Selective Aromatization of the *A* Ring of Steroids through Demethylation by an Electrophilic Ruthenium Fragment

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The reaction of '$(C_5Me_5)Ru^+$', produced by the protonation of $[(C_5Me_5)RuOMe]_2$ by CF_3SO_3H, with various steroids leads to selective aromatization of the *A* ring *via* demethylation of the 19 methyl group and/or dehydration and/or dehydrogenation reactions.

In recent years, new reactivity pathways have been discovered in organometallic chemistry concerning C–H[1] and C–C[2] bond activation. However, whereas synthetic applications of C–H bond activation are promising (for example: photochemical carbonylation, silylation and dehydrogenation,[3] or alkylation of pyridines and lutidines through σ bond metathesis[4]), little is known on C–C bond activation and virtually no synthetic application has been reported, excepting the isomerization of hydrocarbons using scandium[5] or electrophilic palladium derivatives.[1e]

We have recently demonstrated that the electrophilic fragment '$(C_5Me_5)Ru^+$' could aromatize C_6 hydrocarbons *via* cleavage of C–H, C–O or C–C bonds.[6] For example 4,4-dimethylcyclohexenone was transformed selectively into *p*-cresol upon reaction with this ruthenium fragment.

In order to test the potential of our system in organic synthesis, we have considered its reactions with steroids, which are multifunctional molecules and show a wide range of structures. Furthermore π-complexes of oestrogens with similar Ru or Rh moieties have been prepared and used for different applications recently by the groups of Jaouen[7] and Moriarty.[8] Dehydrogenation of the alcohol function on the *A* ring of steroids *via* hydrogen transfer catalysed by ruthenium compounds[9] and even aromatization through cleavage of a C–O bond[10] are also known. Elimination of the 19-methyl group is a difficult process achieved in nature by a cytochrome P-450 enzyme (P-450 arom.) through successive oxidation steps.[11] A model study of this process was recently reported.[12] Reductive aromatization of steroidal dienones has been previously observed upon treatment with lithium metal.[13]

This prompted us to attempt aromatization of the *A* rings of different types of steroids, all of them having a quaternary carbon atom on the *A* ring, namely testosterone, progesterone, cholesterol, dehydroisoandrosterone, androsterone and prednisolone. We report in this communication the first selective application of a carbon–carbon bond cleavage reaction.

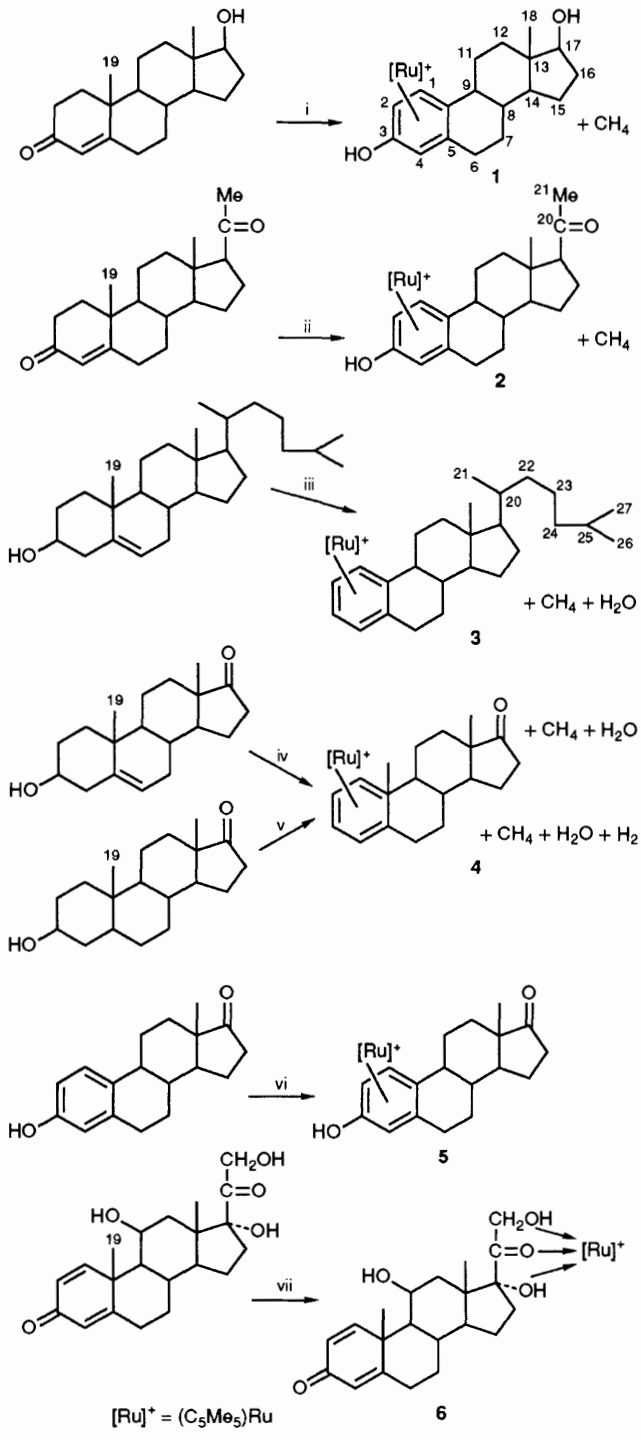
The '$(C_5Me_5)Ru^+$' fragment was prepared as previously reported by protonation of $[(C_5Me_5)Ru(OMe)]_2$ by CF_3SO_3H in CH_2Cl_2 or tetrahydrofuran (THF).[3,14] The reactions with steroids were carried out in closed vessels allowing the identification by GC of the gaseous products. Solid products were isolated and characterized by IR and ^1H and ^{13}C NMR spectroscopy and microanalyses. The disappearance of the NMR signal corresponding to the 19-methyl group and the appearance of aromatic protons or carbon atoms are particularly characteristic. Satisfactory elemental analyses were obtained for **2–6**; it proved impossible to remove THF completely from **1**.

'$(C_5Me_5)Ru^+$' reacts smoothly and nearly quantitatively with testosterone and progesterone at 100 or 120 °C to yield methane and the aromatized *A* ring phenol derivatives **1** and **2** (oestradiol in the case of the testosterone reaction, see Scheme 1). No or little hydrogen was found by GC and no evidence for reaction on the C_5 ring was found by NMR spectroscopy, thus demonstrating the selectivity of the reaction. As in the case of isophorone, previously reported, some C_2H_6 was found by GC which reflects a radical pathway for the carbon–carbon cleavage step and the C-3 OH group was partially transformed into OMe (compounds **1′** and **2′** respectively).[6b]

The reactions with cholesterol and dehydroisoandrosterone are expected to be more complicated (see Scheme 1), since three pathways are possible: (*a*) aromatization of the *B* ring (evolution of $CH_4 + H_2$); (*b*) aromatization of the *A* ring with retention of the OH group (evolution of $CH_4 + H_2$; in the case of dehydroisoandrosterone, formation of oestrone); (*c*) aromatization of the *A* ring with loss of the OH group (evolution of $CH_4 + H_2O$).

Only CH_4 is observed by GC and spectroscopic data confirm that pathway (*c*) is followed in both cases leading to compounds **3** and **4** (see Scheme 1). This is in agreement with what was found with simple C_6 molecules (dehydration easier than dehydrogenation). An authentic sample of **5** was prepared to confirm our assignments and in particular the loss of the OH function in **4**.

Interestingly, the function present on the C_5 *D* ring is now important. Thus the reaction with cholesterol is quantitative at 90 °C after 40 h, whereas no dealkylation is observed with dehydroisoandrosterone at 100 °C after 70 h. In the latter case it is necessary to heat the reaction mixture at 120 °C for 40 h to observe a selective demethylation. This can be related to the competitive coordination of the ketone function on the C_5 ring to ruthenium. It is noteworthy that prednisolone (see Scheme 1) gives a 1 : 1 adduct with '$(C_5Me_5)Ru^+$' (compound **6**), but which does not involve coordination of the *A* ring but rather of the oxygenated functions on the C_5 ring. Heating compound **6** does not lead to dealkylation but to evolution of CO and



Scheme 1 Reactions of '$(C_5Me_5)Ru^+$' with various steroids. *Conditions and yields*: i, in THF, 100 °C, 40 h, 70%; ii, in THF, 100 °C, 40 h, 80%; iii, in THF, 100 °C, 40 h, 100%; iv, in THF, 120 °C, 40 h, 80%; v, in THF, 140 °C, 40 h, 15%; vi, in THF room temp., 24 h; vii, in THF, room temp., 24 h.

Table 1 Steroid aromatization reactions

Starting steroid	Solvent	Reaction time/h	Temp./°C	Gas evolved	Product	Yield (%) Spectroscopic	Yield (%) Isolated
Testosterone	CH_2Cl_2	40	100	CH_4	**1**	30	—
	THF	40	100	CH_4	**1**	70	50
	THF	70	120	CH_4	**1**	100	60
Progesterone	THF	40	100	CH_4	**2**	85	75
	THF	40	120	CH_4	**2**	95	80
Cholesterol	CH_2Cl_2	40	90	CH_4	**3**	100	
Cholesterol	THF	40	100	CH_4	**3**	100	30
Cholesterol	THF	40	120	CH_4	**3**	100	33
Dehydroisoandrosterone	THF	72	100	$H_2 + CH_4$	?		
	THF	42	120	CH_4	**4**	80	51
Androsterone	THF	40	140	$H_2 + CH_4$	**4**	15	—

Table 2 Selected NMR data for **1–6** in $(CD_3)_2CO$ (200 MHz)

Compound	^1H C_5Me_5	^1H Steroid Me (position)	^1H ArH
1	2.06[a]	0.91 (18)	5.82–6.14
2	2.07[a]	0.76 (18), 2.21 (20)	5.82–6.17
3	2.08	0.85 (18), 1.08 (21),[b] 0.99 (26, 27)[c]	5.99–6.29 (ABCD)
4	2.10	1.03 (18)	6.02–6.31 (ABC)
5	2.04	1.02 (18)	5.85–6.17
6	2.01	1.03, 1.61 (18, 19)	

[a] For 3-OMe analogues **1'** and **2'**, $\delta_H(C_5Me_5)$ 2.04, δ (OMe) 3.98. [b] J_{HH} 6.38 Hz. [c] J_{HH} 6.48 Hz.

formation of a complicated mixture of organometallic derivatives which was not characterized.

Finally a compound showing no unsaturation such as androsterone can itself react with '$(C_5Me_5)Ru^+$' to give aromatization on the *A* ring. This time, the mechanism involves dehydrogenation, dehydration and demethylation. The reaction at 140–160 °C for 40 h produces a moderate yield of compound **4** (15%) and H_2 and CH_4 detected by GC.

In conclusion, the ease and selectivity of the cleavage of the 19-methyl group in enone type compounds are unprecedented and lead to a new method for synthesis of oestrogens. The reaction with cholesterol and dehydroisoandrosterone leads to compounds containing an unfunctionalized aromatic *A* ring *via* a mechanism implying isomerization of a C–C double bond, dehydration and demethylation. These compounds could be subject to nucleophilic attack and thus to introduction of new functions. This possibility is presently under study. The reaction with androsterone demonstrates the wide range of applicability of our method (no unsaturation in the starting material). Finally decoordination from the ruthenium moiety is possible by photochemical ring exchange with CD_3CN. This reaction has been performed in NMR tubes but not optimized yet.

We thank Dr D. Labroue for helpful discussions and experimental assistance, A. I. France-Espagne and CNRS for support, and Johnson Matthey for a generous loan of $RuCl_3 \cdot 3H_2O$.

Received, 6th August 1991; Com. 1/04115K

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