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Dimethyl isosorbide *via* organocatalyst *N*-methyl pyrrolidine: scaling up, purification and concurrent reaction pathways†

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Dimethyl isosorbide (DMI) is a well-known bio-based green replacement for conventional dipolar solvents such as dimethyl sulfoxide and dimethylformamide. The synthesis of DMI mainly relies on the etherification of the bio-based platform chemical isosorbide in the presence of basic or acid catalysts and by employing different alkylating agents. Among them, dimethyl carbonate (DMC) is considered one of the most promising for its good biodegradability and low toxicity. In this work, we report on a comprehensive investigation on high yielding methylation of isosorbide *via* DMC chemistry promoted by nitrogen organocatalyst *N*-methyl pyrrolidine (NMPy). Reaction conditions were optimized and then efficiently applied for the methylation of isosorbide epimers, isoidide and isomannide, and for some preliminary scale-up tests (up to 10 grams of isosorbide). The purification of DMI from the reaction mixture was achieved by both column chromatography and distillation at reduced pressure. NMPy demonstrated to be an excellent catalyst also for the one-pot conversion of D-sorbitol into DMI. Furthermore, for the first time, all seven methyl and methoxycarbonyl intermediates observed in the etherification of isosorbide were synthetised, isolated and fully characterised. This has provided an insight on the concurrent reaction pathways leading to DMI and on the role played by NMPy in the methylation of isosorbide. Finally, the reaction mechanisms for the methylation, methoxycarbonylation and decarboxylation promoted by NMPy partaking in the conversion of isosorbide into DMI *via* DMC chemistry have been proposed.

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1. Introduction

Non aqueous solvents – still mainly produced from fossil fuel sources – represent the vast majority of waste derived from organic syntheses, both at laboratory and industrial scale. The replacement of hazardous and toxic organic media with alternatives derived from renewables is a priority to realize more sustainable industrial processes.[1]

Pharmaceutical companies, in particular, are highly affected by the use of organic solvents that are employed in the preparation and purification of active pharmaceutical ingredients.[2] By considering the extent of the issue, GlaxoSmithKline, Pfizer, AstraZeneca and Sanofi, have all established custom-made solvent guides that provide a quick tool to select greener alternative media.[3]

The viable replacement for polar aprotic and halogenated solvents is also highlighted as one of the Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective.[4]

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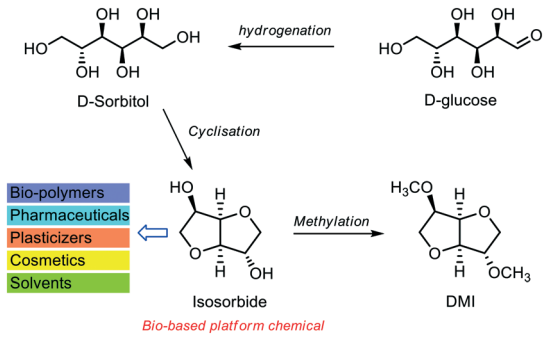
This ever-growing demand for green alternatives to petroleum-based solvents has spurred, in the last ten years, the exploitation of new bio-based reaction media. Ideally, a biomass or waste derived solvent should encompass the required physical–chemical properties to guarantee reagents solubility in combination with low environmental impact, human health preservation, sustainable lifecycle and easy availability at competitive price.

Some relevant examples of bio-based green solvents include:

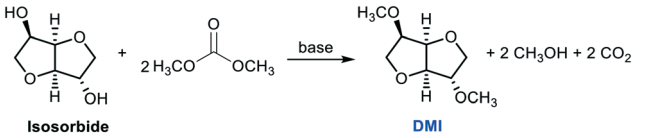
- Weak polar solvents as *p*-cymene, limonene, and terpinene;
- Intermediately polar solvents as 2-MeTHF, 2,2,5,5-tetramethyloxolane (TMO), glycerol, carbohydrates, gluconic acid and ethyl lactate;
- Strong polar solvents as γ-valerolactone, Cyrene™ and dimethyl isosorbide (**DMI**).

Compared to the abovementioned solvents, **DMI** (b.p. 236 °C), is a unique molecule due to its high polarity and water solubility that render it a good replacement for conventional dipolar media, such as dimethyl sulfoxide and dimethylformamide.

Dimethyl isosorbide is one of the simplest derivatives of well-known bio-based platform chemical isosorbide (Scheme 1), an anhydro sugar readily synthesised by D-sorbitol dehydration reaction.[5] D-Sorbitol has an estimated global market of 800 kt per year, thus isosorbide and



Scheme 1 Isosorbide as bio-based platform chemical and DMI precursor.



Scheme 2 DMI synthesis *via* DMC chemistry.

consequently **DMI** are both easily available at relatively cheap price also in large-scale.

DMI has been efficiently used in Pd-catalysed cross-coupling reactions *i.e.*, Suzuki–Miyaura, Mizoroki–Heck and Sonogashira reactions as substitute of hazardous solvents 1,4-dioxane and DMF.[6] Besides, it was recently employed in the preparation of poly(vinylidene fluoride)- and poly(ether sulfone)-based membranes with a pore size in the range of ultrafiltration and microfiltration that render them ideal for applications in water treatment processes.[7] **DMI** use in cosmetics and as efficient thinning agent were also described in the literature.[8]

Despite such wide interest, only a scarce number of synthetic procedures to dimethyl isosorbides are reported in the literature. Nowadays, main synthetic approaches to **DMI** are based on the reaction of isosorbide with alkylating agents including toxic halogen chemicals such as alkyl halide.[9]

Methanol and ethanol have been explored as viable reagents for the synthesis of **DMI** and diethyl isosorbide (DEI) in the presence of numerous catalysts, such as potassium salts of 12-tungsto-phosporic acid, zeolites, zirconia-based catalysts.[10] Isosorbide conversion was in all cases good (up to 78%), whereas selectivity toward **DMI** and DEI resulted only moderate (24 and 34% respectively).

In another approach, 1,2-dimethoxyethane was used as reagent and solvent for isosorbide etherification, by heating to 150 °C in the presence of heteropolyacids.[11] Among them 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) exhibited superior activity leading to almost quantitative conversion of isosorbide (>90%) with **DMI** selectivity up to 80%. The catalyst was recycled three times, although the product was never isolated from the reaction mixture.

DMI was also prepared in moderate yield (54%) by solvent-free reaction of isosorbide with methylphosphates in the presence of iron triflate as Lewis acid at 100 °C.[12]

Dialkyl carbonates (DACs), well known green solvents and reagents,[13] have been extensively investigated for the alkylation of isosorbide. The reaction of isosorbide with DMC is highly attractive as it combines the advantages of a bio-based starting material with a green solvent and reagent leading to a sustainable alternative for conventional dipolar solvents. In the methylation reaction *via* DMC chemistry (Scheme 2) two moles of DMC are consumed to form **DMI** along with the equivalent amount of CO_2 and MeOH as the only by-products formed.

It should be also mentioned that isosorbide has a peculiar V-shaped structure that incorporates four oxygens in β-position to each other, conferring to the molecule a high reactivity, which is atypical of secondary alcohols.[14] The different configuration of the two hydroxyl groups, *endo* (–OH group in the 2-position directed toward the V-shaped cavity) and *exo* (–OH in the 5-position pointing outside of cavity), combined with the reactivity of ambident electrophile DMC, render the synthesis of **DMI** complicated by the presence of numerous intermediates (Scheme 3) and yet captivating.

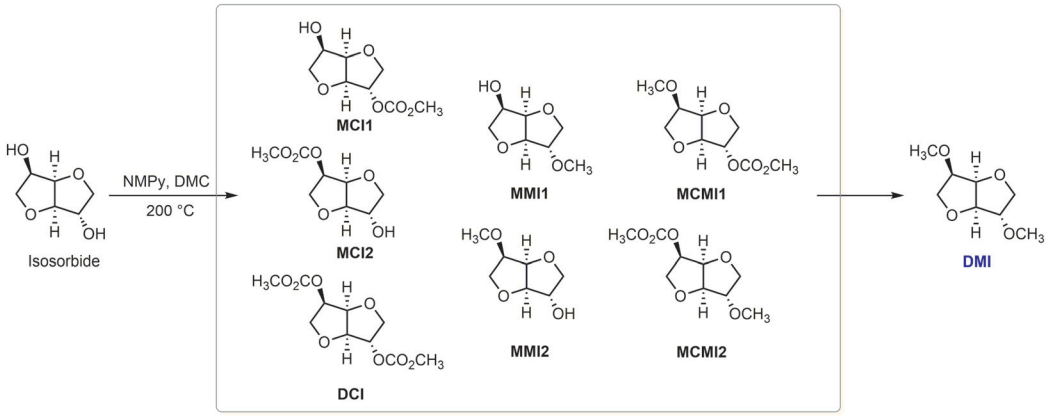
In previous investigations, the methylation of isosorbide was carried out at the reflux temperature of DMC (90 °C) in the presence of freshly prepared NaOMe; **DMI** was isolated as pure compound in quantitative yields, however a large amount of the strong base was required.[15]

In an alternative approach, isosorbide was reacted with DMC at high pressure in autoclave (at 200 °C) in the presence of hydrotalcite KW2000 ($Mg_{0.7}Al_{0.3}O_{1.15}$), (1 : 1 w/w ratio).[16] **DMI** was recovered in high yield (*ca.* 90%) after purification *via* column chromatography, although, to ensure high activity of the catalyst, the hydrotalcite must be calcinated overnight at 400 °C to eliminate interstitial water.

Few patents report additional investigations where DMI was synthetised *via* DMC chemistry in the presence of Brønsted bases at high temperature[17] or employing alternative reaction conditions (MW irradiation);[18] unfortunately these procedures were not described in detail.

Recently a one-pot procedure to **DMI** starting from D-sorbitol *via* DMC chemistry using nitrogen superbase 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst was also described. The reaction was carried out in an autoclave at high pressure and **DMI** selectivity was 70%.[19]

In this work we report on a systematic investigation on the methylation of isosorbide *via* DMC chemistry promoted by *N*-methyl pyrrolidine, that resulted the most efficient nitrogen organocatalysts among the ones investigated. Reaction conditions were first optimized to achieve quantitative conversion and selectivity towards **DMI** and then tested on isosorbide epimers, isomannide and isoidide. Preliminary scale-up experiments (5–10 grams of isosorbide) were also carried out and issues related to **DMI** purification addressed. *N*-Methyl pyrrolidine was then tested in the one-pot direct conversion of D-sorbitol into **DMI** resulting more efficient than TBD used as preferred catalyst in previous investigations.[18] Besides, for the first time, all the reaction intermediates (seven compounds) forming during the reaction of isosorbide with DMC have been isolated and fully characterised *via* a custom-built synthetic



Scheme 3 Methylation of isosorbide *via* DMC chemistry. The scheme outlines all the observed reaction intermediates.

Table 1 DMI *via* DMC chemistry and nitrogen organocatalysts

		Selectivity%					
#	Base	**MMI1**	**DMI**	**MMI2**	**MCI1 MCI2**	**MCMI1 MCMI2**	**DCI**
1	—	1	**1**	1	30	31	35
2	TBD	5	**78**	0	0	17	0
3	DBU	13	**51**	0	0	34	0
4	DABCO	8	**54**	0	0	38	0
5	Pyridine	19	**20**	11	0	49	0
6	NMPy	2	**98**	0	0	0	0
7	Et_3N	5	**95**	0	0	0	0
8	DMAP	6	**94**	0	0	0	0

Isosorbide : DMC : catalyst 1.0 : 50.0 : 0.5 mol ratio. Reactions were conducted in autoclave at 200 °C. Pressure was 13–17 bar; isosorbide conversion was always quantitative. Conversion and selectivity were calculated *via* GC-MS.

strategy. This has provided a clearer insight on the reaction pathways leading to **DMI** and on the role of NMPy as the catalyst. Finally, a mechanism for each concurrent reaction contributing to **DMI** formation, *i.e.*, methylation, methoxycarbonylation and decarboxylation, has been proposed.

2. Results and discussion

In this case study, the methylation of isosorbide was conducted in an autoclave by employing DMC as reagent and solvent in the presence of a nitrogen organocatalyst (Table 1). Scheme 3 reports all the seven reaction intermediates forming by the combined reactivities of isosorbide and DMC, *i.e.*, mono- and di-methoxycarbonyl derivatives (**MCI1**, **MCI2** and **DCI**), mono methyl isosorbides (**MMI1** and **MMI2**) and methoxycarbonyl methyl products (**MCMI1** and **MCMI2**).‡

A first experiment was carried out reacting isosorbide and DMC in the absence of a catalyst. The quantitative conversion of isosorbide was observed although most of the obtained products are methoxycarbonyl derivatives; some methylated products were also present in the reaction mixture.

When superbases 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 1,5-diazabiciclo(5.4.0)undec-7-ene (DBU) were used, **DMI** formed in good to moderate selectivity respectively. 1,4-Diazabicyclo[2.2.2]octane (DABCO) showed modest result, meanwhile pyridine efficiency was quite poor. On the other hand, organocatalysts incorporating aliphatic, less sterically hindered amines such as *N*-methyl pyrrolidine (NMPy), triethyl amine and 4-dimethylaminopyridine (DMAP) resulted more efficient. In particular, NMPy led to the almost quantitative formation of **DMI** and it was selected as the preferred nitrogen organocatalyst.

Interestingly, the catalyst activity seems not related to its basicity as NMPy pK_a value is lower than DBU and TBD, both less efficient in promoting isosorbide etherification.§

Several experiments were then conducted to optimize the reaction conditions (Table 2). Attempts to reduce the amount of NMPy resulted in lower **DMI** selectivity (#1–3; Table 2). By decreasing the reaction temperature to 180 °C, the methylation efficiency has been affected as well. On the other hand, when the reaction was performed at 220 °C, **DMI** formed in quantitative yield in only 6 hours (#5–6; Table 2).

‡ All the carboxymethyl and methyl derivatives of isosorbide have been identified according to their retention time in the GC-MS trace reported in the supplementary information.
§ More data reported in ESI.†

Table 2 DMI: optimization of the reaction conditions

	NMPy	*T*	*t*	Selectivity%			
	mol eq.	°C	h	**MMI1**	**DMI**	**MMI2**	**MCMI1 MCMI2**
1	0.50	200	12	2	**98**	0	0
2	0.35	200	12	5	**90**	0	5
3	0.25	200	12	13	**67**	2	18
4	0.50	180	12	6	**81**	0	13
5	0.50	220	12	1	**99**	0	0
6	0.50	220	6	1	**99**	0	0
7	0.50	200	6	3	**85**	0	12
8	0.50	200	8	4	**85**	0	11
9	0.50	200	10	4	**92**	0	4

Isosorbide : DMC : 1.0 : 50.0 mol ratio; reactions were conducted in an autoclave. Pressure was about 13–17 bar. Isosorbide conversion was always quantitative. Selectivity and conversion were calculated *via* GC-MS.

Methylations performed by reducing the reaction time were also less efficient in terms of **DMI** selectivity.

According to data collected, the best reaction conditions involved the heating of the reaction mixture to 200 °C for 12 h in the presence of 0.5 mol eq. of NMPy (#1; Table 2). In fact, the test carried out at 220 °C led to a dark brown mixture due to the presence of a certain amount of degraded material (#5–6; Table 2).

With the optimized reaction conditions in hand, some scale-up reactions were then performed (Table 3); the amount of the isosorbide was increased up to 10 grams. In all experiments (#1–4; Table 3) the selectivity toward **DMI** was always almost quantitative confirming the efficiency of the procedure.

The purification of dimethyl isosorbide from the reaction mixture was also addressed. **DMI** achieved from relatively small-scale reactions (#1–3; Table 3) was purified *via* column chromatography, meanwhile the larger scale reaction (#4; Table 3) was purified by distillation. In both cases **DMI** was recovered as transparent liquid; the lower yield achieved *via* distillation can be ascribed to product loss in the apparatus. Most likely, by performing the distillation in larger scale, it may result more efficient.

DMC was also recovered by quick distillation in all tests and reused in further experiments.

Methylation of isosorbide epimers, isomannide and isoidide, was next investigated (Scheme 4). Reactions were performed in an autoclave at 200 °C on one- and five-grams scale of the two anhydro sugars.§ Interestingly both dimethyl isomannide (DMIm) and dimethyl isoidide (DMIi) were achieved in excellent selectivity (94–95%) confirming the robustness of this synthetic procedure.§

Table 3 DMI scaling-up syntheses

	Isosorbide	Selectivity%			**DMI** yield
	G	**MMI1**	**DMI**	**MMI2**	%
1	1.0	2	**98**	0	85[a]
2	3.0	1	**99**	0	85[a]
3	5.0	1	**99**	0	75[a]
4	10.0	8	**92**	0	65[b]

Isosorbide : DMC : 1.0 : 50.0 mol ratio, 200 °C, 12 hours; reactions were conducted in autoclave. Selectivity was calculated *via* GC-MS. [a] Purification *via* column chromatography. [b] Purification *via* distillation.

D-Sorbitol one-pot conversion into **DMI** promoted by NMPy was also attempted. A first experiment was conducted according to our previously reported best reaction conditions.[18] Thus, D-sorbitol was reacted with DMC in the presence of NMPy at 90 °C for 48 hours to ensure high yield cyclisation into isosorbide; then the temperature was risen to 200 °C for further 24 hours. As a result, **DMI** was the only product detected in the reaction mixture *via* GC-MS (#2; Table 4). By comparison with our previously reported experiment (#1; Table 4) **DMI** selectivity was higher and no epimerisation was observed, although a certain amount of degraded material was also present in the reaction mixture affecting the isolated yield (55%).

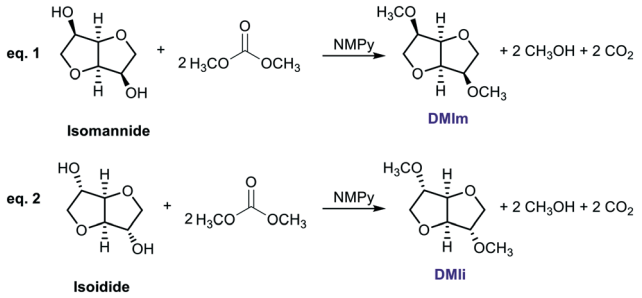
One-pot D-sorbitol conversion to **DMI** was then attempted at 200 °C for 20 hours without any temperature variation. In this trial **DMI** was still the main reaction product, but several other isosorbide derivatives were also present in the reaction mixture (#3; Table 4).

2.1. Concurrent reaction pathways leading to DMI, role of the catalyst and proposed reaction mechanisms

From a mechanistic point of view, the methylation of isosorbide is quite complicated by numerous concomitant reaction pathways. In this scenario, the first issue to be addressed was to develop a strategic approach for the preparation of all seven methoxycarbonyl and methyl derivatives, which were observed as intermediates in the methylation of isosorbide (Scheme 5).‡

The dimethoxycarbonyl isosorbide (**DCI**) was easily prepared in high yield by reaction of isosorbide with an excess of DMC in the presence of potassium carbonate. A Dean–Stark apparatus was set up to push the equilibrium toward **DCI** that was achieved in quantitative yield.

Monocarboxymethyl isosorbides **MCI1** and **MCI2**, reported in the literature as intermediates of isosorbide-based polycarbonate,[20] were previously either isolated in small amounts from complicated reaction mixture[15] or more recently

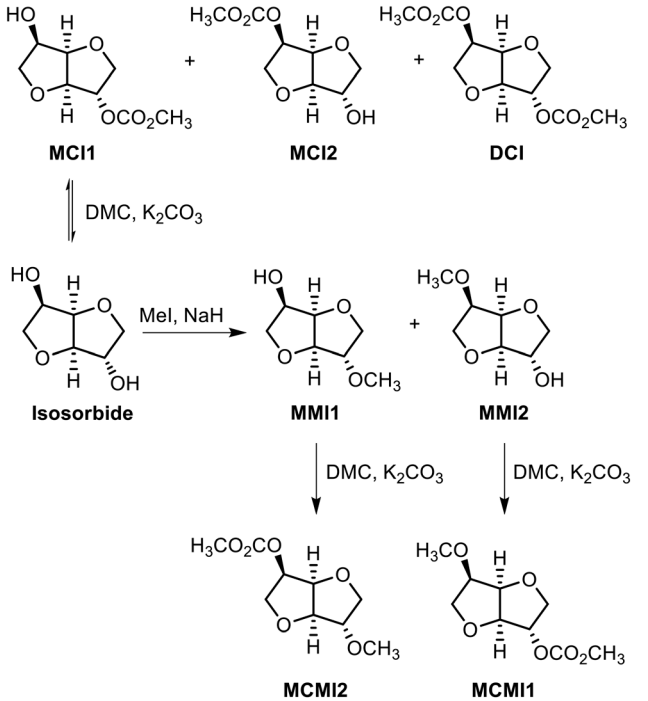


Scheme 4 Synthesis of dimethyl isomannide (eq. 1), dimethyl isoidide (eq. 2) *via* DMC chemistry in the presence of *N*-methylpyrrolidine.

synthetised *via* DMC-mediated isosorbide transesterification in the presence of a task-specific phosphonium ionic liquids.[21] Herein, we developed a convenient synthesis to **MCI1** and **MCI2** by reacting isosorbide with a diluted solution of DMC in acetonitrile employing 1.0 mole eq. of potassium carbonate. Both products formed in moderate yields and were isolated as pure compounds *via* column chromatography. **MCI1** was the major product (**MCI1**:**MCI2** ratio 2:1), inasmuch the methoxycarbonylation reaction of the less sterically hindered *exo* hydroxyl group was favoured.

Monomethyl derivatives **MMI1** and **MMI2** have been scarcely reported in the literature. A typical synthetic approach for these derivatives relies on the selective acetylation of an isosorbide (*exo*) hydroxyl group followed by reaction with methyl halide and deprotection of the acetyl moiety.[22] However, we discovered that a direct methylation of isosorbide in the presence of sub-stoichiometric amount of iodomethane (1.0 mol eq.) led to the formation of a reasonable amounts of the monomethyl derivatives. In the reaction mixture **MMI1** and **MMI2** were present in 1:4 mol ratio due to the strong hydrogen bond involving the *endo* hydroxyl group that renders it more reactive toward alkylation. Both monomethyl derivatives were isolated as pure compounds by purification *via* column chromatography.

Finally, **MCMI1** and **MCMI2** were synthetised in quantitative yield by methoxycarbonylation reaction of **MMI1** and **MMI2** *via* DMC chemistry.

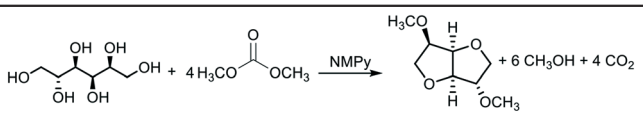


Scheme 5 Synthetic strategy used for the preparation of methoxycarbonyl and methyl derivatives of isosorbide.

All compounds depicted in Scheme 5 were fully characterised *via* (1D and 2D) NMR spectroscopy and high-resolution mass spectrometry that confirmed the proposed structures. The identification of the stereoisomers was also supported by comparing NMR spectra of dimethyl and dimethoxycarboxyl derivatives of isoidide and isomannide available in our laboratory.

By having all the possible intermediates as pure compounds, the reaction pathway leading to DMI was further investigated (Fig. 1). Several experiments were conducted in the best-found reaction conditions (#6; Table 1) and monitored over time (0–12 h). The reaction time zero was conventionally fixed when the autoclave reached the temperature of 200 °C. However, as isosorbide already started

Table 4 D-Sorbitol direct conversion into DMI



#	*T* °C	*t* h	*P* bar	Selectivity% MMI1 MMI2	DMI	MCMI1 MCMI2	DCI
1[a]	90/200	48/24	26	0	**69**	00	0
2	90/200	48/24	30	0	**100**[b]	0	0
3	200	20	20	29	**55**	5	11

Isosorbide:DMC:NMPy 1.0:50.0:1.0 mol ratio; reactions were conducted in autoclave. Selectivity was calculated *via* GC-MS. [a] TBD was used as the catalyst.[18] [b] Isolated yield *via* column chromatography was 55%; a certain amount of insoluble (degraded) material was present in the reaction mixture.

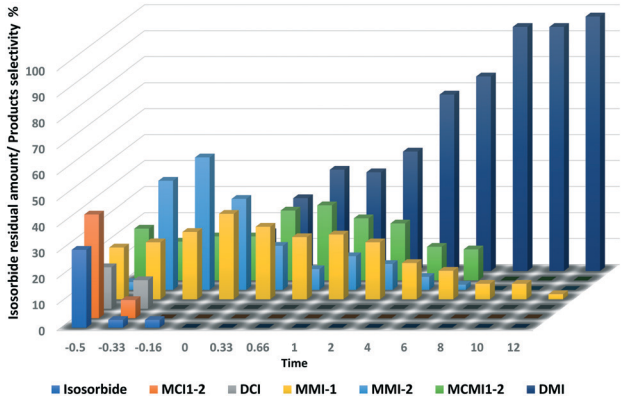


Fig. 1 Methylation of isosorbide over time.§

reacting with DMC at lower temperatures (#1; Table 1), three extra experiments were conducted by heating the mixture to 120, 140 and 160 °C. These temperatures were reached at 30, 20 and 10 minutes before the reaction time zero and are reported in Fig. 1 with negative values (−0.50, −0.33 and −0.16 hour, respectively).

All the experiments were conducted separately rather than performing sampling on a single trial and each reaction was repeated twice to confirm results reliability.§

As expected, the conversion of isosorbide was already quantitative when the autoclave reached the 200 °C. **DCI** and the two monocarboxymethyl derivatives **MCI1** and **MCI2**, once formed, were promptly converted in the other intermediates. **MMI2** formed in larger amount and more rapidly than **MMI1** due to higher reactivity of the *endo* hydroxyl group. Furthermore, **MMI1** resulted the less reactive derivatives as it was the only intermediate still present in the reaction mixture after 8 hours.

According to these data, in Fig. 2 a comprehensive overview of all the possible concurrent reaction pathways leading to DMI *via* DMC chemistry is depicted. Three different reactions might take place: i) methoxycarbonylation *via* $B_{Ac}2$ mechanism; ii) methylation *via* $B_{Al}2$ mechanism and iii) decarboxylation (Fig. 3). Thus, as an example, formation of isosorbide methyl derivatives **MMI1-2** and **DMI** may occur either *via* direct methylation reaction *via* $B_{Al}2$ mechanism or *via* decarboxylation of methoxycarbonyl monomers (**MCI1-2**, **MCMI1-2** and **DCI**).

In the literature, DACs decarboxylation has been extensively reported as viable route to achieve symmetrical and unsymmetrical DACs, however it required high temperature and the presence of a proper catalyst.[23]

For the scope of our investigation some decarboxylation experiments were conducted by employing dimethoxycarbonyl isosorbide as reaction substrate (Fig. 3; Table 5).

When pure **DCI** was reacted with DMC at 200 °C and in the presence of NMPy, **DMI** was the major product observed. Fig. 3 reports on the reaction pathway observed in the conversion of **DCI** into **DMI** (#1; Table 5).

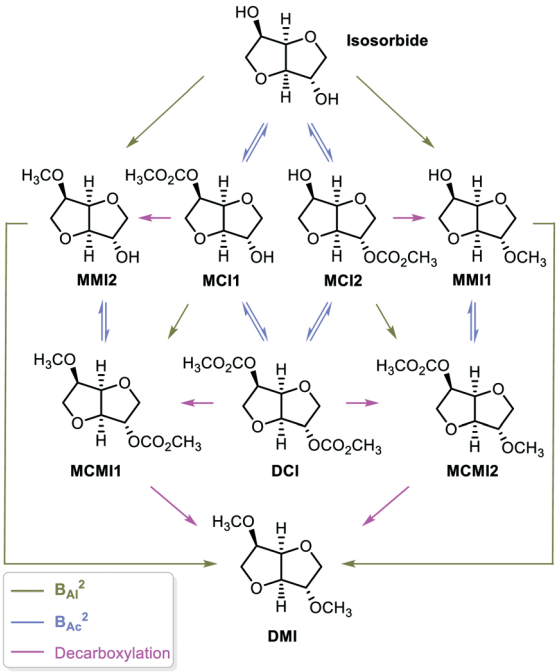


Fig. 2 From isosorbide to DMI *via* DMC: possible reaction pathways.

Data collected showed that monomethyl derivatives **MMI1-2** are present in trace, meanwhile **MCI1-2** formed rapidly in large amount, probably due to the existing thermodynamically driven equilibrium ($B_{Ac}2$ mechanism). After 12 hours small amounts of **MMI1** and **MCMI** derivatives are still present in the reaction mixture, even if DMI selectivity (84%) was comparable to the previously observed results. Although this experiment seems to suggest that the decarboxylation is partaking to the formation of **DMI**, it cannot be excluded that dimethyl isosorbide formed *via* $B_{Ac}2$ equilibrium reaction followed by $B_{Al}2$ direct methylation of the hydroxylic groups. In this view, **DCI** decarboxylation was tested without DMC employing 2-methyl tetrahydrofuran (2-MeTHF) and acetonitrile as reaction media (#2–3; Table 5).

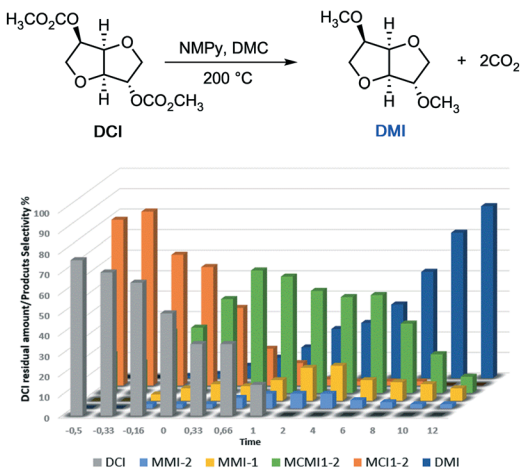


Fig. 3 DCI decarboxylation reaction.

Table 5 DCI conversion into DMI

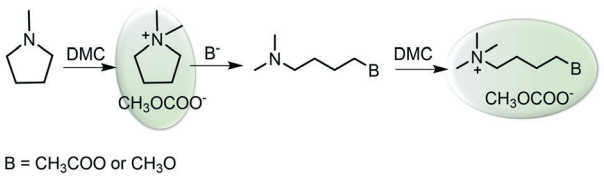
#	Catalyst	Solvent	Selectivity% MMI1	DMI	MMI2	Others
1	NMPy	DMC	6	**86**	0	8
2	NMPy	2-MeTHF	23	**6**	67	4
3	NMPy	CH_3CN	35	**5**	59	0
4	DMPyC	CH_3CN	46	**45**	9	0

Isosorbide : DMC : catalyst 1.0 : 0.5 mol eq. in 30 mL of solvent; temperature 200 °C, autogenous pression 15–17 bar.

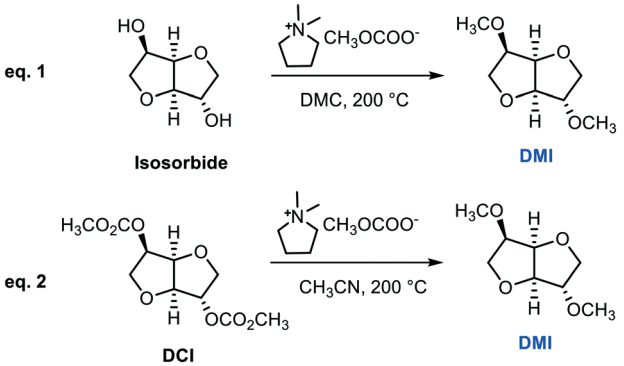
In both experiments, monomethyl derivatives **MMI1** and **MMI2** were the major products, while only traces of **DMI** were observed.

In order to better understand these results, the role of *N*-methylpyrrolidine in the synthesis of **DMI** needed to be disclosed. In our reaction conditions, the nitrogen atom of NMPy, can easily react as a nucleophile with DMC leading to a *N*,*N*-dimethylpyrrolidinium methylcarbonate (DMPyC). This compound was already reported in the literature and a sample was then prepared and collected for further study (Scheme 6).[24] The evidence of its presence in the etherification of isosorbide was confirmed by carrying out a test reaction between NMPy and DMC at 200 °C for 12 hours. Although NMPy resulted fully converted and DMPyC was present and observable up to 160 °C, NMR studies of the final reaction mixture (after 12 hours) showed the presence of other unforeseen products barely identifiable through spectra interpretation. Interestingly, a recent investigation on pyrrolidinium cations stability demonstrated that *N*,*N*-dimethyl pyrrolidinium ions are not stable in basic conditions at high temperature degrading *via* pyrrolidinium ring opening in a linear amine (Scheme 6).[25] In fact when a thermogravimetric analysis on freshly prepared pyrrolidinium methylcarbonate DMPyC was carried out, a slow degradation process was detectable starting at 160 °C.§ Most likely, in the adopted reaction conditions, the basic environment can be ascribed to the methoxycarbonate anion or to methoxide formed by its degradation. The so-formed trialkylamine can eventually methylate once again to the corresponding linear tetraalkyl ammonium ion (Scheme 6) that might also aid the methylation of isosorbide.

As further proof, isosorbide was reacted with DMC in the presence of freshly prepared DMPyC (0.5 mol eq.) and indeed DMI was obtained in high yield (90% yield), confirming the catalytic activity of the pyrrolidinium ion (eq. 1; Scheme 7).



Scheme 6 Catalytic species promoting the methylation of isosorbide.



Scheme 7 Etherification of isosorbide catalysed by DMPyC (eq. 1); decarboxylation of DCI catalysed by DMPyC.

DMPyC was then tested in the conversion of **DCI** into **DMI** (eq. 2; Scheme 7) resulting more efficient than NMPy itself (#4; Table 5). The experiment was performed in CH_3CN in order to avoid any other concurrent reactions that might take place in the presence of DMC and led to **DMI** in 45% selectivity.

This result clearly explained the data observed in the previous decarboxylation experiments (#1–3; Table 5). In the absence of DMC, NMPy first reacts with **DCI** to give the pyrrolidinium species that then promotes the decarboxylation of the residual methoxycarbonates moieties giving mostly **MMI** derivatives. The reaction conducted in the presence of DMPyC not only confirmed that the decarboxylation is one of the concurrent reactions leading to **DMI**, but also outlined that the tetra alkyl ammonium species were the most active catalysts in the etherification of isosorbide. The evidence that the **DCI** decarboxylation was not quantitative in the presence of DMPyC accounts for the complexity of the overall reaction mechanism. Most probably, this reaction contributes only to some extent to **DMI** formation that is also supported by direct methylation *via* $B_{Al}2$ mechanism.

By considering these observations, a better understanding of the three reaction mechanisms partaking in the methylation of isosorbide was attained. Fig. 4 reports the proposed mechanisms for the methoxycarbonylation, methylation and decarboxylation reactions contributing to the formation of **DMI**. As above mentioned, the most effective catalytic species are the quaternary ammonium salts eventually aided by the methyl carbonate anion. Most probably in the methoxycarbonylation and methylation reactions there is a cooperative effect of DMPyC cation and anion where the first activates DMC, while the latter acts as a base on isosorbide hydroxylic groups (Fig. 4). In the literature, a similar mechanism was already reported for methoxycarbonylation of isosorbide catalysed by several nitrogen organocatalysts.[26]

Regarding the decarboxylation reaction, it could be assumed that it is promoted mostly by the quaternary ammonium salts. The isosorbide methoxycarbonyl moiety most probably undergoes CO_2 elimination *via* a four-member intermediate that was already described as typical route for DACs pyrolysis.[23]

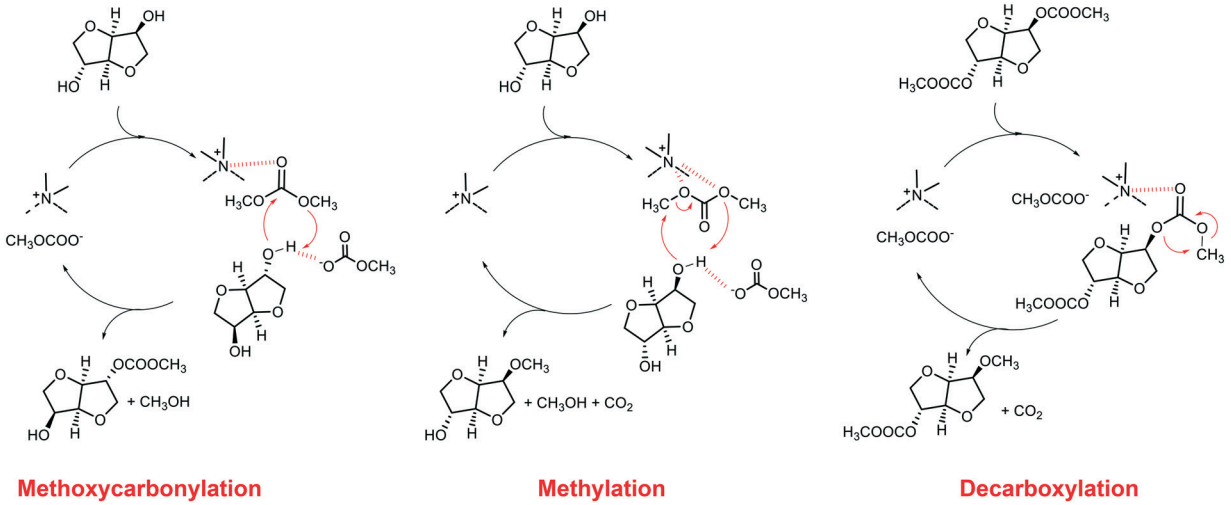


Fig. 4 Possible reaction mechanisms for the methoxycarbonylation, methylation and decarboxylation of isosorbide and its derivatives.

3. Experimental

General

All reagents and solvents were purchased from Sigma Aldrich.

The reactions were monitored through GC-MS (GC System 6890N; Agilent Technologies mass selective detector 5973) with chromatography column (HP-5MS). Compounds were injected with micro-syringe Hamilton (10 μL).

NMR spectra were recorded with Bruker 300 MHz and 400 MHz spectrometer, in $CDCl_3$, CD_3OD and D_2O.

The high-pressure reactions were conducted in autoclave (capacity 220 mL) with thermocouple for the control of temperature and under magnetic stirring.

HR-MS spectra for have been acquired by means of Bruker compact QTOF with a mass resolution of 30 000 in positive polarity mode. The mass calibration has been conducted using a sodium formate cluster's solution and the data have been processed in a HPC mode. The acquisition has been conducted in full scan mode in the range of 50 to 500 *m*/*z*, with a 4 l min^{-1} at 180 °C of source dry gas. The ion formula of each compound has been calculated with the Smart formula tool within the Bruker software platform, using a 4 mDa of mass confidence and considering the isotopic pattern ratio.

Thermogravimetric analysis was recorded with INSEIS STA PT-1000, starting from 30 °C to 500 °C with a temperature ramp rate of 10 °C min^{-1}, under nitrogen flow.

Synthesis of dimethyl isosorbide (#4; Table 1)

In a typical reaction in an autoclave, 1.00 g of isosorbide (6.84 mmol, 1.0 mol eq.) was reacted with 30 mL of dimethyl carbonate (0.35 mol, 50.0 mol eq.) in presence of 0.29 g of *N*-methyl pyrrolidine as base (3.41 mmol, 0.5 mol eq.), at 200 °C for 12 h. The autogenous pressure reached the value of 20 bar. After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor. The resulting mixture was analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity.

DMI was obtained as pure *via* chromatographic column (Et_2O/*n*-hexane 7/3; Rf = 0.80). The pure compound was isolated as a light yellow liquid in 85% yield (1.01 g).

^1H NMR (400 MHz $CDCl_3$) δ ppm = 4.64 (t, 1H), 4.54 (d, 1H), 3.89–3.88 (m, 4H), 3.85 (m, 1H), 3.61–3.53 (m, 1H), 3.49 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 85.8, 81.7, 79.9, 72.9, 69.7, 58.1, 57.1. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_8H_{14}O_4 + H]^+$: 175.0965; found: 175.0967.

Synthesis of dimethyl isosorbide – large scale (#4; Table 3)

In a typical reaction in autoclave, 10.00 g of isosorbide (68.4 mmol, 1.0 mol eq.) was reacted with 100 mL of dimethyl carbonate (1.18 mol, 18.0 mol eq.) in presence of 2.91 g of *N*-methyl pyrrolidine as base (34.1 mmol, 0.5 mol eq.), at 200 °C for 12 h. The autogenous pressure reached the value of 31 bar. After cooling, the reaction crude was filtered and analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity. The product was obtained as pure *via* vacuum distillation (T = 110 °C, p = 40 mbar *ca.*) as a yellowish liquid in 65% yield (7.73 g).

Synthesis of dimethyl isosorbide from isosorbide (#2; Table 4)

In a typical reaction in autoclave, 2.00 g of D-sorbitol (10.97 mmol, 1.0 mol eq.) was reacted with 47 mL of dimethyl carbonate (0.55 mmol, 50.0 mol eq.) in presence of 0.91 g of *N*-methyl pyrrolidine as base (10.91 mmol, 1.0 mol eq.), at 90 °C for 48 h then 200 °C for 24 h. After cooling, the reaction crude was filtered and concentrated *via* rotavapor. The resulting mixture was analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity.

The product was obtained as pure *via* chromatographic column in 55% yield (1.02 g).

Synthesis of dimethyl Isoidide (DMIi)

In an autoclave, 1.00 g of isoidide (6.84 mmol, 1.00 mol eq.) was reacted with 30 mL of dimethyl carbonate (0.35 mol, 50.00 mol eq.) in presence of 0.29 g of *N*-methyl pyrrolidine as base (3.41 mmol, 0.50 mol eq.), at 200 °C for 12 h. The autogenous pressure reached the value of 20 bar.

After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor. The resulting mixture was analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity.

The product was obtained as pure *via* chromatographic column (Et_2O/*n*-hexane 1/1; Rf = 0.30). The pure compound was isolated as a yellowish liquid.

^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 4.61 (s, 2H), 3.91–3.83 (m, 6 H), 3.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 85.1, 84.9, 71.8, 57.2.

Synthesis of dimethyl Isomannide (DMIm)

In an autoclave, 1.00 g of isoidide (6.84 mmol, 1.0 mol eq.) was reacted with 30 mL of dimethyl carbonate (0.35 mol, 50.0 mol eq.) in presence of 0.29 g of *N*-methyl pyrrolidine as base (3.41 mmol, 0.5 mol eq.), at 200 °C for 12 h. The autogenous pressure reached the value of 20 bar.

After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor. The resulting mixture was analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity.

The product was obtained as pure *via* chromatographic column (Et_2O/*n*-hexane 6/4; Rf = 0.40). The pure compound was isolated as an amber coloured solid.

^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 4.53 (m, 2H), 4.01 (t, 2H), 3.90 (m, 2H), 3.63 (t, 2H), 3.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 81.9, 80.3, 70.9, 58.3.

Synthesis of dicarboxymethyl isosorbide (DCI)

In a 250 mL double-necked bottom round flask equipped with a Dean–Stark trap and condenser, 5 g of isosorbide (34.21 mmol, 1.0 mol eq.) was reacted with 90 mL of dimethyl carbonate (1.07 mol, 30.0 mol eq.) in presence of K_2CO_3 as base (0.95 g, 6.80 mmol, 0.2 mol eq.), at 90 °C for 6 h. After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor to achieve **DCI**.

A pure sample of **DCI** was obtained as *via* chromatographic column (DCM/MeOH 99/4; Rf = 0.50).

^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 5.13–5.12 (m, 1H), 5.10–5.08 (t, 1H), 4.92–4.89 (t, 1H), 4.57–4.56 (d, 1H), 4.12–4.02 (m, 2H), 3.97–3.89 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 155.1, 154.8, 85.9, 81.2, 80.8, 76.7, 73.2, 70.5, 55.1, 55.1. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_{10}H_{14}O_8 + H]^+$: 263.0761; found: 263.0766.

Synthesis of monocarboxymethyl isosorbides MCI1 and MCI2

Isosorbide (1.00 g, 6.84 mmol, 1.0 mol eq.), dimethyl carbonate (2.88 mL, 34.20 mmol, 5.0 mol eq.), K_2CO_3 (0.95 g, 6.84 mmol, 1.0 mol eq.) were reacted in 20 mL of acetonitrile, at 80 °C for 42 h. After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor.

The products were obtained as pure *via* chromatographic column (*n*-hexane/EtOAc 7/3; Rf_{MCI1} = 0.3, Rf_{MCI2} = 0.2).

The pure **MCI1** was isolated as a white solid in 33% yield (0.49 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 5.17–5.15 (m, 1H), 4.68 (t, 1H), 4.57–4.55 (m, 1H), 4.35 (m, 1H), 4.17–4.14 (dd, 1H), 4.06–4.02 (dd, 1H), 3.94–3.90 (m, 1H), 3.80 (s, 3H), 3.63–3.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 154.7, 85.4, 81.9, 81.6, 73.6, 73.3, 72.3, 55.1. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_8H_{12}O_6 + H]^+$: 205.0707; found: 205.0706.

The pure **MCI2** was isolated as a white solid in 16% yield (0.23 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 5.11–5.07(m, 1H), 4.93–4.91 (t, 1H), 4.44–4.43 (d, 1H), 4.38–4.36 (m, 1H), 3.95 (m, 2H), 3.93–3.86 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 155.2, 88.4, 80.4, 76.9, 76.3, 75.7, 70.4, 55.1. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_8H_{12}O_6 + H]^+$: 205.0707; found: 205.0706.

Synthesis of monomethyl isosorbides – MMI1 and MMI2

To a solution of D-isosorbide (1.00 g, 6.84 mmol) in THF (30 mL), NaH 60% w/w (0.27 g, 6.84 mmol) was added under N_2 atmosphere. Then the mixture was cooled to 0 °C and a solution of CH_3I (0.43 mL, 6.84 mmol) in THF (10 mL) was added dropwise within 15 min. The ice bath was removed, and the mixture was heated to 60 °C for 20 h under stirring. The mixture at this point appears as a clear orange solution. This solution was quenched with MeOH (2 mL) and concentrated under vacuum to give a crude product.

The products were obtained as pure *via* chromatographic column (DCM/MeOH 7/3; Rf_{MMI1} = 0.3, Rf_{MMI2} = 0.2).

The pure **MMI1** was isolated as a yellow oil in 35% yield (0.39 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 4.53 (t, 1H), 4.40 (d, 1H), 4.21 (m, 1H), 4.01–3.97 (m, 1H), 3.85 (dd, 1H), 3.84–3.77 (m, 2H), 3.53–3.49 (m, 1H), 3.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 85.6, 85.4, 81.7, 73.6, 73.0, 72.2, 57.2. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_7H_{12}O_4 + H]^+$: 161.0808; found: 161.0812.

The pure **MMI2** was isolated as a pale-yellow oil in 15% yield (0.16 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 4.67 (t, 1H), 4.40–4.38 (m, 1H), 4.27–4.25 (m, 1H), 3.92–3.85 (m, 4H), 3.54–3.48 (m, 1H), 3.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 88.4, 81.8, 79.8, 76.8, 75.9, 70.0, 58.3. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_7H_{12}O_4 + H]^+$: 161.0808; found: 161.0812.

Synthesis of monomethylcarboxy methyl isosorbide – MCMI1

MMI2 (0.20 g, 1.25 mmol, 1.0 mol eq.), dimethyl carbonate (7.50 mL, 89.10 mmol, 72.0 mol eq.), K_2CO_3 (0.35 g, 2.50 mmol, 2.0 mol eq.) were reacted at 90 °C for 24 h, in a 25 mL bottom round flask. After 24 h, potassium carbonate (0.175 g, 1.25 mmol, 1.0 mol eq.) was added to mixture reaction and it was left for another 24 h. After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor.

The product was obtained as pure without purification as a clear oil in 99% of yield (0.23 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 5.10–5.08 (m, 1H), 4.74–4.72 (t, 1H), 4.60–4.58 (m, 1H), 4.10–4.09 (t, 2H), 4.00–3.94 (m, 2H), 3.8 (s, 3H), 3.66–3.62 (m, 1H), 3.49–3.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 154.8, 86.2, 81.7, 81.6, 80.3, 73.4, 70.1, 58.3, 55.0. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_9H_{14}O_6 + H]^+$: 219.0863; found: 219.0869.

Synthesis of monomethylcarboxy methyl isosorbide – MCMI2

MMI1 (0.20 g, 1.25 mmol, 1.0 mol eq.), dimethyl carbonate (7.50 mL, 89.10 mmol, 72.0 mol eq.), K_2CO_3 (0.35 g, 2.50 mmol, 2.0 mol eq.) were reacted at 90 °C for 24 h, in a 25 mL bottom round flask. After 24 h, potassium carbonate (0.175 g, 1.25 mmol, 1.0 mol eq.) was added to mixture reaction and it was left for another 24 h. After cooling, the reaction crude was filtered and concentrated under vacuum *via* rotavapor.

The product was obtained as pure without further purification as a clear oil in 99% of yield (0.23 g). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm = 5.00–4.96 (m,1H), 4.77–4.74 (t, 1H), 4.41–4.40 (d, 1H), 3.94–3.91 (m, 1H), 3.86–3.83 (m, 4H), 3.80 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 155.2, 85.9, 85.8, 80.6, 76.9, 72.9, 70.2, 57.0, 55.1. HRMS: *m*/*z* $[M + H]^+$ calc. for $[C_9H_{14}O_6 + H]^+$: 219.0863; found: 219.0869.

Synthesis del *N*,*N*-dimethyl pyrrolidinium methylcarbonate

N,*N*-Dimethyl pyrrolidinium methylcarbonate was prepared accordingly the procedure previously reported in the literature.[24]

^{1}H NMR (400 MHz D_2O) δ ppm = 3.45 (m, 4H), 3.28 (s, 3H), 3.07 (s,6H), 2.17 (m, 4H). ^{13}C NMR (100 MHz, D_2O) δ ppm = 160.2, 66.8, 51.6, 48.8, 21.6.

Decarboxylation of DCI

In a typical reaction in autoclave, 1.79 g of **DCI** (6.84 mmol, 1.00 mol eq.) was reacted with 30 mL of dimethyl carbonate (0.35 mol, 50.0 mol eq.) in presence of 0.29 g of *N*-methyl pyrrolidine as base (3.41 mmol, 0.5 mol eq.), at 200 °C for 12 h. The autogenous pressure reached the value 20 bar.

After cooling, the reaction crude was filtered and concentrated *via* rotavapor. The resulting mixture was analysed *via* GC-MS to evaluate conversion of the substrate and products selectivity.

4. Conclusions

In this work, we have explored the activity of various nitrogen organocatalysts in the conversion of isosorbide into **DMI** *via* DMC chemistry. The reaction conditions for the etherification of isosorbide in the presence of NMPy have been optimized and efficiently employed in larger scale reaction, as well as, for the synthesis of dimethyl isomannide and dimethyl isoidide. Purification of **DMI** was achieved both by column chromatography and distillation.

A synthetic strategy was developed so to prepare all the seven methoxycarbonyl and methyl derivatives of isosorbide, intermediates forming during the methylation reaction. This approach has allowed to study in more detail the reaction pathway leading to **DMI**, which includes three concurrent reactions, *i.e.*, methylation, methoxycarbonylation and decarboxylation. In particular, the investigation conducted on the less studied decarboxylation reaction of **DCI** showed that the most active catalytic species are the *N*,*N*-dimethyl pyrrolidinium methylcarbonate and eventually its tetraalkyl ammonium derivative formed *via* pyrrolidinium ring opening. This observation also explains why the catalyst basicity is not a prominent factor in promoting the methylation reaction. In fact, most probably it is the high NMPy nucleophilicity, promoting the pyrrolidinium formation, that has a predominant effect of the reaction outcome.

Finally, a reaction mechanism was proposed for each reaction involved in **DMI** formation. It is suggested that the anion and cation of the active specie *N*,*N*-dimethyl pyrrolidinium methylcarbonate both support isosorbide in the methoxycarbonylation and the methylation reaction by coordinating an hydroxyl moiety and the DMC oxygen atoms (cation). The decarboxylation reaction may be a typical four membered intermediate with CO_2 release, already reported in the literature for DAC pyrolysis reactions.

In conclusion this work represents a comprehensive investigation on isosorbide methylation *via* DMC chemistry that might open the way to further exploitation also on large scale reactions. In particular the use of continuous-flow in combination with an efficient catalytic system could be the key for the development of a more sustainable synthetic approach to **DMI** at industrial scale.

Author contributions

Dr. Mattia Annatelli, Dr. Manuele Musolino and Davide Dalla Torre: investigation, data curation and some conceptualization. Prof F. Aricò: conceptualization, visualization and writing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) F. Gao, R. Bai, F. Ferlin, L. Vaccaro, M. Li and Y. Gu, *Green Chem.*, 2020, **22**, 6240–6257; (*b*) A. Jordan, P. Stoy and H. F. Sneddon, *Chem. Rev.*, 2021, **121**(3), 1582–1622.
2 R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.
3 (*a*) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M.

Stefaniak, *Green Chem.*, 2008, **10**, 31–36; (*b*) D. Prat, O. Pardigon, H. W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**, 1517–1525; (*c*) L. J. Diorazio, D. R. J. Hose and N. K. Adlington, *Org. Process Res. Dev.*, 2016, **20**, 760–773; (*d*) C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, *Green Chem.*, 2016, **18**, 3879–3890; (*e*) J. Esteban, A. J. Vorholt and W. Leitner, *Green Chem.*, 2020, **22**, 2097–2128.

4 M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082.

5 F. Aricò, *Curr. Opin. Green Sustain. Chem.*, 2020, **21**, 82–88.

6 (*a*) A. Watson, K. Wilson, J. Murray, H. Sneddon and C. Jamieson, *Synlett*, 2018, **29**, 2293–2297; (*b*) J. Sherwood, *Beilstein J. Org. Chem.*, 2020, **16**, 1001–1005.

7 F. Russo, F. Galiano, F. Pedace, F. Aricò and A. Figoli, *ACS Sustainable Chem. Eng.*, 2020, **8**, 659–668.

8 M. Windisch and H. Wieland, EP2574329, 2013.

9 (*a*) P. Fuertes and V. Wiatz, WO 2007/096511 Al, 2007; (*b*) A. East, M. Jaffe, Y. Zhang and L. H. Catalani, US2008/0021209 A1, 2008; (*c*) S. Chatti, M. Bortolussi and A. Loupy, *Tetrahedron*, 2001, **57**, 4365–4370; (*d*) S. Chatti, M. Bortolussi and A. Loupy, *Tetrahedron Lett.*, 2001, **41**, 3367–3370.

10 M. Ibert, N. Essayem, C. Feche and A. Perrard, US9321783, 2016.

11 P. Che, F. Lu, X. Si and J. Xu, *RSC Adv.*, 2015, **5**, 24139–24143.

12 M.-C. Duclos, A. Herbinski, A.-S. Mora, E. Métay and M. Lemaire, *ChemSusChem*, 2018, **11**, 547–551.

13 P. Tundo, M. Musolino and F. Aricò, *Green Chem.*, 2018, **20**, 28–85.

14 G. Flèche and M. Huchette, *Starch/Staerke*, 1986, **38**, 26–30.

15 P. Tundo, F. Aricò, G. Gauthier, L. Rossi, A. E. Rosamilia, H. S. Bevinakatti, R. L. Sievert and C. P. Newman, *ChemSusChem*, 2010, **3**, 566–570.

16 F. Aricò and P. Tundo, *Beilstein J. Org. Chem.*, 2016, **12**, 2256–2266.

17 K. Stensrud and P. Venkitasubramanian, WO2015/094716, 2015.

18 J. S. Howard and A. J. Sanborn, WO12/015616 A1, 2015.

19 F. Aricò, A. S. Aldoshin and P. Tundo, *ChemSusChem*, 2017, **10**, 53–57.

20 (*a*) W. Qian, X. Ma, L. Liu, L. Deng, Q. Su, R. Bai, Z. Zhang, H. Gou, L. Dong, W. Cheng and F. Xu, *Green Chem.*, 2020, **22**, 5357–5368; (*b*) W. Qian, L. Liu, Z. Zhang, Q. Su, W. Zhao, W. Cheng, L. Dong, Z. Yang, R. Bai, F. Xu, Y. Zhang and S. Zhang, *Green Chem.*, 2020, **22**, 2488–2497.

21 W. Qian, X. Tan, Q. Su, W. Cheng, F. Xu, L. Dong and S. Zhang, *ChemSusChem*, 2019, **12**, 1169–1178.

22 (*a*) D. Abenhaïm, A. Loupy, L. Munnier, R. Tamion, F. Marsais and G. Quéguiner, *Carbohydr. Res.*, 1994, **261**, 255–266; (*b*) A. L. Shaikh, A. S. Kale, Md. Abrar Shaikh, V. G. Puranik and A. R. A. S. Deshmukh, *Tetrahedron*, 2007, **63**, 3380–3388.

23 P. Tundo, F. Arico, A. E. Rosamilia and S. Memoli, *Green Chem.*, 2008, **10**, 1182.

24 C. Chiappe, A. Sanzone and P. J. Dysonb, *Green Chem.*, 2011, **13**, 1437–1441.

25 F. Gu, H. Dong, Y. Li, Z. Sun and F. Yan, *Macromolecules*, 2014, **47**, 6740–6747.

26 J. R. Ochoa-Gómez, L. Lorenzo-Ibarreta, C. Diñeiro-Garcìa and O. Gómez-Jiménez-Aberasturi, *RSC Adv.*, 2020, **10**, 18728–18739.