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SYNTHESIS OF BROPARESTROL USING PALLADIUM-CATALYZED CROSS-COUPLING

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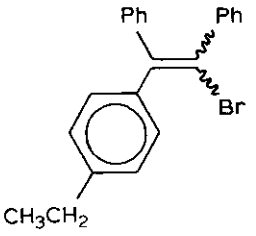
Summary

The synthesis of broparestrol, a biologically active tetrasubstituted olefin used in dermatology, was achieved via palladium-catalyzed cross-coupling to form a C–C bond followed by bromination.

Broparestrol (a *cis-trans* mixture of α-bromo-α,β-diphenyl-β-(*p*-ethylphenyl)ethylene) (**1**) is an estrogen, used in dermatology [1,2]. In this paper we report two advantageous methods of synthesizing broparestrol involving palladium-catalyzed cross-coupling.



(1)

We found that the broparestrol precursor, α,β-diphenyl-β-(*p*-ethylphenyl)ethylene (**2**) could be synthesized by a method based on that used in our recently described synthesis of tamoxifen [3]. Thus diphenylacetylene (**3**) was hydroaluminated with diisobutylaluminium hydride to give a vinylalane intermediate [4], which was cross-coupled with *p*-bromo(ethyl)benzene in presence of a catalytic amount (0.05%) of tetrakis(triphenylphosphine)palladium [5] to give the desired precursor **2**. Precursor **2** was also synthesized by cross-coupling of α-bromo-α,β-diphenylethylene (**4**) with *p*-ethylphenylzinc chloride in the presence of catalytic amount (0.05%) of tetrakis(triphenylphosphine)palladium. It was found that *p*-ethylphenylzinc chloride needed for this coupling could be prepared in situ by reaction

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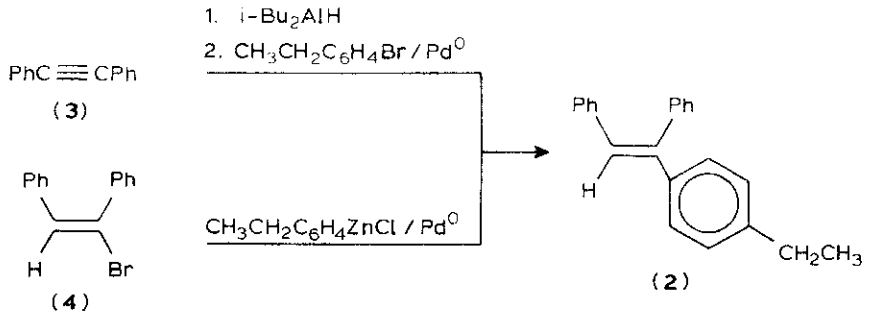
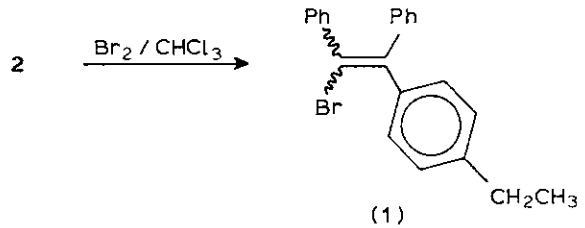
of *p*-bromo(ethyl)benzene with lithium metal followed by treatment with anhydrous zinc chloride in dry tetrahydrofuran.



Finally, **2** was converted into broparestrol by treatment with bromine in dry chloroform.



This new methodology for the synthesis of broparestrol appears to have distinct advantages over previously described methods [6].

Preparation of broparestrol (1)

From diphenylacetylene (3)

To 5 mmol of diphenylacetylene (**3**) in 6 ml of hexane was added dropwise 6 ml of 1 *M* diisobutylaluminium hydride in hexane (3 mmol, 1.2 equiv) at 0°C, and the mixture was allowed to warm to room temperature, then stirred at that temperature for 1 h and at 55°C for 18 h. The mixture was subsequently treated with a mixture of 5 mmol (1 equiv) of *p*-bromoethylbenzene and 0.25 mmol (0.05 equiv) of tetrakis(triphenylphosphine)palladium in 12 ml of dry tetrahydrofuran. The mixture was refluxed for 24 h, cooled to room temperature, and quenched with 3 *N* hydrochloric acid. The usual work-up and evaporation of solvents gave a colorless product, which was treated with 5.25 mmol (1.05 equiv) of bromine in 12 ml anhydrous chloroform. The solution was refluxed for 3 h during which hydrogen bromide was evolved. Work-up and evaporation of the solvents left a residue, which was recrystallized from ethanol to give 3 mmol (60% overall yield) of broparestrol as a white crystalline solid, m.p. 95–102°C (lit. [9] 89–101°C). Its spectra were superimposable upon those of an authentic sample and a single peak was obtained when a mixture of the product with an authentic sample was examined by GLC (OV1 glass column).

From α-bromo-α,β-diphenylethylene (4)

A solution of *p*-ethylphenylzinc chloride was prepared by adding (*p*-ethylphenyl)lithium (prepared by treating *p*-ethylbromobenzene (8 mmol, 2 equiv) with lithium metal (24 mmol, 6 equiv) in 5 ml of anhydrous ether at room temperature for 2 h) to a solution of anhydrous zinc chloride (8 mmol, 2 equiv) in anhydrous tetrahydrofuran (12 ml). The solution was refluxed for 30 min then cooled to room temperature. To 0.2 mmol (0.05 equiv) of tetrakis(triphenylphosphine)palladium contained in a separate flask was added 4 mmol of α-bromo-α,β-diphenylethylene (**4**) in 8 ml of anhydrous tetrahydrofuran, followed by the (*p*-ethylphenyl)zinc chloride solution. The mixture was refluxed for 10 h. Work-up and evaporation of solvents gave a colorless product which was treated with bromine as previously described to give the desired broparestrol in 65% overall yield.

Acknowledgement

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