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Oxidative Aromatic C−O Bond Formation: Synthesis of 3-Functionalized Benzo[*b*]furans by $FeCl_3$-Mediated Ring Closure of α-Aryl Ketones

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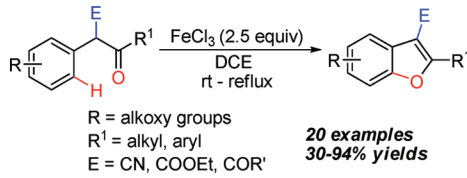
ABSTRACT



A variety of 3-functionalized benzo[*b*]furans were achieved by way of a $FeCl_3$-mediated intramolecular cyclization of electron-rich α-aryl ketones. The alkoxy substituent on the benzene ring in the substrates was essential for an efficient cyclization to occur. This novel method allows the construction of benzo[*b*]furan rings by joining the O-atom on the side chain to the benzene ring via direct oxidative aromatic C−O bond formation.

Benzo[*b*]furan derivatives have drawn extensive and enduring attention for their wide occurrence in natural products, broad range of biological activities, and significant pharmaceutical potentials.[1] It is not surprising therefore that great efforts have been directed toward developing synthetic approaches for the construction of this privileged structure.[2]

The predominant strategy involves the formation of an annulated furan ring from the benzene derivatives. On the basis of the bond formation patterns, the methods of this strategy can be generalized into the following types:[2f] (1) The *O*-atom of the benzo[*b*]furan ring is introduced by utilizing *O*-containing arenes as starting materials in the early synthetic stage (**a**, **b**, and **c** in Figure 1). (2) The *O*-atom is connected to the benzene ring by the transition-metal-catalyzed *O*-arylation of *o*-halobenzyl ketones (**d** in Figure 1). (3) The *O*-moiety on the side chain is joined to the benzene ring without any substituent in the *ortho* position, through the direct formation of a bond between the oxygen

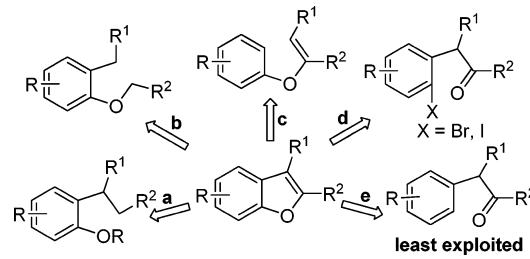


Figure 1. General bond formation patterns for the construction of benzo[*b*]furan skeletons from benzene derivatives.

(1) (a) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, pp 259−287. (b) Hou, X. L.; Yang, Z.; Yeung, K. S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2008**, *19*, 176. For selected papers on the biological activities and pharmacological interest of benzofurans, see: (c) Ziegert, R. E.; Toraeng, J.; Knepper, K.; Braese, S. *J. Comb. Chem.* **2005**, *7*, 147. (d) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2005**, *17*, 142. (e) Carlsson, B.; Singh, B. N.; Temciuc, M.; Nilsson, S.; Li, Y.-L.; Mellin, C.; Malm, J. *J. Med. Chem.* **2002**, *45*, 623. (f) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670.

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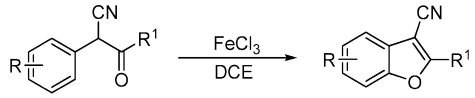
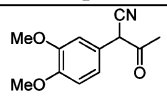
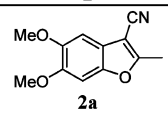
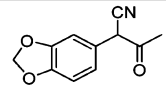
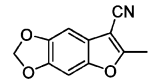
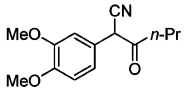
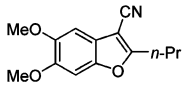
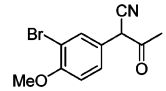
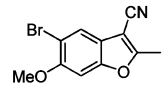
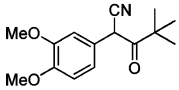
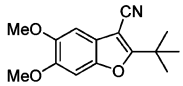
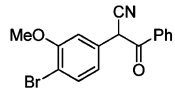
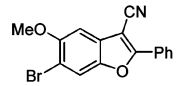
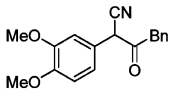
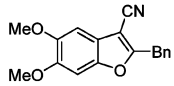
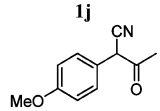
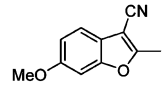
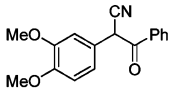
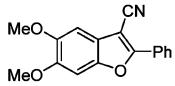
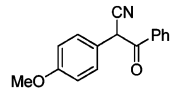
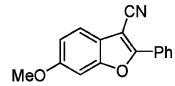
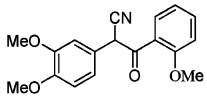
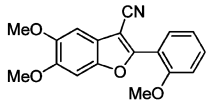
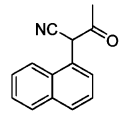
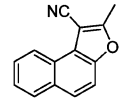
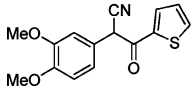
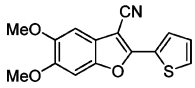
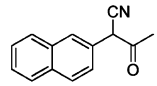
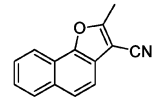
Table 1. Synthesis of 3-Functionalized Benzo[*b*]furans by $FeCl_3$-Mediated Ring Closure of α-Aryl Ketones[a]



1 **2**

entry	α-aryl ketones **1**	benzo[*b*]furans **2**	time (h)	yield[b] (%)	entry	α-aryl ketones **1**	benzo[*b*]furans **2**	time (h)	yield[b] (%)
1	 **1a**	 **2a**	1	70	8	 **1h**	 **2h**	4	94
2	 **1b**	 **2b**	3	64	9[c]	 **1i**	 **2i**	2	68
3	 **1c**	 **2c**	4	50	10[d]	 **1j**	 **2j**	5	60
4[c]	 **1d**	 **2d**	5	67	11[d]	 **1k**	 **2k**	6	30[e]
5	 **1e**	 **2e**	1	55	12[d]	 **1l**	 **2l**	5	45[e]
6[c]	 **1f**	 **2f**	3	51	13	 **1m**	 **2m**	2	55
7[c]	 **1g**	 **2g**	2	60	14	 **1n**	 **2n**	1	56

[a] Optimal conditions: 1 equiv of **1**, 2.5 equiv of anhydrous $FeCl_3$ in DCE at rt unless otherwise stated. [b] Isolated yields after silica gel chromatography. [c] Reaction occurred at 40 °C. [d] Reaction occurred at reflux temperature. [e] With the concomitant formation of other unidentified byproducts.

and an aryl sp^2 carbon (**e** in Figure 1). This last strategy provides a unique access to benzo[*b*]furan compounds since such a method would avoid using the "privileged" phenol drivatives as starting materials and postpone the introduction of the oxygen atom to a later synthetic step. Furthermore, there is no need to install a halogen atom in the *ortho* position of the benzene ring since such a substituent is not indispensable by this approach. To our knowledge, a methodology of constructing benzo[*b*]furans in such a way has rarely been exploited, and only a photoinduced approach falls into this category.[3] In this communication, we describe such an intramolecular cyclization pathway for the construction of 3-functionalized benzo[*b*]furans by direct C−H functionalization of an electron-rich aromatic ring with a side chain *O*-moiety.

In recent decades, the development of novel methodologies that directly functionalize aromatic C−H bonds to construct C−N/O bonds using transition-metal catalysis has received considerable attention.[4] In our previous work, we realized

(2) For selected reviews on synthetic approaches to benzo[*b*]furans, see: (a) Dell, C. P. *Sci. Synth.* **2001**, *10*, 11. (b) Steel, P. G. *Sci. Synth.* **2001**, *10*, 87. (c) Greve, S.; Friedrichsen, W. *Prog. Heterocycl. Chem.* **1999**, *11*, 144. (d) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (e) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (f) Kadieva, M. G.; Oganesyan, E. T. *Chem. Hetercycl. Compd.* **1997**, *33*, 1245. (g) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167. (h) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67. (i) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. For recent selected papers on synthesis of benzo[*b*-]furans, see: (a) Duan, X.-F.; Zeng, J.; Zhang, Z.-B.; Zi, G.-F. *J. Org. Chem.* **2007**, *72*, 10283. (b) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (c) Farago, J.; Kotschy, A. *Synthesis* **2009**, 85. (d) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525. (e) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (f) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467. (g) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (h) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955. De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955. (i) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508. (j) Martinex, C.; lvarez, R. A.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083. (k) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (l) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144.

(3) (a) Pandey, G.; Krishna, A.; Bhalerao, U. T. *Tetrahedron Lett.* **1989**, *30*, 1867.

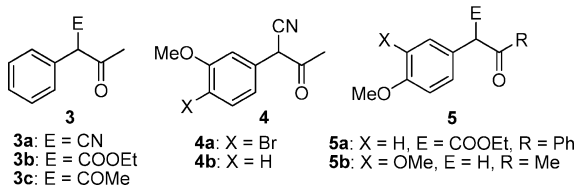


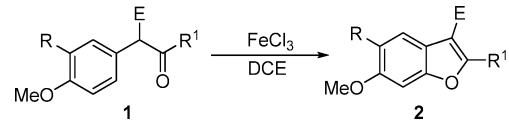
Figure 2. Other models that failed to afford benzo[*b*]furans.

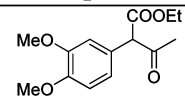
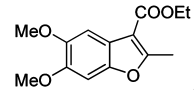
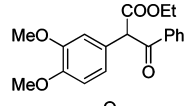
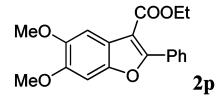
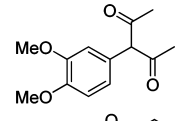
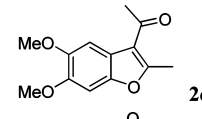
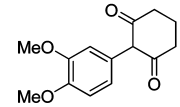
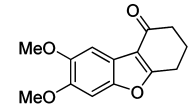
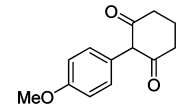
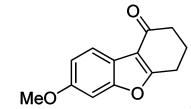
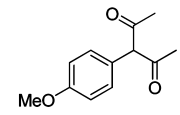
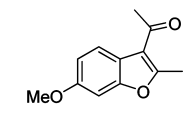
the formation of a series of *N*-alkoxyindole-3-carbonitriles via a novel $FeCl_3$-mediated intramolecular aromatic C−N bond formation.[5] Inspired by this finding, we were interested in investigating the construction of benzo[*b*]furan skeletons by a similar intramolecular oxidative C−O coupling of α-aryl ketonitriles **1**, which are readily available by the condensation of substituted benzyl cyanides with carboxylic esters. To initiate our study, the unsubstituted α-aryl ketonitrile **3a** (Figure 2) was chosen to test the feasibility of the ring closure mediated by $FeCl_3$. However, it was found that substrate **3a** was inert, and no desired benzo[*b*]furan compound was achieved when applying various oxidants under many conditions.[6] A further screen of the substrate pattern led us to discover that substrate **1a**, with 3,4-dimethoxy substituted on the benzene ring, could be conveniently converted to the desired benzo[*b*]furan **2a** in 70% yield when oxidized by $FeCl_3$ in DCE at room temperature (entry 1, Table 1). This result implies that the presence of electron-donating methoxy groups on the benzene ring of the substrate was crucial for the oxidative intramolecular cyclization to occur.

Since the importance of an electron-rich substrate is obvious, we first sought to probe the substrate scope of this $FeCl_3$-mediated oxidative reaction by changing the R^1 groups while keeping the 3,4-dimethoxy benzene moiety intact. The results listed in Table 1 demonstrated that when R^1 was a relatively long-chained propyl group (entry 2, Table 1), a bulkier *tert*-butyl group (entry 3, Table 1), or benzyl group (entry 4, Table 1), the substrates could undergo ring closure to give the desired corresponding benzo[*b*]furan products in moderate yields, although these substrates needed relatively longer reaction times. For the substrates with R^1 being an aryl group, the reactions also furnished the desired cyclized products in acceptable yields, with shorter reaction times (entries 5−7, Table 1).

Next, we decided to investigate the substitution variations of the electron-rich substrates. It was observed that substrate **1h**, with a methylenedioxy substitution on the benzene ring, could afford the benzo[*b*]furan product **2h** in an excellent 94% yield by the method. By replacing the *meta*-methoxy group with a bromo group in **1a**, we found that substrate **1i** could also give the desired **2i** in good yield. However, we were disappointed to find that substrate **4a** (Figure 2), an analogue of **1i** by exchanging the position of the methoxy and the bromo group, yielded no benzo[*b*]furan product under the same conditions. Gratifyingly, substrate **1j**, structurely differing from compound **4a** by replacing the methyl group with a phenyl group, gave the cyclized product **2j** in relatively lower yield, with the cost of a longer reaction time and a higher reaction temperature. Further reducing one methoxy group on the benzene ring in substrate **1a** led us to discover that the solely *para*-methoxy-substituted **1k** furnished the desired **2k** in a poor 30% yield after the reaction mixture was refluxed for 5 h, while the *meta*-methoxy-substituted compound **4b** (Figure 2) was unreactive under the same conditions. Interestingly, when the methyl group in **1k** was replaced with a phenyl group, we were pleased to see that benzo[*b*]furan **2l** could be obtained in moderate yield, although at the expense of a higher reaction temperature and a longer reaction time. On the basis of the above experimental facts, we tentatively conclude that a *para*-methoxy group is more determinant than a *meta*-methoxy group in the substrate for the ring closure to occur. Furthermore, when R^1 was a

Table 2. Further Variations of E groups in Substrate **1**[a]



entry	α-aryl ketones **1**	benzo[*b*]furans **2**	time (h)	yield[b] (%)
1	 **1o**	 **2o**	3	50
2	 **1p**	 **2p**	3	65
3	 **1q**	 **2q**	2	62
4	 **1r**	 **2r**	2	57
5[c]	 **1s**	 **2s**	4	50
6[c]	 **1t**	 **2t**	5	32[d]

[a] Conditions: See Table 1. [b] Isolated yields after silica gel chromatography. [c] Reaction occurred at 40 °C. [d] Complex mixture, 30% of **1t** recovered.

(4) (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (e) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (f) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411.

(5) Du, Y.; Chang, J.; Reiner, J.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 2007.

(6) (a) No desired product achieved when using $FeCl_3$ as oxidant and carrying out the reaction in DCE at rt to reflux. (b) Other oxidative conditions: $K_3Fe(CN)_6$/MeCN, $Cu(OAc)_2$/AcOH, $Mn(OAc)_3$/AcOH, CAN/CH_3CN, and MnO_2/CH_2Cl_2 were also ineffective for this conversion, since substrate **3a** would dimerize under these conditions. For such homocoupling reactions, see: De Jongh, H. A. P.; De Jonge, C. R. H. I.; Mijs, W. J *J. Org. Chem.* **1971**, *36*, 3160, and references cited therein.

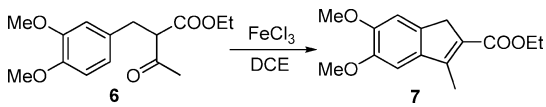
phenyl group, the cyclization process was somewhat enhanced compared to in the cases when it was a methyl group.

The reaction proceeded equally well with substrates **1m**,**n**, in which the naphthyl ring could be taken as an electron-rich benzene ring. Thus, two furan-fused heterocycles **2m**,**n** could be obtained by the approach (entries 13 and 14, Table 2).

To further extend the substrate scope, we finally came to change the benzylic *cyano* group in the substrates into other electron-withdrawing groups. To our delight, substrates **1o**−**r**, bearing an ethoxycarbonyl or alkyl acyl group, also successfully rendered the corresponding benzo[*b*]furan products in moderate yields (entries 1−4, Figure 2). When the substrate was solely substituted with a *para*-methoxy group in the benzene ring (**1s**,**t**, in which E represents an alkyl acyl group), we found that the desired benzo[*b*]furan products **2s**,**t** were obtained in relatively low yields. However, for susbtrate **5a**, differing from **1l** by changing the *cyano* group into an ethoxycarbonyl group, no desired cyclized product was separated under the same conditions. Similarly, we found that when the two methoxy groups were both removed from the benzene ring in the substrate compounds **3b** and **3c** (Figure 2) failed to provide any cyclized products under the same conditions.

It is worth mentioning that when compound **6**, differing from **1o** by one more methylene group, was subjected to the same reaction conditions an unexpected indene **7** was achieved in 45% yield,[7] with no formation of the desired chromene-3-carboxylate derivative (Scheme 1).

Scheme 1. Formation of Indene Derivatives **10** from Compound **9**

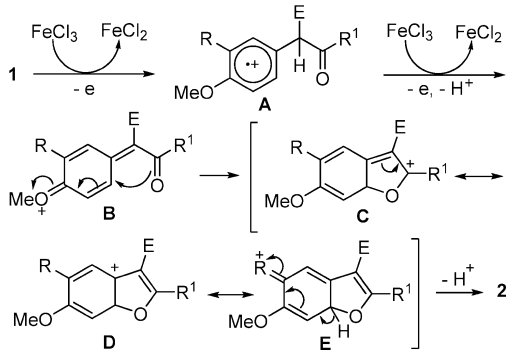


All the structures of the cyclized products were determined by detailed study of the spectroscopic data. Furthermore, product **2p** was unambiguously confirmed through X-ray crystallographic analysis (see Supporting Information).

A tentative mechanistic pathway is shown in Scheme 2. Initially, one electron would be abstracted from the electron-rich aromatic ring **1** by ferric chloride, which acts as a single electron oxidant, to afford the aromatic radical cation **A**. Mediated by ferric chloride, a second single-electron transfer (SET) process would convert the radical cation **A** to the oxonium intermediate **B**. The benzylic electron-withdrawing group is thought to promote the loss of the acidic proton in

(7) For formation of such indene compounds catalyzed by H_3PO_4, see: Koo, J. *J. Am. Chem. Soc.* **1953**, *75*, 1891.

Scheme 2. Proposed Mechanistic Pathway



the process, based on the fact that compound **5b**, without an electron-withdrawing group (E = H) at the benzylic position, failed to provide the desired cyclized product under the described conditions. Next, a conjugated cycloaddition process would occur to transform **B** into the carbocation intermediate **C**, which would be greatly stabilized if R^1 represents a phenyl group. Further tautomerization of **C** would lead to the stable **D**, or even the more stable **E**, if R was an electron-donating group, e.g., a methoxy or bromo group. Finally, rearomatization of **C**−**E** by loss of a proton would give the title compound **2**.

In summary, we demonstrated herein a novel synthetic approach to 3-functionalized benzo[*b*]furan derivatives starting from readily available α-aryl ketones. The underpinning strategy is the $FeCl_3$-mediated ring closure of the electron-rich α-aryl ketones, which realized the construction of benzo[*b*]furan rings by joining the O-atom on the side chain to the benzene ring via direct oxidative aromatic C−O bond formation. Efforts toward the development of proper oxidative conditions for the α-aryl ketones without alkoxy substituents on the aromatic ring, as well as the application of the current reaction in organic synthesis, are in progress in our laboratory.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds (PDF) and X-ray structural data of **2p** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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