Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 58

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5-Membered *N*-heterocyclic compounds by dimethyl carbonate chemistry†

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Received 15th June 2011, Accepted 28th September 2011
DOI: 10.1039/c1gc15698e

Aliphatic and aromatic 1,4-bifunctional compounds bearing a primary alcoholic function and an amine can be efficiently cyclised with dimethyl carbonates in the presence of a base to achieve 5-membered *N*-heterocyclic compounds. This novel synthetic pathway is quantitative, one-pot and green as it does not involve the use of chlorine solvents or reagent.

N-Based heterocycles are very abundant in nature since they are present as structural subunits in many natural products such as vitamins, hormones and alkaloids.[1] These compounds are also interesting from an industrial point of view especially for the synthesis of pharmaceuticals, herbicides, pesticides, dyes, *etc.*[1]

Among the reaction pathways leading to nitrogen-containing heterocycles, many involve heavy metals, *e.g.* metal-catalyzed *intramolecular* cyclisation of aliphatic α,ω-diamine,[2] *intramolecular* and *intermolecular* Ru-catalyzed reactions,[3] *intramolecular* cyclisation of diallyl amine by Grubb's catalyst,[4] or gas-phase high-temperature reaction using zeolites.[5] In recent years, more sustainable approaches for the synthesis of *N*-based heterocycles have been reported,[6] such as photocatalytic cyclisation of α,ω-diamine carboxylic acids by aqueous semiconductor suspensions[7] and microwave-assisted synthesis from alkyl dihalides and primary amines.[8]

However, most of the above-mentioned reactions still require high temperature and long reaction time, utilize chlorine-based chemistry or eventually organic chlorinated solvents.

Short chain dialkyl carbonates such as dimethyl carbonate (DMC), produced nowadays by clean processes,[10] are renowned for possessing properties of low toxicity and high biodegradability, which make them true green solvents and reagents.[11] DMC has been used as efficient eco-sustainable substitute of the most common methylating and carboxymethylating agents such as phosgene, methyl halides or methylsulfate that are toxic and highly corrosive.[12] Dialkyl carbonates and in particular DMC have shown high selectivity with different monodentate and bidentate nucleophiles acting as methylating and/or carboxymethylating agent.[13] The reactivity of the two electrophilic centers of DMC can be selectively tuned, temperature being the key factor. In fact, usually at reflux temperature (T = 90 °C) DMC acts as methoxycarbonylation agent by $B_{Ac}2$ mechanism while at higher temperature (T > 150 °C) the methylation reaction occurs *via* the $B_{Al}2$ mechanism. Both reactions produce as by-product only methanol and eventually CO_2.[11–13]

Exploiting the DMC ($B_{Al}2$-$B_{Ac}2$) chemistry, recently we reported a novel, one-pot, environmentally benign and chlorine-free synthetic pathways for the synthesis of 5-membered cyclic ethers by *intramolecular* cyclisation of 1,4-diols.[9]

In this work, we report a DMC-promoted *intramolecular* cyclisation for the selective synthesis of 5-membered *N*-based cyclic molecules.

4-Amino-1-butanol **1** was selected as starting material as it is the simplest aliphatic model available for this study. It is noteworthy thatthe family of the carboxyalkyl pyrrolidine has been recently used as key intermediates in the synthesis of heterocyclic arylsulphones that showed to be efficient in the treatment of diseases of the central nervous system, *e.g.* Alzheimer's disease and schizophrenia.[4]

Preliminary experiments on this substrate were carried out using DMC as solvent and reagent with different catalysts (Table 1): metallic homogenous catalysts (entries 1–2), alkali carbonates (entries 3–4), heavy metal basic carbonates (entry 5), strong base (entry 6) and hydrotalcite[14] (entry 7).‡

All the reactions were conducted in autoclave with catalytic amount of base/catalyst and in the presence of DMC.

Table 1 Synthesis of *N*-methoxycarbonyl pyrrolidine **4** starting from 4-amino-1-butanol **1** using DMC as solvent and reagent in the presence of catalytic amount of base (10% mol)[a]

Entry	Catalyst	Time (h)	Conversion (%)	*N*-Methoxycarbonyl pyrrolidine[b] (%)
1	$Zn(OAc)_2$	3	100	34.7
2	$SnOBu_2$	3	100	27.5
3	K_2CO_3	3	100	49.3
4	Cs_2CO_3	3	100	62.3
5	$(ZnCO_3)_2{\cdot}[Zn(OH)_2]_3$	3	100	38.7
6	MeONa	3	100	46.0
7	HT KW2000	3	100	47.8

[a] All reactions were carried out in autoclave. [b] Yields were calculated by GC-MS in the presence of an internal standard (decane); in all the cases the methyl 4-(methoxycarbonyloxy)butylcarbamate (its anion **3** is shown in Scheme 1) was the only other product observed.

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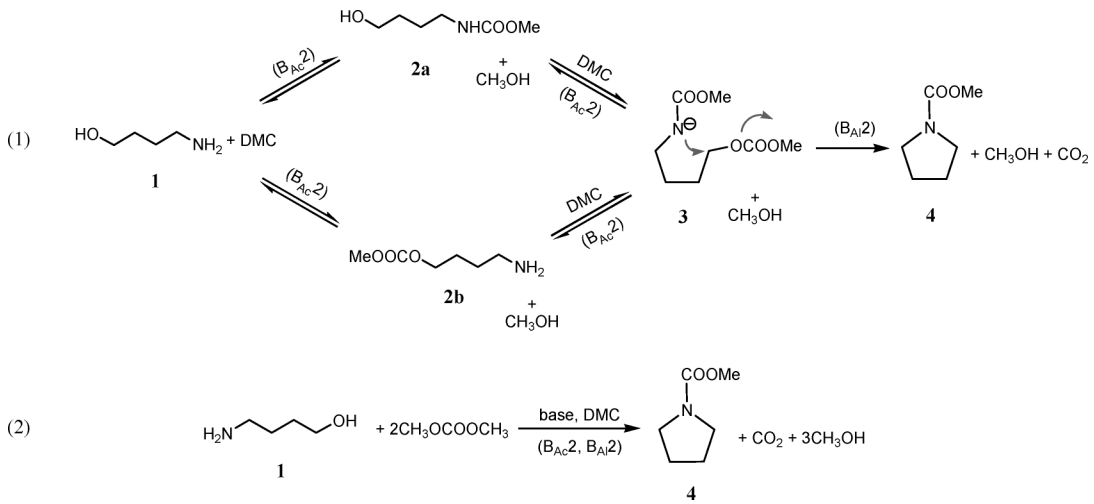
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra, GC-MS analysis. See DOI: 10.1039/c1gc15698e



Scheme 1 *Intramolecular N*-heterocyclisation of 4-amino-1-butanol **1** to form the *N*-carboxymethyl pyrrolidine **4**; (eqn (1)) Reaction mechanism; (eqn (2)) Stoichiometry of the reaction.

Results collected showed in any case the formation of the *N*-methoxycarbonyl pyrrolidine **4** from modest to good yields (34–62%).

Among the catalysts used, alkali carbonates and in particular Cs_2CO_3 resulted the more efficient ones (62% yield). In any case the only by-product formed was the methyl 4-(methoxycarbonyloxy)butylcarbamate that was isolated as pure and fully characterised.‡

This reaction is a remarkable example of hard-soft acid–base theory applied to the DMC, as the starting substrate include two different nucleophiles, *i.e.* a primary amine and a primary alcohols, that discriminate between the two electrophilic centers of the DMC leading to the carboxymethyl pyrrolidine by one-pot cyclisation.

Most probably the reaction proceeds by a sequence of carboxymethylation and alkylation reactions (Scheme 1): the 4-amino-1-butanol **1** firstly undergoes carboxymethylation at the hydroxyl (or amine) group ($B_{Ac}2$), then, or most probably at the same time, the amine (or hydroxyl) moiety will also carboxymethylate ($B_{Ac}2$). As a consequence, the amino group of the so formed carbamate (its related anion **3** is shown in Scheme 1) results softer in character, as demonstrated by previous investigations,[11c] and it undergoes fast alkylation to form selectively the carboxymethyl pyrrolidine **4** ($B_{Al}2$).[15] It is noteworthy that the formation of the *N*-based cyclic **4** is favoured because all the reactions ($B_{Ac}2$) depicted in Scheme 1 are of equilibrium, except the one related to the cyclic formation ($B_{Al}2$).

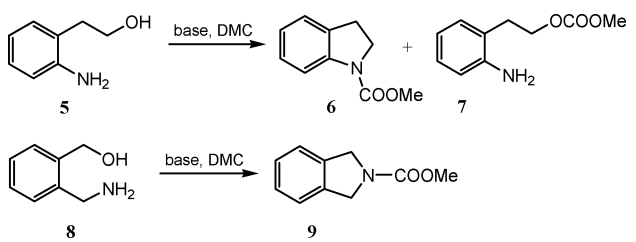
Further investigations of the 4-amino-1-butanol **1** were also conducted at reflux temperature and atmospheric pressure using a base and DMC as solvent and reagent. Results collected are reported in Table 2. High-yielding *N*-heterocyclisation of the starting material was achieved by employing potassium *tert*-butoxide as base (entries 1–2). Most probably the excess of base used in the reaction is needed for the three subsequent reactions to take place (Scheme 1). In fact, performing the reaction using only 0.5 eq mol of base at higher temperature also in autoclave resulted in lower yield (entry 3).

Investigations were also conducted on two simple aromatic bifunctional nucleophile *i.e.* 2-(2-aminophenyl)ethanol and 2-(aminomethyl)benzyl alcohol (Scheme 2). Results, reported in Table 3 and Table 4, respectively, demonstrated that also in this case *N*-carboxymethyl indoline **6** and *N*-carboxymethyl isoindoline **9** were formed in quantitative yield by *intramolecular* cyclisation.

Table 2 Synthesis of *N*-methoxycarbonyl pyrrolidine using DMC and excess of base at different temperature

Entry	Temp. (°C)	KOtBu (eq. mol)	Conv. (%)	*N*-Methoxycarbonyl pyrrolidine[a] (%)
1	90	2	100	77
2	90	2.5	100	86
3	160[b]	0.5	100	76

[a] Yields were calculated by ^{1}H NMR spectrometry; [b] Reaction conducted in autoclave.



Scheme 2 Synthesis of *N*-carboxymethyl indoline **6** and *N*-carboxymethyl isoindoline **9**.

In particular, when 2-(2-aminophenyl)ethanol **5** was used as substrate the products formed were the carboxymethyl indoline **6** and small amount of the cyclisation intermediate 2-aminophenethyl methyl carbonate **7**, the only intermediate observed (entries 1, 3 Table 3).‡ Column chromatography of the reaction mixture allowed isolation of the pure compounds and their characterisation. It is noteworthy that in all the above-mentioned reactions DMC is employed in excess since it serves as solvent and reagent, however it can be easily recycled after filtration of the reaction mixture and evaporation under vacuum. In fact, performing the cyclisation reaction by using recycled DMC (entry 2, Table 3) resulted in the high yielding conversion

Table 3 Synthesis of carboxymethyl indoline **6** by DMC as solvent and reagent[a]

Entry	Base (eq. mol)	Temp. (°C)	Conv. (%)	Carboxymethyl indoline (GC-MS%)
1	NaOMe (2.5)	90	100	82
2[b]	NaOMe (2.5)	90	100	83
3	KOtBu (2.5)	90	100	95 (78)[c]
4[d]	KOtBu (0.1)	180	100	93

[a] The reaction time is 6 hours, yields were calculated by GC-MS data, the intermediate **6** was the only other compounds observed. [b] Using DMC recycled from entry 1 (Table 3). [c] Isolated yield. [d] In autoclave.

Table 4 Synthesis of carboxymethyl isoindoline **9** by DMC as solvent and reagent[a]

Entry	Base (eq. mol)	Temp. (°C)	Conv. (%)	Carboxymethyl isoindoline (GC-MS%)
1	KOtBu (2.5)	90	100	95 (80)[b]
2	NaOMe (2.5)	90	100	80
3[c]	KOtBu (0.1)	180	100	71

[a] The reaction time is 6 h, yields were calculated by GC-MS data. [b] Isolated yield. [c] In autoclave.

of the starting material into the carboxymethyl indoline **5**.‡ Furthermore, when the cyclisation reaction was conducted in autoclave at high temperature and in the presence of catalytic amount of base (entry 4 Table 3), carboxymethyl indoline formed, once again, in good yield (83%).

Table 4 reports the results achieved for the cyclisation of 2-(aminomethyl)benzyl alcohol **8**. This substrate was synthesised by reduction of ethyl 2-cyanobenzoate according to literature procedure.[16] When the cyclisation reaction of **8** was conducted in the presence of a strong base (2.5 eq. mol.) at reflux conditions, the carboxymethyl isoindoline **9** formed in quantitative yield as sole product. (entry 1–2, Table 4). It is also possible to carry out the reaction using catalytic amount of base (0.1 eq. mol.), but this require the use of autoclave and high temperature (entry 3, Table 4)

The reaction of aliphatic and aromatic 4-amino-1-butanol compounds with DMC in the presence of a base and in mild condition led to the corresponding *N*-based cyclic in high yield and short reaction time. The formation of the *N*-based cyclic **4**, **6** and **9** is favoured due to the reaction mechanism comprising of several equilibrium reactions ($B_{Ac}2$), meanwhile the cyclic formation ($B_{Al}2$) is the only kinetically driven reaction (Scheme 1). The cyclisation reaction was conducted at reflux condition in the presence of 2.5 eq. mol. of base or utilizing a catalytic amount of base (0.1 eq. mol.) in an autoclave. Both reactions resulted in the high yielding formation of the 5-membered *N*-heterocyclic compound, although using small amount of base required higher temperature.

Comparing this reaction with the other avaiable synthetic pathways, the DMC-mediated reaction is green, high yielding, occurs in one step, do not require any chlorine-based chemical or strong acid and do not produce any chlorinated waste material. DMC, employed as solvent and reagent in the cyclisation reaction, can be easily recovered by distillation and reused. General applicability of the new synthesis on other suitable substrates is currently under investigation.

‡ Synthesis of carboxymethyl pyrrolidine in autoclave (Table 1): in a typical experiment 4-amino 1-butanol (0.26 mL, 2.80 mmol), DMC (10 mL) and 10% mol of catalyst were heated at $T = 180$ °C while stirring continuously under nitrogen atmosphere for three hours. Results were collected by gas chromatography in the presence of an internal standard (decane). Gradient elution chromatography using Et_2O/hexane (3/2) on silica gel allowed all of the products to be isolated as pure compounds. Carboxymethyl pyrrolidine **4**: analysis conducted on the isolated product were consistent with the one present in the literature.[3b] 4-(Methoxycarbonyloxy)butylcarbamate: as white oil $C_8H_{15}NO_5$; M = 205.2084 g mol^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ = 1.5–1.72 (m, 4H), 3.12 (7, 2H), 3.6 (s, 3H), 3.75 (s, 3H), 4.12 (t, 2H), 5.7 (s, 1H); ^{13}C NMR (75 MHz, CD_3CN) δ = 155.5, 67.3, 54.1, 51.1, 39.9, 25.8, 25.5. Synthesis of carboxymethyl pyrrolidine at reflux conditions (Table 2): in a typical experiment 4-amino 1-butanol (0.5 mL, 5.60 mmol), DMC (15 mL) and potassium *tert*-butoxide were heated at T = 90 °C while stirring continuously under nitrogen atmosphere for three hours. The reaction outcome was followed by ^{1}H NMR spectrometry (see ESI).† Synthesis of carboxymethyl (iso)indoline (Table 3, Table 4): in a typical experiment the substrate, *i.e.* 2-(2-amino phenyl)ethanol (0.5 mL, 3.64 mmol), DMC (15 mL) and potassium *tert*-butoxide (2.5 eq. mol.) were heated at T = 90 °C while stirring continuously under nitrogen atmosphere for six hours. The reaction outcome was followed by GC-MS analysis. If necessary, gradient elution chromatography using hexane/EtOAc (5/2) on silica gel allowed isolation of the pure carboxymethyl indoline **5** and of a small amount of the intermediate 2-aminophenethyl methyl carbonate **6**. Carboxymethyl indoline: Analysis conducted on the isolated product were consistent with the one obtained present in the literature.[17] Mp 69–72 °C (lit. mp 68–72 °C).[17] 2-Aminophenethyl methyl carbonate **7**: as a light red oil $C_{10}H_{13}NO_3$ M = 195.2 g mol^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.88–2.92 (t, 2H), 3.76 (s, 3H), 4.28–4.32 (t, 2H), 6.71–6.74 (m, 2H), 7.1–7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 145.0, 130.4, 128.0, 121.1, 118.7, 115.9, 67.0, 54.8, 31.0. Carboxymethyl isoindoline: analyses conducted on the isolated product were consistent with the one obtained present in the literature.[18] Synthesis of carboxymethyl indoline with recycled DMC (entry 2, Table 3): DMC was distilled from the reaction mixture (entry 1, Table 3). Pure DMC (5 mL) was added to the recovered DMC (10 mL) in order to have enough solvent/reagent to conduct the experiment (15 mL). The reaction was then conducted in the same conditions reported for the synthesis of carboxymethyl indoline **6**.

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