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Novel 17α-ethynylestradiol derivatives: Sonogashira couplings using unprotected phenylhydrazines

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Abstract

The Pd/Cu catalyzed coupling of 17α-ethynylestradiol with halogenated amino-substrates was investigated. Iodophenylhydrazine and its protected derivatives reacted with 17α-ethynylestradiol to give 4-hydrazinophenyl derivatives without any degradation of the hydrazine group. Unprotected 3-, and 4-iodoaniline reacted similarly to produce the aminophenyl-derivatives. Protection of the amino group of halogenated benzylamines was required for alkyne coupling reactions, in order to avoid competing *ortho*-palladation of the benzylamine substrates. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: amine; hydrazine; palladium; steroid.

There has been a great deal of interest in the synthesis of estradiol derivatives with enhanced binding affinity for the estrogen receptor. We desired a direct route for preparing aniline, benzylamine, and phenylhydrazine derivatives appended to the ethynyl group of 17α-ethynylestradiol **1a**. The Sonogashira coupling of alkynes with aryl iodides and bromides catalyzed by Pd(O) and Cu(I) provides a mild, and efficient way to synthesize aryl alkynes;[1–5] however, very few examples of the coupling reaction with amino-substrates have been reported,[6–8] and there are no examples of the alkyne coupling reaction with halogenated unprotected phenylhydrazines. Herein we describe the synthesis of eight derivatives of 17α-ethynylestradiol, and identify the scope and limitations of the Sonogashira coupling reaction with hydrazine, and amine-containing substrates.

The Pd/Cu(I) catalyzed coupling reaction between **1a** and 3-iodoaniline **2a** in diethylamine at 25°C gave the desired *m*-aniline derivative **3a** in excellent yield (Scheme 1). The coupling was also successful using 4-iodoaniline **2b** to give the *p*-substituted compound **3b** in 89% yield (Table 1). Attempts to couple **1a** with 3-iodobenzylamine or 4-bromobenzylamine directly using these conditions were unsuccessful, and only self-coupling of the alkyne and degradation of the starting benzylic amines were observed. Benzylamines have been reported to undergo a direct *ortho*-palladation reaction with $Pd(OAc)_2$,[9,10]

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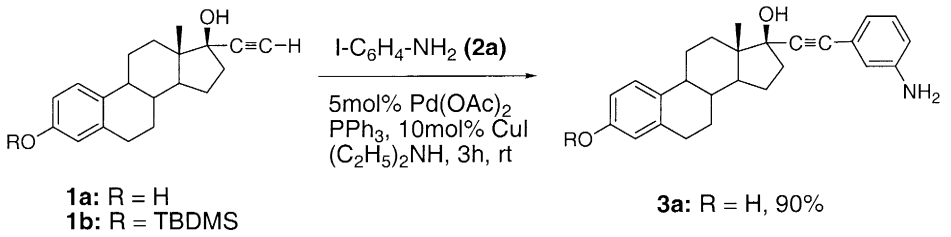
which would prevent the desired catalytic cycle for alkyne coupling. The first step in the *ortho*-palladation involves coordination of the benzylamine, therefore we converted the amine to a non-coordinating derivative. The ^{t}butoxycarbonyl-protected (BOC-) 3-iodobenzylamine **2d** reacted smoothly with **1a** to produce the coupled product **3d** in 75% yield.[7] Deprotection of this compound in 3N HCl/EtOAc gave the benzylic amine derivative **3c** in 80% yield. The coupling reaction was also successful using the BOC-protected 4-bromobenzylamine **2e**, but due to the reduced reactivity of aryl bromides, heating for 4 h at 60°C was required for complete conversion.



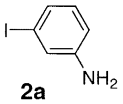
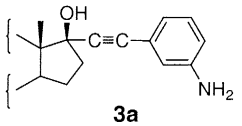
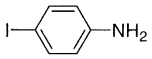
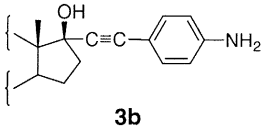
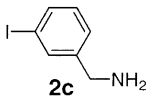
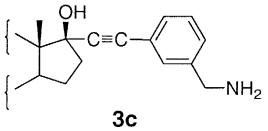
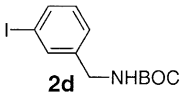
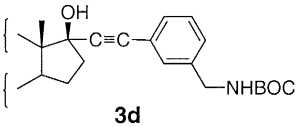
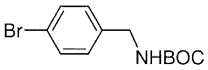
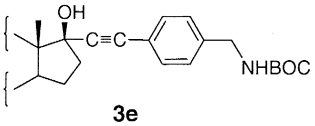
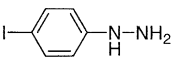
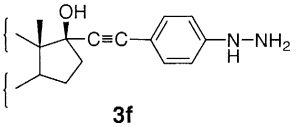
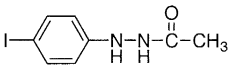
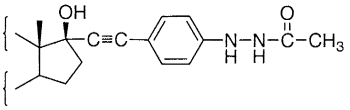
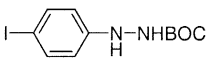
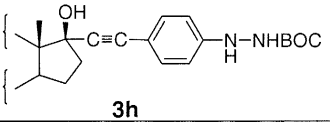
Scheme 1.

The catalytic coupling of hydrazine derivatives is complicated by the competing possibilities of hydrogen transfer chemistry, and reductive cleavage of the N–N bond.[11] The monoarylhydrazine **2f** underwent the coupling reaction catalyzed by Pd/Cu(I) to give the *p*-phenylhydrazine derivative **3f** in 87% yield. This is the first example of a coupling reaction involving an unprotected mono-substituted hydrazine. The acetyl- and BOC-protected hydrazine derivatives **2g**, and **2h** were also converted to the alkyne products in very good yields. The ^{t}butyldimethylsilyl ether group (TBDMS) of the protected estradiol derivative **1b** and the BOC group of **2h** were stable under the mild reaction conditions which were used to produce **3h**. The hydrazine products were easily isolated by evaporation of the diethylamine solvent followed by silica gel chromatography eluted with 5% CH_3OH/CH_2Cl_2.

In summary, the Sonogashira coupling with amine and hydrazine substrates provides an efficient method for derivatizing 17α-ethynylestradiol. The mild reaction conditions, protecting group tolerance, simple workup procedures, and very good product yields are particularly advantageous. No complications from side reactions of the hydrazine group, or degradation of the sensitive phenol and tertiary alcohol functional groups of the steroid were observed. Benzylic amine substrates must first be protected before undergoing the coupling reaction, and the BOC group can be easily removed from the alkyne product. This procedure should be of general utility for the synthesis of conjugated aniline, benzylamine, and phenylhydrazine derivatives.

Typical experimental procedure: Synthesis of 17α-(3′-aminophenyl)ethynylestradiol (**3a**): A solution of palladium acetate (6.0 mg, 0.025 mmol) and triphenylphosphine (13 mg, 0.05 mmol) in diethylamine (3 mL) was stirred under argon for 10 min. Copper(I) iodide (10 mg, 0.05 mmol) and 3-iodoaniline **2a** (110 mg, 0.50 mmol) were added; after 5 min **1a** (148 mg, 0.50 mmol) was added and the reaction stirred for 3 h. Diethylamine was removed in vacuo. The residue was chromatographed on a silica gel column (25 g), eluted with 5% CH_3OH/CH_2Cl_2 to give **3a** (170 mg, 89% yield) as a white solid: mp 151–153°C; FT-IR (KBr, cm^{-1}) 3376, 1601, 1499, 786, 688; ^{1}H NMR (25% DMSO-d_6/$CDCl_3$) δ 8.62 (br s, 1H), 7.08 (d, J=8.8 Hz, 2H), 7.02 (t, J_1=9.0 Hz, J_2=8.2 Hz, 1H), 6.80–6.45 (m, 5H), 4.95 (br s, 1H), 2.76 (s, 2H), 2.40–1.20 (m, 14H), 0.88 (s, 3H); ^{13}C NMR δ 154.39, 146.87, 137.09, 130.41, 128.50, 125.61, 123.28, 120.06, 116.74, 114.67, 114.17, 112.35, 92.95, 84.68, 78.68, 49.05, 46.96, 43.15, 39.9, 39.5, 32.54, 29.05, 26.75, 25.99, 22.33, 12.44; anal. calcd for $C_{26}H_{29}NO_2$–$0.5H_2O$: C, 78.75; H, 7.63; N, 3.53. Found: C, 78.47; H, 7.49; N, 3.81.

Table 1
Coupling of 17α-ethynylestradiol **1a** with amines, and hydrazines[a]

Entry	Aryl halide	Coupled product	Yield (%)[b]
1	 **2a**	 **3a**	90
2	 **2b**	 **3b**	89
3	 **2c**	 **3c**	0
4	 **2d**	 **3d**	75
5	 **2e**	 **3e**	76
6	 **2f**	 **3f**	87
7	 **2g**	 **3g**	76
8	 **2h**	 **3h**	80[c]

[a] All reactions were carried out under argon at room temperature except entry 5 which was heated to 60 °C. [b] All yields are of pure products isolated by silica gel column chromatography, and all the products gave satisfactory spectral and analytical data. [c] Alkyne **1b** was used

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