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Synthesis of 2-Substituted 7-Hydroxybenzofuran-4-carboxylates via Addition of Silyl Enol Ethers to *o*-Benzoquinone Esters

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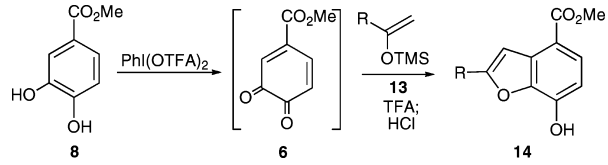
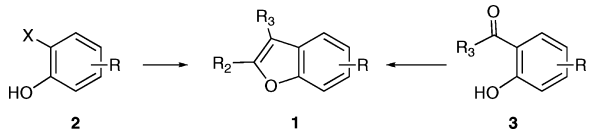
ABSTRACT



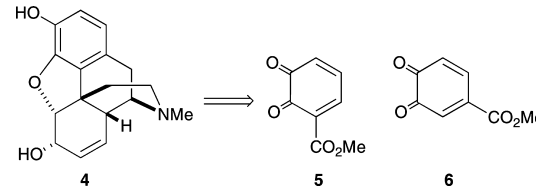
Mukaiyama Michael addition of silyl enol ethers 13 to the 1,2-quinone-4-carboxylate 6 (formed in situ by oxidation of the catechol ester 8) afforded the 2-subsituted 7-hydroxybenzofuran-4-carboxylates 14 in fair to good yields. Alkyl and aryl systems work well, but highly electron-rich silyl enol ethers could not be used because of competing oxidation.

The benzofuran structural unit **1** is often found in natural products and in biologically active materials.[1] Several general methods for its synthesis have been reported, many involving an *o*-substituted phenol, e.g., *o*-halo **2** or *o*-acyl phenols **3** (Scheme 1).[2] However the methods available for the synthesis of highly functionalized benzofurans are fewer in number. In this paper we report a novel synthesis of benzofurans that arose from our interest in a new approach (Scheme 2) for the total synthesis of morphine **4**.[3] We were interested in whether *o*-benzoquinone esters esters could be used as dienophiles in the Diels−Alder reaction with very

Scheme 1



Scheme 2



(1) (a) Zhang, J.; Zhang, Y.; Zhang, Y.; Herndon, J. W. *Tetrahedron* **2003**, *59*, 5609. (b) Dat, N. T.; Jin, X.; Lee, K.; Hong, Y.-S.; Kim, Y. H.; Lee, J. J. *J. Nat. Prod.* **2009**, *72*, 39. (c) Chen, Y.; Wei, X.; Xie, H.; Deng, H. *J. Nat. Prod.* **2008**, *71*, 929. (d) Lin, Y.-L.; Chang, Y.-Y.; Kuo, Y.-H.; Shiao, M.-S. *J. Nat. Prod.* **2002**, *65*, 745. (e) Naya, K.; Takai, K.; Nakanishi, M.; Omura, K. *Chem. Lett.* **1977**, 1179.

(2) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Cambridge, 2000; pp 380−391.

(3) For recent syntheses of morphine, see: (a) Tanimotoa, H.; Saitoa, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358. (b) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449. (c) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311. (d) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 1454.

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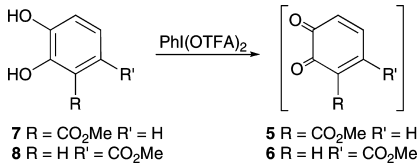
substituted dienes to produce intermediates for the synthesis of morphine. Therefore we examined the reaction of the two *o*-benzoquinone esters, **5** and **6**, with silyloxy dienes (Scheme 3). The required dienophiles **5** and **6** were each prepared by

Scheme 3

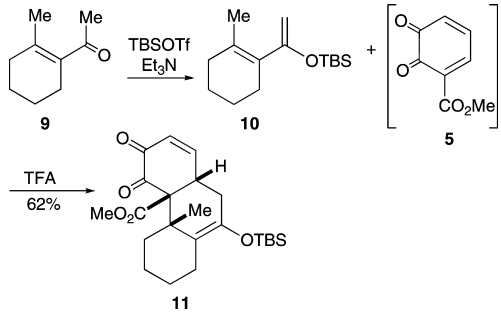


7 R = CO_2Me R' = H
8 R = H R' = CO_2Me

5 R = CO_2Me R' = H
6 R = H R' = CO_2Me

the in situ oxidation of the corresponding known catechols **7**[4] and **8**.[5] These compounds are generally too reactive to be isolated pure but rather were used in solution. Oxidation of **7** with iodosobenzene bis(trifluoroacetate)[6] to give **5** in the presence of the very hindered silyloxy diene **10**, which was prepared by silyl enol ether formation from the ketone **9**,[7] afforded the Diels−Alder adduct **11** as mainly the diastereomer shown in 62% yield (Scheme 4).[8] The stereochemistry of the

Scheme 4

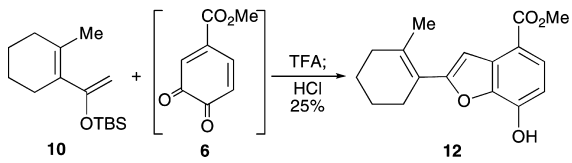


9 **10** **5** **11**

adduct **11** was assigned by extensive NOE analysis. This compound has some structural similarity to morphine and might prove to be a useful intermediate for its synthesis in the future.

However, when the regioisomeric *o*-benzoquinone ester **6** (prepared by in situ oxidation of **8**) was reacted with the diene **10**, a different product was obtained in 25% yield (Scheme 5). The structure of the 7-hydroxybenzofuran-4-

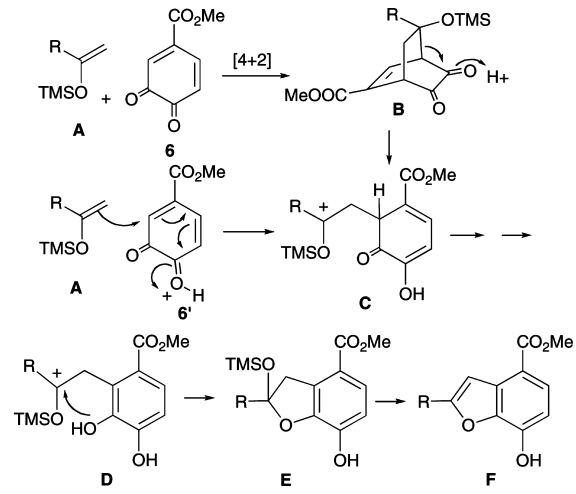
Scheme 5



10 **6** **12**

carboxylate **12** was easily assigned on the basis of proton and carbon NMR spectra and also by the fact that the compound exhibited a blue fluorescence as do many 7-hydroxybenzofurans.[9] There are two possible mechanisms for this process (Scheme 6), namely, an initial [4 + 2] cycload-

Scheme 6

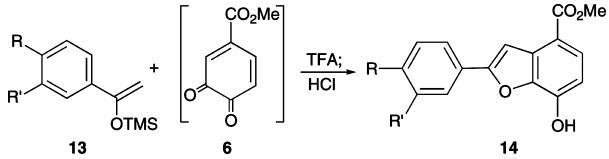


dition (concerted or stepwise) of the electron-rich silyl enol ether **A** and the electron-deficient diene **6** to produce the cycloadduct **B**,[10] which could then open the ring via a retro-aldol-type process to give, with protonation of the phenoxide, the very stabilized cation **C**. This intermediate could also be prepared via the direct Mukaiyama Michel addition of the silyl enol ether **A** to the *o*-quinone ester **6** (or more likely the protonated form **6′**) to generate the same intermediate. The cyclohexadienone of unit **C** would tautomerize and the system would aromatize to give the catechol **D**. The cation of **D** would be trapped by the *o*-phenol group to generate the five-membered ring **E**, which would lose the silyloxy group to afford the benzofuran **F**. Because we do not see any evidence for intermediates such as **B**, we favor the Mukaiyama Michael pathway. There is one similar process reported in the literature, namely, a side product obtained in only two cases when the silyl enol ether of dibenzyl ketone was added to 4-methyl and 4-*tert*-butyl *o*-benzoquinone.[11] In this publication several other Mukaiyama Michael reactions occurred without benzofuran formation.[11]

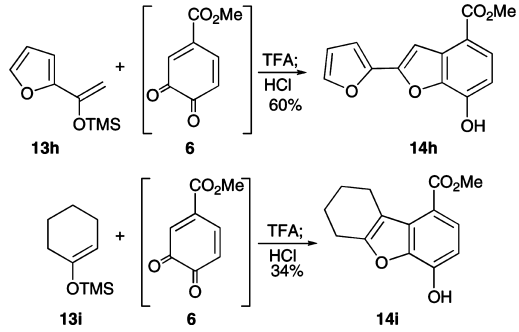
(4) Dallacker, F.; Thiemann, E.; Uddrich, P. *Chem. Ber.* **1971**, *104*, 2347.
(5) Rama Rao, A. V.; Deshmukh, M. N.; Sivadasan, L. *Chem. Ind.* **1981**, 164.
(6) (a) Carlini, R.; Fang, C.-L.; Herrington, D.; Higgs, K.; Rodrigo, R.; Taylor, N. *Aust. J. Chem.* **1997**, *50*, 271. (b) Sayre, L. M.; Nadkarni, D. V. *J. Am. Chem. Soc.* **1994**, *116*, 3157.
(7) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649.
(8) The Diels−Alder reaction of **5**, or alkyl analogues, with much less hindered dienes has been reported: (a) Forte, M.; Orsini, F.; Pelizzoni, F.; Ricca, G. *Gazz. Chim. Ital.* **1985**, *115*, 41. (b) Weller, D. D.; Stirchak, E. P. *J. Org. Chem.* **1983**, *48*, 4873.
(9) Hwu, J. R.; Chuang, K.-S.; Chuang, S. H.; Tsay, S.-C. *Org. Lett.* **2005**, *7*, 1545.
(10) Such [4 + 2] cycloadditions are known, as are the simple dimerization of *o*-benzoquinones. (a) Al-Talib, M.; Gerstenberger, I.; Jones, P. G.; Winterfeldt, E. *Liebigs Ann./Recl.* **1997**, 893. (b) Nair, V.; Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 443. (c) Sinclair, I. W.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2485. (d) Horner, L.; Spietschka, W. *Liebigs Ann. Chem.* **1955**, *591*, 1.

We decided to examine the generality and scope of this new benzofuran synthesis by varying the silyl enol ether starting material. Therefore a variety of silyl enol ethers of ketones **13a**−**i** were prepared by either deprotonation of the ketone and trapping with trimethylsilyl chloride or by treatment of the ketone with trimethylsilyl triflate and base. The *o*-benzoquinone ester **6** was prepared by oxidation of the catechol **8** in the presence of these silyl enol ethers and the mixtures stirred for 24 h. Workup and careful column chromatography[12] provided the expected benzofurans **14a**−**i** in fair to good yields (Scheme 7). Some of the trends in

Scheme 7



enol ether	R	R'	prod	yield
13a	H	H	**14a**	73%
13b	Me	H	**14b**	74%
13c	NO_2	H	**14c**	74%
13d	OMe	H	**14d**	29%
13e	Br	H	**14e**	54%
13f	CH=CH=CH=CH		**14f**	79%
13g	H	OMe	**14g**	33%



reactivity deserve comment. The simple acetophenone silyl enol ether **13a** afforded the expected product, 2-phenyl-7-hydroxybenzofuran-4-carboxylate **14a**, in 73% yield. Substituents in the *para* position of the phenyl ring were generally well tolerated with 4-methyl and 4-nitroacetophenones, **13b** and **13c**, respectively, giving good yields of the products **14b** and **14c** (each 74%). However, 4-methoxyacetophenone **13d** gave only a 29% yield of the desired product **14d**. Here the major side reaction is direct oxidation of the silyl enol ether to give the α-oxygenated acetophenone. Such α-oxidations of silyl enol ethers with oxidants such as iodosobenzene diacetate are well-known.[13] We believe that is the reason that the 3-methoxy analogue **13g** also gave a relatively poor yield (33%) of **14g**. The 4-bromo analogue **13e** gave a moderate yield of **14e** due to decomposition of the starting silyl enol ether. Other aromatic systems worked well, e.g., the silyl enol ether from 2-acetylnaphthalene **13f** gave an excellent 79% yield of the 2-naphthyl analogue **14f**, and the silyl enol ether of 2-acetylfuran **13h** also gave the desired 2-furyl analogue **14h** in 60% yield. Finally nonaromatic ketones could be used, e.g., the silyl enol ether of cyclohexanone **13i** afforded a 34% yield of the tetrahydro dibenzofuran analogue **14i**. Here again direct oxidation of the silyl enol ether was the major side reaction.[14]

In conclusion, we have developed a new method for the synthesis of functionalized benzofurans via the Mukaiyama Michael addition of silyl enol ethers of ketones to the *o*-benzoquinone-4-carboxylate followed by cyclization and aromatization. Further work on the use of this process in synthesis is underway in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Sagawa, Y.; Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1988**, 1105. For a different mode of 1,4-addition, see: Nair, V.; Rajesh, C.; Dhanya, R.; Rath, N. P. *Tetrahedron Lett.* **2002**, *43*, 5349.

(12) These compounds were quite difficult to separate and purify by normal silica gel chromatography because of their tendency to adhere to the column, which made elution difficult at times.

(13) Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273.

(14) **General Procedure for the Oxidation-Cyclization.** To a solution of methyl 3,4-dihydroxybenzoate **8** (1.0 mmol) and the silyl enol ether **13** (4 mmol) in 8 mL of THF at 0 °C was added 2 mL (1.1 mmol) of bis(trifluoroacetoxy) iodobenzene (0.55 M solution in THF) dropwise over 10 min, forming a green solution initially. The reaction was allowed to stir at 0 °C (unless specified otherwise) for 4 h, the solution becoming a dark yellow. To the solution was added 0.5 mL of HCl (4 M solution in dioxane) and 1.0 mL of methanol. The mixture was refluxed for 1 h, and the solution lightened in color. The solution was extracted with 30 mL of diethyl ether, washed with 2 × 10 mL saturated $NaHCO_3$ and 1 × 10 mL brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield an oily residue. The residue was purified by flash column chromatography over silica gel (ether and hexanes) to yield the benzofuran product **14**. The products were often recrystallized to give purer material.