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N-Heterocyclic Carbene Catalyzed Nucleophilic Substitution Reaction for Construction of Benzopyrones and Benzofuranones

Jinmei He,[†] Jiyue Zheng,[†] Jian Liu,[†] Xuegong She,*[,†,‡] and Xinfu Pan*[,†]

Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, P. R. China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

shexg@lzu.edu.cn

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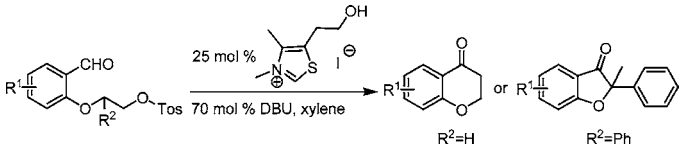
ABSTRACT



N-Heterocyclic carbene as an efficient organic catalyst was employed to catalyze an intramolecular nucleophilic substitution reaction. When R^2 was a phenyl group, the cyclization process underwent isomerization, leading to generation of benzofuranone.

Efficient and selective organocatalytic transformations have been intensely investigated and have attracted a great deal of attention in the past decades.[1] They are becoming powerful tools in the construction of complex molecular skeletons. N-Heterocyclic carbenes (NHCs) generated in situ from thiazolium salts and triazolium salts in the presence of a weak base have been known for a long time.[2] Established catalytic reactions include the benzoin[3] and Stetter reactions[4] in which carbonyl units of aldehydes are converted into nucleophiles upon the addition of a nucleophilic catalyst. Although the development of these carbonyl anion addition reactions has received significant attention,[5,6] nucleophilic substitution reactions catalyzed by NHC have received considerably less. There have been only a few reports on the application of NHCs to these types of organocatalytic transformations.[7] Herein, we report a facile route of nucleophilic substitution reaction catalyzed by NHC to construction of benzopyrones

[†] Lanzhou University.

[‡] Chinese Academy of Sciences.

(1) For reviews on organocatalytic transformations, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Tian, S. K.; Chen, Y. G.; Hang, J. F.; Tang, L.; Mcdaid, P.; Deng, L. *Acc. Chem. Res*. **2004**, *37*, 621. (c) France, S.; Guerin, D. J.; Miller, S. J.; Leclka, T. *Chem. Rev*. **2003**, *103*, 2985. (d) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res*. **2004**, *37*, 580. (e) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.; Houk, K. N. *Acc. Chem. Res*. **2004**, *37*, 558.

(2) (a) Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296. (b) Mizuhara, S.; Handler, P. *J. Am. Chem. Soc.* **1954**, *76*, 571. (c) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(3) For the benzoin condensation, see: (a) Sheehan, J. C.; Hara, T. *J. Org. Chem*. **1974**, *39*, 1196. (b) Enders, D.; Kallfass, U. *Angew. Chem., Int. ed.* **2002**, *41*, 1743. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc*. **2003**, *125*, 8432. (d) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463.

(4) For the Stetter reaction, see: (a) Kerr, M. S.; Read de Alaniz, j.; Rovis, T. *J. Am. Chem. Soc*. **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc*. **2004**, *126*, 8876. (c) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (d) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (e) Mennen, S. M.; Glpson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc*. **2005**, *127*, 1654. (f) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

(5) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534.

(6) Other reaction have been developed. For internal redox of unsaturated aldehydes, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc*. **2004**, *126*, 14370. (b) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (c) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. For internal redox of epoxyaldehydes, see: (d) Chow, K. Y.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. for internal redox of haloaldehydes, see: (e) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. For umpolung of Michael acceptors, see: Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.

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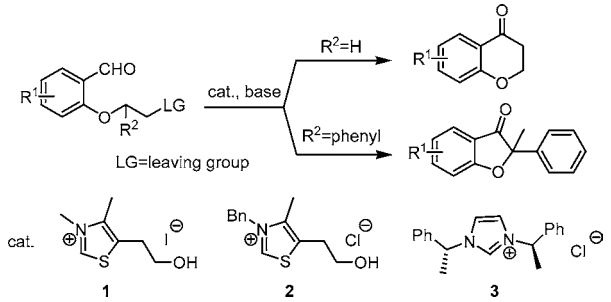
and benzofuranones. In this process, a carbonyl anion catalyzed by NHC was utilized to attach to a suitable leaving group. Benzopyrones and benzofuranones were obtained when the reaction occurred intramolecularly (Scheme 1).

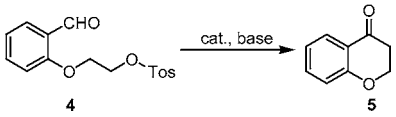
Scheme 1. Intramolecular Nucleophilic Substitution Reaction



According to the traditional approach of analogous nucleophilic substitution reaction, the carbonyl anions could be formed from corresponding aldehydes by thioacetalization.[8] However, the conventional methods are mostly noncatalytic and lack step economy and aesthetic appeal. Our new strategy for construction of benzopyrones and benzofuranones had more advantages and can potentially provide a sustainable, environmentally benign process.

Using aromatic aldehyde **4** as a test substrate, the conditions for this intramolecular nucleophilic substitution reaction were investigated (Table 1). A number of solvents were screened. THF and benzene gave the product in moderate yield (entries 1, 2, and 5), and the use of CH_2Cl_2 or CH_3OH as solvents provided little or none of the desired product (entries 3 and 4). An initial survey of solvents demonstrated that xylene was the solvent of choice (entry 6). Furthermore, the activity of catalysts was also examined. The thiazolium salt **1** was found to be superior to the thiazolium salt **2**,[9] whereas the Herrmann imidazolium salt **3**[10] proved to be inactive in the intramolecular nucleophilic substitution reaction (entry 7). Subsequent optimization indicated that DBU was the optimum base, and the reaction was accelerated by increased amount of DBU. It was found that the reaction proceeded better in the presence of 25 mol % catalyst **1** and 70 mol % DBU at 160 °C.[11]

Table 1. Optimization of Reaction Conditions for the Synthesis of Benzopyrone from Aromatic Aldehyde

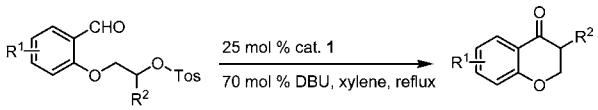


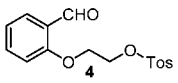
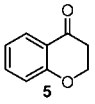
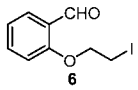
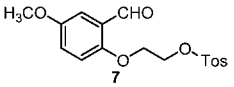
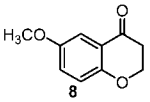
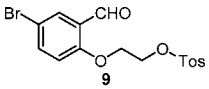
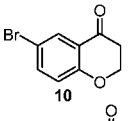
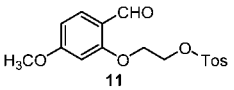
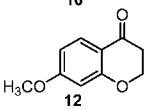
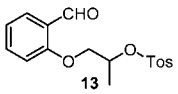
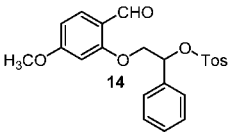
entry[a]	solvent	base	catalyst	temp	time (h)	yield (%)
1	THF	DBU	**1**	reflux	24	50
2	THF	NEt3	**1**	reflux	24	46
3	CH_2Cl_2	DBU	**1**	reflux	24	<5
4	CH_3OH	DBU	**1**	reflux	24	<5
5	benzene	DBU	**1**	reflux	12	58
6	xylene	DBU	**1**	reflux	4h	72
7	xylene	DBU	**3**	reflux	12	0
8	xylene	DBU	**2**	reflux	12	56
9[b]	THF	DBU	**1**	140 °C	4	62
10[b]	CH_2Cl_2	DBU	**1**	140 °C	4	<5

[a] All reactions were performed on a 0.5 mmol scale at 0.02 M. [b] The experiment was conducted in a sealed tube.

With the optimal experimental conditions, the scope of the nucleophilic substitution reaction catalyzed by NHC was explored using a series of aromatic aldehydes (Table 2).

Table 2. Generation of Benzopyrones



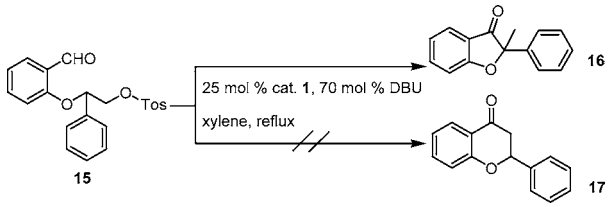
entry[a]	aldehyde	time	product	yield (%)
1		4 h		72
2[b]		4 h		45
3		4 h		75
4		4 h		76
5		10 h		48
6		12 h	no reaction	0
7		12 h	no reaction	0

[a] All reactions were performed on a 0.5 mmol scale at 0.02 M. [b] When the leaving group was chlorine or bromine, product **5** was obtained in low yield.

Reaction of aldehydes **7** and **9** provided benzopyrones **8** and **10** in moderate yield. In the case of aldehyde **11**, the transformation was rather sluggish, and the corresponding

(7) (a) Suzuki, Y.; Toyota, T.; Imada, F. *Chem. Commun.* **2003**, 1314. (b) Miyashita, A.; Suzuki, Y.; Iwamoto, K. L.; Oishi, E.; Higashino, T. *Heterocycles* **1998**, *49*, 405. (c) Miyashita, A.; Suzuki, Y.; Iwamoto, K. L. *Chem. Pharm. Bull.* **1998**, *46*, 390.

Scheme 2. Survey of Another Aldehyde Substrate



benzopyrone was afforded in only 48% yield after prolonged reaction time. Presumably, it was ascribed to the electronic effects. *p*-OMe depressed the electrophilicity of aldehyde, and this made the additon of the catalyst to the carbonyl disadvantageous. When the R^2 group was methyl or phenyl (entries 6 and 7), the corresponding products were not obtained, perhaps as a result of the steric congestion that the carbonyl anion encountered when approaching the sulfonate unit. In this process, any trace of the corresponding acyloin dimmers was not observed.

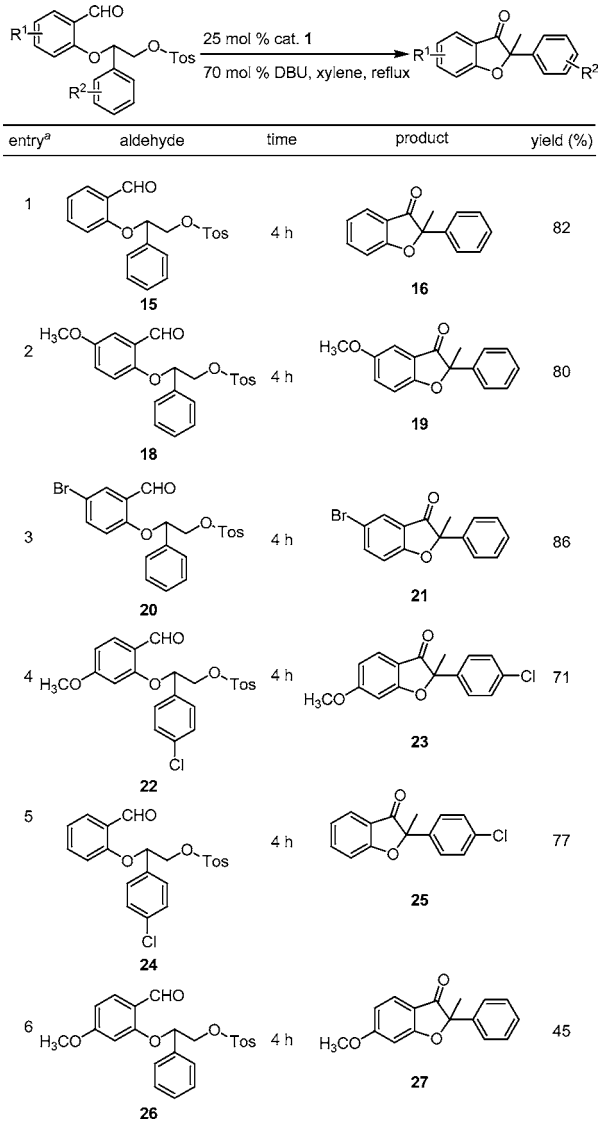
To investigate the impact of structural variations on the aromatic aldehyde substrate for this process, substrate **15** was prepared and underwent the reaction (Scheme 2).

A significant exception was noted; when aldehyde **15** was subjected to these reaction conditions, benzofuranone **16** as the main product was isolated in 82% yield. None of the prospective flavanone **17** was observed. The result suggested that the process underwent an isomerization that delivered the product benzofuranone.

To examine the generality of the methodology, another five analogous aldehyde substrates were scrutinized (Table 3). Aldehydes **18**, **20**, **22**, and **24** reacted in a similar fashion to give satisfactory yields of the product benzofuranones **19**, **21**, **23**, and **25**, and none of the flavanones was detected. Nevertheless, aldehyde **26** still gave product in poor yield.[12]

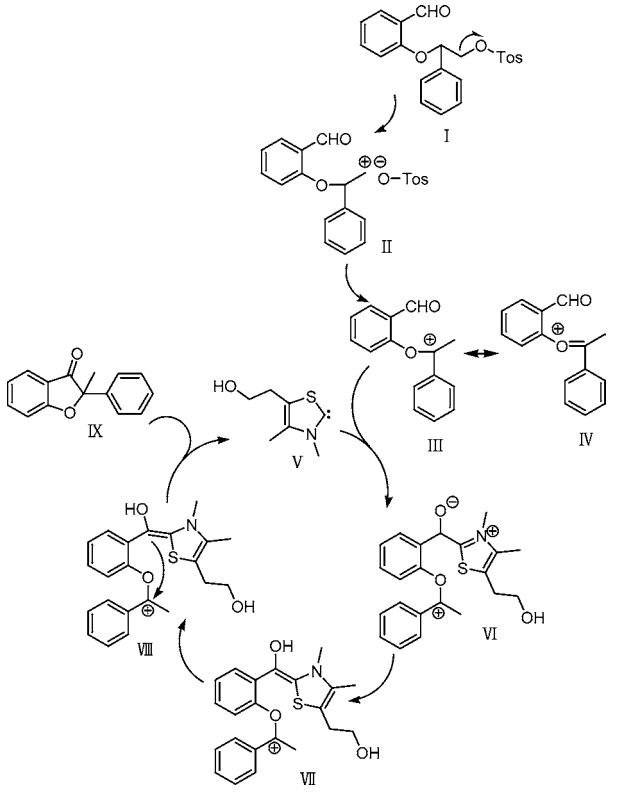
Several experiments producing benzofuranones supported the postulated catalytic cycle outlined in Scheme 3. First,

Table 3. Generation of Benzofuranones



[a] All reactions were performed on a 0.5 mmol scale at 0.02 M.

Scheme 3. Postulated Catalytic Cycle for Benzofuranone Formation



the ion pair **II** may be formed under these reaction conditions, and the carbon cation rearranged to give the more stable

(8) Organic chemists found recourse in the conversion of aldehyde into umpolung reagents such as dithianes and protected cyanohydrin derivatives, which may be converted into the derived carbanionic species with a strong base in traditional way.

(9) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639.

intermediate **III**. Then, the carbene catalyst **V** added to aromatic aldehyde **III** to form intermediate **VI**, which underwent deprotonation to the thiazole-enamine **VII**. Finally, the umpolung aldehyde attached to the electrophilic center, leading to benzofuranone forming **IX** followed by catalyst turnover.

In conclusion, we have developed a novel intramolecular nucleophilic substitution reaction catalyzed by NHC, which is a more direct and efficient way to construct skeletons of benzopyrones and benzofuranones. A variety of substrates underwent the reaction in satisfactory yield, and we presumed a mechanism of this reaction forming benzofuranone, which was likely to undergo rearrangement of cation. Further investigations into the precise mechanism of this reaction as well as the use of chiral carbenes as organocatalysts in other asymmetric reaction are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Herrmann, W. A.; Goossen, L. J.; Artus, G. R. J.; Kocher, C. *Organometallics* **1997**, *16*, 2472.

(11) The reaction solution was refluxed intensely, heated by an oil bath kept at 160−170 °C.

(12) The thermal elimination of the sulfonate **26** was detected (30%); the elimination reaction was a competitive process with cyclization catalyzed by NHC