SYNTHESIS OF 6,7-BENZO-3-METHOXYESTRA-1,3,5(10),8,14-PENTAEN-17-ONE

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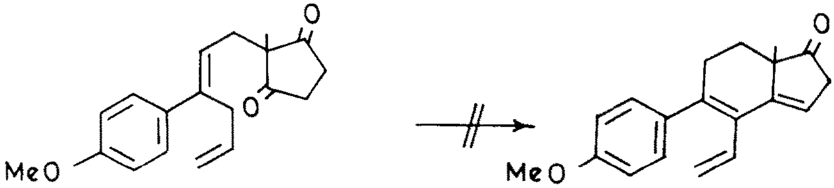
Received July 1, 1986
Revised December 29, 1986

ABSTRACT

A facile synthesis of 6,7-benzo-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one from anisole is reported.

INTRODUCTION

In an earlier publication (1), we have reported the synthesis of 3-methoxy-5,6-secosteroid in an attempt to utilize the A ⟶ AD ⟶ ACD ⟶ ABCD approach to steroid synthesis. However, our efforts to effect cyclization of compound 1 to the crucial intermediate 2 - from which construction of the B ring by an electrocyclic process was contemplated - were unsuccessful (Figure 1).



1

2

Figure 1

It was conjectured that the extensive polymerization observed during the attempted cyclization with a variety of acid catalysts was due to the formation of the sensitive phenyl butadiene moiety incorporated in compound 2.

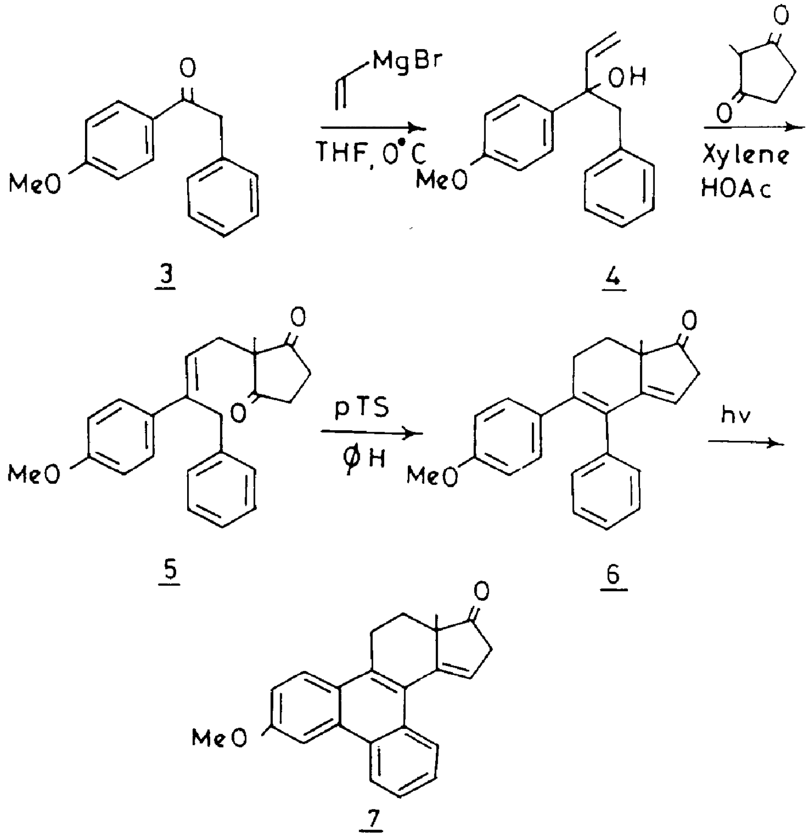


Figure 2

It was envisaged that the above problem could be obviated if the 6,7-double bond were to form part of an aromatic ring. With this objective in mind the synthesis of the title compound was undertaken. The reaction sequence leading to the final product is depicted in Figure 2.

RESULTS AND DISCUSSION

The ketone 3 was prepared from anisole as per literature procedure (2) in 70% yield. Reaction of the ketone 3 with vinylmagnesium bromide in dry THF furnished the vinyl carbinol 4 in 80% yield. The spectral features of this carbinol 4 supported the assigned structure. 2-Methylcyclopentane-1,3-dione underwent a smooth condensation with the carbinol 4 in refluxing xylene containing acetic acid (3). A pure sample of the condensation product 5, obtained by chromatography, gave spectral data that were in total agreement with the structure assigned. Based on nmr and steric reasons an 'E' configuration has been assigned to this compound. About 5% of the 'Z' isomer was also found to be present.

Refluxing a benzene solution of the compound 5 in the presence of equimolar amounts of p-toluene sulfonic acid furnished the cyclized product 6 in 60% yield. The ^{1}H nmr spectrum, besides containing other features, showed a triplet at 5.48 δ (J = 2Hz) characteristic of the vinyl proton at C_{15}.

Irradiation (4) of a cyclohexane solution of the product 6 with light of wavelength 3000 Å in the presence of a catalytic amount of iodine gave a highly colored reaction product. After laborious chromatography a small amount of a pink-colored solid, possessing ^{1}H NMR features characteristic of the cyclized product 7, was obtained.

It is apparent that the presence of the double bond and the carbonyl group in ring D are contributing a great deal to the complex nature of the photochemical reaction products.

EXPERIMENTAL

3-(p-Methoxyphenyl)-4-phenyl-but-1-en-3-ol 4 :

A suspension of vinylmagnesium bromide in dry THF (25 mL) was prepared from magnesium (1.44 g, 0.06 g atom) and vinyl bromide (7 g, 0.06 mol).

A solution of benzyl p-methoxyphenyl ketone 3 (6.78 g, 0.03 mol) in dry THF (25 mL) was added dropwise during 15 min to a stirred and cooled (ice-salt bath) solution of vinylmagnesium bromide. The reaction mixture was stirred at this temperature for 1 h, then warmed to room temperature and stirred for another 1 h. The solution was then refluxed for 2 h. The Grignard complex was decomposed with saturated NH_4Cl solution (25 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent yielded a yellow oil. Chromatography over a column of silica gel (benzene - hexane 3:1) furnished a colorless viscous liquid. On storage it solidified to a colorless solid which was crystallized from petroleum ether (40-60°) (6.10 g, 80%) m.p. 42-44°. IR($CHCl_3$) : 3600 (OH), 1620 cm^{-1} (C=C); NMR ($CDCl_3$/TMS) δ 2.03 (s, 1H, OH), 3.23(s, 2H, benzylic CH_2), 3.86 (s, 3H, OCH_3), 5.13-5.43(m, 2H, olefinic CH_2), 6.26-6.59(dd,1H,olefinic CH),6.93-7.59(m,9H,aromatic).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found : C, 80.50, H, 7.03%.

Condensation of vinyl carbinol 4 with 2-methylcyclopentane-1,3-dione :

To a stirred solution of vinyl carbinol 4 (3.8 g, 0.015 mol) in xylene (25 mL) was added 2-methylcyclopentane-1,3-dione (2.24 g, 0.02 mol) and acetic acid (15 mL). The mixture was refluxed for 7 h and the solvent was removed under vacuum. To the residue, benzene (100 mL) was added and the benzene solution was washed successively with water, 10% $NaHCO_3$ solution, and water. Drying and solvent removal yielded a viscous liquid which was chromatographed over silica gel (benzene). A colorless oil was obtained (3.4 g, 65%); UV($CHCl_3$) λ max : 263 nm; IR($CHCl_3$) : 1780 (C=O), 1740 (C=O), 1620 cm^{-1} (C=C); NMR ($CDCl_3$/TMS) δ 1.15 (s, 3H, CH_3), 2.55 (d, 2H, J = 8Hz, C_{12} methylene protons), 2.68 (s, 4H, cyclopentanedione methylenes), 3.72 (s, 3H, OCH_3), 3.80 (s, 2H, C_8 methylene), 5.61 (t, 1H, J = 8Hz, C_{11} proton), 6.66-7.36 (m, 9H, aromatic).

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found : C, 79.36; H, 6.92%.

6,7-Benzo-3-methoxy-5,6-secoestra-1,3,5(10),8,14-pentaen-17-one 6 :

To a solution of compound 5 (0.70 g, 0.002 mol) in benzene (35 mL) was added p-toluenesulfonic acid (0.35 g, 0.002 mol), and the mixture was refluxed for 2 h on a steambath. It was then cooled and diluted with benzene (100 mL). The benzene solution was washed successively with water, saturated $NaHCO_3$ solution, and finally with water. After drying, the solution was concentrated to a viscous liquid. Chromatography over silica gel (hexane-benzene 1:1) yielded a yellow solid which was crystallized from hexane (0.39 g, 60%); m.p. 138-139°; UV($CHCl_3$) : λ max 248, 287 nm; IR($CHCl_3$) : 1740 (C=O), 1610 cm^{-1} (C=C); NMR ($CDCl_3$/TMS) δ 1.30 (s, 3H, CH_3), 1.66-2.20 (m, 2H, C_{12} protons), 2.59-3.26 (m, 4H, C_{11} and C_{16} methylenes), 3.69 (s, 3H, OCH_3), 5.48 (t, 1H, J = 2Hz, C_{15} proton), 6.59-7.40 (m, 9H, aromatic); MS : m/z 330 (M^+).

Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.70. Found : C, 83.30; H, 6.74%.

6,7-Benzo-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one 7 :

To a solution of the secosteroid 6 (0.1 g) in cyclohexane (75 mL) was added a crystal of iodine, and it was irradiated for 6 h using a light of wavelength 3000 Å. The reaction mixture was diluted with benzene (100 mL) and washed successively with water, sodium thiosulfate solution and water. Drying and solvent removal under reduced pressure gave a fluorescent red liquid. Chromatography over silica gel (hexane-benzene 3:1) yielded a pink solid which was crystallized from hexane (20 mg); IR($CHCl_3$) : 1740 cm^{-1}; NMR ($CDCl_3$/TMS) δ 1.13 (s, 3H, CH_3), 1.77- 2.23(m, 2H, C_{12} methylene), 3.07-3.36 (m, 4H, C_{11} and C_{16} methylenes), 3.95 (s, 3H, OCH_3), 6.26(t, 1H, J = 2Hz, C_{15} proton), 7.00-8.60 (m, 7H, aromatic).

ACKNOWLEDGMENTS

The authors are extremely thankful to Dr. Eberhard Schroder, Schering AG, West Germany for a generous gift of 2-methylcyclopentane-1,3-dione.

NOTES AND REFERENCES

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4. See Mallory, F.B., and Mallory, C.W., J AM CHEM SOC <u>94</u>, 6041 (1972) for photolysis of stilbene derivatives to phenanthrenes.