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An Improved and facile method for the synthesis of 1,1-bis(4-hydroxyphenyl)-2-phenylethylene and its derivatives

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ABSTRACT

The synthesis of 1,1-bis(4-hydroxyphenyl)-2-phenylethylene, which is of biological interest, has been reported by several authors in the past. In this article an improved method is introduced. Different (and commercially available) starting materials are adopted. Also a protective group which is easily attached and removed is used. This procedure provides milder reaction conditions and better yields while the number of steps involved in the synthesis of the compound are reduced. Furthermore the reactions are clean and formation of byproducts which lead to poorer yields are avoided.

INTRODUCTION

Triphenylethylenes are of medical interest due to their estrogen receptor binding properties (1). This category of compounds labeled with radioactive halogens have shown promise in the diagnosis and treatment of certain types of cancer (2).

The synthesis of triphenylethylenes in general is easily accomplished through the condensation of benzophenones and benzylgrignards (3). Furthermore, tetrahydropyranyl (THP) group offers protection for the hydroxy groups in the basic medium, while placement and removal of this moiety can be easily accomplished under mild conditions (4).

Results and Discussion

The procedure reported here (scheme I) has the following advantages over the published procedures (2,5) for the synthesis of III:

It is clean i.e. it is free of side products. The side products which arise from metallation of the benzylic hydrogens in the procedure involving condensation of a ketone and arylgrignards are a nuisance (for example see Ref 6). Removal of these side products are accomplished with difficulty (if at all) and at the expense of yield, time and resources. Secondly, the harsh conditions i.e. high temperatures and pressures and strong acidic or basic conditions which are employed in the published methods (2,5)

for removing the protecting alkoxy groups are avoided. Third, the commercial availability of the starting material exploited in this procedure reduces the number of the steps involved. Finally the yield in this method is higher than the methods already reported (2,5).

However, the procedure which leads to the formation of the organometallic derivatives of BHPE (i.e. III) (2) has not been improved substantially (scheme II). Noteworthy is the use of diethylether instead of THF in the lithium-halogen exchange step (scheme III). The formation of the lithium derivative VI is best indicated by the clear orange solution. This is in contrast to the vinylbromide precursor V which is sparingly soluble in the solvent medium. If THF is used instead of ether as the solvent at the lithium-halogen exchange step, a dark red transparent solution results which does not react with the added tributyltinchloride. This is presumably due to an electron transfer from n-butyllithium to V assisted by THF.

The tin compound reported here (i.e. VII) is used for radioiodination. Following the radiolabeling step, the compound I*-BHPE is purified via HPLC (2) and is ultimately of interest and is used for treatment in cancer research. Therefore, the synthesis of the cold iodo derivative (i.e. IX), which we report here, was also essential for studying the chemical toxicity of the compound.

Experimental Procedures

The ^1H NMR spectra were recorded by Argonne National Laboratory's Nicolet NTC 200 and Bruker AM-300 spectrometers. The mass spectrum was recorded using Argonne's Kratos MS 50 high resolution triple focus ion mass spectrometer. Melting points were measured by electrothermal melting point apparatus and are uncorrected. Elemental analysis were performed by Atlantic Microlab, Inc.

All the glassware were treated in KOH-Ethanol bath for 10 h before use. All reactions involving organometallic compounds were carried under a dry and oxygen free atmosphere of pure argon. The chemicals were obtained from Aldrich chemical company (unless otherwise indicated) and were used without purification except for

3,4-dihydropyran which was distilled from lithiumaluminumhydride (LAH) and was stored under argon for later use. All solvents used in the reactions involving organometallic compounds were freed of moisture and oxygen by refluxing over and distilling from appropriate material under an atmosphere of dry and oxygen free argon gas and were used fresh. The solvents were transferred to the reaction apparatus using syringe and needle.

Tetrahydrofuran (THF) and diethylether were refluxed over LiAlH_4 (LAH) for at least 2 h before distillation.

Synthesis of 4, 4'-bis[(2-tetrahydropyranyl)oxy]-benzophenone I

In a 500 mL round bottomed flask (r.b.f.) equipped with a magnetic stirrer was placed 15.0 g (70 mmol) of 4,4'-dihydroxybenzophenone (Lancaster Synthesis) and 1 g (4 mmol) of pyridinium-p-toluenesulfonate (PPTS). Then CH_2Cl_2 (200 mL) and 20 mL (220 mmol) of 3,4-dihydropyran were added. The flask was then surmounted by a reflux condenser and topped by a drying tube. The slurry was stirred at R.T. for 2 h before a clear orange colored solution resulted. This was then refluxed for 0.5 h. The flask contents were then transferred to a separatory funnel and washed with water (200 mL) followed by brine (i.e. Saturated salt-water solution, 200 mL). The organic phase was then separated, dried (Na_2SO_4) and filtered to give a clear orange solution. TLC of this orange solution vs. the starting material (silicagel, 2:1, hexanes: ethylacetate) showed one spot $R_f = 0.45$, while starting material had $R_f = 0.12$. Rotary evaporation gave a light orange oil weighing 29 g. This oil was extracted with hot hexanes (4 x 100 mL) and the combined extracts produced 21.4 g of white fluffy crystals of I (not reported in the literature), 80% yield, mp 105- 107°C.

^1H NMR (CDCl_3): δ 7.9-7.7 (d, 4), 7.3-7.0 (d, 4), 5.55 (t, 2), 3.5-4.0 (m, 4), 2.1-1.5 (m, 12).

Elemental analysis: Calc'd. C = 72.25%, H = 6.80%
C₂₃ H₂₆ O₅ Found C = 72.08%, H = 6.90%

Synthesis of 1, 1-bis[(4-tetrahydropyranyloxy)phenyl]-2-phenylethanol II

In a set up consisting of a 250 mL r.b.f. which was surmounted by a condenser and topped with a gas inlet adapter was placed 27.5 g (72 mmoles) of I and the apparatus was purged with argon. Then 150 mL of freshly distilled ether (LAH) was added. To this slurry was then added 40 mL (80 mmoles) of benzylmagnesium chloride in THF (Aldrich). A clear light brown solution resulted. This mixture was stirred for 15 h at R.T. after which a milky white solution resulted. This was transferred to a separatory funnel containing 200 mL of water. The organic phase was then separated, dried (brine and then Na₂SO₄) and filtered. The colorless solution was then rotary evaporated until a pale yellow oil was obtained weighing 33 g. This oil was extracted with hot hexanes (5 x 150 mL) and the pale yellow and clear solution yielded 32 g (97%) of white crystals of II (not reported in the literature); (mp 110-111°C).

Elemental analysis: Cal'd C=75.90%, H=7.17%
C₃₀ H₃₄ O₅ Found C=75.86%, H=7.37%

¹H NMR (CDCl₃): δ 7.5 - 6.8 (m, 13 H), 5.4 (s, 2 H), 3.9 (m, 2H), 3.6 (s, 4 H) 2.3 (s, 1 H), 2.1-1.4 (m, 12 H).

Formation of 1,1-bis(4-hydroxyphenyl)-2 Phenylethylene (BHPE) III

In a 250 mL r.b.f. equipped with a magnetic follower was placed 10 g (22 mmoles) of II and 100 mL of methanol. To this slurry was then added 5 mL of conc. HCl. After stirring for 1 h at ambient temperature, TLC of the reaction mixture vs. II showed 1 spot with a smaller R_f value (silicagel, 2:1 hexanes: ethylacetate). This was neutralized with CO₃Na₂ and extracted with CH₂Cl₂, dried (Mg SO₄) and filtered. Rotary evaporation of this solution gave a light orange oil weighing 6 g (95% yield). A portion of this oil was crystalized from toluene, mp 181-4°C (Lit (2) 188°C).

Synthesis of 1,1 bis[4-hydroxyphenyl]-2-bromo-2-phenylethylene (Br-BHPE) IV

The above compound was prepared according to the procedure of Meese and DeSombre (2) in similar yields.

1,1-bis(4-(2-tetrahydropyranyl)oxy)-2-phenylvinylbromide V

In a 250 mL r.b.f. was placed a magnetic stirrer and 8 g (21 mmoles) of IV and 1 g (4 mmoles) of PPTS. The flask was then surmounted with a reflux condenser and a gas inlet adaptor. The flask was then purged with argon and then 100 mL of freshly distilled THF (from LAH) was added. The mixture was made into a solution via stirring and then 6 mL (66 mmoles) of distilled dihydropyran was added via syringe and under argon. The mixture was stirred at R.T. for 10 h and then refluxed for 2 h. After cooling down to R.T., the TLC of the reaction mixture vs. the starting material showed a spot with greater R_f value than V. The reaction mixture was then shaken with 100 mL of brine in a separatory funnel and the organic phase was separated, dried (Na_2SO_4), and then filtered. Rotary evaporation gave an orange colored solid which was crystallized from methanol yielding 7 g (62% yield) of pale yellow crystals, mp 142-3°C (Lit.(7) 142-5°C).

$^1\text{H NMR}$ (CDCl_3): δ 7.5-6.6 (m, 13), 5.4 (s, 1), 5.3 (s, 1), 4.0-3.7 (m, 4), 2.1-1.4 (m, 12).

Elemental Analysis: Calc'd. C= 67.29%, H= 5.79%

$\text{C}_{30}\text{H}_{31}\text{BrO}_4$ Found C= 66.72%, H= 5.84%

1,1-bis(4-(2-tetrahydropyranyl)oxy)-2-phenylvinyl lithium VI

In a typical reaction 2 g (3.7 mmoles) of V was placed in a Schlenk flask and purged with argon. Then 40 mL of freshly distilled diethylether (LAH) was added. This led to a slurry which was chilled to -78°C using dry ice/acetone bath. Then 4 mmoles of n-butyllithium in hexanes (Aldrich) were added. Following the addition of the lithium

reagent, the cold bath was removed and the reaction mixture was allowed to reach ambient temperature during a 2 h period. This led to a clear light orange solution of VI.

Formation of the vinyltributyltin derivative VII

To this solution (VI) was then added 5 mmoles of tributyltinchloride (Aldrich) and allowed to stir at room temperature for 16 h. A milky white solution signaled the completion of the reaction. TLC of the reaction solution revealed one spot which had distinctly different R_f value from that of V on a side by side run. The product VII was purified by passing it through a silicagel column using 4:1 / hexanes: ethyl acetate as the mobile phase. Pure VII is obtained in the form of a colorless oil which shows instability at R.T. as is indicated by new spots on periodic TLC checks.

Deprotection of vinyltributyltin compound and formatin of VIII

A 1 g sample of VII was dissolved in 40 mL of CH_2Cl_2 . To this solution was added a crystal of PPTS and allowed to stir at R.T. The progress of the reaction was monitored periodically via TLC (silicagel, 2 : 1 / hexanes : ethylacetate). When BHPE started to show up on TLC the reaction mixture was quenched by adding dilute sodiumbicarbonate solution. After shaking well in a separatory funnel the organic phase was separated and dried (Na_2SO_4), filtered and rotary evaporated. The residual oil was then purified via column chromatography (silicagel, 4 : 1 / hexanes: ethylacetate) and stored at -80°C .

Formation of 1,1-bis(4-hydroxyphenyl)-2-phenyl-2-iodoethylene (I-BHPE) IX

1 g (4 mmoles) of iodine (Aldrich) was placed in a Schlenk flask and purged with argon gas. To this was then added 25 mL of dry ether and mixed until the iodine was dissolved. A solution of VI prepared from 1 g (2 mmoles) of V as described above. The iodine solution was then added dropwise to the vinyl lithium solution via syringe

until the red color of iodine persisted. The solution was then worked up by treating it with 50 mL of a saturated solution of sodiumthiosulfate (in order to reduce the excess

iodine), dried (MgSO_4) and then filtered. Rotary evaporation yielded an orange colored oil (one spot on TLC, 2:1 / hexanes : ethylacetate, R_f identical to V). This oil was consequently dissolved in 50 mL of methylene chloride and a crystal of PPTS was added. The progress of the reaction was monitored via TLC (silicagel, 2:1 / hexanes : ethylacetate, R_f identical to IV). After the reaction was completed the product was purified by passing it through a silicagel column. Crystallization from toluene yielded 0.5 g (60% yield) of reddish brown crystals (mp $177-80^\circ\text{C}$, Lit. (7) 175°C).

^1H NMR (CDCl_3): δ 7.5-7, 6.95-6.6, 6.5-6.3 (m, 14), 5.5-4 (m, 2), 2.4 (s, 1)

MS : 414 (M^+ peak), 100%; 287 ($\text{M}^+ - \text{I}$), 96%

Elemental Analysis:	Calc'd. C= 55.50%, H= 3.93%, I= 29.40%
$\text{C}_{20}\text{H}_{17}\text{I}\text{O}_3$ (I-BHPE. H_2O)	Found C= 55.53%, H= 3.94%, I= 29.46%

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Scheme I

Scheme II

IV

IVa

IVb

V

Scheme III

VI

VII

VIII

IX