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An Evaluation of the Green Credentials of a Multicomponent Reaction for the Synthesis of Isothioureas Through the Use of the Holistic CHEM21 Green Metrics Toolkit

S. Abou-Shehada,^[a] P. Mampuyts,^[b] B. U. W. Maes,^{[b]*} J. H. Clark^[a] and L. Summerton^{[a]*}

^[a] Green Chemistry Centre of Excellence, University of York, Heslington, York, YO10 5DD, UK.

E-mail: louise.summerton@york.ac.uk

^[b] Department of Chemistry, University of Antwerp, Groenenborgerlaan, 171, 2020 Antwerp, Belgium.

E-mail: bert.maes@uantwerpen.be

Abstract

Multicomponent reactions (MCRs) are considered green and material efficient methods for the synthesis of organic compounds, however very few studies have investigated the metrics of the upstream

processes involved to achieve the starting materials used in these reactions. A novel MCR-approach for the synthesis of N-cyclohexyl-S-methyl-N'-phenylisothiourea from S-methyl methanethiosulfonate, cyclohexyl isocyanide and aniline was appraised in terms of its green metrics using the CHEM21 green metrics toolkit and compared with those of the state of the art approach. The upstream process leading to the component starting materials for both approaches were also appraised to gain an insight into how the greenness of both methods translate from the raw materials to the final product.

Introduction

The twelve principles of green chemistry provide an excellent set of guidelines for designing greener chemical reactions.¹ However over the years they have been subjected to misuse because of a variety of misconceptions. The green chemistry community has developed a variety of green chemistry metrics to better quantify the green credentials of a process, such as atom economy (AE), reaction mass efficiency (RME), process mass intensity (PMI) and E-factor.^{2,3} No reaction can be strictly qualified as “green” especially within the remit of synthetic chemistry as our efforts to better optimise our methodologies are still ongoing and we still need to make better use of renewable resources. However, metrics can be used to quantify improvements in the greenness of new approaches by comparing them against the current state of the art methodologies.

PMI and E-factor are regularly used in the pharmaceutical industry to measure the improved “greenness” of their manufacturing methods against the current technology. However, when considering the development of methodologies from idea inception, there is a distinct lack in the use of green metrics to guide reaction design. Furthermore, though the use of mass-based metrics can give an idea of the inherent efficiency of a transformation it only addresses 1-2 of the principles of green chemistry. Ideally, metrics should be used in

amanner that can give the “whole picture” of the greenness of a reaction including an appraisal of the inherent hazards of the process and materials used, which should encompass reagents as well as reactants and solvents, an idea of the renewability of the materials used and the scarcity of the elements employed.⁴

These aspects and others are encompassed in the holistic CHEM21 metrics toolkit developed by Clark et al.⁴ as part of the CHEM21 project. CHEM21 or Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries is a consortium of academics, pharmaceutical companies and SMEs working collaboratively to develop a broad based portfolio of technologies for the green manufacture of active pharmaceutical ingredients. The consortium uses the CHEM21 metrics toolkit to guide their research and demonstrate the advantages of their novel techniques with improved green chemistry metrics.

With important medicinal properties, isothioureas are an important class of compounds to the pharmaceutical industry; which have found use as anti-histamines, anti-bacterials, for treatment of peptic ulcers, HIV and influenza.⁴⁻⁹ In addition, isothioureas are important synthetic intermediates for the synthesis of guanidines, as illustrated by the many procedures that have been reported.¹⁰ As part of the CHEM21 project, Maes et al. have recently developed a multicomponent reaction for the synthesis of isothioureas from thiosulfonates, isocyanides and (hetero)aromatic amines.¹¹ This method is considered a greener and more efficient alternative to the classical synthesis approach for *S*-substituted isothioureas. For example, *S*-methyl isothioureas are synthesized by methylation of thioureas with methyl iodide (MeI), a known carcinogen and neurotoxic. The key disadvantages of the classical methods to *S*-alkyl isothioureas include the associated health risks of the reagents used, their flammability and high reactivity.

Multi-component reactions (MCRs) are convergent reactions, in which three or more starting materials react in a single operation to form a single product, where basically all or most of the atoms contribute to the newly formed product. Such reactions have attracted much interest by the synthetic organic community over the past two decades, specifically in the areas of biotechnology, drug discovery and materials science.¹² MCRs boast of several advantages; the use of a single pot transformation dictates that the route is a convergent one, thus limiting the use of reaction auxiliaries, work-up and purification stages.¹³ Clearly MCRs should have an improved efficiency in terms of mass usage, which is why many would intuitively consider such a transformation as “green”. We sought to test this hypothesis on the route developed by Maes and co-workers towards isothioureas,¹¹ and take this further and investigate the upstream process that leads to the starting materials used in the process which are usually neglected. Though there have been some investigations into the production of various compounds,¹⁴⁻²⁰ they have typically been limited to discrete reaction steps, with the exception of Andraos and Hudlicky’s investigations into the greenness of the synthesis of Oseltamivir.²⁰

We appraised the metrics of the MCR and classical approach to isothioureas. This was carried out for both the discrete transformations as well the upstream processes that lead to the starting materials; with the aim of gaining a clearer perspective of the impact of upstream processes on the overall greenness of a reaction. The approaches detailed herein were subjected to assessment using the First Pass CHEM21 Metrics Toolkit.⁴ This assessment aims to provide a preliminary assessment of new reactions performed on a small scale (mg

scale) in the laboratory to identify where a reaction is performing well in terms of its greenness whilst highlighting areas where improvements could be made.

The aim of this work was also to highlight how the CHEM21 Metrics Toolkit can be readily used in everyday practice as a means of:

- examining reactions in a more holistic manner, incorporating both quantitative and qualitative parameters;
- assessing the state of the art to provide a benchmark against which new methodologies can be compared (via available literature methods including patents);
- identify where reactions are performing well in terms of their greenness;
- highlighting issues in methodologies where improvements could be made.

By facilitating a quick and user-friendly way of analysing reactions even at an early stage of development, for example at the discovery level in the laboratory, allows chemists to work towards an optimum process, taking into consideration a wide range of parameters. It also encourages continuous improvement, rather than postponing assessment until the reaction is carried out on a much larger scale.

Although the First Pass Chem21 Metrics Toolkit is fairly comprehensive in its assessment, it does not incorporate Life Cycle Assessment (LCA). LCA is not included until Second Pass, whereby the reaction has showed promise, has undergone some optimisation and is now at the stage of being scaled up. The reason for this is that a balance had to be struck between being comprehensive enough to provide a meaningful assessment, but remaining straightforward enough to be incorporated into everyday practice in the laboratory to support regular monitoring of reactions and iterative improvements to be made. This is why the CHEM21 Toolkit was structured into a series of passes with a level of complexity commensurate with the scale of the experiment.

Results and discussion

N-Cyclohexyl-*S*-methyl-*N'*-phenylisothiourea was selected as the model compound for our investigations as its preparation via both the new three-component reaction and the classical synthesis approach has been reported.

Initially we appraised the metrics for the synthesis of the model compound for the two discrete approaches shown in Scheme 1.^{21,22} A qualitative appraisal of the two methodologies would indicate that despite the use of MeI, the classical approach (CA) uses fairly mild conditions in both synthetic steps. They also use green solvents (acetone and ethyl acetate) as the reaction solvents.²³ The CA also achieves the product in good yield for each step, although the system is not catalytic and uses at least stoichiometric amounts of reaction auxiliaries, and requires a purification step for the thiourea prior to the *S*-alkylation. By comparison the MCR method is run at a higher temperature though still mild, the process is mediated by a catalyst based on an earth abundant metal (copper), but does use biorenewable 2-methyl tetrahydrofuran (2-MeTHF), which is now considered as a problematic solvent.²³ However, it is noteworthy that Maes et al.¹¹ reported that the reaction can proceed in a number of solvents, thus this MCR methodology is not limited to 2-MeTHF as a reaction solvent.

Scheme 1 Classical and MCR approaches for the synthesis of *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Classical Approach

MCR Approach (Maes *et al.*)^[11]

The metrics for the discrete transformations are given in Table 1. From these resultant metrics, it is clear that although the classical methodology does provide excellent yield for both steps, the cumulative yield shows that it does not surpass the MCR, with similar yields reported for both approaches. As would be expected, the AE of the MCR approach supersedes that of the classical approach by 10%, interestingly it does not perform as well when the RME is considered. With an RME value of 53%, the classical approach outperforms the MCR; this is due to the fact the latter uses the reactants in a 1.7 : 1 : 2.5 equivalence of aniline : *S*-methyl methanesulfonate : cyclohexyl isocyanide, respectively.

Table 1 Quantitative metrics of classical and MCR approaches for the synthesis of *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Route	Yield (%)	AE (%)	RME (%)	PMI (g g ⁻¹)	PMI Rxn ^a (g g ⁻¹)	PMI Solv ^b (g g ⁻¹)	PMI WU ^c (g g ⁻¹)
CA	84	66	53	817.1	26.9	742.3	790.2
MCR	88	76	39	324.5	13.8	312.5	310.7

^a Process Mass Intensity: Reaction; ^b Process Mass intensity: Solvents; ^c Process Mass Intensity: Work Up

The impact of the two isolation stages for the CA is made clear when observing the process mass intensity (PMI) values, with an overall PMI of the transformation being 817.1 g of input material per g of product produced (g g⁻¹), with the solvents accounting for the majority of the mass usage at 742.3 g g⁻¹. By comparison, the MCR approach has a total process mass intensity of 324.5 g g⁻¹, less than half of that of the CA.

This appraisal of the two approaches is a little surprising, though as one might predict, the MCR approach is certainly more economical, displaying a significant improvement in material efficiency, although the RME does not perform quite as well as expected. We were interested to see how these material efficiencies translated when considering the upstream processes that lead to the formation of the reaction starting materials for these discrete steps. As such, the routes leading to the starting materials for each approach were assessed, through to the final compound and can be found in Scheme 2.

The CA commences with the synthesis of carbon disulphide (CS_2); on the industrial scale CS_2 is produced from the reaction of natural gas with elemental sulfur over a silica or alumina catalyst to give the product in 90% yield.²⁴ Alternatively, on the lab scale CS_2 can be produced by the reaction of acetylene with elemental sulfur to give CS_2 in 84% yield;²⁵ although not strictly an industrial process, this transformation was also included in our investigations. The classical approaches follow the same route from CS_2 to the final product (Scheme 2).

Scheme 2 Overall synthetic routes to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

The MCR approach by comparison is either 4 steps, if the route commences with phosphorus red,²⁶ or 3 steps if the route commences with calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$)²⁵ (Scheme 2). The material metrics for each can be found in Table 2. When calculating the cumulative green metrics, only the metrics of the transformations in the longest branch of the synthetic route were used as per Andraos' guidelines² However, we decided to include the synthetic branches of both approaches (syntheses of MeI for CA and *S*-methyl methanethiosulfonate of the MCR)^{29,33} in the process mass intensity calculations to gauge their impact on the overall process, and the mass-metrics were not considered. For output metrics found in Table 2, the mass inputs were scaled for the production of 10 mmol of the target *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Table 2 Overall quantitative metrics for the 4 routes to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Route	Overall						
	Yield (%)	AE (%)	RME (%)	PMI (g g ⁻¹)	PMI Rxn ^a (g g ⁻¹)	PMI Solv ^b (g g ⁻¹)	PMI WU ^c (g g ⁻¹)
CAM (Methane)	12	40	7	1645.6	74.4	1493.4	1571.2
CAA (Acetylene)	11	44	8	1764.4	72.1	1606.4	1692.3
MCRP (phosphorus)	74	43	30	757.2	95.5	563.5	661.7
MCRCa (Ca ₃ (PO ₄) ₂)	65	32	10	645.4	65.2	563.5	580.2

^a Process Mass Intensity: Reaction; ^b Process Mass intensity: Solvents; ^c Process Mass Intensity: Work Up

A prominent result of the cumulative metrics (Table 2) for all four routes is the ample material savings observed in the MCR approaches which give an overall yield of 74% and 65% for the route commencing with phosphorous (MCRP) and the one commencing with Ca₃(PO₄)₂ (MCRCa) respectively. By comparison, the classical approaches, CA commencing with methane (CAM) and the CA commencing with acetylene (CAA) gave yields of 12% and 11% respectively. The MCR approach thus produces 62% more products in the best-case scenario and 52% more in the worst case, compared to CAM.

Interestingly, the best performing route with respect to AE is CAA with an atom economy of 44%, which is followed by MCRP at 43%, closely followed by CAM at 40% AE, and the weakest performance demonstrated by MCRCa with an AE of 32%.

Although the MCR approach did not perform as well relative to the state of the art in terms of RME when considering the discrete transformations (Table 1), when considering the metrics for the overall synthetic route, the RME for both MCR processes (30% and 10%) outperform CAs, which have RME values of 7% and 8%.

With 6 synthetic steps in the CAs, it is no surprise that their PMI values (1645.6 and 1764.4 g g⁻¹) far exceeded those of the MCR approaches (MCRP: 757.2 g g⁻¹, MCRCa: 645.4 g g⁻¹). Interestingly, commencing the process with calcium phosphate does mitigate the mass usage slightly, which is attributed to the fact that the MCRCa approach is a shorter route.

As would be expected, the material sink for all four processes is due to the work-up procedures; the shorter MCR routes again have a much lower PMI with respect to work up at 661.7 g g⁻¹ and 580.2 g g⁻¹ for MCRP and MCRCa respectively. In order to gain a clearer understanding of the resultant overall metrics, the discrete and cumulative mass based at each step were evaluated for better understanding the areas where the methodologies are failing/performing well.

The discrete and cumulative mass based metrics of CAM, CAA, MCRP and MCRCa are given in Figures 1-4 respectively. The high overall yields observed for MCR approaches are due to the limited number of synthetic steps and the good to excellent yields exhibited at each of those steps. As touched upon earlier, despite having the shorter route MCRCa exhibits a lower overall yield, which is due to the lower yield in the reaction of calcium phosphate to produce POCl₃. In contrast MCRP has one extra synthetic step in order to

Figure 1 Yield, AE, RME and PMI of the classical route from methane to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Figure 2. Yield, AE, RME and PMI of classical route from acetylene to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiourea.

Figure 3. Yield, AE, RME and PMI of MCR route from phosphorous to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiurea.

Figure 4. Yield, AE, RME and PMI of MCR route from calcium phosphate to *N*-cyclohexyl-*S*-methyl-*N'*-phenylisothiurea.

reach POCl₃ however, the yield of POCl₃ is similar cumulatively over two steps compared to the singular step in MCRCa; 94% for MCRP and 83% for MCRCa.

In the case of the classical approaches, though CAM shows a marginally higher yield (within experimental error) for the production of CS₂ compared with CAA (90% and 84% respectively), the overall yield is not hugely affected between the two approaches. When examining the cumulative yield in the graphs in Figures 1 and 2, it can be seen that the step that has the most significant impact on the yield for these approaches is step 3 (production of thiophosgene from thiocarbonyl perchloride in only 24% yield).

The impact is observed in the cumulative yield where, using CAM as an example, the cumulative yield of 90% at step 2, plunges to 22% by step 3. The impact is further highlighted when we consider that the other reaction steps boast of yields between 65-95%. The impact of this step on the overall efficiency is also demonstrated in the RME of both synthetic approaches, showing a significant drop in the cumulative RME on going from step 2 (RME CAM: 53%, RME CAA: 64%) to step 3 at 8% and 10% for CAM and CAA respectively. Notably, the AE for step 3 is not the poorest performing step for both approaches; indeed, in this instance it is step 1 for CAM, but still step 3 for CAA. This divergence between metrics is an excellent example of why examining a single metric in isolation can be misleading.

From the overall metrics, CAM is marginally less atom economical than CAA, as can be seen in the graphs for atom economy in Figures 1 and 2, and is a direct result of the use of methane as the starting material over acetylene. This can be explained by examining the balanced equations for the reactions of both methane and acetylene in the production of CS₂ (Scheme 3); when methane is used as the starting material two molecules of hydrogen sulfide are produced for every one molecule of CS₂, by comparison one molecule of hydrogen sulfide is produced for every two molecules of CS₂ produced from acetylene.

Similarly for MCRP, examining the discrete AEs shows that step 3 (formation of the isocyanide) is the largest material sink. However, the discrete RME values indicate that step 4 is the material sink. The only approach that shows correlation between both these metrics is MCRCa, for which the AE and RME for the discrete steps show that the first step (synthesis of POCl₃) is the largest material sink in the route. The low AE observed for this step is due to the production of three molecules of calcium chloride and six molecules of carbon monoxide for every two molecules of POCl₃ produced - clearly a very inefficient method for the production of POCl₃. This inefficiency is also reflected in the RME, due to the use of reactants and reagents in more than stoichiometric quantities (Scheme 3).

Scheme 3. i) Balanced equations for formation of CS₂ from methane and acetylene; ii) Balanced equation for formation of POCl₃ from calcium phosphate.

The bar charts for the process mass intensities for each of CAM, CAA, MCRP and MCRCa given in Figures 1-4 include the additional steps for the synthesis of methyl iodide and S-methyl methanethiosulfonate for the classical and MCR approaches respectively, corresponding to step 6 in the classical approaches and step 4 for MCRP and step 3 for MCRCa. A brief evaluation of the cumulative metrics for the classical approaches indicate that the material intensive steps come towards the end of the synthetic routes and include steps 4, 5 and 7; as indicated in the overall metrics for all the approaches, the material intensity demonstrated by these approaches are a result of solvent usage, predominantly in the work up. What we can infer from the discrete and cumulative PMI for the classical approaches is that the latter synthetic steps in these routes (steps 4, 5 and 7) use material intensive work up methods, specifically chromatographic purification.

The MCR approaches result in overall PMI values of less than half that of the classical approaches, however, in this instance the shorter MCRCa route is the least mass intensive. The production of POCl₃ from phosphorus is significantly more mass intensive with cumulative PMI over two steps of 54 g g⁻¹ versus a PMI value of 3.2 g g⁻¹ for the production of POCl₃ from calcium phosphate. The largest contributor to the PMI final step, again mostly due to the solvent usage in the work up stage, which in this case is also column chromatography. In the spirit of only reporting on published data, the authors have used the purification methods reported in their original article for the MCR approach;¹¹ however, in the interest of observing the material saving that can be made by taking the extra effort to explore different purification techniques, the Maes group was able to purify the product using recrystallization. The resultant overall PMI for the two MCR approaches would thus be reduced from 787.2 and 675.4 g g⁻¹ to 403.4 and 306.1 g g⁻¹ for MCRP and MCRCa respectively if the final product was purified by recrystallisation.

As a point of interest, the cumulative PMI for the linear route (excluding the branch reactions) was calculated for each of the four approaches and are shown in Table 3. From the values shown, it is clear that the classical approaches show little change in the overall PMI when the synthesis of methyl iodide is included; a change of ~2 g g⁻¹ is observed. By comparison the more material intensive synthesis of S-methyl methanethiosulfonate demonstrates a significant impact on the MCR approach with a 60.6 g g⁻¹ increase.

Table 3 Comparison of linear and convergent PMI values for the classical and MCR approaches to *N*-cyclohexyl-S-methyl-*N'*-phenylisothiourea

	CAM	CAA	MCRP	MCRCa
PMI Linear ^a (g/g)	1643.6	1762.4	696.6	584.8
PMI Convergent ^b (g/g)	1645.6	1764.4	757.2	645.4

^a PMI calculation does not include process mass intensity for the synthesis of Mel in the classical approaches and S-methyl methanethiosulfonate in the MCR approaches;

^b PMI calculation includes process mass intensity for the synthesis of Mel in the classical approaches and S-methyl methanethioulfonate in the MCR approaches.

Qualitative metrics

The CHEM21 metric toolkit does not focus on the mass based metrics alone, especially as they can give little insight into the innate safety of the materials used. In addition to the aforementioned mass based metrics, at First Pass the toolkit also appraises methodologies with respect to the solvents used, health and safety, reagent used, critical elements, energy

use, batch/flow and work up methods. These are appraised and designated a green, amber or red flag to denote “preferred”, “acceptable - some issues” and “undesirable”. The breakdown of the requirements for each flag under each category can be found in the publication by Clark *et al.*⁴

The toolkit is essentially constructed to guide reaction design, in order to aid the researchers within the consortium to home in on problem areas at the reaction discovery stage. As such the flag system set up for this toolkit is perhaps not ideally placed for the task at hand, however a holistic viewpoint of the four methodologies results in some interesting findings that are worthy of note. The qualitative appraisal of each route is given in Table 4.

As all of the transformations use reagents/reactants that contained either sulfur or phosphorus, both elements which have reserves that are projected to last 50–100 years, the steps in all the routes were denoted by an amber flag and were therefore omitted from Table 4. An assumption was made that all transformations were carried out in batches and were also denoted by an amber flag and omitted from the table. The categories that remain are solvent, reagent and energy use, health and safety as well as work up methods. Reagent used and workup methods closely mirror the results from the mass based metrics, highlighting the steps in each synthetic route that could perform poorly with respect to RME. The PMI values demonstrated by the classical approaches were because of mass intensive work up stages, clearly highlighted in Table 4 as chromatographic purification for steps 4, 5 and 7. Thus far, qualitative and quantitative metrics are in harmony.

Despite performing poorly in the overall mass based metrics, the classical approaches perform marginally better than the MCR approaches when health and safety, solvent and energy use are considered. For the two classical approaches the first three steps are carried out under solvent free conditions, and the branched reaction uses methanol as a solvent, all of which are denoted as “preferred” according to the toolkit. By comparison, the majority of the solvents used in the MCR approaches are problematic or hazardous.

Although none of the four transformations perform well when considering the health and safety of the materials used at each step, the authors would be amiss not to highlight that the majority of the synthetic steps in the MCR approaches are deemed “undesirable”. The CHEM21 green metrics toolkit at First Pass assigns the health and safety flags according to the Globally Harmonised System of classification and labelling of chemicals (GHS). It worth bearing in mind that at First Pass, assessments are limited to optimised lab scale methods and as such, are not as stringent as they would be at second and third pass (pilot and large scale processes). According to the National Fire Protection Association standards, the majority of the reagents used in all the approaches are classified as dangerous or corrosive/toxic substances scoring 3 or 4 on the fire diamond, with the exception of S-methyl methanethiosulfonate and cyclohexyl isocyanide which are assigned a score of 2 and dimethyl sulfoxide, which is assigned a score of 1. The NFPA fire diamond would result in red flags for all the steps in the classical routes, whereas the MCR approach does show an improvement, especially with respect to the MCR step developed by Maes *et al.*¹¹ which would be considered much safer.

Table 4 Qualitative appraisal of solvents used, inherent hazards of reagents and reactants, reagent used, energy and work up methods for all approaches.

Step	Solvents	Flag	Health and Safety	Flag	Reagent used	Flag	Energy	Flag	Work up	Flag
Classical Approach starting from Methane (CAM)										
1	None	Green	Methane: H220	Yellow	Reaction without any catalyst/reagents	Green	570-620 °C	Red	Low temperature distillation	Green
2	None	Green	CS ₂ : H372, Chlorine: H400	Red	Reaction without any catalyst/reagents	Green	Reflux	Red	High temperature distillation	Red
3	None	Green	CSCl ₄ : unknown hazards	Yellow	Use of reagents in excess	Red	rt	Green	Low temperature distillation	Green
4	Heptane, THF	Yellow	Aniline: H372, H400, H410	Red	Use of reagents in excess	Red	90 °C	Yellow	Chromatography	Red
5	Heptane	Yellow	Cyclohexylamine: H301, H331, H361 Phenyl isothiocyanate: H301	Yellow	Reaction without any catalyst/reagents	Green	rt	Green	Chromatography	Red
6	DCM	Red	Mel: H331, H301	Yellow	Use of stoichiometric quantities of reagents	Yellow	rt	Green	Chromatography	Red
7	MeOH	Green	Methanol: H370	Red	Use of stoichiometric quantities of reagents	Yellow	rt	Green	Low temperature distillation	Green
Classical Approach starting from acetylene (CAA)										
1	None	Green	H ₂ S: H330, H400	Red	Reaction without any catalyst/reagents	Green	360 °C	Red	High temperature distillation	Red
2	None	Green	Chlorine: H400	Red	Reaction without any catalyst/reagents	Green	Reflux	Red	High temperature distillation	Red
3	None	Green	CSCl ₄ : unknown hazards	Yellow	Use of reagents in excess	Red	rt	Green	Low temperature distillation	Green
4	Heptane, THF	Yellow	Aniline: H372, H400, H410	Red	Use of reagents in excess	Red	90 °C	Yellow	Chromatography	Red
5	Heptane	Yellow	Cyclohexylamine: H301, H331, H361 Phenyl isothiocyanate: H301	Yellow	Reaction without any catalyst/reagents	Green	rt	Green	Chromatography	Red
6	DCM	Red	Mel: H331, H301	Yellow	Use of stoichiometric quantities of reagents	Yellow	rt	Green	Chromatography	Red
7	MeOH	Green	Methanol: H370	Red	Use of stoichiometric quantities of reagents	Yellow	rt	Green	Low temperature distillation	Green
MCR Approach starting from Phosphorous (MCRP)										
1	None	Green	Chlorine: H400	Red	Reaction without any catalyst/reagents	Green	Reflux	Red	Low temperature distillation	Green
2	None	Green	PCl ₃ : H300, H330, H370	Red	Reaction without any catalyst/reagents	Green	rt	Green	Filtration	Green
3	DCM	Red	POCl ₃ : H300, H330, H372	Red	Use of reagents in excess	Red	80 °C	Yellow	Low temperature distillation	Green
4	DMSO	Yellow	Chlorotrimethylsilane: H301, H331	Yellow	Use of reagents in excess	Red	60 °C	Green	Low temperature distillation	Green
5	2-MeTHF, Heptane	Yellow	Aniline: H372, H400, H410	Red	Catalyst: CuI	Green	75 °C	Yellow	Chromatography	Red
MCR Approach starting from Calcium Phosphate (MCRCa)										
1	None	Green	Chlorine: H400	Red	Use of stoichiometric quantities of reagents	Yellow	760 °C	Red	Low temperature distillation	Green
2	DCM	Red	POCl ₃ : H300, H330, H372	Red	Use of reagents in excess	Red	80 °C	Yellow	Low temperature distillation	Green
3	DMSO	Yellow	Chlorotrimethylsilane: H301, H331	Yellow	Use of reagents in excess	Red	60 °C	Green	Low temperature distillation	Green
4	2-MeTHF, Heptane	Yellow	Aniline: H372, H400, H410	Red	Catalyst: CuI	Green	75 °C	Yellow	Chromatography	Red

In a similar vein, though the novel MCR reaction operates at an “acceptable” temperature and therefore has a relatively low energy demand, the remaining steps in the upstream processes are dominated by red or amber flags in comparison to the classical approaches, which boast of 4 synthetic steps carried out at a “preferred” temperature. However, when taking both the mass based metrics and qualitative metrics into account for all the transformations, an argument can be made for the MCR approaches. Given their higher efficiencies and lower mass intensities as well as the superior overall yields, one could argue that a smaller amount of the hazardous solvent or material is needed to produce the final product. Moreover, the energy required to reach the desired temperatures for the smaller material mass would in the long run make the MCR approaches less energy intensive. The opposing argument can be made with respect to the classical approaches.

Conclusions

In this study, we highlight how the First Pass CHEM21 Metrics Toolkit can easily be used to appraise the greenness of reactions on a small scale, allowing identification of where reactions are performing well and highlighting where improvements could be made at an early stage of the development process. The tool also readily facilitates benchmarking exercises, allowing new methodologies to be directly compared to the state of the art. The greenness of the multicomponent reaction to synthesize *S*-substituted isothioureas identified as a case study in this paper and the material savings that can be achieved through their development have been exemplified. Moreover, the investigation of the green credentials of a synthetic methodology cannot be truly understood until the upstream processes to reach the starting materials are also scrutinised and these are often neglected in analyses. The use of the CHEM21 metric toolkit clearly highlights the importance of a holistic approach to metrics and the potential pitfalls of appraising a parameter in isolation and how only interrogating the mass based metrics can give a skewed view of a transformation’s green credentials.

The greenness of the novel three-component reaction could potentially be improved further through a number of additional investigations:

- 1) study whether the reactions can be run at a higher concentration and study whether a greener solvent can be used based on the CHEM21 solvent selection guide.²³
- 2) Reinvestigate the stoichiometry of the three-component reaction for the specific isothiourea selected in this study, as optimisation of the method was done on a different compound, namely *S*-methyl-*N*-*tert*-butyl-*N'*-phenylisothiourea¹¹
- 3) The recuperation of the methane sulfinic acid waste was not investigated during the development of the MCR, but when recovered as its sodium salt, the generated waste could be immediately transformed into the *S*-methyl methanethiosulfonate reaction partner for the MCR.
- 4) Recently several new methods to synthesise thiosulfonates have been disclosed. They have not been evaluated from a green chemistry point of view, which might offer further improvements.³⁴
- 5) The synthesis of the isocyanide reaction partner is a large material sink in the cumulative metrics. In order to improve the overall PMI of the three-component

reaction further research should be devoted to improve the PMI of this coupling partner by applying alternative dehydrating agents.

If after these modifications were made, the MCR reaction was to be scaled up, additional considerations would need to be incorporated and more in depth assessments would be performed. The CHEM21 metrics toolkit at Second Pass additionally assesses Renewables Intensity, LCA, Cost and Safety. At the industrial scale, the cost of a process may still be a dominating factor in selecting a route. Improved green metrics can result in the lowering of costs due to increased efficiency, however many other factors need to be taken into consideration such as disposal costs, cost of reagents etc.

The study into the upstream processes for the multicomponent reactions highlighted the importance of considering the origin of the materials used in the design of novel methodologies. As the synthetic community moves towards greener approaches to the synthesis of industrially relevant compounds, we hope this study serves as a good guide in taking a holistic viewpoint with respect to green metrics and bearing in mind the origin from which the starting materials are sourced.

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