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Copper-catalyzed cascade reactions of *N*-(2-bromoallyl)amines with $KHCO_3$ as the C1 source: an efficient process for the synthesis of oxazolidin-2-ones†

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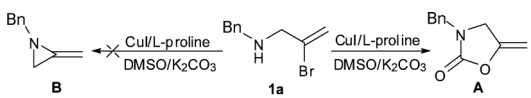
A novel synthesis of oxazolidin-2-ones by carbamic acid formation and a subsequent copper-catalyzed intramolecular vinylation from *N*-(2-bromoallyl)amines and $KHCO_3$ was developed. $KHCO_3$ was used as a C1 source and base in this efficient and convenient cascade process.

As an abundant, cheap and nontoxic C1 source for the production of organic chemicals, carbon dioxide is attractive to both industrial and academic scientists.[1] Extensive research has been conducted on the transformation of carbon dioxide into useful bulk products.[2] Nevertheless, the critical conditions regarding the transportation and storage of carbon dioxide as well as the safety factors associated with high-pressured batch reaction processes affect its utilization in scientific research and industrial production to some extent. Meanwhile, as a safe, cheap and commercially available carbon dioxide equivalent, inorganic carbonate is rarely used in organic synthesis as a C1 source, and its application is undoubtedly desirable.[3]

The classical copper-mediated Ullmann coupling reaction has been developed over one hundred years,[4] and great achievements have been made in the copper-mediated C–N, C–O and C–C bond formation reactions in the past two decades.[5] Although various ethers and oxygenated heterocycles can be constructed using a copper-mediated C–O formation reaction,[6] to our knowledge results have rarely been reported on the copper-mediated vinylation of carboxylic acid.[7] During the course of our continued research on the copper-catalyzed synthesis of heterocycles,[8] we unexpectedly discovered a novel cascade reaction of *N*-(2-bromoallyl)amine with $KHCO_3$, in which $KHCO_3$ acted as a C1 source, leading to the formation of oxazolidin-2-ones in moderate to good yields. The resulting heterocycles are important ubiquitous substructural units



Scheme 1 The reaction of *N*-(2-bromoallyl)benzylamine with K_2CO_3.

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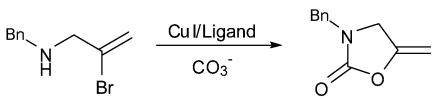
Table 1 Optimization of the reaction conditions for the formation of **2a**[a]



1a **2a**

Entry	Base/equiv.	Ligand[b]	Solvent	Yield[c] (%)
1	K_2CO_3/2.0	A	DMSO	45
2	K_2CO_3/2.0	B	DMSO	40
3	K_2CO_3/2.0	C	DMSO	48
4	K_2CO_3/2.0	D	DMSO	37
5	Cs_2CO_3/2.0	C	DMSO	Trace
6	$KHCO_3$/2.0	C	DMSO	55
7	$KHCO_3$/1.0 K_2CO_3/1.0	C	DMSO	68
8	$KHCO_3$/2.0 K_2CO_3/1.0	C	DMSO	74
9	$KHCO_3$/2.0 K_2CO_3/0.1	C	DMSO	74
10	$KHCO_3$/2.0 K_2CO_3/0.1	C	DMF	60
11[d]	$KHCO_3$/2.0 K_2CO_3/0.1	C	DMSO	59
12[e]	$KHCO_3$/2.0 K_2CO_3/0.1	C	DMSO	33

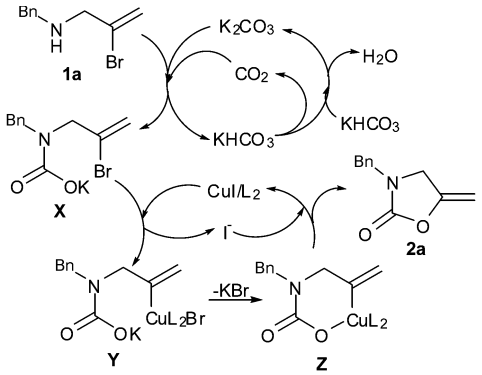
[a] Reaction conditions: **1a** (0.5 mmol), CuI (0.1 mmol), ligand (0.2 mmol), carbonate base (1.0 mmol), and 2 mL of solvent were sealed in a pressurized process vial at 120 °C for 4 h. [b] Ligand: A = L-proline, B = *N*,*N*-diethylglycine, C = *N*,*N*-dimethyl-ethane-1,2-diamine, D = 1,10-phenanthroline. [c] Isolated yield for **2a**. [d] The temperature of the reaction was 110 °C. [e] The temperature of the reaction was 100 °C.

which exist in many natural products and biologically active compounds,[9] and can be obtained from CO_2 fixing reactions.[10]

Using 0.2 equivalent of CuI as the catalyst and 0.4 equivalent of L-proline as the ligand, *N*-(2-bromoallyl)benzylamine (**1a**) was treated with 2 equivalents of K_2CO_3 in DMSO at 120 °C for 2 hours. After analyzing the ^{13}C-NMR and IR spectra of the final product, we surprisingly found that oxazolidin-2-one **A** (45% yield) was obtained instead of the expected aziridine **B** through a direct intramolecular Ullmann-type C–N formation (Scheme 1).

This unexpected and interesting result prompted us to screen the reaction conditions (Table 1). Firstly, we set out to screen the ligands in this reaction, *N*,*N*-dimethyl-ethane-1,2-diamine was found to be the best choice among the ligands (Table 1, entry 3).

We then turned our attention to other C1 sources such as Cs_2CO_3 and $KHCO_3$. A higher yield was obtained when $KHCO_3$ was used (Table 1, entry 6). To our delight, the yields were improved when additional K_2CO_3 was used in the reaction (Table 1, entries 7 and 8). Finally, we found that the highest yield of **2a** was obtained when a mixture of 2.0 equivalents of $KHCO_3$ and 0.1 equivalent of K_2CO_3 was used (Table 1, entry 9). Varying the solvent from DMSO to DMF did not enhance the yield of product (Table 1, entry 10). Lower yields were obtained when the reaction temperature was reduced to 110 °C or 100 °C (Table 1, entries 11 and 12).



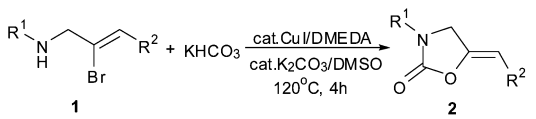
Scheme 2 The proposed mechanism for the formation of **2a**.

With the optimal conditions established, various *N*-(2-bromoallyl)amines were tested to form the corresponding oxazolidin-2-ones **2** (Table 2). As shown in Table 2, the products corresponding to the alkylamine substrates were obtained in good yields (Table 2 **2a–l**), and it is noteworthy that even a strained cyclopropyl substituted amine could give a corresponding ring preserved product **2j**. In contrast, the reactions of arylamines led to lower yields, probably due to the poor nucleophilicity of the arylamines (Table 2 **2m and n**). However, the yield could be improved when an electron donating group was introduced to the benzene ring (Table 2 **2o**). Importantly, this process could be extended to the reactions of internal alkenyl bromides, and modest yields of the products were obtained under identical reaction conditions (Table 2 **2p–r**).

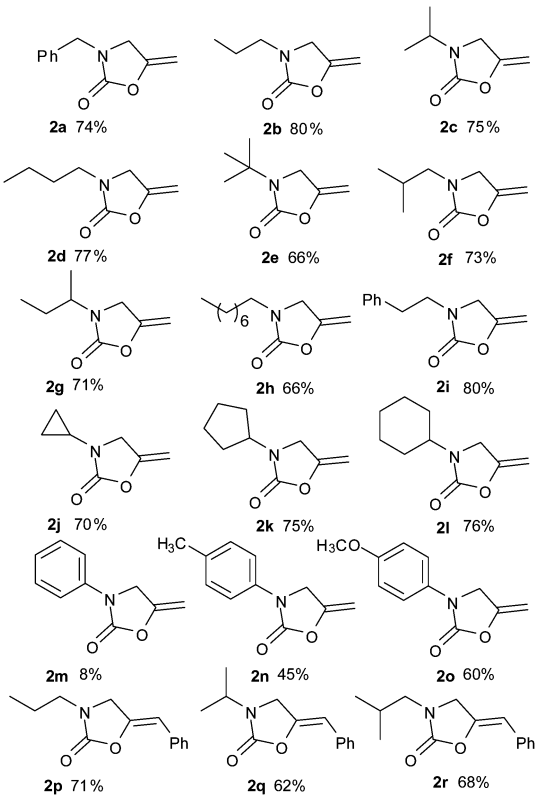
According to the previous reports and results above,[11] a proposed mechanism for this oxazolidin-2-one formation process is described in Scheme 2. When $KHCO_3$ is heated, it produces CO_2 and K_2CO_3. The substrate **1a** reacts with CO_2 in the presence of the base K_2CO_3 to form the carbamic acid salt **X**. The oxidative addition of **X** with the copper catalyst offers the intermediate **Y**. An intramolecular nucleophilic substitution in **Y** generates **Z**. The subsequent reductive elimination in **Z** readily affords the final product **2a** and regenerates the copper species to fulfil the catalytic cycle.

To further demonstrate the applicability and efficiency of this cascade methodology, a gram-scale reaction was performed. When 1.00 g (4.4 mmol) of **1a** was used as the starting material, the reaction could readily offer 0.60 g of **2a** (72%).

Table 2 Synthesis of various oxazolidin-2-ones **2**[a]



1 2



[a] Reaction conditions: **1** (0.5 mmol), CuI (0.1 mmol), DMEDA (0.2 mmol), $KHCO_3$ (1.0 mmol), K_2CO_3 (0.05 mmol), and 2 mL of DMSO were sealed in a pressurized process vial at 120 °C for 4 h.

Conclusions

In conclusion, we have developed a novel protocol for the synthesis of oxazolidin-2-ones *via* a cascade process of carbamic acid formation and a sequential copper-catalyzed

intramolecular vinylation of carboxylic acid. The utilization of $KHCO_3$ as the C1 source made this method efficient and convenient. Further applications of $KHCO_3$ as a C1 source are being investigated in our laboratory.

Acknowledgements

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