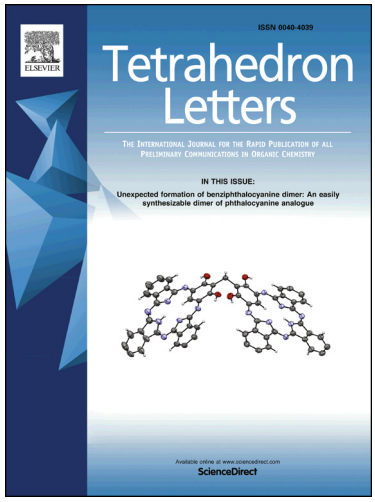

Synthesis of 16-*E*-([aryl]idene)-3-methoxy-estrones by a Palladium catalysed Mizoroki-Heck reaction

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Graphical Abstract

Synthesis of 16-*E*-([aryl]idene)-3-methoxy-estrones by a Palladium catalysed Mizoroki-Heck reaction

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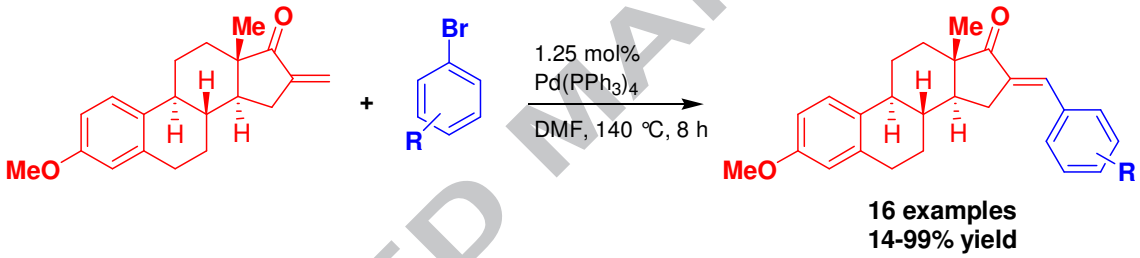

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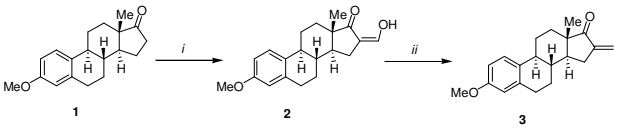
ABSTRACT

16-*E*-Arylidene-3-methoxy-estrones were synthesized using a palladium catalysed Mizoroki-Heck reaction. This methodology tolerates various functional groups and gives the corresponding products in yields between 14 and 99%, which were strongly dependent on the electronic character of the aryl halides.

Estrogenic hormones have been recognized as important contributors of estrogen dependent diseases.[1] Thus, derivatisation of estrone derivatives at various positions has been the focus of intensive research for potential pharmaceutical applications.[2] Functionalised estrones have been mainly employed as inhibitors of estrogenic receptors or imaging agents in the treatment of breast cancer.[3] In particular, the majority of breast cancers are primary initiated and stimulated by estrogenes. Especially, estradiol is known to play a crucial role as a growth factor of such tumor cells.[3,4]

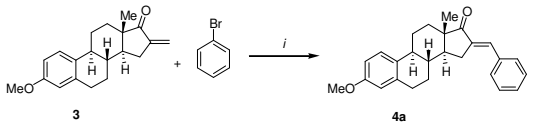
Several D-ring alkylated estrones display high affinity towards estrogenic receptors and could block the biosynthesis of estrondiol and other estrogenes, leading to a depletion of the circulation and tissue concentration of estrogenes.[5] Recently, 16-arylidene estrones have been employed in the synthesis of several bioactive compounds which show antiproliferative activity against human cancer cells.[6] Thus, the synthesis of new antiestrogenes, which influence cell growth of estrogen receptor related tumors, is of considerable current interest. As part of our ongoing interest in the palladium catalysed functionalisation of estrone, we studied the synthesis of 16-benzylidene-3-methoxy-estrones using the Mizoroki-Heck reaction.[7] The Mizoroki-Heck reaction of non-steroid exo-methylene compounds has previously been studied by other groups and has been most famously applied by Tietze and co-workers in the synthesis of enantiopure estrone.[8]

16-Methylene-3-methoxy-estrone **2** was synthesized from commercially available 3-methoxyestrone by a literature procedure (Scheme 1).[9] Next, the Mizoroki-Heck reaction was tested using phenyl bromide under different catalytic reaction conditions using DMF as solvent in the presence of NEt_3 as the base (Table 1). It became obvious that $Pd(PPh_3)_4$ was a suitable catalyst for this reaction, while the more sterically encumbered and electron-rich ligands $PtBu_3 \cdot HBF_4$ and XPhos gave lower yields. We were also able to reduce the catalyst loading to 1.25 mol% which gave even higher yields than the use of 5 mol%.



Scheme 1. Synthesis of starting material **3**; *i*: **1**, NaOMe (4 eq.), ethyl formate (30 eq.), benzene, reflux, 4 h; *ii*: **2**, formaldehyde (4 eq.), pyridine, r.t., 24 h

Table 1. Optimisation of the Mizoroki-Heck reaction[a]



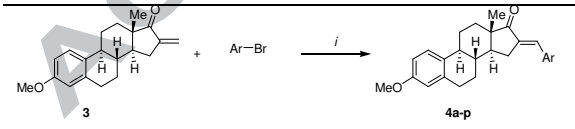
3 4a

Entry	Catalyst [mol%]	Ligand [mol%]	Yield[a] (%)
1	$Pd(OAc)_2$ [5]	XPhos [10]	74
2	$Pd(OAc)_2$ [5]	P*t*Bu$_3$·HBF$_4$ [10]	70
3	$Pd(PPh_3)_4$ [5]	-	90
4	$Pd(PPh_3)_4$ [2.5]	-	90
5	$Pd(PPh_3)_4$ [1.25]	-	96
6	$Pd(PPh_3)_4$ [0.63]	-	88
7	$Pd(PPh_3)_4$ [0.31]	-	72

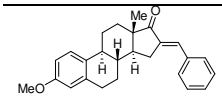
[a] Isolated yield; *Reagents and conditions i*: catalyst, ligand, DMF (4 mL), NEt_3 (0.5 mL), **3** (0.5 mmol), PhBr (0.75 mmol), 140 °C, 8 h

With our optimized conditions in hand, we started to examine the scope of the reaction.[10] Several aryl bromides could be successfully employed to give the desired products **4a-p** in 14-96% yield (Table 2). In all cases, the *E*-isomers were formed selectively. It should be noted that, while compounds **4a**, **4j**, **4k** and **4l** have previously been synthesized *via* aldol condensation, these reactions usually require highly alkaline conditions and thus result in low *E*-selectivity.[11] A broad range of functional groups were tolerated, including nitro, cyano, and acetyl groups, as well as heterocyclic starting materials. The yields were found to be strongly dependent on the substitution patterns. In general, electron poor aryl bromides gave higher yields than electron rich substrates. Aryl halides containing electron donating groups in the *ortho* or *para* positions (e.g. methoxy) resulted in a decreased yield. The presence of such a group in the *meta* position was no problem and resulted in a good yield (70%). Interesting, sterically hindered 1-bromonaphthalene gave an excellent 86% yield. Practical aspects, such as isolation of the product from by-products by column chromatography, also played an important role. In some cases, the separation from by-products was difficult and resulted in a loss of material. The use of aryl iodides or triflates did not result in an improvement of the yield.

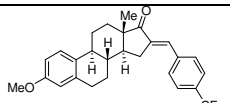
Table 2. Mizoroki-Heck reaction of **3**[a]



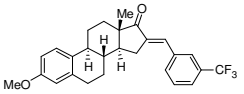
3 4a-p



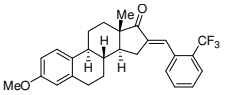
4a (96%)[b]



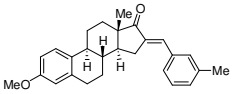
4b (40%)
mp 89-90 °C



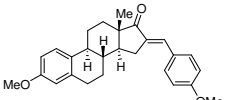
4c (15%)
mp 150-151 °C



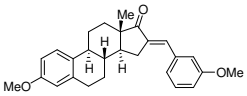
4d (38%)
mp 81-82 °C



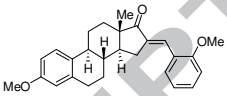
4e (99%)
mp 97-98 °C



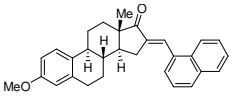
4f (17%)
mp 101-102 °C



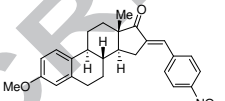
4g (70%)
mp 138-139 °C



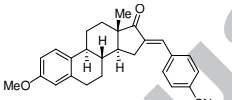
4h (24%)
mp 127-128 °C



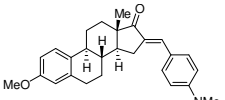
4i (86%)
mp 124-125 °C



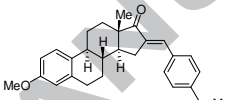
4j (58%)[b]



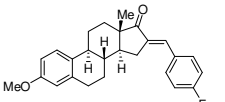
4k (33%)[b]



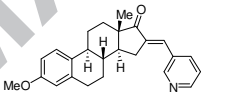
4l (14%)[b]



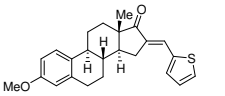
4m (51%)
mp 127-128 °C



4n (39%)
mp 172-173 °C



4o (72%)
mp 203-204 °C



4p (27%)
mp 167-168 °C

[a] *Reagents and conditions i:* $Pd(PPh_3)_4$ (1.25 mol%), **3** (0.5 mmol) ArBr (1.5 eq.), DMF (4 mL), NEt_3 (0.5 mL), 140 °C, 8 h; Isolated yield; [b] Known compound.[11a,11b]

The structures of compounds **4a**, **4n** and **4p** were independently confirmed by single crystal X-ray structural analyses (Fig. 1-3).[12] The structures clearly show the *E*-configuration of the exocyclic double bond in all cases, using electronically different substituents (phenyl, 4-fluorophenyl, 2-thienyl).

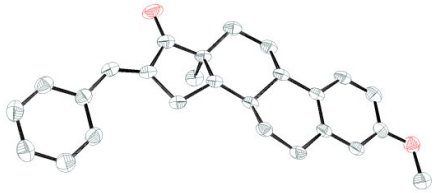


Figure 1. ORTEP plot of compound **4a**.

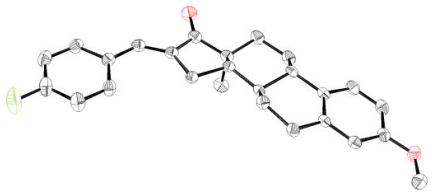


Figure 2. ORTEP plot of compound **4n**.

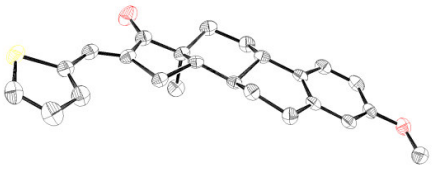


Figure 3. ORTEP plot of compound **4p**.

In conclusion, we have developed a new method for the synthesis of 16-benzylidene-3-methoxy-estrones using the Mizoroki-Heck reaction. Advantageously, the reaction can be performed with relatively low catalyst loading of $Pd(PPh_3)_4$, tolerates a wide range of functional groups and gives exclusively the *E*-configured products.

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10. **General synthetic procedure.** 3-Methoxy-16-methylene-estra-1,3,5(10)-triene-17-one **1** (1 equiv.) and $Pd(PPh_3)_4$ (1.25 mol%) were dissolved in dry DMF (4 mL) and NEt_3 (0.5 mL) in a glass tube, followed by the aryl bromide (1.5 equiv.). The tube was sealed and stirred at 140 °C for 8 h. Afterwards, water (5 mL) was added and extracted using CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using heptane/ethyl acetate.

16-*E*-(Benzylidene)-3-methoxy-1,3,5 (10)-estratriene-17-one (4a): colourless solid; (Hep/EA; 6/1), (180.2 mg, 96%); Rf (Hep/EA; 6/1) = 0.35. mp. 175-176 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.59 (d, ^4J = 1.4 Hz, 1H, Ar), 7.56 (bs, 1H, C=*C*-*H*), 7.52–7.31 (m, 4H, Ar), 7.23 (d, ^3J = 8.6 Hz, 1H, Ar), 6.74 (dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz, 1H, Ar), 6.67 (bs, 1H, Ar), 3.79 (s, 3H, OMe), 3.10–2.85 (m, 3H), 2.65–2.23 (m, 3H), 2.19–1.98 (m, 2H), 1.83–1.45 (m, 5H), 1.01 (s, 3H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ = 209.58 (C=O), 157.63 (*C*-OMe), 137.66 (C), 136.01 (C), 135.63 (C), 133.17 (CH), 132.06 (C), 130.31 (CH), 129.23 (CH), 128.68 (CH), 126.28 (CH), 113.91 (CH), 111.58 (CH), 55.20 (OMe), 48.58 (CH), 47.82 (C), 44.04 (CH), 37.98 (CH), 31.69 (CH_2), 29.64 (CH_2), 29.13 (CH_2), 26.84 (CH_2), 25.97 (CH_2), 14.55 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061 (w), 3029 (w), 2976 (w), 2920 (m), 2897 (w), 2881 (w), 2858 (w), 2842 (m), 2817 (w), 1709 (s), 1682 (w), 1651 (w), 1624 (s), 1608 (s), 1583 (m) 1572 (m), 1557 (w), 1538 (w), 1502 (s), 1465

(m), 1447 (s), 1377 (m), 1340 (m), 1334 (m), 1316 (m), 1296 (m), 1286 (m), 1246 (s), 1234 (s), 1186 (s), 1165 (m), 1116 (m), 1101 (m), 1088(s), 1074 (m), 1051 (m), 1033 (s), 1019 (m), 1001 (m), 992 (m), 970 (m), 943 (s), 924 (w), 906 (s), 864 (s), 844 (m), 822 (s), 788 (m), 772 (s), 745 (m), 686 (s), 630 (m), 614 (m), 588 (m), 566 (s), 540 (m). MS (EI, 70 eV): m/z (%) = 373 (29), 372 (M^+, 100), 228 (20), 227 (84), 186 (16), 174 (22), 160 (20), 116 (88), 115 (55), 91 (30). HRMS (EI): calculated $C_{26}H_{28}O_2$ ($[M]^+$) 372.208, found 372.208.

11. (a) J. C. Touchstone, W. H. Elliot, S. A. Thayer, E. A. Doisy *J. Am. Chem. Soc.* **1955**, *77*, 3562-3564; (b) M. Minu, D. P. Jindal, B. Leclercq *Indian J. Chem., Sect. B* **2003**, *42*, 166-172.

12. CCDC-1550963, 1550964 and 1550965 contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

- First Pd catalyzed Heck reactions of steroids
- Synthesis of various 16-*E*-Arylidene-3-methoxy-estrones
- High *E*-selectivity