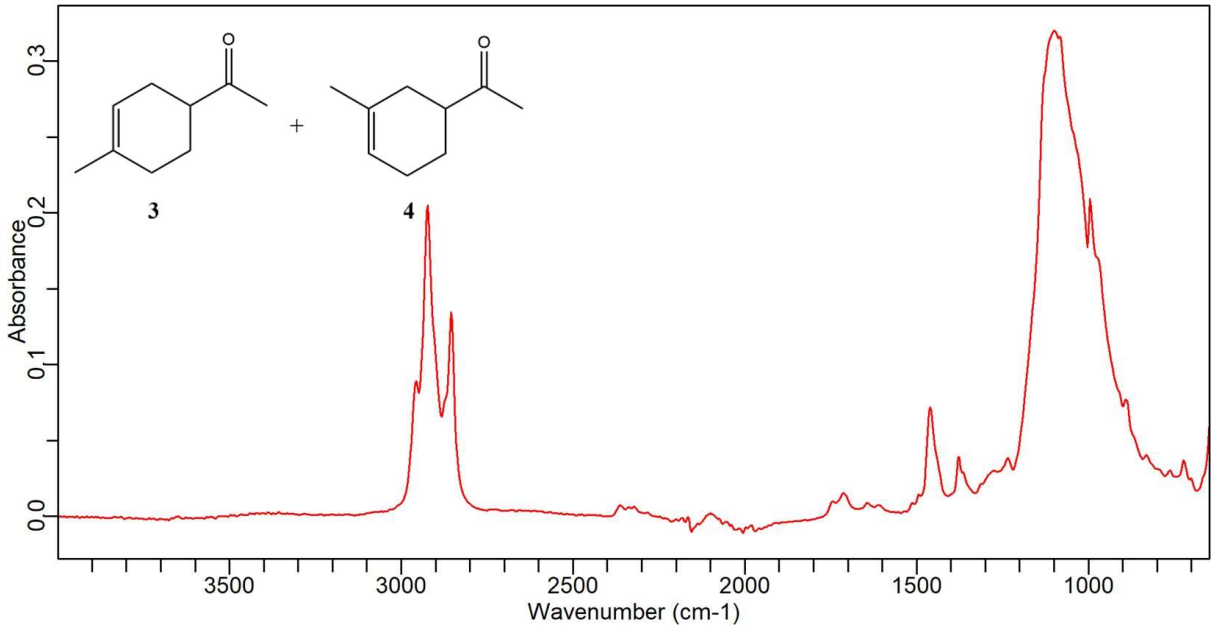

Figure A33. IR-spectrum for compound **3** and **4**.

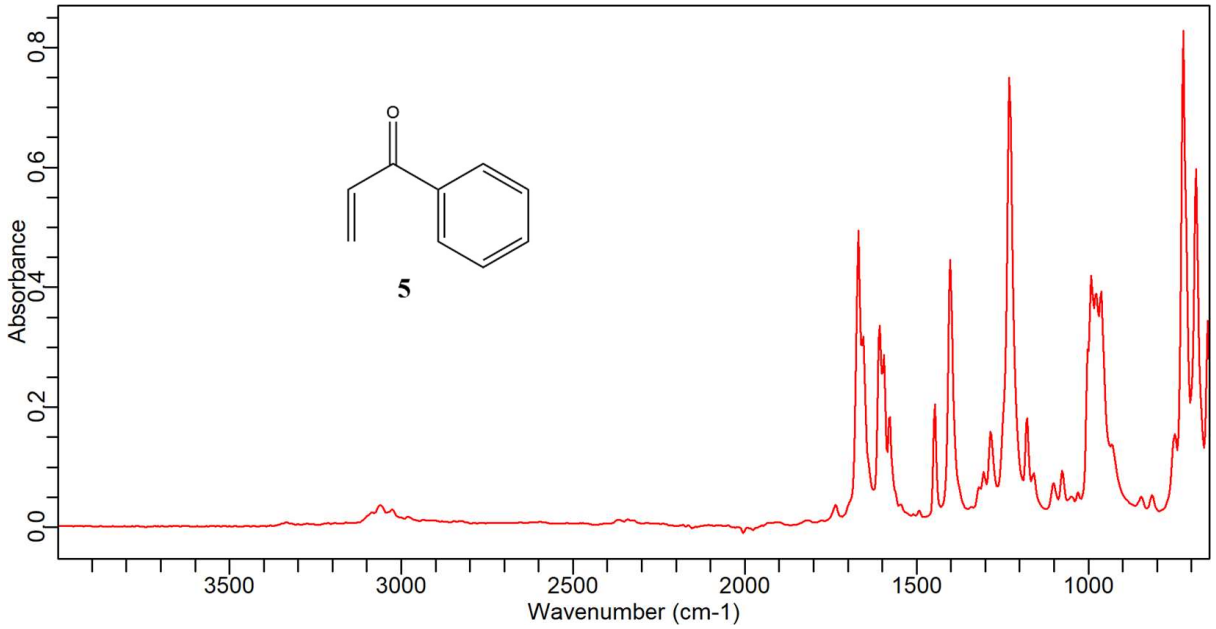

Figure A34. IR-spectrum for compound **5**.

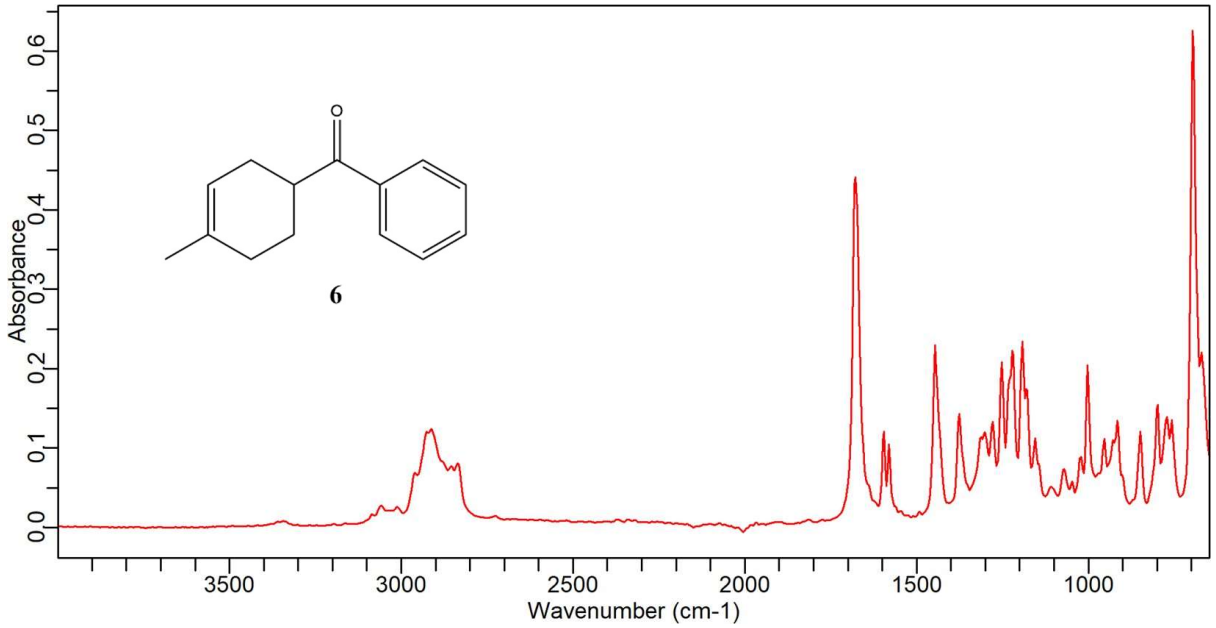

Figure A35. IR-spectrum for compound **6**.

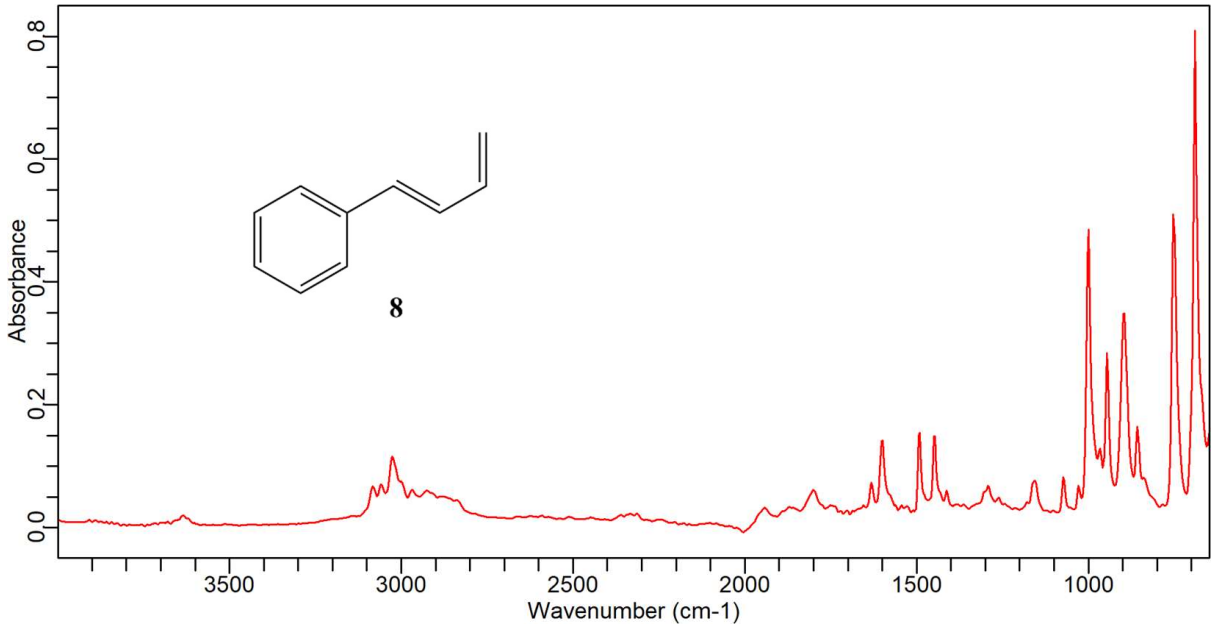

Figure A36. IR-spectrum for compound **8**.

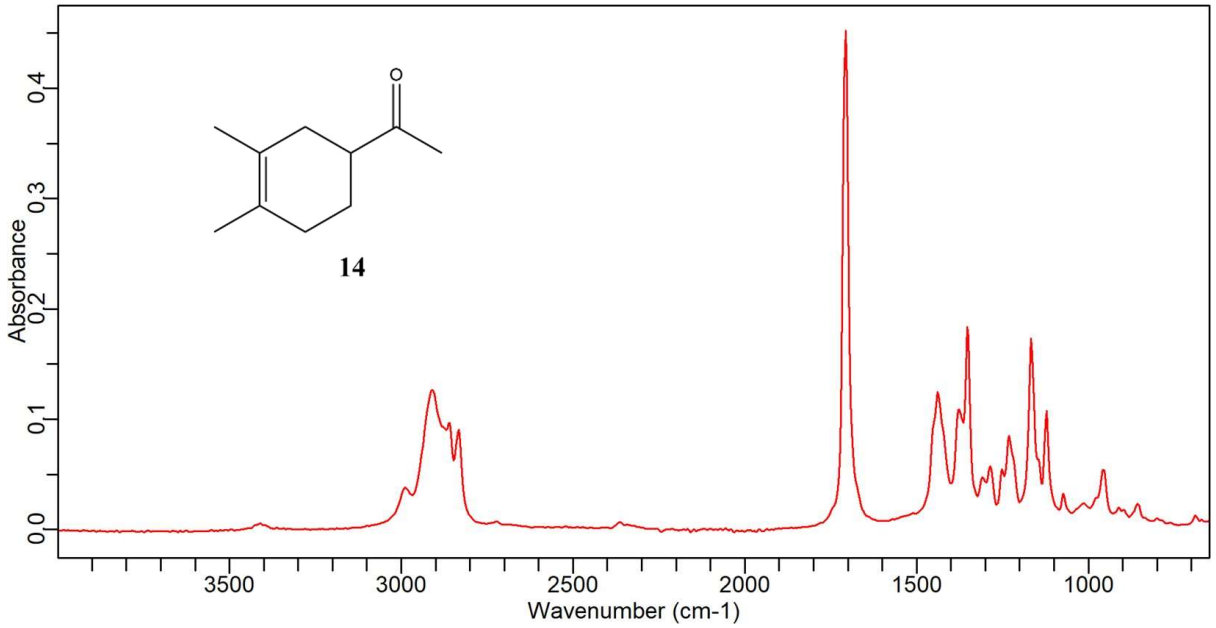

Figure A37. IR-spectrum for compound **14**.

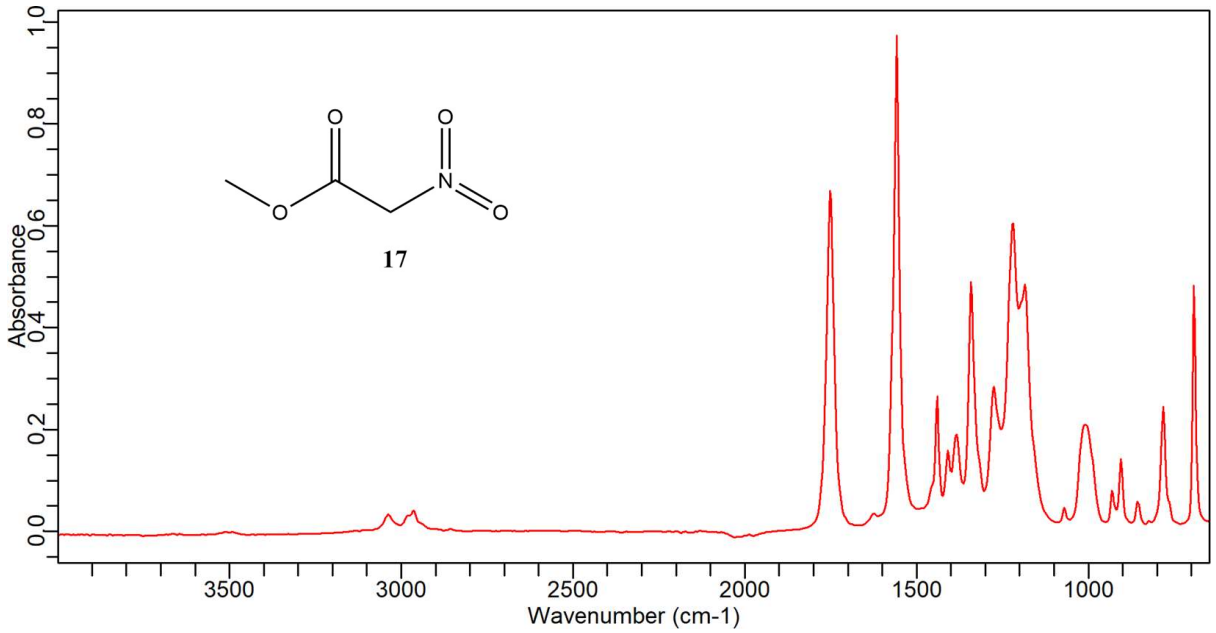

Figure A38. IR-spectrum for compound **17**.

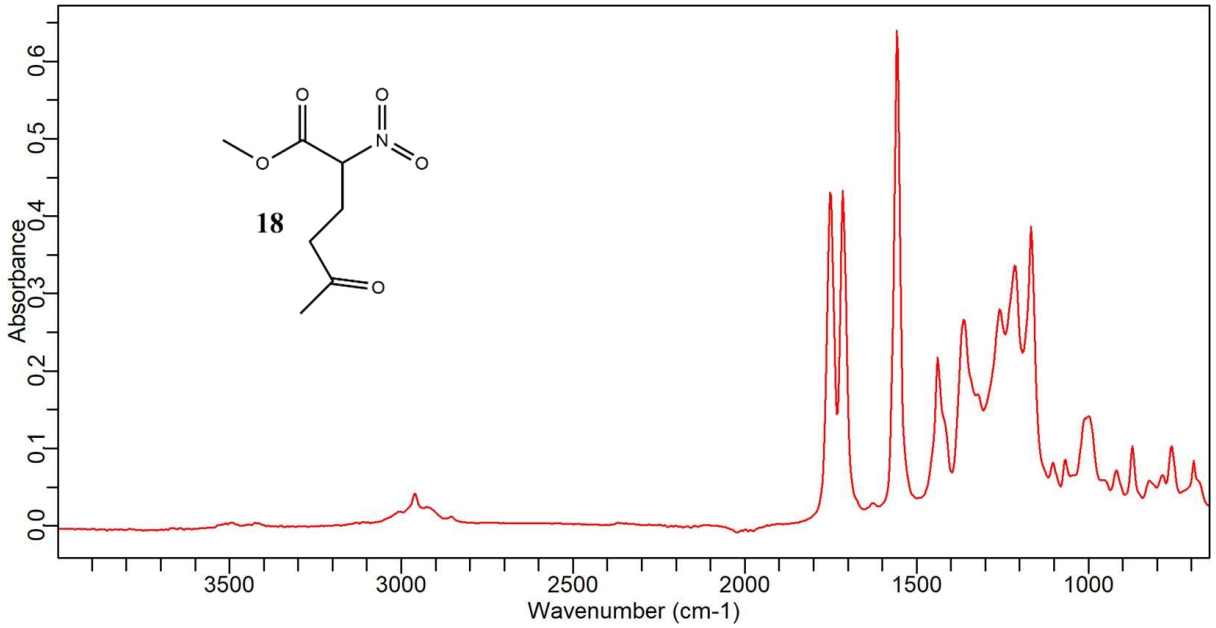

Figure A39. IR-spectrum for compound **18**.

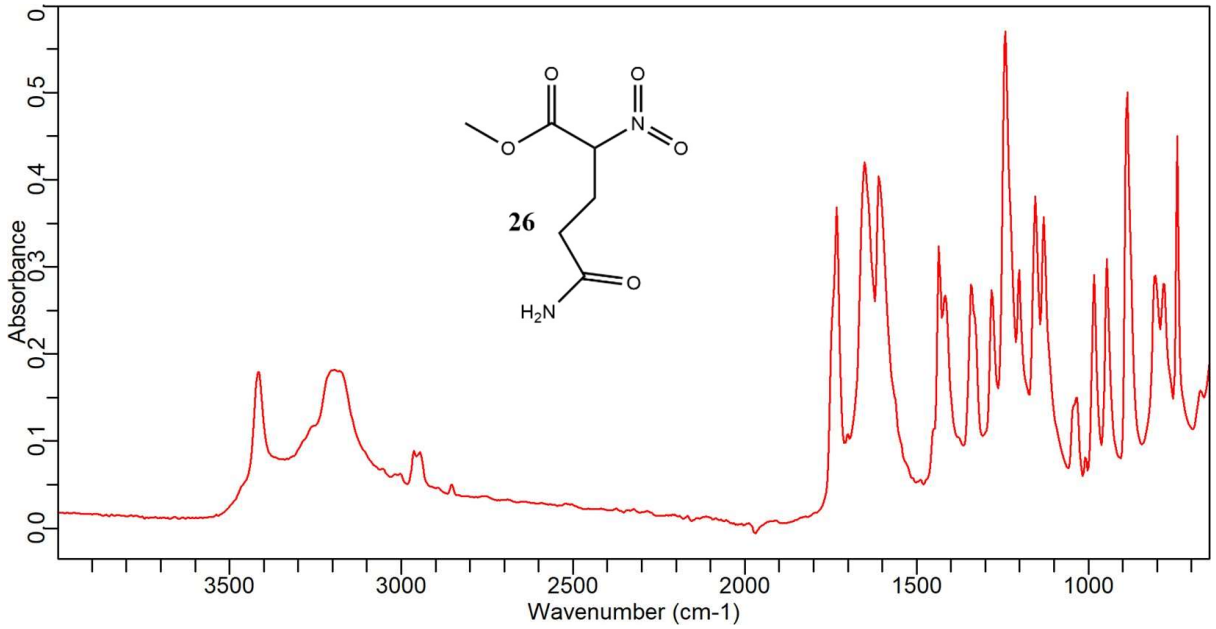

Figure A40. IR-spectrum for compound **26**.

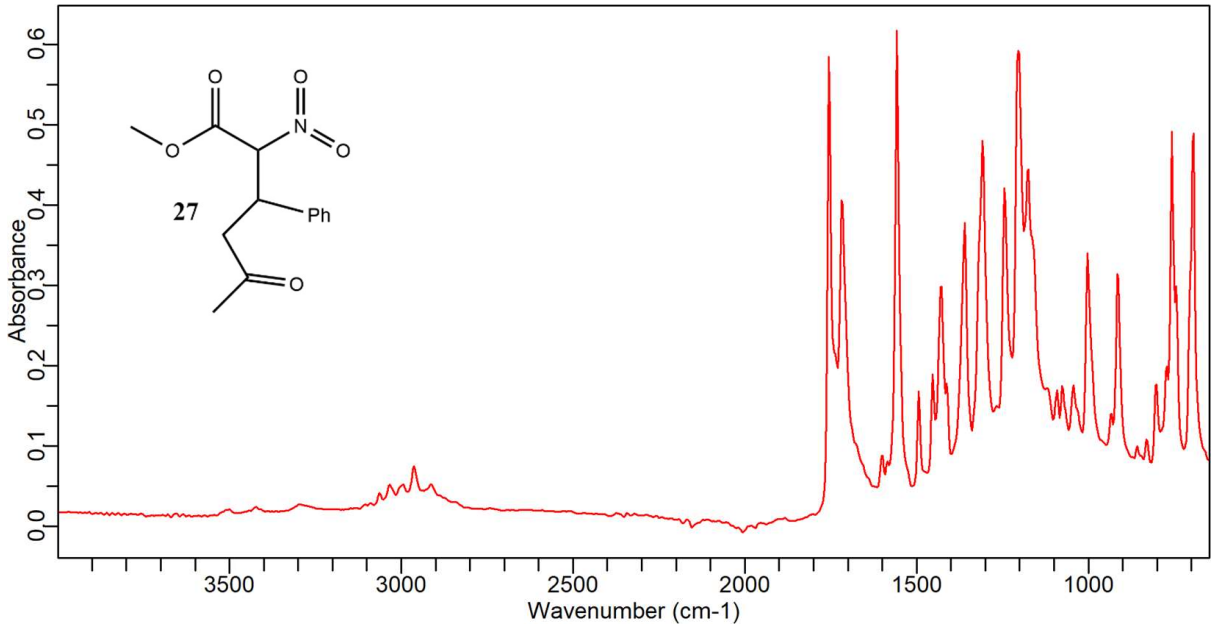

Figure A41. IR-spectrum for compound **27**.

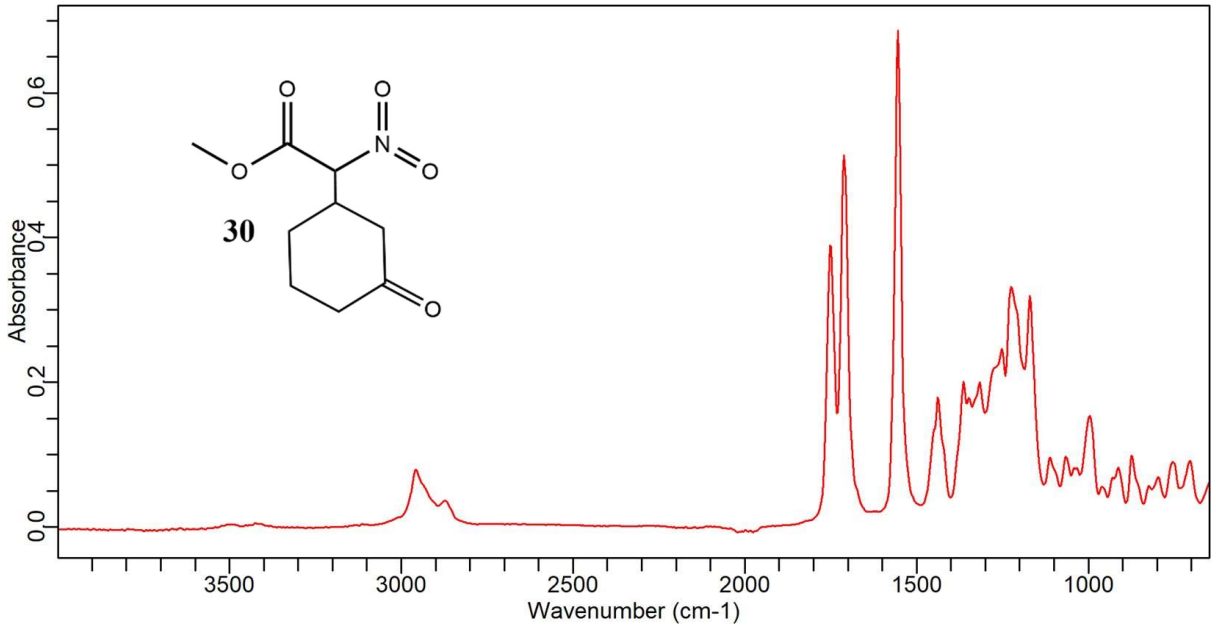

Figure A42. IR-spectrum for compound **30**.

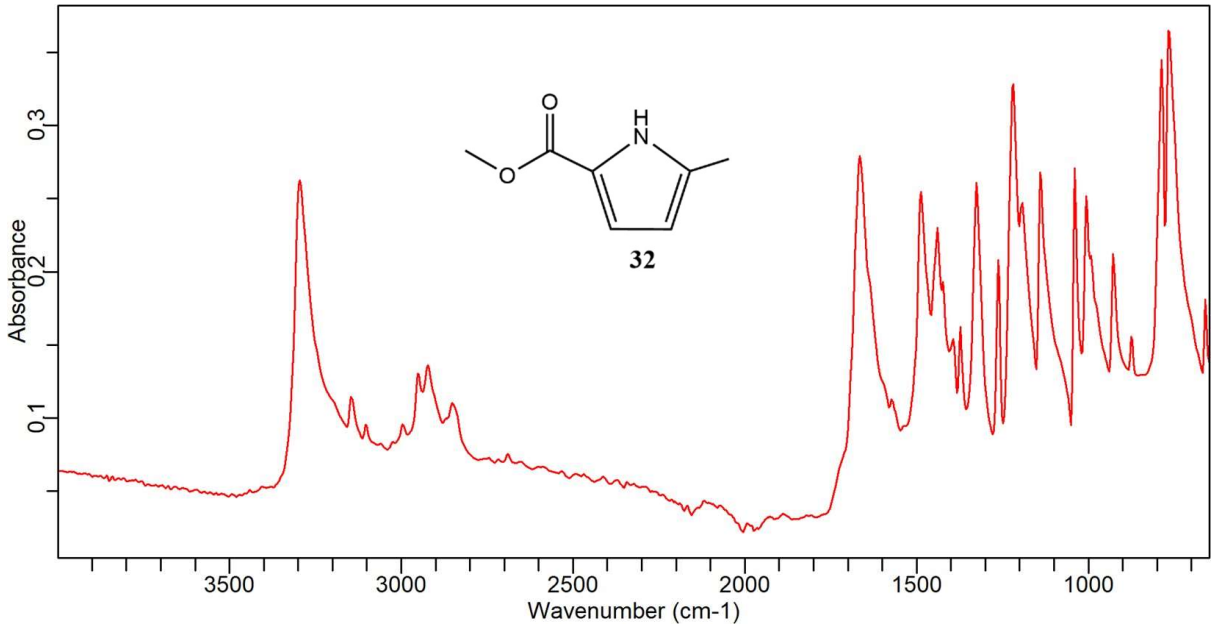

Figure A42. IR-spectrum for compound **32**.

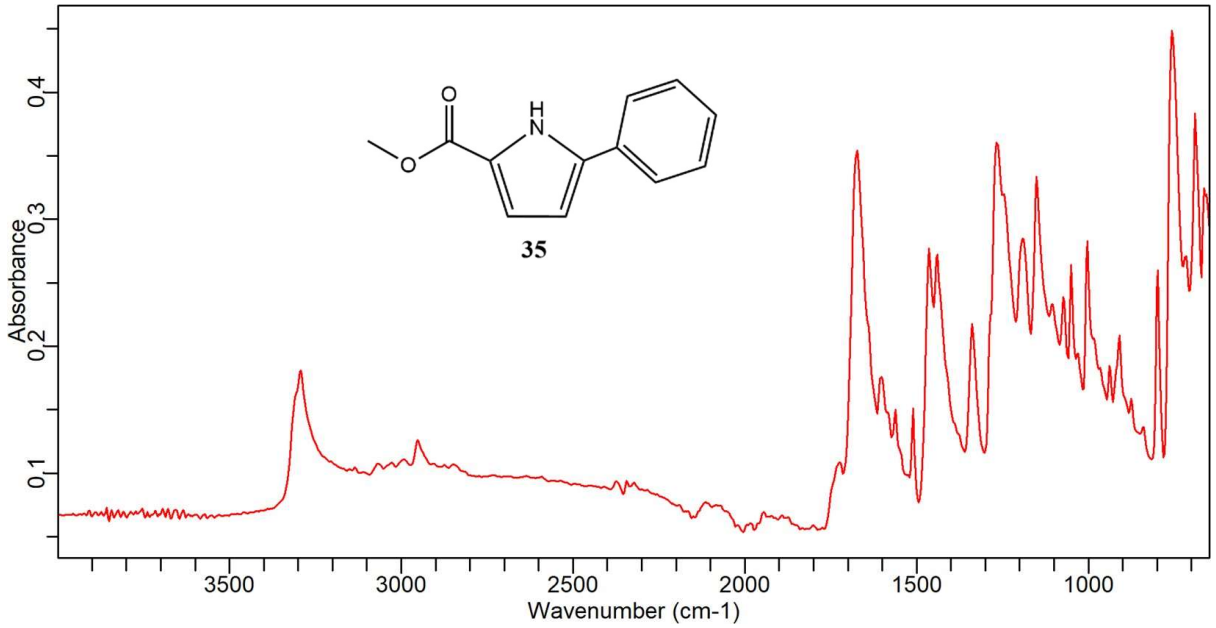

Figure A43. IR-spectrum for compound **35**.