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Benzo-Fused 1,4-Heterocycles via Dialkyl Carbonate Chemistry

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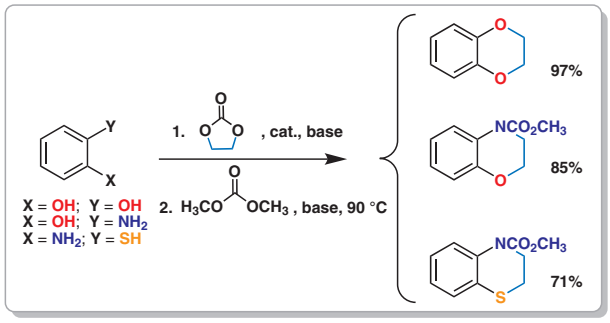


Received: 17.10.2018
Accepted after revision: 10.12.2018
Published online: 18.02.2019
DOI: 10.1055/s-0037-1611710; Art ID: ss-2018-z0704-fa

Abstract A novel halogen-free synthesis of benzo-fused six-membered 1,4-heterocycles through the chemistry of dialkyl carbonates is reported. Commercially available catechol, 2-aminophenol, and 2-aminothiophenol were reacted first with ethylene carbonate in an autoclave to give *O*-hydroxyethyl, *N*-hydroxyethyl, and *S*-hydroxyethyl derivatives respectively, through a $B_{Al}2$ mechanism. Then 2-(2-hydroxyethoxy)phenol and 2-(2-hydroxyethylamino)phenol were cyclized in excellent yields by reaction with dimethyl carbonate (DMC) and DABCO as a bicyclic organic base to give the corresponding benzodioxine and benzoxazine derivative, respectively. Moreover, 2-(2-aminophenylthio)ethanol afforded the benzothiazine derivative in good yield by reaction with DMC with an excess of a strong base such as NaH. The investigation on the cyclization reaction has highlighted that several equilibria are involved leading to the formation of carbonate and carbamate intermediates through $B_{Ac}2$ mechanisms. Depending on the reaction conditions employed, these intermediates may undergo either kinetic-controlled ring closure by a $B_{Al}2$ mechanism or by-product formation.

Key words heterocycles, cyclization reaction, green chemistry, alkylation, chemoselectivity

1 Introduction

Six-membered bicyclic 1,4-heterocycles containing oxygen, nitrogen, and sulfur atoms neighboring an aromatic ring, 1,4-benzodioxane, 3,4-dihydro-2*H*-1,4-benzoxazine, and 3,4-dihydro-2*H*-1,4-benzothiazine are incorporated in numerous natural products and biologically active pharmaceuticals.[1] Piperoxan (Figure 1), fluparoxan, and americanol A are few examples of well-known pharmaceuticals incorporating a 1,4-benzodioxane backbone.[2] This structural unit is also present in sweetening agent isovanillyl and in many natural products, such as silybin, isosilybin, haedoxan A, eusiderin, etc.

Six-membered bicyclic fused 1,4-heterocycles containing nitrogen neighboring an aromatic ring, such as 3,4-dihydro-2*H*-1,4-benzoxazines (benzomorpholines) and 3,4-dihydro-2*H*-1,4-benzothiazines have also received considerable attention due to their wide range of biological and therapeutic properties.[3–6]

Benzomorpholines are important building blocks in many drugs, bioactive molecules, and herbicides. Several 1,4-benzoxazine derivatives exhibit pharmaceutical properties such as potassium channel openers (PCOs), inhibitor of nitric oxide synthase (Figure 1), central nervous system depressants, antipsychotic agents, calcium antagonists, and antibacterial agents. Specific derivatives are potential drugs for treating neurodegenerative, inflammatory, autoimmune, cardiovascular, and diabetic disorders.[3] Numerous examples of benzomorpholines drugs, such as levofloxacin (Figure 1), ciprofloxacin, norfloxacin, and efavirenz incorporate in the core structure a fluorine atom that has been demonstrated to enhance solubility, lipophilicity, metabolic stability, and binding selectivity.[4] Recently, chiral 1,4-benzoxazines have attracted increasing attention not only as a result of their biological activities, but also as interesting catalysts for the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[5]

3,4-Dihydro-2*H*-1,4-benzothiazine derivatives are also very interesting heterocycles that display diverse biological activities and pharmaceutical properties (Figure 1) as antibacterial, antidiabetic, antiarrhythmic, antitumor, and neurodegenerative diseases.[6]

Considering their remarkable biological relevance, several methodologies have been developed for the synthesis of this type of benzo-fused 1,4-heterocycles. The most common procedures include direct cyclization using a metal catalyst, such as palladium,[7] copper-catalyzed intramolecular direct ring closure,[3d,8] and several other methods based on chlorine or halogen chemistry.[9]

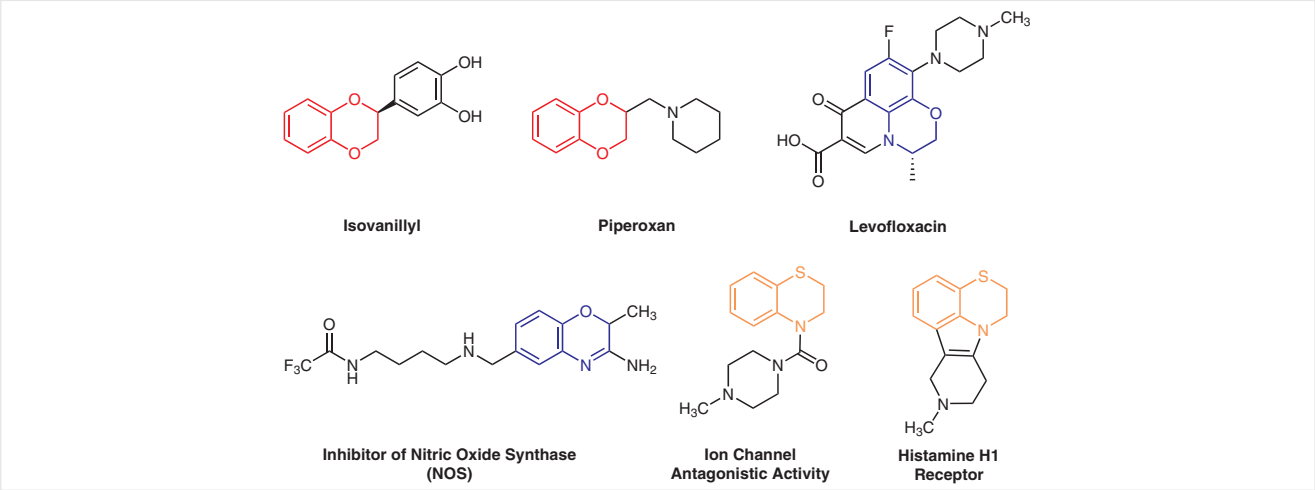


Figure 1 Examples of pharmaceutically and biologically active 1,4-benzodioxines, 3,4-dihydro-2*H*-1,4-benzoxazines, and 3,4-dihydro-2*H*-1,4-benzothiazines

Some of these synthetic approaches have limitations, that is, availability of the starting materials or reagents, high costs of the catalysts, and lack generality of the procedure; thus, exploiting new, routinely applicable and greener methodologies to construct these heterocycles is highly desirable.[3d,7–9]

Short-chain dialkyl carbonates (DACs), and in particular dimethyl carbonate (DMC), are achieving increasing importance as green reagents and solvents in laboratory scale reactions, as well as, in the chemical industry processes.[10] This is mainly due to the versatility of DACs as reagents and solvents, and to their non-toxicity for the human health and the environment.[11]

Recently, DMC has been used in the synthesis of several five-membered N- and O-heterocycles. In these reactions DMC acts as a sacrificial molecule, since it is not present in the final products, but only in the reaction intermediates as a halogen-free leaving group.[12] DMC-based synthesis of heterocycles takes place via a $B_{Ac}2$ followed by a $B_{Al}2$ mechanism resulting in general application, as it is effective for

Biographical Sketches

Prof. Fabio Aricò obtained his master degree in Chemistry from the University of Messina in 1999. He then moved to UK where he was awarded a Ph.D. at Reading University; work was focusing on macrocycle-polymer interconversion. He then spent two years as post-doctoral fellow in Sir Fraser Stoddart group at the UCLA (USA) working on supramolecular systems. In 2005, he moved back to Italy where he joined the Interuniversity Consortium of Chemistry for the Environment collaborating with the University Ca' Foscari. Since 2016 he is an associate Professor at Ca' Foscari University (Venezia); main research interests are green chemistry, chlorine-free chemistry, dialkyl carbonates, and new synthetic pathways.

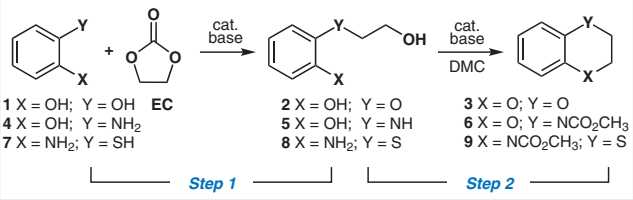
After the graduation in organic chemistry at the University of Milan in 2006, **Dr. Manuele Musolino** has worked as medicinal chemist for both academia (University of Milan) and industry (Sanofi-Aventis Spa) covering the role of research assistant. In 2012, he was awarded a Scottish Universities Life Sciences Alliance (SULSA) four-year Ph.D. fellowship in Medical Sciences, which was successfully carried out at the University of Aberdeen, Scotland. Since March 2017 he has been working as a Research Fellow at Ca' Foscari University of Venice, deeply involved in the development and uses of dialkyl carbonate (DAC) chemistry as a valid and prospective alternative to the halogen chemistry.

aliphatic and aromatic 1,4-diols, incorporating several functionalities. It is noteworthy that DMC or other small DACs are also efficient reagents in the preparation of heterocycles via transposition reaction in the one-pot three-component synthesis of six-membered cyclic carbamates and in a base-free synthesis of large macrocycles.[13]

In this work, we have undertaken a study to synthesize via DAC chemistry, different six-membered benzo-fused 1,4-heterocycles, 1,4-benzodioxines, 1,4-benzoxazines, and 1,4-benzothiazines starting from commercially available reagents (catechol, 1,2-aminophenol, and 1,2-aminothiol, respectively). The cyclization reactions have been achieved in two steps having in common the use of an organic carbonate as the key reagent. Reaction conditions, chemoselectivity, and general application of this novel synthetic approach have been addressed.

2 Results and Discussion

The herein proposed synthetic approach to benzo-fused 1,4-heterocycles encompasses two steps as depicted in Scheme 1.



Scheme 1 Synthesis of benzo-fused 1,4-heterocycles via DAC chemistry

1. Synthesis of the cyclic precursors **2**, **5**, and **8** by reaction of a bis-functionalized benzene (catechol, 2-aminophenol, 2-aminothiophenol) with the cyclic carbonate, ethylene carbonate (EC);

2. Cyclization of the precursors employing DMC as a reagent and solvent in the presence of a base or a catalyst to achieve the desired six-membered heterocycles **3**, **6**, and **9**.

Synthesis of 1,4-Benzodioxane

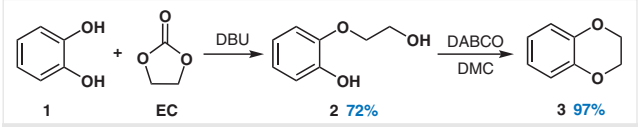
In order to investigate the feasibility of the proposed synthetic approach, we first attempted the preparation of the 1,4-benzodioxane moiety that we have previously prepared starting from the commercially available 2-(2-hydroxyethoxy)phenol (**2**).[12c] However, this substrate is quite expensive when compared to 1,2-dihydroxybenzene, namely catechol.

The most common synthetic procedures for the cyclic precursor **2** include reaction of catechol with ethylene oxide[14] or with 2-haloethanol.[15] In few examples, EC has been used as reagent in the presence of a tetrabutylammonium salt as a catalyst; however, rather harsh reaction conditions were necessary to collect the product in moderate to good yield.[16]

In this case study, the alkylation reaction was investigated both in batch and autoclave conditions, by reacting catechol (**1**) with EC in acetonitrile and testing the efficiency of weak bases such as $NaHCO_3$, K_2CO_3, and Cs_2CO_3; and strong bases, NaH, bicyclic amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo [2.2.2]octane (DABCO), and a heterogeneous catalyst NaY faujasite (see Supporting Information for details).

Best found reaction conditions involved the reaction of catechol and EC in the presence of DBU (1 mol equiv) as base in acetonitrile at 150 °C for 14 hours. The alkylation proceeded with a conversion of 84% and a selectivity of 90% toward intermediate **2** (calculated by NMR analysis). Purification through chromatography on silica gel afforded pure compound **2** in 72% yield. The bis-alkylated derivative represented the only reaction by-product.

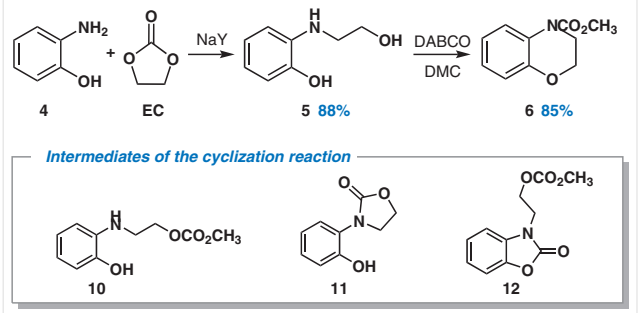
2,3-Dihydro-1,4-benzodioxine (**3**) was then obtained straightforwardly by reaction of compound **2** with DMC at reflux using DABCO as a base.[12c] The filtration of the reaction mixture through a silica pad followed by the solvent concentration under vacuum afforded the cyclic compound **3** in a quantitative yield (Scheme 2).



Scheme 2 Synthesis of 1,4-benzodioxane **3**

Synthesis of 1,4-Benzoxazine

Scheme 3 reports in detail the two-step synthetic approach set up for the preparation of benzomorpholine **6**. Similar to the procedure used for 1,4-benzodioxane DAC approach, in the first step 2-aminophenol was reacted with EC. For the purpose of this work, the preparation of 1,4-benzomorpholine, it would make no difference if the alkylation reaction led to 2-(2-aminophenoxy)ethanol or to 2-(2-hydroxyethylamino)phenol (**5**). Both substrates can undergo cyclization, although previous investigations



Scheme 3 Synthesis of 1,4-benzoxazine **6**

outlined that intramolecular reaction between phenol and an aliphatic alcohol is favored compared to the one involving an aniline and an alcohol.[12]

In this view, it has been previously reported that, in the presence of NaY faujasite as the catalyst, the reaction of bifunctional anilines such as aminophenols with an excess of DMC (used as solvent and reagent) proceeds with a very high mono-*N*-methyl chemoselectivity.[17]

It should be also mentioned that few synthetic approaches to 2-(2-hydroxyethylamino)phenol (**5**) have been reported in the literature mainly involving the use of chlorine chemistry or ring opening of epoxides.[18]

In our first attempt, a solution of 2-aminophenol and EC in acetonitrile was heated at reflux (90 °C) in the presence of NaY. In this case study, ethylene carbonate was used in stoichiometric amount as an aqueous workup would be necessary to separate the excess of unreacted EC from the product. Analyses of the reaction mixture showed that, despite the low yield achieved (ca. 5%), the only product formed was the 2-(2-hydroxyethylamino)phenol (**5**). When the same reaction was performed in an autoclave at 150 °C the alkylated product **5** was isolated in 88% yield confirming the high chemoselectivity of the *N*-alkylation reaction due to the presence of the faujasite. The product was recovered as light-yellow crystals after an easy purification by crystallization in dichloromethane. Besides, the faujasite employed for the alkylation, can be re-used several times without losing its efficiency.

The isolated 2-(2-hydroxyethylamino)phenol (**5**) was then subjected to the cyclization reaction (Table 1). To the best of our knowledge, the synthesis of the *N*-methoxycarbonylbenzomorpholine (**6**) has been previously reported in the literature exclusively via chlorine-based chemistry (74% yield).[19]

In the herein proposed procedure, several bases have been tested: weak base K_2CO_3 and Et_3N (Table 1, entries 1, 2); nitrogen bicyclic Lewis bases, DABCO, DBU, and triazabicyclodecene (TBD) (entries 3–5); and strong bases sodium methoxide and potassium *tert*-butoxide (entries 6, 7). All the experiments have been conducted in the presence of a stoichiometric amount of base at the refluxing temperature of DMC (90 °C) used as both reagent and solvent.

DABCO and superbase TBD were the only bases capable of promoting the cyclization reaction in quantitative yield (Table 1, entries 3 and 5). *N*-Methoxycarbonylbenzomorpholine (**6**) was easily recovered from the reaction mixture by simple filtration on a silica gel pad followed by evaporation of the residual solvent (85% isolated yield). It should be mentioned that DABCO was a more efficient base than TBD as the cyclization reaction reached completion already after six hours (entry 8).

All the other bases (Table 1, entries 1, 2, 4, 6, and 7) promoted the quantitative conversion of 2-(2-hydroxyethylamino)phenol (**5**) into the five-membered cyclic carbamate **12** that was isolated as a pure compound and fully characterized. It should be mentioned that the reaction intermediate **12** is also an interesting heterocycle, because many drugs containing a benzoxazolinone core have been studied for their hypnotic and pharmacological properties, such as anticonvulsant, antipyretic, analgesic, cardiotonic, and antibacterial effect[20] and have been found effective as indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors.[21]

Table 1 Synthesis of the *N*-Methoxycarbonylbenzomorpholine **6**[a]

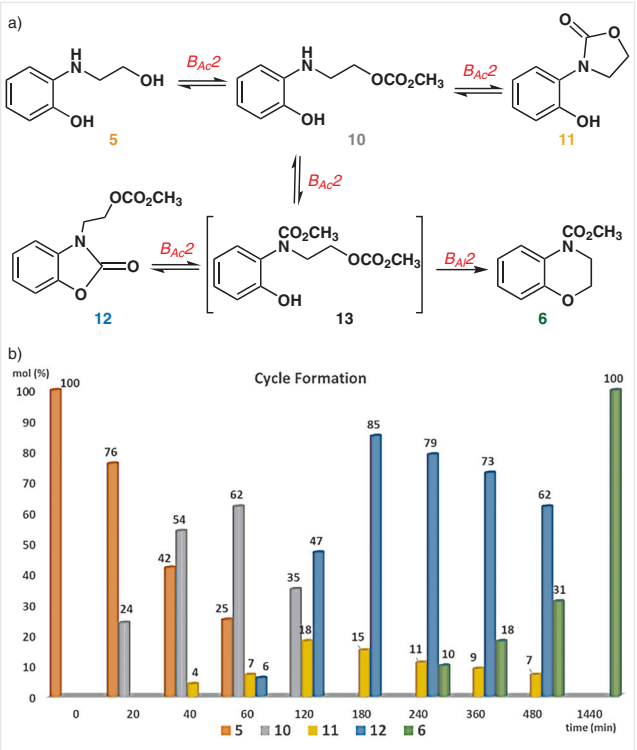
Entry	Base	Mol equiv	Time (h)	Selectivity (%)[b]		
				10	**12**	**6**
1	K_2CO_3	1.00	24	–	100	–
2	Et_3N	1.00	24	–	100	–
3	DABCO	1.00	24	–	–	100
4	DBU	1.00	24	–	100	–
5	TBD	1.00	24	–	–	100
6	NaOMe	1.00	24	–	100	–
7	*t*-BuOK	1.00	24	–	73	27
8	DABCO	1.00	6	–	–	100
9	DABCO	0.50	6	–	–	100
10	DABCO	0.25	6	–	75	25
11	DABCO	0.25	24	–	–	100
12	DABCO	0.10	6	68	32	–
13	DABCO	0.10	24	–	100	–

[a] Reaction conditions: 2-(2-hydroxyethylamino)phenol **5** (1 equiv), DMC (50 equiv), 90 °C. Conversion of the starting reagent **5** was quantitative in all experiments.
[b] Selectivity was calculated by ^{1}H NMR spectroscopy.

The Lewis acid, boron trifluoride diethyl etherate, strongly acidic cation exchanger Amberlyst-15, and amphoteric catalyst hydrotalcite KW2000 have also been tested for the cyclization reaction (1:1 w/w with the substrate); however, analysis of the reaction mixture showed only the presence of the unreacted starting reagent.

In a second set of experiment, the effect of the amount of DABCO on the formation of the benzomorpholine **6** was investigated. Data reported in Table 1 showed that this bicyclic base can be used in substoichiometric amounts (Table 1, entries 9–13), from 0.10 to 0.50 equivalent although the cyclization rate was slower (24 h). When the reaction was performed with 10% mol of DABCO for six hours the methoxycarbonylated intermediate **10** was the major product observed.

In order to elucidate a possible reaction mechanism, the cyclization reaction was performed employing 25% mol of DABCO (Table 1, entry 11). Samples were taken at time intervals, and intermediates and product formation were analyzed by ^{1}H NMR spectroscopy. The results are depicted in Scheme 4 (stacked spectra are included in the Supporting Information).



Scheme 4 a) Plausible reaction mechanism for the formation of the *N*-methoxycarbonylmorpholine **6**; **b**) Cyclization reaction over time according to the experiment in Table 1, entry11. Samples taken at time intervals (20 min, 40 min, 1 h, 2 h, 3 h, 6 h, 8 h, and 24 h). Intermediates and product formation were analyzed via ^{1}H NMR spectroscopy.

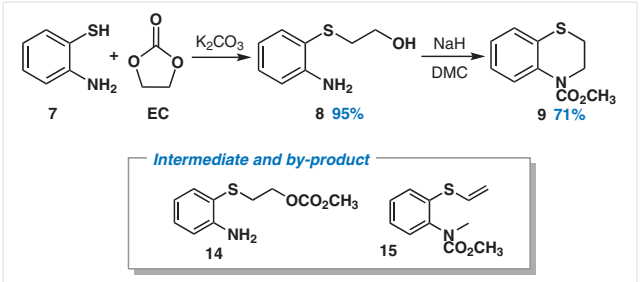
According to the data collected, the starting 2-(2-hydroxyethylamino)phenol (**5**) first undergoes a carboxymethylation of the aliphatic hydroxyl group forming the intermediate **10**. At this point the amino group is most probably methoxycarbonylated by DMC forming a very reactive bismethyl carbonate **13** that was not isolated. The latter compound is the key intermediate, as it can be converted into either the five-membered cyclic carbamate **12** or the desired benzomorpholine **6**.

It is interesting to note that the cyclic carbamate **12** is indeed a reaction intermediate as, once formed, it is slowly converted into the cyclic product **6**. A rather small amount of cyclic carbamate **11** is also formed from the intermediate **10** through an intramolecular $B_{Ac}2$ mechanism. It should be noted that all the reactions of the proposed mechanism are thermodynamically controlled except for the formation of the final product **6** that takes place via a kinetically controlled and irreversible $B_{Al}2$ mechanism (Scheme 4).

As proof of concept, an experiment was carried out employing a pure sample of the five-membered cyclic carbamate **12** isolated by column chromatography. This compound was dissolved into DMC (50 equiv) in the presence of DABCO (1 equiv) and heated at 90 °C according to the reaction conditions previously used for the cyclization of 2-(2-hydroxyethylamino)phenol (**5**) (Table 1, entry 8). Samples of the reaction mixture were taken at time intervals and their ^{1}HNMR spectra showed the quantitative conversion of the substrate **12** into the benzomorpholine **6**. This result confirms the proposed mechanism involving most likely the ring opening of the cyclic carbamate **12** to the bismethyl carbonate intermediate **13** followed by the formation of the heterocycle **6** via $B_{Al}2$ mechanism.

Synthesis of 1,4-Benzothiazine

2-Aminothiophenol was selected as the starting reagent to prepare 1,4-benzothiazine **9** (Scheme 5). The synthesis of the acyclic intermediate 2-(2-aminophenylthio)ethanol (**8**) was straightforward, as a result of the higher nucleophilicity of the thiol group compared to the amino one. The alkylation reaction of 2-aminothiophenol was carried out in an autoclave at 150 °C in the presence of K_2CO_3 resulting in the formation of 2-(2-aminophenylthio)ethanol (**8**) in a quantitative yield. Attempts to perform the reaction in the presence of faujasite led to lower yield, due to the formation of a considerable amount of a 2-aminothiophenol dimer via disulfide bond.[22] The synthesis of compound **8** (in 84% yield) was previously reported in the literature, although the procedure was based upon chlorine chemistry.[23]



Scheme 5 Synthesis of *N*-methoxycarbonyl-1,4-benzothiazine **9**

Conversion of compound **8** to the desired *N*-methoxycarbonyl-3,4-dihydro-2*H*-1,4-benzothiazine (**9**), was investigated by employing a variety of bases in different reaction conditions, as depicted in Table 2. The obtained results show that the reaction course strictly depends on the type of base used to activate the NH_2 group toward a six-membered ring closure by an irreversible $B_{Al}2$ mechanism.

In a first set of experiments, the reaction was conducted at the reflux temperature of DMC (60 equiv) in the presence of stoichiometric amount of a base. In these conditions, the use of potassium carbonate or DBU led to the formation of the methoxycarbonylated intermediate **14** as the major product (Table 2, entries 1, 2). DABCO or TBD, which provided the best outcomes in the synthesis of the morpholine derivative **6**, was inefficient to promote the formation of the benzothiazine derivative **9**. Both experiments gave by-product **15** as the major reaction product (entries 3, 4). A stoichiometric amount of strong base *t*-BuOK and NaOMe

Table 2 Synthesis of the *N*-Methoxycarbonyl-3,4-dihydro-2*H*-1,4-benzothiazine (**9**)[a]

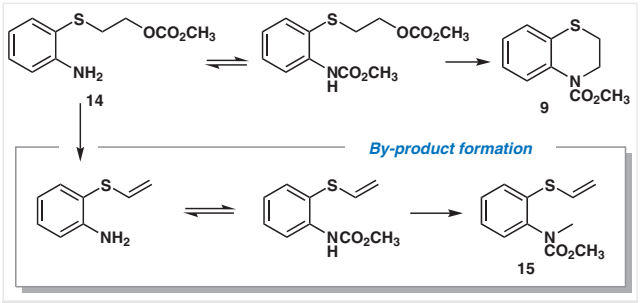
Entry	Base	Mol equiv	Time (h)	Selectivity (%)[b]		
				14	**15**	**9**
1	K_2CO_3[c]	1	24	100	–	–
2	DBU	1	24	93	7	–
3	DABCO	1	24	14	78	8
4	TBD	1	24	–	100	–
5	NaOMe	1	24	100	–	–
6	*t*-BuOK[d]	1	24	100	–	–
7	NaH	1	24	75	0	25
8	NaOMe[e]	3	3	–	21	79
9	NaH	3	3	41	45	14
10	DABCO	3	24	41	59	–
11	NaOMe[f]	3	3	–	34	66
12	NaH[f]	3	3	–	25	75[g]
13	DABCO[f]	3	24	25	67	8

[a] Reaction conditions: 2-(2-aminophenylthio)ethanol **8** (1 equiv), DMC (60 equiv), 90 °C. Conversion of the starting reagent **5** was quantitative in all experiments, unless otherwise specified.
[b] Selectivity was calculated via ^{1}H NMR spectroscopy.
[c] 90% conversion.
[d] 81% conversion.
[e] **9** was isolated in 63% yield.
[f] With 180 equiv DMC.
[g] 71% isolated yield.

led to the formation of the *O*-methoxycarbonylated intermediate **14** as the major product (entries 5 and 6). Sodium hydride was the only base – used in stoichiometric amount – that promoted the cyclization reaction to 1,4-benzothiazine **9** although in moderate yield (entry 7).

Better results were achieved using an excess of bases (Table 2, entries 8–10). Freshly prepared NaOMe employed in three equivalents promoted the formation of the benzothiazine **9** in high yield (79%); the reaction was complete after only three hours at reflux temperature (entry 8). An excess of NaH and DABCO did not favor the cyclization even when the reaction was carried out for 24 hours (entries 9, 10). However, it should be mentioned that higher amount of base causes inhomogeneous stirring and the reaction workup to isolate benzothiazine **9** was more difficult, especially in the case of sodium methoxide (entry 8). In this view, further experiments were conducted in more diluted conditions (180 mol equiv of DMC). As a result, the cyclization reaction was efficiently promoted both by NaOMe and NaH in three hours (entries 11, 12). Pure 1,4-benzothiazine **9** was isolated in 71% yield by chromatography on silica gel. Among the bases tested, only DABCO was ineffective in these reaction conditions (entry 13).

According to the results reported in Table 2, the reaction mechanism for the formation of benzothiazine **9** involves most probably, first the reaction of compound **8** with DMC to give the methoxycarbonylated intermediate **14** (Scheme 5). Then, the compound **14** may undergo either elimination reaction to afford the *N*-methyl carbamate by-product **15** or *N*-carboxymethylation followed by cyclization reaction to give the desired compound **9** (Scheme 6).



Scheme 6 Possible reaction mechanism for the formation of the *N*-methoxycarbonyl-3,4-dihydro-2*H*-1,4-benzothiazine (**9**)

In conclusion, we have developed and optimized a novel two-step synthetic strategy to achieve in good to excellent yields three different benzo-fused 1,4-heterocycles, by exploiting the versatility of DACs as carboxymethylating and methylating agents and solvents. This general procedure consisted in the selective monoalkylation of starting compounds, catechol, 2-aminophenol, and 2-aminothiophenol by reaction with EC in an autoclave followed by cyclization at 90 °C by using DMC as both solvent and reagent. In order to maximize the process yields, different conditions have been tested for both alkylation and cyclization steps by taking into account the nucleophilicity of the heteroatom directly involved in the reaction. Benzodioxine **3** and benzomorpholine derivative **6** were prepared quickly and in quantitative yield from 2-(2-hydroxyethoxy)phenol and 2-(2-hydroxyethylamino) phenol, respectively, employing DABCO as a base.

The benzothiazine derivative **9** was instead prepared in good yield from 2-(2-hydroxyethylthio)phenol by using an excess of strong base, NaH and NaOMe, respectively. Eventually, for each synthesis the main reaction intermediates and by-products were identified, isolated, and characterized via NMR spectroscopy and MS spectrometry and cyclization mechanisms have been proposed.

It should also be mentioned that the simplicity of this synthetic approach can lead to the preparation of a range of differently substituted benzo-fused 1,4-heterocycles. In particular, the use of commercially available 4-chloro-1,3-dioxolan-2-ones (chloroethylene carbonate) or 4-vinyl-1,3-dioxolan-2-one (vinyl ethylene carbonate) instead of EC may allow the introduction of a chlorine or vinyl moiety into heterocycles leading to further modification. This could be used to achieve structures such as piperoxan and isovanillin. Glycerol carbonate can be also employed as building block although its hydroxyl moiety would have to be protected to avoid formation of by-products in the cyclization steps.

Acidic hydrolysis or palladium-catalyzed hydrogenolysis of *N*-methoxycarbonylbenzomorpholine **6** and *N*-methoxycarbonyl-3,4-dihydro-2*H*-1,4-benzothiazine (**9**) in mild conditions would lead to the related benzomorpholine and 3,4-dihydro-2*H*-1,4-benzothiazine with a free amino group that could be also easily subject to further modification. In the specific case of 1,4-benzothiazine, this could be used to prepare compounds with ion channel antagonistic activity.[6]

Regarding the possibility to introduce substituents on the aromatic moiety of benzo-fused 1,4-heterocycles, several commercially available 2-aminophenol, such as 2-amino-4-chlorophenol, 2-amino-3-nitrophenol, and 4-amino-3-hydroxybenzoic acid are available and can be investigated as substrates.

Finally, numerous synthetic approaches are reported in the literature, which allow the introduction of reactive groups such bromine, nitro and acyl moieties, in the aromatic ring of 1,4-benzodioxane.[24] Modifications of the herein discussed benzo-fused 1,4-heterocycles will be the subject of further investigations.

All reagents were purchased from Sigma Aldrich and used without any further purification. NaOMe (Table 2, entries 5, 8, 9) was freshly prepared at 0 °C and under N_2 flow by adding portionwise Na to anhyd MeOH. After the complete dissolution of Na, the solvent was concentrated under vacuum to give NaOMe as a white solid.

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Ascend TM 400 spectrometer. The chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm; CD_3OD: 3.33 ppm) as well as TMS. Data are reported as follows: chemical shift, integration multiplicity (standard abbreviations) and coupling constants (Hz). ^{13}C NMR spectra were recorded at 100 MHz on a Bruker AscendTM 400 spectrometer. Chemical shifts are reported in ppm from the solvent resonance as internal standard ($CDCl_3$: 77 ppm; CD_3OD: 49 ppm).

DIP-EI-MS spectra of compounds **9**, **10**, **11**, **14**, and **15** were recorded on a large-scale tandem mass spectrometer (Waters AutoSpec 6F – Organic Synthesis and Mass Spectrometry Lab – University of Mons, Belgium) combining six sectors of E1B1c1E2c2E3B2c3E4 configuration (E stands for electric sector, B for magnetic sector and c for collision cell). General conditions were, 8 kV accelerating voltage, 70 eV ionizing electron energy and 200 °C ion source temperature. The PEI samples (1 mg), introduced in small Pyrex capillaries, were directly introduced into the ion source without any external heating. The ions were obtained under electron ionization in positive ion mode (200 µA trap current). The full scan mass spectra were recorded by scanning the field of the first magnetic sector and collecting the ions with an off-axis photomultiplier detector. Accurate mass measurements were acquired using perfluorokerosene (PFK) as the internal standard.

HRMS spectra of compounds **5**, **6**, **8**, and **12** were recorded on a Thermo Scientific LTQ Orbitrap XL mass spectrometer, via a full scan mode and with a mass resolution R = 100000.

1,4-Benzodioxane

2-(2-Hydroxyethoxy)phenol (2)[14–16]

In an autoclave, to a solution of catechol (**1**; 1.00 g, 9.08 mmol) and EC (0.80 g, 9.08 mmol) in MeCN (30 mL) was added DBU (1.34 mL, 9.08 mmol) and the mixture was heated to 150 °C for 24 h under stirring. Then, the mixture was cooled to r.t., filtered through a silica gel pad, and concentrated under vacuum to give a brown oil. Purification by flash chromatography (FC) on silica gel eluting with hexane/EtOAc (4:1, R_f = 0.42) gave the compound **2** as a grey solid; mp 99–101 °C; yield: 1.01 g (72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.01–6.81 (m, 4 H), 6.23 (br, 1 H), 4.22–4.15 (m, 2 H), 4.07–3.96 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.5, 145.9, 122.5, 120.2, 115.6, 113.4, 70.6, 61.4.

2,3-Dihydro-1,4-benzodioxine (3)[12c]

To a solution of **2** (1.00 g, 6.49 mmol) in DMC (30 mL, 350.00 mmol) was added DABCO (0.73 g, 6.49 mmol) and the mixture was refluxed under stirring for 3 h. Then, the mixture was filtered through a silica gel pad and the solvent was concentrated under vacuum to give compound **3** as a yellow oil; yield: 0.86 g (97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.76–6.64 (m, 3 H), 6.58–6.53 (m, 1 H), 3.77 (t, *J* = 6.1 Hz, 2 H), 6.24 (t, *J* = 6.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.6 (2 C), 121.4 (2 C), 117.3 (2 C), 64.4 (2 C).

1,4-Benzoxazine

2-[(2-Hydroxyethyl)amino]phenol (5)[19]

In an autoclave, to a solution of 2-aminophenol (4.00 g, 36.65 mmol) and EC (3.23 g, 36.65 mmol) in ACN (100 mL) was added NaY faujasite (4.00 g, 100% wt.) and the mixture was heated to 150 °C for 5 h under stirring. Then, the mixture was cooled to r.t., filtered through a silica gel pad and concentrated under vacuum to give a dense orange oil. Crystallization from CH_2Cl_2 afforded **5** as a brownish solid; mp 87–89 °C; yield: 4.94 g (88%).

^{1}H NMR (CD_3OD, 400 MHz): δ = 6.76–6.64 (m, 3 H), 6.58–6.53 (m, 1 H), 3.77 (t, *J* = 6.1 Hz, 2 H), 6.24 (t, *J* = 6.1 Hz, 2 H).

^{13}C NMR (CD_3OD, 100 MHz): δ = 144.9, 137.6, 119.8, 117.6, 113.5, 111.3, 60.4, 45.8.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_8H_{10}NO_2$: 152.0717; found: 152.0720.

2-[(2-Hydroxyphenyl)amino]ethyl Methyl Carbonate (10)

The cyclization intermediate **10** was synthesized by the reaction of **5** (0.20 g, 1.31 mmol) in DMC (6.00 mL, 65.50 mmol) by adding DABCO (0.04 g, 0.33 mmol) to the reaction mixture and heating to reflux under stirring. After 40 min, the mixture was cooled to r.t., filtered through a silica gel pad and the solvent was concentrated under vacuum to give a crude brown oil. Purification by FC on silica gel by eluting with hexane/EtOAc (9:1; R_f = 0.23) gave **10** as a brown oil; yield: 0.12 g (43%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.91–6.84 (m, 1 H), 6.79–6.63 (m, 1 H), 4.37 (t, *J* = 5.5 Hz, 2 H), 3.82 (s, 3 H), 3.47 (t, *J* = 5.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.9, 144.2, 136.1, 121.5, 118.6, 114.6, 112.8, 66.6, 55.0, 43.3.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_{13}NO_4$: 211.0845; found: 211.0848.

3-(2-Hydroxyphenyl)oxazolidin-2-one (11)

The cyclization intermediate **11** was synthesized by dissolving compound **10** (0.10 g, 0.47 mmol) in aq 2 M NaOH (5 mL). After 10 min under stirring, the solution was neutralized with aq 2 M HCl (5 mL) and extracted with Et_2O (3 × 5 mL). Then the organic phase was dried (anhyd Na_2SO_4) and concentrated under vacuum to give **11** as a brown wax; yield: 0.08 g (97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.90 (br, 1 H), 7.24–7.16 (m, 1 H), 7.11–7.04 (m, 2 H), 7.00–6.94 (m, 1 H), 4.68–4.59 (m, 2 H), 4.21–4.13 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.6, 149.7, 127.8, 125.7, 121.4, 121.1, 120.7, 63.6, 47.0.

HRMS: *m*/*z* [M]$^+$ calcd for $C_9H_9NO_3$: 179.0582; found: 179.0585.

Methyl [2-(2-Oxobenzo[*d*]oxazol-3(2*H*)-yl)ethyl] Carbonate (12)

The cyclization intermediate **12** was synthesized by reaction of **5** (1.00 g, 6.53 mmol) in DMC (27.50 mL, 326.50 mmol) by adding NaOMe (0.35 g, 6.53 mmol) to the reaction mixture and heating to reflux under stirring. After 24 h, the mixture was cooled to r.t., filtered 53975-2193811 through a silica gel pad and the mixture was concentrated under vacuum to give **12** as a yellow oil; yield: 1.10 g (71%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.18 (m, 2 H), 7.16–7.11 (m, 1 H), 7.09–7.05 (m, 1 H), 4.48 (t, *J* = 6.0 Hz, 2 H), 4.14 (t, *J* = 6.0 Hz, 2 H), 3.75 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.3, 154.4, 142.7, 131.1, 123.9, 122.7, 110.1, 108.5, 64.8, 55.1, 41.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_5$: 238.0710; found: 238.0719.

Methyl 2,3-Dihydro-4*H*-1,4-benzoxazine-4-carboxylate (6)[19]

A solution of **10** (0.50 g, 3.27 mmol) and DABCO (0.36 mL, 3.27 mmol) in DMC (13.76 mL, 163.50 mmol) was heated to reflux for 4 h under stirring. Then the mixture was filtered through a silica gel pad and concentrated under vacuum to give **6** as a yellow wax; yield: 0.54 g (85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.31 (m, 1 H), 7.30–7.33 (m, 1 H), 6.99–6.92 (m, 2 H), 4.46–4.39 (m, 2 H), 3.98–3.91 (m, 2 H), 3.83 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.5, 155.0, 128.9, 128.3, 126.1, 120.9, 112.1, 62.5, 55.6, 47.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}NO_3$ + Na^+: 216.0631; found: 216.0633

1,4-Benzothiazine

2-[(2-Aminophenyl)thio]ethan-1-ol (8)[23]

In an autoclave, to a solution of 2-aminothiophenol (**7**; 4.00 g, 31.95 mmol) and EC (2.81 g, 31.95 mmol) in MeCN (100 mL) was added K_2CO_3 (4.42 g, 31.95 mmol) and the mixture was heated to 150 °C for 5 h under stirring. Then the mixture was filtered through a silica gel pad and concentrated under vacuum to obtain a crude oil, which was dissolved in Et_2O (20 mL), washed with H_2O (3 × 20 mL) and dried (anhyd Na_2SO_4). The compound **8** was obtained as a dense brown oil by solvent evaporation under vacuum; yield: 5.14 g (95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1 H), 7.20–7.14 (m, 1 H), 6.79–6.72 (m, 1 H), 3.75 (br s, 2 H), 3.66 (t, *J* = 5.8 Hz, 2 H), 2.91 (t, *J* = 5.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.5, 136.7, 130.3, 118.2, 116.8, 115.4, 60.5, 38.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}NOS$: 170.0634; found: 170.0627.

2-[(2-Aminophenyl)thio]ethyl Methyl Carbonate (14)

The cyclization intermediate **14** was synthesized by the reaction of **8** (1.00 g, 5.91 mmol) with DMC (29.90 mL, 354.60 mmol) by adding K_2CO_3 (0.82 g, 5.91 mmol) to the reaction mixture and heating to reflux under stirring. After 24 h, the mixture was cooled to r.t., salts were filtered off, and the solvent was concentrated under vacuum to give **14** as a yellow oil; yield: 1.23 g (99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1 H), 7.20–7.10 (m, 1 H), 6.77–6.65 (m, 2 H), 4.27 (br, 2 H), 4.23 (t, *J* = 6.7 Hz, 2 H), 3.78 (s, 3 H), 3.00 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.5, 148.7, 136.6, 130.4, 118.6, 116.1, 115.1, 66.2, 54.9, 33.1.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_{15}NO_3S$: 227.0616; found: 227.0618.

Methyl Methyl[2-(vinylthio)phenyl]carbamate (15)

The cyclization by-product **15** was synthesized by reaction of **8** (0.20 g, 1.19 mmol) with DMC (6.4 mL, 59.5 mmol) by adding TBD (0.17 g, 1.19 mmol) to the reaction mixture and heating to reflux under stirring. After 48 h, the mixture was cooled to r.t., filtered through a silica gel pad and the solvent was concentrated under vacuum to give a crude brown oil. Purification by FC on silica gel eluting with hexane/EtOAc (9:1, R_f = 0.18) gave **15** as a bright yellow oil; yield: 0.19 g (72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46–7.40 (m, 1 H), 7.33–7.17 (m, 3 H), 6.48 (dd, J_1 = 15.7 Hz, J_2 = 9.7 Hz, 1 H), 5.51–5.40 (m, 2 H) 3.73 (br s, 3 H, OCH_3 rotamers), 3.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.1, 142.1, 134.1 131.0, 130.4, 128.4, 128.2, 128.0, 117.3, 53.0, 37.3.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{11}H_{13}NO_2S$: 223.0667; found: 223.0669.

Methyl 2,3-Dihydro-4*H*-1,4-benzothiazine-4-carboxylate (9)

To a solution of compound **8** (0.50 g, 2.95 mmol) in DMC (45 mL, 534.52 mmol) was added NaH (60% dispersion in mineral oil, 0.35 g, 8.85 mmol) and the mixture was heated to reflux for 24 h under stirring. Then, the mixture was filtered through a silica gel pad and the solvent concentrated under vacuum to give a brown oil. Purification by FC on silica gel eluting with hexane/Et_2O (97:3, R_f = 0.19) gave **9** as a reddish oil; yield: 0.44 g (71%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (br, 1 H), 7.19–7.14 (m, 1 H), 7.12–7.02 (m, 2 H), 3.98–3.92 (m, 2 H), 3.81 (s, 3 H), 3.25–3.19 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.9, 136.4 127.0, 126.7, 126.6, 125.4, 124.0, 53.2, 42.9, 28.3.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_{11}NO_2S$: 209.0510; found: 209.0507.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611710.

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