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CYCLOADDITION OF SILYLENE PROTECTING DIHYDROXYSTYRENE DERIVED FROM ORTHO-HYDROXYACETOPHENONE: ONE-STEP SYNTHESIS OF PERI-HYDROXYLATED POLYCYCLIC COMPOUNDS

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Summary: Thermal treatment of the silylene protecting dihydroxystyrene derived from *o*-hydroxyacetophenone with dienophiles caused a [4+2]cycloaddition to give the corresponding *peri*-hydroxylated polycyclic aromatic compounds in a single step.

The current interest in the synthesis of *peri*-hydroxylated aromatic compounds which contain potent and biologically active materials such as anthracycline,[1] pyranonaphthoquinone,[2] and chromomycin antibiotics[3] or potently carcinogenic 7,12-dimethylbenz[a]anthracenes[4,5] has prompted us to study facile and direct methods for the *peri*-hydroxylated polycyclic aromatic compounds.[6] We now report here a novel and simple method for the synthesis of these compounds by employing a Diels-Alder reaction of the silylene protecting dihydroxystyrene (1) derived from *o*-hydroxyacetophenone with suitable dienophiles.

Although cycloaddition of styrene diene system itself, consisting of the vinyl group and one of the aromatic ring double bonds to some dienophiles is known as a direct method for the preparation of polycyclic aromatic compounds,[5,7,8] it has not been applied to the synthesis of the *peri*-hydroxylated polycyclic compounds probably because of the following reasons: generally, [4+2]cycloaddition reaction of styrene derivatives requires quite tedious conditions (high temperature and long reaction period) and the yields are usually low due to the sluggish reactivity of the diene systems. Moreover, it seems to be quite difficult to obtain the requisite *peri*-hydroxylated polycyclic compounds by using cycloaddition reaction of α-hydroxystyrene derivatives from a consideration of Manning's report.[8] In fact, reaction of α-trimethylsilyloxystyrene (2) with a slightly excess of naphthoquinone or dimethyl acetylenedicarboxylate (DMAD) in benzene at 130°C for 2 days gave no [4+2]cycloadducts and with a 3-fold excess of DMAD gave a small amount of the [2+2+2]cycloadduct (3) [12%, mp 168-169°C, IR ($CHCl_3$) 3600, 3475, and 1720 cm^{-1}] as the only isolable adduct (Scheme I). The bis-trimethylsilyl protecting dihydroxystyrene (4) [bp 110-112°C/2 mmHg, IR

($CHCl_3$) 1610, 1600, 1080, and 1010 cm^{-1}], obtained from the dianion of α-hydroxyacetophenone and trimethylsilyl chloride, was treated with naphthoquinone or DMAD under similar conditions to give complex mixtures and both [4+2]- and [2+2+2]cycloadducts could not be formed. It is possibly because steric interaction between the trimethylsilyloxy group on benzene and the *o*-trimethylsilyloxyvinyl group should cause the vinyl group and benzene ring to lie out of plane with respect to each other as shown in Fig. 1.

Scheme I

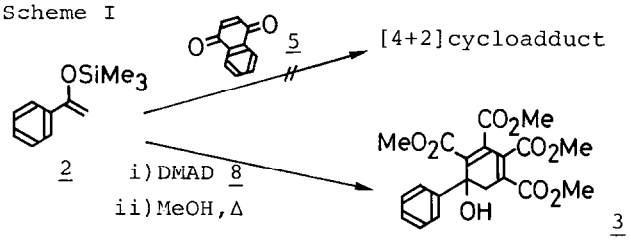
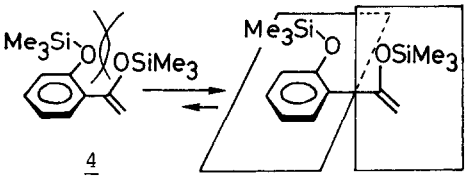


Fig. 1



In contrast, the silylene protecting dihydroxystyrene (1), which may involve a rigid planar diene system, reacted with some dienophiles to give the Diels-Alder adducts in a single step.

The starting styrene (1) was prepared by the reported method.[9] The cycloaddition reaction was generally carried out by employing 1 and 0.5-1.0 equivalents of dienophiles (5-8) in absolute benzene at 130°C for 2 days. A typical experimental procedure is as follows for the reaction of 1 with naphthoquinone (5). A solution of 1 and 5 in benzene was heated in a sealed tube and the mixture was concentrated. Due to the anticipated unstability of the adduct, the crude residue was immediately oxidized[10] and desilylated in refluxing methanol for 1 h to give the aromatized compound, which was acetylated with acetic anhydride-pyridine to give 4,5-diacetoxybenz[a]-anthracene-7,12-dione (9). In a similar fashion, the styrene (1) reacted with some dienophiles (6-8) to give the corresponding *peri*-hydroxylated compounds, which were isolated as acetylated compounds (10-12). Lewis acid ($BF_3 \cdot Et_2O$ and $TiCl_4$) catalyzed reaction of 1 was also examined. The reaction of 1 with 5 in the presence of Lewis acid led to the disappearance of 1, but no trace of cycloadduct was found and the desilylated parent hydroxyketone was obtained. The regiochemical outcome of this cycloaddition was determined by the reaction of 1 with 6 (see, entry 2). The reaction of 1 with DMAD (8) gave the [2+2+2]-cycloadduct (13) beside the normal [4+2]cycloadduct (12). The use of a large excess of 8 in the reaction gave 13 predominantly. The difference in the reaction pathways seems to be due to the different reactivity between the dienophiles as demonstrated in the cycloaddition of vinylpyrroles to some dienophiles.[11] The structures of all products were assigned on the basis of spectral evidence and analytical data. The results are summarized in Table I.

The present silylene protecting dihydroxystyrene (1) is found to act as active diene against dienophiles, probably due to the planar diene system and the electron donating silyloxy groups. The attractive feature of these

reactions is that regiocontrolled adducts are obtained in a direct way and the *peri*-hydroxy groups are incorporated into the produced polycyclic rings without elimination of α-silyloxy group.

Application of this method to the intramolecular cycloaddition leading to natural *peri*-hydroxylated polycyclic compounds is under way.

Scheme II

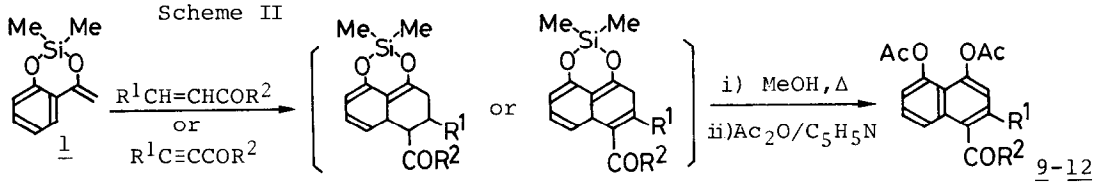
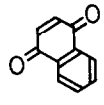
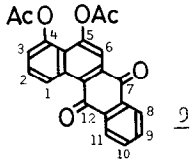
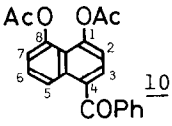
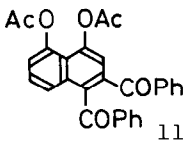
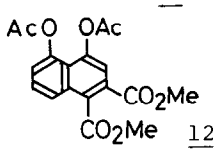
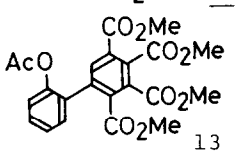


Table I. Cycloaddition of 1 with Dienophiles (5-8)

Entry	Dienophiles	Products[a]	Yield[b] %	M.p. (°C) (solvent)	I.R. ($CHCl_3$) νcm^{-1}	^1H-N.M.R. δ ($CDCl_3$)
1	1 eq.[c]  5	 9	37(52)	229-232 (benzene)	1770 1675 1600	2.36(3H,s,OAc),2.40 (3H,s,OAc),7.1-8.1 (7H,m,ArH),9.60(1H, brd,J=9,C_1-H)
2	1 eq. PhCOC≡CH 6	 10	26(43)	171-172 (benzene-n·hexane)	1760 1655 1600	2.43(6H,s,OAc×2), 7.17(1H,d,J=8 Hz, C_2-H),7.18(1H,dd, J=7.8 and 1.2 Hz,C_7-H),7.46(1H,d,J=8 Hz C_3-H),8.01(1H,dd, J=9 and 1.2 Hz,C_5-H),7.4-7.9(6H,m,ArH)
3	1 eq. PhCOC≡CCOPh 7	 11	40(59)	197-197.5 (benzene-n·hexane)	1765 1660	2.39(3H,s,OAc),2.42 (3H,s,OAc),7.1-7.8 (14H,m,ArH)
4	0.5 eq. $MeO_2CC{\equiv}CCO_2Me$ 8	 12	16[d]	162-163 (benzene-n·hexane)	1770 1730	2.36(6H,s,OAc×2), 3.91(3H,s,OMe),4.04 (3H,s,OMe),7.1-7.8 (4H,m,ArH)
		 13	16[d]	198-199 (ethyl acetate-benzene-n·hexane)	1770 1730	2.31(3H,s,OAc),3.64 (3H,s,OMe),3.87(3H, s,OMe),3.93(3H,s, OMe),4.09(3H,s,OMe), 6.31(1H,s,ArH),7.1-7.8(4H,m,ArH)
5	10 eq. 8	12 13	7(10) 34(48)			

a) The microanalyses of all products (9-13) were in satisfactory agreement with the calculated values.
b) Yields were based on 1 and given after purification by column chromatography or recrystallization. Isolated yields based on the reacted 1 were given in parentheses.
c) The yield was not improved by the addition of an excess of naphthoquinone or chloroanil to the reaction mixture.
d) Yield was based on the dienophile (8).

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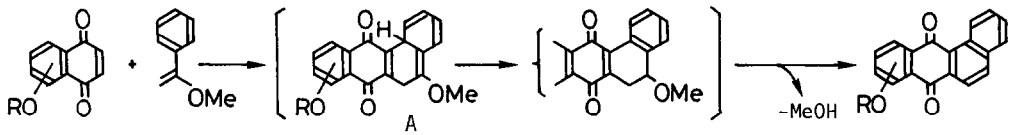

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