

# Combined Use of Macro and Microscale Chemistry in Undergraduate Organic Laboratory

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**Abstract** The current study represents a pilot experiment conducted at University Hassan II of Casablanca, which aims to introduce gradually a new practical teaching approach combining macro and microchemistry into organic chemistry curriculum for the third-year undergraduate chemistry students. A set of fast and simple experiments were introduced over two phases, a simple level of practical instruction in the functional organic chemistry course taught in semester 5 and an advanced level in the practical teaching of green chemistry course taught in semester 6. We used both macro and microscale laboratory techniques and equipment which allowed us to use fewer reagents and organic solvents and to enhance students' skills in mastering macro and micro techniques often used in industrial and research laboratories. Several green metrics as well as Green Star metric were calculated to evaluate the greenness of the implemented experiments. It appeared from the results that aldol, phospho-aldol and Knoevenagel condensations gives a very interesting environmental performance and can be considered as an excellent example of green experiments for undergraduate organic chemistry labs. The survey conducted among third-year chemistry students showed that 84% of the students agreed that introducing macro and microscale chemistry approach has enhanced their interest in learning organic chemistry.

**Keywords** Macro and micro-scale organic experiments, Third-year undergraduate students, Green metrics, Students' perception

## 1. Introduction

Organic chemistry is a part of science that has a large application in everyday lives, the mastery of the basic concepts and techniques of organic chemistry can lead improving competence in many other fields [1]. At the same time and according to many publications, organic chemistry is perceived as a challenging and difficult undergraduate science course. Students prefer to resort to memorization in order to pass their exams and they are unable to reason [2-4].

Practical work is one of the effective ways to enhance students' knowledge and skills and the laboratory work has a rightful place in undergraduate courses, it helps students to get better understanding especially when the aim of the experimentations is clearly defined [5]. However, considerable time and money are spent on practical activities, this may limit its development in institutions with a financial shortfall [6]. In this case, microscale chemistry

seems to be an adequate way to solve this problem.

Indeed, microchemistry has been very well developed in high schools due to the efforts made by the National Microscale Chemistry Center (NMCC) in Boston which has released this concept with the support of the Environment Protection Agency (EPA) and has been able to generalize microchemistry to high schools in the United States. In other parts of the world, microscale chemistry is becoming increasingly prevalent in the curriculum. Recently, in India, a manual of the microscale chemistry laboratory was developed based on the national curriculum framework, highlighted the use of microscale chemistry techniques in schools [7].

At universities, despite the efforts made by some professors to integrate microchemistry experiments in practicals [8-11], there is very slow progress in setting-up this approach, according to Bradley [12] several factors are involved, among them, insufficient government support, resistance to change, non-adaptation to one's own context, etc. Additionally, Breuer has raised in his study the reasons why some people develop a resistance to the adoption of microscale chemistry, we quote, the low skillfulness of students, they don't meet standard equipment, the price of specific equipment required, the inadequacy with industry techniques and the negligence of safety on this scale [13].

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To solve these problems, the use of a new approach that combines micro and macrochemistry seems to be interesting. For this reason, we developed several experiment labs that mutually use macro and micro scale chemistry approaches. Our objective is to reduce the consumption of reagents and organic solvents, to work in a cleaner and more secure conditions and to allow students to become familiar with laboratory equipment and practices used in both industrial and research laboratories, especially that industrial analysis and control laboratories use small quantities to carry out their tests. Thereby, students should master both macro and micro techniques.

We evaluated the greenness of the developed experiments and assessed the students' perception regarding the relevance of introducing microchemistry in their learning process.

## 2. Experimental Section

### 2.1. General Procedures

Two sets of experiments were designed and implemented. The first one includes three experimentations whose main objective is to learn about aldol condensation, saponification and haloform reaction with a focus on the reaction mechanism studied in functional organic chemistry classes in semester 5. The second one is focused on the ecological aspect by applying the principles of green chemistry previously seen in green chemistry course thought in semester 6, specifically catalysis.

For all experiments, the reaction medium was conducted at the microscale, the rest of the operations were performed using conventional macroscale equipment and techniques.

0.1 to 1 gram of starting material were used. The reactions were carried out in small-scale glassware included conical flask of 10 mL or small pill container. Liquid reagents were often measured using 100 - 1000  $\mu$ L automatic micropipette or syringe with capacities ranging from 1 to 5 mL, and masses were measured using electronic balance with precise accuracy of 0.001 g.

For working up the reaction, classical equipment usually required in macroscale experiments were used. The product isolation operations and characterization were performed using conventional macroscale laboratory analysis techniques.

For the first set of experiments, the reaction products were solids and were collected by filtration using macroscale vacuum filtration apparatus and then washed with an appropriate solvent.

The recrystallization process was used to purify the obtained crude products (experience 1 and 3). During the purification steps, we used the smallest glassware generally available in a traditional organic chemistry laboratory and a classic laboratory hot plate.

For experiment 4 and 5, thin-layer chromatography (TLC) was used to monitor the progress of reactions. We used the

classic system with silica gel TLC plate immersed in the eluting solvent previously transferred into an Empty Jam jar. A small spot of products was sufficient to conduct the test.

The product of a reaction does not crystallize from the reaction mixture and was isolated by macroscale simple distillation using Rotary evaporator. We used a reduction adapter, to avoid transferring the reaction mixture to a larger container (evaporation flask) and therefore prevent the loss of the product.

To verify the purity of the product, we conducted a melting point analysis using a standard capillary melting point apparatus requiring only a few crystals trapped in the capillary tube to perform the analysis."

Once the purity has been verified, structure determination was accomplished by using UV/Vis and IR spectroscopies methods since they require a very small amount of product to carry out the tests. Table 1 presents the required material for the experiments and shows that a large part can be used on both scales.

**Table 1.** Materials, Glassware and apparatus required

	Macroscale	Microscale
Electronic balance (accuracy: 0.001 g)	√	√
Magnetic stirring hot plate	√	√
Micromagnetic stirring bar (10/5 mm)		√
Vacuum filtration apparatus	√	√
Thin-Layer Chromatography (TLC): silica gel TLC plates	√	√
Melting point apparatus (standard capillary tube method)	√	√
Rotary evaporator	√	√ *
UV-Visible spectrophotometer	√	√
IR spectrophotometer	√	√
pH-meter paper	√	√
<b>Glassware</b>		
Automatic micropipette 100-1000 $\mu$ L		√
Erlenmeyer flasks of 10 and 25 mL		√
Short-necked, round-bottomed of 25 mL		√
<b>Everyday materials</b>		
Empty Jam jars for TLC	√	√
Small pill containers		√
1.0 and 5.0 mL Syringe		√

\*: Rotary evaporator with reduction adapter.

In this experience, we were helped by post-graduate students acting as teaching assistants, they participated in all experiments to help students at their workplace.

The developed experiments require 2h to complete.

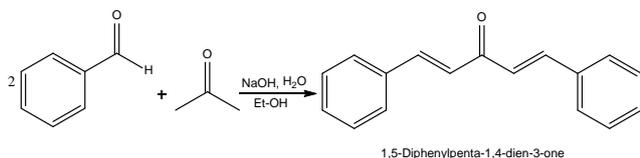
### Part I: Functional organic chemistry practical classes - Semester 5 -

#### Experiment 1: Synthesis of dibenzylideneacetone

The objective of this experiment is to carry out a double mixed-aldol condensation reaction between acetone and

benzaldehyde following scheme 1.

This reaction is qualified by Mestres [14] as the most powerful and best-known C–C forming synthetic reactions, it's widely used either in bulk production and in the fine chemical and pharmaceutical industry.



**Scheme 1.** Reaction Scheme of DBA synthesis

3 mL of NaOH (100 g/l) was added to 2.4 mL of 95% ethanol in a conical flask of 10 mL (A) or in a small pill container which can alternatively be used as reaction vessels.

In a covered conical flask of 10 mL (B) mixture containing 303  $\mu\text{L}$  (1.5 mmol) of acetone and 110  $\mu\text{L}$  (3 mmol) of benzaldehyde were prepared. Using a syringe of 5 mL, half of this mixture was transferred into the conical flask (A) and shaken vigorously until the appearance of a yellow precipitate after 2 or 3 minutes.

After 15 minutes, the rest of the mixture (B) was added while stirring, the conical flask was rinsed with approximately 2 mL of ethanol, the mixture was stirred for 20 minutes.

The product was filtered on a Buchner funnel and washed with ice water.

The obtained product was squeezed between sheets of filter paper to dry it, and then the crude dibenzalacetone was recrystallized using a minimum of 70:30 ethanol-water mixture.

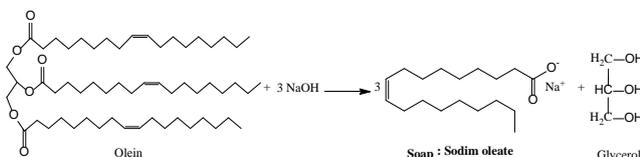
The purified product was dried in a preheated oven at 80 °C for 15 min.

The weight and yield of the product were determined.

Characterization: The melting temperature was determined, as well as the wavelength of maximum absorbance ( $\lambda_{\text{max}}$ ) using UV-Visible spectroscopy ( $2.10^{-4}$  M of DBA in Ethanol 95%).

### Experiment 2: Saponification of olive oil

The saponification reaction is shown in the scheme 2. Olive oil is composed of the mixed triglyceride esters of fatty acids. Olein is a triglyceride ester of oleic acid which represents the major saponifiable fraction.



**Scheme 2.** Saponification of olein

**Saponification Reaction:** In a 25 mL short-necked, round-bottomed flask, 1 mL of olive oil, 2 mL of NaOH solution (300 g/L) and 2 mL of 95% ethanol and a few granules of pumice stone were added; an air condenser was placed and the mixture was gently refluxed for 30 minutes, taking care not to boil away the ethanol.

**Precipitation of soap:** At the end of the reaction period, the mixture was transferred to a 10 mL Erlenmeyer flask containing a saturated NaCl solution (300 g/l).

**Filtration and drying:** The precipitated soap was collected on a Büchner funnel and washed thoroughly using distilled ice water to remove glycerol and excess sodium hydroxide. The obtained soap was pressed between several layers of filter paper till dry.

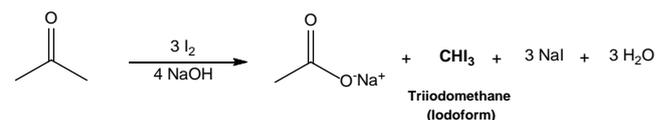
**Testing the Properties:** 5 g/l soapy solution has been prepared by dissolving 1 g of our laboratory made soap in 250 mL of Distilled water. This solution is kept in the refrigerator for future uses.

**Alkalinity measurement:** The pH of a soap solution was assessed using pH-meter paper.

**Krafft temperature measurement:** 100 mL of a soapy solution (previously prepared) has been placed in an ice-water bath for about 15 minutes before the test. The cooled solution was then introduced in a water bath provided with a magnetic stirrer and heated up gradually. The temperature at which turbidity disappeared and the foam begins to form was taken as the approximate Krafft temperature.

### Experiment 3: Synthesis of triiodomethane

Triiodomethane ( $\text{CHI}_3$ ) was prepared from propanone by the haloform reaction following scheme 3.



**Scheme 3.** Reaction Scheme of triiodomethane synthesis

In a 25 mL Erlenmeyer flask, 126  $\mu\text{L}$  (1.72 mmol) of acetone and 2 mL of deionized water is introduced, the mixture was stirred for 10 min; 2 mL of 5% NaOH was added, stirring was continued for 2 min; 2 mL of potassium iodide-iodine reagent (2g KI + 1g  $\text{I}_2$  dissolved in 10 mL of deionized water) was added dropwise; the mixture was kept stirring until stable coloration appeared.

**Recrystallization:** 2 mL of deionized water was added, and the solution was left for decantation for 5-10 min.

The yellow crystals were isolated by vacuum filtration on Buchner funnel and washed thoroughly using distilled water. The obtained product was dried at 100°C for 20 min.

**Characterization:** The melting temperature was determined as well as the wavelength of maximum absorbance ( $\lambda_{\text{max}}$ ) using UV-Visible spectroscopy ( $C = 1.2 \cdot 10^{-4}$  M of iodoform in ethanol).

## Part II: Green chemistry and clean processes practical classes - Semester 6 -

Natural phosphate (NP) was used as a heterogeneous catalyst for the following experiments.

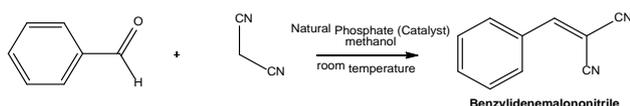
10 g of catalyst was prepared before starting class and were largely sufficient to conduct all practical work sessions. The catalyst was prepared following the same procedure published in our previous work [15]. Briefly, the fraction of 100 – 400  $\mu\text{m}$  grain size has been washed with

water, calcined at 900°C for 2 h, washed again, recalcined at 900°C for 0.5 h and finally grounded to obtain a fine powder with a particle size between 63 and 125  $\mu\text{m}$ . The catalyst can be stored in an oven at 150°C or kept in a desiccator.

#### Experiment 4: Synthesis of benzylidenemalononitrile

Benzylidenemalononitrile and its derivatives have been successfully used as an effective anti-fouling agent, fungicides, insecticides and cytotoxic agents against tumors or riot control agents [16,17]. Several researchers are always interested to explore new methods of synthesizing these interesting compounds, among them, our research laboratory published a single step synthesis of benzylidenemalononitrile in less than 10 minutes [18].

We synthesis benzylidenemalononitrile ( $\text{C}_{10}\text{H}_6\text{N}_2$ ) by the condensation of benzaldehyde and malononitrile at room temperature in methanol (Scheme 4). This synthesis occurs via Knoevenagel condensation.



**Scheme 4.** Reaction Scheme of benzylidenemalononitrile synthesis

In a 25 mL short-necked, round-bottomed flask equipped with a magnetic stirrer, 1.2 mmol of benzaldehyde (123  $\mu\text{L}$ ) and 1 mmol of malononitrile (0.066 g) were placed and stirred with 0.3 g of Natural Phosphate (catalyst) and 1 mL of methanol for 10 min at room temperature, after complete conversion of starting materials to product (TLC; hexane : ethyl acetate 9:1, v/v), 5 mL of methanol was added, the mixture was stirred, and catalyst was separated by filtration. The filtrate was concentrated by rotary evaporator to give a white residue, which was recovered for further analysis.

Characterization: The melting point was determined using a standard capillary tube method which requires less than a few milligrams of the sample. The wavelength of maximum absorbance ( $\lambda_{\text{max}}$ ) was determined by UV-Visible spectroscopy ( $10^{-4}$  M in methanol). IR spectrum of benzylidenemalononitrile was recorded in the range of 4000-400  $\text{cm}^{-1}$  using KBr pellets.

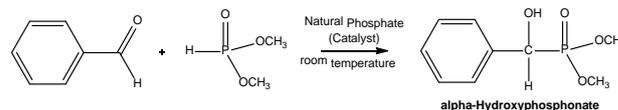
#### Experiment 5: Synthesis of $\alpha$ -Hydroxyphosphonate

$\alpha$ -Hydroxyphosphonates are a very important organophosphorus compound because of the potential biological activity of these derivatives. They are widely used in pharmaceutical and pesticide chemistry and enzyme inhibition [19].

The synthesis of  $\alpha$ -hydroxyphosphonate is conducted by direct condensation of benzaldehyde and dimethylphosphite following the reaction in scheme 5. This is a one-pot procedure, carried out at room temperature and catalyzed by NP as a reusable catalyst [20].

In a 25 mL short-necked, round-bottomed flask, 1 mmol of benzaldehyde (102.5  $\mu\text{L}$ ) and 1 mmol of dimethylphosphite (93.5  $\mu\text{L}$ ) were placed and stirred with 0.4 g of Natural Phosphate (catalyst), the mixture was

vigorously stirred with a spatula at room temperature and left for 30 min. 5 mL of dichloromethane was added, and the catalyst was filtered off. The filtrate was concentrated by rotary evaporator to give a residue (the product) which was recovered for further analysis.



**Scheme 5.** Reaction Scheme of  $\alpha$ -Hydroxyphosphonate synthesis

Characterization: The melting temperature was determined using a standard capillary tube. The wavelength of maximum absorbance ( $\lambda_{\text{max}}$ ) was determined by UV-Visible spectroscopy ( $10^{-4}$  M in ethanol). The IR spectrum of  $\alpha$ -Hydroxyphosphonates was recorded in the range of 4000-400  $\text{cm}^{-1}$  using KBr pellets.

## 3. Results and Discussion

### 3.1. Reactions Yield

Through the results obtained in table 2, we noticed that despite the low quantities used of the starting materials, the products are obtained in reasonable quantities. However, a decrease in yield was observed due to the reduced scale. The rate of this decrease depends on the experimental protocol followed in each experiment.

**Table 2.** Comparison of microscale versus micro-macroscopic reactions yield

Experiments	Micro-macroscopic			Macroscopic
	$m_{\text{exp}}$ (g)	$m_{\text{the}}$ (g)	Yield (%)	Yield (%)
1. synthesis of dibenzylideneacetone	0,150	0,351	43	68 [21]
2. saponification of olive oil	0,213	0,928	23	78 [22]
3. synthesis of triiodomethane	0,101	0,677	15	20 [23]
4. synthesis of benzylidenemalononitrile	0,124	0,154	80	-
5. synthesis of $\alpha$ -Hydroxyphosphonate	0,108	0,216	50	-

### 3.2. Environmental Assessment

Carbon Efficiency, Atom Economy, Reaction Mass Efficiency and E-Factor are the parameters used to compare the environmental performance of the developed experiments.

The Green Star metric was also considered to assess the benignness of experiments by considering simultaneously all of the principles of green chemistry.

#### 3.2.1. Carbon Efficiency

The carbon efficiency (CE) is calculated as the weight ratio of the number of carbon atoms of the product to that of the reactants (equation 1).

$$CE = v_p n_c(P) / \sum v_R n_c(R) \quad (1)$$

Were  $n_c(P)$  is the number of carbon in a product;  $n_c(R)$  is the number of carbon in reactants and  $v_p$  et  $v_R$  are stoichiometric coefficients of the product and reactants respectively.

As indicated in figure 1, a value of 1 has been recorded for Aldol reaction, Knoevenagel condensation and phospho-aldol reaction which indicates no disappearance of carbon compounds in the byproducts. A very low carbon loss of CE is registered for saponification reaction due to the formation of glycerol as a byproduct.

The lowest value of 0.33 is recorded for the haloform reaction that generates carboxylate ion in addition to the desired haloform.

### 3.2.2. Atom Economy

Trost stated in his article, that the Atom Economy (AE) of a chemical reaction measures the number of atoms in the reactants that end up in the final product [24].

$$AE = v_p MW_p / \sum v_R MW_R \quad (2)$$

$MW_p$ : Molecular weight of the product.

$MW_R$ : Molecular weight of reactants.

$v_p$  et  $v_R$ : stoichiometric coefficients of the product and reactant respectively.

From the figure 1, it can be seen that aldol reaction, saponification, Knoevenagel condensation (C-C) and phospho-aldol reaction (C-P) are atom-economic reactions, their AE values are close to 1.

The haloform reaction is not atom economical, only 48% of the mass of the reactants ends up in the desired product. This reflects a large amount of waste product produced in water, sodium acetate and sodium iodide. We can describe this reaction as a wasteful reaction.

### 3.2.3. Reaction Mass Efficiency

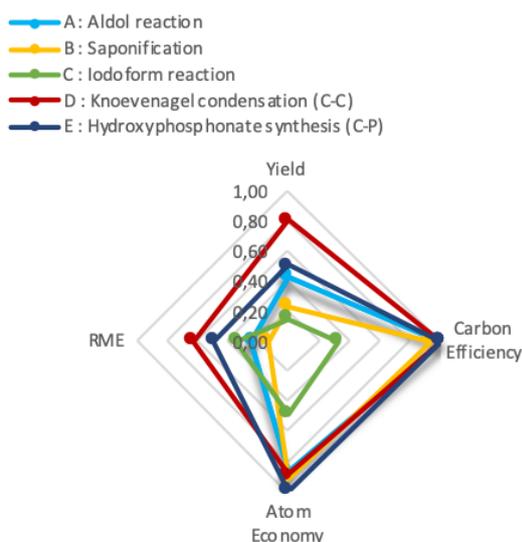


Figure 1. Green metrics for the implemented experiments

Reaction Mass Efficiency (RME) was mentioned for the first time by Clark in 1999 [25], to describe green practices.

The general expression for reaction mass efficiency (RME) is given by equation 3.

$$RME = mp / \sum mR \quad (3)$$

Where  $mp$  is the mass of the product (Kg) and  $mR$  is the mass of reactants (Kg).

An RME of 1 means that there was both 100% of yield and no loss of atoms.

It is apparent from figure 1 that Knoevenagel condensation and phospho-aldol reaction scored the highest values of 0.63 and 0.49 respectively, this is partially due to the recycling of the catalyst. For the rest of the experiments, low values are recorded, 0.14 for the saponification and 0.3 for aldol and iodoform reactions.

### 3.2.4. E-Factor

Sheldon proposed the E-Factor (E) parameter in the late 1980s [26] and considered it as the most and popular parameter used to assess the environmental impact of manufacturing processes and to illustrate the problem of waste in different segments of the chemical industry. It can be calculated as illustrated in equation 4.

$$E\text{-Factor} = \text{Waste (Kg)} / \text{Product (Kg)} \quad (4)$$

The amount of waste can be determined by calculating the difference between the entrants' mass and the desired product's mass. The post-reaction treatment was included in the calculation. Recyclable materials such as catalyst (NP) are not considered as waste and thus ignored.

According to Sheldon, a higher E-factor means more waste and, consequently, greater negative environmental impact. The best organic synthesis is one that produces no waste and its E-factor equals zero.

A mass balance of products and waste for each experiment was carried out, the results in table 3 showed that the higher value of E-factor was registered for Knoevenagel condensation and phospho-aldol reaction which generates respectively 94.12 and 126 Kg of waste per Kg of product. These values fall within the E-factor range specific to the pharmaceutical industry (25 - >100) [27]. These high values are mainly due to a large amount of solvent used for pure product recovery. The solvents recovery for subsequent recycling is essential to reduce the E-factor. In the future, we plan to recycle solvents as much as possible.

For the saponification reaction, 28.8 kg of waste is generated to produce 1 kg of soap.

Table 3. E-factor

	E-factor
Aldol reaction	15.85
Saponification	28.8
Iodoform reaction	6.84
Knoevenagel condensation	94.12
Phospho-aldol reaction	126

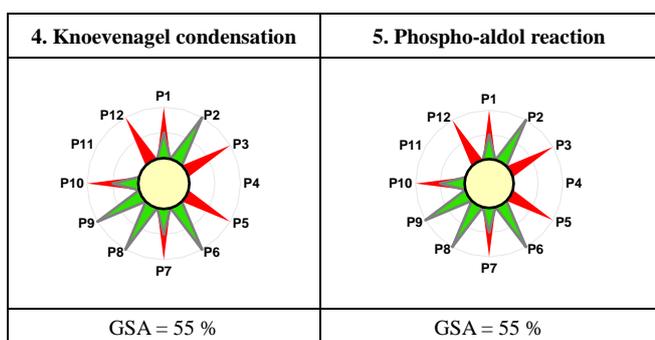
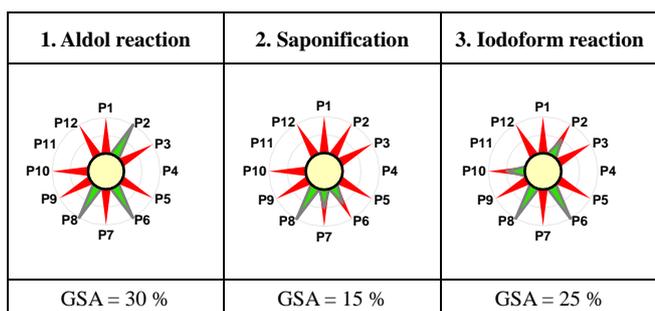
The formation of glycerol with soap caused the increase of this parameter. The recovery of glycerol from soap should be considered in order to reduce substantially the E-factor of the saponification reaction since it is considered a major industrial raw material.

For aldol condensation, 15.85 kg of waste was produced for 1 kg of dibenzylideneacetone. This amount of waste is attributed to the solvents and auxiliary materials used in the reaction.

The lowest value of the E-factor was recorded for the iodoform reaction, 6.84 Kg of waste per Kg of triiodomethane ( $\text{CHI}_3$ ). Waste production is mainly due to the use of excess NaOH and Iodine ( $\text{I}_2$ ) with the **formation** in addition to the desired product, Sodium iodide (NaI) and Sodium acetate ( $\text{CH}_3\text{COONa}$ ). Water molecules were not considered waste.

### 3.2.5. Green Star Metric

The Green Star is a holistic metrics graphic developed by Ribeiro et al., [28] for evaluation of the global greenness of chemical reactions used in teaching laboratories by evaluating the accomplishment of each of the 12 principles of green chemistry.



P1: Prevention, P2: Atom Economy, P3: Less hazardous chemical synthesis, P5: Safer solvents and auxiliary substances, P6: Increase energy efficiency, P7: Use renewable feedstocks, P8: Reduce derivatives, P9: Catalysts, P10: Design for degradation, P12: Safer chemistry for accident prevention.

**Figure 2.** Green Stars of the developed experiments

The construction of the graphical representation of GS was described in detail by Ribeiro et al., [29]. First, we made an inventory of all the substances involved in each experiment: reactants, products, byproducts, solvents, catalyst, etc. We thus assign scores of 1 to 3 to each

substance according to the information on the hazards to human health and the environment, the potential chemical accidents for each substance, as well as renewability and tendency to break down into innocuous degradation products (Table S1).

The needed information's were collected from safety data sheets (SDS) obtained in WEB (Sigma Aldrich and Merck Chemicals). The Criteria and scores to construct the GS are described by Ribeiro et al., [29].

A Green Star Area Index (GSAI) is calculated as a percentage of green area of the green star/area of the green star of maximum greenness [29]. Its values vary from 0 (minimum greenness) to 100 (maximum greenness).

For each experiment, the GS was constructed, the results are presented in figure 2.

The visual comparison of the five GS shows that experiments 4 and 5 are greener than experiments 1, 2 and 3.

The values for GSAI included in figure 2 confirm the visual evaluation of the GS.

For all the experiments, the chemical safety (P3, P5, and P12) has to be improved to avoid accident in laboratory. We foresee in future studies, the possibility of replacing dangerous products by safer ones (substitution of dichloromethane by 2-methyltetrahydrofuran).

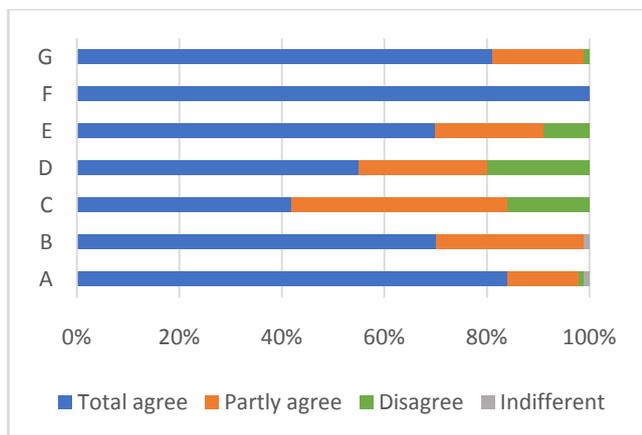
### 3.3. Student's Perception toward Microscale Organic Chemistry Experimentations

79 students having followed macro and microscale experiments, filled the questionnaire at the end of the practical sessions. The students' responses are presented in figure 3.

84% of students are in a total agreement that performing organic macro and microscale experiments is highly interesting and 70% consider that practical work allows them to gain a better understanding of theoretical aspects studied in class. This confirmation is very important since organic chemistry is perceived by many students as a very difficult area [30]. These findings were similar to those of Mashita et al. [31], who raised the importance of using microscale chemistry experimentation in secondary school, to enhance student's understanding of chemistry concepts. Comparable observations were made by Hanson et al. [32] who showed that the micro chemistry approach made chemistry lessons interesting in university classrooms.

It was also important to see that 70% of students consider the learning environment safe and convenient. They use a very small amount of solvents and other organic compounds that can be nauseating and narcotic especially when the hoods are not efficient. No smell was perceived in all practical sessions which is almost impossible in our previous organic chemistry lab.

55% find easy to handle microscale equipment as well as a small amount of chemicals, for the rest of the students we planned, in the next practical sessions, an introductory session to familiarize them with small equipment and small quantities.



**Figure 3. Survey Results:** A: The introduction of macro and microscale experiments in organic practical work is highly interesting. B: The macro and microchemistry practical works allows to gain a better understanding of theoretical aspects studied in class. C: The work time is sufficient. D: Handling easily micro instruments as well as a very small amount of materials. E: The conditions are better than classical practical works in terms of work organization, security, chemical compounds smell, cleanliness of the bench, supervision, etc. F: More macro-microscale organic chemistry experimentations should be integrated into the curriculum. G: Generalizing this approach to other practical chemistry teaching

In addition to the set questions, the questionnaire allowed for free comment on the advantages and disadvantages of the experiments.

Analysis of results revealed that student's perceptions were strongly positive. Here are the advantages raised:

- The macro-microscale experiments provide better conditions than classical chemistry practical works: cleanliness, no chemical smell, work organization.
- Using small quantities of chemicals can potentially save costs, holds safety, preserve health and save the environment as well.
- Being able to handle small glassware and small quantities of chemicals.
- Having the opportunity to repeat the experiment when the reaction does not work well.
- Better control of organic syntheses when the amount of chemicals is small.
- Saving time and generating less waste.
- Making a link between the theoretical teachings and our real-life issues.

As for the disadvantages, 44 % of students reported no disadvantages. for the rest, here are the raised comments:

- Microscale chemistry is not known and needs to be promoted further.
- Because of the small quantities, there is low visibility of what is going on (6 of the 79 students)
- Difficulties in handling small glassware and small quantities of chemicals.

Finally, the use of macro and microscale experiments allowed us to reduce the duration of the practical works from four to two hours. We asked the students to write their lab-reports and return it at the end of the session which led 16% of them to confirm that the duration is not sufficient.

It appears that 81% of students are in favor of generalizing this approach to all practical chemistry teaching.

### 3.4. Specific Laboratory Handling Rules

In addition to the classical rules commonly used in an organic chemistry laboratory, specific practices are to be considered.

**Material Cleanliness:** The smooth running of the reaction is conditioned by a very clean material. The presence of impurities can reduce the percent yield and sometimes inhibits the reaction. The glassware should be rinsed 3 times with deionized water and then rinsed with acetone and dried in an oven, excepting volumetric material, we let them air dry.

**Weighing solids:** Glass weighing boat is highly recommended. We should never use filter paper as containers, the weighed material will stick with the fibers of the filter paper which will lead to a significant loss of mass.

**Handling liquids:** Automatic micropipette is the key equipment for successful experiments, it allows the sampling and the transfer of solutions. Syringe can also be used for transferring solutions to the reaction flask. These equipments should be kept clean after every use to avoid any possible contamination.

### 3.5. Safety and Waste

We did not raise any particular safety precautions to be taken into consideration. Students should wear standard safety equipment, such as laboratory coat, safety glasses, and gloves.

Solvent wastes were collected in a non-halogenated organic solvents waste container, except for the dichloromethane which was transferred into a container for halogenated organic solvents.

## 4. Conclusions

The developed experiments are easy to implement and require equipment often available in organic chemistry labs with very low consumption of chemicals. Through the use of small amounts of chemicals, the reactions proceed quickly and generate less waste which is beneficial both financially and environmentally.

Significant improvements can be made in almost all undergraduate organic chemistry practical class which require a large quantity of very often dangerous organic solvents and a large amount of reagents. By adopting this teaching strategy, the laboratory becomes less consumer of chemicals, cleaner, more secure and less pollutants while ensuring students' better adherence to the practical learning process.

To compare the efficiency of the experiments, several green metrics are calculated. It appears from the results that aldol reaction, Knoevenagel condensation, and phospho-aldol reaction showed the best environmental profile, while, haloform reaction and saponification

showed the lowest environmental performance because of byproducts.

Thus, the mutual use of macro and microscale chemistry in the same experiment allows not only the achievement of educational objectives in convenient conditions, but it also

brings students closer to micro and macro techniques usually practiced in both industrial and research laboratories. Through this work, we showed that it is possible to benefit from the advantages of mixed approaches in the same experiment.

## Supporting Information

**Table S1.** Scores attributed to hazards

**Experiment 1:** Synthesis of dibenzylideneacetone

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Stoichiometric reagents</b>				
Benzaldehyde	H227, H302	2	0	2
Acetone	H225, H319, H336	2	0	3
<b>Auxiliary substances</b>				
Ethanol	H225, H319	2	0	3
Sodium Hydroxide	H290, H314	3	0	2
<b>Product</b>				
Dibenzylideneacetone	NA*	0	0	0
<b>Waste</b>				
Sodium Hydroxide	H290, H314	3	0	2
Ethanol	H225, H319	2	0	3

\*: Not Applicable

**Experiment 2:** Saponification of olive oil

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Stoichiometric reagents</b>				
Oleine	NA	0	0	0
Sodium hydroxide	H290, H314	3	0	2
<b>Auxiliary substances</b>				
Ethanol	H225, H319	2	0	3
NaCl	NA	0	0	0
<b>Product</b>				
Soap : Sodium oleate	NA	0	0	0
<b>Waste</b>				
Glycerol	NA	0	0	0
Sodium hydroxide	H290, H314	3	0	2
NaCL	NA	0	0	0

**Experiment 3:** Synthesis of triiodomethane

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Stoichiometric reagents</b>				
Acetone	H225, H319, H336	2	0	3
Iodine	H312, H332, H315, H319, H335, H372, H400	3	3	0
<b>Auxiliary substances</b>				
Sodium hydroxide	H290, H314	3	0	2

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Product</b>				
CHI <sub>3</sub>	H302, H312, H332, H315, H319, H335	2	0	0
<b>Waste</b>				
CH <sub>3</sub> COONa	NA	0	0	0
NaI	H315, H319, H400	2	3	0
Sodium hydroxide	H290, H314	3	0	2

**Experiment 4: Synthesis of benzylidenemalononitrile**

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Stoichiometric reagents</b>				
Benzaldehyde	H227, H302	2	0	2
Malononitrile	H301, H311, H331, H410	3	3	0
<b>Auxiliary substances</b>				
Methanol	H225, H301, H311, H331, H370	3	0	3
Natural phosphate	NA	0	0	0
<b>Product</b>				
Benzylidenemalononitrile	H302, H312, H332, H319, H335	2	0	0
<b>Waste</b>				
Methanol	H225, H301, H311, H331, H370	3	0	3

**Experiment 5: Synthesis of  $\alpha$ -Hydroxyphosphonate**

Reagents	Hazards			
	Hazard codes	Health (S)	Environment (S)	Physical (S)
<b>Stoichiometric reagents</b>				
Benzaldehyde	H227, H302	2	0	0
Dimethylphosphite	H317, H341, H351, H412	3	2	0
<b>Auxiliary substances</b>				
Dichlorometahne	H315, H319, H336, H351	3	0	0
Natural Phosphate	NA	0	0	0
<b>Product</b>				
$\alpha$ -hydroxyphosphonate	NA	0	0	0
<b>Waste</b>				
Dichlorometahne	H315, H319, H336, H351	3	0	0

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