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Unprecedented Formation of Spirobicyclo[3.1.0]hexanes through Tandem Acetylene-Addition - Michael Cyclization

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Abstract: Reaction of 4-pentynyltriphenylphosphonium bromide **2** with oestrone methyl ether in the presence of potassium *tert*-butylate produced a spirobicyclo[3.1.0]hexane rather than the anticipated Wittig product. The reaction appears to be general for pinacolone-type ketones, as was demonstrated by several examples. A mechanism for this anomalous reaction is proposed.

In the course of our work on synthetic steroid derivatives, we needed a steroid with a pentynylidene side chain at position 17. Thus, we treated oestrone methyl ether **1** with five equivalents of 4-pentynyltriphenylphosphonium bromide[1] **2** (toluene/KO^{t}Bu/100 °C), expecting the desired product **3** (figure 1). To our surprise, however, none of that product could be detected; instead we obtained[2], after

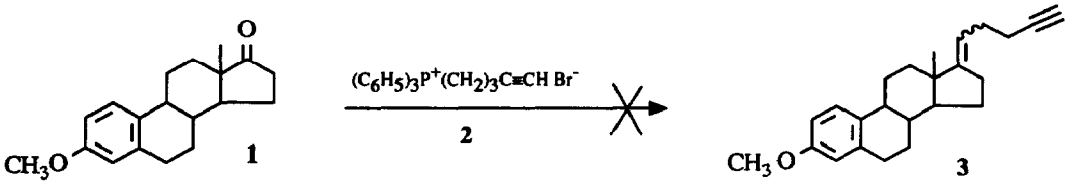


Figure 1

chromatography, 70% of a crystalline product, m.p. 186.6-187.8 °C, $[\alpha]_D$ +86.3° (c = 1, $CHCl_3$), which, from its IR spectrum[3], had retained the carbonyl group. The NMR spectrum of this compound did not show the signals expected for the olefinic protons in the side chain. Instead, the absence of the C-16 protons indicated that α,α-disubstitution of the 17-ketone had taken place, and the ^{13}C-NMR indicated the addition of 2 CH's and 3 CH_2's to the structure. However, the exact structure of the product could not be established with certainty at this stage. When the enol ether of norandrostenedione **4** was subjected to the same reaction conditions, a similar product was formed in 89% yield, m.p. 139-142.5, $[\alpha]_D$ -145.6° (c = 1.18, $CHCl_3$), which was hydrolysed to the corresponding 3-keto-Δ^4 compound, m.p. 163.7-165, $[\alpha]_D$ = +2.5° (c = 1.18, $CHCl_3$). The NMR spectra of the latter compound again indicated the presence of a $=C_5H_8$ moiety at C-16.

To simplify the task of defining the correct structure for the adducts, we subjected a number of simpler ketones to the same reaction conditions. Thus, when 2,2-dimethylcyclopentanone **5** was treated with Wittig reagent **2**, an oily product was obtained in 70% yield for which the ^{13}C-NMR showed only 9 peaks, indicating a symmetrical structure. The spectral data strongly point to a spirobicyclo[3.1.0]hexane-type structure **6** (table 1). Both cyclopropyl protons, which normally would be found at 0.6 ppm, now lie at 1.79 ppm due to the strong deshielding effect of the carbonyl group. Moreover, when the spectrum was recorded in C_6D_6 all signals except for these two were moved upfield. Together, these results strongly point to a cis-relationship between H1, H5 and the carbonyl group.

Somewhat surprisingly, even the simplest *tert*-butyl ketone, pinacolone (**7**), gave the reaction, producing compound **8** (m.p. 74.5-75.7) in 55% yield after chromatography, a second product was isolated which could be identified as triphenylphosphine. In the ^{1}H-NMR spectrum of **8**, a coupling of 3Hz between H6 and H1/H5 could be observed, again pointing to an "exo" position of the acyl substituent. Thus, the structures for the steroid adducts are **9**[4] and **10** respectively, as was confirmed by an X-ray analysis[5] of compound **9**, which completely supported our conclusions about the stereochemistry of the ring junction.

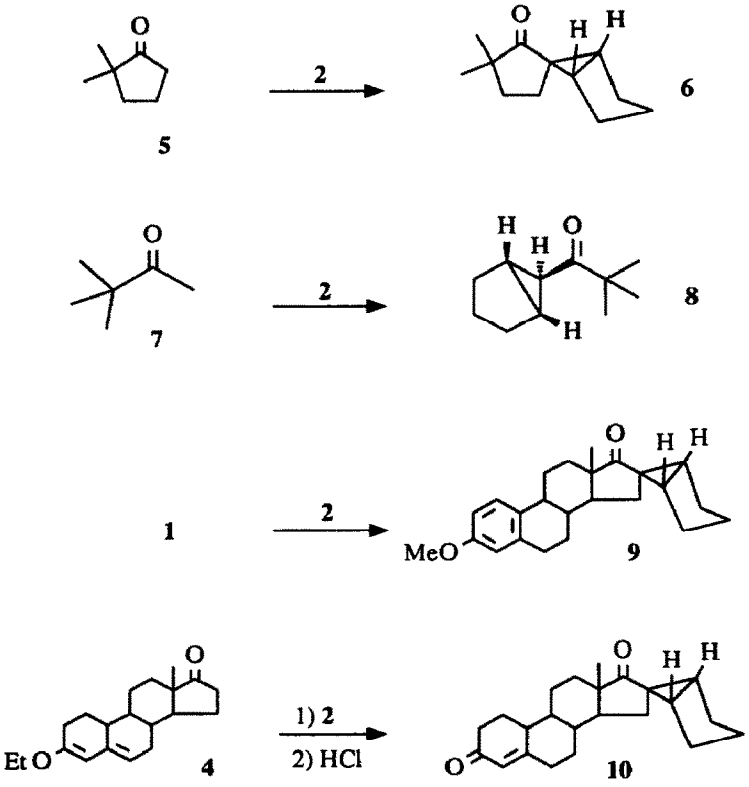
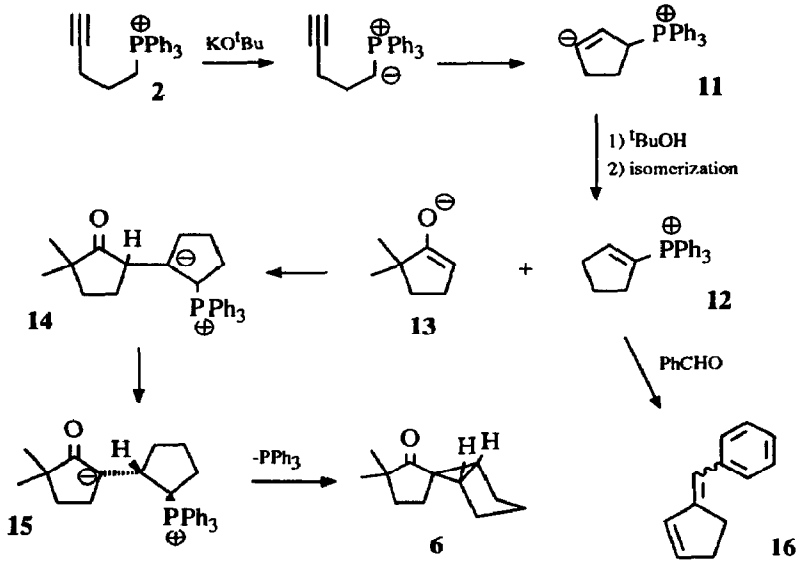


Table 1

A possible mechanism is outlined in scheme 1. The ylid of **2**, generated in the first step, undergoes an intramolecular addition to the triple bond. After protonation and isomerization of the vinyl anion **11**, the cyclopentenylphosphonium salt **12**[6] acts as a Michael acceptor for the enolate **13**, generated from the ketone by reaction with potassium *tert*-butoxide. Proton exchange within the resulting adduct **14** produces **15**, for which the depicted trans configuration is anticipated on grounds of steric considerations. The subsequent substitution step then causes inversion of configuration of this centre to give the cis-fused cyclopropane ring **6** with the acyl substituent in the "exo" position. The proposed mechanism was corroborated by refluxing **2** with KO^{t}Bu in toluene for 15 mins, followed by quenching with benzaldehyde. Work-up produced **16** (as a 2:1 (E:Z) mixture of isomers) as the sole identifiable product, thus establishing that **12** must have formed[7].



Scheme 1

There is little precedent for the first step in this sequence. Addition of carbanions derived from phenylacetonitrile[8] to unactivated acetylenes are known; also, the intramolecular addition of malonate anions[9] has been reported, as have additions of sulfur ylids to activated acetylenes[10]. In our case, because the normal rapid Wittig addition to the ketone is impeded by steric hindrance[11], formation of **12** is made possible; for the same reason, products of type **16** are not formed.

Thus, 6-acylbicyclo[3.1.0]hexanes can be obtained in high yields by an unprecedented addition-cyclization process. Extension of this reaction to other bicyclic systems is currently under active investigation.

Acknowledgement We would like to thank Dr. R.W.W. Hooft and Prof. J. Kroon of the Department of Crystal and Structural Chemistry of the State University of Utrecht, the Netherlands, for obtaining the X-ray diffraction of compound **9**. We are indebted to a referee for a suggestion with regard to the mechanism.

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2. To a suspension of 0.49 g (1.72 mMol) of **1** in 40 ml of dry toluene under a nitrogen atmosphere was added 0.93 g (8.3 mMol) of KO^{t}Bu. The mixture was heated to 100 °C and 3.6 g (8.8 mMol) of **2** was added. After one hour, the mixture was poured into ice-water and extracted into ethyl acetate. Chromatography afforded 0.42 g (70%) of the product.
3. All new compounds gave spectral and analytical data in full accordance with the structures proposed: (**6**): IR (neat): 3020 (cyclopropane CH), 1719 (C=O), 1381, 1203, 1071 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.99-1.87(m, 2H, H2 and H4), 1.84(ddd, 2H, J=8, 7 and 2 Hz, H4'), 1.79(dd, 2H, J=4 and 1.5Hz, H1 and H5), 1.73(ddd, J=8, 7 and 2 Hz, H5'), 1.70(m, 2H, H2 and H4), 1.68(m, 1H, H3eq), 1.27-1.15(m, 1H, H3ax), 1.05(s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$): 222(C=O), 45.7(s), 36.5(t), 36.0(s), 34.7(d), 25.7(t), 23.8(q), 23.3(t), 19.9(t). (**8**): IR (KBr): 3040 (cyclopropane CH), 1674 (C=O), 1468, 1400, 1366, 1098, 1075, 845 cm^{-1}; ^{1}H-NMR: 1.92(t, 1H, J=3 Hz, H6), 1.85-1.60(m,7H), 1.16(br s, 10H, H3ax and ^{t}Bu). ^{13}C-NMR: 214.4(C=O), 43.7(s), 31.5(d), 27.3(t), 26.3(q), 25.2(d), 20.6(t). (**9**): IR (neat): 2835 (OCH_3), 1721 (C=O), 1612, 1575, 1496, 1259, 1056, 1018, 871, 786, 723 cm^{-1}; ^{1}H-NMR: 7.11(d, 1H, J=9Hz, H1'), 6.78(dd, 1H, J=9 and 3 Hz, H2'), 6.72(d, 1H, J=3Hz, H4'), 3.43(s, 3H, OCH_3), 2.82-2.66(m, 2H), 2.15-2.0(m, 3H), 1.98(1H, H12'β), 1.80-1.57(m, 4H), 1.53-1.10(m, 10H), 1.05-0.9(m, 1H), 0.80(s, 3H, CH_3). ^{13}C-NMR: 220.2(C=O), 157.6(s), 137.8(s), 132.2(s), 126.3(d), 113.9(d), 111.6(d), 55.2(q), 49.1(d), 48.4(s), 44.1(d), 38.3(d), 36.3(s), 35.3(d), 31.9(d), 31.6(t), 29.7(t), 26.7(t), 25.9(t)(2x), 25.8(t), 23.4(t), 23.2(t), 14.7(q). (**10**): IR (neat): 3013 (cyclopropane CH), 1714 (17-C=O), 1659 (3-C=O), 1608, 1370, 1256, 1210, 1050, 1046, 890 cm^{-1}; ^{1}H-NMR: 5.85(s, 1H, H4'), 2.54(1H, H6'α), 2.47-2.23(m, 4H), 2.2-2.1(m, 1H), 2.0-1.8(m, 6H), 1.75-1.45(m, 9H), 1.35-1.1(m, 4H), 0.99(s, 3H, CH_3), 1.0-0.9(m, 1H). ^{13}C-NMR: 220 (C=O), 199.9(s), 166.1(s), 125.0(d), 49.8(d), 49.1(d), 48.2(s), 42.7(d), 40.0(d), 36.7(t), 36.4(s), 35.5(t), 32.2(d), 31.5(t), 30.2(t), 26.8(t), 26.0(t), 23.7(t), 23.3(t), 14.8(q). (**16**): ^{1}H-NMR: 7.40-7.25(m, 7H, Ar), 6.8(m, ½H, =CH, Z), 6.35(m, ½H, ArCH=, E), 6.32(m, ½H, =CH, E), 6.30(m, ½H, =CH, Z), 6.25(m, ½H, ArCH=, Z), 6.18(m, ½H, =CH, E), 2.9-2.8(m, ½H, CH_2, E), 2.75-2.6(m, 1H, CH_2), 2.6-2.5(m, ½H, CH_2, Z).
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