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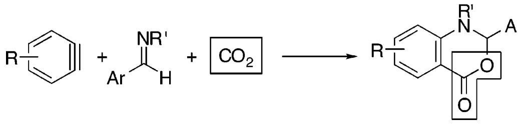
CO_2 Incorporation Reaction Using Arynes: Straightforward Access to Benzoxazinone

Hiroto Yoshida,* Hiroyuki Fukushima, Joji Ohshita, and Atsutaka Kunai*

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan

Received June 13, 2006; E-mail: yhiroto@hiroshima-u.ac.jp; akunai@hiroshima-u.ac.jp

In view of the strong demand for efficacious utilization of CO_2 as a C_1 source, development of CO_2 incorporation reactions into valuable organic molecules has been an essential subject in synthetic organic chemistry.[1] Recently, we have demonstrated that diverse benzo-annulated heterocyclic structures can directly be fabricated via three-component coupling reactions using arynes,[2,3] in which zwitterions arising from nucleophilic attack of neutral nucleophiles to arynes act as pivotal intermediates.[4,5] These reactive zwitterions are readily trapped by such carbon electrophiles as aldehydes[2a] or sulfonylimines,[2b] and thus, we envisaged that they should be appropriate molecular scaffolds for the capture of CO_2 of enough electrophilicity. We report herein the new CO_2 incorporation reaction based upon three-component assembly by the use of arynes and imines, which produces six-membered heterocycles, benzoxazinones of structural diversity (eq 1).

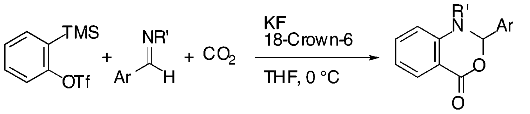


(1)

First we carried out the reaction of in situ-generated benzyne (from **1a**[6] and KF/18-crown-6) with *N*-(2,4,6-trimethylbenzylidene)-methylamine (**2a**) under a CO_2 atmosphere (1 atm) and found that the three-component coupling product, benzoxazinone **3aa**, was produced in 82% yield (Table 1, entry 1). Electron-rich (**2b**−**2d**) or -neutral (**2e** or **2f**) imines also reacted smoothly with benzyne and CO_2 to afford high yields of the respective products (**3ab**−**3af**) (entries 2−6), whereas the reaction of **2g** or **2h** resulted in moderate yield (entries 7 and 8). A substituent on the nitrogen atom affected the course of the reaction considerably. Thus, *N*-benzyl (**2i**) or *N*-*n*-Bu (**2j**) imine could participate in the reaction efficiently to give **3ai** or **3aj** in good yield (entries 9 and 10), in contrast to the reaction of *N*-*i*-Pr (**2k**, 36% yield), *N*-*t*-Bu, or *N*-Ph imine (**2l** or **2m**, benzoxazinone was not formed at all) (entries 11−13), which indicates that steric congestion or decreased nucleophilicity of the nitrogen moiety strictly retards the reaction.

In addition to simple benzyne, variously substituted arynes were also applicable to the reaction (Scheme 1). For example, treatment of 4-methylbenzyne (from **1b**) with **2a** and CO_2 offered a 74% yield of two regioisomers (ratio = 50:50), confirming the intermediacy of an aryne in the present three-component coupling. In contrast, the reaction of 4-fluorobenzyne (from **1c**) or 3-methylbenzyne (from **1d**) proceeded regioselectively to provide **3ca** or **3da** as the major product, respectively. Similarly to other nucleophilic couplings using 3-methoxybenzyne (from **1e**), exclusive formation of **3ea**, which possesses the nitrogen moiety at the *meta* position of the methoxy group, was observed, as well. The use of symmetrical arynes further enhanced the versatility of the reaction, and thus, benzoxazinones of structural diversity (**3fa**−**3ia**) could be synthesized in a straightforward manner. Moreover, 3,6-dimethylbenzyne (from **1j**) underwent the reaction to furnish the product in 57% yield, regardless of its steric hindrance around the triple bond.

Table 1. Three-Component Coupling of Benzyne, Imines, and CO_2[a]



1a **2** *1 atm* **3**

entry	R′	Ar		time (h)	yield (%)[b]	product
1	Me	2,4,6-$Me_3C_6H_2$	**2a**	15	82	**3aa**
2		2,4-$(MeO)_2C_6H_3$	**2b**	15	80	**3ab**
3		2,4-$Me_2C_6H_3$	**2c**	11	76	**3ac**
4		4-$MeOC_6H_4$	**2d**	16	73	**3ad**
5		Ph	**2e**	15	72	**3ae**
6		1-naphthyl	**2f**	18	70	**3af**
7		2-thienyl	**2 g**	17	49	**3ag**
8		4-$CF_3C_6H_4$	**2h**	18	31	**3ah**
9	Bn	4-$MeOC_6H_4$	**2i**	15	72	**3ai**
10	*n*-Bu		**2j**	12	62	**3aj**
11	*i*-Pr		**2k**	15	36	**3ak**
12[c]	*t*-Bu		**2l**	5	0	
13[c]	Ph		**2m**	5	0	

[a] The reaction was carried out at 0 °C in THF (1 mL) using **1a** (0.30 mmol), **2** (0.15 mmol), KF (0.60 mmol), and 18-crown-6 (0.60 mmol) under a CO_2 atmosphere (1 atm). [b] Isolated yield based on **2**. [c] At room temperature.

Considering the salient electrophilicity of arynes, the three-component coupling would be triggered by a nucleophilic attack of an imine as described in Scheme 2. The resulting zwitterion (**4**) then captures CO_2, and a subsequent intramolecular cyclization affords the product. The observed regioselectivities in the reaction of the unsymmetrical arynes should be ascribable to electronic and/or steric effects of a substituent on the arynes. Owing to an electron-withdrawing inductive effect ($-I$ effect) of a fluorine atom (4-fluorobenzyne), the developing negative charge at the closer position to the fluorine atom is stabilized markedly in the transition state for the nucleophilic attack, which results in the preferential generation of **3ca**. Similarly, exclusive formation of **3ea** can rationally be explained by the electron-withdrawing effect together with a steric effect, which directs the nucleophilic attack toward the *meta* position of the methoxy moiety and avoiding a disfavored steric repulsion between the methoxy moiety and an incoming imine. In the case of 3-methylbenzyne, the steric effect would be in conflict with an electron-donating inductive effect ($+I$ effect) of the methyl moiety, leading to the production of a mixture of **3da** and **3′da**. In contrast, a methyl group at position 4 should not

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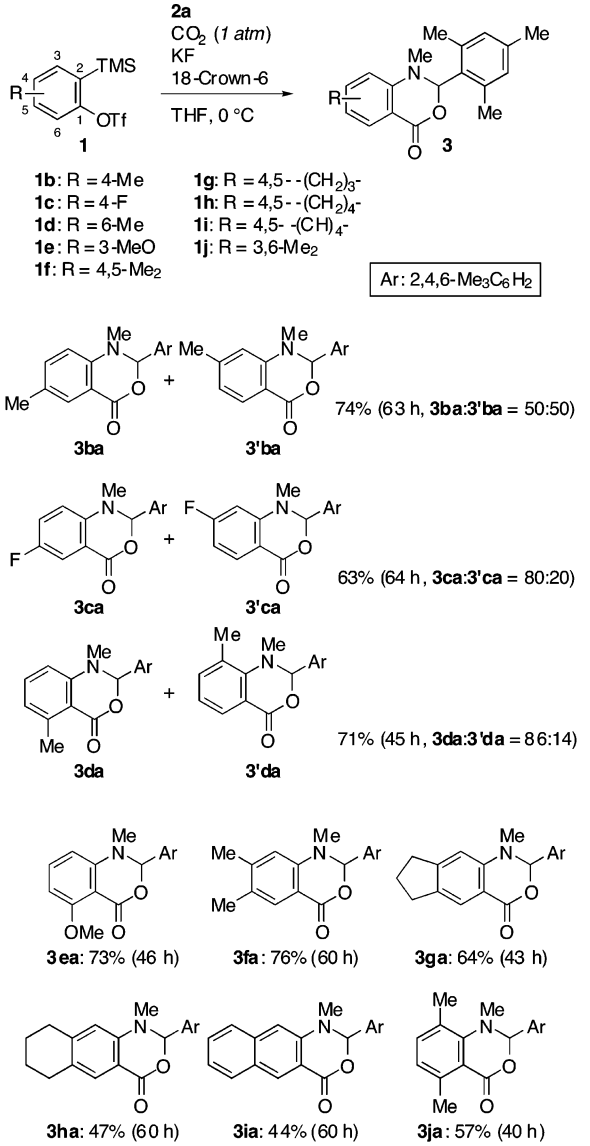
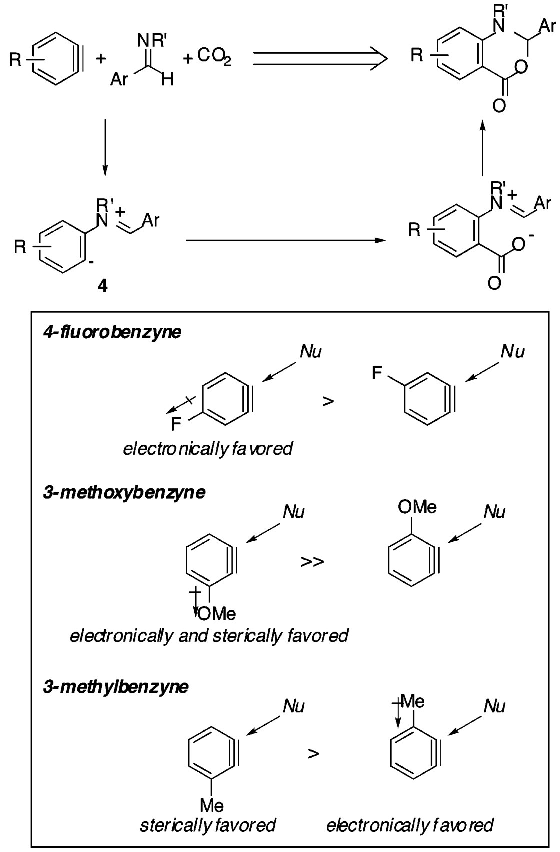
Scheme 1



induce electronic and steric differences, so 4-methylbenzyne accepts the nucleophilic attack on both ends of the triple bond equally.

In conclusion, we have demonstrated that a zwitterion arising from nucleophilic addition of imines to arynes is an excellent molecular scaffold for capturing CO_2, leading to the production of benzoxazinone derivatives, which attract considerable attention by their interesting pharmacological activity, including anti-HCoV and anti-inflammatory effects.[7] Further studies on the CO_2 incorporation−multicomponent reaction by use of arynes and other nucleophiles are in progress.

Scheme 2



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Supporting Information Available: Experimental details. This material is available free of charge via Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Louie, J. *Curr. Org. Chem.* **2005**, *9*, 605. (b) Sakakura, T.; Yasuda, H.; Choi, J.-C. *J. Synth. Org. Chem., Jpn.* **2004**, *62*, 716. (c) Shi, M.; Shen, Y.-M. *Curr. Org. Chem.* **2003**, *7*, 737.
(2) (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (b) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659.
(3) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454.
(4) For a review on nucleophilic coupling with arynes, see: Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 483.
(5) We also reported other nucleophilic coupling reactions using arynes: (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (b) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049. (c) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.
(6) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
(7) (a) Wu, C.-C.; Wang, T.-W.; Wang, W.-I.; Hsieh, P.-W.; Wu, Y.-C. *Eur. J. Pharmacol.* **2005**, *527*, 37. (b) Hsieh, P.-W.; Hwang, T.-L.; Wu, C.-C.; Chang, F.-R.; Wang, T.-W.; Wu, Y.-C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2786. (c) Hsieh, P.-W.; Chang, F.-R.; Chang, C.-H.; Cheng, P.-W.; Chiang, L.-C.; Zeng, F.-L.; Lin, K.-H.; Wu, Y.-C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4751.

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