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Palladium-Catalysed Sonogashira Reactions of 16-(Hydroxymethylidene)-3-methoxy-α-estrone

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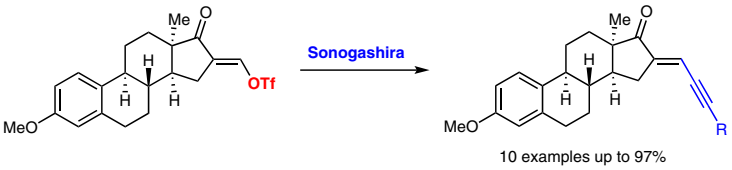

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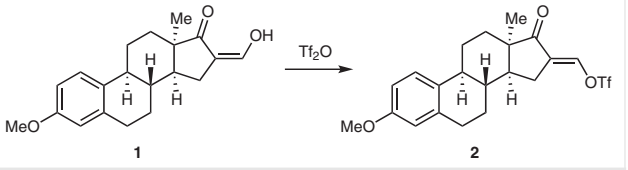
Abstract Sonogashira reactions of steroids have been studied. The reaction of α-estron-16-methylidenyloxy triflate with various alkynes afforded novel alkynylvinylidene steroids. The reactions proceeded in good to quantitative yields, with excellent *E*-selectivity and with a broad synthetic scope.

Key words estrone, steroids, Sonogashira coupling, palladium, alkynes

Steroids are widespread in nature and fulfil functions such as hormones or vitamins. They are incorporated in cell membranes and are found in several bioactive compounds. Hormones such as estrogens, which contain a characteristic aromatic A-ring, are part of the signal system in several organisms. Estradiol as well as estrone and estratriol, in their oxidized forms, have found many pharmaceutical applications.[1] Undoubtedly, one of the most famous synthetic estrone derivatives is 17α-ethynylestradiol, which is a component of contraceptive prescriptions.[2] Other estrone derivatives are known for their enzyme-inhibiting as well as antiproliferative activity.[3]

Despite the intensive research on β-estrone derivatives, reactions of α-estrones are much less studied.[4] In general, transition-metal-catalysed reactions of steroids have not been widely studied to date. In fact, Sonogashira coupling reactions of steroids have, to the best of our knowledge, not been reported in the literature. Thus, due to our ongoing interest related to the application of cross-coupling reactions on the estrone framework,[5] we were interested to study the cross-coupling reaction of the α-estrone framework, particularly on 16-(hydroxymethylidene)-3-methoxy-α-estrone (**1**), which was considered to be readily converted into its corresponding triflate **2**. In this regard we synthesized **2** from **1** using triflate anhydride, adapting a procedure known for formylcyclopentanones.[6] With this we acquired our starting material in a good yield of 76% (Scheme 1).



Scheme 1 Synthesis of the starting material **2**

Interestingly, during the reaction an isomerization occurred and the *E*-isomer was formed with excellent selectivity, which was additionally proven by X-ray crystallography (Figure 1).[7]

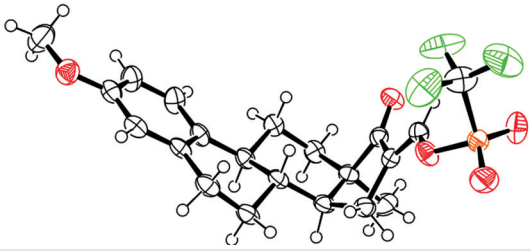
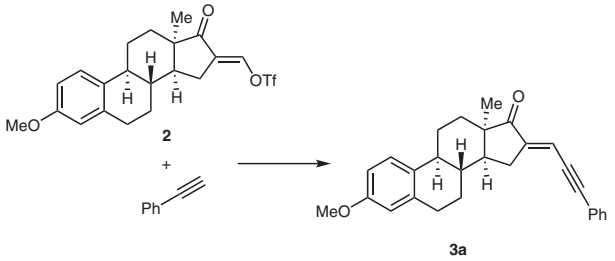


Figure 1 ORTEP of **2**

With triflate **2** in hand, we studied the Sonogashira reaction (Table 1). Our initial attempts were unsuccessful. Reaction of **2** with phenylacetylene under standard conditions, namely the use of $PdCl_2(PPh_3)_2$ and CuI as catalysts in THF/NEt_3, did not give the desired product (Table 1). Thus,

Table 1 Optimization of the Sonogashira Reaction[a]



Catalyst [mol%]	Ligand [mol%]	CuI [mol%]	Base	Temp	Time [h]	Yield [%][b]
$PdCl_2(PPh_3)_2$ [5.0]	–	5	NEt_3	65 °C	8	–
$Pd(OAc)_2$ [5.0]	$P(tBu)_3{\cdot}HBF_4$ [10]	5	NEt_3	r.t.	8	15
$Pd(OAc)_2$ [5.0]	XPhos [10]	5	NEt_3	r.t.	8	95
$Pd(OAc)_2$ [5.0]	XPhos [10]	5	$HN(iPr)_2$	r.t.	8	42
$Pd(OAc)_2$ [2.5]	XPhos [5]	2.5	NEt_3	r.t.	6	97
$Pd(OAc)_2$ [1.5]	XPhos [3]	1.5	NEt_3	r.t.	6	84
$Pd(OAc)_2$ [1.0]	XPhos [2]	1.0	NEt_3	r.t.	6	74
$Pd(OAc)_2$ [0.5]	XPhos [1]	0.5	NEt_3	r.t.	6	69

[a] Reaction conditions: **2** (0.225 mmol), CuI, Pd catalyst, ligand, phenyl acetylene (0.338 mmol), THF, base.
[b] Isolated yields.

more active ligands were tested. $P(tBu)_3{\cdot}HBF_4$ gave the target product **3a**, albeit, in low yield (15%). In contrast, **3a** was isolated in nearly quantitative yield when XPhos was employed as the ligand.[8] Interestlingly, the reaction proceeded very well at room temperature. Using this ligand allowed us to reduce the catalyst loading to 2.5 mol% without decrease of the yield, resulting in an excellent yield of **3a** of 97%. Further reduction of the catalyst amount led to lower yields.

Next, the scope of the reaction was studied (Scheme 2). The developed conditions allow for the coupling of various acetylenes and gave the desired products in moderate to excellent yields. Interestingly, the TMS group and a free amino group are tolerated under the optimized reaction conditions and lead to **3j** and **3g** in moderate to good yields of 45 and 69%, respectively. Furthermore, products containing a thienyl moiety as well as an alkyl side chain were successfully synthesized in good yields of 70 and 61%, respectively. The *E*-configuration of the products could not be specifically proven by NMR analysis; however, Sonogashira reactions are generally well known to have a high stereospecificity. Furthermore the vinylic proton of the products **3a–j** shows a coupling towards the nearest CH_2 group of approximately 2.40 Hz. The same coupling constant could be found in starting material **2**.

In summary, we have synthesized (*E*)-16-(trifluoromethane-sulfonyloxymethylidene)-3-methoxy-α-estrone (**2**) and applied it successfully in the Sonogashira reaction under mild conditions. To the best of our knowledge, these reactions represent the first examples of Sonogashira reactions of steroids. The developed methodology[9] is compatible with the presence of various functional groups and gave desired products in moderate to excellent yields.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588537.

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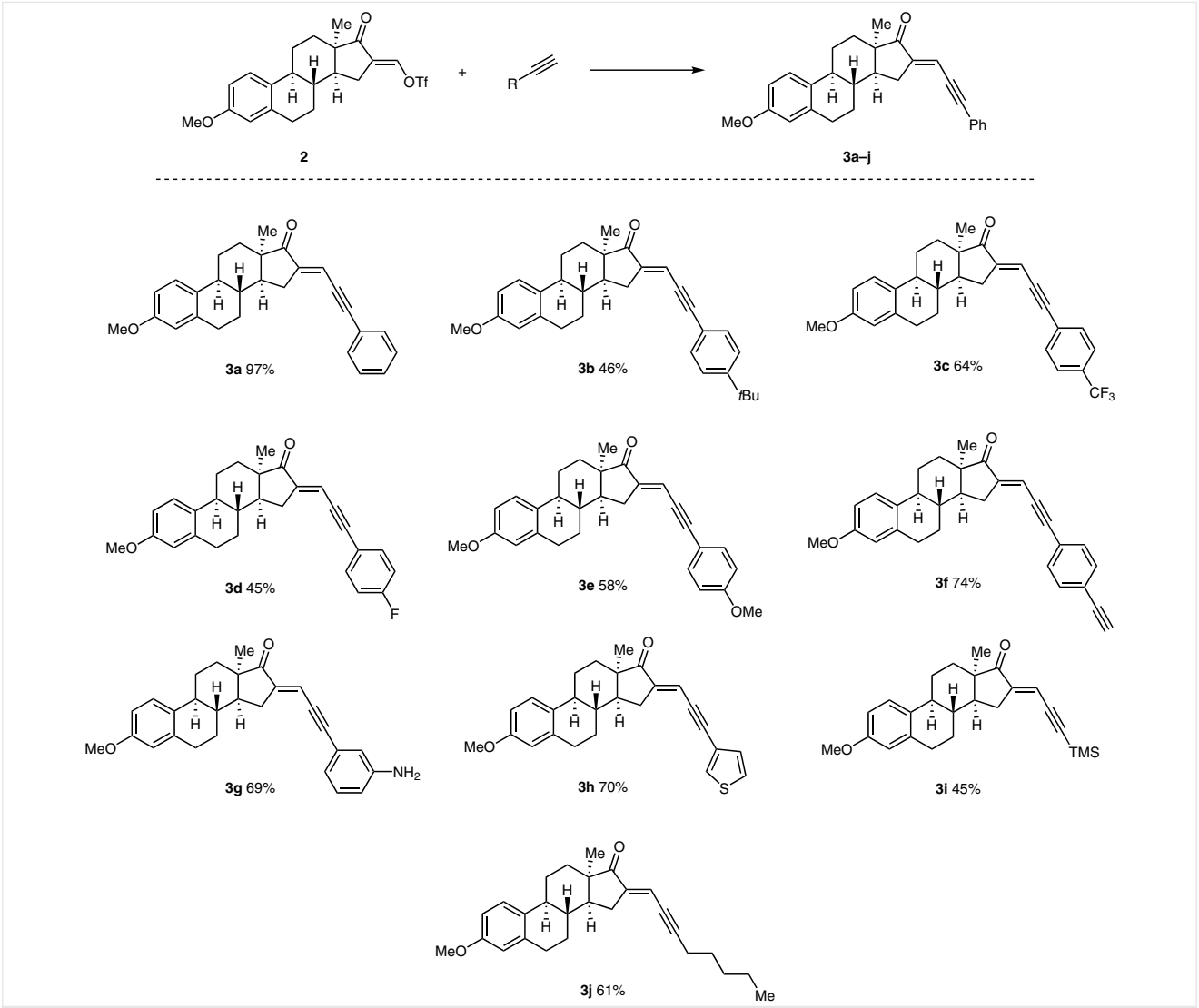
(9) **(*E*)-16-(3-Phenylprop-2-ynylidene)-3-methoxy-α-estrone (3a)**
Compound **2** (0.225 mmol, 100 mg), CuI (0.006 mmol, 2.5 mol%,



Scheme 2 Synthesis of compounds **3a–j**. *Reagents and conditions*: **2** (0.225 mmol), CuI (2.5 mol%), $Pd(OAc)_2$ (2.5 mol%), XPhos (5.0 mol%), phenyl acetylene (0.338 mmol), THF, Et_3N, r.t., 6 h; all isolated yields.

1.1 mg), $Pd(OAc)_2$ (0.006 mmol, 2.5 mol%, 1.3 mg), XPhos (0.012 mmol, 5.0 mol%, 5.7 mg), and phenylacetylene (0.338 mmol, 35 mg) were dissolved in THF (5 mL) and NEt_3 (1 mL). The reaction mixture was stirred at r.t. for 6 h. The solution was diluted with H_2O and extracted with EtOAc (3×). The crude product was purified by column chromatography on silica (elution system heptane/EtOAc, 20:1). Yield: 86 mg (97%); mp 54–55 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79–0.88 (m, 3 H), 1.10 (s, 3 H, Me), 1.43–1.51 (m, 2 H), 1.76–1.83 (m, 1 H), 2.09–2.17 (m, 1 H), 2.24–2.32 (m, 2 H), 2.40–2.48 (m, 1 H), 2.79–2.92 (m, 3 H), 3.76 (s, 3 H, OMe), 6.59 (d, ^4J = 2.71 Hz, 1 H), 6.67–6.72 (m, 2 H), 7.18 (d, ^3J = 8.58 Hz, 1 H), 7.36–7.39 (m, 3 H), 7.50–7.54 (m, 2 H).^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.5 (CH_3), 28.1, 28.3, 29.9, 30.3, 32.2 (CH_2), 41.3, 43.0, 47.6 (CH), 50.8 (C), 55.2 (OCH_3), 87.2, 101.0 (C≡C), 111.7, 113.5, 114.5 (CH), 122.7 (C), 126.9, 128.5, 129.2 (CH), 131.8 (C), 131.9 (CH), 138.0, 146.1, 157.5 (C), 207.4 (C=O). IR (ATR,): 2918 (w), 2187 (w), 1711 (w), 1609 (w), 1498 (w), 1448 (w), 1257 (m), 1076 (m), 1016 (s), 870 (w), 793 (s), 755 (m), 688 (m), 531 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 397 (16), 396 (M^+, 78), 227 (15), 210 (14), 186 (10), 178 (11), 174 (15), 173 (12), 165 (24), 160 (14), 158 (13), 153 (13), 152 (12), 147 (11), 145 (15), 144 (11), 141 (23), 140 (100), 139 (96), 129 (16), 128 (17), 126 (17), 115 (25), 114 (18), 102 (18), 91 (21), 65 (11). ESI-HRMS: *m/z* calcd for $C_{28}H_{29}O$ [M + H^+]: 397.21621; found: 397.21644.