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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 CO₂ based transformation chemistry, we demonstrate the fixation of CO₂ for oxazolidinedione synthesis *via* a novel multicomponent synthesis. In the presence of a catalytic amount of Cu₂O, various 2-bromo-3-phenylacrylic acid derivatives reacted with CO₂ and amines are transformed to the corresponding oxazolidinedione 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, CO₂ is a less electrophilic and thermodynamically stable molecule. Therefore, strong nucleophiles such as Grignard reagents and organolithium compounds are required for the activation. In the past decade, transition-metal mediated chemical fixation of CO₂ has emerged as a potential approach towards the synthesis of a variety of useful commodity chemicals such as carboxylic acids by the activation of C–H bonds in heterocycle synthesis.³ Recently, Yoshida and coworkers reported that CO₂ 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 CO₂ 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

Decades of significant efforts toward exploring technologies for CO₂ transformation, however, have allowed only a handful of heterocycles 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 CO₂ in combination with a multicomponent reaction (MCR) for the synthesis of heterocycles such as oxazolidinedione is highly desirable for its applications from pharmaceuticals to polymers, which could potentially open access to a library of diverse oxazolidinedione scaffolds.

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

Herein we describe the use of CO₂ as a C1 source in the three-component reaction involving amines and 2-bromo-3-phenylacrylic acid derivatives for the synthesis of oxazolidinediones with a copper catalyst. Diverse oxazolidinediones were syn-

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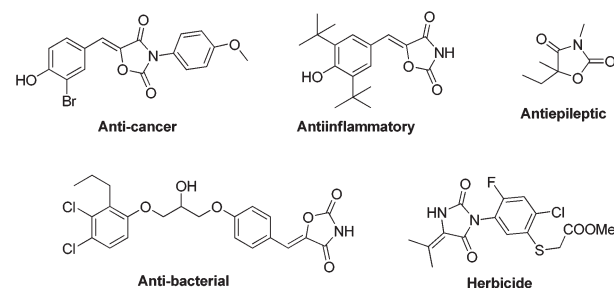


Fig. 1 Some biologically important oxazolidinedione derivatives.

thesized in good to excellent yields, where an 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.

Results and discussion

Originally, we were encouraged by the result reported on the base mediated reaction of amine and CO₂ for the synthesis of a carbamic acid type reactive intermediate.⁹ We anticipated that such an intermediate could be incorporated into 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 acid¹¹ **1a** and *p*-anisidine **2a'** under CO₂ 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 Cs₂CO₃ (2.0 equiv. relative to amount of **1a**) as a base under atmospheric CO₂ 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 conditions at 80 °C using Cs₂CO₃ as a

base. As shown in Table 1, DMF (Table 1, entries 2–6), and a Cu₂O catalyst showed the best activity with an isolated yield of 81% (Table 1, entry 5). The isolated product was characterized by NMR and GC-MS. It was further confirmed by a single crystal X-ray diffraction study (Fig. 2, ESI S1.3.1, S1.4 and Fig. S1†).

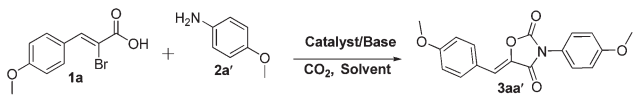
Encouraged by this result, we investigated the effect of bases and solvents with Cu₂O as an optimum catalyst. Different bases such as K₂CO₃, K₃PO₄, 4-dimethylaminopyridine (DMAP), potassium *tert*-butoxide (KO^tBu) and 1,8-diazabicycloundec-7-ene (DBU) were used (entries 8–12) to find that the best result was obtained with the inorganic base Cs₂CO₃ although DBU was equally capable of accelerating the reaction.

In the preliminary examination of solvents such as DMSO, dioxane, DMA, and 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 and 18). An alternative attempt to utilize a heterogeneous catalyst for the CO₂ fixation reaction *via* a Cu₂O/N-doped reduced graphene oxide (Cu₂O/N-rGO) catalyst was unsuccessful with only a moderate yield (entry 19). It is noteworthy that this reaction is very simple with a relatively high yield. The preliminary result is all the more interesting as no further addition of any ligand was required with metal catalysts.

As shown in Fig. 3, the scope of the CO₂ 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 optimized conditions: 1 mol% of Cu₂O catalyst, 2 equiv. of Cs₂CO₃ base, DMF solvent.

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 ESI S1.2†). Then, the synthesized bromoacrylic acid compounds were reacted with aliphatic and aromatic amines under the derived optimal conditions (see ESI 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 an aromatic amine containing oxazolidinedione ring systems, and comparatively moderate to high yields in the range of 58–86% of oxazolidinediones were obtained as shown in Fig. 3. Mostly, the *p*-OCH₃ electron

Table 1 Optimization of reaction conditions for the formation of oxazolidinedione *via* CO₂ fixation multicomponent reactions of alkylacrylic acid with amine^a



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

^a **1a** (0.50 mmol), **2a** (0.60 mmol), Cu/Pd source (1.0 mol%), CO₂ (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%.

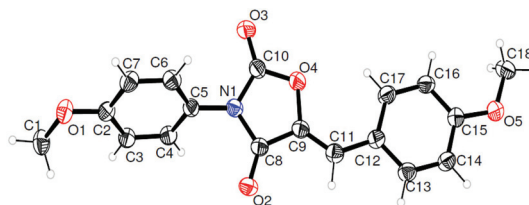


Fig. 2 Single-crystal X-ray diffraction analysis for (**3aa'**). Thermal ellipsoids are shown at the 30% probability level.

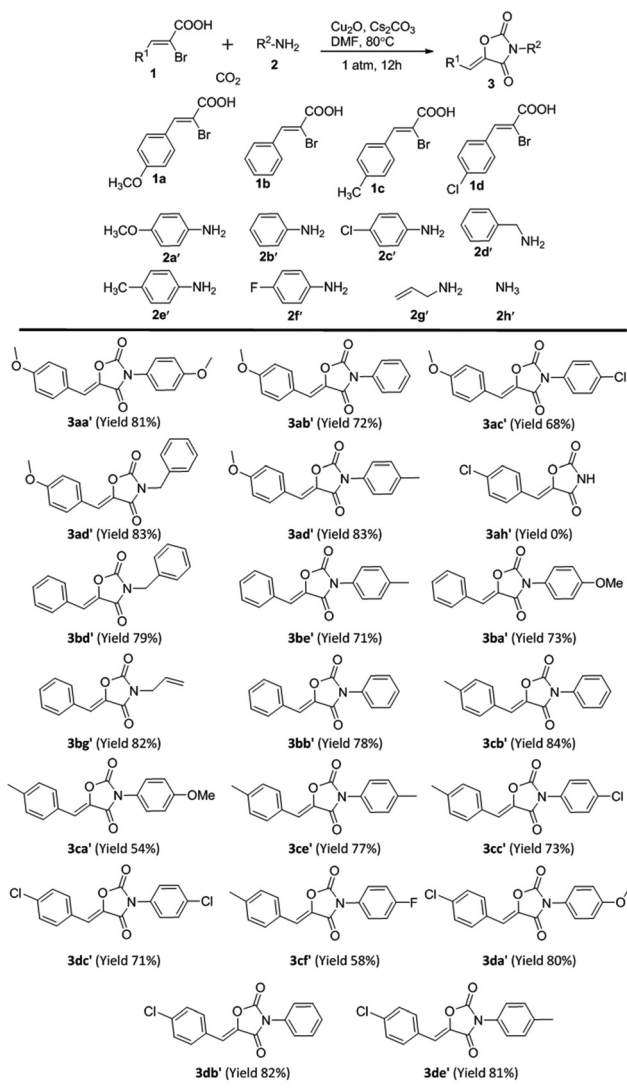
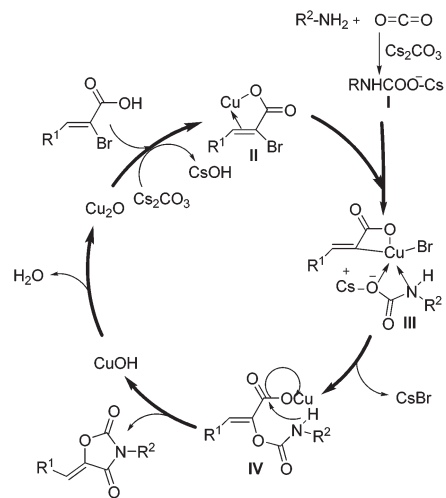


Fig. 3 Copper-catalyzed cascade synthesis of oxazolidinediones via CO_2 fixation multicomponent reactions; **1** (1.0 mmol), **2** (1.2 mmol), Cu_2O (1.0 mol%), Cs_2CO_3 (2.0 mmol), CO_2 (1 atm), solvents (4 mL) at 80°C for 12 h.

donating group on aromatic amines (**3aa'**, **3ba'**, **3ca'**) furnished the products with superior yields over 80% in comparison with yields in the range of 68–73% for the *p*-Cl electron withdrawing group present on the amines (**3ac'**, **3cc'**, **3dc'**). Alternatively, the bromoacrylic acid derivatives with *p*-methoxyphenyl, phenyl, *p*-tolyl, and *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.

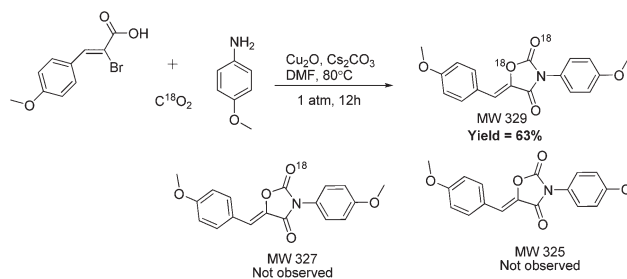
To further enhance the synthetic profile of the three component coupling reactions of 2-bromo-3-alkylacrylic acid (**1a**), amine (**2a**), and CO_2 , we also performed a scale-up synthesis of this copper-catalyzed reaction to obtain a 2.3 gram product (**3aa'**) with 72% yield by the identical protocol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



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

Scheme 1 shows a 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} Furthermore, the corresponding 2-bromo-3-alkylacrylic acid coordinates with a $\text{Cu}(\text{I})$ ion and forms **II** in the presence of a base (Cs_2CO_3). Next, 2-bromo-3-alkylacrylic acid Cu complex **II** undergoes intramolecular oxidative addition followed by complex formation with carbamic acid **I** to generate copper 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, the Cu -catalyzed three component reaction was carried out at an 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 (M_w 329) was detected by mass spectral analysis, and the non-labeled oxazolidinedione (M_w 325, M_w 327) was not detected at



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

all (see ESI Fig. S2†). This result clearly supports the proposed reaction mechanism by demonstrating that two oxygen atoms originated from carbon dioxide, indicating the participation of the whole CO₂ molecule in forming the heterocyclic ring during the three component reaction.

Conclusion

In conclusion, we have demonstrated the fixation of carbon dioxide for oxazolidinedione synthesis *via* a novel multicomponent synthesis. This reaction employed catalytic Cu₂O in the presence of Cs₂CO₃ 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 CO₂ utilization.

Experimental details

To a solution of a substituted 2-bromo-3-phenylacrylic acid (1.0 mmol), amines (1.2 mmol), Cu₂O (1.0 mol%) and DMF (4 mL) in a Schlenk flask was added Cs₂CO₃ (2.0 mmol, 2 equiv.). The reaction container was purged with CO₂ by a balloon three times (~1.0 atm.). The reaction mixture was stirred at 80 °C for 12 hours. An aqueous solution of NaHCO₃ was added to the reaction mixture and the water layer was separated with a separatory funnel using CHCl₃. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The pure corresponding oxazolidinone was obtained with no further purification. Oxazolidinone have been further crystallized by methanol.

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References

- (a) P. N. Pearson and M. R. Palmer, *Nature*, 2000, **406**, 695; (b) M. Pagani, Z. H. Liu, J. L. Riviere and A. C. Ravelo, *Nat. Geosci.*, 2010, **3**, 27.
- (a) CO₂ as a Chemical Feedstock, ed. M. Aresta, Wiley-VHC, Weinheim, 2010; (b) K. Huang, C. L. Sun and Z. J. Shi, *Chem. Soc. Rev.*, 2011, **40**, 2435; (c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann and F. E. Kuehn, *Angew. Chem., Int. Ed.*, 2011, **50**, 8510; (d) T. Sakakura, J. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365.
- (a) K. Sasano, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2013, **135**, 10954; (b) I. I. F. Boogaerts and S. P. Nolan, *J. Am. Chem. Soc.*, 2010, **132**, 8858; (c) L. Zhang, J. Cheng, T. Ohishi and Z. Hou, *Angew. Chem., Int. Ed.*, 2010, **49**, 8670; (d) O. Vechorkin, N. Hirt and X. Hu, *Org. Lett.*, 2010, **12**, 3567; (e) A. Correa, T. León and R. Martín, *J. Am. Chem. Soc.*, 2014, **136**, 1062; (f) K. Inamoto, N. Asano, Y. Nakamura, M. Yonemoto and Y. Kondo, *Org. Lett.*, 2012, **14**, 2622; (g) H. Inomata, K. Ogata, S. Fukuzawa and Z. Hou, *Org. Lett.*, 2012, **14**, 3986; (h) W. J. Yoo, M. G. Capdevila, X. Du and S. Kobayashi, *Org. Lett.*, 2012, **14**, 5326; (i) D. Yu and Y. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20184; (j) H. Mizuno, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2011, **133**, 1251; (k) Y. Sugawara, W. Yamada, S. Yoshida, T. Ikeno and T. Yamada, *J. Am. Chem. Soc.*, 2007, **129**, 12902; (l) S. Kikuchi, K. Sekine, T. Ishida and T. Yamada, *Angew. Chem., Int. Ed.*, 2012, **51**, 6989.
- (a) H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *J. Am. Chem. Soc.*, 2006, **128**, 11040; (b) H. Yoshida, T. Morishita and J. Ohshita, *Org. Lett.*, 2008, **10**, 3845.
- W. J. Yoo, T. V. Q. Nguyen and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 10213.
- T. Kaicharla, M. Thangaraj and A. T. Biju, *Org. Lett.*, 2014, **16**, 1728.
- (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 and 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 and J. W. Venslavsky, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3771.
- K. Harada, H. Kubo, A. Tanaka and K. Nishioka, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 504.
- (a) S. H. Kim, K. H. Kim and S. H. Hong, *Angew. Chem., Int. Ed.*, 2014, **53**, 771; (b) S. L. Peterson, S. M. Stucka and C. J. Dinsmore, *Org. Lett.*, 2010, **12**, 1340; (c) M. Yoshida, Y. Komatsuzaki and M. Ihara, *Org. Lett.*, 2008, **10**, 2083.
- T. Ishida, S. Kikuchi and T. Yamada, *Org. Lett.*, 2013, **15**, 3710.
- X. Gong, H. Yang, H. Liu, Y. Jiang, Y. Zhao and H. Fu, *Org. Lett.*, 2010, **12**, 3128.