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Synthesis of oxazolidinones in supercritical CO_2 under heterogeneous catalysis

Raimondo Maggi,[a,*] Chiara Bertolotti,[a] Emilia Orlandini,[a] Chiara Oro,[a] Giovanni Sartori[a] and Maurizio Selva[b]

[a] *'Clean Synthetic Methodologies Group', Dipartimento di Chimica Organica e Industriale dell'Università, and Consorzio Interuniversitario 'La Chimica per l'Ambiente' (INCA), UdR di Parma2, Viale G.P. Usberti 17A, I-43100 Parma, Italy*

[b] *Dipartimento di Scienze Ambientali dell'Università Ca' Foscari, and Consorzio Interuniversitario 'La Chimica per l'Ambiente' (INCA), UdR di Venezia, Calle Larga S. Marta 2137, I-30123 Venezia, Italy*

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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[1] and chiral auxiliaries[2] in organic synthesis, and as antibacterial drugs in pharmaceutical chemistry.[3] The three main strategies for the preparation of oxazolidinones are represented by (i) the reaction of aminoalcohols with phosgene,[4] urea,[5] or dialkyl carbonates,[6] (ii) the insertion of carbon dioxide in the aziridine moiety,[7] and (iii) the reaction of propargylamines (or propargylic alcohols and amines) with carbon dioxide.[8]

As a part of our program on the development of eco-friendly and high atom economy[9] syntheses of fine chemicals through heterogeneous catalysis,[10] 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.[11] However, due to the inert nature of CO_2, its activation and incorporation into organic substrates still remain a difficult target.[12]

We wish to report herein the use of commercial basic alumina as an efficient catalyst for the reaction of propargylamines[13–16] 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,[17] 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],[18] 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 $pK_b = 25$; Et_3N $pK_b = 11$).

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

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Keywords: Carbon dioxide; Heterogeneous catalysis; Oxazolidinones.

* Corresponding author. Tel.: +39 0521 905411; fax: +39 0521 905472; e-mail: raimondo.maggi@unipr.it

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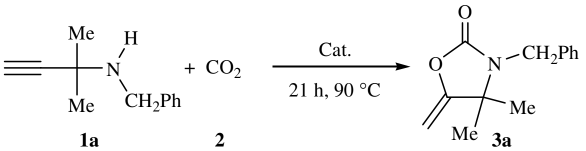
Table 1. *N*-Benzyl-4,4-dimethyl-5-methylen-2-oxazolidinone synthesis promoted by heterogeneous basic catalysts



1a **2** **3a**

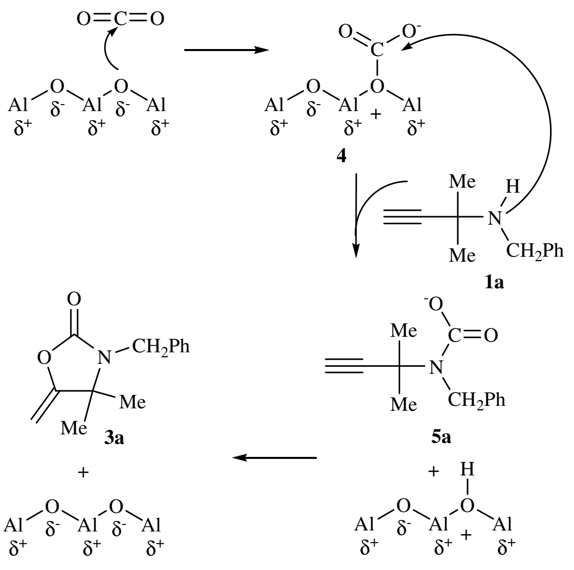
Entry	Catalyst	**3a** Yield (%)	**3a** Selectivity (%)
a	SiO_2–$(CH_2)_3$–NEt_2[a]	72	96
b	SiO_2–TBD[a]	88	99
c	Hydrotalcite MG30	67	97
d	Hydrotalcite MG70	58	98
e	Basic alumina	85	98

[a] The amounts of the catalysts were 0.09 g for SiO_2–NEt_2 and 0.11 g for SiO_2–TBD, corresponding to the same amount of supported base (0.10 mmol).

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-methylen-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_2O_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]



Scheme 1. Reaction pathway for the formation of *N*-benzyl-4,4-dimethyl-5-methylen-2-oxazolidinone.

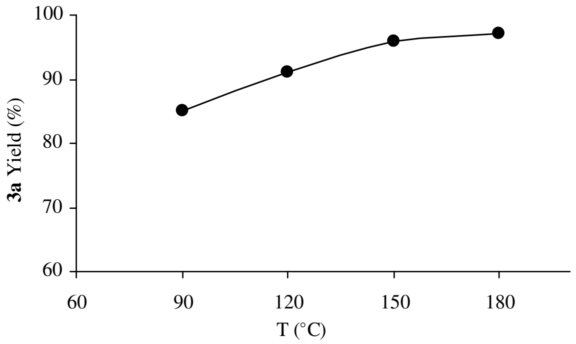
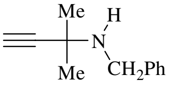
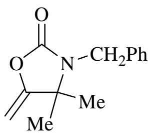
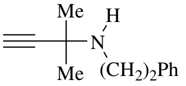
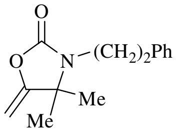
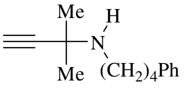
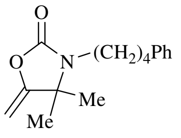
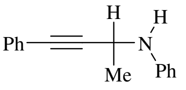
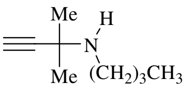
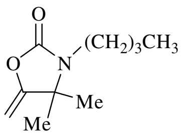
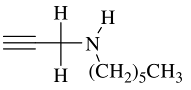
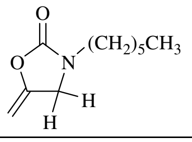


Figure 1. Temperature effect on the *N*-benzyl-4,4-dimethyl-5-methylen-2-oxazolidinone synthesis. $P(CO_2) = 80$ bar; $t = 21$ h; $Al_2O_3 = 0.4$ g.

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 2. Synthesis of variously substituted oxazolidinones promoted by basic alumina

Entry	Propargylamine **1**	Product **3**	Yield [Selectivity] (%)
a			96 [99]
b			70 [98]
c			66 [93]
d			0 [—]
e			67 [95]
f			87 [96]

In a subsequent experiment, we observed that at 150 °C, the reaction of **1a** with $scCO_2$ 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 CO_2 with terminal propargylamines were investigated (Table 2, entries a–c and e, f).[21] The corresponding oxazolidinones with exocyclic double bonds were obtained in acceptable to good yields (66–96%) and with excellent selectivities (93–99%): after separation of the catalyst by filtration they are easily isolated from the reaction crude by methanol crystallization. On the contrary, when a disubstituted alkyne was utilized (Table 2, entry d), the desired product was not detected, suggesting that the present methodology could be specific for terminal propargylamines.

In conclusion we have shown that alumina, able to promote a large variety of organic reactions,[22] can also be utilized as an efficient catalyst for the highly selective preparation of oxazolidinones. Moreover, the absence of VOC, the use of CO_2 as solvent–reagent and the possibility to recycle the catalyst for several runs, make this approach practical and environmentally acceptable.

Acknowledgements

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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 CO_2, then CO_2 (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.[8c]
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 $C_{14}H_{17}NO_2$: C, 72.29; H, 7.42; N, 6.06). δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.28 (6H, s, $2CH_3$), 2.99 (2H, t, $J = 7.4$ Hz, CH_2Ph), 3.33 (2H, t, $J = 7.4$ Hz, CH_2N), 4.18 (1H, d, $J = 3.3$ Hz, $1/2CH_2$), 4.63 (1H, d, $J = 3.3$ Hz, $1/2CH_2$), 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 $C_{16}H_{21}NO_2$: C, 74.20; H, 8.17; N,

5.41). δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.37 (6H, s, $2CH_3$), 1.6–1.7 (4H, m, CH_2CH_2), 2.6–2.7 (2H, m, CH_2Ph), 3.1–3.2 (2H, m, CH_2N), 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). δ_H (300 MHz; $CDCl_3$; Me_4Si): 0.88 (3H, t, $J = 6.7$ Hz, CH_3), 1.2–1.3 (4H, m, $CH_3\mathit{CH_2CH_2}$), 1.5–1.6 (4H, m, $NCH_2\mathit{CH_2CH_2}$), 3.29 (2H, t, $J = 7.3$ Hz, $CH_2\mathit{CH_2}N$), 4.14 (2H, t, $J = 2.6$ Hz, $N\mathit{CH_2}C{=}CH_2$), 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).

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