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Novel *Friedel-Crafts* Alkylation of Estrogens in the Presence of Anhydrous $FeCl_3$ or $FeCl_3$–Graphite as Catalyst

György Göndös[1,*] and **György Dombi**[2]

[1] Department of Organic Chemistry, University of Szeged, H-6720 Szeged, Hungary
[2] Department of Pharmaceutical Analysis, University of Szeged, H-6720 Szeged, Hungary

Summary. The introduction of a *tert*-butyl group at position 2 of the A ring of estrogens leads to enhanced antioxidant effects. Therefore, a generally applicable and convenient method was developed using $FeCl_3$–graphite or anhydrous $FeCl_3$ as catalysts in the *Friedel-Crafts* alkylation of estrogens. The rates and yields of the alkylations were lower with $FeCl_3$–graphite than with anhydrous $FeCl_3$, but the regioselectivity of the former were higher. Both catalysts proved to be more effective than typical $AlCl_3$.

Keywords. Estrogen; Antioxidant; *Friedel-Crafts* alkylation; $FeCl_3$–graphite; intercalation compound.

Introduction

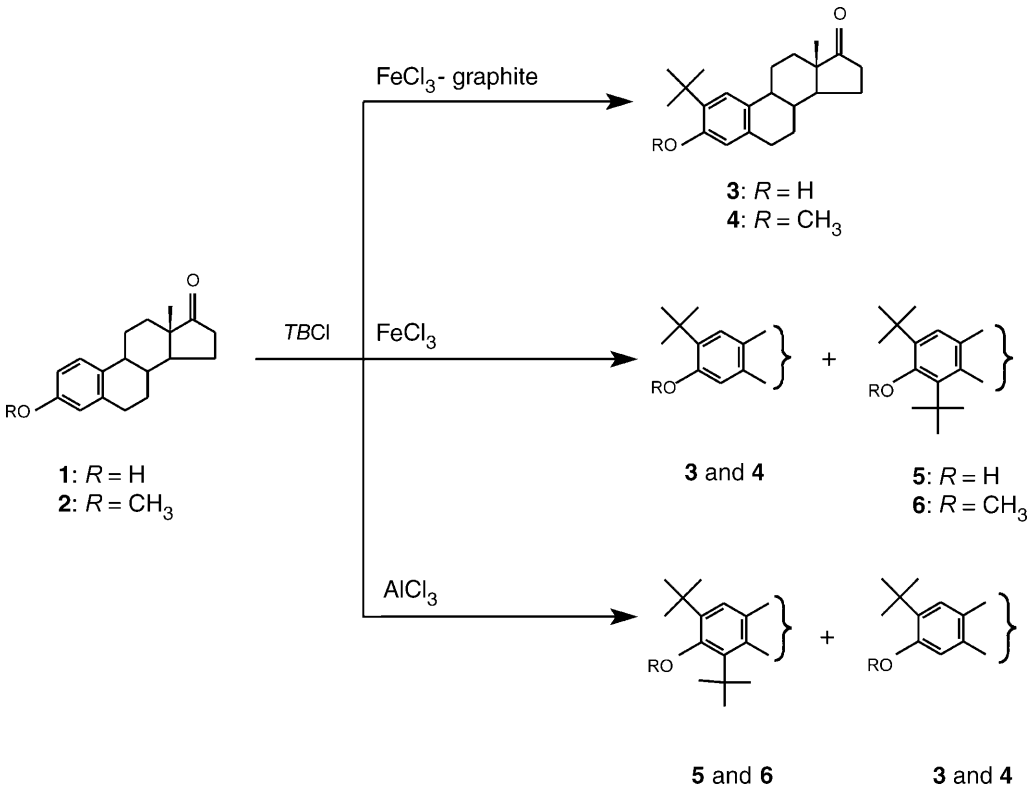
The *Friedel-Crafts* reaction is one of the most widely studied organic transformations [1]. The typical catalyst is aluminum trichloride. Previous research [2] has described the synthesis of alkyl estrogens using boron trifluoride or BF_3–etherate as a *Lewis* acid for this purpose. This variant, however, turned out to be not sufficiently convenient and yielded only 62%.

Recently it has been reported that alkylated estrogens [3], especially those with a bulky substituent at position 2 or 4 of the aromatic ring, display high antioxidant and free radical scavenger abilities. We therefore set out to find a selective and convenient catalyst and procedure for the *Friedel-Crafts* alkylation of estrogens. Our previously published [4] procedure for the alkylation of benzene with *tert*-butyl chloride (*TB*Cl) with $FeCl_3$–graphite as catalyst proceeds with high selectivity for monosubstitution. Thus, a similar procedure was applied here for the synthesis of 2-*tert*-butylestrogens.

Results and Discussion

The *Friedel-Crafts* alkylation of estrone (**1**) and estrone-3-methyl ether (**2**) with *TB*Cl in the presence of a stoichiometric amount of anhydrous $FeCl_3$ or $FeCl_3$–graphite

* Corresponding author. E-mail: gondos@chem.u-szeged.hu



Scheme 1. *Friedel-Crafts* alkylation of estrogens

proved to be successful. The reactions were carried out in *THF* or without solvent using a large excess of *TB*Cl. The experimental section provides details for the latter procedure (Methods A, B, and C), because the yield was higher than in the former method. The results obtained with $FeCl_3$–graphite (Method B) during a reaction time of 72 h indicated that both estrogens afforded exclusively 2-*tert*-butyl-estra-1,3,5(10)-trien-17-one (**3**) in 52% yield or 2-*tert*-butyl-3-methoxyestra-1,3,5(10)-trien-17-one (**4**) in 62% yield (Scheme 1). Unfortunately, appreciable amounts of the starting materials remained unchanged. Efforts to promote the conversion by the addition of fresh catalyst as well as by increasing the reaction time or the reaction temperature were unsuccessful.

With anhydrous $FeCl_3$ as the catalyst and standard reaction conditions, there was a marked acceleration of the rate of alkylation, and with this catalyst the conversions were quantitative. The regioselectivities observed in these reactions, however, were slightly decreased. Thus, **3** (81.2%) and **4** (85.3%) were accompanied by 2,4-di-*tert*-butylestra-1,3,5(10)-trien-17-one (**5**; 9.1%) or 2,4-di-*tert*-butyl-3-methoxyestra-1,3,5(10)-trien-17-one (**6**; 10%) (Scheme 1).

The higher yields of **3** and **4** using anhydrous $FeCl_3$ instead of $FeCl_3$–graphite led us to choose the former as the better catalyst, despite the fact that anhydrous $FeCl_3$ resulted in the formation of minor amounts of the disubstituted products **5** and **6**. After removal of the catalyst from the crude oily products on a neutral alumina column, **3** and **4** were crystallized as pure products in excellent yields.

Although exclusively 2-substituted products (**3** and **4**) were formed in the presence of $FeCl_3$–graphite, the chromatographic separation of the products from the starting materials proceeded very slowly and involved considerable product losses. However, the advantage of the latter catalyst is that $FeCl_3$–graphite can be filtered off from the reaction mixture and that, after a simple washing procedure, the same catalyst can be reused. The activity of the catalyst dropped by only 10–15% after the first use. In general, *Friedel-Crafts* catalysts cannot be reused; this appears to be the first example of a reusable catalyst for a *Friedel-Crafts* reaction.

In addition, we compared the reactivity of the traditional *Friedel-Crafts* catalyst, *i.e.* $AlCl_3$, with that of anhydrous $FeCl_3$ and $FeCl_3$–graphite in the alkylation of estrogens **1** and **2**. The amounts of catalyst and substrates employed were stoichiometric. The results indicated that $AlCl_3$ is less active than anhydrous $FeCl_3$ or $FeCl_3$–graphite in a given estrogen alkylation.

In the presence of $AlCl_3$ (Method C), a mixture of mono- and di-*tert*-butyl compounds was formed in very low yields (**3** and **5**: 18%; **4** and **6**: 20%). The pure compounds were not isolated from the reaction products. The ratios of 2-substituted and 2,4-disubstituted products in the crude reaction mixtures were determined by GC-MS and ^{1}H NMR spectroscopy. For both starting materials, the major products were 2,4-di-*tert*-butylestra-1,3,5(10)-trien-17-one (**5**; 60%) and 2,4-di-*tert*-butyl-3-methoxyestra-1,3,5(10)-trien-17-one (**6**; 84%); the minor products were **3** (40%) and **4** (16%). In different solvents, *e.g. THF* or CS_2, the yields in the *Friedel-Crafts* reactions with $AlCl_3$ as catalyst were very similar to those with *TB*Cl as both solvent and reagent.

Experimental

All melting points were determined on a Kofler hot-stage melting point instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX 400 Avance 400 spectrometer at ambient temperature; the internal reference was *TMS*. Elemental analyses were performed with a Kovo (Czech Republic) CHN automatic analyzer and found to be in good agreement with the calculated values. GC-MS analyses were carried out on a Hewlett-Packard model 5890 gas chromatograph equipped with a quadrupole mass-selective detector and a 12 m × 0.25 HP-1 cross-linked Me–silicone rubber capillary column using He as carrier gas; the initial solvent delay was 5 min at 5°C, the ramp rate 8°C · min^{-1} to 250°C, the electron impact ionization energy 70 eV. TLC was performed with glass plates precoated with silica gel (Kieselgel 60 F_{254}; Merck, Darmstadt); spots were visualized by short-wavelength UV light or spraying with EtOH:H_2SO_4 = 1:1 and heating the plates to 100°C. Column chromatography was carried out with 230–400 mesh silica gel (Merck Grade 60, Aldrich Chemical Company). *TB*Cl was purchased from Aldrich, anhydrous $FeCl_3$ from Janssen Co., Graphimet $FeCl_3$-15 from Alfa Products Research Chemicals and Materials, and estrone and estrone-3-methyl ether from Steraloids; all chemicals were used as received.

2-tert-Butylestra-1,3,5(10)-trien-17-one (**3**) [3]

Method A. 0.97 g Anhydrous $FeCl_3$ (6 mmol) were added to a stirred suspension of 1.63 g **1** (6 mmol) in 55.5 g *TB*Cl (600 mmol). The reaction mixture was stirred for 24 h at room temperature and monitored by TLC. After the reaction appeared to be complete, ice-water was added to the stirred reaction mixture, and the steroid was extracted with diethyl ether (3 × 30 cm^3). The combined organic layers were washed with aqueous $NaHCO_3$ (20 cm^3) and brine. The Et_2O solution was dried over Na_2SO_4. Removal of the solvent

gave a dark-green oil, which was passed through a small column (neutral Al_2O_3; toluene:$Et_2O = 2:1$) and then recrystallized from EtOH to give 1.6 g **3** (81%) as yellow crystals.

M.p.: 242–244°C (Ref. [3]: m.p.: 244–245°C); the analytically pure material melted at 245–247°C; TLC (toluene:$Et_2O = 1:1$): $R_f = 0.76$; ^{1}H NMR ($CDCl_3$): $\delta = 7.19$ (s, 1H), 6.43 (s, 1H), 4.65 (s, 1H), 1.40 (s, 9H), 0.91 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 221.20$, 152.10, 135.11, 124.10, 116.60, 50.40, 48.00, 44.21, 38.51, 35.90, 34.52, 31.62, 29.70, 28.70, 26.52, 26.00, 21.61, 13.80 ppm.

The mother liquor of compound **3** was concentrated *in vacuo* to 1.5 cm^3, and the residue was purified by preparative TLC on neutral silica gel G. The plate (0.5 mm × 20 cm × 20 cm) was developed with toluene:$Et_2O = 1:1$ to give two bands detectable by UV light. The silica gel corresponding to each band was removed from the plate, and the compound was recovered by elution with Et_2O or EtOAc. The main zone gave 0.18 g 2,4-di-tert-butylestra-1,3,5(10)-trien-17-one (**5**, $C_{26}H_{38}O_2$; 9.1%) as an oil which solidified on standing to a waxy solid. Recrystallization from EtOH gave colorless needles of m.p. 162–165°C.

The analytical sample was recrystallized from *n*-hexane:EtOAc = 95:5. M.p.: 168–170°C; TLC (toluene:$Et_2O = 1:1$): $R_f = 0.86$; ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (s, 18-CH_3), 1.41 (s, *tert*-Bu), 6.68 (s, 1-H) ppm; GC-MS: $t_R = 40.15$ ($m/z = 381$).

Method B. A 10 cm^3 two-neck round-bottomed flask was charged with 95 mg estrone (0.35 mmol) and 3.24 g *TB*Cl (35 mmol). The suspension was stirred at ambient temperature under N_2 for 2 h; then, 0.37 g $FeCl_3$–graphite (15%) (0.35 mmol) were added over 40 min. The mixture was stirred gently while HCl gas was passed over the surface of the mixture for 72 h (monitored by TLC). Subsequently, the catalyst was filtered off and washed with 3 × 5 cm^3 *TB*Cl, and the solvent was removed to give a sticky yellowish solid which was purified by chromatography (silica gel, EtOAc:hexane = 8:2) to afford 60 mg **3** (52%) as white crystals of m.p. 246–247°C. Its spectroscopic and analytical data were identical with those of **3**.

Method C. Anhydrous $AlCl_3$ (0.13 g, 1 mmol) was added in small portions over 45 min to a stirred suspension of 0.27 g estrone (1 mmol) in 9.26 g dry *TB*Cl (100 mmol) at 0°C. The reaction mixture was stirred for further 2 h at 0°C and then for 72 h at room temperature. Subsequently, the mixture was poured onto stirred crushed ice and extracted with 3 × 20 cm^3 Et_2O. The combined organic layers were washed with 15 cm^3 aqueous $NaHCO_3$ and 20 cm^3 brine and dried over Na_2SO_4. The solvent was removed to yield a dark-yellow oil. The crude product was analyzed by ^{1}H NMR spectroscopy and GC-MS; ratio of products: unchanged estrone **1**: 88%, **5**: 7%, **3**: 5%. Approximately the same ratios were obtained when anhydrous *THF* or CS_2 were used as solvent.

2-tert-Butyl-3-methoxyestra-1,3,5(10)-trien-17-one (**4**; $C_{23}H_{32}O_2$)

Method A. Anhydrous $FeCl_3$ (0.97 g, 6 mmol) was added in small portions to a stirred suspension of 1.7 g **2** (6 mmol) in 55.5 g *TB*Cl (600 mmol) over 1 h at room temperature. The reaction mixture was then stirred at room temperature for 60 h, diluted with ice-water, and extracted with 3 × 25 cm^3 Et_2O. The organic layer was dried over $MgSO_4$, and the solvent was removed to give a yellow oil which was purified by chromatography (silica gel, 3% EtOAc in hexane) to yield 1.7 g **4** (85%) as pale-yellow crystals of m.p. 185–187°C (EtOH). The analytical sample was obtained as white crystals by recrystallization from EtOH.

M.p.: 190–191°C; TLC (toluene:$Et_2O = 1:1$): $R_f = 0.83$; ^{1}H NMR ($CDCl_3$): $\delta = 7.23$ (s, 1H), 6.63 (s, 1H), 3.83 (s, 3H), 2.90 (m, 2H), 1.38 (s, 9H), 0.93 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 221.00$, 156.60, 135.71, 134.92, 130.80, 123.74, 111.90, 55.00, 50.40, 48.12, 44.30, 38.51, 35.90, 34.71, 31.60, 29.84, 29.31, 26.60, 25.92, 21.60, 13.90 ppm.

The mother liquor of compound **4** was concentrated *in vacuo* to 0.8 cm^3, and the residue was purified by preparative TLC on neutral silica gel G. The plate (0.5 mm × 20 cm × 20 cm) was developed with toluene:$Et_2O = 1:1$ to give two bands detectable by UV light. The silica gel corresponding to

each band was removed from the plate and eluted with EtOAc. The upper zone gave 0.2 g **6** (10%) as a pale-yellow oil.

The 2,4-di-*tert*-butyl-3-methoxyestra-1,3,5,10-triene-17-one (**6**; $C_{27}H_{40}O_2$) did not crystallize. TLC (toluene:$Et_2O = 1{:}1$): $R_f = 0.96$; ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (s, 18-CH_3), 3.79 (s, 3-OCH_3), 6.70 (s, 1-H); GC-MS: $t_R = 37.50$ ($m/z = 395$).

Method B. 0.37 g $FeCl_3$–graphite (15%) (0.35 mmol) was added in small portions to a stirred suspension of 0.1 g **2** (0.35 mmol) in 3.24 g *TB*Cl (35 mmol) at room temperature. The mixture was stirred at ambient temperature under N_2 for 72 h, filtered, and the catalyst was washed with $3 \times 5\,cm^3$ *TB*Cl. The solvent was concentrated *in vacuo* to give a light-brown oil which was purified by column chromatography (silica gel, 230–400 mesh, 3% EtOAc in *n*-hexane) to give 74 mg **3** (62%) as white crystals of m.p. 187–190°C. The analytical and spectroscopic data were identical to those given above.

Method C. 0.13 g anhydrous $AlCl_3$ (1 mmol) was added in small portions over 45 min to a stirred suspension of 0.284 g **2** (1 mmol) in 9.26 g dry *TB*Cl (100 mmol) at 0°C. The reaction mixture was stirred for another 2 h at 0°C and then for 72 h at room temperature. Subsequently, the mixture was poured under stirring into crushed ice and extracted with $3 \times 20\,cm^3$ Et_2O. The combined organic layers were washed with aqueous 15 cm^3 aqueous $NaHCO_3$ and 20 cm^3 brine and dried over Na_2SO_4. Removal of the solvent gave a solid residue which was analyzed by ^{1}H NMR spectroscopy; ratio of products: unchanged **2**: 80%, **6**: 17%), **4**: 3.2%. The yields and product ratios were not changed when anhydrous *THF* or CS_2 were used as solvent.

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