Synthesis of cis- and trans-tamoxifen

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Summary: The synthesis of cis-tamoxifen, non antiestrogenic tetrasubstituted olefin, was achieved via carboalumination of diphenylacetylene as a key step. Conversion to the antiestrogenic trans-tamoxifen was achieved by facile cis-trans isomerization of the corresponding phenol by acid or catalysts.

Tamoxifen "1-[4-(2-dimethylaminoethoxy)phenyl]1,2-diphenyl-1-butene" is a biologically active tetrasubstituted olefin. The cis-form (1) is not antiestrogenic. On the other hand, the trans-form "Nolvadex" (2) has antiestrogenic activity and is used as antibrast cancer agent and for infertility problems."
In this paper we report the synthesis of cis-tamoxifen (1) via carboalumination of diphenylacetylene as a key step. Conversion to trans-tamoxifen (2) was also achieved by facile cis-trans isomerization of the corresponding phenol (6) by acid catalyst.

Diphenylacetylene (3) was carboaluminated in a syn manner either with triethylaluminium alone or in conjunction with stoichiometric amounts of titanocene dichloride to give vinylmetal, which was cleaved with iodine to give vinyl iodide (4). It should be mentioned here that diphenylacetylene reacts better with triethylaluminium complexed with titanocene dichloride$^{2,3}$.

Attempts to couple 4-[2-(dimethylamino)ethoxy]phenyl-zinc chloride with vinyl iodide (4) proved unsuccessful under a variety of conditions; however, vinyl iodide (4) coupled very nicely with (p-methoxyphenyl) zinc chloride by palladium-catalyzed cross-coupling$^4$ to give the methoxyaryl compound (5).

The methoxyaryl compound (5) was transformed into cis-tamoxifen (1) by first demethylation with sodium ethylthiolate in refluxing dimethylformamide to give the corresponding phenol (6) followed by reaction of the phenoxide ion with 2-(dimethylamino)ethyl chloride.

Finally, the facile isomerization of the corresponding phenol (6) by acid or radical catalysts followed by reaction of the corresponding phenoxide ion with 2-(dimethylamino)ethyl chloride gave the antiestrogenic trans-tamoxifen (2) as a major
product (65%) and cis-tamoxifen (1) as a minor product (35%). Separation of the two isomers is possible either by thin layer chromatography\textsuperscript{6} or by recrystallization\textsuperscript{7}.

**General procedure**

To a slurry of sodium hydride [0.398 g (8.29 mmol) of a 50% mineral oil dispersion washed twice with dry tetrahydrofuran (10 mL)] in dry dimethylformamide (18 mL) cooled to 90°C was added ethanethiol (0.593 g, 9.55 mmol) dropwise at such a rate as to prevent foaming. The mixture was stirred for 10 min after the addition was complete and then the methoxyaryl compound 5 (0.71 g, 2.39 mmol) in dry dimethylformamide (5 mL) was added in one portion. The resultant mixture was refluxed for 10 h, cooled to room temperature, poured into 3N hydrochloric acid, and extracted with ether. The combined organic layers were washed with 3N hydrochloric acid and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent
gave the demethylated product (0.61 g, 90% crude yield) which was used without further purification: IR 3400 cm\(^{-1}\) (s).

To a solution of sodium ethoxide in ethanol [prepared by adding sodium metal (0.15 g, 6.53 mmol) to absolute ethanol (15 mL)] was added crude demethylated product prepared above (0.61 g), in absolute ethanol (15 mL). To this mixture was then added in one portion a solution of 2-(dimethylamino)ethyl chloride hydrochloride (0.607 g, 4.21 mmol) in warm absolute ethanol (15 mL). The resultant mixture was refluxed for 24 h, cooled to room temperature, poured into water, and extracted with ether. The combined organic layers were washed with 5% sodium hydroxide solution (3 times) and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave crude product as a viscous oil. Recrystallization from methanol gave cis-tamoxifen in 62% yield as a white crystalline solid, mp 70–72° (Lit\(^7\), mp 72–74°).

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References:

1. For review, see: Hell, R.C., Brogdon, R.N., Speight, T.M., Avery, G.S., Drugs 1978, 16,1.


