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Authors: Fabio Arico', Pietro Tundo, and Alexander Aldoshin

To be cited as: *ChemSusChem* 10.1002/cssc.201601382

Link to VoR: http://dx.doi.org/10.1002/cssc.201601382

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One-pot Preparation of Dimethyl Isosorbide from D-Sorbitol via Dimethyl carbonate Chemistry

F. Aricò, A. S. Aldoshin, P. Tundo*

Abstract: Direct synthesis of dimethyl isosorbide (DMI) from D-sorbitol via dimethyl carbonate (DMC) chemistry is herein firstly reported. High yield of DMI was achieved using nitrogen superbase 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst and performing the reaction in a stainless steel autoclave by increasing the temperature from 90 °C to 200 °C. In this procedure DMC features its full capacity, acting in the different steps of the process as carboxymethylating, leaving group (cyclization) and methylating agent; DMC is also employed as the reaction media.

D-sorbitol is considered one of the top-ten bio-based platform chemicals especially due to the numerous applications of its anhydro sugar cyclic derivative isosorbide, namely 1,4:3,6-dianhydro-D-glucitol (Figure 1). [1]
Nowadays, cyclization of D-sorbitol to achieve isosorbide is mainly carried out by a twofold dehydration acid-catalyzed reaction via 1,4-sorbitan intermediate. [2]
Isosorbide has a characteristic V-shaped structure [3] constituted by two *cis*-connected tetrahydrofuran where each hydroxyl group is in the β-position to both furanic oxygens.[4] The OH directed toward the V-shaped cavity is labeled as *endo* whereas the *exo* OH group is the one pointing outside of the sugar cavity (Figure 1). The configuration of the two hydroxyl groups drives the reactivity of the cyclic sugar as confirmed by isomannide and isoidide, the two epimers of isosorbide that incorporate only *endo* or *exo* hydroxyl groups, respectively. As a consequence these epimers show diverse reactivity of the hydroxyl groups (Figure 1).

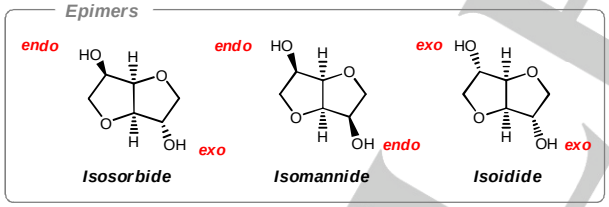
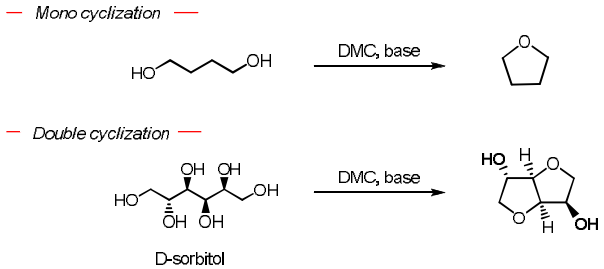


Figure 1. Molecular structure of isosorbide, isomannide and isoidide.

Isosorbide has, in fact, a considerable potential for the production of versatile new chemicals as its hydroxyl groups can be easily functionalized or directly processed. Examples of industrial applications include mono- and dinitrate isosorbide commonly used as vasodilators [5], isosorbide alkyl esters investigated as–plasticizers [6], short-chain aliphatic isosorbide ethers employed as coalescent in the paint industry [7] and mono- and di-substituted isosorbide used as surfactants.[8]
Isosorbide and its derivates have also been exploited as monomers in the manufacture of polymers, i.e., poly-(ethylene-co-isosorbide)terephthalate (PEIT), poly(isosorbide oxalate) and poly(isosorbide carbonate) [9] such as DURABIO® and PLANEXT®.
Another very interesting derivate is dimethyl isosorbide (DMI), a bio-based high-boiling green industrial solvent (b.p. 235 °C) that has also found applications as pharmaceutical additives and in personal care products. [10-11]
In this prospect, we have recently investigated the synthesis of isosorbide and therefore its derivatization *via* green reagent and solvent dimethyl carbonate (DMC).[12]
DMC is an extensively investigated green substitute of phosgene in carboxymethylation reactions (base-catalysed bimolecular acyl cleavage mechanism, $B_{Ac}2$) and dimethyl sulphate (DMS) or methyl halides in methylation reactions (base-catalysed bimolecular alkyl cleavage, $B_{Al}2$) mechanism).[13-14] Besides DMC has recently found applications as cyclization agent for the synthesis of several heterocycles, i.e. 5- and 6-membered cyclic ethers, pyrrolidines, indolines and 1,3-oxazin-2-ones.[14]

The synthesis of isosorbide and its further functionalization employing dialkyl carbonate, and in particular DMC, are appealing processes as they encompass the preparation, as well as, the transformation of a bio-based chemical via a chlorine-free sustainable approach. In particular, the synthesis of isosorbide was efficiently achieved by reacting D-sorbitol and DMC in the presence of sodium methoxide. In this approach DMC constitutes the leaving group which is generated *in situ* and acts as a sacrificial molecule for the synthesis of five-membered heterocycles (Scheme 1).



Scheme 1. Synthesis of cyclic ethers via DMC chemistry.

The cyclization reaction proceeds via carboxymethylation ($B_{Ac}2$) followed by an intramolecular alkylation reaction ($B_{Al}2$). Using this approach, isosorbide was synthesized in high yield and the pure product recovered without any time consuming purification technique. [11a]
More recently the cyclization of D-sorbitol was carried out in the presence of catalytic amount of a nitrogen base 1,8-diazabicycloundec-7-ene (DBU) resulting in the quantitative formation of the cyclic sugar. [11c]

[a] Prof. F. Aricò, Dr. A. S. Aldoshin, Prof. P. Tundo
Department of Environmental Science, informatics and Statistics,
Ca' Foscari University
Campus Universitario, Via Torino 155, 30170 Venezia mestre (Italy)
E-mail: tundop@unive.it

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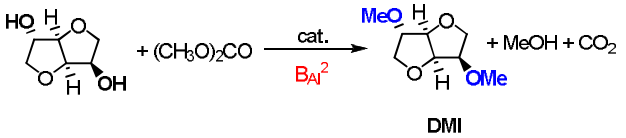
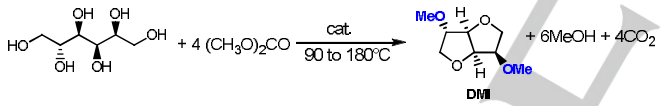
DMC was also employed for the synthesis of DMI by methylation of isosorbide both at reflux conditions (90 °C) in the presence of a large excess of a strong base [10] and in autoclave (≥180 °C) using hydrotalcite as catalyst. [12] The methylation of isosorbide in both reactions was quantitative. This result is particularly relevant as the hydroxyl group of isosorbide are secondary alcohols generally very difficult to alkylate even at high temperature.[15]



Scheme 2. Methylation of isosorbide via DMC chemistry

The greenness and the bio-based properties of cyclic sugar D-sorbitol and the valuable application of DMI prompted us to investigate a new one-pot route to this compound starting directly from its cheap and easy available parent alcohol. In fact, according to the reported procedures, the synthesis of isosorbide and its subsequent methylation (Scheme 1 and Scheme 2) required different reaction conditions and catalysts/bases. In this work for the first time we aim at investigating a single catalyst able to promote both the preparation and the derivatization of isosorbide in one-pot.

In this synthetic approach DMC would be used at its full extent acting as carboxymethylating, leaving group in the cyclization reaction and methylating agent; furthermore DMC is the reaction media (Scheme 3).



Scheme 3. One-pot synthesis of DMI starting from D-sorbitol.

In a first set of experiments D-sorbitol was dissolved in DMC and the mixture was placed into a stainless steel autoclave in the presence of a base or a catalyst. The synthesis was conducted at 180 °C under autogenic pressure and by continuous stirring of the solution. After 24 hours the reaction was stopped and the resulting mixture analyzed via GC-MS; the concentration of DMI was determined using a calibration curve (internal standard). Results are reported in Table 1.

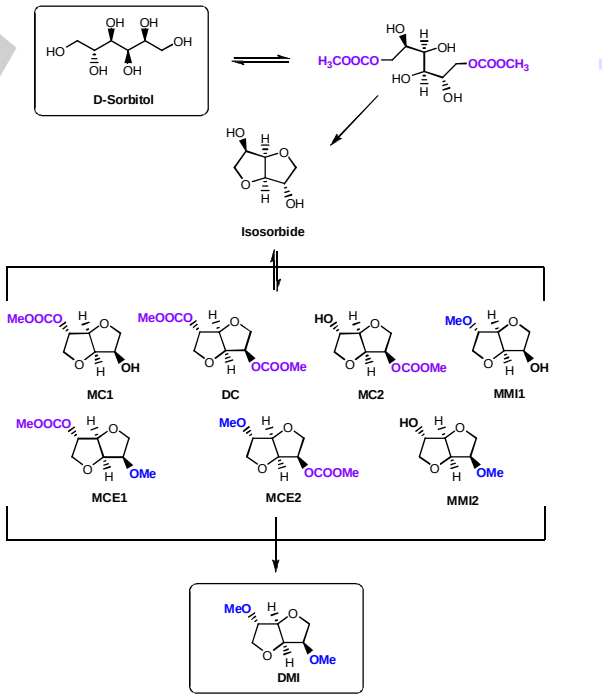
Several catalysts were investigated including a weak base (K_2CO_3), strong bases (NaOMe, KOBut), linear and cyclic nitrogen bases (Et_3N, 4-dimethylaminopyridine (DMAP)), superbases (DBU and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)), basic (Al_2O_3) and amphoteric (hydrotalcite KW2000) catalysts. Formation of dimethyl isosorbide was observed in all the reactions (Table 1) except when sodium methoxide or alumina were used. DMI yield ranged from 2 to 24%; the latter result achieved when triethyl amine was used as a base.

Table 1. D-sorbitol direct conversion into DMI[a]

#	Base (equiv.)		Temp. (°C)	P. (bar)	DMI (%)[b]
1	K_2CO_3	(3)	180	10	2
2	NaOMe	(3)	180	10	0
3	KOBut	(3)	180	12	16
4	Et_3N	(3)	180	50	24
5	Et_3N	(1)	180	20	18
6	DMAP	(3)	180	12	11
5	DBU	(3)	180	12	7
7	TBD	(3)	180	10	22
8	Al_2O_3	(3)	180	10	0
9	KW2000	(1/1 w/w)	180	10	23

[a] Reaction conditions: D-sorbitol:DMC:catalyst 1:50:3 equiv. at 180 °C in autoclave for 24 hours. [b] Calculated via calibration curve on GC-MS.

In this view, it should be pointed out that the modest yield of DMI is not surprising considering the complexity of the reaction pathway. In fact, in order to achieve DMI, D-sorbitol has to undergo a double carboxymethylation (B_{Ac}^2) followed by a double intramolecular alkylation (B_{Al}^2) where the carboxymethyl group acts as the leaving group leading to the formation of isosorbide (Scheme 4).

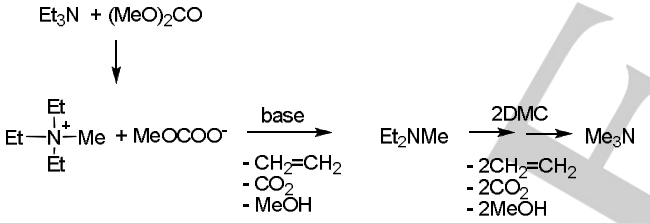


Scheme 4. Simplified reaction pathway for the synthesis of DMI starting from D-sorbitol via DMC chemistry. Reaction intermediates includes monomethyl derivatives (MMI1, MMI2), carboxymethyl derivatives MC1, MC2, DC) and methyl carboxymethyl derivatives (MCE1, MCE2).

Besides, as reported in the literature,[10] the methylation of isosorbide via DMC leads to the formation of seven intermediates as a result of numerous succeeding reactions where carboxymethylations are equilibrium reactions, meanwhile methylations are kinetically driven irreversible reactions. Thus, once formed, DMI accumulates in the reaction mixture as it cannot undergo any further transformation.

Simplifying the methylation reaction we should, in any case, account for two further intermolecular $B_{Al}2$ reactions in order to form the DMI molecule from isosorbide. Therefore, the one pot synthesis of DMI takes place through, at least, six subsequent reactions (Scheme 4).

Results reported in Table 1 show also that among the base investigated Et_3N is the most promising one (entry 4, Table 1). The use of Et_3N is quite interesting since, despite being a homogenous base, it can be easily removed by evaporation at the end of the reaction. However, in the triethylamine catalyzed reaction, it was also detected an almost linear increasing of the pressure up to 50 bar. Most probably this might be ascribed to the continuous quaternization of Et_3N performed by DMC [16] that finally leads to the formation of four products, i.e., trimethylamine and ethylene due to Hoffman elimination; methanol and CO_2 (Scheme 5). The formation of these volatile or low boiling side-products enhances the reaction pressure. In order to validate this hypothesis, the one-pot synthesis of DMI was also attempted with a reduced amount of Et_3N (1.0 equiv.). As a result the autogenic pressure was more than halved, albeit the yield of DMI slightly diminished (entries 4-5, Table 1).



Scheme 5. Quaternization of triethyl amine by DMC with consequent formation of several gaseous by-products.

In all the experiments reported in Table 1, GC-MS analysis of the reaction mixture did not show the presence of any other derivatives of isosorbide which were previously observed in the methylation reaction of this cyclic sugar.[8] This led us to the consideration that, under these reaction conditions, the limiting step was most probably the cyclization reaction (carboxymethylation of the primary alcohols followed by intramolecular nucleophilic attack of the secondary hydroxyl group) rather than the subsequent methylation of isosorbide, which is an easier reaction in comparison.

Thus, in a second set of experiments the synthesis of DMI was carried out modifying the reaction conditions. A mixture of D-sorbitol, DMC and the catalyst (1 equiv.) was charged into the autoclave. The reaction was first heated at 90 °C (DMC boiling point temperature) and then the temperature was increased to 200 °C.

In this reaction condition we aimed to ensure a higher efficiency of the cyclization step before increasing the temperature required for the methylation reaction. A test reaction was conducted to prove this hypothesis; D-sorbitol (1.0 equiv.) and TBD (1.0 equiv.) were dissolved in 50 mL of DMC and the mixture was heated at 90 °C. After 48 hours the solution was cooled to room temperature and *p*-xylene was added as external standard. GC-MS analysis of the solution showed that, under this reaction condition, isosorbide was formed in 85 % yield (calculated via calibration curve).

Table 2. D-sorbitol direct conversion into DMI[a]

#	Base	Temp. (°C)	P. (bar)	**DMI** yield %[b]	**DMIm** yield %[b]	**DMIi** yield %[b]
1	Et_3N	90/200	85	60	14	26
2	TDB	90/200	26	69	14	17
3	DBU[c]	90/200	58	59	19	22
4[d]	KW2000[e]	90/200	50	41	0	0

[a] Reaction conditions: D-sorbitol:DMC:catalyst 1:50:1 equiv. in autoclave at 90 °C for 48h and then at 200 °C for 24 hours. [b] Calculated via GC-MS; [c] Purification via column chromatography led to isolation of DMI in 43% yield amd DMIm in 9% yield. [d] In this case it was observed also the presence of monomethyl derivatives MMI1 and MMI2 (16% and 11% respectively) and methyl carboxymethyl derivatives MCE1 and MCE2 derivatives 32% (Scheme 4); [e] (1/1 w/w).

Table 2 reports the results observed for the most efficient catalysts previously investigated, i.e., Et_3N, TBD and hydrotalcite showing an evident increase of the DMI yield. The best result, 69 %, was achieved when TBD was used as catalyst (entry 2, Table 2).

In some experiments (entries 1-3, Table 2), the presence of dimethyl isomannine (DMIm) and isoidide (DMIi) was also detected [17] possibly due to the epimerization of residual isosorbide carbonate precursor (Scheme 4) that takes place when the temperature is increased at 200 °C.[18]

The high pressure observed in all the experiments can be ascribed to the decarboxylation of DMC over a long period of time. Under this reaction condition, the use of Et_3N resulted once again in the highest autogenic pressure (entry 1, Table 2).

When hydrotalcite was used as catalyst, although the observed yield was only modest, i.e. 40%, the formation of O-methylated epimers DMIm and DMIi was not observed. Besides, GC-MS showed also the presence of a good percentage of several isosorbide derivatives in the reaction mixture, i.e., monomethyl derivatives (MMI1, MMI2) and methyl carboxymethyl derivatives (MCE1, MCE2) (entry 4, Table 2, note c). This result can be ascribed to the catalyst that due to the presence of both acidic and basic sites might lead to a different reaction mechanism compared to the other base investigated.

Hydrotalcite is, in fact, a well known catalyst for decarboxylation reaction that might improve the reaction outcome, but can also lead to the faster decomposition of DMC into dimethyl ether.
For all the experiments (entries 1-4, Table 2), purification of the reaction mixtures was conducted via column chromatography resulting in the isolation of pure sample of DMI (see experimental section).

In conclusion, it is herein reported the first example of direct synthesis of DMI starting from cheap and easy available D-sorbitol. Several bases have been investigated showing a discrete conversion of the linear sugar into DMI. The relatively modest yield was ascribed to the low efficiency in the cyclization step. In order to address this issue the reaction was then conducted in two sequential steps; first at 90 °C (atmospheric pressure, boiling point of DMC) and thus increasing the temperature to 200 °C. As a result the yield of DMI drastically increased, up to 69% when TBD was employed as catalyst.
The direct synthesis of DMI from D-sorbitol encompasses a quite complicated reaction pathway that includes two carboxymethylations and two intramolecular cyclizations for the synthesis of isosorbide followed by two methylations that are most probably preceded by carboxymethylation reaction.
This work demonstrates that it is possible to synthesize DMI in a one-pot approach employing a single catalyst although optimization of the procedure is still needed.
It is noteworthy that this reaction is the first example in which DMC is used as carboxymethylating, leaving group, methylating agent and reaction media at the same time. The result achieved confirm the versatility of DMC as green reagent and solvent for bio-based platform chemical synthesis and derivatization leading in our case at the synthesis of DMI a valuable industrially relevant product.

Experimental Section

All reagents were purchased from Sigma Aldrich and used without any further purification. Mass spectra were run on GC-MS Agilent Technologies (GC System 6890N Network, Agilent Technologies Mass Selective Detector 5973, capillary column of silice HP-5). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300 Ultra Shield apparatus. The chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm) and regarding the tetramethylsilane (TMS). ^{13}C NMR spectra were recorded at 75 MHz on a Bruker apparatus 300 Ultra Shield. Chemical shift are reported in ppm from the solvent resonance as internal standard ($CDCl_3$: 77 ppm). The reactions carried out at high pressure were conducted in a stainless steel autoclave with a capacity of 220 mL equipped with a thermostat and thermocouple, heated by jacketed and equipped with magnetic stirring. Hydrotalcite KW2000 was calcined in a muffle at 500 °C for 6 hours.

General procedure for experiments reported in Table 1: In an autoclave, equipped with a magnetic stir bar, was prepared a solution of D-sorbitol sugar (2.0 g, 11.0 mmol), a base (33.0 mmol) and DMC (50.0 g, 555.6 mmol). Biphenyl (1.7 g, 11.0 mmol) was added to the reaction mixture and the autoclave was hermetically sealed under a nitrogen atmosphere and then heated to 200 °C. After 24 hours the mixture was cooled, filtered on paper and the eventual catalyst/base residue (in the case of experiments with K_2CO_3, NaOMe, KOBut, Al_2O_3 and KW2000) washed with DMC. The reaction mixture was the injected on the GC-MS and the yield of DMI was calculated using a calibration curve (biphenyl was used as internal standard).

General procedure for experiments reported in Table 2: In an autoclave, equipped with a magnetic stir bar, was prepared a solution of D-sorbitol (2.0 g, 11.0 mmol), a base (11.0 mmol) and DMC (50.0 g, 555.6 mmol). Biphenyl (1.7 g, 11.0 mmol) was added to the reaction mixture and the autoclave was hermetically sealed under a nitrogen atmosphere and then heated to 90 °C. After 48 hours the mixture was heated at 200 °C for other 24 hours. Then the reaction was cooled, filtered on paper and the eventual catalyst residue (in the case of experiments with KW2000) washed with DMC. The reaction mixture was the injected on the GC-MS and the yield of DMI was calculated using a calibration curve.

Purification of DMI can be conducted via gradient column chromatography using as elution system CH_2Cl_2:MeOH (98:2). As for entry 3; Table 2 DMI was isolated as colourless liquid in 43% yield: $C_8H_{14}O_4$; M=174.09 gmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): d= 4.64 (t, 1H), 4.50 (d, 1 H), 3.88–3.99 (m, 4 H), 3.85 (m, 1 H), 3.53–3.61 (m, 1 H), 3.45 (s, 3H), 3.36 ppm (s, 3 H). All spectroscopic features of this product correspond to those reported in the literature.

Keywords: Isosorbide • Dimethyl carbonate • Cyclization • Methylation • Cyclic sugar

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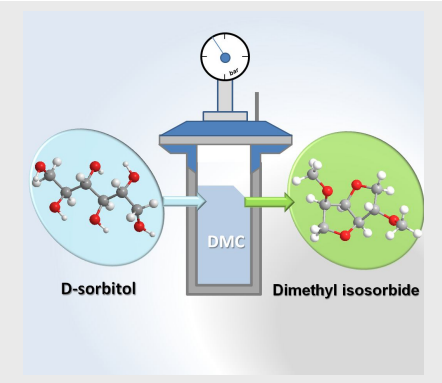
[17] Pure samples of dimethyl isoidide and dimethyl isomannide are available in our laboratory and have been used for comparison in GC-MS analysis.

[18] Most probably the residual carboxymethyl derivatives of D-sorbitol that did not form isosorbide at 90 °C can undergo cyclization when the temperature is increased to 200 °C forming either isosorbide or its epimers. In order to prove this hypothesis, isosorbide was reacted with TBD (1.0 equiv.) at 200 °C in the presence of an excess of DMC (50.0 equiv.) for 24 hours. GC-MS analysis of the reaction mixture showed mainly DMI and small amount of MCE. Epimerization products were not detected.

Another possibility would be a S_N2 reaction of the methoxide anion on the carbon bearing the carboxymethyl moiety of DCI leading to the inversion of the corresponding chiral center configuration.

COMMUNICATION

Dimethyl isosorbide is synthesized for the first time via one-pot reaction starting from its parent alcohol D-sorbitol via dimethyl carbonate chemistry.



*F. Aricò, A. Aldoshin, P. Tundo**

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One-pot Preparation of Dimethyl Isosorbide from D-Sorbitol via Dimethyl carbonate Chemistry