ChemPubSoc Europe

DOI: 10.1002/chem.201402368

CHEMISTRY
A European Journal
Communication

Carbon Dioxide Fixation

Direct Assembly of 2-Oxazolidinones by Chemical Fixation of Carbon Dioxide

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Abstract: The reaction of β- and γ-haloamines with carbon dioxide to give pharmaceutically relevant 2-oxazolidinones and 1,3-dioxazin-2-ones, was found to proceed efficiently in the presence of a base and in the absence of catalyst. After optimization of reaction conditions, the system was successfully expanded to a variety of haloamines, even at multigram scale. The reaction was further studied *in silico* by DFT calculations.

The chemical activation and fixation of carbon dioxide has been pivotal at the forefront of research development towards sustainable chemical transformations.[1a–c] The structural diversity, value, and applications of those molecules accessible utilizing carbon dioxide are instrumental to stimulate research programs. These factors also predetermine the economic and environmental impact in addition to the viability of a given process at the industrial and pharmaceutical level.[2] Furthermore, the value-driven nature of this research is underpinned by the abundance, low cost, optimum atom economy, and environmental features underlying the use of carbon dioxide as a C-1 feedstock.[3]

In this connection, 2-oxazolidinones constitute a prominent family of molecules amenable to be constructed by chemically fixating CO_2.[4] Widely applied in asymmetric synthesis as chiral auxiliaries,[5a–b] these compounds have recently shown unparalleled biological profiles. In particular, *N*-aryl-2-oxazolidinones (Scheme 1) are regarded as the last resort treatment against a broad variety of gram-positive bacterial pathogens of rising prevalence, which are resistant to other potent antibiotics such as the methicillins or vancomycins.[6a–d] Additionally, the analogous 6-ring scaffold, 1,3-dioxazin-2-one, is found in novel antiretroviral and antibacterial drugs.[7a–b] Most industrial processes contemplate the construction of the 2-oxazolidinone heterocyclic core as the key step through phosgenation of β-aminoalcohols or the use of expensive building blocks and/or sacrificial reagents.[8a–e] Greener alternatives are mainly limited to a recent report on the assembly of 2-oxazolidinones through the catalytic condensation of readily available glycerol derivatives with urea. However, this approach is hitherto hampered by modest selectivities and yields as well as a narrow substrate scope.[9] This affects the costs associated with the industrial production of 2-oxazolidinones significantly enough to restrict their public administration, and trigger research on methods that are simultaneously sustainable and effective, such as those based on the chemical fixation of CO_2.[5,10]

In the last decade, research on the construction of 2-oxazolidinones by chemical fixation of CO_2 has experienced considerable progress. However, a close examination reveals that careful selection of substrates still continues to determine the success of this task. In this sense, β-aminoalcohols represent the most intuitive and highly desirable substrates given their availability and cost. However, previous studies required either high temperatures and supercritical conditions,[11] toxic organometallic catalysts,[12,13] electrochemical procedures based on precious metals,[14] or, more recently, stoichiometric additives to capture the water generated in situ.[15a–c] In contrast, the use of activated aziridine derivatives as substrates have widely met with better results by employing either catalytic,[16a–e] or solvent and catalyst-free conditions.[17a–b] Unfortunately, the relatively high cost of these building blocks coupled with the prefunctionalization generally required on the aziridine nitrogen atom and other positions of the ring have a deleterious effect on their industrial implementation.

In the course of our ongoing research on the activation of small molecules,[18a–c] we became aware of the non-existence of a simple direct method involving CO_2-based construction of 2-oxazolidinones and 1,3-dioxazin-2-ones with the structural features showcased on any member of the 2-oxazolidinone family of antibiotics, namely no substitution on ring position 3 (Scheme 1) and a hydroxymethyl or methyl group on position 4. Furthermore, we envisaged that such a method would be compatible with subsequently performing a well-known and efficient catalytic N-arylation protocol with a broad scope of aryl halides.[19]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402368. It includes spectroscopic data, methods used, and computational details.

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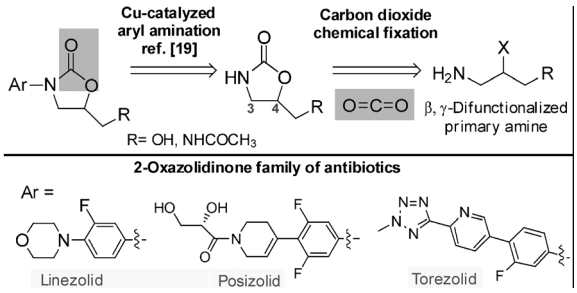
The resulting approach would possess a modular character providing access to a diverse array of highly valuable candidates for further medicinal screening (Scheme 1).

Herein, we report the first direct construction of 2-oxazolidinones by chemical CO_2 fixation on primary β- and γ-haloamines. In contrast to the majority of precedents using aminoalcohols, our system exploits the reactive nature of the C–X bond to facilitate CO_2 chemical fixation in the presence of stoichiometric amounts of a conventional base with high yields and selectivities even at multigram scale.



Scheme 1. Proposed modular route to 2-oxazolidinone antibiotics.

Preliminary inspection of our hypothesis led us to quantitatively convert a simple primary β-haloamine, such as 2-bromoethylamine, into the desired 2-oxazolidinone (**1**) after a reaction time of one hour with potassium hydroxide at 80 °C and 40 bar of CO_2 in EtOH. Further evaluation demonstrated that these reaction conditions were also amenable for the conversion of 3-bromopropylamine into the analogous 6-membered-ring 1,3-dioxazin-2-one (**2**). We then set out to optimize the reaction conditions by using the readily available 3-bromopropylamine as the model substrate.

Ethanol and KOH were our original solvent and base of choice owing to their inexpensiveness and sustainable nature. Substituting EtOH with other solvents capable of dissolving the reagents involved (that is, H_2O and MeCN) led to the isolation of product in lower yields, 66% and 50%, respectively. A solvent-free reaction was also attempted, but no reaction was observed because of starting material decomposition caused by insufficient heat transfer. Other bases investigated, namely, K_2CO_3 and Et_3N, gave conversions of 88% and 98%, respectively. KOH was deemed the most suitable base for further studies.

We next studied the effect of temperature on conversion (Figure 1). It is seen that quantitative conversion is first observed at temperatures exceeding 60 °C, and no drop in efficiency is observed until above 100 °C. At 150 °C, conversion is significantly affected by the emergence of side reactions. Meanwhile, concerning the effect of CO_2 pressure, a reaction under 1 bar at the optimum temperature of 65 °C only managed to afford the product in 11% yield after 1 h. In fact, a remarkably higher yield of 91% was not achieved until the pressure of CO_2 was raised to 10 bar. However, when the reaction pressure was increased to 30 bar, the yield was improved by 7%. Further increase of pressure to 40 bar led yields to reach >99%. We thus concluded that a temperature of 65 °C and a pressure of 35 bar were optimal for this reaction.

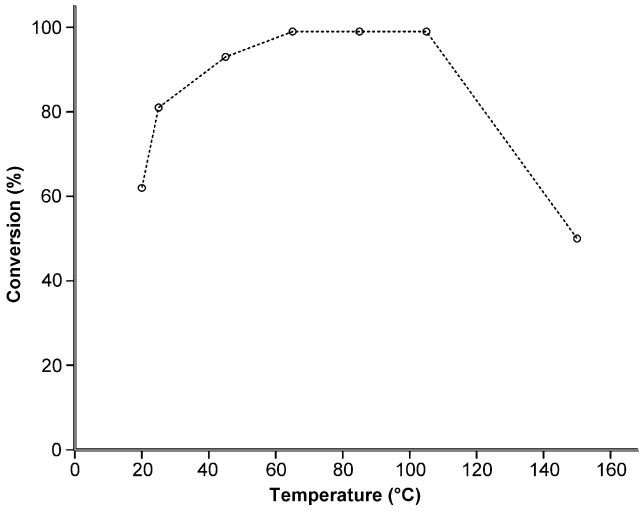


Figure 1. Effect of temperature on the cyclization of 3-bromopropylamine and CO_2. Reaction conditions: 2 mmol substrate, 1.2 equiv KOH, 10 mL EtOH, 1 h, 40 bar. Conversions recorded by GC/MS and ^1H NMR spectroscopy.

Having established optimal reaction conditions, we expanded the reaction to other primary β- and γ-haloamines. Table 1 summarizes the results. Under these conditions, chlorinated and brominated amines show similar reactivity, and all studied 2-haloethylamines and 3-halopropylamines were quantitatively converted into the corresponding 5- and 6-membered-ring products, which were isolated in excellent yields (Table 1, entries 1–4). The reaction between 2,5-dichloropentylamine and carbon dioxide (Table 1, entry 5) also proceeds selectively and efficiently to give **3**. Attempts to use 2,3-dichloropropylamine

Table 1. Cyclization of various β- and γ-haloamines with carbon dioxide.[a]

Entry	Substrate	Product	Yield [%][b]
1	Cl, NH_2	**1**	>99
2	Br, NH_2	**1**	>99
3	Cl, NH_2	**2**	98
4	Br, NH_2	**2**	99
5	Cl, NH_2, Cl	**3**	91
6	Cl, NH_2, Cl	**4** / **5**	37:15
7[c]	Cl, NH_2, Cl	**4** / **5**	63:28
8[d]	Cl, NH_2, Cl	**4** / **5**	81:17

[a] Reaction conditions unless otherwise noted: 2 mmol substrate, 1.2 equiv KOH, 10 mL EtOH, 65 °C, 35 bar CO_2, 1 h. [b] Yield of isolated product. [c] Reaction time of 18 h. [d] 1.2 equiv Cs_2CO_3 used in place of KOH.

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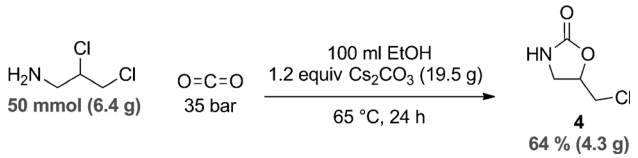
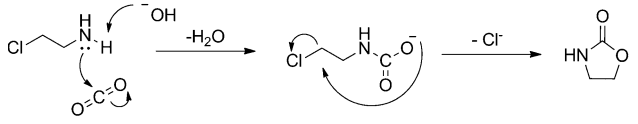
as substrate initially yielded moderate results, in that a mixture of products was obtained (Table 1, entry 6). The use of longer reaction times leads to higher conversions but does little to improve the selectivity of the reaction (Table 1, entry 7). However, replacing potassium hydroxide with cesium carbonate, a base previously employed in cyclic carbonate synthesis[20], a higher selectivity is obtained and the 5-membered-ring product can be isolated in good yields (Table 1, entry 8).

To demonstrate the power of our approach, we studied the reaction of 2,3-dichloropropylamine, which allows direct access to the 2-oxazolidinone key precursor, **4**, which has suitable ring functionality for the rapid assembly of 2-oxazolidinone antibiotics (Scheme 1). Because of this relevance, the synthesis of **4** was chosen as a model reaction for scale-up experiments. Using a larger reactor and a longer reaction time of 24 h to account for the higher volume of the reaction, the scale was successfully increased 25 fold to 50 mmol, with a 74% conversion into **4** (Scheme 2). After column chromatography, the pure product was isolated in 64% yield, indicating that the reaction is applicable at multigram scale.



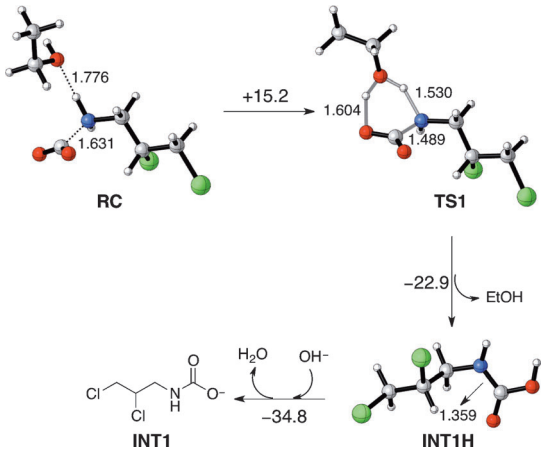
Scheme 2. Multigram scale synthesis of 2-oxazolidinone precursor **4**.

Based on these results, we propose a mechanism in which the amine first reacts with CO_2 and the base in a single concerted step to give a carbamate anion, which then undergoes an intramolecular nucleophilic substitution to furnish the cyclic urethane and the inorganic byproduct (Scheme 3). The occurrence of a concerted mechanism in the first step has been recently deemed feasible through computation.[21]



Scheme 3. Proposed mechanism for CO_2-based assembly of 2-oxazolidinones.

To gain more insight into the reaction mechanism and the regioselectivity of the process, we carried out Density Functional Theory (DFT) calculations on the transformation of 2,3-dichloropropylamine into cyclic carbamates **4** and **5** by using the PCM(EtOH)-M06-2X/6-311+G*&def2-TZVPP(for Cs) level.[22] Our calculations suggest (see Scheme 4) that amine addition to CO_2 begins from the initial reactant complex **RC**, which involves both reactants and a molecule of EtOH. This species is transformed into intermediate **INT1H** via transition state **TS1** with a computed activation barrier, $\Delta\Delta G^{\ddagger}$, of 15.2 kcal mol^{-1}



Scheme 4. Formation of **INT1** from the initial reactant complex **RC**. Values close to arrows indicate the computed free energies (in kcal mol^{-1} at 65 °C). Bond distances are given in Å. All data have been computed at the PCM-(EtOH)-M06-2X/6-311+G* level.

(at 65 °C) in a highly exergonic process ($\Delta\Delta G_R = -7.7$ kcal mol^{-1}). The saddle point, **TS1**, which resembles that suggested previously for the absorption of CO_2 by 2-amino-2-methyl-1-propanol,[21] is associated with the concerted formation of the new N–C bond and proton transfers from the amino group to EtOH and from EtOH to CO_2. Once formed, **INT1H** rapidly evolves to anion **INT1** through a highly exergonic acid/base reaction promoted by OH^- (Scheme 4).

The intramolecular cyclization reaction was studied next. As shown in Scheme 5, **INT1** evolves to cyclic carbamates **4** and **5** through an intramolecular nucleophilic substitution reaction via transition states **TS2** and **TS3**, respectively. Both saddle points are associated with the synchronous displacement of the chloride substituent (placed at positions C2 or C3, respectively) by the nucleophilic (O=)C–O$^-$ group to form the new C–O bond of the corresponding carbamate. In this sense, the optimized geometries of these transition states resemble those found for typical backside S_N2 reactions.[23] Interestingly, our calculations suggest that the regioselectivity of the process takes place under thermodynamic control, in view of the negligible barrier energy difference computed for the processes involving **TS2a** and **TS3a** ($\Delta\Delta G^{\ddagger} = 0.1$ kcal mol^{-1} at 65 °C). Similar results were obtained when the cation K^+ is considered in the calculations ($\Delta\Delta G^{\ddagger} = 0.2$ kcal mol^{-1} involving transition states **TS2b** and **TS3b**). Therefore, the selectivity of the reaction in the presence or absence of K^+ is directly related to the thermodynamic stability of five- and six-membered cyclic carbamates **4** and **5**. Thus, the latter species lies 1.8 kcal mol^{-1} (1.5 kcal mol^{-1} in the presence of K^+) over the former, which is in nice agreement with the experimentally observed favored formation of **4** over **5** (see Table 1) and previously published thermodynamic studies.[24]

At variance, the barrier energy difference significantly increases when Cs^+ is involved in the process. The computed $\Delta\Delta G^{\ddagger}$ value of 1.7 kcal mol^{-1} for the reactions involving **TS2c** and **TS3c** is translated into a Boltzmann's ratio of 92:8 (at 65 °C), which nearly matches the experimentally observed

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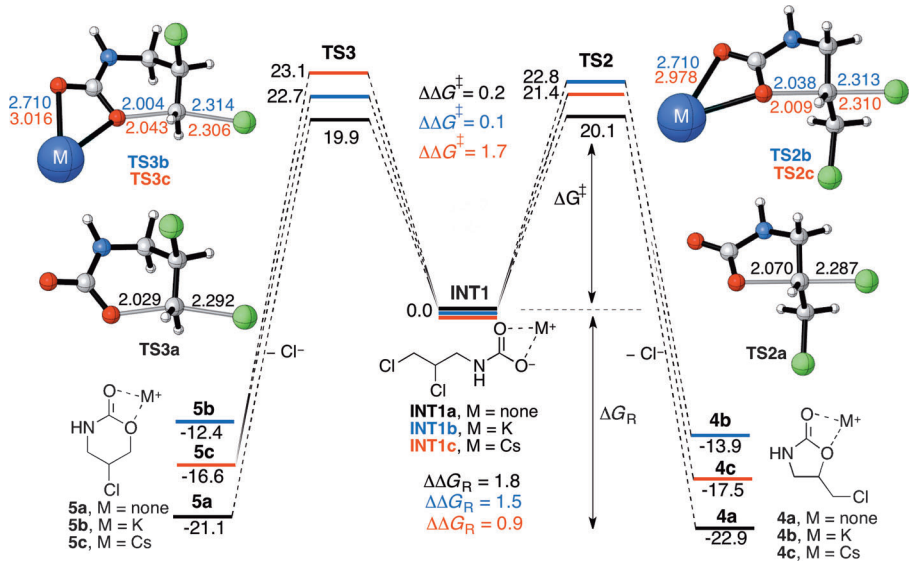

Scheme 5. Computed intramolecular nucleophilic substitution reactions from **INT1**. All data have been computed at the PCM(EtOH)-M06-2X/6-311+G*&def2-TZVPP (for Cs) level. See Scheme 4 for additional caption details.

81:17 ratio of **4** and **5** (see Table 1). Therefore, it can be concluded that the regioselectivity of the process in the presence of Cs^+ takes place under kinetic control as well (see also Figure 1S in the Supporting Information).

In conclusion, we have successfully achieved catalyst-free chemical fixation of carbon dioxide to give a diverse range of primary β- and γ-haloamines in a single step. The reaction efficiently transforms readily available material into high-value 2-oxazolidinones antibiotic precursors by using a cheap and environmentally benign combination of solvent and base. Furthermore, this method is amenable for multigram scale synthesis. DFT calculations show the participation of one solvent molecule in the initial carbamate formation and the inorganic base in activating the carbamate moiety during the latter cyclization. The observed regioselectivity for this process arises from the thermodynamic nature of our conditions, given the similarity in the calculated kinetic barriers for the 5- and 6-membered-ring products. At variance, when the process is carried out in the presence of Cs^+, the regioselectivity of the process takes place under kinetic control as well. Further studies are currently ongoing in our laboratories to extend the scope of this approach to secondary and aromatic amines.

Acknowledgements

Funding from Academy of Finland, Magnus Ehrnrooth Foundation, and TES - Tekniikan Edistämissäätiö is gratefully acknowledged. I.F. is also grateful for financial support from the Spanish MINECO (grants CTQ2010–20714-C02–01/BQU and Consolider-Ingenio 2010, CSD2007–00006) and CAM (grant S2009/PPQ-1634, AVANCAT).

Keywords: 2-oxazolidones · antibiotics · carbon dioxide activation · carbon dioxide fixation · density functional calculations

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Received: February 26, 2014
Published online on ■■ ■■, 0000

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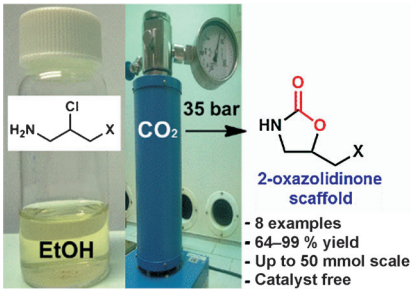

The reaction of β- and γ-haloamines with carbon dioxide to give pharmaceutically relevant cyclic urethanes was found to proceed efficiently in the presence of a base and in the absence of catalyst (see figure). After optimization of reaction conditions, the system was expanded to a variety of haloamines, even at multigram scale. The reaction was further studied in silico by DFT calculations.

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