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Friedel-Crafts Acylation, Lab Guide, Use of GC-MS, The Organic Chemistry Notebook Series, a Didactical Approach, N°17

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Abstract We present a lab guide of the Friedel-Crafts (F-C) acylation (synthesis of aromatic ketones) for its application in undergraduate teaching laboratories of organic chemistry as part of the educational series in organic synthesis: "The Organic Chemistry Notebook Series, a Didactical Approach". This guide is enriched by a short bibliographic-historical on the F-C reaction including proposals on mechanistic views. The synthesis of acetophenone (**1**) from benzene and *p*-methylacetophenone (**2**) from toluene was carried out using aluminum chloride as Lewis acid and acetyl chloride and acetic anhydride as acylating agents, respectively. The introduction of new technologies/instrumentation into educational laboratory settings could be seen in the identification of the products that was carried out by gas chromatography coupled with mass spectrometry (GC-MS) not of common use in undergraduate laboratories nowadays, the sample quantity ranged between 1 to 3 mL. This technique is more easily accessible and less expensive than $^{1}H/^{13}C$ NMR analysis and has the additional advantage of quantifying the product (yield) and assessing its purity, sometimes allowing impurities to be characterized. The results obtained present the somewhat distinctive feature of high and medium yields and purity of the synthesized products (**1** and **2**).

Keywords Friedel-Crafts Acylation, Organic Chemistry Lab, Synthesis, Mechanistic Approach, Aromatic Ketones, GC-MS, Chemistry Didactics

1. Introduction

Charles *Friedel* (1832-1899), French chemist born in Strasbourg, and James Mason *Crafts* (American chemist, Boston, MA, 1839-1917) authored in 1877 three short communications of *Comptes Rendues* about the synthesis of aromatic ketones [1-3]. This reaction named *Friedel-Crafts acylation* reaction [4], is a powerful and industry employed reaction from then until the present. This contemplates the use of $AlCl_3$, an inexpensive and recoverable catalyst.

The account of the historical and technical evolution of Friedel-Crafts' alkylation and acylation was detailed in the publication by Wisniak (2009) [4]. The way to the affination of the F-C reaction debuted with the heat treatment of some alkyl or acyl chlorides with metallic aluminum, a low-rate reaction. Then, the authors changed metallic Al for aluminum chloride, giving a fast reaction at low temperature with evolving gases (HCl and C_nH_{2n+2}). This panorama let CF and JC envisage a high potent method for the synthesis of hydrocarbons or their oxygenated derivatives (ketones).

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A first mechanism attempt was proposed by CF and JC, with $AlCl_3$ in the catalyst role, *i.e.* used and recovered. Such hypothesis was based on the appearing of a small quantity of a phenyl aluminum compound (supposed to be $C_6H_5{\bullet}Al_2Cl_5$). This intermediate reacted with the alkyl chloride to afford a new hydrocarbon *secundum*: $C_6H_5{\bullet}Al_2Cl_5 + RCl \rightarrow C_6H_5R + Al_2Cl_6$, [4]. This reaction can be broken down by means of the mentioned mechanism as shown in Figure 1.

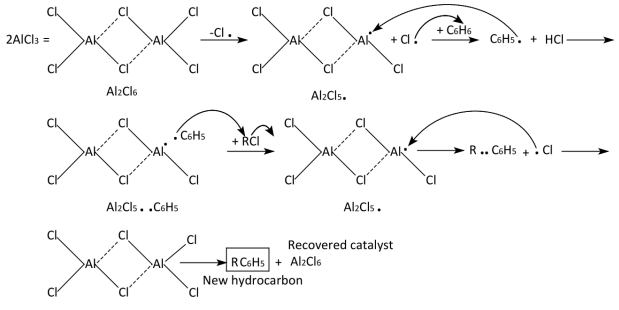


Figure 1. Benzene/Alkyl Chloride Coupling Reaction, Mechanism

The reaction takes place by interaction of the catalyst in its dimeric form. The excision of a Cl atom from the aluminum chloride provokes extraction of an H atom from benzene to afford HCl. The coupling between C_6H_5 and Al_2Cl_5 occurs and the adduct is formed. The Al-catalyzed species is now

well-fitted for an attack over the organic chloride to generate a new C-C bond, or said otherwise a new hydrocarbon RC_6H_5 and subsequent recovery of the aluminum catalyst. In a posterior communication [4,5], FC and JC proposed a correction of their mechanism however it implied the consumption of $AlCl_3$ during reaction [4].

Later on, CF and JC investigated other possibilities of aluminum halides as catalysts. For example, the interchange of chloride by iodide in amyl chloride as shown in Figure 2 [4,6].

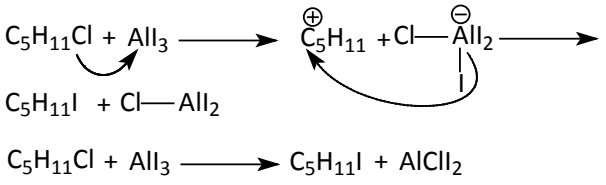


Figure 2. Use of Previously Prepared AlI_3 during Iodide Chloride Interchange in Hydrocarbons (Mechanism and Global reaction)

From these experiments CF and JC envisaged the possibility of given the presence of a benzene ring the interaction between this with the halogenated hydrocarbon would afford a mixture of both greasy moieties as the result of the coupling between them in a new hydrocarbon weighing the sum of the parts. Such result was possible thanks to the presence of aluminum chloride [4,5], see Figure 3.

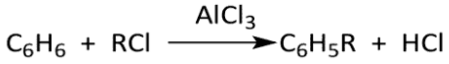


Figure 3. Friedel-Crafts Alkylation, Catalyzed by $AlCl_3$

Friedel-Crafts reaction originally intended for the synthesis of halogenated aliphatic compounds with benzene with the catalytic competition of aluminum trichloride, (cf. Figure 4 [7]), was similarly employed to synthesize aromatic ketones produced from the coupling of an aliphatic or aromatic acid chloride (instead of an alkyl chloride) with an aromatic hydrocarbon (*e.g.* benzene), Figure 4.

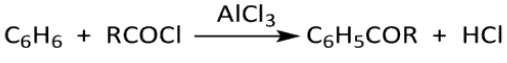


Figure 4. Friedel-Crafts Acylation

Other assays on acylation by CF and JC [4,5] included the attachment of other species (*e.g.* acid anhydrides) to benzene or its homologues according to the generic reaction $C_6H_6 + O + Al_2Cl_6 = C_6H_5O + Al_2Cl_5 + HCl$. The supposed mechanism involved evolution of HCl from $AlCl_3$ (experimentally proven) [4]. Figure 5.

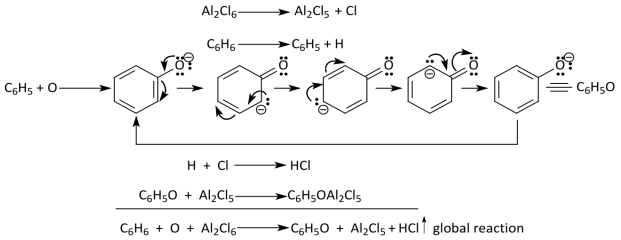


Figure 5. Other Assays by Friedel and Crafts

The mixture of benzene or toluene and aluminum chloride was exposed to airby oxygen giving rise to phenol (C_6H_5OH) or cresol ($HOC_6H_4CH_3$), respectively after addition of water. Also, the procedure employing S, CO, SO_2, or $CH_2{=}CH_2$ instead of O produced C_6H_5SH (thiophenol), C_6H_5COOH, $C_6H_5SO_2H$ (phenyl sulphinic acid), $C_6H_5CH_2CH_3$, $C_6H_4(CH_2CH_3)_2$ or $C_6H_3(CH_2CH_3)_3$.

Conclusively, CF and JC proposed the resumed mechanism as shown in Figure 6 [4].

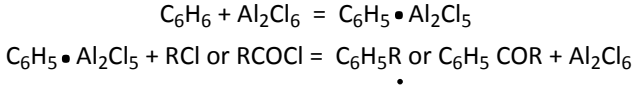


Figure 6. Alkylation or Acylation Mechanism as Proposed by CF and JC [4]

We present a lab guide of the Friedel-Crafts (F-C) acylation (synthesis of aromatic ketones) for its application in undergraduate teaching laboratories of organic chemistry as part of the educational series in organic synthesis: "The Organic Chemistry Notebook Series, a Didactical Approach". The lab guide conducts to the synthesis of acetophenone (**1**) as well as 4-methylacetophenone (**2**). Mechanistic views are provided for some reactions. Also, innovation is intended for laboratory practices by means of the application of GC-MS technique for identifying the obtained ketones and minor derivatives; this is suitable given that both products are liquid at room temperature.

2. Friedel-Crafts Acylation Lab Guide

This lab guide comprises two parts, materials and reagents section, and experimental procedure section. These items must be available and correctly assembled in conformity to the Experimental Procedure Section below before the practice should be get started.

2.1. Reagents and Materials Section

2.1.1. Reagents' Data, Table 1

Table 1. F-C Reaction, Reagents

Item	Reagents		
	Name and Formula	**Quantity**	**Reference**
1	Aluminum Chloride $AlCl_3$	12g 0.09 mol	CAS 7446-70-0
2	Lithium Chloride LiCl	1.60g 0.038 mol	CAS 7447-41-8
3	Toluene $C_6H_5CH_3$	10mL 0.094 mol	CAS 108-88-3
4	Benzene C_6H_6	10mL 0.112 mol	CAS 71-43-2
5	Acetyl Chloride CH_3COCl	5mL 0,070 mol	CAS 75-36-5
6	Hydrochloric Acid HCl (37%)	200mL 2.416 mol	CAS 7647-01-0
7	Sodium Hydroxide NaOH	10g 0.250 mol	CAS 1310-73-2
8	Anhydrous Magnesium Sulphate $MgSO_4$	400g 3.323 mol	CAS 7487-88-9
9	Dichloromethane CH_2Cl_2	-	CAS 75-09-2
10	Diethyl Ether $(C_2H_5)_2O$	-	CAS 60-29-7
11	Acetic Anhydride $(CH_3CO)_2O$	10mL 0.106 mol	CAS 108-24-7

2.1.2. Materials, Table 2

Table 2. F-C Reaction, Materials

Item	Materials		
	Object	**Volume/Other**	**Units**
1	Round Bottom Flask	100 mL	25
2	Two-Neck Round Bottom Flask (Option A, Fig. 12)	100 mL	1
3	Graduated pipettes	10mL	5
4	Pasteur pipettes	-	-
5	Graduated Cylinder	25mL	1
6	Beaker	25mL	3
7	Universal Support	-	1
8	Clamp/Nut	-	1
9	Glass Rod	-	1
10	Spatula(s)	-	2+
11	Condenser	-	1
12	Oil Bath	-	1
13	Ice Bath	-	1
14	Microscale Simple Distillation Equipment	-	1
15	Addition Funnel (option A, Fig. 8)	25mL	1
16	Syringe (option B, Fig. 8)	10ml	1
17	Separatory Funnel	50mL	1
18	Erlenmeyer Flask	25 ml	5
19	Magnetic Stirrer	-	1
20	Magnetic Stirring Bars	-	-
21	Thermometer	-20°C to 200°C	1
22	Rotavapor	-	1

2.2. Experimental Procedure Section

2.2.1. Acetophenone Synthesis (1)

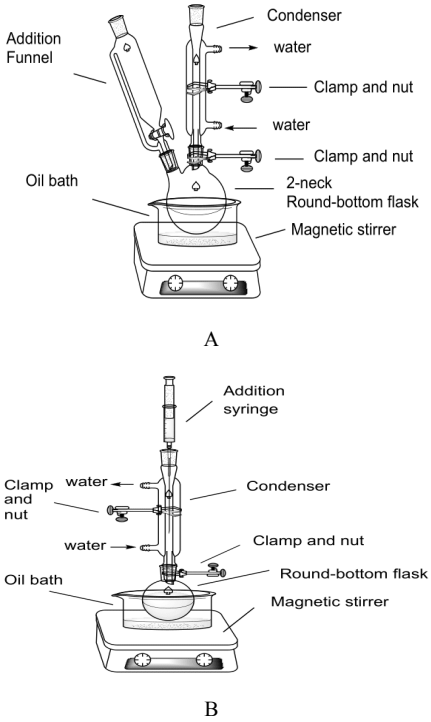


Figure 7. Synthesis of Acetophenone (**1**), Two Equipment Options A or B

The flask/reflux/shaker/bath system was assembled as shown in Figure 8. A mixture of aluminum chloride (1.30 g, 0.0750 mol) and benzene (1.85 mL, 0.0207 mol) was prepared in the flask (Figure 7 A, B). Acetic anhydride (3.92 mL, 0.0415 mol) was added to the flask slowly (dropwise) over period of 30 min, via addition funnel or syringe (Figure 8 A, B). It was heated under reflux for one hour. The reaction mixture turned a deep orange/brown color during the addition of acetic anhydride. It was allowed to cool to room temperature and it was added to a mixture of 45 ml of concentrated hydrochloric acid and 45 g of ice. After all of the reaction mixture had been poured, it was stirred for an additional 15 minutes. The mixture was then transferred to a separatory funnel with 25 ml of diethyl ether and the organic and aqueous phases were separated. The aqueous phase was extracted with another 25 ml portion of diethyl ether. The combined organic layer was washed with two 25 mL portions of 10% sodium hydroxide solution. The combined organic phase was separated and dried over magnesium sulphate. The dry organic phase was distilled in a simple distillation equipment under vacuum, a micro-scale equipment is suggested. The product obtained was acetophenone (**1**, 0.86 g, 34.4% yield).

2.2.2. 4–Methylacetophenone Synthesis (2) [8]

Set the experimental equipment of Fig. 8.

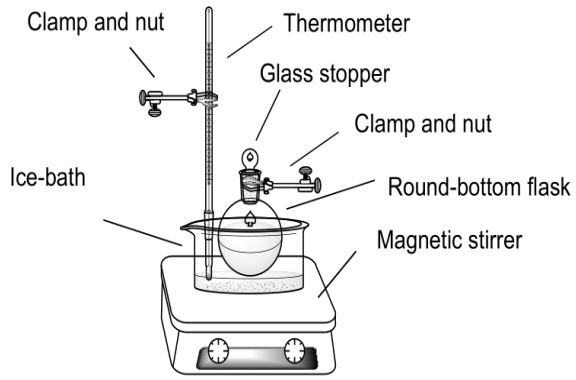


Figure 8. Synthesis of *p*-Methylacetophenone (2)

A mixture of aluminum chloride (10.00 g, 0.0750 mol) and lithium chloride (1.59 g, 0.0375 mol) in dichloromethane (15.00 mL) was prepared at -15°C. Toluene (2.66 mL, 0.0250 mol) and acetyl chloride (1.78 mL, 0.0250 mol) were added. The reaction mixture was left at -15°C for one hour (see Fig. 9), allowed to stand at room temperature overnight. 100 ml of a mixture of ice and dilute hydrochloric acid (concentration of 20%.) was slowly added to the reaction mixture, the organic phase was separated and the aqueous phase was extracted with two 50 ml aliquots of diethyl ether. The combined organic phases were then washed with 50 ml of dilute sodium hydroxide solution (concentration of 10%) and then with water, separated and dried over anhydrous magnesium sulphate. The dried solution was filtered to remove the drying agent and the solvents removed on a rotary evaporator. This ends manipulations. The product obtained was *p*-methylacetophenone (**2**, 2.86 g, 885.3%).

2.2.3. GC-MS Analyses and IR Spectrometry

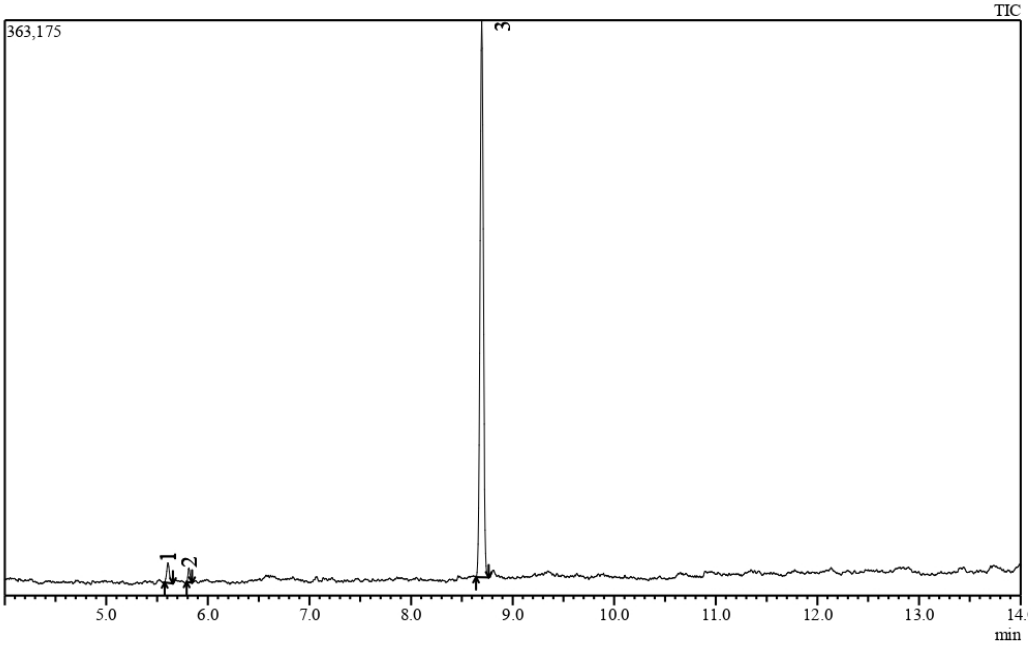
The Gas chromatography coupled to EI mass spectroscopy (GC-MS) analyses were performed in a Shimadzu QCMS-QP2020 instrument, with a 30 m long Rxi ®-5Sil MS RETEK (Centre County, PA, U.S.) capillary column. 0.25 mm i.d. and helium carrier with flow rate of 1.0 mL/min; the temperature was programmed to be maintained at 60°C for 1 min and then increased at a rate of 5°C/min for 15 min and ended with 2 min at 250°C. Thus, the total ion chromatograms and mass spectra for acetophenone (**1**, Figure 9) and p-methylacetophenone (**2**, Figure 10) were obtained.

01/12/2022

Qualitative Analysis Report

Sample Information

Analyzed by	: M.Sc. Santiago Tarqui Tarqui
Analyzed	: 01/12/2022 10:32:15 a.m.
Sample Type	: Unknown
Level #	: 1
Sample Name	: Acetofenona
$EndIf$IS Amount	: [1]=1
Sample Amount	: 1
Dilution Factor	: 1
Vial #	: 6
Injection Volume	: 1.00
$EndIf$Modified by	: Admin
Modified	: 01/12/2022 10:48:15 a.m.



Peak Report TIC

Peak#	R.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	5.607	24338	2.89	12515	3.35	1.94		NN
2	5.814	13733	1.63	9097	2.44	1.51		NN
3	8.695	804765	95.48	351549	94.21	2.29		Acetophenone

Figure 9. GC-MS Acetophenone (**1**) Chromatogram

01/12/2022

Qualitative Analysis Report

===== Analytical Line 1 =====

[AOC-20i]

# of Rinses with Presolvent	:3
# of Rinses with Solvent(post)	:1
# of Rinses with Sample	:1
Plunger Speed(Suction)	:Middle
Viscosity Comp. Time	:0.2 sec
Plunger Speed(Injection)	:High
Syringe Insertion Speed	:High
Injection Mode	:Normal
Pumping Times	:5
Inj. Port Dwell Time	:0.3 sec
Terminal Air Gap	:No
Plunger Washing Speed	:High
Washing Volume	:8uL
Syringe Suction Position	:0.0 mm
Syringe Injection Position	:0.0 mm
Use 3 Solvent Vial	:1 vial

[GC-2010]

Column Oven Temp.	:60.0 °C
Injection Temp.	:280.00 °C
Injection Mode	:Split
Flow Control Mode	:Linear Velocity
Pressure	:90.7 kPa
Total Flow	:103.7 mL/min
Column Flow	:1.00 mL/min
Linear Velocity	:36.4 cm/sec
Purge Flow	:3.0 mL/min
Split Ratio	:100.0
High Pressure Injection	:OFF
Carrier Gas Saver	:OFF
Splitter Hold	:OFF

Oven Temp. Program

Rate	Temperature(°C)	Hold Time(min)
-	60.0	1.00
5.00	135.0	0.00

< Ready Check Heat Unit >	
Column Oven	: Yes
SPL1	: Yes
MS	: Yes
< Ready Check Detector(FTD/BID) >	
< Ready Check Baseline Drift >	
< Ready Check Injection Flow >	
SPL1 Carrier	: Yes
SPL1 Purge	: Yes
< Ready Check APC Flow >	
< Ready Check Detector APC Flow >	
External Wait	:No
Equilibrium Time	:3.0 min

[GC Program]

[GCMS-QP2020]

IonSourceTemp	:220.00 °C
Interface Temp.	:280.00 °C
Solvent Cut Time	:3.00 min
Detector Gain Mode	:Relative to the Tuning Result
Detector Gain	:0.91 kV +0.00 kV
Threshold	:0

[MS Table]

--Group 1 - Event 1--	
Start Time	:3.00min
End Time	:16.00min
ACQ Mode	:Scan
Event Time	:0.30sec
Scan Speed	:1111
Start m/z	:50.00
End m/z	:350.00
Sample Inlet Unit	:GC

[MS Program]

Use MS Program :OFF

Figure 9. Cont. GC-MS Acetophenone (**1**), Method

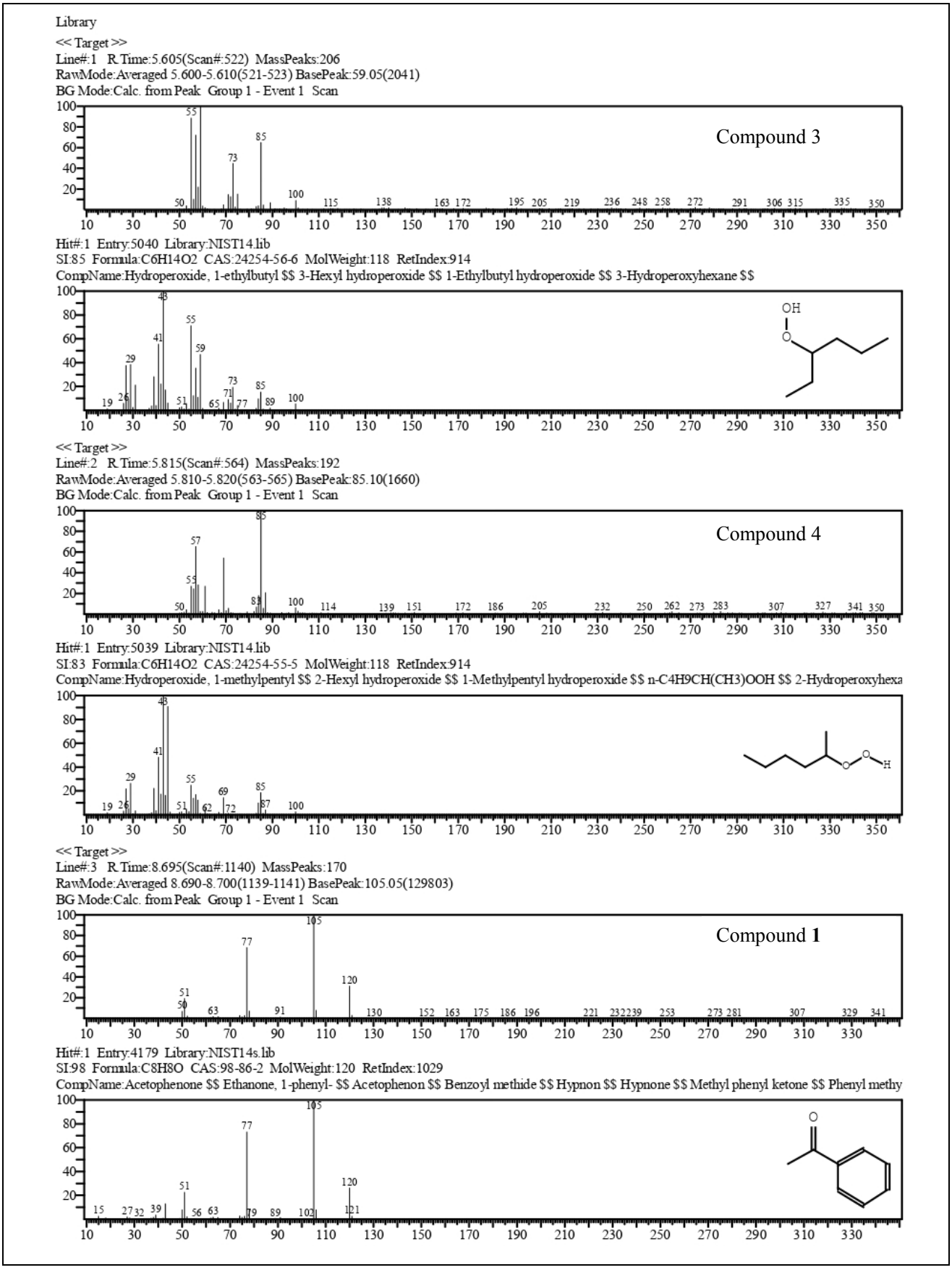


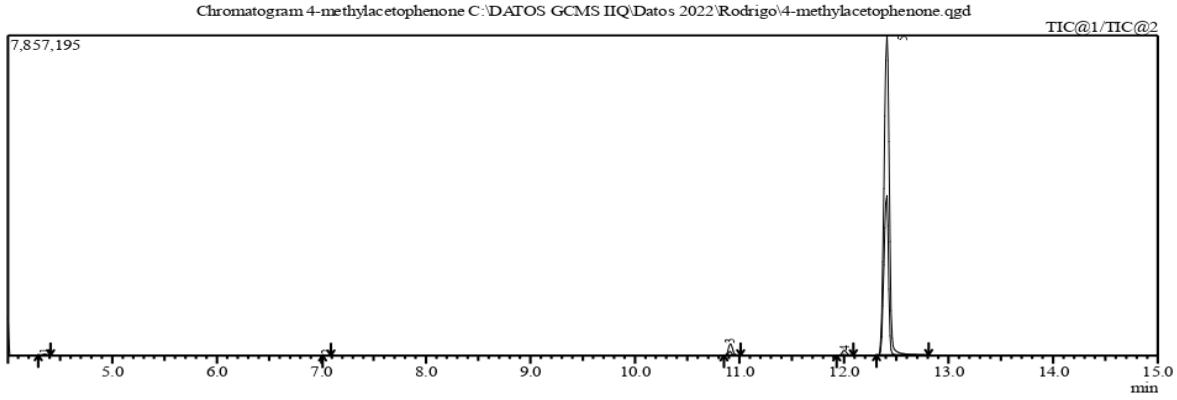
Figure 9. Cont. GC-MS Acetophenone (1), EIMS Spectra of Compounds. Top: Experimental, Bottom: Library

15/06/2022

Qualitative Analysis Report

Sample Information - RVA

Analyzed	: M.Sc. Saniago Tarqui T. - IIQ
Sample Type	: Unknown
Level #	: 1
Sample Name	: 4-methylacetophenone
Sample ID	: 4-methylacetophenone
IS Amount	: [1]=1
Sample Amount	: 1
Dilution Factor	: 1
Vial #	: 2
Injection Volume	: 1.00
$EndIf$Modified by	: Admin
Modified	: 14/06/2022 06:53:36 p.m.



Peak Report TIC

Peak#	R.Time	Area%	Height%	Mark	Name
1	4.356	0.3	0.3		1,3-dimethyl-benzene
2	7.050	0.1	0.1		1,2,3-trimethyl-benzene
3	10.913	2.7	3.4		2-methyl-acetophenone
4	12.002	1.2	1.4		3-methyl-acetophenone
5	12.410	95.8	94.8		4-methyl-Acetophenone

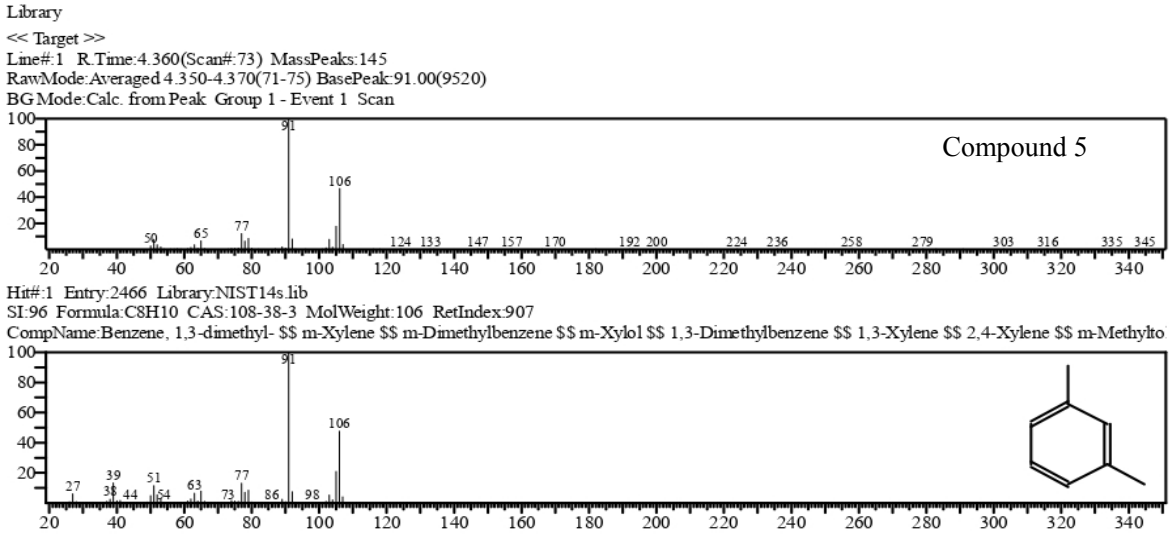


Figure 10. GC-MS 4-Methylacetophenone (2), Chromatogram, EIMS Spectra of Compounds, Top: Experimental, Bottom: Library

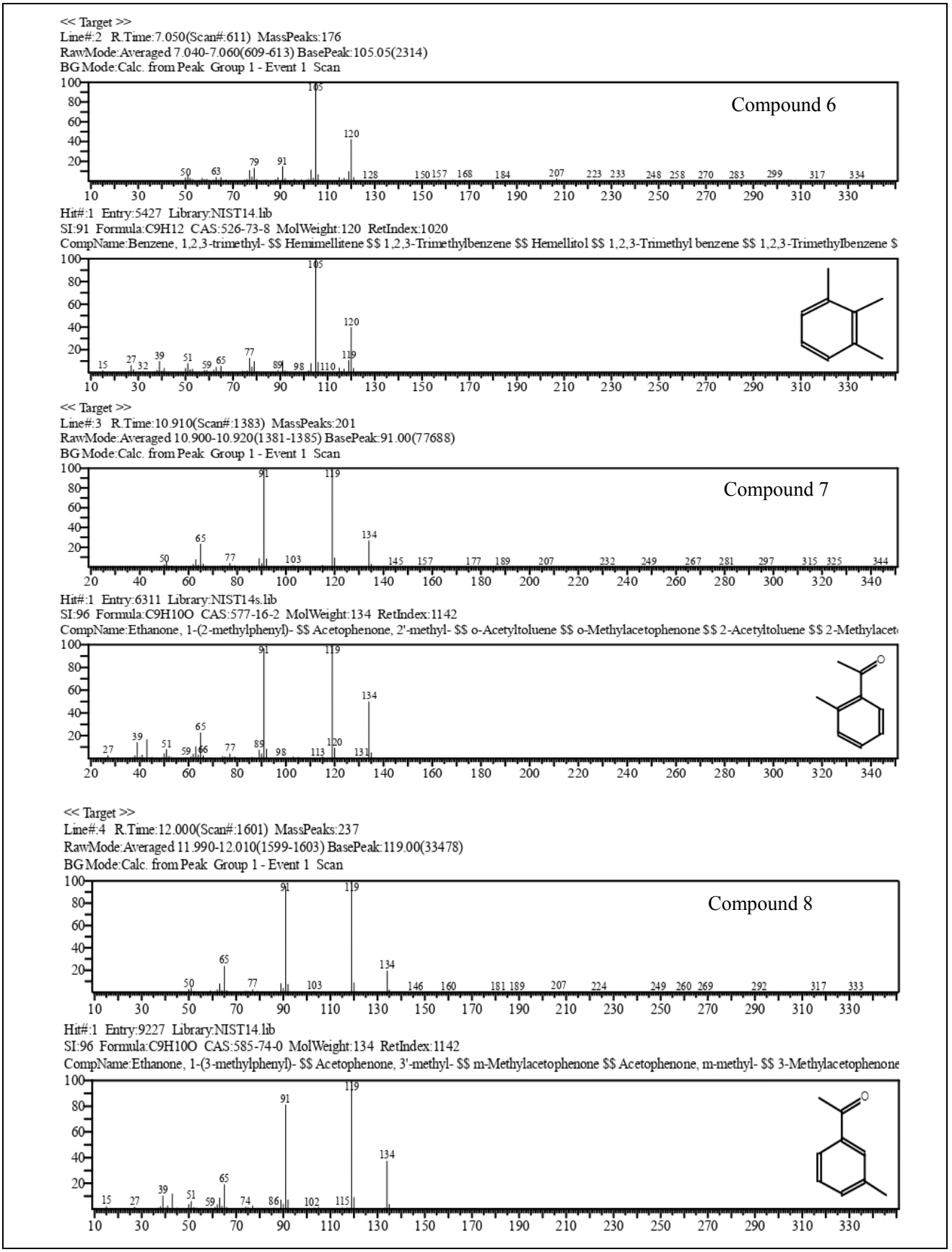


Figure 10. Cont. GC-MS 4-Methylacetophenone (**2**), EIMS Spectra of Compounds, Top: Experimental, Bottom: Library

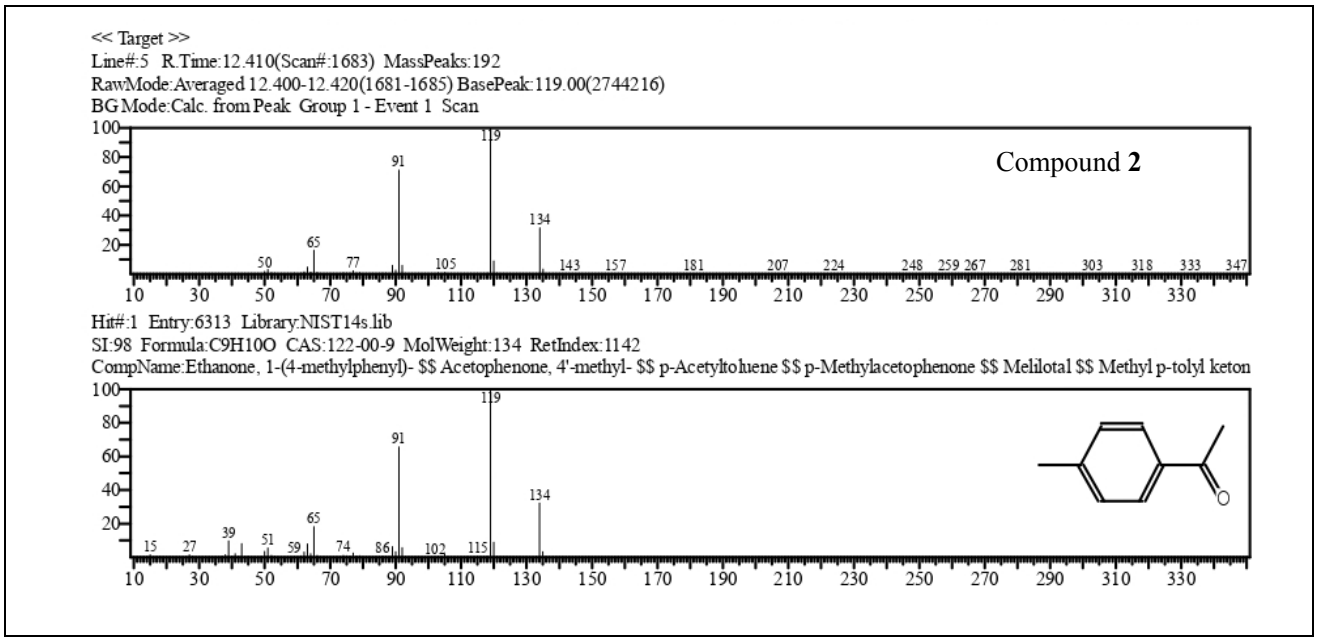


Figure 10. **Cont.** GC-MS 4-Methylacetophenone (**2**), EIMS Spectra of Compounds, Top: Experimental, Bottom: Library

2.2.4. IR Analyses of Acetophenone (1) and 4-Methylacetophenone (2)

IR apparatus was Perkin-Elmer Spectrum 1000, FTIR-IR and NEAR-IR spectroscopy using ZnSe support.

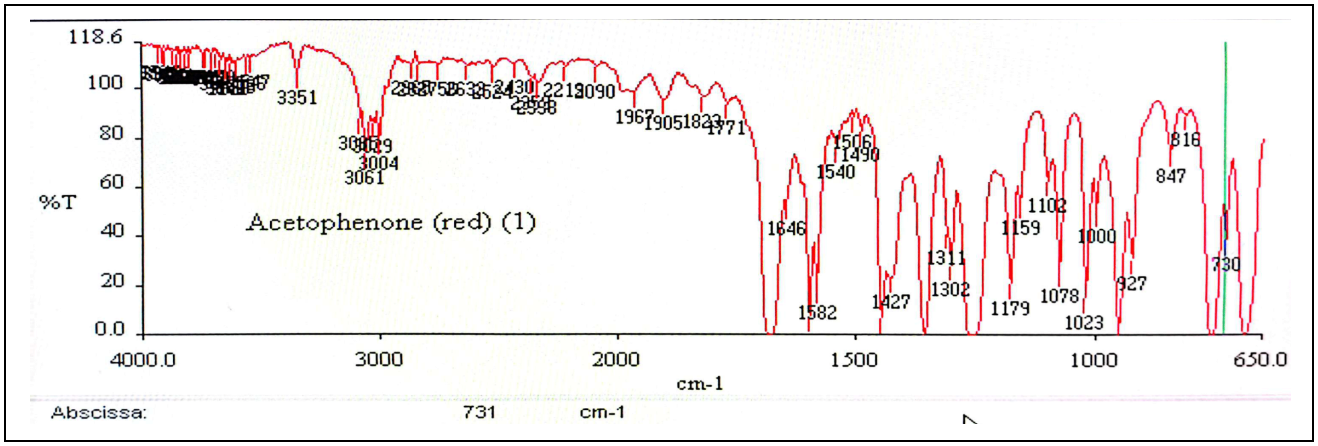


Figure 11. IR Spectrum of Acetophenone (**1**)

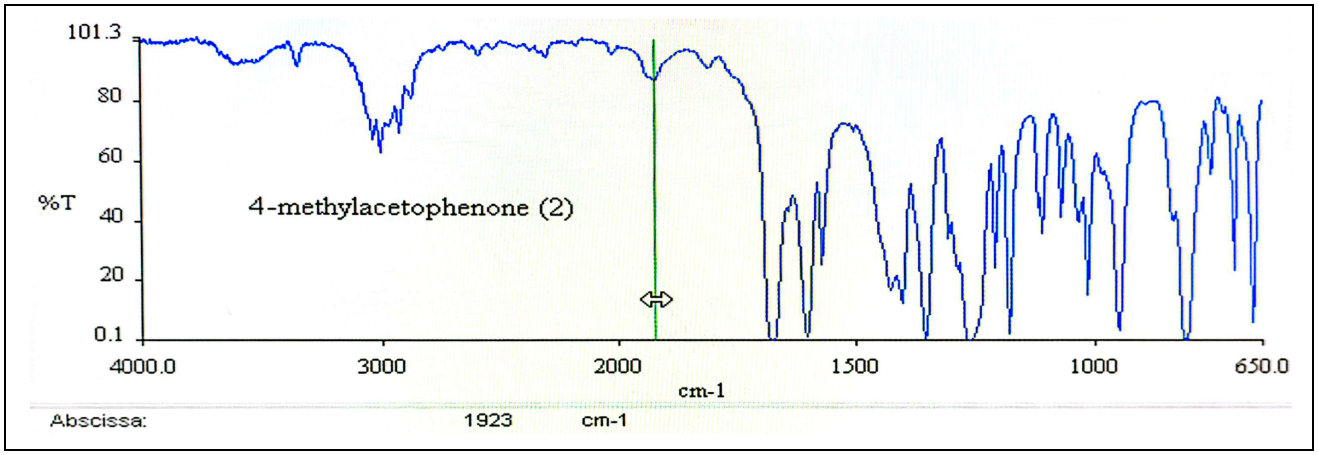


Figure 12. IR Spectrum of 4-Methylacetophenone (**2**)

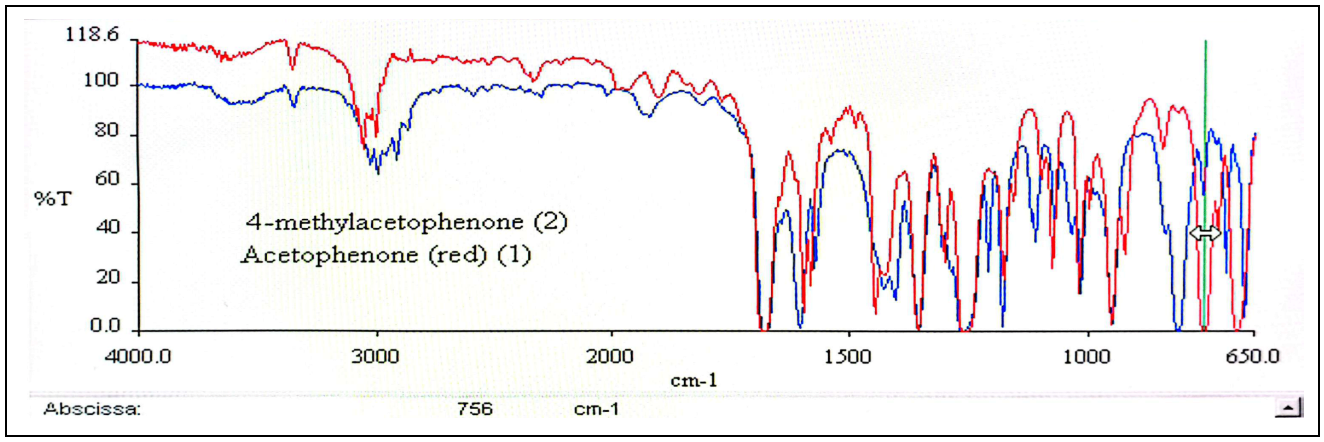


Figure 13. IR Spectra, Comparative Overlapped View of **1** and **2**

2.2.5. Comments on the Experimental Procedure Section

Friedel-Crafts acylation does not always give acceptable yields due to a number of factors; we proceed to a brief analysis of them below. It is important to mention that the Friedel-Crafts reaction mechanism (Figures 12 and 13) in the case of acid anhydrides is the same as that of acyl chlorides, but the aluminum complex formed would be aluminum trichloride acetate [9].

Polar solvents (nitrobenzene, nitroalkanes) are used for acylation in a homogeneous phase, conversely, non-polar solvents (dichloromethane, carbon disulfide, petroleum ether, carbon tetrachloride), for acylation in heterogeneous phase. A frequent practice is to use as solvent an excess of the aromatic compound to be substituted. The main influence of the solvent is manifested on the yield of the reaction, although it also influences the orientation of the substitution, fundamentally in polycyclic aromatics [10].

Slight variations in temperature cause the formation of oils or resinous materials (*cf.* Introduction), reducing performance. It has also been found that an increase in temperature usually produces variations in the distribution percentages of the possible isomers.

Aluminum trichloride is the most widely used catalyst in the Friedel-Crafts reaction due to its low cost and high catalytic power. However, other catalysts are also used such as metals, mineral acids, other metal halides, etc. Various series of transition metal halides have been examined and their catalytic power has been evaluated, with the maximum value generally corresponding to aluminum halides and particularly to chloride [11]. Among chlorides, the order of catalytic activity is:

$$AlCl_3 > SbCl_5 > FeCl_3 > TeCl_2 > SnCl_4 > TiCl_4 > TeCl_4 > BiCl_3 > ZnCl_2$$

These effects can generally be minimized in the presence of solvents or reagents that complex aluminum trichloride such as lithium chloride [12]. The degree of purity of the aluminum trichloride is a particularly important factor and it is advisable to use freshly sublimated and anhydrous aluminum trichloride (Although anhydrous aluminum chloride is necessary to obtain high yields, it is not recommended to do this process for an undergraduate practice, as it is time consuming and expensive).

Friedel-Crafts acylation and alkylation are homologous but not identical processes. The F-C alkylation requires relatively small (catalytic) amounts of aluminum chloride. On the other hand, at least one molar equivalent of aluminum chloride is needed for each carbonyl group present in the acylating agent in acylation. The Friedel-Crafts acylation is free of two features that complicate the alkylation reaction, (i) polysubstitution and (ii) rearrangements of the carbocations formed. There is usually no difficulty in stopping acylation with the introduction of a single acyl group into the aromatic nucleus, since the acyl group deactivates the nucleus and prevents further electrophilic attack.

2.2.6. Physicochemical Data of Compounds

Major Compounds

Compound **1**. Acetophenone. GC Ret time: 8.695 min; EIMS 70 eV: *m/z* (rel. int.): 120 $[M]^+$ (33), 105 (100), 91 (1), 77 (69), 63 (2), 51 (20), 50 (8); IR (cm^{-1}) υ_{max} 3351 (Overtone of C=O Stretch), 1646 (C=O Stretch), 1596, 1452, 1355, 1258, 936, 761 [13].

Compound **2.** .4-Methylacetophenone. GC Ret time: 12.410 min; EIMS 70 eV: *m/z* (rel. int.): 134 $[M]^+$ (32), 119 (100), 91 (67), 65 (19), 51 (7). IR (cm^{-1}) u_{max} 3357 (Overtone of C=O Stretch), 1675 (C=O Stretch), 1607, 1428, 1357, 1268, 948, 790 [13].

Minor Compounds

Compound 3. 3-Hydroperoxyhexane. GC Ret time: 5.607 min; EIMS 70 eV: *m/z* (rel. int.): 118 $[M]^+$ (0), 100 (9), 85 (66), 73 (46), 59 (100), 57 (71), 55 (89), 50 (1).

Compound 4. 2-Hydroperoxyhexane. GC Ret time: 5.814 min; EIMS 70 eV: *m/z* (rel. int.): 118 $[M]^+$ (0), 100 (7), 85 (100), 69 (54), 61 (29), 57 (66), 55 (29), 50 (1).

Compound 5. 1,3-Dimethylbenzene. GC Ret time: 4.356 min; EIMS 70 eV: *m/z* (rel. int.): 106 $[M]^+$ (48), 91 (100), 77 (13), 65 (12), 50 (7).

Compound 6. 1,2,3-Trimethylbenzene. GC Ret time: 7.050 min; EIMS 70 eV: *m/z* (rel. int.): 120 $[M]^+$ (42), 119 (10), 105 (100), 91 (14), 79 (14), 63 (4), 50 (4).

Compound 7. 2-Methylacetophenone. GC Ret time: 10.913 min; EIMS 70 eV: *m/z* (rel. int.): 134 $[M]^+$ (28), 120 (10), 119 (100), 103 (1), 91 (100), 77 (5), 65 (23), 50 (6).

Compound 8. 3-Methylacetophenone. GC Ret time: 12.002 min; EIMS 70 eV: *m/z* (rel. int.): 134 $[M]^+$ (20), 120 (10), 119 (100), 103 (1), 91 (100), 77 (4), 65 (22), 50 (6).

2.2.7. Hazards

All reagents comport a degree of toxicity when handling. The student must check out the hazards in the references of Table 1 (CAS number).

2.2.8. Tasks for the Student

Prepare a written report that includes:

1. A flow chart of the manipulations
2. A table with products, their yields and their degree of purity
3. Mention of the isolation and purification procedures
4. Notable comments on possible difficulties in handling
5. New information on the Friedel-Crafts reaction and its industrial applications

3. Results and Discussion

3.1. Synthesis of 1 (Acetophenone)

The synthesis of **1** gave a low yield of 34% after the final distillation. This low yield can be attributed to the fact that the aluminum chloride was not completely dried for this procedure since its drying is a complex and tedious process which is not convenient for an undergraduate laboratory practice. Despite the low yield, gas chromatography (Figure 9) shows that acetophenone was obtained with high purity. The first two peaks (RT = 5.61 and 5.81 min) were identified as 3-Hydroperoxyhexane and 2-Hydroperoxyhexane (compounds 3 and 4 respetively by GC-MS (see section 2.2.6). Together they have a contribution to the product of 4.5%. Hydroperoxy function (Compounds 3 and 4) makes suspicion of EIMS rearrangements during run of spectra a fact signalled by T. Lund [14]. On the other hand, the third peak (RT = 8.695 min) corresponds to **1** with a contribution of 95.5%. In this case, despite the fact of a low yield the product obtained has a high purity being suitable for subsequent synthesis.

3.2. Synthesis of 2 (4-Methylacetophenone)

The synthesis of **2** gave a good yield (85%) after the final distillation. In order to verify the purity of the product obtained it was analyzed by gas chromatography -mass spectrometry (GC-MS, Fig. 10). The chromatogram shows five compounds. Compounds 5, 1,3-Dimethylbenzene, and compound 6, 1,2,3-Trimethylbenzene (see section 2.2.6.). These compounds are minor products of the synthesis F-C. For instance, 1,2,3-methylbenzene also called hemimellitene (CAS [526-73-8]) is industrially produced during petrol distillation in the C_9 fraction of aromatic hydrocarbons; also, Trimethylbenzenes are products from methylation of toluene or xylene according to Friedel – Crafts reaction when chloromethane in the presence of aluminum chloride is employed [15]. Compounds 7, 8 and **2** correspond after the GC-MS analysis to three isomers, 2-, 3- and 4-acetophenone, respectively. Compound 7 (RT 10.913) with a contribution to the product of 2.7%, compound 8 (RT 10.002) with a contribution of 1.2% and compound **2** (RT 12.410) 95.8%.

The elution order in GC of the three isomers (cmpds 7, 8 and **2**) is, according to the recorded retention times, 7, first, 8, second, and the last one is **2**. However, when an equimolar mixture of these three compounds is separated by GC, the most volatile of the three (lowest boiling point) elutes first (lowest retention time), and sequentially after elute the other two with higher boiling points, namely the order is **2** (4-MeAcOPhenone, 226°C, 1st), 8 (3-MeAcOPhenone, 234°C, 2nd) and 7 (2-MeAcOPhenone, 242°C, 3rd).

Boiling points
4-Methylacetophenone (*p*-Methylacetophenone): 226°C. (**2**)
3-Methylacetophenone (*m*-Methylacetophenone): 234°C. (8)
2-Methylacetophenone (*o*-Methylacetophenone): 242°C. (7)

This poses the reverse order with respect to the results obtained. We can explain this if we consider that the products of the three isomers after a Friedel-Crafts acylation aren't in equimolar proportions. Actually, the percentages according to Figure 10 are 7 (*ortho*-methyl isomer, RT 10.913, 2.7%), 8 (*meta*-methyl isomer, RT 10.002, 1.2%) and **2** (*para*-methyl isomer, RT 12.410, 95.8%). Thus, the less abundant component of the mixture should boil first (8, 1.2%), then the following in increasing mass (7, 2.7%), and finally the most abundant (**2**, 95.8%). What we observe here is two driving forces for boiling-elution. The first one is the boiling point, and the second is the mass of each component. One of them predominates over the other, temperature vs. mass. It is clear according to the results (chromatogram of Figure 10), that 2 elutes last, here mass predominates over boiling point (T°). For the minor components 7 and 8, the fact that 8 (lower relative boiling point) weighs more than 7, precludes the influence of 7's higher boiling point. Thus 7 elutes before 8.

The next important aspect to be discussed is why in this acylation (toluene's acylation) the *para*-isomer product is favored over the other two isomers, *ortho* and *meta,* and also why *meta* overshadows *ortho.* The answers will emerge of the focus on the mechanisms, exposed in the next section.

3.3. Friedel-Crafts Acylation Mechanisms

The F-C method allows the direct union of an acyl group to an aromatic ring and is called Friedel-Crafts acylation. In this reaction, benzene (or derivative) undergoes electrophilic aromatic substitution (EAS) when treated with an acylating agent, acyl halide or acid anhydride in the presence of a Lewis acid catalyst. Two possible mechanisms [9].

3.3.1. Mechanism for Acetophenone. Acylation of Benzene, See Figure 14 [9]

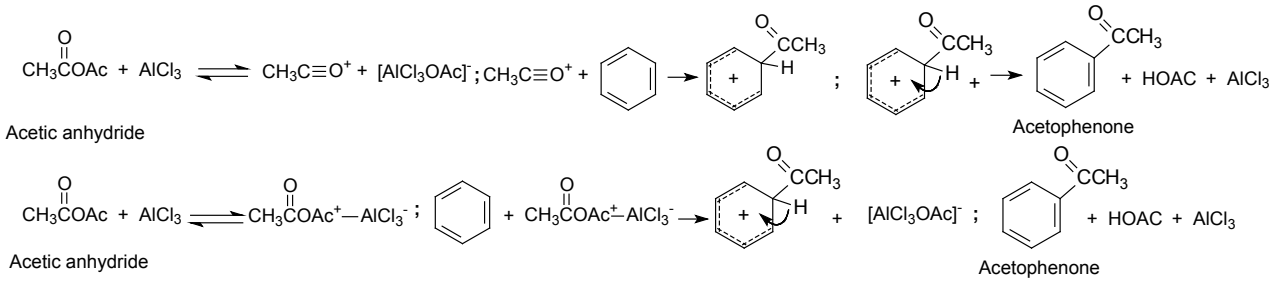


Figure 14. Friedel Crafts Acylation of benzene and acetyl chloride to form acetophenone

3.3.2. Mechanism for 4-Methylacetophenone. Acylation of toluene, see Figure 15 [9,16]

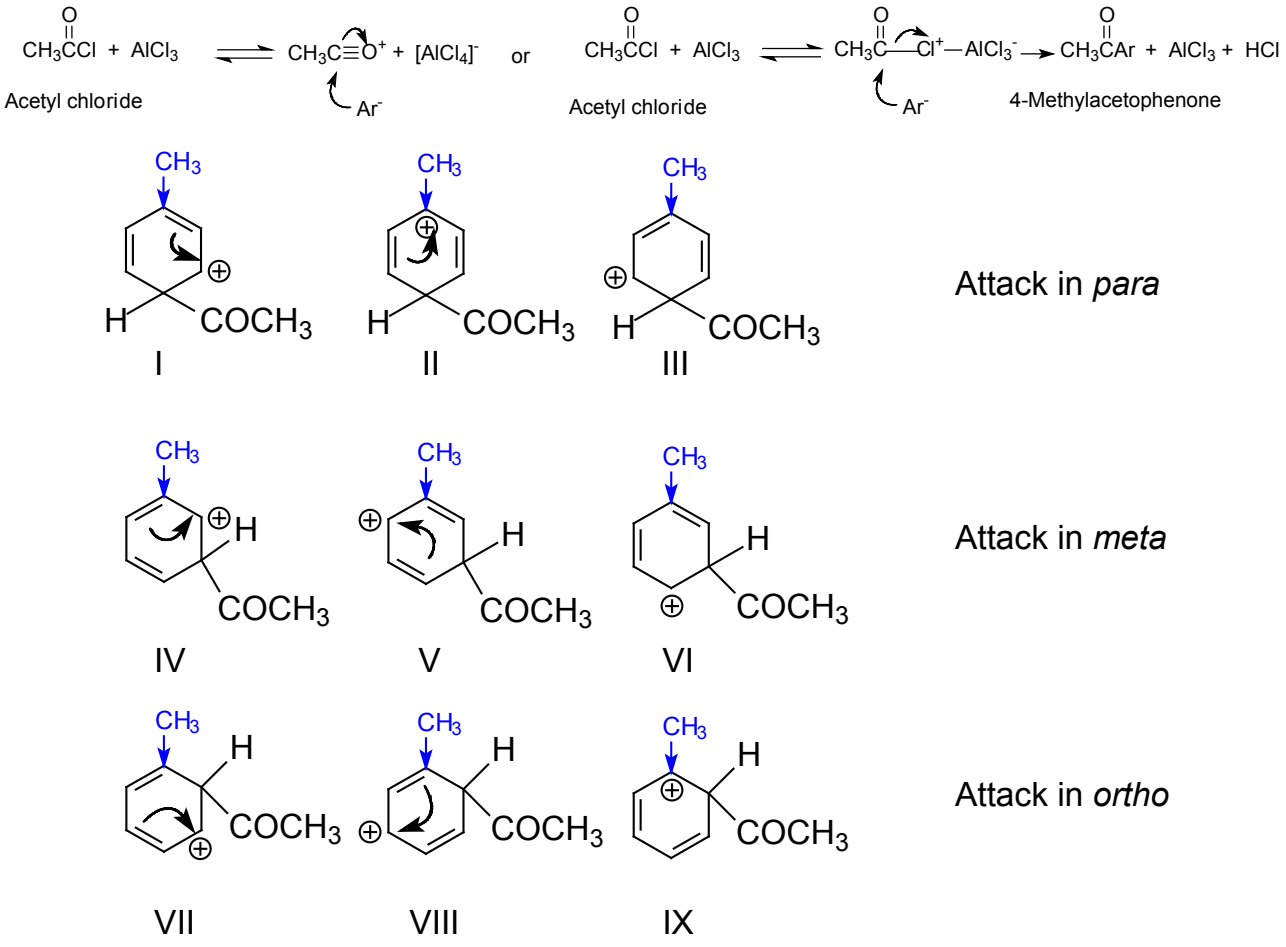


Figure 15. Mechanism of Acylation of Toluene to form 4-Methylacetophenone (2) [9,16]

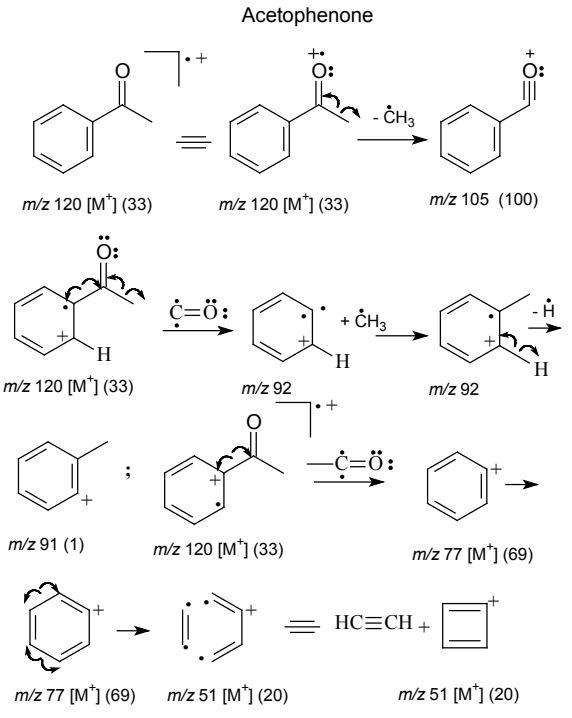
The activating group methyl of toluene, activates all positions of benzene, and it's an *ortho*/*para* director because these positions become more activated than the *meta* position. Figure 15 shows the same mechanisms exposed for acetophenone. The methyl group in toluene directs a preferential attack on Ar^- on the *ortho*/*para* positions. Let us compare, for example, the carbocations generated by the attack on positions *para* and *meta* of toluene. Each cation is a hybrid of three structures I-III for *para* and IV to VI for *meta*. In structure II, the positive charge is located on the carbon supporting the methyl group. Even though this one liberates electrons for all positions in the ring, its charge in electrons is preferentially addressed to the closest carbon. Hence structure II is particularly stable. Due to this contribution of structure II, the hybrid carbocation resulting from an attack in position *para* is more stable that the one afforded by an

attack in *meta* (IV–VI). Hence, substitution is faster on *para* than *meta*. The same feature can be observed when the attack in on *ortho* (VII-IX), here, also a more stable carbocation is generated, because of the contribution of IX, in comparison to the *meta* attack [16]. Thus, this mechanism supports the obtained relative amounts of the three isomers of methyl acetophenone by F- C. The much faster attack on the *para* position, overwhelms the attacks on the other positions. The ortho position attack is slower than *para* in spite of having the same hybrid carbocation. The reason is steric hindrance generated by the proximity of both substituents in the ring, methyl and acetyl.

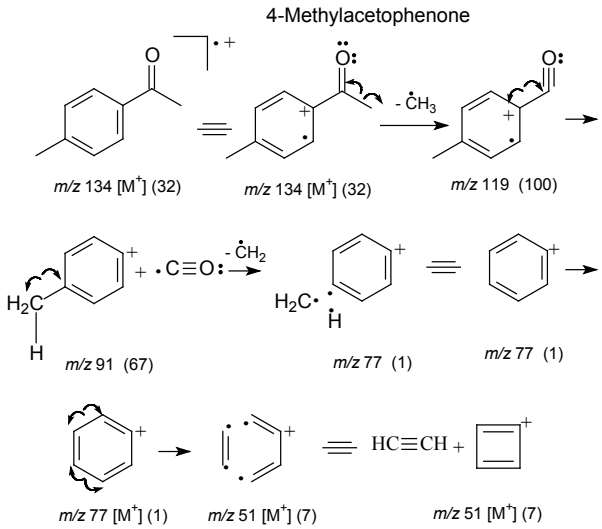
3.4. Identification of Products

All major and minor products of the F-C acylation were characterized, 8 products in all (see section 2.2.6). The main tool was Gas Chromatography-Mass Spectrometry (GC.MS). An easily profitable and easy doing technique for fast results in quantification and identification, particularly as complement in synthesis works by undergraduate students. Figures 9 and 10 show the chromatograms and mass spectra for both synthesis products. The target products of the syntheses were compound 1 (acetophenone) and compound 2 (*p*-methylacetophenone), both major products of these experiments. The technique gives very clearly the identification of all products based on the retention times and EIMS spectra. Hence, no ambiguity in characterization is possible. We'll expose the EIMS fragmentation pattern of the major products, main goal of this lab guide, compounds 1 and 2. As complementary identification tool, the IR spectra of 1 and 2 were run.

3.4.1. EIMS' Fragmentation Pattern of Acetophenone (1)



3.4.2. EIMS' Fragmentation Pattern of 4-Methylaceto-Phenone (2)



4. Conclusions

A practical guide for organic chemistry laboratory was proposed on the subject of synthesis with the preparation of two aromatic ketones using the acylation method according to Friedel-Crafts with real and verifiable results. The identification of the syntheses products was carried out with the GC-MS technique due to its lower costs compared to a NMR analysis. The exposition of the manipulation was done in a detailed manner with a supplementary character beyond what is found as bibliography available to undergraduate chemistry students. For this, this guide deals with basic synthetic tools such as Friedel-Crafts acylation simple operation to be mastered for future even more interesting synthetic forays. Given the fact of high altitude of our laboratory (3600 m.a.s.l., about 486.9 mmHg of atmospheric pressure) some synthetic experiments can show lower yield in comparison to values reported from literature of the homologue treatment at sea level. This could be a cause for the poor yield of acetophenone (**1**) by F-C.

The Organic Chemistry Notebook Series, a Didactical Approach pretends, besides proposing mechanistic views, to vow simple and accessible practices making use of starting materials and reagents that are common in the organic chemistry laboratory. Some other didactical approaches on the F-C acylation devoted to students in the lab have been surveyed as bibliography precedingly, and have inspired and guided somehow the present job. It is worth mentioning A. M. Reeve, that proposed A Discovery-Based Friedel–Crafts Acylation Experiment: Student-Designed Experimental Procedure [17]. In this regard, two of the authors, J. J. D. and A. C. are currently undergraduate and graduate students, respectively in our Chemical Research Institute. Another interesting paper deals with the structure determinations of the final products of the F-C acylation, by employing IR spectrometry [18]. A more recent approach to the F-C

acylation was the employing of MW synthesis with Microwave -Assisted Friedel-Crafts Acylation of Toluene with Anhydrides. Compounds were characterized by ^{1}H NMR, ^{13}C NMR and DEPT pulses [19]. Thus, to the best of our knowledge, the present guide is innovating regarding the identification of products with a more modern technique, that presents multiple advantages regarding previous works on educational themes like synthesis of simple compounds like Friedel-Crafts Acylation.

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