Practice

Crossed Aldol Reaction: Synthesis Optimization of Dehydrozingerone

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SUPPORTING MATERIAL

Contents

NOTE: The instructions in RED color are for laboratory instructors only!

1. LIST OF CHEMICALS AND HAZARDS

Chemicals	**CAS No.**	**Labelled as**	**GHS Hazard Statements**[1]	**Hazard Pictograms**
Vanillin ($C_8H_8O_3$)	121-33-5	Vanillin	H319	
Sodium Hidroxide (NaOH)	1310-73-2	NaOH 2.5 M	H314	
Acetone (C_3H_6O)	67-64-1	Acetone	H225, H319, H336	
Hydrochloric Acid (HCl)	7647-01-0	HCl 6M	H314, H335	
Lithium Chloride (LiCl)	7447-41-8	Anhydrous LiCl	H302, H315, H319	
Niquel (II) Chloride Hexahydrate ($NiCl_2$*$6H_2O$)	7791-20-0	$NiCl_2$*$6H_2O$	H301+H331, H315, H317, H334, H341, H350i, H360D, H372, H410	
Toluene (C_7H_8)	108-88-3	Toluene	H225, H304, H315, H336, H361, H373, H402	
Ethanol (C_2H_6OH)	64-17-5	EtOH	H225	
Ethyl Acetate ($C_4H_8O_2$)	141-78-6	EtOAc	H225, H319, H336	
Vanillin TLC Stain*	NA	Vanillin Revelator	H225, H302, H314, H340	
Distilled water (H_2O)	7732-18-5	Distilled H_2O	Not Hazardous	None

[1] The meaning of each Hazard Statement is explained in section 1.1, shown below.

*The Vanillin TLC stain can be prepared in the laboratory previous to the synthesis. The solution contains 0,5 g of Vanillin, 0,5 mL of H_2SO_4 and 9 mL of Ethanol.

1.1. Definition of GHS Hazard Statements

The GHS hazard statements of reagents used in this practice are defined as follow:

Physical Hazards

H225 - Highly flammable liquid and vapor.

Health Hazards

H302 Harmful if swallowed

H304 May be fatal if swallowed and enters airways.

H314 Causes severe skin burns and eye damage.

H315 Causes skin irritation.

H317 May cause an allergic skin reaction.

H319 Causes serious eye irritation.

H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.

H335 May cause respiratory irritation.

H336 May cause drowsiness or dizziness.

H340 May cause genetic defects.

H341 Suspected of causing genetic defects.

H350i May cause cancer by inhalation.

H360D May damage the unborn child.

H361 Suspected of damaging fertility or the unborn child.

H372 Causes damage to organs through prolonged or repeated exposure.

H373 May cause damage to organs (central nervous system, liver, heart) through prolonged or repeated exposure.

H301+H331 Toxic if swallowed or if inhaled.

Environmental Hazards

H402 Harmful to aquatic life.

H410 Very toxic to aquatic life with long-lasting effects.

2. EQUIPMENT AND MATERIALS

- 50 mL round bottom flask
- Magnetic stirrer
- Hot plate

- Reflux condenser
- Büchner flask
- Filter paper
- Spatula
- Büchner funnel
- Crystallizer
- Glass rod
- Capillaries
- Analytical balance
- TLC silica plate
- Chamber for TLC
- UV-Vis Lamp

2.1. List of quantities of reagents

Reagents	**Molecular Formula**	**Molecular Weight**	**Quantity**
Vanillin	$C_8H_8O_3$	152.15 g/mol	0.5 g
Sodium Hidroxide (2.5M)	NaOH	39.997 g/mol	2.63 mL
Acetone	C_3H_6O	58.08 g/mol	5 mL
Hydrochloric Acid (6M)	HCl	36.46 g/mol	2.5 mL
Lithium Chloride	LiCl	42.394 g/mol	0.013 g – 0.139 g[1]
Nickel (II) Chloride Hexahydrate	$NiCl_2 \times 6H_2O$	129.594 g/mol	0.0425 g
Toluene	C_7H_8	92.14 g/mol	9 mL
Ethanol	C_2H_6OH	46.07 g/mol	5 mL[2]
Ethyl Acetate	$C_4H_8O_2$	88.11 g/mol	1 mL
Distilled water	H_2O	18.018 g/mol	10 mL

1 The amount of lithium chloride depends on the equivalents of each group, which goes from 0.1 equiv to 1 equiv

2 The amount of ethanol used can vary, depending on the crystallization process.

3. STUDENT HANDOUT

3.1. Theoretical Introduction

Aldol Reaction

The Aldol condensation is one of the most important reactions for C-C bond formation and has been a very useful tool in the synthesis of complex natural and synthetic products for pharmaceutical purposes[1].

Carbonyl compounds can enolize in acidic or basic media (see Figure 1). In acidic media, carbonyl compounds can be protonated and a proton on the alpha carbon can be extracted to produce a double bond. On the other hand, protons on alpha carbons to carbonyl are slightly acidic (pKa ~25) and when a strong base is used that proton can be removed to produce either an enolate as oxoanion or a carbanion with the dual nucleophilic site. When a weak base as NaOH (pKa ~15) is used, only a small portion of enolate is produced, however in the presence of electrophiles, it can react, then equilibrium keto-enolate couse generation of more enolate species. So even the NaOH is not strong enough to remove quantitavly the proton from alpha carbon, the reaction is still possible whenever the enolate can find electrophile. The reactivity of nucleophilic sites of enolates is explained in the coursebook – Organic Chemistry by Clayden, Greeves and Warren on page 453 in the second edition[2].

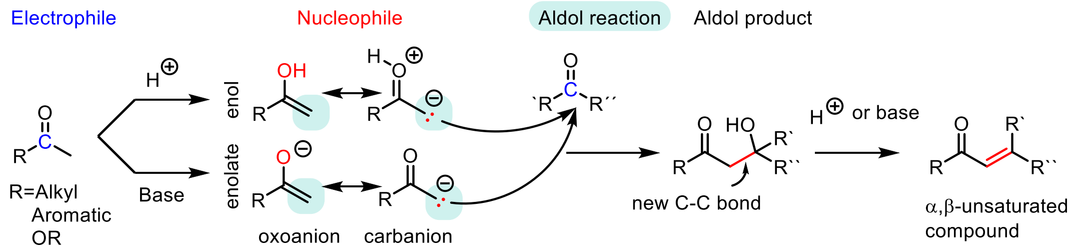


Figure 1. Aldol reaction. Enolization in acidic media to produce enol and in basic media to produce enolate. Both enol and enolate act as nucleophiles and attack another carbonyl to produce a new C-C bond.

An aldol reaction, when the alpha carbon acts as a nucleophile and attacks the carbonyl of the same species, is called auto condensation. When enol or enolate attack another carbonyl species, more electrophilic than themselves, it is called crossed aldol reaction. From a synthetic point of view, the last one is much more useful.

Crossed Aldol Reaction

In order to achieve a successful crossed-aldol reaction, some characteristic must be fulfilled (see Figure 2):

- One of the partners should be enolizable and only one enolate should be possible, in the case of unsymmetrical ketones only one side should be enolizable. In the case of symmetrical ketones, only one enolate is possible.
- The second partner should be more electrophilic than the first pre-enolized partner.

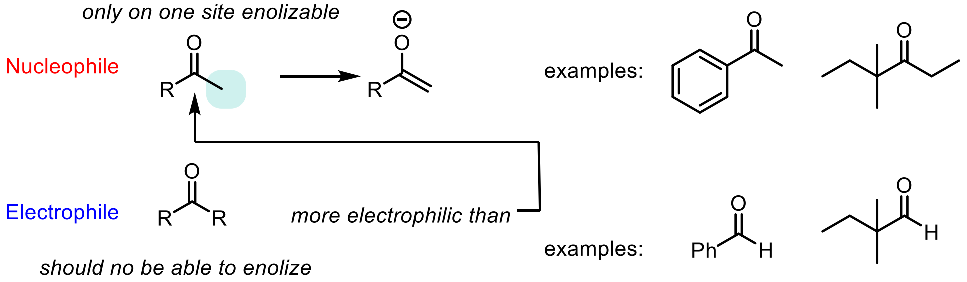


Figure 2. Requirements for nucleophile and electrophile in order to carry out a crossed aldol reaction with a unique product

Vanillin: A natural aldehyde and our electrophile used for the crossed aldol reaction

Vanillin and acetone fulfil the requirements for a crossed aldol condensation. Vanillin can be easily condensed with acetone to give *E*-4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one (also known as dehydrozingerone or vanillideneacetone).

Vanillin can be easily obtained from a natural source by extraction from vanilla plants, however, the compound is also available in drug- and hygiene stores, because vanillin is commonly used as a flavoring agent in the food industry. Interestengly, the high demand of the vanillin made imposible to obtained it in industrial scal by extraction and other biotechnological protocols are applied to semisynthetise the vanillin from biomass [3].

Dehydrozingerone or DHZ is a remarkable scaffold comprising of a phenyl ring bearing a methoxy group ortho to the phenolic OH and an α,β-unsaturated carbonyl group with a terminal methyl group. It is present in a natural source as rhizomes of ginger, it also exhibits a wide range of biological activities such as anti-inflammatory, antioxidant, antimicrobial, and cytotoxic activity[4–6].

The synthesis reported in literature has some disadvantages: the reaction is carried out for up to 48h and the reported yields are poor to moderate, around 50%.[7] In this laboratory practice, you will try to optimize the reaction in terms of time and yield of the reaction. Since using some metal halide salts was previously reported to improve the yield of the aldol reaction[8], you will use lithium chloride and/or nickel chloride (see Figure 3) at different temperatures. The progress will be monitored by TLC. Since acetone is volatile, doesn´t have a chromophore moiety in its structure and is used in excess, the vanillin consumption will be monitored and the disappearance of the spot on the TLC will be the sign of the end of the reaction. For that, it is important to separate the starting material (vanillin) and the product (dehydrozingerone).. For the procedure to visualize and separate starting material and product, see the experimental section

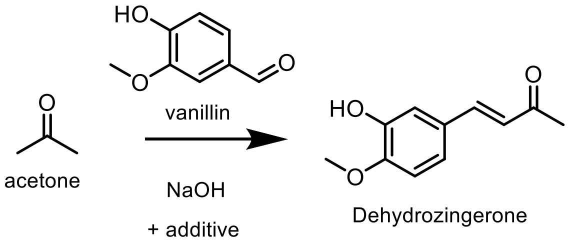


Figure 3. Scheme of reaction using acetone and vanillin.

Each group will be work using a different reaction condition and the goal at the end of the session is to asses which conditions are the best in terms of reaction ratio, economy, waste production, energetic efficiency and yield.

Optimization of the reaction in terms of atomic and energetic economy, low waste production and hazard prevention – The Principles of Green Chemistry

One aspect that is sometimes underrated in chemical research and chemical industry is the pursuit to avoid materials that are hazardous to humans and to the environment, as much as possible. This approach has been called “Green Chemistry” and is defined by 12 fundamental principles[9]:

- Prevention of waste: Try to prevent the production of waste, rather than treat or clean it up after its formation
- Atom Economy: All materials used in the process should be incorporated in the product
- Implementation of less hazardous chemical synthesis routes: Use and generate substances that are as little toxic as possible to human health and the environment
- Design of safer chemicals: Products should be designed to be as harmless as possible while maintaining their desired properties
- Use of safer solvents and auxiliary substances: Chosen solvents and other agents should have minimal toxicity and be recyclable if possible
- Design energy efficient chemical routes: Routes should be carried out at room temperature and pressure to minimize energy demands
- Use renewable materials: Renewable feedstocks should be used, such as chemicals derived from biological sources to avoid substances derived from petrochemicals.
- Use the least reaction steps: Try to avoid the use protecting groups or other derivatives, as these steps require additional reagents and generate waste
- Use efficient catalysts: The use of catalysts enables reactions of higher atom efficiency and the catalyst itself can be reused many times over
- Design degradable products: Where possible, products that are capable to be degraded by UV light, water or bio-degradation should be the goal
- Prevent pollution through constant monitoring: Monitoring in real-time can prevent accidents that cause unwanted reactions and release toxic material

- Design safer chemical procedures: By eliminating the use of hazardous chemicals from (industrial) chemical process, risks are largely minimized in the first place.

3.2. Objectives

- Synthesis of biologically active dehydrozingerone by crossed aldol protocol.
- Application of thin layer chromatography in the reaction optimization process.
- Determination of the optimal conditions.
- Introduction of the role of Lewis acids in organic synthesis.

3.3. Experimental Procedure

The instructor needs first to divide the students into six groups, each one working with different conditions (see Table 1). If the laboratory conditions permit, one student per group can be made and each condition can be studied by two or more groups. In that case, it will be much easier to detect human errors.

Synthesis of Dehydrozingerone

1. In a 50 mL round-bottom flask, add 0.5 g (3.3 mmol) of vanillin then 5 mL (67.5 mmol) of acetone with vigorous stirring. After vanillin has dissolved completely (usually very fast) add 2.63 mL NaOH 2.5 M (the concentration of NaOH is important as using more concentrated NaOH will produce a thick paste mixture which extends reaction time and further complicates the precipitation process). Now add the additive/s (check the table below and workgroup to know which additive to add, perform calculations,and the corresponding time for each reaction). If the reaction is heated you need to assemble a condenser to the flask to avoid evaporation of acetone.

Table 1. The proposal of different conditions and expected results

Work Group	Additives (Equivalents)	Temperature conditions/°C	Time after vanillin is consumed
1	LiCl (0.1 equiv)	Room Temperature	8-10h
2	LiCl (0.1 equiv)	40	3h00
3	LiCl (0.1 equiv)	50	2h30
4	LiCl (0.5 equiv)	40	3h30
5	LiCl (1 equiv)	40	3h30

6	LiCl (0.1 equiv) + $NiCl_2 \times 6H_2O$ (0.1 equiv)	40	2h00

2. In the cases of groups 2 to 6, you need to assemble a water bath with a thermometer to control the temperature. Also, the condenser assembles in a flask to avoid evaporation. (DO NOT forget to control the temperature, if it is too hot, add some ice cubes to quickly achieve the correct temperature). The instructor must demonstrate the assembly of both pieces of equipment.
3. In all reactions, be prepared to do TLC every 30 min (Since none of the reaction finishes before 2h, the first two samples can be done at time 0 and then after 1h or 1h30) in order to control the kinetic progress of the reaction.

   TLC Conditions:

   - (Toluene: AcOEt / 9:1)
   - Visualization in UV-light + Vanillin stain (For vanillin stain visualization, wet the silica plate with the solution, dry and burn it gently by applying heat from hotplate or heat gun.
4. Once the reaction is complete (or if laboratory session is about to finish –consult your instructor) stop it. Is a good idea that all students quench the reaction at least 30 min before the session is finished as is the usual time that they need to precipitate, filter and clean the working area
5. Add drop by drop, 2.5 mL of HCl 6M to the round bottom flask and cool to room temperature for about 5 min.
6. Assemble a cold bath with ice and place the round bottom flask in it. By using the glass rod, scratch the bottom of the flask to improve the precipitation of the compound. The precipitate is usually free of starting material and 5 min is the usual time for the precipitate to start appearing in an ice bath, however sometimes it needs up to 15 min, in which case the temperature can be lowered using ice and salt to force the precipitation. If there is no precipitation (few cases), in the next

session the student should evaporate acetone and extract the aqueous layer with CH_2Cl_2 or AcOEt.

7. Filter by vacuum and washwith little very cold distilled water several times
8. The yellow crystals will be recrystallized from hot ethanol in a water bath while vigorously stirring. Once precipitated, filter the crystals once again by vacuum.
9. Weight, label and store the product properly for characterization.

Characterization of Dehydrozingerone

- TLC 9:1 (Toluene/AcOEt).
- Determine Comparison of the melting point (MP) of the product with the literature (See Entry 5).
- Infrared Spectroscopy (IR). (See Entry 5)
- If available in the teaching laboratory – HPLC, MS spectrometry (see Entry 5) and ^{1}H NMR

Students should use MP and IR spectroscopy to determine the identity of the product. If available, HPLC/UPLC, mass or NMR spectroscopy can be used to determine the purity of the product . HPLC and FT-IR spectra are attached at the end of this file

3.4. Laboratory Questions

1. Draw the mechanism of the aldol reaction generated in this session.
2. Calculate the reaction yield and compare with all groups.
3. Collect all the data from all groups. What is your conclusion?. Which conditions and additive(s) accomplish the purpose of optimization? The instructor must warn thestudents that the yield is not the definitive factor to base of the final decision on, as our experience has shown that occasionally yields can be misleading as the quantity of precipitate is sometimes erratic and depends on students handling abilities as well as the post recrystallization process.
4. How do you think that LiCl or $NiCl_2$ improve the reaction ratio? What is a Lewis acid?

5. Describe the product obtained by IR spectroscopy and compare with literature (ask the instructor for a copy of IR spectra or check the database: https://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_index.cgi). What difference can you observe regarding the starting material?
6. Describe with your own words, what the pursuit of green chemistry entails.
7. Name at least 6 of the 12 Principles of Green Chemistry

3.5. Laboratory Answers

1. The mechanism is shown as follow:

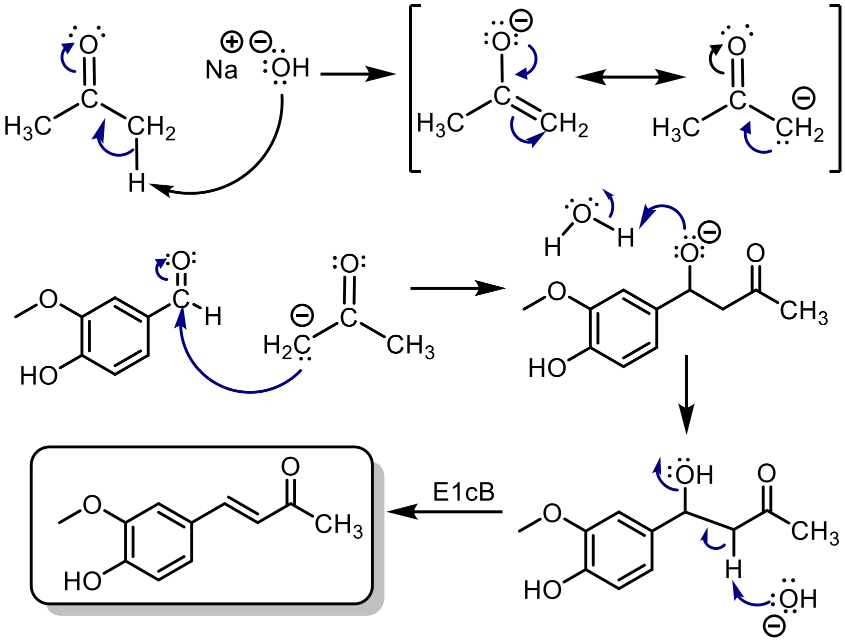


Figure 4. Mechanism of crossed aldol reaction for vanillin.

2. $Reaction\,yield = \frac{Experimental\,mass\,of\,DHZ}{Theorethical\,mass\,of\,DHZ} x\,100$

3. The best condition is using LiCl (0.1 eq) with $NiCl_2{\cdot}6H2O$ (0.1 eq) at 40 °C or just LiCl (0.1 eq) at 50 °C where the time of full conversion is shortened from 24 h as reported in the literature to 2 h and 2.30 h, respectively. The first mentioned condition requires additional reagents and even at a 10% molar ratio, it will still result as waste, so lithium chloride alone as an additive only requires 0.5 h longer heating but the reaction is greener.

4. The lithium cation has a great affinity to the oxygen. When enolate-ketone is established with a weak base as NaOH only small portion of enolate can be observed which can act as a nucleophile. However, the presence of lithium cations probably favour the generation of more enolates, which accelerates the reaction. On the other hand, the presence of metals such as nickel interact with the carbonyl oxygen increasing the electrophilicity of the aldehyde. In the Lewis theory of acid-base reactions, acids accept pairs of electrons. A Lewis acid is, therefore, any substance, such as the H+ ion, that can accept a pair of nonbonding electrons. In other words, a Lewis acid is an electron-pair acceptor.
5. The students must identify at least the next IR bands values in the spectrum: strong C=O stretching for a conjugated ketone at 1685-1666 cm^{-1}. C=C stretching for an alkene at 1662-1626 cm^{-1}. O-H stretching for hydroxyl (phenolic) at 3550-3200 cm^{-1} with a strong appearance. C=C bending for alkene at 730-665 cm^{-1} with a strong appearance. The differences in spectra for starting material and final product are C=O stretching for ketone at 1685-1666 cm^{-1} and C=O stretching for aldehyde at 1710-1665 cm^{-1} for dehydrozingerone and vanillin, respectively. Also, C-H stretching for aldehyde at 2850-2695 cm^{-1} and C-O stretching for ether at 1000-1300 cm^{-1}; 1070-1150 cm^{-1} appears only in the vanillin IR spectrum.
6. Green Chemistry aims to reduce negative effects on human health and the environment and maximizing efficiency by implementation of 12 fundamental principles in chemical research and also in chemical industry.
7. The 12 Principles of Green Chemistry are:

   - Prevention of waste
   - Atom Economy
   - Implementation of less hazardous chemical synthesis routes
   - Design of safer chemicals

- Use of safer solvents and auxiliary substances
- Design energy efficient chemical routes
- Use renewable materials
- Use the least reaction steps
- Use efficient catalysts
- Design degradable products
- Prevent pollution through constant monitoring
- Design safer chemical procedures

4. ECONOMIC ANALYSIS OF EXPERIMENTAL CLASS

Chemicals	**Amount per semester**[a]	**Source**	**Sigma Aldrich Code**	**Cost ($)**	**Cost ($) by group**
Vanillin ($C_8H_8O_3$)	3 g	Drugstore-Ibarra	NA	15$ - 300g	0.15 $
Sodium Hidroxide (NaOH-5M)	15.78 mL (2.5M) *	Local Chemical SupplierIbarra (M&M)	NA	17$ - 500mL	0.26 $
Acetone (C_3H_6O)	30 mL	Sigma-Aldrich	8222511000	26$ - 1L	0.78 $
Hydrochloric Acid (HCl)	15 mL	Sigma-Aldrich	320331	81$ - 500mL	2.43 $
Lithium Chloride (LiCl)	0.30 g	Sigma-Aldrich	73036	82$ - 100g	0.24 $
Niquel (II) Chloride Hexahydrate ($NiCl_2 {*} 6H_2O$)	0.05 g	Sigma-Aldrich	223387	70$ - 25g	0.14 $
Toluene (C_7H_8)	9 mL	Sigma-Aldrich	1083231000	39.5$ - 1L	0.35 $
Ethanol (96%) (C_2H_6OH)	30 mL	Drugstore-Ibarra	NA	9$ - 1gallon	0.07 $
Ethyl Acetate ($C_4H_8O_2$)	1 mL	Sigma-Aldrich	8222772500	61$ -2.5L	0.024 $
Total cost by semester	4.44$				
Cost by group	0.74 $				

[a]The amount of chemicals is approximated for 6 groups in a laboratory practice over one semester.

* 7.89 mL of 5M solution of NaOH are needed to prepare the 15.78 mL 2.5M of NaOH.

5. CHARACTERIZATION OF STARTING MATERIAL AND FINAL PRODUCT

5.1. Melting point

Reported[10]

Vanillin: 81°C – 83°C

Dehydrozingerone: 127°C – 131°C

Experimental

Vanillin: 81°C

Dehydrozingerone: 129°C-130°C

5.2. Infrared Spectroscopy (IR)

Vanillin

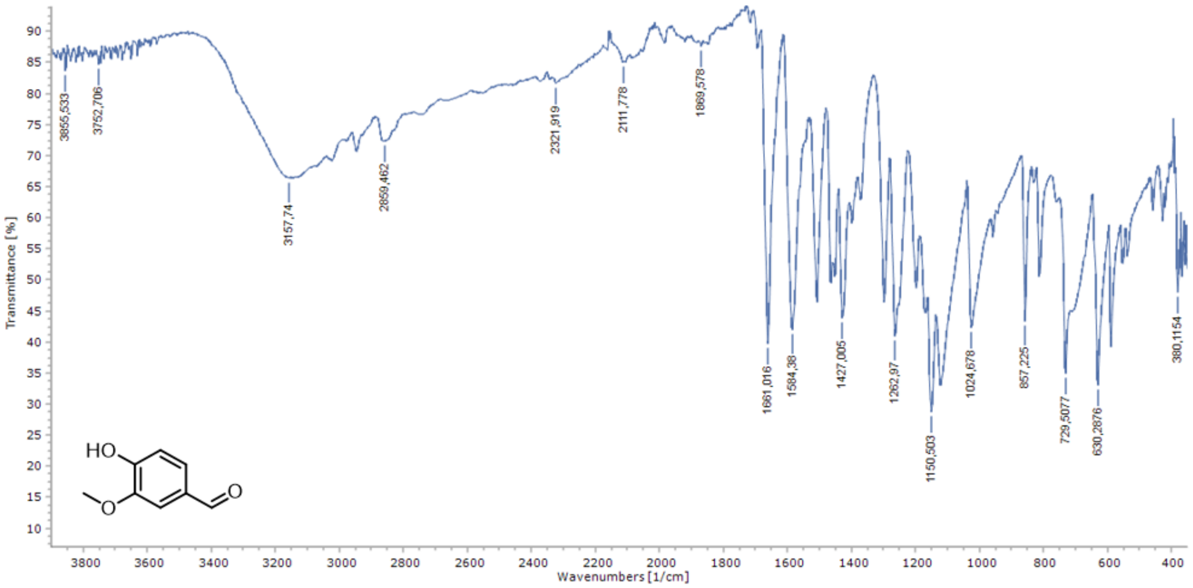


Fig. 4. IR spectrum (ATR sampling technique) of starting material (Vanillin) for crossed aldol reaction.

Dehydrozingerone

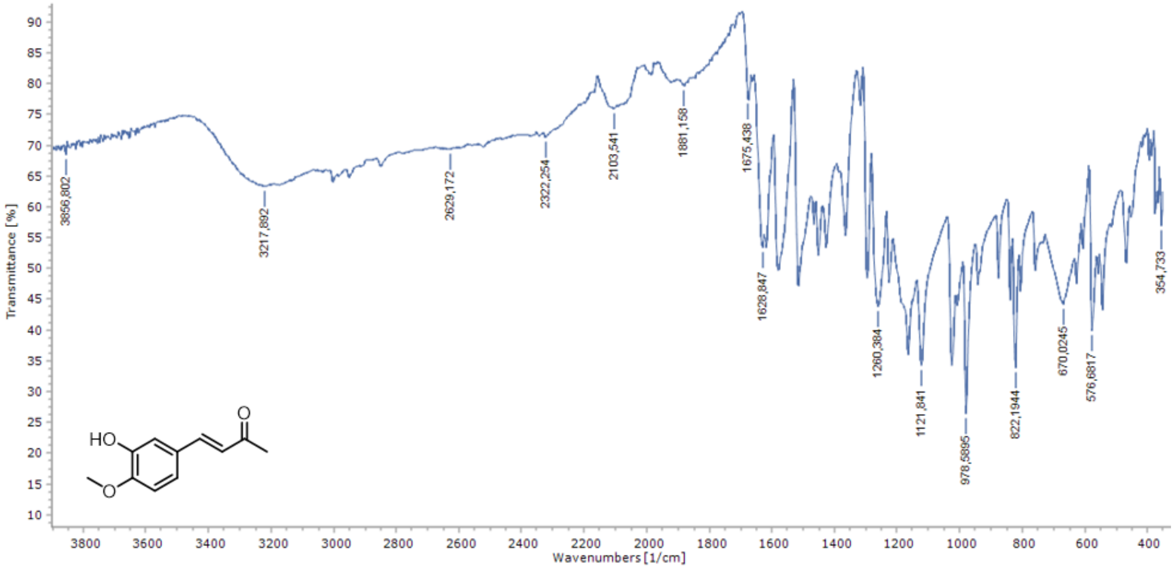
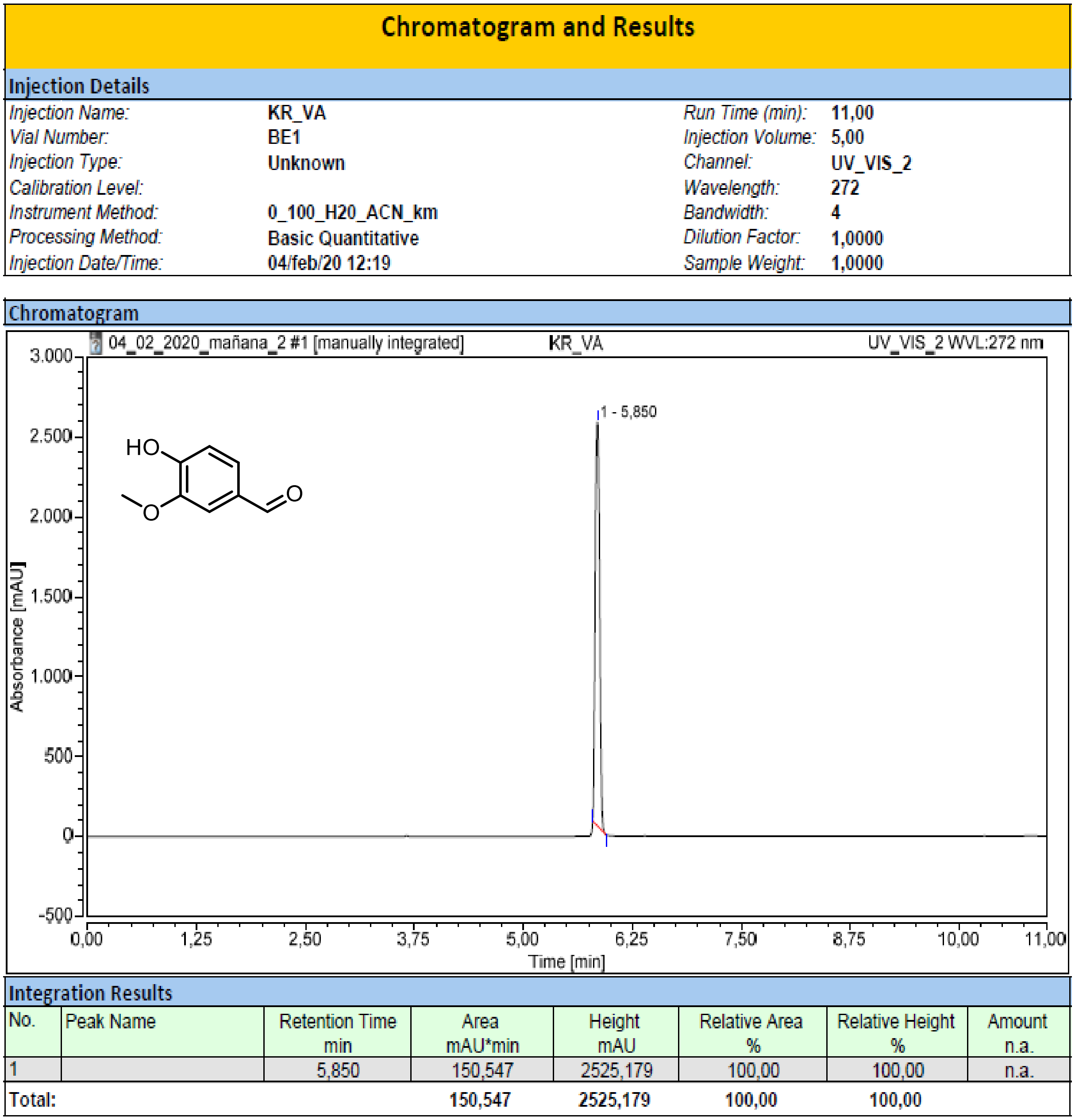


Fig. 5. IR spectrum (ATR sampling technique) of reaction product (Dehydrozingerone) from crossed aldol reaction of vanillin.

5.3. High Performance Liquid Chromatography (HPLC)

The analytical method was developed by using HPLC apparatus UltiMate 3000, C-18 column for HPLC Hypersil GOLD™ (150 mm x 4.6 mm, 5µ particle size). The instrument method used was 0-100 H_20 and Acetonitrile gradient.

Vanillin



Chromatogram and Results

Injection Details

Injection Name:	KR_VA	*Run Time (min):*	11,00
Vial Number:	BE1	*Injection Volume:*	5,00
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	272
Instrument Method:	0_100_H20_ACN_km	*Bandwidth:*	4
Processing Method:	Basic Quantitative	*Dilution Factor:*	1,0000
Injection Date/Time:	04/feb/20 12:19	*Sample Weight:*	1,0000

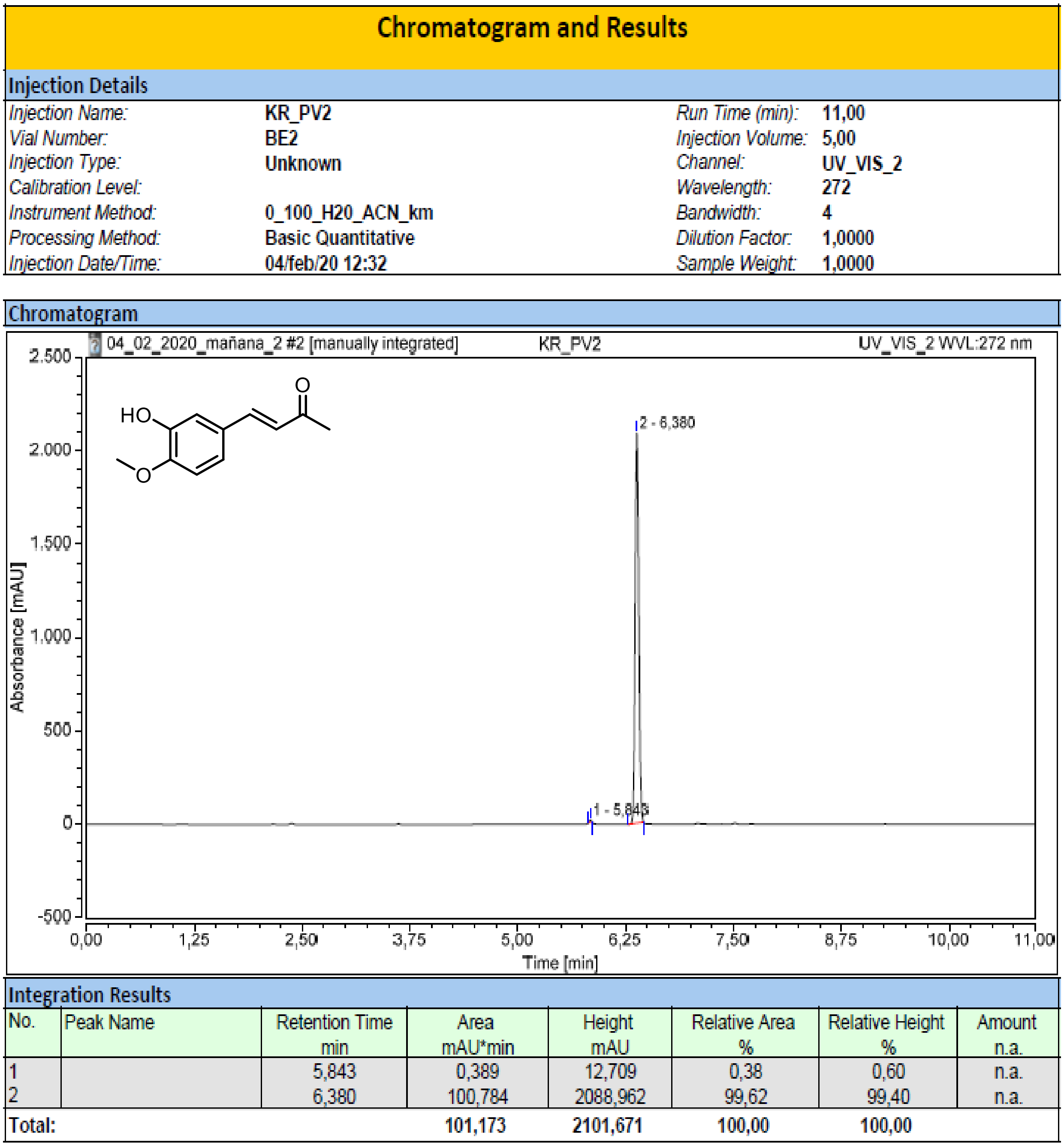
Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5,850	150,547	2525,179	100,00	100,00	n.a.
Total:			150,547	2525,179	100,00	100,00	

Fig. 6. HPLC Chromatogram starting material (Vanillin) for crossed aldol reaction.

Dehydrozingerone



Chromatogram and Results

Injection Details

Injection Name:	**KR_PV2**	*Run Time (min):*	**11,00**
Vial Number:	**BE2**	*Injection Volume:*	**5,00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**272**
Instrument Method:	**0_100_H20_ACN_km**	*Bandwidth:*	**4**
Processing Method:	**Basic Quantitative**	*Dilution Factor:*	**1,0000**
Injection Date/Time:	**04/feb/20 12:32**	*Sample Weight:*	**1,0000**

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5,843	0,389	12,709	0,38	0,60	n.a.
2		6,380	100,784	2088,962	99,62	99,40	n.a.
Total:			**101,173**	**2101,671**	**100,00**	**100,00**	

Fig. 7. HPLC Chromatogram reaction product (Dehydrozingerone) from crossed aldol reaction of vanillin.

5.4. Mass Spectrometry (MS)

ESI/MS spectra were obtained using nitrogen as the collision gas within a mass range of m/z 100–800. MS parameters were as follows: the cone and capillary voltages were set at

20 kV and 2,5 kV, respectively, the source temperature was 80°C, and desolvation flow was 600 (L/hr). The analytical method was developed using an Acquity BEH C-18 column (2.1 × 100 mm, 1.7 µm) (Waters).

ESI+ $[M+H]^+$ calculated 193.0786 and found 193.1237

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