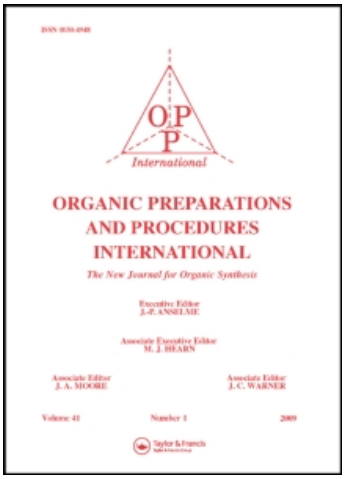

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A ONE-STEP SYNTHESIS OF CLOMID INTERMEDIATE

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A ONE-STEP SYNTHESIS OF CLOMID INTERMEDIATE

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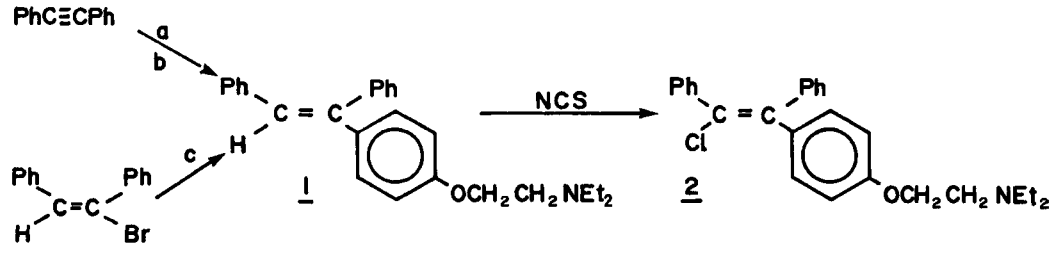
Clomiphene citrate (Clomid), a mixture of the citrate salt of E- and Z-isomers of N,N-diethyl-2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]ethanamine (1), is one of the most common drugs used for the treatment of infertility; it is used to induce ovulation and hence promote fertility in anovulatory women who have functional ovaries and adenohypophysis. Clomid acts directly on the hormone regulatory process in the brain to cause increased pituitary hormone release which in turn triggers ovulation.[1] Clomid is an expensive drug, due in part to the difficulty in preparing it.[2] This paper reports a short method for the preparation of a key clomid intermediate 2. Compound 2 could be obtained by hydroalumination of diphenylacetylene followed by C-C cross-coupling of the resulting vinylalane with the aryl bromide[3] using catalytic amount of tetrakis(triphenylphosphine)palladium (60% yield) and by direct palladium-catalyzed cross-coupling of vinyl bromide[4] with arylzinc chloride (70% yield). This direct cross-coupling failed in the past[5] because of the difficulty in obtaining the corresponding arylzinc chloride. This problem has been resolved by treatment of one equivalent of 4-[2-(diethylamino)ethoxy]phenyl bromide with magnesium in the presence of two equivalents of ethylene dibromide which was added in small portions over 3 hrs to facilitate formation of Grignard reagent. The intermediate 2 could be transformed into clomid by treatment with N-chlorosuccinimide in chloroform, followed by treatment of the



a) i-Bu_2AlH b) p-$(Et_2NCH_2CH_2O)C_6H_4Br$, $(Ph_3P)_4Pd$
c) p-$(Et_2NCH_2CH_2O)C_6H_4ZnCl$, $(Ph_3P)_4Pd$

chlorinated product with equivalent amount of citric acid as previously described.[2] Compared to the published methods,[2] this route clearly is the shortest and most efficient known and appears to be promising for the synthesis of clomid and derivatives.

Though previously investigated, the stereochemistry of the hydroalumination[4] and the cross-coupling[6] is not important here (the chlorination step gives a mixture of E and Z isomers) because clomid is a mixture of isomers.

EXPERIMENTAL SECTION

Mps are uncorrected. IR spectra were recorded on a Beckman IR-8 spectrophotometer and calibrated against polystyrene. ^{1}H NMR spectra were obtained on JEOL JNM FX-100 spectrometer; chemical shifts are reported as δ values in part per million (ppm) downfield from internal TMS. Glpc analyses were performed on PYE Unicam series 304 chromatograph with OV1 glass column. Diisobutylaluminium hydride (Fluka) was used as 1M solution in hexane. All reactions were stirred magnetically and carried out under an atmosphere of nitrogen in oven-dried (160°) glassware. Tetrahydrofuran and hexane were distilled over sodium benzophenone ketyl. Other solvents were distilled and dried prior to use.

cis-1,2-Diphenyl-1-[4-(2-diethylaminoethoxy)phenyl]ethylene (2). Route A (via Palladium-catalyzed Cross-coupling of Vinylalane).- A solution of the vinylalane was prepared by the dropwise addition of 15 mL (15 mmol, 1.2 equiv) of 1M diisobutylaluminium hydride in hexane to 2.23 g (12.5 mmol, 1 equiv) of diphenylacetylene in 15 mL of hexane at 0°; it then was allowed to warm up with stirring to room temperature for 1 hr and then heated at 55° for 18 hrs and then cooled to room temperature.

To a separate flask containing tetrakis(triphenylphosphine)palladium (0.722 g, 0.625 mmol, 0.05 equiv) was added 4-[2-(diethylamino)ethoxy]phenyl bromide[3] (3.1 g, 12.5 mmol, 1 equiv) in dry tetrahydrofuran (24 mL); this mixture was then added to the vinylalane solution prepared above. The reaction mixture was refluxed for 24 hrs. At the end of this time, the resulting mixture was cooled to room temperature and quenched with 40 ml water and throughly extracted with 3 x 60 ml of ether. The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent and treatment of the crude product with hydrogen chloride gas followed by recrystallization (ethyl acetate-hexane) gave 3.05 g (60%) of the desired hydrochloride salt of 2 as a white crystalline solid, mp. 129-132°, lit.[7] 137-140°; ^{1}H NMR ($CDCl_3$): δ 1.51 [m, 6H, $(\underline{CH_3}CH_2)_2$], 3.33 [m, 4H, $(CH_3\underline{CH_2})_2$], 3.54 [m, 2H, NCH_2], 4.50 [m, 2H, $-CH_2O$] and 6.85-7.33 [m, 15H, aromatic H and vinyl H]. Comparison with an authentic sample[7] gave superimposable spectra and a single peak upon co-injection by glpc (OV1 glass column).

Route B (via Palladium-catalyzed Cross-coupling of Vinyl Bromide).- A solution of 4-[2-(diethylamino)ethoxy]phenylzinc chloride was prepared by addition of the corresponding Grignard reagent [prepared by refluxing the corresponding aryl bromide (0.754 g, 3.1 mmol,

1 equiv) with magnesium (0.225 g, 9.3 mmol) in 45 ml THF; ethylene bromide (1.16 g, 6.17 mmol) was added in small portions over 3 hrs to facilitate formation of Grignard reagent] to a solution of anhydrous zinc chloride (0.42 g, 3.1 mmol, 1 equiv) in dry tetrahydrofuran (5 ml).

The resultant solution was refluxed for 30 min and then cooled to room temperature. To a separate flask containing tetrakis(triphenylphosphine)palladium (0.179 g, 0.155 mmol, 0.05 equiv) was added 1-bromo-1,2-diphenylethene (0.803 g, 3.1 mmol, 1 equiv) in dry tetrahydrofuran (5 mL); this mixture was then added to the arylzinc chloride solution prepared above. The reaction mixture was refluxed for 24 hrs, cooled to room temperature and worked-up as previously described. Evaporation of solvents and treatment of the crude product with hydrogen chloride followed by recrystallization (from ethyl acetate/hexane) gave 0.81 g (70% yield) of the desired hydrochloride salt. The ^{1}H NMR spectrum was identical to that reported above.

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