Communications to the Editor

Regiospecific and Stereospecific Functionalization of Benzylic Sites by Tricarbonylchromium Arene Complexation

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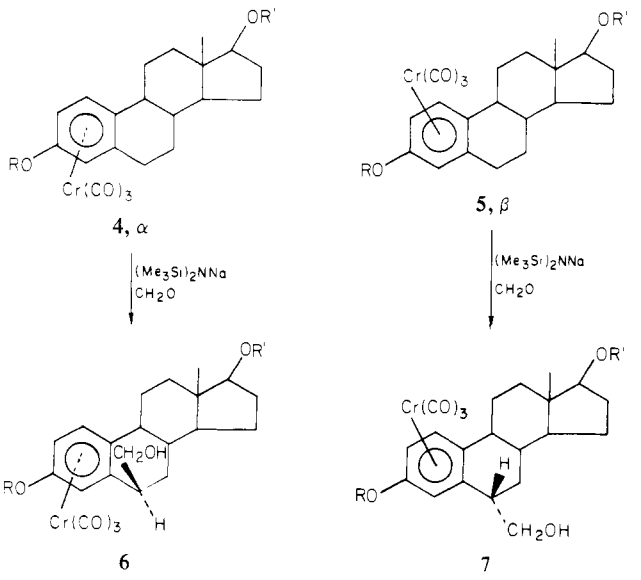
In the rapidly expanding field of transition-metal-promoted reactions,[1-3] we are not aware of any regiospecific and stereospecific functionalization of extra arenic sites in a natural product mediated by an organometallic temporary activation technique. We show here how a very selective α-carbanion generation in substituted (arenetricarbonylchromium) model molecules may be extended to new syntheses in the estrogen series.

With the aim of studying the selectivity of proton abstraction from $Cr(CO)_3$ benzylic sites[4] a homogeneous series of model molecules was prepared in high yields from hexacarbonylchromium and arene ligands using the method of Pauson[5] (Table I). Owing to the interest of functionalization in chemistry, the behavior of stabilized benzylic anions, generated by *t*-BuOK, in the presence of formaldehyde has been particularly analyzed.[6] A selection of results obtained for 2 equiv of HCHO are listed in Table I.

The table shows a striking difference in the behavior of the complexes depending on the position of the substituents. It is clear that the meta alkyl substrates (**1a–c**) were much more reactive than the para alkyl compounds (**1d–f**). While, in the first examples, the yields in isolated products were superior to 63%, the second series appears to be inert (**1e,f**) or very slightly reactive (**1d**, yield 10%). Moreover, on alkyl substituents that are meta to a methoxy group, a double attack may take place leading to the diol (**3b**) or the corresponding ethylene complex (**3a**) as major products.

Interestingly, when the two potential sites of attack (namely the meta and para positions with respect to the methoxy substituent) are present in the same molecule (**1g,h**) only products bearing the hydroxymethyl group on the meta α carbon atom were produced. The last instance is particularly demonstrative of the stereochemical scope of this reaction since the alicyclic complex **2h**, obtained in good yields (95%), results from both a regiospecific and stereospecific addition of the carbonyl compound in exo position.[7]

Scheme I



At this stage of the work, conformational effects of the tripod[8,9] and differences in the kinetic acidity of the para and meta alkyl substituents seem important factors to be taken into account to explain the encountered regioselectivity.[10]

However, the original stereochemical features of the above reaction (specially with **1h**) are sufficiently promising to try to extend its scope to natural products for which subtle and specific modifications are, very often, of interest. Obvious substrates to begin with, for such an examination, may be selected among the estrogen derivatives.

The suitably protected (3-*O*-benzyl-17β-*O*-(*tert*-butyldimethylsilyl)estradiol)tricarbonylchromium α (**4**) and β (**5**) derivatives were prepared as follows. Estradiol was complexed by heating with $Cr(CO)_6$ in dibutyl ether. The mixture of the two $Cr(CO)_3$ estradiol α and β diastereomers was rapidly treated with NaH and $C_6H_5CH_2Br$.[11] The two (3-*O*-benzylestradiol)-tricarbonylchromium complexes were separated on a silica gel column (eluent, ether/petroleum ether 2/1). Each diastereomer was then treated with NaH and *t*-$BuMe_2SiCl$[12] to give the products **4** and **5** in 45% yield (ratio, 4/5 = 56/44 based on isolated complexes). The identification of the diastereomers **4** and **5** has been ascertained by chemical correlation with (3-*O*-(*tert*-butyldimethylsilyl)estradiol)dicarbonyl(thiocarbonyl)chromium "α" for which a X-ray structural analysis has been carried out.[13]

The functionalization reaction has been studied on both **4** and **5**. For this purpose it was necessary to replace the base *t*-BuOK by $(Me_3Si)_2NNa$,[14] to avoid removal of the protecting groups in

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(1) "Principles and Applications of Organotransition Metal Chemistry"; Collman, J. P., Hegedus, L. S., Eds.; Univ Sci Books: New York, 1980.

(2) Jaouen, G. In "Transition Metal Organometallics in Organic Synthesis"; Alper, H., Ed.; Academic Press: New York, 1978; Vol. 2, p 65–120.

(3) Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379.

(4) (a) Simonneaux, G.; Jaouen, G., *Tetrahedron* **1979**, 2249. (b) Trahanovsky, W. S.; Card, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 2897.

(5) Mahaffy, C. A.; Pauson, P. L. *Inorg. Synth.* **1979**, *19*, 154.

(6) Brocard, J.; Lebibi, J.; Couturier, D. *Bull. Soc. Chim. Fr.* **1982**, *2*, 357.

(7) The stereochemistry of several unequivocal anti additions has previously been ascertained for (arenetricarbonylchromium) complexes.[4,6]

(8) Jackson, W. R.; Rae, I. D.; Wang, M. G.; Semmelhack, M. F.; Garcia, J. N. *J. Chem. Soc., Chem. Commun.* **1982**, 1359 and references therein.

(9) Albright, J. A.; Carpenter, B. K. *Inorg. Chem.*, **1980**, *19*, 3092 and references therein.

(10) Calculations in progress.

(11) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

(12) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Arzano, H. B.; Barton, D. H. R.; Davies, S. G.; Lusinchi, X.; Meunier, B.; Pascard, C. *Nouv. J. Chim.* **1980**, *4*, 369.

(13) (a) Louër, M., et al., manuscript in preparation. (b) The (estradiol)tetracarbonylchromium derivatives are named α or β diastereomers depending on the location of the tripod on the α and β side of the hormone.

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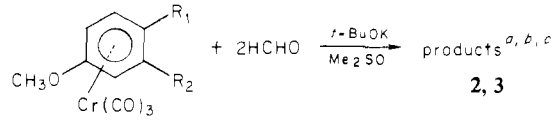
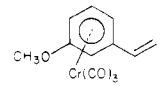
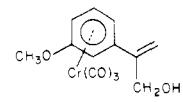
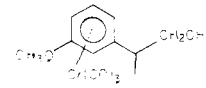
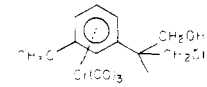
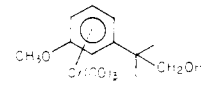
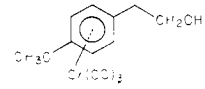
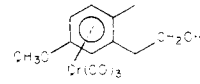
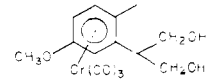
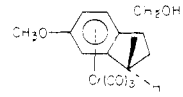
Table I. Reaction of (Methoxyarene)tricarbonylchromium Complexes with Formaldehyde



1

substrate	R_1	R_2	products
1a	H	CH_3	 2a, 10%  3a, 53%
1b	H	C_2H_5	 2b, 12%  3b, 52%
1c	H	$CH(CH_3)_2$	 2c, 65%
1d	CH_3	H	 2d, 10%
1e	C_2H_5	H	no reaction
1f	$CH(CH_3)_2$	H	no reaction
1g	CH_3	CH_3	 2g, 8%  3g, 53%
1h[d]	$-(CH_2)_3-$		 2h, 95%

[a] The reactions were carried out at room temperature. The products were purified by column chromatography (silica gel), crystallized, and fully characterized by ^1H and ^{13}C NMR, mass spectroscopy, elemental analysis, and unequivocal synthesis (2h). [b] The stereochemical results were unchanged when using 1 equiv of HCHO. [c] No products resulting from ring proton abstraction were detected. [d] 2h was the only observed isomer and the yield was calculated by taking into account the recovered starting material (≃10%).

the 3- and 17-positions.[15] Compound **4** led to complex **6** (56% yield in isolated product) (mp 170 °C) with the CH_2OH group exclusively in the 6-position on the hormone skeleton and anti with respect to the $Cr(CO)_3$ moiety. A similar regio- and stereospecificity resulted from the reaction of the β diastereomer **5** giving rise to **7** (mp 188 °C) in 62% yield. It is interesting to note that, for this β location of the tripod, the 6 and 9-benzylic sites of the complexed hormones are available for proton abstraction (compare with the meta and para positions in complexes of Table I), but only the product corresponding to a meta attack with respect to the OCH_2Ph protecting group has been observed. Products such as **6** and **7**, for which the $Cr(CO)_3$ group can be removed without detriment to the organic molecule,[16] might be valuable precursors in current endocrinology problems such as designed fixation of cytotoxic groups, γ-emitting estrogen and affinity markers.[17]

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Registry No. 1a, 12109-01-2; **1b**, 88729-81-1; **1c**, 88729-82-2; **1d**, 12109-02-3; **1e**, 88729-83-3; **1f**, 33409-10-8; **1g**, 77490-94-9; **1h**, 32915-66-5; **2a**, 88729-84-4; **2b**, 88729-85-5; **2c**, 88729-86-6; **2d**, 88729-87-7; **2g**, 88729-88-8; **2h**, 88729-89-9; **3a**, 88729-90-2; **3b**, 88729-91-3; **3g**, 88729-92-4; **4**, 88729-93-5; **5**, 88765-18-8; **6**, 88729-94-6; **7**, 88765-19-9; **8**, 88729-95-7; **9**, 88729-96-8.

(14) Interestingly, this base also promotes proton abstraction from $Cr(CO)_3$ modified benzylic positions as does *t*-buOK (Wannagat, U.; Niedergrüm, H. *Chem. Ber.* **1961**, *94*, 1540).[12b]

(15) (3-*O*-Benzyl-17β-*O*-(*tert*-butyldimethylsilyl)estradiol)-α-tricarbonylchromium (**4**), 0.612 g (1 mmol), and 0.370 g (2 mmol) of $(Me_3Si)_2NNa$ were stirred in 10 mL of Me_2SO under argon at 40 °C for 5 min. The solution was cooled to room temperature, and 0.300 g of powder of paraformaldehyde was added. After 2 h, the solution was hydrolyzed with HCl 1/10. The product was extracted with ether and purified by TLC (silica gel; eluent, ether/petroleum ether 1/1). A yellow solid **6**, 0.360 g (56%), was isolated and recrystallized in ether/petroleum ether (*m/e* 506 (M − $Cr(CO)_3$), 449 (M − $Cr(CO)_3$-*t*-Bu); mp 170 °C; $(\alpha)^{20}_D$ +5° (*c* 0.02, CH_2Cl_2); ^{13}C NMR (C-6) 34.65, (C-9) 44.28, (δ, CD_3COCD_3); compare with **4** (C-6) 25.94, (C-9) 43.24 (δ, $CDCl_3$). Starting from (3-*O*-benzyl-17β-*O*-(*tert*-butyldimethylsilyl)estradiol)-β-tricarbonylchromium (**5**), the compound **7** was prepared in 62% yield according to the same procedure: (mp 188 °C; *m/e* 642 (M), 558 (M − 3CO), 506 (M - $Cr(CO)_3$), 449 (M - $Cr(CO)_3$ - *t*-Bu); $(\alpha)^{20}_D$ +54° (c 0.025, CH_2Cl_2); ^{13}C-NMR (C-6) 39.01, (C-9) 42.47 (δ, CD_3COCD_3); compare with **5**: (C-6) 26.63, (C-9) 42.86 (δ, $CDCl_3$).

(16) By sunlight decomplexation in air (Jaouen, G.; Dabard, R. *Tetrahedron Lett.* **1971**, 1015) compound **6** gave rise to the free ligand **8** in 90% yield (mp 78 °C; $|\alpha|^{23}_D$ +20° ($CHCl_3$, *c* 0,03 g/mL); *m/e* 506; ^1H NMR 7.22 (dd, H_1), 6.78 (dd, H_2), 6.84 (d, H_4), 3.71 (dd, CH_2OH), 5.02 (s, $PhCH_2$), 7.58 (m, Ph), 0.75 (s, Me-13), 0.04 (s, Me_2), 0.90 (s, *t*-Bu), (δ, $CDCl_3$)), Whereas **7** led to **9** (mp 129 °C; $|\alpha|^{20}_C$ +27.5° ($CHCl_3$, *c* 0,03 g/mL); *m/e* 506; ^1H NMR 7.24 (d, H_1), 6.81 (dd, H_2), 6.94 (d, H_4), 3.80 (dd, CH_2OH), 5.04 (s, $PhCH_2$), 7.4 (m, Ph), 0.72 (s, Me-13), 0.04 (s, Me_2), 0.90 (s, *t*-Bu) (δ, $CDCl_3$)).

(17) (a) "Cytotoxic Estrogens in Hormone Receptive Tumors"; Raus, J., Martens, H., Leclercq, G., Eds.; Academic Press: New York, 1980. (b) See, for example: Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J.; Neeley, R. J. *J. Med. Chem.* **1980**, *23*, 994. Mazaitis, J. K.; Gibson, R. E.; Komai, T.; Eckelman, W. C.; Francis, B.; Reba, R. C. J. *J. Nucl. Med.* **1980**, *21*, 142. (c) Simons, S. S., Jr.; Thompson, E. B. *Biochem. Actions Horm.* **1982**, *9*, 221–254.