DEEP EUTECTIC SOLVENTS (DES) AS CATALYST AND SOLVENT FOR

KNOEVENAGEL CONDENSATION REACTIONS

by

Hanan Almuzaini

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Thesis Committee:

Dr. Scott Handy, Major Professor

Dr. Keying Ding

Dr. Kevin L. Bicker

ABSTRACT

The Knoevenagel condensation reaction is one of the most important condensation reactions that can be used in different areas such as cosmetics, perfumes, pharmaceuticals, calcium antagonists and polymers [1]. Usually, it is carried out in organic solvents. Bases such as ammonia, primary or secondary amines, and their salts can catalyze a Knoevenagel reaction [2-3]. Several heterogeneous catalysts such as aluminum oxide [4], alkali-containing MCM-41 [5], and zeolites [6] can also be used to catalyze this reaction. Recently, with the development of the green chemistry concept, which seeks to reduce negative environmental impact [8], the Knoevenagel condensation reaction was rewritten under greener conditions. It was found that deep eutectic solvents (DES), a mixture of two or three cheap and safe solid components that are capable of associating with each other through hydrogen bond interactions [19], are a good option to catalyze this type of reaction. DES is inexpensive, safe, and easy to recycle. This type of reaction conditions gave a high yield under a smooth process in a short time [28]. By using a deep eutectic solvent (choline chloride/urea) as a catalyst and solvent, different factors that could affect the Knoevenagel condensation reaction, such as the effect of substituted groups in active methylene compounds on the yield of the products, can be studied.

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CHAPTER ONE: INTRODUCTION

Knoevenagel condensation reaction:

The Knoevenagel condensation reaction is a special case of the aldol condensation in which α,β-unsaturated compounds are the major products. The basic reaction of the aldol condensation is the reaction between two carbonyl compounds as shown in Scheme 1. Alternatively, the Knoevenagel condensation reaction can occur between an active methylene, a compound that has a methylene group flanked on both sides by electron withdrawing groups, and a carbonyl compound, an aldehyde or ketone as shown in Scheme 2. α,β-unsaturated compounds, the products of the Knoevenagel condensation, have been used for cosmetics, perfumes, pharmaceuticals, calcium antagonists and polymers. [1]
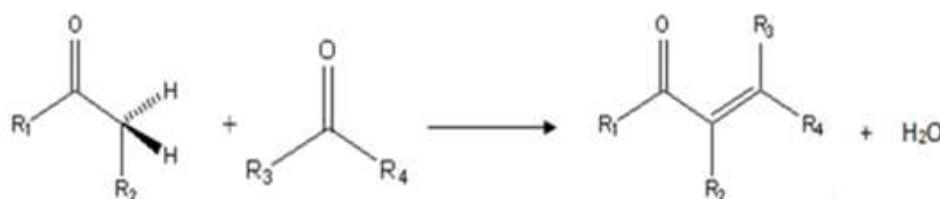
Scheme 1: The general reaction of aldol condensation
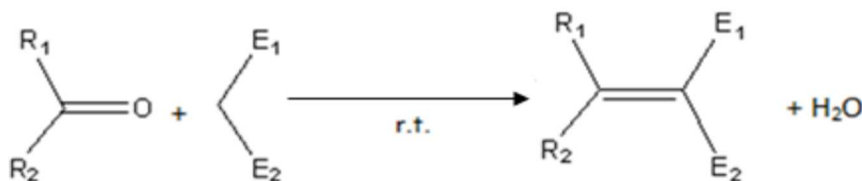
R_1, R_2= alkyl, aryl, H E_1, E_2= CN, COMe, COOMe, COOEt, COOH

Scheme 2: The general reaction of Knoevenagel condensation

In general, Knoevenagel condensation reactions are carried out in organic solvents. Bases such as ammonia, primary or secondary amines and their salts can catalyze the Knoevenagel reaction [2-3]. Several heterogeneous catalysts such as aluminum oxide [4], alkali-containing MCM-41 [5], and zeolites [6] can also be used to catalyze this reaction.

Mechanism of Knoevenagel condensation reaction:

A recent study used task-specific ionic liquids such as $[H_3N^+-CH_2-CH_2-OH]$ $[CH_3COO^-]$ as a catalyst for the Knoevengel condensation reaction [7]. By using this type of catalyst, the hydroxyl group and ammonium group of a catalyst combined to activate the active methylene and the carbonyl group of the aromatic aldehydes, mediating the proton transfer necessary to get to a simple aldol-like intermediate, which undergoes dehydration to afford the final product. It was found that the Knoevenagel reaction affords just the E-isomer with no Z-isomer detected in the NMR, likely to thermodynamic reasons. According to this result, a mechanism obtained for the Knoevenagel condensation reaction is shown in Scheme 3.
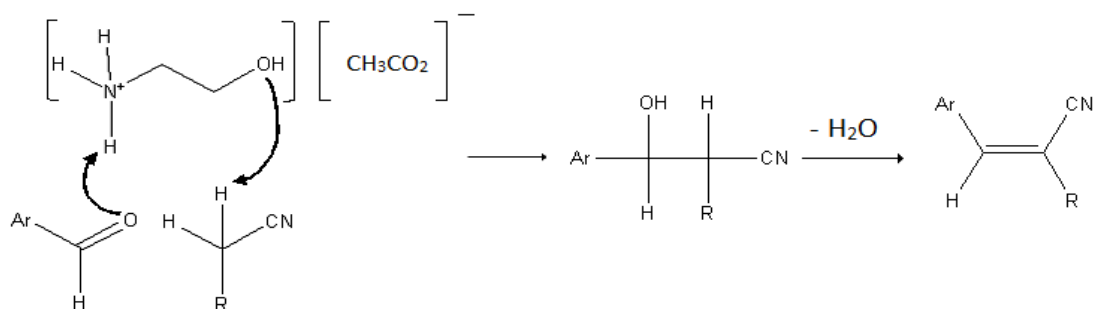
Scheme 3: The Knoevenagel condensation reaction gives E- isomers

Green chemistry:

Green chemistry is a new approach that has been developed in recent years. It focuses on the safety of the environment by designing chemical products processes that reduce or eliminate the generation of hazardous substances. [8]

In fact, there are some key principles to make a greener chemical, process, or product. The process, solvents, and raw materials should be safe. It should use fewer chemicals and solvents and less energy. Green chemistry focuses on using recyclable solvents and catalysts to prevent waste which is better than treating or cleaning up waste after it has been created. The process should be efficient with use fewer hazardous materials. If a process follows these principles, it will be friendly to the environment [8].

In general, the Knoevenagel condensation reactions are done using organic solvents and basic catalysts such as primary or secondary amines and their salts. Heterogeneous catalysts such as aluminum oxide have been used to catalyze this reaction [4]. Even though the Knoevenagel condensation is carried out under these conditions, there are still a lot of limitations such as long reaction time, the need of a high temperature, harder recovery, and complex reaction conditions. In addition to all of these limitations, organic solvents have toxicity problems, and these catalysts are harder to re-use and recover. So, a new set of conditions is needed to avoid all of these disadvantages.

With the development of the green chemistry concept, the Knoevenagel condensation reaction has been studied under different conditions, which could reduce environmental issues. The organic solvents have been replaced by other types of solvents

such as water. Water is used as a solvent for different types of organic reactions such as Diels–Alder reactions. The Diels-Alder reaction has been reviewed by Chanda and Fokin et al. [9]. They also reviewed other types of heterogeneous reactions for several important reactions such as Passerini and Ugi, 1,3-dipolar cycloadditions and Claisen. All of these reactions were done by using water as a solvent [9].

Water is not only friendly to the environment but also cheap. The Knoevenagel reaction can be done in a shorter time with water than with organic solvents, and it can occur at room temperature when poly-guanidine is used as a catalyst (Figure 1). Poly-guanidine **1** is easy to reuse, which makes it greener than other catalysts [10].

Scheme 4 illustrates the reaction of benzaldehyde **2** with malononitrile **3** in water with poly-guanidine **1**. It clearly shows the reaction needs more time when organic non-polar solvents or solvent-free conditions are used (Table 1, entries 1, 2, and 3). On the other hand, water is just as good as any highly polar organic solvent (such as methanol and DMF, Table 1, entries 4, 5, and 7); however, organic solvents have toxicity problems compared to water.
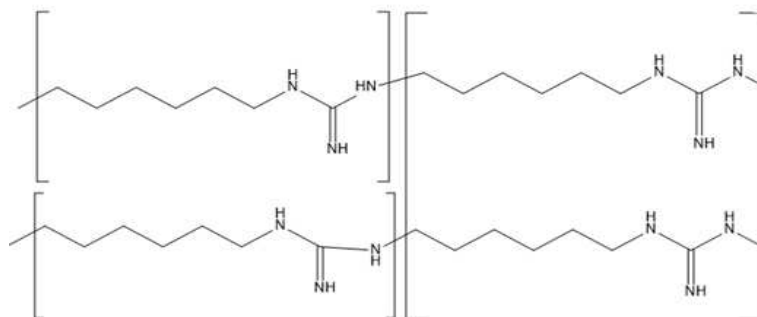
Figure 1: The structure of poly-guanidine **1**
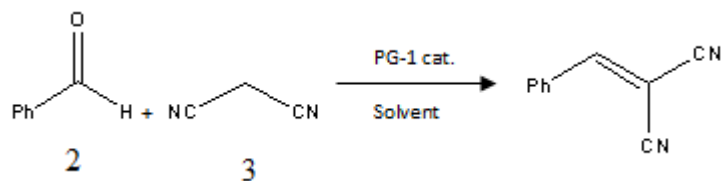
Scheme 4: The reaction of **2** with **3** in water catalyzed by PG-1

Table 1: Solvent effects on the reaction of **2** with **3**

Entry	Solvent	Reaction time [min]	Yield of 3a %
1	CH_2Cl_2	90	86
2	THF	90	88
3	CH_3CN	90	91
4	CH_3OH	10	90
5	DMF	15	92
6	-	6 h	93
7	H_2O	10	94

Ionic liquids have been used with solvent or solvent-free conditions to catalyze the Knoevenagel condensation reaction because they have the unique chemical and physical properties of non-volatility, nonflammability, thermal stability, and controlled miscibility

[11]. Several ionic liquids have been used in the reaction under several different sets of reaction conditions including grinding, microwave irradiation, and melting [11]. These conditions give a high yield of α,β-unsaturated compounds in short time, as is shown in Scheme 5 and Table 2.
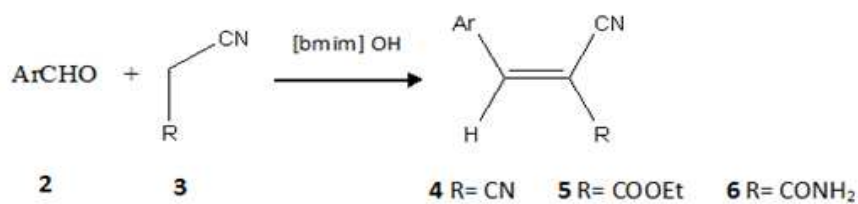
Scheme 5: The Knoevenagel condensation reaction is catalyzed by ionic liquids

Table 2: Condensation reactions of aromatic aldehydes with active methylene compounds

Entry	Ar	R	Yield[a] (%)	Time[b] (S)	Yield[b] (%)	Time[c] (min)	Yield[c] (%)	Mp (^{0}C)	Mp[lit] (^{0}C)
1	4-Cl-C_6H_4	CN	93	90	93	1	90	162.5-163.6	160-162
2	4-OH-C_6H_4	CN	93	60	88	1	91	188-189	188-189
3	4-Cl-C_6H_4	COOEt	-	30	95	3	82	93.5-94	92-94
4	4-Cl-C_6H_4	CONH$_2$	-	90	88	5	82	205-206.5	206-207

[a] Grinding reaction   [b] Microwave irradiation reaction   [c] Melting reaction

Several papers were published about how to catalyze Knoevenagel condensation reaction by ionic liquids [12-13-14]. It seems that they achieve the goal of doing this reaction under safe reaction conditions with less complex conditions than using water. However, many ionic liquids are expensive, toxic, and minimally biodegradable [15-16]. So the study of potential new approaches continues.
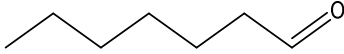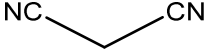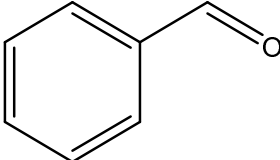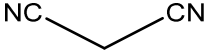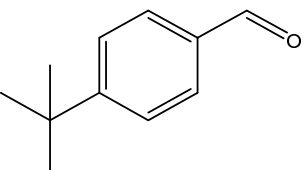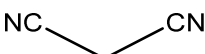
Another option to catalyze the Knoevenagel condensation reaction is by using Lu(III) metal-organic frameworks as a Lewis acid. This option can give a high yield in a short time, about 8 hours. However, a high temperature is needed. Also, it was found that the activity of this type of catalyst for aliphatic aldehydes is higher than aromatic aldehydes and the conversion and selectivity is affected by the time as shown in Scheme 6 and Table 3 [17].
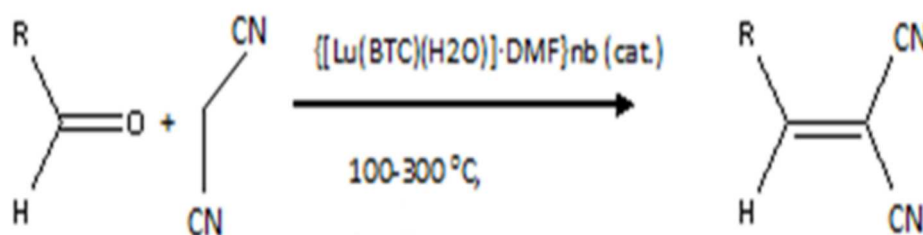
Scheme 6: Knoevenagel condensation of aldehydes with active methylene compounds using Lu framework catalyst.

The Knoevenagel condensation reaction can be done under free solvent conditions using gallium chloride as a catalyst, as shown in Scheme 7. The reaction is done in a short time and at room temperature. However, the catalyst cannot be recycled [18].

Table 3: Conversion and selectivity in Knoevenagel condensation

Aldehyde	Methylene compound	Reaction temperature ^{0}C	Conversion after 480 min	Selectivity after 480 min
	NC⁀CN	130	100	87
	NC⁀CN	130	46	65
	NC⁀CN	130	36	Not detected

R=Ph, furfuryl, pyridyl

X=CN or COOEt
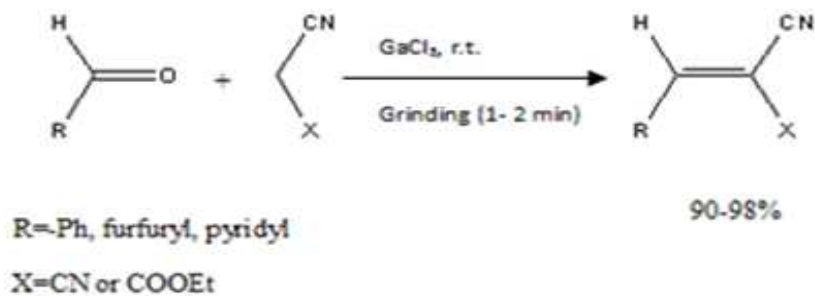
Scheme 7: Knoevenagel condensation reaction using gallium chloride as a catalyst

Deep eutectic solvents (DES):

In 2003, deep eutectic solvents (DES) were first introduced by Abbott and co-workers [19]. DES are mixtures of two or three cheap and safe solid components that are capable of associating with each other through hydrogen bond interactions. These types of solvents can be used in polymer chemistry and synthetic organic chemistry due to their extremely low vapor pressure [20].

There are three main families of DES. The first family involves the mixture of a ioniz salt and a hydrogen-bond donor with a 1:2 molar ratio and is the most heavily studied. An example of this family is the mixture of choline chloride and urea, as shown in Scheme 8. The second family involves the combination of a ioniz salt with a metal salt such as choline chloride and zinc chloride, in a 1:2 molar ratio and the expected reaction is shown in Scheme 9 [21]. The third family, which is more complex, is the combination of a carbohydrate, a urea, and an ammonium salt in varying ratios. The combination of choline chloride and d-fructose, as shown in Scheme 10, is an example of the third family [22]. All of these families of DES have very similar characteristics. The high cost and toxicity of ionic liquids are generally avoided by using inexpensive, non-toxic, and biodegradable compounds to make the DES.
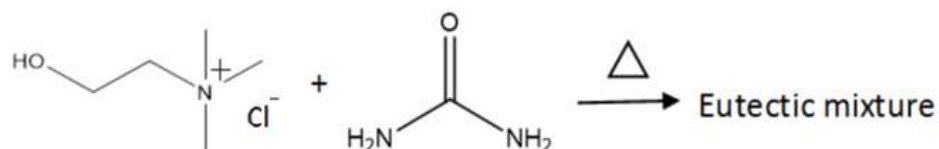
Scheme 8. An example of the first family of DES
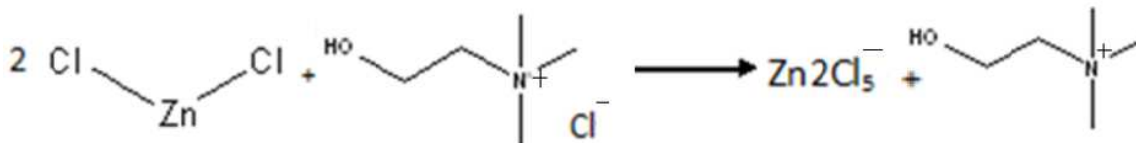
Scheme 9. An example of the second family of DES
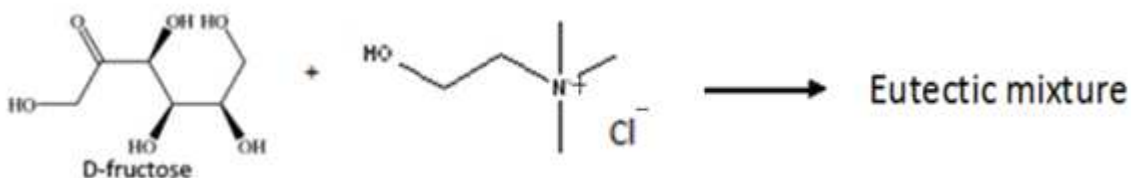
Scheme 10. An example of third family of DES, mixture of d-fructose and choline

chloride.

Due to the variety of salts and hydrogen-bond donors or metal salts that can be

used to form different types of DES, a number of fundamental properties such as Lewis

or Bronsted acidity, polarity, and solvent miscibility can be controlled. In addition, the

different types of DES have found many significant areas of application. DES are

excellent solvents for enzymatic reactions [23]. They have also been used as solvents for

the development of prebiotic chemistry [24]. One of the most common application for

DES is their use in organic synthesis [25].

The most common solvent that has been used for all areas of application,

including organic synthesis, is choline chloride/urea (CC/U). This is because both urea

and choline chloride are available in very large quantities at a very low cost and have

very low toxicity. CC/U can be recycled. It can be dried *in vacuo* after the reaction

products are separated by extraction with an organic solvent. One can avoid using an

organic solvent by dissolving the DES in water to separate it from the reaction products and then removing the water *in vacuo* to recover the DES.

Many chemical reactions have been explored using CC/U due to its advantages. For example, it has been used for the alkylation of anilines using simple alkyl bromide in the absence of any added base as seen in Scheme 11 [26]. CC/U has also been used to catalyze many types of condensation reactions, such as the Perkin reaction seen in Scheme 12, which shows the reaction of an aromatic aldehyde with an anhydride in CC/U at room temperature to afford the cinnamic acid derivatives in good yield [27]. In addition, CC/U has been used to catalyze heteroaromatic synthesis and multicomponent reactions.
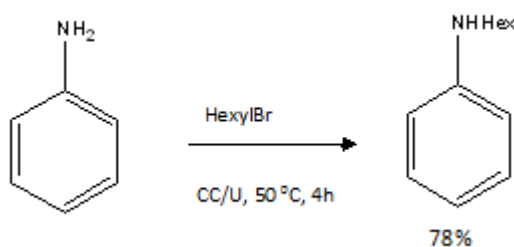
Scheme 11. Alkylation of anilines
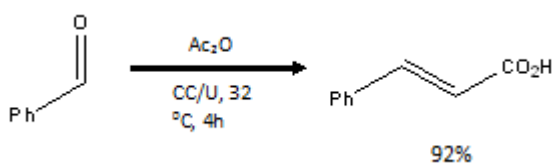
Scheme 12. Perkin reaction

Deep eutectic solvents (DES) as catalyst for Knoevenagel condensation reaction:

As shown above, a lot of chemical reactions have been studied in DES due to their advantages compared with other types of green conditions. The Knoevenagel condensation has also been very recently reported [28]. The reaction of malononitrile with aromatic aldehydes using a DES prepared from choline chloride and urea in 1:2 ratio was reported, as shown in Scheme 13. These conditions gave a high yield under a smooth process. In Table 4, different percent yields are generated from reacting benzaldehyde with malononitrile by using different types of solvents at room temperature for 20 minutes.
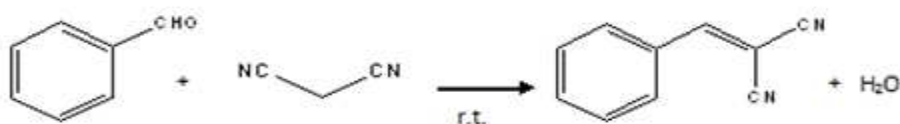
Scheme 13: The Knoevenagel condensation reaction is catalyzed by DES

Table 4. Different percent yields are generated under different solvents

Sample no.	Solvent	DES	Yield %
1	Methanol, Toluene , or DMF	-	-
2	-	ChCl: Urea= 1:1	54
3	-	ChCl: Urea= 1:2	86
4	-	ChCl: Urea= 1:3	72
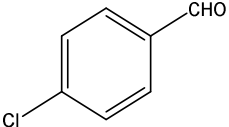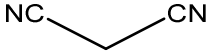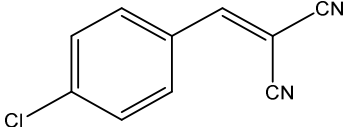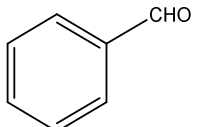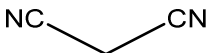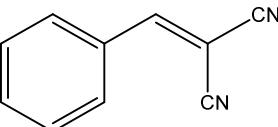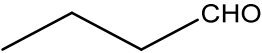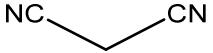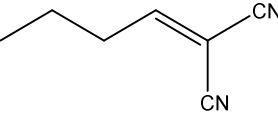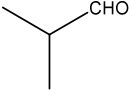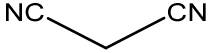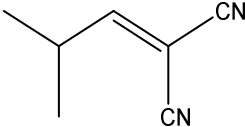
As shown in Table 4, the starting materials do not react using organic solvents at room temperature. However, different percent yields of were obtained using different molar ratios of choline chloride with urea even when no catalyst was used. As a result, using a 1:2 ratio of choline chloride and urea gives the highest percent yield.

Consequently, using deep eutectic solvents such as choline chloride with urea as a solvent without any addition of a catalyst seems to be the best reaction conditions for the Knoevenagel condensation. Compared to other methods, using DES is safe, inexpensive, and simple.

The effect of aldehyde and active methylene on Knoevenagel reaction:

It is important to note that aromatic aldehydes and aliphatic aldehydes undergo the Knoevenagel condensation reactions under different conditions. Aromatic aldehydes, whether electron-rich or electron-deficient, work well and give high yields of the products. They are very facile and addressed in all procedures. However, aliphatic aldehydes afforded complex mixtures, including Aldol products and Michael addition products. Table 5 shows the different percent yields of reacting different types of aldehydes. The results show clearly that aromatic aldehydes give a high yield in a short time, where aliphatic aldehydes do not give a yield even in after a longer reaction time [10].

Table 5. The effect of aromatic and aliphatic aldehydes on the Knoevenagel

condensation
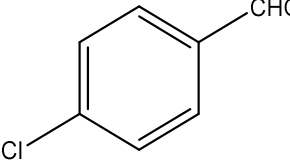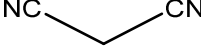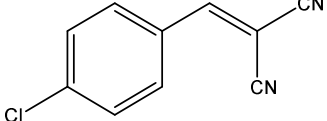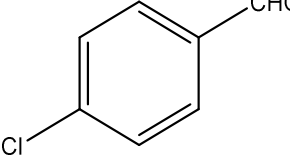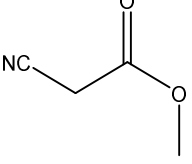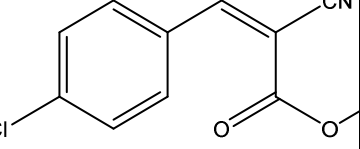
Aldehydes	Active methylene	Time [min]	Products	Yield %
		10		93
		10		94
		40		-
		40		-

* Reaction conditions: aldehyde (1 mmol), active methylene compound (1 mmol), PG-cat

1 (20 mol-%) in H_2O (3 mL), room temperature.

In addition, the substituted groups on the active methylene impact the Knoevenagel

condensation reactions. When electron-withdrawing ability increases, the activity of the

methylene group increases, too. Active methylenes with a CN group, such as malnonitrile,

react faster than other active methylenes that have a simple carbonyl group, such as ethyl

cyanoacetate, because the ethyloxy group, which is a donating group by resonance, makes

the carbonyl group a less effective withdrawing group. This is illustrated in Table 6. When

the electron-withdrawing ability decreases, the reaction needs more time and gives a lower

yield [10].

Table 6. The effect of different substituted groups on active methylene

Aldehydes	Active methylene	Time [min]	Products	Yield %
		10		93
		15		90

*Reaction conditions: aldehyde (1 mmol), active methylene compound (1 mmol),

PG-2 (20 mol-%) in H_2O (3 mL), room temperature.

Current research:

At the time this project started, Knoevenagel reactions had not been explored using DES. As a result, the primary goal was to explore Knoevenagel condensation reactions under environmentally friendly conditions using deep eutectic solvents. In particular, the DES formed from choline chloride and urea in a 1:2 molar ratio was used as the solvent and catalyst for these reactions. More specifically, the influence of both electronic and steric effects on the aromatic aldehyde and the nature of the active methylene compound were also studied using a common set of reaction conditions.

CHAPTER TWO: EXPERIMENTAL

Materials:

The following materials were obtained from Alfa Aesar: 99% malononitrile, 99+% ethyl acetoacetate, 98% dimedone, 98% 4-chlorobenzaldehyde, 98% o-tolualdehyde, 97% 2-chlorobenzaldehyde, 99% barbituric acid, 98% 4-dihydroxy-2-mercaptopyrimidine; 98% p- tolualdehyde, 98% choline chloride, and 98% urea. The following materials were obtained from Sigma- Aldrich: acetylacetone, 98% 2,2-dimethyl-1,3-dioxane-4,6-dione; 98% 4-nitrobenzaldehyde, and 98% 2-thiophenecarboxaldehyde. Acros Organics supplied 99%, 4-hydroxybenzaldehyde. Bulk A.C.S reagent-grade hexanes and ethylacetate were obtained from Pharmco Aaper. Silica gel (230–400 mesh) for flash chromatography as purchased from Natland International Corporation. Thin layer chromatography (TLC) was performed on silica gel F coated on aluminum plates from Analytech. Cambridge Isotope Labs provided 99.8% deuterated chloroform and 99.9% acetone-D6 which were used for nuclear magnetic resonance (NMR) analysis.

Instrumentation:

All Knoevenagel condensation reactions were heated on a Barnstead Thermolyne heated stirplate. The solvent was pre-formed on a J-Kem Scientific at 70 ^{0}C. Solvents were evaporated under reduced pressure on a Buchi R200 rotary evaporator. A Sartorius A/C 210-S balance was used to record the masses. All ^{1}H and ^{13}C NMR spectra were collected using JEOL ECX 300 and ECA 500 NMR spectrometers.

Methods:

Preparation of the Deep Eutectic Solvent (Choline Chloride/Urea):

In a clean vial, a mixture of 7 g of choline chloride and 6 g urea (1:2 molar ratio) was heated at 70º C overnight. Then 1 mL of this solvent was allowed to cool to room temperature to use as a solvent for all Knoevenagel condensation reactions.

General Procedure for the Knoevenagel Condensation Reaction:

A mixture of 1 mmol of an active methylene compound, 1 mmol of an aldehyde and 1 mL of deep eutectic solvent were combined in a small vial. The reaction vial was stirred and heated on a Barnstead Thermolyne stirring hotplate at 80 ºC overnight. Then in a separatory funnel, the reaction mixture was washed alternately with both water and methylene chloride. The methylene chloride layer was collected and the solvent removed under reduced pressure on a rotary evaporator to afford the crude product. Some products required further purification using column chromatography as indicated. The product was separated over 10 g of silica gel, using different ratios of hexanes and ethyl acetate as eluent. The identification of known products were confirmed by comparison with the literature as indicated, while new products were fully characterized.

Propanedinitrile, 2-[(4-methoxyphenyl)methylene]- [10]
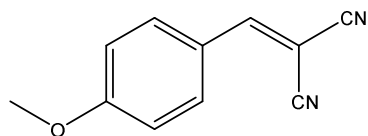
The reaction of malononitrile and 4-anisaldehyde gave a 97% yield. ^{1}HNMR (CDCl$_3$, 500 MHz): δ (ppm): 8.18 (s, 1H), 8.01 (d, J = 9.2 Hz, 2H), 7.00 (d, J = 9.2 Hz, 2H), 3.92 (s, 3H).
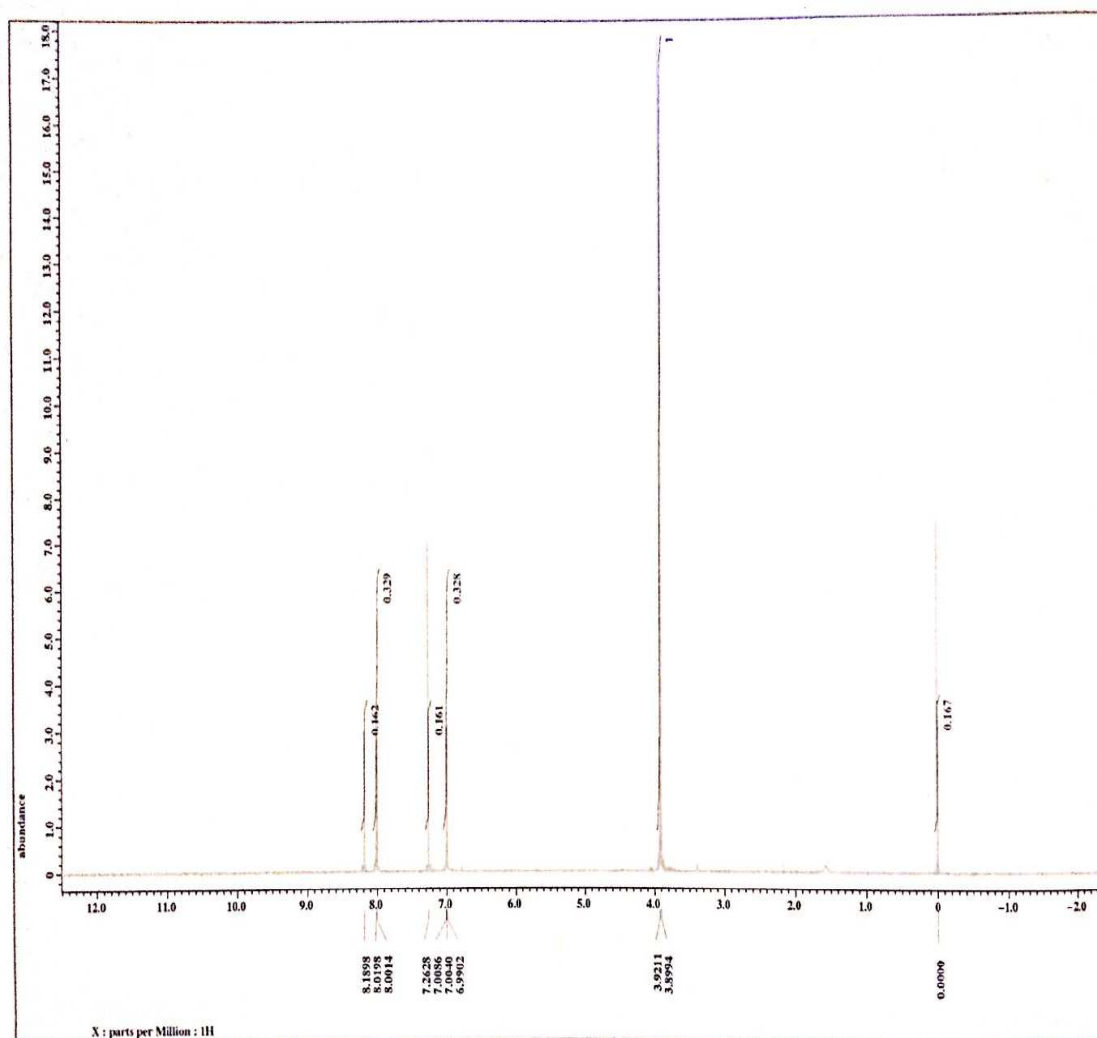
Propanedinitrile, 2-[(4-chlorophenyl)methylene]- [10]
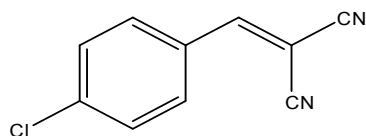
The reaction of malononitrile and 4-chlorobenzaldehyde gave an 82% yield. ^{1}HNMR (CDCl$_3$, 500 MHz): δ (ppm): 8.21 (s, 1H), 7.95 (d, J = 7.0 Hz, 2H), 7.49 (d, J = 7.0 Hz, 2H), 7.26 (s, 1H).
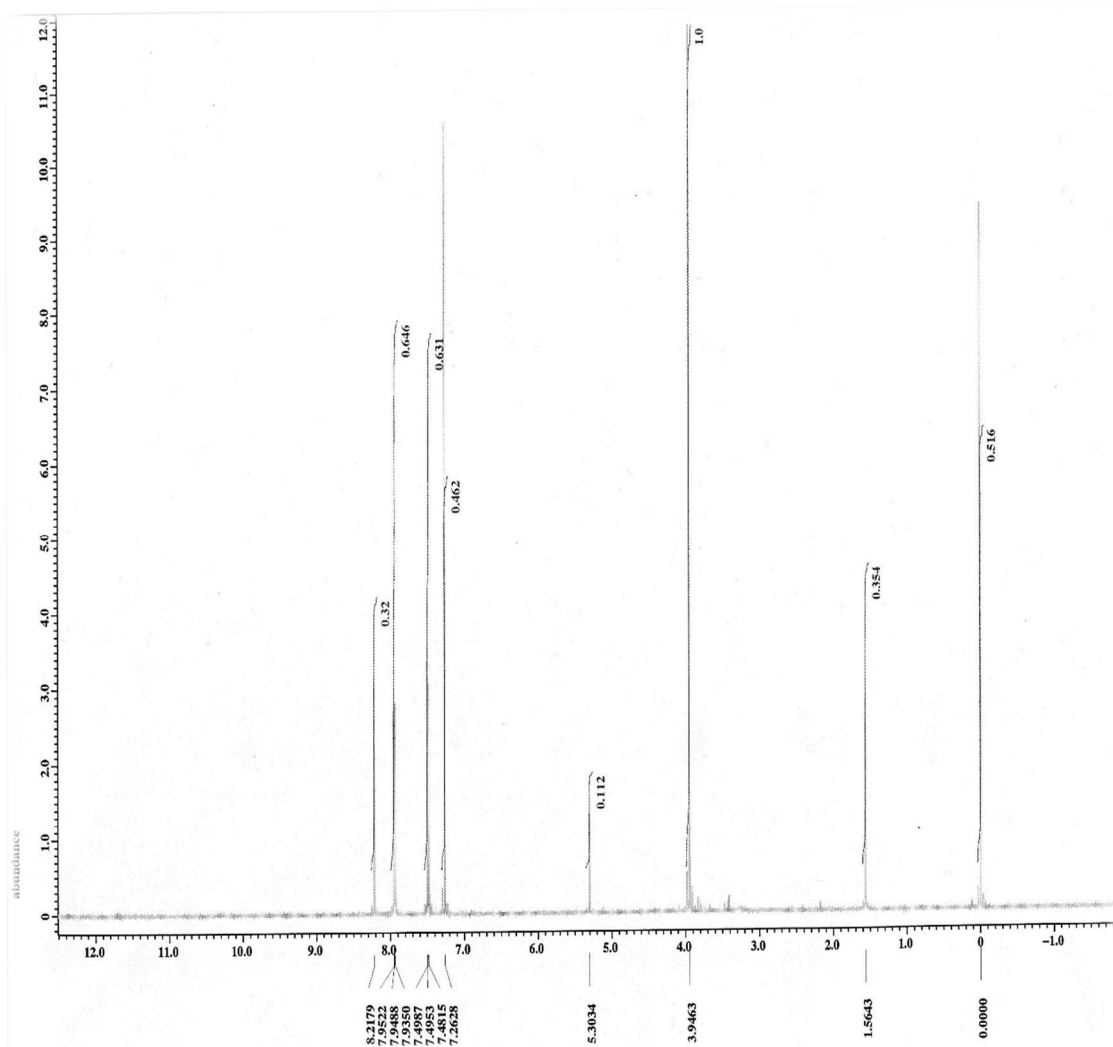
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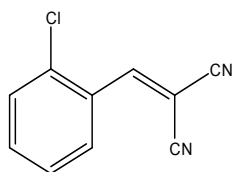
The reaction of malononitrile and 2-chlorobenzaldehyde gave a 96% yield. ^{1}HNMR (CDCl$_3$, 500 MHz): δ (ppm): 8.27 (s, 2H), 8.19 (d, J = 7.4 Hz, 1H), 7.56 (s, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.45 (s, 1H).
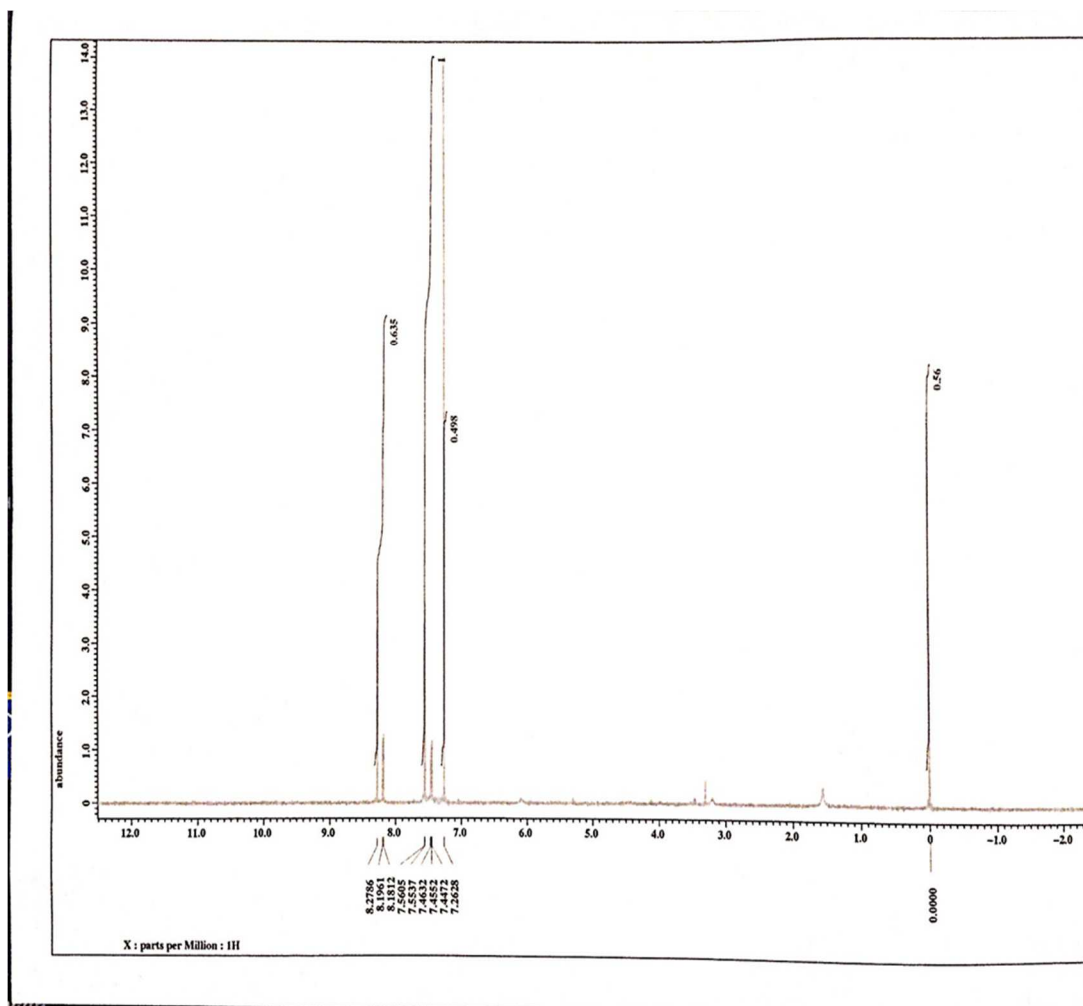
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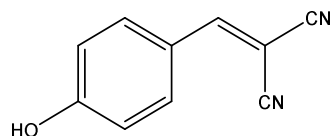
The reaction of malononitrile and 4-hydroxyphenyl gave a 74% yield. ^{1}HNMR (CDCl₃, 300 MHz): δ (ppm): 8.06 (s, 1H), 7.96 (d, J = 7.4 Hz, 2H), 7.05 (d, J = 7.4 Hz, 2H).
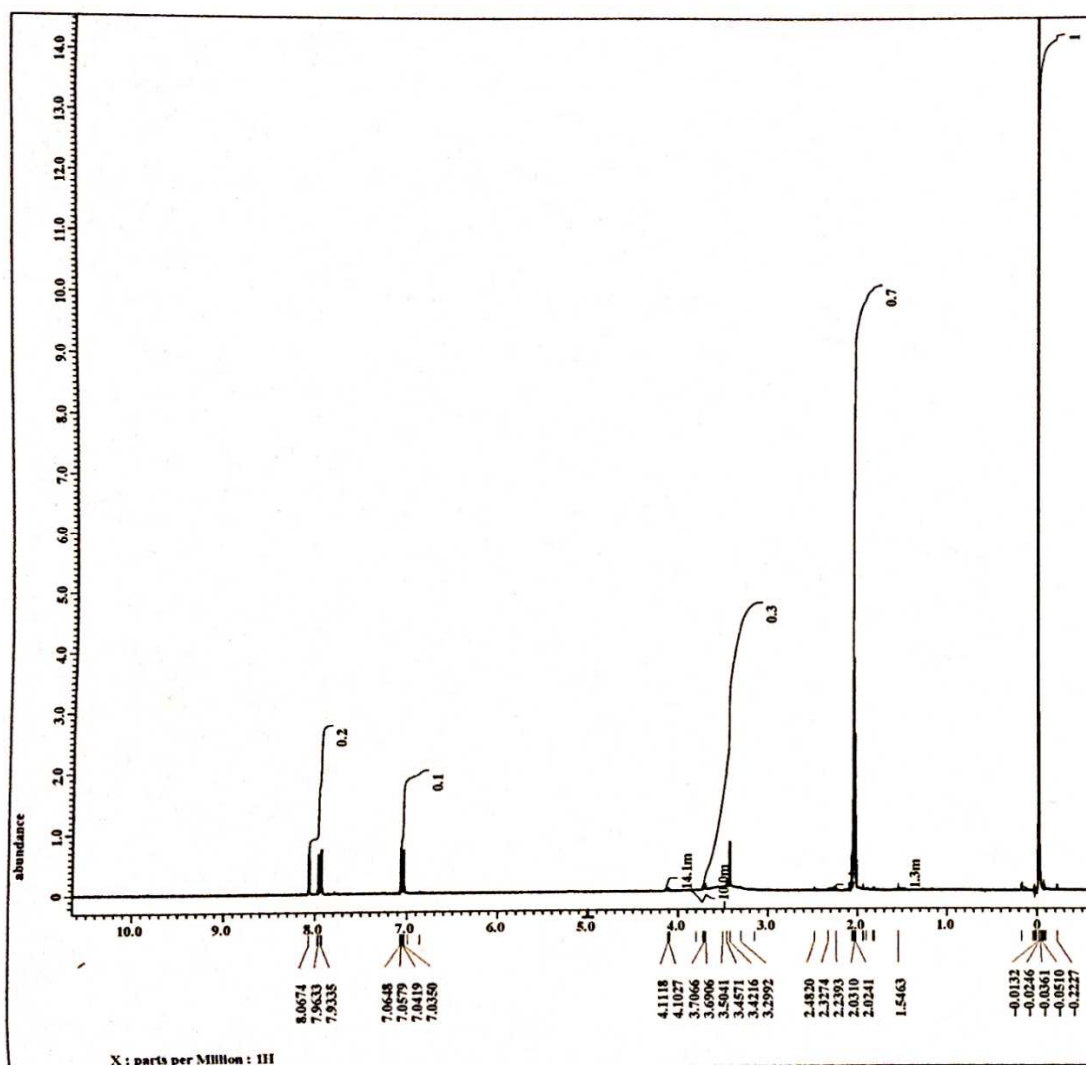
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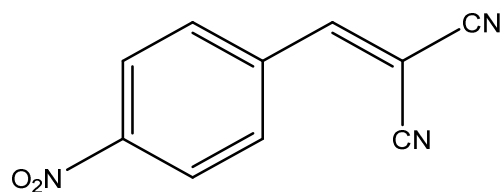
The reaction of malononitrile and 4-nitrobenzaldehyde gave a 90% yield. ^{1}HNMR (CDCl₃, 300 MHz): δ (ppm): 8.31 (d, 2H), 7.56 (d, 2H), 7.25 (s, 1H).
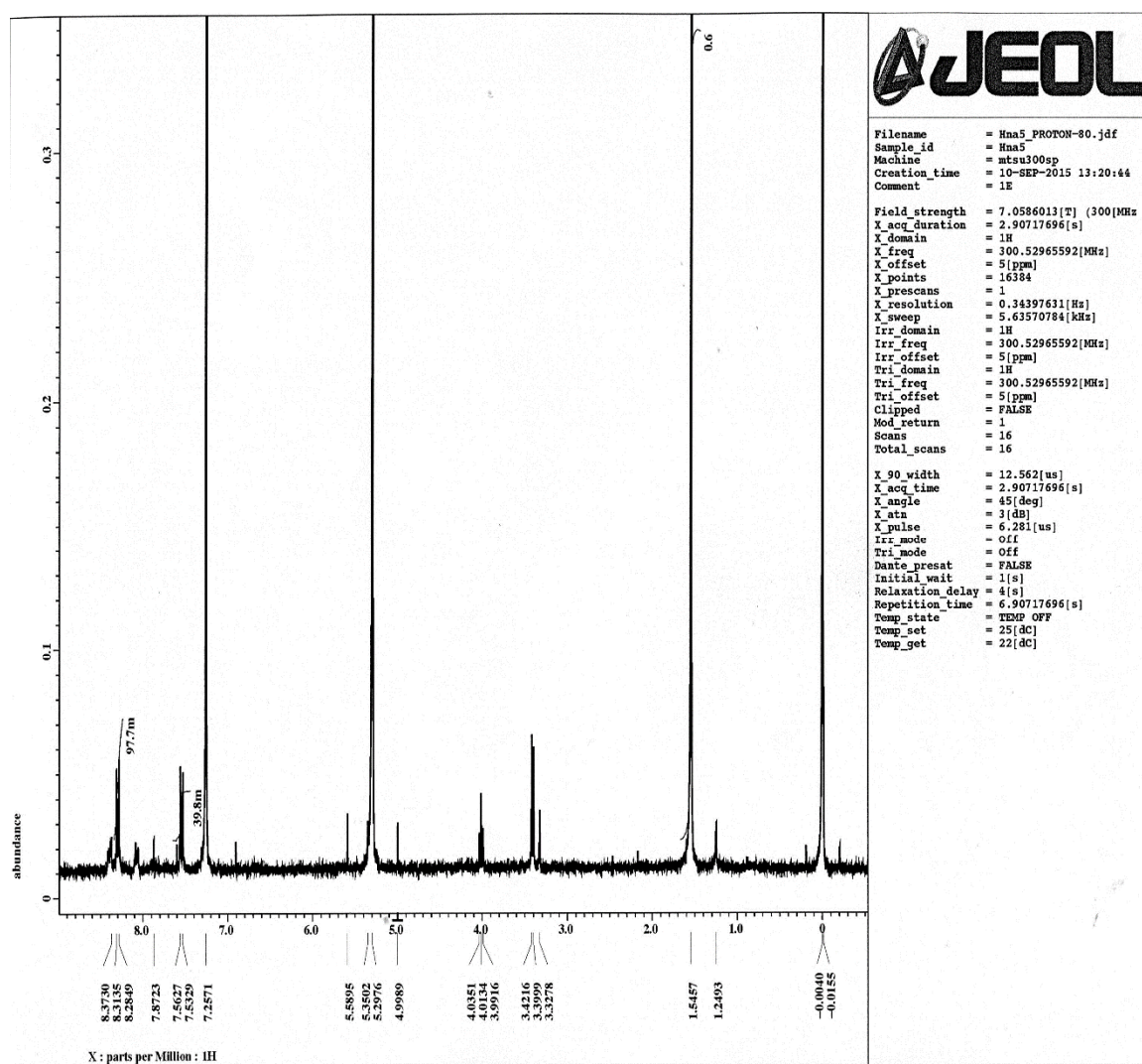
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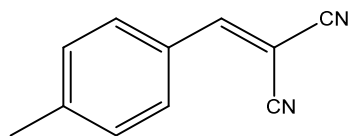
The reaction of malononitrile and p-tolualdehyde gave a 99% yield. ^{1}HNMR (CDCl3 300 MHz): δ (ppm): 7.81 (d, J = 7.4 Hz, 2H), 7.71 (s, 1H), 7.33 (d, J = 7.4 Hz, 2H), 2.16 (s, 3H).
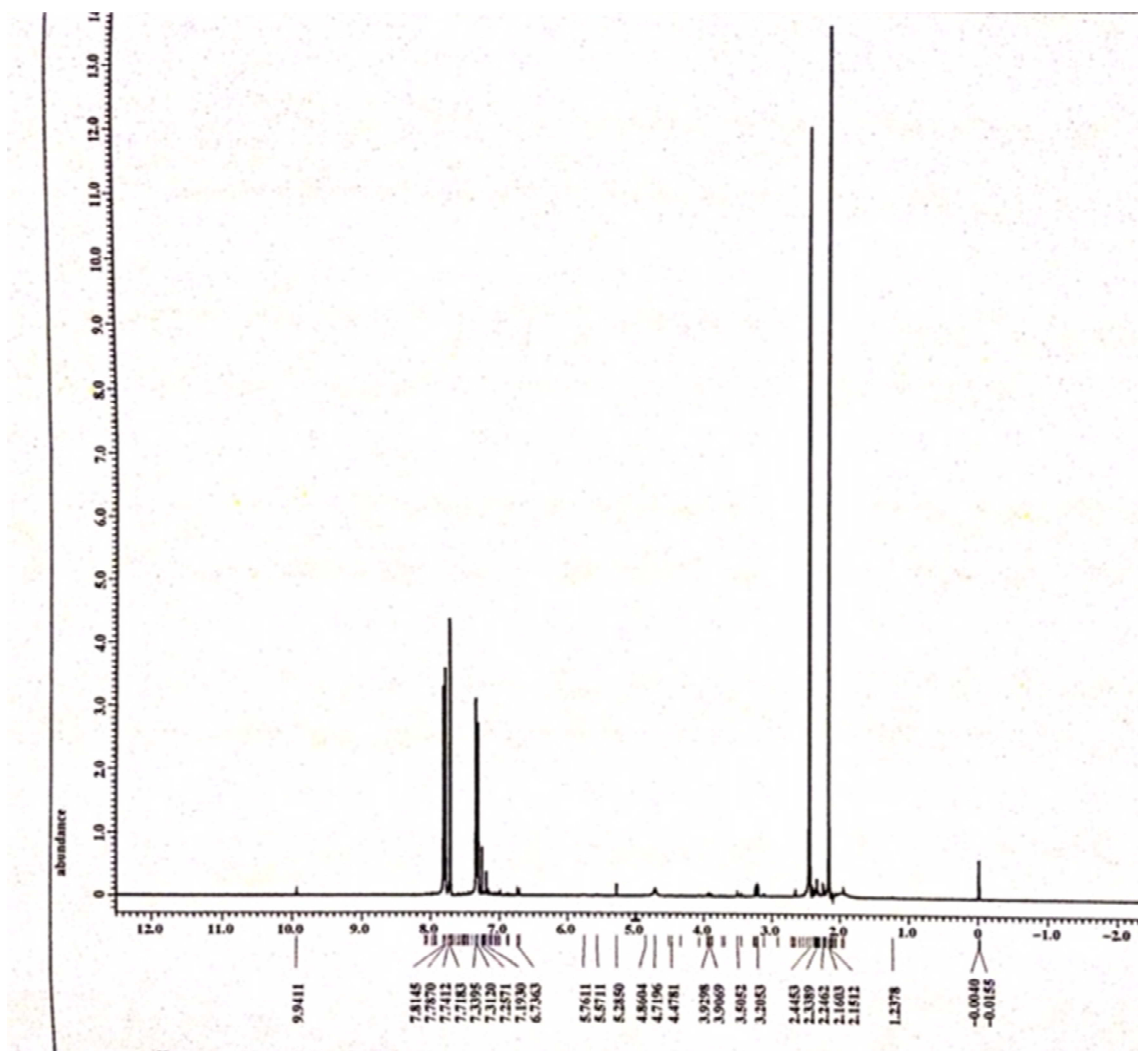
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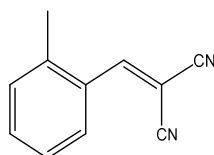
The reaction of malononitrile and o-tolualdehyde gave a 99% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): δ (ppm): 8.10 (s, 1H), 8.09 (d, J= 7.2 Mz, 1H), 7.43- 7.25 (m, 3H), 2.39 (s, 3H).
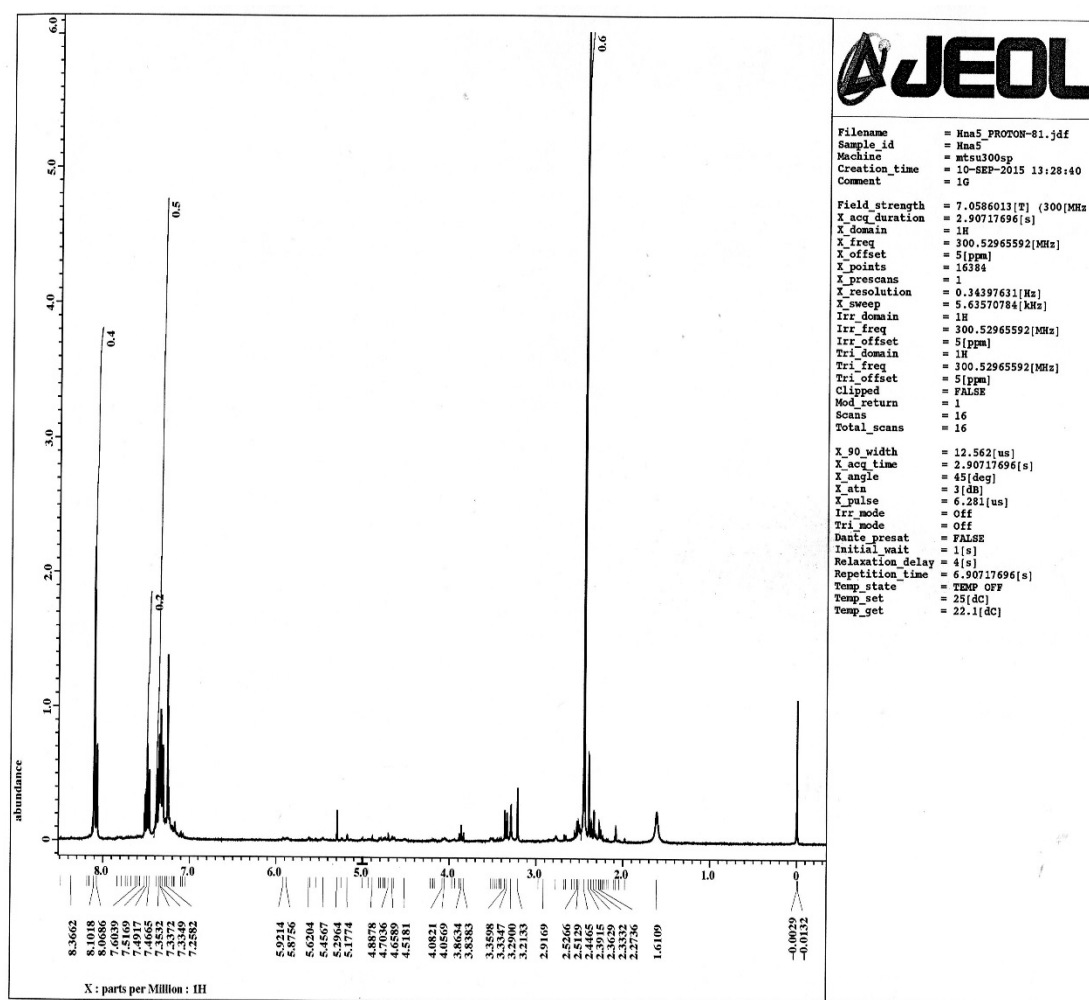
Propanedinitrile, 2-(2-thienylmethylene)- [10]
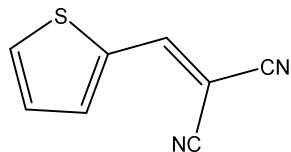
The reaction of malononitrile and 2-thiophenecarboxaldehyde gave a 99% yield.

^{1}HNMR (CDCl$_3$ 300 MHz): δ (ppm): 7.89 (d, J= 6.4 Mz, 1H), 7.87 (s. 1H), 7.80 (d, J= 3.5 Mz, 1H), 7.27 (dd, J=3.5, 6.4 Mz, 1H).
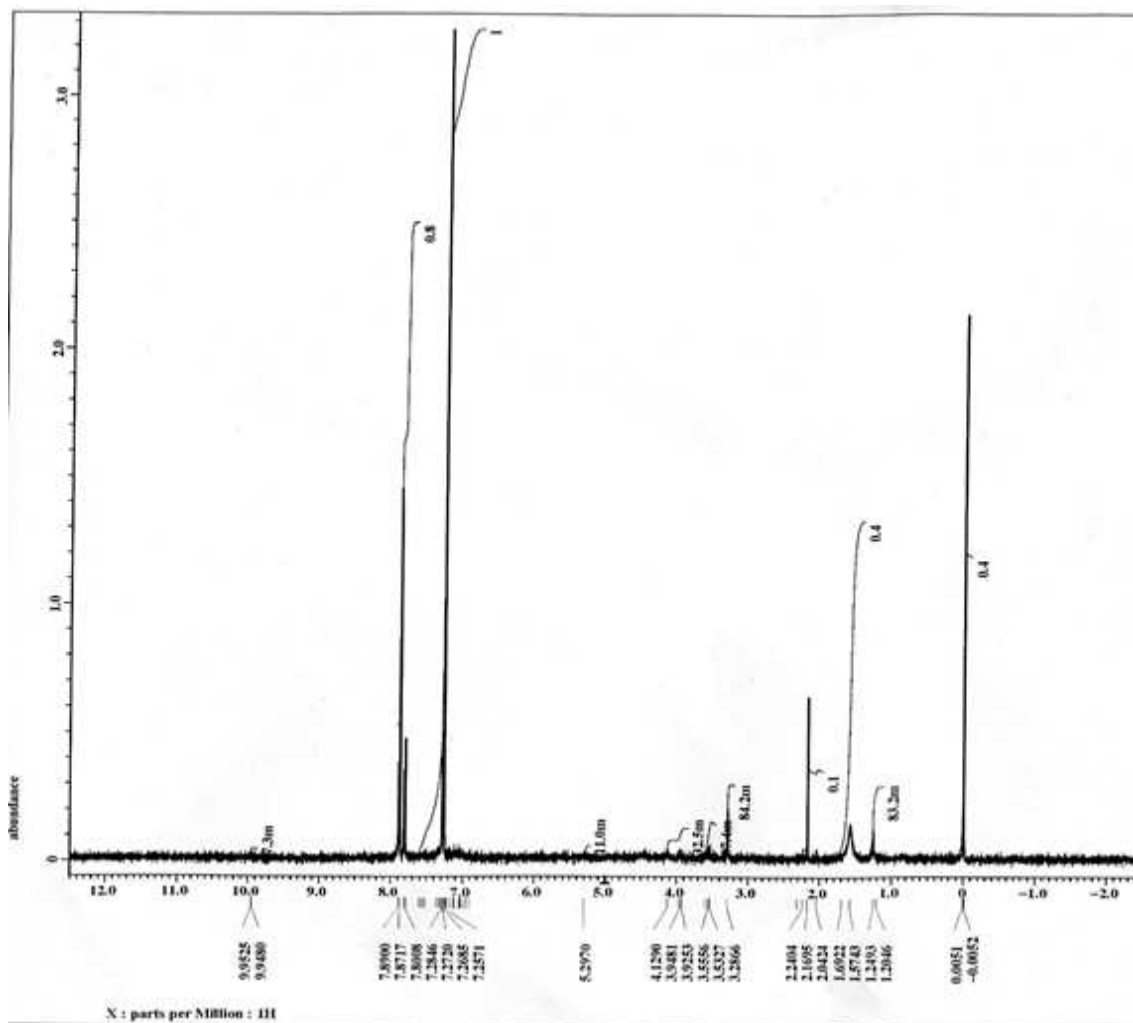
Methyl 2-cyano-3-(4-methoxyphenyl)-2-propenoate [10]
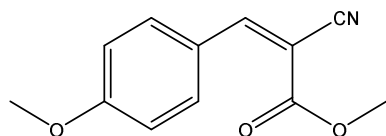
The reaction of methyl cyanoacetate and 4-anisaldehyde gave a 92% yield. ^{1}HNMR (CDCl₃ 500 MHz): δ (ppm): 7.92 (d, J = 7.4 Hz, 2H), 7.65 (s, 1H), 7.23 (d, J = 7.4 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H).

X : parts per Million : 1H
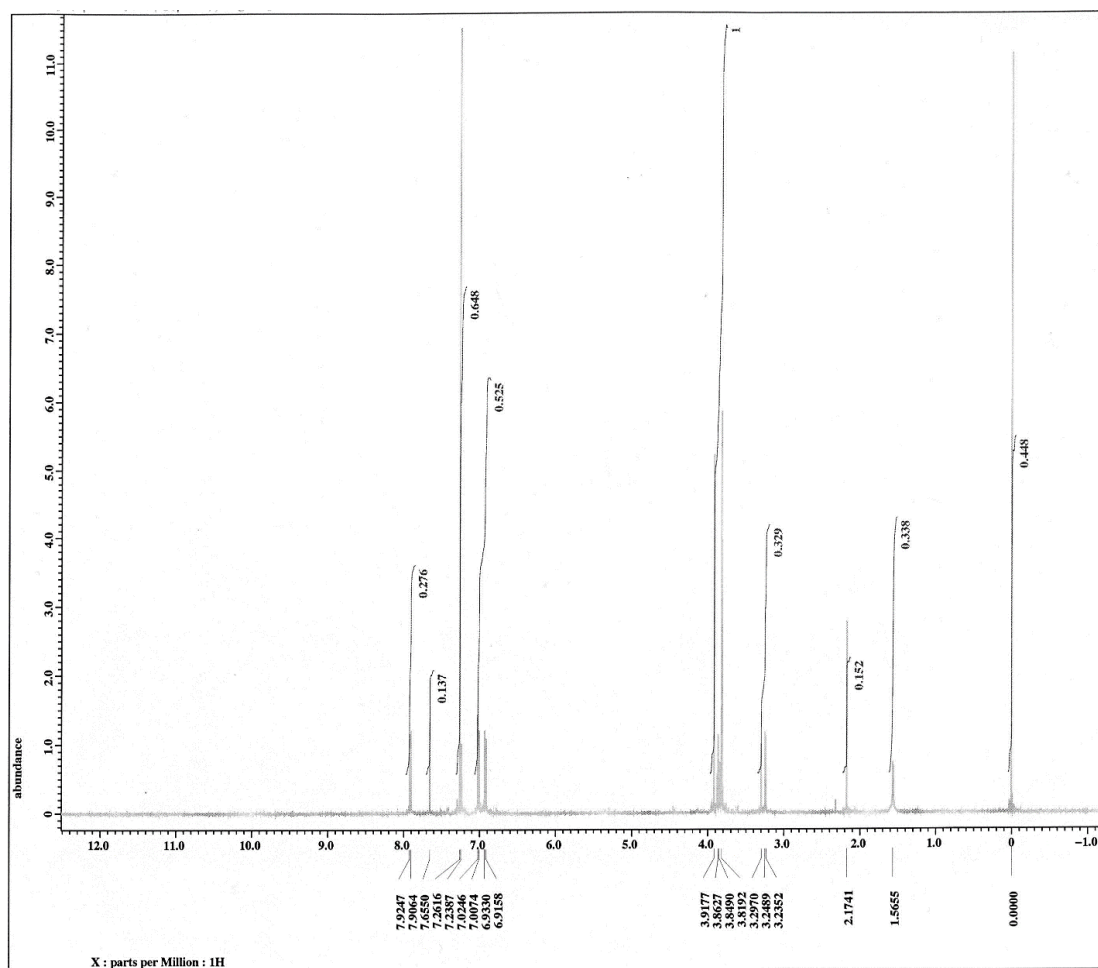
Methyl 2-cyano-3-(4-chlorophenyl)-2-propenoate [10]
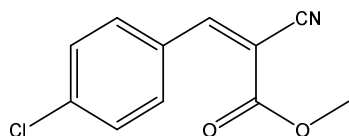
The reaction of methyl cyanoacetate and 4-chlorobenzaldehyde gave a 94% yield.

^{1}HNMR (CDCl$_3$ 500 MHz): δ (ppm): 8.21 (s, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.48 (d, J = 7.4 Hz, 2H), 3.97 (s, 3H).

X : parts per Million : 1H
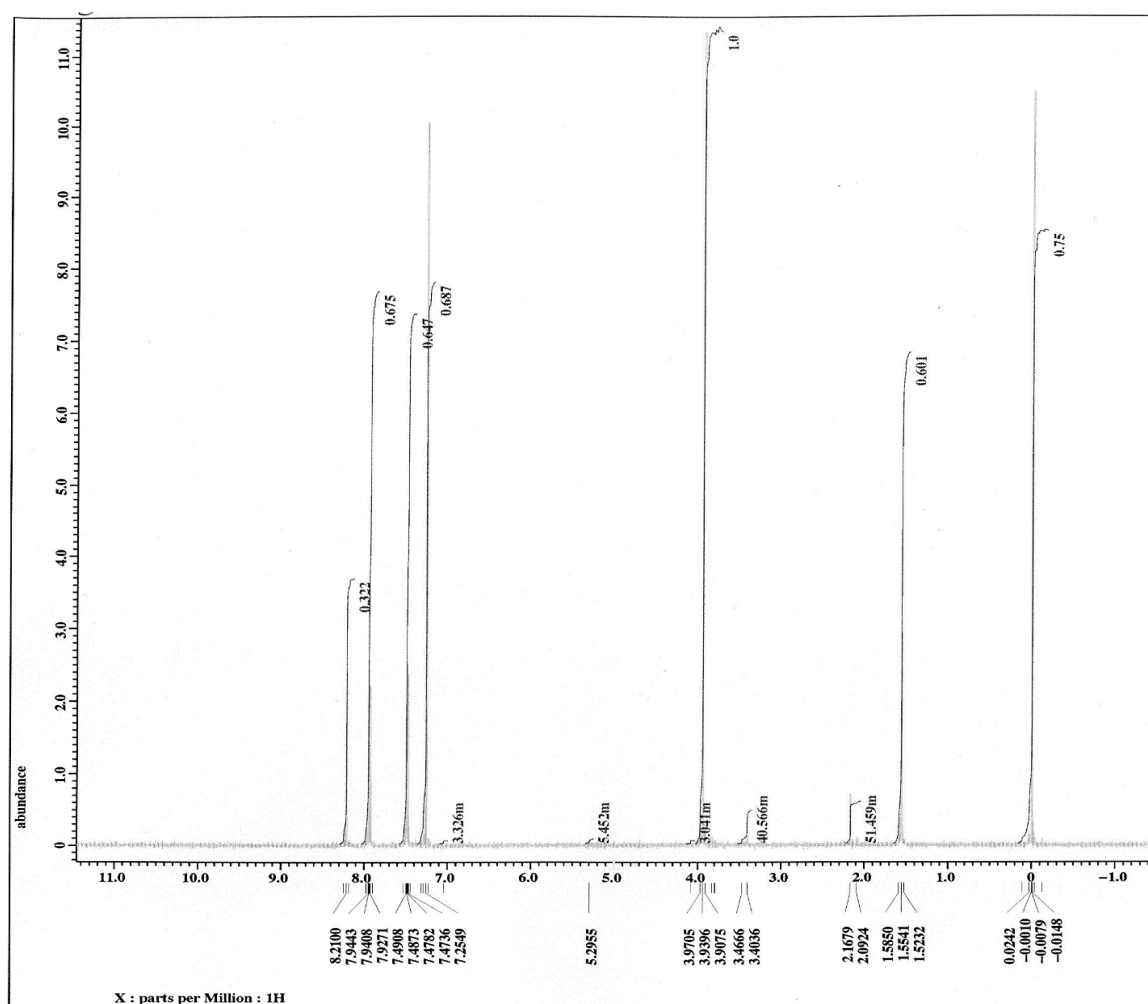
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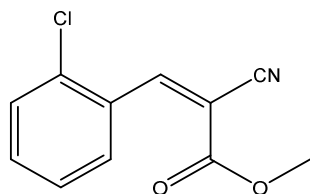
The reaction of methyl cyanoacetate and 2-chlorobenzaldehyde gave a 98% yield.

^{1}HNMR (CDCl3 500 MHz): δ (ppm): 8.71 (s, 1H), 8.23 (d, J = 7.4 Hz, 1H), 7.51-7.48 (m, 3H), 3.96 (s, 3H).
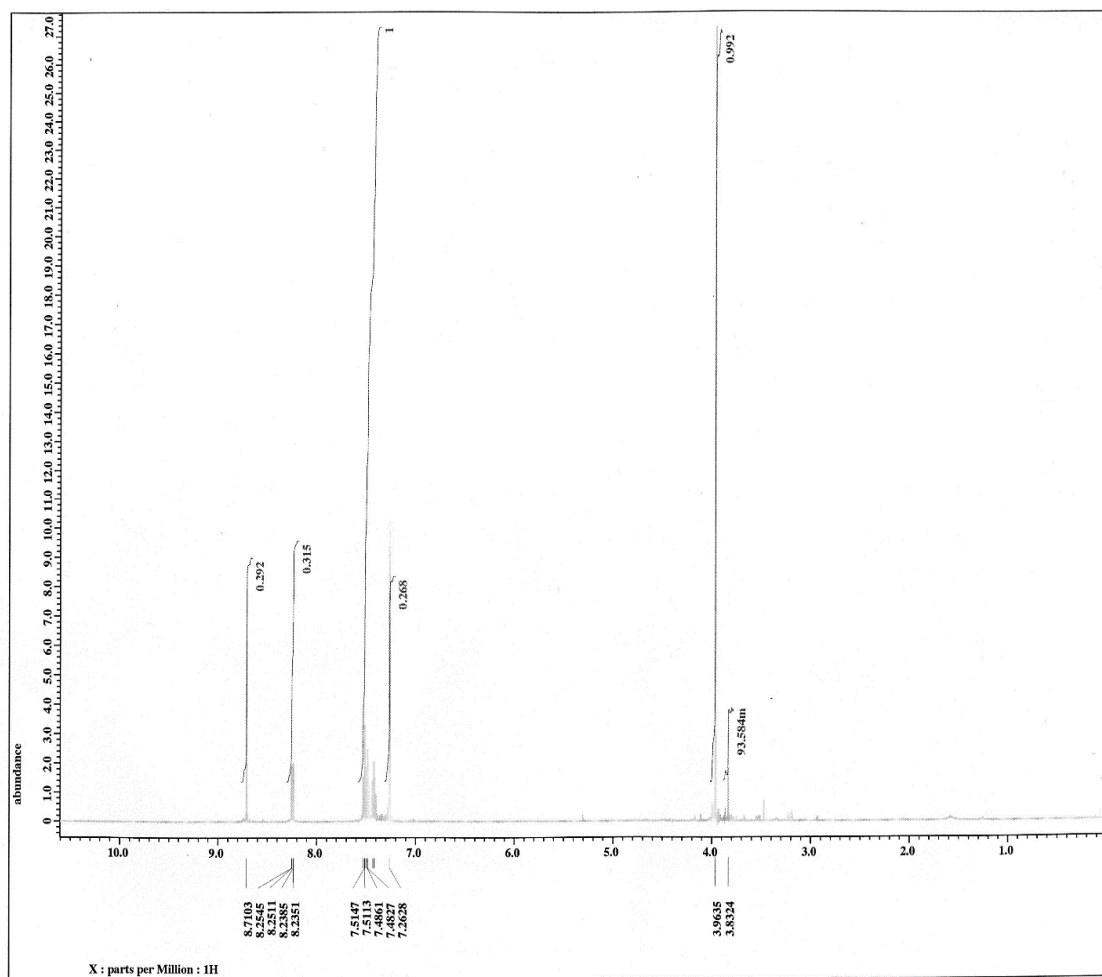
Methyl 2-cyano-3-(4-hydroxyphenyl)-2-propenoate [10]
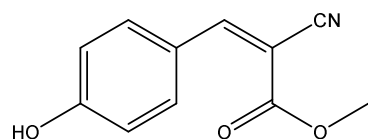
The reaction of methyl cyanoacetate and 4-hydroxyphenyl gave a 99% yield.
^{1}HNMR (Acetone-D6 500 MHz): δ (ppm): 8.18 (s, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.02 (d, J = 7.2 Hz, 2H), 3.84 (s, 3H).
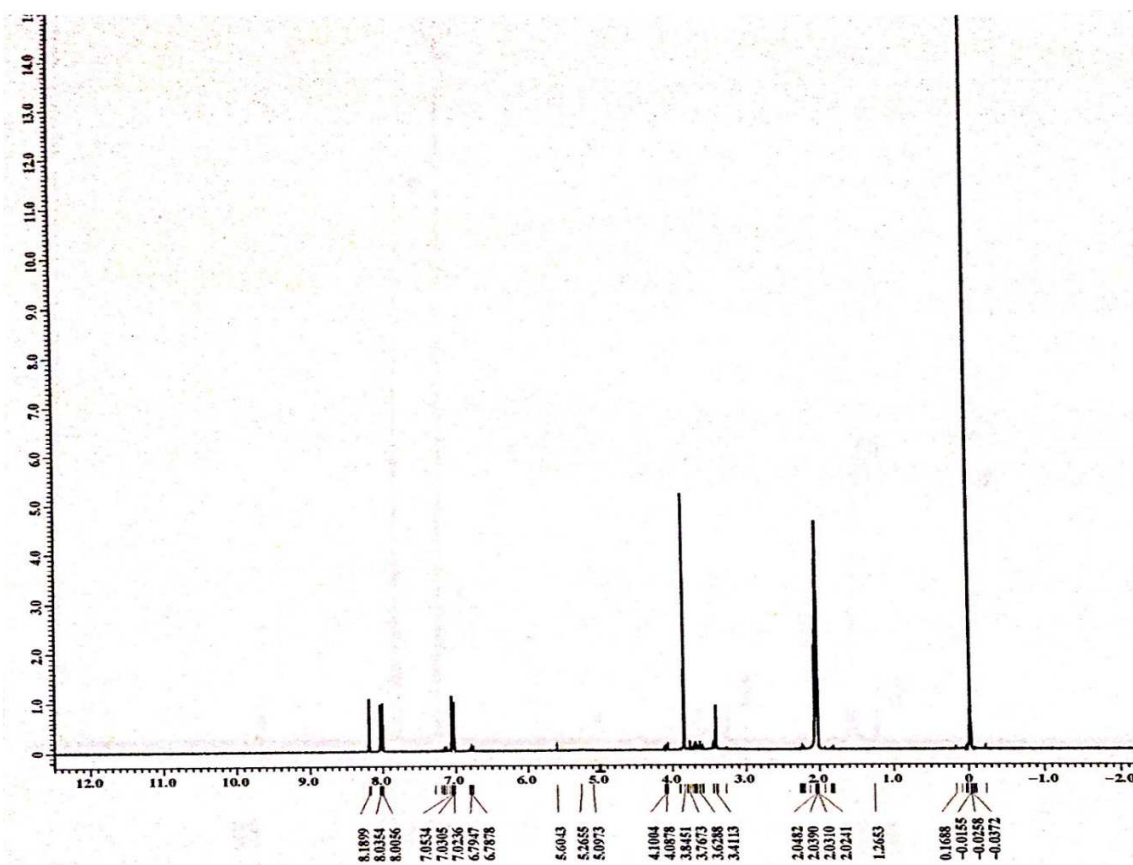
Methyl 2-cyano-3-(4-nitrobenzaldehyde)-2-propenoate [10]
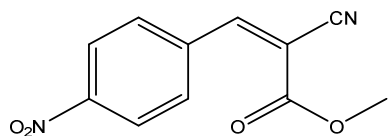
The reaction of methyl cyanoacetate and 4-nitrobenzaldehyde gave a 99% yield.

^{1}HNMR (CDCl$_3$ 300 MHz): δ (ppm): 8.36 (d, J = 7.2 Hz, 2H), 8.11 (d, J = 7.2 Hz, 2H), 7.25 (s, 1H), 3.97 (s, 3H).
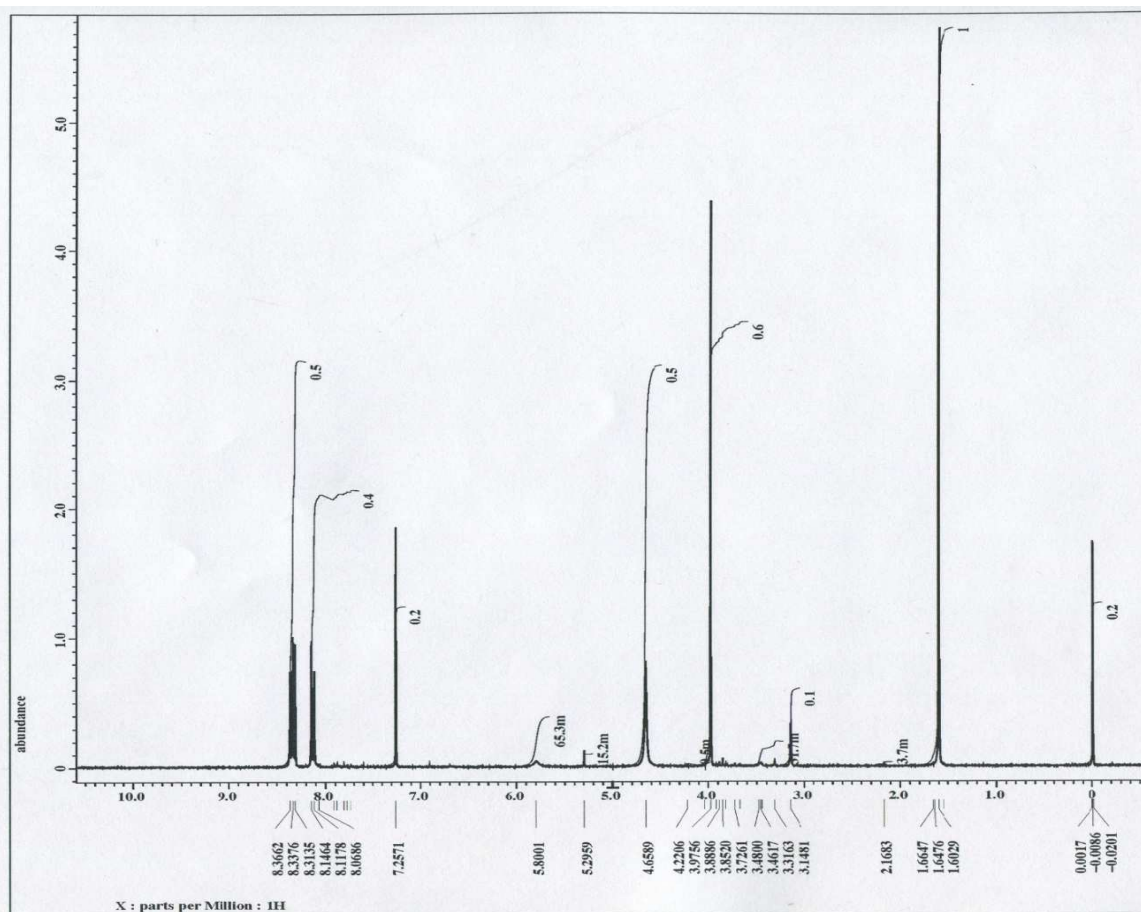
Methyl 2-cyano-3-(p-tolualdehyde)-2-propenoate
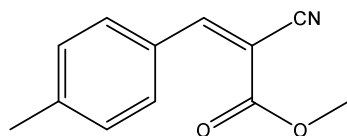
The reaction of methyl cyanoacetate and p-tolualdehyde gave a 99% yield. ^{1}HNMR (CDCl$_3$, 300 MHz): δ (ppm): 8.21 (s, 1H), 7.90 (d, J = 7.4 Hz, 2H), 7.30 (d, J = 6.4 Hz, 2H), 3.91 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ (ppm): 153.72, 139.70, 132.99, 131.11, 130.46, 128.72, 126.84, 115.27, 103.93, 53.51, 19.96.

50.0

40.0

30.0

(thousandths)

20.0

10.0

0

220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 −10.0 −20.0

153.7263

139.7049
132.9900
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115.2773

103.9362

53.5166

19.9608

X : parts per Million : 13C
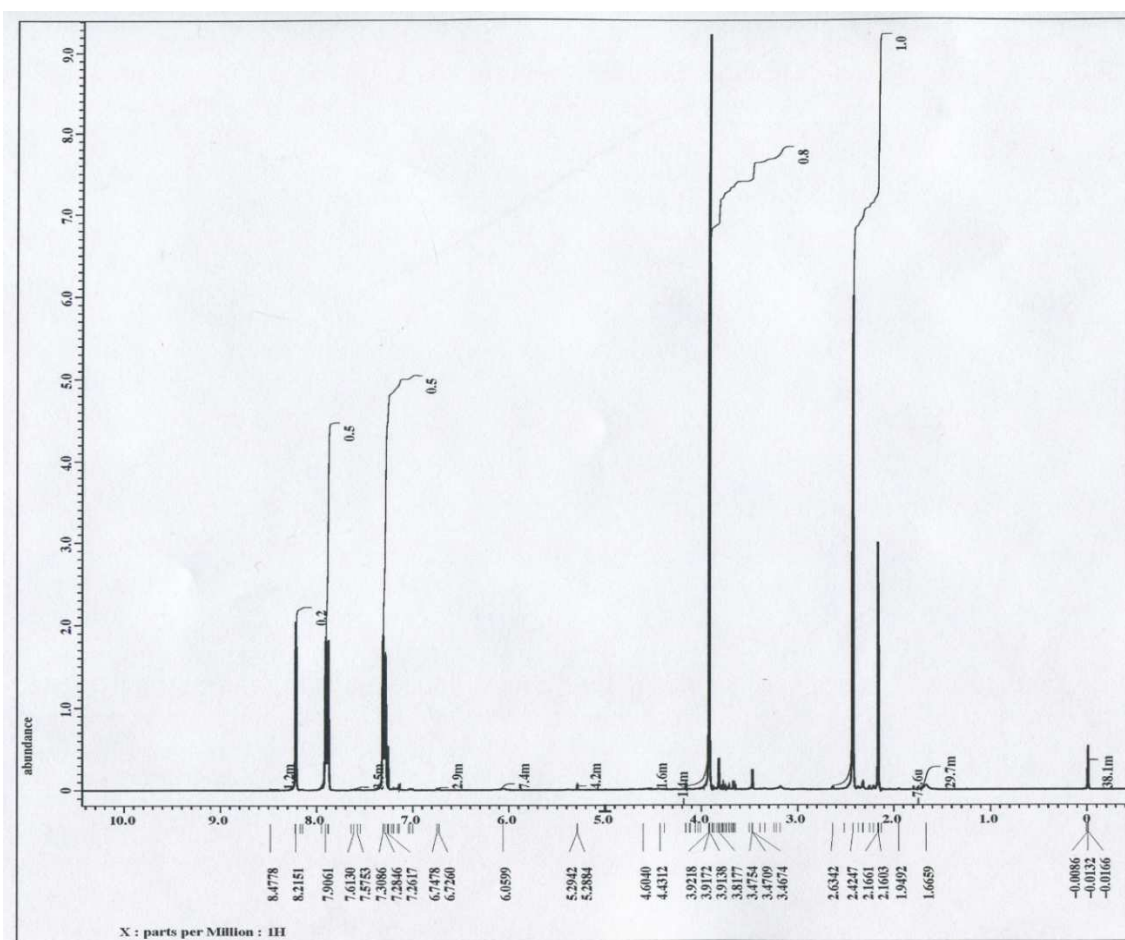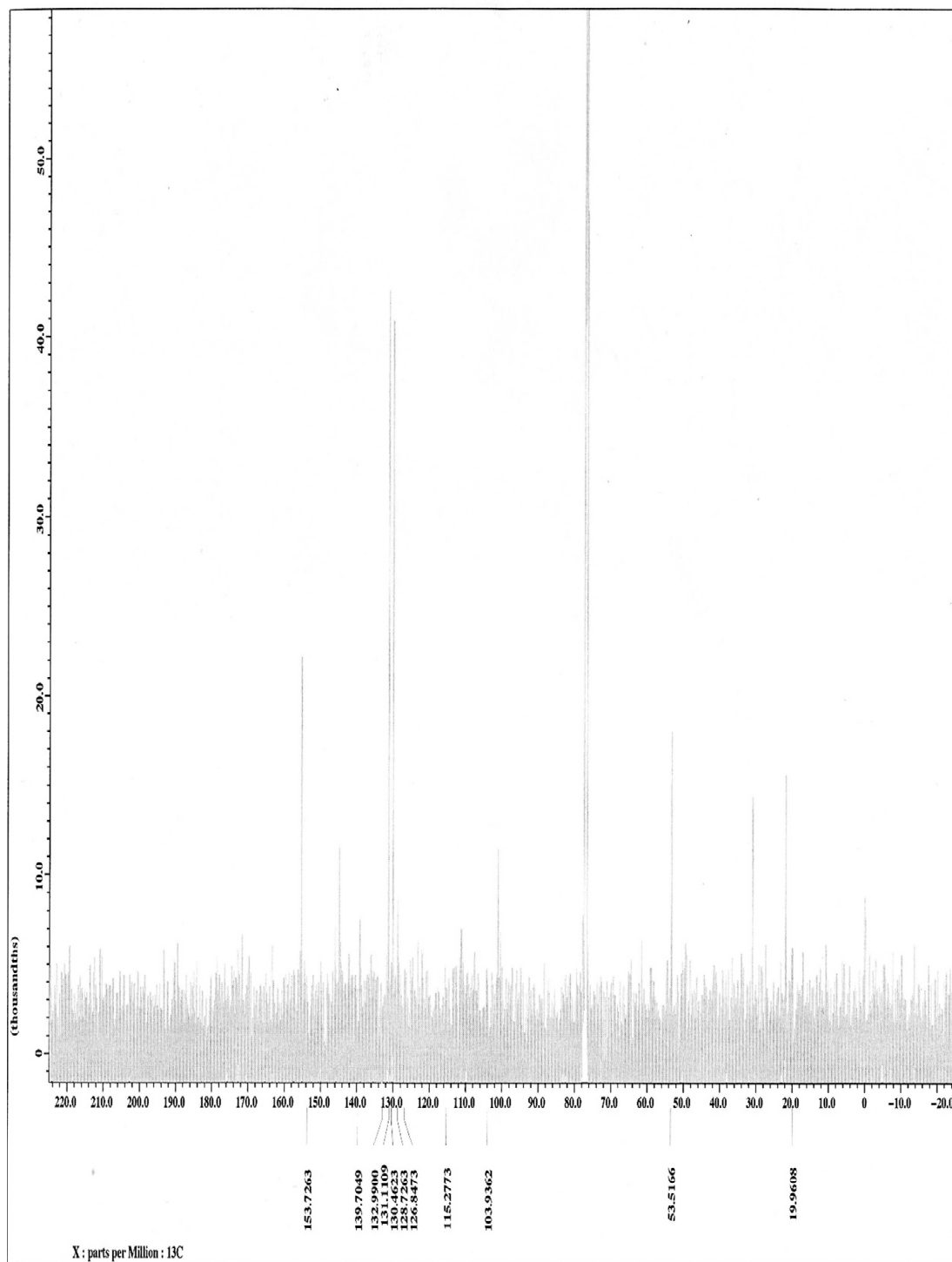
Methyl 2-cyano-3-(o-tolualdehyde)-2-propenoate
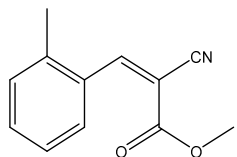
The reaction of methyl cyanoacetate and o-tolualdehyde gave an 81% yield.
1HNMR (CDCl₃, 500 MHz): δ (ppm): 8.57 (s, 1H), 8.13 (s, 1H), 7.42 (s, 1H), 7.29-7.24 (m, 2H), 3.96 (s, 1H), 2.44 (s, 3H). 13C NMR (CDCl₃, 125 MHz): δ (ppm): 162.78, 152.54, 139.77, 132.88, 131.00, 130.34, 128.61, 126.67, 115.36, 104.05, 53.40, 19.58.

abundance

0.28 0.26 0.24 0.22 0.2 0.18 0.16 0.14 0.12 0.1 0.08 0.06 0.04 0.02 0

220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0

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152.5435
139.7717
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X : parts per Million : 13C
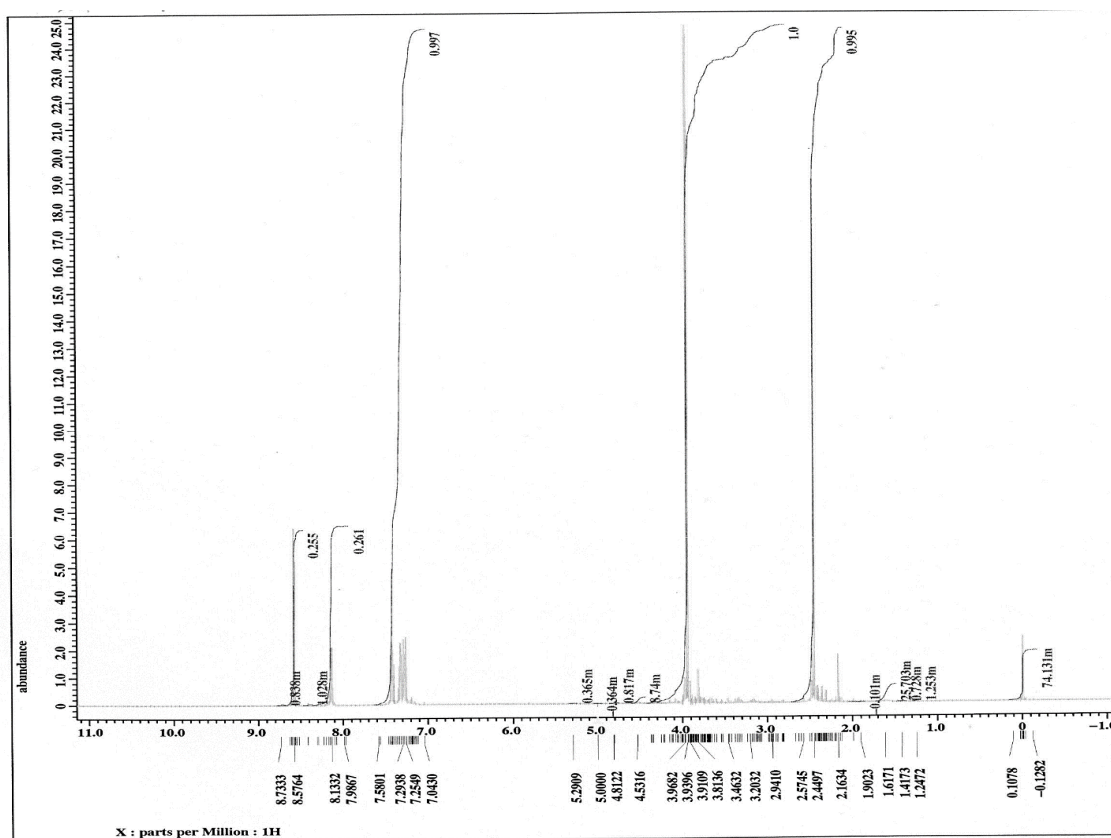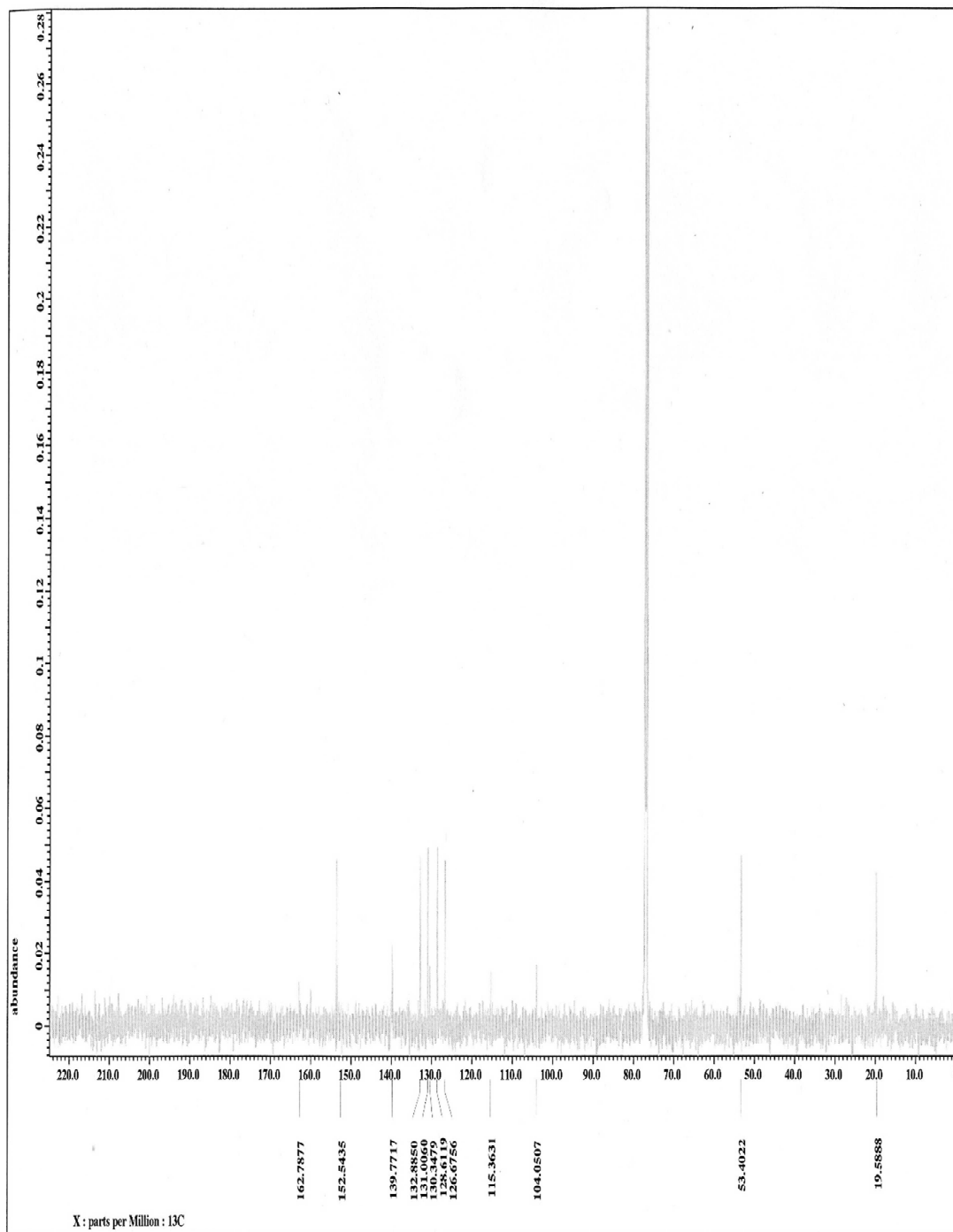
Methyl 2-cyano-3-(2-thienyl)-2-propenoate [10]
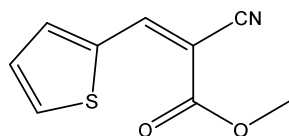
The reaction of methyl cyanoacetate and 2-thiophenecarboxaldehyde gave a 99% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): δ (ppm): 8.36 (s, 1H), 7.84-7.81 (m, 2H), 7. 23 (d, J = 2.1 Hz, 1H), 3.91 (s, 3H).
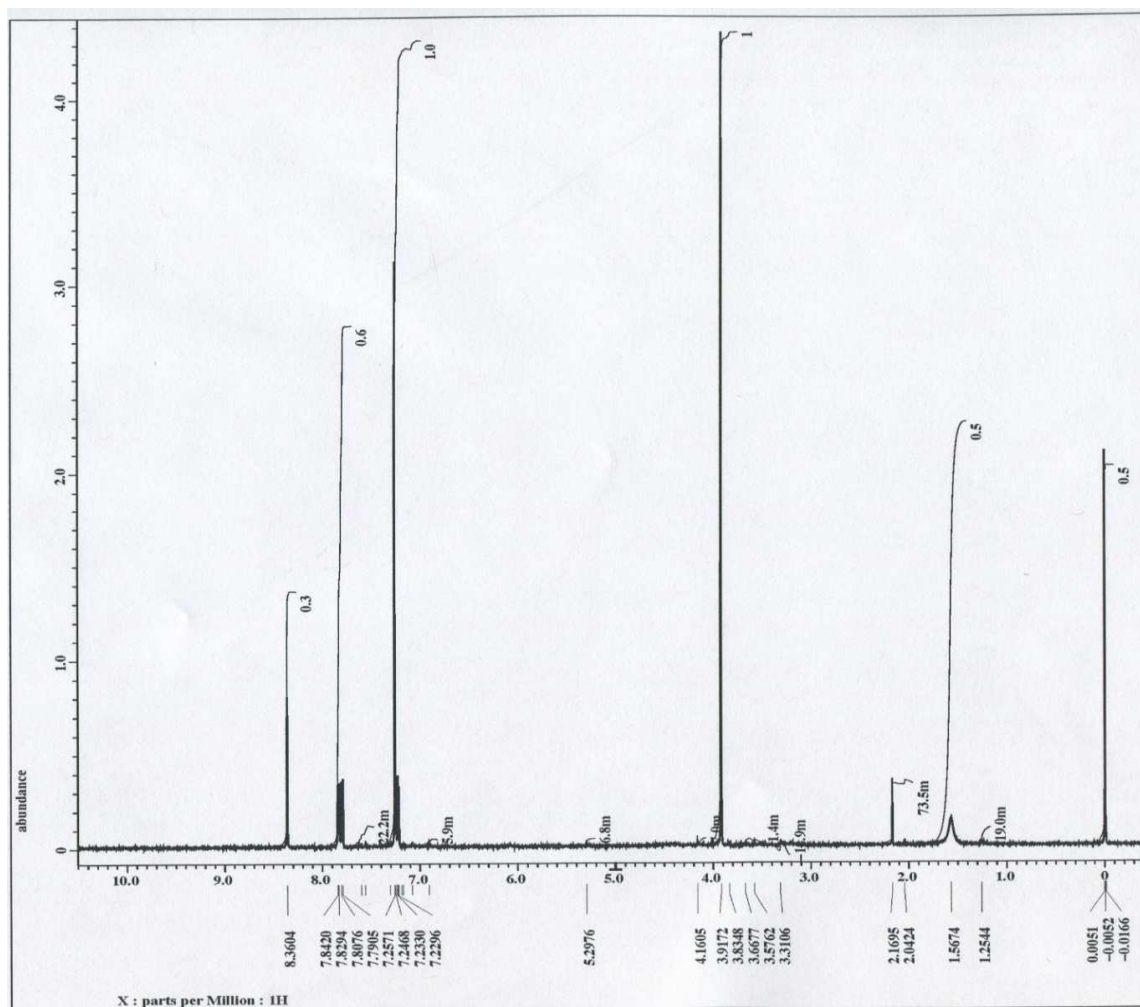
Ethyl 2-[(4-methoxyphenyl)methylene]-3-oxo-butanoate [28]
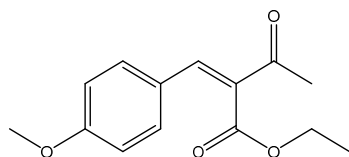
Ethyl 2-[(4-methoxyphenyl)methylene]-3-oxo-butanoate demonstrated an R_f of 0.46 in the eluting solvent that was a 8:2 mixture of hexanes to ethyl acetate. It was isolated via colum chromatography in 99% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): 7.24 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.30 (s, 1H), 4.11 (q, 2H), 3.78 (s, 3H), 2.04 (s, 3H), 1.25 (t, 3H).
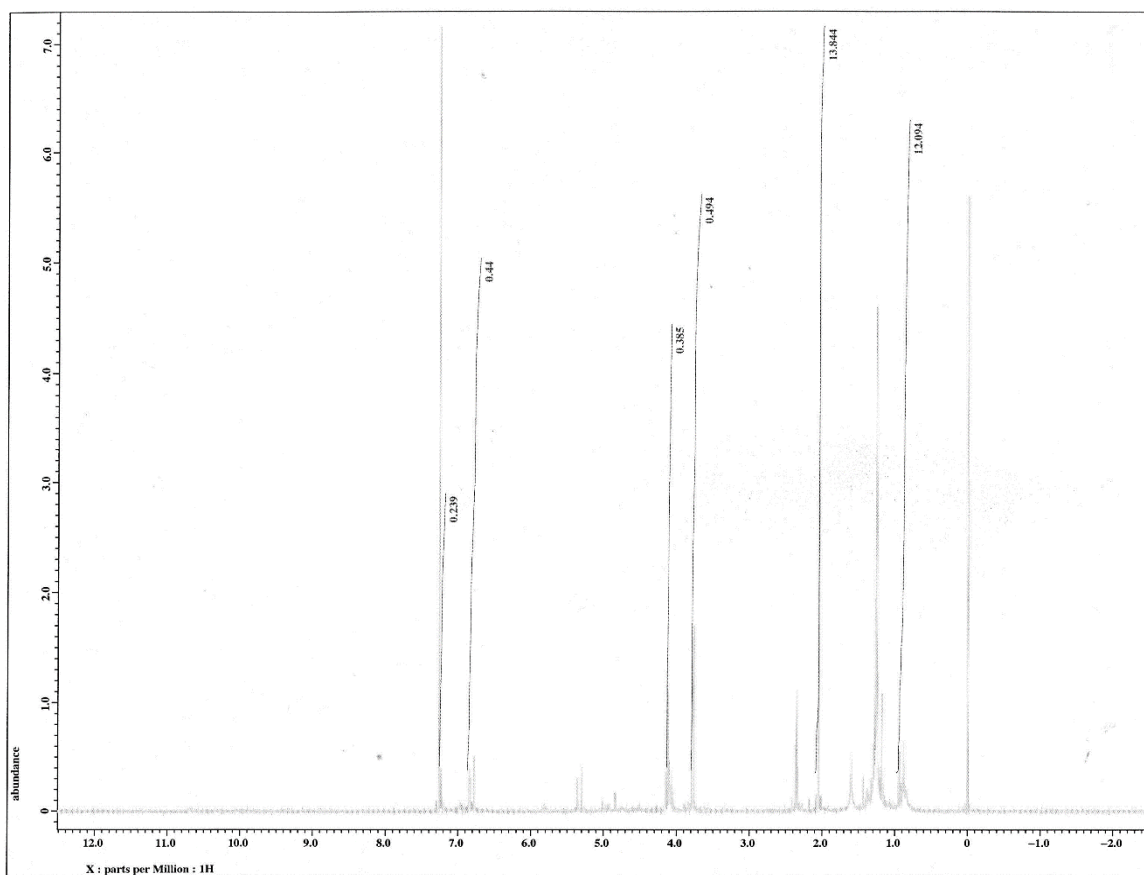
Ethyl 2-[(4-chlorophenyl)methylene]-3-oxo-butanoate
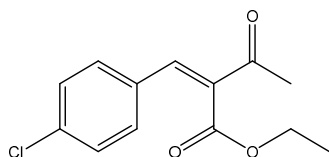
The ethyl 2-[(4-chlorophenyl)methylene]-3-oxo-butanoate demonstrated an R_f of 0.44 in the eluting solvent that was a 8.5:1.5 mixture of hexanes to ethyl acetate. It was isolated via column chromatography in 99% yield. ^{1}HNMR (CDCl$_3$ 300 MHz): 7.26 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H), 4.94 (s, 1H), 4.08 (q, 2H), 2.36 (s, 3H), 1.26 (t, 3H). ^{13}C NMR (CDCl$_3$ 75 MHz): 207.22, 167.53, 143.99, 129.25, 128.72, 128.54, 128.19, 103.96, 59.71, 30.89, 19.31.

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X : parts per Million : 13C

Ethyl 2-[(4-hydroxybenzaldehyde)methylene]-3-oxo-butanoate [30]

The reaction of butanoic acid, 3-oxo-, ethyl esterof and 4-hydroxybenzaldehyde afforded the product in 85.5% yield. ^{1}HNMR (Acetone-D6 300MHz): 7.08 (d, J = 7.5 Hz, 2H), 6.62 (d, J = 7.5 Hz, 2H), 4.97 (s, 1H), 4.03 (q, 2H), 2.28 (s, 3H), 1.16 (t, 3H).
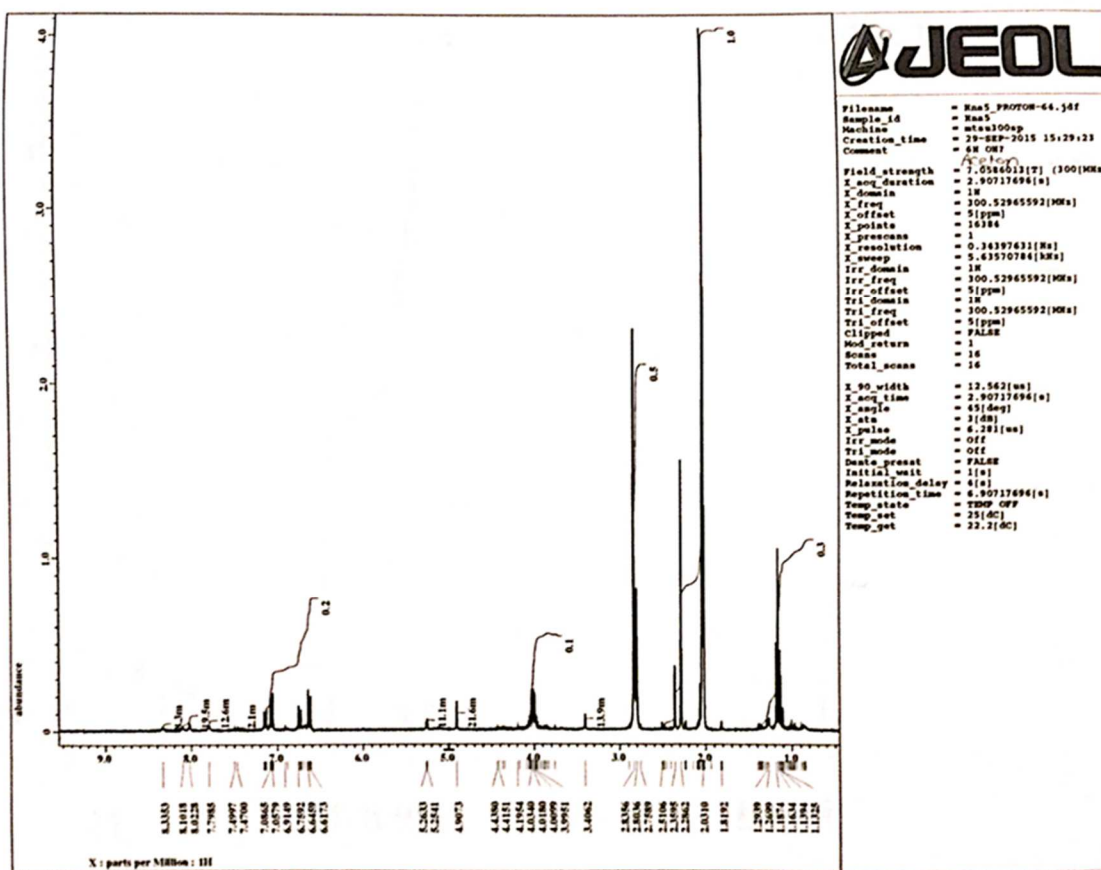
Ethyl 2-[(4-nitrobenzaldehyde)methylene]-3-oxo-butanoate [30]
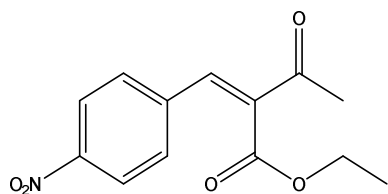
The reaction butanoic acid, 3-oxo-, ethyl ester and 4-nitrobenzaldehyde gave the anticipated product in 85% yield. ^{1}HNMR (CDCl$_3$ 300 MHz): 8.17 (d, J = 7 Hz, 2H), 7.52 (d, J = 7 Hz, 2H), 5.08 (s, 1H), 4.12 (q, 2H), 2.37 (s, 3H), 1.25 (t, 3H).
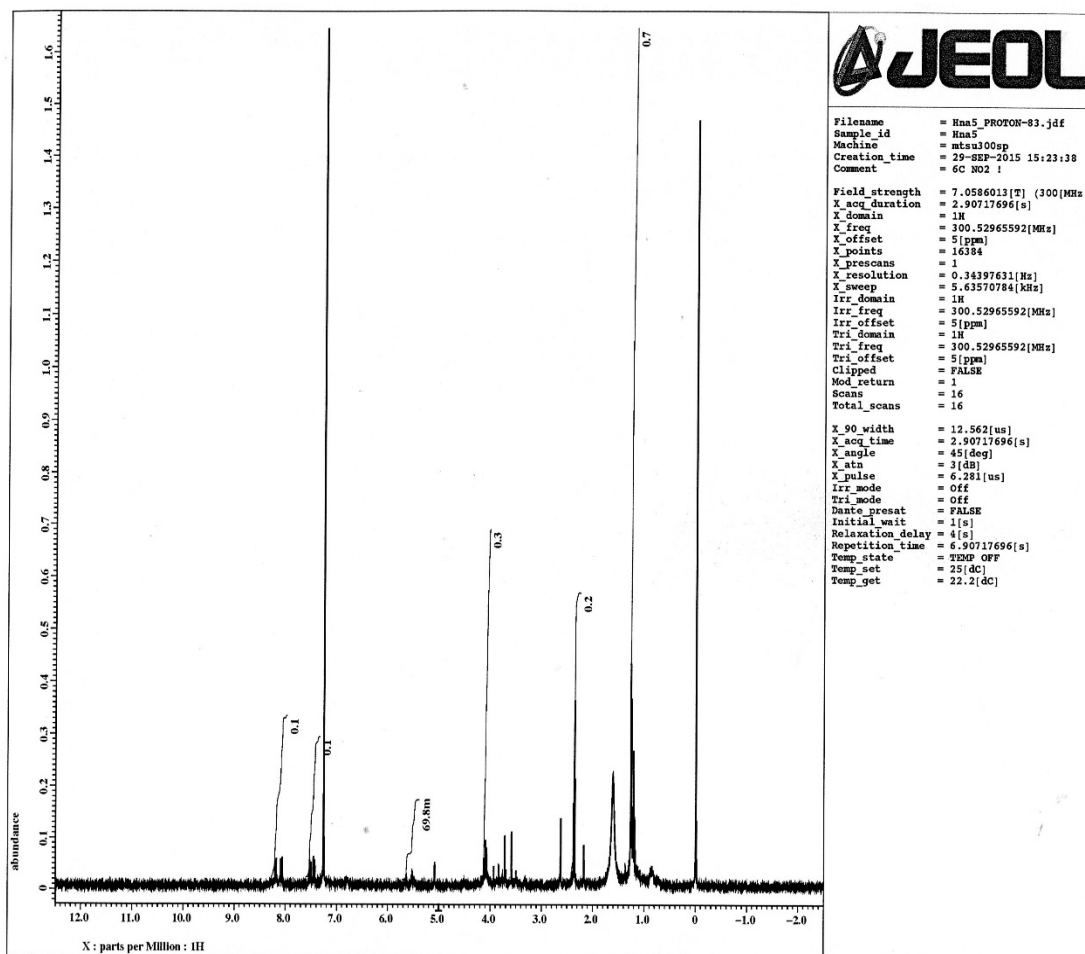
Ethyl 2-[(4-methylphenyl)methylene]-3-oxo-butanoate [31]
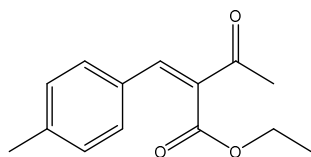
The butanoic acid, 2-[(4-methylphenyl) methylene]-3-oxo-, ethyl ester demonstrated an R_f of 0.44 in the eluting solvent that was a 8:2 mixture of hexanes to ethyl acetate. It was isolated via column chromatography in 99% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): 7.24-7.02 (m, 4H), 4.94 (s, 1H), 4.06 (q, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 1.26 (t, 2H).
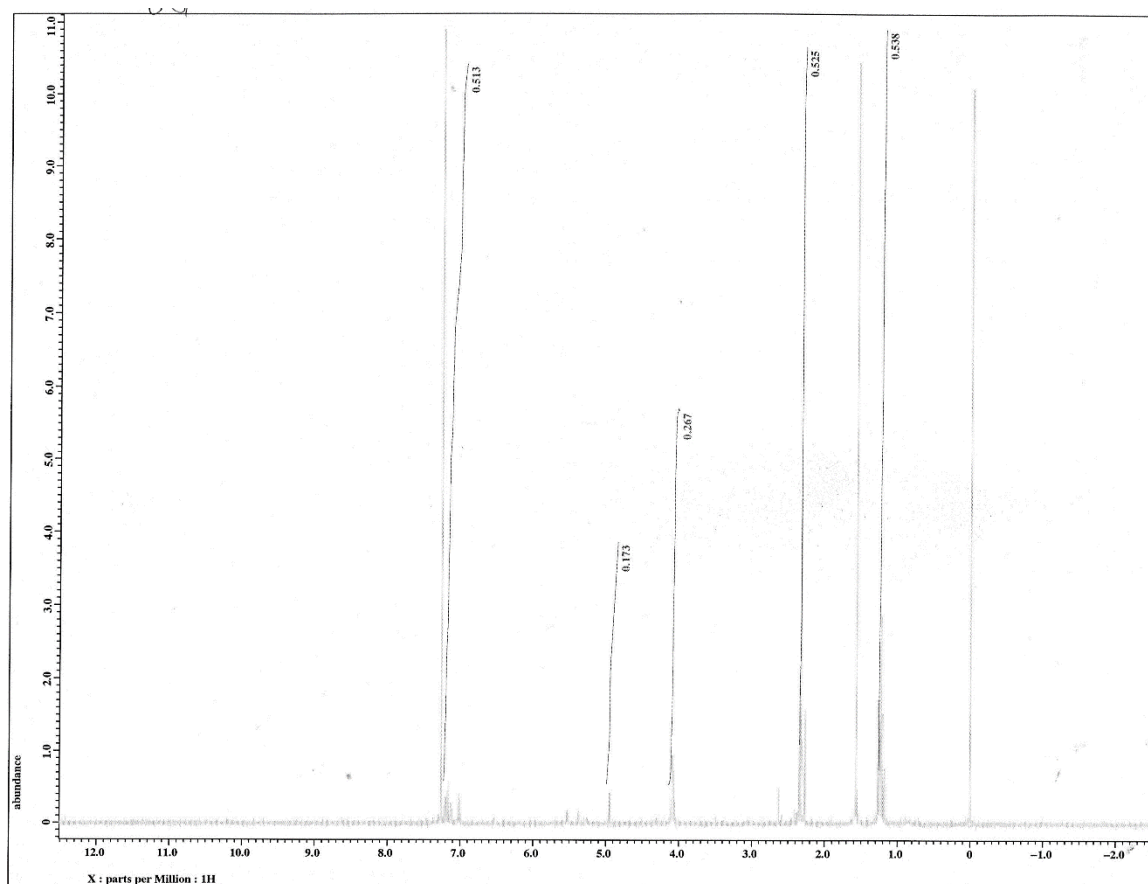
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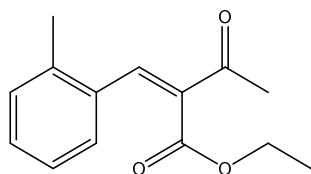
The reaction of butanoic acid, 3-oxo-, ethylester of and 2-methylbenzaldehyde gave the anticipated product in 80 % yield. ^{1}HNMR (CDCl$_3$ 300 MHz): 7.61 (m, 1H), 7.16-7.13 (m, 3H), 5.41 (s, 1H), 4.00 (q, 2H), 2.49 (s, 3H), 2.38 (s, 3H), 1.03 (t, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz): 218.82, 165.25, 151.99, 146.23, 141.17, 134.19, 130.36, 127.56, 126.68, 100.52, 59.86, 52.01, 18.86, 13.63.
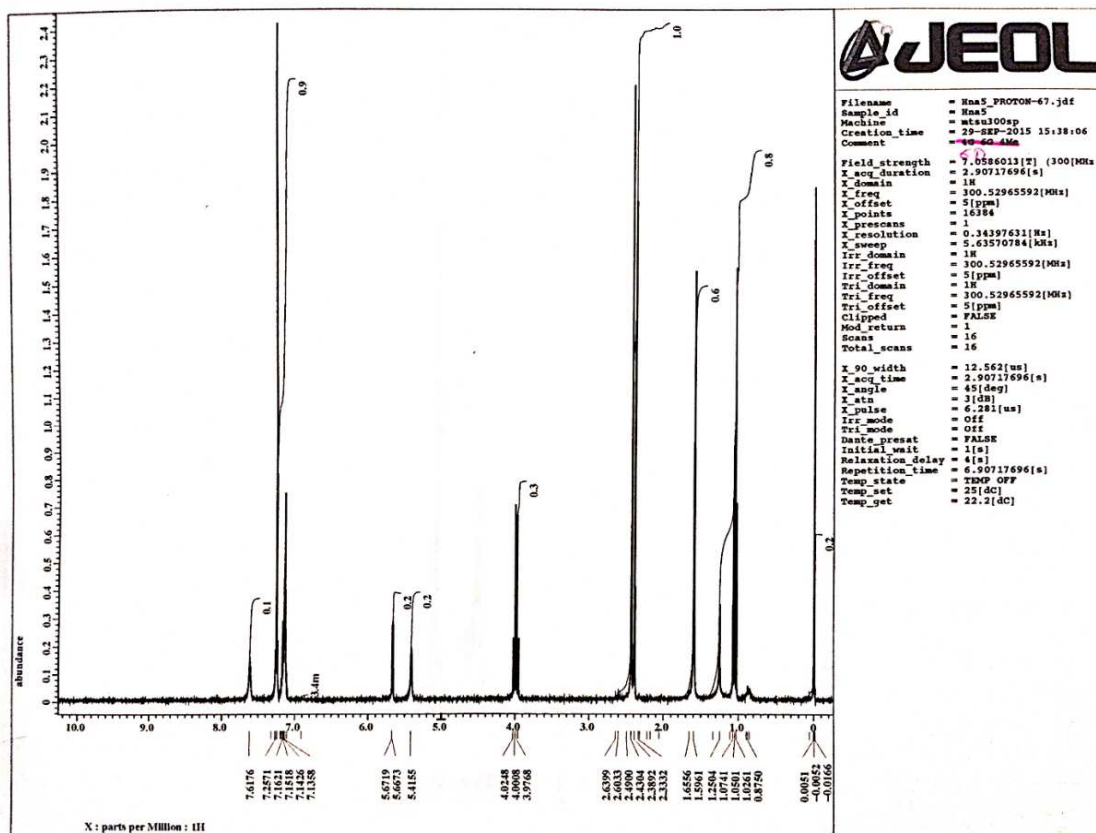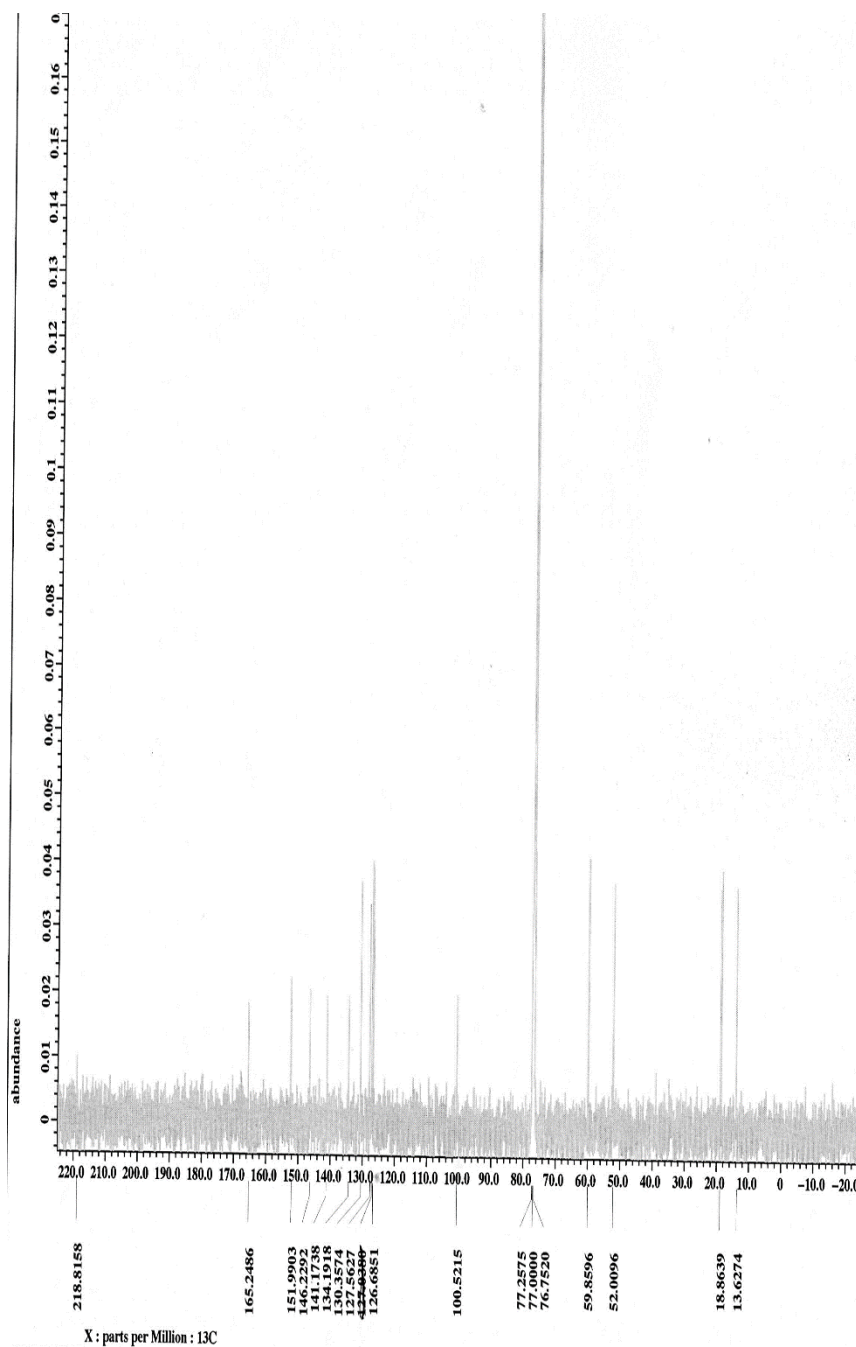
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X : parts per Million : 13C

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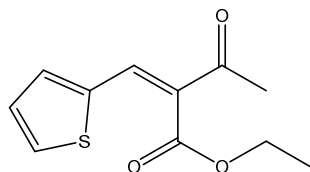
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X : parts per Million : 13C

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167.1658

143.9590

125.8171
122.8507

103.8313

77.2575
77.0000
76.7520

59.6879

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14.1520

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2-[(4-chlorophenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione [32]

The reaction of dimedone and 4-chlorobenzaldehyde gave the anticipated product in 22% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): 7.26 (d, J = 7 Hz, 2H), 7.21 (d, J = 7 Hz, 2H), 5.47 (s, 1H), 2.44 (m, 4H), 1.05 (s, 6H).
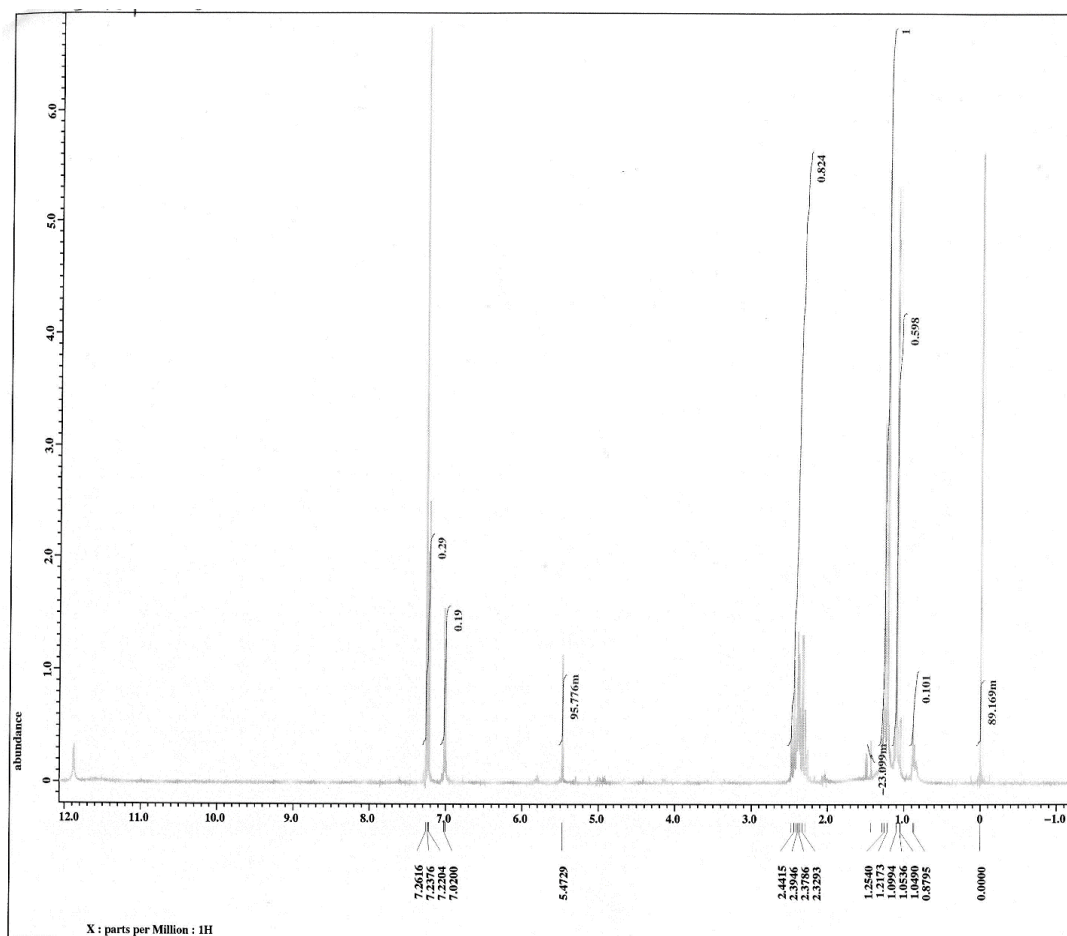
2-[(2-chlorophenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione
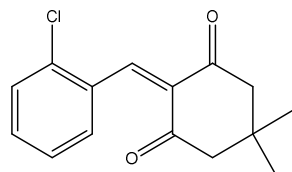
The reaction of dimedone and 2-chlorobenzaldehyde gave the anticipated product in 64% yield. ^{1}HNMR (CDCl$_3$ 500 MHz): 7.29-7.19 (4H, m, Ar H and C-H), 5.63 (s, 1H), 2.40-2.16 (m, 4H), 1.11 (s, 6H). ^{13}C NMR (CDCl$_3$ 75 MHz): 189.80, 130.44, 129.48, 127.77, 126.54, 118.78, 46.75, 32.46, 31.59, 29.79, 29.14.

X : parts per Million : 1H

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X : parts per Million : 13C

2-[(4-nitrobenzaldehyde)methylene]-5,5-dimethyl-1,3-cyclohexandione

The reaction of dimedone and 4-nitrobenzaldehyde gave the anticipated product in 99% yield. ^{1}HNMR (CDCl 300 MHz): 8.13 (d, J = 7 Hz, 2H), 7.25 (d, J = 7 Hz, 2H), 5.43 (s, 1H), 2.41-2.16 (m, 4H), 1.01 (s, 6H). ^{13}C NMR (CDCl$_3$ 75 MHz): 190.95, 189.37, 146.52, 127.55, 124.25, 123.81, 123.34, 114.73, 77.43, 77.00, 76.57, 33.06, 30.78, 29.37, 27.27.

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189.3757

146.5249

127.5566
124.2582
123.8184
123.3404
114.7358

77.4302
77.0000
76.5793

33.0689
30.7839
29.3785
27.2751

X : parts per Million : 13C

2-[(2-methylbenzaldehyde)methylene]-5,5-dimethyl-1,3-cyclohexandione

The reaction of dimedone and 2-methylbenzaldehyde gave the anticipated product in 62% yield. ^{1}HNMR (CDCl 300 MHz): 7.14-7.09 (m, 4H), 5.51 (s, 1H), 2.53-2.16 (m, 4H), 1.06 (s, 6H). ^{13}C NMR (CDCl$_3$ 75 MHz): 207.81, 135.97, 131.89, 127.00, 126.84, 126.32, 106.30, 57.48, 45.54, 44.48, 28.50, 19.37.

JEOL

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207.8086

135.9796
131.5912
127.0117
126.8492
126.3233

106.3034

77.4207
77.0000
76.5793

57.4772

45.5359
44.4843

28.4989

19.3685

X : parts per Million : 13C

5-[(4-methoxyphenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione [10]

The reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione and 4-anisaldehyde gave an 80% yield. ^{1}HNMR (CDCl$_3$ 300 MHz): 7.15 (d, J = 7 Hz, 2H), 6.86 (d, J = 7 Hz, 2H), 6.85 (s, 1H), 3.74 (s, 3H), 2.16 (s, 6H).
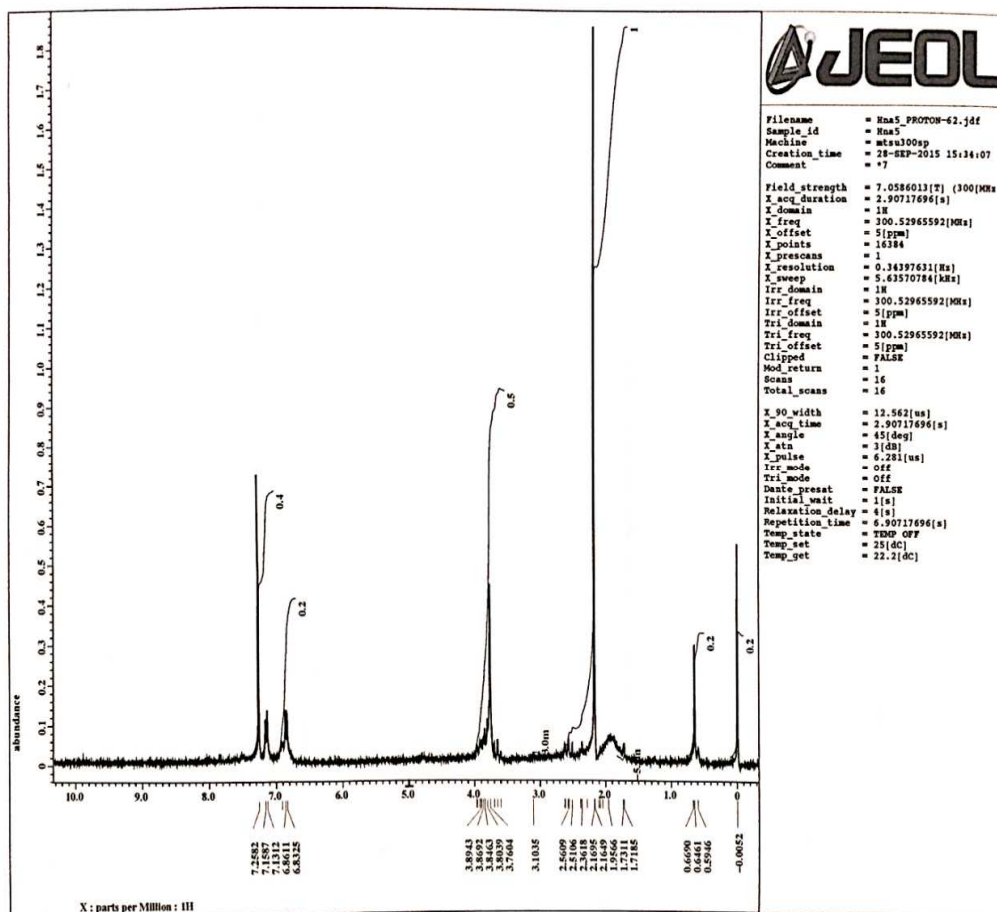
CHAPTER THREE: RESULTS AND DISCUSSION

The Knoevenagel condensation reaction in this study was catalyzed by the deep eutectic solvent formed by a 1:2 molar ratio combination of choline chloride and urea. Different types of active methylene compounds were allowed to react with different types of aromatic aldehyde to determine how general this method was. The NMR was used to detect all of the Knoevenagel reaction products. In fact, all of these different reactions between list of aromatic aldehydes and active methylene compounds gave E isomer and no Z isomer was detected by the NMR.

With respect to the aromatic aldehydes, two main factors were considered: electronics (electron-rich with donating groups, and electron-deficient with withdrawing groups) and steric hindrance. Steric hindrance was examined by the comparison of ortho and para substituted compounds with the same group (such as ortho and para chloro substituted benzaldehyde in Figure 2). The percent yields of these reactions are calculated and compared to study this effect. Electronic effects can be compared by the use of aromatic aldehydes with different groups on them, ranging from highly elecrron-deficient (nitro groups), to electron-rich (with hydroxyl or methoxy groups) as seen in Figure 3.

Para-chlorobenzaldehyde   ortho-chlorobenzaldehyde
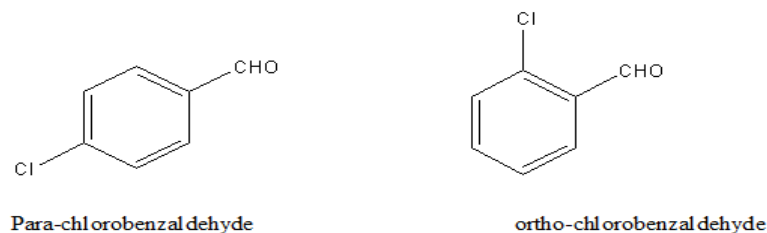
Figure 2. Aldehydes used to study steric effects
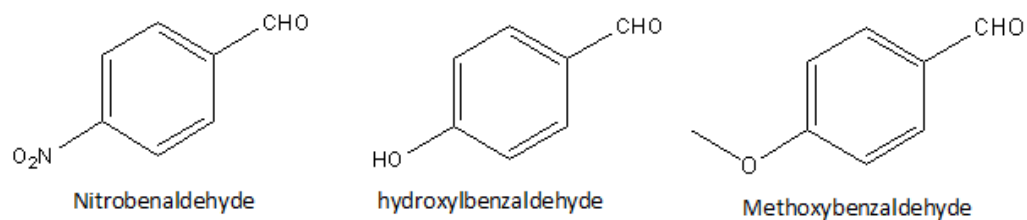
Figure 3. Aldehydes used to study electronic effects

The scope of the active methylene compound was studied by using the range of compounds shown in Table 7, which goes from the very active malononitrile to the weakly active dimethyl malonate.

Table 7. Active methylene compounds used in this research

Active methylene compound	Active methylene compound

EDG = electron donating group   *EWG = electron withdrawing group

Malononitrile is a very active compound because the methylene group is flanked on both sides by cyano groups. Cyano groups withdraw electrons, making them strongly deactivating. So, the methylene group in this compound is strongly activated (easily enolized). As a result, the reaction of malononitrile with different types of aldehydes gives high yields. In fact, the products did not need any further purification. Table 8 shows the different percent yields of the Knoevenagel condensation products of the reaction between malononitrile and various aromatic aldehydes.

Table 8. The reaction of malononitrile with different aldehydes

Aldehyde	Time (h)	Temperature (°C)	Product	Yield (%)
4-anisaldehyde	20	80	Propanedinitrile, 2-[(4-methoxyphenyl)methylene]-	97
4-chlorobenzaldehyde	20	80	Propanedinitrile, 2-[(4-chlorophenyl)methylene]-	82
2-chlorobenzaldehyde	20	80	Propanedinitrile, 2-[(2-chlorophenyl)methylene]-	96
4-hydroxyphenyl	20	80	Propanedinitrile, 2-[(4-hydroxyphenyl)methylene]-	74
4-nitrobenzaldehyde	20	80	Propanedinitrile, 2-[(4-nitrophenyl)methylene]-	90
p-tolualdehyde	20	80	Propanedinitrile, 2-[(4-methylphenyl)methylene]-	99
o-tolualdehyde	20	80	Propanedinitrile, 2-[(2-methylphenyl)methylene]-	99
2-thiophenecarboxaldehyde	20	80	Propanedinitrile, 2-(2-thienylmethylene)-	99

Methyl cyanoacetate is also a very active compound. Both cyano and ester groups that flank the methylene group in this compound are electron-withdrawing, although the

ester is less withdrawing than the cyano. The reaction of different aromatic aldehydes with methyl cyanoacetate yields plentiful and pure products. Table 9 shows the different yields of the reaction between different aldehydes and methyl cyanoacetate.

Table 9. The reaction of methyl cyanoacetate with different aldehydes

Aldehyde	Time (h)	Temperature (°C)	Product	Yield (%)
4-anisaldehyde	20	80	Methyl 2-cyano-3-(4-methoxyphenyl)-2-propenoate	92
4-chlorobenzaldehyde	20	80	Methyl 2-cyano-3-(4-chlorophenyl)-2-propenoate	94
2-chlorobenzaldehyde	20	80	Methyl 2-cyano-3-(2-chlorophenyl)-2-propenoate	98
4-hydroxyphenyl	20	80	Methyl 2-cyano-3-(4-hydroxyphenyl)-2-propenoate	99
4-nitrobenzaldehyde	20	80	Methyl 2-cyano-3-(4-nitrobenzaldehyde)-2-propenoate	99
p-tolualdehyde	20	80	Methyl 2-cyano-3-(p-tolualdehyde)-2-propenoate	99
o-tolualdehyde	20	80	Methyl 2-cyano-3-(o-tolualdehyde)-2-propenoate	81
2-thiophenecarboxaldehyde	20	80	Methyl 2-cyano-3-(2-thienyl)-2-propenoate	99

As shown in Table 8 and 9, the reaction of different aromatic aldehydes with malononitrile or methyl cyanoacetate gives high and pure yields regardless of aldehyde structure. Upon going to a less reactive active methylene compound – ethyl acetoacetate – differences could be noted. The first change was that some reactions did not give pure products after simple extraction and needed to be purified. Table 10 shows the yields of

the reactions between ethyl acetoacetate with different aromatic aldehydes. The reactions with anisaldehyde and p-tolualdehyde needed to be purified. In addition, 2-chlorobenzaldehyde did not afford any isolable product. Although this might be due to steric effects, o-tolualdehyde did afford the anticipated product in fairly good yield, so the influence of sterics is unclear.

Table 10. The reaction of ethyl acetoacetate with different aldehydes

Aldehyde	Time (h)	Temperature (°C)	Proudct	Yield (%)
4-anisaldehyde	22	80	Ethyl 2-[(4-methoxyphenyl)methylene]-3-oxo-butanoate	60*
4-chlorobenzaldehyde	22	80	Ethyl 2-[(4-chlorophenyl)methylene]-3-oxo-butanoate	99
2-chlorobenzaldehyde	22	80	Ethyl 2-[(2-chlorophenyl)methylene]-3-oxo-butanoate	n.r.
4-hydroxyphenyl	22	80	Ethyl 2-[(4-hydroxybenzaldehyde)methylene]-3-oxo-butanoate	85.5
4-nitrobenzaldehyde	22	80	Ethyl 2-[(4-nitrobenzaldehyde)methylene]-3-oxo-butanoate	85
p-tolualdehyde	22	80	Ethyl 2-[(4-methylphenyl)methylene]-3-oxo-butanoate	55*
o-tolualdehyde	22	80	Ethyl 2-[(2-methylphenyl)methylene]-3-oxo-butanoate	80
2-thiophenecarboxaldehyde	22	80	Ethyl 2-[(2-thienylmethylene)methylene]-3-oxo-butanoate	99

(*) the product needed to be purified   (n.r.) no reaction

Another type of active methylene that has been studied in this research is

dimedone. It is slightly more reactive that ethyl acetoacetate due to both the higher

withdrawing characteristics of the ketone groups compared to ester groups and due to the

lack of steric hindrance about the active methylene carbon. As a result, it would be

expected that higher yields would be obtained from these reactions. In fact, however,

yields were generally poorer than those with ethyl acetoacetate as seen in Table 11.

Although the aldehydes were generally consumed, isolated yields of the products were

not high. One possible explanation may be the ease with which the initial Knoevenagel

product can undergo a second Michael reaction to afford a compound such as the reaction

of dimedone with 4-methoxybenzaldehyde as shown in Scheme 14. These products have

been reported before using DES [33]. Thus it may be that lower temperatures are required

to obtain better yields of the desired Knoevenagel products.
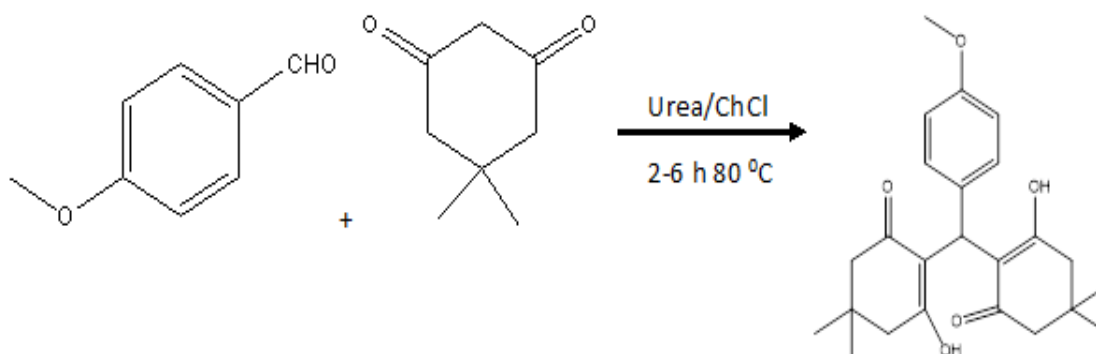
Scheme 14. The initial Knoevenagel product can undergo a second Michael reaction

Table 11. The reaction of dimedone with different aldehydes

Aldehyde	Time (h)	Temperature (°C)	Product	Yield (%)
4-anisaldehyde	22	80	2-[(4-methoxyphenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione	n.d.
4-chlorobenzaldehyde	22	80	2-[(4-chlorophenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione	22
2-chlorobenzaldehyde	22	80	2-[(2-chlorophenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione	64
4-hydroxyphenyl	22	80	2-[(4-hydroxyphenyl)methylene]-5,5-dimethyl-1,3-cyclohexandione	n.r.
4-nitrobenzaldehyde	22	80	2-[(4-nitrobenzaldehyde)methylene]-5,5-dimethyl-1,3-cyclohexandione	99
p-tolualdehyde	22	80	2-[(4-methylbenzaldehyde)methylene]-5,5-dimethyl-1,3-cyclohexandione]-	n.r.
o-tolualdehyde	22	80	2-[(2-methylbenzaldehyde)methylene]-5,5-dimethyl-1,3-cyclohexandione	62
2-thiophenecarboxaldehyde	22	80	2-[(2-thienylmethylene)methylene]-5,5-dimethyl-1,3-cyclohexandione	n.r.

n.d.: not detected   n.r.: no reaction

Finally, one last active methylene compound – 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) – was also explored. The two ester groups flanking the

methylene group are not as withdrawing as keto or cyano groups, although the lack of

steric hindrance serves to still make it generally quite reactive. Still, its Knoevenagel

condensation reaction with several aromatic aldehyde did not afford the anticipated

products. Only in the case of reaction with 4-anisaldhyde was the product obtained in

reasonable yield (Table 12). The failure of these reactions may be the result of faster

reaction of Meldrum's acid with the hydroxyl group present in chlorine chloride to afford

a choline ester that could not be readily isolated.

Table 12. The reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione with different aldehydes

Aldehyde	Time (h)	Temperature (°C)	Product	Yield (%)
4-anisaldehyde	22	80	5-[(4-methoxyphenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	80
4-chlorobenzaldehyde	22	80	5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	n.r.
2-chlorobenzaldehyde	22	80	5-[(2-chlorophenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	n.r.
4-hydroxyphenyl	22	80	5-[(4-hydroxyphenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	n.r.

This study examined the activity of four additional active methylene compounds

by combining them with 4-anisaldehyde. The four active methylene compounds were

acetylacetone, barbituric acid, 4,6-dihdroxy-2-mercaptopyrimidine, and tetronic acid. None of these compounds afforded the anticipated products with 4-anisaldehyde. Further efforts may be able to identify conditions that will work with these less reactive active methylene compounds.

Finally, the activity of the active methylene compound is not the only factor that influences the Knoevenagel condensation reaction. The position of the substituted group in aromatic aldehyde, whether the group is on ortho or para, affects this type of reaction too. Table 13 illustrates this factor by studying the different yield generated from the reaction of 4-chlorobenaldehyde, 2-chlorobenzaldehyde, p-tolualdehyde or o-tolualdehyde with a variety of active methylene compounds.

Table 13. The effect of the position of substituted group in aromatic aldehyde in the yield of the Knoevenagel condensation reaction

	malononitrile	methyl cyanoacetate	ethyl acetoacetate	Dimedone
4-chlorobenaldehyde	82	94	99	22
2-chlorobenzaldehyde	96	98	n.r.	64
p-tolualdehyde	99	99	55	n.r.
o-tolualdehyde	99	81	80	62

As shown in Table 13, the reaction of 2-chlorobenzaldehyde with different active methylene compounds gives higher yields than the reaction of 4-chlorobenzaldehyde with these active methylene compounds. However, the reaction of p-tolualdehyde gives higher

yields than the reaction of o-tolualdehyde with active methylene compounds, rendering

any conclusions regarding the influence of sterics uncertain.

CHAPTER FOUR: CONCLUSIONS

The Knoevenagel condensation reaction is a special case of aldol condensation reaction. The α,β unsaturated compounds, the main products from this type of reaction, can be used in cosmetics, perfumes, pharmaceuticals, calcium antagonists and polymers. In the past, the Knoevenagel condensation reaction has occurred under organic, complicated, and unsafe reaction conditions. However, with the development of the green chemistry concept, the Knoevenagel condensation reaction was rewritten under safe conditions. In this study, a deep eutectic solvent (choline chloride/urea) was used as a catalyst for this type of reaction. DES is safe, inexpensive and easy to recycle. Different percent yields were formed depending on the type of substituted groups on the active methylene compounds and the position of substituted groups on aromatic aldehyde. The activity of the methylene group increases as the electron-withdrawing ability of the two groups flanking the methylene group increases. When the activity of an active methylene compound increases, the reaction is done in a short time and gives high yields without the need for any purification.

Indeed, the deep eutectic solvent is a good catalyst for the Knoevenagel condensation reaction. Even though there are several reactions which could not be formed under this type of condition, the temperature or the time of reaction could be changed to generate some of these products. As a future plan for this area of research, deep eutectic solvents could be used as a catalyst and solvent for other types of active methylene compounds and aldehydes. In addition, other factors that could effect this type

of reaction can be studied such as the time and temperature that is required for this type

of reaction.

REFERENCES

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2. Jones, G. 2011. The Knoevenagel Condensation. *Organic Reactions* **2011**, *15*, 204–599.

3. Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115–136.

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