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Federico Mundo, Sylvain Caillol, Vincent Ladmiral, Michael a R Meier. On Sustainability Aspects of the Synthesis of Five-Membered Cyclic Carbonates. ACS Sustainable Chemistry & Engineering, 2024, 12 (17), pp.6452-6466. 10.1021/acssuschemeng.4c01274 . hal-04564897

**HAL Id: hal-04564897**

**<https://hal.science/hal-04564897v1>**

Submitted on 1 May 2024

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# On sustainability aspects of the synthesis of five-membered cyclic carbonates

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**Keywords:** Sustainability, E-factor, cyclic carbonates, synthetic methods.

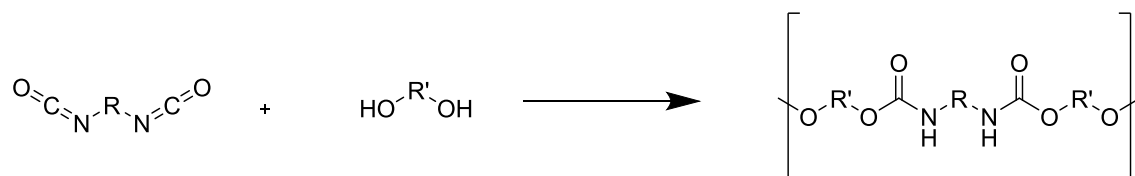
## ABSTRACT

The synthesis of cyclic carbonates, substrates gaining growing interest due to their broad spectrum of applications, is analyzed from a Green Chemistry perspective. Extensive research has been carried out on the synthesis of these substances, which are of interest especially for the preparation of so-called non-isocyanate polyurethanes (NIPUs). Often, the renewability of the raw materials, derived for instance from carbon dioxide, diols, urea, or alkyl carbonates is taken into account, without considering sustainability aspects of their synthesis protocols. In this review, we employ E-factors and discuss basic toxicity information to compare numerous approaches and data reported in the literature for synthesizing the most common cyclic carbonates to provide a useful, although not exhaustive, first sustainability evaluation. This study highlights that to achieve a more sustainable manufacture of cyclic carbonates, the renewability of the starting materials has to be matched with safer chemicals and mild and efficient reaction protocols in order to limit the environmental impact of their synthesis.

## INTRODUCTION

The increasing awareness concerning the environmental impact of fossil fuels and the safety of workers led to an increased interest in renewable resources and alternative synthetic strategies in order to reduce environmental and human risks. In this respect, polyurethanes (PUs) are a very important class of materials on the market and their demand is constantly increasing with an expected combined annual growth rate of 4,4% for the period 2023/2030. In addition, the global polyurethane market was valued to more than USD 82 billion and is projected to grow to USD 123 billion by 2030.<sup>1</sup> Polyurethanes are classically synthesized by a polyaddition process of (poly)isocyanates and (poly)alcohols (Scheme 1). This class of polymers is typified by the presence of urethane (carbamate)

linkages and their incredible versatility, leading to a broad spectrum of applications, including thermoplastics and thermosets, with products ranging from highly elastic to rigid foams (insulation, panels, car seats), rigid and flexible moldings (car shock absorbers, window frames), coatings, and many others.



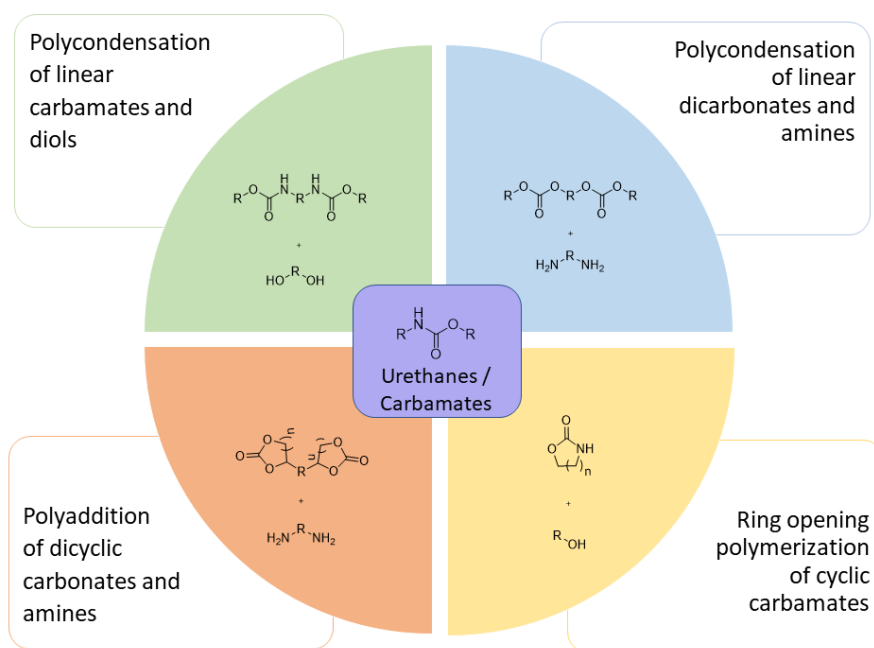
**Scheme 1.** Schematic representation of the polyaddition of polyisocyanates and polyalcohols to yield polyurethanes.

More than 90% of the commercially available PUs are produced from aromatic polyisocyanates.<sup>2,3</sup> Compared to the aliphatic and the cycloaliphatic isocyanates, the aromatic ones show higher reactivity toward hydroxyl groups and yield materials with better mechanical properties. Among them, toluene diisocyanate (TDI: LD<sub>50,oral, rat</sub> = 5130 mg/kg) and methylene diphenyl 4,4'-diisocyanate (MDI: LD<sub>50,oral, rat</sub> = 4130 mg/kg) are most widely used in the PU industry, with relative demands of 61.3% and 34.1% respectively.<sup>4,5</sup> On the other hand, aliphatic and cycloaliphatic polyisocyanates are used to obtain PUs that do not become discolored on exposure to heat or light, this feature is particularly relevant for coating materials.<sup>6</sup> Among the aliphatic isocyanates, hexamethylene diisocyanate (HDMI: LD<sub>50, oral, rat</sub> = 18200 mg/kg) and isophorone diisocyanate (LD<sub>50, oral, rat</sub> = 4814 mg/kg) are of major practical importance, although with a smaller relative demand of 3,4% and 1,2%, respectively.<sup>5</sup> Isocyanates are classified as CMR (carcinogenic, mutagenic, reprotoxic) with high inhalation toxicity and irritant power, which can result in health effects such as skin or eye irritation, asthma and cancer.<sup>7</sup> Therefore, prolonged exposure should be avoided. Another major concern is related to the synthesis of isocyanates. Several methods are reported in the literature, such as the Curtius and Lossen rearrangement.<sup>8-12</sup> However, these methods are not suitable for large-scale operations, because of the potential hazards involved in using large quantities of the reagents for the Curtius rearrangement<sup>13</sup> and the little availability of the hydroxamic acids.<sup>14</sup> In contrast, phosgenation of amine hydrochlorides,<sup>15</sup> carbamate salts,<sup>16-18</sup> or ureas<sup>19-21</sup> are used commercially on industrial scale.<sup>20-22</sup> Among all these routes, the most common method is the phosgenation of an amine or its salt, which is by far the most efficient and economically attractive.<sup>11,22</sup> Deploying phosgene as synthetic precursor for isocyanates requires elaborate safety measures and high investment. Moreover, the growing awareness towards our environment and the continuous strive to ensure the health, safety and well-being of both operators and final customers have sparked research interest related to the use of alternative, less problematic reagents.

Conventional PUs are obtained from fossil-based and often hazardous reagents. In recent years, a class of polymers termed non-isocyanate polyurethanes (NIPUs) emerged as a possible and promising substitute for PUs, meeting the demands of new stringent regulations and addressing the concerns towards harmful reagents<sup>23</sup> and CO<sub>2</sub> emissions.

One synthetic approach towards NIPUs relies on cyclic carbonates, which also have different applications including chemical intermediates, solvents, fuel additives, electrolytes solvents for Li-ion batteries, coatings, paints, binders, and adhesives.<sup>24</sup>

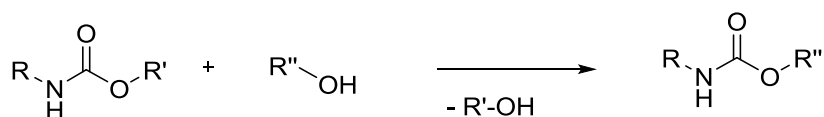
More generally, NIPUs are currently produced via four synthetic pathways, including high-temperature polycondensation of bis-alkyl carbamates with diols, copolymerization of CO<sub>2</sub> with aziridines, ring-opening polymerization (ROP) of cyclic carbamates, and polyaddition of mainly 5-membered-polyfunctional cyclic carbonates with polyamines (Scheme 2).<sup>25-27</sup> Noteworthy, of these approaches, the ROP approach of 5CCs is rather limited in scope and it should be mentioned that the polyaddition of cyclic carbonates with polyamines leads to regioisomers.



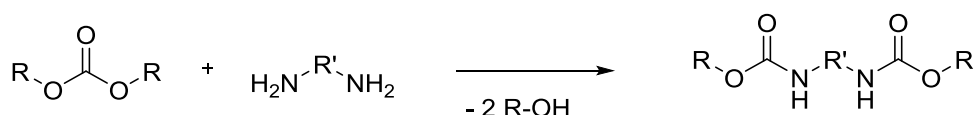
**Scheme 2.** Main synthetic pathways to non-isocyanate polyurethanes.

The copolymerization of aziridines with carbon dioxide does not depend on phosgene and isocyanates, but aziridines are typically manufactured starting from 1,2-dichloroethane (Dow process), haloamines ( $\beta$ -chloroethylamine process) or 2-aminoethanol (Nippon Shokubai and Wenker processes), of which only the latter two are still used today.<sup>28</sup> All these routes however require toxic aziridines (aziridine,  $LD_{50, rat} = 15 \text{ mg/kg}$ ; 2-methylaziridine  $LD_{50, oral, rat} = 19 \text{ mg/kg}$ )<sup>29,30</sup> and greener access to such chemicals remains a major issue.<sup>31</sup>

The polycondensation of alcohols with polyalkyl carbamates, a transurethanization reaction (also called transcarbamoylation, Scheme 3), yields polyurethanes and typically a lower molar mass alcohol as side product. Bis-alkyl carbamates can be easily synthesized by reacting diisocyanates with alcohols, which would not be an improvement in terms of sustainability. They can also be obtained via phosgene-free routes by reacting dialkyl carbonates with diamines (Scheme 4) or by rearrangement reactions of carboxylic acid derivatives.



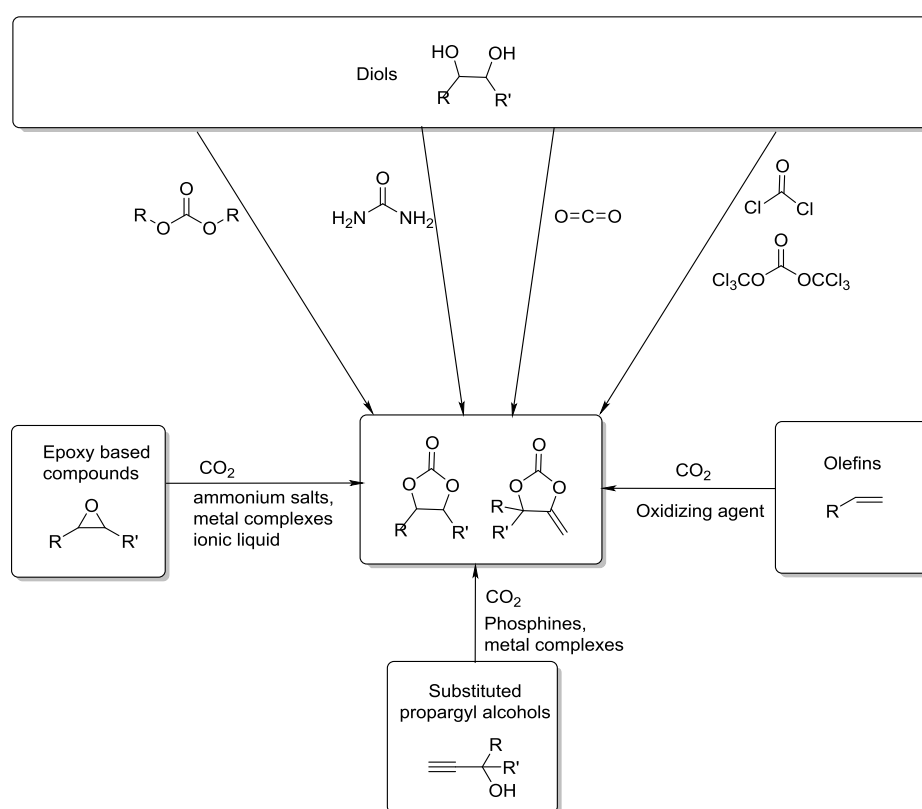
**Scheme 3.** Example of a transcarbamoylation reaction.



**Scheme 4.** Example of bis-alkyl carbamate synthesis by reacting dialkyl carbonates with diamines.

The most used dialkyl carbonate in this process is dimethyl carbonate (DMC). Several commercial processes to make DCM are currently in use: the older (and least sustainable) based on phosgene and methanol,<sup>32</sup> the more favorable liquid phase oxidative carbonylation of methanol,<sup>33</sup> the vapor phase oxidative carbonylation of methanol<sup>34</sup> and transesterification of ethylene carbonate with methanol.<sup>35</sup> Another route consists in urea alcoholysis, where urea and methanol are the raw materials to yield DMC and ammonia as co-product, which can be recycled to synthesize urea.<sup>36</sup>

The synthesis of 5-membered cyclic carbonates (5CCs) has been widely studied, their simplest representatives, ethylene and propylene carbonate, have been commercially available for decades.<sup>37-39</sup> In general, the main approaches for their synthesis (Scheme 5) involve diols, linear carbonates, olefins, urea, propargyl alcohols, and epoxides. Diols and polyols, together with epoxides, are the main reagents for the synthesis of 5CCs. To a lower extent, precursors such as propargyl alcohols are crucial to yield unsaturated cyclic carbonates. In this review, we will analyze the main synthetic routes to yield the most often discussed 5CCs. Moreover, a few more “exotic” CCs will also be included in the discussion. The carbonates evaluated in this review are summarized in Scheme 6.



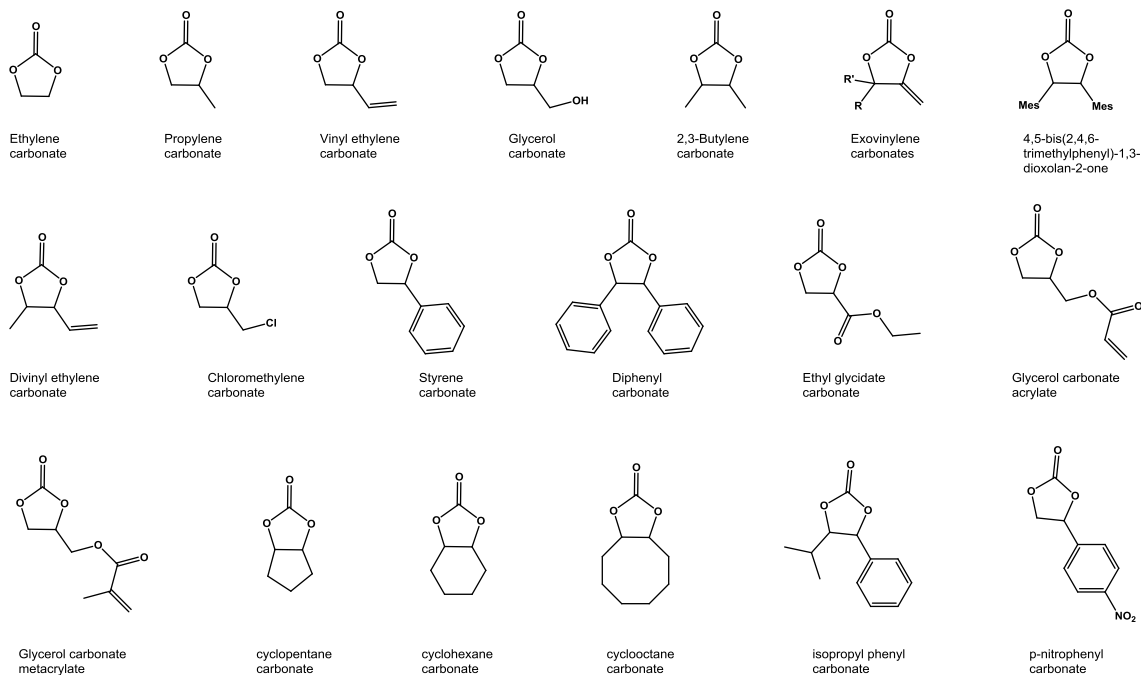
**Scheme 5.** Summary of main synthetic routes of 5CCs.

### Approach used to compare the sustainability of different 5CC syntheses

In order to compare and evaluate the different synthetic routes to 5CCs in terms of sustainability, the E-factor, developed in the early 1990s by Sheldon,<sup>40</sup> was used in this review. Manuscripts with exhaustive experimental information were selected to apply this metric. However, many protocols had to be excluded due to missing, yet nonetheless necessary experimental details to calculate E-factors. The E-factor is now generally accepted to assess the potential environmental acceptability of a chemical process and it is defined as the mass ratio of waste to desired product (Equation 1). The ideal E-factor for a process is zero,<sup>41</sup> the higher the value, the higher the quantity of waste and the negative environmental impact. Thus, as the main aim of this review is to evaluate and compare the sustainability of the synthesis of the most widespread used 5CCs (Scheme 6), we will use the E-factor

in combination with toxicity data of the reagents as well as considering solvent selection guides (which are considering both toxicity and CO<sub>2</sub> footprints) to provide general guidelines for more sustainable 5CCs synthesis and compare different synthetic routes.

$$E - factor = \frac{\text{weight of raw materials} - \text{weight of desired product}}{\text{weight of desired product}} \quad \text{Eq. 1}$$



**Scheme 6.** 5CCs analyzed in this review.

## Synthesis of 5CCs from diols

Diols are important chemicals that have numerous applications as solvents, constituents of pharmaceuticals, and monomers for polymer synthesis, for instance polycarbonates (PCs) or poly(ethylene terephthalate) (PET). Moreover, diols can be used as reagents for the synthesis of cyclic carbonates. The high diversity and availability of diols make possible the synthesis of cyclic carbonates having different ring sizes and functional groups. For instance, vicinal diols give access to 5CCs, 1,3- diols make the synthesis of 6CCs possible, and longer chain diols give access to macrocyclic cyclic carbonates. The focus of this review is to assess the sustainability of 5CCs, the most often applied and most easy to access CCs. Hence, only this class of compounds will be highlighted. At present, most of the diols on the market are petroleum-derived and based on building blocks such as ethylene, propylene and benzene.<sup>42</sup> Moreover, 1,2-diols such as ethylene glycol, propylene glycol, 2,3-butanediol or glycerol can be obtained from biomass sources, namely cellulose, starch and plant oils.<sup>43</sup>

Diols can be used for the synthesis of 5CCs in combination with different reactants, including carbon dioxide, urea, phosgene, or dialkyl carbonates. These different approaches will be discussed in the following paragraphs.

## Syntheses of 5CCs from diols and carbon dioxide

The reaction between 1,2-diols and carbon dioxide is certainly one of the most challenging to yield cyclic carbonates, for instance if compared to the commonly used carbonation of epoxides. Typically, this requires harsh reaction conditions and thus considerable amounts of energy as well as specific equipment. Therefore, catalysts leading to milder conditions and higher yields are crucial for the development of this route. Numerous articles describing harsh conditions have been published,<sup>44,45</sup> for instance requiring high temperatures (up to 180 °C) and CO<sub>2</sub> pressures (50 atm). The reported yields are reasonable to good, ranging from 67% to 99%. However, as far as reaction conditions and calculated E-factors values are concerned (Table 1), some differences should be highlighted. The work of Chul-Choi et al. clearly shows, for the majority of the substrates synthesized, lower yields, harsher reaction conditions and higher E-factors (up to 4-fold) compared to the work described by Tomishige et al. The latter approach consists of a carboxylation/hydration cascade reaction carried out with cerium oxide as catalyst and 2-cyanopyridine used as reagent and solvent. In the first step of the reaction, 1,2-diols undergo carboxylative coupling with carbon dioxide, yielding the corresponding cyclic carbonate and water. Subsequently, the water molecules react with 2-cyanopyridine in a hydration reaction, leading to 2-picolinamide, a valuable intermediate for the synthesis of fungicides and antibacterias.<sup>46,47</sup> In our E- factor evaluations, 2-picolinamide was not taken into account as desired product, yet further use of 2- picolinamide would significantly lower the E-factor. By analyzing the reagents employed in the two protocols, Tomishige et al. are proposing a synthetic protocol with more toxic reagents. Indeed, 2- cyanopyridine has a lower LD<sub>50, oral, rat</sub> than *N*-methyl-2-pyrrolidinone (NMP) (2-cyanopyridine LD<sub>50, oral, rat</sub> = 1000mg/kg; *N*-methyl-2-pyrrolidinone LD<sub>50, oral, rat</sub> = 4150mg/kg). However, we have to underline that NMP is classified as reprotoxic. Another interesting synthetic protocol has been described by Kitamura et al., requiring considerably milder reaction conditions compared to the two protocols discussed above. Indeed, this protocol yields cyclic carbonates at room temperature with 1 atm of carbon dioxide in 24h. Moreover, the experimental yields are considerably high (<89%) and the calculated E-factors are comparable with the ones observed for the protocols of Tomishige et al. However, some of the reagents used, namely DBU (LD<sub>50, oral, rat</sub> = 215 mg/kg) and 1-bromobutane (BuBr) (LD<sub>50, oral, rat</sub> = 2761 mg/kg), are respectively labeled as toxic and CMR. These reagents are furthermore used in rather high amounts, respectively 2 and 2.4 equivalents per equivalent of diol.

To sum up, among the protocols discussed, the most promising considering E-factors and reaction conditions seem to be the ones described by Kitamura et al., as the reactions are carried out under the mildest conditions and the E-factors are among the lowest. However, there are some major concerns regarding the hazardousness of the chemicals used in this protocol. For instance, replacing DBU with less toxic bases or minimizing the amount used could render the process safer and more sustainable. As a general advice, we suggest trying to recycle the solvents and the catalysts, indeed, all the

protocols we have analyzed in this chapter showed a significantly high solvent contribution to the E-factor value up to 73%. With regard to the Tomishige et al. synthetic route, there is room to improve the overall sustainability considering that 2-cyanopyridine could be separated from the heterogeneous catalyst and the products of the reaction to further used as precursor for herbicides or fungicides (see above).

**Table 1.** Summary of the synthetic protocols reacting diols and carbon dioxide.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
Propylene carbonate	180 °C, 24h, 30 atm	98	83.0	i) N-methyl-2-pyrrolidone (CMR)	Chul-Choi et al. <sup>45</sup>
Glycerol carbonate	180 °C, 24h, 30 atm	72	99.0	i) N-methyl-2-pyrrolidone (CMR)	Chul-Choi et al. <sup>45</sup>
4-phenyl-1,3-dioxolan-2-one	180 °C, 24h, 30 atm	77	66.1	i) N-methyl-2-pyrrolidone (CMR)	Chul-Choi et al. <sup>45</sup>
Ethylene carbonate	130 °C, 1h, 50 atm	99	26.6	i) 2-cyanopyridine (acute toxicity)	Tomishige et al. <sup>44</sup>
Propylene carbonate	130 °C, 1h, 50 atm	99	23.2	i) 2-cyanopyridine (acute toxicity)	Tomishige et al. <sup>44</sup>
4-phenyl-1,3-dioxolan-2-one	180 °C, 48h, 50 atm	95	14.9	i) 2-cyanopyridine (acute toxicity)	Tomishige et al. <sup>44</sup>
Vinyl ethylene carbonate	160 °C, 1h, 50 atm	67	31.0	i) 2-cyanopyridine (acute toxicity)	Tomishige et al. <sup>44</sup>
Ethylene carbonate	25 °C, 24h, 1 atm	95	13.9	i) 1-bromobutane (CMR) ii) DBU (acute toxicity)	Kitamura et al. <sup>48</sup>
Propylene carbonate	25 °C, 24h, 1 atm	96	31.9	i) 1-bromobutane (CMR) ii) DBU (acute toxicity)	Kitamura et al. <sup>48</sup>
4-phenyl-1,3-dioxolan-2-one	25 °C, 24h, 1 atm	89	21.3	i) 1-bromobutane (CMR) ii) DBU (acute toxicity)	Kitamura et al. <sup>48</sup>

## Synthesis of 5CCs from diols and urea

Urea is a white crystalline substance with the chemical formula  $\text{NH}_2\text{CO}_2\text{NH}_2$ . This nitrogen-containing compound is a product of protein metabolism and is industrially manufactured using the Basarov reaction by reacting ammonia and carbon dioxide, typically at high temperature and pressure to yield ammonium carbamate, which in turn dehydrates to form urea and water.<sup>49</sup> Urea is widely used in agriculture as a fertilizer because it is a source of nitrogen, which is an essential nutrient for plant growth. Furthermore, urea is also used as raw material in the manufacture of cosmetics, pharmaceuticals, flame-proofing reagents, explosives, adhesives, and plastics. Moreover, urea can react with vicinal diols to yield cyclic carbonate monomers. The reaction between urea and a diol can be compared to the synthetic route described in the previous section in terms of reaction conditions, as it also requires harsh conditions and thus considerable amounts of energy as well as specific equipment, such as vacuum systems to remove the generated by-products to accelerate the process. Numerous articles describing harsh conditions have been published, for instance high temperatures ranging from 140°C to 160°C.<sup>50–53</sup> The reported yields are fairly high in the majority of cases, ranging from 21% to 95%. Regarding the calculated E-factor values (Table 2), some differences between the different reactions become more obvious. The works of Cheng et al. and Patti et al. show the best E-factors and the mildest conditions for the majority of the substrates synthesized. In fact, the reaction temperatures and times are lower compared to the work of Beller et al., leading to lower energy consumption. On the other hand, the Cheng and Patti synthetic routes require vacuum systems in the majority of the cases, which contribute to increase the energetic demand of the process. From a qualitative point of view, we could assume that this additional amount of energy, which will be



increasingly renewable in the foreseeable future, can be compensated by the lower amount of waste produced per gram of product and the lower reaction time and temperature required. By considering the reagents employed in the two synthetic protocols, it has to be positively noted that no CMRs or acutely toxic reagents are employed. In addition, Cheng et al. used 1-hexadecyl-3-methylimidazolium chloride (C<sub>16</sub>mimCl), an ionic liquid (IL), which is well known for its non-flammability, negligible vapor pressure, recyclability, chemical and thermal stability.<sup>54</sup> On the other hand, many ILs, including the imidazolium-based ones, show low biodegradability, phytotoxicity and could bioaccumulate in both terrestrial and aquatic living beings.<sup>55</sup> Another synthetic protocol has been described by Beller et al., requiring slightly harsher reaction conditions and generally longer reaction times compared to the two protocols discussed so far. Indeed, this protocol yields cyclic carbonates at 150 °C in 18h at atmospheric pressure. Moreover, even though the yields are among the highest (up to 90%), the calculated E-factors are rather high ranging from 2.53 to 81.14. In addition, some of the reagents used, namely 1,4-dioxane (LD<sub>50, oral, rat</sub> = 5150 mg/kg) and 3-chloro-1,2-propanediol (LD<sub>50, oral, rat</sub> = 26 mg/kg), both labeled as CMR and toxic, contradict the principles of green chemistry.

In conclusion, for the synthesis of 5CCs from urea and diols, the most promising procedures considering E-factors, reaction conditions and hazardousness of the reagents seem to be the ones proposed by Patti et al., as the reactions are performed under the mildest conditions and the E-factors are the lowest. Moreover, the reactions are carried out in neat conditions by mixing the two main reagents and the catalyst. However, even though this protocol does not show any obvious sustainability issues, in our opinion there is still room to improve. Indeed, urea is used in stoichiometric excess (2 equivalents of urea per equivalent of diol), while by using a stoichiometric ratio or recycling of urea, the E-factors could potentially decrease at least threefold. Concerning the protocol described by Beller et al., replacing the highly carcinogenic 1,4-dioxane with the less hazardous cyclopentyl methyl ether (CMPE), which is considered as a greener substitute for such solvents,<sup>56,57</sup> could lead to considerable sustainability improvements.

**Table 2.** Summary of the synthetic protocols reacting diols and urea.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
Ethylene carbonate	150 °C, 18h	65	37.3	i) 1,4-dioxane (CMR)	Beller et al. <sup>53</sup>
4-phenyl-1,3-dioxolan-2-one	150 °C, 18h	90	14.8	i) 1,4-dioxane (CMR)	Beller et al. <sup>53</sup>
4-chloromethyl-1,3-dioxolan-2-one	150 °C, 18h	21	81.1	i) 3-chloro-1,2-propanediol (CMR, acute toxicity) ii) 1,4 – dioxane (CMR)	Beller et al. <sup>53</sup>
4,5-dimethyl-1,3-dioxolan-2-one	150 °C, 18h	86	21.6	i) 1,4-dioxane (CMR)	Beller et al. <sup>53</sup>
4,5-diphenyl-1,3-dioxolan-2-one	150 °C, 18h	87	2.5	i) 1,4-dioxane (CMR)	Beller et al. <sup>53</sup>
Ethylene Carbonate	140 °C, 3h, 0.15 atm	95	14.9		Cheng et al. <sup>52</sup>
4-phenyl-1,3-dioxolan-2-one	140 °C, 3h, 0.15 atm	81	2.8		Cheng et al. <sup>52</sup>
4-chloromethyl-1,3-dioxolan-2-one	140 °C, 3h, 0.15 atm	87	2.5		Cheng et al. <sup>52</sup>
Glycerol carbonate	140°C, 7h, 1 atm	83	1.2		Patti et al. <sup>50</sup>
Ethylene carbonate	140°C, 24h, 0.04 atm	30	5.9		Patti et al. <sup>50</sup>
Propylene carbonate	140°C, 24h, 0.04 atm	79	1.5		Patti et al. <sup>50</sup>

## Syntheses of 5CCs from diols and dialkyl carbonates

Dialkyl carbonates are important organic compounds and chemical intermediates and are considered more sustainable solvent and reagent alternatives due to their comparably low toxicity, decrease of irritating or mutagenic effects, as well as biodegradability for important representatives. Owing to these features, dialkyl carbonates are gaining interest as alternatives for toxic and carcinogenic chemicals, most prominently phosgene.<sup>58</sup> Among linear carbonates, the most important ones are dimethyl carbonate (DMC) and diethyl carbonate (DEC). They are used as monomers for polymers and in transesterification reactions to produce other carbonates such as diphenyl carbonate (DPC), which is another important organic carbonate, but is toxic for aquatic life. DMC and DEC can be synthesized by numerous routes, namely by phosgene alcoholysis,<sup>59</sup> oxidative carbonylation of alcohols,<sup>33</sup> urea alcoholysis and a methanol oxidative carbonylation route. This last route can be performed either in vapor-phase (developed by Dow, USA) or liquid-phase (Enichem process).<sup>60</sup> Among these routes, methanol oxidative carbonylation is the most used one. It is worth mentioning that renewable DMC obtained via urea alcoholysis is gaining momentum on the market owing to moderate reaction conditions, limited safety problems related to the production of ammonia, and the possibility to re-use this byproduct in urea production plants.<sup>61,62</sup> Linear carbonates can react with vicinal diols to yield various cyclic carbonates. The reaction between these two reagents is quite different from the routes reacting diols with either carbon dioxide or urea. In fact, the reaction conditions are considerably milder with temperatures ranging from 30 °C to 110 °C and generally shorter reaction times ranging from 2h to 24h, resulting in reduced energy consumption. Moreover, such routes can be performed using basic laboratory equipment. Numerous articles describing such synthetic routes have been published,<sup>63–67</sup> reporting yields that are reasonably high, ranging from 43% to 99%. Differences concerning reaction conditions, calculated E-factors and toxicity of the reagents are summarized in Table 3. The works of Pyo et al., Olsén et al. and Selva et al. show the harshest reaction conditions and the longest reaction times among the protocols analyzed. Indeed, temperatures ranging from 90 °C and 110 °C were applied for reaction times between 4h and 24h. The calculated E-factor values range from 2.6 to 24.5, mainly a result of the excess of organic carbonate used. Pyo et al. and Selva et al. applied a diol:carbonate ratio of 1:18 and 1:20, respectively, while Olsén et al. used a 1:2 ratio, explaining the notable difference of E- factors (up to 9-fold). By considering the reagents employed in the three synthetic routes, no CMRs or acutely toxic reagents are employed, except for the Olsén et al. protocol, where 1,5-hexadiene-3,4-diol is labeled as toxic ( $LD_{50, \text{oral, rat}} = 1652 \text{ mg/kg}$ ). This is however not a general disadvantage of the described protocol, but relates to the specific substrate used. In addition, some concerns can be raised regarding the high corrosivity and flammability of sodium hydride used in sub-stoichiometric amount (0.1 equivalents per equivalent of diol). Another synthetic protocol has been described by Kim et al., requiring notably milder reaction conditions and reaction times compared to all the other protocols discussed so far. Indeed, this protocol yields cyclic carbonates at 30 °C in 2h, leading to lower energy consumption. Furthermore, the yields are the highest reported (> 90%) and the E-factors are in line with the other protocols in the majority of the cases. In this case, the calculated E-factors are more influenced by the amount of solvent used (solvent contribution to E-factor  $\geq 78\%$ ) rather than the diol:carbonate ratio, which is 1:1.1. In addition, some of the reagents used, i.e. DPC ( $LD_{50, \text{oral, rat}} = 1500 \text{ mg/kg}$ ), are labeled as very toxic for aquatic life and 3-chloro-1,2-propanediol ( $LD_{50, \text{oral, rat}} = 26 \text{ mg/kg}$ ) is labeled as CMR and toxic. At last, the protocol described by Meier et al. is carried out at 80°C for 22h, the yields are not the highest but still acceptable ranging from 43% (4,5-dimethyl-1,3-dioxolan-2-one) to 81% (ethylene carbonate). Despite the lower yields obtained compared to the other protocols mentioned here, this procedure was conceived to avoid toxic reagents while employing DMC both as solvent and reagent in slight stoichiometric excess (ratio diol:DMC 1:1.2). E-factors for this procedure are among the lowest, ranging from 1.6 to 3.3.

To sum up, among the protocols discussed, the most promising protocol considering E-factors, reaction conditions, and hazardousness of the reagents seems to be the one proposed by Meier et al., as the reaction produces the least amount of waste per gram of product. Even though the reaction conditions are not the mildest, leading to higher energy consumption, this protocol was developed by following green chemistry principles. Hence, toxic chemicals were avoided, catalyst loading was minimized and stoichiometry was optimized. Moreover, it is worth mentioning that Meier et al. paid

attention to finding the best purification by assessing their E-factor values, although this is not described or taken into consideration in the analysis of this review. Concerning the protocols of Pyo et al. and Selva et al., in our opinion, there is still room to improve. In fact, DMC is used in stoichiometric excess (up to 20 equivalents of carbonate per equivalent of diol), while by using a stoichiometric ratio E-factors could potentially decrease at least 21-fold. Similarly, the E-Factor could be reduced by recycling the excess of reagent used, which should be easily achievable by distillation. Finally, regarding the protocol of Kim et al., performing the reaction in neat conditions or recycling the solvent (2-methyl-THF) could potentially decrease the E-factor up to 7-fold.

**Table 3.** Summary of the synthetic protocols reacting diols and dialkyl carbonates.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
Propylene carbonate	110 °C, 24h	98	21.2		Pyo et al. <sup>63</sup>
Glycerol carbonate	110 °C, 24h	73	24.5		Pyo et al. <sup>63</sup>
4,5-diphenyl-1,3-dioxolan-2-one	30 °C, 2h	99	9.8	i) Diphenyl carbonate (very toxic to aquatic life)	Kim et al. <sup>67</sup>
Propylene carbonate	30 °C, 2h	90	17.3	i) Diphenyl carbonate (very toxic to aquatic life)	Kim et al. <sup>67</sup>
Ethylene carbonate	30 °C, 2h	91	19.8	i) Diphenyl carbonate (very toxic to aquatic life)	Kim et al. <sup>67</sup>
4-chloromethyl-1,3-dioxolan-2-one	30 °C, 2h	91	12.3	i) Diphenyl carbonate (very toxic to aquatic life) ii) 3-chloro-1,2-propanediol (CMR, acute toxicity)	Kim et al. <sup>67</sup>
1,2-divinylethylene carbonate	100 °C 16h	70	2.6	i) 1,5-hexadiene-3,4-diol (acute toxicity)	Olsén et al. <sup>64</sup>
Propylene carbonate	90 °C, 4h	92	19.3		Selva et al. <sup>65</sup>
Ethylene carbonate	80 °C, 22h	81	1.6		Meier et al. <sup>66</sup>
Propylene carbonate	80 °C, 22h	65	2.0		Meier et al. <sup>66</sup>
4,5-dimethyl-1,3-dioxolan-2-one	80 °C, 22h	43	3.3		Meier et al. <sup>66</sup>

## Syntheses of 5CCs from diols and phosgene

Phosgene is a colorless gas at ambient temperature and pressure. It is manufactured from a reaction of carbon monoxide and chlorine gas over activated carbon.<sup>68</sup> The importance of phosgene was initially its various uses in the production of intermediates in many different fields of chemistry. Currently, most of the phosgene produced is used in the manufacture of diisocyanates, key reagents for the synthesis of polyurethanes, and for the synthesis of polycarbonates. However, the toxicity of phosgene is a major concern and, hence, exceptional effort has been to be taken to ensure an as safe as possible handling of this reagent. An additional concern in terms of sustainability is the produced HCl byproduct upon 5CC synthesis, which typically is quenched by stoichiometric amounts of base and thus relates to high amounts of salt waste. Even though the phosgene route is not the most preferable, we would like provide a summary on this synthetic pathway in order to compare its strengths and weaknesses to the other discussed approaches.

The reaction between phosgene and diols requires the lowest temperatures and reaction times among all the synthetic routes analyzed herein. The reaction temperatures applied are, in the majority of the cases, close to 0 °C, ranging from -78 °C to room temperature, and the reaction times range from 15 minutes to 3h. Such reaction conditions are considerably milder and they require significantly shorter

reaction time compared to the other protocols we analyzed until now. Mild reaction conditions might be required for some substrates, yet cooling also remains highly energy intense. Numerous articles describing this synthetic pathway have been published,<sup>64,69–72</sup> reporting modest to high yields ranging from 39% to 97% and E-factor values in the order of hundreds in the majority of the cases. Nevertheless, as far as reaction conditions and calculated E-factor values are concerned (Table 4), some differences should be emphasized.

First, it is noticeable that all the protocols described were performed applying fairly similar reaction times and temperatures. Hence, the analysis of these aspects leads to neglectable differences. The works of Itaya et al. show the shortest reaction times among all the protocols discussed here, ranging from 15 minutes to 2h. E-factor values and yields described in these two works range from 104 to 256 and from 39% and 76%, respectively. However, these values are not the best compared to other protocols. In contrast, the works of Wallace et al. and Matsumoto et al. show the best E-factors and yields for this synthetic route, ranging from 31.8 to 64.3 and from 67% to 97%, respectively. Finally, the work of Olsén et al. shows a high yield (95%), however the E-factor and reaction time are significantly higher compared to other protocols (respectively up to 325-fold and 24-fold). Concerning the toxicity of the reagents, all the protocols discussed use either phosgene, labeled as CMR and highly toxic ( $LC_{50, \text{inhalation}, 4h} = 0.501 \text{ mg/l}$ ), or triphosgene, which is also highly toxic ( $LC_{50, \text{inhalation}, 4h} = 0.005 \text{ mg/l}$ ). Moreover, these chemicals can cause severe skin burns and eye damage. In addition, some of the reactions performed by Itaya et al. use triethylamine, which is labeled as highly toxic ( $LD_{50, \text{oral, rat}} = 730 \text{ mg/kg}$ ) as well.

In conclusion, among the protocols discussed, the most promising considering E-factors, reaction conditions and hazardousness of the reagents, seem to be the one proposed by Matsumoto et al. All the protocols discussed here might be improved by following some precautions. First, using stoichiometric amounts of reagents and less solvent could drastically reduce the E-factors. As an example, reagents such as pyridine are used in considerable stoichiometric excess (up to 13-fold) and might be reduced. Moreover, reaction solvents contribute significantly to the E-factor with percentages up to 97%. Reducing or recycling the solvent could reduce the E-factors up to 33-fold.

**Table 4.** Summary of the synthetic protocols reacting diols and phosgene.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
1,2-divinylethylene carbonate	0 °C → r.t., 6h,	95	10339.0	i) Triphosgene (acute toxicity)	Olsén et al. <sup>64</sup>
4,5-Bis(2,4,6-trimethylphenyl)-1,3-dioxolan-2-one	0 °C, 3h	67	46.4	i) Phosgene (acute toxicity, CMR)	Wallace et al. <sup>69</sup>
4,5-bis(2-methylphenyl)-1,3-dioxolan-2-one	0 °C, 3h	97	64.3	i) Phosgene (acute toxicity, CMR)	Wallace et al. <sup>69</sup>
cyclooctene carbonate	0 °C, 30 min	48	256.0	i) Triphosgene (acute toxicity)	Itaya et al. <sup>70</sup>
cyclopentane carbonate	0 °C, 30 min	68	104.0	i) Phosgene (acute toxicity, CMR)	Itaya et al. <sup>70</sup>
cyclohexane carbonate	0 °C, 30 min	39	203.0	i) Phosgene (acute toxicity, CMR) ii) triethylamine (acute toxicity)	Itaya et al. <sup>70</sup>
4,5-dimethyl-1,3-dioxolan-2-one	0 °C, 15 min	76	106.0	i) Phosgene (acute toxicity, CMR)	Itaya et al. <sup>71</sup>
4-phenyl-1,3-dioxolan-2-one	0 °C, 1h	57	233.7	i) Phosgene (acute toxicity, CMR)	Itaya et al. <sup>71</sup>
4-(4-nitrophenyl)-1,3-dioxolan-2-one	25 °C, 2h	61	134.0	i) Phosgene (acute toxicity, CMR) ii) triethylamine (acute toxicity)	Itaya et al. <sup>71</sup>
4-isopropyl-5-phenyl-1,3-dioxolan-2-one	0 °C, 15 min	66	161.3	i) Phosgene (acute toxicity, CMR) ii) triethylamine (acute toxicity)	Itaya et al. <sup>71</sup>
4,5-dimethyl-1,3-dioxolan-2-one	-78 °C → 0 °C, 1h	92	31.8	i) Triphosgene (acute toxicity)	Matsumoto et al. <sup>72</sup>



## Syntheses of 5CCs from epoxides and CO<sub>2</sub>

The reaction between epoxides and carbon dioxide is an efficient route to yield cyclic carbonates, also at industrial level. Moreover, this reaction has numerous advantages from a green chemistry perspective, as it uses carbon dioxide as a renewable, non-toxic and abundant reactant. It furthermore shows 100% atom economy, since all the reactants are incorporated in the product. Moreover, reactions can be carried out under solvent-free conditions.<sup>73</sup> The carbonation of epoxides is a synthetic route that requires high temperatures and CO<sub>2</sub> pressures, thus considerable amounts of energy are required as well as specific equipment. Therefore, the use of catalysts, leading to milder reaction conditions, is crucial for the development of this route. Numerous articles describing harsh conditions have been published,<sup>58,74–78</sup> high temperatures ranging from 60 °C to 120 °C and CO<sub>2</sub> pressures up to 100 atm were reported. The yields were among the highest described in this review, ranging from 40% and 100%. The works of Shi et al. and Deng et al. clearly show, in the majority of the substrates synthesized, comparable conversions, which are in most of the cases almost quantitative. This is a clear advantage and points to the reproducibility and generalizability of this approach. The two protocols are carried out using fairly similar reaction conditions, i.e., similar temperature and CO<sub>2</sub> pressure are described (respectively, 40 and 30 atm). Moreover, the protocol of Deng et al. leads to lower E-factors. The average calculated values are 0.55 vs. 1.1 for the other protocol. Both are very low compared to the above discussed protocols. By analyzing the reagents employed in the two protocols, Shi et al. and Deng et al. are both using toxic and CMR epoxides, namely propylene oxide (LD<sub>50, oral, rat</sub> = 382 – 587 mg/kg), epichlorohydrin (LD<sub>50, oral, rat</sub> = 175 mg/kg), glycidol (LD<sub>50, oral, rat</sub> = 463 mg/kg), or styrene oxide (LD<sub>50, oral, rat</sub> = 4290 mg/kg). Other hazardous reagents employed in the two protocols are phenol (LD<sub>50, oral, estimated</sub> = 100 mg/kg), triphenylphosphine (LD<sub>50, oral, rat</sub> = 700 mg/kg) and tetrabutylammonium bromide (TBAB) (LD<sub>50, oral, rat</sub> = >300 – <2.000 mg/kg). However, the latter reactants are used in very low quantities, ranging from 2 mol% to 3.6 mol% of epoxide. The works of Lozano et al. and Kleij et al. were carried out at lower CO<sub>2</sub> pressures (10 atm) and reaction temperatures are slightly different (respectively 70 °C and 60 °C). However, reaction times are significantly different, especially Kleij et al. describe three times longer reactions, thus also possibly requiring more energy. Another important difference concerns the E-factor values. Despite the significantly lower yields, the protocol of Kleij et al. shows half the E-factor values. This considerable difference in the calculated E-factor is due to the higher excess of CO<sub>2</sub> employed in the other protocols. Moreover, another advantage of this protocol is the absence of toxic reagents employed, while in the protocol of Lozano et al., some of the reagents used, namely vinyl acrylate (LD<sub>50, oral, estimated</sub> = 0.0847 mg/kg), is labeled as highly toxic and glycidol is labeled as highly toxic and CMR. Finally, the work of Peppel et al. showed the best E-factors (E = 0.045), but the harshest reaction conditions. Indeed, this protocol yields cyclic carbonates at 170 °C with 100 atm of carbon dioxide in 1h. CMR and toxic reagents, such as ethylene oxide and propylene oxide, have been used also here.

To sum up (see also Table 5), the best protocol considering the E-factor is the one proposed by Peppel et al. However, considering also the reaction conditions, the protocol proposed by Deng et al. shows advantages despite the slightly higher E-factor. For instance, the milder reaction conditions make the process safer. However, it is difficult to establish which protocol is quantitatively better considering the minor differences in E-factors described. The major issues of the analyzed protocols concern the high temperature and pressures required and the inherent toxicity of the necessary epoxide precursors. The protocols we discussed have, in the majority of cases, E-factors values less than 1, making further improvements difficult, but demonstrating their advantage.

**Table 5.** Summary of the synthetic protocols reacting epoxides and CO<sub>2</sub>.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
Propylene carbonate	120 °C, 4h, 40 atm	96	1.3	i) Propylene oxide (CMR, acute toxicity)	Shi et al. <sup>58</sup>
4-phenyl-1,3-dioxolan-2-one	120 °C, 4h, 40 atm	85	1.1	ii) Phenol (CMR, acute toxicity) iii) triphenylphosphine (CMR) i) Styrene oxide (CMR, acute toxicity)	Shi et al. <sup>58</sup>
4-chloromethyl-1,3-dioxolan-2-one	120 °C, 4h, 40 atm	99	0.9	ii) Phenol (CMR, acute toxicity) iii) triphenylphosphine (CMR) i) Epichlorohydrin (CMR, acute toxicity)	Shi et al. <sup>58</sup>
Ethylene carbonate	170°C, 1h, 100 atm	99	0.045	ii) Phenol (CMR, acute toxicity) iii) triphenylphosphine (CMR) i) Ethylene oxide (CMR, acute toxicity)	Peppel et al. <sup>75</sup>
Propylene carbonate	170 °C, 1h, 100 atm	98	0.046	i) Propylene oxide (CMR, acute toxicity)	Peppel et al. <sup>75</sup>
4-chloromethyl-1,3-dioxolan-2-one	120 °C, 1h, 30 atm	99	0.13	i) Epichlorohydrin (CMR, acute toxicity)	Deng et al. <sup>76</sup>
4-phenyl-1,3-dioxolan-2-one	120 °C, 1h, 30 atm	96	0.13	ii) TBAB (acute toxicity) i) Styrene oxide (CMR, acute toxicity)	Deng et al. <sup>76</sup>
Glycerol carbonate	120 °C, 2h, 30 atm	91	0.2	ii) TBAB (acute toxicity) i) Glycidol (CMR, acute toxicity)	Deng et al. <sup>76</sup>
4,5-dimethyl-1,3-dioxolan-2-one	120 °C, 24h, 30 atm	93	0.2	i) TBAB (acute toxicity)	Deng et al. <sup>76</sup>
4,5-diphenyl-1,3-dioxolan-2-one	120 °C, 24h, 30 atm	56	2.1	i) TBAB (acute toxicity)	Deng et al. <sup>76</sup>
glycerol carbonate methacrylate	60 °C, 6h, 10 atm	100	12.8	i) Glycidol (CMR, acute toxicity)	Lozano et al. <sup>77</sup>
glycerol carbonate acrylate	60 °C, 6h, 10 atm	100	12.5	i) Vinyl acrylate (acute toxicity)	Lozano et al. <sup>77</sup>
ethyl 2-oxo-1,3-dioxolane-4-carboxylate	70°C, 18h, 10 atm	40	6.4		Kleij et al. <sup>79</sup>

## Syntheses of 5CCs from olefins and CO<sub>2</sub>

The reaction between olefins, an oxidizing agent and CO<sub>2</sub> is an interesting one-pot synthetic pathway that directly yields cyclic carbonates. This route avoids the synthesis and purification of epoxides by generating them *in-situ*, and further cycloaddition of CO<sub>2</sub> occurs in the presence of a catalyst. Moreover, as the epoxide is *in-situ* generated, exposure to these hazardous chemicals with typically high LD<sub>50</sub> (see above) is reduced. However, highly toxic chemicals such as *tert*-butyl hydroperoxide (TBHP) (LC<sub>50, inhalation, 4h</sub> = 1,2 mg/kg) and olefins that show CMR properties are employed in some procedures. This synthetic route includes the carbonation step of epoxides and is hence related to the pathway discussed in the previous section. Thus, high temperatures and CO<sub>2</sub> pressures are also required here and significant amounts of energy are necessary as well as specific equipment. Numerous articles describe harsh conditions,<sup>80–83</sup> high temperatures ranging from 80 °C to 100 °C and CO<sub>2</sub> pressures (up to 100 atm) were reported. The yields are fairly high in the majority of the cases, but show a wide range from 11% to 97%. Table 6 summarizes some differences concerning reaction conditions as well as calculated E-factor values.

The works of Motavalizadehkakhky et al. and Jain et al. show fairly harsh reaction conditions. Indeed, the reaction temperature and pressure are among the highest. On the other hand, yields (over 70%)

and E-factors are the best among the protocols analyzed, the latter ranging from 1.2 to 5.7. In addition, the protocol of Motavalizadehkakhky et al. is performed under solvent-free conditions, while the protocol of Jain is not. With regards to reagent toxicity, some of the reagents employed, namely styrene ( $LD_{50, \text{oral, rat}} = 2650 \text{ mg/kg}$ ) and cyclohexene ( $LD_{50, \text{oral, rat}} = 1300 \text{ mg/kg}$ ) are labeled as CMR, and TBHP is labeled as highly toxic and CMR. However, these two protocols have the lowest number of hazardous reagents employed (up to two). Another interesting synthetic protocol has been described by Ghosh et al., requiring the mildest conditions and reaction times. Indeed, this protocol yields cyclic carbonates at 80 °C in 10h at 17 atm of pressure. However, the yields are relatively poor (less than 34%) and calculated E-factor values are among the highest (up to 29.7). This significant difference in the E-factors is due to the insufficient yields, the higher excess of  $CO_2$  employed and the presence of a solvent. In addition, many hazardous reagents are employed in this protocol namely styrene, cyclohexene, TBHP and TBAB. Finally, the work of Arai et al. yields cyclic carbonates in 4h at 80°C and 80 atm. Also in this protocol, yield (31%) and E-factor (10.9) are unsatisfactory compared to other protocols. This fairly high E-factor value relates to a high excess of  $CO_2$  (7.75 equivalents of  $CO_2$  per equivalent of substrate).

To sum up, among the protocols discussed, the most promising considering E-factor values and yield seems to be the one proposed by Motavalizadehkakhky et al. However, this protocol does not employ the lowest number of hazardous chemicals. In this respect, the protocol described by Jain et al. is the one that uses the least number of dangerous reagents. Nevertheless, the E-factors and the yields are not the highest, but are still fairly satisfying. As a general advice, in order to improve sustainability, we suggest to perform reactions in neat conditions and using stoichiometric amounts of reagents could drastically reduce E-factors up to 5-fold.

**Table 6.** Summary of the synthetic protocols reacting olefines with an oxidizing agent and  $CO_2$ .

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
4-phenyl-1,3-dioxolan-2-one	80 °C, 4h, 80 atm	31	10.9	i) Styrene (CMR) ii) TBHP (CMR, acute toxicity) iii) TBAB (acute toxicity)	Arai et al. <sup>80</sup>
4-phenyl-1,3-dioxolan-2-one	100 °C, 10h, 30 atm	97	1.2	i) Styrene (CMR) ii) TBHP (CMR, acute toxicity)	Motavalizadehkakhky et al. <sup>82</sup>
4-phenyl-1,3-dioxolan-2-one	100 °C, 10h, 30 atm	70	4.7	i) Styrene (CMR)	Jain et al. <sup>82</sup>
propylene carbonate	100 °C, 10h, 30 atm	85	5.7		Jain et al. <sup>82</sup>
4-chloromethyl-1,3-dioxolan-2-one	100 °C, 10h, 30 atm	80	4.8		Jain et al. <sup>82</sup>
cyclohexane carbonate	100 °C, 10h, 30 atm	80	4.6	i) cyclohexene (CMR)	Jain et al. <sup>82</sup>
4-phenyl-1,3-dioxolan-2-one	80°C, 10h, 17atm	34	8.0	i) Styrene (CMR) ii) TBHP (CMR, acute toxicity) iii) TBAB (acute toxicity)	Ghosh et al. <sup>83</sup>
cyclohexene carbonate	80°C, 10h, 17atm	11	29.7	i) cyclohexene (CMR) ii) TBHP (CMR, acute toxicity) iii) TBAB (acute toxicity)	Ghosh et al. <sup>83</sup>

### Synthesis of exovinylene 5CCs from propargyl alcohols and $CO_2$

The carboxylative coupling of  $CO_2$  to propargyl alcohols is an efficient route to yield unsaturated and thus highly reactive cyclic carbonates (i.e. exo-vinylene carbonates). These monomers are promising,



as they find broad applications in biological compounds, pharmaceuticals, and polymer chemistry. Indeed, the presence of an exocyclic olefin on the five-membered cyclic carbonate significantly enhances the reactivity towards S-, N-, and O-nucleophiles in the ring-opening of the cyclic carbonates.<sup>84</sup> However, these substrates have limited availability compared to conventional cyclic carbonates, especially bis-functional ones, thus requiring further development before possible applications in NIPU synthesis. This synthetic pathway requires reaction conditions that are in the majority of the cases milder than carboxylative coupling routes. Generally, temperatures ranging from 25 °C to 100 °C, CO<sub>2</sub> pressures (up to 50 atm) as well as specific equipment are required. The protocols discussed herein<sup>79,85–89</sup> report reasonably good yields ranging from 70% to 98%. In addition, according to the nature of the propargyl alcohol used in the protocol (primary, secondary, tertiary), different reaction conditions are described to yield the desired product. For this reason, we are going to evaluate the protocols by sorting them according to the substrate used, i.e. primary, secondary, and tertiary propargyl alcohol-based 5CCs. Here, we would like to point out the differences concerning reaction conditions, calculated E- factors and toxicity of the reagents (Table 7).

The works of Cervantes-Reyes et al. and Schaub et al. describe the carboxylative coupling of CO<sub>2</sub> to primary and secondary propargyl alcohols showing the mildest reaction conditions. Thus, cyclic carbonates yielded from primary propargyl alcohol were produced within 24h at 25 °C and 15 atm in high yields (>86%). Carbonates yielded from secondary propargyl alcohols require higher carbon dioxide pressures (25 atm) with yields up to 94%. The calculated E-factors are among the highest ranging from 7.6 to 100.7. Such high values are due to the stoichiometric excess of carbon dioxide, particularly in the Cervantes-Reyes et al. protocol (up to 60-fold) and the use of solvents (DCM or acetonitrile) that contribute up to 82% to the total E-factor value. The described protocols all employ propargyl alcohol or 3-butyn-2-ol and 1-pentyn-3-ol, which are labelled as CMR and toxic (LD<sub>50, oral, rat</sub> = 56 mg/kg; LD<sub>50, oral, rat</sub> = 45 mg/kg; LD<sub>50, oral, rat</sub> = 70 mg/kg respectively)

The works of Kimura et al., Ikariya et al., and Detrembleur et al. describe the carboxylative coupling of CO<sub>2</sub> with tertiary propargyl alcohols. These protocols describe higher temperatures (up to 100°C) and pressures ranging from 45 atm to 100 atm. Moreover, such conditions can lead to supercritical carbon dioxide, as described in the work of Detrembleur et al. ( $p_{\text{CO}_2} = 100 \text{ atm}$ ,  $T = 50 \text{ °C}$ ), which require specific equipment. However, these protocols show better E-factor values ranging from 2.1 to 6.8, reasonably high yields (>70%) and shorter reaction time in the majority of the cases. Lower E-factor values are mainly due to solvent-free conditions, however, in the majority of the cases, high stoichiometric excesses of carbon dioxide (up to 18-fold) were used. By analyzing the reagents employed in these protocols, all of them use the CMR labeled compound 2-methyl-3-butyn-2-ol (LD<sub>50, oral, rat</sub> = 1420 mg/kg) and, in addition, Detrembleur et al. use triethylamine (LD<sub>50, oral, rat</sub> = 730 mg/kg) labeled as highly toxic.

In conclusion, among the protocols reported, the most promising considering the E-factor is the one proposed by Detrembleur et al., even though the yield is not the highest, but the stoichiometric excess of carbon dioxide is the lowest (1.25 eq of CO<sub>2</sub> per equivalent of alcohol). Moreover, reaction time and temperature are fairly low. The E-factor of this route could be further improved by up to 27% by recovering ZnI<sub>2</sub> and by using a modest stoichiometric excess of CO<sub>2</sub>. In order to improve these protocols, we suggest to recycle the solvents and catalysts, as indeed the majority of the procedures we have discussed in this chapter showed high solvent contribution to the E-factor value up to 82%. Moreover, carbon dioxide excess should be reconsidered in the protocol of Cervantes et al.

**Table 7.** Summary of the synthetic protocols reacting propargyl alcohols and CO<sub>2</sub>.

Synthesized substrate	Reaction conditions	Yield (%)	E-factor	Toxic reagents	Reference
4-methylene-1,3-dioxolan-2-one	25 °C, 16h, 10 atm	95	19.3	i) Propargyl alcohol (CMR, acute toxicity)	Cervantes-Reyes et al. <sup>85</sup>
4-methyl-5-methylene-1,3-dioxolan-2-one	25 °C, 24h, 20 atm	94	100.7	i) CsF (CMR, acute toxicity) ii) 3-butyn-2-ol (acute toxicity)	Cervantes-Reyes et al. <sup>85</sup>

4-ethyl-5-methylene-1,3-dioxolan-2-one	25 °C, 24h, 20 atm	90	93.8	i) CsF (CMR, acute toxicity) ii) 1-pentyn-2-ol (acute toxicity)	Cervantes-Reyes et al. <sup>85</sup>
4-methylene-1,3-dioxolan-2-one	25 °C, 16h, 10 atm	98	20.2	i) Propargyl alcohol (CMR, acute toxicity)	Schaub et al. <sup>79</sup>
4-methylene-1,3-dioxolan-2-one (synthesis with silver decanoate)	25 °C, 16h, 10 atm	97	20.5	i) Propargyl alcohol (CMR, acute toxicity)	Schaub et al. <sup>79</sup>
4-methylene-1,3-dioxolan-2-one	25 °C, 16h, 10 atm	86	7.6	i) Propargyl alcohol (CMR, acute toxicity)	Schaub et al. <sup>86</sup>
4,4-dimethyl-5-methylene-1,3-dioxolan-2-one	25 °C, 16h, 20 atm	87	16.5	i) 2-methyl-3-butyn-2-ol (CMR)	Schaub et al. <sup>86</sup>
4,4-dimethyl-5-methylene-1,3-dioxolan-2-one	100 °C, 16h, 50 atm	86	3.9	i) 2-methyl-3-butyn-2-ol (CMR)	Kimura et al. <sup>87</sup>
4,4-dimethyl-5-methylene-1,3-dioxolan-2-one	60 °C, 15h, 45 atm	90	6.8	i) 2-methyl-3-butyn-2-ol (CMR)	Ikariya et al. <sup>88</sup>
4,4-dimethyl-5-methylene-1,3-dioxolan-2-one	50 °C, 8h, 100 atm	70	2.1	i) 2-methyl-3-butyn-2-ol (CMR) ii) triethylamine (acute toxicity)	Detrembleur et al. <sup>89</sup>

## CONCLUSIONS

We reviewed the main synthetic routes to yield mono-5CCs and evaluated basic toxicity information, reaction conditions, and E-factors to provide a basic sustainability assessment of 5CC synthesis. However, our chosen approach cannot replace deeper quantitative analysis, such as LCA, but provides a first insight. The data discussed in this review are summarized in Scheme 7, providing an overview on the E-factor averages for each of the discussed synthetic routes (Scheme 2).

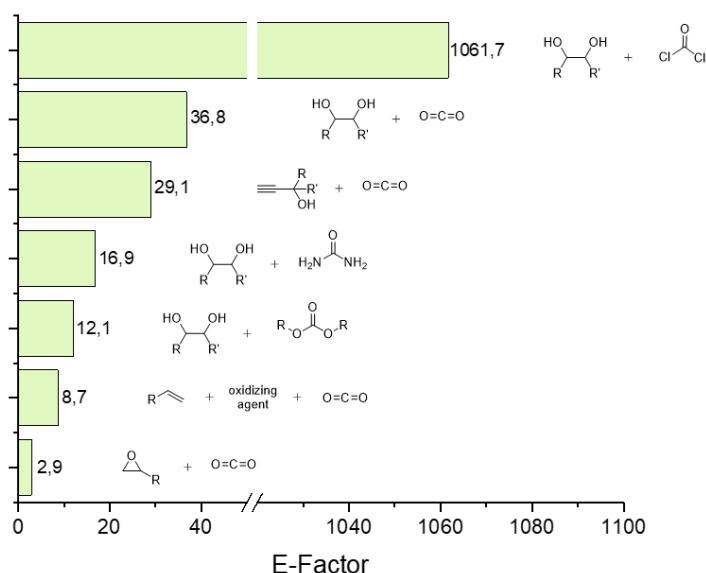
Despite the harsh conditions and toxicity of the epoxides, the cyclization reaction of epoxides and carbon dioxide shows the lowest average E-factor (Scheme 7) and excellent yields in the majority of the cases. Furthermore, this approach can be implemented in flow reactor systems, as reported by Kleij et al.<sup>90</sup> and by Montbaliu et al.<sup>91</sup> in his latest contribution, showing outstanding productivity output and efficiency in glycidol coupling reactions with stoichiometric amount of CO<sub>2</sub>. A similar synthetic route worth mentioning is the carboxylative cyclization of propargyl alcohols, which showed an average E-factor value of 29.1. This value is not the lowest, mostly related to the excess of CO<sub>2</sub>, but this might be targeted in future research. This route remains important, as it yields exo-vinylene cyclic carbonates, that are of great interest for their properties and applications in NIPU and polycarbonate chemistry.<sup>92</sup> Reasonably low E-factors have been calculated for other synthetic protocols. Among them, the synthetic route based on olefins showed an average E-factor value of 8.7, a value that demonstrates the viability of this process in terms of green metrics. Moreover, this route might avoid the direct employment of toxic epoxides by yielding and reacting them with carbon dioxide *in situ*. Another advantage not considered herein is the avoidance of an additional reaction step, as olefins are precursors for other routes, i.e. the ones based on diols and epoxides, which by themselves lead to waste and require toxic substances. Moreover, this approach seems to be the most promising to be applied to natural resources, i.e. to plant oils or terpenes,<sup>93-100</sup> which would also be far less toxic than the herein compared olefin substrates. The reaction of dialkyl carbonates and diols, which is particularly promising considering that it avoids toxic or harmful reagents in most cases, also remains promising. For instance, dialkyl carbonates and diols can be obtained sustainably from renewable resources. Even though this strategy reported higher average E-factor values compared to other approaches, we believe that an optimal synthetic design, such as the one reported Meier et al.,<sup>66</sup> will

lead to much lower E- factors and make this route very attractive from a green chemistry perspective. Moreover, this route does not depend on autoclaves, making it accessible to every chemistry lab. Additionally, this route was successfully implemented in flow reactors to carbonate various 1,2-diols toward mono- and bis-cyclic carbonates.<sup>101</sup> Considering the assumptions made about the route based on dialkyl carbonates, also the synthetic protocol based on urea and diols is noteworthy. In fact, urea can be produced from renewable resources and it is comparably non-toxic. However, the reaction conditions are notably harsher, leading to higher energy consumption and making them dangerous for the operators. Finally, carbonates synthesized from phosgene and diols are the least attractive in terms of E-factor, sustainability, and safety, since the employment of acute toxic phosgene gas poses major concerns for the safeguard of workers and the environment. Despite the strict safety standards and regulations currently in place for these chemicals (ECHA, Seveso directive), lethal accidents are occasionally reported.<sup>102–104</sup> All these considerations should discourage the use of phosgene and spur its substitution with safer and more sustainable chemicals, consistently with the principles of green chemistry.

Generally, all protocols would benefit from strictly adhering to the principles of green chemistry, or, phrased differently, by not contradicting any of the principles of green chemistry, as is often the case by using highly toxic or even CMR labelled compounds. All routes, but especially the ones based on CO<sub>2</sub> activation, would benefit from the further development of catalysts and the reduction of the necessary CO<sub>2</sub> equivalents. The latter could also be achieved by recovering the excess CO<sub>2</sub>, which should be easy to realize in industrial operations, but was not reported in the herein studied protocols.

## Acknowledgements

We kindly acknowledge funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955700.



**Scheme 7.** Main synthetic routes to 5CCs analyzed herein ordered by decreasing E-factor mean values.



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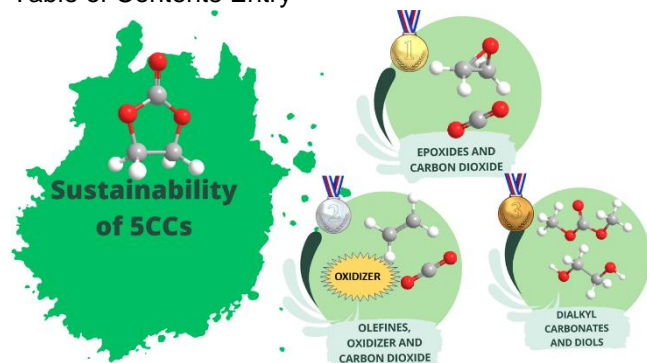
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## Table of Contents Entry



The synthesis of 5-membered cyclic carbonates is reviewed, utilizing E-Factors and general sustainability aspects such as reagent toxicity and solvent selection criteria.