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# Mild and Rapid Method for the Generation of *ortho*-(Naphtho)quinone Methide Intermediates

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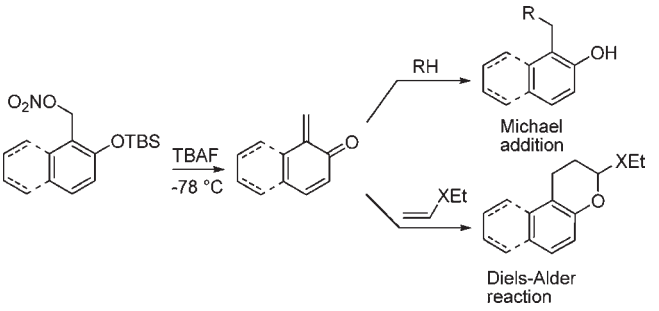
## ABSTRACT




**A new mild method has been devised for generating *o*-(naphtho)quinone methides via fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl(or 1-naphthylmethyl) nitrate. The reactive *o*-(naphtho)quinone methide intermediates were trapped by C, O, N, and S nucleophiles and underwent "inverse electron-demand" hetero-Diels–Alder reaction with dienophiles to give stable adducts. The method has useful potential application in natural product synthesis and drug research.**

Short-lived, highly reactive, *ortho*-quinone methide (*o*-QM) species are generated *in situ* by a large variety of synthetic methods. When these intermediates are produced in the absence of other reagents they form dimers and trimers; otherwise, they undergo 1,4-conjugate addition with nucleophiles as well as Diels–Alder cycloadditions with various dienophiles.[1a,b] *o*-QMs have been used for the synthesis of several natural products[1c,d] and are the cytotoxins responsible for the effect of some antitumor drugs, antibiotics,[1e] and DNA alkylators.[1a,f] A recent example of *o*-QM application in drug chemistry is the hybrid drug NO-ASA[1g] (Figure 1). The main synthetic methods of generating *o*-QMs are by tautomerization; oxidative, thermal, or photochemical initiation; using acid or base catalysis; and olefination of *o*-quinones, as described in a review by Van de Water and Pettus.[1h] Since that time photochemical excitation has been the most frequently used method to generate *o*-QMs.[1i–k] Suitable precursors for generating *o*-QMs thermally are 2-hydroxy benzyl acetates,[2a–d] *N*,*N*-dialkyl-9-aminomethyl-10-phenanthrols, and their naphthalene analogues[1q] and methyl-4*H*-1,2-benzoxazine-3-carboxylates.[2e,f] *o*-QMs can also be generated from either chemical or enzymatic oxidation of 3-(4-hydroxyphenyl)- 4-methyl-2*H*-chromen-7-ol derivatives,[2g] from Lewis acid catalyzed dehydration of *o*-hydroxyl benzyl alcohols,[2d] or from the Lewis acid cleavage of the MOM group of 2-(methoxymethoxy)benzyl acetates.[2h] Strong bases and weak nucleophiles generate *o*-QMs equally well from appropriate precursors.

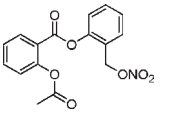



**Figure 1.** Structure of hybrid drug NO-ASA.

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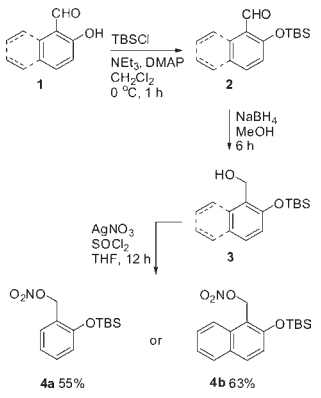
Recent examples include the treatment of *o*-hydroxybenzyl acetate with isopropylmagesium chloride,[3a] the reaction of [trialkyl(or triaryl)silylmethyl]-1,4-benzoquinones with oxygen nucleophiles,[3b] fluoride induced desilylation of silyl derivatives of *o*-hydroxybenzyl acetates[1r] and -benzyl iodides,[3c] and the base catalyzed or sodium dithionite reduction of (2-hydroxy-1-phenyl)-methyltrimethylammonium iodides.[3d] Less popular methods for *o*-QM generation involve the use of metal complexes such as the selective alkyl deprotonation of oxo-dienyl rhodium complexes {Cp*Rh[$\eta^5$-($MeC_5H_4O$ or *i*-$PrC_5H_4O$)][$BF_4$]} by base to give rhodium−*o*-QM complexes {Cp*Rh[$\eta^4$-($C_7H_6O$ or $Me_2C_7H_4O$)]}.[3e]

Considering the importance of *o*-QMs as active intermediates in many biological processes and in drugs, we became interested in developing a mild and efficient method for *o*-QM production that would be useful in drug research. We therefore present a novel fluoride-induced desilylation of nitrate esters **4a**,**b** and **8** (Schemes 1, 3) leading to *o*-QMs or *o*-naphthoquinone methides that are then trapped by a range of nucleophiles or dienophiles. The starting materials used to synthesize nitrate esters **4a,b** are the commercially available 2-hydroxybenzaldehyde (**1a**) and 2-hydroxy-1-napthaldehyde (**1b**) (Scheme 1). In the first step of this synthesis, the hydroxy group of **1a,b** undergoes protection using *tert*-butyldimethylsilyl chloride (TBSCl), DMAP, and $NEt_3$ in dichloromethane, to yield the silyl ethers **2a,b**. The silyl ethers were then reduced using $NaBH_4$ in methanol to give the alcohols **3a,b**. The alcohol derivatives were then reacted with $AgNO_3$ and $SOCl_2$ to afford the desired nitrate esters **4a,b** in 55 and 63% yields, respectively. In order to test the viability of the aforementioned method of *in situ o*-QM generation, Michael addition was the first reaction chosen to trap these intermediates. Thus the nitrate ester **4a** (Table 1) was dissolved in dry THF under an argon atmosphere, the temperature was lowered to −78 °C, and then the appropriate nucleophile (RH) was added followed by dropwise addition of TBAF. The reaction is postulated to proceed by attack of the fluoride anion onto the silyl ether, breakage of the Si−O bond, and elimination of a nitrate anion to generate the corresponding *o*-QM *in situ*. The latter is then trapped by different C, O, S, and N nucleophiles to generate Michael addition products **5a**−**m**. The type of nucleophiles used, the products, and the yields obtained are shown in Table 1.

**Scheme 1.** Synthesis of 2-(*tert*-Butyldimethylsilyloxy)benzyl Nitrate **4a** and (2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-naphthyl)-methyl Nitrate **4b**




The ability of a dienophile to react with the *in situ* generated *o*-QM was explored next. The nitrate ester **4a** (Scheme 2) was dissolved in dry THF under an argon atmosphere, the temperature was lowered to −78 °C, and then a 100-fold excess of the appropriate dienophile, ethyl vinyl ether (EVE), or ethyl vinyl sulfide was added followed by dropwise addition of TBAF. The *o*-QM generated in this reaction acts as a heterodiene which reacts with the respective dienophile and undergoes "inverse electron-demand" hetero-Diels−Alder reaction to yield the corresponding chromanes **6a**,**b** in 20 and 17% yields, respectively. The low yield of these reactions may be accounted for by the competing facile trimerization of the very reactive *o*-QM. The insoluble material from the reaction mixtures of **6a**,**b** was recrystallized from acetone, and the

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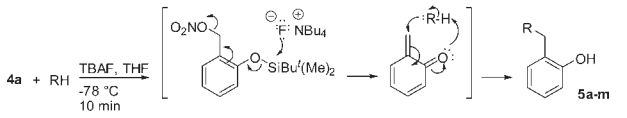
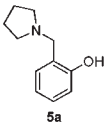
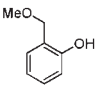
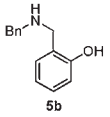
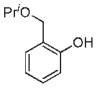
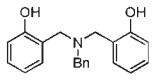
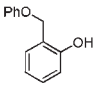
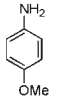
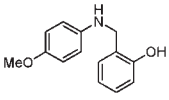
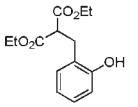
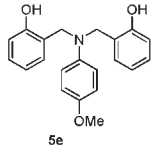
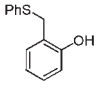
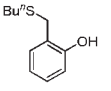
(4) (a) Cavitt, S. B.; Sarrafizadeh, H. R.; Gardner, P. D. *J. Org. Chem.* **1962**, *27*, 1211. (b) Mao, Y. L.; Boekelheide, V. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1732.

**Table 1.** Michael Addition of C, O, S, and N Nucleophiles to the *in Situ* Generated *o*-QM

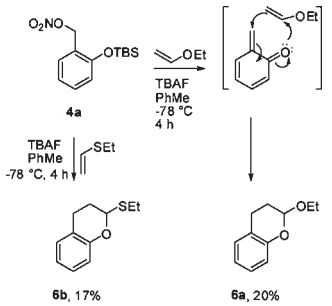



| entry | RH | product | yield (%)[a] | entry | RH | product | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 |  |  **5a** | 80 | 5 | MeOH[c] |  **5g** | 94 |
| 2 |  |  **5b** | 13 | 6 | *i*-PrOH[c] |  **5h** | 65 |
| | |  **5c** | 20 | 7 | PhOH |  **5i** | 52 |
| 3 |  |  **5d** | 30 | 8 | $CH_2(CO_2Et)_2$[d] |  **5j** | 60 |
| | |  **5e** | 20 | 9 | PhSH |  **5k** | 68 |
| 4 | $NaN_3$[b] |  **5f** | 63 | 10 |  |  **5l** | 56 |
| | | | | 11 | *n*-BuSH |  **5m** | 66 |

[a] Isolated yields. [b] 18-crown-6 was added as a catalyst. [c] Instead of using THF as a solvent, methanol and isopropanol were used. [d] Sodium hydride was used to generate the carbanion from diethyl malonate.

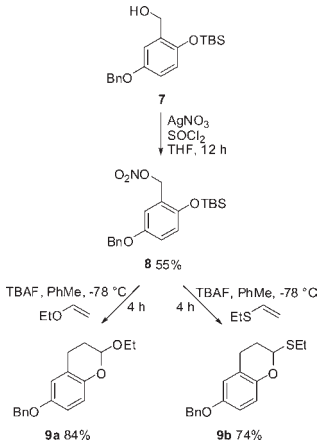
melting point was found to be the same as that of the trimer reported by Cavitt et al.[4a] and confirmed later by Mao and Boekelheide.[4b]

**Scheme 2.** Hetero Diels–Alder Reaction of the *in Situ* Generated *o*-QM with EVE and Ethyl Vinyl Sulfide




Since an electron-donating substituent on the *o*-QM would increase the net nucleophilicity of the heterodiene and hence encourage an "inverse electron-demand" hetero-Diels–Alder reaction, nitro ester **8** (Scheme 3) was chosen as a substrate for this purpose and synthesized from known alcohol **7**.[3c]

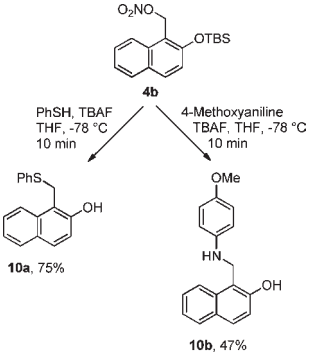
**Scheme 3.** Synthesis of 5-(Benzyloxy)-2-(*tert*-butyldimethylsilyloxy)benzyl Nitrate **8** and Its Hetero-Diels–Alder Reaction with EVE and Ethyl Vinyl Sulfide




Compound **8** was reacted with a 100-fold excess of ethyl vinyl ether or ethyl vinyl sulfide, in the same way as described for compound **4a**, to give chromanes **9a** and **9b** in 84 and 74% yields, respectively. The high yields of compounds **9a** and **9b** compared to the low yields of the corresponding compounds **6a** and **6b** reflect the more efficient cycloaddition reaction between the electron-poor heterodiene and electron-rich dienophiles.

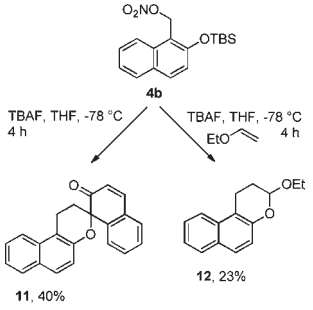
The applicability of this reaction was next tested with naphthylmethyl nitrate **4b** as a substrate (Scheme 4). Again, using the reaction conditions applied to the ester **4a**, ester **4b** was reacted with thiophenol or 4-methoxyaniline in dry THF under argon at −78 °C and TBAF to afford Michael addition products **10a** and **10b** in 75 and 47% yields, respectively. Once again, this is assumed to occur, *via* the *in situ* generation of the *o*-naphthoquinonemethide.

**Scheme 4.** Michael Addition of Thiophenol and 4-Methoxy Aniline to the *in Situ* Generated *o*-Naphthoquinone Methide



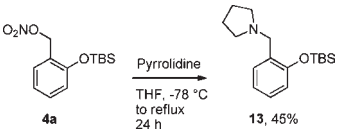
Indeed when the reaction of compound **4b** was repeated in the absence of a dienophile in THF, with dropwise addition of TBAF, the transient *o*-naphthoquinone methide underwent diene-dienophile cycloaddition to give the spiro dimer **11** (Scheme 5) in 40% yield. The absence of the trimerization product in this reaction is presumably because the benzene ring of the naphthalen-2(1*H*)-one **11** blocks the $\gamma$- and $\delta$-carbons of the cyclohexa-2,4-dien-1-one ring and stops further diene-dienophile cycloaddition, as in the case of the dimer derived from *o*-QM. Furthermore, applying the reaction conditions of compound **4b** used for the Michael additions but substituting the nucleophiles for EVE lead to a hetero-Diels–Alder reaction occurring with the transient *o*-naphthoquinone methide to give 3-ethoxy-2,3-dihydro-1*H*-benzo[*f*]chromene **12**, in 23% yield (Scheme 5).

**Scheme 5.** Hetero-Diels–Alder Reaction of *in Situ* Generated *o*-Naphthoquinone Methide by Dimerization and with EVE




Finally, reaction of nitrate ester **4a** with pyrrolidine (Scheme 6) at −78 °C in THF for 6 h did not produce any product that could be detected by TLC. However, heating the reaction mixture for 24 h afforded compound **13** where nucleophilic substitution of nitrate by pyrrolidine had occurred. This reaction confirms beyond doubt the intermediacy of *o*-(naphtho)quinone methides in the aforementioned reactions.

**Scheme 6.** Substitution Reaction of a Nitrate Anion in **4a** by Pyrrolidine




In conclusion, we have presented a new method of producing *o*-(naphtho)quinone methides from benzo and naphtho precursors bearing methylnitrate and *tert*-butyldimethylsilyloxy substituents at adjacent positions of the aromatic ring. The method of *o*-(naphtho)quinone methide generation involves fluoride anion nucleophilic cleavage of the silyloxy $\sigma$-bond by *n*-tetrabutylammonium fluoride followed by concomitant elimination of a nitrate anion. The intermediate *o*-(naphtho)quinone methides were trapped by nucleophiles and dienophiles showing the wide applicability of this method.

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