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Synthesis of Hydroxytamoxifen

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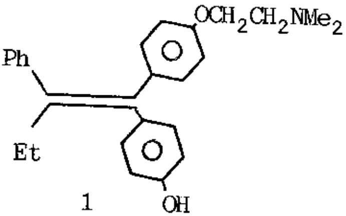
Summary: The synthesis of hydroxytamoxifen, antiestrogenic tetrasubstituted olefin was achieved via palladium-catalyzed cross-coupling of vinyl bromide with arylzinc chloride.

Hydroxytamoxifen (1) "1-(4-[2-(dimethylamino)ethoxy] phenyl)-1-(4-hydroxyphenyl)-2-phenyl-1-butene" is a biologically active tetrasubstituted olefin, which has antiestrogenic activity.[1,2]

In animal studies, antiestrogenic potency is greater in hydroxytamoxifen(1) relative to z-tamoxifen.[2,3,4]



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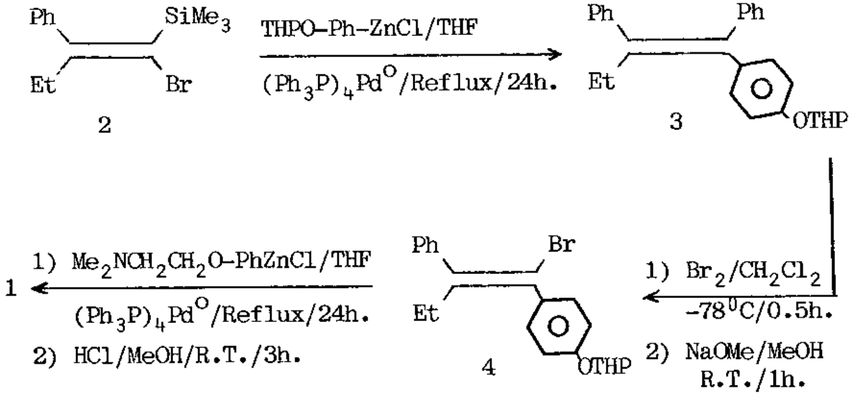
In this paper we report the synthesis of hydroxytamoxifen (1) via palladium-catalyzed cross-coupling of vinyl bromide with arylzinc chloride.

Bromovinylsilane (2) has been previously synthesized by us[5] via treatment of phenyl(trimethylsilyl)acetylene with diethylaluminium chloride-titanocene dichloride to give vinylmetal which was cleaved with N-bromosuccinimide. Compound (2) was converted to compound (3) via treatment of 2 with 4-[(2-tetrahydropyranyl)oxy]phenylzinc chloride in the presence of catalytic amount of palladium zero. Trimethylsilyl group was replaced by bromine by treatment of 3 with bromine-sodium methoxide[6]. It was observed that ~ 15% cleavage of the tetrahydropyranyl ether was obtained in the crude reaction product. This material could either be separated from 4 by column chromatography or reprotected by treating the crude reaction product with dihydropyran and a catalytic amount of phosphorus oxychloride[7]. Compound (4) was converted to the desired hydroxytamoxifen (1) via treatment of 4 with 4-[2-(dimethylamino)ethoxy]phenylzinc chloride in the presence of catalytic amount of palladium zero followed by removal of the tetrahydropyranyl ether by exchange with methanol, using hydrochloric acid as a catalyst.[7]



Experimental

All reactions were stirred magnetically and carried out under an atmosphere of nitrogen in oven-dried (160^{0}C) glassware. Tetrahydrofuran and hexane solvents were distilled over sodium and benzophenone. Other solvents were dried and distilled prior to use.

Preparation of 1-(trimethylsily)-1-(4-[(2-tetrahydropyranyl)oxy]phenyl)-2-phenyl-1-butene(3).

A solution of 4-[(2-tetrahydropyranyl)oxy]phenyl zinc chloride was prepared by adding the corresponding aryllithium [prepared by reacting the corresponding aryl bromide (5 mmol) with n-butyllithium (5 mmol) in 15 ml of dry tetrahydrofuran at -78^{0}C for 0.5 h] to a solution of anhydrous zinc chloride (5 mmol) in 10 ml of dry tetrahydrofuran. The resultant solution was refluxed for 0.5 h and then cooled to room temperature.

To a separate flask containing tetrakis (triphenylphosphine) palladium (0.25 mmol, 0.05 equiv) was added (z)-1-bromo-1,2-diphenyl-1-butene (4.5 mmol) in 15 ml of dry tetrahydrofuran, followed by addition of 4-[(2-tetrahydropyranyl)oxy]phenylzinc chloride prepared above. The resulting mixture was refluxed for 24 h. At the end of this time the reaction mixture was quenched with water. Usual work-up and evaporation of solvents gave 4.2 mmol of the crude olefin(3).

Preparation of 1-bromo-1-(4-[(2-tetrahydropyranyl)oxy]phenyl)-2-phenyl-1-butene(4):

To a solution of 4 mmol of compound(3) in 4 ml of dichloromethane cooled to -78^{0}C was added dropwise a 1M solution of bromine (4.8 mmol) in dichloromethane, followed by addition of 1M solution of sodium methoxide (5 mmol) in methanol. The reaction mixture was allowed to warm to room temperature and then stirred for 1h. Usual work-up and evaporation of solvents gave a residue which was chromatographed to give 3 mmol of vinyl bromide(4) in 60% overall yield from compound (2).

Preparation of Hydroxytamoxifen(1):

A solution of 4-[2-(dimethylamino)ethoxy]phenyl zinc chloride was prepared by adding the corresponding Grignard reagent [prepared by refluxing the corresponding aryl bromide (2 mmol) with magnesium (6.15 mmol) in 30 ml of dry tetrahydrofuran, ethylene bromide (4.10 mmol) was added in small portions over a 3 h period to facilitate formation of Grignard reagent] to a solution of anhydrous zinc chloride (2 mmol) in 5 ml of dry tetrahydrofuran. The resulting solution was refluxed for 1 h and then cooled to room temperature.

In a separate flask containing tetrakis (triphenylphosphine) palladium (0.1 mmol, 0.05 equiv) was added 1.8 mmol of vinylbromide (4) in 5 ml of dry tetrahydrofuran, followed by addition of 4-[2-(dimethylamino)ethoxy]phenyl zinc chloride prepared above. The resulting mixture was refluxed for 24 h. At the end of this time the reaction mixture was quenched with water. Usual work-up and evaporation gave crude dihydropyranyl ether of hydroxytamoxifen which was dissolved in 4 ml methanol and treated with three drops of 3M hydrochloric acid at room temperature for 3 h. At the end of this time, the reaction mixture was treated with aqueous sodium hydroxide. Usual work-up and evaporation gave viscous oil. Recrystallization from hexane-tetrahydrofuran gave 0.9 mmol (50% yield) of the desired hydroxytamoxifen.

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