Synthesis of oxazolidinones in supercritical CO$_2$
under heterogeneous catalysis

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Abstract—Basic alumina efficiently promotes the reaction of propargylamines with scCO$_2$ for the synthesis of variously substituted oxazolidinones that, after catalyst filtration, are easily isolated by methanol crystallization.

Oxazolidinones are important heterocyclic compounds showing a large application as intermediates and chiral auxiliaries in organic synthesis, and as antibacterial drugs in pharmaceutical chemistry. The three main strategies for the preparation of oxazolidinones are represented by (i) the reaction of aminoalcohols with phosgene, urea, or dialkyl carbonates, (ii) the insertion of carbon dioxide in the aziridine moiety, and (iii) the reaction of propargylamines (or propargylic alcohols and amines) with carbon dioxide.

As a part of our program on the development of eco-friendly and high atom economy syntheses of fine chemicals through heterogeneous catalysis, we were particularly interested in methodologies (ii) and (iii). These reactions in fact, represent good examples of green processes involving carbon dioxide as a C$_1$ source.

In addition to its intrinsic eco-compatibility, CO$_2$ offers advantages in terms of costs, availability, and easy separation from reaction mixtures. However, due to the inert nature of CO$_2$, its activation and incorporation into organic substrates still remain a difficult target.

We wish to report herein the use of commercial basic alumina as an efficient catalyst for the reaction of propargylamines with CO$_2$ carried out under supercritical conditions (scCO$_2$). Accordingly, variously substituted oxazolidinones can be prepared. On the basis of our previously reported results on the cycloaddition of CO$_2$ to epoxides for cyclic carbonate formation, organic bases such as trialkylamine and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) supported on silica [named SiO$_2$–(CH$_2$)$_3$–NEt$_2$ and SiO$_2$–TBD], were initially used to promote the model reaction between N-benzyl-1,1-dimethyl-propargyl amine 1a and scCO$_2$ (Table 1, entries a and b).

Experiments were carried out in a stainless steel autoclave (45 ml): a mixture of 1a (2 mmol) and the organic supported catalyst (5 mol % with respect to 1a) was pressurized with CO$_2$ (80 bar), and heated at 90 °C under magnetic stirring for 21 h. The more basic TBD-supported catalyst afforded better results in terms of yield and selectivity of product 3a with respect to the SiO$_2$–NEt$_2$ (TBD pK$_a$ = 25; Et$_3$N pK$_a$ = 11).

Nevertheless, the main problem with these catalysts was their deactivation on recycling, for example, the following yields were achieved with SiO$_2$–TBD: 1st cycle 88%, 2nd cycle 70%, 3rd cycle 62%, and 4th cycle 45%. Probably, part of the organic moiety of the catalyst was lost because of the quite high reaction temperature. An
hypothesis which was confirmed by FT-IR analyses: a decrease of the signals of the TBD moiety (1600–1400 cm$^{-1}$) was observed after each catalytic run.

To overcome this drawback, we decided to test commercially available solid bases such as alumina (Merck) and hydrotalcites (Pural) [0.4 g each], under the same reaction conditions. All the catalysts afforded $N$-benzyl-4,4-dimethyl-5-methylene-2-oxazolidinone 3a as the sole product (selectivities >97%). Basic alumina was a better catalyst (Table 1, entry e) with respect to basic anionic clays (Table 1, entries c and d; MG30 and MG70: MgO/Al$_2$O$_3$ ratio of 30/70 and 70/30, respectively).

The good performance of basic alumina could be ascribed to the presence of ‘superficial’ carbonate species (4) originated by electrostatic interactions between CO$_2$ and the oxygen atoms of the solid framework (Scheme 1).$^{19}$

The reaction of propargylamine 1a with carbonate 4 may proceed through intermediate 5a that finally produces the desired oxazolidinone 3a. This last step follows a 5-exo-dig cyclization process according to the Baldwin rules for digonal systems.$^{20}$

The effect of the reaction temperature was then examined (Fig. 1). The increase of the temperature from 90 to 150 °C increased the conversion of propargylamine up to 95%, while the excellent selectivity (>97%) toward compound 3a, was preserved.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargylamine 1</th>
<th>Product 3</th>
<th>Yield [Selectivity] (%)</th>
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<tbody>
<tr>
<td>a</td>
<td>$\text{N-CH}_2\text{Ph}$</td>
<td>$\text{H}$</td>
<td>Me</td>
</tr>
<tr>
<td>b</td>
<td>$\text{N-(CH}_2\text{Ph)}$</td>
<td>$\text{H}$</td>
<td>Me</td>
</tr>
<tr>
<td>c</td>
<td>$\text{N-(CH}_4\text{Ph)}$</td>
<td>$\text{H}$</td>
<td>Me</td>
</tr>
<tr>
<td>d</td>
<td>$\text{Ph-}$</td>
<td>$\text{N}$</td>
<td>$\text{H}$</td>
</tr>
<tr>
<td>e</td>
<td>$\text{N-(CH}_2\text{CH}_3)$</td>
<td>$\text{H}$</td>
<td>Me</td>
</tr>
<tr>
<td>f</td>
<td>$\text{N-(CH}_5\text{CH}_3)$</td>
<td>$\text{H}$</td>
<td>Me</td>
</tr>
</tbody>
</table>

Scheme 1. Reaction pathway for the formation of $N$-benzyl-4,4-dimethyl-5-methylene-2-oxazolidinone.
In a subsequent experiment, we observed that at 150 °C, the reaction of 1a with scCO2 took place also with a lower amount (0.2 g) of alumina: the same high yield (96%) in 3a was obtained. Below this quantity of catalyst (<0.2 g), a longer reaction time (more than 48 h) was necessary to get the same result.

In all cases, after each cycle, the basic alumina could be simply recovered by filtration, and reused without any thermal activation, for at least seven runs (96, 95, 96, 94, 95, 97, and 96% yield, respectively). Finally, the reactions of CO2 with terminal propargylamines were investigated (Table 2, entries a–c and e,f). The corresponding oxazolidinones with exocyclic double bonds were obtained in acceptable to good yields (66–96%) and with excellent selectivities (93–94, 95, 97, and 96% yield, respectively).

In conclusion we have shown that alumina, able to promote a large variety of organic reactions, can also be utilized as an efficient catalyst for the highly selective preparation of oxazolidinones. Moreover, the absence of VOC, the use of CO2 as solvent–reagent and the possibility to recycle the catalyst for several runs, make this approach practical and environmentally acceptable.

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References and notes

21. Synthesis of oxazolidinones 3a–c and 3e,f: the selected amine (2 mmol) and basic alumina (0.2 g) were charged in a small autoclave (45 ml). The autoclave was washed twice with CO2, then CO2 (80 bar) was introduced. The reaction mixture was stirred for 21 h at 150 °C; the autoclave was cooled to room temperature, the catalyst was separated by Büchner filtration and washed with hot methanol. The crude was purified by crystallization (MeOH). Spectral data of known oxazolidinones 3a, 3e were in accordance with the literature data.74
N-Phenethyl-4,4-dimethyl-5-methylene-2-oxazolidinone 3b: mp 71–72 °C (from MeOH) (Found: C, 72.20; H, 7.31; N, 6.15. Calcd. for C12H18NO2: C, 73.62; H, 7.42; N, 6.06); δH (300 MHz; CDCl3, Me4Si): 1.28 (6H, s, 2CH3), 2.99 (2H, t, J = 7.4 Hz, CH2Ph), 3.33 (2H, t, J = 7.4 Hz, CH2N), 4.18 (1H, d, J = 3.3 Hz, 1/2CH3), 4.63 (1H, d, J = 3.3 Hz, 1/2CH3), 7.2–7.3 (5H, m, Ar), m/z 231 (M+, 18), 216 (10), 140 (100), 91 (19).
N-Phenylbutyl-4,4-dimethyl-5-methylene-2-oxazolidinone 3c: mp 87–88 °C (from MeOH) (Found: C, 74.11; H, 8.05; N, 5.49. Calcd. for C14H21NO2: C, 74.20; H, 8.17; N,
5.41). $\delta_H$ (300 MHz; CDCl$_3$; Me$_4$Si): 1.37 (6H, s, 2CH$_3$), 1.6–1.7 (4H, m, CH$_2$CH$_3$), 2.6–2.7 (2H, m, CH$_2$Ph), 3.1–3.2 (2H, m, CH$_2$N), 4.21 (1H, d, $J = 3.3$ Hz, 1/2CH$_2$), 4.63 (1H, d, $J = 3.3$ Hz, 1/2CH$_2$), 7.1–7.6 (5H, m, Ar). $m/z$ 259 ($M^+$, 24), 244 (29), 112 (45), 91 (100).

N-Hexyl-5-methylene-2-oxazolidinone 3f: bp 110–111 °C (0.02 mm Hg) (Found: C, 65.52; H, 9.26; N, 7.74. Calcd. for C$_{10}$H$_{17}$NO$_2$: C, 65.63; H, 9.36; N, 7.65). $\delta_H$ (300 MHz; CDCl$_3$; Me$_4$Si): 0.88 (3H, t, $J = 6.7$ Hz, CH$_3$), 1.2–1.3 (4H, m, CH$_3$CH$_2$CH$_2$), 1.5–1.6 (4H, m, NCH$_2$CH$_2$CH$_2$), 3.29 (2H, t, $J = 7.3$ Hz, CH$_2$CH$_2$N), 4.14 (2H, t, $J = 2.6$ Hz, NCH$_2$C═CH$_3$), 4.27 (1H, d, $J = 2.6$ Hz, 1/2CH$_2$), 4.73 (1H, d, $J = 2.6$ Hz, 1/2CH$_2$). $m/z$ 183 ($M^+$, 34), 140 (13), 112 (100).