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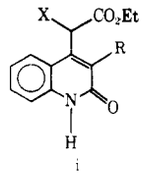

i

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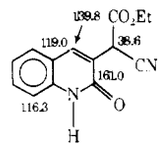
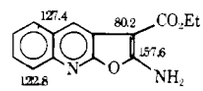


11a



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(13) A referee suggested that the ethyl moiety might sterically drive the ester function out of planarity with the double bond, thus destablizing any partial charge in a transition state such as **5**.

Thallium in Organic Synthesis. 53. Simple Procedures for the Replacement of a Phenolic OH Group by N=NAr, N=O, H, NH_2, and C Substituents[1,2]

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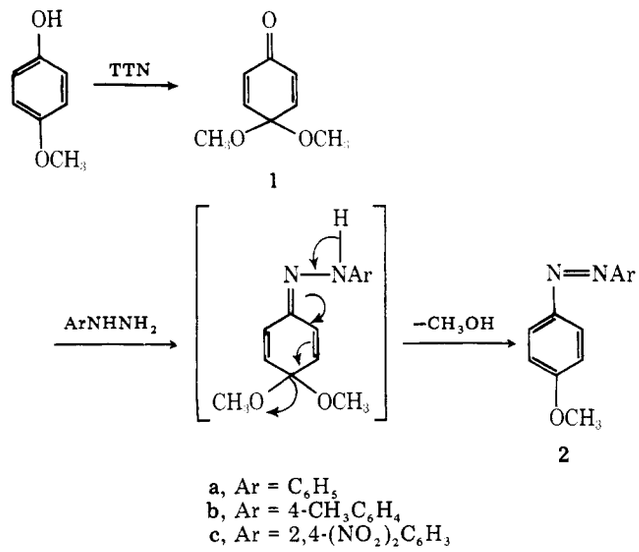
Evans et al.[3] have recently described an ingenious synthetic approach to the Amaryllidaceae alkaloid cherylline via a quinone methide prepared by a Wittig-type reaction of 4,4-dimethoxycyclohexadienones. We have recently described a general, efficient, and mild procedure for the oxidation of a variety of 4-substituted phenols to 4-substituted 4-methoxycyclohexadienones utilizing thallium(III) nitrate (TTN) in methanol or methanol/trimethyl orthoformate as solvent.[4] We now report a series of simple transformations of these cyclohexadienones which effect overall replacement of the OH group of the precursor phenol by N=NAr, N=O, H, NH_2, and C substituents.

In 1963 Hecker and Lattrell[5] reported the conversion of several 4-hydroxy-4-substituted cyclohexadienones (prepared by thallium(III) or lead(IV) acetate oxidation of the corresponding phenols) to 2,4-dinitrophenylazobenzenes by reaction with 2,4-dinitrophenylhydrazine. Because of the inaccessibility of the requisite precursor cyclohexadienones, however, there has been no subsequent synthetic exploitation

Scheme I

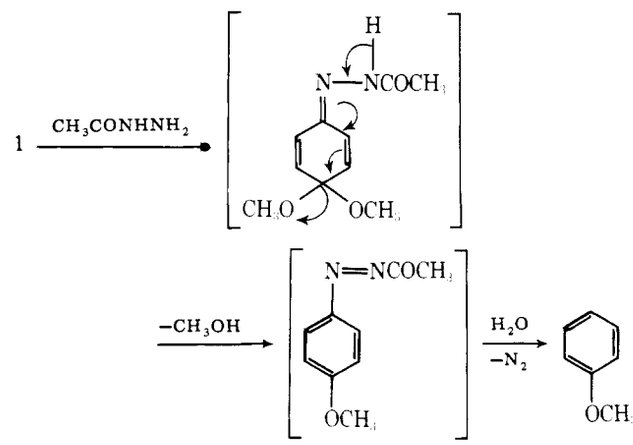


1

2

a, Ar = C_6H_5
b, Ar = 4-$CH_3C_6H_4$
c, Ar = 2,4-$(NO_2)_2C_6H_3$

Scheme II



of this type of transformation, but it appears to be general. Thus, treatment of **1** with phenylhydrazine smoothly gave 4-methoxyazobenzene **2a** in 90% yield (Scheme I). Similarly, reaction of **1** with 4-methyl- and 2,4-dinitrophenylhydrazine gave 4-methyl-4′-methoxyazobenzene (**2b**) and 2,4-dinitro-4′-methoxyazobenzene (**2c**) in 92 and 98.5% yield, respectively. This transformation can also be carried out without isolation of the intermediate cyclohexadienone; 3,4-dimethylphenol, for example, was converted to 3,4-dimethylazobenzene in 55% overall yield. Extrapolation of these results to the replacement of a phenolic OH group by H was somewhat less successful. Reaction of **1** with acethydrazide followed by addition of water resulted in the evolution of nitrogen, and anisole was isolated in 50% yield (Scheme II); 6-hydroxytetralin was similarly converted to tetralin in 31% yield.[6] Despite the moderate yields, this simple transformation could represent a mild procedure for effecting a potentially useful reduction.[7]

The principle illustrated in these transformations—conversion of **1** to an imine possessing an acidic α-hydrogen atom which can be lost in a subsequent, and spontaneous, aromatization step—appears to be capable of considerable extension. Thus, treatment of **1** with hydroxylamine led directly to 4-methoxynitrosobenzene in 91% yield (Scheme III). The overall conversion of 4-methoxyphenol to 4-methoxynitrosobenzene can also be carried out as a one-pot operation without isolation of the intermediate cyclohexadienone, although this procedure gave a somewhat lower yield (70%). Using the latter technique, 4-methylphenol, 3,4-dimethyl-

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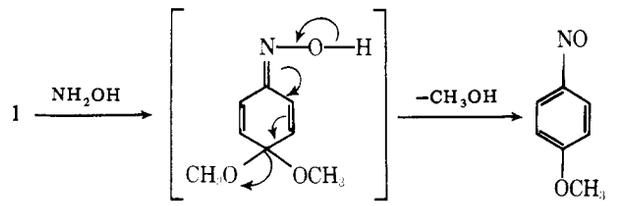
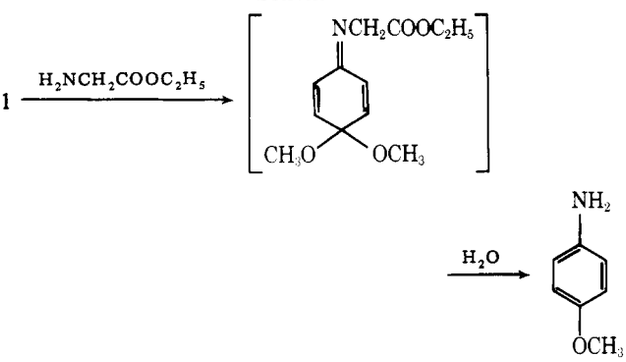
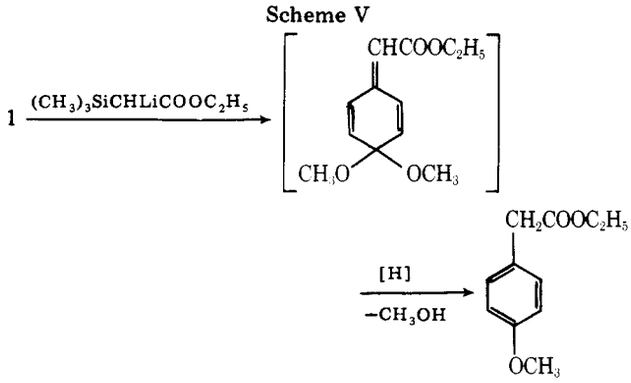
Scheme III



Scheme IV



Scheme V



phenol, 2-chloro-4-methoxyphenol, 4-hydroxybiphenyl, and 6-hydroxytetralin were converted to the aromatic nitroso compounds (in which the nitroso group has replaced the OH substituent of the phenolic precursor) in 41, 62, 54, 40, and 31% yield, respectively.

The cyclohexadienone 1 can also be converted to 4-methoxyaniline (isolated as the acetanilide) in 56% yield by reaction with ethyl glycinate followed by acid hydrolysis of the (presumed but not isolated) imine (Scheme IV). This mild conversion of a phenol to an aniline derivative should be contrasted with the extremely vigorous conditions required by current methodology.[8]

Finally, by analogy with the recently described conversion by Evans et al.[3] of 1 to *N,N*-dimethyl-α-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetamide with the lithium enolate of *N,N*-dimethyl-α-trimethylsilylacetamide, we have found that reaction of 1 with the lithium enolate of ethyl α-trimethylsilylacetate gave the corresponding quinone methide dimethyl ketal (Scheme V). Catalytic reduction then led directly to ethyl 4-methoxyphenylacetate (68%). This transformation, and that reported by Evans, represent an attractive potential synthetic method for arylation of carbanions.

Experimental Section[9]

General Procedure for the Conversion of 4,4-Dimethoxycyclohexadienone to 4-Methoxyazobenzenes. A solution of the arylhydrazine hydrochloride (7 mmol) in methanol (20 mL) containing pyridine (3.75 mmol) was added dropwise to a stirred solution of 4,4-dimethoxycyclohexadienone (5 mmol) in methanol (20 mL) cooled to 0 °C. The mixture was stirred at room temperature for 2.5 h; 6 drops of boron trifluoride etherate were then added and stirring was continued for a further 8–10 h. The reaction mixture was diluted to a total volume of 200 mL with methylene chloride and the resulting solution washed with water (50 mL), saturated aqueous sodium bicarbonate solution, and water (50 mL); it was then dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. Chromatography of the residue on silica gel using methylene chloride as the eluent gave the pure (mp, IR, NMR, TLC) 4-methoxyazobenzene.

One-Pot Procedure for the Conversion of Phenols to Azobenzenes: Preparation of 3,4-Dimethylazobenzene. A solution of thallium(III) nitrate trihydrate (2.22 g, 5 mmol) in anhydrous methanol (20 mL) was added dropwise to a stirred solution of 3,4-dimethylphenol (0.61 g, 5 mmol) in anhydrous methanol (20 mL) cooled to −78 °C. The temperature of the reaction mixture was allowed to rise to room temperature, and stirring was continued for 1 h. The reaction mixture was then cooled to 0 °C, a solution of phenylhydrazine (0.76 g, 7 mmol) in methanol (20 mL) containing pyridine (0.5 g, 6.25 mmol) was added dropwise, and stirring was continued at room temperature for 4 h. Six drops of boron trifluoride etherate was then added and stirring was continued for a further 12 h. The product was isolated using the technique described above; this gave 0.58 g (55%) of pure 3,4-dimethylazobenzene, mp 63–65 °C. Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.92; H, 6.64; N, 13.02.

Conversion of 4,4-Dimethoxycyclohexadienone to Anisole. 4,4-Dimethoxycyclohexadienone (0.77 g, 5 mmol) was dissolved in anhydrous methanol (20 mL) containing 2 g of Davidson Type 4A molecular sieves. In a separate flask, anhydrous acethydrazide (0.55 g, 7.5 mmol) was dissolved in anhydrous methanol (20 mL) containing 2 g of Davidson Type 4A molecular sieves and concentrated hydrochloric acid (0.25 g). The two solutions were stirred for 30 min; then the latter was added to the former, which had been chilled to 0 °C. The mixture was stirred for 1.5 h, 20 drops of boron trifluoride etherate were then added during 3 min, and stirring was continued for 2.5 h. Water (100 mL) was added all at once and the molecular sieves were removed by filtration; the filtrate was stirred for 30 min, after which 10% hydrochloric acid (5 mL) was added. The resulting mixture was stirred at room temperature for 6 h, then at 60 °C for 1 h; water (100 mL) was added and the aqueous solution was extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (50 mL) and aqueous sodium bicarbonate solution (50 mL) and dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was chromatographed on silica gel using methylene chloride as eluent; this gave 270 mg (50%) of pure (IR, GLC) anisole.

Conversion of 6-Hydroxytetraline to Tetralin. 6-Hydroxytetralin (5 mmol) was oxidized to the cyclohexadienone by the procedure described above for the oxidation of 3,4-dimethylphenol with thallium(III) nitrate trihydrate. The cyclohexadienone was not isolated, but was treated in situ with acethydrazide as described in the preparation of anisole; this gave pure (IR, GLC) tetralin in 31% yield.

General Procedure for the Conversion of Phenols to Nitroso Compounds. A solution of thallium(III) nitrate trihydrate (2.22 g, 5 mmol) in methanol (15 mL) was added to a stirred solution of the phenol (5 mmol) in methanol (15 mL) cooled to −78 °C. The temperature of the reaction mixture was allowed to rise to room temperature, and stirring was continued for 1 h. A solution of hydroxylamine hydrochloride (6.5 mmol) and pyridine (11.5 mmol) in methanol was then added dropwise and the mixture was stirred for a further 5 h.[10] Six drops of boron trifluoride etherate were then added,[11] and stirring was continued overnight. The reaction mixture was diluted to a volume of 150 mL with ether and filtered to remove inorganic salts; the filtrate was washed with aqueous sodium chloride solution (75 mL). The aqueous layer was extracted with ether (2 × 75 mL), and the combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel using methylene chloride as eluent to give the pure product.

Conversion of 4,4-Dimethoxycyclohexadienone to 4-Nitrosoanisole. A solution of hydroxylamine hydrochloride (0.84 g, 12 mmol) and pyridine (1 g, 12.5 mmol) in methanol (25 mL) was added dropwise to a stirred solution of 4,4-dimethoxycyclohexadienone (1.54 g, 10 mmol) in methanol (50 mL), and the reaction mixture was stirred at room temperature for 5 h. Product isolation as described above gave 1.24 g (91%) of pure (IR, NMR, TLC) 4-nitrosoanisole.

Conversion of 4,4-Dimethoxycyclohexadienone to 4-Methoxyacetanilide. A mixture of ethyl glycinate hydrochloride

(1.05 g, 7.5 mmol) and sodium bicarbonate (0.55 g, 6.5 mmol) in ethanol (50 mL) and water (10 mL) was added to a solution of 4,4-dimethoxycyclohexadienone (0.77 g, 5 mmol) in ethanol (50 mL), and the resulting mixture was heated under reflux for 1 h. Ten drops of 10% hydrochloric acid was added and the mixture was heated under reflux for 24 h; 6 N hydrochloric acid (80 mL) was then added and reflux continued for 2 h. The reaction mixture was then cooled, neutralized with sodium bicarbonate, and extracted with chloroform (3 × 150 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give crude 4-methoxyaniline. This was acetylated with acetic anhydride and the crude anilide (86%) purified by chromatography and crystallization; this gave 0.46 g (56%) of pure (IR, NMR) 4-methoxyacetanilide, mp 130–132 °C.

Conversion of 4,4-Dimethoxycyclohexadienone to Ethyl 4-Methoxyphenylacetate. The lithium enolate of ethyl α-trimethylsilylacetate[12] (5.5 mmol) was prepared in THF using the procedure described by Evans[3] for the preparation of the corresponding acetamide. A solution of 4,4-dimethoxycyclohexadienone (5 mmol) in THF (3 mL) was added to the enolate solution, and the mixture was stirred at 0 °C for 5 h. It was then added to a mixture of saturated aqueous sodium bicarbonate solution (40 mL) and methylene chloride (150 mL) which had been prechilled to 0 °C. The organic layer was separated, washed with 5% aqueous sodium chloride solution (40 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude quinone methide ketal (1.10 g) was catalytically hydrogenated (5% Pd/charcoal) at atmospheric pressure in ethyl acetate and the product chromatographed on silica gel using methanol/methylene chloride (3:97) as eluent. This gave 0.22 g of 4-methoxyphenol and 0.43 g (68% based on dienone consumed) of pure (IR, NMR, GLC) ethyl 4-methoxyphenylacetate.

Registry No.—**1**, 935-50-2; **2a**, 2396-60-3; **2b**, 29418-44-8; **2c**, 51640-06-3; $ArNHNH_2$ (Ar = Ph), 100-63-0; $ArNHNH_2$ (Ar = 4-$CH_3C_6H_4$), 539-44-6; $ArNHNH_2$ (Ar = 2,4-$(NO_2)_2C_6H_3$), 119-26-6; TTN, 13746-98-0; 3,4-dimethylphenol, 95-65-8; 3,4-dimethylazobenzene, 67425-70-1; acethydrazide, 1068-57-1; anisole, 100-66-3; 6-hydroxytetralin, 1125-78-6; tetralin, 119-64-2; hydroxylamine hydrochloride, 5470-11-1; 4-nitrosoanisole, 100-17-4; 4-methoxyacetanilide, 51-66-1; ethyl glycinate hydrochloride, 623-33-6; 4-methoxyaniline, 104-94-9; ethyl 2-trimethylsilylacetate lithium enolate, 54886-62-3; 4-methoxyphenol, 150-76-5; ethyl 4-methoxyphenylacetate, 14062-18-1.

References and Notes

(1) For the previous paper in this series, see E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, *J. Org. Chem.*, **43**, 3632 (1978).
(2) We are indebted to the National Science Foundation (Grant No. CHE76-16506) and to Eli Lilly and Co. for financial support of this work.
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(4) A. McKillop, D. H. Perry, M. Edwards, S. Antus, L. Farkas, M. Nógrádi, and E. C. Taylor, *J. Org. Chem.*, **41**, 282 (1976).
(5) E. Hecker and R. Lattrell, *Justus Liebigs Ann. Chem.*, **662**, 48 (1963).
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(8) See, e.g., D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964); R. A. Scherrer and H. R. Beatty, *ibid.*, **37**, 1681 (1972); R. A. Rossi and J. F. Bunnett, *ibid.*, **37**, 3570 (1972); R. Bayles, M. C. Johnson, R. F. Maisey, and R. W. Turner, *Synthesis*, 31, 33 (1977).
(9) Mp's were determined using a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer Model 467 grating infrared spectrophotometer, and NMR spectra using a Varian A-60 60 MHz spectrometer. GLC was performed on an F and M Model 810R-29 S/N B-273 gas chromatograph equipped with a Honeywell Electronik 15 strip chart recorder. TLC refers to the use of Baker-flex silica gel 1B2-F thin-layer chromatography sheets. Microanalyses were performed by Hoffmann-La Roche, Inc., Nutley, N.J.
(10) When 4-methoxyphenol is used as the substrate the reaction temperature should be held at 0 °C both before the addition of the hydroxylamine and for 1 h afterwards to prevent acid-catalyzed decomposition of the quinone ketal.
(11) Azoxyarenes are produced as by-products in small amounts in these reactions and are difficult to separate from the desired nitroso compounds. Addition of boron trifluoride eliminates this problem.
(12) R. J. Fessenden and J. S. Fessenden, *J. Org. Chem.*, **32**, 3535 (1967).

Eutectic Potassium–Sodium–Aluminum Chloride as a Mild Catalyst for Ene Reactions: Simple Synthesis of the Sex Pheromone from Douglas Fir Tussock Moth

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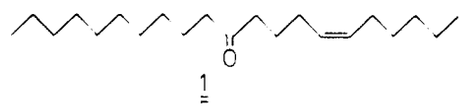
Several syntheses of the sex pheromone of the Douglas fir tussock moth (**1**) have recently been published.[1-4] These



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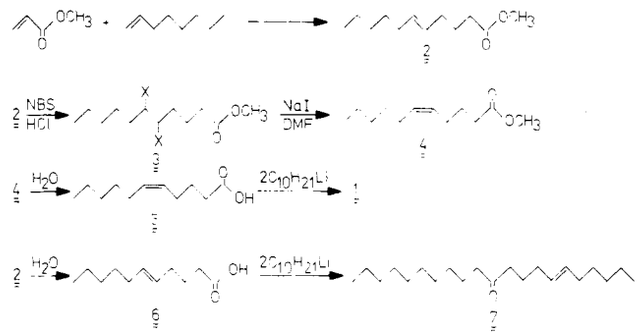
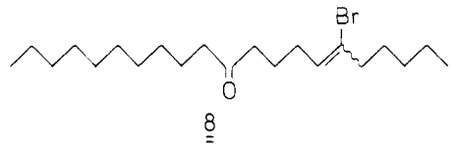
syntheses make use of fairly complicated reactions and sophisticated starting materials. During our studies of acid-catalyzed ene reactions, we have explored a simpler synthesis both for the natural isomer and the also active[5] *E* isomer (**7**). The principles of this synthesis are outlined in Scheme I.

Scheme I



The ene reaction between methyl acrylate and 1-octene has been reported not to occur with aluminium chloride.[6] This is probably due to isomerization of the 1-octene to other internally substituted octenes and subsequent formation of branched adducts. In contrast to this, the eutectic mixture of $AlCl_3$, NaCl, and KCl has been found to be a superior catalyst for the reactions of methyl acrylate with 1-olefins. Using this catalyst, a 40% yield of ene adducts was obtained as a 94:6 mixture of normal and branched isomers. Careful GC analysis (see Experimental Section) showed that the ratio of **2**/**4** was 86:14. After hydrolysis of the product mixture and reaction with decyllithium,[7] the *E* isomer **7** can be obtained by recrystallization. The conversion of the acid mixture to **5** could not be carried out satisfactorily via the straightforward bromination–dehydrobromination[8]–hydrogenation[9] reaction sequence. The overall yields were low, and the presence of **8**,



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in the product mixture, from the reaction with decyllithium indicated the interference of the carboxylate group somewhere in the bromination–dehydrobromination sequence.

Inversion of the **2**/**4** ratio could, however, be carried out very smoothly by conversion of the ester mixture to the corresponding vicinal bromochloride[10] and subsequent elimination[11] to form the inverted olefin. GC analysis showed that the inversion is not 100% stereospecific in this case since the ratio **2**/**4** of the inverted mixture was 20:80. Hydrolysis and reaction