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E-Ring extended estrone derivatives: introduction of 2-phenylcyclopentenone to the estrone D-ring via an intermolecular Pauson–Khand reaction

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Abstract—An expedient synthetic route to E-ring extended estrone derivatives is reported. Estrone-derived cyclopentenones were accessed by an intermolecular Pauson–Khand (PK) cycloaddition. It was found that electron donating and withdrawing substituents in the arylalkyne increased and decreased the yields of PK products, respectively. The stereochemistry of the products was elucidated by X-ray and NMR studies.

Several D-ring alkylated estrone analogues display exceptionally high affinity for estrogen receptors.[1] In particular, compounds in which an E-ring is formed are known to be involved in the inhibition of steroidogenic enzymes.[2,3] Such compounds also have an effect on steroid dehydrogenase activity and the ability to inhibit the detrimental action of the steroid sulfatase enzyme.[4]

Generally, E-ring extended steroids have been accessed by modification of the C17-ketone in the D-ring by either arylimine or oximino formation,[5] addition of a carbon nucleophile[2] or hydrazone formation.[4] Other approaches have included ketone reduction, silyl enol ether formation or ring-closing metathesis (giving five- or six-membered E-rings).[6,7]

While a number of skeletal variations of steroids have been examined and other cycloaddition—mediated approaches to D-ring modification have been developed,[1,8] ring extension via an intermolecular Pauson–Khand reaction (PK) has not hitherto been described.

The PK reaction has been considered a valuable and convergent method for the synthesis of five-membered rings.[9] This carbon–carbon bond forming reaction converts an alkyne, an alkene and carbon monoxide into a cyclopentenone unit under the influence of a transition metal carbonyl compound, usually dicobaltoctacarbonyl, (Fig. 1).[10] Since its discovery in the early seventies,[11] the usefulness of the reaction has been broadened through the development of promoters and catalytic techniques. Although the reaction was discovered in its intermolecular form, the scope of the intermolecular PK reaction has always been limited by the poor reactivity and selectivity of simple alkenes. Since only low to modest yields have been reported for unstrained alkenes, most of the intermolecular PK applications have been restricted to the use of strained, norbornene-type alkene structures. An additional limitation is the possible mixture of regioisomers as reaction products, thus, there are only a few examples of intermolecular PK reactions where unsymmetrical rings have been used as the alkene substrate.[12]

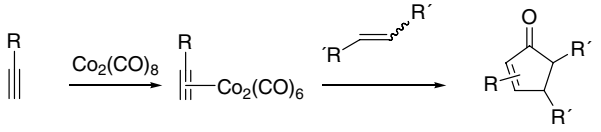

Figure 1. The Pauson–Khand cycloaddition reaction.

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† X-ray crystallography.

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During the course of our studies towards the synthesis of skeletally modified estrone analogues, it was shown that 3-methoxy-estra-1,3,5(10),16-tetraene derived from estrone undergoes an intermolecular PK cycloaddition leading to estrone analogues which contain a 2-phenylcyclopentenone E-ring.

In the first phase of our work, estrone **1** was converted to 3-methoxy-estra-1,3,5(10),16-tetraene **3** via the Shapiro reaction[13] as shown in Scheme 1. The 3-hydroxy group of estrone **1** was methylated with MeI in the presence of K_2CO_3 yielding 78% of **2** after crystallisation.[14] The Shapiro reaction of estrone has previously been performed with tosyl hydrazide and catalytic HCl in THF followed by elimination with 30% overall yield.[15] In our hands, the tosyl hydrazone was formed in 82% yield with *p*-TsOH as catalyst in toluene. Subsequent elimination of the tosyl hydrazone with excess base[16] afforded alkene **3** in a yield of 78% after column chromatography.

The PK reaction of alkene **3** with phenylacetylene **4** and *t*-butyl methyl sulfide promoter in dichloromethane[17] afforded cyclopentenones **8a** and **8b** in 55% combined yield after purification by column chromatography (Scheme 2).[18] The isomers **8a** and **8b** were separated by crystallisation.

To determine the influence of the electronic nature of the alkyne, the reaction was performed with different aryl alkynes substituted at the 4-position. Substituents with an electron donating character, i.e. a 4-Me group, (alkyne **6**), increased the yield of the desired product **10** (59%). Further increasing the electron donating nature of the substituent (4-OMe), the reaction of *p*-methoxyphenylacetylene **5** with **3** afforded product **9** with an excellent yield of 83%. As expected, if the electron donating character of the alkyne is decreased by an electron withdrawing ester group, such as in alkyne **7**, a considerably lower yield was obtained (29% of **11**).[19a]

The PK reaction with alkene **3** and alkyne **4** (as well as alkynes **5–7**) gave rise to a mixture of two cyclopentenone isomers **8a** and **8b**. The regio- and stereochemistries were determined by crystal structural analysis and using a combination of NMR techniques: COSY, HSQC and ROESY. We succeeded in growing crystals of PK adduct **8a**, which were suitable for X-ray analysis[19b] (Fig. 2), and which allowed us to determine the configuration of **8a** based on the known stereochemistry of the optically pure estrone **1** and chiral space group $P2_1$. NMR studies were used to determine whether **8a** and **8b** were regio- or stereoisomers. The bridgehead methyl group showed a strong ROE effect with both protons H^a and H^b (Scheme 3), indicating that the protons are located on the same side of the fused rings, and thus leading to the conclusion that compound **8b** is a regioisomer of **8a**.

The regiochemistry of the PK reaction can be explained by electronic and steric factors during the insertion of the alkene component into the cobalt–alkyne complex.[12,20] In special cases the regioselectivity is believed

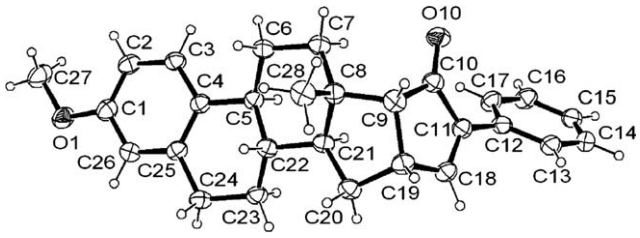
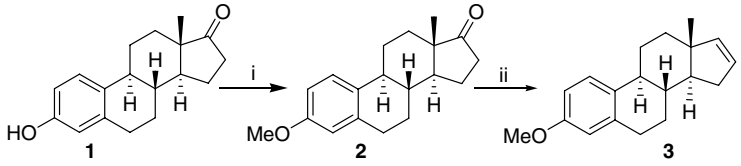
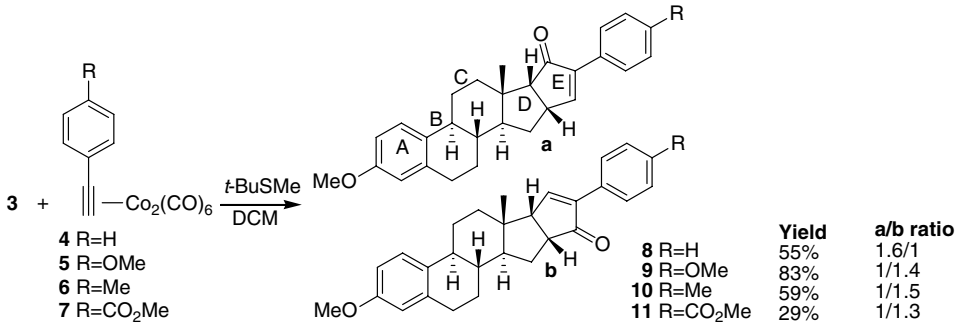


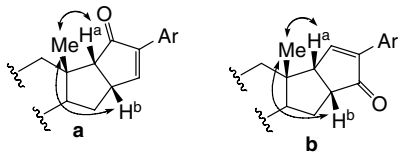
Figure 2. The ORTEP X-ray structure presentation of **8a** at 30% probability level with crystallographic numbering.



Scheme 1. Reagents and conditions: (i) K_2CO_3, MeI, acetone, 78%, (ii) (a) *p*-$TsNHNH_2$, *p*-TsOH, MeOH, 82%, (b) *n*-BuLi, THF, 78%.



Scheme 2. Pauson–Khand reaction with 4-substituted phenylalkynes.



Scheme 3. Observed ROE correlations.

to depend not only on through-bond inductive effects of the remote substituents but also to be controlled by through-space orbital interactions.[21] The only examples of the formation of unsymmetrical rings have been with bridged alkenes, such as norbornyl- or 8-oxabicyclo[3.2.1]oct-6-ene derivatives or strained cyclobutenes.[12] Due to the insertion of the less hindered face of the alkene π-bond into a less substituted C–Co–bond in the cobalt–alkyne complex, the intermolecular PK reaction commonly yields *exo*-fused products with the larger alkyne substrate in the α-position with respect to the carbonyl. Large allylic substituents on the alkene tend to align themselves '*anti*' to the carbonyl group.

The ratios of regioisomers **a** and **b** in adducts **8–11** indicate (Scheme 2) that electronic effects exerted by alkyne substituents have no significant influence on the regioselectivity. However, the fact that the sterically less bulky phenylacetylene **4** leads to adduct **8a** as the major isomer while regioisomers **9–11b** dominate with substituted phenyl alkynes **5–7**, implies that even distant steric effects, i.e. smaller substitution of **4**, may affect the regioselectivity.

To conclude, 2-phenylcyclopentenone was introduced to the estrone D-ring via an intermolecular PK reaction yielding E-ring extended estrone derivatives. Our current efforts are aimed at broadening the scope of this reaction.

Acknowledgements

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17. Representative experimental procedure: Phenylacetylene (0.05 ml, 0.46 mmol) and cobalt octacarbonyl (157 mg, 0.46 mmol) were stirred in DCM (14 ml) under argon for 30 min. Alkene **3** (170 mg, 0.633 mmol) dissolved in 3 ml of DCM was added to the dark red solution. The reaction mixture was stirred for 20 min prior to the addition of *t*-BuSMe (0.14 ml, 1.110 mmol). The reaction mixture was stirred for 15 min at rt and then refluxed for three days. The reaction mixture was adsorbed on silica and purified by column chromatography (hexane–ethyl acetate 80:1 → 1:1) yielding 81 mg (55%) of the desired cyclopentenone **8** as a white solid. $R_f = 0.59$ (hexane–EtOAc = 3:1). ESI HRMS $[M+H]^+$ 399.2327 calculated 399.2324 $\Delta = 0.8$ ppm.
18. The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively in $CDCl_3$ (**8a**); δ_H: 7.74 (2H), 7.71 (1H, d, $J = 3.2$ Hz), 7.39 (2H), 7.33 (1H), 7.19 (1H), 6.70 (1H), 6.61 (1H), 3.76 (s, 3H, CH_3O–), 3.42 (1H, s, =CHC*H*), 2.82 (2H), 2.61 (1H, d, $J = 5.5$ Hz, COC*H*), 2.35 (1H, m), 2.20–2.01 (2H, m), 1.86 (1H, m), 1.77 (2H, m), 1.65–1.44 (2H, m), 1.42–1.14 (3H, m), 1.00 (3H, s, CH_3C); ^{13}C NMR (100 MHz, $CDCl_3$) (**8a**); δ_C: 207.7, 161.6, 157.5, 143.9, 137.7, 132.5, 131.5, 128.5, 128.4, 126.3, 113.8, 111.4, 61.8, 55.2, 49.6, 48.2, 44.6, 43.4, 41.6, 38.4, 34.3, 29.8, 29.6, 27.9, 26.3, 20.9 (**8b**); δ_H: 7.81 (1H, C*H*=), 7.76 (2H, Ph), 7.39 (3H, Ph), 7.17 (1H), 6.70 (1H), 6.61 (1H), 3.76 (s, 3H, CH_3O–), 3.01 (2H, m), 2.82 (2H, m), 2.33 (1H, m), 2.15–1.96 (2H, m), 1.89–1.70 (3H, m), 1.63–1.38 (3H, m), 1.36–1.09 (2H, m), 0.98 (3H, s, CH_3C) (**8b**); δ_C: 210.7, 159.2, 157.5, 145.1, 137.9, 132.2, 131.6, 128.5, 128.4, 127.1, 126.2, 113.7, 111.5, 55.2, 54.9, 49.4, 47.8, 43.4, 42.8, 38.3, 35.1, 30.4, 29.7, 27.8 26.4, 20.6.
19. (a) All new compounds were characterised by ^1H and ^{13}C NMR spectroscopic techniques (400 and 100 MHz, respectively) and by high resolution mass spectroscopy (ESI MS); (b) Crystal data for **8a**: $C_{28}H_{30}O_2$, FW = 398.54, monoclinic $P2_1$, $a = 11.677(2)$ $b = 6.534(1)$, $c = 14.350(3)$ Å, $\beta = 100.03(3)°$, $d_c = 1.221$ g/cm^3, Reflections collected 2922 of which 1875 ($R_{int} = 0.0449$)

independent, 272 parameters, $R1 = 0.0501$, w$R2 = 0.1310$ [$I > 2\sigma I$], $R1 = 0.0555$, $wR2 = 0.1357$ (all data), GOF = 1.129, absolute structure parameter = 0(10), largest diff. peak and hole 0.16 and 0.17 e Å^3. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606000. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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