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# A NOVEL ROUTE TO 3-ALKYLATED ESTRA-1,3,5(10)-TRIENES

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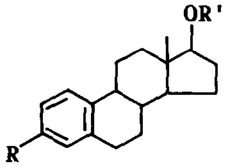
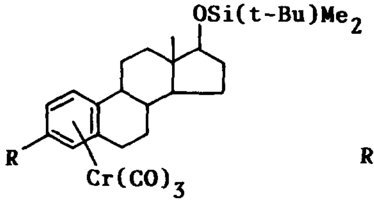
Summary: Nucleophilic attack by the lithium anion of acetonitrile on the diastereomeric chromium tricarbonyl complexes of 17ß-(tert-butyldimethylsilyloxy)-3-methoxyestra-1,3,5(10)-triene leads to the corresponding 3-cyanomethyl complexes, useful intermediates en route to 3-alkylated estra-1,3,5(10)-trienes.

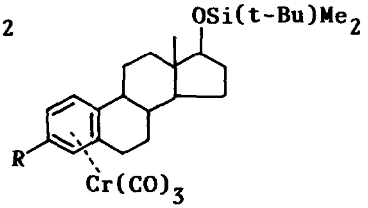
Chromium tricarbonyl complexes of ring A aromatic steroids are emerging as promising intermediates for the partial synthesis of more elaborate derivatives. The well known enhanced acidity of aromatic and benzylic positions in such compounds has been elegantly exploited in regioselective syntheses of catechol estrogens1) and stereospecific alkylations at 6-position2). Virtually unexplored, however, remain additions of carbon nucleophiles to ($\eta^6$-arene)-$Cr(CO)_3$ complexes in the steroid field.
We adumbrate here an essential part of a study on the regiochemical outcome and the synthetic potential of such transformations as exemplified by the reaction of the Li-anion of acetonitrile with the chromium tricarbonyl complexes of 17ß-(tert-butyldimethylsilyloxy)-3-methoxyestra-1,3,5(10)-triene 1.



1 R=OMe, R'=Si(t-Bu)$Me_2$
4 R=OMe, R'=H
5 R=$CH_2CN$, R'=H
6 R=$CH_2CHO$, R'=H
7 R=$CH_3$, R'=H



2 R=OMe
8 R=$CH_2CN$



3 R=OMe
9 R=$CH_2CN$

The transition metal complexes 2 and 3 were obtained as a mixture of diastereomers starting from 3-methoxyestra-1,3,5(10)-triene-17ß-ol 4 (TBDMSCl, DMF, imidazole; $Cr(CO)_6$,α-picoline, argon atmosphere, Δ).
Individual diastereomers are readily isolated by chromatography. For the present study, however, it proved more convenient to carry on the purified mixture. To an excess of the Li-anion of acetonitrile (5 eq.) (LDA, THF, MeCN, -78°C, HMPA) was added a solution of complexes 2 and 3 in THF at -78°C. The cooling bath was removed and the reaction mixture was stirred for 4 hours at ambient temperature. During this period two new complexes were formed as shown by TLC. The reaction was quenched by the addition of aqueous ammonium chloride at 0°C. After decomplexation (THF, $I_2$) and deprotection (THF, aqueous HCl) the crude reaction mixture consisted of two compounds, starting material 4 and a single new product (m.p. 182 -184°C (acetone/hexane), $[\alpha]_D^{22}$= +74.4° ($CHCl_3$, c = 0.5), 46% from 2/3), to which we assign structure 5 on the basis of its spectral properties[3)]. To demonstrate the synthetic potential inherent in this compound and further corroborate our structural assignment the substitution product 5 was correlated via aldehyde 6 with the known 3-methylestra-1,3,5(10)-triene-17ß-ol 7[4)] by a two step sequence (toluene, DIBAH; toluene, $(Ph_3P)_3RhCl$).
The formation of primary ipso substitution products 8 (m.p. 171 - 173°C dec. (ether/pentane), $[\alpha]_D^{22}$= +26.4° ($CHCl_3$, c = 0.5)) and 9 (m.p. 169 -171°C dec. (ether/pentane), $[\alpha]_D^{22}$= +67.8° ($CHCl_3$, c = 0.5)) may involve a fast reversible addition of the anion to C-1[5,6)]. Experiments addressing this question as well as the performance of additional anions will be presented in the full account of this work.

## References and Notes

Dedicated to Prof. R. Wiechert on the occasion of his 60th birthday.

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3. $^1H$ NMR (300MHz, $CDCl_3$) δ 7.30 (1/2 ABq, J= 8.4 Hz, 1H), 7.08 (1/2 ABq, J= 8.4Hz, 1H), 7.06 (s, 1H), 3.74 (t, J= 7.8 Hz, 1H), 3.68 (s, 2H), 2.88-2.85 (m, 2H), 0.78 (s, 3H).
   IR (KBr): 3500, 2950, 2920, 2870, 2840, 2260, 1500, 1410, 1060, 1020 $cm^{-1}$.
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