The Selective Introduction of Organometallic Markers into Oestrogens. C-16 Prop-2-ynylation of Oestrone

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The reactivity of the (prop-2-ynyl)hexacarbonyldicobalt cation (**1**) can be dramatically modified in the presence of hexamethyldisilazane, allowing selective attack onto enol sites in the presence of activated arene rings.

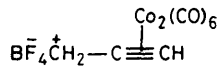
In a recent paper[1] we have described the preparation of A-ring substituted prop-2-ynyl (propargyl) transition metal carbonyl β-oestradiols, compounds which have potential as substrates in steroid hormone receptor assays using Fourier transform (F.t.) i.r. spectroscopy.[2,3] In developing this area of study, an important target was the synthesis of a 16α-substituted metal carbonyl oestradiol since it was hoped that the affinity of the modified hormone towards the specific receptor might not be unduly affected by the presence of a bulky substituent at this position.[4] In principle a (prop-2-ynyl)hexacarbonyldicobalt function can be directly introduced at the C-16 position by reaction of a suitable enol ether with the organometallic cation (**1**),[5] but the desired reaction may be hindered by competitive alkylation of the arene ring.[1] We have found however that specific alkylation of the carbonyl function is possible under the right conditions.

Reaction of the cation (**1**) with enol ether (**2a**) at −10 °C in dichloromethane gave rise to a mixture of five products: the three monoalkylated oestrones (**3a**), (**4a**), and (**7a**) and the two dialkylated products (**5**) and (**6**). The reactivity of the two nucleophilic sites in the molecule were similar, approximately 50% of the starting material being alkylated at the arene ring and 65% at the enol ether. In contrast, under the same conditions, the methoxymethyl protected enol ether (**2b**) gave virtually exclusive ring alkylation,† only products (**3b**) and (**4b**) being isolated in good yield.

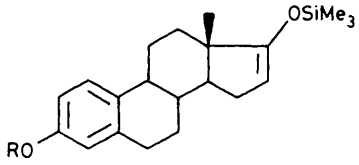
It seems possible that this difference in reactivity may be due to prior complexation of the cation to the $-OCH_2O-$ function in (**2b**), thus favouring alkylation of the adjacent arene over the more remote enol ether. However, this reactivity was found to be completely reversed when the reaction was performed in the presence of two equivalents of hexamethyldisilazane (**8**), alkylation occurring only at C-16 giving (**7b**) in 80% isolated yield. Moreover, in the presence of (**8**) no reaction between cation (**1**) and 3-*O*-methyl oestrone was observed after 3.5 h (−5 °C to room temperature), whereas without the amine alkylation at the C-2 and C-4 positions[1] is complete after 2 h at −5 °C, or within 0.5 h at room temperature. In fact the reactivity of hexamethyldisilazane itself towards cation (**1**) differs from that of other sterically hindered amines. Thus an excess of di-isopropylamine reacts with (**1**) to give the (prop-2-ynyl)hexacarbonyldicobalt complex (**9**) while t-butylamine is readily dialkylated to give (**10**). However, although addition of (**8**) (3 equiv.) to (**1**) (in CH_2Cl_2) results in the immediate dissolution of the sparingly soluble cation, there is no formation of a prop-2-ynyl amine complex corresponding to (**9**). It would therefore appear that there is an association between the amine and the cation to give an intermediate species which reacts preferentially with an enol ether but which does not undergo the proton abstraction which would result in the formation of a neutral tertiary amine.

The product (**7**) thus obtained by alkylation at the C-16 position consists (as determined by n.m.r. spectroscopy and t.l.c.) of a single isomer, consistent with stereospecific attack at the less hindered α-face of the planar enol ether (**2**), and is readily converted into the required oestradiol derivative (Scheme 1). Initial decomplexation to (**11**) reduces the steric encumbrance to facilitate α-attack by BH_4^- in the reduction step. T.l.c. separation yields two products, in approximately equal quantities, one of which is recomplexed with $Co_2(CO)_8$, the other being only polymerized by this reagent; the latter product has vinylic signals in the ^1H n.m.r. spectrum and decomposes within a few days. This result is consistent with borohydride attack at both the α and β faces of the ketone

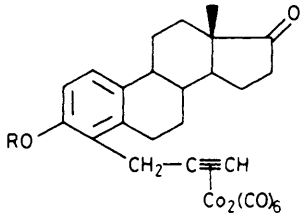
† ^1H n.m.r. spectroscopy of the minor products suggested that small quantities (<5%) of C-16 alkylated compounds may have been present.



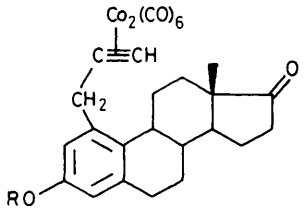
(1)



(2) **a**; R = Me
b; R = CH_2OMe



(3) **a**; R = Me
b; R = CH_2OMe



(4) **a**; R = Me
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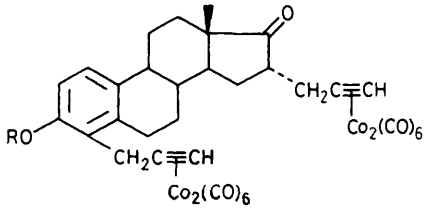
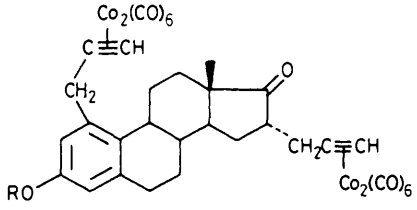
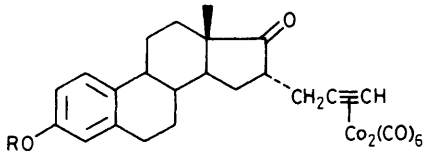


(5) R = Me



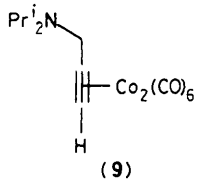
(6) R = Me



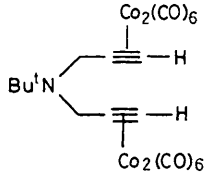
(7) **a**; R = Me
b; R = CH_2OMe

$(Me_3Si)_2NH$

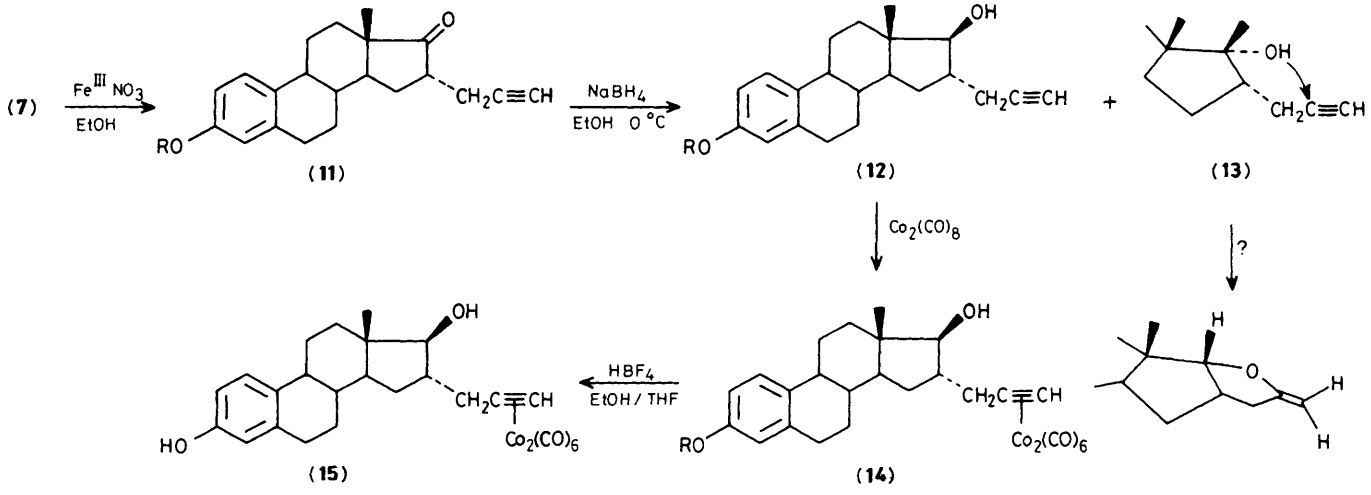
(8)



(9)



(10)



R = CH_2OMe

Scheme 1

(**11**), in the one case giving the *trans* product (**12**) and in the other the equivalent *cis* product (**13**) in which OH addition to the acetylene gives rise to an exocyclic vinyl ether. Finally, the methoxymethyl protecting group in (**14**) is readily cleaved [HBF_4, Et_2O, EtOH, tetrahydrofuran (THF); room temperature, 20 h] giving the 16α-substituted-17β-oestradiol (**15**), the spectral characteristics of which are consistent with the assigned stereochemistry.‡

The application of this methodology allows direct and selective introduction of a cobalt carbonyl prop-2-ynyl group in an α position to a ketone function when an activated aromatic group is present in the molecule.

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‡ All the new products have been identified by elemental analysis, mass spectroscopy, i.r., and ^1H n.m.r. spectroscopy at 250 MHz.

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