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Special Issue

Efficient Access to 2-Pyrones via Carbene-Catalyzed Oxidative [3+3] Reactions between Enals and Nitrogen Ylides

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Abstract: Pyrones are important structural units in natural products and synthetic functional molecules. Here, we report a carbene-catalyzed oxidative [3+3] cycloaddition reaction between enals and nitrogen ylides for quick access to 2-pyrones. Inexpensive and easily prepared 2′-pyridinium acetophenone bromide salts are used as precursors of pyridinium ylides to react with enals in our catalytic reactions.

2-Pyrones are common scaffolds in various natural products and complex biologically active compounds.[1] Simple 2-pyrone-derived functional molecules exhibit proven bio-activities[2] such as enzyme inhibitive,[2a] anti-microbial[2b] and cytotoxic activities[2c] (Figure 1a). Substituted 2-pyrones bear multiple reactive sites and can be used as building blocks for the preparation of sophisticated functional molecules (Figure 1b).[3] Therefore, the syntheses of 2-pyrones have received considerable attention.[4]

N-heterocyclic carbenes (abbreviated as NHCs or carbenes) have proven to be a class of robust organic catalysts. A large number of efficient and unique synthetic transformations have been realized through NHC organocatalysis in recent years.[5] The oxidative LUMO activation of enals with NHC catalysts, first reported by Studer and co-workers,[6] is an efficient way to prepare reactive α,β-unsaturated acylazolium intermediates for cycloaddition reactions.[7] Ylides are versatile synthetic starting materials[8] and shall in principle behave as effective nucleophilic reactants in the NHC-catalyzed reactions. However, the use of ylides in NHC catalysis is rare. In 2012, Studer and co-workers reported an enantioselective cyclopropanation reaction of enals using sulfur ylides in situ generated from sulfonium salts (Scheme 1a).[9] Studer's work afforded 3-membered cyclopropane ring as the product.

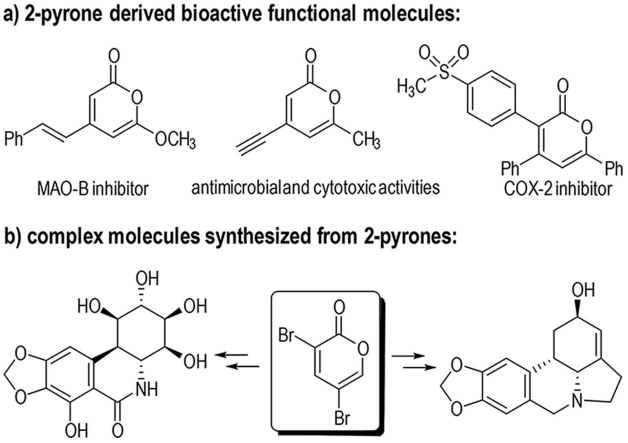

Figure 1. Applications of substituted 2-pyrones in biological and synthetic research.

Here we report the use of a different type of ylides, nitrogen ylides in situ generated from alkyl pyridinium salts, for reaction with enals promoted by NHC catalysts under oxidative conditions (Scheme 1b). Our reaction affords 6-membered lactone **3** as the final product. Notably, although nitrogen ylides are routinely used in organic synthesis,[10] their involvements in NHC-catalyzed reactions are rarely reported.[11]

Our [3+3] cycloaddition reaction between enal and nitrogen ylide is illustrated in Scheme 1b. Mechanistically, the enal substrate **1** is activated by NHC catalyst in the presence of an oxidant to generate α,β-unsaturated acylazolium intermediate **I**. Nucleophilic nitrogen ylide intermediate **II** is generated in situ from the pyridinium salts **2** under basic conditions to react with **I** via a Michael addition process to give adduct **III**. A proton transfer process and the release of a pyridine from **III** afford intermediate **IV**. Proton transfer and isomerization of **IV** give zwiter ion intermediate **V**, which undergoes a lactone formation process and finally gives the 2-pyrone products **3** and regenerates the NHC catalyst. It is worth noting that Studer and co-workers have recently reported the synthesis of 2-pyrones using enals and 2′-nitroacetophenones as the reaction substrates (with the release of a HNO_2 to form a carbon-carbon double bond).[12] The 2-pyrone products are generally afforded

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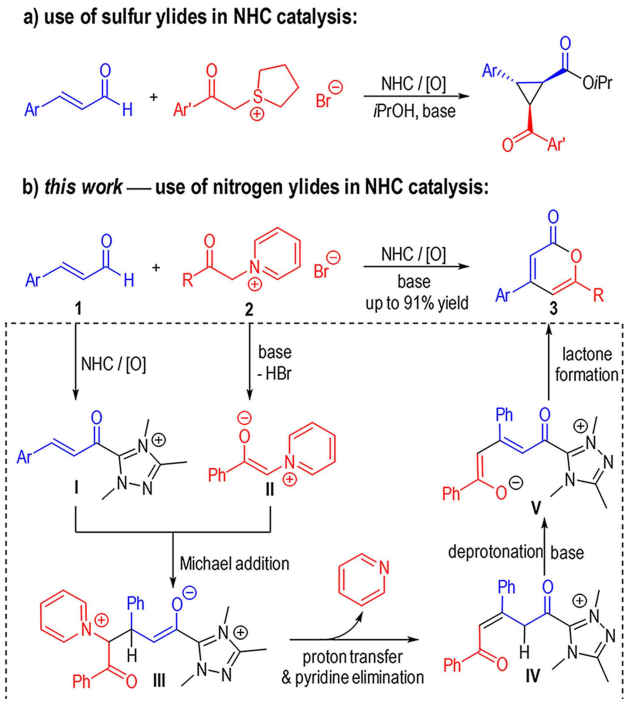
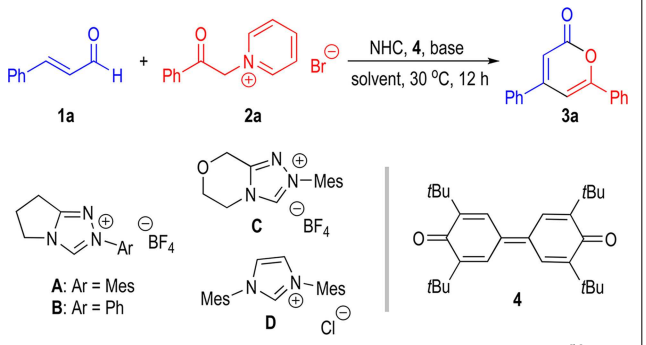


Scheme 1. Ylides used in NHC organocatalysis.

Table 1. Condition optimization.[a]



Entry	NHC	Base	Solvent	Yield [%][b]
1	**A**	K_2CO_3	THF	85
2	**B**	K_2CO_3	THF	< 5
3	**C**	K_2CO_3	THF	< 5
4	**D**	K_2CO_3	THF	56
5	**A**	Cs_2CO_3	THF	81
6	**A**	K_3PO_4	THF	81
7	**A**	Et_3N	THF	40
8	**A**	DBU	THF	< 5
9	**A**	K_2CO_3	EA	82
10	**A**	K_2CO_3	CH_2Cl_2	< 5
11	**A**	K_2CO_3	CH_3CN	< 5

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol), NHC (0.02 mmol), base (0.12 mmol), **4** (0.10 mmol), solvent (1.5 mL), 30 °C, 12 h. [b] Yields were isolated yields after purification by SiO_2 column chromatography.

in higher yields in our reactions and the pyridinium salts used in our methodology are inexpensive and readily available.[13]

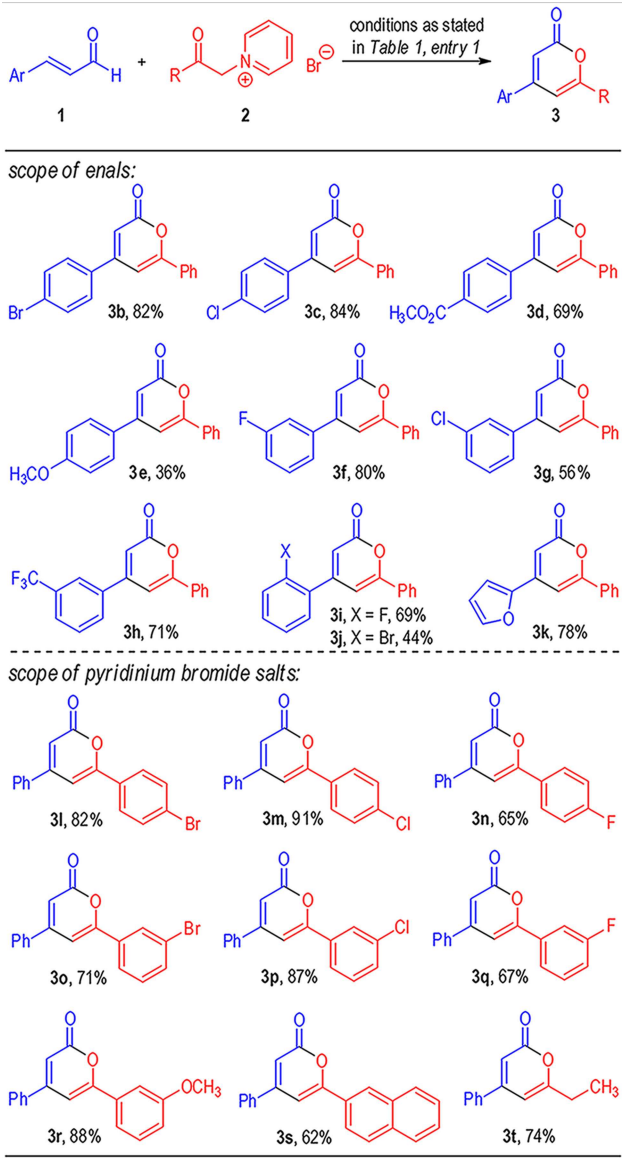
Cinnamylaldehyde **1a** and pyridinium bromide salt **2a** were chosen as the model substrates to test the reaction conditions (Table 1). Different NHC catalysts were first evaluated in THF with K_2CO_3 used as the base and **4** used as the oxidant (Table 1, entries 1 to 4). To our great delight, the 2-pyrone product **3a** could be afforded in 85% isolated yield with triazolium **A** used as the NHC pre-catalyst (entry 1). Only trace products could be observed when using the triazolium derived NHC pre-catalysts **B** and **C** (entries 2 to 3). Notablely, imidazolium **D** also performed well in this transformation, although the product yield was a bit lower (entry 4). Switching the base to inorganic bases such as Cs_2CO_3 and K_3PO_4 gives the 2-pyrone product in similar yields (entries 5 to 6). However, organic bases are not efficient for this transformation, giving the desired products in either low or trace yields (entries 7 to 8). Solvents also have great influence on this catalytic process (entries 9 to 10). For example, the reactions could go well in THF (entry 1) and EA (entry 9), with the 2-pyrone products afforded in good isolated yields. However, almost no products could be formed when carrying out the reactions in CH_2Cl_2 or CH_3CN (entries 10 to 11).

With the optimized reaction condition (as stated in Table 1, entry 1) at hand, we then tested the reaction scope using enals **1** and pyridinium bromide salts **2** with different substitution patterns (Scheme 2). Electron-withdrawing substituents are well tolerated on the benzene rings of the cinnamylaldehydes **1**, with the 4,6-diaryl-2-pyrones afforded in moderate to good isolated yields (**3b** to **3d**, **3f** to **3h**). Enals with electron-donating groups installed on the β-benzene rings did not work well in this process and the products could only be afforded in poor yields (eg., **3e**). Although 2-fluorophenyl enal works well in this catalytic process (**3i**), bulkier enals such as 2-bromophenyl enal could only give the corresponding product **3j** in poor yield. The β-benzene groups on enal substrates **1** could also be replaced with hetero aromatic groups such as pyranyl group, with the corresponding product afforded in good isolated yield (**3k**). Both electron-withdrawing and electron-donating groups are well tolerated on the benzene rings of the pyridinium bromide salts in this catalytic process, with all the products afforded in good to excellent isolated yields (**3l** to **3s**). Notably, the substituted benzene group on substrate **2** could even be switched to a simple aliphatic group without obvious erosion of the product yield (**3t**). However, only trace products could be observed when using alkyl enals as the reaction substrates.

In summary, we have developed an NHC-catalyzed oxidative [3 + 3] cycloaddition reaction between enals and nitrogen ylides for the synthesis of substituted 2-pyrones. The inexpensive and easily prepared 2′-pyridinium acetophenone bromide salts are used as the nitrogen ylide precursors and the 2-pyrone products are afforded in moderate to excellent yields. Further investigations on quick and direct access to valuable functional molecules from readily availasble starting materials through simple catalytic transformations are in progress in our laboratory.

Experimental Section

To a dry Schlenk tube equipped with a magnetic stir bar, was added aldehydes **1** (0.1 mmol), pyridinium bromide salt **2**



Scheme 2. Substrate scope (Reactions were carried out under condition as in Table 1, entry 1. Yields were isolated yields after purification by SiO_2 column chromatography).

(0.11 mmol), triazolium salt **A** (0.02 mmol), and K_2CO_3 (0.12 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (1.5 mL) was added and the reaction mixture was then stirred at 30 °C till **1** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (10:1 petroleum ether/EtOAc) to afford the desired product **3**.

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Conflict of Interest

The authors declare no conflict of interest.

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