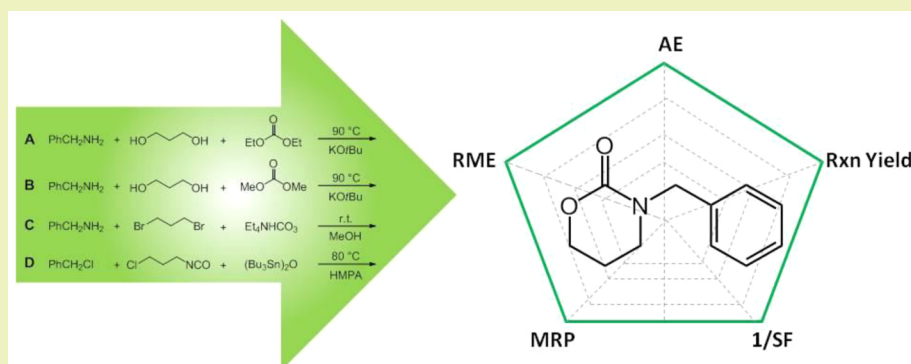# A Comparative Environmental Assessment for the Synthesis of 1,3-Oxazin-2-one by Metrics: Greenness Evaluation and Blind Spots

Sara Toniolo, Fabio Aricò,* and Pietro Tundo

Department of Environmental Science, Informatics and Statistics, University Ca' Foscari of Venice, 2137 Dorsoduro, 30123 Venezia, Italy

S *Supporting Information*

ABSTRACT: Alternative syntheses for the production of 3-benzyl-1,3-oxazinan-2-one are compared and evaluated employing green metrics. An environmental assessment has been performed using the algorithm recently developed by Andraos that takes into account the mass flows and the software EATOS that considers mass flows, environmental impacts of the substances involved, and waste produced. Strengths and critical spots of the environmental tools employed are also discussed. Data collected showed that the synthesis employing diethyl carbonate is the most promising one, having the lowest environmental impact.

KEYWORDS: *Green metrics, Cyclic carbamates, EATOS, Dimethyl carbonate, Andraos algorithm*

INTRODUCTION

One of the tasks of the chemical industry is to lead the challenge of industrial sustainability by providing eco-efficient products and monitoring the environmental impact of the processes used.[1] In theory, there are several well-known Life Cycle Assessment (LCA)-based tools that enable environmental assessment of a chemical process, such as FLASC (Fast Life Cycle Assessment for Synthetic Chemistry)[2] and the Ecosolvent.[3] However, carrying out a LCA study on a chemical process is seldom possible due to the lack of all the necessary information needed especially in the case of new synthetic pathways.[4] Furthermore, the FLASC tool is not freely available for public users,[5] and Ecosolvent focuses mainly on the quantification of the environmental impact of waste solvent treatment. As a consequence, recently, a set of measures, i.e., green metrics, have been developed in order to enable the assessment of chemical processes and to monitor their environmental impacts.[6−9] In particular, the E Factor (E),[10,11] Atom Economy (AE) promulgated by Trost,[12] Mass Index (MI),[13,14] and Reaction Mass Efficiency (RME),[15] which are the most common green metrics, provide information already in the design phase of a chemical process and define consumptions measured as material flows and waste production. Another popular metric used by the pharmaceutical

industry is Process Mass Intensity (PMI), which is very closely related to the E Factor (PMI = E + 1).[16]

Additional metrics have also been proposed for the evaluation of the "greenness" of a chemical process, i.e., the Stoichiometric Factor (SF) inherent to the use of excess reagents and the Material Recovery Parameter (MRP) that takes into account the use of auxiliary materials.[17]

Recently, two easily accessible tools for calculating green metrics have been developed and are extensively used: the EATOS[18] (Environmental Assessment Tool for Organic Synthesis) software and the algorithm developed by Andraos.[19]

The EATOS software allows evaluating a chemical process from a quantitative point of view through two metrics, i.e., S^{-1} and the E Factor. The first refers to the quantity of chemicals used and the latter to the amount of waste.

EATOS also calculates two other indices that refer to the nature of the materials and of the waste: (1) The Environmental Index input (EI_{in}) describes the Potential Environmental Impact (PEI) associated with the input substances involved in the synthesis and related to the reclaiming of resources and to the risk of the chemical reaction (PEI/kg

product). (2) The Environmental Index output (EI$_{out}$) describes the Potential Environmental Impact (PEI) related to several weighting categories such as human toxicity, chronic toxicity, and ecotoxicology (PEI/kg product).

A correct use of EATOS means that all the substances involved in the synthesis must be classified as substrates, solvents, catalysts, byproducts, coupled products, and auxiliary materials and are characterized by a quality factor (Q) from 1 to 10 related to the weighting categories. Thus, the software elaborates all the qualitative and quantitative data supplying, as a result, a histogram that evaluates the "greenness" of the chemical process.

The spreadsheets developed by Andraos measure the greenness of a synthetic pathway leading to a target product starting from the balanced chemical equation. The algorithm elaborates the stoichiometric coefficients and the amounts of material used in the experimental procedure. This tool, after elaborating the data, produces a plot in the form of a radial pentagon whose vertices are the Atom Economy (AE), Reaction Mass Efficiency (RME), Material Recovery Parameter (MRP), yield (Rxn Yield), and inverse of the Stoichiometric Factor (SF). The quantities representing the vertices are all fractions between 0 and 1; the boundary represents the ideal scenario of complete greenness with respect to each of the five metrics. The resulting pentagonal figure enables the comparison between the synthesis under study and an ideal process characterized by a regular pentagon where AE, yield, RME, 1/SF, and MRP are equal to one. Moreover, the algorithm envisages the construction of the synthesis tree[15] and the calculation of various metrics for any kind of synthesis pathway, both linear and convergent. Recently, the Andraos algorithm was extended to radial polygons that include also benign indices and safety hazard indices;[20,21] however, for the scope of this work, the simplest spreadsheets resulting in a radial pentagon have been used.

In this work, the synthesis of 3-benzyl-1,3-oxazinan-2-one has been selected as the case study to investigate the greenness of a reaction by the mean of two computational tools: EATOS and the algorithm developed by Andraos.

Oxazinan-2-ones (Figure 1) are compounds of interest due to their biological activity as they have been employed in the
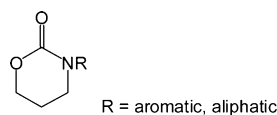

Figure 1. 1,3-Oxazinan-2-one motif.

treatment for Alzheimer's disease,[22] in herbicides with excellent crop–weed selectivity,[23] in the treatment of diseases mediated by the activation of β3-adrenoceptor,[24] in the treatment of diseases related to kinases activity,[25] and for the regulation of cholesterol.[26] There are many routes to oxazinan-2-ones, and the majority involve phosgene and isocyanate[27,28] (synthesis D, Scheme 1) or alkyl halide[29–31] chemistry (synthesis C, Scheme 1), while others require hard to obtain starting materials[32–35] or multiple steps to give the final product.[36,37] Recently, we have reported two new routes to 1,3-oxazinan-2-ones (syntheses A and B, Scheme 1) by a one-pot reaction of an amine with a 1,3-diol and a dialkyl carbonate (DAC) in the presence of a strong base.[38,39]

Short-chain dialkyl carbonates and in particular dimethyl carbonate (DMC) are renowned for possessing properties of low toxicity and high biodegradability,[40–42] which make them true green solvents and reagents.[43–46] DMC has been extensively used as an efficient eco-sustainable substitute of the most common methoxycarbonylating and methylating agents such as phosgene, methyl halides, or dimethylsulfate showing high selectivity with different monodentate and bidentate nucleophiles.[47–53]

Furthermore, it has been reported that substituting a chlorine atom with a carbonate moiety via DAC chemistry resulted in new green synthetic pathways with various applications, i.e., synthesis of linear and cyclic carbamates, preparation of cyclic intermediates for the cosmetic industry, selective mono-C-methylation of CH$_2$-acidic compounds such as arylacetonitriles, and intermediates of anti-inflammatory drugs.[43–53] Compared to their halogen analogues, organic carbonates were green and harmless for the operators and the environment. In particular, the toxicological tests carried out on selected DACs did not show any acute dermal, oral, or skin toxicity, and their olfactory impact was insignificant.[54]

In this study, four synthetic methodologies for 3-benzyl-1,3-oxazinan-2-one have been compared by means of the EATOS software and Andraos' algorithm. These syntheses have been selected, among the ones available in the literature, because they were judged most favorable with respect to availability of starting materials, synthetic methodology (one-pot reaction), and yields.

The two tools selected to evaluate the "greenness" of the chemical reaction under study present similar approaches. They both implement a model from the balanced chemical equation and from the complete experimental procedures of the synthetic pathways. The advantage of using two methods of computation is evident. EATOS calculates the S^{-1} and E Factor, and the algorithm developed by Andraos calculates the Atom Economy, Material Recovery Parameter, Stoichiometric Factor, and Reaction Mass Efficiency. Furthermore, the EATOS software takes into account the quality of the substances involved, such as the hazard. Comparing and evaluating the data collected employing these two tools not only gave a clear picture of the greenness of the syntheses investigated but also allowed insights on the strengths and the blind-spots of the tools used.

■ EXPERIMENTAL SECTION

Environmental Assessment. The tools used for the environmental assessment were the EATOS software and the algorithm developed by Andraos.

The data required for EATOS were obtained from the MSDS of Sigma Aldrich, and in particular, they include information dealing with risk (R phrases), human toxicity (LD$_{50}$ oral or dermal, hazard symbols), chronic toxicity (suspect of carcinogen, teratogen, mutagen by International Agency for Research on Cancer), eco-toxicology (WGK, EC$_{50}$ 48h *Daphnia magna*), and accumulation (BCF, logPow). These data have been also check for consistency with the ChemSpider Database. The prices were taken from Sigma Aldrich catalogue.

The data related to the amounts of material used and the balance equation were taken from the published papers,[28,31,38,39] both for EATOS and for the algorithm of Andraos.

The environmental assessment included the consumption of reactants, catalysts, solvents, and auxiliaries, and the production of waste. The workup and the purification phases were not included. The workup and purification phases are not included in the assessment because these procedures are not always disclosed in details. The costs of the materials were evaluated only using the EATOS software.

Scheme 1. Reaction Schemes of the Four Synthetic Pathways Leading to 3-Benzyl-1,3-oxazinan-2-one Investigated by EATOS Tool and Spreadsheets of Andraos (Modified Synthesis C)
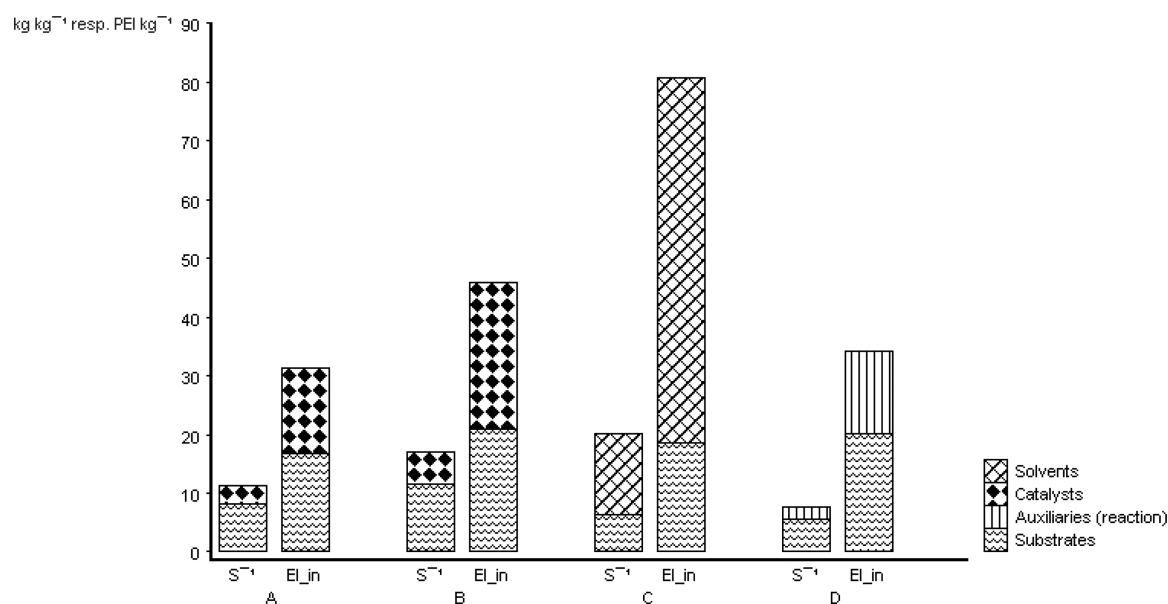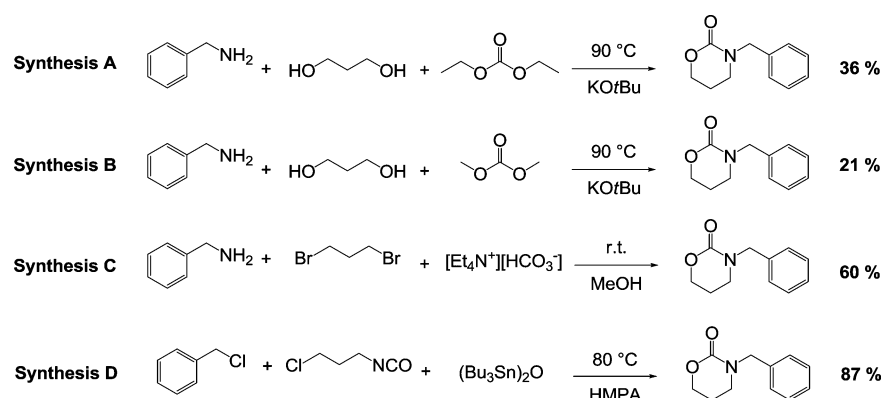
Figure 2. Mass index (S^{-1}) and environmental impact factor (EI_{in}) for syntheses A, B, C, and D.

RESULTS AND DISCUSSION

In this study the greenness of four synthetic pathways of 3-benzyl-1,3-oxazinan-2-one (Scheme 1) have been compared: (1) Synthesis A: Reaction of benzylamine with 1,3-propanediol in the presence of diethyl carbonate (DEC) and potassium *tert*-butoxide (36% yield).[39] (2) Synthesis B: Reaction of benzylamine with 1,3-propanediol in the presence of DMC and potassium *tert*-butoxide (21% yield).[39] (3) Synthesis C: Reaction of benzylamine with 1,3-dibromopropane in the presence of methanol (60% yield).[31] (4) Synthesis D: Reaction of benzylbromide with 3-chloropropyl isocyanate in the presence of hexamethylphosphoramide (HMPA) (87% yield).[28]

The system boundaries encompass the consumption of reactants, utilization of catalysts and solvents, coupled products, and production of byproducts. The metrics evaluation of the selected four syntheses was limited to the reaction step; the workup and purification phases are not included in the assessment because these procedures are not always disclosed in details.

The data collection was carried out in two phases. First, the experimental procedures were investigated taking into account the consumption of input materials and the production of waste. Second, the information dealing with the toxicological and eco-toxicological profile of the substances involved was collected. By means of EATOS, it was possible to calculate four indexes: S^{-1}, E Factor, EI_{in}, and EI_{out}. The software automatically referred the calculated indexes to 1 kg of product, i.e., 1 kg of 3-benzyl-1,3-oxazinan-2-one.

The parameters included in the calculation of EI_{in} are the prices of the starting materials and the risk statements collected from the material safety data sheets (MSDS). The data included in the calculation of EI_{out} are the hazard symbols and LD_{50} for human acute toxicity, any suspect carcinogen, mutagen, or teratogen substance for chronic human toxicity, the Water Endangerment Class (WGK) and EC_{50} (48 h, *Daphnia magna*) for eco-toxicology, and the Bioconcentration Factor (BCF) or the log P_{ow} (octanol–water partition coefficient) when available.

The mass indexes (S^{-1}) and the EI_{in} of the four synthetic pathways studied (A, B, C, D) are depicted in Figure 2.

Synthesis C resulted in the highest S^{-1} value (19.82) mainly ascribed to the amount of solvent used. Synthesis B, that used DMC as solvent and reagent, presents a S^{-1} equal to 16.87 that depends on 67% utilization of the substrates. Synthesis A, which differs from B only for the use of DEC, is characterized
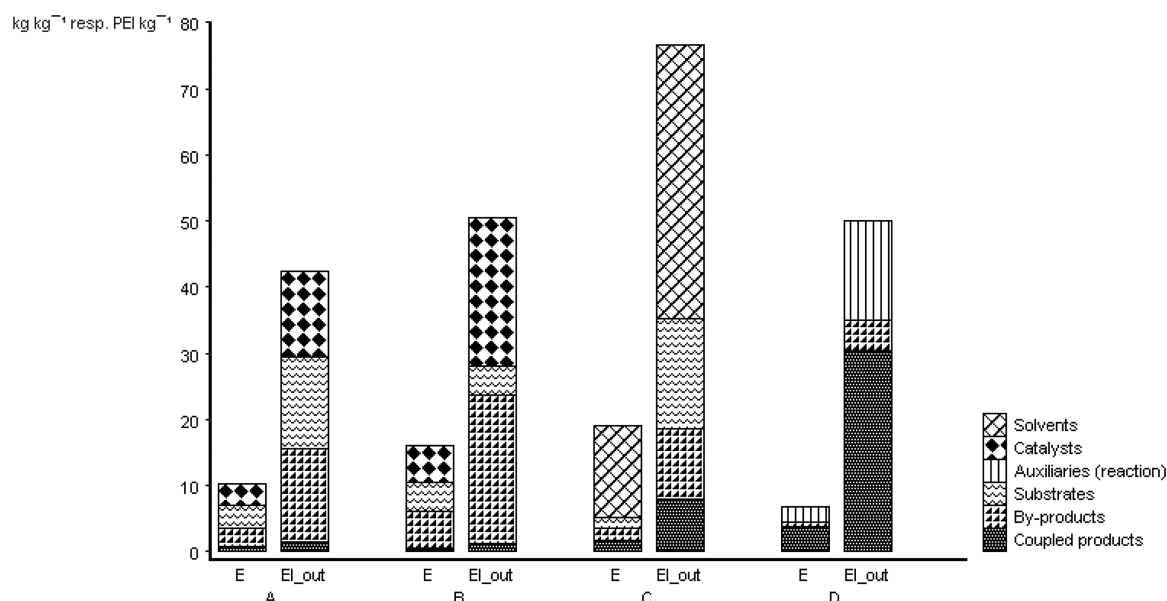
Figure 3. E Factor and Environmental Impact factor (EI_{out}) for syntheses A, B, C, and D.
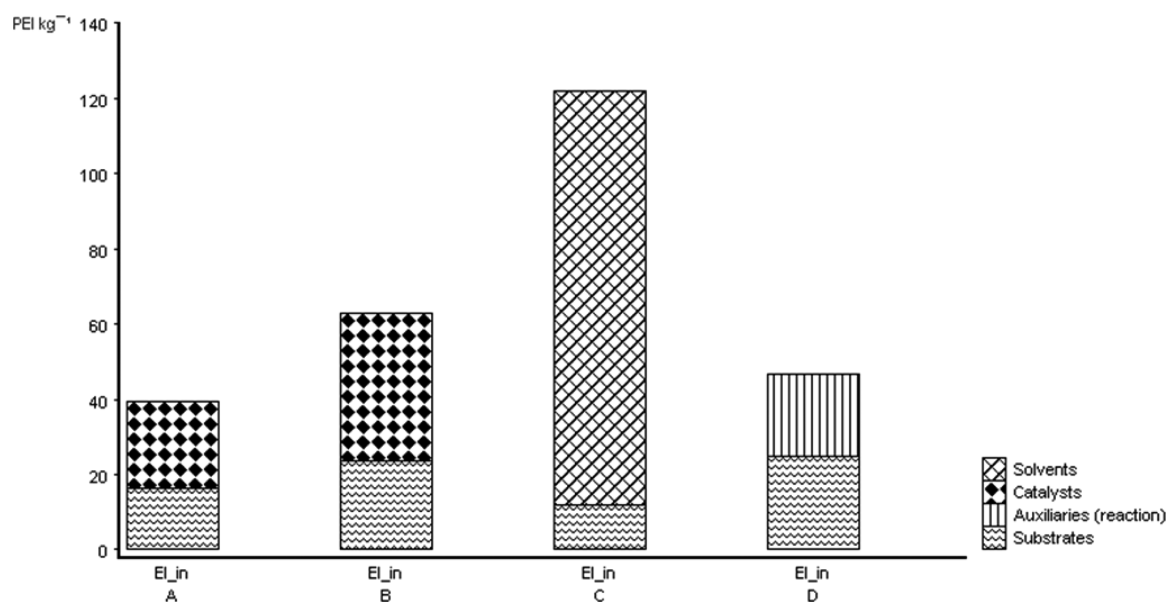

Figure 4. Environmental Index (EI_{in}) for syntheses A, B, C, and D without considering the prices of the substances involved.

by a S^{-1} equal to 11.06, a value that is attributed to 71% of the amount of substrates used. The synthesis characterized by the lowest S^{-1} is D (7.48) because the amounts of input materials are relatively low.

EATOS also calculates the EI_{in} metric combining the S^{-1} and Q values associated with the prices and risk statements in order to assess the nature of the substances involved. The synthesis characterized by the highest EI_{in} (80.4 PEI/kg) is C. This score is mainly associated to the utilization of methanol (77%) to which EATOS assigns a value (Q) of 8 for the risk and of 1 for the claiming of resources. Synthesis B presents an EI_{in} equal to 45.6 PEI/kg that is ascribed to 55% of potassium *tert*-butoxide (Q = 7 for the risk and 2 for the price). However, it is noteworthy that this synthetic pathway presents low risk values for the substrates. Synthesis D is characterized by an EI_{in} equal to 33.9 PEI/kg due to 41% of the HMPA (Q = 10 for the risk)

and for 59% of the substrates, in particular for the use of bis(tributyltin)oxide (Q = 6 for the risk category).

The synthesis characterized by the lowest EI_{in} (31,0 PEI/kg) is A because EATOS assigned low risk values to the substance used.

In order to consider also the waste produced during the synthesis and to take into account its nature, EATOS also calculates the E Factor and EI_{out}. The results are depicted in Figure 3. The comparison of the E Factors shows that synthesis C is more mass intensive than the other ones because the amount of waste produced is 18.81 kg/kg product. This is mainly due to the use of methanol (73% of the waste produced). Syntheses A and B produce, respectively, 10.06 and 15.87 kg waste/kg product. The less mass intensive is synthesis D for which the E Factor is equal to 6.48. In this synthetic pathway, there are no excess of reagents used, and the yield is higher than the other reactions.

The nature of the waste produced is disclosed by EI_{out}, obtained by combining the E Factor and the Q values assigned by EATOS to the substances. The highest environmental impact (76.35 PEI/kg) is calculated for synthesis C. Once again, this result is due to the use of methanol (54%; Q = 7 for the human toxicity) and to $[Et_4N^+][HCO_3^-]$ (22%; Q = 10 for the eco-toxicology). The EI_{out} obtained for synthesis D is equal to 49.90 PEI/kg; this result is mainly due (60%) to the nature of the coupled products: tributyltin bromide (Q = 10 for both human toxicity and eco-toxicology) and tributyltin chloride (Q = 7 and 10 for human and eco-toxicity). Syntheses A and B, that use DACs, present an environmental impact equal to 35.37 and 50.26 PEI/kg, respectively. The value assigned to synthesis A is due to the use of potassium *tert*-butoxide (37%; Q = 4 for the human toxicity) and to the utilization of DEC (24%, Q = 1 for human toxicity and 4 for eco-toxicity). The environmental impact assigned to synthesis B is attributed to 35% of the use of potassium *tert*-butoxide and 34% to the byproducts of the reaction.

In the Supporting Information, further specifications about the contributions of S^{-1}, EI_{in}, E, and EI_{out} due to solvents, catalysts, substrates, byproducts, and coupled products are reported. Overall, the metrics calculated by the mean of EATOS show that syntheses A and B present better results than the synthesis C both for S^{-1} and the E Factor, even if the yields are lower. Besides, although synthesis D presents the lowest values of S^{-1} and the E Factor as it is performed without excess of reagents and with a high yield, the substances involved are characterized by high Q values. In addition, the environmental impact assessment demonstrates that synthesis A has the lowest EI_{out} values because the substances involved in the process present a better toxicological and eco-toxicological profile.

It is noteworthy that EATOS utilizes as a measurement for the claiming of the resources the products prices, which are supposed to reflect the dimension of the environmental impact.[14] Thus, in order to investigate how the price affects the results, the same study previously reported was conducted without considering the costs.[55] It is evident from Figure 4 that the exclusion of the price often increases EI_{in}. In particular, in the case of dangerous substances characterized by a medium cost as the HMPA, the price leads to a reduced environmental impact factor. Also in this case, comparing the four synthetic pathways leading to 1,3-oxazinan-2-one, synthesis A involving DEC has a lower value of EI_{in}.

The comparison between the four syntheses for the production of 3-benzyl-1,3-oxazinan-2-one was also investigated by the mean of the algorithm developed by Andraos that allows the calculation of the raw materials footprint (Table 1).

The results obtained (Table 1, Figure 5) show that synthesis D is closer to the ideal conditions compared to the other reactions. Syntheses A and B are characterized by higher AE but lower SF^{-1} than the other reactions. However, the algorithm does not calculate environmental impact factor and does not take into account the nature of the substances involved in the process.

The assessment performed demonstrates that syntheses A and B present a better environmental profile than synthesis C. AE, MRP, and RME have higher values, whereas the E Factor and S^{-1} are lower. If the environmental impact is taken into account, the EATOS software confirms that the quality of the substances involved in syntheses A and B and the nature of the

Table 1. Comparison of Raw Material Footprint for Syntheses A–D and the Ideal According to the Andraos Spreadsheet.[a]

	AE	Rxnyield	1/SF	MRP	RME
synthesis A	0.63	0.36	0.56	0.70	0.09
synthesis B	0.69	0.21	0.60	0.66	0.05
synthesis C	0.38	0.60	0.72	0.30	0.05
synthesis D	0.21	0.87	1.00	0.71	0.13
ideal	1.00	1.00	1.00	1.00	1.00

[a]AE = Atom Economy. Rxn yield = Reaction yield. SF = Stoichiometric Factor. MRP = Material Recovery Parameter. RME = Reaction Mass Efficiency.
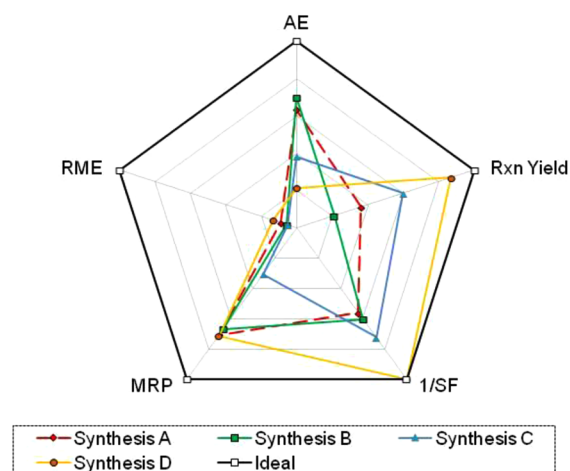

Figure 5. Comparison of the raw material footprint for syntheses A, B, C, and D and the ideal.

waste produced are more eco-friendly than synthesis C. On the other hand, synthesis D is characterized by higher values of MRP and RME and lower values of the E Factor and S^{-1} compared to DACs-based synthetic approaches. However, syntheses A and B showed a similar (synthesis B) or better (synthesis A) environmental impact profile than synthesis D.

Considering all the green metrics investigated for this study, it is evident that a greenness evaluation dealing only with MRP, RME, E Factor, and S^{-1} can be misleading. The EATOS software and Andraos algorithm should be both used in order to investigate the greenness of a reaction. The calculation of MRP, RME, SF, E Factor, and S^{-1} give a clear picture of the mass involved and of the quantity of waste but not of their nature.

■ CONCLUSIONS

An environmental assessment of four syntheses for the production of 3-benzyl-1,3-oxazinan-2-one has been performed. Two tools were employed: the algorithm developed by Andraos that takes into account the quantity of materials involved and waste produced and the EATOS software that considers the amount and the nature of substances and waste.

The study on the synthesis of 3-benzyl-1,3-oxazinan-2-one demonstrates that in order to have a complete picture of the greenness of a synthesis the amounts of materials involved and of waste produced and data about their nature should be taken into account. Indeed, a greenness evaluation only dealing with MRP, RME, E Factor, and S^{-1} via the Andraos algorithm can be misleading because the contribution due to the nature of the

1060

dx.doi.org/10.1021/sc500070t | ACS Sustainable Chem. Eng. 2014, 2, 1056–1062

materials is not disclosed. However, even if EATOS considers also the environmental profile of the substances, the influence of toxic materials results are mitigated by their employment in small amounts. Thus, a careful interpretation of the results obtained is important in order to understand if low values of EI_{in} and EI_{out} are due to an efficient synthesis performance or to a good environmental profile of the substances.

In our case study, i.e., the synthesis of 3-benzyl-1,3-oxazinan-2-one, the procedures involving DACs (syntheses A and B) showed a better environmental profile than the synthetic approach that employs tetraethylammonium bicarbonate (synthesis C). On the other hand, synthesis D, having a high reaction yield and a good stoichiometric factor, seemed to be closer to the ideal reaction conditions for the preparation of the selected 1,3-oxazinan-2-one. This discrepancy suggests that a real green optimization for the synthesis of cyclic carbamates has not yet been achieved as the most material efficient plan (synthesis D) is not also the most benign one (synthesis A). However, an accurate evaluation of the environmental impact profile must take in account the toxicity of the substances involved (Q values) that in the case of synthesis D resulted in higher values than for DACs-based syntheses A and B. This is particularly reflected in the values of EI_{in} and EI_{out}.

We can then conclude that among the synthetic procedures investigated the preparation of the 1,3-oxazinan-2-one employing DEC (synthesis A) resulted in the most promising one having the smaller environmental impact, although an improvement of the raw materials footprint is still necessary and currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

S^{-1}, EI_{in}, E, and EI_{out} data calculated by EATOS software, as well as the spreadsheets of the Andraos algorithm for syntheses A−D. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +39 041 234 8600. Tel: +39 041 234 8642. E-mail: Fabio.arico@unive.it.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Jenck, J. F.; Agterberg, F.; Droescher, M. J. Products and processes for a sustainable chemical industry: a review of achievements and prospects. *Green Chem.* **2004**, *6*, 544−556.

(2) Curzons, A. D.; Jimènez-González, C.; Duncan, A. L.; Constable, D. J. C.; Cunningham, V. L. Fast life cycle assessment of synthetic chemistry (FLASC) tool. *Int. J. LCA.* **2007**, *12*, 272−280.

(3) Capello, C.; Hellweg, S.; Hungerbühler, K. Environmental assessment of waste-solvent treatment options. *J. Ind. Ecol.* **2007**, *12*, 111−127.

(4) Gaber, Y.; Törnvall, U.; Orellana-Coca, C.; Amin, M. A.; Hatti-Kaul, R. Enzymatic synthesis of N-alkanoyl-N-methylglucamide surfactants: Solvent-free production and environmental assessment. *Green Chem.* **2010**, *12*, 1817−1825.

(5) This tool has been developed by Glaxo Smith Kline, and it is used only within its laboratories.

(6) Dunn, P. J.; Galvin, S.; Hattenbach, K. The development of an environmentally benign synthesis of sildenafil citrate (Viagra) and its assessment by green chemistry metrics. *Green Chem.* **2004**, *6*, 43−48.

(7) Demirci, U. B. How green are the chemicals used as liquid fuels in direct liquid-feed fuel cells? *Environ. Int.* **2009**, *35*, 626−631.

(8) Lombardo, M.; Gianotti, K.; Licciulli, S.; Trombini, C. An environmentally friendly α-hydroxyallylation reaction of the Garner aldehyde: A comparative assessment of alternative Barbier conditions. *Tetrahedron* **2004**, *60*, 11725−11732.

(9) Eissen, M.; Mazur, R.; Quebbemann, H. G.; Pennemann, K. H. Atom economy and yield of synthesis sequences. *Helv. Chim. Acta* **2004**, *87*, 524−535.

(10) Sheldon, R. A. Catalysis: The key to waste minimization. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 381−388.

(11) Sheldon, R. A. Atom efficiency and catalysis in organic synthesis. *Pure Appl. Chem.* **2000**, *72*, 1233−1246.

(12) Trost, M. B. The atom economy—A search for synthetic efficiency. *Science* **1991**, *254*, 1471−1477.

(13) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. So you think your process is green, how do you know?—Using principles of sustainability to determine what is green—A corporate perspective. *Green Chem.* **2001**, *3*, 1−6.

(14) Metzger, J. O.; Eissen, M. Concepts on the contribution of chemistry to a sustainable development. Renewable raw materials. *C. R. Chim.* **2004**, *7*, 569−581.

(15) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. Metrics to 'green' chemistry—Which are the best? *Green Chem.* **2002**, *4*, 521−527.

(16) Jiménez-González, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. Using the right green yardstick: Why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes. *Org. Process Res. Dev.* **2011**, *15*, 912−917.

(17) Andraos, J. Global green chemistry metrics analysis algorithm and spreadsheets: evaluation of the material efficiency performances of synthesis plans for oseltamivir phosphate (Tamiflu) as a test case. *Org. Process Res. Dev.* **2009**, *13*, 161−185.

(18) Eissen, M.; Metzger, J. O. Environmental performance metrics for daily use in synthetic chemistry. *Chem.—Eur. J.* **2002**, *8*, 3580−3585.

(19) Andraos, J. On using tree analysis to quantify the material, input energy, and cost throughput efficiencies of simple and complex synthesis plans and networks: Towards a blueprint for quantitative total synthesis and green chemistry. *Org. Process Res. Dev.* **2001**, *10*, 212−240.

(20) Andraos, J. Safety/hazard indices: Completion of a unified suite of metrics for the assessment of "greenness" for chemical reactions and synthesis plans. *Org. Process Res. Dev.* **2013**, *17*, 175−192.

(21) Andraos, J. inclusion of environmental impact parameters in radial pentagon material efficiency metrics analysis: using benign indices as a step towards a complete assessment of "greenness" for chemical reactions and synthesis plans. *Org. Process Res. Dev.* **2012**, *16*, 1482−1506.

(22) Fuchs, K.; Eickmeier, C.; Heine, N.; Peters, S.; Dorner-Ciossek, C.; Handschuh, S.; Nar, H.; Klinder, K. U.S. Patent US 2010/144681 A1, 2010.

(23) Tomokazu, H.; Yasuko, Y.; Toshihiko, S.; Koki, M. European Patent EP 2085392 A1, 2009.

(24) Berger, R.; Chang, L.; Edmonson, L. S. D.; Goble, S. D.; Harper, B.; Kar, N. F.; Kopka, I. E.; Li, B.; Morriello, G. J.; Moyes, C. R.; Shen, D. M.; Wang, L.; Wendt, H. International Patent WO 2009/123870 A1, 2009.

(25) Li, Y.; Yao, W.; Rodgers, J. International Patent WO 2009/64835 A1, 2009.

(26) Ali, A.; Sinclair, P. J.; Taylor, G. E. U.S. Patent US 2009/018054 A1, 2009.

(27) Fujiwara, M.; Baba, A.; Matsuda, H. J. The cycloaddition of heterocumulenes to oxetanes. *Hetrocyclic Chem.* **1989**, *26*, 1659−1663.

(28) Shibata, I.; Nakamura, K.; Baba, A.; Matsuda, H. Formation of n-tributylstannyl heterocycle from bis(tributyltin) oxide and ω-haloalkyl isocyanate. One-pot convenient synthesis of 2-oxazolidinones and tetrahydro-2H-1,3-oxazin-2-one. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 853−859.

(29) Jung, J.; Avery, M. A. An efficient synthesis of cyclic urethanes from Boc-protected amino acids through a metal triflate-catalyzed intramolecular diazocarbonyl insertion reaction. *Tetrahedron Lett.* **2006**, *47*, 7969−7972.

(30) Wang, G.; Ella-Menye, J.; Sharma, V. Synthesis and antibacterial activities of chiral 1,3-oxazinan-2-one derivatives. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2177−2181.

(31) Trifunovic, S.; Dimitrijevic, D.; Vasic, G.; Vukicevic, R. D.; Radulovic, N.; Vukicevic, M.; Heinemann, F. W. New simple synthesis of N-substituted 1,3-oxazinan-2-ones. *Synthesis* **2010**, *6*, 943−946.

(32) Kayaki, Y.; Mori, N.; Ikariya, T. Palladium-catalyzed carboxylative cyclization of α-allenyl amines in dense carbon dioxide. *Tetrahedron Lett.* **2009**, *50*, 6491−6493.

(33) Rice, G. T.; White, M. C. Allylic C−H amination for the preparation of syn-1,3-amino alcohol motifs. *J. Am. Chem. Soc.* **2009**, *131*, 11707−11711.

(34) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. Striking AcOH acceleration in direct intramolecular allylic amination reactions. *Chem.—Eur. J.* **2009**, *15*, 11078−11082.

(35) Mangelinckx, S.; Nural, Y.; Dondas, H. A.; Denolf, B.; Sillanpaa, R.; De Kimpe, N. Diastereoselective synthesis of 6-functionalized 4-aryl-1,3-oxazinan-2-ones and their application in the synthesis of 3-aryl-1,3-aminoalcohols and 6-arylpiperidine-2,4-diones. *Tetrahedron* **2010**, *66*, 4115−4124.

(36) Kim, Y. J.; Varma, R. S. Microwave-assisted preparation of cyclic ureas from diamines in the presence of ZnO. *Tetrahedron Lett.* **2004**, *45*, 7205−7208.

(37) Ella-Menye, J.; Sharma, V.; Wang, G. New synthesis of chiral 1,3-oxazinan-2-ones from carbohydrate derivatives. *J. Org. Chem.* **2005**, *70*, 463−469.

(38) McElroy, C. R.; Aricò, F.; Benetollo, F.; Tundo, P. Cyclization reaction of amines with dialkyl carbonates to yield 1,3-oxazinan-2-ones. *Pure Appl. Chem.* **2012**, *84*, 707−719.

(39) McElroy, C. R.; Aricò, F.; Tundo, P. 1,3-oxazinan-2-ones from amines and 1,3-diols through dialkyl carbonate chemistry. *Synlett* **2012**, *23*, 1809−1815.

(40) Asahi Kasei Chemicals Corporation. World Patent WO2007/34669 A1, 2007.

(41) *The Merck Index*; Budavari, S., Ed.; Merck and Co., Inc.: Ralway, NJ, 1989.

(42) Tundo, P.; Selva, M. The chemistry of dimethyl carbonate. *Acc. Chem. Res.* **2002**, *35*, 706−716.

(43) Aricò, F.; Toniolo, U.; Tundo, P. 5-Membered N-heterocyclic compounds by dimethyl carbonate chemistry. *Green Chem.* **2012**, *14*, 58−61.

(44) Aricò, F.; Tundo, P.; Maranzana, A.; Tonachini, G. Synthesis of five-membered cyclic ethers by reaction of 1,4-diols with dimethyl carbonate. *ChemSusChem* **2012**, *5*, 1578−1586.

(45) Tundo, P.; Aricò, F.; Gauthier, G.; Rossi, L.; Rosamilia, A. E.; Bevinakatti, H. S.; Sievert, R. L.; Newman, C. P. Green synthesis of dimethyl isosorbide. *ChemSusChem* **2010**, *3*, 566−570.

(46) Tundo, P.; Aricò, F. Dimethyl carbonate as a sacrificial molecule for the synthesis of 5-membered N- and O-heterocycles. *J. Chin. Chem. Soc.* **2012**, *59*, 1375−1384.

(47) Rosamilia, A. E.; Aricò, F.; Tundo, P. Reaction of the ambident electrophile dimethyl carbonate with the ambident nucleophile phenylhydrazine. *J. Org. Chem.* **2008**, *73*, 1559−1562.

(48) Tundo, P.; Memoli, S.; Hérault, D.; Hill, K. Synthesis of methylethers by reaction of alcohols with dimethylcarbonate. *Green Chem.* **2004**, *6*, 609−612.

(49) Tundo, P.; Aricò, F.; Rosamilia, A. E.; Memoli, S. Synthesis of dialkyl ethers by decarboxylation of dialkyl carbonates. *Green Chem.* **2008**, *10*, 1182−1189.

(50) Tundo, P.; McElroy, C. R.; Aricò, F. Synthesis of carbamates by reaction of amines with dialkyl carbonates: influence of leaving and entering groups. *Synlett* **2010**, *10*, 1567−1571.

(51) Rosamilia, A. E.; Aricò, F.; Tundo, P. Insight into the hard-soft acid-base properties of differently substituted phenylhydrazines in reactions with dimethyl carbonate. *J. Phys. Chem. B* **2008**, *112*, 14525−14529.

(52) Aricò, F.; Chiurato, M.; Peltier, J.; Tundo, P. Sulfur and nitrogen mustard carbonate analogues. *Eur. J. Org. Chem.* **2012**, 3223−3228.

(53) Aricò, F.; Evaristo, S.; Tundo, P. Chemical behavior and reaction kinetics of sulfur and nitrogen half-mustard and Iprit carbonate analogues. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1319−1325.

(54) A specific example is DACs containing ether functionality ($CH_3OCH_2CH_2OCH_2CH_2OCOOCH_3$) that have a negligible toxicological profile as hereunder reported: (1) Riva, L.; Mangano, R.; Tundo, P. Patent PCT/IB2008/003409, 2008. (2) Acute dermal toxicity (determined according to the Guidelines for Testing of Chemicals, n° 402, February 24, 1987, Organization for Economic Co-operation and Development" (OECD)): non-toxic, not dangerous. (3) Acute oral toxicity (OECD Guidelines for Testing of Chemicals, n° 420, December 17, 2001): category 5/NC of the GHS classification (no symptom). (4) Ocular irritation (OECD Guidelines for Testing of Chemicals, n° 405, February 24, 1987): irritating. (5) Skin irritation (OECD Guidelines for Testing of Chemicals, n° 404, April 24, 2002): non-irritating. (6) Skin sensitivity (OECD Guidelines for Testing of Chemicals, n° 406, July 17, 1992, and UNI EN ISO 19993-10:2004): non-sensitizing.

(55) The source of pricing data used was Sigma Aldrich catalog (March 2013), and the currency is euro.