Pd(0)-Mediated Cross Coupling of 2-Iodoestradiol with Organozinc Bromides: A General Route to the Synthesis of 2-Alkynyl, 2-Alkenyl and 2-Alkylestradiol Analogs

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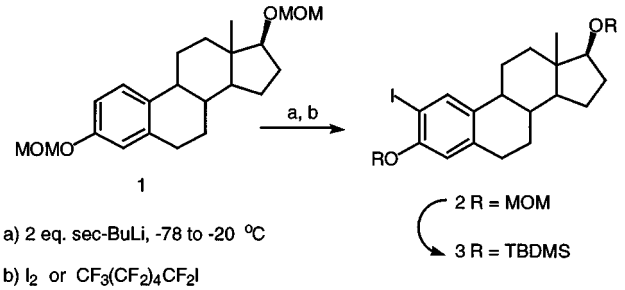
Abstract: Treatment of 3,17-*O*-bis(*tert*-butyldimethylsilyl)-2-iodoestradiol with in situ-generated organozinc bromides in the presence of a catalytic amount of $Pd(PPh_3)_4$ as a Pd(0) source led to efficient displacement reactions.

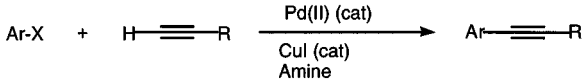
Keywords: estradiol, antitumor compounds, palladium, cross coupling, organozinc bromides

In order to define the structural parameters associated with the antitublin activity[1] and cytotoxicity[2,3] of 2-methoxyestradiol, an array of 2-substituted estradiol analogs were synthesized and evaluated for biological activity.[4,5] Several of them were very potent inhibitors of tubulin polymerization acting at the colchicine binding site. In view of the cytotoxic activities of these compounds in human cancer cell cultures, a systematic study was undertaken to synthesize 2-alkynyl, 2-alkenyl, and 2-alkylestradiols. Regioselective lithiation of 3,17-*O*-bis(methoxymethyl)estradiol **(1)**[6] followed by quenching with I_2 or perfluorohexyl iodide[7] gave the 2-iodoestradiol derivative **2** in 78% yield (Scheme 1). Deprotection of the two hydroxyl groups followed by reprotection with TBDMSCl gave compound **3**.[8]

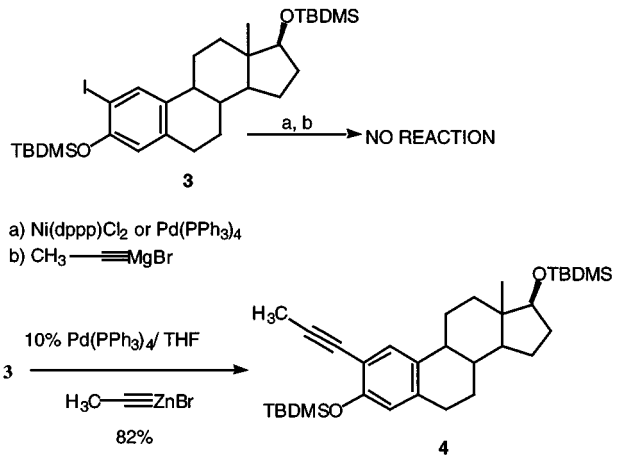


Scheme 1

The Sonogashira procedure involving the reaction of terminal alkynes with aryl halides in the presence of amines and a catalytic amount of Pd(II) complex and CuI (Scheme 2) has been widely used for the synthesis of arylalkynes.[9-11] However, the reaction of compound **3** with propyne under the Sonogashira coupling conditions provided only a 12% yield of the required product.[5] Since relatively large amounts of 2-propynylestradiol were needed for its preclinical development as an anticancer agent, it was decided to develop a more practical route for its synthesis which could possibly be extended to the preparation of related compounds as well.



Scheme 2

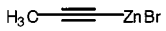
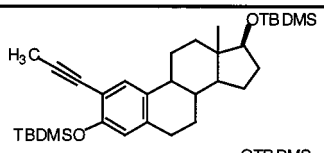
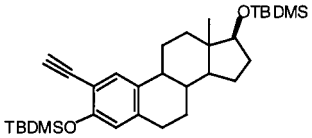
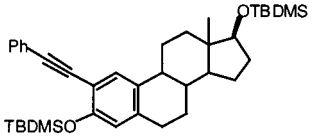
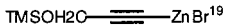
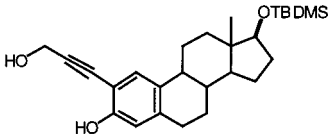
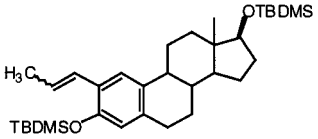
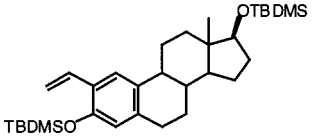
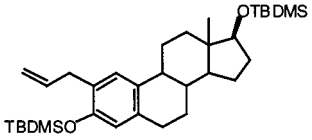
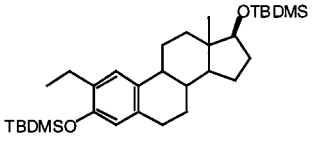


Scheme 3

Initially, the coupling reaction of compound **3** was attempted unsuccessfully under Kumada conditions using commercially available 1-propynylmagnesium bromide. The use of $Pd(PPh_3)_4$ in place of the Ni(II) complex also failed. Finally, the 2-propynylestradiol analog **4** was prepared in 82% yield in the presence of tetrakis(triphenylphosphine)palladium and in situ-generated 1-propynylzinc bromide.[10] Under these conditions the coupling reaction was very facile and the starting material was totally consumed.

Encouraged by the remarkable effect of the employment of the organozinc bromide, the coupling reaction was extended further to the synthesis of several alkynyl, alkenyl and alkyl estradiol analogs. As documented in Table 1, the presently employed Negishi coupling procedure[12] pro-

Table 1. Coupling Reaction of Iodo Compound 3 with Organozinc[18] Reagents.

Entry	Organozinc reagents	Product [15]	Isolated yield(%)
1			82
2			95
3			72
4			73[a]
5	$CH_3CH{=}CH{-}ZnBr$[b]		94[c]
6	$CH_2{=}CH{-}ZnBr$		92[20]
7	$CH_2{=}CHCH_2{-}ZnBr$		75
8	$CH_3CH_2{-}ZnBr$		86

[a]The product was isolated after acidic work-up with *p*-toluene sulfonic acid. [b]This reagent was prepared from commercially available 1-propenylmagnesium bromide of unknown stereochemistry.

ceeds very well with sp (entries 1-4), sp^2 (entries 5 and 6), and sp^3 (entries 7 and 8) carbon-based organozinc reagents.[13-17] Excellent yields were obtained in most of the cases and the formation of side products was minimal.

In summary, we have developed a mild, efficient and general synthetic route to several 2-substituted estradiol analogs using in situ-generated organozinc bromides in the presence of Pd(0). Further studies of the scope and utility of this method are presently under investigation.

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References and Notes

(1) D'Amato, R. J.; Lin, C.; Flynn, E.; Folkman, J.; Hamel, E. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3964.
(2) Seegers, J. C.; Aveling, M.-L.; Aswegen, C. H.; Cross, M.; Koch, F.; Joubert, W. S. J. *Steroid Biochem.* **1989**, *32*, 797.

(3) Lottering, M.-L. Haag, M.; Seegers, J. C. *Cancer Res.* **1992**, *52*, 5926.
(4) Cushman, M.; He, H.-M.; Katzenellenbogen, J. A.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1995**, *38*, 2041.
(5) Cushman, M.; He, H.-M.; Katzenellenbogen, J. A.; Varma, R. K.; Hamel, E.; Lin, C. M.; Ram, S.; Sachdeva, Y. P. *J. Med. Chem.* **1997**, *40*, 2323.
(6) Lovely, C. J.; Gilbert, N. E.; Liberto, M. M.; Sharp, D. W.; Lin, Y. C.; Brueggemeier, R. W. *J. Med. Chem.* **1996**, *39*, 1917.
(7) Shimizu, T.; Koizumi, T.-a.; Yamaguchi, I.; Osakada, K.; Yamamoto, T. *Synthesis* **1998**, 259.
(8) He, H.-M.; Fanwick, P. E.; Wood, K.; Cushman, M. *J. Org.Chem* **1995**, 60, 5905.
(9) Sonogashira, K.; Tohda, Y.; Hagihara, N. A. *Tetrahedron Lett*. **1975**, 4467.
(10) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.
(11) Krause, M.; Ligneau, X.; Stark, H.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1998**, *41*, 4171.
(12) Negishi, E.-i, Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957.
(13) Knochel, P.; Peria, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
(14) Palmgren, A.; Thorarensen, A.; Bäckvall, J.-E. *J. Org.Chem.* **1988**, *63*, 3764.
(15) Betzemeier, B.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2623.
(16) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.
(17) Kristensen, J.; Begtrup, M.; Vedsø,P. *Synthesis* **1998**, 1604.
(18) The organozinc bromides were prepared from the corresponding Grignard reagent and anhydrous $ZnBr_2$ in dry THF.
(19) The corresponding Grignard reagent was not commercially available. It was prepared from propargyloxy trimethylsilane and ethylmagnesium bromide in THF.
(20) The crude product was contaminated with 3,17-*O*-bis(*tert*-butyldimethylsilyl)estradiol. However, when the coupling reaction was carried out with the iodo compound **2** instead of **3**, the corresponding 2-vinyl-3,17-bis(methoxymethyl)-estradiol was isolated in 89% yield as a pure compound.
(21) Satisfactory spectral and analytical data were obtained for all of the products. A typical experimental procedure is as follows (Table 1, entry 2): Anhydrous $ZnBr_2$ (0.289 g, 1.28 mmol) was dissolved in dry THF (40 mL) under argon. A solution of ethynylmagnesium bromide in THF (2.6 mL, 0.5 M) was added, and the reaction mixture was stirred under argon (solution turns turbid). After 10 min, $Pd(PPh_3)_4$ (0.074 g, 0.064 mmol) and iodo compound **3** (0.4 g, 0.64 mmol) were added, and the stirring was continued for 6 h at rt. The reaction mixture was poured into ice water (100 mL), extracted with ethyl acetate (3 X 20 mL), washed with brine (50 mL) and dried (Na_2SO_4). The removal of organic solvent followed by column chromatographic purification (silica gel, 230-420 mesh, 5% ethyl acetate in hexane) gave pure product (0.32 g, 95%) as a pale yellow solid: mp 126-128 °C; IR (KBr) 3307, 2925, 2855, 2101, 1488, 1398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1 H), 6.49 (s, 1 H), 3.61 (t, J = 6 Hz, 1 H), 3.10 (s, 1 H), 2.77-2.75 (m, 13 H), 0.96 (s, 9 H), 0.87 (s, 9 H), 0.71 (s, 3 H), 0.22 (s, 6 H), 0.05 (s, 6 H). Anal. Calcd for $C_{32}H_{52}O_2Si_2$: C, 73.22; H, 9.98. Found: C, 73.14; H, 10.26.

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