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Synthesis of oxazolidine-2,4-diones by a tandem phosphorus-mediated carboxylative condensation–cyclization reaction using atmospheric carbon dioxide†

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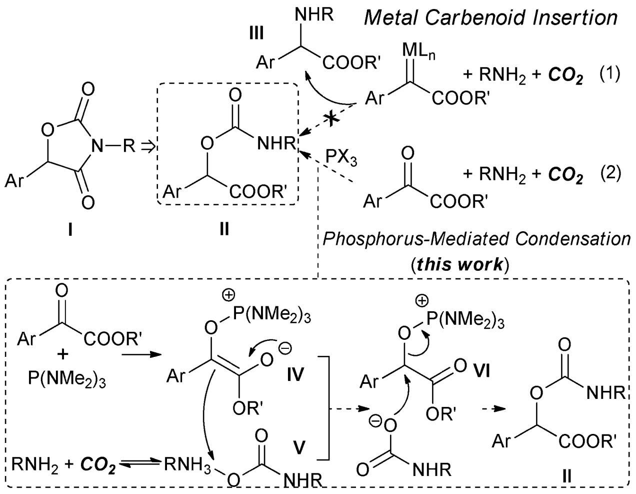
The oxazolidine-2,4-dione motif is found frequently in biologically important compounds. A tandem phosphorus-mediated carboxylative condensation of primary amines and α-ketoesters/base-catalyzed cyclization reaction have been developed. These processes provide a novel and convenient access to various oxazolidine-2,4-diones in a one-pot fashion using atmospheric carbon dioxide and readily available substrates under very mild and transition-metal-free conditions.

Oxazolidine-2,4-diones are important structural motifs frequently found in medicinally relevant and biologically active molecules.[1–5] These compounds have been identified as having diverse properties such as antitumor,[1] cardiotonic,[2] antidiabetic,[3] and anti-inflammatory activity.[4] For example, vinzolidine shows broad inhibitory activity against many cancer cell lines.[1] Anticonvulsants ethosuximide and trimethadione were found to exhibit life-span-extending activity.[5] Vinclozolin has long been established as a common fungicide used to control diseases in fruits and vegetables. With regard to oxazolidine-2,4-diones synthesis, most of the traditional strategies suffer from harsh reaction conditions, multi-steps and the use of very toxic compounds like phosgene and isocyanates. Therefore, a mild, convenient and environmentally friendly method for the synthesis of oxazolidine-2,4-diones is highly desired.

Recently, the development of homogeneous transformation of carbon dioxide into valuable fine chemicals has drawn considerable attention since carbon dioxide is an abundant, nontoxic and renewable carbon resource.[6] Reactions of carbon dioxide with relatively weak carbon nucleophiles, C–H bonds, halide electrophiles have been successfully developed to access functionalized carboxylic acids and derivatives.[7] Due to the thermodynamic and kinetic stability of carbon dioxide, high-energy starting materials or transition-metal catalysts are often used to facilitate these reactions. Despite their good catalytic efficiency, the use of transition metals involves drawbacks including their associated cost, toxicity, and raises the important issue of removing metal impurities from the products, especially in the synthesis of pharmaceutical compounds. Therefore, the development of a transition-metal-free methodology to convert carbon dioxide into value-added compounds is desirable.[8]

Intrigued by the development of a convenient access to oxazolidine-2,4-dione and as a continuation of our interest in carbon dioxide utilization,[9] we envisioned that oxazolidine-2,4-dione **I** could be easily synthesized by cyclization of carbamate **II**, which might be obtained by an insertion reaction of a metal carbenoid and carbamic acid formed *in situ* from primary amines and carbon dioxide (eqn (1), Scheme 1).[10,11] However, our initial investigation revealed that the $Rh_2(OAc)_4$ catalyzed reaction of amine, carbon dioxide and methyl 2-diazo-2-phenylacetate gave no carbamate product **II** (see ESI†). Instead, non-carboxylative product **III** was exclusively formed from the insertion of the N–H bond of the amine into the metal carbenoid, due to that metal



Scheme 1 Synthesis of oxazolidine-2,4-diones *via* a tandem phosphorus-mediated carboxylative condensation–cyclization sequence using atmospheric carbon dioxide.

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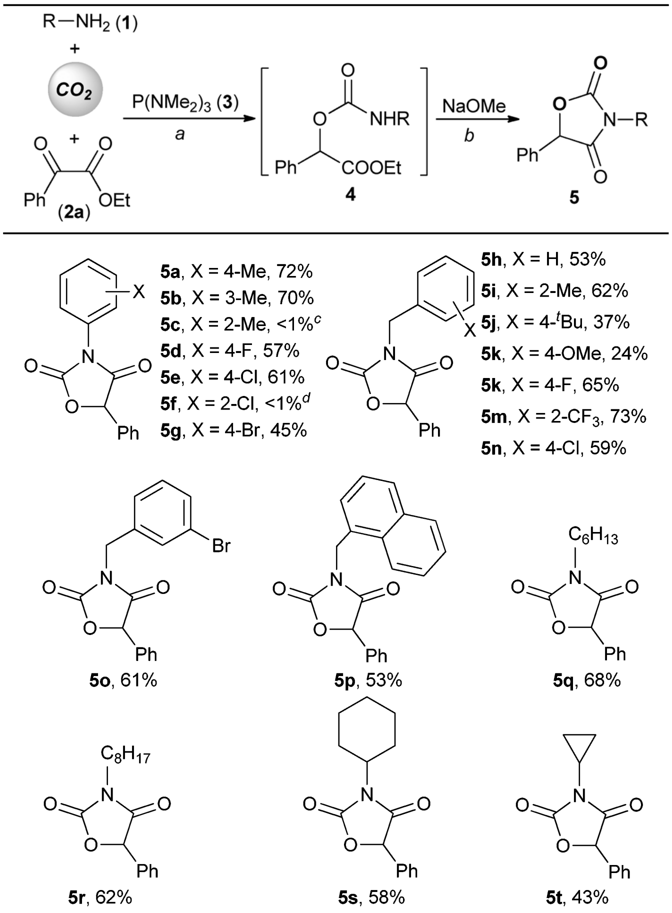
carbenoid is electrophilic[12] and the nitrogen atom in amine shows a much higher nucleophilicity than the oxygen atom in unstable carbamic acid. Very recently, Jiang and co-workers reported an elegant synthesis of carbamate by the reaction of amine, carbon dioxide and *N*-tosylhydrazones promoted by potassium carbonate,[13] in which a carbocation generated by decomposition of carbene in a protic solvent was proposed as a key intermediate. The reaction proceeded under relatively harsh reaction conditions (4 MPa of carbon dioxide and 120 °C), presumably because of the low nucleophilicity of carbamic acid.

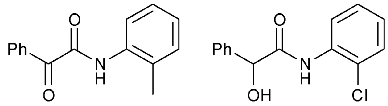
On the other hand, the carbamic acid shows much higher acidity or electrophilicity than the amine and thus prefers to react with an active nucleophile. It was reported that Kukhtin–Ramirez addition of tris(dimethylamino)phosphine to α-ketoester gives adduct **IV**,[14] which reacts formally as a carbene but proves to serve as a nucleophile to react with many electrophilic reagents.[15,16] We reasoned that in our designed reaction system of eqn (2) in Scheme 1, adduct **IV** would rapidly react with carbamic acid **V** rather than the amine *via* proton transfer. It should be noted that proton transfer from phenols, amides and carboxylic acids to the Kukhtin–Ramirez adduct has been recently testified to be feasible by Radosevich and co-workers' elegant studies.[16] The produced alkoxyphosphonium species **VI** would then conduct nucleophilic displacement with the carbamate group to yield target product **II** (Scheme 1). Therefore, this reaction system would offer an access to oxazolidine-2,4-diones from atmospheric carbon dioxide under very mild reaction conditions. Herein, we report a new and convenient synthesis of oxazolidine-2,4-diones *via* a tandem phosphorus-mediated carboxylative condensation/base-catalyzed cyclization sequence in a one-pot fashion using atmospheric carbon dioxide and readily available substrates under transition-metal free conditions.

In initial experiments with *p*-toluidine (**1a**), atmospheric carbon dioxide and ethyl benzoylformate (**2a**), we found that upon employing tris(dimethylamino)phosphine (**3**) the condensation reaction proceeded rapidly and carbamate product **4a** was obtained exclusively in excellent yield, which probably attributed to the high affinity of the Kukhtin–Ramirez adduct toward *in situ* formed carbamic acid rather than amine. To avoid a tedious isolation procedure for **4a**, the residue from the condensation reaction was directly used in the next NaOMe-catalyzed cyclization reaction. After an easy workup to remove the water-soluble byproduct hexamethylphosphoramide, the tandem sequence afforded oxazolidine-2,4-dione **5a** in 72% isolated yield in a one-pot fashion. It is noteworthy that as a carboxylative reagent, carbon dioxide is totally incorporated in the oxazolidine-2,4-dione product as the carboxylate moiety. Other phosphorus(III) reagents such as $P(OMe)_3$ only gave a trace product and PEt_3 proved to be ineffective in this reaction system.

Table 1 Synthesis of oxazolidine-2,4-diones from various primary amines (**1**), atmospheric carbon dioxide and ethyl benzoylformate (**2a**)



[a] Reaction conditions: primary amine **1** (1.2 mmol), ethyl benzoylformate (1.0 mmol), carbon dioxide (1 atm), THF (10 mL), −78 °C to rt, 1.5 h. [b] Reaction conditions: NaOMe (0.1 mmol), toluene, 110 °C, 1 h. Yields of isolated products are given. [c] 81% yield of **4c** was isolated in the first step, compound **6c** was isolated as the main product. [d] 80% yield of **4f** was isolated in the first step, compound **6f** was isolated as the main product.



6c **6f**

With these optimal reaction conditions in hand, the substrate scope with respect to the primary amine was investigated (Table 1). Alkyl (**1a–c**) or halide (**1d–g**) substituted anilines undergo the carboxylative condensation reaction with atmospheric carbon dioxide and ethyl benzoylformate in the presence of tris(dimethylamino)phosphine smoothly. With the exception of **5c** and **5f**, other 3-aryl substituted oxazolidine-2,4-dione products (**5a–b, 5d–e, 5g**) were obtained in moderate to good yields. The *ortho* substitution in **4c** and **4f** may hinder the cyclization step due to steric reasons. In Jiang and co-worker's carbamate synthesis using the coupling reaction of amine, carbon dioxide and *N*-tosylhydrazones,[13] anilines were not suitable substrates due to their low basicity and nucleophilicity. The difference in the reactivity of anilines in their and our reactions might result from the mechanistic distinctions in terms of key intermediates. Benzyl amines bearing a wide range of functional groups including electron-donating alkyl and alkoxy, and electron-withdrawing trifluoromethyl substituents all participate in the tandem reaction efficiently to provide the corresponding oxazolidine-2,4-dione products (**5h–p**) in moderate to good yields. The structure of product **5n** was determined unambiguously by single crystal

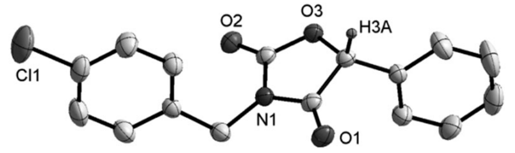
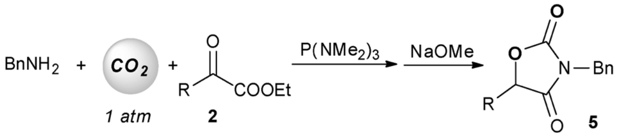
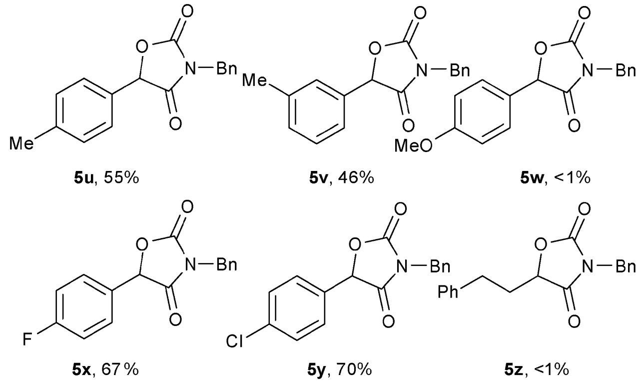


Fig. 1 ORTEP plot of **5n** shown with ellipsoids at the 30% probability level; most hydrogen atoms are omitted for clarity.

Table 2 Synthesis of oxazolidine-2,4-diones from benzyl amine, atmospheric carbon dioxide and various α-ketoester (**2**)[a]





5u, 55% **5v**, 46% **5w**, <1%

5x, 67% **5y**, 70% **5z**, <1%

[a] Reaction conditions: benzyl amine (1.2 mmol), α-ketoester **2** (1.0 mmol), carbon dioxide (1 atm), THF (10 mL), −78 °C to rt, 1.5 h; then NaOMe (0.1 mmol), toluene, 110 °C, 1 h. Yields of isolated products are given.

X-ray diffraction (Fig. 1).[17] The presence of the bromo groups in **5g** and **5o** provides a handle for further functionalization using traditional methods such as cross-coupling reactions. As expected, primary aliphatic amines are also found to be suitable substrates (**5q–t**), and the cyclopropyl group is compatible with the reaction conditions (**5t**).

Moreover, the tandem condensation–cyclization reaction of benzyl amine, atmospheric carbon dioxide and several α-ketoesters can also be carried out (Table 2). The use of alkyl, chloro and fluoro substituted ethyl benzoylformates leads to the formation of the corresponding oxazolidine-2,4-dione products in moderate to good yields (**5u–v**, **5x–y**). The more electron-rich substrates including methoxy substituted ethyl benzoylformate (**2w**) and alkyl substituted α-ketoester (**2z**) are inert under these conditions. The reactions of these two substrates at increased temperature (60 °C) gave complex mixtures and no desired carbamate products were detected in the condensation step.

In summary, we have developed a novel, convenient, and transition-metal-free access to biologically important oxazolidine-2,4-diones *via* a phosphorus-mediated carboxylative condensation of readily available primary amines and α-ketoesters using carbon dioxide as a carboxylative reagent, and a NaOMe-catalyzed cyclization sequence in a one-pot fashion. Due to the high nucleophilic affinity of the Kukhtin–Ramirez adduct formed by the reaction of tris(dimethylamino)phosphine and α-ketoester toward *in situ* formed carbamic acid, the condensation reaction can be easily carried out using atmospheric carbon dioxide under mild reaction conditions. Further mechanistic investigations and extension of this strategy to other reactions involving carbon dioxide incorporation are ongoing in our laboratory.

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