Synthesis of 7-methoxy-4-oxo-*N*-phenyl-4*H*-chromene-2-carboxamide

Supplementary Material

The chromone scaffold has been elected as a privileged structure for drug discovery programs due to its noteworthy pharmacological activities.[1-3] The chemical decoration of the heterocyclic framework allows the obtention of a diversity of chemical libraries namely those enclosing chromone carboxamide derivatives.

Herein we report a three-step synthetic procedure to obtain one chromone carboxamide derivative of the library.[1-3] In general, the experiment was easy to perform and the purification processes easy to undertake.

Students' laboratorial sessions

The experiments were designed for chemistry-based curricula, namely chemistry or medicinal chemistry courses, and are best suited for students that have organic chemistry (theoretical and practical) foundations. The experiments were tested in a first year master chemistry course including 30 students. They were easy to perform and produced clear results which directed the students in a new practical and real organic chemistry lesson. The average success of students in the integrated experience was of 95%. In general, students obtained adequate amount of compounds to complete the hands-on experience of structural characterization. No difficulties in the purification step and acquisition of NMR spectra have been detected. However, in the interpretation of NMR data, some drawbacks have been noticed; students were advised to use molecular model kits to assist in the visualization process. A lab report was written according standard guidelines.[4]

Notes

- Students must read the details of the experiments and prepare a procedure flow chart to be followed in the class;
-Students must check the purity of each product by TLC;
-Students must be aware that the reaction between HCl and sodium ethoxide led to the formation of a white precipitate (NaCl);
-Students can check pH with universal indicator paper;
- Students must be familiar with chromone structural features;
- Students must review NMR spectroscopic concepts.

Additional notes

Considering that the proposed experiment correspond to a three step procedure, it is advised to start the first stage with an appropriate amount of the starting material acetophenone (2 g). The yields of step **1** (formation of the chromone ester) and step **2** (formation of the chromone carboxylic acid) are 70-80% and 80-90%, respectively. In the amidation reaction a moderate yield (around 60-75%) is always obtained. The purification by flash column chromatography allows removing the by-products formed along the reaction. All the NMR spectra should be performed in DMSO-*d6*, except for the chromone ester (**2**) as the product is not soluble enough.

A detailed structural analysis, namely the 1D and 2D NMR spectra of the final compound, was previously reported by the authors.[5]

Structural analysis- key notes

Step 1: Synthesis of ethyl 7-methoxy-4-oxo-4*H*-chromene-2-carboxylate

^{1}H NMR allow to identify the compound, namely by noticing the multiplicity vs integration data of CH_2 (quartet-2H) and of CH_3 protons (triplet-3H) of the ester function that are identified around δ4.46 and δ1.43 ppm, respectively. Furthermore, the aromatic protons of the benzopyrone ring (δ = 8.09 – 6.99 ppm), the hydrogen of the pyrone ring (singlet-1H) and the methoxyl function (singlet-3H) are well recognized in the spectra.

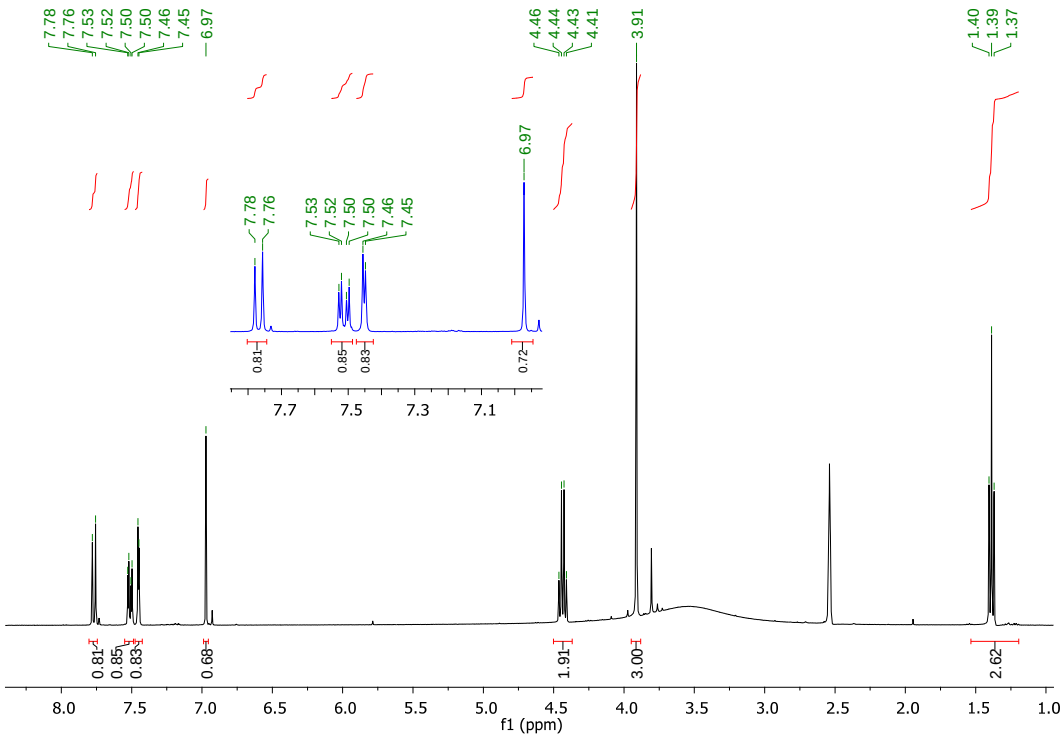


Figure SM 3.2.1.1 - ^{1}H NMR of ethyl 7-methoxy-4-oxo-4*H*-chromene-2-carboxylate (400 MHz, $CDCl_3$)

Step 2: Synthesis of 7-methoxy-4-oxo-4*H*-chromene-2-carboxylic acid

The hydrolysis reaction yield is almost quantitative (100%), as expected for a complete reaction. Since the ^{1}H NMR signal for the proton of the carboxylic group is usually not observed due to proton exchange with the solvent, the presence of the function is confirmed in ^{13}C NMR spectra. The signal of the carbonyl moiety appears at a predictable chemical shift (COOH at δ = 161.89 ppm). Moreover, it is detected in the both spectra the disappearance of the signals corresponding to the ethyl moiety of the ester function.

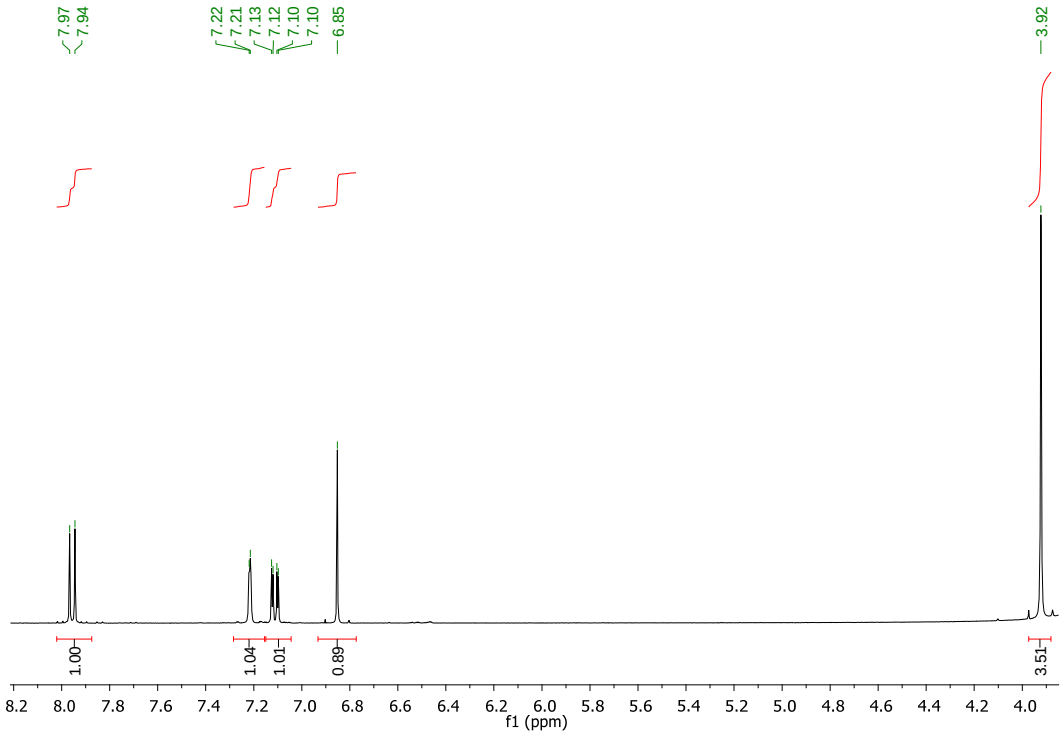


Figure SM 3.2.1.2 - ^{1}H NMR of 7-methoxy-4-oxo-4*H*-chromene-2-carboxylic acid (400 MHz, DMSO-*d6*)

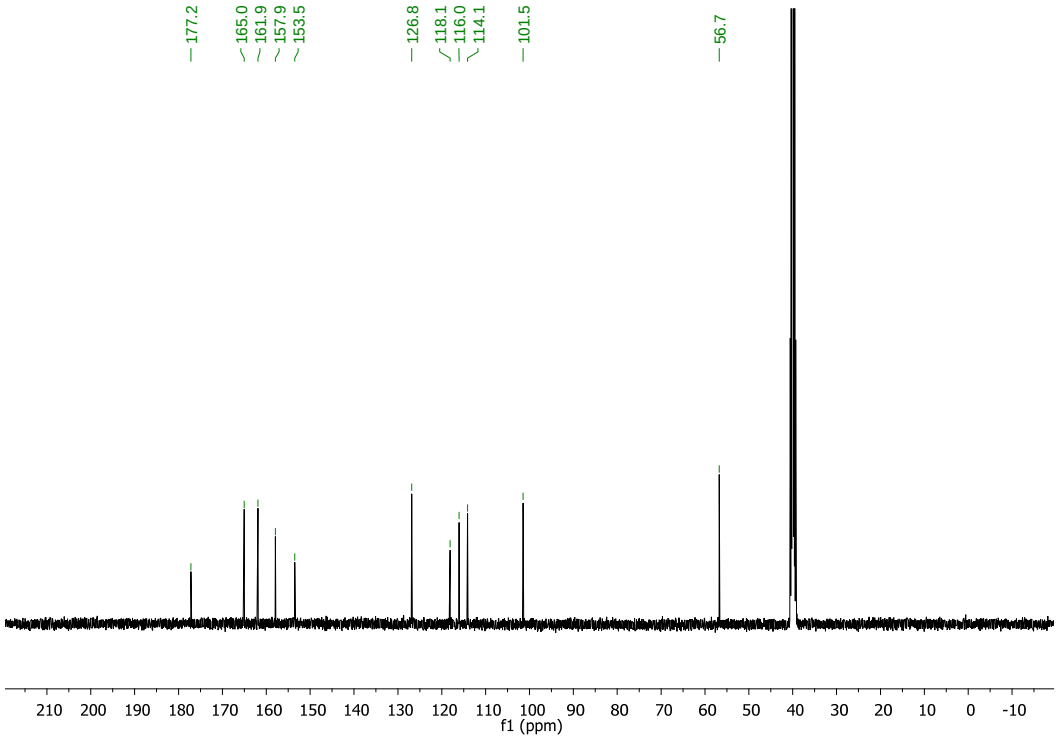


Figure SM 3.2.1.3 - ^{13}C NMR of 7-methoxy-4-oxo-*N*-phenyl-4*H*-chromene-2-carboxamide (101 MHz, DMSO-*d6*)

Step 3: Synthesis of 7-methoxy-4-oxo-*N*-phenyl-4*H*-chromene-2-carboxamide

The chromone carboxylic acid was activated with the coupling agent PyBOP and then the ester intermediate (for more details see reference 13 of the protocol) will react with the amine (aniline). The purification by flash column chromatography (eluent: dichloromethane/methanol 90:10 (v/v))) will remove the by-products. A recrystallization process with dichloromethane/*n*-hexane is strongly advised.

In ^{1}H NMR the signal corresponding to the proton of the amide group (CONH) appears at δ = 10.66 ppm.

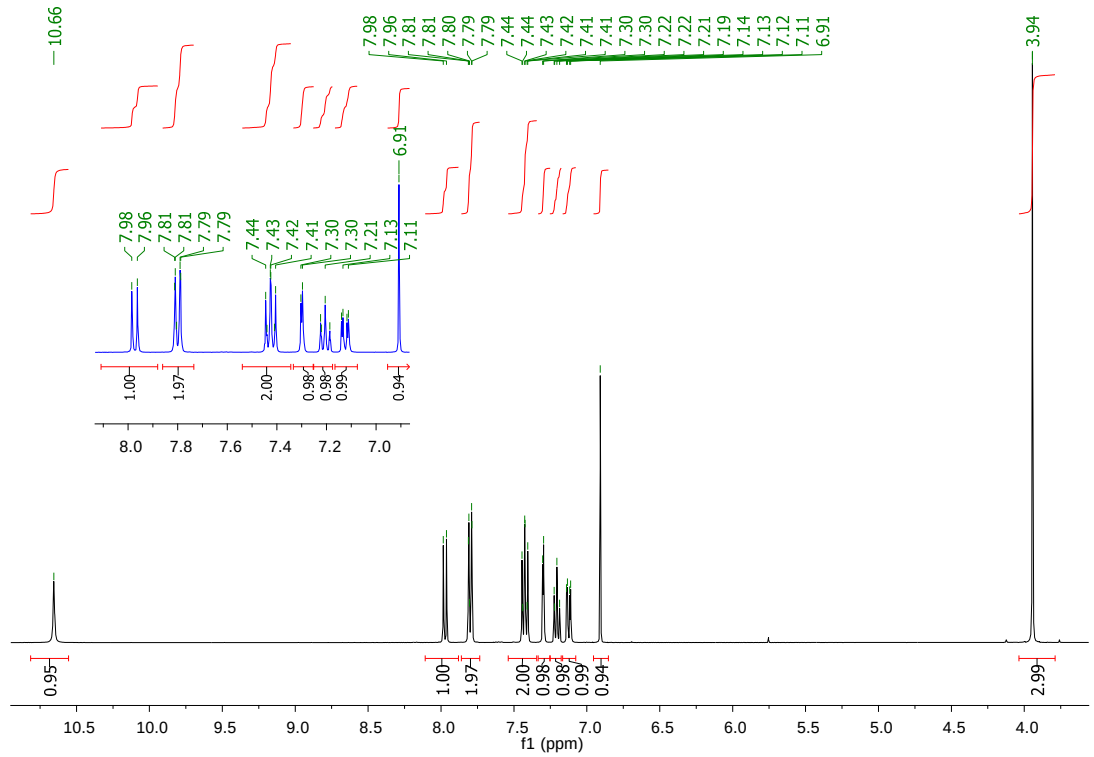


Figure SM 3.2.1.4 - ^{1}H NMR of 7-methoxy-4-oxo-*N*-phenyl-4*H*-chromene-2-carboxamide (400 MHz, DMSO)

References

1. A. Gaspar, M. J.Matos, J. Garrido, E.Uriarte, F. Borges, *Chem. Rev*., 2014, **114** (9), 4960-4992.
2. A. Gaspar, T. Silva, M. Yanez, D. Vina, F. Orallo, F. Ortuso, E. Uriarte, S. Alcaro, F. Borges, *J. Med. Chem*., 2011, **54**, 5165-5173.
3. A. Gaspar, J. Reis, S. Kachler, S. Paoletta, E. Uriarte, K.N. Klotz, S. Moro, F. Borges, *Biochem. Pharmacol*., 2012, **84**, 21-29.
4. W. R. Dolphin, Writing Lab Reports and Scientific Papers; McGraw-Hill: New York, 1997. http://www.mhhe.com/biosci/ genbio/maderinquiry/writing.html
5. J. Reis, A. Gaspar, F. Borges, L. Rebelo Gomes, J. Nicolson Low, *J. Mol. Struct*., 2014, **1056**, 31-37.

Additional Reading

McMurry J. E., Organic Chemistry**,** Brooks Cole, USA, 2011.

Pavia D. L, Lampman G. M., S. Kriz G. S., Vyvyan J. A., Introduction to Spectroscopy, Brooks Cole, USA, 2008.

Ault A.,Techniques and Experiments for Organic Chemistry, University Science Books, Sausalito, CA, 6rd ed, 2008.

Synthesis of 2,3-diphenylindenone

Supplementary Material

This experiment was performed by several groups of graduate students in the Advanced Organic Chemistry Lab. The experimental procedures are essentially those of R. Weiss[1] and T.J. Clark[2] with some modifications. In the first synthesis the phthalic anhydride used should be pure and free from phthalic acid. If necessary, it can be purified by sublimation. Sodium acetate should be molten by heating in a porcelain cap. Note that at the beginning of the heating the hydrated salt dissolves in the crystallization water, becomes solid again and then melts. Benzalphtalide is obtained with an average yield of 72 % (mp=100-101º C).[1] A picture of the reaction apparatus is shown on Figure SM 3.2.2.1.

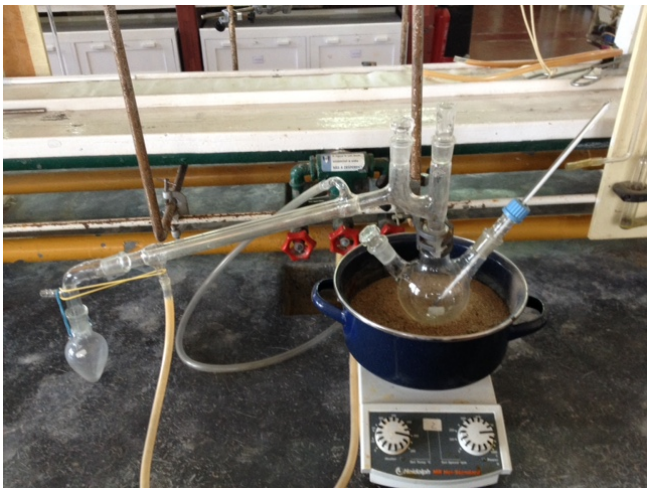


Figure SM 3.2.2.1 Reaction apparatus for the preparation of Benzalphthalide (session 1)

The second synthesis is too long to be performed in a 4 hour lab class. It should be interrupted after the addition of the 6M H_2SO_4 solution, but not before, because the decomposition of the excess of Grignard reagent leads to undesirable by products like phenol and benzoic acid. The initial reaction apparatus is shown on Figure SM 3.2.2.2.

Figure SM 3.2.2.2 Reaction apparatus for the preparation of 2,3-diphenylindenone

2,3-Diphenylindenone is obtained with an average yield of 90 % (mp=150.5-152ºC).[2] Beautiful red prismatic crystals are obtained from the slow evaporation of the recrystallization solution (see Figure SM 3.2.2.3).

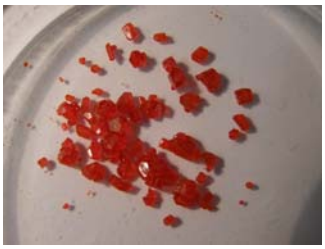


Figure SM 3.2.2.3: Prismatic crystals of 2,3-diphenylindenone

Hints to the questions

An abbreviated mechanism of the two reactions is proposed on Figures SM 3.2.2.4 and SM 3.2.2.5.

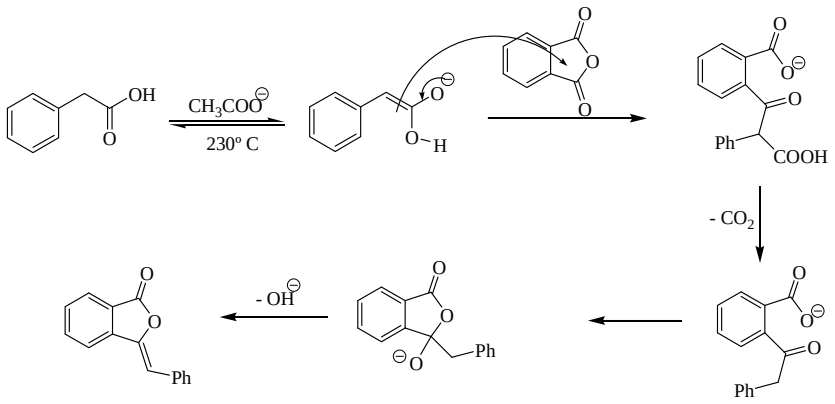


Figure SM 3.2.2.4 Proposed abbreviated mechanism for the formation of Benzalphthalide

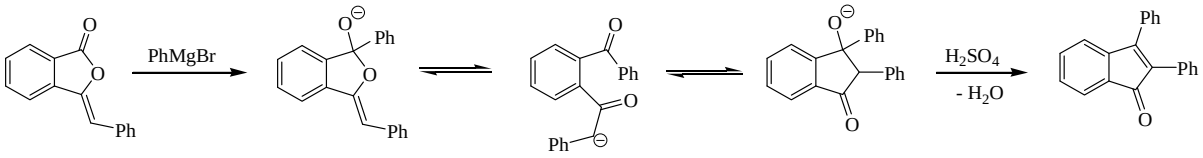


Figure SM 3.2.2.5 Proposed abbreviated mechanism for the formation of 2,3-diphenylindenone

Spectroscopic data:

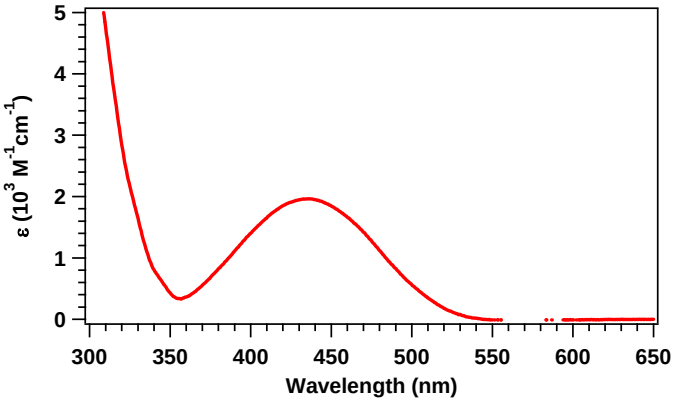


Figure SM 3.2.2.6: UV-Vis spectrum of 2,3-dihenylindenone in toluene.

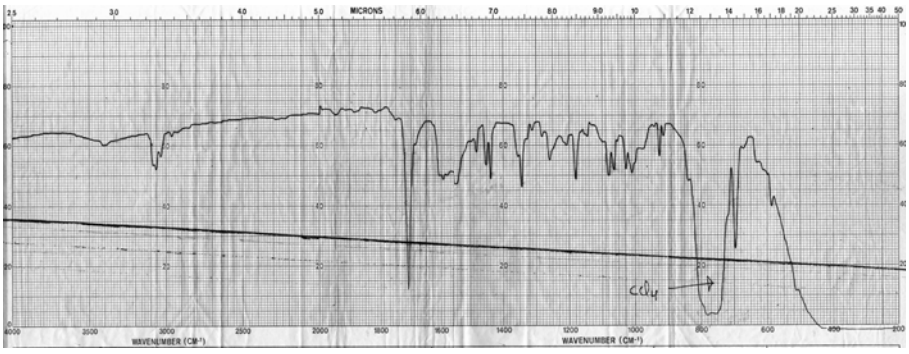


Figure SM 3.2.2.7: IR spectrum of 2,3-dihenylindenone (in CCl_4, NaCl windows)

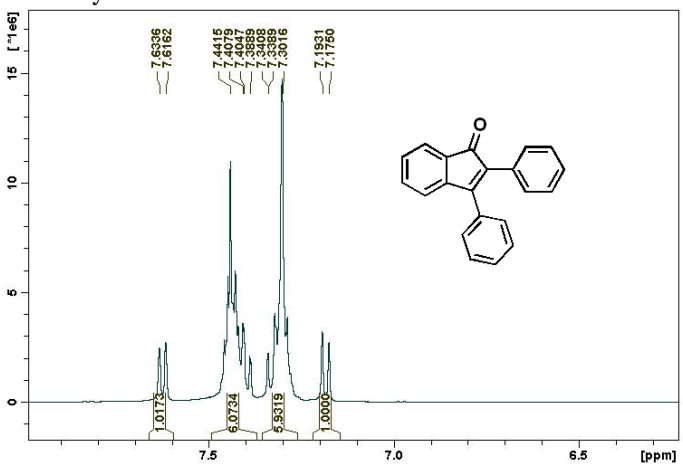


Figure SM 3.2.2.8: ^{1}H NMR (400 MHz) spectrum of 2,3-diphenylindenone in $CDCl_3$

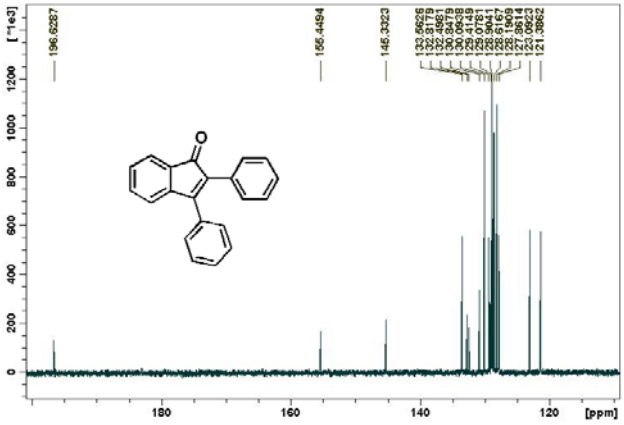


Figura SM 3.2.2.9 - ^{13}C RMN (400 MHz) spectrum ($CDCl_3$) of 2,3-diphenylindenone.

[1] R. Weiss, *Org. Synth. Coll*. 2, 1943, 61.
[2] T.J. Clark, *J. Chem. Educ*., 1971, ***48***, 554.

Synthesis of Dimedone

Supplementary Material

The synthesis of dimedone was introduced first in 2003 to 2nd year undergraduate students of intermediate organic chemistry as a short project involving bibliographic research and experimental work (three groups of two students). They have the opportunity to study several carbonyl group transformations as Michael Addition and Claisen Condensation widely used in organic synthesis as well tautomerism where an enol is formed by proton transfer. Once dimedone forms crystalline derivatives with aldehydes, it is used to aldehydes identification, so if desired, students can perform this reaction in classroom[1].

Additional notes on the preparation of dimedone:

This synthesis is usually made in two sessions of *c.a.* 3 hours each. The first one includes the dissolution of sodium metal in absolute ethanol (which takes some time to complete), two 45-minute periods with refluxing, and dropwise addition of several reactants (Figure **SM 3.2.3.1**).

Figure SM 3.2.3.1 – Reaction set-up apparatus for dimedone

Distillation is usually left for the second session (Figure **SM 3.2.3.2**).

Figure SM 3.2.3.2 – Rotary evaporator for distillation of ethanol-water mixture

On the liquid-liquid extraction step, students must be warned to preserve the aqueous layer instead of the organic one. The final vacuum filtration should be performed only when the product is completely crystallized, which may take anything from 1 to 24 hours. If possible, it is advisable to leave the mixture to precipitate overnight. The yield of dimedone is 20-25%, much lower than the 70% reported in literature[2]. The low yield low could be related to ineffective liquid-liquid extraction and recrystallization. According to this reference, the yield also depends on the purity of mesityl oxide, which should be distilled prior to its use. In this experiment, mesityl oxide purchased from Aldrich was used without further purification. Experimental melting point is 148-150ºC (148-149ºC[1] and 148-150ºC[3]).

IR spectrum:

The students can realize that enolic form does not show the usual absorption of conjugated ketones. A broad band can be observed at 2800-2400 cm^{-1} and near 1600 cm^{-1} due to enol form (Figure **SM 3.2.3.3**). IR spectrum is available online in SDBS[4] under number 3075.

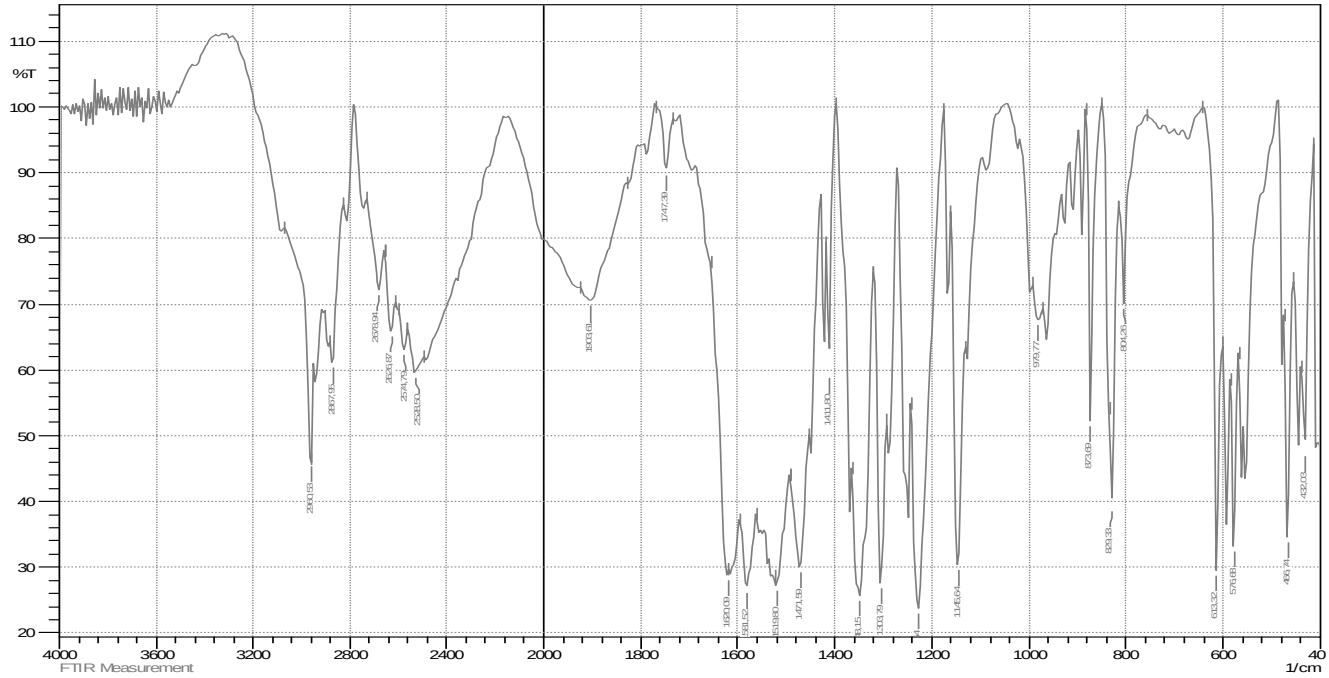


Figure SM 3.2.3.3: IR (KBr) of dimedone

^{1}H NMR spectrum:

^{1}H NMR spectra of dimedone was obtained with student's samples (Figure **SM 3.2.3.4**).

They can easily identify the broad signal at 3.35 ppm OH proton and the signal at 5.19 ppm relative to the proton of sp^2 carbon atom. ^{13}C NMR spectrum of dimedone is available online in SDBS[4] under number 3075, while the ^{1}H NMR spectrum can be found in literature[5,6].

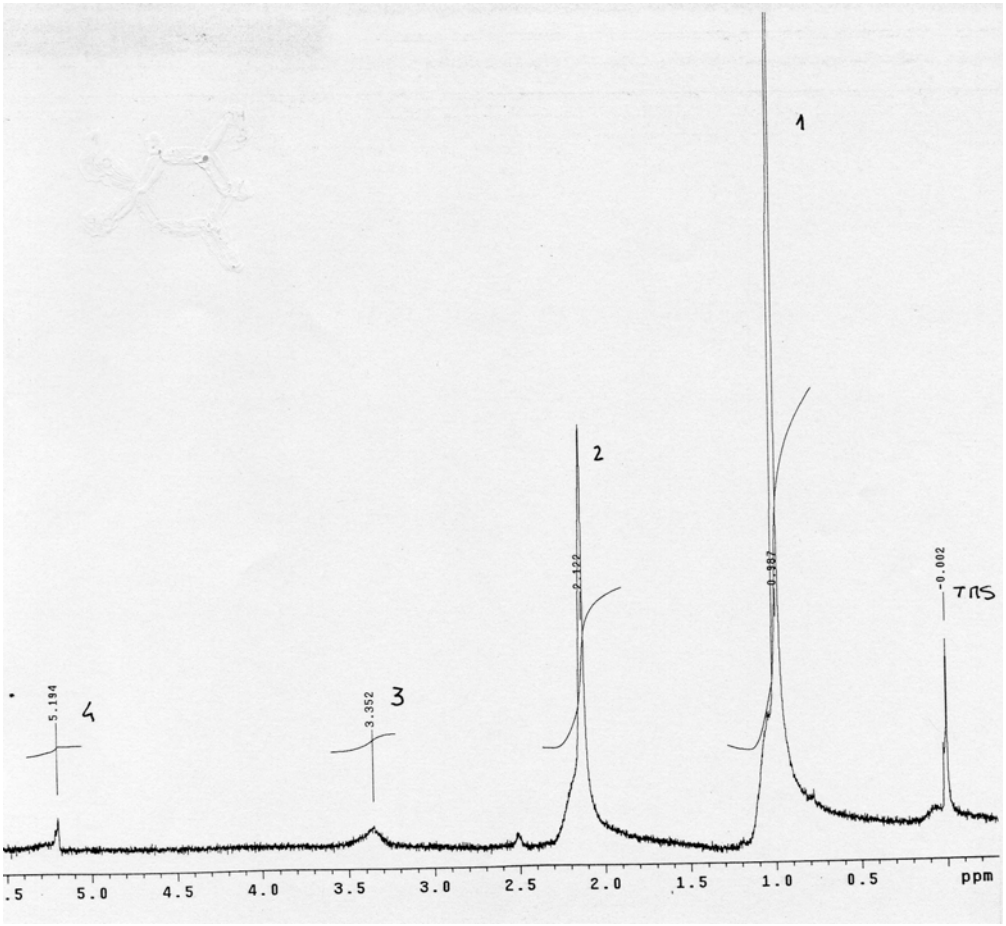


Figure SM 3.2.3.4: ^{1}H NMR ($CDCl_3$) of dimedone

[1] A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, 5th ed. 1989, 1259.
[2] R. L. Shriner, H. R. Todd, *Org.Synth. Coll.*, 1943, **2**, 200.
[3] *The Merck Index*., 11th ed., 1989, 511.
[4] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi accessed in Oct 2015
[5] Clayden, Greeves, Warren and Wothers, Organic Chemistry, Oxford, 2001, 524.
[6] *The Aldrich library of NMR spectra*, 2nd ed., 1, 1983, 391.

Acylation Reaction of Enol Ether Using Ionic Liquid

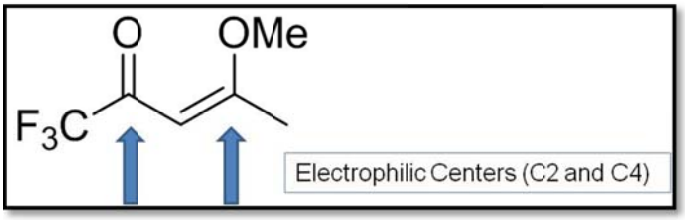
Supplementary Material

This experiment reports the synthesis of acylated enol ether 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones using the ionic liquid (IL) [BMIM][BF_4].

- The system should be free of water to avoid the formation of trifluoroacetic acid, which would decrease the yield.
- The slow addition (drop by drop) and control of the temperature (0 °C) during the whole reaction time is imperative to avoid polymerization of the enol ether and a consequent decrease in the yield.
- The first step of the extraction is the separation of the product from the IL (using diethyl ether), and the second step (washing diethyl ether with water) is to remove the pyridine salt solubilized in the diethyl ether.
- The product is yellow-colored oil, obtained at a yield of 71 %. The experiment was tested in our laboratories by three students, and yields of 79, 80, and 85 % were obtained. Therefore, a synthesis yield between 71 and 85 % can be obtained.
- The conversion of reagents into products cannot be monitored by ^{1}H NMR because the anhydride is a non-hydrogenated compound and the enol ether

has a low boiling point.[1] Loss of the product may occur during extraction with diethyl ether (some of the product could be interacting with the IL).

- Some product could be lost when water is added to the diethyl ether (product shows some solubility in water).
- The acylation results in C-C σ-bond formation through substitution at the non-aryl sp^2 carbons. The electrophilic centers formed can be seen in **Scheme SM 3.2.4.1.**



Scheme SM 3.2.4.1. Electrophilic centers.

- The physical properties of the reactants and the product can be seen in Table SM 3.2.4.1.

Table SM 3.2.4.1. Chemical and physical properties of the reactants and product.

Compound	Chemical formula	Molecular weight (g mol^{-1})	Boiling point (°C)[a]
Enol ether **1**	C_4H_8O	72.1	35–36[2]
Trifluoroacetic anhydride **2**	$C_4F_6O_3$	210.0	40[3]
Pyridine	C_5H_5N	79.1	115[4]
Enone**3**	$C_6H_7F_3O_2$	168.0	42[5]

[a]Pressure: 1atm.

Characterization data

Name: 1,1,1-trifluoro-4-methoxypent-4-en-2-one ($C_6H_7F_3O_2$).Yield: 71–85 %. Aspect: orange oil. Boiling Point (Pressure of 11 Torr): 42 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ, 2.41 (s, CH_3); 3.80 (s, O-CH_3); 5.69 (s, CH); ^{13}C NMR ($CDCl_3$, 150 MHz): δ, 21.17 (CH_3); 56.60 (CH_3-O-); 91.64 (CH); 116.78 (q, CF_3, *J*= 291 Hz); 179.0 (q, C=O, *J*= 33 Hz); 181.63 (C).

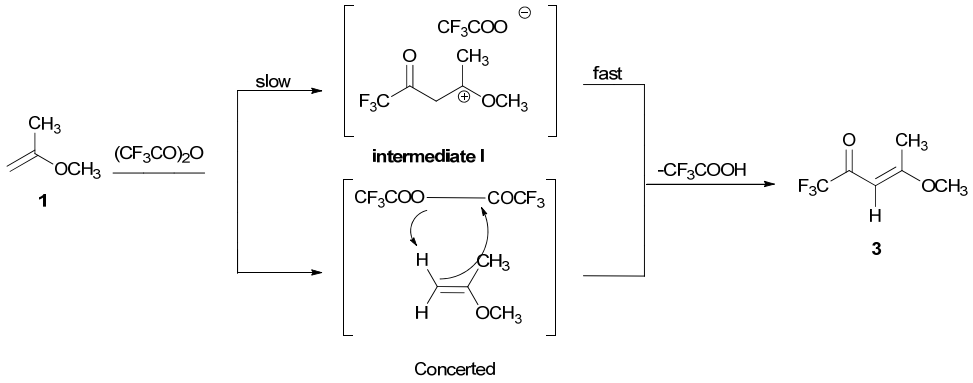
How to prepare a sample for NMR analysis

1. Place 0.020 g (20 mg) of the product (M3) into an NMR tube.

2. Add 600 μL of $CDCl_3$ (containing TMS as an internal reference) to the NMR tube.

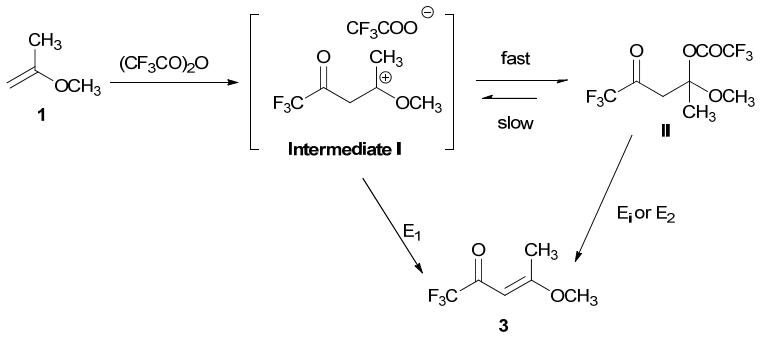
3. Acquire the ^{1}H NMR and ^{13}C NMR spectra.

- Reaction mechanism[6]: The conventional method for the reaction of enol ether with trifluoroacetic anhydride is performed in the presence of pyridine and organic solvents. Two mechanisms for these reactions have been proposed. One is the stepwise mechanism, in which the initial addition of an acyl cation to the vinyl group occurs to form the cationic intermediate **I,** followed by rapid elimination of a proton from **I**. The other mechanism is the single-step mechanism, in which the addition of an acyl group and the elimination of a proton occur concertedly, without the formation of the cationic intermediate **I** (see **Scheme SM 3.2.4.2**).



Scheme SM 3.2.4.2.

In the case of two steps, the elimination in order to obtain trihaloacetylated olefins can be done by following two possible routes: one is E_1 or E_2, in which the cationic intermediates of **I** are converted into **II**; and the other is E_1, in which the intermediates of **I** are converted into the product (**Scheme SM 3.2.4.3**).



Scheme SM 3.2.4.3.

- In this mechanism, an important point is the polymerization reaction that can lead to a decrease in the product yield.[6]
- The mechanism for this acylation in ILs is not discussed here because the manner in which ILs act in these organic reactions is unclear, and there has been, and continues to be, much controversy.
- It is suggested that ILs should be considered to be molecular solvents in terms of the effect on the reaction. ILs are among the most complex solvents, and due to their structure and diverse functionality, they are capable of most kinds of interactions (e.g., dispersive, π-π, n–π, hydrogen bonding, dipolar, ionic/charge–charge). Thus, we postulate that the enhanced rate of the reactions is due to the decrease in activation energy of the slow reaction step. The general IL effect can probably be expected for reactions involving highly polar or charged intermediates such as carbocations or carbanions, and activated complexes which could become more stable and live longer in these media.[7]
- Also, it should be emphasized that [BMIM][BF_4] allows a greener reaction and is an alternative to the hazardous traditional organic solvents, due to its properties such as non-flammability, negligible vapor pressure, high thermal stability, solvating ability, and easy recyclability.

Figures

Photos of the experiment

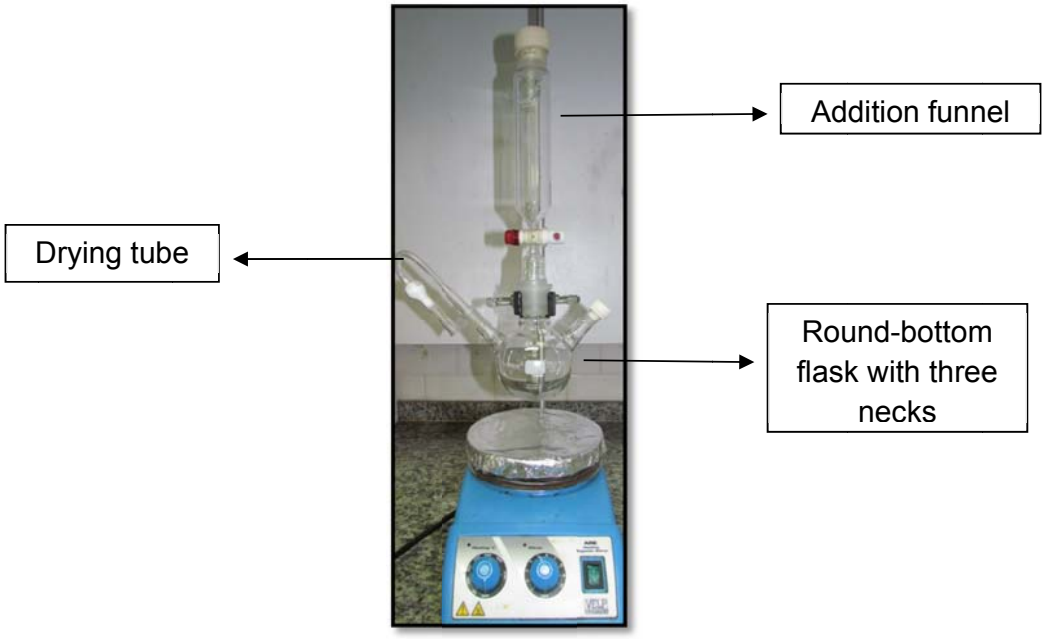


Figure SM 3.2.4.1. Apparatus for acylation.

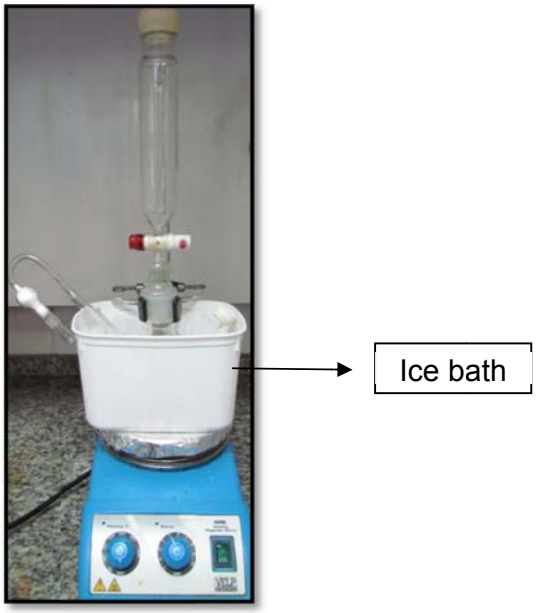


Figure SM 3.2.4.2. Apparatus for acylation with ice bath.

Figure SM 3.2.4.3. A yellow solution can be seen when dropping starts.

Figure SM 3.2.4.4. Crude product.

^{1}H and ^{13}C NMR spectra

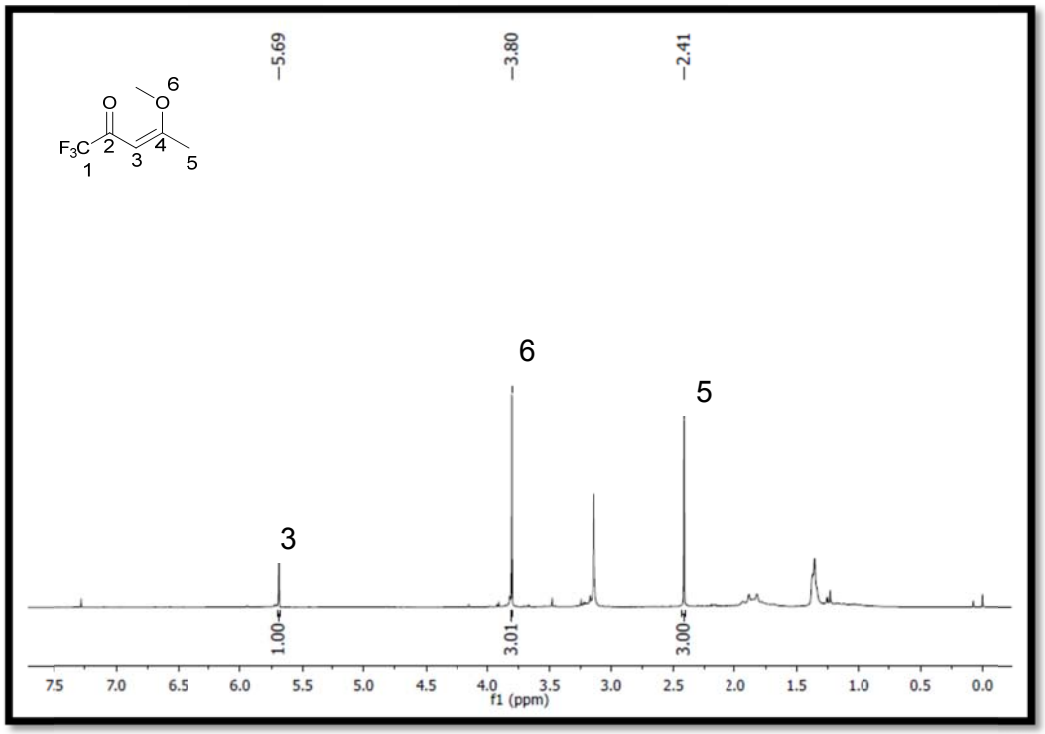


Figure SM 3.2.4.5. Spectrum of NMR ^{1}H, in $CDCl_3$, 600 MHz, 25 °C.

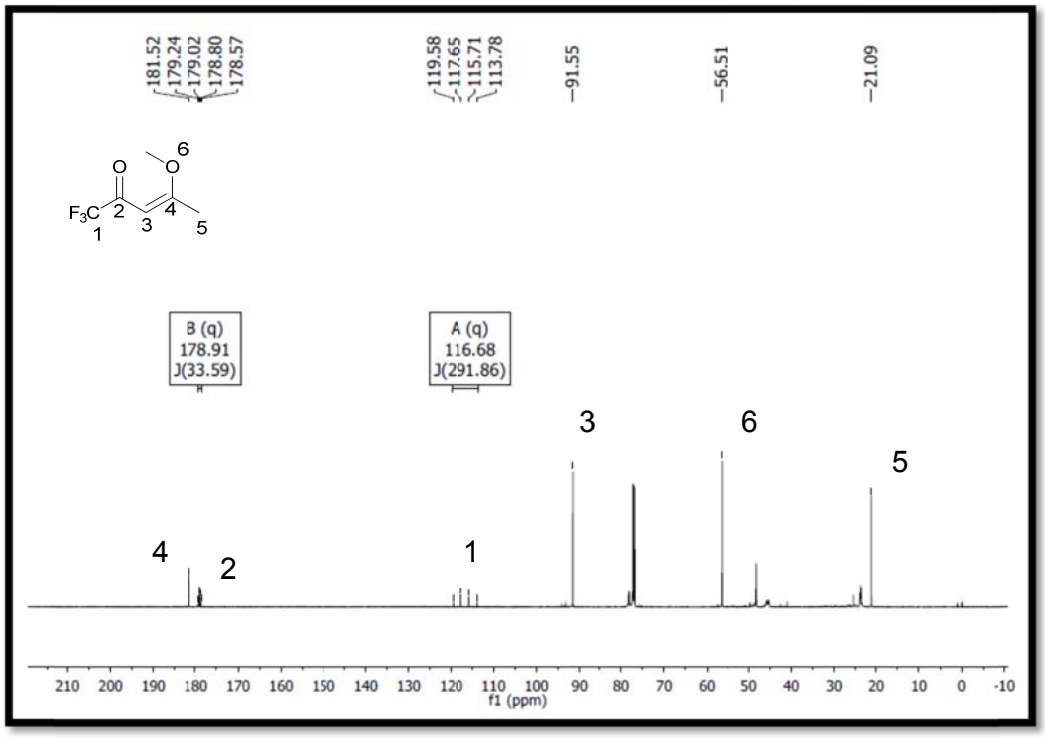


Figure SM 3.2.4.6. Spectrum of NMR ^{13}C, in $CDCl_3$, 150 MHz, 25 °C.

[1]M. A. P. Martins, E. A. Guarda, C. P. Frizzo, E. Scapin, P. Beck, A. C. Costa, N.Zanatta, H. G. Bonacorso, *J. Mol. Catal. A: Chem.,* 2007, **266**, 100.
[2]N. Sebbar, *J. Phys. Chem.A*, 2004, **108**, 8353.
[3]R. F.Clark, *J. Am. Chem. Soc,*1953, **75**, 6305.
[4] B. L.Myron, T. W. Byron,*J. Am. Chem. Soc.*1957, **79**, 1656.
[5]A. P. Martins, W. Cunico, C. M. P. Pereira, A. F. C. Flores, G. Bonacorso, N. Zanatta, *Curr. Org. Synth.* 2004, 391.
[6]Moriguchi, T. and Endo, T. *J. Org. Chem.*1977,**178***,* 389.
[7]M. A. P. Martins, C. P. Frizzo, A. Z. Tier, D. N. Moreira, N. Zanatta, H. G. Bonacorso, Chem. Rev. 2014, **114**, PR1.