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A convenient and inexpensive conversion of an aziridine to an oxazolidinone☆

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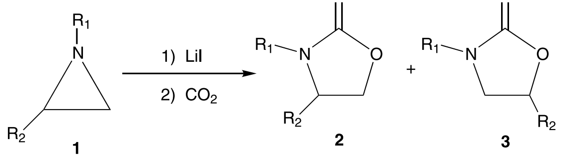
Abstract—The conversion of an aziridine to the corresponding oxazolidinone using only carbon dioxide and a catalytic amount of lithium iodide is discussed. In all cases, either no reaction occurred or a high yield of product was obtained. HMPA has been added to the reaction mixture, as needed, to drastically improve the regioselectivity. Net retention of stereochemistry between the starting aziridine and the product oxazolidinone was observed. © 2003 Elsevier Science Ltd. All rights reserved.

Oxazolidinones are important as chiral auxiliaries and as protecting groups in organic synthesis, as ligands for metal catalysts, and as biologically active pharmaceutical agents.[1–6] In spite of these facts, there are very few reports in the literature of the conversion of a readily available aziridine, such as **1**, and carbon dioxide (CO_2) into an oxazolidinone, such as **2** or **3** (Scheme 1).[7–11] The primary obstacles for this direct conversion are the relative inertness of carbon dioxide, which has been overcome by using a high pressure or electrolysis, and the large amount of polymer typically formed.[12–18] In contrast, carbon dioxide has been successfully utilized in the ring expansion of an epoxide to a carbonate.[19]

Due to our interest in the reactivity of aziridines,[20] we attempted the conversion of aziridine **1a** to oxazolidinone **2a**/**3a** using LiI/CO_2 and obtained a mixture of the two products in over 80% combined isolated yield, the very first time. Encouraged by these results, we have extended this reaction to a large number of aziridines to study the regiochemistry and the stereochemistry of this inexpensive and convenient conversion.



a	$R_1 = CH_2Ph$	$R_2 = CH_3$
b	$R_1 =$ pentyl	$R_2 = CH_3$
c	$R_1 = CH_2Ph$	$R_2 = Ph$
d	$R_1 = Ph$	$R_2 = Ph$
e	$R_1 = Ph$	$R_2 =$ pentyl

Scheme 1.

As shown in Scheme 1, in our first series of experiments, we have varied the R_1 and R_2 groups on the aziridine in order to determine the regiochemistry of this reaction. These reactions were run by heating aziridine **1** with LiI in THF to affect a ring opening, and then bubbling CO_2 into the THF solution for an extended period of time at room temperature to give the product. When the reaction of **1a** was run without the addition of LiI, or in the presence of $LiClO_4$ or I_2 in place of LiI, no product was obtained and the starting aziridine was recovered.

When R_1 and R_2 are both alkyl groups, as in **1a** and **1b**, we obtain about a 2:1 mixture of the two regioisomers of the product in approximately 85% overall yield. In contrast, when R_1 is an alkyl group and R_2 is a phenyl, we get, in almost quantitative yield, exclusively regioisomer **3**, i.e. only the more substituted carbon–nitrogen is carboxylated. Finally, when R_1 is a phenyl group, as in **1d** or **1e**, or for that matter, when R_1 is any electron-delocalizing group, no reaction is observed and the starting aziridine is isolated in high yield.

Two possible mechanisms for this reaction are shown in Scheme 2 for the conversion of **1a** to **2a**. In the first step, which requires refluxing conditions, the iodide opens the aziridine ring of **1a** to generate **4a**, which

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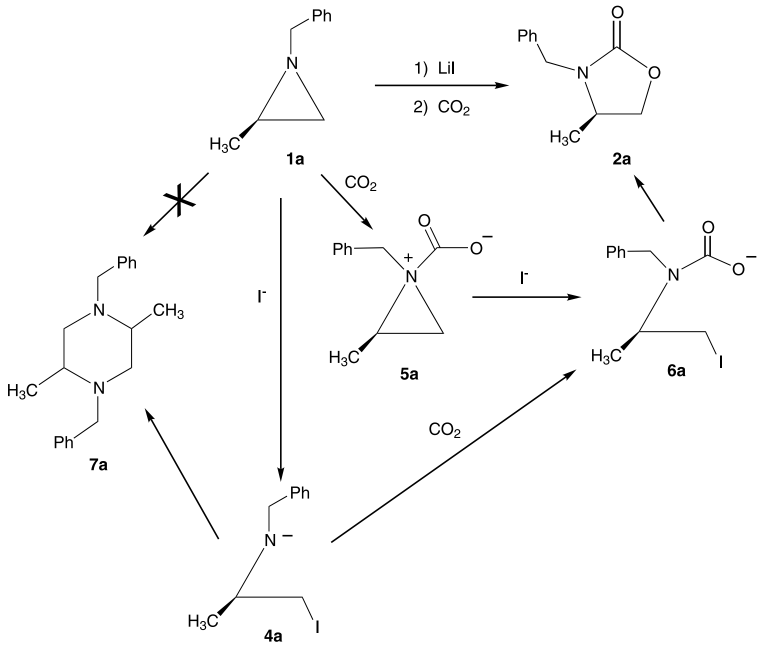


Scheme 2.

then reacts with CO_2 to give **6a**. Consistent with this mechanism, if the reaction is worked-up without the addition of CO_2, aziridine **1a** is not isolated but rather dimer **7a** is obtained. (Subjecting compound **1a** to the work-up conditions gives **1a** and none of **7a**.) However, as pointed out by a reviewer, for the reactions discussed below, in which the aziridine, LiI, and CO_2 are stirred at room temperature, it is likely that the CO_2 reacts first to give aziridinium **5a**, which then reacts with LiI to generate **6a**. In either case, **6a** ring closes to give the product **2a**. In both mechanisms, the regiochemistry is determined by the nucleophilic attack of the iodide. When the nitrogen is substituted by an electron-delocalizing group, the nitrogen is less nucleophilic and the reaction to form **6** probably does not occur.

Schemes 1 and 2 suggest that the reaction should be catalytic in LiI because it is not consumed in the reaction. In addition, Scheme 2 suggests that a higher pressure/concentration of CO_2 might allow for the more facile formation of intermediates **6d** and **6e**. Therefore, we changed the reaction conditions from two separate steps at atmospheric pressure to one step under a higher pressure. The aziridine, 0.25 equiv. of LiI, and an excess of powdered dry ice were mixed together in a sealed thick-walled flask. For the reactions of compounds **1a**, **1c**, **1d** and **1e**, the results from this higher-pressure reaction are no different from those discussed above for the CO_2 bubbling reaction.

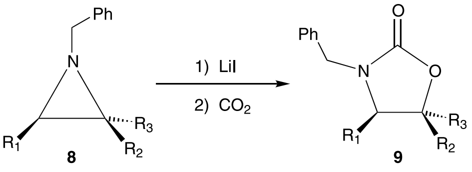
In an attempt to determine how little LiI could be used, we found for the reaction of aziridine **1c** to oxazolidinone **3c** as little as 5 mole percent of LiI will give over a 90% yield of the single product. Unfortunately, for the reaction of **1a** to **2a** and **3a**, the same 2:1 mixture of products was obtained regardless of the amount of LiI used.

In an effort to obtain only one product rather than a mixture from the reaction of **1a**, we added 1 equiv. of hexamethylphosphoramide (HMPA) as a co-solvent. HMPA has been shown to be a potent lithium-complexing agent. Many lithium-complexing agents have been shown to activate organolithium reagents by increasing the ion pair separation.[21] We hypothesized that by increasing the ion pair separation of the lithium iodide, the reaction would exhibit more S_N2 character, and therefore, a reduction in the mixture of regioisomers would occur.

The reaction of aziridine **1a** with lithium iodide and carbon dioxide under the higher pressure/concentration conditions with added HMPA generated oxazolidinone **2a** (97%) and only a very small amount of **3a** (3%, in a 90% overall yield). To further test our hypothesis, we ran the same reaction with compound **1b** and obtained oxazolidinone **2b** (95%) and only a very small amount of **3b** (5%, in a 90% overall yield). We also tried adding HMPA to the reactions of **1d** and **1e**, but unfortunately, still no reaction occurred.

To determine the stereochemistry of this conversion, we next tried the reactions shown in Scheme 3, under the CO_2 bubbling conditions. However, in all cases, either no reaction occurred or less than a 20% yield of product was obtained.

We then changed to the higher-pressure reaction conditions using a stoichiometric amount of LiI. The yields improved a great deal, but unfortunately, mixtures of *cis* and *trans* isomers of the products were formed. We thought that obtaining a stereochemical mixture might be due to a reaction intermediate in Scheme 2 undergoing multiple S_N2 reactions with the LiI to scramble the stereochemistry. Therefore, the conversion of **8** to **9**



a $R_1, R_2 = CH_2CH_2CH_2CH_2$ $R_3 = H$
b $R_1, R_2 = CH_2CH_2CH_2$ $R_3 = H$
c $R_1 = R_2 = CH_3$ $R_3 = H$
d $R_1 = R_3 = CH_3$ $R_2 = H$
e $R_1 = R_2 = Ph$ $R_3 = H$
f $R_1 = R_3 = Ph$ $R_2 = H$

Scheme 3.

using a catalytic amount of LiI was attempted, and high yields (85–90%) and very clean reaction products were obtained.

When the carbons are substituted by two phenyl groups, as in **8e** and **8f**, no reaction occurred and the starting aziridine was recovered unchanged. However, when the carbons are substituted by two alkyl groups, either *cis* or *trans*, net retention of stereochemistry was observed.[22] This result is consistent with the double inversion suggested by the mechanisms in Scheme 2.

Thus, we have developed a convenient, inexpensive, regiospecific, and stereospecific method for the conversion of readily available aziridines to useful oxazolidinones using carbon dioxide. The reactions are catalytic in LiI. In fact, we have shown that the stereochemistry improves as the LiI concentration is decreased. In those cases in which a mixture of regioisomers is obtained, we found that adding HMPA greatly improves the isomeric ratio.[23,24]

Acknowledgements

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22. The determination of the stereochemistry of oxazolidinones **9c** and **9d** was accomplished by comparing the ^1H NMR spectrum for each compound. It has been shown in the literature (Wohl, R. A. *J. Org. Chem.* **1973**, *38*, 3858) that for similar oxazolidinones, the methyl groups at C-4 and C-5 are at higher field in the *cis* isomer than in the *trans* isomer, and the methine protons at C-4 and C-5 are at lower field in the *cis* isomer than in the *trans* isomer.
23. **Method A for the conversion of an aziridine to an oxazolidinone**. A mixture of 1.0 mmol aziridine and 1.0 mmol lithium iodide in 30 mL of THF was allowed to reflux for 15 min. Carbon dioxide was then bubbled through this reaction mixture for 4 h at room temperature. After this time, the mixture was added to 50 mL of ether and washed with 25 mL of 10% sodium bisulfite. The ethereal solution was washed with 100 mL of water, in three portions. The ethereal solution was dried with anhydrous K_2CO_3, and evaporated to dryness yielding the oxazolidinone.

    Method B for the conversion of an aziridine to an oxazolidinone with or without added HMPA. A mixture of 0.4 mmol aziridine, 0.1 or 0.4 mmol lithium iodide, and 0.4

mmol HMPA (when needed) in 15 mL of THF was added to a 25 mL heavy walled round bottom flask that contained a threaded Teflon plug. This reaction mixture was then cooled to -78°C, and 8.0 g (180 mmol) of powdered dry ice (carbon dioxide) was added in two portions. The round bottom flask was then capped with the threaded Teflon plug and allowed to warm to room temperature. The reaction mixture was stirred overnight at room temperature. After that, the mixture was again cooled to -78°C and the pressure was released very slowly. The mixture was worked-up as above.

24. Spectroscopic data for compounds **2a**, **3a**, **3c**, **9a** and **9b** may in found in Refs. 13, 17, 25, and 26. The spectroscopic data for **2b**: ^{1}H NMR: δ 0.91 (t, $J=6.7$ Hz, 3H), 1.27 (d, $J=5.9$ Hz, 3H), 1.30–1.39 (m, 4H), 1.46–1.58 (m, 2H), 2.93–3.17 (m, 1H), 3.33–3.47 (m, 1H), 3.79–3.95 (m, 2H), 4.39 (t, $J=7.3$ Hz, 1H); ^{13}C NMR: δ 14.09, 18.30, 22.47, 27.19, 41.72, 50.96, 68.98, 158.21; IR: 1747 cm^{-1}; MS, m/e 171 (5.4), 156 (19.0), 142 (34.8), 115 (28.8), 114 (82.6), 70 (100), 56 (9.8); high resolution MS found 172.1331, calculated for $C_9H_{18}NO_2^+$ 172.1337. The spectroscopic data for **9c**: ^{1}H NMR: δ 1.10 (d, $J=6.2$ Hz, 3H), 1.33 (d, $J=5.6$ Hz, 3H), 3.65 (pent, $J=6.8$ Hz, 1H), 4.03 (d, $J=14.9$ Hz, 1H), 4.61 (pent, $J=6.7$ Hz, 1H), 4.82 (d, $J=15.5$ Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR: δ 12.61, 15.05, 45.85, 53.19, 73.78, 127.96–128.88, 136.40, 158.08; IR: 1739 cm^{-1}; MS, m/e 205 (30.4), 150 (40.8), 106 (33.7), 92 (14.1), 91 (100), 79 (14.2), 65 (20.7), 56 (17.9); high resolution MS found 206.1171, calculated for $C_{12}H_{16}NO_2^+$ 206.1181. The spectroscopic data for **9d**: ^{1}H NMR: δ 1.18 (d, $J=6.2$ Hz, 3H), 1.33 (d, $J=6.1$ Hz, 3H), 3.18 (pent, $J=6.5$ Hz, 1H), 4.09 (d, $J=14.9$ Hz, 1H), 4.11 (pent, $J=6.5$ Hz, 1H), 4.76 (d, $J=15.2$ Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR: δ 17.46, 19.32, 45.90, 57.46, 127.96–128.93, 136.19, 158.08; ^{13}C NMR (CD_3CN): δ 17.55, 19.32, 46.25, 58.65, 78.47, 128.47–129.61, 138.05.
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