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Bypassing the Inertness of Aziridine/CO<sub>2</sub> Systems to Access 5-Aryl-2-Oxazolidinones: Catalyst-Free Synthesis Under Ambient Conditions

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*Published Version:*

Bresciani G., Antico E., Ciancaleoni G., Zacchini S., Pampaloni G., Marchetti F. (2020). Bypassing the Inertness of Aziridine/CO<sub>2</sub> Systems to Access 5-Aryl-2-Oxazolidinones: Catalyst-Free Synthesis Under Ambient Conditions. CHEMSUSCHEM, 13(20), 5586-5594 [10.1002/cssc.202001823].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/782544> since: 2022-08-24

*Published:*

DOI: <http://doi.org/10.1002/cssc.202001823>

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(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

G. Bresciani, E. Antico, G. Ciancaleoni, S. Zacchini, G. Pampaloni, F. Marchetti, "Bypassing the Inertness of Aziridine/CO<sub>2</sub> Systems to Access 5-Aryl-Oxazolidones: Catalyst-Free Synthesis Under Ambient Conditions", *ChemSusChem*, **2020**, *13*, 5586-5594.

The final published version is available online at:

<https://doi.org/10.1002/cssc.202001823>

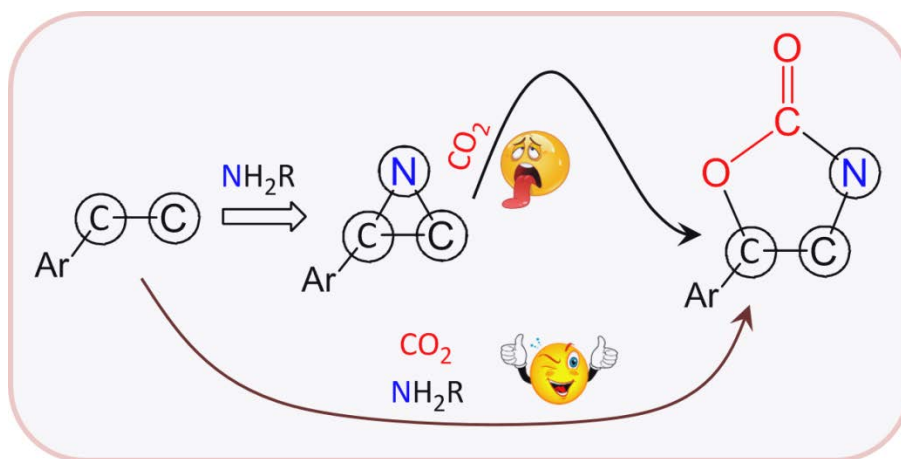
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# Bypassing the Inertness of Aziridine/ $\text{CO}_2$ Systems to Access 5-Aryl-2-Oxazolidinones: Catalyst-Free Synthesis Under Ambient Conditions

Giulio Bresciani, Emanuele Antico, Gianluca Ciancaleoni, Stefano Zacchini, Guido Pampaloni, Fabio Marchetti

The largely investigated catalytic process affording 5-aryl-2-oxazolidinones by two-step assembly of a  $\text{C}_2$  precursor with primary amine and carbon dioxide is replaced by the catalyst-free, direct addition of the amine/ $\text{CO}_2$  adduct to the  $\text{C}_2$  unit in isopropanol or water.



# **Bypassing the Inertness of Aziridine/CO<sub>2</sub> Systems to Access 5-Aryl-2-Oxazolidinones: Catalyst-Free Synthesis Under Ambient Conditions**

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## Abstract

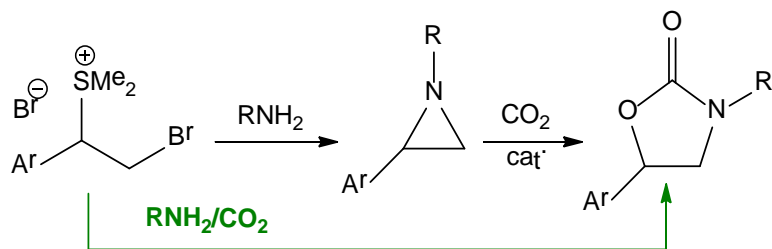
The development of sustainable synthetic routes to access valuable oxazolidinones via CO<sub>2</sub> fixation is currently a hot topic of research, and the aziridine/carbon dioxide coupling has aroused a considerable interest. This reaction is featured by a high activation barrier, so to require a catalytic system, and may present some other critical issues. Here, we describe the straightforward gram-scale synthesis of a series of 5-aryl-oxazolidinones at ambient temperature and atmospheric CO<sub>2</sub> pressure, in the absence of any catalyst/co-catalyst and using isopropanol or water as solvent. The key to this innovative procedure consists in the direct transfer of the pre-formed amine/CO<sub>2</sub> adduct (carbamate) to common aziridine precursors (dimethylsulfonium salts), replacing the classical sequential addition of amine (intermediate isolation of aziridine) and then CO<sub>2</sub>. The reaction mechanism has been elucidated by NMR studies and DFT calculations applied to model cases.

**Keywords:** carbon dioxide activation; sustainability; catalyst free organic synthesis; oxazolidinones; aziridines.

## Introduction

Carbon dioxide is a nontoxic and ubiquitous substance associated to environmental issues, and its utilization as a C<sub>1</sub> synthon for organic synthesis, replacing hazardous compounds, is an ultimate goal of research, in the perspective of a sustainable world.<sup>1</sup> In particular, oxazolidinones are five-membered heterocyclic compounds that find important applications for their biological activity<sup>2</sup> and as synthetic precursors to various natural and bioactive compounds.<sup>3</sup> The recent years have witnessed an intense investigation aimed to develop new straightforward synthetic processes to access such fine chemicals exploiting CO<sub>2</sub> fixation routes.<sup>1b,f,2a,4</sup> All of the reported methods require the use of a catalyst unless high CO<sub>2</sub> pressure or supercritical carbon dioxide is employed.<sup>5</sup> Thus, unsaturated amines,<sup>6,7</sup> haloamines<sup>8</sup> and amino-alcohols<sup>6d,9</sup> have been investigated for their cyclization reactions with CO<sub>2</sub> to afford 2-oxazolidinones; even three-component systems may be effective, and in this regard, several epoxide/amine,<sup>10</sup> alkyne/amine,<sup>11</sup> and alkene/amine<sup>12</sup> combinations have been considered. Repo and co-workers demonstrated that a series of N-aryl-2-oxazolidinones are accessible from the one-pot carboxylation of aniline/1,2-dibromoethane in organic solvents under mild conditions.<sup>13</sup> In this scenario, the coupling of CO<sub>2</sub> with aziridines remains an intriguing and intensively investigated approach.<sup>1b,g,6d,14</sup> However, this reaction is featured by a high activation barrier,<sup>15</sup> therefore both metal<sup>16</sup> and organocatalysts<sup>17</sup> have been explored to the purpose. It should be remarked that the engagement of pressurized carbon dioxide is usually necessary, instead examples of efficient aziridine/CO<sub>2</sub> coupling at ambient temperature and pressure are rare and inevitably associated to either a catalyst,<sup>18</sup> specialized

equipment<sup>19</sup> or limited substrate scope.<sup>20</sup> Furthermore, the catalytic systems may present some critical issues in terms of catalyst loading and the need for a halide co-catalyst (Lewis base) and toxic solvents.<sup>14</sup> It is quite common in the literature that aziridines employed for the cyclization reaction with CO<sub>2</sub> are prepared with a convenient procedure whereby a sulfonium bromide salt, derived from styrene or related ring-substituted species, provides the C<sub>2</sub> unit of the three-membered heterocycle (Scheme 1).<sup>16a-b,17a-c,21</sup> This protocol allows to access a variety of 2-aryl-aziridines using an excess of amine, and conversion into the corresponding aryl-oxazolidinones follows. In principle, two possible regioisomers can be finally obtained, bearing the substituted ring carbon bound to either oxygen (5-aryl-2-oxazolidinone) or nitrogen (4-aryl-2-oxazolidinone), and full regioselectivity is not often realisable.<sup>14,16a-b,22</sup> Looking at the synthetic route in Scheme 1 and at variance to the literature, we wondered whether the two-step incorporation of the carbamate unit {OC(=O)NR}<sup>23</sup> (from RNH<sub>2</sub> and CO<sub>2</sub>) within the final five-membered ring could occur in one pot, avoiding the intermediate aziridine step. Our idea stemmed from the largely documented evidence that carbon dioxide and amines easily form carbamate adducts.<sup>24</sup> Thus, the present work describes a novel and simple CO<sub>2</sub>-fixation strategy to synthesize 5-aryl-2-oxazolidinones bypassing the inertness of the aziridine/carbon dioxide system: exceptional simplicity and increased sustainable value respect to existing procedures is guaranteed by operating at ambient conditions (ambient temperature, atmospheric CO<sub>2</sub> pressure) and the complete absence of any catalyst/co-catalyst.



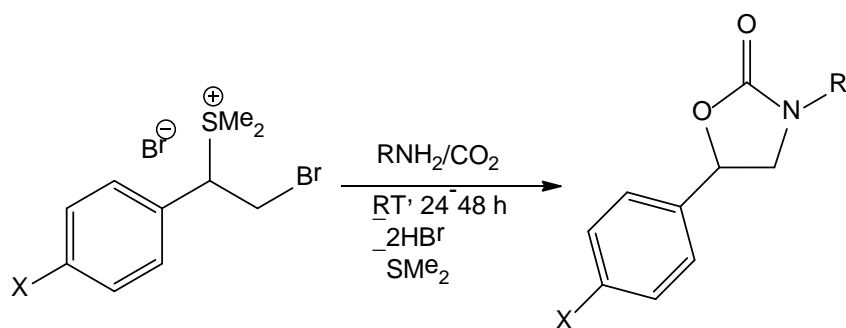
**Scheme 1.** Black: widely investigated synthetic pathway to 5-aryl-2-oxazolidinones via aziridine/CO<sub>2</sub> coupling using a variety of catalytic systems and operating at variable reaction conditions; Green: unprecedented strategy described in this work (ambient temperature and CO<sub>2</sub> pressure; solvent = isopropanol or water; absence of metal/catalyst/nucleophile; full regioselectivity).

## Results and discussion

### 1. Synthesis and characterization of compounds.

In order to obtain 5-aryl-2-oxazolidinones (gram-scale synthesis), deaerated isopropanol saturated with carbon dioxide was left reacting with the primary amine up to completion. Following addition of the sulfonium salt (**1-7**) in an optimal 1:4 molar ratio respect to the amine, the mixture was stirred for 24-48 hours at ambient temperature under CO<sub>2</sub> atmosphere from a balloon. The desired products **8-14**, except **8g**, **8h** and **10g**, were generally isolated after work-up in good to excellent yields (Scheme 2). In comparison, the use of water as solvent required 6 equivalents of the amine and longer reaction times to achieve satisfying yields (see Table S1

in the Supporting Information for details). Nonetheless, water revealed to be the appropriate choice to incorporate hydrazine and ethylenediamine, since the carbamates of these amines are not soluble in isopropanol, and thus **8g**, **8h** and **10g** were obtained. The reaction leading to **8b** was selected as a model one to test further reaction solvents, and isopropanol resulted to be the best option (see SI, page S32). A comparative view of yields after variable times (Table S1) suggests that electronic and steric factors associated to the amine R substituent are influencing, and the best results are achieved with a compromise of electron donor properties and bulkiness. For instance, R = Me is beneficial compared to R = H, while lower yields have been achieved with R = Cy, and our attempts to obtain oxazolidinones from tert-butylamine and aniline were not successful.



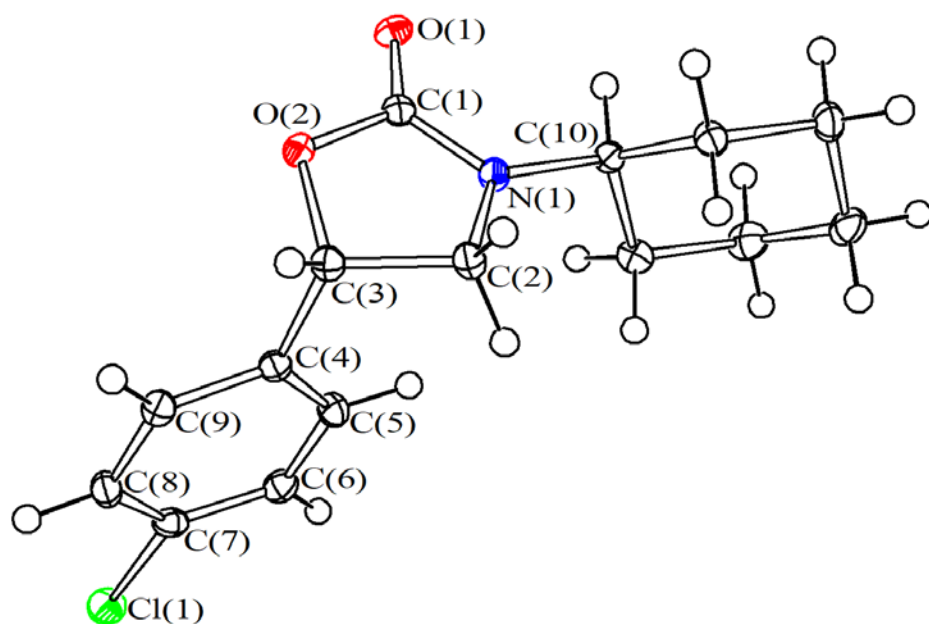
	X	R		Time (h)	Yield% <sup>a</sup>
<b>1</b>	H	H	<b>8a</b>	48	62
		CH <sub>3</sub>	<b>8b</b>	24	96
		CH <sub>2</sub> CH <sub>3</sub>	<b>8c</b>	48	91
		CH(CH <sub>3</sub> ) <sub>2</sub>	<b>8d</b>	48	65
		Cy	<b>8e</b>	48	60
		CH <sub>2</sub> Ph	<b>8f</b>	48	74
		NH <sub>2</sub>	<b>8g</b>	48	87 <sup>b</sup>
		CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>8h</b>	48	71 <sup>b</sup>
		CH <sub>2</sub> CH <sub>2</sub> OH	<b>8i</b>	48	95
<b>2</b>	CH <sub>3</sub>	H	<b>9a</b>	48	58
		CH <sub>3</sub>	<b>9b</b>	24	68
		CH <sub>2</sub> CH <sub>3</sub>	<b>9c</b>	48	84
		CH(CH <sub>3</sub> ) <sub>2</sub>	<b>9d</b>	48	50
		Cy	<b>9e</b>	48	44
		CH <sub>2</sub> Ph	<b>9f</b>	48	68
<b>3</b>	Cl	H	<b>10a</b>	48	67
		CH <sub>3</sub>	<b>10b</b>	24	92
		CH <sub>2</sub> CH <sub>3</sub>	<b>10c</b>	48	87
		CH(CH <sub>3</sub> ) <sub>2</sub>	<b>10d</b>	48	79
		Cy	<b>10e</b>	48	69

		CH <sub>2</sub> Ph	<b>10f</b>	48	87
		NH <sub>2</sub>	<b>10g</b>	48	88 <sup>b</sup>
		CH(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	<b>10h</b>	48	88
<b>4</b>	F	H	<b>11a</b>	48	65
		CH <sub>3</sub>	<b>11b</b>	24	92
		CH(CH <sub>3</sub> ) <sub>2</sub>	<b>11d</b>	48	72
		CH(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	<b>11h</b>	48	82
<b>5</b>	OMe	CH <sub>3</sub>	<b>12b</b>	24	98
		CH <sub>2</sub> CH <sub>3</sub>	<b>12c</b>	48	92
<b>6</b>	NO <sub>2</sub>	CH <sub>3</sub>	<b>13b</b>	24	98
		CH <sub>2</sub> CH <sub>3</sub>	<b>13c</b>	48	92
<b>7</b>	CO <sub>2</sub> Me	CH <sub>3</sub>	<b>14b</b>	24	89
		CH <sub>2</sub> CH <sub>3</sub>	<b>14c</b>	48	67

**Scheme 2.** One pot synthesis of 5-aryl-2-oxazolidinones from (2-bromo-1-arylethyl)dimethylsulfonium bromide, primary amines (4 eq. respect to **1-7**; Cy = cyclohexyl, C<sub>6</sub>H<sub>11</sub>) and CO<sub>2</sub> in isopropanol. T = 298 K, pCO<sub>2</sub> = 1 atm. <sup>a</sup>Yields referred to isolated products. <sup>b</sup>Solvent H<sub>2</sub>O, 6 eq. of amines respect to **1,3**.

All the compounds **8-14** were fully characterized by elemental analysis, IR and multinuclear NMR spectroscopy. According to the respective <sup>1</sup>H NMR spectra, **8-14** are exclusively obtained as a single regioisomer (no traces of 4-aryl-2-oxazolidinones). In addition, the molecular structures of **10a** and **10e** were elucidated by single-crystal X-ray diffraction studies; the representative structure of **10e** is shown in Figure 1, while a view of **10a** is supplied as Supporting Information (Figure S1).



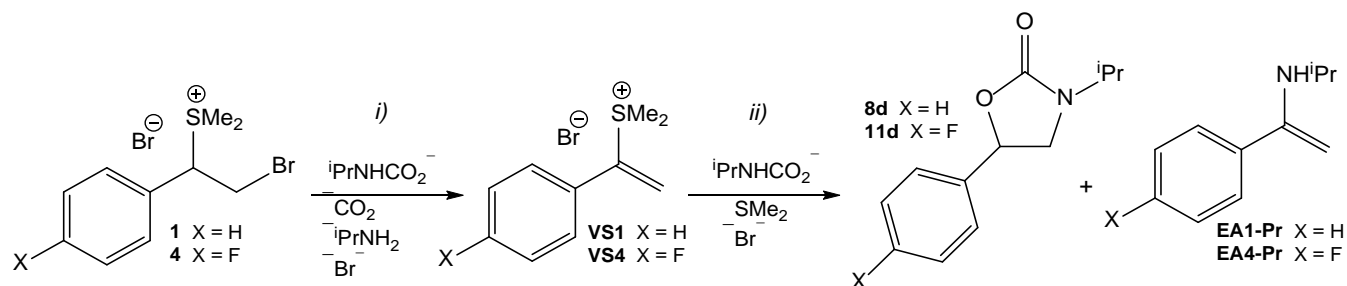


**Figure 1.** Molecular structure of **10e**, with labelling. Displacement ellipsoids are at the 50% probability level. H-atoms have been omitted for clarity. Main bond distances (Å) and angles (°): C(1)-O(1) 1.2124(19), C(1)-O(2) 1.3663(18), C(1)-N(1) 1.3465(19), N(1)-C(2) 1.4522(18), C(3)-O(2) 1.4695(18), C(2)-C(3) 1.534(2), C(3)-C(4) 1.507(2), C(7)-Cl(1) 1.7429(15), N(1)-C(10) 1.4633(19), O(2)-C(1)-N(1) 121.39(13), C(1)-N(1)-C(2) 112.21(12), N(1)-C(2)-C(3) 101.24(12), C(2)-C(3)-O(2) 103.56(11), C(3)-O(2)-C(1) 109.09(11), C(2)-C(3)-C(4) 116.07(13).

Note that **8a-g**, **9a-c**, **9e**, **10a-c**, **10e**, **10h** and **11a-b**, **12b-c** and **14b** were all previously synthesized by means of a catalytic system, often under not mild conditions. Instead, **8h-i**, **9d**, **9f**, **10d**, **10f-g**, **11d-h**, **13b-c** and **14c** are reported here for the first time. In particular, the classical procedure to access **8h-i** may be challenging due to elaborated protocols required for the preparation of the respective aziridine precursors,<sup>25</sup> or polymerization side-reactions favoured by the presence of the alcohol function.<sup>26</sup>

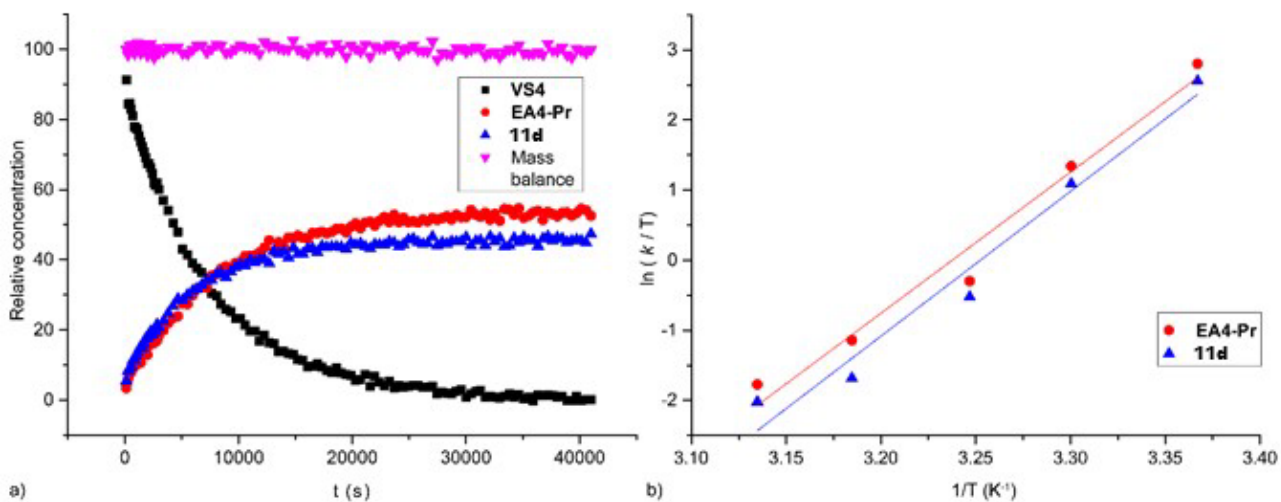
The route depicted in Scheme 2 consists in the preliminary formation of a CO<sub>2</sub>/amine adduct (carbamate), followed by assembly of the latter with the C<sub>2</sub> unit supplied by the (2-bromo-1-aryl)dimethylsulfonium bromide reagent.<sup>27</sup> For sake of comparison, a series of 5-aryl-oxazolidin-2-ones (including **8c,d,f** and **10h**) has been recently prepared by North and co-workers<sup>16b</sup> via the metal-catalysed reaction at 50 °C of CO<sub>2</sub> with aryl-aziridines, the latter being preliminarily obtained and isolated from (2-bromo-1-arylethyl)dimethylsulfonium bromide salts and an excess (up to 5 equivalents) of amine.<sup>21b,28</sup> Calculated E factors related to the synthesis of **8c** from **1** and NH<sub>2</sub>Et were approximately 2.2 and 2.5, respectively for the one pot procedure presented herein (procedure A in the SI) and the two-step one by North and co-workers<sup>16b</sup> (solvent wastes were not considered).

In order to investigate mechanistic and kinetic aspects, the reactions leading to **8d** and **11d** were monitored by NMR spectroscopy (see NMR studies in the SI). Thus, an excess of carbamate (from  $\text{NH}_2^i\text{Pr}/\text{CO}_2$ ) in aqueous solution was added to the precursor (**1** and **4**, respectively) in  $\text{D}_2\text{O}$  in an NMR tube.  $^1\text{H}$  and 2D-HMBC experiments revealed the progressive formation of (1-arylvinyl)dimethylsulfonium salts (**VS1**, **VS4**),<sup>29</sup> promoted by the basicity of the carbamate (Scheme 3, step i). This finding is in alignment with previous reports on the reactivity of **1** with Brønsted bases.<sup>30</sup>



**Scheme 3.** NMR-detected steps of the reaction of (2-bromo-1-aryl)dimethylsulfonium bromide with *N*-isopropyl carbamate in  $\text{D}_2\text{O}$  or  $\text{DMSO-d}_6$ . In  $\text{D}_2\text{O}$ , **EA** are not detected and **8d/11d** separate as an oily phase.

Due to severe resonance broadening determined by the separation of an organic phase containing the oxazolidinone product from the aqueous medium,<sup>31</sup> we repeated the NMR study in  $\text{DMSO-d}_6$ , where **8d** and **11d** are soluble. Thus, the reaction of **1/4** with  $\text{NH}_2^i\text{Pr}/\text{CO}_2$  proceeded much faster than in  $\text{D}_2\text{O}$ , affording almost immediately **VS1/VS4** (Figures S2-S5), which then slowly converted into two different species (Scheme 3, step ii): one corresponded to **8d/11d**, while the second species was identified as an enamine (**EA1-Pr/EA4-Pr**). Such enamines are featured by two diagnostic  $^1\text{H}$  NMR signals (e.g. for **EA4-Pr** at 5.49 and 4.98 ppm) correlating with the same carbon in the  $^{13}\text{C}$  spectrum (107.4 ppm); in addition, a 2D HMBC experiment highlighted that the amino-substituent is geminal respect to the phenyl ring, without any other long-range contact (Figures S6-S10). The kinetic profile for the reaction leading to **11d** (in  $\text{DMSO-d}_6$ ) could be elucidated by  $^{19}\text{F}$  NMR spectroscopy in the 297-319 K temperature range. The trend of [**11d**] and [**EA4-Pr**] concentrations as a function of time is fitted as an exponential growth ( $R^2 > 0.920$  in every case; Figures 2A and S11a-d), providing the values of the reaction kinetic constants at different temperatures (Table 1). Fitting the data with the Eyring equation, the linearity is quite good ( $R^2 > 0.958$ ; Figure 2B), and the activation enthalpies and entropies are comparable for the two products (**11d**:  $\Delta H^\ddagger = 10.4 \pm 1.1 \text{ kcal mol}^{-1}$ ,  $\Delta S^\ddagger = -38 \pm 6 \text{ cal mol}^{-1} \text{ K}^{-1}$ ; **EA4-Pr**:  $\Delta H^\ddagger = 10.2 \pm 1.0 \text{ kcal mol}^{-1}$ ,  $\Delta S^\ddagger = -40 \pm 7 \text{ cal mol}^{-1} \text{ K}^{-1}$ ).



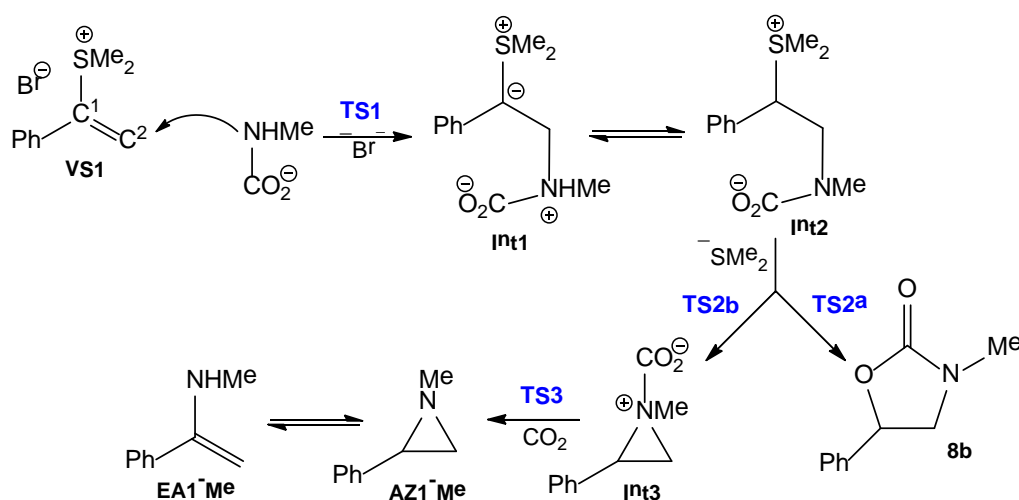
**Figure 2.** a) Concentration of intermediate (**VS4**) and products (**11d** and **EA4-Pr**) along the reaction of **4** with  $\text{NH}_2^i\text{Pr}/\text{CO}_2$  in  $\text{DMSO-d}_6$ , as a function of time ( $T = 297 \text{ K}$ ); b) Eyring plot related to **11d** and **EA4-Pr** ( $R^2 = 0.964$  and  $0.959$ , respectively).

**Table 1.** Kinetic reaction constants at different temperatures (solvent:  $\text{DMSO-d}_6$ ).

T (K)	$k_{8c}(\text{s}^{-1})$	$k_{\text{EA4-Pr}}(\text{s}^{-1})$
297	$4900 \pm 230$	$3800 \pm 150$
303	$1160 \pm 25$	$900 \pm 25$
308	$228 \pm 24$	$182 \pm 7$
313	$100 \pm 5$	$58 \pm 2$
319	$54 \pm 4$	$42 \pm 3$

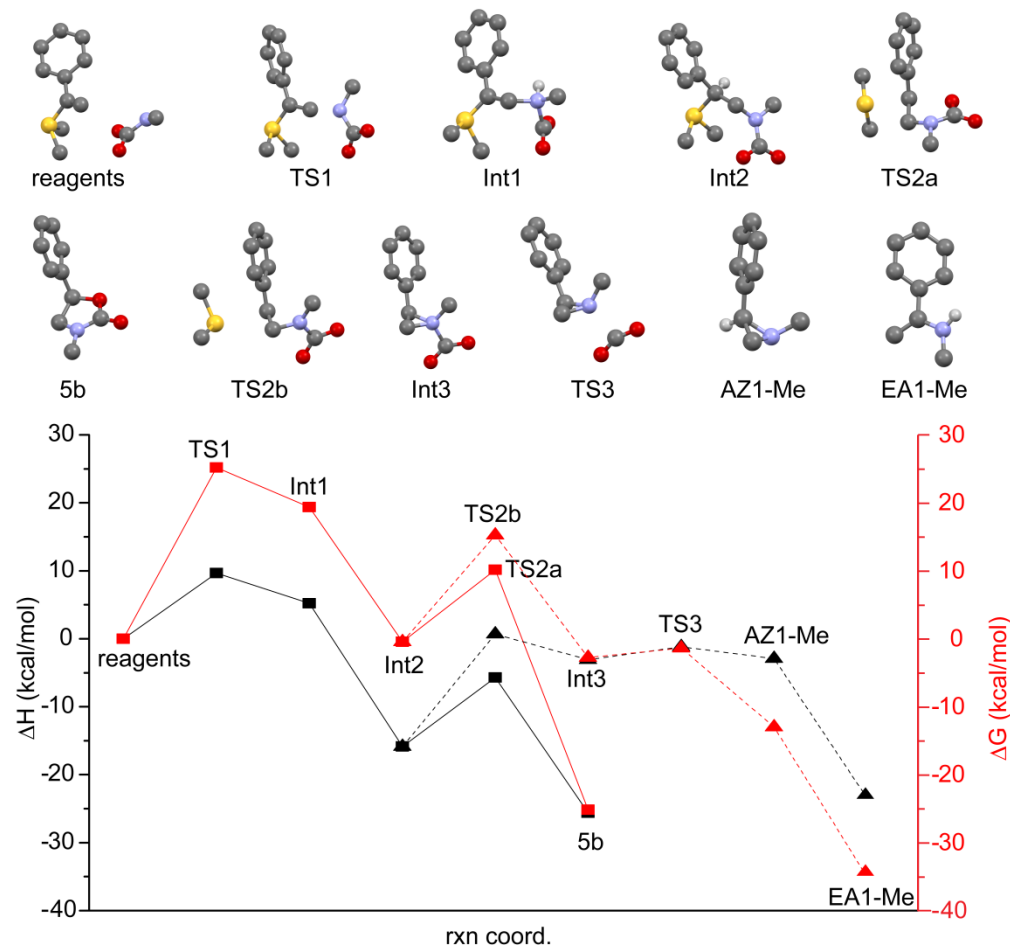
#### DFT calculations.

The reaction affording **8b**, via the preliminary formation of **VS1**,<sup>32</sup> was chosen as a model for detailed DFT calculations, and the overall proposed pathway is shown in Scheme 4.



**Scheme 4.** Proposed DFT mechanism for the reaction of dimethyl(1-phenylvinyl)sulfonium salt **VS1** (from **1**, see Scheme 3) with  $\text{NH}_2\text{Me}/\text{CO}_2$ ; relevant transition states in blue; water as solvent (conductor-like polarisable continuum model).

According to the DFT-computed energies (Figure 3), the rate determining step is the initial nucleophilic addition of the carbamate nitrogen to the less hindered alkenic carbon of **VS1** ( $\text{C}^2$ ), featured by an activation enthalpy of  $9.6 \text{ kcal mol}^{-1}$ . Limited to this key step, the calculation was repeated on the reaction of **VS4** with  $^i\text{PrNHCO}_2^-$  (DMSO as solvent, Scheme 3): the activation enthalpy resulted  $12.9 \text{ kcal mol}^{-1}$ , i.e. in reasonable agreement with the experimental value ( $10.4 \pm 1.1 \text{ kcal mol}^{-1}$ , see above).<sup>33</sup> While any alternative attack to  $\text{C}^1$  is prohibitive ( $\Delta G^\ddagger = 35 \text{ kcal mol}^{-1}$ ),  $\text{C}^2$ -O coupling involving one carbamate oxygen is theoretically possible ( $\Delta H^\ddagger = 9.1 \text{ kcal mol}^{-1}$ ), but the resulting species seems unable to evolve to any product. The intramolecular proton transfer converting **Int1** into **Int2** occurs through a high-energy transition state ( $\Delta G^\ddagger = 40.3 \text{ kcal mol}^{-1}$ ), therefore it is presumably assisted by the excess of carbamate in the solution. The subsequent C-O bond forming cyclization (**TS2a**) yields **8b** and resembles a previously proposed cyclization step for the formation of oxazolidinones from alkenes, chloramine-T and  $\text{CO}_2$ ;<sup>34</sup> the competitive, presumable formation of the enamine **EA1-Me** from **Int2** parallels the experimentally observed formation of **EA1-Pr** and **EA4-Pr** in DMSO (Scheme 3), and may be explained with a ring closure by the nitrogen atom (**TS2b**). The resulting aziridine **AZ1-Me** can rearrange to **EA1-Me** ( $\Delta G^\ddagger = 22 \text{ kcal mol}^{-1}$ ). In general, the route via **TS2b** in water is probably disfavoured since the various equilibria are shifted toward the oxazolidinone product, precipitating from the aqueous reaction medium where instead enamines of the type  $\text{CH}_2=\text{C}(\text{Ar})(\text{NHR})$  are expected to be soluble.<sup>35</sup> According to  $^1\text{H}$  NMR analyses of the crude mixtures, a minor amount of the relevant aziridine (<5%) is generally a side-product of the formation of **8-14**, however this fact might be most properly related to the direct reaction of the amine with **1-7**.



**Figure 3.** (Down) DFT-computed energy paths for the formation of **8b** and **EA1-Me** from **VS1** and NH<sub>2</sub>Me/CO<sub>2</sub>. (Up) DFT-optimized geometries of the species involved in the mechanism; for the sake of clarity, most of hydrogen atoms are omitted.

Alternative, hypothetical reaction pathways were carefully examined by DFT calculations (Scheme S1): all of them exhibit higher activation barriers and are thus ruled out at ambient temperature (Figures S12-S14).

## Conclusions

The synthesis of valuable oxazolidinones from the coupling of aziridines with CO<sub>2</sub> has aroused a notable interest: the use of a catalytic system has been usually taken for granted, often associated to high CO<sub>2</sub> pressure and/or high temperature, and many efforts have been addressed to develop suitable metal catalysts pointing towards a more sustainable process. Herein, we have reported a novel method to access thirty-three 5-aryl-oxazolidinones (twelve reported for the first time) in a gram-scale, consisting in the preliminary facile fixation of CO<sub>2</sub> with NH<sub>2</sub>R, and subsequent reaction of the resulting carbamate with a C<sub>2</sub> synthon. The latter is widely employed in the literature to obtain aryl-oxazolidinones, but through a two-step route with the intermediate

isolation of 2-aryl-aziridines. Our innovative method overcomes the inertness of the aziridine/CO<sub>2</sub> system, and therefore does not require any type of promoter (catalyst or ring-opening nucleophile) and allows to operate under ambient temperature and atmospheric CO<sub>2</sub> pressure. Moreover, avoiding the aziridine-forming step is beneficial even considering that aziridines are toxic, potentially carcinogenic chemicals.<sup>14,36</sup>

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### Acknowledgements

We gratefully thank the University of Pisa for financial support (*Fondi di Ateneo 2018*).

### Supporting Information Available

Experimental procedures and characterization of products; X-ray studies; NMR studies; DFT calculations; NMR and IR spectra of products. Cartesian coordinates of the DFT structures are collected in a separated .xyz file. CCDC reference numbers 1967793 (**10a**) and 1967794 (**10e**) contain the supplementary crystallographic data for the X-ray studies reported in this paper. These data can be obtained free of charge at [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

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