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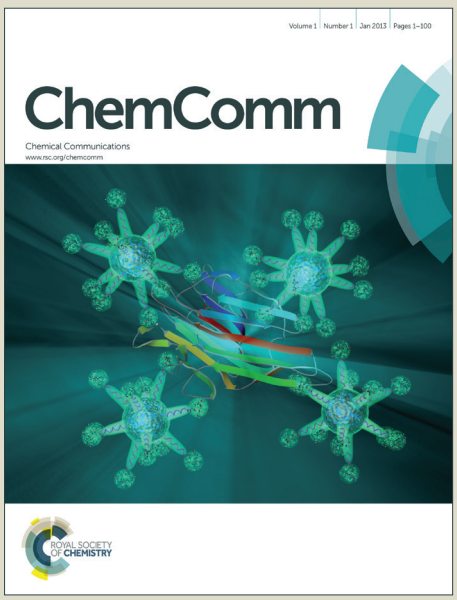

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Synthesis of oxazolidine-2,4-diones by tandem phosphorus-mediated carboxylative condensation/ cyclization reaction using atmospheric carbon dioxide

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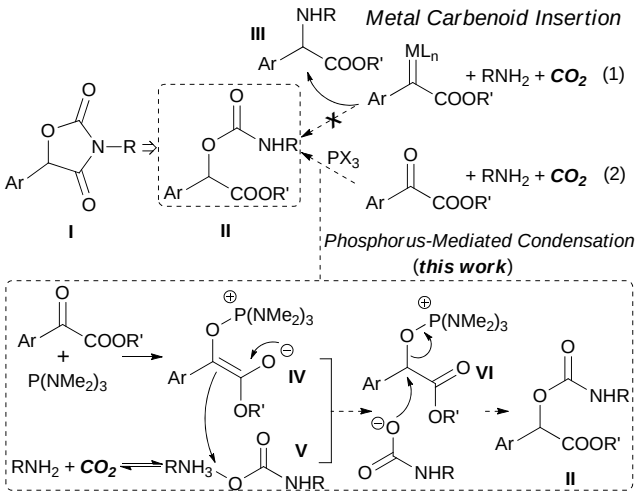
The oxazolidine-2,4-dione motif is found frequently in biologically important compounds. A tandem phosphorus-mediated carboxylative condensation of primary amine and α-ketoester/base-catalyzed cyclization reaction has been developed. This process provides a novel and convenient access to various oxazolidine-2,4-diones in 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] Those 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 on 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 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 attentions since carbon dioxide is an abundant, nontoxic and renewable carbon resource.[6] Reaction 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 those reactions. Despite their good catalytic efficiency, the use of transition metals suffers from drawbacks including its 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 transition-metal-free methodology to convert carbon dioxide into value-added compounds is desirable.[8]



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

Intrigued by developing 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 carbeniod and carbamic acid formed in-situ from primary amine and carbon dioxide (eq 1, Scheme 1).[10,11] However, our initial investigation revealed that $Rh_2(OAc)_4$ catalyzed reaction of amine, carbon dioxide and methyl 2-diazo-2-phenylacetate gave no carbamate product **II** (see Supporting Information). 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 carbenoid is electrophilic[12] and nitrogen atom in amine shows much higher nucleophilicity than

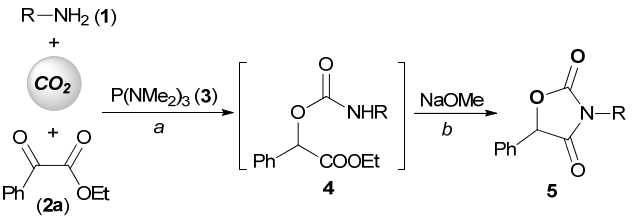
oxygen atom in unstable carbamic acid. Very recently, Jiang and co-worker reported an elegant synthesis of carbamate by the reaction of amine, carbon dioxide and *N*-tosylhydrazones promoted by potassium carbonate,[13] in which a carbocation generated by decomposition of carbene in protic solvent was 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.

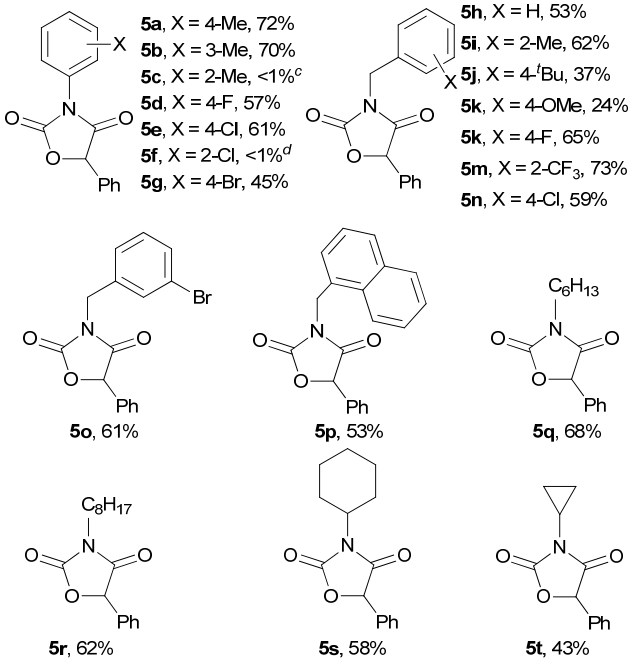
On the other hand, the carbamic acid shows much higher acidity or electrophilicity than amine and thus prefers to react with an active nucleophile. It was reported that Kukhtin-Ramirez addition of tris(dimethylamino)phosphine to α-ketoester gives adduct **IV**,[14] which reacts formally as a carbene but proves to serve as a nucleophile to reacted with many electrophilic reagents.[15,16] We reasoned that in our designed reaction system of equation 2 in Scheme 1, adduct **IV** would rapidly react with carbamic acid **V** rather than amine via proton transfer. It should be noted that proton transfer from phenols, amides and carboxylic acids to Kukhtin-Ramirez adduct have been recently testified to be feasible by Radosevich and co-worker's elegant works.[16] The produced alkoxyphosphonium species **VI** would then conduct nucleophilic displacement with 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 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 when employing tris(dimethylamino)phosphine (**3**) the condensation reaction did proceed rapidly and carbamate product **4a** was obtained exclusively in excellent yield, which probably attributed to Kukhtin-Ramirez adduct's high affinity toward in-situ formed carbamic acid rather than amine. To avoid a tedious isolation procedure for **4a**, the residue from condensation reaction was directly used in 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 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 ineffective in this reaction system.

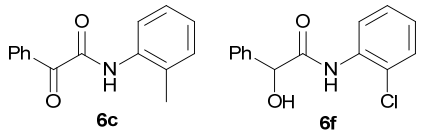
With these optimal reaction conditions in hand, the substrate scope with respect to the primary amine was investigated (Table 1). Alkyl (**1a-c**) or halide (**1d-g**) substituted anilines undergo carboxylative condensation reaction with atmospheric carbon dioxide and ethyl benzoylformate in the presence 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 yield. 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 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 aniline's reactivity 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 X-ray diffraction (Figure 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 cyclopropyl group is compatible with the reaction conditions (**5t**).

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 first step, compound **6c** was isolated as main product. [d] 80% yield of **4f** was isolated in first step, compound **6f** was isolated as main product.



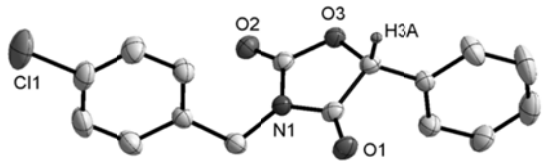
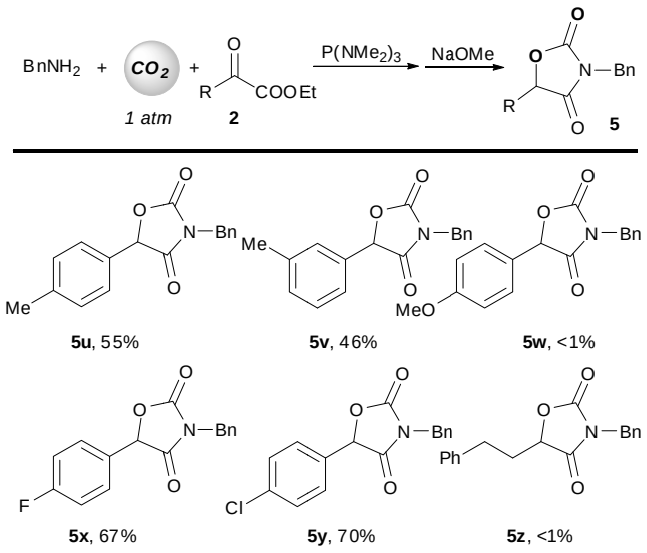


Figure 1 ORTEP plot of **5n** shown with ellipsoids at the 30% probability level; most hydrogen atoms were omitted for clarity.

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 benzoylformates (**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.

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



[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.

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 one-pot fashion. Due to high nucleophilic affinity of the Kukhtin-Ramirez adduct formed by 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 carbon dioxide incorporation reactions are ongoing in our laboratory.

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17 CCDC 1044132 (**5n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

