JOC*Note*

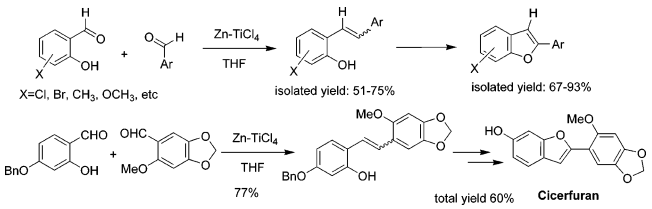
A Facile Two-Step Synthesis of 2-Arylbenzofurans Based on the Selective Cross McMurry Couplings

Xin-Fang Duan,* Jing Zeng, Zhan-Bin Zhang, and Guo-Fu Zi

Department of Chemistry, Beijing Normal University, Beijing 100875, China

xinfangduan@vip.163.com

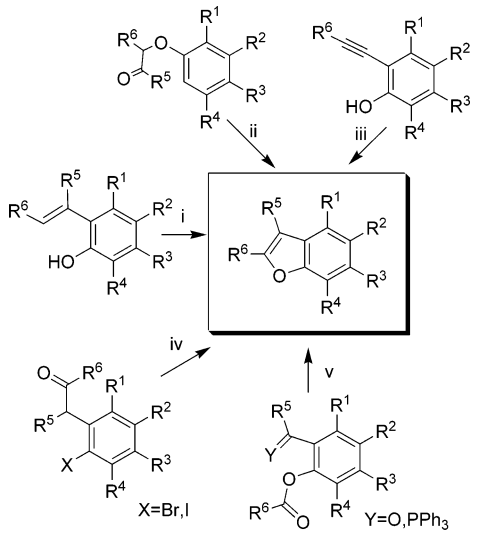
Received September 6, 2007



A novel two-step synthesis of 2-arylbenzofurans has been developed. It involves a selective cross McMurry coupling of a salicylaldehyde or substituted salicylaldehyde with an aromatic aldehyde and a sequential oxidative cyclization of the resulting *ortho*-vinylphenols. Utilizing this synthetic protocol, a variety of 2-arylbenzofurans including cicerfuran (**5**) have been efficiently synthesized.

Benzofurans and their analogues constitute a major group of naturally occurring compounds.[1] Their broad range of biological activities and significant pharmacological potentials have generated extensive and enduring efforts toward the syntheses of these important heterocyclic compounds.[2] Major reported synthetic strategies involve (Scheme 1) (i) oxidative cyclization of *o*-vinylphenols,[3] (ii) dehydrative cyclization of α-phenoxy ketones,[4] (iii) cyclization of *o*-ynylphenol,[5] (iv) copper- or palladium-catalyzed O-arylation of *o*-halobenzyl ketones,[6] and (v) intramolecular McMurry couplings[7] or Wittig reactions.[8]

SCHEME 1



Recently, we have initiated a program to achieve the general and selective cross McMurry couplings between two carbonyl compounds.[9] We reported that, in the presence of a series of groups such as −OH, $-NH_2$, etc., a selective cross McMurry coupling between diaryl or aryl ketones with various ketones was achieved.[9] We now disclose a novel two-step synthetic strategy for 2-arylbenzofurans using the selective cross McMurry couplings between two aromatic aldehydes as a pivotal step, namely, (a) a selective cross McMurry coupling of salicylaldehyde or substituted salicylaldehyde with an aromatic aldehyde yielding an *o*-vinylphenol, and (b) a sequential oxidative

(1) (a) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 259. (b) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: London, 1984; Vol. 4, p 531. (c) Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, p 337.

(2) (a) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2005**, *17*, 142. (b) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167. (c) Dell, C. P. *Sci. Synth.* **2001**, *10*, 11. (d) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67.

(3) For I_2-mediated cyclization, see: (a) Pan, C.-F.; Yu, J.; Zhou, Y.-Q.; Wang, Z.-Y.; Zhou, M.-M. *Synlett* **2006**, 1657. (b) Kim, K. M.; Ryu, E. K. *Heterocycles* **1995**, *41*, 219. For the cyclization using DDQ, see: (c) Takeshi, K.; Koji, I. *Heterocycles* **2005**, *65*, 1641. (d) Fujita, M.; Qi, G.-Z.; Verkerk, U. H.; Dzwiniel, T. L.; McDonald, R.; Stryker, J. M. *Org. Lett.* **2004**, *6*, 2653. (e) Nicolaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E.; Adamopoulos, S. G. *J. Heterocycl. Chem.* **1998**, *35*, 91. (f) Imafuku, K.; Fujita, R. *Chem. Express* **1991**, *6*, 323. (g) Merlini, L.; Cardillo, G.; Cricchio, R. *Tetrahedron* **1971**, *27*, 1875. For other reagents, see: (h) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214. (i) Lattanzi, A.; Senatore, A.; Massa, A.; Scettri, A. *J. Org. Chem.* **2003**, *68*, 3691. (j) Masutani, K.; Irie, R.; Katsuki, T. *Chem. Lett.* **2002**, 36.

(4) (a) Shen, Q.; Peng, Q.; Shao, J.-L.; Liu, X.-L.; Huang, Z.-H.; Pu, X.-Z.; Ma, L.; Li, Y.-M.; Chan, A. S. C.; Gu, L.-Q. *Eur. J. Med. Chem.* **2005**, *40*, 1307. (b) Mashraqui, S. H.; Patil, M. B.; Sangvikar, Y.; Ashraf, M.; Mistry, H. D.; Daub, E. T. H.; Meetsma, A. *J. Heterocycl. Chem.* **2005**, *42*, 947. (c) Santini, C.; Berger, G. D.; Han, W.; Mosley, R.; MacNaul, K.; Berger, J.; Doebber, T.; Wu, M.; Moller, D. E.; Tolman, R. L.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1277. (d) Jørgensen, M.; Krebs, F. C.; Bechgaard, K. *J. Org. Chem.* **2000**, *65*, 8783.

(5) (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (b) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (c) Yue, D.-W.; Yao, T.-L.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (d) Yao, T.-L.; Yue, D.-W.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985 and references therein.

(6) (a) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467. (b) Chen, C.-Y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964. (c) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Eur. J. Org. Chem.* **2005**, *12*, 2481. (d) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755.

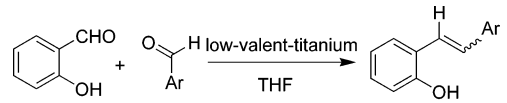
(7) For the preparation of 2,3-disubstituted benzofuran via the intramolecular McMurry couplings, see: (a) Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990. (b) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468. (c) Fürstner, A.; Hupperts, A.; Rock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215. (d) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991. (e) Banerji, A.; Nayak, S. K. *Chem. Commun.* **1990**, 150. The preparation of 2- or 3-monosubstituted benzofurans by this methodology is quite few; see ref 7d, p 5994.

(8) (a) Yuan, Y.; Men, H.-B.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720. (b) Katerina, C.; Miloslav, N.; Pavel, P.; Jiri, S. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1939. (c) Jean, G.; Nicole, B.; Pierre, D. *J. Heterocycl. Chem.* **1990**, *27*, 10. (d) Hercouet, A.; Lecorre, M. *Tetrahedron Lett.* **1979**, *20*, 2145.

(9) Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* **2006**, *71*, 9873.

10.1021/jo7019652 CCC: $37.00
Published on Web 11/21/2007

TABLE 1. The Influence of the Equivalent of Low Valent Titanium on the Cross McMurry Reactions between Salicylaldehyde and Aryl Aldehyde



1a **2a-2b** **3aa-3ab**

a: Ar = Ph; **b**: 4-MeOPh

entry	aldehyde[a]	Ti (equiv)	time (h)	yield[b] (%)
1	**1a** + **2a**	$TiCl_4$−Zn−Py (5)	3.5	43 (**3aa**)
2	**1a** + **2a**	$TiCl_4$−Zn−Py (4)	5	50.2 (**3aa**)
3	**1a** + **2a**	$TiCl_4$−Zn−Py (2.5)	6	58 (**3aa**)
4	**1a** + **2a**	$TiCl_4$−Zn (4)	5	51 (**3aa**)
5	**1a** + **2a**	$TiCl_4$−Zn (2.5)	6	60 (**3aa**)
6	**1a** + **2b**	$TiCl_4$−Zn−Py (5)	3	60 (**3ab**)
7	**1a** + **2b**	$TiCl_4$−Zn−Py (4)	5.5	73 (**3ab**)
8	**1a** + **2b**	$TiCl_4$−Zn−Py (2.5)	6	74 (**3ab**)
9	**1a** + **2b**	$TiCl_4$−Zn (4)	6	72 (**3ab**)
10	**1a** + **2b**	$TiCl_4$−Zn (2.5)	6	75 (**3ab**)

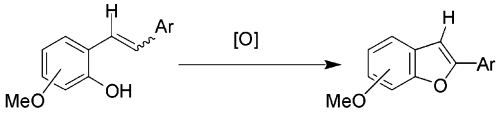
[a] The mole ratios of **1a** to **2a**, **2b** were 1:1.2. [b] Yield of isolated product.

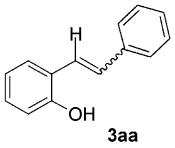
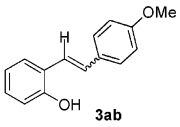
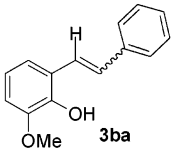
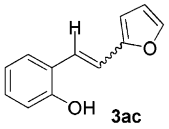
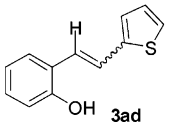
cyclization of the *o*-vinylphenol to afford the corresponding 2-arylbenzofuran. Because the reagents are readily available and the protocols simple to carry out, this new synthetic methodology represents a convenient and effective approach toward a variety of 2-arylbenzofurans.

Initially, we performed the McMurry coupling of salicylaldehyde (**1a**) with benzaldehyde (**2a**) and 4-methoxybenzaldehyde (**2b**) using 5 equiv of low valent titanium ($TiCl_4$−Zn−Py) according to our reported procedure.[9] It was observed that the coupling proceeded significantly faster than those between ketones[9] with isolated yields of the cross couplings products ranging from 43 to 60%, respectively (Table 1, entries 1 and 6). The yields increased to 58 and 74% when 2.5 equiv of low valent titanium was used (Table 1, entries 3 and 8). We observed a yellow precipitate forming during the course of the reaction. Ordinarily, the couplings occur as a black mixture using $TiCl_4$−Zn as a low valent titanium source. The yields were similar to those using $TiCl_4$−Zn−Py (Table 1, entries 4, 5, 9, and 10). Here, optimal conditions for cross McMurry couplings of salicylaldehyde or substituted salicylaldehyde (**1**) with aryl aldehyde (**2**) employed 2.5 equiv of $TiCl_4$−Zn with a 1:1.2 mol ratio of **1** to **2**.

The oxidative cyclization of *o*-vinylphenols was tested using three reagents: (A) DDQ,[3c−g] (B) *m*-CPBA/TsOH,[3h] and (C) I_2/K_2CO_3.[3c−g] The results are outlined in Table 2. Although DDQ is commonly utilized to carry out the oxidative cyclization, we observed that the other two reagents were equally effective. Additionally, the workup of the DDQ reaction required greater effort than the other two methods. The reported cyclization via *m*-CPBA/TsOH was performed in two steps:[3h] epoxidation by *m*-CPBA followed by TsOH-catalyzed cyclization. In our lab, we improved the procedure and performed the two reactions in one pot. We found that this method was suitable for the *o*-vinylphenol without an electron-donating group such as MeO− (Table 2, entry 1). The method employing I_2/K_2CO_3 was highly effective and simple for the oxidative cyclization in most cases. We were able to achieve the oxidative cyclization of *o*-vinylphenols using I_2/K_2CO_3 in most cases that were attempted. For the *o*-vinylphenols without electron-donating groups, we

TABLE 2. The Oxidative Cyclization of *o*-Vinylphenols to 2-Arylbenzofurans



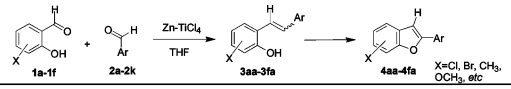
entry	*o*-vinyl phenol	yield (%)[a] *m*CPBA -TsOH	DDQ	I_2/THF
1	 **3aa**		60	89	63
2	 **3ab**		91	90	91
3	 **3ba**		45	61	83
4	 **3ac**		21	19	81
5	 **3ad**		47	55	85

[a] Isolated yield.

obtained the oxidative cyclization product via *m*-CPBA/TsOH.

With the above optimized conditions for the two reactions, we prepared a variety of 2-arylbenzofurans through this two-step synthetic strategy in order to establish the generality of this approach (Table 3). This method proved to be a flexible and convergent protocol for 2-arylbenzofurans. Besides 2-phenyl or substituted phenyl benzofurans, 2-heteroaromatic substituted benzofurans were also conveniently and efficiently synthesized (Table 3, entries 3, 4, and 7). The oxidative cyclization proceeded smoothly, and high yields were achieved. In regards the selective cross McMurry reaction, the following features are highlighted: (1) the hydroxyl group of **1a**−**f** is important to the selective cross coupling as it not only enhances the selective cross coupling over homocoupling but also facilitates the isolation of the products; (2) the presence of electron-donating groups, such as methoxy and piperidinyl, seems beneficial to the enhancement of the selectivity cross coupling

TABLE 3. Preparation of 2-Arylbenzofuran Using the Selective Cross McMurry Reactions



entry	aldehydes[a]	*o*-vinylphenol (yield)[b]	oxidants for cyclization	2-arylbenzofuran (yield)[b]
1	1a + 2a	3aa, 60%	*m*CPBA -TsOH	4aa, 89%
2	1a + 2b	3ab, 75%	I_2/K_2CO_3	4ab, 91%
3	1a + 2c	3ac, 58%	I_2/K_2CO_3	4ac, 81%
4	1a + 2d	3ad, 62%	I_2/K_2CO_3	4ad, 85%
5	1a + 2e	3ae, 61%	I_2/K_2CO_3	4ae, 67%
6	1a + 2f	3af, 65%	I_2/K_2CO_3	4af, 93%
7	1a + 2g	3ag, 62%	I_2/K_2CO_3	4ag, 67%
8	1a + 2i	3ai, 63%	I_2/K_2CO_3	4ai, 83%
9	1a + 2j	3aj, 72%	I_2/K_2CO_3	4aj, 79%
10	1a + 2k	3ak, 52%	*m*CPBA -TsOH	4ak, 63%
11	1b + 2a	3ba, 59%	*m*CPBA -TsOH	4ba, 87%
12	1c + 2a	3ca, 59%	I_2/K_2CO_3	4ca, 77%
13	1d + 2a	3da, 63%	I_2/K_2CO_3	4da, 87%
14	1e + 2a	3ea, 69%	I_2/K_2CO_3	4ea, 83%
15	1f + 2a	3fa, 72%	I_2/K_2CO_3	4fa, 88%

[a] The mole ratios of **1a**−**1f** to **2a**−**2k** were 1:1.2. [b] Yield of isolated product.

(Table 3, entries 2, 6, 8, 9, and 13−15), an effect also observed for the homocoupling of diaryl ketone;[10] (3) to achieve a selective cross coupling, the rates of two carbonyl compounds in the McMurry reaction should not be significantly different; otherwise the coupling of the two carbonyl compounds will result in predominantly homocoupling products. In our hands, the couplings of salicylaldehyde with butyraldehyde, cyclopentanecarboxaldehyde, and cyclohexanone did not significantly afford their respective cross coupling products. We observed that the homocouplings of butyraldehyde, cyclopentanecarboxaldehyde, and cyclohexanone were complete in approximately 1 h, and hardly any cross coupling products were observed.

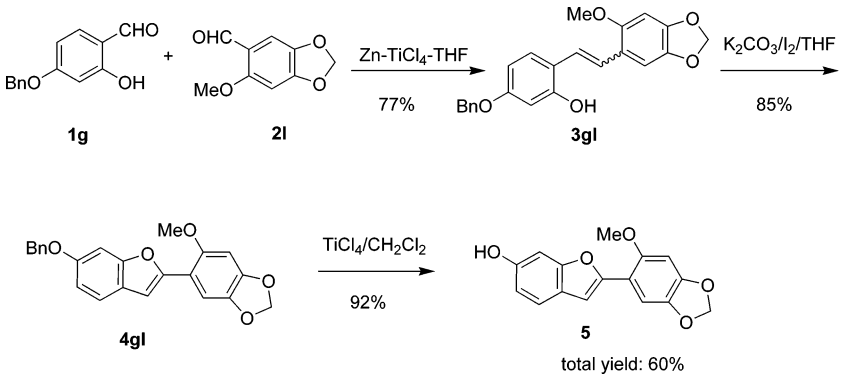
Utilizing the synthetic approach outlined above, we achieved a total synthesis of a naturally occurring benzofuran compound, cicerfuran (**5**),[11] as illustrated in Scheme 2. Our synthesis of cicerfuran is more convenient and effective compared to previously reported procedures,[11a,b] for the reagents are readily available and the procedures are simple. Moreover, the overall yield of 60% is significantly higher than those reported (<20%).[11a,b]

In conclusion, we developed a facile two-step synthetic strategy for 2-arylbenzofurans. The key step is a selective cross McMurry coupling between a salicylaldehyde or substituted salicylaldehyde and an aromatic aldehyde. This synthetic approach further extends the scope of the cross McMurry reaction and provides a novel approach toward the facile syntheses of 2-arylbenzofurans.

(10) Chung, M. K.; Qi, G. Z.; Stryker, J. M. *Org. Lett.* **2006**, *8*, 1491.

(11) (a) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214. (b) Novak, Z.; Timari, G.; Kotschy, A. *Tetrahedron* **2003**, *59*, 7509. (c) Stevenson, P. C.; Veitch, N. C. *Phytochemistry* **1998**, *48*, 995. (d) Stevenson, P. C.; Veitch, N. C. *Phytochemistry* **1998**, *48*, 947.

SCHEME 2. Total Synthesis of Cicerfuran



Experimental Section

General Procedure for Cross McMurry Reactions. Under an Ar atmosphere, a four-necked flask equipped with a magnetic stirrer was charged with zinc powder (0.8 g, 12 mmol) and 40 mL of THF. The mixture was cooled to −5 ∼ 0 °C, and $TiCl_4$ (0.65 mL, 6 mmol) was added by a syringe slowly with the temperature kept under 0 °C. The suspension was warmed to room temperature and stirred for 0.5 h, then heated at reflux for 2.5 h. The mixture was again cooled to −5 ∼ 0 °C, and the solution of two aldehydes (in 1:1.2 mol ratio, 2.4 mmol) in THF (15 mL) was added slowly. After addition, the reaction mixture was heated at reflux until the carbonyl compounds were consumed (monitored by TLC). The reaction was quenched with 10% aqueous $NaHCO_3$ solution and taken up CH_2Cl_2. The organic layer was collected and concentrated. The crude material was purified by flash chromatography to give the desired products.

General Procedure for the Oxidative Cyclization of *o*-Vinylphenols Using *m*-CPBA/TsOH. To a solution of *o*-vinylphenol (5 mmol) in chloroform (100 mL) was added *m*-chloroperbenzoic acid (1.8 g, 8.5 mmol). The mixture was stirred at 35−40 °C until the *o*-vinylphenol was completely oxidized (monitored by TLC). Then a few crystals of *p*-toluenesulfonic acid were added, and the resulting mixture was again stirred at 35−40 °C until the epoxide was consumed (monitored by TLC). The mixture was washed with saturated aqueous $NaHCO_3$ (100 mL), and the organic layer was washed with 2 × 200 mL purified water and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the crude material was purified by flash chromatography to give the desired products.

General Procedure for the Oxidative Cyclization of *o*-Vinylphenols Using I_2/K_2CO_3. To a solution of *o*-vinylphenol (2 mmol) in THF (20 mL) was added anhydrous K_2CO_3 (1.53 g, 11.1 mmol) and was stirred for 10 min. I_2 (2.82 g, 11.1 mmol) was added, and the mixture was stirred at ambient temperature until the *o*-vinylphenol was consumed. The mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and treated with saturated aqueous $NaHSO_3$ to remove the unreacted iodine. The mixture was extracted with EtOAc, and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the crude material was purified by flash chromatography to give the desired products.

Acknowledgment. We gratefully acknowledge the National Nature Science Foundation of China (Grant 20672014) and Drs. Noriyuki Kawahata and Yao Ma for revising this manuscript and their helpful advice.

Supporting Information Available: Typical experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7019652