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PAPER

The solvent-free and catalyst-free conversion of an aziridine to an oxazolidinone using only carbon dioxide†

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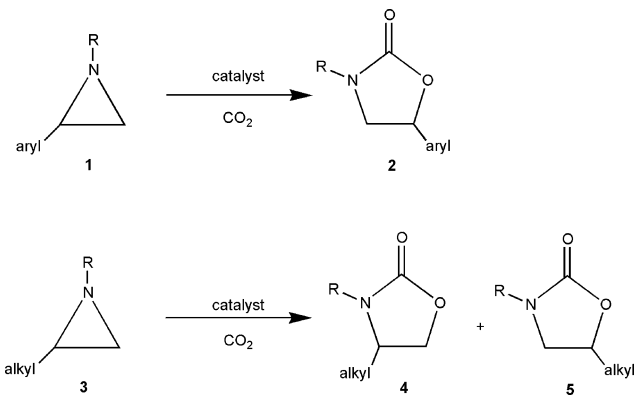
It has been found for the first time at room temperature that the reaction of an unactivated 2-alkyl or 2-aryl aziridine with carbon dioxide to generate the corresponding oxazolidinone does *not* need any form of catalysis or solvent to proceed in high yield, especially when using high speed ball milling.

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, which is an important class of compounds used as chiral auxiliaries, as metal ligands, and as pharmaceuticals (specifically as antibiotics).[1–3] Although carbon dioxide is abundant, renewable, nonflammable, and inexpensive, due to its stability,[4,5] a difficult to synthesize catalyst, high pressure (typically over 100 atm), and/or high temperature (typically over 100 °C) generally are required for these insertion reactions to proceed.[6–9] In addition, most of these reactions only work when the 2-position is substituted with a phenyl group; they do not work when the 2-position is substituted with an alkyl group. Put another way, in most reactions, compound **1** will react to give **2**, but compound **3** is stable.

For the past several years, we have been investigating the reactions shown in Scheme 1 in which both types of unactivated aziridines (**1** and **3**, R = alkyl) are converted to the corresponding oxazolidinones at low pressure and temperature using a salt as a catalyst.[10–12] In a control experiment allowed to go for an extended period of time (12 h *vs.* 4 h or less when a salt is used) at room temperature, it was found that the reaction of compound **3** (Scheme 1, R = $PhCH_2$ and alkyl = CH_3) with CO_2 (3 atm) in THF using no catalyst gives a 7% yield of oxazolidinones **4** + **5**. This result is encouraging and led to an effort to find a method to convert an aziridine plus CO_2 into an oxazolidinone using no catalyst.



Scheme 1

While working on this project, it was reported that *N*-alkyl-2-aryl aziridines (**1**) will generate the corresponding oxazolidinone (**2**) with no catalyst.[13] However, those reactions must be done at 120 °C and at 90 atm of CO_2 pressure.

In this manuscript, it is shown that the reaction of an aziridine with carbon dioxide to generate an oxazolidinone may be done at low pressure and at room temperature in the absence of catalyst and solvent.

Conversion performed in glassware with no solvent

As mentioned above, the reaction of compound **3** (R = $PhCH_2$ and alkyl = CH_3) with CO_2 in THF using no catalyst gives a 7% yield of oxazolidinones **4** + **5**. Extending the reaction time or increasing the pressure did not greatly improve the yield of this reaction.

A solvent is generally used to dissolve the reactants, which in turn facilitates the collisions that must occur in order to transform the reactants into products. It was thought that a solvent may not be necessary for this reaction because it involves

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a gas and a liquid. Thus, the aziridine plus CO_2 reaction was attempted in the absence of solvent.

When aziridine **3** was stirred, with no catalyst or solvent, under a CO_2 pressure of 3 atm for 12 h, the yield of oxazolidinones **4** + **5** increased from the 7% observed in THF to 37%. At 4 atm, the yield increased to about 40%. In each case, compound **4** was the major isomer and constituted 93% of the product mixture.

Due to the low yield, the reaction was allowed to go for a longer period of time. At 4 atm, the yield increased from 40% after 12 h, to 57% after 24 h, to 80% after 48 h, and to 89% after 8 days, with no effect on the regioselectivity.

Not surprisingly, given how much more quickly 2-phenyl substituted aziridines react in comparison to 2-alkyl substituted aziridines, when compound **1** (R = $PhCH_2$ and aryl = Ph) was subjected to CO_2 gas at 4 atm and at room temperature, in the absence of any solvent or catalyst, after 24 h, oxazolidinone **2** was generated in nearly quantitative yield.

These reactions are very sensitive to moisture. When a couple drops of water were added to the reaction, the yield was about half that observed under anhydrous conditions. The reason the yield decreases with water may be due to the reaction of water with carbon dioxide to generate carbonic acid, which in turn, protonates the aziridine. This acid–base reaction would thus greatly decrease the amount of nucleophilic aziridine present in the reaction mixture.

High speed ball milling

In order to greatly decrease the time of the reactions, high speed ball milling (HSBM) was investigated. Mechanical energy from HSBM has been shown to give high yields and increased rates of chemical reactions, especially those reactions done in the absence of any solvent. The HSBM apparatus uses a small steel ball in a steel vial with high speed shaking to achieve small particle sizes through milling. Subsequent collisions of the milling ball with the sides of the reaction vessel provide mechanical energy to overcome the activation barrier of the reaction.[14,15]

These reactions are accomplished by using a 3.5 mL steel vial with a 3.2 mm diameter milling ball. To the vial was added approximately 150 mg of the aziridine and 3 g of dry ice as the CO_2 source. The vial was sealed and shaken in a paint shaker for the appropriate length of time. Table 1 summarizes our HSBM reactions.

Given the ease of the reaction in the glass flask, the first reaction attempted in the HSBM was 2-phenyl substituted compound **1** with dry ice for 17 h (entry 1). This conversion generated compound **2** in nearly quantitative yield with only one regioisomer.

Therefore, the reaction of 2-alkyl aziridine **3** (R = $PhCH_2$ and alkyl = CH_3) with dry ice was subjected to the same HSBM reaction conditions (entry 2). This conversion was completed in 17 h in quantitative yield with over 93% of the product as isomer **4**. As a set of control experiments, when the HSBM reaction conditions were used for the reaction of compound **3**, but with no shaking or no milling ball, the yields obtained were similar to those reported above in the glass apparatus. In other words, the shaking/mechanical energy decreases the time of the reaction from over a week to over night.

Unlike the salt catalyzed reactions, the nitrogen of the aziridine does not have to be substituted by an alkyl group. Aziridine **6** (entry 3) gave the corresponding oxazolidinone **7** in quantitative yield.

To learn about the relative stereochemistry of the products, two different 2,3-disubstituted aziridines were used. The reactions of *cis*-2,3-dimethylaziridine **8** gave a nearly quantitative yield of *cis*-stereoisomer **9** in the HSBM apparatus (entry 4). Similarly, *N*-benzyl-7-azabicyclo[4.1.0]heptane **10** gave a nearly quantitative yield of the corresponding *cis* oxazolidinone **11** (entry 5). Thus, these reactions proceed with net retention of stereochemistry as was observed previously for the LiI catalyzed reactions, in which a double inversion is known to take place.[10]

Given the success of the 2,3-dialkyl aziridine reactions and the ease of the 2-phenyl aziridine reaction, it is surprising that 2,3-diphenyl aziridine **12** gives back only starting material even after shaking for an extended period of time (entry 6). This result is the same as is observed when a salt is used as the catalyst. One explanation is that the phenyl groups have enough electron withdrawing ability that the nitrogen does not have the required electron density to attack the CO_2.

Consistent with this idea, a mild electron withdrawing substituent at the 2-position, such as a *meta*-chloro phenyl group, generates only a trace amount of a compound with the correct molecular weight for the product, even when shaken for an extended period of time (entry 7).

When the nitrogen is substituted by a phenyl, regardless if the 2-position is substituted by a phenyl (entry 8) or by an alkyl group (entry 9), the starting aziridine is recovered unchanged after an extended period of shaking. Even when the nitrogen is substituted with a *para*-methoxy phenyl (entry 10), none of the corresponding oxazolidinone is obtained. These results are similar to the results observed for the high temperature-no catalyst reactions[13] and the salt catalyzed reactions.[10]

It is believed that these observations are due to the greatly decreased basicity and nucleophilicity of *N*-phenyl in comparison to *N*-alkyl aziridine. Specifically, the pK_a of an alkyl azirdine is 8.3 and the pK_a of *para*-methoxy aniline is 5.2.[16,17] Thus, the *N*-phenyl aziridine is much less basic, and thus less nucleophilic, than an *N*-alkyl aziridine.

As was observed previously for the salt catalyzed reactions, *N*-acyl aziridine **17** simply isomerizes to oxazoline **18** (entry 11), regardless of the amount of carbon dioxide present.

Due to the nature of the shaking apparatus, 17 h is a convenient period of time for each reaction. However, we were interested in determining if a shorter reaction time was possible. In other words, we wanted to determine the shortest time that would still give a 95+% yield of the oxazolidinone. For 2-phenyl aziridine **1**, this time was found to be 6 h, and for 2-alkyl aziridine **3**, this time was found to be 12 h.

Mechanism

Based on the stereochemical results, the nucleophilicity of the nitrogen, and the mechanism of the salt catalyzed reaction, there are two possible mechanisms for these transformations. The initial step of each is the nucleophilic ni-

Table 1 High Speed Ball Milling Reactions

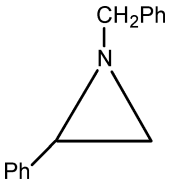
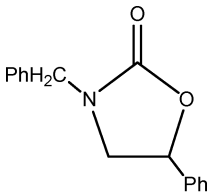
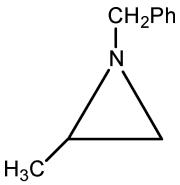
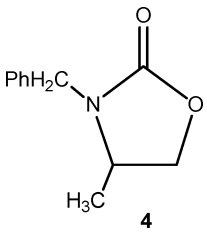
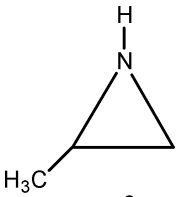
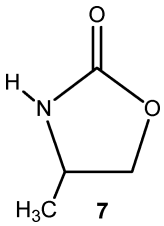
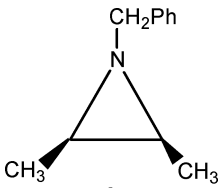
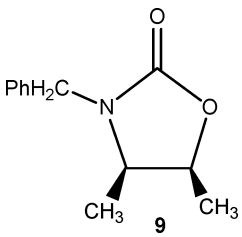
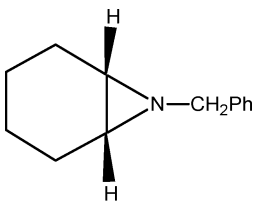
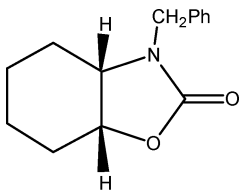
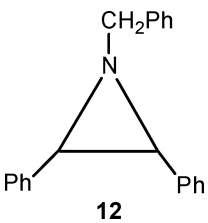
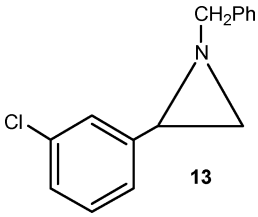
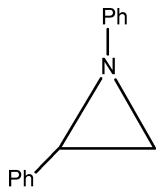
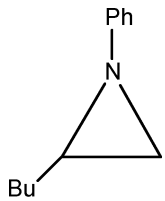
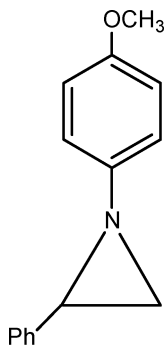
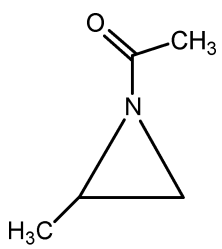
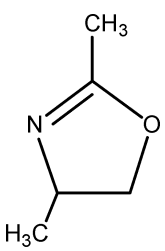
Entry	Starting aziridine	Major product oxazolidinone	Reaction time (h)	Regioselectivity % major product	Total % yield of all products
1	 **1**	 **2**	17	100	quantitative
2	 **3**	 **4**	17	93	quantitative
3	 **6**	 **7**	17	100	quantitative
4	 **8**	 **9**	17	100	quantitative
5	 **10**	 **11**	17	100	quantitative
6	 **12**		43		0
7	 **13**		43		trace

Table 1 (*Contd.*)

Entry	Starting aziridine	Major product oxazolidinone	Reaction time (h)	Regioselectivity % major product	Total % yield of all products
8	 **14**		43		0
9	 **15**		43		0
10	 **16**		43		0
11	 **17**	 **18**	17	100	quantitative

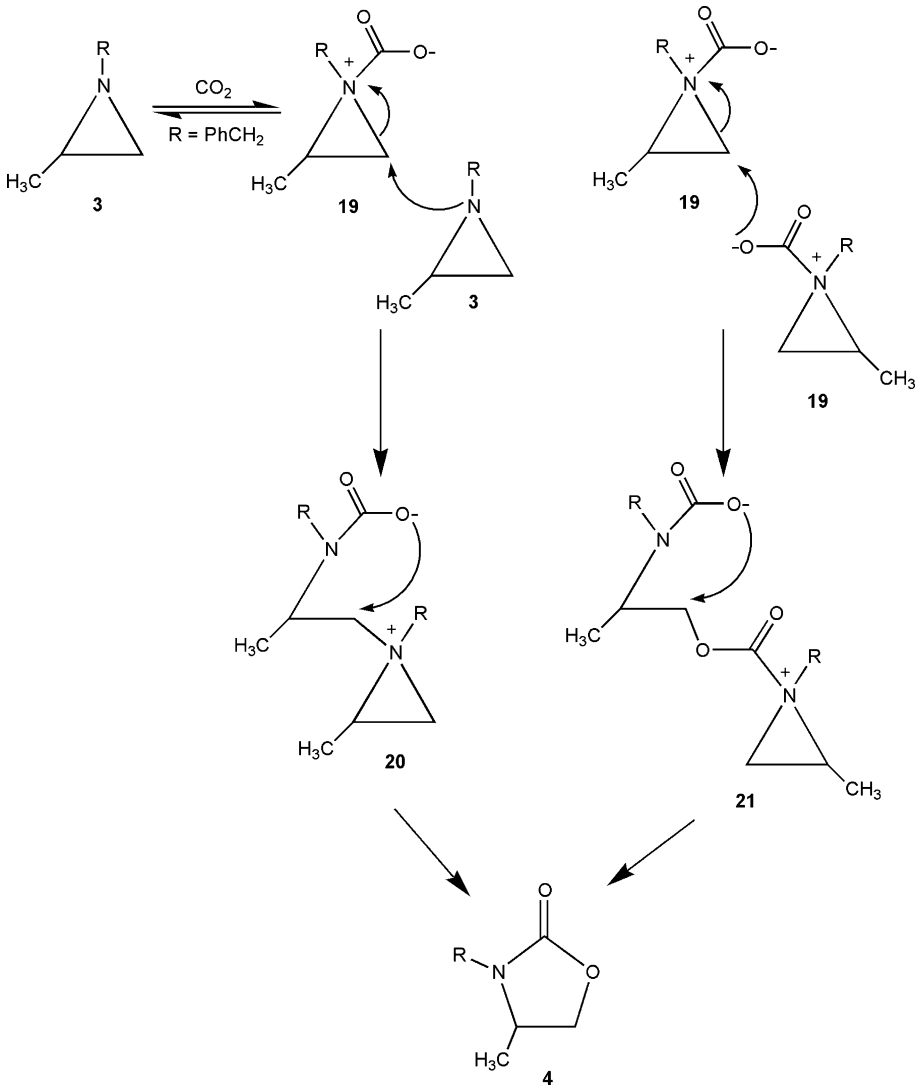
trogen of the aziridine attacking CO_2 to give compound **19**. The mechanisms then differ because a different nucleophile is used for subsequent steps. One mechanism is a variation of the mechanism proposed for the high temperature-no catalyst reaction,[13] in which the nucleophile is a carboxylate, and the other is a variation of the mechanism proposed in a recent study using an amino acid as the catalyst for the aziridine to oxazolidinone conversion,[9] in which the nucleophile is an aziridine. These proposed mechanisms are shown in Scheme 2 for prototypical compound **3**. (The carboxylate in compound **19** cannot undergo a unimolecular reaction and attack the 3-position because (1) this would be a 5-*endo*-tet reaction, which is disfavored by Baldwin's Rules, and (2) this mechanism would give net inversion, which is inconsistent with entries 4 and 5 in Table 1.)

Conclusion

It has been shown that the reaction of an unactivated aziridine with CO_2 does not need a catalyst, a solvent, high temperature, or high pressure if mechanical energy is applied.

General experimental procedure

Into a 48 mL thick walled glass flask, with a stir bar, was added aziridine **3** (0.18 g, 1.2 mmol) and 2 mL of THF, or just the aziridine. The reaction mixture then was subjected to carbon dioxide gas at room temperature for the appropriate length of time. The pressure was monitored by a gauge and adjusted to 3 or 4 atm by bleeding off excess pressure at the beginning of the reaction.



Scheme 2

After the reaction was completed, the THF was evaporated. For those reactions in which no solvent was used, at the end of the reaction, ether was added to the reaction mixture so it could be transferred to a round bottom flask. The ether was then evaporated.

As done previously, GC-MS and NMR spectroscopy were used to analyze the reaction mixture. Spectroscopic data may be found in references 10 and 18 (See ESI†). The product was weighed to determine the yield. Each reaction was run at least three times and the reported yields are the averages of these three runs.

HSBM experimental procedure

Between 0.10 and 0.20 g of the aziridine were placed into a stainless steel reaction vessel (total volume 3.5 mL) with a 3.2 mm diameter milling ball and an excess of dry ice (3.0 g, 68 mmol CO_2). (Because there is such a large excess of carbon dioxide, we have found that it does not matter exactly how much of the aziridine is used.) The vial was tightly sealed with a stainless steel cap containing a Teflon gasket. For the non-shaking control experiments, the vial remained stationary at room temperature for the appropriate time period. For the shaking experiments, the vial was shaken at 18 Hz, using a Spex 8000 M mixer, for 999 min (approx. 17 h). The reaction mixture was transferred and analyzed spectroscopically as above. Spectroscopic data for starting materials and for products may be found in references 10, 18, and in references cited therein (See ESI†). The product was weighed to determine the yield. Each reaction was run at least three times and the reported yields are the averages of these three runs.

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