

Using Green Star Metrics To Optimize the Greenness of Literature Protocols for Syntheses

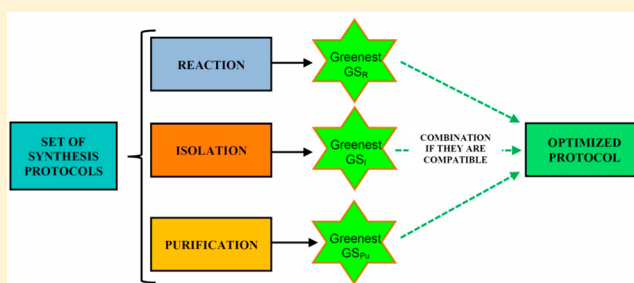
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S Supporting Information

ABSTRACT: A procedure to improve the greenness of a synthesis, without performing laboratory work, using alternative protocols available in the literature is presented. The greenness evaluation involves the separate assessment of the different steps described in the available protocols—reaction, isolation, and purification—as well as the global process, with the tool green star. This proved to be adequate to assess separately the microgreenness of the steps. Two case studies, the syntheses of ethyl acetate and manganese(III) acetylacetonate, are presented. The results show how the different steps limit the global greenness of the synthesis and suggest that the workup may be more problematic than the reaction itself. Moreover, the study showed that the green star can be used for comparing in detail the alternative protocols proposed for a synthesis, finding the best alternative for each step and allowing the design of a greener protocol by combining them.

KEYWORDS: Second-Year Undergraduate, Safety/Hazards, Green Chemistry, Reactions, Synthesis, Problem Solving/Decision Making



INTRODUCTION

The main objective of green chemistry is the design of chemical products and processes that reduce/eliminate the synthesis and use of hazardous substances and other deleterious impacts on the environment and human health.^{1–4} At the academic level, it is essential that chemistry students acquire a vision of chemistry in a global Science–Technology–Society (STS)⁵ context and be aware of how green chemistry is important to support sustainability. Indeed, at present, the use and production of hazardous substances and the output of huge amounts of residues, which means lost natural resources, are major concerns regarding sustainable development that green chemistry can help to overcome.⁶ With reference to this objective, a better teaching practice than prescribing standard protocols for synthesis experiments in the laboratory involves the students in the analysis of the greenness of existing alternative protocols for a synthesis before undergoing experimental work to improve it. These considerations resulted in a study in progress, where synthesis protocols from the literature are assessed by students with a holistic metric, the green star, in experiments to optimize the greenness.^{7–9} In general, synthesis reactions are complex systems that involve not only the stoichiometric reagents but also large amounts of several auxiliary substances, such as solvents, auxiliary reagents, etc. These provide no atoms to the product and constitute residues, therefore limiting the greenness of the global synthesis processes. In particular, the large amounts of solvents often used in synthesis have strong negative impacts on the global greenness. Solvents are usually used in larger amounts in the

workup steps (final isolation and purification of the product) than in the reaction.^{10,11} In our previous work,^{7–9} it eventually became clear that it was necessary to assess separately the several steps of the synthesis to fully understand how each of them limits the greenness. Often, as shown in Figure 1, synthesis procedures used in school laboratories involve two stages (“stage” is a series of successive operations to yield an isolated product¹²) and three steps (reaction, isolation, and purification).

The first stage includes the reaction (R) and the isolation (I) steps, and the second is the step for purification (Pu) of the product. Figure 1 includes the types of materials used in each step, showing an uneven distribution between the reaction and the workup. The greenness of the global process (G) is influenced differently by each of the three steps. Apparently, this situation is not often given enough attention in laboratorial green syntheses, and therefore, it was decided to look for systematic procedures suitable to make students more aware of the issue. In this search, the idea emerged that a practical way to optimize the greenness of a synthesis, when several alternative protocols were accessible in the literature, would be to assemble a protocol greener than the existing ones by looking for the greenest procedure of each of the three steps to constitute a new greener alternative to be used as the starting protocol for the laboratory experiment. This paper reports the exploration of this idea, which was focused on the assessment of the adequacy of the green star metric for the purpose.

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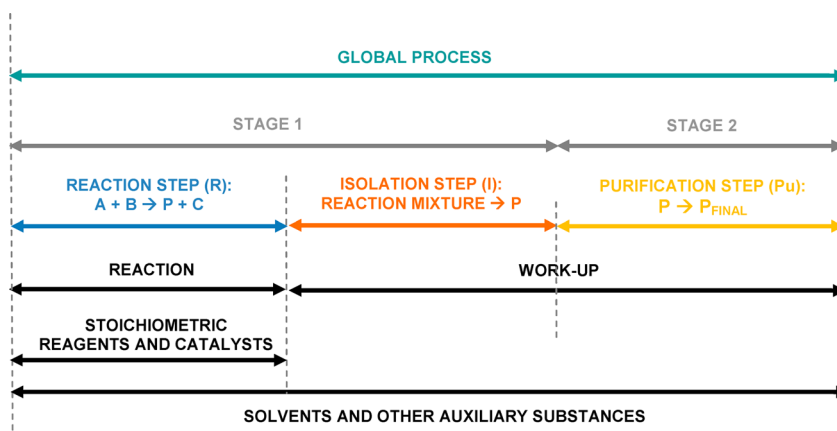


Figure 1. Graphical representation of the model used to define the steps and stages of a synthesis and reagents involved in each: A,B stoichiometric reagents; P product; C byproducts.

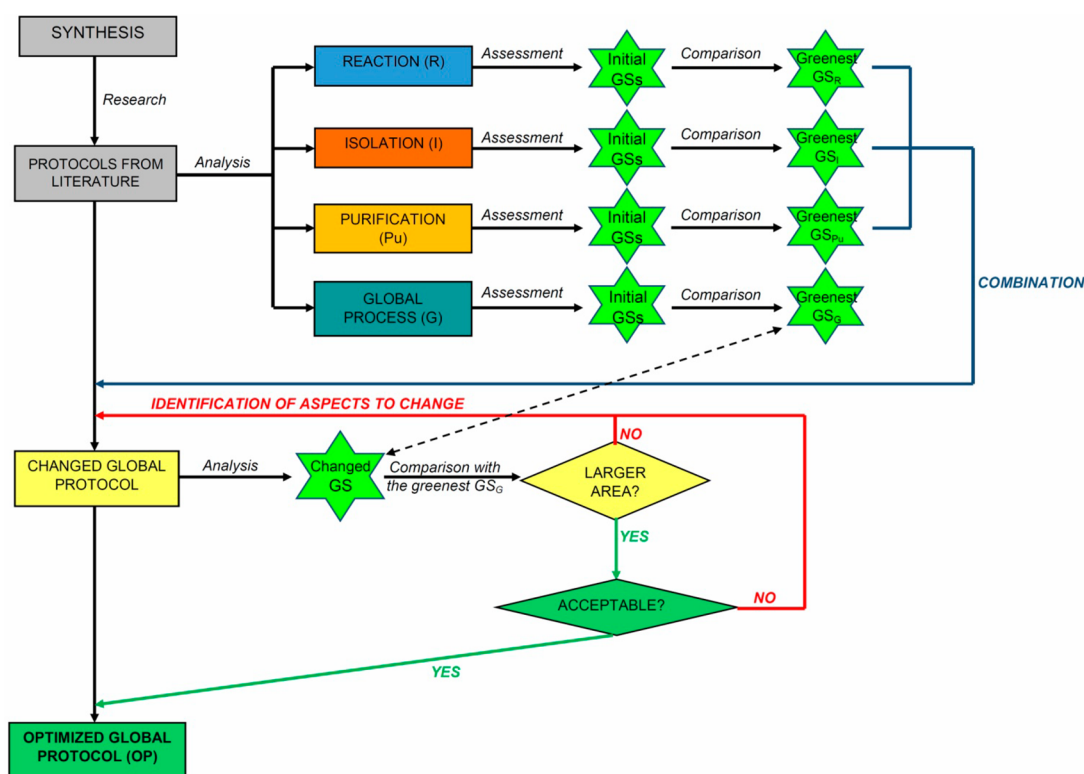


Figure 2. Methodology used to optimize several protocols of the synthesis: GSs, green stars of several procedures; GS_R, the greenest green star of the reaction step; GS_I, the greenest green star of the isolation step; GS_{Pu}, the greenest green star of the purification step; GS_G, the greenest green star of the global process.

More precisely, the main objective of this work was to assess whether an a priori optimization of synthesis protocols is possible based on data from the literature for this procedure. The usefulness of the green star for the greenness assessment of the three steps separately was investigated first. Once the suitability of the green star for this purpose was confirmed, another objective of the work was the evaluation of the relative importance of the three steps above for the global greenness of the synthesis, which required an analysis of how the partial and the global stars are inter-related. Two case studies showing how this methodology works and the type of results it produces are presented below.

METHODOLOGY

The methodology used in the work is presented in Figure 2.

First, different protocols for a synthesis were collected and analyzed, and their greenness was assessed and compared using the green star.¹³ This metric uses the 12 principles of green chemistry¹⁴ to evaluate the greenness and is constructed giving the scores 1, 2 or 3 (the maximum value of greenness, assessed in three levels) to each of the principles following the criteria defined before^{7–9,13} (details in Supporting Information, Table 3S). The star is represented in an Excel radar chart, with the color green (over a red background) of the length of each corner of the star being used to show the degree of accomplishment, 1–3, of the corresponding principle.

Table 1. Principles of Green Chemistry Used in the Evaluation of the Synthesis Reactions and Nonreactive Operations

principle	description	synthesis reaction (10 corners)	nonreactive operations (6 corners)
P1, prevention	It is better to prevent waste than to treat or clean up waste after it has been created.	X	X
P2, atom economy	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.	X	
P3, less hazardous chemical synthesis	Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.	X	
P4, designing safer chemicals	Chemical products should be designed to effect their desired function while minimizing their toxicity.		
P5, safer solvents and auxiliary substances	The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.	X	X
P6, increase energy efficiency	Energy requirements of chemical processes should be recognized for their environmental and economic impacts should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.	X	X
P7, use renewable feedstocks	A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.	X	X
P8, reduce derivatives	Unnecessary derivatization (use of blocking groups, protection/deprotection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible because such steps require additional reagents and can generate waste.	X	
P9, catalysts	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.	X	
P10, design for degradation	Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.	X	X
P11, real-time analysis for pollution prevention	Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.		
P12, safer chemistry for accident prevention	Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents including releases, explosions, and fires.	X	X

The evaluation was made by considering separately the three steps, reaction, isolation and purification of the product as well as the global process. In principle, the green star evaluation of greenness is based on the 12 principles, but in teaching synthesis experiments, some of these are not used. In general, for the reaction step, only 10 are assessed: principles P4 (designing safer chemicals) and P11 (real-time analysis for pollution prevention) are not applied because no new products are prepared (P4) and process monitoring for real-time analysis for pollution prevention is not used (P11). On the other hand, the steps of isolation and purification of the product generally involve no reaction, only physical operations, and therefore, principles P2 (atom economy), P3 (less hazardous chemical synthesis), P8 (reduce derivatives), and P9 (preference for catalysts) are also not applicable—only six principles are assessed.¹³ In summary, two types of green stars are used, depending on the principles involved in the evaluation: 10 corner stars for the reaction and six corner stars for the workup operations. Table 1 shows the principles used in the evaluation of the synthesis reaction (10 corners) and nonreactive operations (isolation, purification, etc., six corners).

After comparison of the results of these evaluations for the alternative protocols found in the literature, the greenest green stars for the reaction, isolation, and purification were selected and combined to create a new, and supposedly greener, global protocol. The greenness of this new protocol was evaluated, and the resulting green star was compared with the greenest green star of the initial global protocols to confirm that an optimized global alternative was indeed achieved.

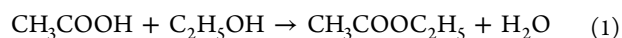
CASE STUDIES

The syntheses presented are carried out in the courses of Laboratory of Organic Chemistry¹⁵ and Laboratory of Chemistry III of Chemistry BSc courses in two Portuguese universities.¹⁶ Protocols (PrX, X = A–K, Table 2, for the synthesis of ethyl acetate,¹⁵ and X = A–G, Table 3, for the

synthesis of manganese(III) acetylacetonate¹⁶) were collected from the Web sites of the courses, as well as others published in scientific journals, textbooks of preparative chemistry experiments, and also from Internet pages of other universities in different countries (see references in Tables 2 and 3). Upon a global analysis of the protocols, the evaluation and comparison of the greenness of the syntheses were made with the green star.¹³ These two cases are part of a study involving 20 organic and inorganic syntheses in which 210 protocols were assessed (a list of the compounds is provided in the Supporting Information, Table 39S).

Synthesis of Ethyl Acetate

The synthesis of ethyl acetate is a simple and very popular preparation often used in organic chemistry laboratories.^{17–19} Of the 11 protocols found,^{15,17–24} five were collected from university Web pages,^{15,20–23} five from Organic Chemistry experimental textbooks,^{15–17} and one from a scientific journal.²⁴ All of these protocols use the reaction



Ten different procedures for the reaction step (R₁–R₁₀, Table 2) were found. The procedures R₁–R₇ differ only in the excess of stoichiometric reagent used and/or the reaction temperature. The procedures R₈–R₁₀ differ from R₁–R₇ only in the catalysts. For the workup, 10 different procedures for the isolation of the product (I₁–I₁₀) and one for purification (Pu₁) were identified. The isolation procedures differ in the washing solvents used (or the concentrations of their solutions) and whether or not a distillation is performed at the beginning of this step (Table 2). The purification, when prescribed, is the same for all of the protocols (Table 2).

The stars of the greenness assessment for the various protocols, detailed for each of the three steps (R, I and Pu) and for the global process (G), the criteria used in the construction of the green star, the hazards and scores of all substances involved, and the scores obtained to construct all the green

Table 2. Summary of the Analyzed Protocols for the Synthesis of Ethyl Acetate^a

PrA ¹⁵	Reaction (R ₁): stoichiometric proportions of ethanol and glacial acetic acid, cooling (ice bath) sulfuric acid (catalyst), reflux, <i>T</i> < 100 °C Isolation (I ₁): simple distillation → washing (10% sodium carbonate solution → calcium chloride solution) → drying (anhydrous calcium chloride) → filtration (gravity) Purification (Pu ₁): simple distillation
PrB ¹⁷	Reaction (R ₁): ≡ PrA (scale enlarged to double) Isolation (I ₂): simple distillation → washing (30% sodium carbonate solution → calcium chloride solution) → drying (anhydrous calcium chloride) → filtration (gravity) Purification (Pu ₁): ≡ PrA
PrC ¹⁷	Reaction (R ₂): ≡ PrA (reflux, but <i>T</i> < 100 °C is used) Isolation (I ₃): ≡ PrB (simple distillation, but decantation instead of filtration is used) Purification (Pu ₁): ≡ PrA
PrD ²⁰	Reaction (R ₃): 96% exc. ethanol, sulfuric acid (catalyst), simple distillation, <i>T</i> ~ 150 °C Isolation (I ₄): washing (saturated sodium carbonate solution → calcium chloride solution) → drying (anhydrous calcium chloride) → filtration (gravity) Purification (Pu ₁): ≡ PrA
PrE ¹⁸	Reaction (R ₄): 10% exc. ethanol, sulfuric acid (catalyst), simple distillation, <i>T</i> ~ 140 °C Isolation (I ₄): ≡ PrD Purification (Pu ₁): ≡ PrA
PrF ²¹	Reaction (R ₅): 23% exc. glacial acetic acid, sulfuric acid (catalyst), reflux, <i>T</i> ~ 100 °C Isolation (I ₅): simple distillation → washing (saturated sodium carbonate solution) Purification: not prescribed
PrG ²²	Reaction (R ₆): ≡ PrF (reflux, but <i>T</i> < 100 °C is used) Isolation (I ₆): washing (saturated sodium carbonate solution) → decantation Purification (Pu ₁): ≡ PrA
PrH ¹⁹	Reaction (R ₇): stoichiometric proportions of ethanol and glacial acetic acid, sulfuric acid (catalyst), simple distillation, <i>T</i> ~ 140–160 °C Isolation (I ₇): washing (dilute sodium carbonate solution) Purification: not prescribed
PrI ²³	Reaction (R ₈): 22% exc. ethanol, hydrochloric acid (catalyst), anhydrous calcium chloride (auxiliary substance), reflux, <i>T</i> < 100 °C Isolation (I ₈): simple distillation → washing (saturated sodium chloride solution → saturated sodium carbonate solution → 45% calcium chloride solution) → drying (anhydrous calcium chloride) Purification (Pu ₁): ≡ PrA
PrJ ¹⁸	Reaction (R ₉): 30% exc. ethanol, hydrogen chloride (catalyst); sulfuric acid (auxiliary substance), cooling (ice bath) Isolation (I ₉): washing (cold water → sodium carbonate solution) → drying (anhydrous sodium sulfate) → decantation Purification (Pu ₁): ≡ PrA
PrK ²⁴	Reaction (R ₁₀): 100% exc. glacial acetic acid, DTPA ^b / K10 ^c (catalyst), reflux, <i>T</i> < 100 °C Isolation (I ₁₀): filtration Purification: not prescribed

^aPr, protocol. ^bDTPA, dodecatungstophosphoric acid. ^cMontmorillonite K10; → sequential.

stars for all protocols, are presented in the Supporting Information (Figure 1S and Tables 1S–25S).

In some of the protocols (abbreviation Pr), only a simple distillation is prescribed, either in the reaction step (PrH) or in the isolation (PrF) or purification (PrG and PrJ) steps. In protocols A, B, C, and I, distillations are prescribed in both the isolation and the purification steps. Protocols D and E prescribe distillation in both the reaction and the purification steps, and in protocol K, no distillation is prescribed, with the reaction mixture being only refluxed. These details are important because distillations affect, in opposite directions, the quality of the product and the greenness of the workup and of the global protocol (obtained by combination of steps from different protocols). The discussion below shows how complex it is to deal with the workup to obtain simultaneously quality of product and greenness of the synthetic procedure. From the assessment, it was concluded that the greenest procedures for each of the steps are reactions R₁ (reflux, PrA and PrB) and R₂ (reflux, PrC), with GSAI = 30; isolation, I₇ (washing, PrH, GSAI = 50); and purification, Pu₁ (simple distillation, GSAI = 42) (details in Supporting Information). The greenest global protocols are the protocols F (R₅, reflux, I₅ simple distillation) and H (R₇, simple distillation, I₇, washing) with GSAI = 25, where no purification is prescribed (Figure 3).

For these protocols, the global green star is equal to the reaction star (GSAI = 25) because the isolation step does not have any influence on the global greenness. Indeed, the principles assigned with green corners (P1, P2, P6, and P8) in the reaction stars either correspond to green corners in the isolation star (P1 and P6) or are not assessed in the isolation star (P2 and P8).

A first optimization, OP1 (OP, from Optimized Procedure), is obtained by combining the greenest procedures for the reaction and isolation steps R₁, R₂, and I₇ (Figure 4, top), but in all of these procedures, no distillation is prescribed; purification was not included as in protocols F and H, the greenest ones, where a simple distillation was included in the isolation (PrF, I₅) or reaction (PrH, R₇) step (Figure 3).

This combination provides a slightly greener protocol (but predictably with quality of the product decreased) than those from the literature, with the global star having GSAI = 30, above the value for protocols F and H (GSAI = 25), the greenest in Table 2.

A second optimization, OP2 (Figure 4, middle), with the same global greenness, is obtained by substituting in OP1 the isolation step I₇ with I₅ (a distillation is included in this isolation step). The greenness of I₅ is more limited than the greenness of I₇ because the principles P5 and P6 of the green

Table 3. Summary of the Analyzed Protocols for the Synthesis of Manganese(III) Acetylacetonate^a

PrA ¹⁶	Reaction (R ₁): eq 2, 122% exc. acetylacetone, water, and sodium acetate (auxiliary substances), <i>T</i> ~ 60–70 °C Isolation (I ₁): filtration (suction) → washing (cold water) → drying (desiccator over anhydrous calcium chloride) Purification (Pu ₁): recrystallization–dissolution (cyclohexane, petroleum ether) → reflux (water bath) → cooling (ice bath) → filtration (suction) → washing (cold petroleum ether) → drying (air)
PrB ²⁵	Reaction (R ₂): ≡ PrA (but 113% exc. acetylacetone is used) Isolation (I ₂): filtration (suction) → washing (water) → drying (air) Purification (Pu ₂): recrystallization–dissolution (cyclohexane, petroleum ether) → reflux (steam bath) → cooling (slowly) → filtration (suction) → drying (air)
PrC ²⁶	Reaction (R ₃): ≡ PrA (but 104% exc. acetylacetone is used) Isolation (I ₁): ≡ PrA Purification: not prescribed
PrD ²⁷	Reaction (R ₄): ≡ PrA (but 108% exc. acetylacetone and <i>T</i> ~ 100 °C are used) Isolation (I ₂): ≡ PrB Purification (Pu ₃): recrystallization–dissolution (hot toluene, petroleum ether) → filtration (gravity) → cooling (slowly)
PrE ²⁸	Reaction (R ₅): ≡ PrD (but 117% exc. acetylacetone is used) Isolation (I ₃): filtration (suction) → washing (water) → drying (oven at 60–70 °C) Purification (Pu ₄): recrystallization–dissolution (benzene, petroleum ether) → filtration (gravity) → cooling (ice bath) → filtration (suction) → drying (oven at 60 °C)
PrF ²⁹	Reaction (R ₆): eq 3, 73.5% exc. acetylacetone, water (auxiliary substance), <i>T</i> ~ 100 °C Isolation (I ₄): filtration (suction) → washing (acetylacetone–water 1:1) → drying (suction) Purification (Pu ₅): recrystallization–dissolution (hot benzene, hot petroleum ether) → cooling (ice bath) → filtration (suction) → drying (air)
PrG ³⁰	Reaction (R ₇): eq 4, slight exc. acetylacetone, sodium acetate (auxiliary substance), room temperature Isolation (I ₅): washing (acetylacetone, acetone, and ethyl ether) Purification (Pu ₆): recrystallization (hot acetone)

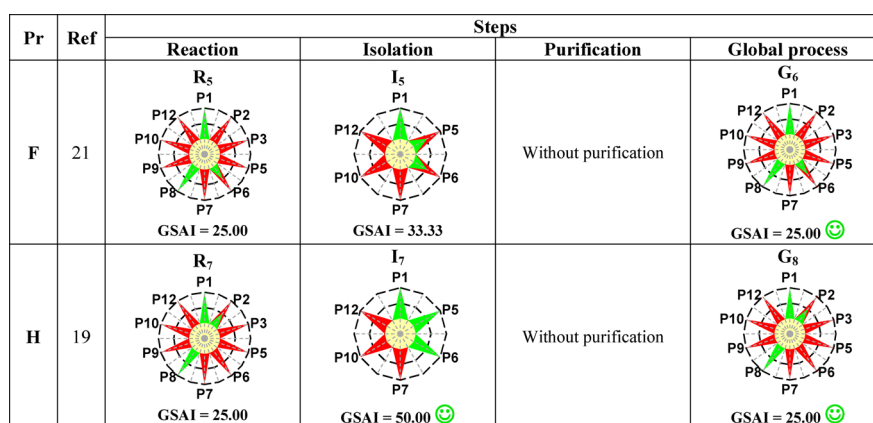
^aPr, protocol; → sequential.

Figure 3. Comparison between the green star obtained for the reaction, isolation, and purification steps and for the global process in protocols F and H of the synthesis of ethyl acetate: GSAI, green star area index (ratio of the area of the green star to the area of the green star of maximum greenness, expressed as a percentage); Pr, protocol; R_i, I_i, Pu_i, and G_i correspond to different procedures found for reaction, isolation, purification and global process, respectively; green smiley face is the greenest protocol.

star for I₅ have a score of 2 due to the solvents used (P5) and the simple distillation performed (P6), but the combined effect of the greenness of the isolation with the greenness of the reaction has no influence on the greenness of the global process. Therefore, when R₅ is replaced with R₁ or R₂ in protocol F, a greener global process is obtained (GSAI is increased from 25 to 30 because the accomplishment of P2 improved). Although OP1 and OP2 present the same global greenness, OP2 has the advantage of including a distillation in the isolation step to increase the purity of the product.

A third optimization, OP3, is obtained by adding the purification step used in protocols A–E, G, I, and J, to OP1, as shown in Figure 4, bottom. This optimization gives a global star different from that of protocols F and H (the greenest ones, where purification is not prescribed, although in these protocols, a distillation is included in the isolation or in the

reaction step, respectively), although with the same GSAI (25). This was achieved because the reaction procedures in protocols F and H (R₅ and R₇, Figure 3) were substituted with a greener one (R₁ and R₂, where distillations are not prescribed, Figure 4). A comparison of OP1 with OP3 (Figure 4) shows that adding the purification step decreases the GSAI from 30 to 25—the decrease in OP3 was a consequence of the reduction of the score of principle P8 to P2, as there are two stages for the synthesis, with the product being isolated twice (first in the isolation step and then in the purification step). This situation exemplifies how repeated isolations of the product, when required, may be responsible for loss of greenness. A global inspection of Figure 3 and 4 shows that the workup does not influence the global greenness scored for principles P5, P6, P7, P10, and P12 because they are equal or higher than their values for the reaction; in contrast, in the case of principle P1, some of

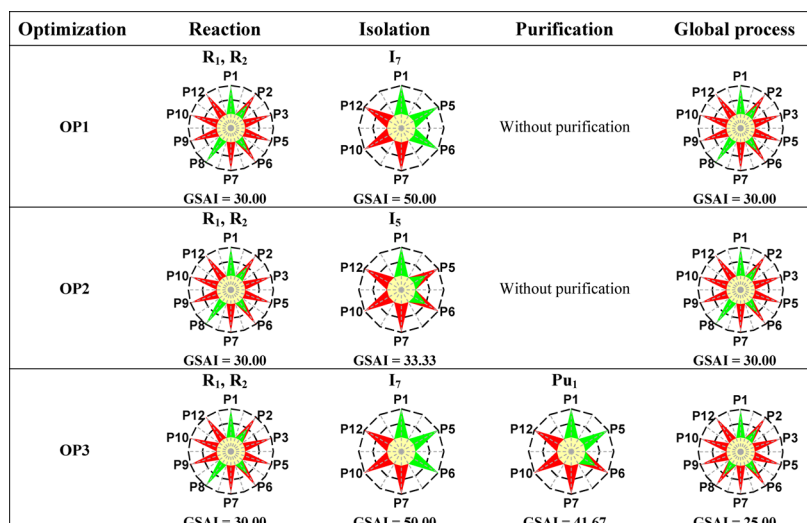


Figure 4. Green star obtained by combining different step procedures for the synthesis of ethyl acetate.

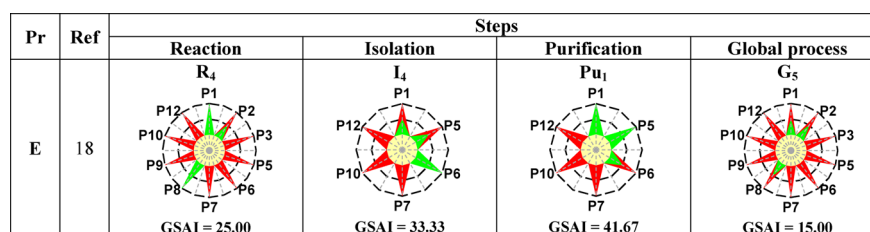


Figure 5. Comparison between the green star obtained for the reaction, isolation, and purification steps and for the global process in protocol E of the synthesis of ethyl acetate: GSAI, green star area index (ratio of the area of the green star to the area of the green star of maximum greenness, expressed as a percentage); Pr, protocol; R_i, I_i, Pu_i, and G_i correspond to different procedures found for reaction, isolation, purification and global process, respectively.

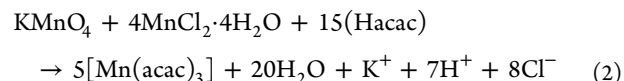
the protocols have a lower score for global green star than for the reaction star, with the difference being due to the workup (example in Figure 5, protocol E, with more examples in Figure 1S in the Supporting Information). This happens because the waste produced in the isolation and/or purification steps is less benign than that from the reaction. The other principles are only punctuated in the reaction step, except principle P8, as mentioned above.

In summary, of all protocols analyzed, a green star with GSAI = 25 is obtained only when purification was not used (protocols F and H, Figure 3). In the combinations presented in Figure 4, the same greenness is obtained when purification is used and higher if it is excluded, which means an improvement of the greenness, albeit modest. In particular, the comparison of OP2 with the other two helps to understand how the details of the workup may have a subtle influence on greenness. Above all, this analysis shows how complex it is to reach, at the same time, purity of the product and greenness of the workup (and of the global process). There is a conflict between these two aims that requires a bidimensional optimization procedure to find a balance. The reaction shows high atom economy (AE = 83%), having good potential to provide a suitable example of green synthesis with reference to the material component of greenness. However, even after optimization, the green star showed limited global greenness (GSAI = 30%), which is mainly due to the hazards of the substances involved and using nonrenewable feedstocks, etc.

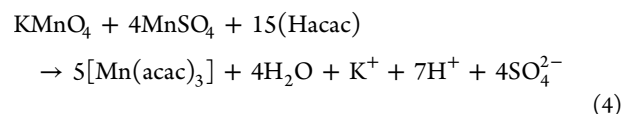
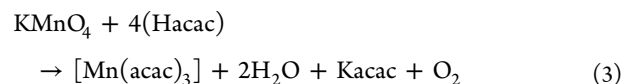
Synthesis of Manganese(III) Acetylacetonate

Seven protocols were found for this synthesis:^{16,25–30} two in university Web pages,^{16,28} two in Inorganic Chemistry experimental textbooks,^{26,27} and three published in scientific journals,^{25,29,30} as summarized in Table 3.

Most protocols use the reaction



except protocols F and G, which use, respectively, the reactions



These protocols involve seven different procedures (R₁–R₇) for the reaction step. Procedures R₁–R₅ differ only in the excess of acetylacetonate used or in the reaction temperature, but R₆ and R₇ use different chemical reactions. For the workup, five different procedures were found for the isolation of the product (I₁–I₅) and six for the purification (Pu₁–Pu₆). In the isolation procedures I₁–I₃, the product is always washed with water but the drying processes are different (air, oven, or desiccator). In procedures I₄ and I₅, different solvents are used for washing the product, and this is air-dried. In the purification procedures

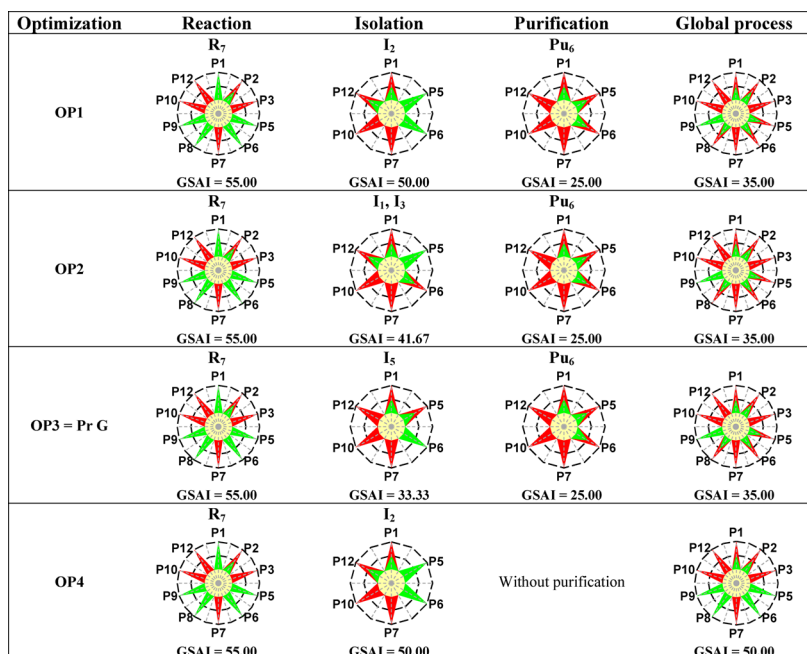


Figure 6. Green star global optimization for the synthesis of manganese(III) acetylacetonate.

Pu₁–Pu₆, different recrystallization solvents are used (cyclohexane, toluene, benzene, or acetone). Purification is not prescribed in protocol C.

The stars of the detailed greenness assessment for the various protocols, as well as the data needed to construct them, are presented in the Supporting Information (Figure 2S and Tables 26S–38S). Here, only the greenest combinations obtained are presented (see Figure 6).

When the greenest procedures for the steps (see Supporting Information) were combined to optimize the greenness, three combinations were found to give the same global greenness (Figure 6, combinations OP1–OP3), with GSAI = 35; OP3 corresponds to protocol G, the greenest protocol analyzed, where purification was prescribed. These involve the greenest procedures for the reaction (R₇, GSAI = 55) and purification (Pu₆, GSAI = 25) but with four different procedures for the isolation (I₁, I₂, I₃ and I₅ with GSAI ranging between 33 and 50). Nevertheless, the isolation procedure I₂ (GSAI = 50) should be chosen because water is used as solvent (in I₅, acetylacetone, acetone, and ethyl ether are used), and it is performed at room temperature (in I₁, the product is washed with cold water, and in I₃, it is dried at 60–70 °C). This shows that when the greenness for the global process is the same for all the combinations, attention should be paid to the greenness of the individual steps to look for further optimization; this may be possible by selecting the greenest procedure for each step. This example stresses the importance of considering individually the greenness of the steps, in parallel with that of the whole synthetic process, to obtain a full panorama of the greenness.

However, a global process with better greenness than OP1–OP3 can be obtained by excluding purification (combination OP4 in Figure 6, GSAI = 50) because the purification step decreases the global greenness, reducing the scores of the principles P1, P5 and P6 (Table 1). This combination is greener than the greenest protocol analyzed (protocol C, GSAI = 40, where purification was also not prescribed) because it considers a greener procedure for the reaction (R₇, GSAI = 55,

instead of R₃, GSAI = 45) and a greener procedure for the isolation (I₂, GSAI = 50, instead of I₁, GSAI = 42) (for details, see Figure 2S, Supporting Information).

In summary, the use of the proposed procedure allowed an improvement of the greenness, but like in the previous case, it was limited. The three reactions considered above show different values of atom economy:

$$\begin{aligned} \text{Reaction 4 (AE} = 78\%) &> \text{Reaction 2} \\ &(\text{AE} = 72\%) > \text{Reaction 3 (AE} = 63\%) \end{aligned}$$

The lowest value for Reaction 3 is the result of the use of a fourth molecule of Hacac, which is not included in the product, which is required to combine with the potassium ion in the co-product, Kacac. In reference to the other two reactions, the higher value (Reaction 4) is the result of the use of the reactant MnSO₄, which has a lower molar mass than MnCl₂·4H₂O (Reaction 2). After optimization, the green star showed a higher global greenness (GSAI = 50) than in the previous case, although the constraints to increase global greenness are the same.

DISCUSSION

The following discussion aims to highlight the most important aspects that emerged during the analysis of the studied cases and to evaluate to what extent the objectives stated in the Introduction have been accomplished.

Procedure for the Optimization of Synthesis Procedures

The results of this work show that it is possible to improve the greenness of a given synthesis procedure, without the need to perform laboratory work, by identifying the best performing reaction, isolation, and purification steps from the different protocols available in the literature, using the green star to assess what is tentatively called the *microgreenness* of these different steps involved, and combining the greenest procedure for each step (e.g., for the synthesis of ethyl acetate, OP1, Figure 4). However, instead of one, several combinations with

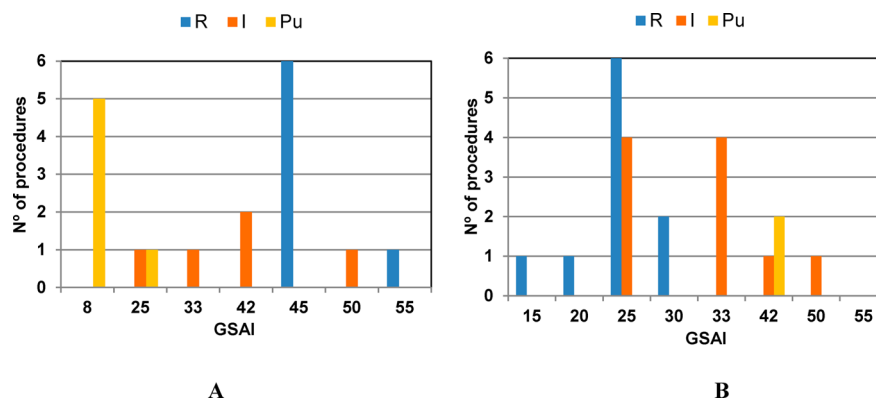


Figure 7. GSAI values for green star of all the syntheses analyzed: A, manganese(III) acetylacetonate; B, ethyl acetate; R, reaction; I, isolation; Pu, purification.

the same level of greenness may be found, as shown in the synthesis of both ethyl acetate, OP1 and OP2 (Figure 4), and manganese(III) acetylacetonate, OP1–OP3 (Figure 6). For the optimization of the synthesis of manganese(III) acetylacetonate (Figure 6), the procedure for the purification step is always the same, and all the principles are scored as 1 except principles P1, P5 and P6, which are scored as 2. When the green stars are combined, these scores limit the maximum score of these principles. Although for the isolation step procedure I_2 is the greenest (GSAI = 50), three other procedures with lower isolation GSAI yield the same global greenness (Figure 6, OP2 with $I_1 = 42$ or $I_3 = 42$ and OP3 with $I_5 = 33$). This happens because the scores of principles P1, P5 and P6 in the purification step are the same as (or lower than) those for the isolation step, limiting the scores of the principles for the global process. Therefore, when combinations are made, the procedures for the isolation and purification steps should be chosen, if possible, so that they do not decrease the initial score of the principles in the reaction step.

In summary, when the use of green star provides no unequivocal choice of the better procedure, further analysis of the situation is needed. These examples are useful to remind chemists that metrics are only tools for helping in the decision making and are to be used in the context of a broader and deeper understanding about the problem of achieving green optimization.

Usefulness of the Green Star for the Evaluation of the Microgreenness Syntheses

The results show that the separate evaluation of the three steps of a given synthesis (reaction, isolation, and purification) with the green star tool provides extra information on how the greenness of the global process depends on the greenness of each of the steps, allowing the discussion of the global greenness in terms of the microgreenness of the successive steps involved in the syntheses.

However, the relations between the global green stars and those of the three steps are complex, deserving some comments. First, the scores of the principles P2 and P9 in the global process are always the same as the scores for the reaction step because they are not evaluated in the isolation and purification steps. Thus, performing the reaction using conditions of stoichiometric or near stoichiometric proportions of reagents (scored in P2, atom economy) and with harmless catalysts (scored in P9, catalysts) increases the greenness of the global process. Second, the score of the principle P3 (less hazardous chemical synthesis) in the global green star includes

the hazards of all substances involved, which means that auxiliary substances used only in workup steps will also affect the score of this principle. Therefore, the global score of P3 may be different from the score of the reaction, although the principle is not assessed in the workup steps. The same situation may happen in the case of principle P8 (reduce derivatives) if a purification is performed—often when the number of stages of the synthesis increases, the global score decreases. The two syntheses presented exemplify this difference (for details, see Figures 1S and 2S, Supporting Information): for both, all protocols that include isolation and purification of the product (two stages) have a score of 2 for principle P8 (reduce derivatives) in the global green star; in contrast, the protocols without purification (only one stage) have a score of 3 for that principle (for details, see Figures 1S and 2S, Supporting Information). For the remaining principles, the score of each principle in the global green star is the lowest of the three steps.

The Importance of Workup for Greenness

The study shows that the workup of a synthesis may influence very much the greenness of a synthetic process, in a way that may depend markedly on the procedure adopted. This is shown in Figure 7, where the frequency distributions of the GSAI values for each step (reaction, isolation, and purification of the product) for all procedures of the two syntheses are presented.

When comparing the frequencies of the GSAI values obtained in the three steps for the synthesis of manganese(III) acetylacetonate, we found that the purification step always shows a more limited greenness than the reaction or the isolation. The decrease of the greenness is due to the use of problematic solvents (benzene, petroleum ether, etc.) and of temperature conditions different from room temperature. In contrast, for the case of ethyl acetate synthesis, the greenness of the isolation and the purification steps is higher than the greenness of the reaction (the use of calcium chloride and sodium carbonate solutions in the workup steps allows higher greenness of isolation). These results illustrate the importance of a careful choice of solvents for the workup, especially with respect to their environmental impact.

Final Remarks

The increases in greenness and its levels reached after optimization for the syntheses discussed in this work, as well as those described previously in other reports,^{7–9} are limited. These results agree with the large amounts of residue produced in Canadian university teaching laboratories found in a

systematic study by Andraos.³¹ This situation is not unexpected because, until recently, greenness was ignored when choosing synthesis reactions for teaching laboratories. Indeed, as the negative impacts of chemistry were altogether ignored, both in industrial and academic environments, it is an inheritance of the pre-green chemistry era, often found when prescribed protocols are evaluated with reference to greenness (as exemplified by GSAI values in Figure 3). Thus, the pre-evaluation of syntheses protocols by students before going to the laboratory may help to make them aware of the problems of the “historic synthetic chemistry” and that there is plenty of room to improve greenness both by revising prevalent synthetic pathways and by designing new ones addressed proactively toward achieving the goals of green chemistry.

■ REMARKS FOR PEGAGOGICAL IMPLEMENTATION

The results of the present study suggest a strategy for teaching synthesis in the laboratory with the purpose of promoting the development of a more creative mind when the students prepare and perform the experimental work. At present, usually, when the students are asked to perform a certain synthesis, a unique protocol is prescribed to them, as if it was the only way to prepare the compound in question. This study proposes an alternative: (i) a chosen compound, some bibliography for its synthesis, consisting of several protocols, is presented to the students (alternatively, the students may be given only the name of the compound and asked to find in the literature as many as possible protocols for its preparation, if literature search is also an aim of the course); then students are asked (ii) to assess, with the green star, the information available in them, having as a goal the greenness of the syntheses, and (iii) to define from the results of the assessment, if possible, a protocol greener than those evaluated to develop the laboratory work. The use of the green star is a fundamental tool for the activity of the students, used for assessing the microgreenness of the protocols a priori, investigating possible combinations to improve the global greenness of the process, and choosing the protocol they think would be the greenest to test in the laboratory as a first approach. After the chosen protocol is performed, another phase of the student's work is reached. The students are asked to evaluate the protocol by applying the green star and to calculate suitable mass metrics to assess whether their decisions on the assembly of the optimized protocol from the literature information were correct or not, that is, whether the protocol was well chosen or needs to be changed or substituted. The students have to evaluate if the yield and purity of the product (values are not always referred in the literature) are adequate for the purpose, and if the values of the reaction mass efficiency and the E-factor (or the mass intensity) mean a reasonable level of greenness, etc. If not, they may continue the work by further experimental optimization of the synthesis, considering parameters that affect purity, yield, and the greenness. These are numerous; for instance, the solvents used and their hazards and efficiency in terms of yield of reaction, the efficiency of the workup operations, the efficiency of catalysts, temperature, etc. may be considered in optimization to be chosen depending on the case. This allows for versatility of the work asked to the student, depending on the level of the course, time allowed for further experiments, etc.

These activities are varied and may have different results. If the chosen protocol delivers poor results in practice and no improvement is possible, the student may even have to

conclude that his work failed—his choice of protocol must be abandoned. This is an extreme situation, and more often, the student will learn that synthesis is a complex process and many inter-related aspects have to be taken into consideration in its optimization. This approach makes students aware of this complexity, which is better understood in the practice of synthesis and should deserve more attention in the planning of synthetic experiments. This strategy involves the students more deeply in the work, trains them in taking personal decisions with fuller responsibility, and provides them with a more realistic vision of what synthetic chemistry is—and that green chemistry involves a persistent fight to revise chemistry to support technosphere sustainability.

So far, this approach has been followed with our students in courses for training future teachers, so that they learn how to evaluate and choose which protocols to use in their lab classes when they move on to secondary schools, allowing in parallel a better understanding of the role of green chemistry as a post of sustainable development. As the students are in the last year of their master course and mature on laboratory work, they are challenged by this new type of work (in the Supporting Information is included what is actually provided to the students to define the work to be developed, file “Preparation of the compound... X...”). The success is assessed by following their work and by an oral presentation, followed by open discussion with colleagues, and a written report. In their reports, they referred that the work contributed to increase their knowledge about (i) green chemistry and the 12 principles; (ii) instruments to assess greenness that may be used in the implementation of laboratory work; and (iii) new ways to develop laboratory work that may provoke a change of attitudes in schools and introduce green chemistry in secondary schools. They also referred that in this way they found the laboratory work more useful and interesting.

■ CONCLUSIONS

This work expands the scope of the usefulness of the green star metric, showing that it is an adequate tool for detailed assessment of the greenness of the different steps of a synthesis—what is tentatively called microgreenness. The results show that the evaluation of the microgreenness shows how the different steps influence the global greenness of the syntheses, providing useful information for pursuing their optimization. The results suggest that the workup of the synthesis may often be more problematic for the greenness than the reaction itself, a detail that has been often forgotten in green chemistry teaching. Moreover, the study demonstrated that the green star can be used for comparing in detail the alternative protocols proposed for a synthesis, finding the best alternative for each step, and assembling a greener protocol by combination of them. In summary, it shows that it is possible to optimize the synthesis using existing procedures and combining their best steps to obtain a greener global protocol.

Finally, this work enables new ways of working with students. For example, they may begin by analyzing a set of alternative protocols and evaluate the possibility of changing some of their prescriptions (solvents, operations, conditions, etc.) to optimize the greenness and make decisions themselves on what to do, instead of just following a prescribed protocol without a previous meditation on its greenness—the practical work will then be to perform the optimized protocol and assess the results to confirm whether the expectations of increasing greenness were fulfilled and their decision was correct. Besides

training the students to assume responsibilities, the proposed procedure allows the students to have direct contact with the principles of green chemistry and feel their importance, possibilities, and advantages for improving the greenness of the synthesis of substances by assessing the improvements with a holistic metric based on those principles, such as the green star.

■ ASSOCIATED CONTENT

■ Supporting Information

Results and discussion of the greenness assessment for the syntheses of ethyl acetate (Figure 1S) and manganese(III) acetylacetonate (Figure 2S); criteria for the construction of the green star: tables where the criteria are defined for scoring human health, environment and physical hazards, as well as the renewability and degradability of the substances involved (Tables 1S and 2S), and the criteria for scoring the principles of green chemistry which are applied (Table 3S); protocols and information for construction of green star for the synthesis of ethyl acetate (Tables 4S–25S) and of manganese(III) acetylacetonate (Tables 26S–38S); file to support students in the work: “Preparation of the compound... X...”; information on the scope of the project in which this work is included; and Excel files to obtain the green star and calculate GSAI. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

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