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Grau de Química

Treball Final de Grau

Synthesis of *para*-substituted cinnamaldehydes as substrates in aminocatalyzed aldol reactions with ketones.

Síntesi de cinnamaldehids *para*-substituïts com a substrats en la reacció aldòlica aminocatalítica amb cetones.

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M’agradaria agrair aquest treball a la gent que hi ha estat durant el trajecte.

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Aquest treball també és vostre.

REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

Organocatalysis is a part of chemistry that seeks to synthesize compounds in a more efficient and sustainable way. It aligns closely with the principles of green chemistry, since it uses an organic catalyst instead of a metallic one. These organocatalysts are typically non toxic, more environmentally friendly, and do not require harsh reaction conditions.

The Sustainability Development Goals consist of 17 goals aimed at promoting sustainable development and ensuring a better future for all. These can be grouped into 5 large groups, called 5Ps: planet, people, peace, prosperity and partnership.

This work aligns with these ideas, particularly contributing to the areas of planet and prosperity. The main objective of the work is the synthesis of α,β-unsaturated aldehydes to be subsequently applied to organocatalyzed asymmetric aldol reactions. As mentioned previously, this methodology avoids the use of metal catalysts and allows the reactions to be carried out under milder conditions, which are less harmful to the environment.

Specifically, this work contributes to the following objectives:

- SDG #12: Responsible production and consumption, developing methodologies that have a lower environmental impact, minimizing by-products, and avoiding the use of heavy metals.
- SDG #9: Industry, innovation and infrastructure, advancing scientific knowledge in the field of organocatalysis, and contributing to more sustainable synthesis, such as those producing less waste and working under milder reaction conditions.

If the research carried out was to be further expanded in the future, it could have a significant impact on industrial processes in the pharmaceutical or fine chemical sectors. Safety in manufacturing processes would improve by eliminating the need to use harsh reaction conditions, in addition to helping to reduce the environmental footprint.

CONTENTS

1. SUMMARY

One of the most important challenges in organic chemistry is the stereoselective formation of C–C bonds using sustainable methods that follow the principles of Green Chemistry. Organocatalytic aldol reactions are especially useful in this regard since a new C–C bond is formed and up to two new stereocenters can be created using nontoxic small organic molecules as catalysts under mild reaction conditions.

The main aim of the project of our research group is to develop aminocatalytic aldol reactions of ketones to α,β-unsaturated aldehydes. In this work, *p*-nitrocinnamaldehyde and *p*-trifluoromethylcinnamaldehyde have been prepared via the Julia–Kocienski and Wittig reactions, to determine which is the best method to prepare them.

Although the Julia–Kocienski method led to the desired aldehyde as a single *E*-diastereomer with good yields, it needs harsh conditions and prior preparation of the sulfone. In contrast, the Wittig reaction is more straightforward and needs milder conditions, but it produces mixtures of *E* and *Z* isomers. To overcome this limitation, isomerization methods were explored. The use of iodine at rt with sunlight proved effective, enriching the *E* isomer in a practical and scalable way.

We have also studied the reactivity of the synthesized aldehydes in organocatalytic aldol reactions using L-proline tetrazole as catalyst. Acetone and cyclohexanone were tested as nucleophilic donors. In the acetone case, the desired aldol product was obtained with a 24% yield. Since the yield was relatively low, different hydrogen bond donors were tested as additives to improve the outcome of the reaction, but none of them led to product formation under the conditions tested.

Keywords: organocatalysis, aldol reaction, Julia–Kocienski reaction, Wittig reaction.

2. RESUM

Un dels reptes més importants de la química orgànica és la formació estereoselectiva d'enllaços C–C mitjançant mètodes sostenibles que segueixen els principis de la química verda. Les reaccions aldòliques organocatalítiques són especialment útils en aquest sentit, ja que es forma un nou enllaç C–C i es poden crear fins a dos nous estereocentres utilitzant molècules orgàniques senzilles i no tòxiques com a catalitzadors, en condicions de reacció suaus i respectuoses amb el medi ambient.

L'objectiu principal del projecte del grup de recerca és el desenvolupament de reaccions aldòliques aminocatalítiques de cetones a aldehids α,β-insaturats. En aquest treball, s'ha preparat *p*-nitrocinamaldehid i *p*-trifluorometilcinamaldehid mitjançant les reaccions de Julia–Kocienski i de Wittig, per determinar quin és el mètode més eficient per obtenir-los.

Tot i que la reacció de Julia–Kocienski va conduir a l'aldehid *E* desitjat com a únic diastereòmer amb bons rendiments, necessita condicions de reacció estrictes i la preparació prèvia de la sulfona. En canvi, la reacció de Wittig és més senzilla i necessita condicions més suaus, però produeix mescles d'isòmers *E i Z*. Per superar aquesta limitació, es van explorar mètodes d'isomerització. L'ús de iode a temperatura ambient amb llum solar va resultar eficaç, enriquint la mescla en l'isòmer *E* d'una manera pràctica i escalable.

També hem estudiat la reactivitat dels aldehids sintetitzats en reaccions aldòliques organocatalítiques utilitzant L-prolina tetrazole com a catalitzador i emprant acetona i ciclohexanona. En el cas de l'acetona, es va obtenir l'aldol desitjat amb un rendiment del 24%. Com que el rendiment era relativament baix, es van provar diferents additius per millorar el resultat de la reacció, però cap d'ells va conduir a la formació del producte esperat en les condicions provades.

Paraules clau: Organocatàlisi, reacció aldòlica, reacció de Julia–Kocienski, reacció de Wittig.

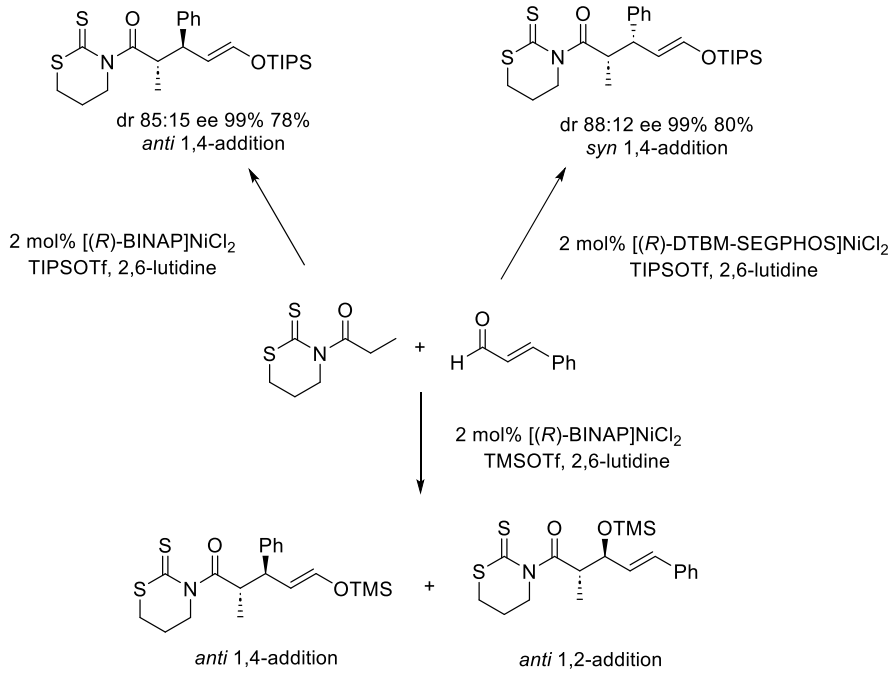
3. INTRODUCTION

The efficient synthesis of most organic molecules, whether pharmaceutical, bioactive or functional materials, relies on the formation of carbon-carbon bonds. For this reason, the development of new methods for the formation of such bonds represents one of the most important goals in organic synthesis. Atom economy, a concept promoted by Barry M. Trost,[1] highlights the importance of designing chemical reactions that are more efficient and environmentally sustainable. Minimizing the use of excess reagents, reducing waste formation, and avoiding multistep synthetic routes are central to this approach. Ideally, such transformations should be direct, catalytic and residue-free, maximizing atom economy by ensuring that all atoms from starting materials are incorporated into the final product.

Traditionally, C–C bonds have been constructed using strong nucleophiles such as organometallic reagents or metal enolates, often employed in excess, which frequently results in the formation of undesirable side products. This generation of waste is precisely what the principle of atom economy seeks to avoid. Also, inert atmospheres, anhydrous conditions and low temperatures are often needed, which limits their applicability. In particular, enolates are formed by treating carbonyl compounds with strong bases such as LDA. Enolates are strong nucleophiles and can react with electrophiles to form a C–C bond. Their application often requires harsh conditions, shows poor functional group tolerance and relies on stoichiometric amounts of metal-based reagents,[2] characteristics far from the principles of atom economy.

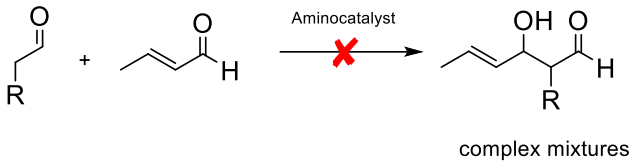
An important current scientific challenge lies in developing mild and efficient synthetic methods that minimize waste formation. In line with this objective, the present work focuses on the synthesis and characterization of α,β-unsaturated aldehydes, that will serve as starting materials for their organocatalytic aldol reaction with ketones.

Research in our laboratory is focused on the development of catalytic methods for C–C bond formation using chiral Ni(II) enolates derived from thioimides. These enolates react efficiently in SN_1-type alkylation reactions and in aldol reactions. When the aldol reaction was first attempted using cinnamaldehyde, as a model α,β-unsaturated aldehyde, a mixture of 1,2- and 1,4-addition products was obtained. Although optimal conditions were identified for the formation of the *syn*-1,4 and *anti*-1,4 adducts, no conditions were found for the predominant formation of the 1,2-addition products (**Scheme 1**).



Scheme 1. Previous results of the group in the aldol addition to cinnamaldehyde using chiral Ni(II) enolates.

Because of that, we changed the focus to organocatalytic aldol reactions, that are environmentally friendly and an attractive alternative. As is well known, enamines from aldehydes can act as nucleophiles in aldol reactions, Mannich reactions and Michael reactions, among others. However, cross-aldol reactions with α,β-unsaturated aldehydes have been less studied. Research from our laboratory shows that low yields of the 1,2-products are obtained. The reaction is complicated by autocondensation of the donor aldehyde (**Scheme 2**).



Scheme 2. Aminocatalytic cross-aldol reaction with cinnamaldehydes.

As a next step, we considered the possibility of using ketones in the aldol reaction, to prevent autocondensation. Ketones are less electrophilic than aldehydes, and that makes their corresponding enamines more appropriate for selective nucleophilic attack on the α,β-unsaturated aldehydes.

3.1. ORGANOCATALYSIS

A catalyst works by decreasing the activation energy of a process, permitting the reaction to occur under milder conditions. It interacts with the reactants and generates intermediates that react giving the products and regenerating the catalyst, facilitating the course of the reaction without affecting its equilibrium position.[3]

In organocatalysis, a small organic molecule is used as a catalyst. This type of catalysis has gained a lot of importance since it follows the atom economy values. Organocatalysts are less toxic, less polluting and usually cheaper than organometallic catalysts. Furthermore, these catalysts don't require the use of anhydrous conditions or inert atmospheres, because they are oxygen and water stable.[4] Organocatalysts are usually compatible with a variety of functional groups, so this avoids the need of protection groups, lowering the final number of steps in the global reaction.[5]

The low catalyst loading (often only a few mol%) combined with its operational simplicity, minimal generation of toxic metal waste and broad substrate compatibility makes organocatalysis a powerful and sustainable method. Consequently, it has become a key tool in the development of environmentally synthetic routes, in line with green chemistry principles.

3.2. ENANTIOSELECTIVITY

An enantiomer is one of the two stereoisomers that are non-superimposable mirror images of each other. While enantiomers share identical physical and chemical properties in achiral environments, they can exhibit vastly different biological activities. Many biomolecules in living organisms are chiral, and there is often a marked difference in the effect of each enantiomer: one may be therapeutic, while the other may be inactive or even toxic.

Enantioselectivity, the preferential formation of one enantiomer over the other, has become a major objective in asymmetric synthesis. Achieving high enantioselectivity requires the catalyst to differentiate between the two possible stereoisomeric transition states and selectively favor one over the other.

In metal-catalyzed asymmetric transformations, the metal center usually plays an organizational role to promote stereocontrol. In contrast, organocatalysis relies on molecular interactions that can be classified as passive -including Van der Waals forces, electrostatic effects and hydrophobic interactions- or dynamic, which involve interactions between catalysts and substrates at the reaction centers. Hydrogen bonding plays a particularly critical role in organocatalytic systems. It helps to stabilize reactive intermediates, influence conformational preferences and helps to define a transition state that favors the formations of one specific enantiomer.[6]

3.3. L-PROLINE TETRAZOLE AS ORGANOCATALYST

As previously mentioned, the preparation of enantiomerically pure compounds is of great scientific interest in organic synthesis. Asymmetric catalysis can provide enantiomerically pure products using only substoichiometric amounts of a chiral compound. Although organic molecules had been previously used as catalysts in enzymatic contexts, the concept of using small, chiral organic molecules as standalone catalysts emerged more recently.

These molecules often function as artificial enzymes, and in some cases, they outperform chiral metal complexes in stereoselective reactions. This is due to mechanistic similarities with enzymes such as aldolases and decarboxylases, which catalyze similar bond-forming reactions in biological systems.[7]

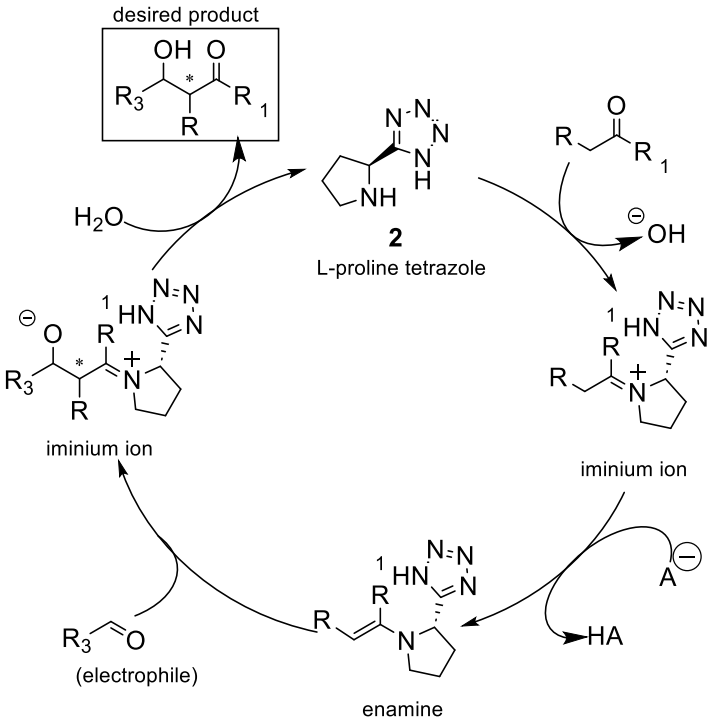
In both enzymatic and organocatalytic systems, a very important part is the formation of an enamine intermediate. During this process, a secondary amine (either coming from the enzyme or the catalyst) reacts reversibly with a carbonyl compound, forming a nucleophilic enamine. Next, the enamine attacks the electrophile, resulting in the formation of a new C–C bond formation.

Among small-molecule organocatalysts, α-amino acids, with proline (**1**), being a paradigmatic example, are among the most widely used catalysts due to their excellent physicochemical and catalytic properties. However, although proline is readily available and inexpensive, it has certain limitations. For example, it is poorly soluble in many non-polar o moderately polar organic solvents and the ee values obtained in some reactions are not excellent. To address this limitation, structural modifications, especially at the carboxyl group, have been introduced. The majority of such studies focus on proline derivatives, many of which maintain simple structures.[7]

1 **2**

Figure 1. Structure of proline and proline tetrazole **2.**

For this work, (*S*)-5-(–)-(2-Pyrrolidinyl)-1*H*-tetrazole (proline tetrazole, **2**) has been selected as catalyst to promote the asymmetric aldol addition of ketone to α,β-unsaturated aldehydes. In this derivative of L-proline (**1**) the carboxylic acid is replaced by a tetrazole ring. This confers **2** with several advantages that make it particularly well-studied to our goals.[8] Importantly, the tetrazole group has been proven to increase the solubility of the catalyst across a wider array of organic solvents, including less polar ones, while retaining the ability to activate ketones through enamine formation. Moreover, the tetrazole ring can participate in hydrogen bonding during the transition state. These interactions are believed to stabilize the transition state complex, enhance stereoselectivity, and correctly orient the electrophile for nucleophilic attack. This dual functionality, enamine activation of the nucleophile and hydrogen-bond-mediated stabilization of the transition state, is a hallmark of modern bifunctional organocatalysts.[9] In addition, the catalyst demonstrates good efficiency at minimal loading, needing a few mol% to reach considerable yields and stereocontrol, which aligns with the green chemistry principles.



Scheme 3. Mechanism for the proline tetrazole-catalyzed aldol reaction.

As shown in **Scheme 3**, the proposed catalytic cycle for this transformation begins with enamine formation between the secondary amine of proline and the ketone. This enamine subsequently reacts with aldehyde, which is activated by the hydrogen-bond donor capability of the tetrazole group (**Figure 2**). Final hydrolysis of the resulting iminium intermediate regenerates the catalyst and yields the aldol product. Thus, L-proline tetrazole plays a dual role by activating both the nucleophile and the electrophile, facilitating the formation of the C–C bond with high enantioselectivity.[8]

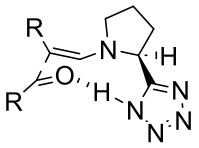


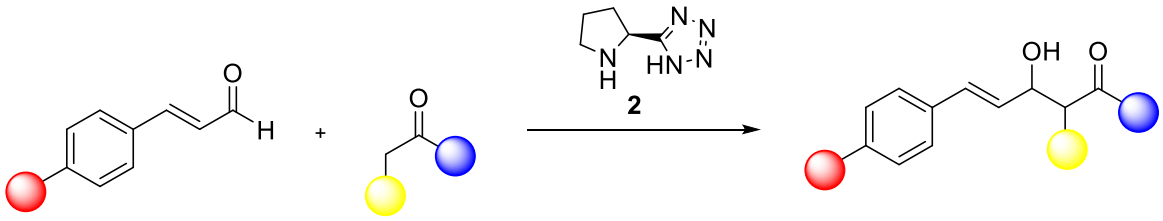
Figure 2. Proposed hydrogen bonded transition state in the aldol reaction catalyzed by proline tetrazole **2.**

4. OBJECTIVES

The main objective of this work is the preparation of several α,β-unsaturated aldehydes using different methods, such as the Wittig and Julia–Kocienski reactions. Additionally, the aldehydes prepared will be used in organocatalytic aldol reactions of ketones as aldol donors (**Scheme 4**).

4.1. SPECIFIC OBJECTIVES

- To prepare *p*-nitrocinnamaldehyde via both the Julia–Kocienski and the Wittig reactions, and to compare the yield and diastereoselctivity obtained from each method.
- To prepare *p*-trifluoromethylcinnamaldehyde via the Wittig reaction.
- To prepare 2,2-dimethyl-1,3-dioxan-5-one.
- To study the aminocatalyzed aldol reaction of different ketones with *p*-nitrocinnamaldehyde.

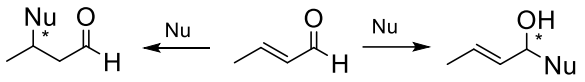


Scheme 4. Organocatalytic reactions with ketones.

5. RESULTS AND DISCUSSION

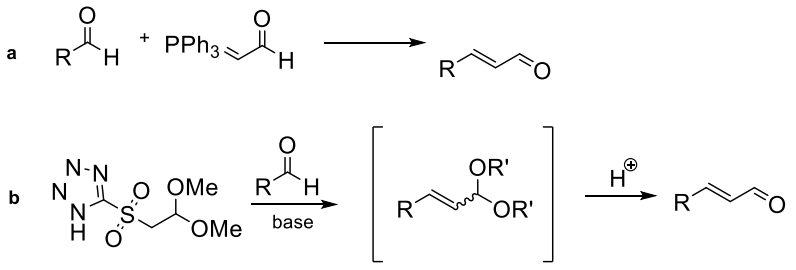
5.1. SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

α,β-Unsaturated aldehydes are valuable synthetic intermediates in organic chemistry as they can react with nucleophiles via attack at the carbonyl carbon (1,2-addition) or to the β-carbon (1,4-addition) (**Scheme 5**). Michael addition is thermodynamically favoured and preferred for weak nucleophiles.[10] The direct addition to the carbonyl carbon is favoured for strong nucleophiles.



Scheme 5. 1,2 and 1,4 nucleophilic additions to an α,β-unsaturated aldehyde.

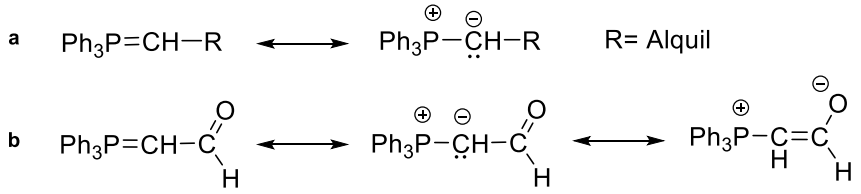
Different methods have been developed for the synthesis of such compounds. Among them, the Wittig reaction (**a in Scheme 6**) and the Julia–Kocienski reaction (**b in Scheme 6**) are routinely used. Both methods offer distinctive advantages depending on the type of substrate and the reaction conditions required. For this reason, both types of reaction have been applied in this work to the synthesis of cinnamaldehydes and their viability and results compared in terms of yield, stereochemical selectivity and purity of the product.



Scheme 6. Preparation of α,β-unsaturated aldehydes using the Wittig (a) and Julia–Kocienski (b) reactions.

Cinnamaldehydes with different substituents on the aromatic ring were needed in our group to use as starting materials in an organocatalytic aldol reaction. The synthesis of these aldehydes had traditionally been performed in the group using the Julia–Kocienski reaction, which affords only the *E*-diastereomer. This is a huge advantage of this reaction. However, this method also has drawbacks because it requires the preparation of the starting sulfone and proceeds under more demanding conditions, making it a lengthier process overall. On the other hand, the Wittig reaction involves only a single step and operates under milder conditions. However, this reaction can afford *E:Z* diastereomeric mixtures. It is well known that with non-stabilized Wittig reagents, *Z* double bonds

are mainly formed (**a in Scheme 7**), while with stabilized ylides, with electron-withdrawing groups (**b in Scheme 7**), the product is predominantly *E***.** We decided to compare the two methods by synthesizing *p*-substituted cinnamaldehydes in both ways.



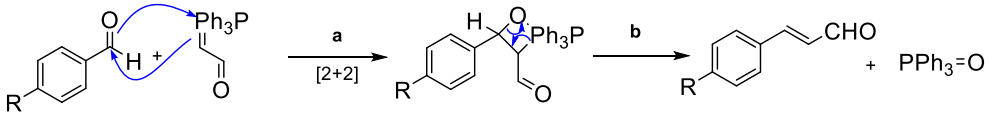
Scheme 7. Non-stabilized ylides (a) and stabilized ylides (b).

5.2. WITTIG REACTION

The Wittig reaction is a classical option to create a C=C bond, especially for the conversion of aldehydes or ketones to alkenes using phosphorus ylides.

In this work we have applied this method for the preparation of *p*-nitrocinnamaldehyde and *p*-trifluoromethylcinnamaldehyde.

The reaction mechanism starts with a formal [2+2] cycloaddition between the phosphonium ylide and the aldehyde carbonyl (**a in Scheme 8**) to form an oxaphosphetane. Finally, a reverse [2+2] cycloaddition generates the desired product (where R= NO_2, CF_3) and triphenylphosphine oxide (**b in Scheme 8**).[11]

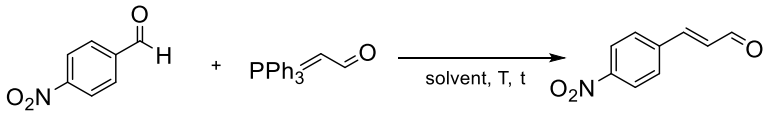


Scheme 8. Li-salt free Wittig reaction mechanism.

The synthesis of the desired α,β-unsaturated aldehyde bearing a *para*-nitro substituent was first carried out under the conditions reported in the literature,[12] using standard reflux in $CHCl_3$. After 2 h, TLC showed the reaction was almost complete. Purification by column chromatography afforded two fractions. The first contained the desired aldehyde as a 95:5 *E*:*Z* mixture, while the second fraction was a 84:16 *E*:*Z* mixture of diastereomers. Recrystallization of the first fraction in absolute EtOH increased the diastereomeric ratio from *E*:*Z* 95:5 to 98:2 (**Table 1**). The yield was 67%. This result was highly satisfactory as the product obtained is suitable for further use in the organocatalytic aldol reaction. The second fraction was also recrystallized obtaining a 16% yield of the product with a 94:6 *E*:*Z* ratio.

We then increased the reaction time to 48 h, until the starting material was completely consumed. Under these conditions the target aldehyde was obtained as a 91:9 *E*:*Z* mixture. After recristallization in absolute ethanol, a moderate yield of 43% of *p*-nitrobenzaldehyde with a diastereomeric *E*:*Z* ratio of 93:7 was obtained (**Table 1**). Recrystallization only marginally increased the diastereomeric ratio. Although the *E*-isomer was predominant, the presence of 7% of the *Z*-isomer was problematic, since we need the aldehyde with a high degree of geometrical purity to achieve optimal stereocontrol in the organocatalytic aldol reaction. The lower yield obtained after 48 h of reaction (43%) compared to the yield obtained after 2 h (83%) can likely be attributed to the significantly smaller reaction scale (5 mmol vs. 30 mmol), which often results in greater relative losses during workup and recrystallization. In an effort to improve the stereoselectivity of the reaction, alternative conditions were explored. A solvent screening was initiated based on reports suggesting that solvent polarity may influence the *E*:*Z* selectivity of Wittig-type reactions.[13] The solvent was switched from $CHCl_3$ to toluene, a less polar solvent, with the aim of favouring the thermodynamically more stable *E*-isomer under the increased reaction temperature. However, this change had a different effect: the *E*:*Z* ratio dropped to 55:45 (**Table 1**), with a significant increase in the *Z*-isomer formation. The reaction mixture was not purified due its low diastereomeric ratio.

Table 1. Summary of experimental conditions tested for the synthesis of (*E*)-*p*-nitrocinnamaldehyde.



Entry	Solvent	T (ºC)	t (h)	Yield [%]	*E*:*Z* before recrystallization	*E*:*Z* after recrystallization
1	$CHCl_3$	reflux	2	67	95:5	98:2
2	$CHCl_3$	reflux	48	43	91:9	93:7
3	Toluene	reflux	48	---	54:45	----

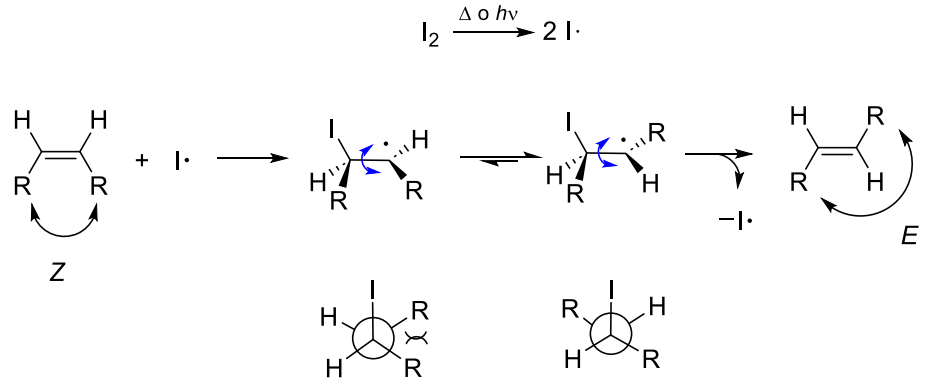
The reported reaction conditions were also applied to the synthesis of *p*-trifluoromethylcinnamaldehyde,[12] using standard reflux in $CHCl_3$ for 48 h. The crude mixture was subjected to column chromatography in an attempt to separate the *E* and *Z* diastereomers, which, as in the case of *p*-nitrocinnamaldehyde, show similar though different Rfs by TLC. Three different fractions were collected. One of the fractions showed a single spot on the TLC, suggesting high purity. This fraction contained the desired *E*-configured product in 38% yield. However, the two other fractions contained a mixture of diastereomers. One of them corresponded to a 65:35 *E*:*Z* mixture and was obtained in 30% yield, while the other one was an 83:17 *E*:*Z* mixture (16% yield). These results point to the difficulty isolating the pure *E* diastereomer by column chromatography.

5.3. ISOMERIZATION

To improve the diastereomeric ratio of the *p*-nitrocinnamaldehyde obtained via the Wittig reaction, we attempted its isomerization using either I_2 or acid catalysis. *p*-Nitrocinnamaldehyde with a diastereomeric ratio of 54:46 was used for these tests.

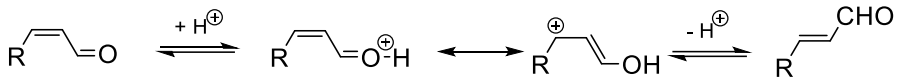
Initially, we treated a solution of *p*-nitrocinnamaldehyde in CH_2Cl_2 with a catalytic amount of I_2 for 24 h at 4 ºC in the dark. Analysis of the product by NMR revealed a *E*:*Z* ratio of 69:31. Then, the experiment was repeated at rt and under exposure to sunlight, obtaining a much better 93:7 diastereomeric ratio.

The mechanism of the double bond isomerization catalyzed by I_2 is believed to proceed via a radical pathway and involves, first of all, the formation of I· atoms, from I_2, either photochemically or thermally. The I· radical then adds to the double bond forming an intermediate that can undergo single bond rotation. Finally, elimination of an I· atom allows reformation of the double bond as the more stable *E* isomer (**Scheme 9**).[14]



Scheme 9. Mechanism of *E*→*Z* isomerization with I_2.

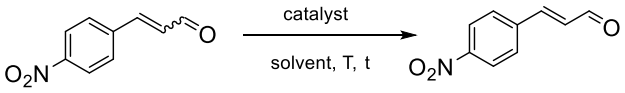
Isomerization with 6 M hydrochloric acid and AcOEt as a solvent, was also attempted. In this case, after 30 min, the dr improved to a lesser extent, generating product with an *E:Z* ratio of 59:41. The mechanism of this acid-catalyzed isomerization can be explained first by protonation of the carbonyl oxygen, which decreases the double bond character of the C=C, allowing single bond rotation. Loss of a proton affords the initial conjugated aldehyde, favouring the formation of the more stable *E* isomer (**Scheme 10**).



Scheme 10. Acid-catalyzed *Z*→*E* isomerization.

Although the diastereomeric ratio improved in the both cases in which iodine was used, the isomerization under sunlight generated a greater ratio of the *E*-isomer, making it more effective (**Table 2**). Therefore, these conditions (sunlight, rt) appear to be the best option for the isomerization of *p*-nitrocinnamaldehyde samples with a low initial *E:*Z ratio. Using the acid-catalyzed process no significant improvement of the diastereomeric ratio was obtained, although longer reaction times could lead to higher percentages of the *E* diastereomer.

Table 2. Summary of experimental conditions tested for the isomerization of α,β-unsaturated aldehydes.

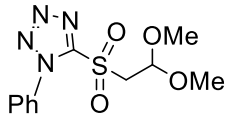


Entry	Reagents	Solvent	Light/Storage conditions	T (ºC)	t (h)	Yield [%]	Initial *E:Z*	Final *E:Z*
1	I_2	DCM	Dark (fridge)	4	24	100	54:46	69:31
2	I_2	DCM	Sunlight	rt	24	30	54:46	93:7
3	HCl (6 M)	AcOEt	-----	0ºC → rt	0.5	74	54:46	59:41

5.4. JULIA–KOCIENSKI REACTION

The Julia–Kocienski olefination is a widely used method for the stereoselective formation of *E*-configured C=C bonds, particularly in α,β-unsaturated systems. It is often used as an alternative to the Wittig reaction when higher stereochemical purity is required.

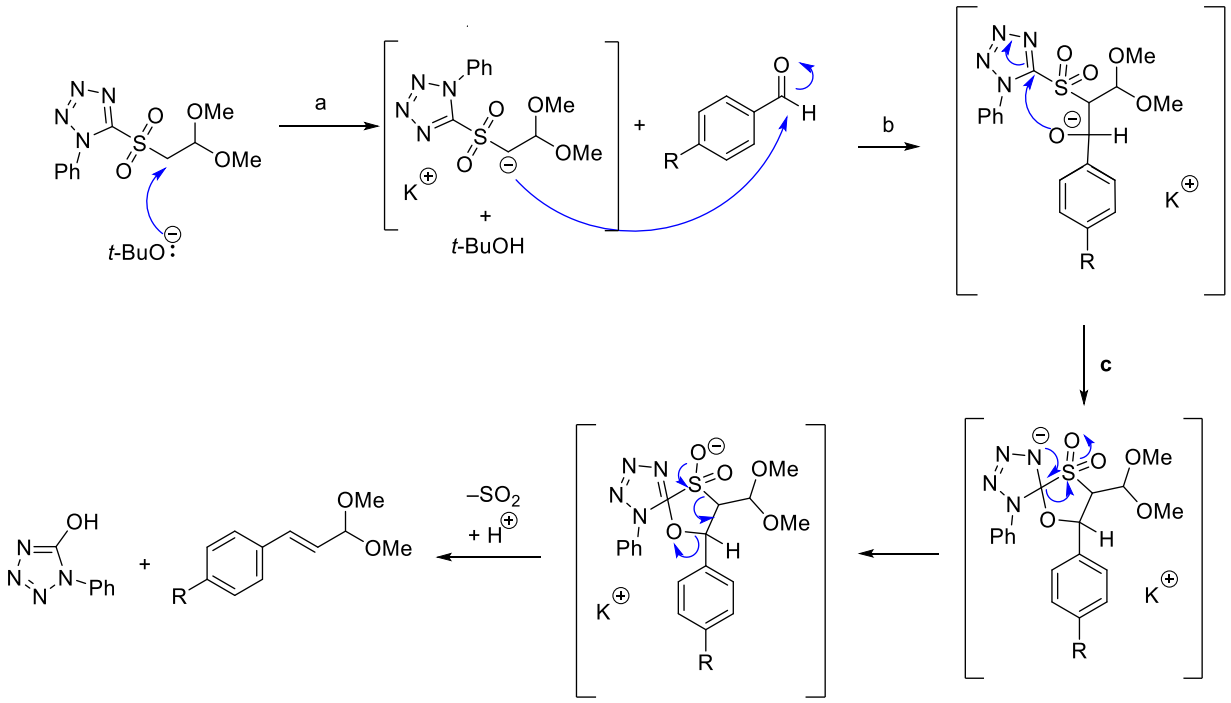
For the preparation of an α,β-unsaturated aldehyde via the Julia–Kocienski reaction, sulfone **3** is needed. This reagent is not commercially available, so it has to be prepared beforehand from 1-phenyl-1*H*-tetrazole, in two steps. In our case, there was no need to prepare it as a sufficient amount of the compound was already available in the laboratory. The sulfone is a key reagent that, upon deprotonation reacts with an aldehyde to generate the desired alkene. The reaction is usually carried out under basic conditions, often using strong bases like potassium *tert*-butoxide, and requires strictly anhydrous and inert conditions to proceed efficiently.



3

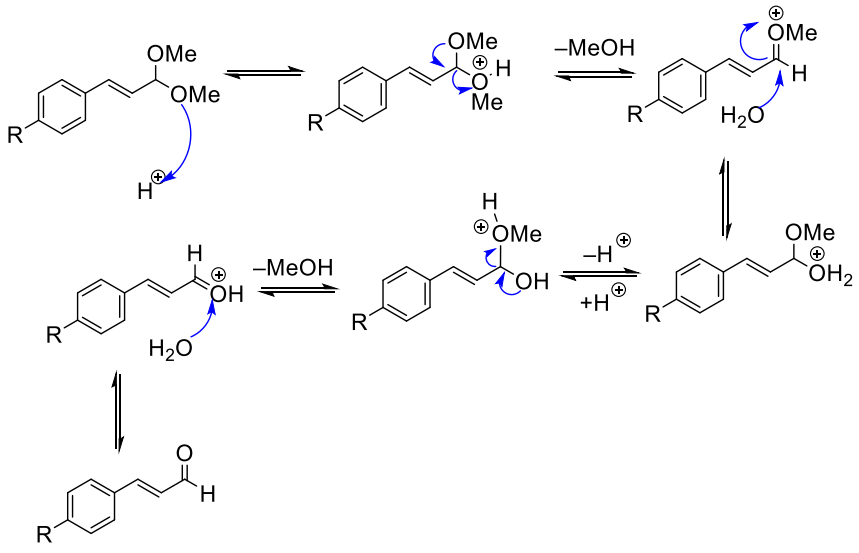
Figure 3. Structure of sulfone **3.**

The mechanism is shown in **Scheme 11** and starts with the deprotonation of the sulfone with a strong base generating the corresponding anion (**a**). This attacks the electrophile (carbonyl of the aldehyde) as we can see on **b in Scheme 11.** After this there is a Smiles rearrangement followed by SO_2 elimination (**c in Scheme 11**).



Scheme 11. Mechanism of the Julia–Kocienski reaction.

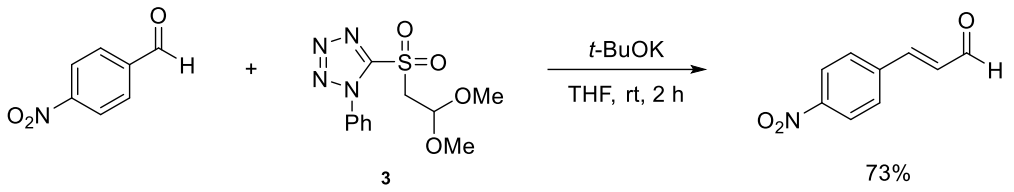
Sulfone **3** is specially designed for the stereoselective synthesis of α,β-unsaturated aldehydes via the Julia–Kocienski reaction.[15] During the reaction, the aldehyde group is protected as an acetal, which is stable in basic conditions, and is unmasked during the final acid-catalyzed hydrolysis step. Deprotection of the acetal in acidic media, shown in **Scheme 12,** is crucial for releasing the free α,β-unsaturated aldehyde and defines the last stage of the synthetic route. The acetal functions not only as a protecting group for the aldehyde but also contributes to the overall stereocontrol of the process, as *Z*-->*E* isomerization takes place during the acid-catalyzed hydrolysis step. The method provides excellent *E*-selectivity, representing a valuable alternative to more traditional olefination approaches such as the Wittig reaction, particularly when high stereochemical purity is required.



Scheme 12. Mechanism of acetal hydrolysis.

Preparation of α,β-unsaturated aldehydes using the Julia–Kocienski reaction is not as straightforward as the Wittig reaction as: i) the sulfone has to be prepared beforehand; ii) the reaction conditions are more strict, as anhydrous conditions and a N_2 atmosphere is required; iii) long reaction times are needed. Also, the addition of the suspension of *t*-BuOK in THF must be very slow, as rapid addition leads to a significant decrease in yield. However, if performed properly, we can achieve good yields with this method and greater stereochemical purity since the product obtained is 100% *E*.

In our hands, preparation of *p*-nitrocinnamaldehyde via the Julia–Kocienski reaction, as shown in **Scheme 13**, afforded the desired product in 73% yield as a single *E* diastereomer.

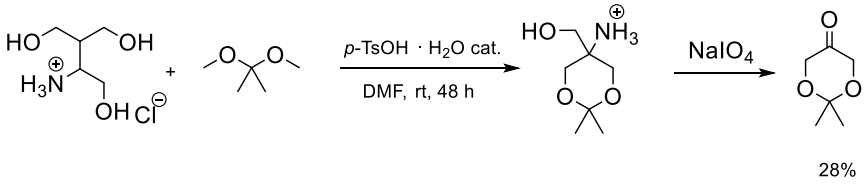


Scheme 13. Julia–Kocienski reaction.

5.5. PREPARATION OF 2,2-DIMETHYL-1,3-DIOXAN-5-ONE

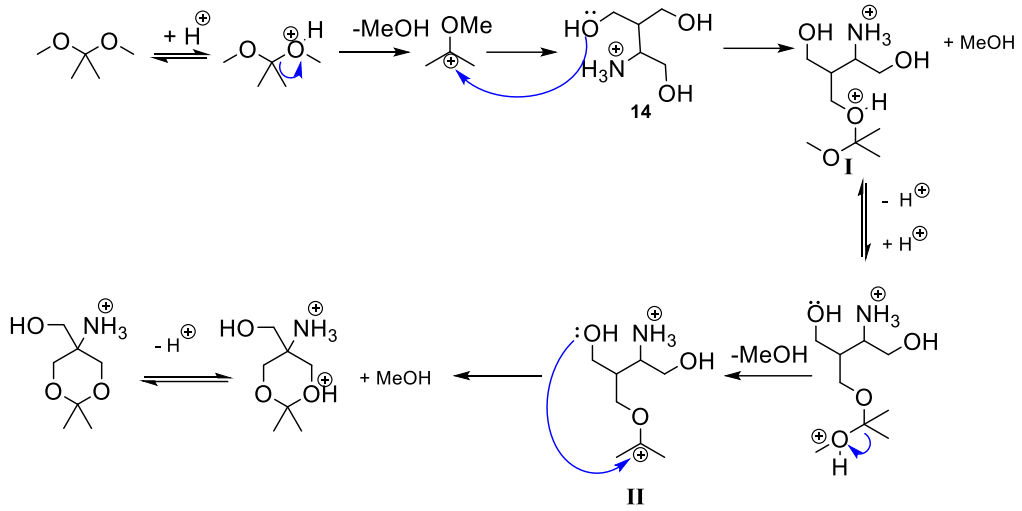
As discussed in the introduction, we wanted to study the aminocatalytic aldol reaction ketones with α,β-unsaturated aldehydes that proceeds via enamine activation of the ketones. Although ketone enamines are not formed as easily as enamines from aldehydes, there are certain ketones for which enamine formation is more favored. This is the case of 2,2-dimethyl-1,3-dioxan-5-one. This cyclic molecule has two oxygen groups that favour the formation of a more stable enamine.[16]

The synthesis of this ketone (**Scheme 14**) began with the formation of a cyclic acetal by treatment of 2-amino-2-hydroxymethyl-1,3-propanediol·HCl with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid, using DMF as solvent, at rt for 48 h.[17]



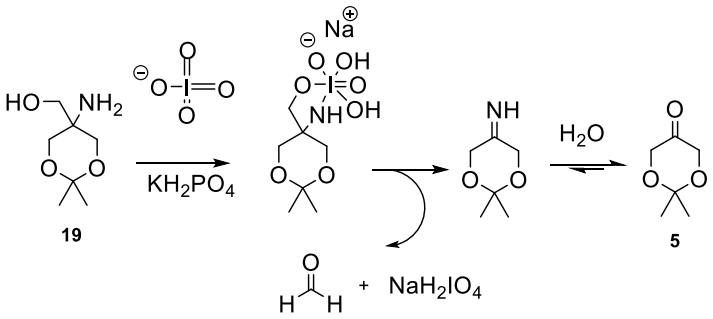
Scheme 14. Global reaction of 2,2-Dimethyl-1,3-dioxan-5-one.

The mechanism for the formation of the ketal is shown on **Scheme 15.** Protonation of 2,2-dimethoxypropane generates an oxocarbenium ion that reacts with a hydroxyl group to generate intermediate **I**. Loss of MeOH from **II**, generates another oxocarbenium ion, that is, again, attacked by another hydroxyl, forming the most stable six-membered ring. The reaction is under thermodynamic control. *p*-TsOH protonates the methoxy group, favouring the loss of methanol and therefore, promoting the formation of the oxocarbenium ion, that can be attacked by a hydroxyl, forming the C-O bond that closes the cycle.



Scheme 15. Mechanism for ketal formation.

The next step is the oxidation of the amino alcohol with $NaIO_4$ in water and KH_2PO_4, at 5 ºC. Sodium periodate acts as an oxidizing agent. It breaks the C-C bond and forms a ketone. The mechanism of this reaction is analogous to that of the cleavage 1,2-diols with $NaIO_4$ (**Scheme 16**). Monopotassium phosphate's acts as a buffer. It controls the pH and prevents decomposition by excessive acid or base. The yield obtained was relatively low, 28%, but enough material was secured for future tests.



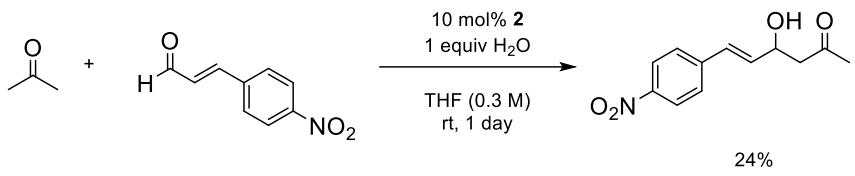
Scheme 16. Selective oxidation with $NaIO_4$.

5.6. ORGANOCATALYTIC ALDOL REACTIONS

The *p*-nitrocinnamaldehyde prepared as discussed previously was tested in aminocatalytic aldol reactions of acetone and cyclohexanone using **2** as catalyst, as discussed in the next sections. The goal was to evaluate whether α,β-unsaturated aldehydes are suitable substrates in aminocatalytic aldol reactions.

5.6.1. Organocatalytic aldol reactions using acetone

The organocatalytic aldol reaction between (*E*)-*p*-nitrocinnamaldehyde and acetone was carried out under mild conditions using L-proline tetrazole **2** as the catalyst (**Scheme 17**).



Scheme 17. Organocatalytic aldol reaction using acetone.

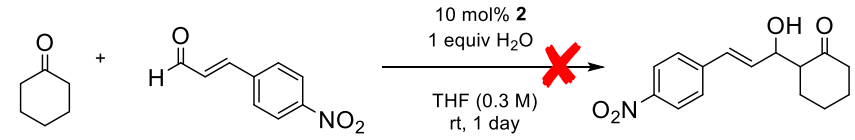
Previous studies in the group determined that addition of 1 equiv of water favors the reaction. Water can play a beneficial role in aminocatalytic reactions since it facilitates catalyst turnover. For example, the final step in the catalytic cycle is the hydrolysis of an iminium intermediate, in which water is needed to release the catalyst (**Scheme 3**).

Under the conditions of **Scheme 17**, the reaction afforded the desired aldol product in 24% yield (determined by ^{1}H NMR analysis using an internal standard). The use of acetone, less electrophilic and more sterically hindered than aliphatic aldehydes, avoids self-condensation and the reaction mixtures are simpler to analyze.

This reaction was used as a starting point for subsequent additive-based experiments, permitting a direct comparison of its effectiveness in the presence and absence of hydrogen-bond donors.

5.6.2. Organocatalytic aldol reactions using cyclohexanone

In addition to the reaction with acetone, the same protocol was carried out using cyclohexanone (**Scheme 18**). The main objective of the experiment was to explore whether other ketones could react with *p*-nitrocinnamaldehyde using 2 as catalyst, with the main idea of expanding the scope and utility of the method. Cyclohexanone is frequently used in reactions involving enamine activation.



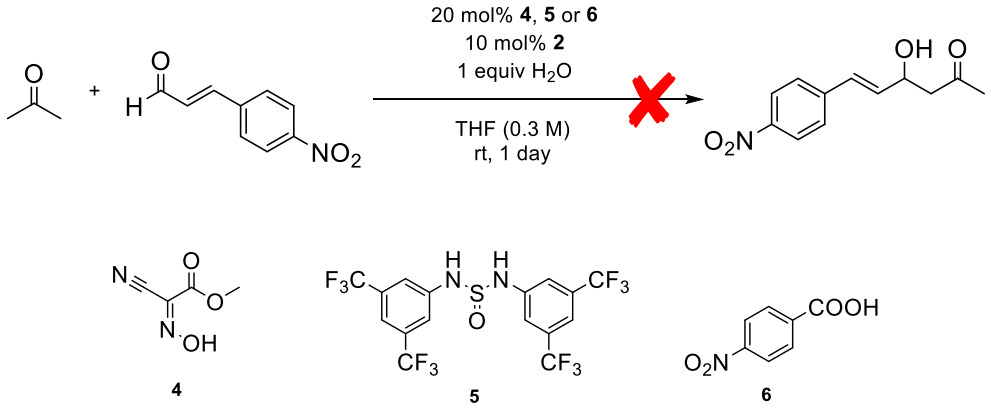
Scheme 18. Organocatalytic aldol reaction using cyclohexanone.

However, under the same conditions as the ones used previously for acetone, the formation of the desired aldol product was not observed.

Although it is known that cyclohexanone forms the corresponding enamine under the reaction conditions used, its concentration is probably too low to be able to react with the poorly electrophilic *p*-nitrocinnamaldehyde.

5.6.3. Organocatalytic aldol reactions using additives

With the aim of improving the yield and selectivity of the aldol reaction with acetone, the same reaction was repeated with the addition of additives **4**, **5** and **6** shown in **Scheme 19**. Hydrogen-bond donor additives **4** and **5** are known to increase enamine formation,[18] while the use of acidic additives, such as **6**, is known to be beneficial in these types of reactions. However, in this case, use of additives resulted in no product formation.



Scheme 19. Organocatalytic aldol reaction using additives.

Therefore, in this case, the reaction was more efficient without the use of any additives. Further work is needed to confirm and justify these results.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

The solvents and reagents used were obtained from commercial sources and were dried and purified when necessary, according to standard procedures.[19]

^{1}H-NMR (400 or 500 MHz) and ^{13}C NMR (100.6 or 126 MHz) spectra were acquired at rt using either a Brüker Avance III HD 400 (400 MHz) spectrometer or Brüker Avance Neo 500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are quoted in Hz. Tetramethylsilane (TMS) was employed as an internal reference (δ 0.00 for ^{1}H-NMR) and $CDCl_3$ (δ 77.0 for ^{13}C-NMR). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), m (multiplet) and their corresponding combinations. Assignment of signals is based on integration, splitting patterns and known chemical environments.

IR spectra (Attenuated Total reflectance, ATR) using a Thermo Scientific Nicolet 6700 FT.IR spectrometer. Only the most representative bands are reported in cm^{-1}.

HPLC analyses were carried out in a Shimadzu LC-20 HPLC system, using isocratic conditions, and detected at 254 nm with a UV-Vis spectrophotometer. The column used, mobile phase and retention times are specified in each case.

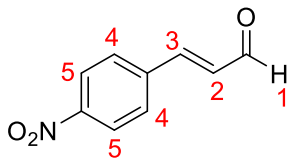
Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates and analyzed with UV light (254 nm). Some plates were stained with a solution of potassium permanganate, phosphomolybdic acid or *p*-anisaldehyde.

Optical rotations were measured using a JASCO P-2000 polarimeter, equipped with a 100 mm glass cell. The instrument operated with a resolution of 0.0001º at 25ºC and 589 nm, using the sodium D-line as light source.

6.2. SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

6.2.1. (*E*)-*p*-Nitrocinnamaldehyde (Wittig method) (7)

(Tryphenylphosphoranylidene)acetaldehyde (1.70 g, 5.60 mmol, 1.12 equiv) was added to a solution of 4-nitrobenzaldehyde (0.76 g, 5.0 mmol, 1.0 equiv) in $CHCl_3$ (50 mL). The reaction mixture was kept under reflux for 48 h. After this period, it was allowed to cool to rt and then concentrated under reduced pressure to remove the solvent. The crude material was purified by column chromatography (hexanes/AcOEt 80:20). The product was a 91:9 mixture of the *E* and *Z* isomers. It was recrystallized with hot absolute ethanol and the resulting crystals were filtered and washed with cold absolute ethanol. The desired product was obtained as a yellow, almost white solid as a 93:7 *E:Z* mixture (0.38 g, 2.1 mmol, 43% yield).

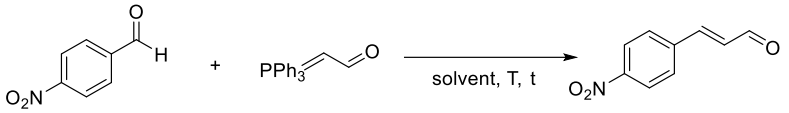


7

Yellow solid. **Rf** = 0.45 (Hexanes/AcOEt 70:30); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 9.78 (1H, d, *J* = 7.5, H_1), 8.33-8.21 (2H, m, H_5), 7.77-7.68 (2H, m, H_4), 7.53 (1H, d, *J* = 16.1, H_3) 6.81 (1H, dd, *J* = 16.1, 7.5, H_2).

The same procedure was repeated with a shorter reaction time (entry 1, Table E1) and with toluene as solvent (entry 3, Table E1).

Table E1. Summary of experimental conditions tested for the synthesis of (*E*)-*p*-nitrocinnamaldehyde.



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Entry	Solvent	T (ºC)	t (h)	Yield [%]	*E:Z* before recrystallization	*E:Z* after recrystallization
1	$CHCl_3$	reflux	2	67	95:5	98:2
2	$CHCl_3$	reflux	48	43	91:9	93:7
3	Toluene	reflux	48	---	54:45	----

6.2.2. Isomerization of 7 with iodine

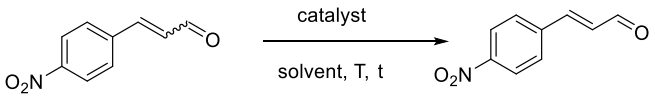
To a solution of *p*-nitrocinnamaldehyde (54:46 *E:Z* mixture) (50 mg, 0.30 mmol, 1.0 equiv) in anhydrous nitrogen CH_2Cl_2 (1.2 mL), iodine (8 mg, 0.06 mmol, 0.2 equiv) was added. The system was kept under nitrogen atmosphere and kept in the fridge at 4 ºC for 24 h. After this period, a saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was added dropwise and the mixture was stirred for 5 min. During this time, the red solution turned yellow. The mixture was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the final yellow solid (50 mg, 0.30 mmol, 100% yield).

The same reaction was repeated at rt and under sunlight exposure. The final *E*:*Z* ratio was 93:7.

6.2.3. Isomerization of 7 with acid

To a solution of *p*-nitrocinnamaldehyde (54:46 *E:Z* mixture) (50 mg, 0.30 mmol, 1.0 equiv), AcOEt (1.50 mL) and 6 M HCl (1 mL) were added at 0 ºC, and the mixture was stirred at rt for 30 min. The mixture was extracted with AcOEt (2 x 10 and 5 mL), and the combined organic layers were washed with 2 M NaOH (5 mL), saturated NH_4Cl (3 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the final yellow solid with an *E:Z* ratio of 59:41 (40 mg, 0.23 mmol, 72% yield).

Table E2. Summary of experimental conditions tested for the isomerization of α,β-unsaturated aldehydes.

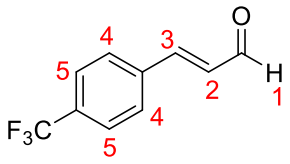


7 **7**

Entry	Reagents	Solvent	Light/Storage conditions	T (ºC)	t (h)	Yield [%]	Initial *E:Z*	Final *E:Z*
1	I_2	DCM	Dark (fridge)	4	24	100	54:46	69:31
2	I_2	DCM	Sunlight	rt	24	30	54:46	93:7
3	HCl (6 M)	AcOEt	-----	0ºC --> rt	0.5	74	54:46	59:41

6.2.4. (*E*)-*p*-Trifluoromethylcinnamaldehyde (Wittig method) (8)

(Tryphenylphosphoranylidene)acetaldehyde (1.70 g, 5.60 mmol, 1.12 equiv) was added to a solution of 4-(trifluoromethyl) benzaldehyde (0.87 g, 5.0 mmol, 1.0 equiv) in $CHCl_3$ (50 mL). The reaction mixture was kept under reflux for 48 h. After this period, it was allowed to cool to rt and then concentrated under reduced pressure to remove the solvent. The crude material was purified by column chromatography (hexanes/AcOEt 80:20). Three fractions were collected based on TLC analysis. The three fractions obtained were a yellow solid. The first has an *E*:Z mixture of 83:17 (0.16 g, 0.82 mmol, 16%), the second corresponded to the pure *E* isomer (0.38 g, 1.90 mmol, 38%), and the third was a diastereomeric mixture with a *E*:*Z* ratio of 65:35 (0.30 g, 1.50 mmol, 30%).



8

Yellow solid. **Rf** = 0.5 (Hexanes/AcOEt 70:30); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 9.76 (1H, d, *J* = 7.6, H_1), 7.74 – 7.65 (4H, m, H_4 + H_5), 7.51 (1H, d, *J* = 16.1, H_3), 6.78 (1H, dd, *J* = 16.1, 7.5, H_2).

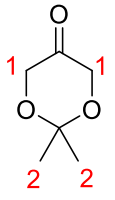
6.2.5. (*E*)-*p*-Nitrocinnamaldehyde (Julia–Kocienski method) (7)

In a 3-necked flask purged with liquid N_2, sulfone **3** (3.48 g, 11.8 mmol, 1.2 equiv), 4-nitrobenzaldehyde (1.49 g, 9.82 mmol, 1.00 equiv) and anhydrous THF (13 mL) were added at a temperature of –40 ºC. Then, a suspension of *t*-BuOK (3.30 g, 29.5 mmol, 3.00 equiv) in THF (28 mL) is added drop by drop. After an hour stirring at rt, AcOEt (28 mL) and HCl 6 M (13 mL) are added at 0 ºC and then left for 45 min at rt. The phases are separated, and the aqueous phase is extracted with AcOEt (3 x 12 mL). The combined organic extracts are washed with NaOH 2 M (14 mL), NH_4Cl (9 mL) and brine (15 mL). The organic phase is dried with anhydrous $MgSO_4$, filtered and the solvent is removed. The crude solid is purified by column chromatography (Hexanes:AcOEt 70:30). The desired product was obtained as a yellow solid (1.28 g, 7.23 mmol, 73% yield).

6.3. SYNTHESIS OF STARTING MATERIALS

6.3.1. 2,2-Dimethyl-1,3-dioxan-5-one (9)

A 2 L round-bottom flask equipped with a magnetic stirring bar was charged with 2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride (7.88 g, 50.0 mmol, 1 equiv), 2,2-dimethoxypropane (6.38 g, 60.0 mmol, 1.2 equiv), *p*-toluenesulfonic acid (0.34 g, 2.50 mmol, 4 mol%) and DMF (16 mL). The mixture was stirred during 40 h at rt. After this time, triethylamine (0.42 mL) was added, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (120 mL) and treated with triethylamine (6.7 mL). After stirring at rt for 10 min, the precipitate was filtered and the solvent was removed under reduced pressure, affording the crude β-amino alcohol. In a 2 L three-necked round-bottom flask equipped with a magnetic stirrer, a dropping funnel and a thermometer, the β-amino alcohol was dissolved in water (45 mL) and KH_2PO_4 (4.24 g, 31.2 mmol) was added. Then, a 0.5 M aq $NaIO_4$ solution (94 mL) was added dropwise at 5 ºC for 3 h. After completion, the cooling bath was removed, and the solution was stirred for 15 h at rt. The aqueous solution was extracted with CH_2Cl_2 (5 x 5 mL) and the combined organic extracts were washed with $NaHSO_3$ aq. (70 mL) and brine (70 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by distillation using a Vigreux column under reduced pressure, affording a colorless oil (1.778 g, 13.66 mmol, 28%).



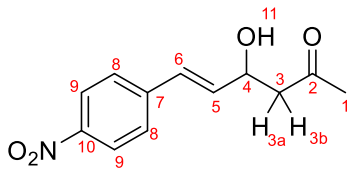
9

Colourless oil. **Rf** = 0.7 (DCM/Hexanes/AcOEt 50:30:20); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 4.15 (4H, s, H_1), 1.45 (6H, s, H_2)

6.4. ORGANOCATALYTIC ALDOL REACTIONS

6.4.1. Organocatalytic aldol reactions acetone with *p*-nitrocinnamaldehyde

In a small glass vial, (*E*)-*p*-nitrocinnamaldehyde (53.1 mg, 0.30 mmol, 1.00 equiv) and catalyst **2** (98%, 4.26 mg, 0.03 mmol, 0.1 equiv) were added and stirred for 5 min. A 0.3 M aqueous THF solution (0.8 mL), previously prepared by diluting 16.2 µL of water in 2.40 mL of THF, was then added to the glass vial. Finally, anhydrous acetone (174.2 mg, 3.00 mmol, 10 equiv) was added. The reaction mixture was stirred for 24 h at 25 ºC in a water bath. The reaction was then quenched with brine (3 mL) and extracted with dichloromethane (3 x 5mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR and ^{13}C NMR using methyl 4-nitrobenzoate as internal standard to estimate the yield. The crude solid was purified by column chromatography (DCM: hexanes: AcOEt 50:30:20). The desired product was obtained as a yellow oil (0.017 g, 0.07 mmol, 24% yield).



10

Yellow oil. **Rf** = 0.3 (Hexanes/AcOEt 70:30); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.16 (2H, d, *J*= 8.8, H_9), 7.49 (2H, d, 8.7, H_8), 6.74 (1H, dd, 16.0, 1.6, H_6), 6.38 (1H, dd, 15.9, 5.4, H_5), 4.80 (1H, dt, 8.7, 4.3, H_4), 3.28 (1H, s, H_{11}), 2.82 (1H, dd, 17.7, 3.8, H_{3a}), 2.75 (1H, dd, 17.8, 8.3, H_{3b}), 2.23 (3H, s, H_1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 (C_2), 147.1 (C_{10}), 143.2 (C_7), 135.1 (C_5), 128.2 (C_6), 127.1 (C_8), 124.1 (C_9), 68.0 (C_4), 49.6 (H_3), 30.9 (C_1).

Polarimetry (Conditions: 1 dm cell, temperature 25 ºC, D line (589 nm)) $[\alpha]_D^{25}$ =+0.0642

CHIRAL HPLC (Phenomenex Lux iCellulose i5, 15:85 IPA:hexane, flow rate 1mL/min):
Rt1 : 28.6 min, Rt2 : 31.7 min, 63:35 e.r.

IR (ATR) 3424, 1705, 1593, 1508, 2926 cm^{-1}. The IR bands are consistent with those reported in the literature.[20]

6.4.2. Organocatalytic aldol reactions of cyclohexanone with *p*-nitrocinnamaldehyde

To a small glass vial, (*E*)-*p*-nitrocinnamaldehyde (53.1 mg, 0.30 mmol, 1 equiv) and catalyst **2** (98%, 4.26 mg, 0.03 mmol, 0.1 equiv) were added and stirred for 5 min. A 0.3 M aqueous THF solution (0.8 mL), previously prepared by diluting 16.2 µL of water in 2.40 mL of THF, was then added. Then, cyclohexanone (294.4 mg, 3.00 mmol, 10.0 equiv) was added. The reaction mixture was stirred for 24 h at 25 ºC in a water bath. After completion, the reaction was quenched with brine (3 mL) and extracted with dichloromethane (3 x 5 mL). The ^{1}H NMR showed that the reaction did not proceed.

6.4.3. Organocatalytic aldol reaction with additives

In a small glass vial, (*E*)-*p*-nitrocinnamaldehyde (53.1 mg, 0.30 mmol, 1.00 equiv), catalyst **2** (98%, 4.26 mg, 0.03 mmol, 0.1 equiv) and additive **4**, **5** or **6** (7.69 mg, 0.06 mmol, 0.2 equiv), were added and stirred for 5 min. A 0.3 M aqueous THF solution (0.8 mL), previously prepared by diluting 16.2 µL of water in 2.40 mL of THF, was then added to the glass vial. Finally, anhydrous acetone (174.2 mg, 3.00 mmol, 10 equiv) was added. The reaction mixture was stirred for 24 h at 25 ºC in a water bath. The reaction was then quenched with brine (3 mL) and extracted with dichloromethane (3 x 5mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR using methyl 4-nitrobenzoate as internal standard to estimate the yield. Only starting material was detected by ^{1}H NMR analysis.

7. CONCLUSIONS

The main objective of this work was the preparation of *p*-substituted cinnamaldehydes and their application in an aminocatalytic aldol reaction.

p-Nitrocinnamaldehyde was successfully synthesized using both the Wittig and Julia–Kocienski reactions. Although the Wittig route is experimentally more straightforward and benefits from the commercial availability of the required ylide, it led to mixtures of *E*:*Z* diastereomers that were difficult to separate by column chromatography. While recrystallization improved the diastereomeric ratio, it did so at the expense of yield. Isomerization of the *E*:*Z* mixtures using iodine as catalyst was effective, although some *Z* isomer remained and involves an additional synthetic step. In contrast, the Julia–Kocienski reaction, though more demanding in terms of reagent preparation and setup, afforded the *E* isomer selectively and in good yield, making it the preferred method overall.

p-Trifluoromethylcinnamaldehyde was similarly prepared via the Wittig reaction. The cyclic ketone 2,2-dimethyl-1,3-dioxan-5-one was also successfully synthesized.

The organocatalyzed aldol reaction of *p*-nitrocinnamaldehyde with acetone, using catalyst **2**, proceeded with low yield and enantioselectivity. The use of hydrogen-bond donor additives was counterproductive, completely suppressing the reaction. Cyclohexanone proved unreactive under the tested conditions.

These results suggest that, for the preparation of stereodefined *E*-α,β-unsaturated aldehydes, the Julia–Kocienski method offers a more reliable approach than the Wittig reaction. Further optimization is required to improve both the efficiency and selectivity of the subsequent organocatalytic aldol reactions.

8. REFERENCES

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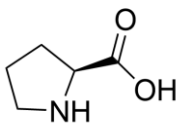
9. ACRONYMS AND ABBREVIATIONS

[α]	Specific rotation
aq	Aqueous
ºC	Degrees Celsius
cat	Catalyst
cm^{-1}	Wavenumber (s)
δ	Chemical Shift
DCM	Dicloromethane
dr	Diastereomeric ratio
ee	Enantiomeric excess
e.r	Enantiomeric ratio
equiv	Equivalent
g	Gram(s)
h	Hour(s)
Hz	Hertz
HPLC	High performance liquid chromatography
LDA	Lithium diisopropylamide
M	Molar
Me	Methyl
min	Minute(s)
mL	Milliliter(s)
nm	Nanometer(s)
NMR	Nuclear magnetic resonance
pH	Potential of hydrogen
ppm	Part(s) per million
p-TsOH	*p*-Toluenesulfonic acid
Rf	Retention factor

rt	Room temperature
SN_1	Unimolecular nucleophilic substitution
THF	Tetrahydrofuran
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
UV-vis	Ultraviolet-visible

APPENDICES

APPENDIX 1: STRUCTURE INDEX



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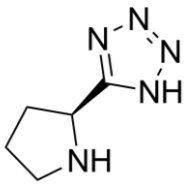

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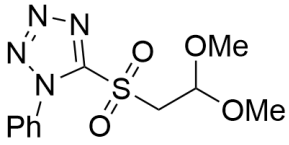

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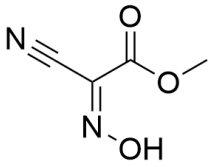

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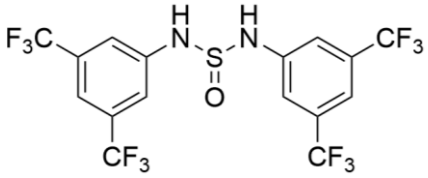

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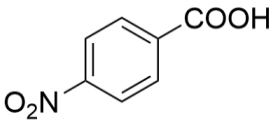

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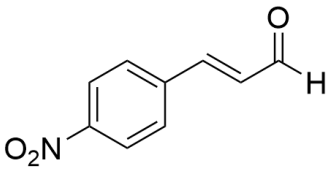

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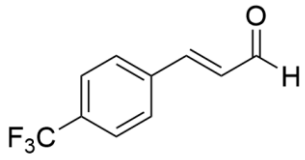

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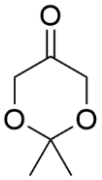

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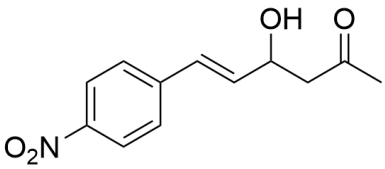

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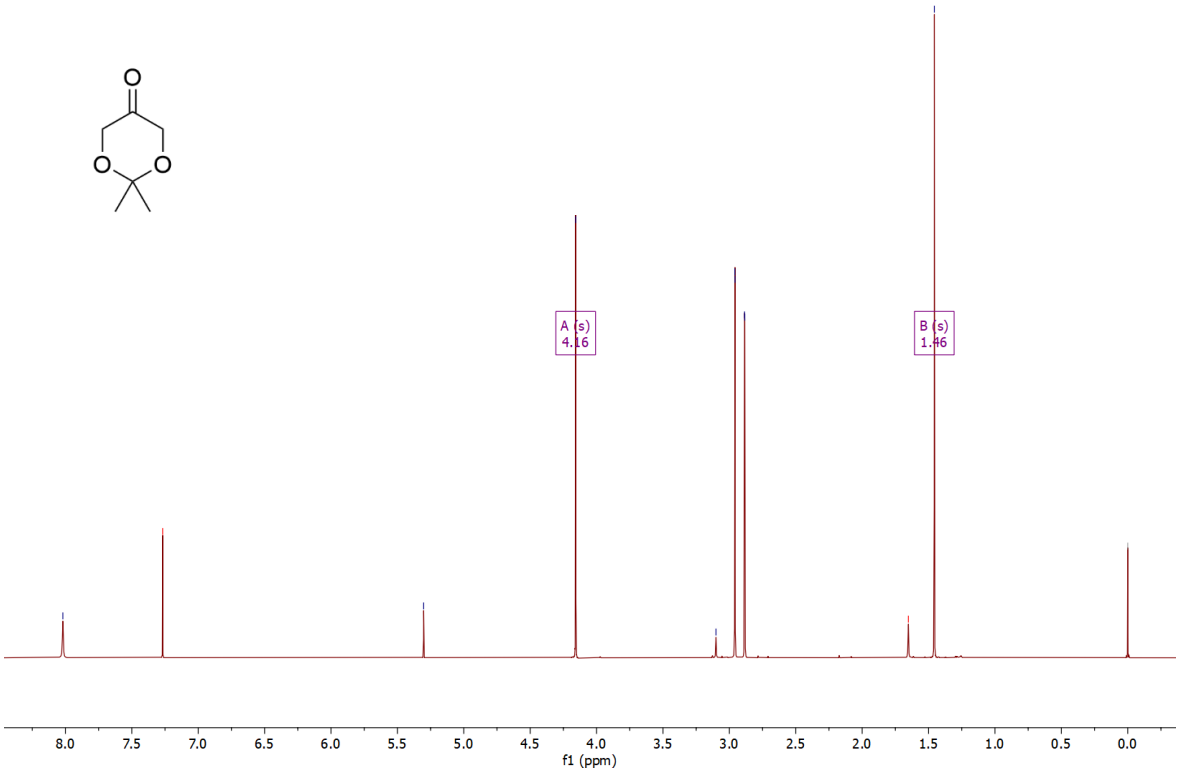
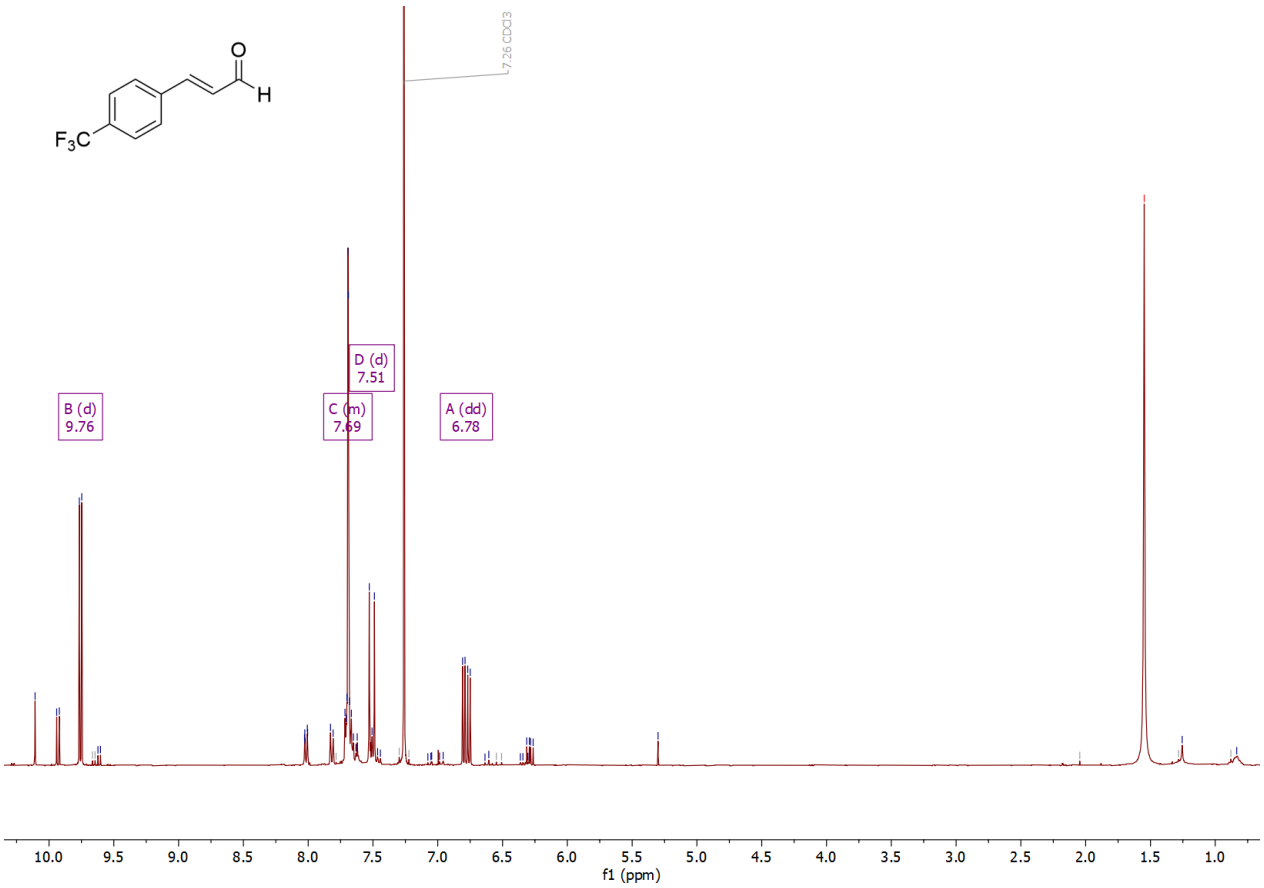
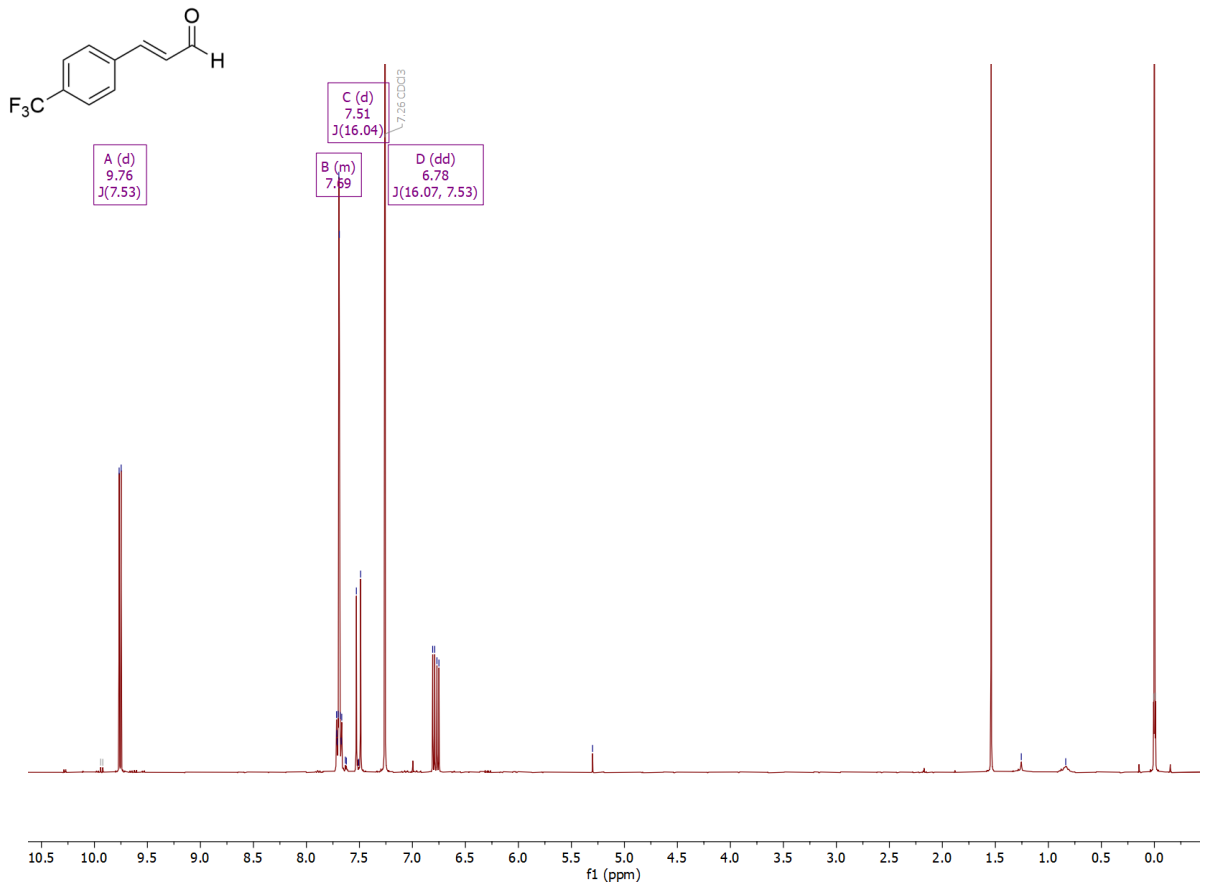
APPENDIX 2: ^{1}H-NMR, ^{13}C-NMR AND IR OF THE PRODUCTS OBTAINED



^{1}H-RMN of . 2,2-Dimethyl-1,3-dioxan-5-one **9** in $CDCl_3$.



^{1}H-RMN of *p*-trifluoromethylcinnamaldehyde **8** in $CDCl_3$. Wittig reaction.
E:*Z* ratio 83:17



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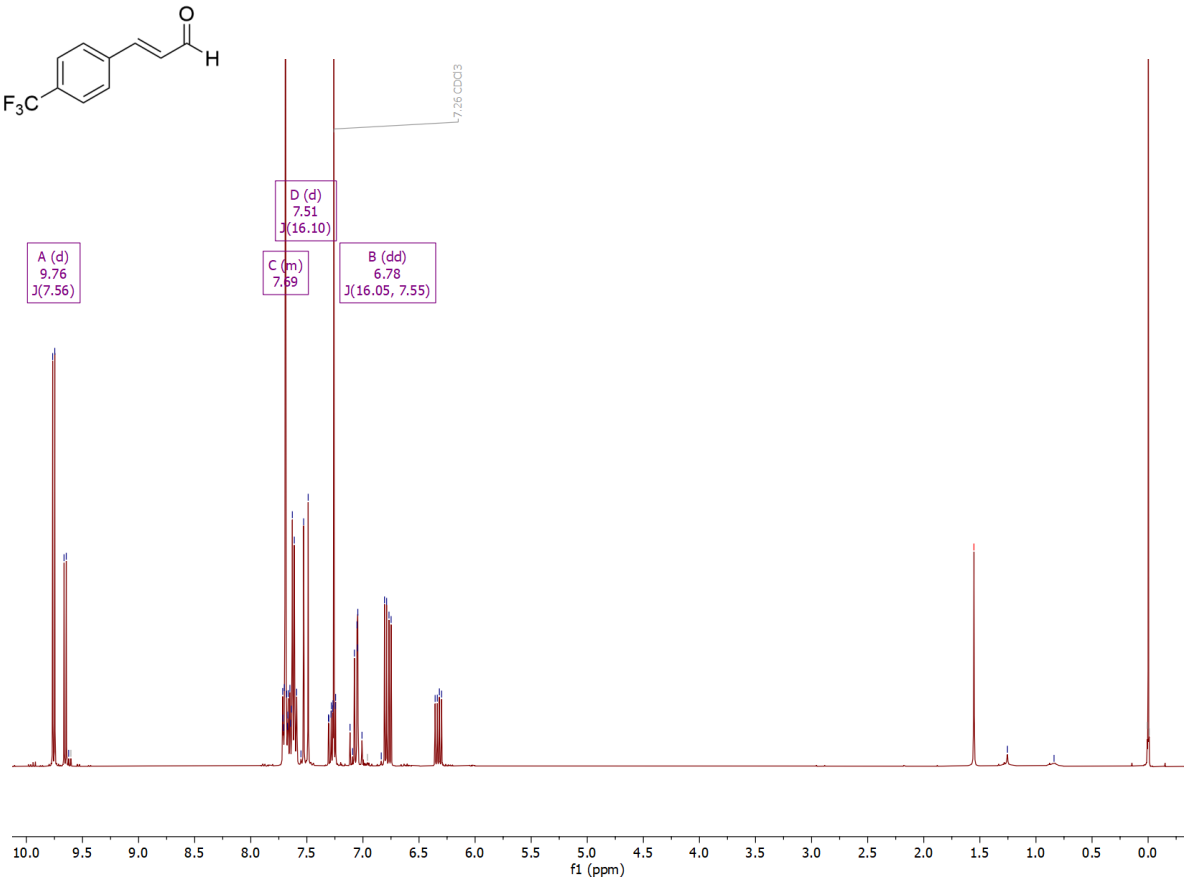
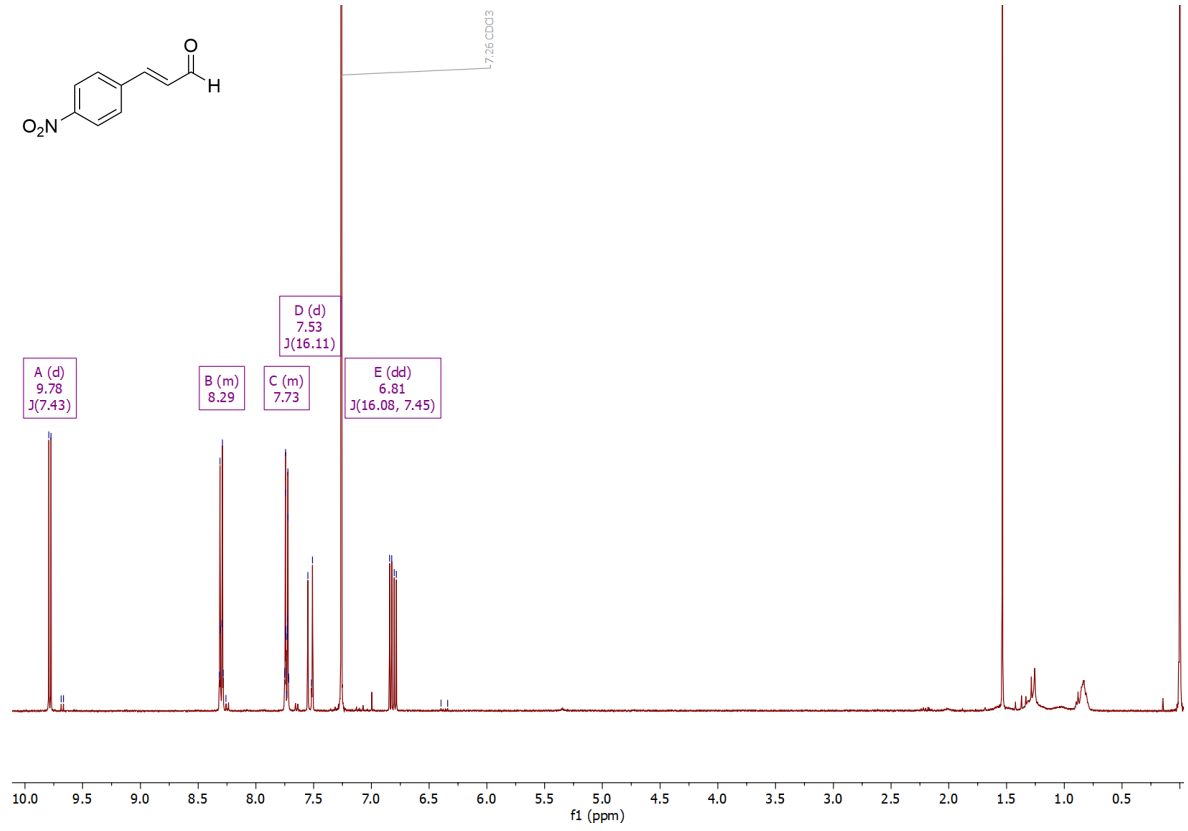
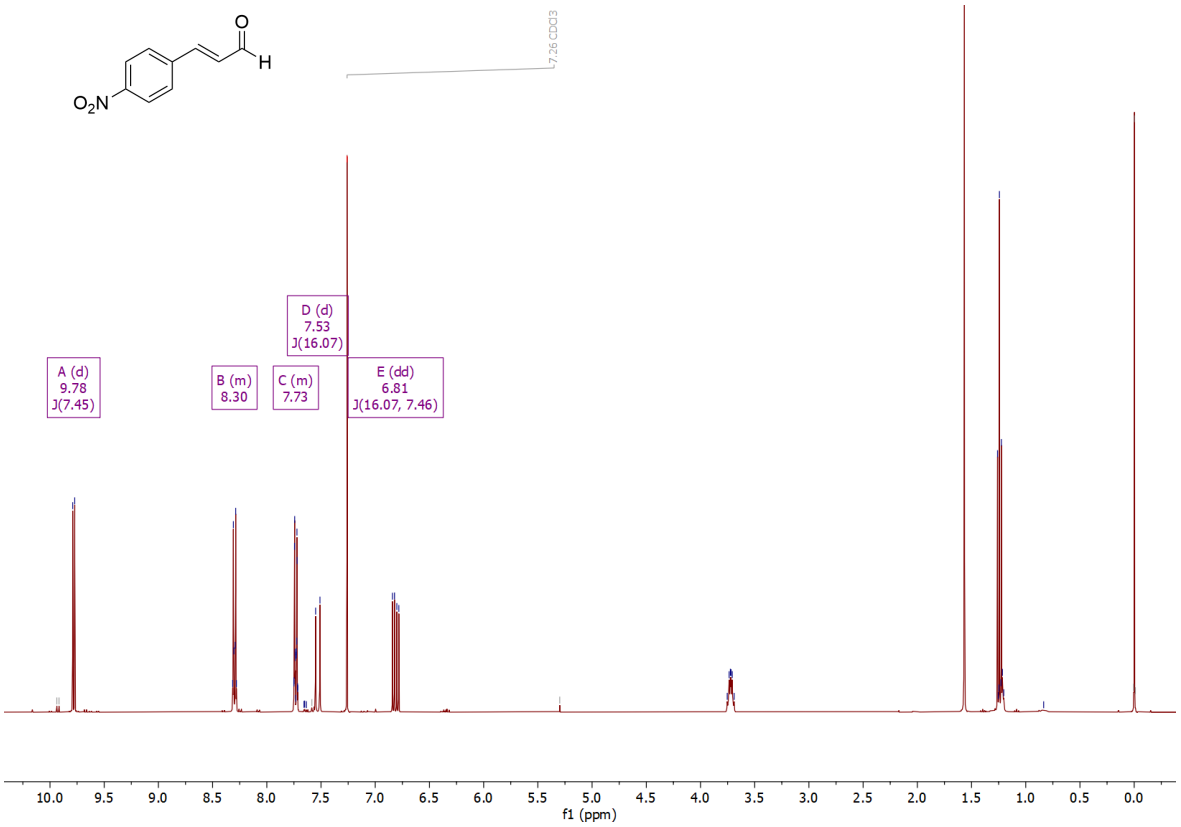


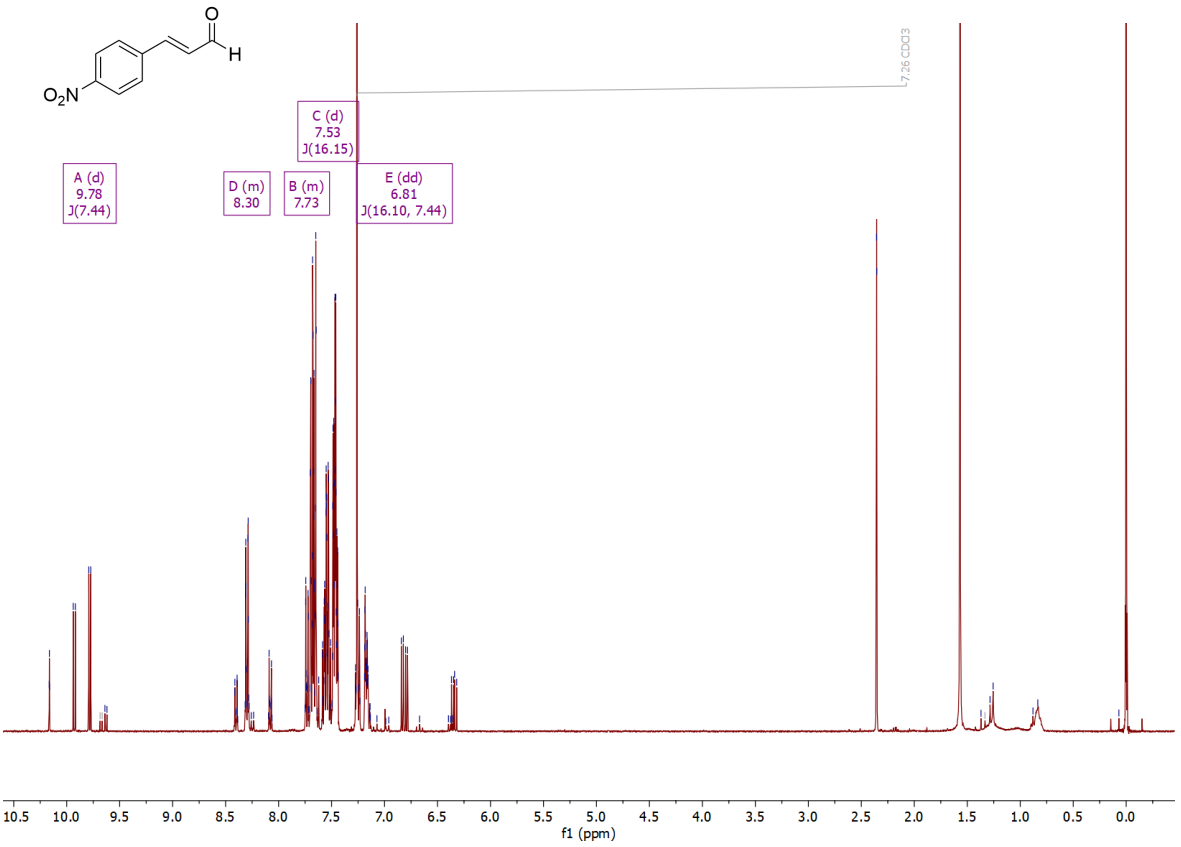
^{1}H-RMN of *p*-trifluoromethylcinnamaldehyde **8** in $CDCl_3$. Wittig reaction.
E:*Z* ratio 65:35.



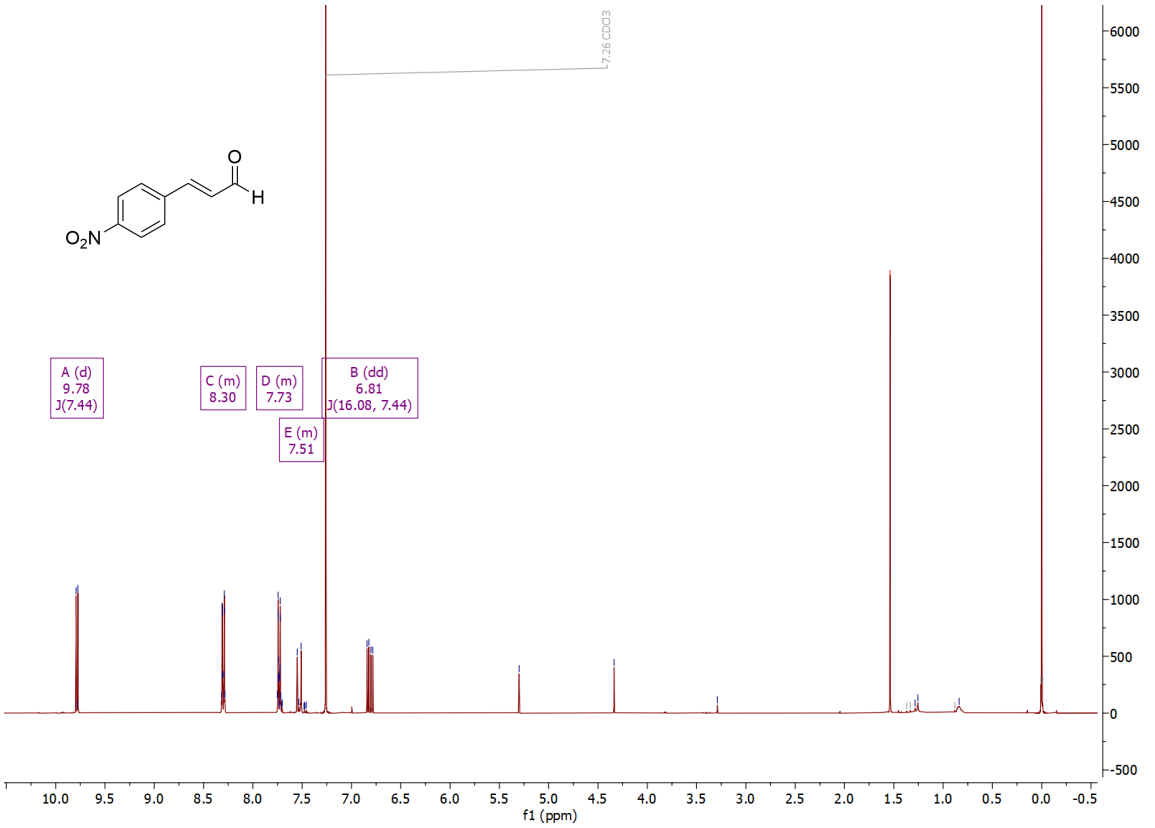
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Wittig reaction.
E:*Z* ratio 93:7.



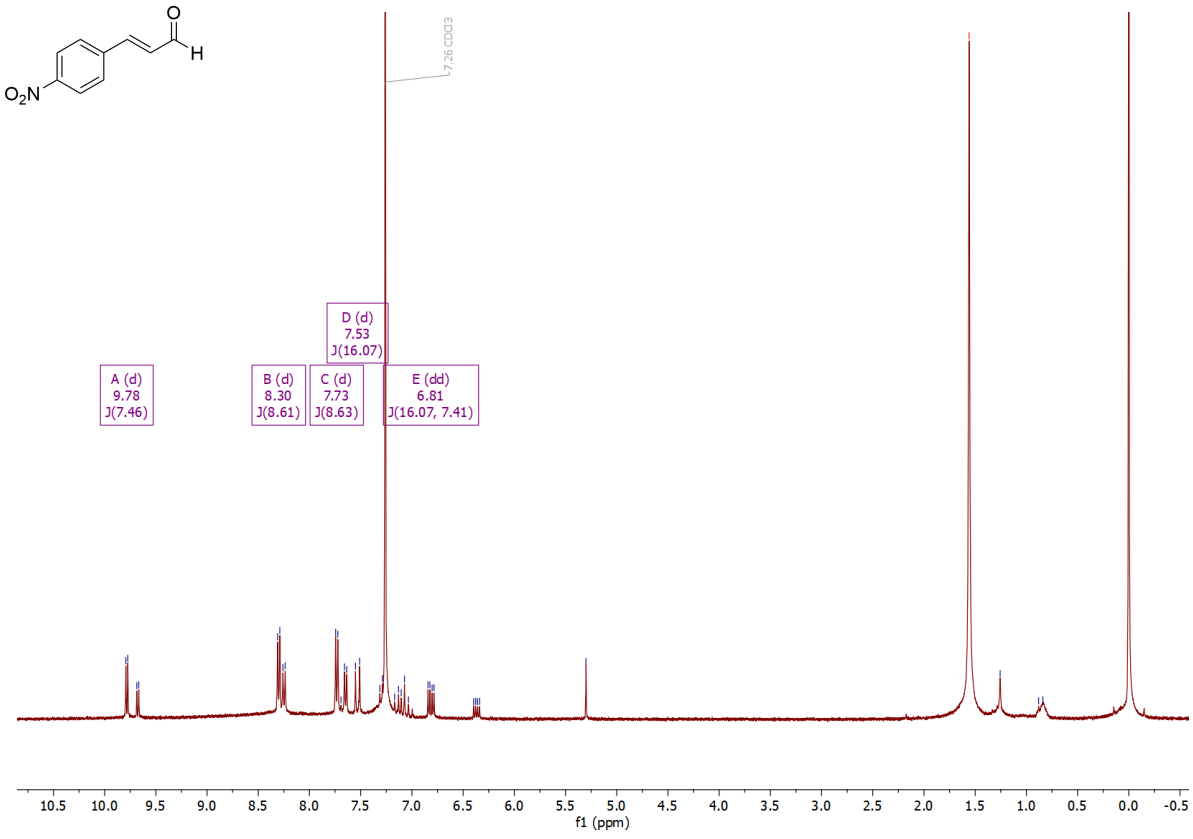
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Wittig reaction (shorter reflux time).
E:*Z* ratio 98:2.



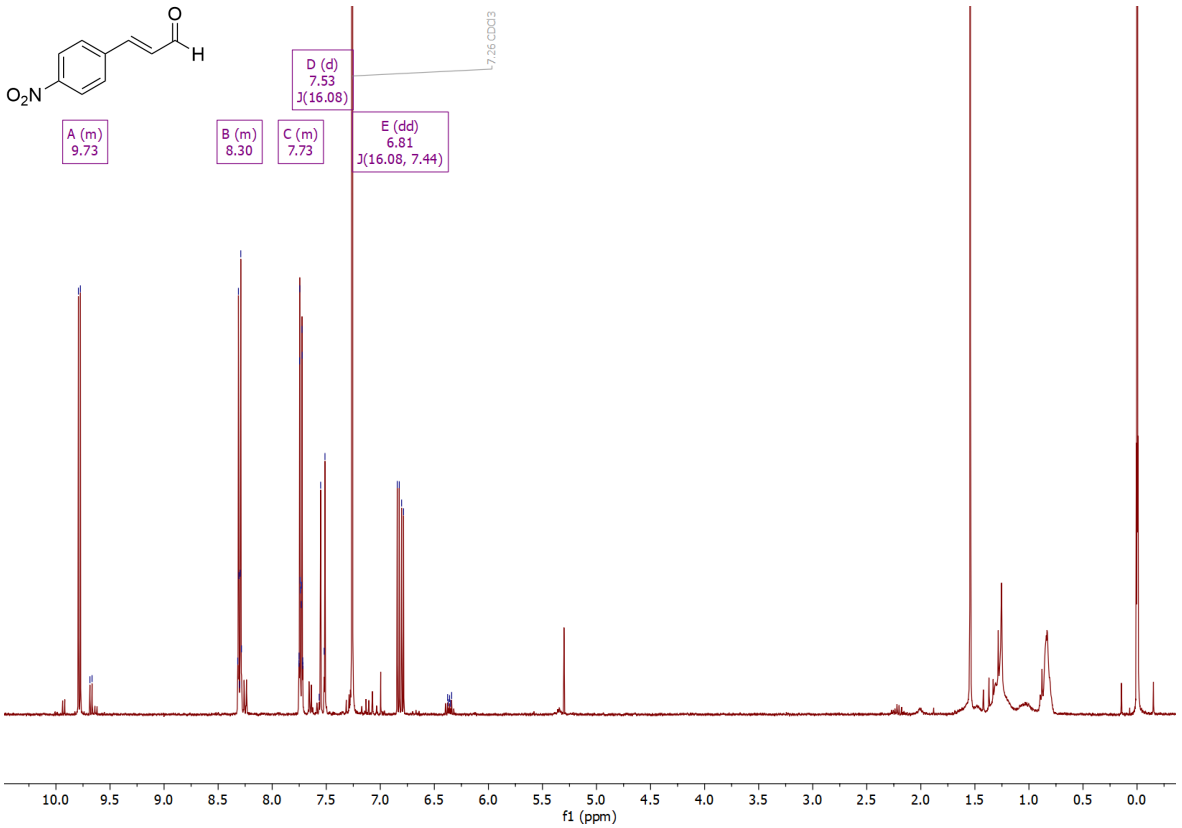
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Wittig reaction (toluene).
E:*Z* ratio 54:45.



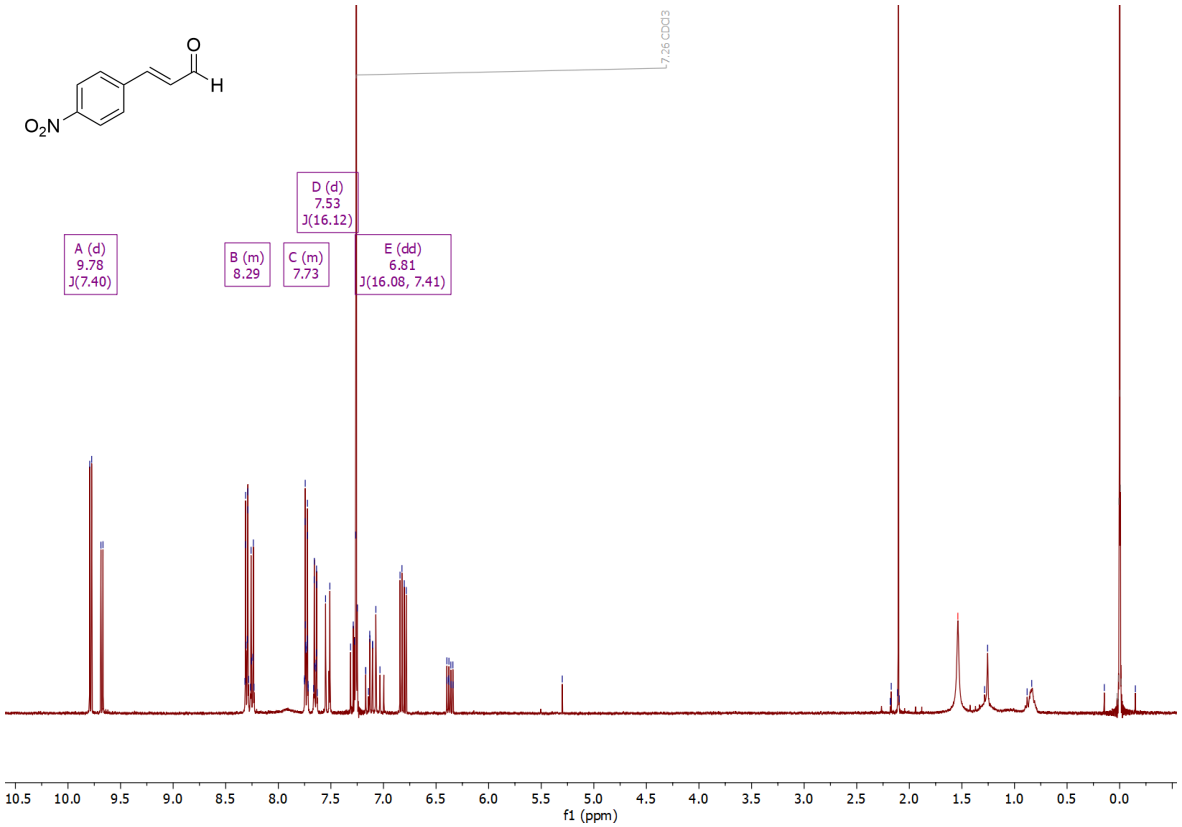
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Julia–Kocienski reaction.



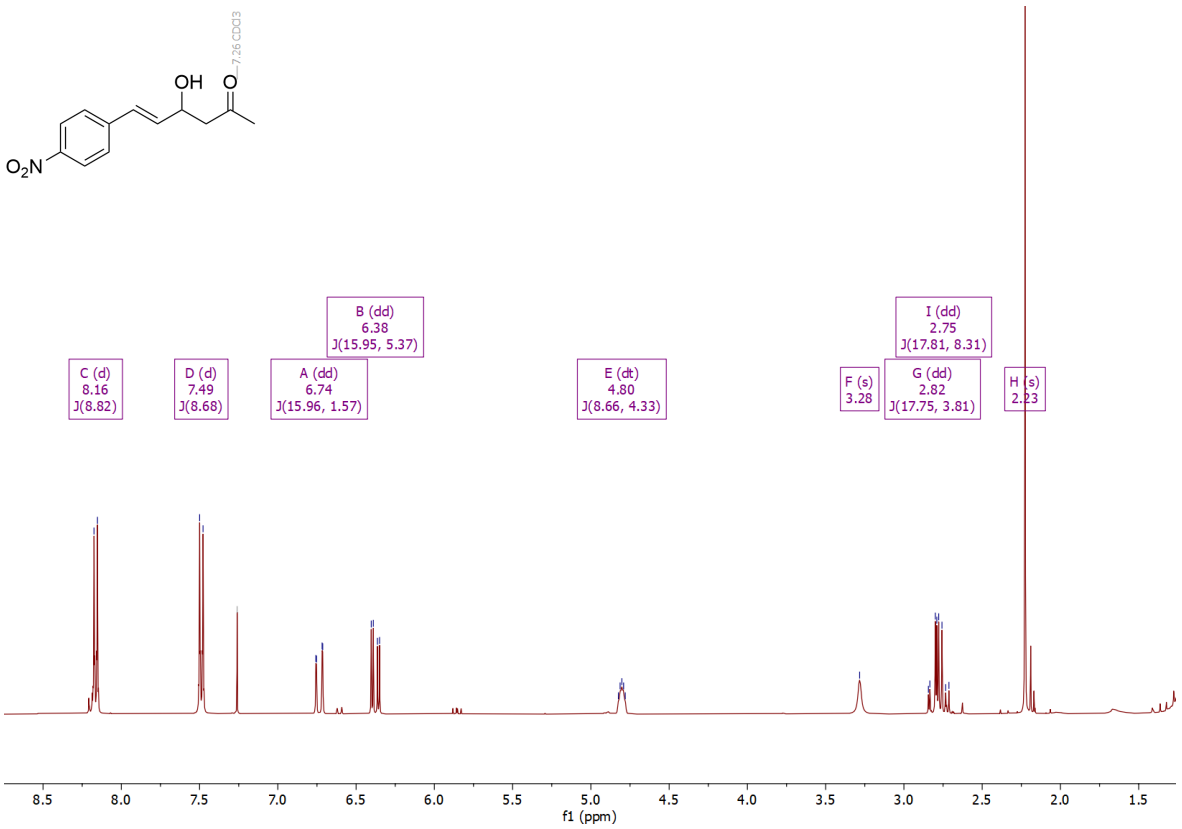
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Isomerization with I_2 (dark).
E:*Z* ratio 69:31.



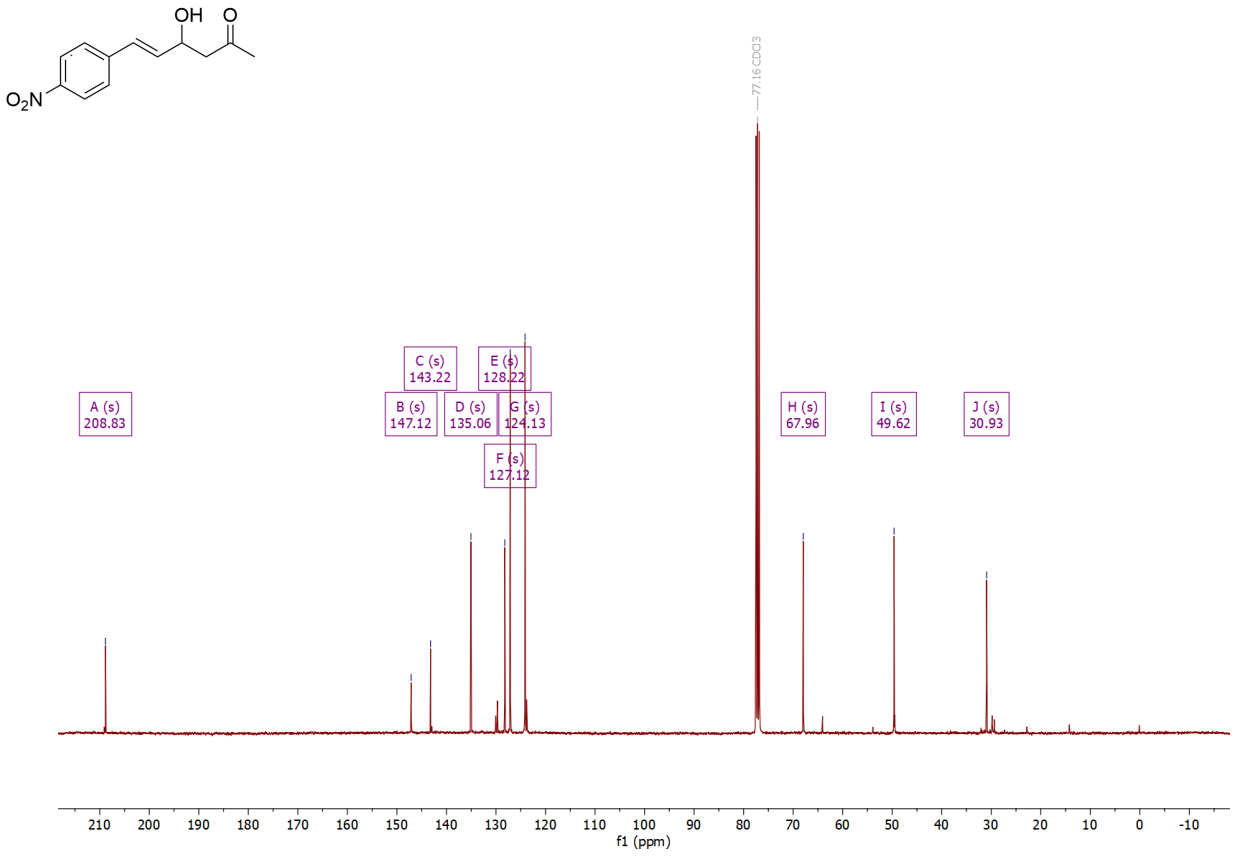
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Isomerization with I_2 (sunlight).
E:*Z* ratio 93:7.



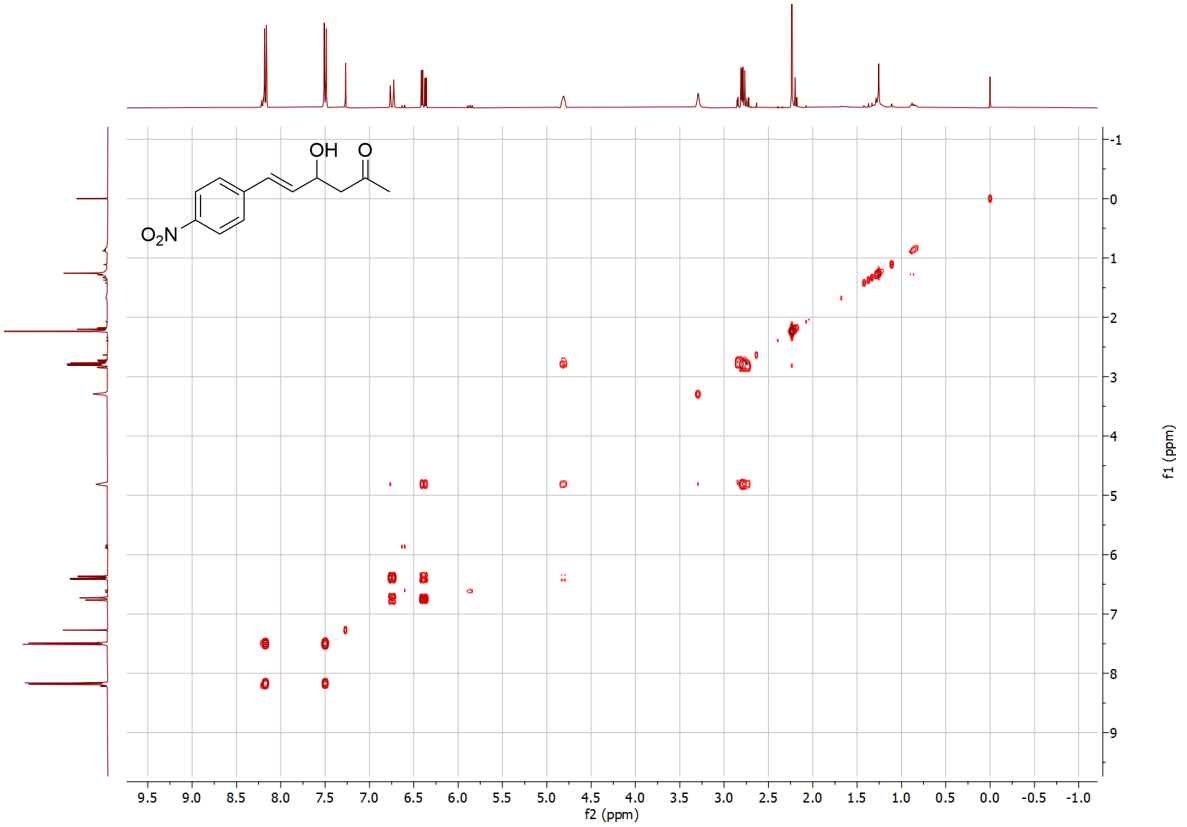
^{1}H-RMN of *p*-nitrocinnamaldehyde **7** in $CDCl_3$. Isomerization with acid.
E:*Z* ratio 59:41.



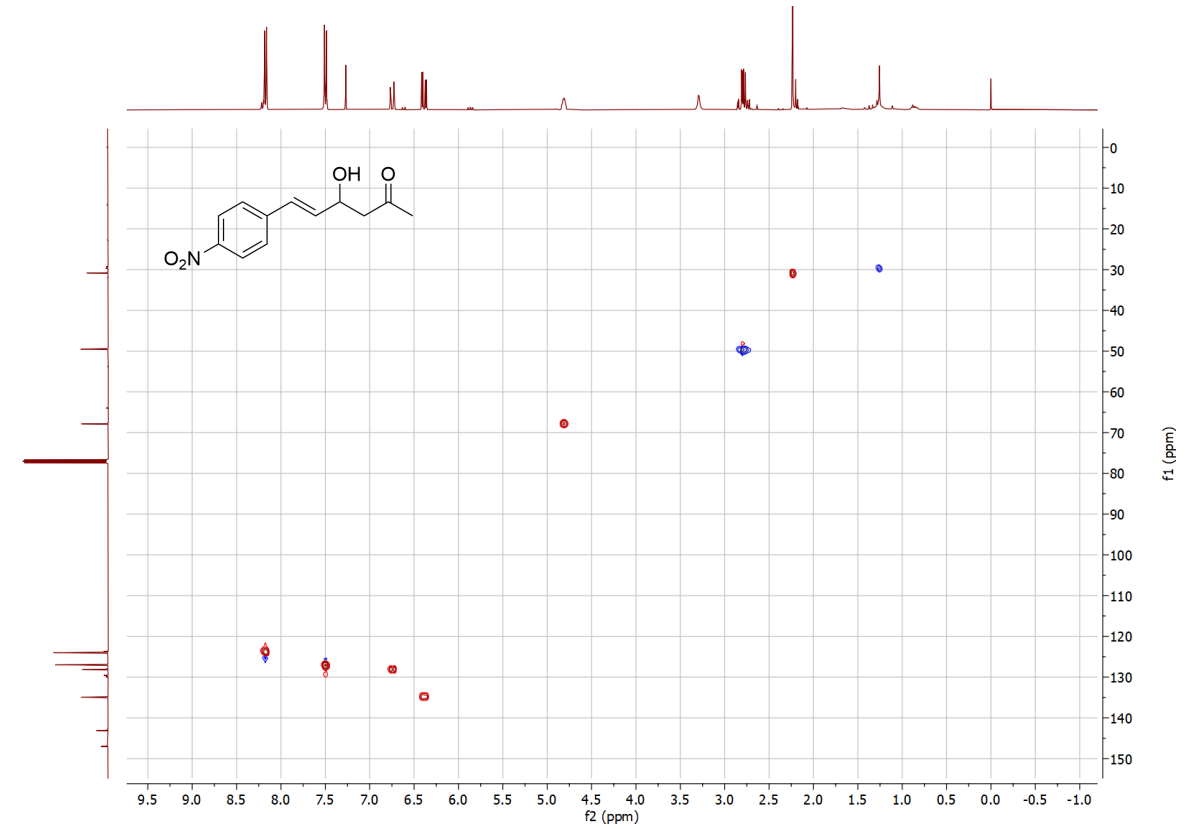
^{1}H-RMN of (5*E*)-4-Hydroxy-6-(4-nitrophenyl)-5-hexen-2-one **10** in $CDCl_3$.



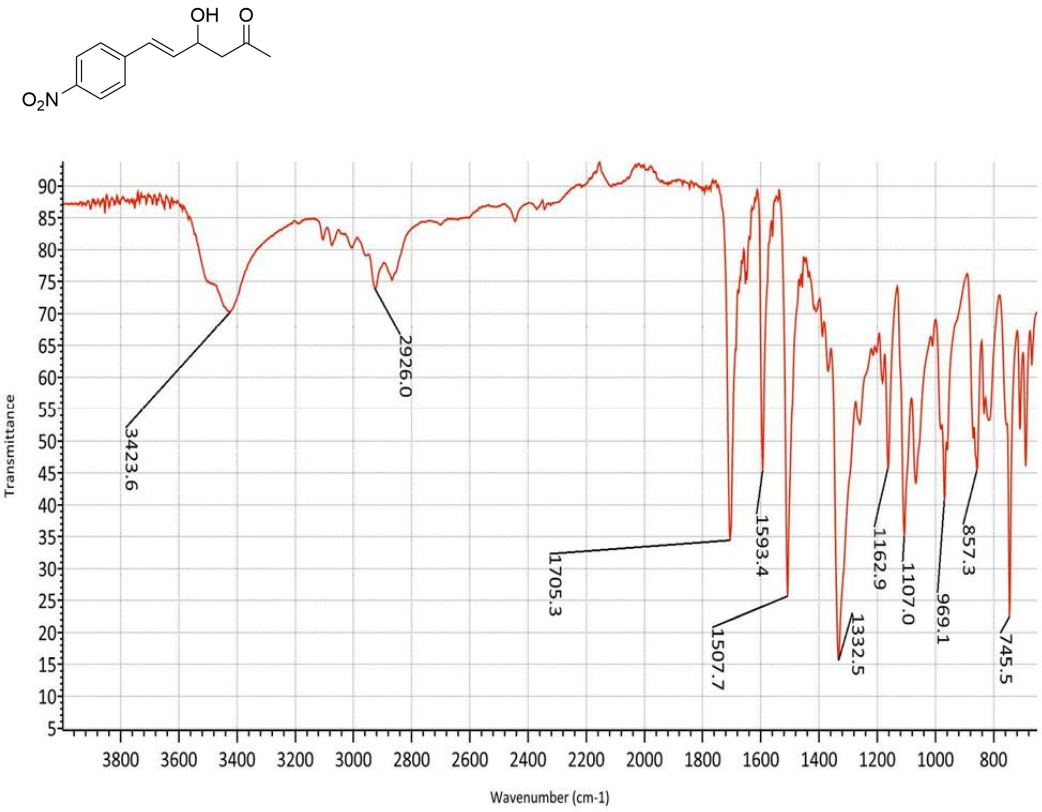
^{13}C-RMN of (5*E*)-4-Hydroxy-6-(4-nitrophenyl)-5-hexen-2-one **10** in $CDCl_3$.



2D ^{1}H-^{1}H COSY (400 MHz) of (5*E*)-4-Hydroxy-6-(4-nitrophenyl)-5-hexen-2-one **10**.



2D ^{1}H-^{13}C HSQC (400 MHz) of (5*E*)-4-Hydroxy-6-(4-nitrophenyl)-5-hexen-2-one **10**.



IR of (5*E*)-4-Hydroxy-6-(4-nitrophenyl)-5-hexen-2-one **10**.