Preparation of chalcone and its further Robinson annulation with ethyl acetoacetate

Supplementary Material

Notes to the instructor:

This experiment has been implemented at Tampere University of Technology to students of MSc in Chemistry. The average yield for the chalcone preparation is 76 % and the yields are between 58 and 89 %. The average yield for the Robinson annulation is 36 % and the enone has been obtained from 23 to 61 % yields (9 students).

This experiment is given to the students in the context of studies on carbonyl chemistry, intending to show them the different reactivity of the carbonyl group. Emphasis is given to the crossed aldol reaction mechanism and mechanistic aspects related to the background self-condensation aldol reaction of the ketone is also discussed. The experiment is further used to strength the students' background in the chemoselective reactivity of enones (direct vs conjugate additions), and the usefulness of the Robinson annulation for ring synthesis.

The procedure can be adapted to show the students how to handle reactions under anhydrous atmosphere but no significant differences on the reaction yields have been observed when performing the reactions under Ar.

Notes for the Claisen-Schmidt condensation:

Although not absolutely necessary for this reaction, the students are usually instructed to use a three-necked round bottomed flask equipped also with a condenser. This will avoid any problems arising from an accidental fast addition of benzaldehyde. The typical reaction apparatus used by the students is as illustrated in SM 4.2.4.1.1. Benzaldehyde is usually added for 5-10 min, as the fast addition of this reactant has shown to have a detrimental effect in the reaction yield. The occurrence of a Cannizzaro reaction might be on the basis of the lower yield, but this aspect was never confirmed by the authors.

The students are usually instructed to follow the reaction by TLC, using Hexane 9/1 AcOEt as eluent. Acetophenone and the chalcone have similar Rf's and so the reaction is followed by checking the consumption of benzaldehyde, using UV lamp (254 nm). Nevertheless, when developing the TLC plates with Cerium Molybdate benzophenone is not visible whilst the product develops into a yellow/greenish color (SM 4.2.4.1.2). A standard of the previously prepared chalcone is usually provided to the students for the sake of comparison. Students are instructed to prepare much diluted samples of starting materials as spots usually get spread in the TLC. Other combinations of eluents for the TLC were unsuccessfully tested (Toluene/AcOEt; CH_2Cl_2/$CHCl_3$; CH_2Cl_2/Hexane; Et_2O/Hexane).

The reaction takes 2-3 hours to reach completion and usually results in a very thick mixture containing the precipitated chalcone (SM 4.2.4.1.3). In some instances the product does not precipitate and two layers are visible in the reaction flask, even though the benzaldehyde has been completely consumed. In such cases the reaction is stirred in an ice bath for some minutes to induce precipitation of the chalcone, or a minimum amount of cold water can be added. In order to keep the schedule, the reaction mixture can be kept overnight in the fridge and the filtration done in session 2.

The recrystallization of the chalcone should be done at 50 °C, since its melting point is only 55-57 °C. The amount of ethanol needed for the recrystallization is 5 mL/g of crude chalcone. The dissolution of the chalcone in ethanol has been performed aided by a water bath at 50 °C. The recrystallization of the compound is performed by cooling the mixture at room temperature to get the first crystals and then moved to the fridge (4 °C) for about 20 min. The beaker walls have been scratched with a glass rod to induce crystallization when needed.

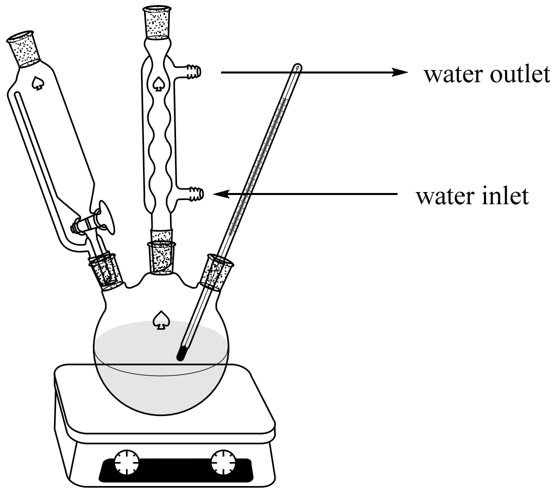
Notes for the Robinson Annulation:

The use of different amounts of barium hydroxide and different reaction temperatures allow the preparation and isolation of the intermediaries of this reaction, as described by Delaude.[1] In order to show the students the presence of such intermediaries, samples of the 1,5-diketone and the hydroxy ketone have been prepared beforehand according to the procedure developed by Delaude,[1] and given to the students for them to prepare TLC standards for comparison. TLC's of the reaction mixture are performed by diluting the reaction mixture in ethanol and eluting twice with AcOEt 15/85 Hexane. Observation of the spots can be achieved either with a UV lamp (254 nm) or by developing with $KMnO_4$ solution followed by heating. After 1h it is possible to observe 4 spots in the reaction mixture, corresponding to the starting chalcone, the 1,5-diketone, the hydroxy ketone and the cyclic enone (SM 4.2.4.1.4). After overnight reaction traces of chalcone are still visible, nevertheless the reaction can be quenched as the desired product is obtained pure after crystallization.

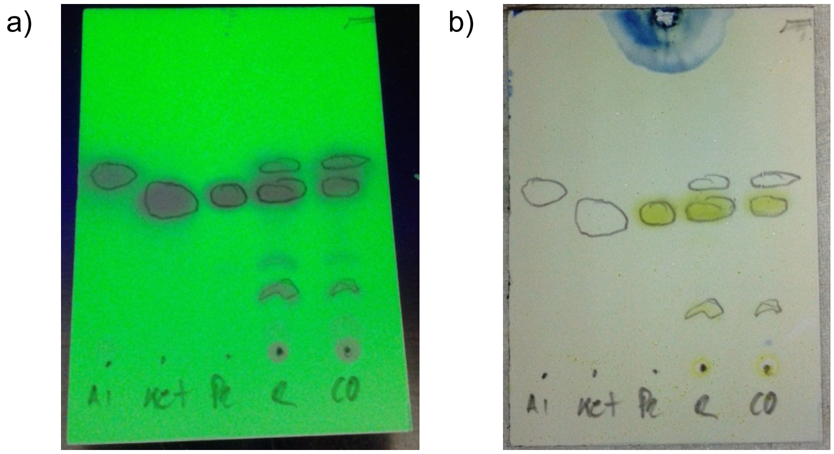
It is important to keep vigorous reflux (around 90 °C), as longer reaction times are needed for gentle refluxes due to the low solubility of the barium hydroxide in ethanol.

After overnight reflux, it is important to efficiently cool the reaction mixture and to use very cold water in the dilution step. If not, a yellow gum will form and clog the surface of the sintered glass funnel, making the filtration to take long time and decreasing the purification yield.

Enough ethanol just to dissolve the crude enone lumps is used in the recrystallization. During the dissolution of the product in boiling ethanol the mixture becomes milky and care should be taken in order to avoid the use of excess ethanol (25-40 mL of ethanol have been used).

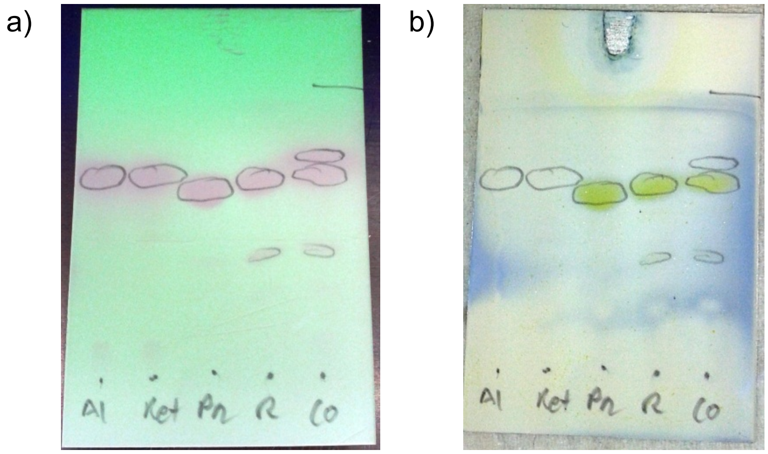


SM 4.2.4.1.1 – Reaction apparatus used for the aldol condensation



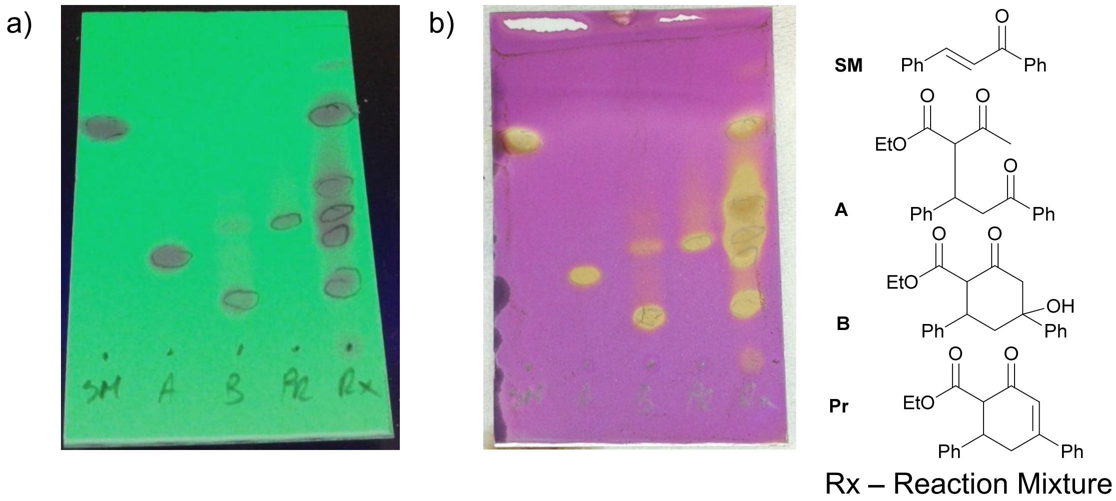
Al – Benzaldehyde
Ket – Acetophenone
Pr – Chalcone
R – Reaction Mixture
Co – co-spot of benzaldehyde + reaction mixture

SM 4.2.4.1.2 – TLC of the reaction mixture after 1h stirring (AcOEt 1/9 Hexane). a) Spots revealed with UV lamp. b) Spots developed with Cerium molybdate – chalcone spot develops to yellow/greenish



Al – Benzaldehyde
Ket – Acetophenone
Pr – Chalcone
R – Reaction Mixture
Co – co-spot of benzaldehyde + reaction mixture

SM 4.2.4.1.3 – TLC of the reaction mixture after 3h stirring. (AcOEt 1/9 Hexane) a) Spots revealed with UV lamp. b) Spots developed with Cerium molybdate – chalcone spot develops to yellow/greenish



SM 4.2.4.1.4 – TLC of the Robinson annulation reaction mixture after 1h at reflux (AcOEt 15/85 Hexane, eluted twice). a) Spots revealed with UV lamp. b) Spots developed with $KMnO_4$.

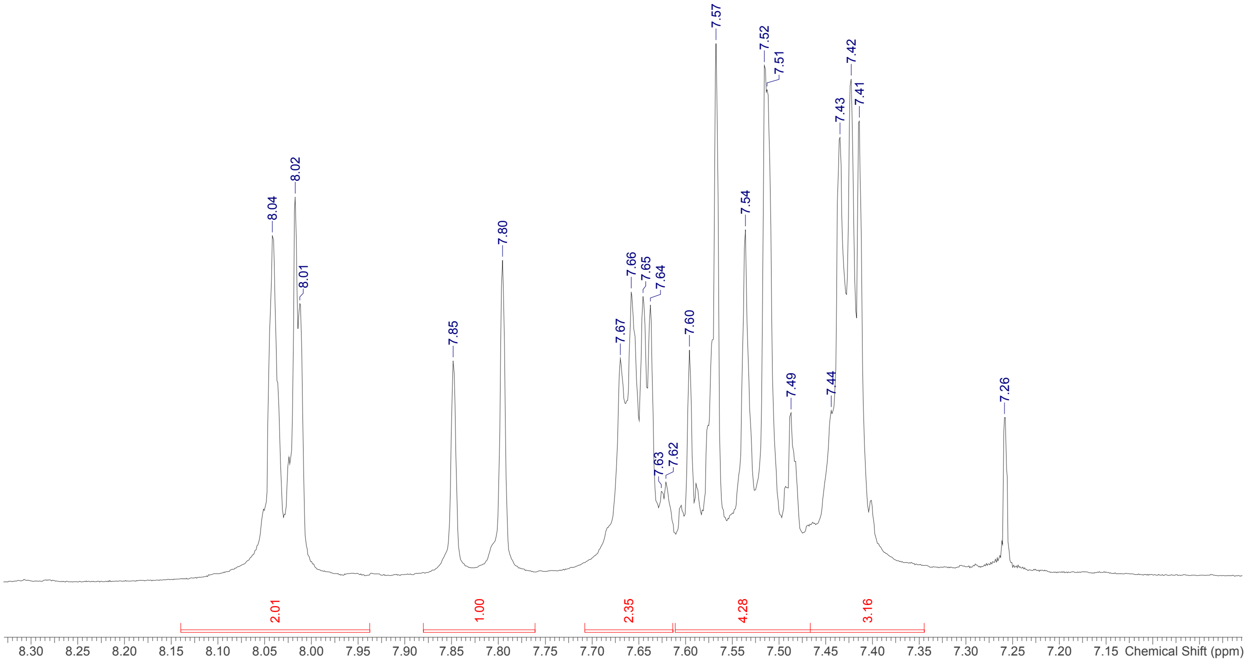
Tips to answer the questions

1. This question intends to make the student think about the different electrophilicity of the aldehyde and the ketone. It is expected the student to identify the formation of the aldol self-condensation of acetophenone as the main possible side product of this reaction.
2. Performing crystallizations at a higher temperature than the melting point is detrimental to yield of the process, as the compound can decompose. In this case the melting point of the product is 55-57 °C.
3. The analysis of the ^1H NMR of the prepared chalcone clearly shows a duplet at 7.82 ppm. The large coupling constant of that duplet (J = 15.5 Hz) and the absence of any other visible duplet indicate the exclusive formation of the *E*-alkene. The student should be instructed to think on the possibility of the Z-alkene to form and equilibrate to the *E*-alkene because of thermodynamic control.[2]
4. The students should be able to easily identify the spots on the TLC below the desired product, even if the instructor does not provide intermediary samples for comparison.
5. It is intended that the students think about the amount of catalyst used, as well as the need for higher temperatures in order to trigger the dehydration of the tertiary alcohol.
6. The atom economy of the Robinson annulation reaction studied in this experiment is 95 %, as only water is produced as a side-product. However, due to the difficulty in the precipitation of the reaction product, the experimental atom economy has been determined by the students to be only 34 % - (1.53 g average obtained product) / (3.38 g total mass of reactants).

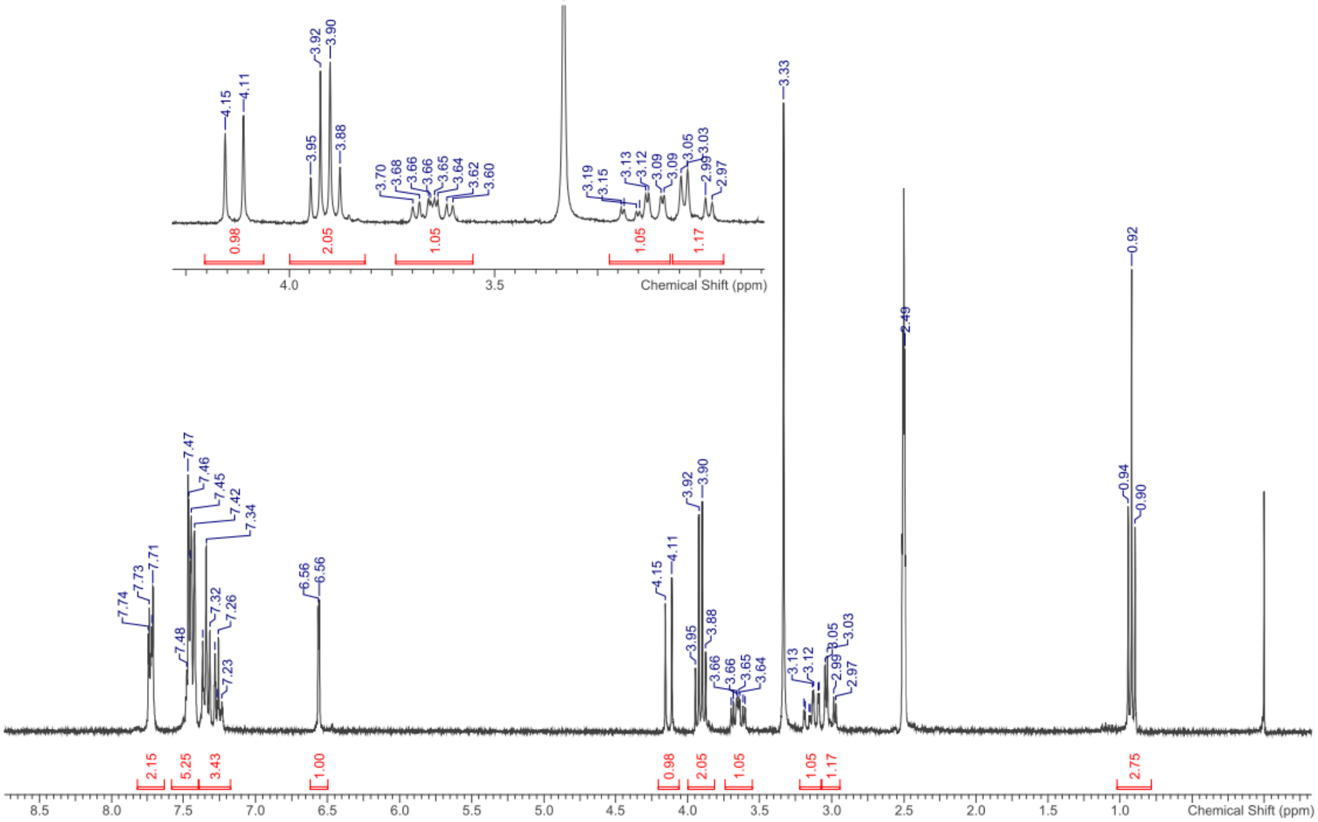
^{1}H NMR spectrum of the chalcone can be found in the literature,[3] in SDBS (No. 5818).[4] Students are encouraged to look also for the spectra of the starting materials. Spectra for benzaldehyde (No. 672) and acetophenone (No. 722) can be found in SDBS[4] or at Sigma-Aldrich website.[5]

Spectra of the Robinson annulation product in $CDCl_3$ can be found in the literature,[6] as well as the exhaustive structural characterization in DMSO-d_6.[1] The use of DMSO as deuterated solvent is advised if the instructor is planning to go deep into the structural analysis of the compound. In $CDCl_3$, the benzylic proton and the vicinal α-carbonyl proton resonate at the same frequency and so cannot be distinguished. A coupling scheme based on the previous analysis of the Robinson annulation product and the spectra obtained by the students is indicated as SM – 4.2.4.1.7.

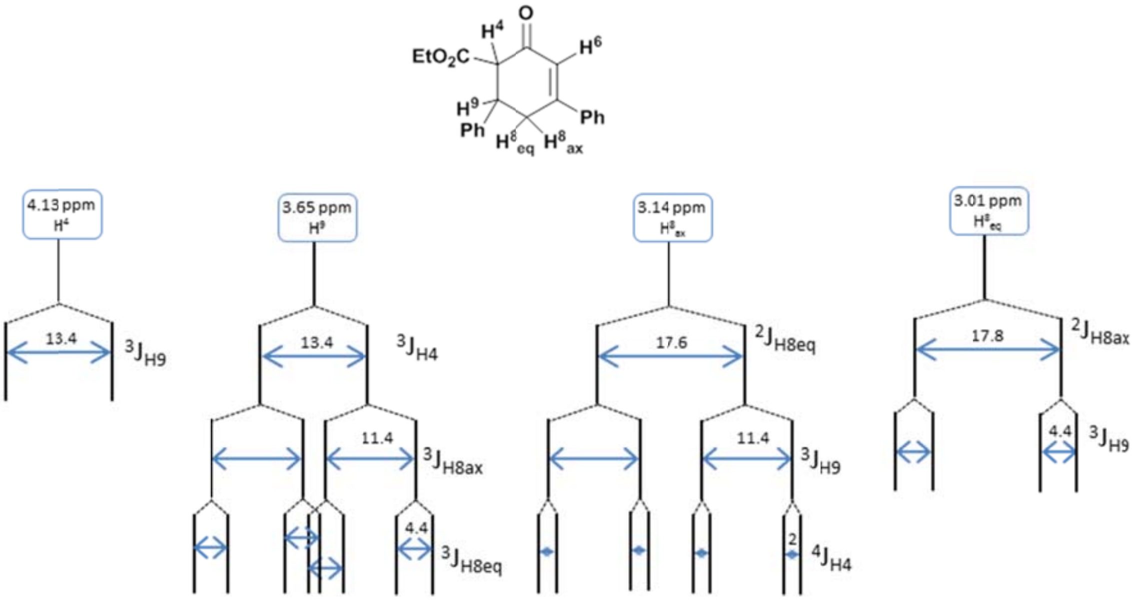
Copies of the spectra obtained by the students



SM 4.2.4.1.5 - 300 MHz ^{1}H NMR ($CDCl_3$) of chalcone obtained by the students.



SM 4.2.4.1.6 - 300 MHz ^{1}H NMR (DMSO-d_6) of Robinson annulation product obtained by the students.



SM 4.2.4.1.7 – Scheme of the ^{1}H NMR spectrum based on the coupling constants of the hydrogens of the cyclohexenone moiety of the Robinson annulation product. (Coupling constants indicated in Hz, and chemical shifts for the analysis performed in DMSO-d_6).

1. L. Delaude, J. Grandjean and A. F. Noels, *J. Chem. Educ.*, 2006, **83**, 1225.
2. J. Clayden, N. Greeves and S. G. Warren, *Organic chemistry*, 2nd edn., Oxford University Press, Oxford ; New York, 2012, pp. 679-680.
3. Compound **12** in T. Yamakawa, H. Kinoshita and K. Miura, *J. Organomet. Chem.*, 2013, **724**, 129-134.
4. SDBSWeb : http://sdbs.riodb.aist.go.jp (National Institute of Advanced Industrial Science and Technology), August 2014
5. Benzaldehyde spectra: http://www.sigmaaldrich.com/spectra/fnmr/FNMR009397.PDF, August 2014; Acetophenone spectra: http://www.sigmaaldrich.com/spectra/fnmr/FNMR009167.PDF, August 2014.
6. Compound **16a** in N. A. Shakil, M. K. Singh, M. Sathiyendiran, J. Kumar and J. C. Padaria, *Eur. J. Med. Chem.*, 2013, **59**, 120-131.

Conjugate Addition of Organocuprates to α,β-Unsaturated Ketones: Synthesis of 3,3-Dimethylcyclohexanone from 3-Methyl-2-cyclohexen-1-one

Supplementary Material

The aim of this experiment is to familiarize the student in handling reagents and reactions sensitive to moisture and air. This experiment can be performed individually (ten students) or in pairs (twenty students). The experiment can be performed on a smaller scale, for example using half the amounts indicated in the experiment.

1) The starting 3-methyl-2-cyclohexen-1-one is prepared as per L. M. Harwood, C. J. Moody, *Experimental Organic Chemistry. Principles and Practice*, Blackwell Scientific Publications, 1989, p 569. This ketone can be purchased from Aldrich (Ref. M39105)

2) Originally, technical grade diethyl ether (distilled from sodium benzophenone ketyl) is used (Fig 4.2.4.2.1). Alternative drying with anhydrous Na_2SO_4 under air atmosphere using an Erlenmeyer flask provides the same result. Technical grade *tert*-butyl methyl ether (TBME) (300 mL, Scharlau extra pure Ref: ME0550025A or similar) is transferred to a round bottomed flask (500 mL) and dried over anhydrous Na_2SO_4 (~50 g). The flask is capped with a rubber septum and connected to a balloon with a needle as an argon inlet. After 30 min the dry TBME is ready to be transferred (10 mL) to the reaction flask via syringe.

3) CuI (Aldrich, Ref: 205540) is used without further purification.

4) The round-bottomed flask is oven-dried, capped with a rubber septum and allowed to reach room temperature under a stream of argon. Anti-thermal gloves or clamps are recommended. Alternatively the reaction flask can be heated with a heat gun under a stream of argon (Fig 4.2.4.2.2). The flask is connected

to a balloon-argon inlet by a needle and one-way stopcock with luer (Cole Parmer, Ref. EW30600-05 or similar)

5) The argon is transferred directly from an argon-containing cylinder to a balloon. The balloon is connected to an empty luer-hypodermic syringe through one-way stopcock (Fig 4.2.4.2.3).

6) The dry-ice acetone bath is prepared in a propylene bath (or similar) by addition of acetone over dry-ice pellets purchased from Air Liquide. The dry-ice pellets are handled with anti-thermal gloves.

7) Disposable polypropylene hypodermic syringes can be purchased from any medical store. Needles with luer hub were purchased from Aldrich (Ref. Z117102-1EA).

8) A solution of methyllithium in diethyl ether (MeLi, 2x100 mL, M = 1.6, Aldrich Ref. 197343) is transferred via cannula (double-tipped needle Aldrich, Ref. Z101095-1EA) to an oven-dried and flushed under argon reagent storage round-bottomed flask (500 mL) provided with a rubber septum and connected by a needle to a balloon which serves as an argon inlet. The transfer of the MeLi solution to a proper round-bottomed flask greatly facilitates the intake of the required amount of MeLi by means of the available syringe needles. The remaining small amount of MeLi in the round bottomed flask is destroyed at the end of the session. The required solution of MeLi is taken from the flask by a polypropylene hypodermic syringe equipped with a metallic needle (Fig 4.2.4.2.4) and transferred to the round-bottomed reaction flask (Fig 4.2.4.2.5). Before the experiment, the student must be instructed by the supervisor in handling air and moisture sensitive reagents and in the transfer of flammable liquids via syringe (https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Bulletin/al_techbull_al134.pdf). During the transfer of MeLi, the student must wear safety glasses and latex gloves.

9) The 3-methyl-2-cyclohexen-1-one was transferred by means of a Pasteur pipette to a 25 mL round-bottomed flask in a balance and weighed (1.00 g). The flask is capped with a septum and purged with argon as described in paragraph 4. Dry TBME (10 mL) is transferred to the flask by syringe to dissolve the enone (Fig 4.2.4.2.6). The enone-solution is transferred to the reaction flask as described for MeLi (paragraph 8).

10) The reaction is monitored by thin-layer chromatography (TLC) (Fig 4.2.4.2.7) using 2x5 cm aluminium-

backed silica gel plates (0.2 mm thickness). 30% EtOAc /hexanes is used as the eluent mobile phase in a beaker (100 mL) covered with a watch glass (Fig 4.2.4.2.8). The glass capillaries are made by heating and stretching Pasteur glass pipettes with a Bunsen lighter. The plate is first examined by ultraviolet illumination at 254 nm (Fig 4.2.4.2.9) and then visualized by immersion in a *p*-anisaldehyde stain followed by heating with a heat gun (Ref. Bosch PHG500-2 or similar) (Fig 4.2.4.2.10).

11) Filtration through a pad of Celite® S facilitates separation of solids (Fig 4.2.4.2.11).

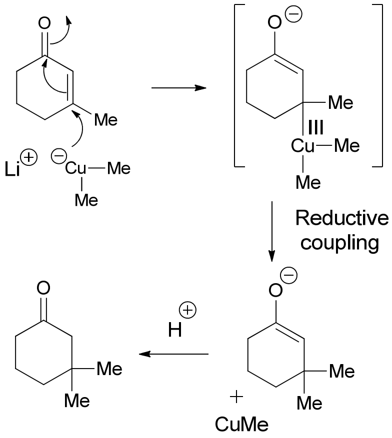
12) Flash column chromatography (https://www.youtube.com/watch?v=fF1gXUvyGb4); W. C. Still et al. *J. Org. Chem*. **1978**, *43*, 2923) is performed with 230-400 mesh silica gel. Home-made 2x10 cm column chromatography equipped with a SAV® 29/32 threaded joint is used. Air-pressure is accomplished with a Richardson rubber bulb (Fig 4.2.4.2.12). Flash chromatography is suggested in this experiment for the following reasons: a) It takes less time to purify the reaction product. b) It allows the student to become familiar with this efficient and currently used method for separation of organic compounds. The combined chromatography fractions containing product are concentrated in the rotary evaporator and the residual solvent is removed using a high vacuum pump (Fig 4.2.4.2.13) to give a colorless oil which is weighed. The time under the vacuum pump is suggested to be half a minute at 3 mmHg. Prolonged vacuum drying result in lower yields due to the volatility of the product (3,3-dimethylcyclohexan-1-one, b.p. 174-175 ºC).

13) The yields on reaction product from 45 experiments developed by students are described (table 4.2.4.2.1). A reaction product was randomly chosen to run representative ^{1}H and ^{13}C NMR and DEPT spectra (Fig 4.2.4.2.14, 4.2.4.2.15, 4.2.4.2.16).

Range of Yields (%)	Number of experiments
35-45	6
46-55	7
56-65	11
66-75	21

Table 4.2.4.2.1

14) Possible mechanism for the reaction between Me_2CuLi and α,β-unsaturated ketone (Scheme 4.2.4.2.1)



Scheme 4.2.4.2.1

FIGURES

Fig 4.2.4.2.1 Drying and distillation of solvent under argon

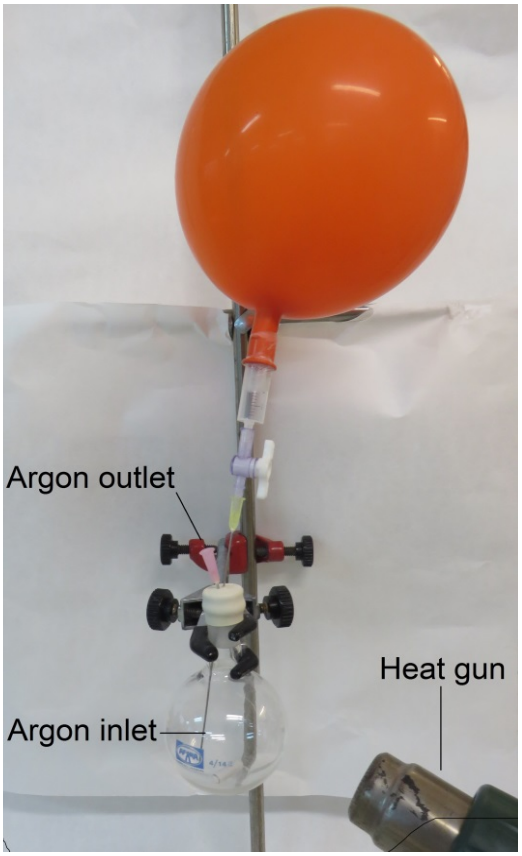


Fig 4.2.4.2.2 Drying the reaction flask under argon.

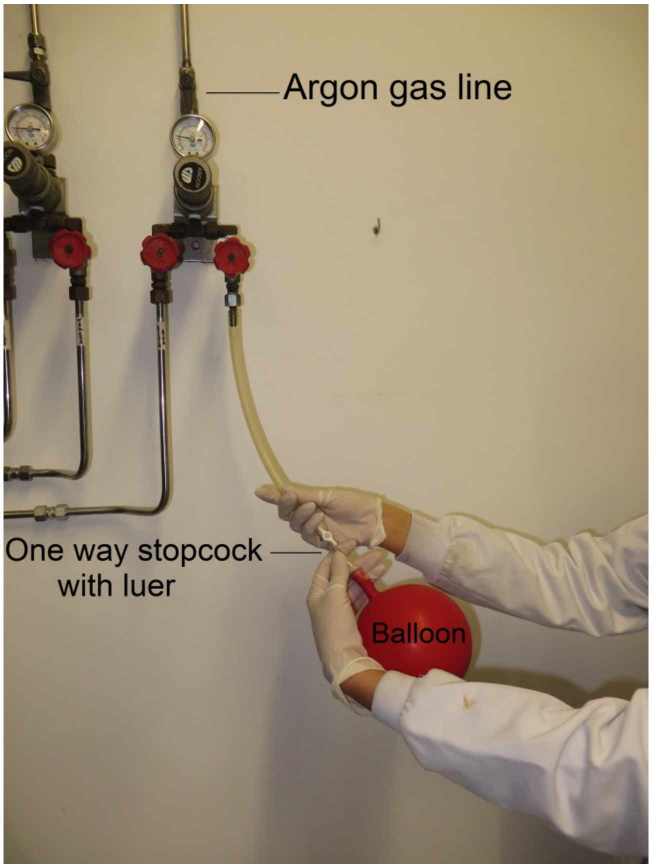


Fig 4.2.4.2.3 Filling the balloon with argon gas

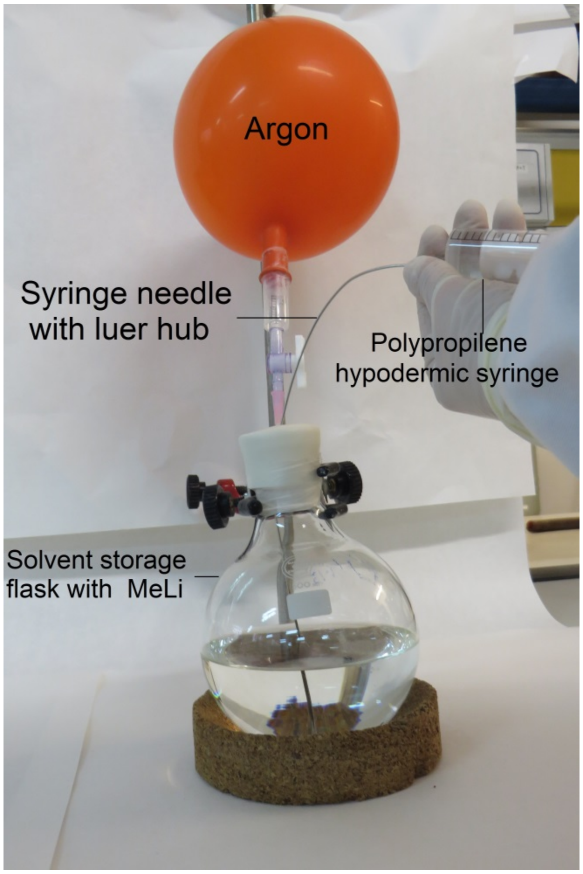


Fig 4.2.4.2.4 Taking MeLi via syringe

Fig 4.2.4.2.5 Transfer MeLi to the reaction flask

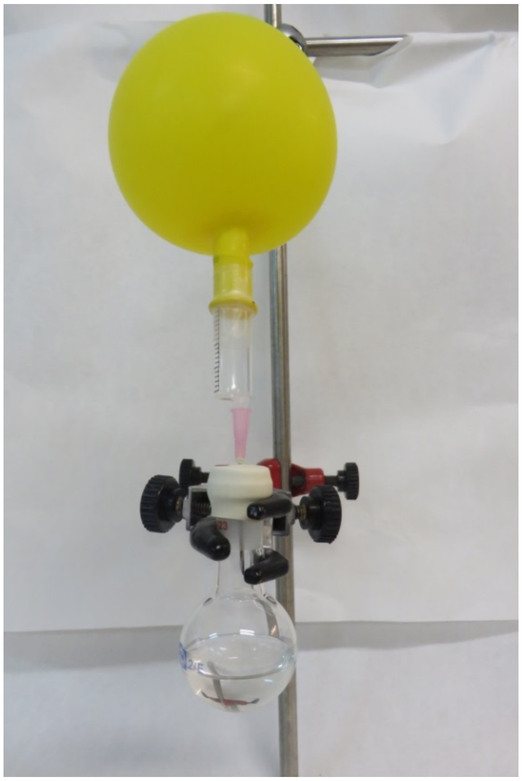


Fig 4.2.4.2.6 Solution of starting enone in TBME

Fig 4.2.4.2.7 Taking a sample for TLC with a glass capillary

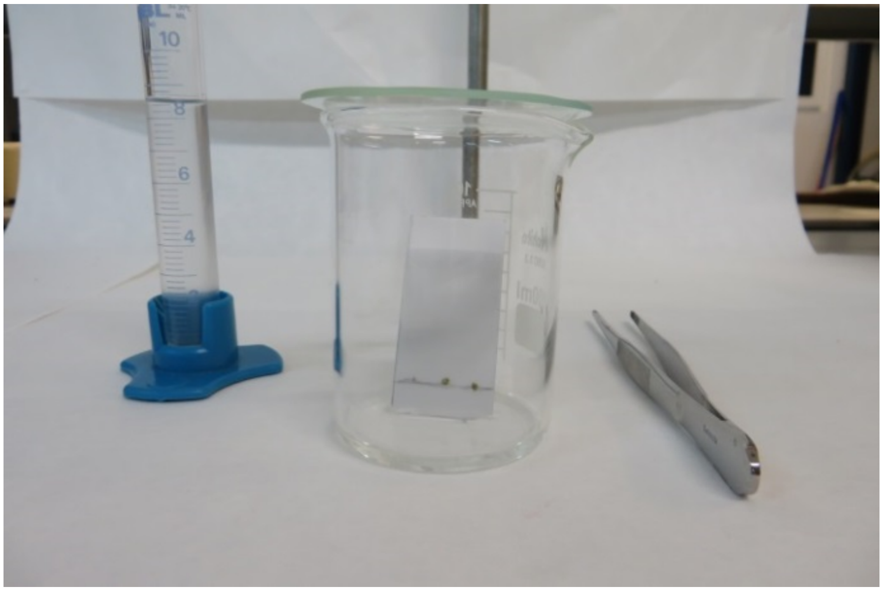


Fig 4.2.4.2.8 Monitoring the reaction by TLC.

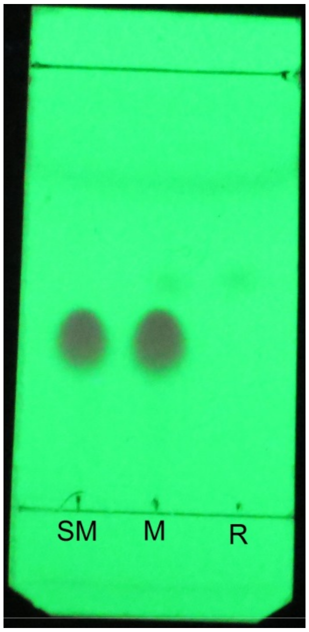


Fig 4.2.4.2.9 Visualization with UV light (λ = 254 nm)
SM: Starting material
M: Mixture SM + R
R: Reaction

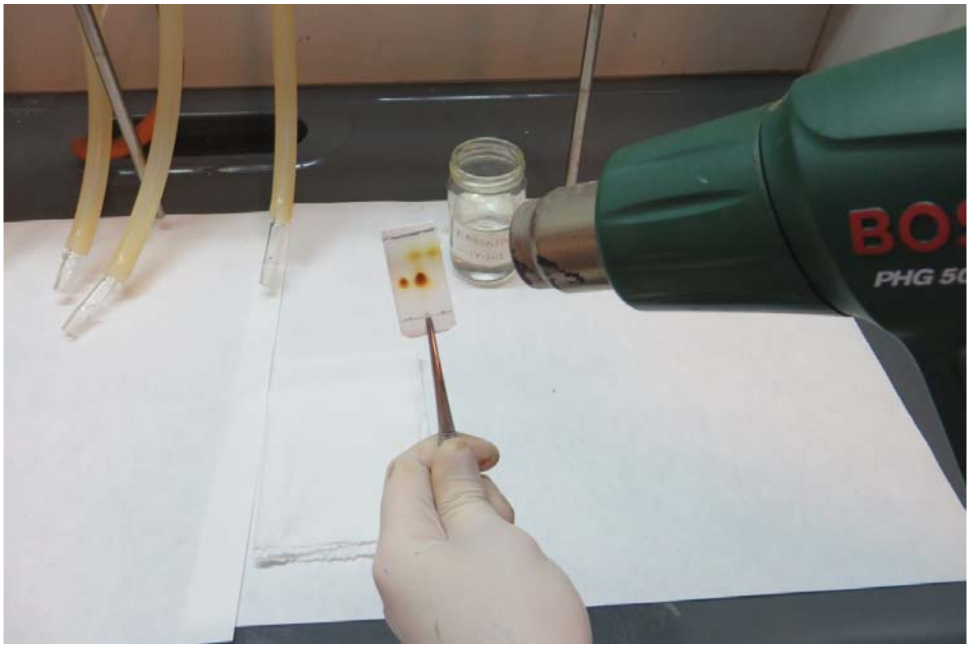


Fig 4.2.4.2.10 Visualization of reaction products on TLC plate with *p*-anisaldehyde stain under heating

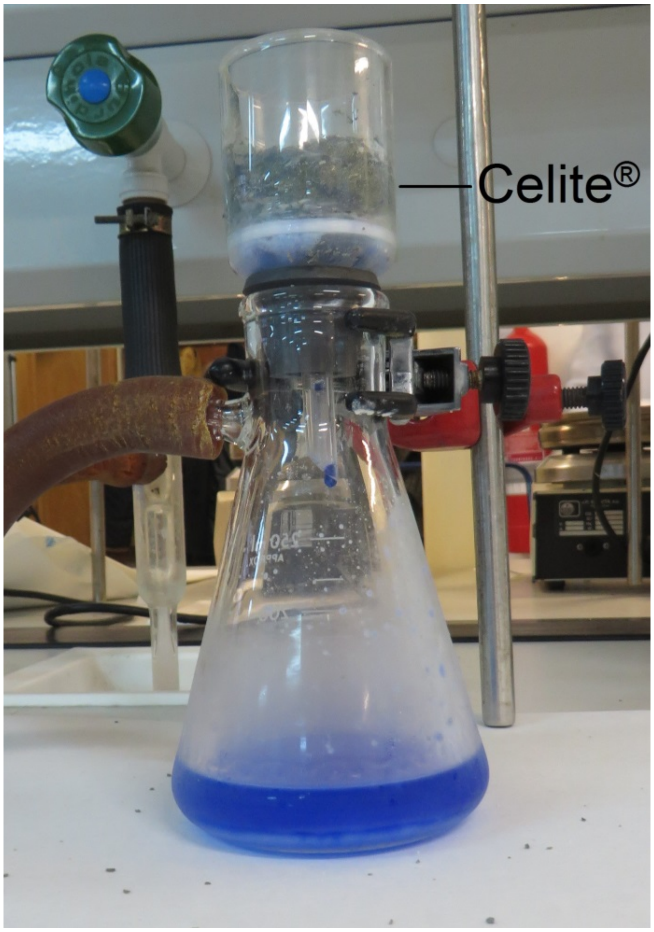


Fig 4.2.4.2.11 Filtration through a pad of Celite® S

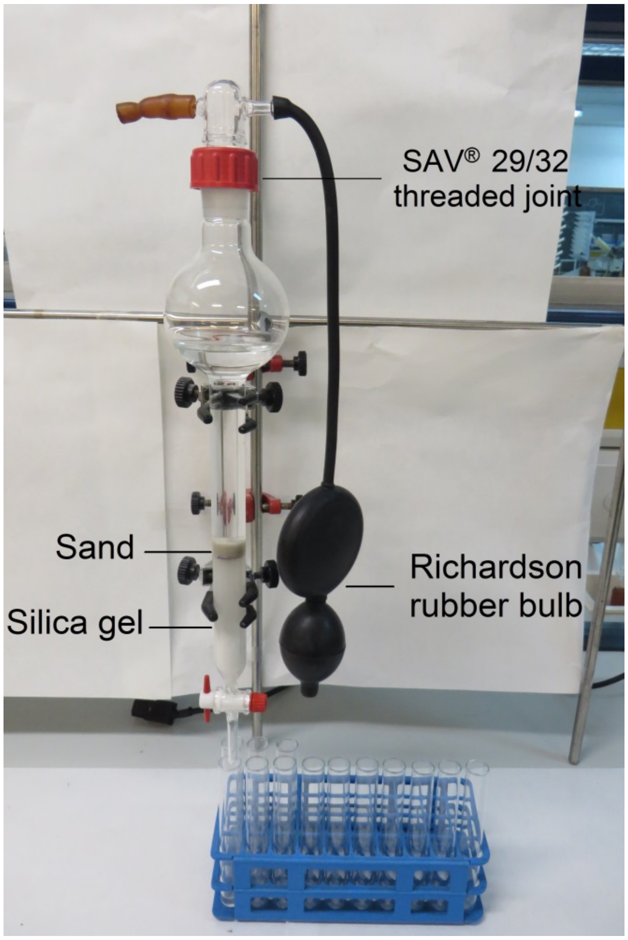


Fig 4.2.4.2.12 Flash Column Chromatography

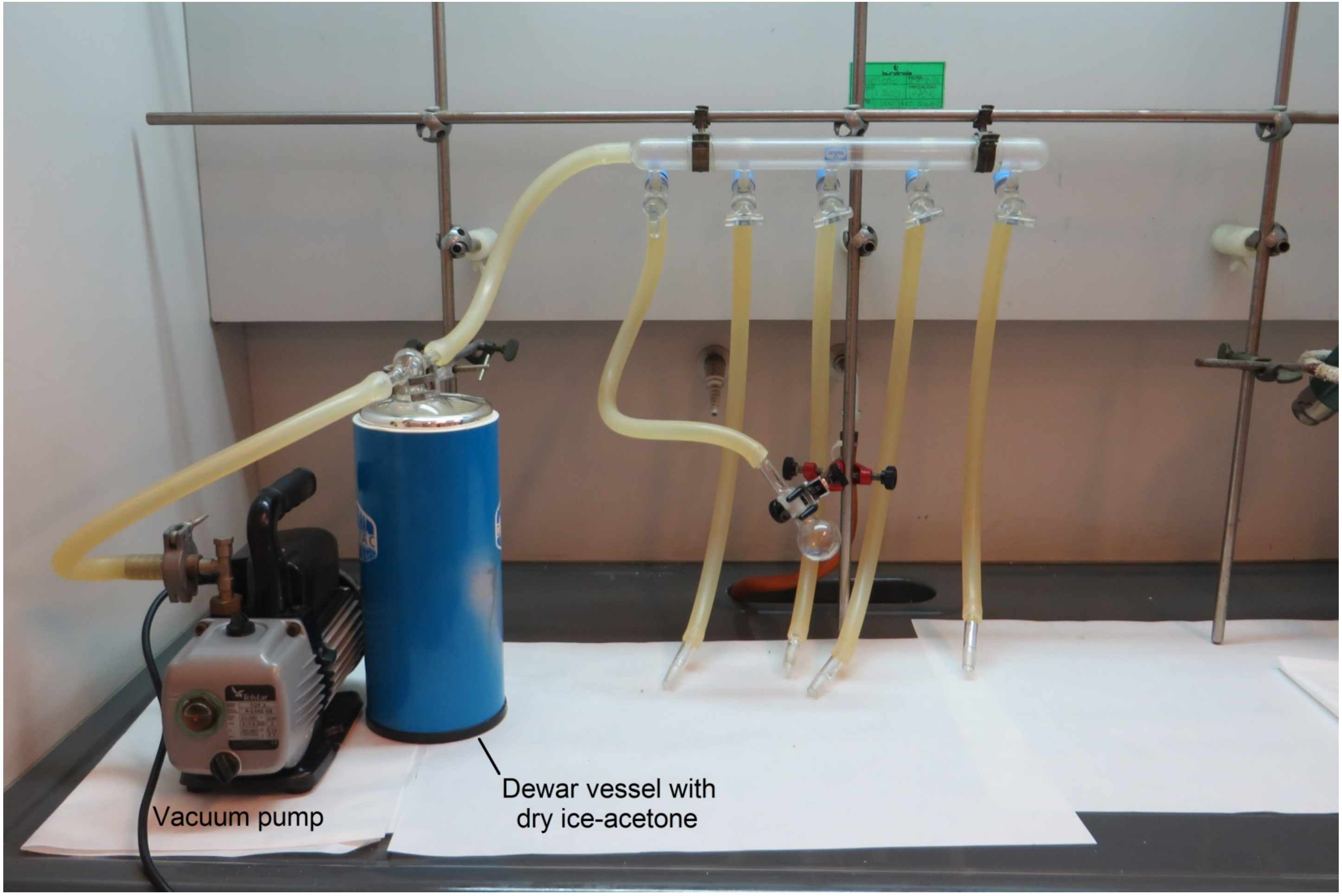


Fig 4.2.4.2.13 Removing solvent residues under vacuum

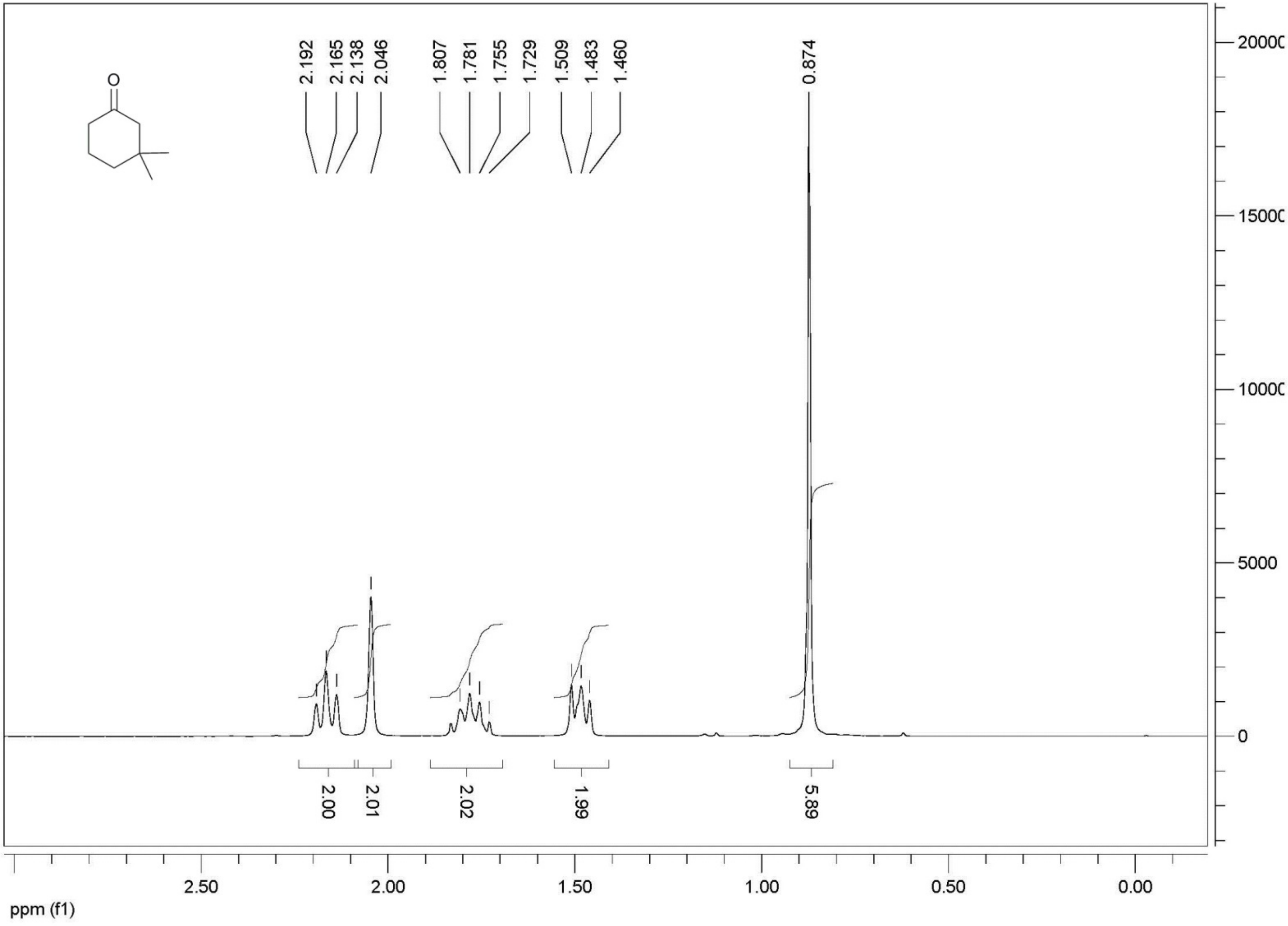


Fig 4.2.4.2.14 ^{1}H NMR Spectrum (250 MHz, $CDCl_3$,δ) of 3,3-dimethylcyclohexanone

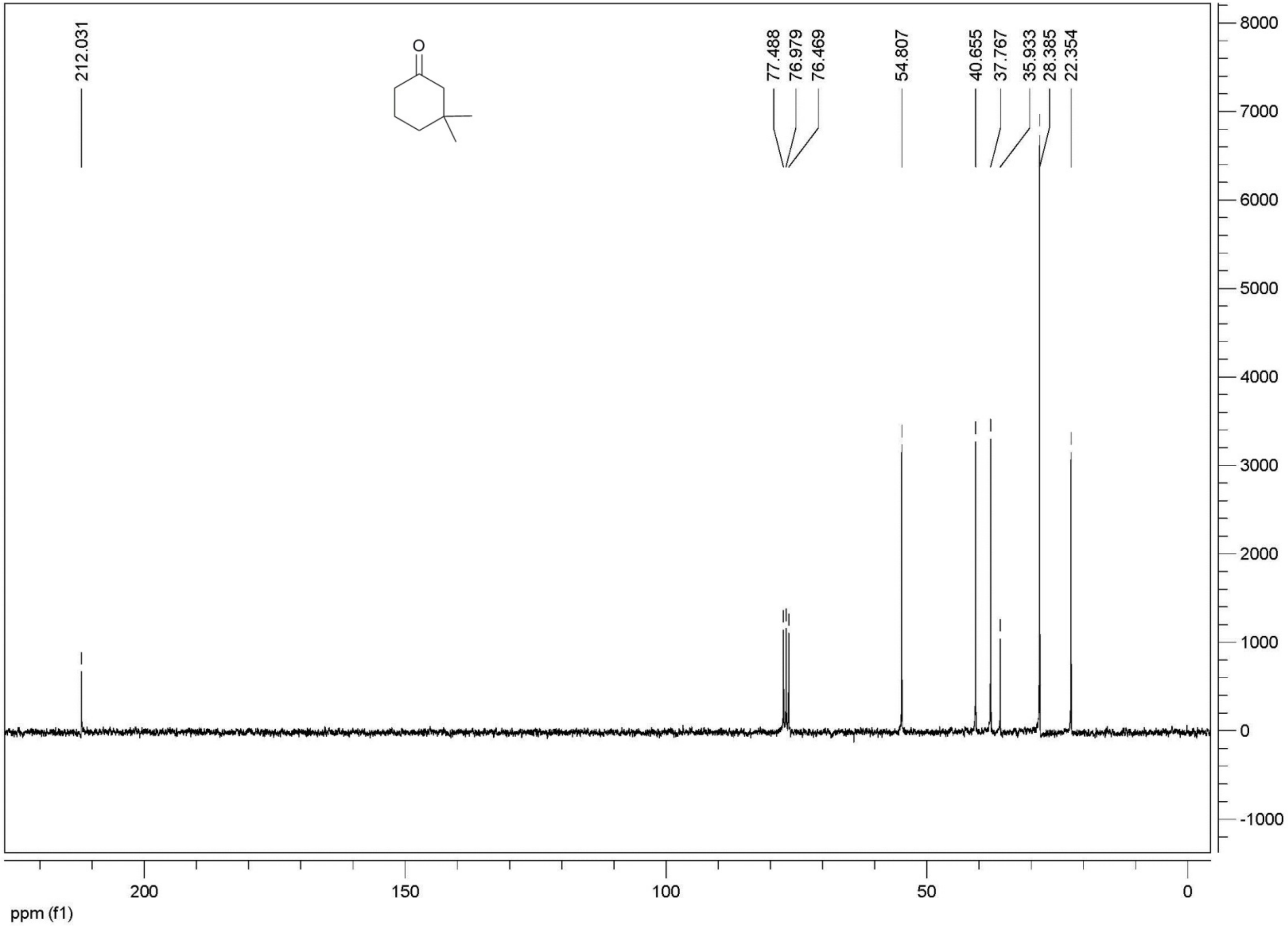


Fig 4.2.4.2.15 ^{13}C NMR Spectrum (250 MHz, $CDCl_3$, δ) of 3,3-dimethylcyclohexanone

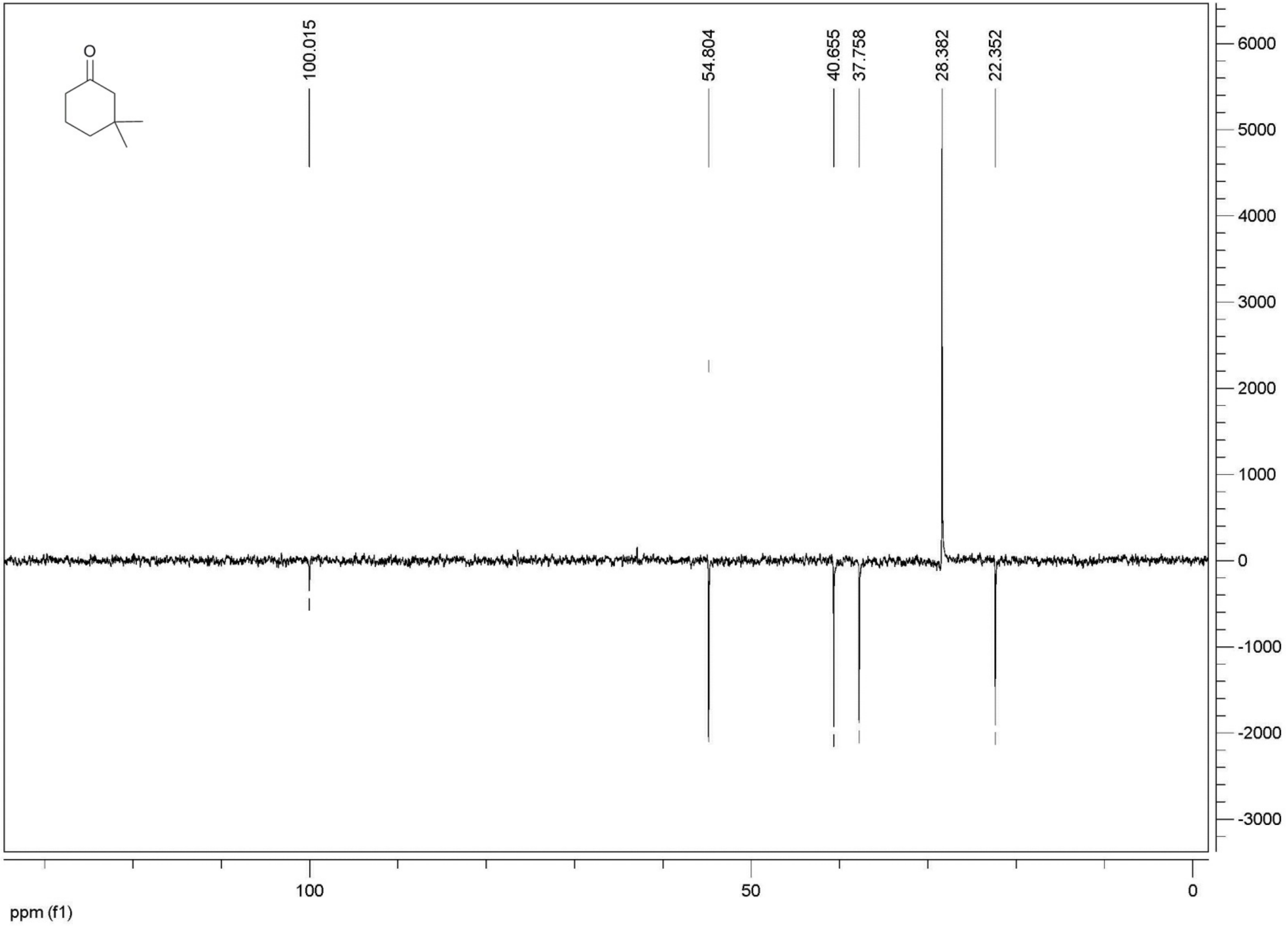


Fig 4.2.4.2.16 DEPT Spectrum (250 MHz, $CDCl_3$, δ) of 3,3-dimethylcyclohexanone