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N-Heterocyclic carbene catalyzed intramolecular nucleophilic addition of carbonyl anion equivalents to enol ethers

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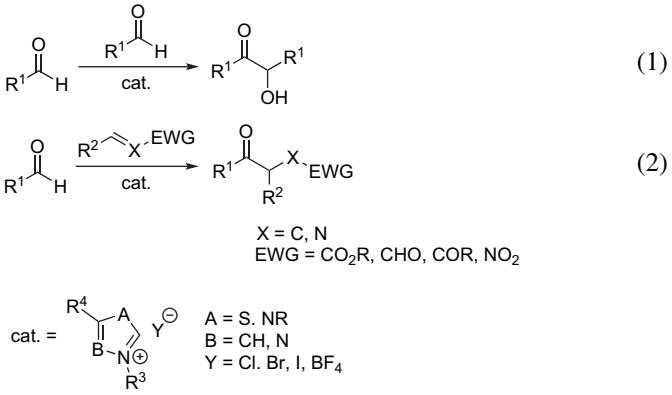
ABSTRACT

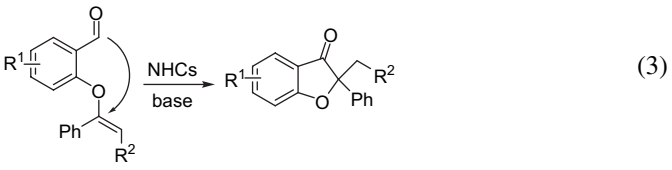
The intramolecular nucleophilic addition reaction of acyl anion equivalents to enol ethers is described, which was catalyzed by *N*-heterocyclic carbenes generated in situ from readily available thiazolium salt. In this transformation, benzofuranones were obtained in excellent yield. In combination with our previous work, the precise mechanistic elucidation for the formation of benzofuranones has been further investigated. A labeling experiment implied that the transformation proceeds through a nucleophilic addition mechanism.

1. Introduction

Umpolung reactivity of functional groups is a powerful strategy for the construction of organic molecules in unconventional ways.[1] Among this field, *N*-heterocyclic carbenes (NHCs), as a kind of versatile organocatalysts, have been known for a long time[2] and successfully utilized in a variety of transformations.[3] These highly nucleophilic carbenes, which are generated in situ from thiazolium salts, diazolium salts, and triazolium salts[4] in the presence of weak base, can react with aldehydes, resulting umpolung aldehyde or acyl anion equivalents.[5] The umpolung aldehydes are induced to undergo various nucleophilic addition reactions. Typically, the benzoin condensation[6] and the Stetter reaction[7] are two of the most important examples. In the benzoin condensation, the acyl anion equivalent is added to another aldehyde (Scheme 1, Eq. 1). In the Stetter reaction, the umpolung aldehyde is added to Michael acceptor (Scheme 1, Eq. 2). Recently, the continued development of the two related reactions has received significant attention and offered new opportunities for unusual synthetic strategies.[8,9] However, the nucleophilic addition reaction of umpolung aldehydes to unactivated olefins was rarely reported. In this context, we described the first example of the NHCs-catalyzed addition reaction of umpolung aldehydes to enol ethers (Scheme 2, Eq. 3). In this process, the enol ethers, as a type of unactivated olefin, performed as electrophiles and reacted with acyl anion equivalents for the construction of benzofuranones. This reaction is another kind of nucleophilic addition reaction catalyzed by NHCs, which presented a novel addition reaction and broadened the scope of application of NHCs.



Scheme 1. Benzoin condensation and Stetter reaction catalyzed by NHCs.



Scheme 2. Nucleophilic addition of carbonyl anion equivalents to enol ethers catalyzed by NHCs.

2. Results and discussion

We have previously reported[10] that NHCs were fairly effective for the construction of benzopyrones and benzofuranones (Scheme 3), which were mainly depended on the substitution nature of the

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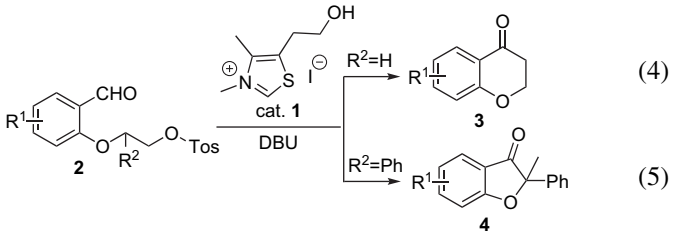
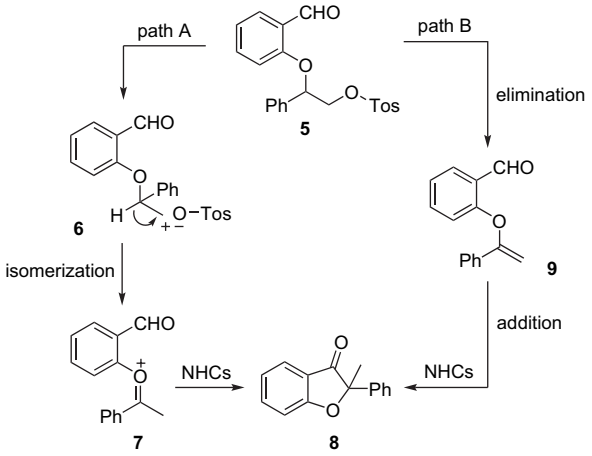
substrate. When R^2 was hydrogen, six-membered ring benzopyrone **3** was obtained via the nucleophilic substitution reaction (Eq. 4). For R^2 as phenyl group, the cyclization process underwent isomerization, leading to generation of five-membered ring benzofuranone **4** (Eq. 5). For this significant exception, the mechanism of nucleophilic substitution was proposed in our previous work (Scheme 4, path A) to proceed via **6**, probably formed under these reaction conditions firstly, then the carbon cation rearranged to give the more stable intermediate **7**, which could be regarded as the most important intermediate in this process. Finally, the umpolung aldehyde catalyzed by NHCs was attached to the electrophilic center, leading to the formation of the benzofuranone **8**. Inspired by the result of the unusual structures of the products **8**, we supposed that the benzofuranone **8** could be formed via a quite different way (Scheme 4, path B). It was proposed that the aldehyde **5** was most likely to undergo the thermal elimination to provide the enol ether **9**, then the umpolung aldehyde was taken the way of intramolecular nucleophilic addition of carbonyl anion equivalents to enol ethers, leading to the formation of benzofuranone **8**. In this proposed mechanism, enol ether **9** is the key intermediate, which undergoes an intramolecular nucleophilic addition.



Scheme 3. Construction of benzopyrones and benzofuranones.



Scheme 4. The two proposed paths for benzofuranone formation.

On the basis of the above hypothesis, a series of salicylaldehyde-derived enol ethers were prepared for the confirmation of the mechanism (Table 1). Initially, the readily prepared thiazolium salt **1** was utilized as optimum catalyst. Xylene and DBU were chosen as the solvent and base, respectively. Excessive DBU was employed to ensure complete consumption of the reactants. Fortunately, benzofuranone **8** was obtained in quantitative yield when enol ether **9** was subjected to this reaction at 140 °C for 6 h. Substrate **10** required longer reaction time to afford the product in excellent yield (entry 2). Similarly, substrates **12** and **14** underwent cyclization in excellent yield and formed the benzofuranones **13** and **15** (entries 3 and 4). The satisfactory results were also obtained with enol ethers **16** and **18** (entries 5 and 6). When R^2 was methyl group, the substrate **20** also gave product **21** in excellent yield (entry 7). 2-(Vinyloxy)benzaldehyde **22** was subjected to the nucleophilic addition reaction, however, the desired product was not obtained. In this nucleophilic addition reaction, the acyl anion equivalents were capable of cyclizing onto unactivated olefins, not just good Michael acceptors, and this type of addition reaction can be regarded as the integration of benzoin condensation and the Stetter reaction.

The mechanism of this nucleophilic addition of carbonyl anion equivalents to enol ethers depicted in Scheme 5 was analogous to that proposed for the benzoin condensation[11] and the Stetter reaction.[12] The carbene catalyst **23** was added to the aromatic aldehyde **9** and resulted in intermediate **24**, which underwent deprotonation to give the thiazole-enamine **25**. The umpolung aldehyde was added to the enol ether and provided the product **8**, followed by the catalyst turnover.

To confirm the more precise mechanism for this transformation, which started from the aldehyde **5** and finished as the benzofuranone **8** (Scheme 4), substrate **27** was prepared for the further investigation, in which the benzylic position was deuterated (Scheme 6). It was supposed that deuterated benzofuranone **30** would be obtained if this transformation takes the way of nucleophilic substitution reaction (Scheme 6, path A), otherwise takes the way of nucleophilic addition reaction (Scheme 6, path B). When deuterated substrate **27** was subjected to this reaction, benzofuranone **8** was obtained in 33% yield,[13] and none of the deuterated product **30** was observed. The result of the lack of deuterium in the product implied that the transformation from aldehyde **27** to the product probably took the way of nucleophilic addition of carbonyl anion equivalents to enol ethers, rather than the nucleophilic substitution mechanism. In this transformation, the substrate **27** took the elimination way firstly, then the addition of carbonyl anion equivalents to enol ethers. The primary cation **28** may be not formed, probably it is extremely unstable.

3. Conclusions

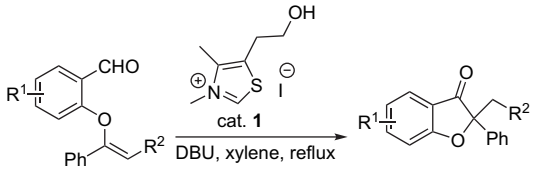
In summary, we have discovered that the readily available thiazolium salt in the presence of base promoted the addition of acyl anion equivalents to enol ethers. A variety of substrates underwent the reaction and gave excellent yields. Combining our earlier results, more precise mechanistic studies on this transformation has been further investigated. The use of chiral carbenes as organocatalysts in other asymmetric reaction is currently underway in our laboratory.

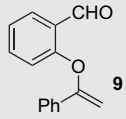
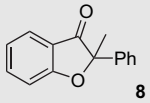
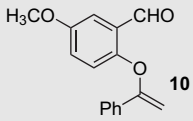
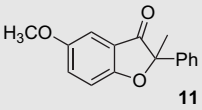
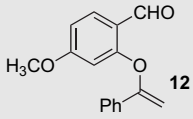
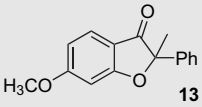
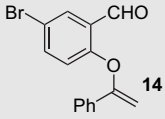
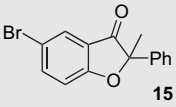
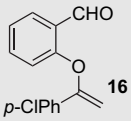
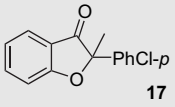
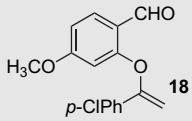
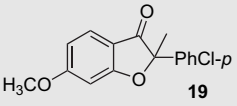
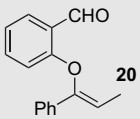
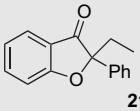
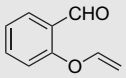
4. Experimental

4.1. General remarks

The ^1H and ^{13}C NMR data were recorded on a Mercury Plus-300 or a Bruker-400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million and coupling constants (J) in hertz. IR spectra were recorded on a Nicolet 670 FTIR spectrophotometer and reported in wavenumbers (cm^{-1}). Mass spectral (MS) data were obtained on a V.G. ZAB-HS mass spectrometer. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel GF_{254} plates. Xylene purchased was analytically pure. DBU was purchased from commercial suppliers and used without further treatment. Thiazolium salts were synthesized according to the literature procedure.

Table 1
Examples of NHCs-catalyzed addition reaction



Entry[a]	Substrate	Cat. (%)	Time (h)	Product	Yield (%)
1	 **9**	25	6	 **8**	>99
2	 **10**	25	12	 **11**	90
3	 **12**	25	12	 **13**	95
4	 **14**	25	12	 **15**	92
5	 **16**	25	12	 **17**	86
6	 **18**	25	12	 **19**	94
7	 **20**	25	12	 **21**	95
8	 **22**	25	12		

[a] All reaction were performed on a 0.5 mmol scale at 0.02 M in xylene at reflux temperature.

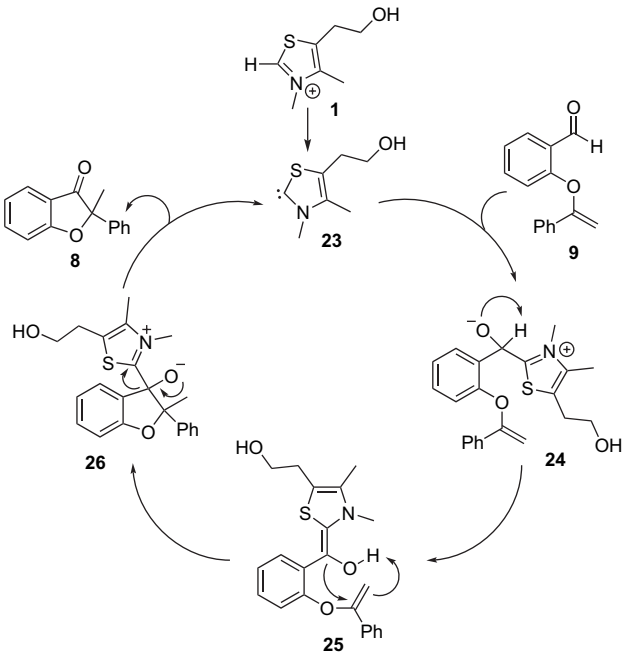
4.2. General procedure

*4.2.1. 3-Methyl-5-(2-hydroxyethyl)-4-methyl-l,3-thiazolium iodine (cat. **1**)*

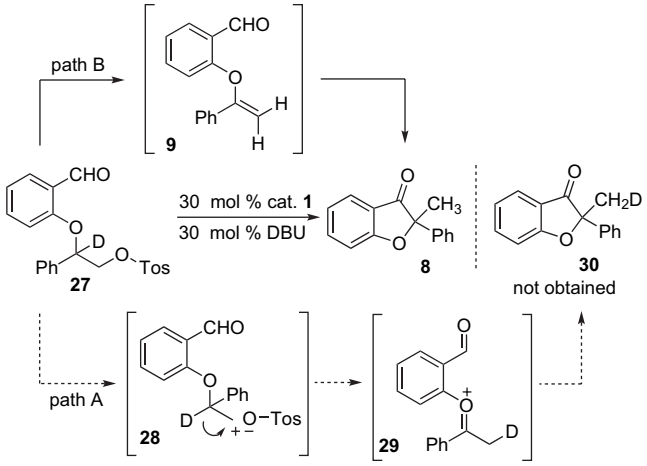
5-(2-Hydroxyethyl-4-methyl-1,3-thiazole (14.3 g, 0.1 mol), iodomethane (21.3 g, 0.15 mol), and dry acetonitrile (60 ml) were mixed in a 250 ml round-bottomed flask with a reflux condenser (potassium hydroxide drying tube) and heated under reflux for 24 h. After cooling, the acetonitrile was removed and the residue treated with isopropyl alcohol (30 ml). Ether was then added until the solution retains a very slight turbidity. After crystallization is complete the precipitate was filtered off under suction, washed with ether, and the ether-moist product dried in a water-pump vacuum. Yield 23.66 g (83%).

*4.2.2. Synthesis of enol ether **9***

To compound **5** (198 mg) in xylene (5 ml) was added DBU (152 mg). The resultant mixture was stirred at 140 °C for 4 h. The solvent was removed under ordinary pressure; the residue was extracted with brine and ethyl acetate, dried over anhydrous Na_2SO_4,



Scheme 5. Proposed catalytic cycle.



Scheme 6. The labeling experiment.

filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, elution with 20:1 petroleum ether/EtOAc) afforded enol ether **9** (108 mg, 96%) as yellow oil.

4.2.3. Synthesis of benzofuranones

A round bottom flask was charged with DBU (53 mg, 0.35 mmol) in 25 ml xylene and thiazolium salt (36 mg, 0.125 mmol) was added. The resulting mixture was stirred at 50 °C for 30 min and then substrate (0.5 mmol) was added. The reaction mixture was stirred for 12 h at reflux temperature. The solvent was removed under ordinary pressure; the residue was chromatographed using 20:1 petroleum ether/EtOAc to afford the product.

*4.2.3.1. 6-Methoxy-2-methyl-2-phenylbenzofuran-3(2H)-one (**13**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.54 (m, 3H), 7.37–7.26 (m, 3H), 6.67–6.64 (m, 2H), 3.89 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 173.6, 168.5, 138.5, 128.4, 127.9, 126.1, 124.6, 112.3, 111.8, 96.0, 90.4, 55.8, 24.2; IR (KBr) 1708, 1613, 1443, 1284, 1203 cm^{-1}; MS *m*/*z* (%) 254 (M^+, 60), 253 (24), 151 (100), 134 (43), 124 (30), 106 (37), 77 (46), 63 (51). HRMS (ESI) calcd for $C_{16}H_{15}O_3$ $[M+H]^+$ 255.1016, found 255.1011.

*4.2.3.2. 2-Ethyl-2-phenylbenzofuran-3(2H)-one (**21**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7.40–7.25 (m, 4H), 7.07 (t, *J*=7.5 Hz, 1H), 2.29–2.21 (m, *J*=7.5, 1.7 Hz, 2H), 0.91 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 171.6, 138.0, 137.1, 128.4, 127.8, 124.8, 121.9, 120.3, 113.1, 92.6, 31.7, 7.9; IR (KBr) 1721, 1612, 1462, 1323, 1299, 1246, 756 cm^{-1}; MS *m*/*z* (%) 238 (M^+, 41), 223 (55), 209 (100), 121 (52), 117 (52), 115 (68), 77 (94), 63 (52). HRMS (ESI) calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1067, found 239.1070.

Acknowledgements

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13. Thiazolium salt **1** and DBU of 30 mol % were mixed in xylene and stirred at 50 °C for 30 min, and then substrate was added. The reaction mixture was stirred for 12 h at reflux temperature.