

AN IMPROVED PROCEDURE FOR THE CONVERSION OF
3,3-DISUBSTITUTED-1,4-CYCLOHEXADIENES TO 2,5-CYCLOHEXADIEN-1-ONES

Arthur G. Schultz,* Arthur G. Taveras, and Roger E. Harrington
Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Summary: The bis-allylic oxidations of 1,4-cyclohexadienes with tert-butyl hydroperoxide and pyridinium dichromate give 2,5-cyclohexadien-1-ones in good to excellent yields.

Bis-allylic oxidations of 3,3-disubstituted-1,4-cyclohexadienes, derived from Birch reduction-alkylations of benzoic acid derivatives, have provided 2,5-cyclohexadien-1-ones.^{1,2} The cyclohexadienones have proven to be valuable substrates for a variety of chemical and photochemical rearrangements.¹ Chromium reagents such as 1) Na₂CrO₄ in acetic acid-acetic anhydride, 2) CrO₃ in acetic acid-acetic anhydride, 3) pyridinium chlorochromate (PCC) in refluxing chloroform, and 4) pyridinium dichromate (PDC) in refluxing chloroform usually have provided the desired 2,5-cyclohexadien-1-one, but product yields have been in the low to moderate range. In some cases oxidation did not occur or aromatic products were obtained via oxidative fragmentation.

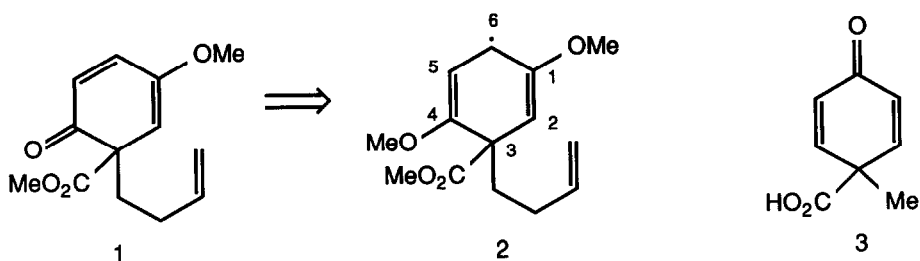
We now report that the 1:1 molar mixture of tert-butyl hydroperoxide and PDC that has been reported to be an effect reagent for allylic and benzylic oxidations³ is a generally superior reagent system for the preparation of 2,5-cyclohexadien-1-ones (Table I).⁴ The reaction procedure is essentially the same as that previously described,³ except that 90 rather than 70% tert-butyl hydroperoxide routinely was used. The effectiveness of both 70 and 90% tert-butyl hydroperoxide was examined (entry 10) and little, if any, difference in product distribution was found.

Excellent yields of 2,5-cyclohexadien-1-ones are obtained from 3-carbomethoxy-1,4-

cyclohexadienes with alkyl and alkenyl substituents at C(3). Entries 3, 6, and 10-12 show that the tert-butyl hydroperoxide and PDC reagent is superior to the other chromium reagents that have been examined. Entries 10-12 (and 16-17) demonstrate that allylic oxidation at the 3'-butenyl side chain is not competitive with bis-allylic oxidation at the cyclohexadiene ring.


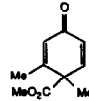
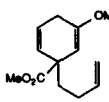
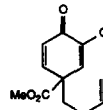
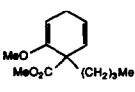
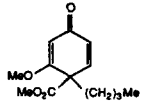
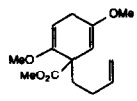
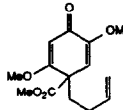
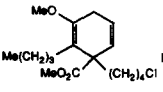
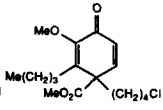
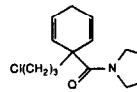
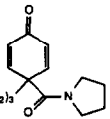

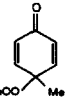
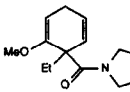
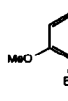
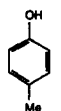
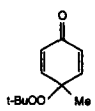
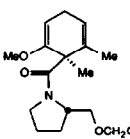
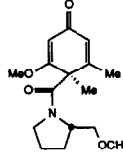
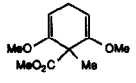
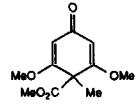
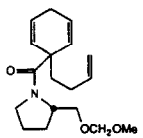
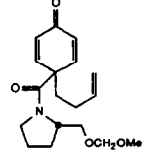
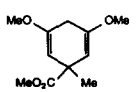
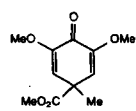
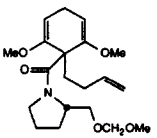
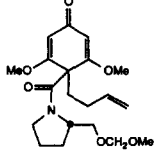
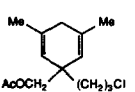
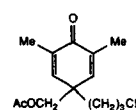
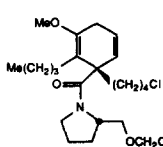
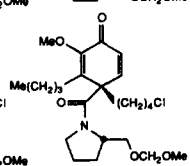

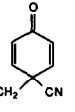
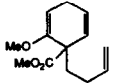
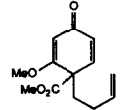
Oxidations of 1,5-dimethoxy-1,4-cyclohexadienes are particularly problematic (entry 7). The tert-butyl hydroperoxide and PDC reagent gave 2,5-cyclohexadien-1-ones with moderate efficiencies, whereas the other reagent systems were found to be ineffective (e.g., entry 7). In contrast, the 1,5-dialkyl substitution is quite compatible with allylic oxidants as previously illustrated by the conversion of 3-acetoxymethyl-3-(3'-chloropropyl)-1,5-dimethyl-1,4-cyclohexadiene to the 2,5-cyclohexadien-1-one (entry 8).^{1d}

A significant quantity of the 2,4-cyclohexadien-1-one 1 (18% yield) was obtained from the oxidation of 3-(3'-butenyl)-3-carbomethoxy-1,4-dimethoxy-1,4-cyclohexadiene (entry 12). The analogous 2,4-cyclohexadien-1-one is not obtained from the 2,4-dimethoxy-1,4-cyclohexadiene (entry 6). Thus, it appears that the putative intermediate bis-allylic radical 2² undergoes oxidation not only at C(6) to give the 2,5-cyclohexadien-1-one, but, because of the methoxy group at C(1), also at C(4) to give 1.



There was an off-chance that the 4-carboxy-2,5-cyclohexadien-1-one 3 might be obtainable⁵ from the corresponding 1,4-cyclohexadiene by virtue of the mild reaction conditions characteristic of the method under consideration. However, only 4-tert-butylperoxy-4-methyl-2,5-cyclohexadiene-1-one was isolated from the oxidation of 3-carboxy-3-methyl-1,4-cyclohexadiene (entry 4). Presumably 3 is formed, but undergoes the expected vinylogous β -keto acid decarboxylation to give p-cresol. Entry 5 shows that p-cresol undergoes oxidation with tert-butyl hydroperoxide and PDC to give the 4-tert-butylperoxy-2,5-cyclohexadien-1-one. This type of phenolic oxidation is well preceded with other transition metal oxidants.⁶

Table I. Oxidations of 3,3-Disubstituted-1,4-cyclohexadienes and *p*-Cresol with a 1:1 Molar Ratio of *tert*-BuOOH:PDC at 25°C

entry	substrate	product	yield % ^a	lit. yield (ref. 1) %	entry	substrate	product	yield % ^a	lit. yield (ref. 1) %
1			74		11			42 (50)	21 ^b
2			76		12			76 (79)	49 ^b
3			77	34 ^b	13			62	
4			20-30		14				ref. 8 ^{b,c,d}
5			47		15			73	44 ^{b,c}
6			97	20 ^b	16			83	
7			23 (40)	0 ^{b,c,d}	17			88	
8			63 ^c		18			85	
9			40	63 ^b					
10			87 (95)	22 ^c , 44 ^b					

^aYields are for products isolated after chromatography of the reaction mixture on silica gel. The yield based on recovered starting material is given in parentheses. ^bCrO₃ in HOAc-Ac₂O. ^cPDC in CHCl₃ at reflux. ^dPCC in CHCl₃ at reflux.

3-Benzyl-3-cyano-1,4-cyclohexadiene was converted to the 2,5-cyclohexadien-1-one with tert-butyl hydroperoxide and PDC (entry 9), albeit in lower yield than with PDC in refluxing chloroform. However, 3-carboxamido-1,4-cyclohexadienes undergo smooth oxidations to the corresponding 2,5-cyclohexadien-1-ones (entries 13, 15-18). This conversion is especially important for the preparation of 2,5-cyclohexadien-1-ones containing the chiral auxiliary L-prolinol. The 1,4-cyclohexadienes are obtained by the stereoselective Birch reduction-alkylation.⁷ Other methods of oxidation resulted in lower yields of 2,5-cyclohexadien-1-ones (cf., entry 15) or the formation of aromatic products by oxidative-fragmentation of the carboxamide group (entry 14).⁸

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References and Notes

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4. Oxidations of 1,4-dienes had not been considered in the earlier work (ref. 3); however, diaryl methanes were reported to give diaryl ketones in excellent yield.
5. Cyclohexadienone 3 is a structural analogue of prephenic acid, a biosynthetically important 4-carboxy-2,5-cyclohexadien-1-ol; see: a) Plieninger, H. Angew. Chem., Int. Ed. Engl. 1962, 1, 367. b) Danishefsky, S.; Hiram, M.; Fritsch, N.; Clardy, J. J. Am. Chem. Soc. 1979, 101, 7013.
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