

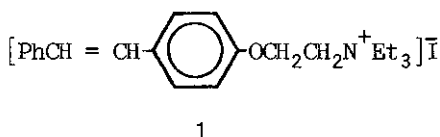
Synthesis of N,N,N-Triethyl-2-[4-(2-phenylethenyl)phenoxy]
ethan ammonium iodide.

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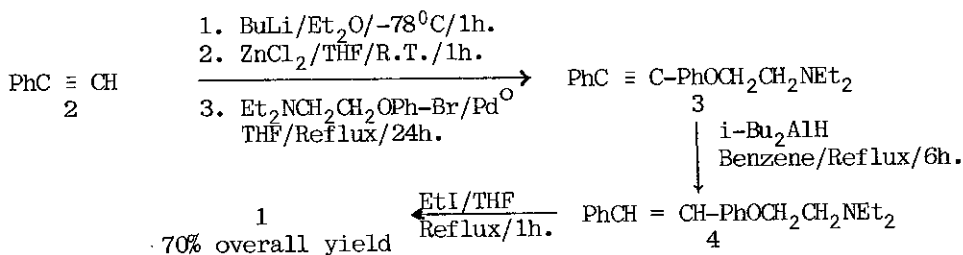
Summary: The synthesis of N,N,N-triethyl-2-[4-(2-phenylethenyl)phenoxy]ethan ammonium iodide, antispasmodic disubstituted olefin, was achieved via palladium-catalyzed cross-coupling of phenylacetylide with aryl bromide followed by hydroalumination.

N,N,N-triethyl-2-[4-(2-phenylethenyl)phenoxy]ethan ammonium iodide (1) is a biologically active disubstituted olefin. It is used as antispasmodic, ganglionic blocker^{1,2}.

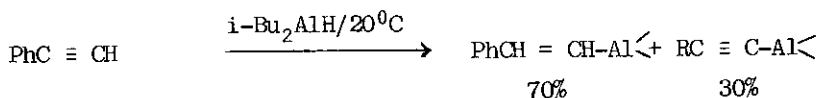


In this paper we report the synthesis of compound (1) via palladium-catalyzed cross-coupling^{3,4} of phenylacetylide with 4-[2-(diethylamino)ethoxy]phenyl bromide followed by hydroalumination/hydration and treatment of the product with ethyl iodide.

Thus phenylacetylene was treated with *n*-butyllithium followed by treatment with anhydrous zinc chloride to give phenylacetylde which was cross-coupled with 4-[2-(diethylamino)ethoxy]phenyl bromide in the presence of catalytic amount (0.05 equiv) of tetrakis (triphenylphosphine) palladium^{3,4} to give the alkyne (3). This compound (3) was transformed into olefin (4) without further purification by first hydroalumination⁵ with diisobutylaluminum hydride in refluxing benzene for 6h followed by treatment with water⁵. This intermediate (4) was transformed into the desired ammonium iodide (1) without further purification by treatment with ethyl iodide in refluxing tetrahydrofuran for 1h. The desired product (1) was obtained in 70% overall yield by recrystallization from ethyl acetate-benzene.



It should be mentioned here that initial attempt to prepare compound 1 via hydroalumination of phenylacetylene followed by palladium-catalyzed cross-coupling of the product with aryl bromide led to low yield of the desired product. This was due to a competition between hydroalumination and metallation of phenylacetylene⁶.



Experimental:

Melting points are reported uncorrected. Glpc analysis were performed on PYE Uican series 304 chromatograph with OV 1 glass column.

Butyllithium and diisobutylaluminum hydride (Fluka) were used as 1M solution in hexane. All reactions were stirred magnetically and carried out under an atmosphere of nitrogen in oven-dried (160°C) glassware. Tetrahydrofuran, diethyl ether and benzene solvents were distilled over sodium and benzophenone.

Preparation of 1-phenyl-2-[4-(2-diethylaminoethoxy)phenyl]acetylene (3):

To 8 mmol of phenylacetylene (2) in 16 ml anhydrous ether was added dropwise 8.5 mmol of 1M butyllithium in hexane at -78°C for 1h, an the mixture was allowed to warm to room temperature, then 8.5 mmol of 1M anhydrous zinc chloride in dry tetrahydrofuran was added. The resulting solution was stirred at room temperature for 1h. This mixture was subsequently treated with a mixture of 8 mmol of 4-[2-(diethylamino)ethoxy] phenyl bromide and 0.4 mmol (0.05 equiv) of tetrakis (triphenylphosphine)palladium in 20 ml of dry tetrahydrofuran. The resulting mixture was refluxed for 24h. At the end of this time the reaction mixture was quenched with water. Usual work-up and evaporation of solvents gave 7.5 mmol' of the crude alkyne (3) which was used for the following experiment without further purification.

Preparation of N,N,N-triethyl-2-[4-(2-phenylethenyl)phenoxy]ethan ammonium iodide (1):

To 5 mmol of alkyne (3) in 6 ml of benzene was added dropwise 6 ml of 1M diisobutylaluminum hydride in hexane (6 mmol, 1.2 equiv) at room temperature for 0.5 hour. The

reaction mixture was then refluxed for 6 hours. At the end of this time the reaction mixture was quenched with water. Usual work-up and evaporation of solvents gave olefin (4) which was refluxed with 5 mmol of ethyl iodide in 15 ml tetrahydrofuran for 1 hour. Work-up and evaporation of solvents left a residue, which was recrystallized from ethyl acetate-benzene to give 3.5 mmol (70% overall yield) of the desired compound (1) as a white crystalline solid, m.p. 210-213⁰C (lit. 211-212⁰C). Examination by GLC (OV1 glass column) gave a single peak.

Acknowledgement:

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References:

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