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ARTICLE TYPE

A comparative approach to the most sustainable protocol for the β-azidation of α,β-unsaturated ketones and acids

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In this contribution we have used our green metrics analysis to compare material efficiency, environmental impact, and safety-hazard impact in order to compare flow and batch procedures for azidation of α,β-unsaturated carbonyls. It has been proved that flow protocols possess a greener profile over the corresponding batch procedures based on identical chemistries. In this work the new flow procedure described is very efficient; however, the significant uncertainties in the environmental and safety-hazard impact scores are due to the lack of available toxicity, hazard, and occupational exposure data on trimethylsilyl azide and the resin catalysts used here. The results for the new flow procedure show significant and definite improvements over previously published work with respect to waste minimization/material efficiency and are consistent with satisfying green chemistry principles. The results obtained in this work prove the usefulness of our flow-approach for realizing highly efficient processes featuring a minimal waste production.

Introduction

In the last decade the importance of applying green metrics analysis in upholding green chemistry principles has been recognized generally[1] and specifically by the pharmaceutical industry.[2] Indeed, metrics analysis is central to the discipline of green chemistry and is the defining feature of this emerging area of chemistry. The use of metrics serves two important purposes: it substantiates claims of greenness through rigorous quantitative reasoning and it upholds ethical standards in the publication of scientific literature with respect to the detailed disclosure of experimental procedures for reproducible syntheses of compounds. However, its application to organic synthesis methodology has only been recently demonstrated in a few cases. Most of these involve the application of material efficiency metrics such as atom economy (AE),[3] E-factor,[1c,e,4] global reaction mass efficiency (RME),[5] and process mass intensity (PMI).[6] Examples include synthesis of 1,3-oxazin-2-ones,[7] isoprene production,[8] synthesis of PEG (polyethylene glycol)-based supports,[9] transition metal catalyzed reactions,[10] pyrazole syntheses,[11] three component synthesis of 1-amidoalkyl-2-naphthols,[12] glyphosate synthesis,[13] phosgene and phosgene-free syntheses of industrial chemicals,[14] oseltamivir phosphate syntheses,[15] *(S)*-3-aminobutanoic acid synthesis,[16] rose oxide synthesis,[17] synthesis of metal salts of acetylacetonate,[18] Biginelli adducts,[19] 1,3,4-thiadiazole-2-thiols,[20] fine chemicals,[21] ionic liquid syntheses,[22] sulfide oxidations,[23] photochemical reactions,[24] Elliott's alcohol,[25] synthesis of various methylating agents,[26] pegylation of menadiol and podophyllotoxin,[27] bromination of olefins,[28] elementary organic reactions,[29] and Ro 24-5904 synthesis.[30] The limitations of applying material efficiency metrics alone have also been discussed.[31] Examples of life cycle analysis including environmental impact and safety/hazard impact applied to organic reactions are still rare.[32] A key feature of metrics analysis that can help to gain further acceptance by the wider chemistry community is the display of results in an easy to understand graphical form that conveys visually both the attributes and weaknesses of a given kind of synthesis methodology, thereby guiding future optimization in a directed manner. In this context the present work details the application of material, environmental impact, and safety/hazard impact metrics to azidation reactions of α,β-unsaturated carbonyl derivatives using flow methodology.[33] This new way of carrying out organic transformations as opposed to the traditional glass vessel is the chemist's version of thinking outside the box. Though this method has often been described as meeting green principles such as improved safety through reduced contact with hazardous reagents and the potential of recycling solvents rather than their disposal after use, there has not yet been a metrics comparison of this method applied to a given reaction with previous literature procedures. This report also offers support for these claims.

Our research has been recently focused on the optimization of synthetic procedures employing eco-friendly reaction protocols based on the use of water,[34] solvent free conditions (SolFC)[35] and highly concentrated conditions (HiCC), combined with the use of heterogeneous catalysts.[36]

In recent years, we have been interested in the use of organic ammonium fluorides as way to activate Si-N and Si-O bonds. In this field, we have reported two alternative protocols for the β-azidation of α,β-unsaturated ketones based on the use of commercially available Amberlite IRA900F as catalyst under

SolFC[35g] and on the use of PS-DABCOF$_2$ as catalyst in water, that was synthesized by our previously reported procedure.[34a] We have also reported a protocol for the β-azidation of α,β-unsaturated carboxylic acids based on the use of PS-DABCOF as catalyst under SolFC.[35a] β-azido-carbonyl compounds have been synthesized by conjugate addition of N-nucleophile such as, N_3^- to α,β-unsaturated carbonyl compounds. A number of target molecules can be prepared via these intermediates, such as γ-amino alcohols and β-amino acids that are common motifs in many natural and biologically active compounds.[37]

According to the fact that our research goal is the definition of efficient protocols with high levels of sustainability, we have also been interested in the application of flow chemistry. In general, flow reactors can be an efficient technology to reduce the environmental impact of synthetic processes. The use of flow methods offer the possibility of realizing synthetic processes in a safe, reproducible and scalable manner; they may offer several advantages as compared to traditional batch reactors[38] such as the minimization of waste and in particular of the amount of organic solvent needed to isolate the final products and the optimization of the recovery and reuse of the solid catalysts.

In accordance with our previous reports in this field,[35c-e,36] we are interested in the definition of generally useful and practical procedures to recover and reuse the catalytic system and the desired product with the minimal cost in terms of time and waste disposal.

Methodology of Metrics Calculations

In carrying out a detailed green metrics analysis three groups of metrics were examined: (a) material efficiency metrics (reaction yield, AE,[3] global RME,[5] E-factor,[1c-e] PMI[6]; (b) environmental impact metrics (see Appendix for list of potentials, benign impact index for waste materials[39]); and (c) safety-hazard metrics (see Appendix for list of potentials, safety-hazard impact index for waste materials[40] and for input materials[40]). To ensure fairness in ranking, a set of reactions chosen for comparison leading to a particular product had a common starting substrate. The only variations were in the azide reagents and auxiliary materials such as catalysts, reaction solvents, work-up materials, and purification materials. All reactions examined were single-step reactions. Most literature procedures disclosed auxiliary material consumption, however, in cases when these were not disclosed the following assumptions were made: volumes of each kind of work-up extraction solvent was set equal to the volume of reaction solvent (e.g., if ether, saturated sodium bicarbonate solution, and brine were used in the work-up and 100 mL of reaction solvent were used, then 100 mL of each wash solvent for a total of 300 mL of work-up solvents was assumed), and the mass of drying agent was set to 2 g if the volume of reaction solvent was less than 20 mL or 10 g if the reaction volume was between 100 mL and 500 mL. Undisclosed masses of silica gel and volumes of eluents in chromatographic procedures could not be estimated reliably; therefore PMI values for such procedures appear as lower limits in the tables, i.e., values appear with a “greater than” inequality sign (>). Reactions with such designations should be interpreted with caution as having an associated uncertainty with respect to rankings. Stoichiometric amounts of water as reagent were used in the calculations for the flow methodology described in this work unless otherwise noted. Uncertainty estimates based on a simple data set incompleteness fraction for the environmental impact (EI) and safety-hazard impact (SHZI) scores were introduced as follows according to equation (1) where, x is the number of missing parameters for all substances used in a given reaction, n is the number of parameters needed to estimate EI (n = 8) or SHZI (n = 11) for each substance, and C is the total number of chemicals required in carrying out a given reaction including reagents, catalysts, additives, ligands, reaction solvents, work-up materials, and purification materials.

$$\%\,\text{uncertainty} = \frac{x}{nC}\ \text{X}\ 100 \qquad (1)$$

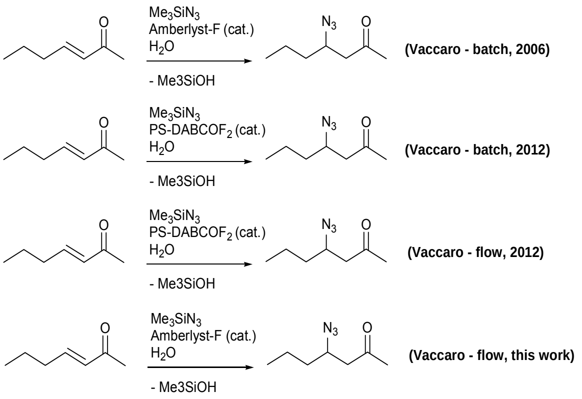
No weightings were attached to any of the parameters used since such an approach is compounded by the problem of arbitrary choice of weighting factors. Actual measures of uncertainty for each parameter value are unknown since these are not reported in the source references (e.g., error estimates for LD50 values are not stated in any database compilation of such parameters). This precludes any possibility of doing a thorough propagation of errors statistical analysis. Though we acknowledge that our approach is crude and simplistic we feel this interpretation of uncertainty is good enough to flag EI or SHZI estimates that are calculated based on key missing data for specific compounds used in a given chemical transformation, and therefore to interpret such estimates with appropriate caution. A complete listing of chemicals and the associated raw data for determining potentials is given in Table S1 in the Supporting Information. Missing data are also indicated in that table. For each reaction, radial polygons were used to display the results of all three groups of metrics to gauge overall performance. The vector magnitude ratio (VMR) obtained from the ratio of the vector magnitude of the variables making up the radial polygon diagrams versus those for the ideal green case as described previously[41] was used as the overall measure of “greenness” for ranking purposes. The trimethylsilyl azide reagent used in the present work has been advertised as a safer azide transfer reagent[42] compared to hydrazoic acid and sodium azide, however there has not been substantive evidence to support these claims as would be required for the present green metrics analysis. For example, this compound has no available data for the following parameters: oral LD50, dermal LD50, occupational exposure limit, water solubility, impact sensitivity, and Trauzl lead block test for explosive power. However, there is only one anecdotal report of an accidental explosion that has occurred with this reagent.[43] This shortcoming along with the uncertainties due to missing parameters described above needs to be considered in the interpretation of the ranking results for the present investigation.

Results and discussion

In this section we describe the results of the green metrics analysis for the synthesis of the four β-azido products from their respective α,β-unsaturated ketone or acid precursors.

(A) *4-azido-heptan-2-one*

For the synthesis of this ketone, the green performances of conventional batch and flow procedures may be directly compared. There were no other literature procedures available for comparison (see Scheme 1).



Scheme 1 Literature plans to synthesize 4-azido-heptan-2-one from hept-3-en-2-one.

From Figure 1, the new flow procedure described in this work lowers PMI by 59 % over the prior published flow procedure[34a] and by 73% and 84 % over the batch procedures.[34a,35g] As expected, the main contributor to E-factor and PMI for inputs is solvent usage. The new flow procedure is not performed under dry conditions and therefore the use of sodium sulfate is eliminated (drying agent) in the work-up. Water is considered in the calculation because it is consumed in a stoichiometric amount according to the reaction mechanism. This reduction is consistent with the highest VMR value found for the new flow procedure (see Figures 2A and 2B and Tables 1 and 2). From Figure 3, the major contributing potential to environmental impact from waste generated for all three methods is ingestion toxicity potential: trimethylsilanol (reaction byproduct) from both flow procedures and ethyl acetate (work-up solvent) from the batch procedure. The skin dose potential is the largest contributor to waste material hazards coming from trimethylsilanol and ethyl acetate.

For the input materials, the main hazard potential in the new flow procedure is risk phrase potential arising from trimethylsilyl azide. Ethyl acetate contributes to skin dose and corrosive liquid potentials. From Table 1, atom economies for all three methods are identical since the balanced chemical equation is the same (see Scheme 1). Reaction yield performances are virtually the same over the three procedures. The least safety-hazard impact score for input materials and the least environmental impact score for waste materials are found for the new flow procedure. Though the new flow procedure has the highest VMR values, it apparently has the lowest values for benign index for waste materials and for safety-hazard index for input materials compared to the batch procedure which has the highest values for these parameters. This apparent paradoxical situation arises since both of these indexes are calculated based on *mass weighted* impact potentials. In the case of the new flow procedure which produces the least amount of waste in absolute terms (as evidenced by its lowest PMI and E-factors), the proportion of the waste coming from the most offending byproduct, trimethylsilanol, is 63 %, whereas for the batch procedure it is only 5 %. This example is an illustration of a key point in striving for truly green syntheses. Optimization in the direction of producing benign and safe waste products suggests that not only the waste materials be composed of inherently lower impact potentials with respect to environment and safety, but also that the mass proportion of the most offending chemical with respect to the overall waste mass profile is kept to a minimum as far as possible.

(B) *3-azidocyclohexanone*

Scheme 2 shows the four known reactions for preparing 3-azidocyclohexanone. The Xia 2003[44] and 2004[45] use sodium azide as the azidation reagent, but only differ in the choice of catalyst; whereas, the Miller[46] and the present flow method use trimethylsilylazide in aqueous solution using DBU and Amberlyst-F as catalysts, respectively. From Figure 4, the new flow procedure has the lowest PMI overall. In the Miller plan, in which was generated controlled stoichiometries of HN_3 during the reaction, the solvent usage is very large. These are conservative estimate since the amounts of chromatographic solvents were not disclosed; hence, the true E-factor and PMI results for this method are much worse than present estimates indicate. The new flow procedure has the highest VMR (see Figures 5A and 5B and Table 3 and 4). From Figure 6, the greatest environmental impact from waste material is ingestion toxicity potential from trimethylsilanol (new flow procedure), sodium azide (both Xia plans), and acetic acid (Miller plan). For the safety-hazard impact from waste material, the skin dose potential from trimethylsilanol (new flow procedure), occupational exposure limit potential from sodium azide (both Xia plans) and dichloromethane (Miller plan) are the main contributors. For the safety-hazard impact from input material, the corrosive liquid potential from cyclohexenone (new flow procedure), OELP from sodium azide (both Xia plans) and dichloromethane (Miller plan) are the main contributors.

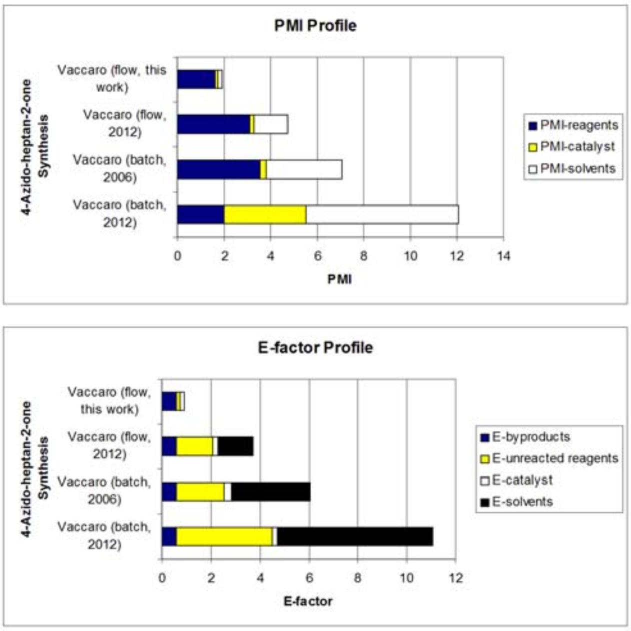


Figure 1 PMI and E-factor profiles showing individual contributions for the synthesis of 4-azido-heptan-2-one according to plans shown in Scheme 1.

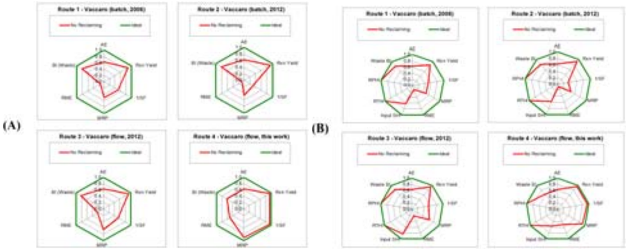


Figure 2 Figure 2. (A) Radial polygons showing results of material and environmental impact metrics; (B) Radial polygons showing results of material, environmental impact, and safety-hazard metrics for the synthesis of 4-azido-heptan-2-one according to plans shown in Scheme 1.

From Tables 3 and 4, we find that the Miller plan has the lowest atom economy, both Xia plans have the highest EI scores due to sodium azide reagent, and the new flow procedure has the lowest EI and SHZI scores. The variation in waste benign index values is small over the four synthesis methods - all are high. The new flow procedure has a lower input safety-hazard index compared to the Miller plan though the chemistry is very similar. The value for the Miller plan needs to be interpreted with caution since its SHI was determined with omission of the chromatographic purification solvents ethyl acetate and hexane since the masses of these were not disclosed. It is very likely that the new flow procedure would score higher if the details of the Miller plan were fully known. It is certain that these purification solvents will account for the bulk of the total mass of input materials used for the entire reaction.

Table 1 Summary of material and environmental impact metrics results for the synthesis of 4-azido-heptan-2-one according to plans shown in Scheme 1.

Plan	AE %	Yield %	PMI	BI (waste)	VMR	Total EI score	% U^a in EI
Vaccaro (batch, 2006)	63.3	87	7.05	0.8243	0.6291	26.05	27.1
Vaccaro (batch, 2012)	63.3	91	12.07	0.8040	0.6055	26.05	27.1
Vaccaro (flow, 2012)	63.3	93	4.73	0.8199	0.6728	36.38	23.2
Vaccaro (flow, this work)	63.3	95	1.92	0.6243	0.7848	20.95	30.0

^{a} % Uncertainty in total in total EI score

Table 2 Summary of safety-hazard metrics results for the synthesis of 4-azido-heptan-2-one according to plans shown in Scheme 1.

Plan	Input SHI	VMR	Total SHZI score	% U^a in SHZI
Vaccaro (batch, 2006)	0.6167	0.7268	53.1	25.8
Vaccaro (batch, 2012)	0.5718	0.7092	53.1	23.4
Vaccaro (flow, 2012)	0.8349	0.7755	53.6	24.7
Vaccaro (flow, this work)	0.5656	0.8175	29.1	38.6

^{a} % Uncertainty in total in total EI score

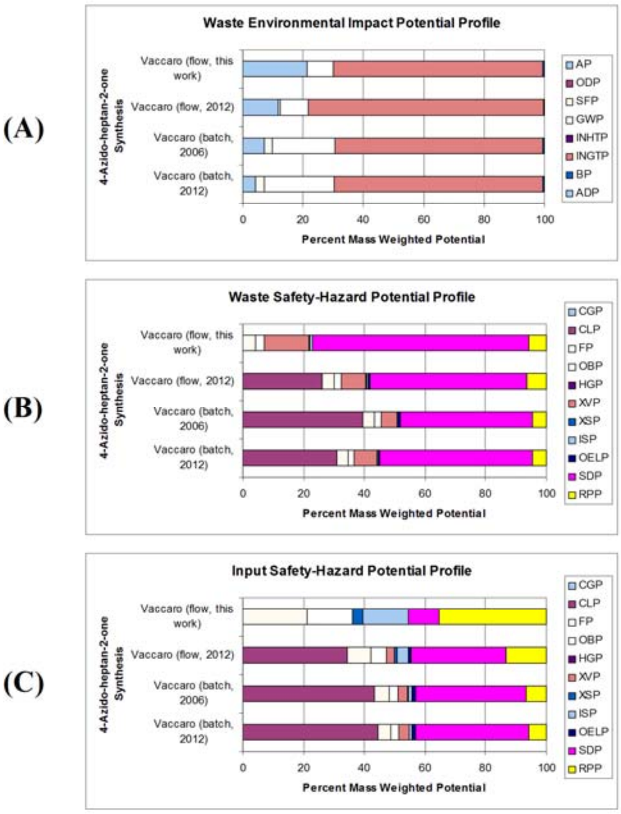
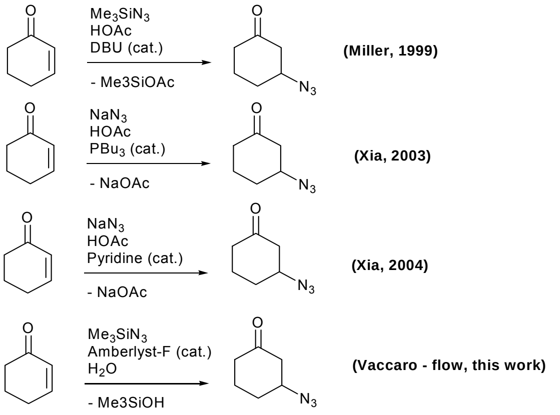


Figure 3 (A) Waste environmental impact, (B) waste safety-hazard, and (C) input safety-hazard potential profiles showing percent contributions of potentials for the synthesis of 4-azido-heptan-2-one according to plans shown in Scheme 1.

For the safety-hazard impact of waste materials, the skin dose potential from unreacted acrylic acid (new flow procedures), occupational exposure limit potential from unreacted sodium azide (Boyer and Blagg method) are the main contributors. For the safety-hazard impact of input materials, the same profile arises as for the safety-hazard impact of waste materials. There is little variation in values of waste benign indexes - all are high.



Scheme 2 Literature plans to synthesize 3-azidocyclohexanone from cyclohexenone.

Table 3 Summary of material and environmental impact metrics results for the synthesis of 3-azidocyclohexanone according to plans shown in Scheme 2.

Plan	AE %	Yield %	PMI	BI (waste)	VMR	Total EI score	% U^a. in EI
Vaccaro (this work)	60.7	98	3.2	0.9761	0.7572	290.1	20.8
Xia (2004)	62.9	95	25.2	0.9429	0.6277	4913.4	16.7
Xia (2003)	62.9	94	> 19.8	0.9267	0.6239	5025.5	8.3
Miller (1999)	51.3	90	> 59	0.9890	0.5987	558.0	20.8

^{a} % Uncertainty in total in total EI score

Table 4 Summary of safety-hazard metrics results for the synthesis of 3-azidocyclohexanone according to plans shown in Scheme 2.

Plan	Input SHI	VMR	Total SHZI score	% U^a in SHZI
Vaccaro (this work)	0.7733	0.8190	89.8	22.7
Xia (2004)	0.9343	0.7628	1389.1	15.2
Xia (2003)	0.9029	0.7565	1173.5	10.6
Miller (1999)	0.8747	0.7391	207.4	19.7

^{a} % Uncertainty in total in total EI score

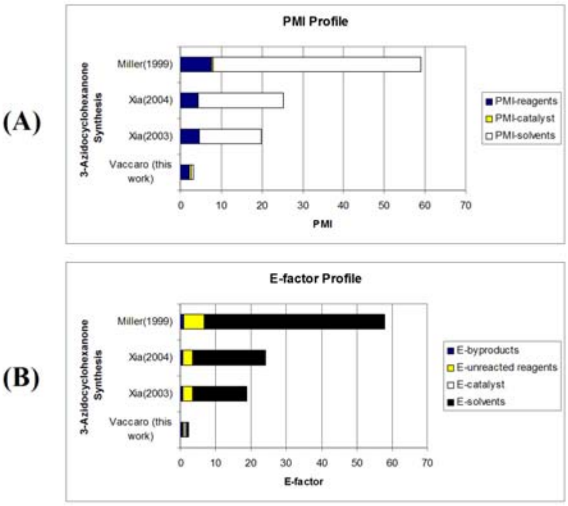


Figure 4 PMI and E-factor profiles showing individual contributions for the synthesis of 3-azidocyclohexanone according to plans shown in Scheme 2.

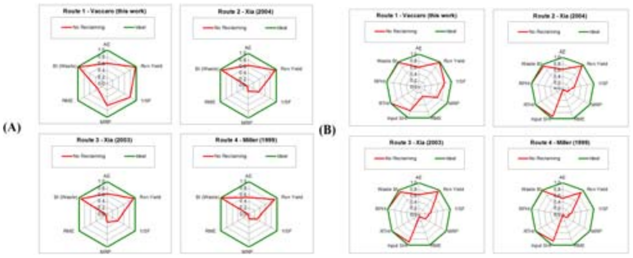


Figure 5 (A) Radial polygons showing results of material and environmental impact metrics; (B) Radial polygons showing results of material, environmental impact, and safety-hazard metrics for the synthesis of 3-azidocyclohexanone according to plans shown in Scheme 2.

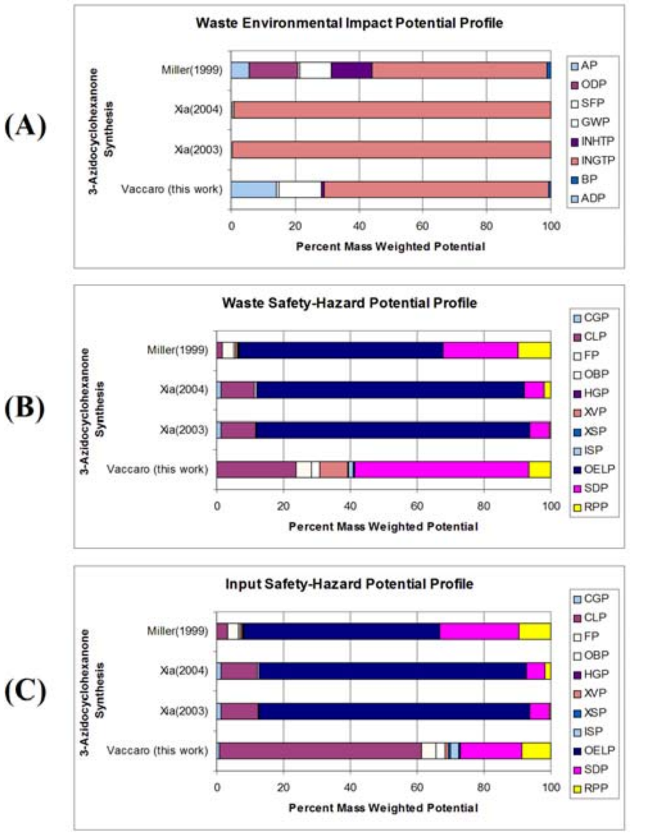
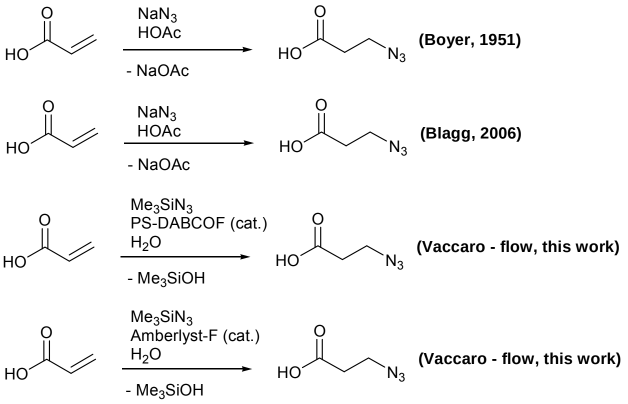


Figure 6 (A) Waste environmental impact, (B) waste safety-hazard, and (C) input safety-hazard potential profiles showing percent contributions of potentials for the synthesis of 3-azidocyclohexanone according to plans shown in Scheme 2.

The input SHI value for the new flow procedure is apparently lower than the other methods for the same reason as described for the synthesis plans for 3-azidocyclohexanone – the SHI determinations for the other methods suffer from omission of purification materials which were not disclosed.



Scheme 3 Literature plans to synthesize 3-azidopropanoic acid from acrylic acid.

Table 5 Summary of material and environmental impact metrics results for the synthesis of 3-azidopropanoic acid according to plans shown in Scheme 3.

Plan	AE %	Yield %	PMI	BI (waste)	VMR	Total EI score	% U^a in EI
Vaccaro (Amb-F)	56.1	80	4.5	0.9541	0.6978	3270.8	16.7
Vaccaro (PS-DABCOF)	56.1	99	3.6	0.9955	0.7519	3270.8	16.7
Boyer (1951)	58.4	24	> 39	0.9287	0.5349	7916.0	5.4
Blagg[48] (2006)	58.4	50	> 296	0.9910	0.5279	7797.9	3.6

[a] % Uncertainty in total in total EI score

Table 6 Summary of safety-hazard metrics results for the synthesis of 3-azidopropanoic acid according to plans shown in Scheme 3.

Plan	Input SHI	VMR	Total SHZI score	% U in SHZI
Vaccaro (Amb-F)	0.8151	0.7878	216.0	19.7
Vaccaro (PS-DABCOF)	0.8109	0.8199	216.0	19.7
Boyer (1951)	0.9058	0.7101	1315.2	6.5
Blagg (2006)	0.9689	0.7158	1320.6	5.2

[a] % Uncertainty in total in total EI score

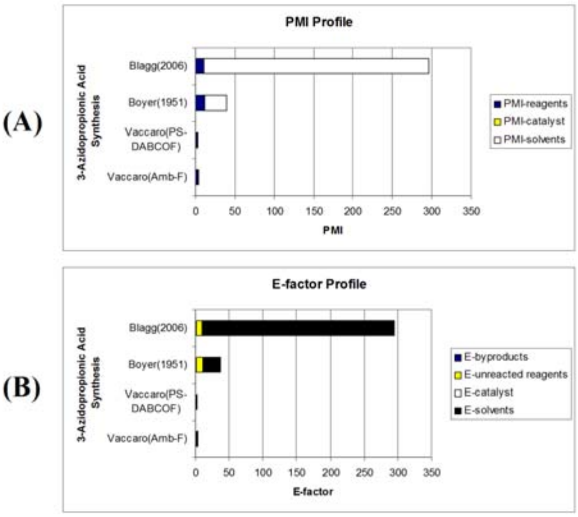


Figure 7 PMI and E-factor profiles showing individual contributions for the synthesis of 3-azidopropanoic acid according to plans shown in Scheme 3.

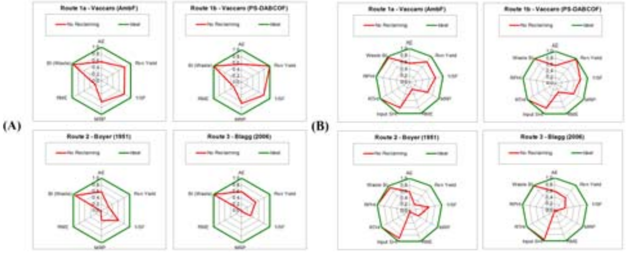


Figure 8 (A) Radial polygons showing results of material and environmental impact metrics; (B) Radial polygons showing results of material, environmental impact, and safety-hazard metrics for the synthesis of 3-azidopropanoic acid according to plans shown in Scheme 3.

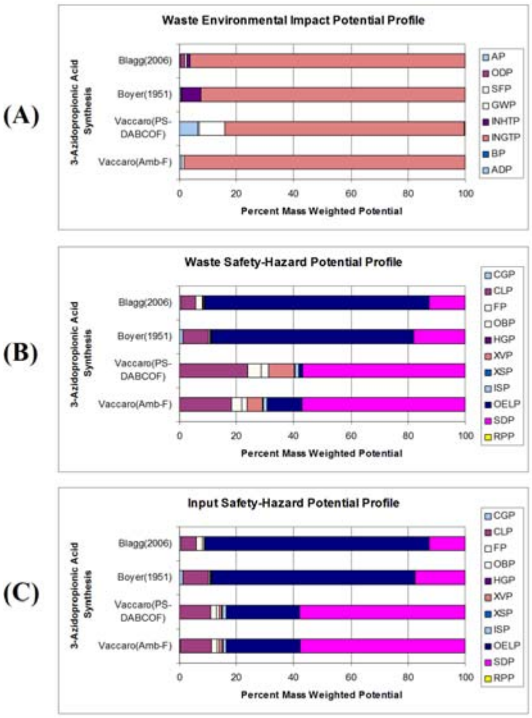
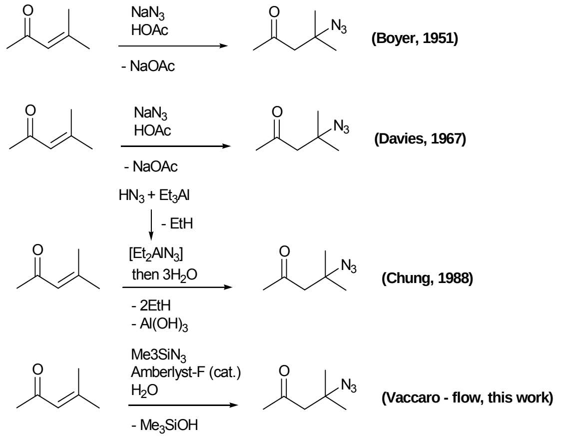


Figure 9 (A) Waste environmental impact, (B) waste safety-hazard, and (C) input safety-hazard potential profiles showing percent contributions of potentials for the synthesis of 3-azidopropanoic acid according to plans shown in Scheme 3.

(D) *4-azido-4-methyl-pentan-2-one*

From Scheme 4, the Boyer[47] and Davies[49] plans employ sodium azide in aqueous acetic acid to make 4-azido-4-methyl-pentan-2-one, whereas, the Chung[50] and Vaccaro plans use hydrazoic acid and trimethylsilyl azide, respectively. Figure 10 shows that the flow procedure has the lowest PMI and E-values. The Chung plan has the highest solvent usage due to reaction solvents (chloroform and hexane) and work-up solvents (dichloromethane) which contributes to the high PMI and E-values. From Table 7, it also has the lowest atom economy at 46 % compared with best plans at 63 %. The Boyer plan has the lowest yield (38%) compared with the flow procedure which has the highest (90%). The Boyer, Davies, and Chung plans all have minimum estimates for PMI due to the lack of disclosure of work-up and purification materials. The flow procedure has lowest EI score and the lowest SHZI score. The large EI scores for other plans arise from sodium azide (INGTP, Boyer and Davies) and from hydrazoic acid (INGTP, Chung). For the environmental impact for waste materials, the main contributions are skin dose potential from trimethylsilanol (flow procedure), OELP from sodium azide (Boyer and Davies plans), and OELP from dichloromethane and chloroform solvents (Chung plan) (see Figure 12). For the safety-hazard impact for waste materials, the same results apply as for the environmental impact for waste materials. For the safety-hazard impact for input materials, the skin dose potential from ethyl acetate and 4-methyl-pent-3-en-2-one (mesityl oxide) (flow procedure), OELP from sodium azide (Boyer and Davies plans), and OELP from dichloromethane and chloroform solvents (Chung plan) are the main contributors. The waste BI for the new flow procedure is noticeably lower than for the other plans – the most offending chemical, trimethylsilanol byproduct, represents 26 % of total mass of waste. For the Boyer plan the most offending unreacted sodium azide represents 5 % of the total waste; whereas, for the Davies plan unreacted sodium azide is only 0.9 % of the total waste. For the Chung plan unreacted hydrazoic acid represents 0.2 % of the total waste. From Table 8, the new flow procedure has the lowest SHI score: ethyl acetate represents 20 % of input materials mass; mesityl oxide presents 22 % of input materials mass; and trimethylsilyl azide which does not have all its impact parameters known represents 39 % of input materials mass. For the Boyer plan, sodium azide represents 6 % of the total input mass; whereas, for the Davies plan it is 1 % of input mass. For the Chung plan, chloroform and dichloromethane represent 10 % and 23 % of the total input mass, respectively. No OELP data are known for hydrazoic acid which accounts for 0.3 % of the input mass. From the radial polygons shown in Figure 11 and the results in Tables 7 and 8, the new flow procedure comes out on top with the highest VMR score.



Scheme 4 Literature plans to synthesize 4-azido-4-methyl-pentan-2-one from 4-methyl-pent-3-en-2-one (mesityl oxide).

Table 7 Summary of material and environmental impact metrics results for the synthesis of 4-azido-4-methyl-pentan-2-one according to plans shown in Scheme 4.

Plan	AE %	Yield %	PMI	BI (waste)	VMR	Total EI score	% U in EI
Vaccaro (this work)	61	90	3.5	0.8921	0.7220	76.3	16.7
Boyer (1951)	63.2	38	> 30.3	0.9493	0.5619	4721.5	5.4
Davies (1967)	63.2	66	> 137	0.9896	0.5657	4633.9	6.9
Chung (1988)	45.6	88	> 238	0.9975	0.5804	4074.8	6.9

[a] % Uncertainty in total in total EI score

Table 8 Summary of safety-hazard metrics results for the synthesis of 4-azido-4-methyl-pentan-2-one according to plans shown in Scheme 4.

Plan	Input SHI	VMR	Total SHZI score	% U in SHZI
Vaccaro (this work)	0.7697	0.7972	73.9	19.7
Boyer (1951)	0.9352	0.7279	1173.2	6.5
Davies (1967)	0.9697	0.7349	1400.2	7.1
Chung (1988)	0.9349	0.7376	227.1	7.1

[a] % Uncertainty in total in total EI score

Figure 10 PMI and E-factor profiles showing individual contributions for the synthesis of 4-azido-4-methyl-pentan-2-one according to plans shown in Scheme 4.

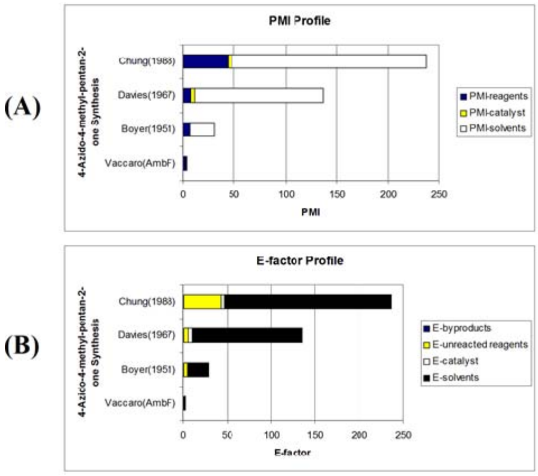


Figure 11 (A) Radial polygons showing results of material and environmental impact metrics; (B) Radial polygons showing results of material, environmental impact, and safety-hazard metrics for the synthesis of 4-azido-4-methyl-pentan-2-one according to plans shown in Scheme 4.

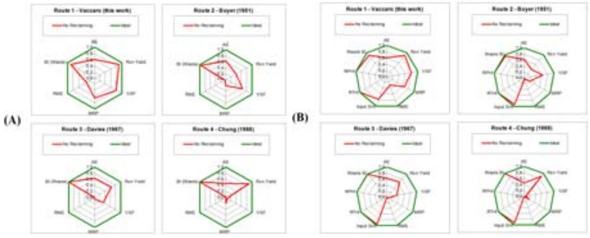
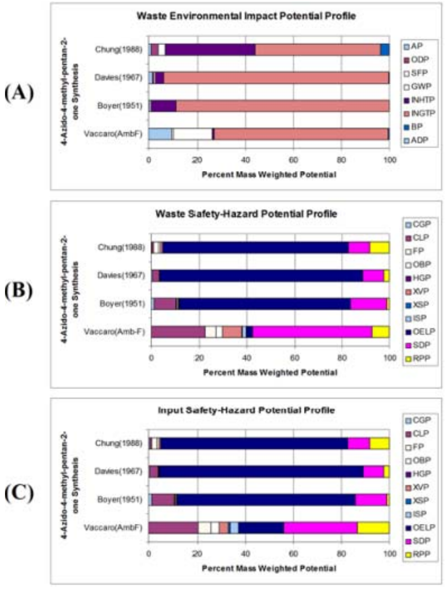


Figure 12 (A) Waste environmental impact, (B) waste safety-hazard, and (C) input safety-hazard potential profiles showing percent contributions of potentials for the synthesis of 4-azido-4-methyl-pentan-2-one according to plans shown in Scheme 4.



Experimental section

Unless otherwise stated, all solvents and reagents were used as obtained from commercial sources without further purification. GC analyses were performed by using Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), a FID detector and hydrogen as gas carrier. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^{1}H at 400 MHz and ^{13}C at 100.6 MHz) in $CDCl_3$ using TMS as the internal standard. Elemental Analyses were conducted on a Fisons EA1108CHN.

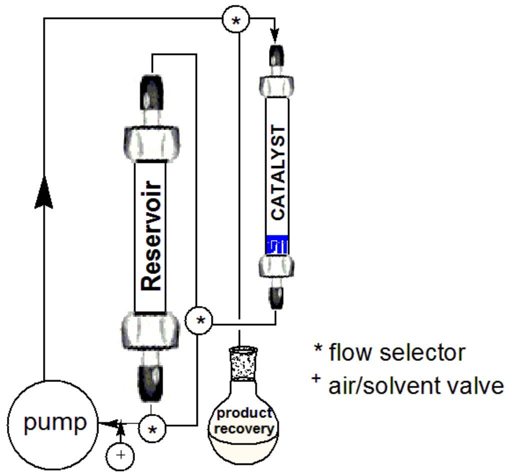


Figure 13 General schematic representation of the flow reactor used. Thermostated chamber is not shown for clarity.

Flow experimental procedure for the β-azidation of (3E)-hept-3-en-2-one with Amberlist-F as catalyst.

(3E)-hept-3-en-2-one (100 mmol, 11.216 g) and $TMSN_3$ (110 mmol, 14.6 mL) were charged into a glass column functioning as a reservoir. Amberlyst-F (10 mol%, 2.632 g), suitably dispersed in 1 mm diameter solid glass beads, was charged on a glass column; the equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 ml/min) through the catalyst column at 60 °C for 2.5 h to reach the complete conversion to 4-azidoheptan-2-one. After this time the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the product into the reservoir and empty the Amb-F column. To completely recover the product and clean the reactor, ethyl acetate (2 x 5 mL at a 1.5 mLmin^{-1}, 0.1 mL/mmol of enone) was pumped from the air/solvent valve through the catalyst column for 10 minutes (each fraction) and then collected in the reservoir as well. The solvent was removed (88% of recovered solvent) under vacuum to furnish pure 4-azidoheptan-2-one as an oil in 95% yield (14.725 g, 95 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

Flow experimental procedure for the β-azidation of Cyclohex-2-enone with Amberlist-F as catalyst.

Cyclohex-2-enone (100 mmol, 9.6 g) and $TMSN_3$ (150 mmol, 19.91 mL) were charged into a glass column functioning as a reservoir. Amberlyst-F (25 mol%, 6.316 g), suitably dispersed in 1 mm diameter solid glass beads, was charged on a glass column; the equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 ml/min) through the catalyst column at 30 °C for 6 h to reach the complete conversion to 3-azidocyclohexan-1-one. After this time the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the product into the reservoir and empty the Amb-F column. To completely recover the product and clean the reactor, ethyl acetate (2 x 5 mL at a 1.5 mLmin^{-1}, 0.1 mL/mmol of enone) was pumped from the air/solvent valve through the catalyst column for 10 minutes (each fraction) and then collected in the reservoir as well. The solvent was removed (88% of recovered solvent) under vacuum to furnish pure 3-azidocyclohexan-1-one as an oil in 98% yield (13.622 g, 98 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

Flow experimental procedure for the β-azidation of 4-methylpent-3-en-2-one with Amberlist-F as catalyst.

4-methylpent-3-en-2-one (100 mmol, 9.8 g) and $TMSN_3$ (150 mmol, 19.91 mL) were charged into a glass column functioning as a reservoir. Amberlyst-F (25 mol%, 6.316 g), suitably dispersed in 1 mm diameter solid glass beads, was charged on a glass column; the equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 ml/min) through the catalyst column at 60 °C for 3 h to reach the complete conversion to 3-azidocyclohexan-1-one. After this time the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the product into the reservoir and empty the Amb-F column. To completely recover the product and clean the reactor, ethyl acetate (2 x 5 mL at a 1.5 mLmin^{-1}, 0.1 mL/mmol of enone) was pumped from the air/solvent valve through the catalyst column for 10 minutes (each fraction) and then collected in the reservoir as well. The solvent was removed (88% of recovered solvent) under vacuum to furnish pure 3-azidocyclohexan-1-one as an oil in 90% yield (12.69 g, 90 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

Flow experimental procedure for the β-azidation of acrylic acid with Amberlist-F as catalyst.

Acrylic acid (100 mmol, 7.2 g) and $TMSN_3$ (150 mmol, 19.91 mL) were charged into a glass column functioning as a reservoir. Amberlyst-F (25 mol%, 6.316 g), suitably dispersed in 1 mm diameter solid glass beads, was charged on a glass column; the equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 ml/min) through the catalyst column at 30 °C for 3 h to reach the complete conversion to 3-azidopropionic acid. After this time the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the product into the reservoir and empty the Amb-F column. To completely recover the product and clean the reactor, ethyl acetate (2 x 5 mL at a 1.5 mLmin^{-1}, 0.1 mL/mmol of acrylic acid) was pumped from the air/solvent valve through the catalyst column for 10 minutes (each fraction) and then collected in the reservoir as well. The solvent was removed (88% of recovered solvent) under vacuum to furnish pure 3-azidopropionic acid in 80% yield (9.2 g, 80 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

Flow experimental procedure for the β-azidation of acrylic acid with PS-DABCOF as catalyst.

Acrylic acid (100 mmol, 7.2 g) was charged in a glass column functioning as reservoir and $TMSN_3$ (150 mmol, 19.91 mL) was slowly added into it. PS-DABCOF (15 mol%, 5.4 g), suitably dispersed in 1 mm diameter solid glass beads, was charged into a second glass column. The equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 ml/min) through the catalyst column at 60 °C for 0.5 h to reach the complete conversion to 3-azidopropionic acid. After this time the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the product into the reservoir and empty the PS-DABCOF column. To completely recover the product and clean the reactor, ethyl acetate (2 x 5 mL at a 1.5 $mLmin^{-1}$, 0.1 mL/mmol of acrylic acid) was pumped from the air/solvent valve through the catalyst column for 10 minutes (each fraction) and then collected in the reservoir as well. The solvent was removed (90% of recovered solvent) under vacuum to furnish pure 3-azidopropionic acid in >99% yield (11.4 g, 99.9 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

Conclusions

Based on the findings from this investigation, our green metrics analysis covering material efficiency, environmental impact, and safety-hazard impact corroborates that flow procedures for azidation of α,β-unsaturated carbonyl substrates have a greener profile over their published traditional batch procedures when identical chemistries of reactions are compared. However, for the analyses of a set of reactions to the same products by different azide reagents and catalysts, these results need to be interpreted with caution since some procedures did not disclose all auxiliary material consumption. More importantly, the significant uncertainties in the environmental and safety-hazard impact scores for the new flow procedure described in this work are due to the lack of available toxicity, hazard, and occupational exposure data on trimethylsilyl azide and the resin catalysts used here. Despite these shortcomings, the present results for the new flow procedure show significant and definite improvements over past published work with respect to material efficiency and are consistent with satisfying green chemistry principles. Waste production has been significantly reduced by adopting our flow conditions; in fact, the PMI has been considerably reduced for all substrates. The flow protocol is characterized by the use of minimal amounts of reagents and organic solvents during the reaction and the workup and by an easy procedure for the recovery and reuse of the catalyst. The results obtained in this work prove the usefulness of our flow-approach for realizing highly efficient processes featuring a minimal waste production. We hope to test further the greenness of other flow procedures on other chemical transformations to see if we find similar advantages over conventional batch processes.

Appendix

List of Abbreviations

AE = atom economy
BI = benign index
EI = environmental impact
PMI = process mass intensity
RPHI = reaction pressure hazard index
RTHI = reaction temperature hazard index
SHI = safety-hazard impact
SHZI = safety-hazard index
VMR = vector magnitude ratio
Abbreviations for Environmental Impact Potentials (8 parameters):
AP = acidification-basification potential
ODP = ozone depletion potential
SFP = smog formation potential
GWP = global warming potential
INHTP = inhalation toxicity potential
INGTP = ingestion toxicity potential
BP = bioconcentration potential
ADP = abiotic resource depletion potential
Abbreviations for Safety-Hazard Potentials (11 parameters):
CGP = corrosive gas potential
CLP = corrosive liquid/solid potential
FP = flammability potential
OBP = oxygen balance potential
HGP = hydrogen gas generation potential
XVP = explosive vapour potential
XSP = explosive strength potential
ISP = impact sensitivity potential
OELP = occupational exposure limit potential
SDP = skin dose potential
RPP = risk phrase potential

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Notes and references

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