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LETTERS

A Straightforward Oxidation of Dienones to 2-Acetylfurans by Selenium Dioxide

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Abstract: Direct oxidation of (*E*)-4-(6-substituted-1-cyclohexenyl)-3-buten-2-ones (**4a~7a**) by selenium dioxide afforded 2-acetyltetrahydrobenzofurans (**4b~7b**) in moderate to good yields. An inverse, stepwise [2+4] cycloaddition mechanism of the intermediate formation was proposed from conformational and electronic requirements of conjugated dienones and solvent effects of SeO_2 oxidation. © 1998 Elsevier Science Ltd. All rights reserved.

For the synthesis of allylic alcohols and diketones selenium dioxide has been used as a conventional reagent *via* the oxidation of olefins and ketones.[1] Oxidations of α,β-unsaturated carboxylic acids with SeO_2 were also known to give γ-acetoxy derivatives[2] and α,β-unsaturated-γ-butyrolactone derivatives.[3] In reports of A. Takeda and his collegues[4] oxidations of conjugated alkadienoic esters with SeO_2 gave mixtures of furans and selenophenes with low isolated yields of each products. In our recent interests in functional derivatization of conjugated dienones to biologically active isosteres aromatization of conjugated dienones for the selective formation of 2-acetylfurans was studied. We now report our preliminary results of direct oxidations of conjugated dienones by SeO_2 in this letter.

For the general scope of this oxidation and mechanistic investigations of the proposed intermediate formation[4b] we first prepared acyclic 2,4-dienones by Stille's coupling method of enol triflate[5] with methyl vinyl ketone in the presence of palladium catalyst.[6] Two isomeric dienones (**1a** and **2a**) coupled between thermodynamic enol triflates and methyl vinyl ketone were separated by silica gel column chromatography and identified through NOE difference spectra.[7] Refluxing (3*E*,5*E*)-5,7-dimethyl-3,5-octadien-2-one (**1a**) with 2 eq. of SeO_2 in anhydrous benzene for 18 hrs gave 34 % of 2-acetylfuran (**1b**) after column chromatography without any formation of selenophenes. However, (3*E*,5*Z*)-5,7-dimethyl-3,5-octadien-2-one (**2a**) gave only 21 % of a oxidized product (**1b**) with a recovered starting dienone (**2a**, 28 %) even after 52 hr refluxing in benzene. From the consideration of s-*cis* conformation of diene moiety to be more feasible for [2+4] cycloaddition, we next designed and prepared (*E*)-4-(6-substituted-1-cyclohexenyl)-3-buten-2-ones by the same method as above. With a purpose to increase the rate of the formation of the intermediate (**d** in Scheme 2) oxidations were carried out in the presence of excess SeO_2 (4 eq.) under refluxing conditions. (*E*)-4-(1-cyclohexenyl)-3-buten-2-one (**3a**) gave a mixture of tetrahydrobenzofuran (**3b**), benzofuran (**3c**), and benzoselenophene (**3d**) with 32 %, 16 %, and 5 % of isolated yields, respectively, after silica gel chromatographic separation.[9] Each products were identified by ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy.

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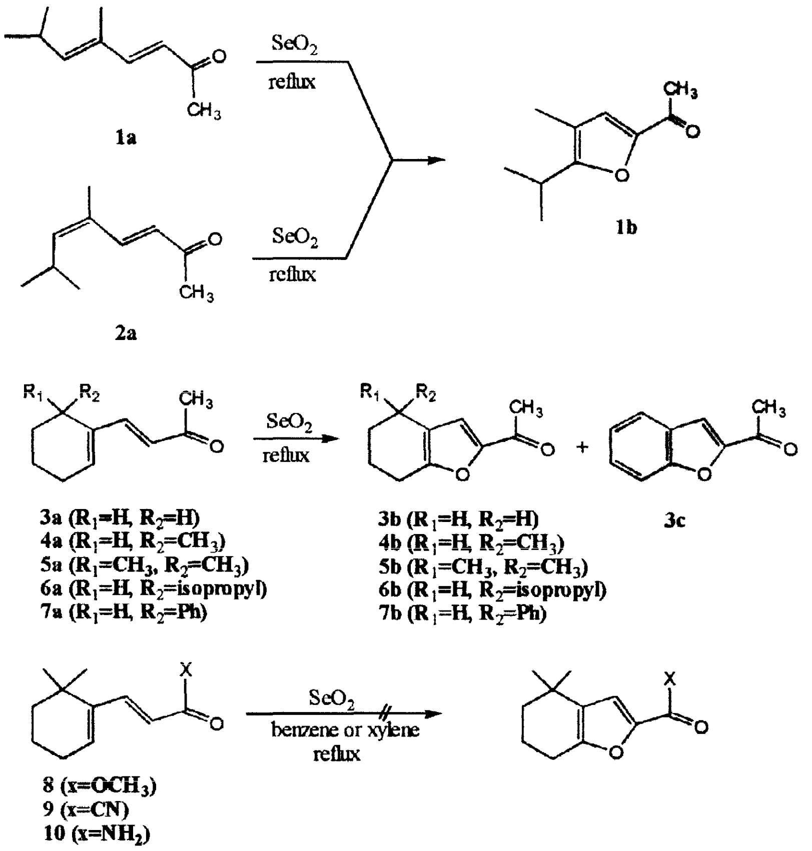


Scheme 1. Oxidation of 2,4-Dienones by SeO_2

Table 1. Reaction Conditions and Products of Conjugated Dienone Oxidation by SeO_2[a]

Cpd.	Solvent	Rxn Time[b] (hr)	Prod.	Yield[c] (%)	^{1}H-NMR ($CDCl_3$, 200 MHz, δ in ppm)
1a	benzene	18	**1b**	34	1.28 (d, J=6.9 Hz, 6H), 2.01 (s, 3H), 2.40 (s, 3H), 3.06 (septet, J=6.8 Hz, 1H), 6.97 (s, 1H).
2a[d]	benzene	52	**1b**	21	
3a	benzene	52	**3b** **3c** **3d**	32 16 5.0	**3b**: 1.80 (m, 4H), 2.41 (s, 3H), 2.47 (t, J=6.3Hz, 2H), 2.66 (t, J=5.9 Hz, 2H), 6.99 (s, 1H). **3c**: 2.62 (s, 3H), 7.73-7.31 (m, 5H). **3d**: 2.66 (s, 3H), 7.39 (m, 2H), 7 .90 (m, 2H), 8.14 (s, 1H).
3a	xylene	3.0	**3b**	25	
4a	benzene	16	**4b**	49	1.16 (d, J=6.9Hz, 3H), 1.76 (m, 2H), 1.95 (m, 2H), 2.40 (s, 3H), 2.58-2.72 (m, 3H), 7.05 (s, 1H).
4a	xylene	4.5	**4b**	32	
5a	benzene	6.0	**5b**	94	1.18 (s, 6H), 1.55 (m, 2H), 1.86 (m, 2H), 2.40 (s, 3H), 2.62 (t, J=6.3 Hz, 2H), 7.07 (s, 1H).
6a	1,4-dioxane	0.4	**6b**	73	0.83 (d, J=6.9 Hz, 3H), 1.05 (d, J=6.9 Hz, 3H), 1.48 (m, 1H), 1.73 (m, 2H), 2.02 (m, 2H), 2.43 (s, 3H), 2.53 (m, 1H), 7.07 (s, 1H).
7a	benzene	24	**7b**	47	1.63-1.88 (m, 2H), 1.97-2.17 (m, 2H), 2.37 (s, 3H), 2.76 (m, 2H), 3.86 (m, 1H), 6.80 (s, 1H), 7.34-7.12 (m, 5H).

[a] Reactions were done with 4 eq. of SeO_2 under refluxing in a given solvent except **1a** and **2a** which were oxidized with 2 eq. of SeO_2. [b] Reaction times were determined by gas chromatography. [c] Isolated yields after silica gel column chromatography. [d] 28 % of starting compound, **2a**, was recovered.

Noteworthy is that further *in situ* oxidations of 2-acetyltetrahydrobenzofuran (**3b**) and an intermediate, 2-acetyltetrahydrobenzo-selenophene which was not isolated, to 2-acetylbenzofuran (**3c**) and 2-acetylbenzoselenophene (**3d**), respectively, in the presence of excess SeO_2. Oxidation of (*E*)-4-(6-methyl-1-cyclohexenyl)-3-buten-2-one (**4a**) after 16 hr refluxing in benzene gave a corresponding product of furan (**4b**) with an improved isolated yield of 49 % and traces of aromatized products unidentified. Refluxing **4a** in xylene required only 4.5 hr to complete oxidation with some decompositions to lower the yield of **4b** (32 %). Compounds of **5a** and **6a** with their sterically-enforced s-*cis* conformation of dienes reacted with SeO_2 much faster than **3a** or **4a** with a modest (73 % of **6b** in 1,4-dioxane at 80 °C) to a high yield of 94 % (**5b** in benzene). However, (*E*)-4-(6-phenyl-1-cyclohexenyl)-3-buten-2-one (**7a**) gave only a moderate yield (47 %) of **7b** after 24 hr refluxing in benzene. Molecular modeling of **7a** was performed on Silicon Graphics workstation using SYBYL 6.3 software from Tripos. The structure of **7a** was fully geometry optimized using the standard Tripos molecular mechanics force field. The result showed a more stable s-*trans* conformation of **7a** and 6-phenyl group in **7a** to be orthogonal to the plane of dienone. Aromatic π–clouds of **7a** were close enough to overlap with 3-methynyl hydrogen of conjugated butadienone moiety which might result in anisotropic effects of H-3.[8] In ^{1}H-NMR of **7a**, a doublet due to H-3 (H-3 at 5.77 ppm, d, J=16.0 Hz) was in fact 0.53 ppm up-field shifted relative to that of 6,6-dimethyl-substituted **5a** (H-3 at 6.30 ppm, d, J=16.2 Hz) while doublets of H-4s' remained constant (7.15 ppm in **5a** and 7.10 ppm in **7a**). Thus, 6-phenyl group of **7a** influenced less steric interaction with dienone and s-*trans* diene moiety was preferred to be stable. Oxidations of less activated dienes conjugated to ester (**8**), nitrile (**9**), or amide (**10**) did not occur even after 5 days refluxing in benzene or in xylene with 4 eq. of SeO_2. It might prove the formation of the intermediate (**d** in Scheme 2) to be an inverse [2+4] cycloaddition type.[10]

Moreover, SeO_2 oxidation rates of (*E*)-4-(6,6-dimethyl-1-cyclohexenyl)-3-buten-2-one (**5a**) were dependent on solvent polarity as is shown in Table 2. In polar solvent of 1,4-dioxane or acetic acid oxidation rates were increased to be completed within 25 minutes (in 1,4-dioxane) or 15 minutes (in acetic acid) at the same temperature (80 °C). Therefore, the TS for the formation of the intermediate may reveal a polar addition of a oxygen nucleophile of selenium dioxide to the electrophilic dienone. In acetic acid oxidation showed some decomposed products which decreased the yield of **5b** (60 %).

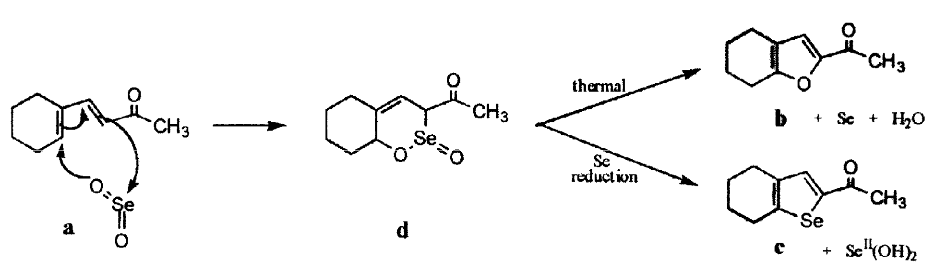
Table 2. Solvent Effects for Oxidation of Compound 5a by SeO_2[a]

Reaction	Solvent	Temp. (°C)	Rxn. Time[b]	Yield (%)[c]
1	benzene	80	13 hr	82.2
2	1,4-dioxane	80	25 min	83.7
3	acetic acid	80	15 min	60.1

[a]Oxidations were done with 2 eq. of SeO_2. [b]Reactions were monitored by G.C.
[c]Isolated yields after silica gel column chromatography.

Thus, considering above conformational and electronic requirements of conjugated dienones and solvent effects of SeO_2 oxidation we propose again a stepwise formation of the intermediate (**d**)[4b] as is shown in Scheme 2 by an initial nucleophilic selenium dioxide additions to dienones similar to the adduct of butadiene derivatives with SeO_2.[11] Thermal rearrangements of the intermediate will give the product, furan, along with water.

The present method provides a straightforward oxidation of conjugated dienones to 2-acetyltetrahydrobenzofurans with a simple and mild procedure. We are now in further studies for the diversity of this SeO_2 oxidation.



Scheme 2. Proposed Mechanism of Oxidation by SeO_2

Acknowledgement: We thank Korean Ministry of Science and Technology for financial support of this research.

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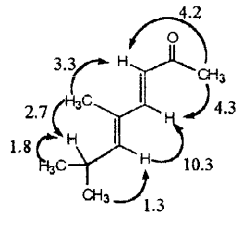
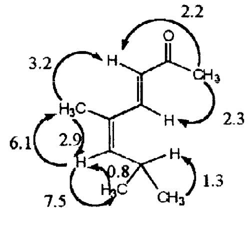
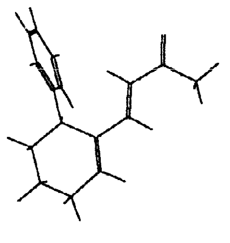
7. NOE Difference Spectra of **1a** and **2a** are summarized below.
8. s-*trans* conformation of **7a** using SYBYL 6.3



1a



2a



9. General procedure for the oxidation of conjugated dienones with SeO_2: To a stirred solution of **5a** (178 mg, 1.0 mmol) in 10 mL of dry benzene was added SeO_2 (445 mg, 4.0 mmol). During refluxing the solution at 80 °C reaction was monitored by G.C. with capillary column (HP-1, cross linked 5 % PhMe silicone, 12 m x 0.2 mm x 0.33 μm film thickness, 80 °C–250 °C, 8.5 °C/min.). After completion of the reaction benzene evaporated and the syrup was subjected to Silica Gel column chromatography using hexane:ethyl acetate (10:1) as eluent. Products isolated were anlalyzed by ^{1}H-NMR, ^{13}C-NMR, and GC-Mass spectroscopy.
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