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Chemical Fixation of Carbon Dioxide by Copper Catalyzed Multicomponent Reactions for Oxazolidinedione Syntheses

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The quest to reduce greenhouse gases has triggered the development of new chemical fixation of carbon dioxide. Given the importance of CO_2 based transformation chemistry, we demonstrate fixation of CO_2 for oxazolidinedione synthesis via a novel multicomponent synthesis. In the presence of a catalytic amount of Cu_2O, various 2-bromo-3-phenylacrylic acid derivatives reacted with CO_2 and amines are transformed to the corresponding oxazolidinediones derivatives in high yields.

Introduction

With the alarming rise in global temperature, sustainable technologies need to give serious consideration to fixing carbon dioxide, a prominent greenhouse gas.[1] It is a C1 building block for chemical synthesis because of its ubiquitous, low cost and nontoxic nature. It has a tremendous potential as fuels, polymers or other chemicals through renewable energy utilization.[2] However, CO_2 is a less electrophilic and thermodynamically stable molecule. Therefore, strong nucleophiles have been required such as Grignard reagents and organolithium compounds for the activation. In the past decade transition-metal mediated chemical fixation of CO_2 has emerged as a potential approach towards synthesis of a variety of useful commodity chemicals such as carboxylic acids by the activation of C-H bonds in heterocycles synthesis.[3] Recently, Yoshida and coworkers reported that CO_2 could readily be incorporated by a three-component coupling reaction using arynes and imines, where generated zwitterions from nucleophilic attack of imines to arynes captured CO_2 as a route to biologically important functionalized benzoxazinones.[4] More recently Kobayashi et al. utilized a similar strategy for the synthesis of isocoumarins *via* new NHC-Cu catalyzed reactions involving ortho-arynes, terminal alkynes, and carbon dioxide.[5]

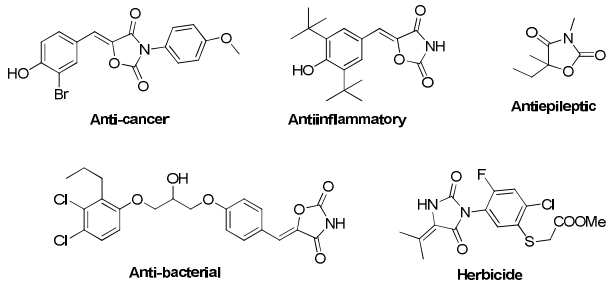

Figure 1. Some biologically important oxazolidinedione derivatives.

The decades of significant efforts toward exploring technologies for CO_2 transformation, however, have allowed only a handful of heterocyles to be synthesized, which is considered to be one of the most prominent areas of organic synthesis.[4-6] Hence, development of efficient methods utilizing CO_2 in combination with multicomponent reaction (MCR) for the synthesis of heterocyles such as oxazolidinedione is highly desirable for its applications from pharmaceuticals to polymers, which could potentially open access to a library of diverse oxazolidinediones scaffold.

Oxazolidinedione is a versatile component of many biologically active compounds. A vast number of pharmaceuticals containing these skeletons are being used for therapeutic purposes (Figure 1). For instance, it is used for anticonvulsant drugs such as ethadione, paramethadione, and trimethadione.[7] It has also been reported recently for their bioactivities such as sodium channel blocker, anti-diabetic and anti-cancer.[8]

Herein we describe the use of CO_2 as a C1 source in the three-component reaction involving amines and 2-bromo-3-phenylacrylic acid derivatives for the synthesis of oxazolidinediones with copper catalyst. Diverse oxazolidinediones were synthesized in good to excellent yields,

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where amine component has been changed from aliphatics to aromatics. This catalytic system is a simple and practical protocol with great potential for further applications especially in medicinal chemistry.

Result and Discussion

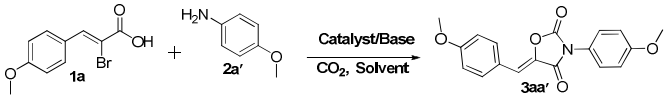
Originally, we were encouraged by the result reported on the base mediated reaction of amine and CO_2 for the synthesis of carbamic acid type reactive intermediate.[9] We anticipated that such an intermediate could be incorporated in alkene to generate newer heterocycles by metal catalysts.[10] To prove our working hypothesis, studies were initiated with benchmark reactions of 2-bromo-3-(4-methoxyphenyl)acrylic acid[11] **1a** and *p*-anisidine **2a'** under CO_2 transformation conditions for oxazolidinedione synthesis (**3aa'**) (Table 1), involving optimization with respect to catalysts, bases, solvents, and temperature. Several metal catalysts were initially investigated for the reaction of **1a** as a model substrate in DMF at 80°C in the presence of Cs_2CO_3 (2.0 equiv relative to amount of **1a**) as a base under atmospheric CO_2 pressure for 12 h (Table 1). The reaction did not proceed in the absence of the metal salt (Table 1, entry 1). Palladium salt, which was expected to activate the cross coupling reaction, hardly worked for this reaction (Table 1, entry 7). Hence, a series of various copper catalysts were investigated under identical reaction condition at 80 °C in Cs_2CO_3 as a base. As shown in Table 1, DMF (Table 1, entries 2-6), and Cu_2O catalyst showed the best activity with isolated yield of 81% (Table 1, entry 5). The isolated product was characterized by NMR and GC-MS. It was further confirmed by single crystal X-ray diffraction study (Figure 2, Supplementary information section S1.3.1, S1.4 and Figure S1).

Encouraged by this result, we investigated the effect of bases and solvents with Cu_2O as an optimum catalyst. Different bases such as K_2CO_3, K_3PO_4, 4-Dimethylaminopyridine (DMAP), Potassium *tert*-butoxide (KOtBu) and 1,8-Diazabicycloundec-7-ene (DBU) were used (entries 8-12) to find that the best result was obtained with inorganic base Cs_2CO_3 although DBU was equally capable of accelerating the reaction.

In the preliminary examination of solvents such as DMSO, dioxane, DMA, toluene (entries 13-16), nonprotic polar solvents were found to promote the reaction smoothly, and DMF was revealed as the best solvent for the model reaction. We also found that a milder reaction temperature at 60°C and a lower catalyst loading (0.5 mol%) resulted in a lower yield (entries 17-18). An alternative attempt to utilize heterogeneous catalyst for CO_2 fixation reaction *via* Cu_2O/N-doped reduced graphene oxide (Cu_2O/N-rGO) catalyst was not successful only with moderate yield (entry 19). It is noted in this regard that this reaction is very simple with relatively high yield. The preliminary result is all the more interesting as no further addition of any ligand was required with metal catalyst.

As shown in Figure 3, the scope of CO_2 fixation multicomponent reaction of 2-bromo-3-alkylacrylic acids with amines can be extended to the formation of various products by employing different amines and various bromoacrylic acid derivatives under the optimized conditions: 1 mol% of Cu_2O catalyst, 2 equiv. of Cs_2CO_3 base, DMF solvent.

Table 1: Optimization of reaction conditions for the formation of oxazolidinedione via CO_2 fixation multicomponent reactions of alkylacrylic acid with amine.[a]



Entry	Catalyst	Solvent	Base	Yield[b]
1	-	DMF	Cs_2CO_3	0
2	CuI	DMF	Cs_2CO_3	56
3	CuBr	DMF	Cs_2CO_3	45
4	CuCl	DMF	Cs_2CO_3	23
5	Cu_2O	DMF	Cs_2CO_3	81
6	$Cu(OAc)_2$	DMF	Cs_2CO_3	39
7[c]	$Pd(OAc)_2$	DMF	Cs_2CO_3	0
8	Cu_2O	DMF	K_2CO_3	69
9	Cu_2O	DMF	K_3PO_4	29
10	Cu_2O	DMF	KO^{t}Bu	0
11	Cu_2O	DMF	DBU	77
12	Cu_2O	DMF	DMAP	13
13	Cu_2O	DMSO	Cs_2CO_3	67
14	Cu_2O	Dioxane	Cs_2CO_3	34
15	Cu_2O	DMA	Cs_2CO_3	68
16	Cu_2O	Toluene	Cs_2CO_3	12
17[d]	Cu_2O	DMF	Cs_2CO_3	51
18[e]	Cu_2O	DMF	Cs_2CO_3	32
19	Cu_2O/N-rGO	DMF	Cs_2CO_3	46

[a]**1a** (0.50 mmol), **2a** (0.60 mmol), Cu/Pd source (1.0 mol %), CO_2 (1 atm), solvents (2 ml) at 80 °C for 12 h. [b]Isolated yield. [c]1,3-bis(4-methoxyphenyl)urea (**4**) was isolated (12% yield). [d]Reaction temperature was 60°C. [e]Catalyst loading was 0.5 mol%.

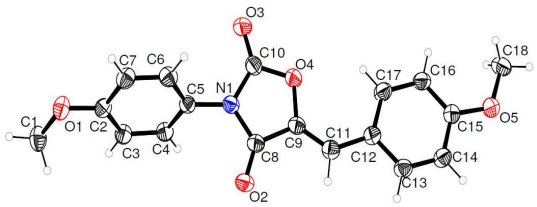
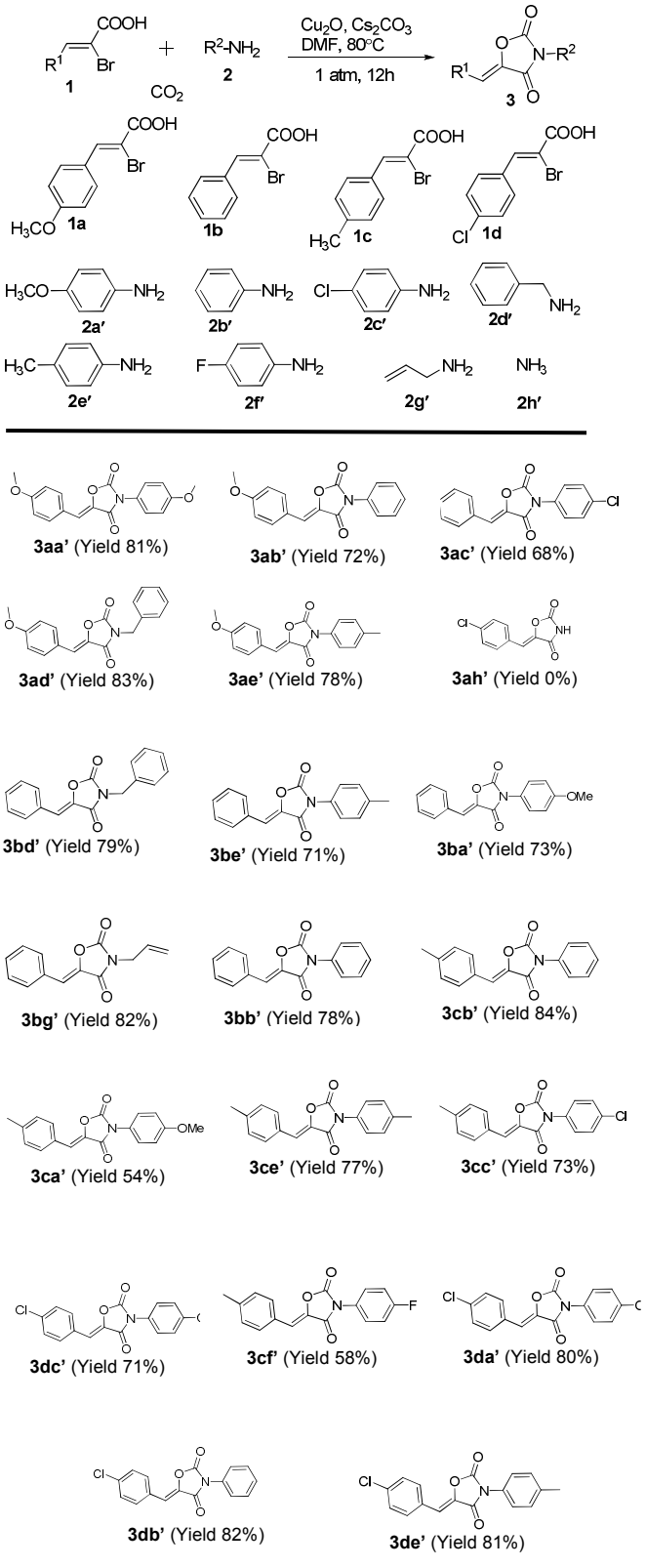


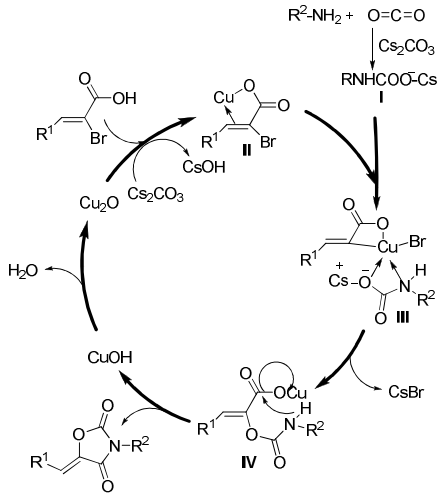
Figure 2. Single-crystal X-ray diffraction analysis for (**3aa'**). Thermal ellipsoids are shown at 30% probability level.

Four types of 2-bromo-3-alkylacrylic acid derivatives with *p*-methoxyphenyl (**1a**), phenyl (**1b**), *p*-tolyl (**1c**), and *p*-chlorophenyl (**1d**) substitutes were first synthesized by multistep reactions (See supplementary information section S1.2). Then, the synthesized bromoacrylic acid compounds were reacted with aliphatic and aromatic amines under the derived optimal conditions (See supplementary

Figure 3. Copper-catalyzed cascade synthesis of oxazolidinediones via CO_2 fixation multicomponent reactions; [a]**1** (1.0 mmol), **2** (1.2 mmol), Cu_2O (1.0 mol %), Cs_2CO_3 (2.0 mmol) CO_2 (1 atm), solvents (4 mL) at 80 °C for 12 h. [b]Isolated yield.



information section S1.3). In the synthesis of oxazolidinedione with various aliphatic amines, benzyl amine, and allyl amine produced the corresponding oxazolidinediones (3ad', 3bd', 3bg') in high yields (79-83%), while the use of ammonia instead of aliphatic amines did not allow isolation of the product (**3ah'**). Furthermore, we synthesized aromatic amine containing oxazolidinedione ring systems, and comparatively moderate to high yields in the range of 58-86% of oxazolidinediones were obtained as listed in Figure 3. Mostly, *p*-OCH_3 electron donating group on aromatic amines (**3aa'**, **3ba'**, **3ca'**) furnished the products with superior yields over 80% in comparison to yields in range of 68-73% for the *p*-Cl electron withdrawing group presented on the amines (**3ac'**, **3cc'**, **3dc'**). Alternatively, the bromoacrylic acid derivatives with *p*-methoxyphenyl, phenyl, *p*-tolyl, *p*-chlorophenyl groups on the alkene gave moderate to high yields (58-88%), irrespective of the electron-withdrawing (**3ac'**, **3cc'**, **3cf'**, **3dc'**) or electron-donating (**3aa'**, **3ba'**, **3ca'**, **3da'**) nature of the group on the phenyl ring.

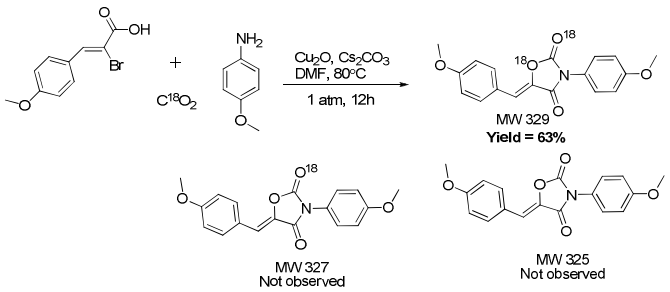


Scheme 1. Proposed reaction pathways for the synthesis of oxazolidinedione via CO_2 fixation multicomponent reactions

To further enhance the synthetic profile of the three component coupling reactions of 2-bromo-3-alkylacrylic acid (**1a**), amine (**2a**), and CO_2, we also performed a scale-up synthesis of this copper-catalyzed reaction to obtain 2.3 gram product (**3aa'**) with 72 % yield by the identical protocol with no chromatography filtration step as aforementioned, indicating further upscaling potential. (See supplementary information scheme S1).

Scheme 1 shows hypothetical reaction mechanism. Firstly, the amine and the CO_2 react together to form an intermediate as a conjugate base of carbamic acid **I**.[9b] Further, the corresponding 2-bromo-3-alkylacrylic acid coordinates with a Cu(I) ion and forms **II** in the presence of base (Cs_2CO_3). Next, 2-bromo-3-alkylacrylic acid Cu complexes **II** undergo intramolecular oxidative addition followed by complex formation with carbamic acid **I** to generate coper complex **III**, and subsequent reductive elimination of copper complex **III** provides the intermediate **IV**. Intramolecular nucleophilic attack of amino to carbonyl in **IV** affords oxazolidinedione, freeing the copper catalyst. Eventually, in this proposed mechanism, the corresponding oxazolidinedione derivative contains carbon dioxide that is inserted into a heterocyclic ring.

To gain a better insight into this Cu catalyzed three-component reaction with carbon dioxide, control experiments were performed. Normally, Cu-catalysed three component reaction was carried out at atmospheric pressure of CO_2. To prove the origin of inserted carbon dioxide, isotope-labelling experiments with $C^{18}O_2$ were conducted to investigate the presence of carbon dioxide in the oxazolidinedione molecule (Scheme 2).[10] As a result, the ^{18}O-labeled oxazolidinedione (MW 329) was detected by mass spectral analysis, and the non-labeled oxazolidinedione (MW 325, MW 327) was not detected at all (See supplementary information Figure S2). This result clearly supports the proposed reaction mechanism by demonstrating that two oxygen atoms were originated from carbon dioxide, indicating the participation of whole CO_2 molecule in forming the heterocyclic ring during the three component reaction.



Scheme 2. Mechanistic prove for the synthesis of oxazolidinedione via CO_2 fixation multicomponent reactions by isotopic labelling experiments.

Conclusion

In conclusion, we demonstrate fixation of carbon dioxide for oxazolidinedione synthesis via a novel multicomponent synthesis. This reaction employed catalytic Cu_2O in the presence of Cs_2CO_3 base to synthesize oxazolidinedione derivatives in good-to-high yields. A number of aliphatic and aromatic amines as well as acrylic acid derivatives can be transformed in high yields to pharmaceutically relevant oxazolidinedione compounds even on a large scale. This catalyst system does not need any sensitive ligands or expensive additives. The results indicate that carbon dioxide can conceptually be further utilized in various multicomponent reactions. Therefore, we anticipate that this work would contribute substantially to the development of next-generation CO_2 utilization.

Experimental Details.

To a solution of a substituted 2-bromo-3-phenylacrylic acid (1.0 mmol), amines (1.2 mmol) Cu_2O (1.0 mol%) and DMF (4mL) in a Schlenk flask was added Cs_2CO_3 (2.0 mmol, 2eq.). The inside of the reaction container was purged with CO_2 by a balloon three times (~1.0 atm). The reaction mixture was stirred at 80 °C for 12 hours. Aqueous solution of $NaHCO_3$ was added to reaction mixture and the water layer was separated with separatory funnel using $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The pure corresponding oxazolidinone was obtained with no further purification. Oxazolidinone have been further crystallize by the methanol.

Acknowledgements

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References

1. a) P. N. Pearson, M. R. Palmer, *Nature*, 2000, **406**, 695; b) M. Pagani, Z. H. Liu, J. L. Riviere, A. C. Ravelo, *Nat. Geosci.* 2010, **3**, 27.
2. CO_2 as a Chemical Feedstock, ed. M. Aresta, Wiley-VHC, Weinheim, **2010**; b) K. Huang, C. L. Sun, Z. J. Shi, *Chem. Soc. Rev.* 2011, **40,** 2435; c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kuehn, *Angew. Chem., Int. Ed.* 2011, **50**, 8510; d) T. Sakakura, J. Choi, H. Yasuda, *Chem. Rev*. 2007, **107**, 2365.
3. K. Sasano, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* 2013, **135**, 10954; b) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* 2010, **132**, 8858; c) L. Zhang, J. Cheng, T. Ohishi, Z. Hou, *Angew. Chem. Int. Ed.* 2010, **49**, 8670; d) O. Vechorkin, N. Hirt, X. Hu, *Org. Lett.* 2010, **12**, 3567; e) A. Correa, T. León, R. Martin, *J. Am. Chem. Soc.* 2014, **136**, 1062; f) K. Inamoto, N. Asano, Y. Nakamura, M. Yonemoto, Y. Kondo, *Org. Lett.* 2012, **14**, 2622; g) H. Inomata, K. Ogata, S. Fukuzawa, Z. Hou, *Org. Lett.* 2012, **14**, 3986; h) W. J. Yoo, M. G. Capdevila, X. Du, S. Kobayashi, *Org. Lett.* 2012, **14**, 5326; i) D. Yu, Y. Zhang, *P. Natl. Acad. Sci.* 2010, **107**, 20184; j) H. Mizuno, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* 2011, **133**, 1251; k) Y. Sugawara, W. Yamada, S. Yoshida, T. Ikeno, T. Yamada, *J. Am. Chem. Soc.* 2007, **129**, 12902; l) S. Kikuchi, K. Sekine, T. Ishida, T. Yamada, *Angew. Chem. Int. Ed.* 2012, **51**, 6989.
4. H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.* 2006, **128**, 11040; b) H. Yoshida, T. Morishita, J. Ohshita, *Org. Lett.* 2008, **10**, 3845.
5. W. J. Yoo, T. V. Q. Nguyen, S. Kobayashi, *Angew. Chem. Int. Ed.* 2014, **53**, 10213.
6. T. Kaicharla, M. Thangaraj , A. T. Biju, *Org. Lett.*, 2014, **16**, 1728.
7. a) J. W. C. Lewis, *Chem. Rev.*, 1958, **58**, 63; *b*) P. C. Unangst, D. T. Connor, W. A. Cetenko, R. J. Sorenson, C. R. Kostlan, J. C. Sircar, C. D. Wright, D. J. Schrier, R. D. Dyer, *J. Med. Chem.* 1994, **37**, 322; *c*) D. A Heerding, L. T. Christmann, T. J. Clark, D. J. Holmes, S. F. Rittenhouse, D. T. Takata, J. W. Venslavsky, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3771
8. K. Harada, H. Kubo, A. Tanaka, K. Nishioka, *Bioorg. Med. Chem. Lett.* 2012, **22**, 504.
9. S. H. Kim, K. H. Kim, S. H. Hong, *Angew. Chem. Int. Ed.* 2014, **53**, 771; b) S. L. Peterson, S. M. Stucka, C. J. Dinsmore, Org. Lett. 2010, **12**, 1340; c) M. Yoshida, Y. Komatsuzaki, M. Ihara, *Org. Lett.* 2008, **10**, 2083.
10. T. Ishida, S. Kikuchi, T. Yamada, *Org. Lett*. 2013, **15**, 3710.
11. X. Gong, H. Yang, H. Liu, Y. Jiang, Y. Zhao, H. Fu, *Org. Lett.* 2010, **12**, 3128.

Graphical Abstract: