Synthesis of 2-Substituted 7-Hydroxybenzofuran-4-carboxylates via Addition of Silyl Enol Ethers to \( \alpha \)-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-substituted 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. Several general methods for its synthesis have been reported, many involving an \( \alpha \)-substituted phenol, e.g., \( \alpha \)-halo 2 or \( \alpha \)-acyl phenols 3 (Scheme 1). 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. We were interested in whether \( \alpha \)-benzoquinone esters could be used as dienophiles in the Diels–Alder reaction with very

Scheme 1

Scheme 2


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 the in situ oxidation of the corresponding known catechols 7 and 8. These compounds are generally too reactive to be isolated pure but rather were used in solution. Oxidation of 7 with iodosobenzene bis(trifluoroacetate) 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, afforded the Diels-Alder adduct 11 as mainly the diastereomer shown in 62% yield (Scheme 4).<ref>
\[ \text{Scheme 3} \]
\[
\begin{align*}
\text{5} & \quad \text{R} = \text{CO}_2\text{Me} \quad \text{R'} = \text{H} \\
\text{6} & \quad \text{R} = \text{H} \quad \text{R'} = \text{CO}_2\text{Me}
\end{align*}
\]

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-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. There are two possible mechanisms for this process (Scheme 6), namely, an initial [4 + 2] cycloadition (concerted or stepwise) of the electron-rich silyl enol ether A and the electron-deficient diene 6 to produce the cycloaduct B, which could then open the ring via a retroaldol-type process to give, with protonation of the phenoxide, the very stabilized cation C. This intermediate could also be prepared via the direct Mukaiyama Michael 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-butylo-o-benzoquinone. In this publication several other Mukaiyama Michael reactions occurred without benzofuran formation.

\[ \text{Scheme 6} \]

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 chromatography12 provided the expected benzofurans 14a–i in fair to good yields (Scheme 7). Some of the trends in 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-acetyl naphthalene 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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(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.