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The high yield and regioselective conversion of an unactivated aziridine to an oxazolidinone using carbon dioxide with ammonium iodide as the catalyst

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ABSTRACT

The conversion of an unactivated 2-alkylaziridine to the corresponding oxazolidinone generally requires a very high pressure of carbon dioxide, a high temperature, an expensive catalyst, and/or a long reaction time. Here, a new, high yield (over 95%), and highly regioselective (over 95%) conversion of an unactivated aziridine to an oxazolidinone is reported. This reaction is easy to perform because it requires a low pressure of carbon dioxide, low temperature, no co-solvent, and the catalyst is the salt ammonium iodide.

1. Introduction

According to recent reviews, in comparison to activated aziridines, few papers have been published on the chemistry of readily available unactivated *N*-alkyl aziridines. One reaction of an *N*-alkyl aziridine is the insertion of carbon dioxide into a C–N bond to generate an oxazolidinone, an important compound used as a chiral auxiliary, as a metal ligand, and as a pharmaceutical (specifically as an antibiotic).[1–3] Although carbon dioxide is abundant, renewable, nonflammable, and inexpensive, it is chemically stable.[4,5] Therefore, the insertion reaction generally requires the presence of a difficult to synthesize catalyst, high pressure (typically over 100 atm), and/or high temperature (typically over 100 °C).[6–9]

A number of years ago, to the best of our knowledge for the first time, we showed that a salt, specifically LiI, can promote the insertion of CO_2 into the C–N bond of an unactivated *N*-alkylaziridine (Scheme 1).[10,11] When the 2-position of the ring is substituted by an aryl group (**1**), almost a quantitative yield of one regioisomer (**2**) is obtained. However, when the 2-position is substituted by an alkyl group (**3**), the yield is still very high but two isomers are formed in a 2:1 ratio (major isomer **4** and minor isomer **5**). When HMPA was added to the reaction of **3**, the ratio of the isomers became 97% to 3%. All alkyl groups studied so far behave very similarly. Thus, the specific R or alkyl group does not have an effect on the yield or the regioselectivity. A theoretical study has shown that both the Li^+ and the I^- must bond to the aziridine for the insertion reaction to occur.[12]

Since that time, a couple of other salts have been shown to catalyze this type of insertion reaction; however, as mentioned above, those methods typically require pressures greater than 100 atm, temperatures greater than 100 °C, and/or 2-phenyl substitution for the C–N insertion reaction to proceed.[6–9]

In this Letter, a high yield and highly regioselective conversion of an unactivated 2-alkylaziridine to the corresponding oxazolidinone is discussed. The reaction proceeds at room temperature or below, at 1–4 atm CO_2, with ammonium iodide as the catalyst, and with THF as the solvent.

2. Results and discussion

2.1. Comparison of different salts

Initially, our goal was to test the theoretical prediction[12] that both the Li^+ and I^- of LiI were needed to catalyze the CO_2 insertion reaction. Following our typical procedure[10] for the transformation shown in Scheme 1 (**3** R = $PhCH_2$, alkyl = CH_3, room temperature, 3 atm pressure, 4 h), but using a variety of salts, the data in Table 1 were obtained. Consistent with the theoretical analysis of this reaction, the lithium salts give higher yields than the sodium salts, which give higher yields than the potassium salts. In addition, the iodides give higher yields than the bromides, which give higher yields than the chlorides.

However, the best yield is obtained with ammonium iodide. This result is probably because the ammonium ion ($pK_a = 9.5$) coordinates with the aziridine to generate an aziridinium ($pK_a = 8.3$),[13] a ring system known to readily ring open.[14,15] Therefore, we decided to study the reaction of NH_4I in greater detail.

2.2. Effect of pressure

To determine the effect of pressure on this reaction, the conversion of **3** in THF with NH_4I was examined at three different pressures (Table 2, entries 1–3). These pressures were chosen because they are easily obtained from a tank of carbon dioxide and because they can be used in normal laboratory glassware. It was found that the higher the pressure, the higher the yield and regioselectivity.

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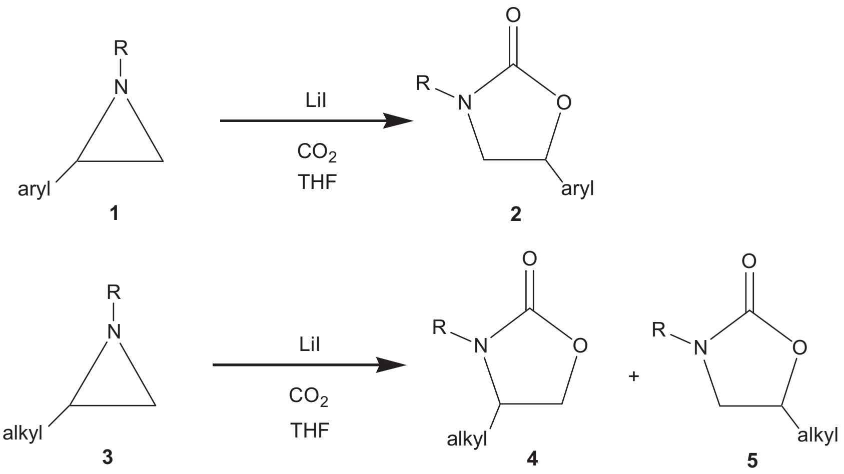

Scheme 1.

Table 1
Comparing different salts to promote the conversion of **3** to **4** + **5**

Entry	Salts	Yield[a] (%)	Regioselectivity[a] (% isomer **4**)
1	LiI	85	66
2	LiBr	76	84
3	LiCl	33	99
4	NaI	83	69
5	NaBr	27	97
6	NaCl	0	–
7	KI	Trace	–
8	KBr	0	–
9	KCl	0	–
10	NH_4I	94	84
11	NH_4Br	Trace	–
12	NH_4Cl	0	–
13	No salt	0	–

[a] All reactions were repeated at least three times, and all yields and regioselectivity values are reproducible to less than ±3%.

2.3. Effect of reaction time

Based on previous experience, the reaction of **3** + CO_2 using LiI as the catalyst takes a minimum of 4 h in THF or in THF/HMPA. However, monitoring the NH_4I reaction as a function of time (10, 20, 40, 60, 120, 180, and 240 min, Table 2 entries 3–9) showed that the yield of 96% was obtained in about 40 min and it did not change with longer time, including after two days (Table 2, entry 10). In addition, the regioselectivity actually increased very slightly at shorter time. Specifically, at 40 min, the percentage of isomer **4** is 91% in comparison to the 88% at 4 h.

The yield and regioselectivity obtained with NH_4I are very similar to those observed with LiI when HMPA is added and are higher than those reported in the literature with a variety of other salts. Another important part of this reaction is that no co-solvent is needed and the time required for the reaction is fairly short (40 min vs, greater than 4 h).

2.4. Effect of moisture

Because NH_4I is hygroscopic, the effect of water on this reaction needed to be determined. It was found that the addition of water to the reaction has no effect on the yield; however, the regioselectivity decreases from 91% to about 82%. Therefore, care needs to be taken to avoid moisture in these reactions.

2.5. Effect of temperature

Based on theoretical calculations, it has been suggested that for an aziridinium ion, the ring opening reaction of the less substituted C–N bond has lower activation energy than the ring opening reaction of the more substituted C–N bond.[14] This idea implies that at a lower temperature, a higher regioselectivity would be obtained. Thus, the effect of temperature on the reaction of **3** + CO_2 was investigated (Table 2, entries 3, 11 and 12).

Consistent with the calculations, when the reaction of **3** is run at 0 °C for 4 h, the yield increases to 99%, with 96% of that material

Table 2
Dependence of percentage yield and regioselectivity on different variables

Entry	Pressure (atm)	Temperature (°C)	Time (min)	NH_4I amount (equiv)	Yield[a] (%)	Isomer **4** [a](%)
1	1	rt	240	1	91	77
2	3	rt	240	1	94	84
3	4	rt	240	1	97	88
4	4	rt	10	1	43	95
5	4	rt	20	1	87	92
6	4	rt	40	1	96	91
7	4	rt	60	1	97	90
8	4	rt	120	1	98	90
9	4	rt	180	1	96	90
10	1	rt	2 days	1	96	80
11	4	0	240	1	99	96
12	4	45	40	1	91	78
13	4	rt	40	0.05	53	94
14	4	rt	120	0.05	98	91

[a] All reactions were repeated at least three times, and all yields and regioselectivity values are reproducible to less than ±3%.

being the major isomer **4**. In contrast, when the temperature of the reaction is increased from room temperature to 45 °C, the regioselectivity decreases to less than 80% of the major isomer.

2.6. Catalytic NH_4I

Rather than using a stoichiometric amount of NH_4I, this reaction also can be performed using a catalytic amount of NH_4I (Table 2, entries 13 and 14). However, when catalytic NH_4I (5 mol %) is used for the reaction of **3** + CO_2, the product formation occurs much more slowly (53% yield vs, 97% yield in 40 min). When this catalytic reaction is allowed to proceed for 2 h, the yield increases to 98%, with 91% of the mass as isomer **4**.

2.7. Maximization of isomer 4

Thus as shown in Table 2, using NH_4I as the catalyst and THF as the solvent, unactivated 2-alkylaziridine **3** will undergo insertion of CO_2 into the less substituted C–N bond to give isomer **4** in high yield (over 95%), in high regioselectivity (over 95%), at low pressure (3 or 4 atm), at low temperature (room temperature or below), and in a short time (40 min at rt or 4 h at 0 °C).

2.8. Maximization of isomer 5

For turning around the results in the previous section, larger amounts of insertion into the more substituted C–N bond to give isomer **5** should be obtained with LiI, at lower pressure, higher temperature, and longer reaction time. When the reaction of compound **3** with CO_2 was run in THF with LiI, at 1 atm CO_2, at 55 °C, for 3 days, only 33% of the oxazolidinone was isomer **4** and 67% was what was formerly minor isomer **5**. Unfortunately, the yield was only 70%, because at the higher temperature, a large amount of piperazine (a six-membered ring dimer of an aziridine) was formed.

3. Experimental section

Into a 48 mL thick walled flask, with a stir bar, was added aziridine **3** (0.180 g, 1.22 mmol), 1.22 mmol of salt (LiI, 0.162 g; LiBr, 0.106 g; LiCl, 0.052 g; NaI, 0.184 g; NaBr, 0.126 g; NaCl, 0.071 g; KI, 0.203 g; KBr, 0.146 g; KCl, 0.091 g; NH_4I, 0.177 g; NH_4Br, 0.120 g; or NH_4Cl, 0.066 g), and 2 mL of THF. The reaction mixture was then subjected to carbon dioxide gas at room temperature for the appropriate length of time. The pressure was monitored by a gauge and adjusted to 1, 3, or 4 atm by bleeding off excess pressure at the beginning of the reaction. For the 45 °C reaction and for the 0 °C reaction, the flask was put into an oil bath or an ice/water bath before the CO_2 was added. For the reaction with added water, 0.25 mL of water was added to the THF solution before the CO_2 was added. For the catalytic reaction, only 9.0 mg (0.060 mmol) NH_4I was used.

After the reaction was completed, the THF solution was added to 50 mL of diethyl ether. The ether solution was washed once with 20 mL of 10% sodium bisulfate and twice with 20 mL of water. The ether then was dried with anhydrous K_2CO_3 and evaporated to dryness, yielding the oxazolidinone mixture. As done previously, GC–MS and ^1H NMR spectroscopy were used to analyze the reaction mixture.[10]

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15. One reviewer suggested a control experiment using KI and a catalytic amount of CF_3COOH. When this was tried, the results were the same as the reaction using only KI, and thus, the $NH_4^+ I^-$ is not simply a proton source. The second reviewer suggested an alternative mechanism in which instead of the NH_4^+ reacting with the aziridine, it is coordinating with the CO_2. The coordinated CO_2 and the I^- then react with the aziridine ring.