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COMMUNICATION

Protic onium salts-catalyzed synthesis of 5-aryl-2-oxazolidinones from aziridines and CO_2 under mild conditions†

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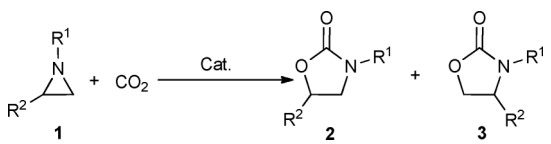
Protic onium salts, *e.g.* pyridium iodide, proved to be highly efficient and recyclable catalysts for the selective synthesis of 5-aryl-2-oxazolidinones under a CO_2 atmosphere at room temperature, presumably due to aziridine activation assisted by hydrogen bonding on the basis of ^{1}H NMR and *in situ* FT IR under CO_2 pressure study.

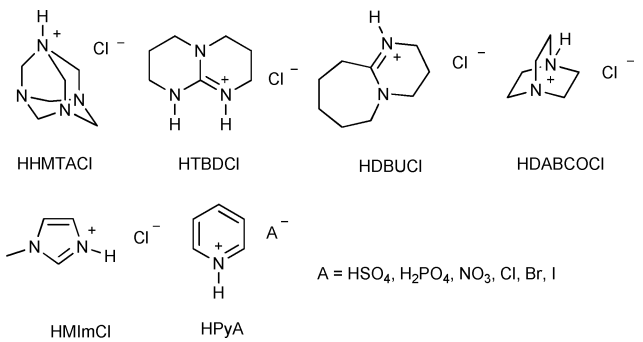
Carbon dioxide is an easily available renewable carbon resource, which has the advantages of being nontoxic, abundant, and economical.[1] The [2 + 3] coupling reaction between CO_2 and aziridines is one of the few commercial routes using CO_2 as a raw material to afford the 5-membered materials (Scheme 1), which are important heterocyclic compounds showing wide applications as intermediates[2a–d] and chiral auxiliaries[2e–g] in organic synthesis. Therefore, a growing effort has been devoted to developing efficient methodologies for producing oxazolidinones. From the viewpoint of green chemistry, the cycloaddition procedure utilizing CO_2 as a feedstock is more attractive in comparison with those processes including carbonylation of amino alcohols with phosgene,[3a,b] CO,[3c] and reaction of propargylamine/propargylic alcohol with CO_2.[3c–g]



Scheme 1 Synthesis of 2-oxazolidinones from aziridines and CO_2.

In the past decades, numerous catalysts particularly Lewis acid ionic liquids (ILs) have been proposed for this reaction.[4a–m] Although significant advances have been seen, toxic organic solvents/co-catalysts, high catalyst loading, high CO_2 pressure or longer reaction time are generally required to perform the reaction smoothly. Therefore, development of an easily prepared, efficient and recyclable single component catalyst for selective formation of 5-aryl-2-oxazolidinone under mild conditions is still highly desirable.

Because of the distinctive properties such as high thermal stability, negligible vapor pressure, high loading capacity and easy recyclability, ILs can potentially be used as environmentally friendly solvents and/or efficacious catalysts and have attracted significant attention from the scientific community.[5] In the framework of our continuous effort on the synthesis of oxazolidinones from CO_2,[4j–m] we found that a series of protic onium salts (Scheme 2) were proved to be highly effective catalysts for this transformation under ambient conditions. Interest in those protic onium salts stems from facile preparation from relatively inexpensive starting materials, gratifyingly thermal behaviour and air/water stability. It is particularly worth mentioning that hydrogen bonding formation between an aziridine and an protic onium salts could lead to aziridine's activation and thus promote the reaction. Indeed, HPyI (*N*-proton pyridium iodide) displayed excellent activity even without any additional organic solvent/additive.



Scheme 2 Protic onium salts used in this study.

In the preliminary study, a series of the Cl^--containing protic onium salts were examined to evaluate the cation influence by performing the reaction of 1-ethyl-2-phenylaziridine (**1a**) and CO_2 at 100 °C and 5 MPa of CO_2 for 1 h. The results listed in Table 1 reveal that the cation has a remarkable impact on the catalytic performance. NH_4Cl was almost inactive (entry 1, Table 1). The catalytic efficiency increased in the following order: $HHMTA^+ < HTBD^+ < HDBU^+ \sim HDABCO^+ < HMIm^+ <$

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† Electronic supplementary information (ESI) available: General experimental methods, characterization for ionic liquids, aziridines, oxazolidinones and piperazines and copies of NMR, ESI-MS spectra. See DOI: 10.1039/c1gc15581d

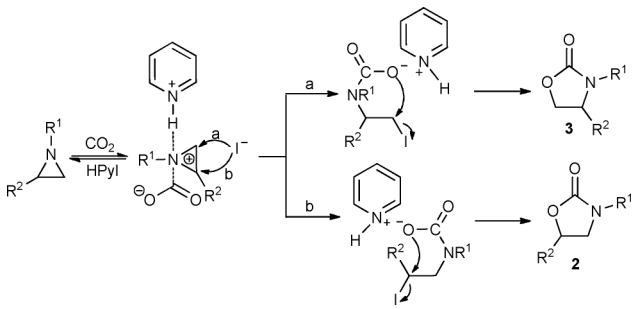
Table 1 Cation effect of the protic onium salts on the reaction[a]

Entry	Catalyst	Conv./%[b]	Yield/%[b,c]	Regio-sel.[d]
1	NH_4Cl	10	8	88 : 12
2	HHMTACl	89	43	93 : 7
3	HTBDCl	87	77	92 : 8
4	HDBUCl	94	90	90 : 10
5	HDABCOCl	99	92	92 : 8
6	HMImCl	95	94	88 : 12
7	HPyCl	97	97	93 : 7
8	C_4DABCOCl	73	45	93 : 7

[a] Reaction conditions: **1a** (1 mmol, 0.147 g); catalyst loading (3 mol%); CO_2 (5 MPa); 100 °C; 1 h. [b] Determined by GC. [c] Total yield of **2a** and **3a**. [d] Molar ratio of **2a** to **3a**.

HPy^+ (entries 2–7). This is understandable because those delocalized cations could help stabilize the intermediate (Scheme 3) and thus gave better results. The $HDABCO^+$ cation with a tertiary nitrogen able to activate CO_2 showed high catalytic activity (entry 5).[4l] Whereas, *N*-butyl protic onium salt *i.e.* C_4DABCOCl, incapable of forming hydrogen bonds with the aziridine, showed much lower activity (entry 5 *vs.* 8). Therefore, hydrogen bonding formation could play a crucial role in facilitating the reaction. On the other hand, low efficiency of $HHMTA^+$ would presumably be ascribed to its steric hindrance (entry 2). Table 2 shows the anion effect of HPyA on the reaction. HSO_4^-, $H_2PO_4^-$ and NO_3^- were found to be ineffective due to poor nucleophilicity and leaving ability (entries 1–3,Table 2). Interestingly, the halide activity follows the order of $Cl^- < Br^- < I^-$ (entries 4–6), consistent with the trend of nucleophilicity and leaving ability. As a result, HPyI gave a quantitative result even within 15 min and was therefore chosen as the model catalyst for further investigation.

Influence of the reaction parameters on the reaction was also examined. The results are summarized in Table 3. When 0.25 mol% catalyst was used, 82% yield of **2a**+**3a** was obtained



Scheme 3 The proposed mechanism.

Table 2 Anion effect[a]

Entry	Catalyst	Conv./%[b]	Yield/%[b,c]	Regio-sel.[d]
1	$HPyHSO_4$	4	0	—
2	$HPyH_2PO_4$	13	0	—
3	$HPyNO_3$	49	6	96 : 4
4	HPyCl	48	34	90 : 10
5	HPyBr	>99	70	97 : 3
6	HPyI	>99	97	97 : 3

[a] Reaction conditions: **1a** (1 mmol, 0.147 g); catalyst loading (3 mol%); CO_2 (5 MPa); 100 °C; 15 min. [b] Determined by GC. [c] Total yield of **2a** and **3a**. [d] Molar ratio of **2a** to **3a**.

Table 3 Reaction conditions screening[a]

Entry	Cat./ mol%	T/°C	CO_2 pressure/ MPa	Time/ min	Conv./%[b]	Yield/%[b]
1	0.25	100	5	15	86	82
2	1	100	5	15	>99	98
3	3	100	5	15	>99	97
4	1	25	5	15	>99	98
5	1	120	5	15	>99	76
6	1	25	0.1	300	89	85
7	1	25	3	15	>99	98
8	1	25	7	15	99	98
9	1	25	9	15	85	84
10	1	25	3	5	>99	91

[a] Reaction conditions: **1a** (1 mmol, 0.147 g). [b] Determined by GC.

alongside small amounts of 1,4-diethyl-2,5-diphenyl-piperazine (**4a**) and 1,4-diethyl-2,3-diphenyl-piperazine (**5a**) being detected by GC-MS and ^{1}H NMR (see electronic supplementary information†). Nearly quantitative yield was attained in the presence of 1 mol% HPyI. A further increase in the catalyst amount to 3 mol% has little influence on the reaction outcome (entries 1–3). Notably, high regio-selectivity was kept in the range of 0.25 to 3 mol% HPyI. To our delight, HPyI worked very well even at r.t. (entries 2, 4, 5). Temperatures over 120 °C caused a slight decrease in the yield due to facile formation of piperazines **4a** and **5a**. On the other hand, an almost quantitative yield together with excellent selectivity could be retained in the range of 3–7 MPa CO_2, demonstrating the preferential effect of the hydrogen-bonding for accelerating the reaction (entries 4, 7, 8). Moreover, 85% yield could also be attained even at 1 atm CO_2 when prolonging the reaction time to 5 h (entry 6). However, CO_2 pressure over 9 MPa caused the yield to decrease because of CO_2's dilution effect, whereas chemo-selectivity was still > 99% (entry 9).[6] Therefore, the suitable CO_2 pressure would be *ca.* 3 MPa. Notably, excellent results can also be obtained within 5 min under mild reaction conditions (entry 10). To test catalyst stability, a subsequent cycle was run by adding fresh substrate to the reaction mixture upon completion of the reaction without product separation. The total product was separated after 5 cycles. The results indicate that no substantial drop in catalytic activity was detected after five successive cycles (Table 4).

The generality of this protocol was also examined. Various oxazolidinones were selectively formed in good yields (Table 5). However, increasing steric hindrance of the *N*-substituted group R^1 gave rise to a reactivity decrease (entries 9–11). High regioselectivity could be attained from 97 : 3 (**2**/**3**) to >99 : 1 with variation of the alkyl substituent at the nitrogen atom. On

Table 4 Catalyst reusability[a]

Cycle	t/min	Conv./%[b]	Yield/%[b,c]	Regio-sel.[d]
1	15	>99	98	98 : 2
2	15	>99	97	97 : 3
3	30	99	95	98 : 2
4	30	98	94	98 : 2
5	30	99	95	98 : 2

[a] Reaction conditions: **1a** (1 mmol, 0.147 g); catalyst loading (1 mol%); CO_2 (3 MPa); 25 °C. [b] Determined by GC. [c] Total yield of **2a** and **3a**. [d] Molar ratio of **2a** to **3a**.

Table 5 Various oxazolidinones synthesis[a]

Entry	R^1, R^2	T/°C	Time	Conv./%[b]	Yield/%[b]	Regio-sel.[c]
1	Et, Ph	25	15 min	>99	98	97 : 3
2	Et, *p*-Cl-Ph	25	15 min	>99	>99	98 : 2
3	Et, *p*-Me-Ph	70	15 min	>99	>99	99 : 1
4	*n*-Pr, Ph	25	15 min	98	94	98 : 2
5	*i*-Pr, Ph	25	2 h	72	71	99 : 1
6	*n*-Bu, Ph	25	30 min	>99	98	97 : 3
7	*i*-Bu, Ph	25	4 h	>99	98	97 : 3
8	Bn, Ph	80	15 min	>99	98	97 : 3
9	*c*-Hex, Ph	25	48 h	46	45	>99 : 1
10	*c*-Hex, p-Cl-Ph	60	48 h	>99	>99	>99 : 1
11	*c*-Hex, p-Me-Ph	55	48 h	73	73	>99 : 1

[a] Reaction conditions: **1** (1 mmol); catalyst loading (1 mol%); CO_2 (3 MPa). [b] Determined by GC. [c] Molar ratio of **2** to **3**.

the other hand, an electron-withdrawing group on the benzene ring showed higher activity than an electron-donating group (entry 10 *vs.* 11).

Previously, we have reported CO_2 activation induced by nucleophilic tertiary nitrogen based on studies using *in situ* FT-IR spectroscopy under CO_2 pressure.[4l,m] Indeed, almost the same result was observed for this catalytic system. The absorption peak of the carbonyl group was migrated from 1770 cm^{-1} (**1a**-CO_2 carbamate salt, Scheme 3) to 1740 cm^{-1} (oxazolidinone), when **1a** was used as the substrate (Fig. S1, see electronic supplementary information†), implying the activation of CO_2 by the tertiary nitrogen atom of aziridine. To further gain insight into the reaction mechanism, ^{1}H NMR technique was also employed to identify aziridine activation presumably induced by hydrogen bonding formation between the aziridine and the *N*-proton onium salt *e.g.* HPyI. It was found that the *para*-proton showed a upfield shift from 8.59 to 8.50, while *ortho*-proton gave a downfield shift from 8.92 to 9.38 (Fig. 1), plausibly indicating hydrogen bonding formation between HPyI and **1a**.

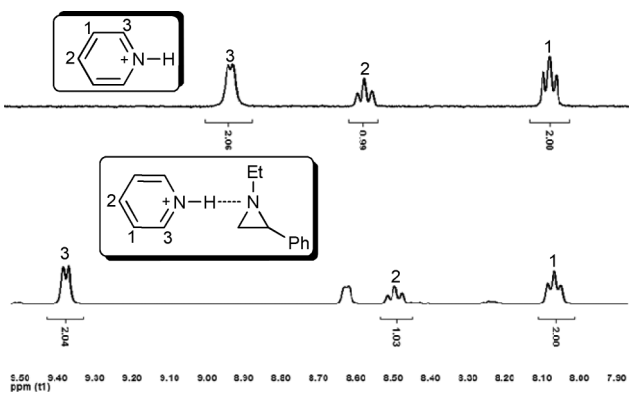


Fig. 1 The ^{1}H NMR ($CDCl_3$, 400 MHz) of HPyI without and with **1a**.

On the basis of previous reports[4c,j] and the experimental results herein, a possible mechanism for the HPyI-catalyzed cycloaddition of CO_2 with aziridine was proposed as shown in Scheme 3. Firstly, aziridine could coordinate with CO_2 to afford the carbamate salt, which was detected by *in situ* FT-IR.[4l,m] Simultaneously, the aziridine itself could also interact with HPy^+ through hydrogen bonding, thus resulting in aziridine's activation. Subsequent nucleophilic attack by the iodide anion and the final intra-molecular ring-closure, form oxazolidinone and regenerate the catalyst. The main product **2** could originate from ring-opening of the aziridine through nucleophilic attack at the most substituted carbon (path b), in agreement with typical ring-opening of the 3-membered heterocycles.[7]

In summary, protic onium salts, such as HPyI proved to be highly efficient and stable catalysts for the cycloaddition of CO_2 to aziridines without utilization of any organic solvent or additive under modest reaction conditions. The protic onium salts used in this study represent cheap, easily synthesized, robust *etc.* protic onium-based catalysts, which can effectively activate aziridine through hydrogen bonding formation. Further extending the application of protic onium salt towards broad reactions is currently under investigation in our laboratory.

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