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Direct Access to Anthranilic Acid Derivatives via CO_2 Incorporation Reaction Using Arynes

Hiroto Yoshida,* Takami Morishita, and Joji Ohshita

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

yhiroto@hiroshima-u.ac.jp

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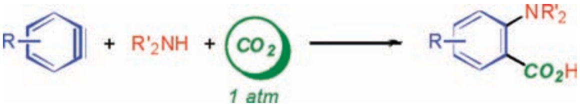
ABSTRACT



CO_2 was found to be directly convertible into anthranilic acid derivatives of great synthetic value through a three-component coupling using arynes and amines. Zwitterions arising from nucleophilic attack of amines to arynes serve as key intermediates in the coupling.

Much attention has been focused on development of new CO_2 incorporation reactions, because of increasing demand for efficacious application of CO_2 as a C_1 source for constructing valuable organic compounds.[1,2] Recently, we have disclosed that CO_2 could readily be incorporated into diverse benzoxazinones of synthetic significance under mild conditions based on a three-component coupling reaction using arynes and imines,[3] where zwitterions generated from nucleophilic attack of imines to arynes serve as key intermediates for capturing CO_2.[4,5] This result implies that similar species containing zwitterionic structure should have a potential affinity for CO_2, and thus, we envisioned that use of other neutral nucleophiles in lieu of imines in the three-component coupling would result in a novel method for incorporating CO_2 into valuable organic compounds. Herein, we report a direct and efficient synthesis of anthranilic acid derivatives, which attract considerable attention by their interesting pharmacological activity,[6] through a three-component coupling using amines as nucleophiles.[7]

The new coupling reaction could be achieved when benzyne, generated in situ from **1a**[8] and a fluoride ion, was treated with dipropylamine (**2a**) in THF at 0 °C under a CO_2

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(1) For a recent review, see: Sakakura, T.; Choi, J. -C.; Yasuda, H *Chem. Rev.* **2007**, *107*, 2365.

(2) For recent examples, see: (a) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195. (b) Nakano, K.; Kamada, T.; Nozaki, K. *Angew. Chem., Int. Ed.* **2006**, *43*, 7274. (c) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706. (d) Aoki, M.; Izumi, S.; Kaneko, M.; Ukai, K.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2007**, *9*, 1251. (e) Greco, G. E.; Gleason, B. L.; Lowery, T. A.; Kier, M. J.; Hollander, L. B.; Gibbs, S. A.; Worthy, A. D. *Org. Lett.* **2007**, *9*, 3817.

(3) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040.

(4) Other three-component coupling reactions of arynes which proceed through a zwitterionic intermediate have been reported: (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. (c) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793. (d) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454.

(5) Transition-metal-catalyzed three-component coupling of arynes: (a) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (b) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686. (c) Jeganmohan, M.; Cheng, C.-H *Org. Lett.* **2004**, *6*, 2821. (d) Jayanth, T. T.; Jeganmohan, M.; Cheng, C. -H *Org. Lett.* **2005**, *7*, 2921. (e) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (f) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921. (g) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589. (h) Bhuvaneswari, S.; Jeganmohan, M.; Yang, M. -C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2158.

(6) (a) Congiu, C.; Cocco, M. T.; Lilliu, V.; Onnis, V. *J. Med. Chem.* **2005**, *48*, 8245. (b) Nittoli, T.; Curran, K.; Insaf, S.; DiGrandi, M.; Orlowski, M.; Chopra, R.; Agarwal, A.; Howe, A. Y. M.; Prashad, A.; Floyd, M. B.; Johnson, B.; Sutherland, A.; Wheless, K.; Feld, B.; O'Connell, J.; Mansour, T. S.; Bloom, J. *J. Med. Chem.* **2007**, *50*, 2108.

(7) We have already reported on synthesis of 2-aminobenzhydrols (or 2-aminobenzhydrylamines) based on three-component coupling reactions of arynes, aminosilanes, and aldehydes (or sulfonylimines). In these reactions, the use of amines as nucleophiles in lieu of aminosilanes led to considerable lowering of the product yields in contrast to the results described herein. (a) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367. (b) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452.

(8) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

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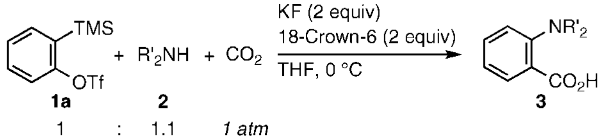
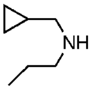
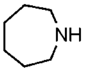
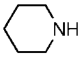
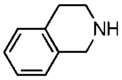
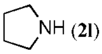
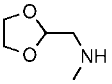
atmosphere (1 atm), giving *N*,*N*-dipropylanthranilic acid (**3aa**) in 84% yield (Table 1, entry 1). The high selectivity for the formation of the anthranilic acid is worth noting because amines are apt to be arylated in the reaction with arynes to produce aniline derivatives.[9] The reaction of dibutyl- (**2b**), diethyl- (**2c**), or bis(2-methoxyethyl)amine (**2d**) also took place efficiently to afford the respective products (**3ab**−**3ad**) in good yields (entries 2−4). Regardless of the steric hindrance around the nitrogen atom, amines bearing a secondary alkyl group (**2e**−**2g**) smoothly coupled with benzyne and CO_2, furnishing 74−79% yields of **3ae**−**3ag** (entries 5−7). In addition, *N*-(cyclopropylmethyl)-*N*-propylamine (**2h**) could participate in the reaction to give **3ah** in 77% yield, leaving the strained cyclopropyl group intact (entry 8). Seven- or six-membered cyclic amines (**2i**−**2k**) produced moderate yields of anthranilic acids **3ai**−**3ak** (entries 9−11), whereas the reaction of pyrrolidine (**2l**) resulted in a low yield (entry 12). Although the yield was rather lower than those described above, the reaction of an amine containing an acetal functionality also offered the desired product **3am** (entry 13).[10,11]

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

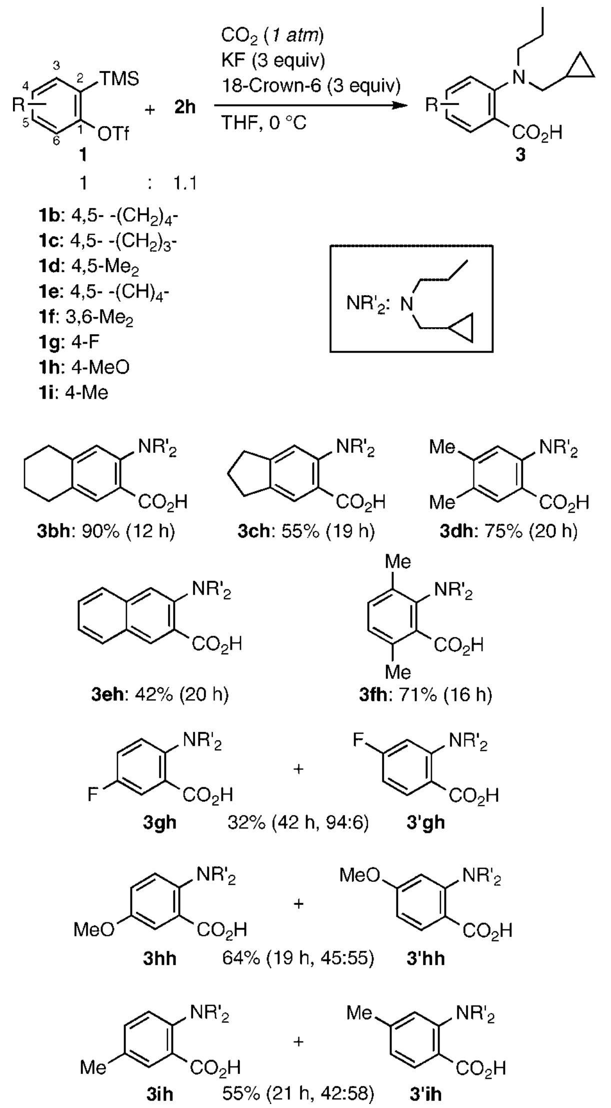


entry	2	3	time (h)	yield (%)[b]
1	*n*-Pr_2NH (**2a**)	**3aa**	50	84
2	*n*-Bu_2NH (**2b**)	**3ab**	18	74
3	Et_2NH (**2c**)	**3ac**[d]	21	54
4	$(MeOCH_2CH_2)_2NH$ (**2d**)	**3ad**[d]	39	64
5	*i*-Pr_2NH (**2e**)	**3ae**[d]	20	79
6	Cy_2NH (**2f**)	**3af**	97	78
7	CyMeNH (**2g**)	**3ag**[d]	40	74
8[c]	 NH (**2h**)	**3ah**	22	77
9	 (**2i**)	**3ai**[d]	18	62
10	 (**2j**)	**3aj**[d]	25	53
11	 (**2k**)	**3ak**	66	38
12	 (**2l**)	**3al**[d]	84	7
13	 (**2m**)	**3am**[d]	22	29

[a] The reaction was carried out in THF (1 mL) at 0 °C using **1a** (0.15 mmol), **2** (0.165 mmol), 18-crown-6 (0.30 mmol), and KF (0.30 mmol) under a CO_2 atmosphere (1 atm). [b] Isolated yield based on **1a**. [c] KF = 3 equiv; 18-crown-6 = 3 equiv. [d] Anthranilic acids were converted into the respective methyl esters before isolation.

The versatility of the present reaction could further be enhanced by application to substituted arynes (Scheme 1). Thus, a 90% yield of product **3bh** was obtained by treatment of cyclohexane-fused aryne (from **1b**) with **2h** and CO_2. Multisubstituted anthranilic acids of structural diversity (**3ch**−**3eh**) could readily be constructed in the reactions using 4,5-disubstituted arynes (from **1c**−**1e**), and moreover, 3,6-dimethylbenzyne (from **1f**) was smoothly transformed into the respective product (**3fh**), despite its steric congestion. The reaction of 4-fluorobenzyne (from **1g**) proceeded with a high regioselectivity, giving **3gh** and **3′gh** in a ratio of

Scheme 1. Three-Component Coupling of Arynes, **2h**, and CO_2



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(9) (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

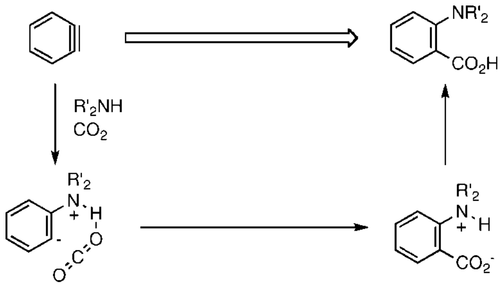
(10) In the reactions with low yields of **3**, an aniline derivative and some unidentified compounds were formed as side products.

(11) The reason for the longer reaction time (for example, entries 6, 11, and 12) is due to slow consumption of benzyne precursor **1a**.

94:6,[12] while almost equal amounts of regioisomers were formed in the reaction using 4-methoxybenzyne (from **1h**) or 4-methylbenzyne (from **1i**).

The three-component coupling would be initiated by a nucleophilic attack of an amine to an aryne as depicted in Scheme 2. The resulting zwitterion (**4**) is then trapped by CO_2 to provide anthranilic acid **3** through proton migration. The high selectivity for the three-component coupling compared with the amine arylation[9] may be ascribable to attractive hydrogen bonding between the amine H in **4** and CO_2, which enhance the electrophilicity of CO_2 to a great extent.

Scheme 2. Plausible Reaction Pathway



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In conclusion, we have demonstrated that CO_2 could efficaciously be incorporated into diverse anthranilic acid derivatives under extremely mild conditions based upon the three-component coupling by use of arynes and amines.[13] The result exemplifies that zwitterionic species are prominent molecular scaffolds for capturing CO_2, and hence studies on CO_2 incorporation reactions utilizing other neutral nucleophiles are in progress in our laboratory.

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Supporting Information Available: Experimental procedure and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] A similar regioselectivity, which can be attributed to the strong electron-withdrawing effect of a fluorine atom, was observed in other three-component couplings with 4-fluorobenzyne. See refs 3, 4, and 7.

[13] Preliminary experiments revealed that primary amines and aminosilanes also gave the respective three-component coupling products, which will be reported in due course.