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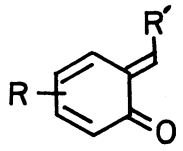
A New Generation of o-Quinone Methides from o-(1-(Alkylthio)alkyl)phenols under Mild Conditions

Tsutomu INOUE, Seiichi INOUE, and Kikumasa SATO*
Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240

o-(1-(Alkylthio)alkyl)phenols are converted into o-quinone methides in good yield by treatment with silver oxide under mild conditions. Since the methides tend to prefer (E) configuration, cis-4-alkyl-2-alkoxychromans are exclusively obtained as a result of endo [4+2] cycloaddition of the methides and vinyl ethers.

o-Quinone methides (**1**)[1] are reactive and unstable intermediates involved in chemistry and biochemistry. According to their great reactivity, the chroman ring systems are led by their easy di- or trimerization in which one molecule acts as heterodiene and another as dienophile.[2] However, in the presence of competing dienophiles with electron donating groups, the methides often react with these reagents to afford interesting chroman compounds.[3]

A variety of methods of o-quinone methide generation have been reported; for example, pyrolysis of o-(methoxymethyl)- or o-(hydroxymethyl)phenols,[2a,4a] one-electrone oxidation of o-substituted phenols,[4b] desilylation of disilylated o-hydroxybenzyl alcohol,[3c] etc.[3b,4c,d] Generally these methods need relatively high temperature, because of o-quinone methides possessing high energy quinoid structure.



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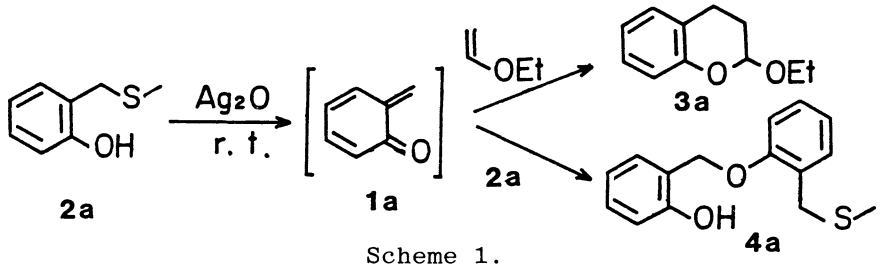
We describe herein a new general procedure for generation of o-quinone methides from o-(1-(alkylthio)alkyl)phenols under mild conditions.

Recently it was reported that o-(1-(alkylthio)alkylphenols (**2**) were prepared from phenoxysulfonium ylides via [2,3]sigmatropic rearrangement in good yields.[5] Utilizing the alkylthio group as a leaving group, the generation of o-quinone methides would be carried out more easily than the reported methods because the alkylthio group is to be eliminated easily from the benzyl position due to its small bond dissosiation energy (51 kcal/mol) as measured by Darwent.[6]

In this respect the first trial we began was to treat o-(methylthiomethyl)-phenol (**2a**) with a variety of metal oxides. A mixture of the phenol (1.0 mmol) and a metal oxide (1.2 mmol) in ethyl vinyl ether (15 mL), which has been known to trap o-quinone methide in the manner of [4+2] cycloaddition in high efficiency, was vigorously stirred at room temperature for 18 h. Silver oxide afforded 2-ethoxychroman (**3a**) and 2-(2-(methylthiomethyl)phenoxy)methylphenol (**4a**) in 32% and



Scheme 1.

30% yield, respectively (Scheme 1). The latter would have been formed by the 1,4-addition reaction between **2a** and the o-quinone methide **1a** as an electrophile.

On the contrary, other oxides, such as CuO, SnO_2, and NiO failed to afford the chroman **3a**; Mn_2O, PbO_2 and basic ferricyanide, which were reported to yield a o-quinone methide from 2,6-dimethyl-4-t-butylphenol in the manner of one-electron oxidation by Bolon,[4b] also failed to give **3a**. The stoichiometry of the reaction was then investigated using 2-(α-(isopropylthio)benzyl)phenol (**2b**) as the precursor of **1b** in which the formation of the dimerization product **4b** is very small due to resonance stabilization of the o-quinone methide by the phenyl substituent (Table 1). The reaction of **2b** with Ag_2O in a 1:0.5 molar ratio gave a 73% yield of the o-quinone methide. This fact indicates that the yield of the o-quinone methides based on Ag_2O is nearly twice as much of that of Bolon's method. In addition, metalic silver was not detected in the reaction mixtures.[7] It therefore seems that the present reaction may involve other processes than the one-electron oxidation of phenols.

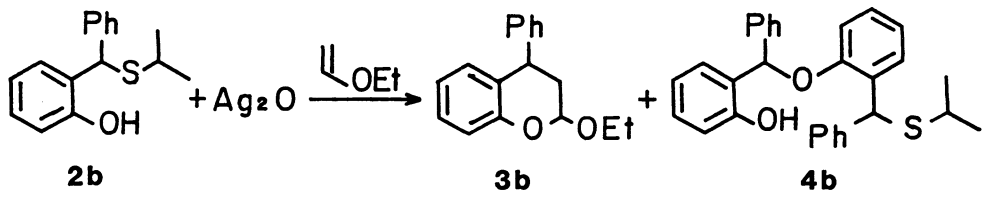
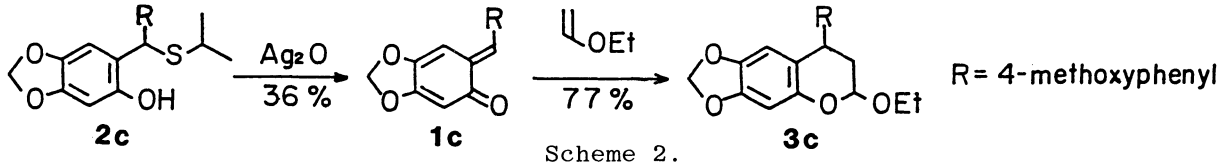


Table 1. The Reaction of 2-(α-(Isopropylthio)benzyl)phenol (**2b**) with Ag_2O

Ag_2O/**2b** (mole ratio)	Conversion/%	Yield/%		
		3b	**4b**	Total
0.3	62	47	3	50
0.5	100	62	11	73
1.2	100	79	trace	79

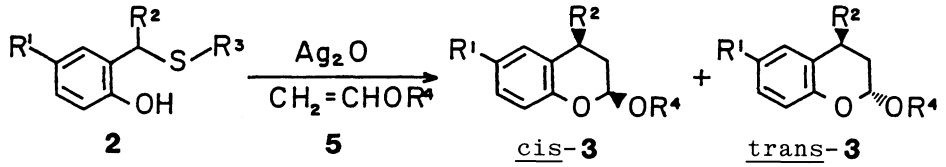
When 2-(α-(isopropylthio)-4-methoxybenzyl)-4,5-methylenedioxyphenol (**2c**) was treated with silver oxide (0.6 mol equiv.) in diethyl ether in the absence of ethyl vinyl ether at room temperature for 18 h, an orange-colored crystalline material, (E)-6-(4-(methoxybenzylidene)-3,4-methylenedioxy-2,4-cyclohexadienone (**1c**)[8,10] was isolated in 36% yield by the concentration of the filtrate of the reaction mixture (Scheme 2). On standing in ethyl vinyl ether at room temperature, the o-quinone methide **1c** was converted to chroman **3c** in 77% yield. When **2c** was treated with silver oxide in ethyl vinyl ether in a separate experiment, chroman **3c** was directly obtained in 64% yield. The fact proved the generation of o-quinone methides in this procedure.



2c 1c 3c

Scheme 2.

A variety of phenols **2b-g** were treated with silver oxide in vinyl ethers **5** under similar conditions. After the completion of the reactions, the reaction mixture were filtered to remove the silver salt and the filtrates were concentrated. The corresponding cis-chromans **3b-g** were predominantly isolated by column chromatography of the residual oil in good yields (Table 2). Cis configuration is thought to result from endo cycloaddion between o-quinone methide possessing (E) configuration and vinyl ether **5**, and the observed high stereoselectivity compared with that in the case of thermally generated o-quinone methides[4a] is due to the mild reaction conditions.[9]



2 5 cis-3 trans-3

Table 2. Chroman Synthesis from Phenols **2** by Treatment with Ag_2O in Vinyl Ether **5**[a]

	R^1	R^2	R^3	R^4	Yield/% cis-**3**	Yield/% trans-**3**[b]
b	H	Ph	i-Pr	Et	76	3
d	H	Et	i-Pr	Et	60[c]	trace
e[c]	CH_3	$CH=CH_2$	i-Pr	Et	73[c]	-
f	H	$CH=CH_2$	i-Pr	n-Bu	26[c]	-
g	CH_3	CH=CHPh	i-Pr	Et	49[c]	-

a) Reaction conditions: Phenol 1.0 mmol; Ag_2O 1.2 mmol; Vinyl ether 15 mL; 25 °C; 18 h. b) Determined by ^1H NMR. c) Spectral data are summarized in Ref. 10.

In conclusion, we have found a new o-quinone methide generation procedure which is more effective and general to obtain various o-quinone methides than previously described routes. Moreover, the resulting methides are converted predominantly into cis-4-alkyl-2-alkoxychromans in the manner of endo [4 + 2] cycloaddition with vinyl ethers on account of the mild reaction conditions.

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7) Silver mercaptide was detected as the only silver-containing species in the reaction mixture of **2** which contained a higher alkylthio group instead of methylthio or isopropylthio groups.
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10) Physical and spectral data are as follows.
1c: mp 138-142 °C; IR(KBr) 1610, 1590, 1240, 1170, and 810 cm^{-1}, ^1H NMR(CCl_4) δ=3.83 (3H, s), 5.76 (1H, s), 5.94 (2H, s), 6.61 (1H, s), 6.96 (2H, d, J=7.20 Hz), 7.55 (2H, d, J=7.20 Hz), and 7.63 (1H, s). **2e**: IR(neat) 3300, 2900, 1490, 1240, 1030, and 840 cm^{-1}; ^1H NMR($CDCl_3$) δ=1.08 (6H, d, J=6.83 Hz), 2.77 (1H, hept, J=6.83 Hz), 3.78 (3H, s), 5.28 (1H, s), 5.87 (2H, s), 6.49 (2H, s), 6.85 (2H, d, J=8.30 Hz), 7.27 (1H, s), and 7.32 (2H, d, J=8.30 Hz). **3d**: IR(neat) 2900, 1480, 1210, and 750 cm^{-1}; ^1H NMR($CDCl_3$) δ=0.98 (3H, t, J=7.58 Hz), 1.25 (3H, t, J=6.92 Hz), 1.71 (1H, ddq, J=9.32, 14.14, and 7.58 Hz), 1.83 (1H, ddd, J=13.51, 6.59, and 8.24 Hz), 1.95 (1H, ddq, J=4.50, 14.14, and 7.58 Hz), 2.15 (1H, ddd, J=2.46, 6.26, and 13.51 Hz), 2.8 (1H, m), 3.62 (1H, dq, J=9.65 and 6.92 Hz), 3.96 (1H, dq, J=9.56 and 6.92 Hz), 5.15 (1H, dd, J=2.64 and 6.59 Hz), 6.84 (1H, dd, J=8.24 and 1.31 Hz), 6.89 (1H, ddd, J=7.25, 7.25, and 1.31 Hz), 7.11 (1H, ddd, J=8.24, 7.25, and 0.99 Hz), and 7.14 (1H, dd, J=7.25 and 0.99 Hz). **3e**: IR(neat) 2900, 1490, 1210, 1010, 910, and 810 cm^{-1}, ^1H NMR($CDCl_3$) δ=1.23 (3H, t, J=6.92 Hz), 1.92 (1H, ddd, J=13.52, 6.59, and 7.70 Hz), 2.19 (1H, ddd, J=13.52, 6.59, and 2.63 Hz), 2.25 (3H, s), 3.6 (1H, m), 3.62 (1H, dq, J=6.92 and 9.56 Hz), 3.96 (1H, dq, J=6.92 and 9.56 Hz), 5.1-5.2 (3H, m), 5.9-6.0 (1H, m), 6.74 (1H, d, J=7.91 Hz), 6.90 (1H, s), 6.92 (1H, d, J=7.91 Hz). **3f**: IR(neat) 2910, 1490, 1210, 1020, 920, 820 cm^{-1}, ^1H NMR($CDCl_3$) δ=0.90 (3H, t, J=6.25 Hz), 1.35 (2H, m), 1.56 (2H, m), 1.92 (1H, ddd, J=6.17, 7.33, and 13.19 Hz), 2.19 (1H, ddd, J=2.64, 6.60, and 13.19 Hz), 2.24 (3H, s), 3.5-3.6 (2H, m), 3.91 (1H, dt, J=9.23 and 6.60 Hz), 5.1-5.2 (3H, m), 5.95 (1H, dt, J=6.81 and 9.23 Hz), 6.74 (1H, d, J=7.91 Hz), 6.90 (1H, s), 6.92 (1H, d, J=7.91Hz). **3g**: IR(neat) 2900, 1490, 1140, 1050, 1020, 900, 820, 750, 690 cm^{-1}, ^1H NMR($CDCl_3$) δ=1.26 (3H, t, J=7.25 Hz), 2.01 (1H, ddd, J=6.26, 7.52, and 13.52 Hz), 2.22 (3H, s), 2.26 (1H, ddd, J=2.64, 6.59, and 13.52 Hz), 3.6-3.7 (2H, m), 4.00 (1H, dq, J=7.25 and 9.56 Hz), 5.22 (1H, dd, J=2.64 and 6.26 Hz), 6.36 (1H, dd, J=8.9 and 15.49 Hz), 6.54 (1H, d, J=15.49 Hz), 6.77 (1H, d, J=8.57 Hz), 6.93 (1H, s), 7.07 (1H, d, J=8.57 Hz), 7.2-7.4 (5H, m).

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