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[a013]

Oxidative degradation of a steroidal isoxazoline: 1-formyl-7-methoxy-2-methylphenanthrene from 3'-methoxyestra-1',3',5'(10')-trieno(16',17':4,5)isoxazoline.

Masao Imai,[a] Masataka Watanabe,[a] Christian Burmester,[b] Shuntaro Mataka,[b] Thies Thiemann[a]*[c]

[a]Interdisciplinary Graduate School of Engineering Sciences and [b]Institute of Materials Chemistry and Engineering, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi 816-8580, Fukuoka-ken, Japan. E-mail: thies@cm.kyushu-u.ac.jp

[c]new address: Department of Chemistry, Faculty of Sciences, United Arab Emirates University, PO Box 17551, Al Ain, United Arab Emirates. E-mail: thies@uaeu.ac.ae

Abstract: Estra-1,3,5(10),16-tetraene was converted to an estra-1',3',5'(10')-trieno(16',17':4,5)isoxazoline. The isoxazoline was transformed to a substituted 1-formylphenanthrene by the action of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Keywords: Estrane, steroid, isoxazole, dehydrogenation, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)

1. Introduction

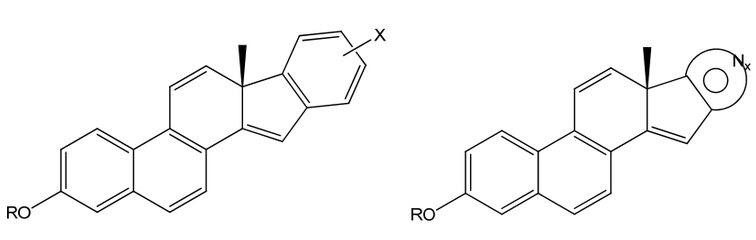
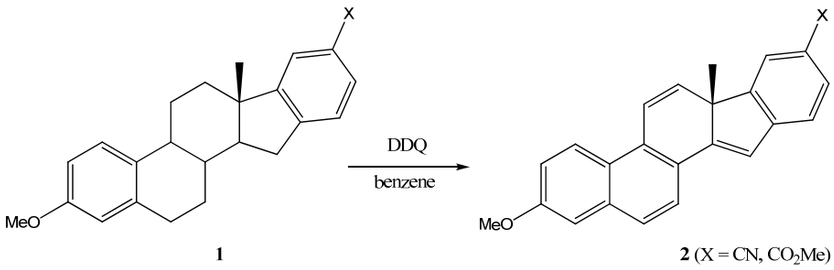


Figure 1.

In our search for steroid derived, chiral, polycondensed π-systems such as **A** and **B** (Figure 1), we have carried out syntheses of 16,17-arenoestrane derivatives and have studied their dehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (DDQ).[1] Many of these arenoestranes

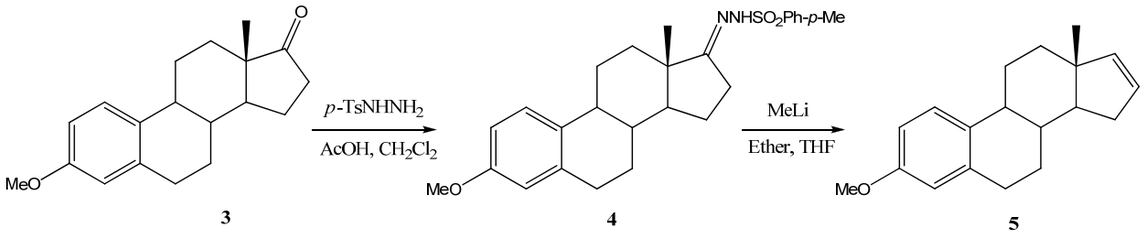
could be dehydrogenated with relative ease (Scheme 1). Next, we turned our attention to the dehydrogenation of 16,17-heteroareno annelated estranes.[2] In the following, we communicate our experience with reacting 16,17-isoxazoloestranes with DDQ.



1 **2** (X = CN, CO_2Me)

Scheme 1.

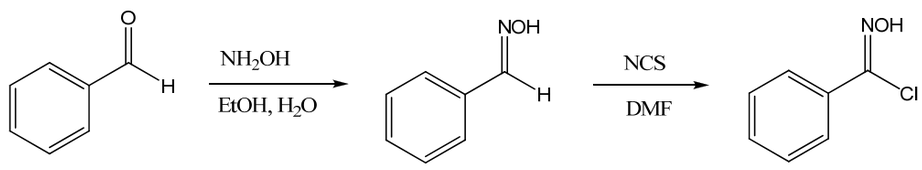
Results and Discussion



3 **4** **5**

Scheme 2.

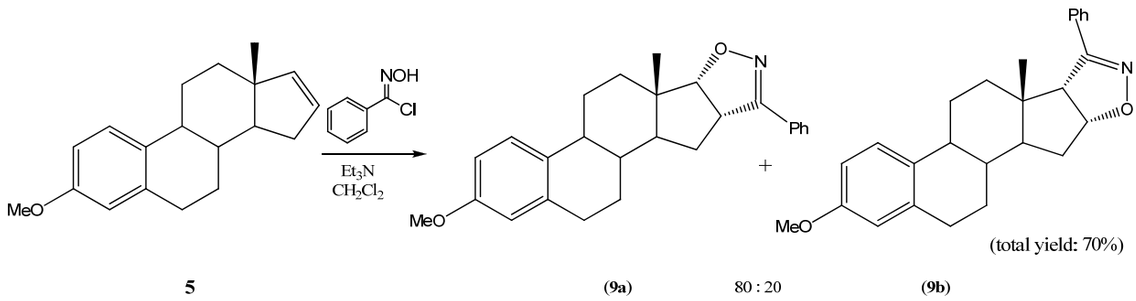
An easy access to 16,17-heteroarenoestranes is obtained through addition reactions of 1,3-dipoles to estra-1,3,5(10),16-tetraene **5**.[3,4] **5** itself can be synthesized easily from estra-1,3,5(10)-trien-17-one **3** via its *p*-toluenesulfonylhydrazone **4** by Shapiro reaction[5] (Scheme 2). A 1,3-dipolar cycloaddition of **4** to phenylnitrile oxide gives estra-1',3',5'(10')-trieno(16',17':4,5)isoxazoline **5a** in a mixture of regioisomers (Scheme 4), which can be separated by column chromatography on silica gel.



6 **7** (95%) **8** (44%)

Scheme 3.

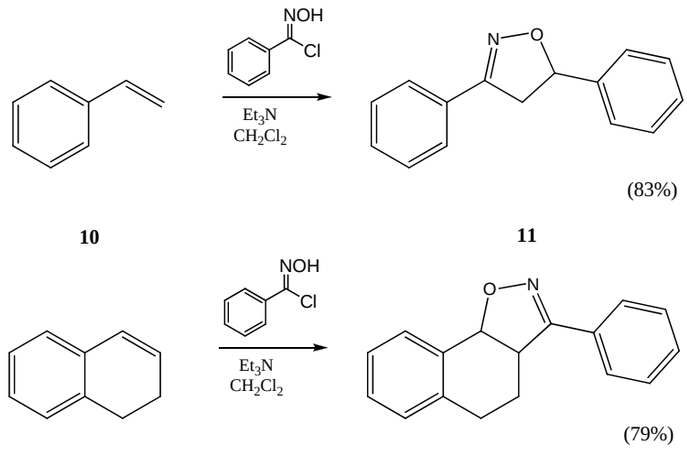
Phenylnitrile oxide itself was prepared *in situ* by dehydrochlorination of the corresponding hydroxamic chloride **8**, which is accessible in two steps from benzaldehyde (**6**) via the oxime **7**. Formerly the reaction to benzhydroxamic chlorides and related compounds was carried out with chlorine[6] or with nitrosyl chloride in ether.[7] Here, the transformation has been carried out with *N*-chlorosuccinimide (NCS) in DMF.[8] The stereochemistry of the two formed isomers of **9** was determined by evaluating the NMR patterns of the H_{C16} and H_{C17}. In the formation of both of the isomers, the nitrile oxide approaches **5** from the α-side, away from the angular methyl group. The stereochemistry of products **9** has been investigated by NOE experiments.



5 **(9a)** 80 : 20 **(9b)**

Scheme 4.

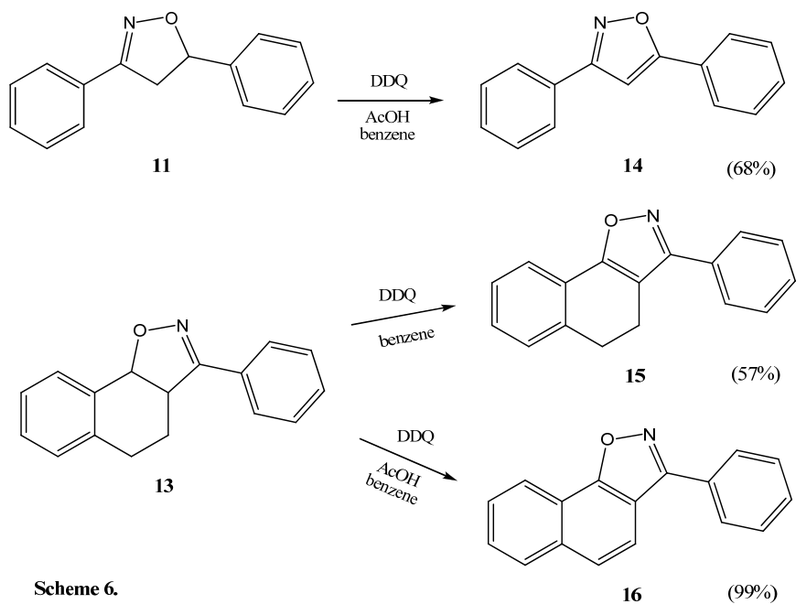
For comparative purposes, 3,5-diphenylisoxazoline (**11**) was synthesized from styrene (**10**) and phenylnitrile oxide (starting from **8**) and 3-phenyltetrahydronaphtho[2,1-*d*]-isoxazoline (**13**) from **12** and **8**. **11** was subjected to the action of DDQ under different conditions. Heating **11** with DDQ in benzene at 60 °C did not give any appreciable product. The same reaction in the presence of a little acetic acid, however, gave the dehydrogenated compound, 3,5-diphenylisoxazole (**14**), in good yield. The reaction of 3-phenyltetrahydronaphtho[2,1-*d*]-isoxazoline (**13**) with DDQ in benzene gave 3-phenyldihydronaphtho[2,1-*d*]-isoxazoline (**15**) in moderate yield. In the presence of acetic acid, 3-phenylnaphtho[2,1-*d*]-isoxazoline (**16**) was produced in almost quantitative yield.



10 **11**

12 **13**

Scheme 5.

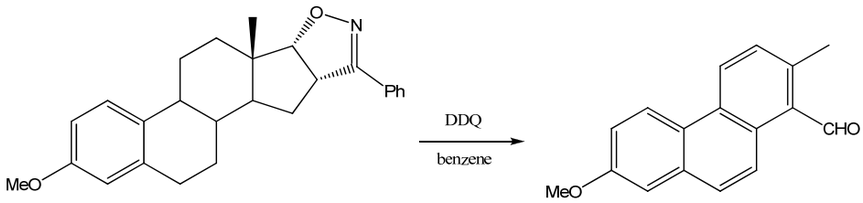


11 **14**

13 **15** **16**

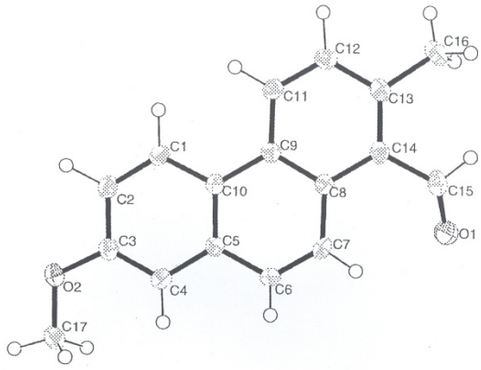
Scheme 6.

A very different result was obtained when submitting **9a** to these conditions, albeit in absence of acetic acid. While the main isolable substance **17** showed the expected absorptions in the aromatic region of the ^{1}H NMR spectrum, an absorption for a carbaldehyde function at δ = 11.0 ppm was very much in evidence. Further information on **17**, gained from its ^{13}C NMR and MS spectra, readily indicated its structure to be that of 1-formyl-7-methoxy-2-methylphenanthrene (**17**). A single crystal X-ray structural analysis of **17** showed the structural assignment to be true.



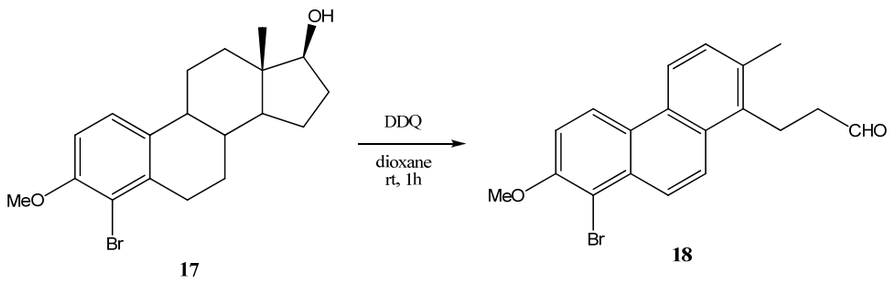
9a **17** (45%)

Scheme 7.



ORTEP drawing of 1-formyl-7-methoxy-2-methylphenanthrene (**17**). Cell constants and the orientation matrix for data collection correspond to a C-centered monoclinic cell with dimensions: a = 43.13(2) A; b = 6.074(3) A; c = 9.756(4) A; V = 2483.8(2) A^3; γ = 95.76(3); V = 2483.8(2) A^3. For Z=6 and FW = 268.35, the calculated density is 1.08 g/cm^3. Based on the systematic absences of: hkl: h+k+/-2n and h0l: l +/-2n, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: C2/c(#15).

The oxidative degradation of the D ring in an estrane by the action of DDQ in itself is not unusual. Thus, a different study from our laboratory also shows estradiol derivatives such as **17** to undergo this type of degradation (Scheme 8, see also ref. 10). Nevertheless, a *structured approach* to utilize steroids as starting materials for non-steroidal and non-triterpenoidal target molecules through degradation or fragmentation reactions has not yet been forwarded. It is evident that steroids in general and estrane derivatives in particular are high-value starting materials. Clearly, they are also much less abundant in nature than many carbohydrates, for which C-C cleavage reactions[11] to target molecules other than carbohydrates are well-established. Nevertheless, for target compounds such as aromates with certain substitution patterns the possibility of transforming steroids through degradation or fragmentation reactions should be reexamined.



17 **18**

Scheme 8.

2. Experimental Section

3-Methoxyestra-1',3',5'(10')-trieno(16',17')3-phenylisoxazolines **9**. - Benzohydroxyiminoyl chloride (**8**, 390 mg, 2.5 mmol) was dried *in vacuo* and dissolved in dry dichloromethane (30 mL). The solution was cooled to 0 °C and to it was added triethylamine (0.37 mL, 2.75 mmol). After 5 min., 3-methoxyestra-1,3,5,(10),16-tetraene (**5**, 540 mg, 2.0 mmol) was added to the mixture, which was stirred subsequently for 5h at rt. The reaction was quenched by addition of water (10 mL). Then, the mixture was extracted with dichloromethane (3 X 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (ether/hexane 2:1) gave 3-methoxyestra-1',3',5'(10')-trieno(16',17':4,5)3-phenylisoxazoline (**9a**) (433 mg, 56%) as a colorless solid; mp 204 – 205 °C; IR (KBr) ν 2938, 2858, 1610, 1501, 1455, 1358, 1314, 1234, 1034, 911, 765, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.07 (1H, dd, ^3J = 8.2 Hz, ^3J = 8.3 Hz), 4.71 (1H, ^3J = 8.2 Hz), 6.61 (1H, d, ^4J = 2.5 Hz), 6.71 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz), 7.22 (1H, d, ^3J = 8.8 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.57, 28.06, 28.14, 29.76, 31.82, 38.40, 43.29, 47.04, 47.19, 50.24, 55.22, 94.21, 111.52, 113.83, 126.43, 126.97, 128.75, 129.31, 129.74, 132.43, 137.77, 157.52, 159.10. MS (70 eV) *m/z* (%): 387 (M^+, 100). HRMS Found: 387.2203; Calcd. for $C_{26}H_{29}O_2N$: 387.2203, and 3-methoxyestra-1',3',5'(10')-trieno(16',17':5,4)3-phenylisoxazoline (**9b**) (108 mg, 14%) as a colorless solid; ^1H NMR (395 MHz, $CDCl_3$) δ 1.04 (3H, s, CH_3), 1.39 - 1.60 (7H, m), 1.75 (1H, ddd, ^2J = 13.4 Hz, ^3J = 12.6 Hz, ^3J = 4.8 Hz), 1.90 - 1.93 (1H, m), 2.13 - 2.17 (1H, m), 2.22 (1H, dd, ^2J = 13.4 Hz, ^3J = 5.7 Hz), 2.84 - 2.86 (2H, m), 3.75 (3H, s, OCH_3), 3.86 (1H, d, ^3J = 8.9 Hz), 5.29 (1H, dd, ^3J = 8.9 Hz, ^3J = 4.8 Hz), 6.61 (1H, d, ^4J = 2.9 Hz), 6.66 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.9 Hz), 7.06 (1H, d, ^3J = 8.6 Hz), 7.36 - 7.41 (3H, m), 7.64 - 7.67 (2H, m). MS (70 eV) m/z (%): 387 (M^+, 100). HRMS Found: 387.2201; Calcd. for $C_{26}H_{29}O_2N$: 387.2203.

3,5-Diphenylisoxazole (**14**). – A mixture of 3,5-diphenylisoxazoline (**11**, 60 mg, 0.27 mmol), acetic acid (0.2 mL), and dichlorodicyanobenzoquinone (240 mg, 1.06 mmol) in benzene (3 mL) was heated at 60 °C for 5h. Thereafter, the cooled reaction mixture was poured in to water (10 mL) and extracted with ether (3 X 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 4:1) to give **14** a colorless solid (41 mg, 68%), mp. 130 °C; IR (KBr) ν 3313, 3047,

1612, 1592, 1450, 1401, 1321, 1292, 1161, 1091, 1075, 1025, 949, 915, 764, 692 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.76 (1H, s), 7.38 – 7.62 (6H, m), 7.75 – 7.82 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 97.45, 125.82, 126.79, 127.13, 127.44, 128.28, 129.00, 129.11, 130.21, 130.55, 162.96; MS (EI) m/z (%) = 221 (M^+, 30).

1-Formyl-7-methoxy-2-methylphenanthrene (**17**). – A solution of xx (31.6 mg, $8.1 \cdot 10^{-2}$ mmol) and DDQ (130 mg, 0.57 mmol) in benzene (3 mL) was heated at 60 °C for 5h. Thereafter, the cooled reaction mixture was poured into water (15 mL) and extracted with ether (3 X 25 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel to yield **17** (10 mg, 45%) as a pale brown solid, mp. 143 °C; IR (KBr) ν 2960, 2931, 1677, 1608, 1608, 1268, 1206, 1170, 900, 861, 815, 728, 716, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.82 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 7.30 (1H, dd, ^{3}J = 8.9 Hz, ^{4}J = 1.8 Hz), 7.47 (1H, d, ^{4}J = 1.8 Hz), 7.82 – 7.84 (2H, m), 8.54 (1H, d, ^{3}J = 9.2 Hz), 8.70 (1H, d, ^{3}J = 8.7 Hz), 8.82 (1H, d, ^{3}J = 8.7 Hz), 11.0 (1H, s, CHO); MS (EI, 70 eV) *m/z* (%) = 250 (M^+) (27).

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