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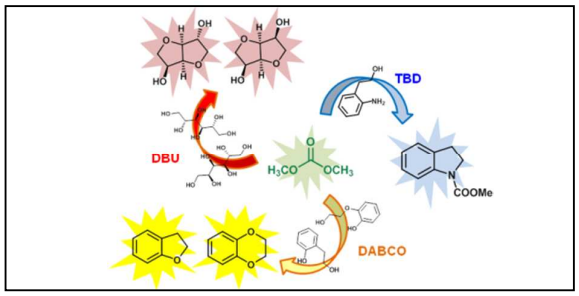
Five- and six-memebered N- and O-heterocycles have been prepared by DMC chemistry in the presence of catalytic amount of a homogenous nitrogen bicyclic base in neat conditions.



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Synthesis of five- and six-membered heterocycles by dimethyl carbonate with catalytic amount of nitrogen bicyclic bases

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Catalytic amount of a nitrogen bicyclic base, i.e., DABCO, DBU and TBD is effective for the one-pot synthesis of heterocycles from 1,4-, 1,5-diols and 1,4-bifunctional compounds via dimethyl carbonate chemistry under neat conditions. Nitrogen bicyclic bases, that previously showed to enhance the reactivity of DMC in methoxycarbonylation reaction by $B_{Ac}2$ mechanism, are herein used for the first time as efficient catalysts for cyclization reaction encompassing both $B_{Ac}2$ and $B_{Al}2$ pathways. This synthetic procedure was also applied to a large scale synthesis of cyclic sugars isosorbide and isomannide starting from D-sorbitol and D-mannitol, respectively. The resulting anhydro sugar alcohols were obtained as pure crystalline compounds that did not require any further purification or crystallization.

Introduction

N- and O-based heterocycles are ubiquitous in nature as molecules incorporating their skeleton display remarkably biological activity.

Substituted 2,3-dihydrobenzofuran moiety, for instance, is a common motif in natural products and is the key structural element in biologically active neolignans (obtusafuran and kadsurenone) and lithospermic acids, (Figure 1).[1] Many of these natural products are used as pharmaceuticals with several applications as antimicrobial, antioxidant, antimitotic, antiangiogenic and neuritogenic.[2]

Furthermore, five-membered O-based heterocycles are incorporated in cyclic sugars isosorbide and isomannide widely used as scaffold for green solvents (dimethyl isosorbide), surfactants (monosubstituted isosorbide) and pharmaceuticals, i.e., isosorbide dinitrate extensively used as vasodilator.[3]

Six-membered benzo-fused 1,4-heterocycles such as benzodioxines are also important pharmaceuticals.[4] Benzodioxane derivatives such as piperoxan, an α-adrenergic blocking agent, fluparoxan, a potent antidepressant and andamericanol A, that shows interesting neurotrophic properties are just few examples.[5] Simple 2,3-dihydro-1,4-benzodioxine is present in isovanillyl sweetening agents that are 500 times sweeter than sucrose. In addition, this core molecule is included in many natural products, such as silybin, isosilybin, haedoxan A and eusiderin.

Similarly, N- based five-membered heterocycles are present as structural subunits in many natural products such as vitamins, hormones and alkaloids and are also interesting from an industrial point of view especially for the synthesis of pharmaceuticals, herbicides, pesticides, dyes, etc.[6]

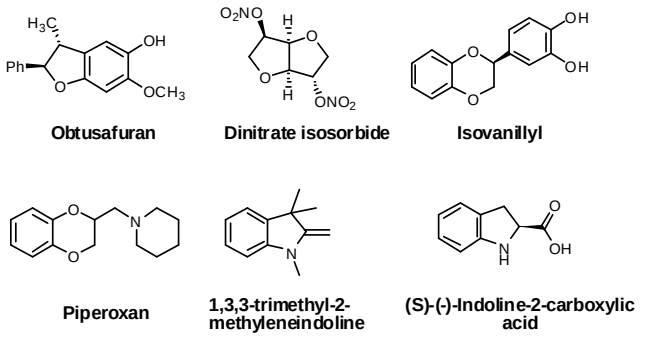

Figure 1. Some examples of biological active and industrially relevant N- and O-based heterocycles: obtusafuran (exhibits antiplasmodial activity); dinitrate isosorbide (vasodilatator); piperoxan (antihistaminic compound); isovanillyl (sweetening agent); 1,3,3-trimethyl-2-methyleneindoline (dye-intermediate); (S)-(-)-Indoline-2-carboxylic acid (chiral auxiliary, chiral catalyst, and present in heterocyclic alkaloid natural products).

A variety of methodologies has been reported for specific heterocycles, i.e., 5- and 6-membered N- and O-based heterocycles. The most common synthetic approaches are generally based on cyclization and/or cycloaddition involving

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heavy metals[7] or chlorine chemistry (e.g., tosylate through the chlorosulfonation of toluene, mesylate).[8]

In some cases, cyclization reactions are conducted under acidic conditions, however these syntheses might also lead to a mixture of elimination and/or rearrangement products especially when tertiary alcohols are involved.[9]

Short chain dialkyl carbonates (DACs) such as dimethyl carbonate (DMC), produced nowadays by clean processes,[10] are renowned for their applications as green solvents and reagents.[11] In particular, DMC is a versatile electrophile that can act as methylating agent via a $B_{Al}2$ mechanism or carboxymethylating agent by $B_{Ac}2$ mechanism[12] showing high selectivity with different monodentate and bidentate nucleophiles.[13-15]

Recently it has been extensively reported that nitrogen bicyclic Lewis bases, i.e., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and triazabicyclodecene (TBD),[16] are capable of enhance the reactivity of DMC in methoxycarbonylation reaction.[17-21]

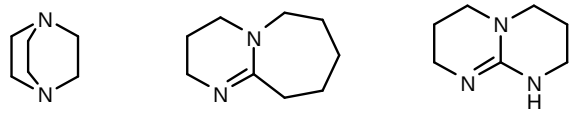


Figure 2. Chemical structures of DABCO, DBU and TBD.

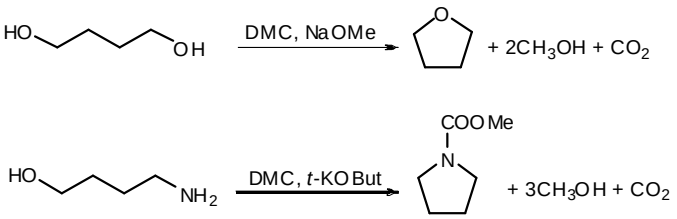
DABCO, compared to the amidine DBU, is a simple amine, meanwhile TBD has a guanidine structure resulting the strongest base among the ones selected (Figure 2).[16]

DBU has showed a nucleophilic behavior towards a variety of electrophiles.[17] It has also been reported that DBU can act as a nucleophile reacting with electrophilic substrates, such as DMC and dibenzyl carbonate, and activate them by forming a N-alkoxycarbonyl DBU derivative.[18-19] This species plays a key role in several important DBU-catalyzed esterification of carboxylic acids, i.e., methylation of phenols, indoles, and benzimidazoles with DMC, benzylation of the N, O, and S atoms with dibenzyl carbonate.[18]

TBD is a strong guanidine base,[16] utilized as organocatalysts in the synthesis of fine chemicals[20] and in several polymerization reactions.[21]

We have previously reported a convenient one-pot, chlorine-free synthetic procedure for O-based 5-membered heterocycles, i.e., the reaction of aliphatic and aromatic 1,4-diols with DMC in a stoichiometric excess of a strong base (NaOMe) and acetonitrile as solvent led to quantitative synthesis of the related 5-membered cyclic ethers (Scheme 1).[14] Computational investigation demonstrated that the formation of the cyclic ethers was energetically the most favourable pathway due to a large entropy reduction that occurs at the relevant transition states.[14b]

Similarly, aliphatic and aromatic 1,4-bifunctional compounds bearing a primary alcoholic function and an amine were efficiently cyclized with DMC in the presence of an excess of potassium *tert*-butoxide to achieve 5-membered *N*-heterocyclic compounds (Scheme 1).[15]



Scheme 1. Synthesis of N- and O-based 5-membered heterocycles by DMC chemistry.

In this work, we investigated if nitrogen bicyclic bases could be used as promoters in the synthesis of 5- and 6-membered heterocycles by DMC chemistry. These cyclization reactions are particular interesting as they encompass both methoxycarbonylation via $B_{Ac}2$ mechanism, i.e., formation of the intermediate **2**, and cyclization via $B_{Al}2$ mechanism, i.e., formation of cyclic **1**. So far the activation of DMC in the presence of TBD, DBU and DABCO has only been reported for methoxycarbonylation reaction by a $B_{Ac}2$ mechanism.[17-21]

Our intent is to investigate if DACs activation by nitrogen bicyclic bases in $B_{Al}2$ pathway might occur. Thus, we have selected as first model study the cyclization via DMC chemistry as the mechanism for the formation of these heterocyclic compounds was already investigated.[14]

The cyclization reactions were performed in neat and on substrates incorporating different functionalities, i.e., two aliphatic primary alcohols (1,2-bis(hydroxymethyl)benzene), a primary and a secondary alcoholic units (D-sorbitol and D-mannitol), an aliphatic alcohol and a phenol unit (2-hydroxyphenethyl alcohol and 2-(2-hydroxyethoxy)phenol), an aliphatic alcohol and an aniline units (2-(2-aminophenyl)ethanol).

The new synthetic procedure resulted indeed very efficient and required only catalytic amount of nitrogen bicyclic base. A reaction mechanism for the cyclization catalyzed by these nitrogen Lewis bases is tentatively proposed and discussed.

Results and discussion

In a first set of experiments a 1,4-diol incorporating a phenolic group and a primary alcohol has been selected as substrate for the preparation of its related cyclic ethers via DMC chemistry in the presence of decreasing amount of DBU, TBD and DABCO. The efficiency of these bases has been compared with a simple Lewis base (Et_3N) and NaOMe. The latter base showed, in our previous investigation,[14] the best activity in cyclization reaction with DMC.

Thus, this synthetic procedure has been tested for the preparation of aromatic 6-membered O-based heterocycles and aromatic 5-membered N-based heterocycles. Finally glucose derivate sugars D-sorbitol and D-mannitol have been also tested

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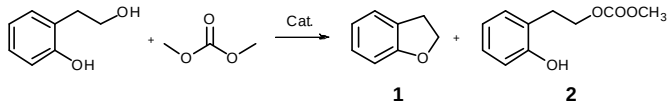
as substrates for the synthesis of isosorbide and isomannide in the same reaction conditions.

Aromatic 5-membered O-based heterocycles

2-(2-Hydroxyethyl)phenol was reacted with DMC (4.0 eq. mol.) in the presence of stoichiometric amount DBU in refluxing acetonitrile (entry 1, Table 1).
In this reaction conditions, the substrate gave 2,3-dihydrobenzofuran **1** in quantitative yield. The cyclic compound was isolated as pure by a quick filtration on a silica pad to remove the excess of DBU followed by the evaporation of the residual DMC and solvent.



Scheme 2. Synthesis of 2,3-dihydrobenzofuran **1** by DMC chemistry.

When the amount of DBU was decreased, i.e., 0.5 and 0.25 eq. mol. the conversion of the substrate was still quantitative and the selectivity increased to 99% (entries 2-3, Table 1).
In order to further improve the reaction conditions, an experiment was attempted mixing the two reagents with DBU (0.25 eq. mol.) without any solvent. The reaction reached completion after only 4 hours resulting in the quantitative formation 2,3-dihydrobenzofuran **1** as the only product of the reaction (entry 4, Table 1).

Table 1. Reaction of 2-hydroxyphenethyl alcohol with DMC.[a]

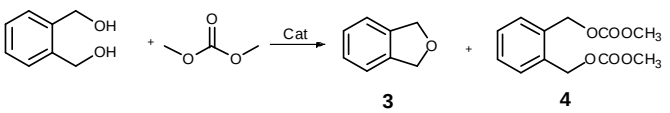
#	Catalyst (eq. mol)	CH_3CN (mL)	Time (h)	Conv.[b] (%)	Isolated yield % **1** (%)
1	DBU (1.0)	10	3	100	92
2	DBU (0.5)	10	8	100	90
3	DBU (0.25)	10	17	100	99
4	DBU (0.25)	-	4	100	98
5	DBU (0.1)	-	8	100	96
6	DBU (0.05)	-	8	100	92
7	DABCO (0.05)	-	8	100	83
8	TBD (0.05)	-	8	100	91
9	Et_3N[c] (0.05)	-	24	n.q.[d]	48
10	NaOMe[e](0.05)	-	24	n.q.[d]	6

[a] Reaction conditions: 2-(2-hydroxyethyl)phenol (1 eq. mol) DMC (4 eq. mol), 90 °C; [b] The reaction was followed by TLC as the cyclic intermediate **2** is unstable on the GC-MS conditions; [c] Reaction conducted at 85 °C; **2** was isolated in 12% yield; [d] Conversion of the starting diol was not quantitative; [e] Intermediate **2** was isolated in 21% yield.

Further experiments in neat were conducted employing catalytic amount of DBU, i.e., 10% and 5% mol. (entries 5-6, Table 1); conversion and selectivity towards the cyclic ether **1** remained unaffected resulting both quantitative.
Cyclic nitrogen bases DABCO and TBD were then tested as catalysts for the cyclization reaction. Both bases, used in catalytic amount, resulted very efficient for the preparation of 2,3-dihydrobenzofuran **1** (entries 7-8, Table 1).

For comparison, a simple acyclic amine i.e., Et_3N, was also used as catalyst, however, the cyclic product **1** formed only in modest yield (entry 9, Table 1).
Finally, NaOMe, the base previously used in stoichiometric excess (3.0 eq. mol.) for this reaction, was also tested.[14] In this case, the conversion was not quantitative and the isolated yield of compound **1** was only scarce (entry 10, Table 1).
For this substrate all nitrogen bicyclic bases investigated are efficiently catalysts for the synthesis of the aromatic cyclic ether **1** in neat conditions. They all showed an enhanced efficiency and short reaction time in comparison to simple Lewis base (Et_3N) and strong base as NaOMe.
It should be noted that the cyclization step ($B_{Al}2$ see eq. 3 Figure 4) of this reaction release CO_2 as by-product which is known to deactivate strong bases i.e. NaOMe.[14] Conversely, tertiary ammines establish an equilibrium reaction with CO_2 thus they maintain their activity as catalysts. This might explain why cyclic nitrogen bases can be employed in less than a stoichiometric amount in these cyclization reactions.

Similar reaction conditions were employed on a substrate that incorporates two aliphatic hydroxyl groups, i.e., 1,2-bis(hydroxymethyl)benzene (Scheme 3).



Scheme 3. Synthesis of 1,3-dihydrobenzofuran by DMC chemistry.

Table 2 reports the data collected for the preparation of the phtalan **3**.
Despite the complete conversion of the substrate, none of the bicyclic nitrogen catalysts resulted efficient for the synthesis of 1,3-dihydroisobenzofuran **3** (entries 1-3, Table 2). DBU was the best catalyst with an isolated yield of 58%. The monocarboxymethyl derivates of 1,2-bis(hydroxymethyl)benzene has never been observed.

Table 2. Reaction of 1,2-bis(hydroxymethyl)benzene via DMC chemistry.[a]

#	Catalyst (eq. mol)	Time (h)	Conv.[b] (%)	Isolated yield **3** (%)	**4** (%)
1	DBU (1.0)	24	100	58	37
2	DABCO (1.0)	24	100	29	65
3	TBD (1.0)	24	100	17	70

[a] Reaction conditions1,2-bis(hydroxymethyl)benzene (1 eq. mol) DMC (8 eq. mol) 90 °C; [b] As observed by TLC.

These results could be ascribed to the lower acidity of the hydroxyl group incorporated in the starting material in comparison with the phenol unit of the 2-(2-hydroxyethyl)phenol.

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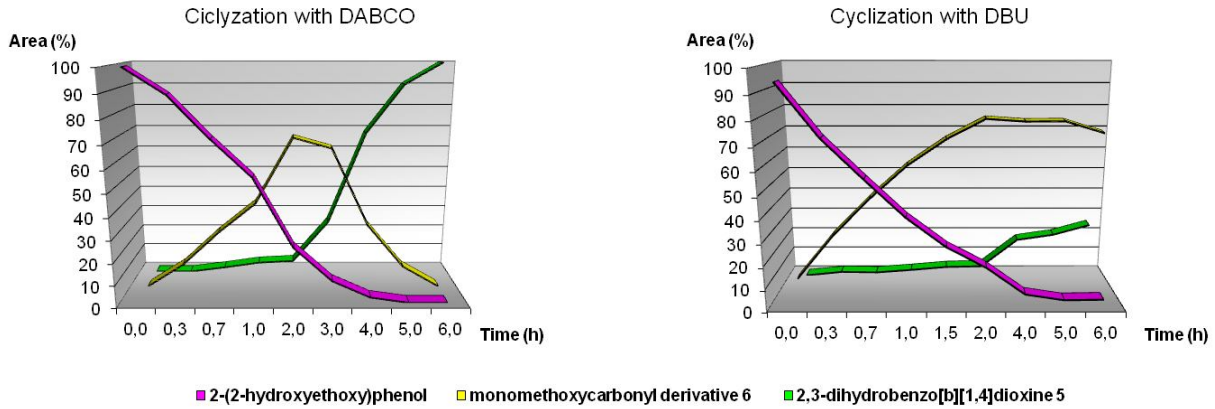
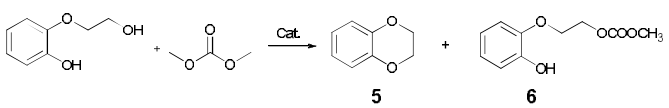


Figure 3. Reaction profiles of the synthesis of 6-membered cyclic **5** with DABCO (0.1 eq. mol.) and DBU (0.1 eq. mol.) according to GC-MS analysis.



5 **6**

Scheme 4. Synthesis of 2,3-dihydrobenzo[b][1,4]dioxine **5** by DMC chemistry.

Most probably, the nitrogen bicyclic bases used weren't strong enough to deprotonate the benzyl alcohol moiety and promote the cyclization reaction (see eq. 3 Figure 4). It is interesting to point out that TBD gave the lower yield of the phthalan **3**, despite being the strongest base among the ones used suggesting that the basicity of the catalyst is not the only factor affecting the cyclization reaction.

Aromatic 6-membered O-based heterocycles

2-(2-Hydroxyethoxy)phenol was selected as substrate for the preparation of six-membered heterocycle 2,3-dihydrobenzo[b][1,4]dioxine **5** (Scheme 4).

In a first set of experiments, the cyclization reaction was carried out in neat conditions using stoichiometric amount of DBU, DABCO or TBD (entries 1-3, Table 3).

Table 3. Reaction of 2-(2-hydroxyethoxy)phenol via DMC chemistry [a]

#	Catalyst (eq. mol)	Time (h)	Conv.[b] (%)	Selectivity[b] (Isolated) **5** (%)	**6** (%)
1	DBU (1.0)	5	100	88 (69)	12
2	DABCO (1.0)	2	100	100 (92)	0
3	TBD (1.0)	3	100	100 (92)	0
4	DABCO (0.5)	2	100	98 (80)	0
5	DABCO (0.1)	7	100	95 (90)	0
6	DABCO (0.05)	15	100	94 (83)	0
7	DABCO (0.01)	24	100	10	90
8	TBD (0.05)	24	100	91 (77)	7

[a] Reaction conditions: 2-(2-hydroxyethyl)phenol (1 eq. mol) DMC (8 eq. mol) 90 °C; [b] Calculated via GC-MS analysis.

The reactions performed employing DBU or TBD as base required longer reaction time. Furthermore, when DBU was used as catalyst, small amount of the monomethoxycarbonyl derivative **6** was also observed.

Among the catalysts, DABCO (1.0 eq. mol) resulted very efficient (reaction time 2 hours) (entry 2, Table 3) in promoting the cyclization of 2-(2-hydroxyethoxy)phenol also when used in catalytic amount, i.e, 0.05 eq. mol (entries 4-6, Table 3).

For comparison TBD was also tested as catalyst at the concentration of 5% mol. The experiment showed comparable results and reaction time to DABCO.

Finally, an attempt has been also made using only 1% mol. of DABCO. In this case the starting material resulted completed converted although the selectivity was shifted toward the monomethoxycarbonyl derivative **6**.

For this substrate the nitrogen bases showed a different behaviour in activating DMC and methylcarbonate derivatives. Thus, a comparative study has been conducted performing the cyclization reaction in the presence of 10% mol. of the catalysts.[†] Figure 3 shows the reaction profiles for the reactions conducted in the presence of DABCO and DBU. Samples taken at time intervals and analysed by GC-MS confirmed that DABCO was the best catalyst resulting in quantitative conversion and selectivity toward the cyclic compound **5** after 6 hours. DBU on the other hand resulted the less efficient nitrogen base.

DABCO- and DBU-catalyzed reaction showed a similar reaction rate in the $B_{Ac}2$ mechanism (consumption of the 2-(2-hydroxyethoxy)phenol). On the contrary, the conversion of the reaction intermediate **6** into the cyclic compound **5** depended on the catalyst used. This result is not surprising as $B_{Ac}2$ and $B_{Al}2$ mechanism are controlled by different factors.

Aromatic 5-membered N-based heterocycles

Reaction of bifunctional nucleophile 2-(2-aminophenyl)ethanol with DMC in the presence of stoichiometric amount of nitrogen bicyclic catalysts DABCO, DBU or TBD (entries 1-3, Table 4)

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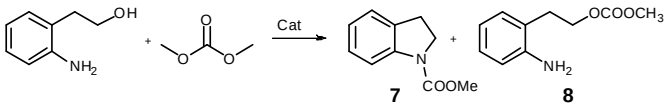
gave a quantitative conversion toward the *N*-carboxymethyl indoline **7**. Although the results are similar, TBD resulted the best base in terms of isolated yield and reaction time.



Scheme 5. Synthesis of N-carboxymethyl indoline **7** by DMC chemistry.

This reaction trend was confirmed performing the reaction in neat in the presence of 0.5 eq. mol. of the selected catalyst.[†] Data showed that, when TBD was used, the selectivity toward the *N*-carboxymethyl indoline **7** after 4 hours was already 85% (64% with DABCO). Conversely a conversion of only 25% was observed with DBU. When the amount of TBD was further decreased, i.e., 0.1 mol. eq. the selectivity also diminished to 65% (entry 5, Table 4).

In this case study, 2-(2-aminophenyl)ethanol incorporates two different nucleophiles, i.e., a primary amine and a primary alcohol, that discriminate between the two electrophilic centers of the DMC leading to the *N*-carboxymethyl indoline by one-pot cyclization. Thereforethe reaction, most probably, proceeds by a sequence of carboxymethylation and alkylation reactions.

Overall the one-pot synthesis of the *N*-carboxymethyl indoline **7** includes two methoxycarbonylations ($B_{Ac}2$) and an intramolecular alkylation ($B_{Al}2$); this complex sequence of reactions might explain the higher amount of catalyst required for a selective formation of the cyclic product **7**.[15a]

Table 4. Reaction 2-(2-aminophenyl)ethanol with DMC.[a]

#	Catalyst (eq. mol)	Time (h)	Conv.[b] (%)	Selectivity[b] (Isolated) **7** (%)	**8** (%)
1	DBU (1)	24	100	89 (75)	11
2	DABCO (1)	18	100	95 (72)	0
3	TBD (1)	7	100	100 (91)	0
4	TBD (0.5)	21	100	100 (97)	0
5	TBD (0.1)	24	100	65 (54)	35

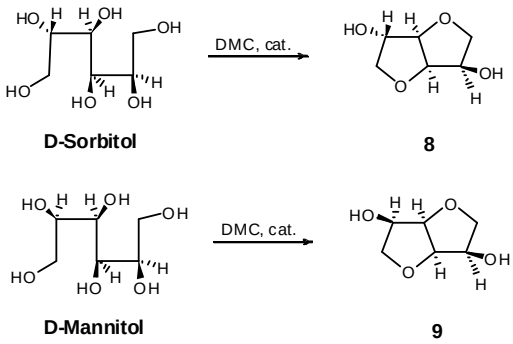
[a] Reaction conditions: 2-(2-aminophenyl)ethanol (1 eq. mol), DMC (8 eq. mol) 90 °C; [b] Calculated via GC-MS analysis.

Anydro sugar alcohols

Anhydro sugar alcohols have many applications in food and pharmaceutical field, as well as monomers in the formation of polymers and copolymers.[22] Isosorbide and its epimer isomannide are industrially synthesized by dehydration of their parent alcohols D-sorbitol and D-mannitol by an acid catalyzed reaction.[23] In our previous work we have reported a convenient synthesis of isosorbide by DMC-mediated double cyclization reaction in the presence of an excess of a strong base (4 eq. mol. of NaOMe) and methanol as solvent (Scheme 6).[14]

Herein, D-sorbitol was tested according to the new reaction condition, i.e, in neat using DBU as catalyst in stoichiometric amount. The reaction outcome was followed by ^{1}H NMR spectroscopy until disappearance of the starting material and of the eventual reaction intermediates.

When the reaction was attempted employing a stoichiometric amount of DBU, isosorbide showed to form quantitative after 7 hours (entry 1, Table 5).



Scheme 6. Synthesis of isosorbide **8** and isomannide **9** by DMC chemistry.

Table 5. Reaction of D-sorbitol and D-mannitol with DMC.[a]

#	Sugar	Cat. (eq. mol)	Time (h)	Conv.[b] (%)	Isolated yield (%)
1	D-sorb.	DBU (1.0)	7	100	**8** 98
2	D-sorb.	DBU (0.5)	7	100	**8** 98
3	D-sorb.	DBU (0.25)	8	100	**8** 98
4	D-sorb.	DBU (0.05)	24	100	**8** 98
5	D-Mann.	DBU (0.5)	7	100	**9** 80
6	D-Mann.	DBU (0.05)	24	100	**9** 92

[a] Reaction conditions: D-sugar (1 eq. mol) DMC (8 eq. mol), methanol (2 mL) 90 °C; [b] Calculated via ^{1}H NMR spectroscopy.

Crystalline isosorbide can be easily recovered by filtration on a silica pad and evaporation of the residual DMC. Reducing the amount of DBU to 0.5 eq. mol and then to 0.25 eq. mol., resulted in any case in a quantitative and highly selective formation of the cyclic sugar (entries 2-3, Table 5). It was possible to decrease the amount of DBU up to 5% mol without affecting the efficiency of the cyclization outcome (entry 4, Table 5). However, when the reaction was conducted employing catalytic amount (5% mol) of DABCO or TBD, NMR spectra showed, after 24 h, the presence of several reaction intermediates and of the starting reagent.

The same synthetic approach was then used on D-mannitol employing 0.25 mol of DBU in neat. As a result, isomannide was obtained in quantitative yield (entry 5, Table 5). The amount of DBU can be reduced up to 5% mol without affecting the reaction outcome. Attempts to further reduce the amount of catalyst resulted in both cases, i.e., isosorbide and isomannide, in partial conversion of the substrate.

It must be pointed out that despite anhydro sugars isosorbide and isomannide are formed through a one-pot double cyclization reaction, the amount of DBU used remains catalytic, i.e. 2.5% mol. for each tetrahydrofuranic cycle formed.

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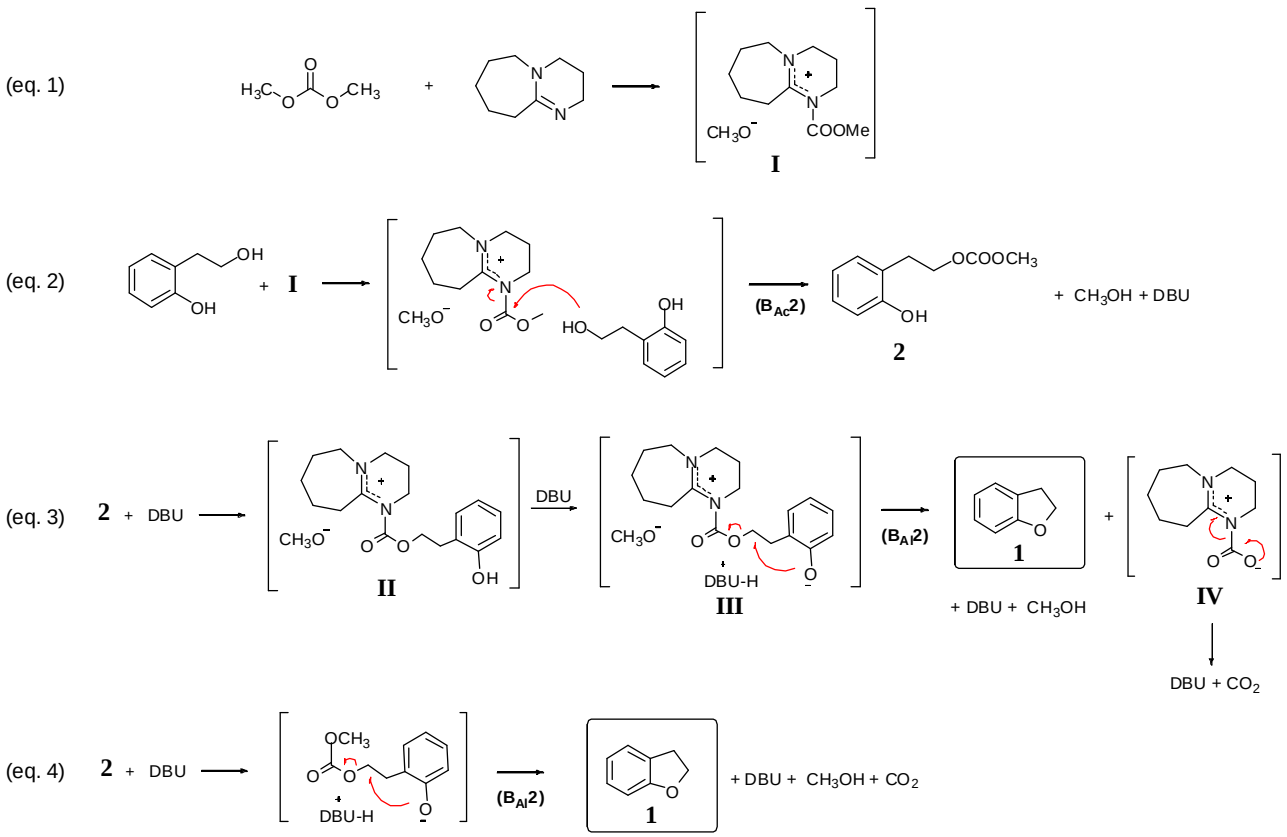

Figure 4. Possible reaction mechanism of the DBU-catalysed cyclization via DMC chemistry (all reactions reported are equilibrium except for the cyclization by $B_{Al}2$ mechanism).

Reaction Mechanism

The reactivity of DMC and in general of DACs in the presence of the nitrogen bicyclic base DBU has been previously investigated. Organic carbonates are activated by DBU via the formation of N-alkoxycarbonyl DBU derivative (eq. 1, Figure 4).[19] However, in our case study, most probably DBU has a more complex double role in the cyclization reactions acting both as activator in the formation of methoxycarbonyl reaction intermediate ($B_{Ac}2$ mechanism), but also as a base or a leaving group in the alkylation reaction ($B_{Al}2$ mechanism). A possible reaction mechanism for the synthesis of 5- and 6-membered heterocycles is depicted in Figure 4.

Eq. 1 shows the activation of DMC by DBU in the case of the aromatic substrate 2-(2-hydroxyethyl)phenol resulting in the formation of the N-alkoxycarbonyl-amidinium adduct (**I**).

The resulting intermediate is a better electrophile compared to DMC,[19] thus it can be easily attacked by a nucleophile, i.e., 2-(2-hydroxyethyl)phenol (eq. 2, Figure 4) leading to the formation of the methoxycarbonyl derivative **2**.

Carbonate intermediate **2** can also be activated by DBU forming the N-alkoxycarbonyl-amidinium adduct **II**. At this point, most probably, another molecule of DBU acts as a base deprotonating the aromatic hydroxyl group of the intermediate **III** (eq. 3, Figure 4). Although we cannot rule out that the methoxide group might act as base itself.

The subsequent intramolecular cyclization by $B_{Al}2$ mechanism leading to the formation of the 2,3-dihydrobenzofuran **1** is thus aided by the specie **IV** that acts as leaving group and then rapidly decomposes in DBU and CO_2 (eq. 3, Figure 4). It should be mentioned that the intermediate **IV**, being neutral charged, is a better leaving group compared to alkoxycarbonate anions.

Overall in the cyclization reaction methanol and CO_2 are released as the only reaction by-products, meanwhile DBU is restored so that it can catalyse another cycle.

It is also noteworthy that the nitrogen Lewis bases used have a different strength, i.e., TBD>DBU>>DABCO.[24] Consequently, we should expect a faster cyclization reaction for the stronger base according to the mechanism reported in eq. 4. However, the basicity of the catalysts doesn't reflect the trend observed for the cyclization reactions.

In fact, TBD, the strongest base, is not always the best catalyst for the cyclization by DMC chemistry.

This might indeed validate that nitrogen bicyclic bases lead to the formation of the intermediate **II,** which is similar to the

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specie **I** although it has a different fate. In fact, the latter follows a $B_{Ac}2$ mechanism meanwhile intermediate **II** undergoes a $B_{Al}2$ mechanism.

Each substrate investigated showed a peculiar preference for one of three nitrogen bicyclic catalysts: aromatic 1,4- and 1,5-diols resulted more reactive in the presence of DABCO, 1,4-amino alcohol cyclized preferably with TBD and finally anhydro sugars showed to form rapidly in the presence of DBU. Conversely, nitrogen bicyclic catalysts do not seem to be equally effective in the cyclization of substrates incorporating less acidic groups such as aliphatic alcohols or amines. In fact, experiments conducted on 1,2-bis(hydroxymethyl)benzene (Table 2), 2-(aminomethyl)benzyl alcohol, 4-aminobutan-1-ol gave only moderate yield of the respective cyclic compound (see also supporting information).

Besides the activation of DMC and the basicity of the nitrogen bicyclic catalysts involved, other factors might affect the catalyst affinity with the substrate, i.e. steric and entropic effects as they influence in different way the $B_{Ac}2$ and $B_{Al}2$ mechanisms.

Ii should be also mention that , in any case, we cannot rule out the possibility that the mechanisms reported in eq. 3 and eq. 4 (Figure 4) take place simultaneously or cooperate to the formation of the cyclic product **1**. In this prospect, further studies on this reaction mechanism are at the moment ongoing.

When other nitrogen bicyclic bases have been used, i.e., DABCO or TBD, the cyclization most probably undergoes via a similar reaction mechanism.

Experimental

All reagents were purchased by Sigma Aldrich and used without any further purification. The HPLC method was performed using an UV detector and the wavelength was set at 254 nm. Samples were analysed on a C18 column (4.6 mm x 150 mm, 3µm). The binary mobile phase consisted of 60% (v/v) acidified water as solvent A and 40% (v/v) acetonitrile as solvent B. A flow rate of 1 mL/min was used with the gradient program as follows: 40% solvent B at 0-4 min; 40-50% solvent B at 4-6 min; 50-70% solvent B at 6-8 min; 70-80% solvent B at 8-10 min. The injection volume was 20µL.

General procedure for the synthesis of 2,3-dihydrobenzofuran (example from entry 6, Table 1): In a vessel equipped with a reflux condenser, 2-hydroxyphenethyl alcohol (2.90 mmol, 1.00 mol. eq.), DMC (11.60 mmol, 4.00 mol. eq.) and DBU (0.14 mmol, 0.05 mol. eq.) were heated at reflux while stirring. The progress of the reaction was monitored by TLC. After 8 hours the reaction was stopped, cooled at room temperature and the solvent evaporated. Finally, a pure compound was obtained in 92% yield (0.32 g, 2.66 mmol) by column chromatography on silica gel. THF/Hexane 5/95 can be used as eluent.

Characterization data were consistent with those obtained for the commercially available compound.

General procedure for the synthesis of phthalan (example from entry 1, Table 2): In a vessel equipped with a reflux condenser, 1,2-Bis(hydroxymethyl)benzene (3.62 mmol, 1.00 mol. eq.), DMC (28.90 mmol, 8.00 mol. eq.) and DBU (3.62 mmol, 1.00 mol. eq.) were heated at reflux while stirring. The progress of the reaction was monitored by TLC. After 24 hours the reaction was stopped, cooled at room temperature and the solvent evaporated. Finally, the pure compound was obtained in 58% yield (0.25 g, 2.08 mmol) by column chromatography on silica gel. THF/Hexane 5/95 can be used as eluent.

Characterization data were consistent with those obtained for the commercially available compound.

General procedure for the synthesis of 2,3-dihydrobenzo[b][1,4]dioxine (example from entry 6, Table 3): In a vessel equipped with a reflux condenser, 2-(2-hydroxyethoxy)phenol (1.95 mmol, 1.00 mol. eq.), DMC (15.60 mmol, 8.00 mol. eq.) and DABCO (0.10 mmol, 0.05 mol. eq.) were heated at reflux while stirring. The progress of the reaction was monitored by TLC. After 15 hours the reaction was stopped, cooled at room temperature and the solvent evaporated. Finally, the pure compound was obtained in 83% yield (0.22 g, 1.62 mmol) by column chromatography on silica gel. THF/Hexane 1/9 can be used as eluent.

Characterization data were consistent with those obtained for the commercially available compound.

General procedure for the synthesis of *N*-carboxymethyl indoline (example from entry 1, Table 4): In a vessel equipped with a reflux condenser, 2-(2-aminophenyl)ethanol (2.19 mmol, 1.00 mol. eq.), DMC (17.50 mmol, 8.00 mol. eq.) and DBU (2.19 mmol, 1.00 mol. eq.) were heated at reflux while stirring. The progress of the reaction was monitored by TLC. After 24 hours the reaction was stopped, cooled at room temperature and the solvent evaporated. Finally, the pure compound was obtained in 75% yield (0.29 g, 1.64 mmol) by column chromatography on silica gel. THF/Hexane 1/9 can be used as eluent.

Characterization data correspond to those reported in the literature.[15]

General procedure for the synthesis of cyclic sugars

Isosorbide (example from entry 4, Table 5): In a round bottom flask equipped with a reflux condenser, D-sorbitol (5.49 mmol, 1.00 mol. eq.), DMC (43.90 mmol, 8.00 mol. eq.), DBU (0.27 mmol, 0.05 mol. eq.) and MeOH (2.00 mL) were heated at reflux while stirring. The progress of the reaction was monitored by NMR. After 24 hours the reaction was stopped, cooled at room temperature and the mixture was filtered over Gooch n°4. Finally, DMC was evaporated under vacuum and the product was obtained as pure in 98% yield (0.79 g, 5.40 mmol).

Larger scale synthesis of isosorbide: In a round bottom flask equipped with a reflux condenser, D-sorbitol (0.05 mol, 1.00 mol. eq.), DMC (0.44 mol, 8.00 mol. eq.), DBU (2.70 mmol,

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0.05 mol. eq.) and MeOH (20.00 mL) were heated at reflux while stirring. The progress of the reaction was monitored by NMR. After 48 hours the reaction was stopped, cooled at room temperature and the mixture was filtered over Gooch n°4. Finally, DMC was evaporated under vacuum and the product was obtained as pure in 98% yield (7.90 g, 0.05 mol).
Characterization data were consistent with those obtained for the commercially available compound.

Isomannide (example from entry 6, Table 5): In a round bottom flask equipped with a reflux condenser, D-mannitol (5.49 mmol, 1.00 mol. eq.), DMC (43.90 mmol, 8.00 mol. eq.), DBU (0.27 mmol, 0.05 mol. eq.) and MeOH (2.00 mL) were heated at reflux while stirring. The progress of the reaction was monitored by NMR. After 24 hours the reaction was stopped, cooled at room temperature and the mixture was filtered over Gooch n°4. Finally, DMC was evaporated under vacuum and the product was obtained as pure in 92% yield (0.74 g, 5.06 mmol).
Characterization data were consistent with those obtained for the commercially available compound.

Conclusions

Reacting 1,4-, 1,5-diols or an 1,4-aminoalcohol with DMC in the presence of catalytic amount of DABCO, DBU or TBD allowed an easy and wide ranging synthesis of N- and O-heterocycles. This novel synthetic procedure doesn't use any solvent and results in the quantitative one-pot preparation of 5-membered cyclics 2,3-dihydrobenzofuran **1**, *N*-carboxymethyl indoline **7**, 6-memeberd cyclic 2,3-dihydrobenzo[b][1,4]dioxine **5** and anydro sugar isosorbide **8** and isomannide **9**. All the so formed cyclic products can be isolated as pure crystalline material by simple filtration on a silica pad.
A possible reaction mechanism for the cyclization reaction has been proposed; most probably, in this synthetic approach, the nitrogen bicyclic catalysts have a complex role acting both as DMC activator in the formation of methoxycarbonyl reaction intermediate ($B_{Ac}2$ mechanism), but also as base in the alkylation reaction ($B_{Al}2$ mechanism).
It is noteworthy that this is the first time that the effect of nitrogen bicyclic on $B_{Al}2$ reactions have been reported. More detailed studies on the reaction mechanism are ongoing at the moment so to clarify the role of the cyclic nitrogen base in the intramolecular cyclization step, but also to have a better understanding of the relationship between the substrate and the best catalyst found for its cyclization.
It should be noted that, in these cyclizations, DMC acts as sacrificial molecule, being fully converted at the end of the reaction into methanol and CO_2. This reaction mechanism is reminiscent of chlorine compounds that are typically used as sacrificial molecules, however in our case the intrinsic toxicity of these molecules is avoided.
An important industrial application and validation of this procedure is the synthesis of pure anydro sugar alcohols starting from the related glucose derivatives. In fact, isomannide and isosorbide can be easily synthesised in quantitative yield and high purity, no recrystallization or further purification is necessary.

Notes and references

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† Electronic Supplementary Information (ESI) available includes ^{1}H NMR of compounds **1**, **3**, **5**, **7**-**9** and reaction profiles for the synthesis of heterocycles **1**, **5**, **7**. See DOI: 10.1039/b000000x/

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