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New Reagent Systems Containing CrO_3 Provide Precursors for Syntheses of Neo-lignans[1)]

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Oxidations of 1-aryl-1-propenes with new reagent systems, CrO_3–HBF_4–MeCN and CrO_3–$HClO_4$–MeCN, gave the 4-aryltetralones **1a** and **1c**, and the tetrahydrofuran **4**, which are precursor molecules for aryltetrahydronaphthalene and tetrahydrofuran neo-lignans.

Keywords——reagent system; chromium trioxide; neo-lignan; aryltetrahydronaphthalene; tetrahydrofuran

Chromic oxide has been widely used as a reagent in oxidations of organic compounds, and several kinds of reagent systems[2)] and reagents, namely, Collin's reagent, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC),[3)] and 2,2′-bipyridinium chlorochromate,[4)] have been developed recently. Although several solvents such as water, acetone, acetic acid, acetic anhydride, pyridine, and dimethylformamide are used in different reagent systems using CrO_3, little attention has been paid to solvent effects. However, interest is currently focussed on the solvent effects in reactions of metals and metal ions with a view to activating organic substrates[5)] and forming complexes with donor solvents leading to changes in redox potentials.[6)]

We are interested in the behavior of CrO_3 in the various solvents from the viewpoint of reduction potentials, and we have found large variations. The measured electrode potentials of CrO_3 in some donor solvents are shown in Table I, from which it can be seen that (i) the electrode potentials depend not only on the basicities of the solvents,[6)] but also on other factors such as the oxidation potentials of the solvents,[7)] (ii) MeCN is a useful solvent, giving high reduction potential, and is stable to oxidation.

The electrode potentials of CrO_3 in MeCN or acetone in the presence of aqueous acids, HBF_4, $HClO_4$, or H_2SO_4, in connection with Jones' reagent were also measured, and are shown in Table II. Although a large difference was not observed in the electrode potentials of CrO_3 in MeCN or acetone in acidic media, the reaction behavior of CrO_3 in the above systems was investigated particularly in the oxidations of 1-aryl-1-propenes as possible alternative systems to Jones' reagent. CrO_3 in MeCN in the presence of aqueous HBF_4 or $HClO_4$ gave better results than other reagents, including Jones' reagent.

Oxidation of (*E*)-1-(3,4-dimethoxyphenyl)-1-propene with the reagent system CrO_3 (100 mg) in MeCN (8 ml) with 42% aqueous HBF_4 (2 ml) gave (after 30 s) the tetralone **1a**, mp 124—126 °C, in 16% yield as the only identifiable product. Reduction of **1a** with $NaBH_4$ in CF_3CO_2H[8)] gave **1b**, mp 115—117 °C; this product was identical to (±) galbulin.[9)] The structure of **1a** was assigned by considering the latter result, and from its nuclear magnetic resonance (NMR) data, which showed a coupling constant of 10 Hz between C(3)–H and C(2)–H. Catalytic reduction of **1a** on 10% Pd-C, though, afforded a novel tetralin **2**, mp 102—103 °C, in 90% yield as a sole product, NMR ($CDCl_3$) δ: 0.74 [3H, d, J=5.9 Hz, C(3)–

TABLE I. Electrode Potentials of CrO_3 in Some Donor Solvents

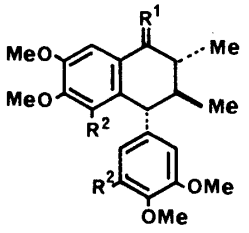
Solvent	Electrode potential (mV)[a]	Solvent	Electrode potential (mV)[a]
Acetonitrile	1632	Propanediol-1,2-carbonate	1010
Acetic acid	1533[b]	Water	875
Nitromethane	1470	Dimethylformamide	845
Sulfolane	1467	Dimethylsulfoxide	541
Acetic anhydride	1361	Pyridine	541
Acetone	1095	Hexamethylphosphoric amide	406
Trimethylphosphate	1052		

a) Electrode potentials (mV *vs.* SCE, using a Pt electrode) were measured with a pH meter (Toa HM20E) with solutions of 100 mg of CrO_3 in 10 ml of solvent at 25 °C.
b) Measured in partial suspension of CrO_3.

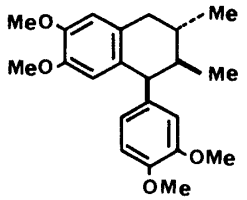
TABLE II. Electrode Potentials of CrO_3 with Acids in Acetonitrile and Acetone

Acid	Electrode potential in MeCN (mV)[a]	Electrode potential in MeCOMe (mV)[a]
HBF_4	1174	1078
$HClO_4$	1160	1048
H_2SO_4	1098	1018

a) Electrode potentials (mV *vs.* SCE, using a Pt electrode) were measured with a pH meter (Toa HM20E) with solutions of 100 mg CrO_3 in 8 ml of solvent and 2 ml of 42% aqueous solution of acid.



1a : $R^1=O$, $R^2=H$
1b : $R^1=H_2$, $R^2=H$
1c : $R^1=O$, $R^2=OMe$
1d : $R^1=H_2$, $R^2=OMe$



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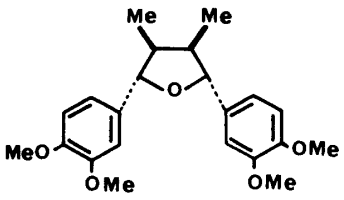

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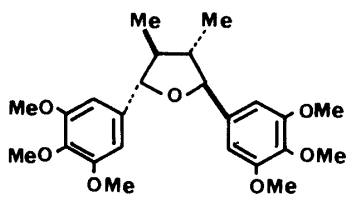

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Chart 1

Me], 1.15 [3H, d, J=6.8 Hz, C(2)–Me], 1.91—2.18 [2H, m, C(2)–H and C(3)–H], 2.45—2.82 [2H, m, C(1)–H], 2.91 [1H, d, J=7.2 Hz, C(4)–H], 3.96 [3H, s, OMe], 3.87 [6H, s, 2×OMe], 3.88 [3H, s, OMe], 6.60—6.74 [4H, m, aromatic H], and 6.78 [1H, s, C(8)–H]. The structure of **2** was deduced from the following NMR data: (i) the C(3)–Me resonance appears at δ 0.74 owing to the shielding effect of the phenyl group, and (ii) there is a coupling constant of 7.2 Hz between C(3)–H and C(4)–H.

The above oxidation at lower temperature or under high dilution gave more complex products including veratraldehyde and **1a**; the latter was obtained in much lower yield than at room temperature. An alternate oxidation in the presence of 42% aqueous $HClO_4$ gave almost the same result, but oxidation in the presence of 42% aqueous H_2SO_4 or Jones' reagent afforded a different product instead of **1a**, that is, *ca.* 50% veratraldehyde together with a small amount of **3**, mp 117—119 °C (identical with *meso*-galgravin[10]).

Oxidation of (*E*)- and (*Z*)-1-(3,4,5-trimethoxyphenyl)-1-propenes with the reagent system CrO_3–HBF_4–MeCN gave the tetralone **1c**, mp 135—137 °C, and the tetrahydrofuran **4**, mp 126—128 °C (identical with (±)-grandisin[11]) in 14.3 and 17.7% yields, respectively. Compound **1c** was reduced to the tetralin **1d**, mp 130—132 °C, with $NaBH_4$ in CF_3CO_2H. Although oxidation of the same arylpropenes with the reagent system CrO_3–$HClO_4$–MeCN afforded similar results, oxidations with other reagent systems, CrO_3 in MeCN with 42% aqueous H_2SO_4 or H_3PO_4 or Jones' reagent, did not gave compounds **1c** and **4**.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, NMR spectra with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ soln.) and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Electrode potentials (mV *vs.* SCE, using a Pt electrode) were measured with a potentiometer (Toa-HM20E). Elemental analyses were done by Ms. M. Takeda and Ms. S. Okamura, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel $60F_{254}$ were used for column chromatography and thin-layer chromatography (TLC), respectively.

Oxidations of (*E*)-1-(3,4-Dimethoxyphenyl)-1-propene——Method A. CrO_3–HBF_4–MeCN at Room Temperature: A solution prepared by adding 88 ml of MeCN to a mixture of CrO_3 (1.1 g, 11 mmol) and 42% aqueous HBF_4 (22 ml) was added in one portion at room temperature to a stirred solution of (*E*)-1-(3,4-dimethoxyphenyl)-1-propene (1.78 g, 10 mmol) in MeCN (50 ml), and the whole was stirred for 30 s. The reaction mixture was poured into ice-water and then extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform elution gave 292 mg (15.8%) of 4α-(3,4-dimethoxyphenyl)-2α,3β-dimethyl-6,7-dimethoxy-1-tetralone **1a** as colorless crystals (ether–hexane), mp 124—126 °C, IR (Nujol): 1680, 1600 cm^{-1}. NMR ($CDCl_3$) δ: 0.98 [3H, d, J=6.1 Hz, C(3)–Me], 1.18 [3H, d, J=6.6 Hz, C(2)–Me], 2.46—2.89 [1H, m, C(3)–H], 3.15—3.31 [1H, m, C(2)–H], 3.90 [6H, s, 2×OMe], 3.94, 3.95 [each 3H, s, 2×OMe], 6.73—6.92 [4H, m, aromatic H], 7.57 [1H, s, C(8)–H]. *Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. MS *m/e*: 370.1781. Found: C, 71.03; H, 7.10. MS *m/e*: 370.1793.

Method B. CrO_3–$HClO_4$–MeCN at Room Temperature: A solution prepared by adding 8.8 ml of MeCN to a mixture of CrO_3 (110 mg, 1.1 mmol) and 42% aqueous $HClO_4$ (2.2 ml) was added dropwise at room temperature to a stirred solution of (*E*)-1-(3,4-dimethoxyphenyl)-1-propene (175 mg, 1 mmol) in MeCN (5 ml), and the whole was stirred for 1 min. The reaction mixture was worked up as in method A to yield the tetralone **1a** in almost the same yield as method A, together with a trace of starting material.

Method C. CrO_3–H_2SO_4–MeCN at Room Temperature: A solution prepared by adding 8.8 ml of MeCN to a mixture of CrO_3 (110 mg, 1.1 mmol) and 42% aqueous H_2SO_4 (2.2 ml) was added dropwise at room temperature to a stirred solution of the 1-aryl-1-propene (175 mg, 1 mmol) in 5 ml of MeCN and the whole was stirred at room temperature for 1 min. The reaction mixture was worked up and subjected to silica gel chromatography as described in method A to yield mainly veratraldehyde as well as starting material, and trace amounts of the tetrahydrofuran **3**, (*meso*-galgravin, *r*-2, *c*-5-bis(3,4-dimethoxyphenyl)-*t*-3,*t*-4-dimethyltetrahydrofuran), as colorless crystals (ether–hexane), mp 117—119 °C. IR (Nujol): 1595 cm^{-1}. NMR ($CDCl_3$) δ: 1.04 [6H, d, J=6.6 Hz, C(3)–Me and C(4)–Me], 2.20—2.46 [2H, m, C(3)–H, C(4)–H], 3.88 [12H, s, 4×OMe], 4.52 [2H, d, J=6 Hz, C(2)–H, C(5)–H], 6.80—7.00 [6H, m, aromatic H]. *Anal.* Calcd for $C_{22}H_{28}O_5$. MS: *m/e* 372.1937. Found: 372.1948.

Method D. Jones' Reagent: A solution of the 1-aryl-1-propene (356 mg, 2 mmol) in acetone (15 ml) was treated with 1.8 ml of Jones' reagent (prepared by adding 6 ml of H_2O to a mixture of CrO_3 2.67 g and conc. H_2SO_4 2.3 ml),

and the whole was stirred at room temperature for 5 min. The reaction mixture was worked up and subjected to silica gel chromatography. From the chloroform elute, 165 mg (49.5%) of veratraldehyde, a trace of the tetrahydrofuran **3**, and starting material were obtained.

Reduction of 1a with $NaBH_4$ in CF_3CO_2H——A solution of **1a** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (3 ml) was treated with CF_3CO_2H (0.58 ml) and the whole was stirred under N_2 at 50—55 °C for 2 h. $NaBH_4$ (32 mg, 0.84 mmol) was added to the reaction mixture at 0 °C and the whole was stirred under N_2 at room temperature overnight. The reaction mixture was poured into ice-water and then extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was recrytallized from benzene to yield 43 mg (90%) of (±)-galbulin **1b**, 1α-(3,4-dimethoxyphenyl)-2β,3α-dimethyl-6,7-dimethoxytetralin, as colorless crystals, mp 115—117 °C. IR (Nujol): 1598 cm^{-1}. NMR ($CDCl_3$) δ: 0.87 [3H, d, J=5.5 Hz, C(3)-Me], 1.05 [3H, d, J=5.5 Hz, C(2)-Me], 1.40—1.80 [2H, m, C(2)-H, C(3)-H], 2.55—2.85 [2H, m, C(1)-CH_2], 3.43 [1H, d, J=9.28 Hz, C(4)-H], 3.55, 3.79, 3.81, 3.88 [each 3H, s, 4×OMe], 6.20 [1H, s, aromatic H], 6.60—6.79 [4H, m, aromatic H]. *Anal.* Calcd for $C_{22}H_{28}O_4$. MS *m/e*: 356.1989. Found: 356.1991.

Catalytic Reduction of 1a——Catalytic reduction of **1a** (100 mg) in 5 ml of AcOH in the presence of 10% Pd-C gave 43 mg (90%) of **2** (benzene), 1β-(3,4-dimethoxyphenyl)-2β,3α-dimethyl-6,7-dimethoxytetralin, mp 102—103 °C. IR (Nujol): 1598 cm^{-1}. *Anal.* Calcd for $C_{22}H_{28}O_4$. MS *m/e*: 356.1989. Found: 356.1991.

Oxidation of (*E*)- and (*Z*)-1-(3,4,5-Trimethoxyphenyl)-1-propene——Method A. CrO_3–HBF_4–MeCN at Room Temperature: A solution prepared by adding 880 ml of MeCN to a mixture of CrO_3 (11 g, 0.11 mol) and 42% aqueous HBF_4 (220 ml), was added dropwise at room temperature to a stirred solution of (*E*)- or (*Z*)-(3,4,5-trimethoxyphenyl)-1-propene (20.8 g, 0.1 mol) in MeCN (500 ml), and the whole was stirred at room temperature for 30 s. The reaction mixture was worked up and the product was subjected to silica gel chromatography. The first chloroform elution gave 3.07 g (14.3%) of 4α-(3,4,5-trimethoxyphenyl)-2α,3β-dimethyl-5,6,7-trimethoxy-1-tetralone **1c** as colorless crystals (ether–hexane), mp 124—126 °C. IR (Nujol): 1690, 1598 cm^{-1}. NMR ($CDCl_3$) δ: 1.10 [3H, d, J=6.35 Hz, C(3)-Me], 1.16 [3H, d, J=6.59 Hz, C(2)-Me], 1.83—1.98 [1H, m, C(3)-H], 2.32—2.45 [1H, m, C(2)-H], 3.14 [3H, s, C(5)-OMe], 3.77, 3.81, 3.82 [each 3H, s, 3×OMe], 3.92 [6H, s, 2×OMe], 6.29 [2H, s, C(2′)-H, C(6′)-H], 7.33 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. MS *m/e*: 430.1991. Found: C, 67.19; H, 7.17; MS *m/e*: 430.2019. The second chloroform elution gave 3.82 g (17.7%) of (±)-grandisin, (*t*-3,*c*-4-dimethyl-*r*-2,*t*-5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran), **4** as colorless crystals (ether–hexane), mp 126—128 °C. IR (Nujol): 1595 cm^{-1}. NMR ($CDCl_3$) δ: 1.10 [6H, d, J=6 Hz, C(3)-Me, C(4)-Me], 1.75—1.85 [2H, m, C(3)-H, C(4)-H], 3.85 [6H, s, 2×OMe], 3.92 [12H, s, 4×OMe], 4.65 [2H, d, J=9.2 Hz, C(2)-H, C(5)-H], 6.65 [4H, s, aromatic H]. *Anal.* Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46. MS *m/e*: 432.2131. Found: C, 66.34; H, 7.55. MS *m/e*: 432.2146.

Method B. CrO_3–$HClO_4$–MeCN at Room Temperature: A solution prepared by adding 8.8 ml of MeCN to a mixture of CrO_3 (110 mg, 1.1 mmol) and 42% aqueous $HClO_4$ (2.2 ml) was added at room temperature to a stirred solution of the 1-aryl-1-propene (208 mg, 1 mmol) in MeCN (5 ml), and the whole was stirred at room temperature for 30 s. The reaction mixture was worked up and subjected to silica gel chromatography to yield the tetralone **1c** and the tetrahydrofuran **4** in almost the same yields as method A.

Reduction of 1c by $NaBH_4$ in CF_3CO_2H——CF_3CO_2H 2.58 ml was added under N_2 to a solution of **1c** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (3 ml), and stirred at 50—55 °C for 2 h. To this mixture, $NaBH_4$ 26.3 mg (0.696 mmol) was added at 0 °C, and the whole was stirred under N_2 at room temperature overnight. The reaction mixture was worked up and the resultant residue was recrystallized from benzene to yield 46 mg (95%) of 5,6,7-trimethoxy-2β,3α-dimethyl-1α-(3,4,5-trimethoxyphenyl)tetralin **1d** as colorless crystals, mp 130—132 °C. IR (Nujol): 1590 cm^{-1}. NMR ($CDCl_3$) δ: 1.08 [6H, d, J=5.13 Hz, C(2)-Me, C(3)-Me], 1.25—1.65 [2H, m, C(2)-H, C(3)-H], 2.62 [2H, d, J=6.84 Hz, C(1)-CH_2], 3.10 [3H, s, C(5)-OMe], 3.56 [1H, d, J=8.4 Hz, C(4)-H], 3.73 [3H, s, OMe], 6.33 [2H, s, C(2′)-H, C(6′)-H], 6.42 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{24}H_{32}O_6$. MS *m/e*: 416.2199. Found: 416.2202.

References and Notes

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