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Transition-metal-free lactamization of C(sp^3)–H bonds with CO_2: facile generation of pyrido[1,2-*a*]pyrimidin-4-ones†

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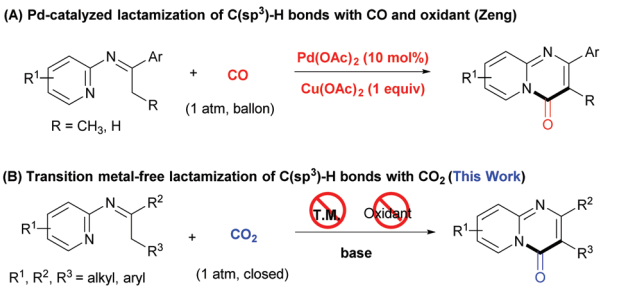
A novel carbonylation of C(sp^3)–H bonds in pyridylamines with one atmosphere of CO_2 is reported to synthesize important pyrimidinones in good yields. This transition-metal-free and redox-neutral process features the use of a nontoxic carbonyl source, broad substrate scope, good functional group tolerance, facile scalability and easy product derivatization.

The development of green and sustainable strategies for organic synthesis has received increasing attention. A green and recyclable building block may play a key role in these strategies. As an ideal C1 building block, CO_2 is nontoxic, abundant, and recyclable. Therefore, it is highly important to utilize CO_2 to synthesize high-value-added chemicals in a sustainable way.[1] Among the diverse organic transformations of CO_2,[2] the carbonylation with CO_2 to synthesize carbonyl-containing heterocycles has attracted increasing attention,[3] replacing highly toxic and user-unfriendly CO and phosgene. Recently, significant progress has been achieved in the carbonylation of C–H with CO_2 due to its high atom- and step-economy.[4] Importantly, as it bears carbon with a higher valence than that of CO, CO_2 can act ideally as the combination of CO and oxidants (CO_2 = CO + [O]), realizing such carbonylations under redox-neutral reaction conditions and reducing the cost and heavy metal residues.[5] However, most of the research in this field is focused on the carbonylation of C(sp^2)–H bonds.[4a–n] In contrast, there are only few examples of carbonylation of C(sp^3)–H bonds with CO_2.[4o–q] Notably, to the best of our knowledge, only one example of lactamization of C(sp^3)–H with CO_2 was reported by Zhang and Lv,[4p] who realized the efficient generation of 4-hydroxy-2(1*H*)-quinolinones from *o*-acetamidoacetophenones, albeit under a high pressure of CO_2 (3 MPa). Herein, we report a novel carbonylation of C(sp^3)–H bonds in pyridylamines with one atmosphere of CO_2 to synthesize important pyrimidinones under transition-metal-free and redox-neutral conditions (Scheme 1B).

Pyrimidinones are important motifs in many drug molecules and widely investigated in medicinal chemistry.[6] Therefore, many groups have developed synthesis methods to generate such a structure efficiently.[7] It is worth noting that Zeng and co-workers developed an elegant Pd-catalyzed lactamization of ketoimines with CO (Scheme 1A), which displays broad substrate scope and high step economy.[8] However, the use of toxic CO and stoichiometric $Cu(OAc)_2$ as the oxidant increases the risk for heavy metal residues and hampers its applications in industry. With our continuous interest in the sustainable organic synthesis with CO_2,[4b,9] we wondered whether we could realize the efficient carbonylation of the C(sp^3)–H bonds in ketoimines with CO_2 to obtain pyrimidinones under redox-neutral conditions. Such a scenario faces several challenges. First, the thermodynamic stability and kinetic inertness of CO_2 render it difficult to realize efficient transformations, especially under low pressure. Second, the dearomatization of pyridines would occur during the reaction, which make such processes even more challenging (Fig. 1).



Scheme 1 Carbonylation of the C–H bond.

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‡These authors contributed equally to this work.

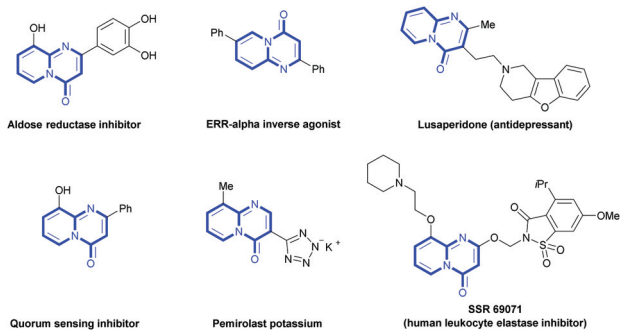


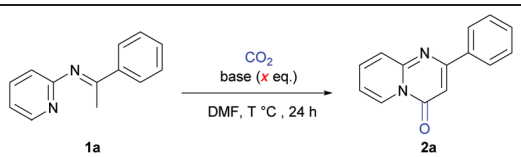
Fig. 1 Selected examples of bioactive pyrimidinones.

With such challenges in mind, we began to investigate the reaction using *N*-(2-pyridyl) ketoimine **1a** as the substrate under one atmosphere of CO_2 (Table 1). To our delight, the desired product **2a** was obtained in 61% yield with lithium *t*-butoxide as the base in DMF at 120 °C for 24 h (Table 1, entry 1). Other bases, such as NaO^{t}Bu, KO^{t}Bu and Cs_2CO_3, were also tested but gave lower yields (Table 1, entries 2–4). When using NaO^{t}Bu or KO^{t}Bu as the base, the reaction system was very viscous and **1a** was transformed to a byproduct (see the ESI† for details), both of which might cause a lower yield of **2a**. The screening of the amount of LiO^{t}Bu demonstrated that 4.5 equivalents was the best choice (Table 1, entries 5–10). Similar to our previous reports,[4b] the desired product was not detected when 1 equivalent of LiO^{t}Bu was used, indicating that LiO^{t}Bu not only acts as a base but also participates in the formation of intermediates. Subsequently, we evaluated the reaction temperature and found that 130 °C gave the highest yield (Table 1, entries 9 and 11–14). Although **2a** was generated in very low yield at 80 °C, the carboxylative product could be detected obviously by ESI-MS (Table 1, entry 11), which indicates that it might be an intermediate for this transformation and the cyclization might not occur easily at lower temperatures. Other solvents, such as DMA, DMSO, diglyme, and THF, were also tested (Table 1, entries 15–19). However, no better results were obtained, indicating the unique role of DMF for this reaction. No desired product was obtained in the absence of CO_2, demonstrating its crucial role as a carbonylative source (Table 1, entry 20).

With the optimal reaction conditions in hand, we began to expand the substrate scope of *N*-(2-pyridyl) ketoimines **1** (Table 2). First, we examined the substrate bearing mono-substituents on the phenyl ring (**1a–n**). As shown in Scheme 2, various functional groups, such as electron-donating groups (EDGs, –OMe, –OCF_3) and electron-withdrawing groups (EWGs, –CF_3, –Cl, –SO_2Me) at the *ortho* (**1c**), *meta* (**1d–e**), and *para* (**1f–m**) positions of the phenyl ring, did not affect the reaction. However, a substrate bearing a strong EWG, such as the nitro group (**1n**), at the *para* position showed low reactivity and was not suitable for this reaction. Besides the mono-substituents, the substrates bearing di- (**1o**) or tri-substituents (**1p**) on the phenyl ring can also undergo this transformation to provide the desired products in good yields. To our delight, our protocol was also suitable for the alkyl-substituted *N*-(2-pyridyl) ketoimine substrate **1q**, which has not been reported *via* Pd-catalysis.[8] Furthermore, substrates bearing substituents on the pyridine ring were also investigated. Similarly, the substrate with EDGs on the pyridine ring (**1s** and **1u**) showed better reactivities than those with EWGs (**1t**) and electron-neutral groups (**1r**). Notably, the product **2r** shows significant bioactivity and acts as an ERR-alpha inverse agonist.[6c] Besides the mono-substituted pyrimidinones, to our delight, we could also generate the di-substituted ones (**2w** and **2x**) in good yields.

After developing this method, we further demonstrated its utility in organic synthesis. First, we conducted the gram-scale

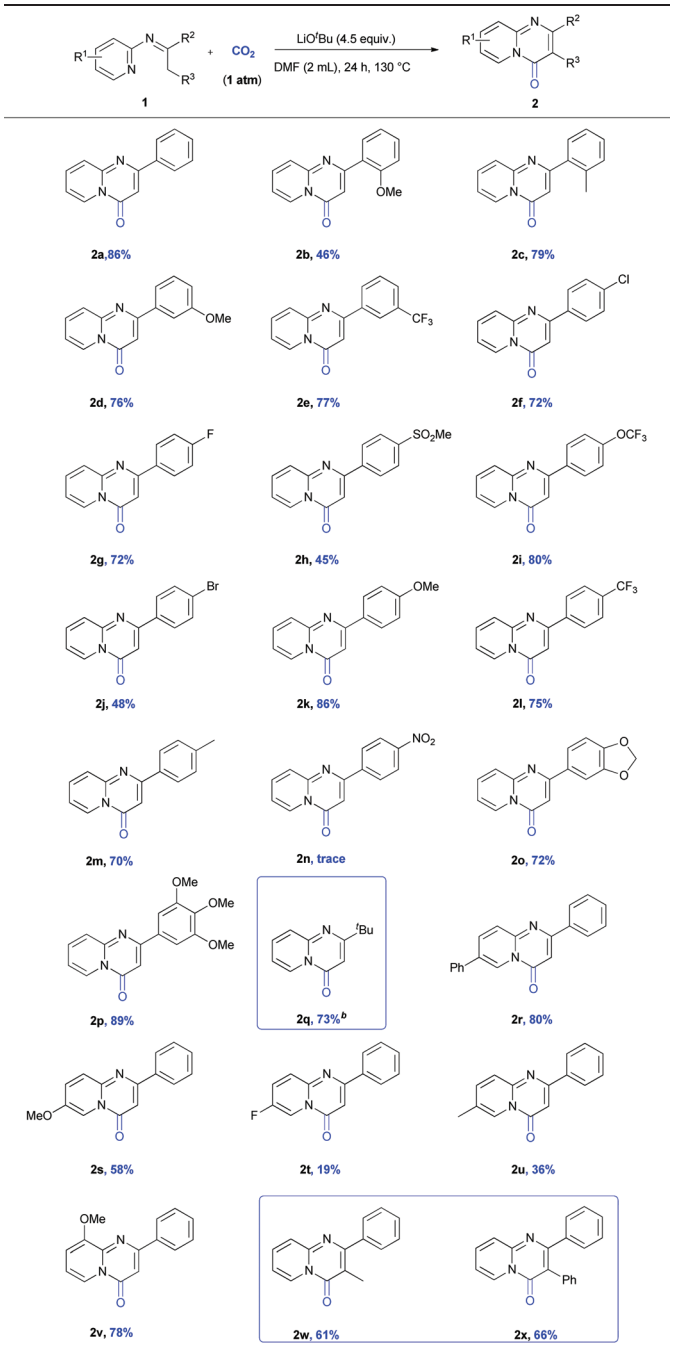
Table 1 Optimization of reaction conditions[a]



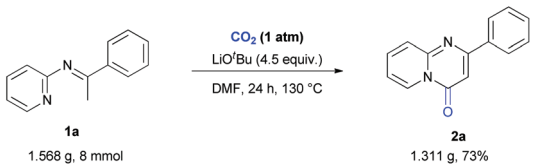
Entry	Base	*x*	*T*/°C	Yield[b] (%)	Entry	Base	*x*	*T*/°C	Yield[b] (%)
1	LiO^{t}Bu	3	120	61	11	LiO^{t}Bu	4.5	80	<5
2	NaO^{t}Bu	3	120	35	12	LiO^{t}Bu	4.5	110	67
3	KO^{t}Bu	3	120	22	**13**	**LiO^{t}Bu**	**4.5**	**130**	**87 (86)**
4	Cs_2CO_3	3	120	12	14	LiO^{t}Bu	4.5	140	86
5	LiO^{t}Bu	1	120	N.D.	15[c]	LiO^{t}Bu	4.5	130	23
6	LiO^{t}Bu	2	120	35	16[d]	LiO^{t}Bu	4.5	130	47
7	LiO^{t}Bu	2.5	120	56	17[e]	LiO^{t}Bu	4.5	130	35
8	LiO^{t}Bu	3.5	120	63	18[f]	LiO^{t}Bu	4.5	130	17
9	LiO^{t}Bu	4	120	74	19[g]	LiO^{t}Bu	4.5	130	5
10	LiO^{t}Bu	4.5	120	77	20[h]	LiO^{t}Bu	4.5	130	0

[a] Reaction conditions: **1a** (0.2 mmol), 1 atm of CO_2, 2 mL of DMF, 24 h. [b] GC yields are given with dodecane as an internal standard and the isolated yield is given in parentheses. [c] DMA (2 mL). [d] DMSO (2 mL). [e] Diglyme (2 mL). [f] THF (2 mL). [g] 1,4-Dioxane (2 mL). [h] Under the atmospheric of N_2 instead of CO_2.

Table 2 Substrate scope investigation[a]



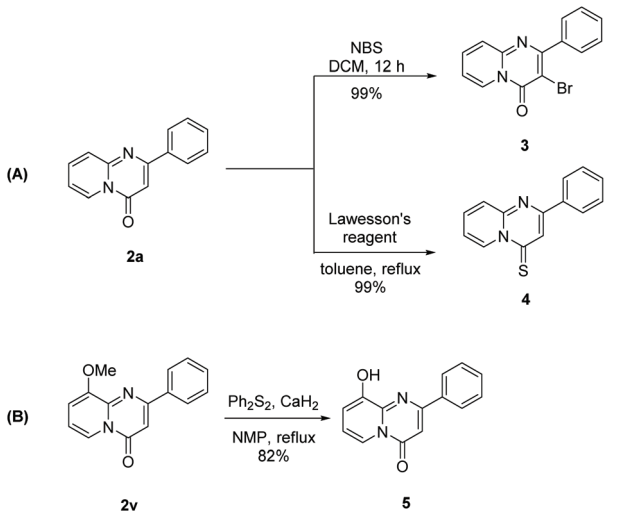
[a] Reaction conditions: **1** (0.2 mmol), LiO^{t}Bu (4.5 equiv.), 1 atm of CO_2, 2 mL of DMF, 24 h, 130 °C. Isolated yields. [b] 30 h.



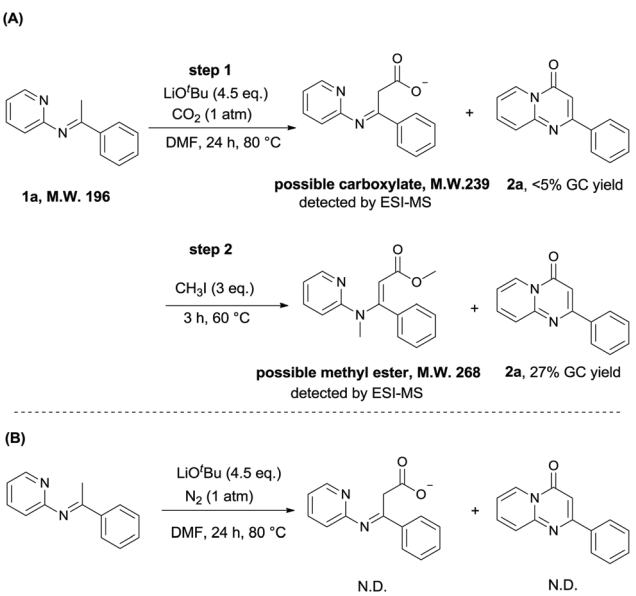
Scheme 2 Gram-scale reaction.

reaction of **1a** and obtained the target product **2a** in 73% yield (Scheme 2). Moreover, product **2a** could be functionalized to give both **3** and **4** in quantitative yields (Scheme 3A). These results indicated the great potential application of this transformation in organic synthesis. In addition to **2r**, a quorum sensing inhibitor **5** [6d] could be rapidly accessed in good yield *via* the carbonylation of **1v** followed by demethylation (Scheme 3B).

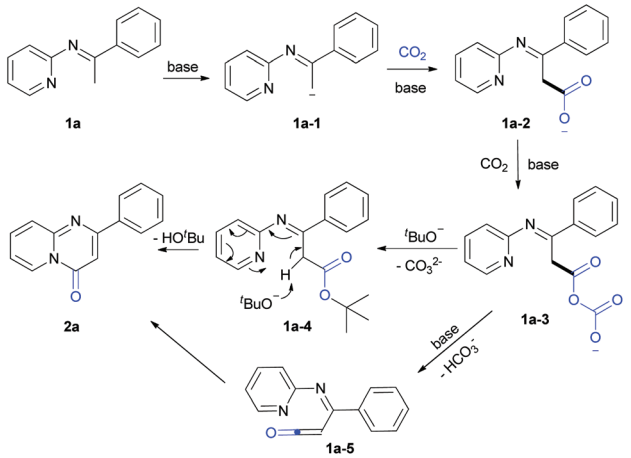
To gain more insight into the lactamization reaction, we did some mechanistic studies (Scheme 4). To confirm the carboxylate as the intermediate (Table 1, entry 11), we added CH_3I to quench the reaction which was performed at 80 °C. We detected the formation of the corresponding methyl ester by ESI-MS and obtained product **2a** in a higher yield (27% GC yield, Scheme 4A). In contrast, neither **2a** nor the intermediate



Scheme 3 Derivatization reaction.



Scheme 4 Mechanism studies.



Scheme 5 Proposed mechanism.

could be detected by ESI-MS in the control experiments under N_2 (Scheme 4B). Therefore, we speculate that both the carboxylate intermediate and the ester could undergo the cyclization reaction to provide the desired product.

Based on the results and previous reports,[7e,10] we proposed the following possible pathway (Scheme 5). **1a** underwent deprotonation in the presence of the strong base LiO^tBu to form **1a-1**, which can further react with CO_2 to generate intermediates **1a-2** and **1a-3**. Under standard conditions, **1a-3** might react with $^tBuO^-$ to generate **1a-4**, which further transforms to **2a** in the presence of a base. In addition, **1a-3** might also transform to **1a-5**, which undergoes a cyclization reaction to provide the desired product **2a**.

Conclusions

In summary, we have developed an efficient transition metal-free and external oxidant-free strategy to generate valuable pyrimidinones *via* the carbonylation of C(sp^3)–H bonds with an atmospheric pressure of CO_2, which is the more environment-friendly carbonylation source. This protocol features broad substrate scope, good functional group tolerance, facile scalability and easy product derivatization, thus providing potential application in organic synthesis and the pharmaceutical industry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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