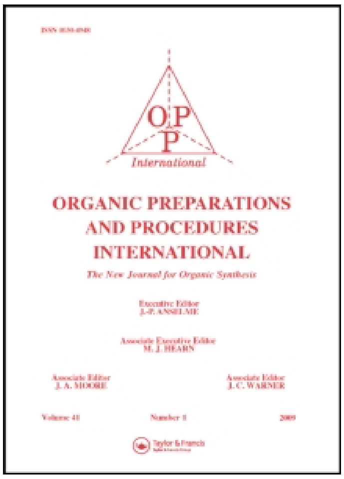

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THE SYNTHESIS OF OLIVETOL. TRIMETHYLSILATION AS A PROTECTIVE GROUP DURING GRIGNARD REACTIONS

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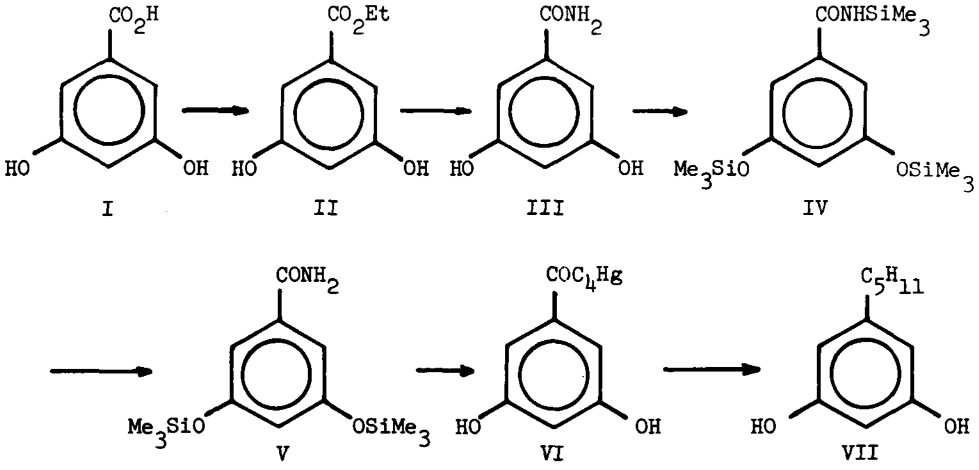
Recently, considerable interest has been shown in the preparation of olivetol (3,5-dihydroxy-n-pentylbenzene, VII) as the precursor for the synthesis of the physiologically active Δ^1-tetrahydrocannabinol and related structures.[1-12] In some cases, alkoxy groups were used to protect the hydroxy groups of the starting material. The use of alkoxy groups while initially synthetically attractive, has lead to significant reduction in yields in the protection and subsequent deprotection of the hydroxyl functions. In other cases, the starting materials used such as 3,5-dimethoxybenzoic acid, 2,4,6-trimethoxybenzoic acid, and/or 3-nonene 2-one, were in



fact either too expensive or as in the later case, not readily available.[12] We now report a simple synthesis of olivetol (VII) from the commercially available 3,5-dihydroxybenzoic acid (α-resorcylic acid, I). The key to the success of this synthetic sequence is the use of trimethylsilylation[13] of reactive hydroxyl groups as a protective-deprotective technique during Grignard synthesis.

Fisher esterification of α-resorcyclic acid (I) with ethanol yielded dihydroxy ester II (95% yield) which was converted to the amide III (90%) by heating under pressure in liquid ammonia. Trimethylsilylation of amide III to trisilylated derivative IV was accomplished almost quantitatively by heating the dihydroxyamide III and hexamethyldisilazane with a catalytic amount of H_2SO_4. Compound IV was converted to the bis-O-trimethylsilylated benzamide V in quantitative yields by shaking with water for short periods of time. Reaction of V with n-butyl magnesium bromide gave an 85% yield of crude ketone VI. A Clemmensen reduction on the crude ketone VI gave a 70% yield (based on V) of olivetol (VII). This product was identical (IR and nmr spectra) with a commercial sample of olivetol (Aldrich Company).

Attempted reaction of IV with n-butyl magnesium bromide yielded two products in poor yields; subsequent work-up gave a large portion of dihydroxyamide. The major product was 3,5-dihydroxyphenyl n-butyl ketone and the minor product was the 3,5-dihydroxyphenyl di-n-butylcarbinol (ratio 85:15). Similar results were obtained when 3,5-dimethoxy-N-trimethylsilylbenzamide was treated with the same Grignard reagent. The fact that a 90% yield of the ketone was obtained from similar treatment of 3,5-dimethoxybenzamide with n-butyl magnesium bromide indicated that the trimethylsilyl group on the amide nitrogen hinders reaction at this site.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian HA 60-IL Spectrometer. Chemical shifts are reported as δ relative to tetramethylsilane. 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and 3,5-dihydroxybenzoic acid were obtained from Columbia Organic Chemical Company and used without further purification. Infrared spectra were obtined on a Beckman IR-20A. Gas chromatographic analysis was done on a Beckman G.C. 45; flame ionization detector; glass column with 6 feet of 5% OV 17 on chromasorb W, 100-120 mesh. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

<u>3,5-Dihydroxybenzamide (III)</u>[15].- To approximately 250 ml of anhydrous liquid ammonia in a one-liter high pressure bomb (Parr high pressure autoclave) was added 11.0 g (60 mmoles) of II.[14] The temperature was maintained at 140-150° for 15 hrs. and a maximum pressure of 1500 psi developed. The bomb was cooled, pressure released and excess ammonia allowed to evaporate. The remaining oily residue was dissolved in ethanol and boiled with 25.0 g of activated charcoal, filtered while hot and the ethanol removed by evaporation. Crystallization from EtOH gave 8.2 g (90%) of a tan solid, mp. 285-287° (dec.).

<u>Anal</u>. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.60; N, 9.15.
Found: C, 55.08; H, 4.57; N, 9.02.

<u>N-Trimethylsilyl 3,5-ditrimethylsilyloxybenzamide (IV)</u>.- To a 100 ml (200 mmoles) of anhydrous HMDS was added 20.0 g (143 mmoles) of III and two drops of conc. H_2SO_4. The reaction mixture was heated to reflux under a N_2 atmosphere for 2 hrs.; ammonia was evolved. The reaction mixture was cooled in an ice bath and the solid collected by filtration. After drying in a vacuum desiccator, 70.0 g (95%) of fine, white needles, mp. 75-80°, were obtained.

<u>Anal</u>. Calcd. for $C_{16}H_{31}NO_3Si_3$: C, 52.00; H, 8.40; N, 3.90.
Found: C, 52.12; H, 8.19; N, 4.02.

3,5-Bis-trimethylsilyloxybenzamide (V).- To a solution of 20.0 g (5.0 mmoles) of IV in 100 ml of ether or carbon tetrachloride in a separatory funnel, was added 50 ml of water. The mixture was shaken vigorously for no more than five minutes; the organic layer was separated and dried on anhydrous $MgSO_4$. Evaporation of the solvent gave a white solid, 15 g. (100%) mp. 90-100°.

Anal. Calcd. for $C_{13}H_{23}NO_3Si_2$: C, 52.50; H, 7.80; N, 4.70.

Found: C, 52.66; H, 7.60; N, 4.88.

3,5-Dihydroxyphenyl n-butyl ketone (VI). To a mixture of 7.2 g (300 mmoles) of magnesium turnings, 200 ml of anhydrous ethyl ether and a crystal of iodine were added dropwise 41.0 g (300 mmoles) of n-butyl bromide in 50 ml of ethyl ether while the mixture was heated to reflux. The reaction mixture was stirred at reflux for 30 min. after addition was complete. A solution of 13.5 g (45 mmoles) of V in 25 ml of ethyl ether was then added dropwise and the reaction mixture was maintained at reflux for 48 hrs. under a N_2 atmosphere. It was then poured over 500 g of ice and acidified with 6 N HCl. The separated layers were both neutralized with solid sodium bicarbonate and each extracted twice with 250 ml of ether. The combined ethereal layer was dried over $MgSO_4$ and evaporated to give a dark reddish oil (7.49, 85%) which was used directly for the next step.

Olivetol (VII).- A mixture of 25 g of mossy zinc, 2.5 g of mercuric chloride, 2 ml of concentrated HCl, and 30 ml of water were stirred for 10 minutes. The aqueous solution was diluted with 25 ml of concentrated HCl; then 7.4 g of the crude product obtained above was dissolved in 30 ml of a 5:1 aqueous ethanol:water solution and added directly to the mixture. The reaction mixture was slowly brought to reflux and maintained for ten hours or until an aliquot of the reaction gave no color with ferric chloride solution;[12] about 2-4 ml of concentrated HCl was added hourly. When the color test indicated the reaction to be complete, the mixture was cooled and the solution (after being decanted from any unchanged zinc amalgam) was neutralized with solid $NaHCO_3$. The solution was then saturated with NaCl and extracted with 250 ml of ethyl ether. The ether was removed by evaporation to give a reddish oil which was distilled in vacuo to give 4.8 g (70%, based on crude ketone) of a resinous oil bp. 145°/0.6 mm, lit.[1] bp. 145-153°/0.65 mm).

Nmr (d_6 acetone): δ 0.95 t (3H); 2.45 t (3H); 6.20 s (3H); 7.80 s (2H) (D_2O ex.).

Anal. Calcd. $C_{11}H_{16}O_2$: C, 73.33; H, 8.88.
Found: C, 73.22; H, 8.96

N-Trimethylsilyl-3,5-dimethoxybenzamide.- N-Trimethylsilyl-3,5-dimethoxybenzamide was prepared in the same manner as the trisilylated benzamide IV, using 18.1 g (100 mmoles) of 3,5-dimethoxybenzamide,[1] mp. 144-146°, and 175 ml of HMDS. Reflux was maintained under a N_2 atmosphere for 2 hrs.; 23.0 g (91%) of small white crystals, mp. 89-92°, were obtained.

Anal. Calcd. for $C_{12}H_{19}NO_3Si$: C, 56.90; H, 7.50; N, 5.50.
Found: C, 56.88; H, 7.53; N, 5.63.

3,5-Dimethoxyphenyl n-butyl ketone and 3,5-Dimethoxyphenyl-di-n-butylcarbinol.- N-Trimethylsilyl 3,5-dimethoxybenzamide (20.0 g, 80 mmoles) was reacted in the same manner as V with 11.5 g (480 mmoles of magnesium turnings, 65.5 g (480 mmoles) of an n-butyl bromide and 200 ml of ether. Reflux was maintained for 72 hrs. and subsequent work-up and distillation gave two compounds in low yield.

3,5-Dimethoxyphenyl n-butyl ketone, mp. 37-40°, lit.[7] 39-41° (20.9 g, 11%).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.30; H, 8.10.
Found: C, 70.22; H, 8.14.

Nmr ($CDCl_3$): δ 0.95 t (3H); 1.5 m (4H); 2.9 t (2H); 3.9 s (6H); 6.7 m (1H); 7.1 s (2H).

3,5-Dimethoxyphenyl-di-n-butylcarbinol (0.69 g, 3%).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 73.00; H, 10.00.
Found: C, 72.89; H, 9.91.

Nmr ($CDCl_3$): δ 0.95 t (6H); 1.2 m (8H); 1.7 m (4H); 3.83 s (6H); 6.35 t (1H); 6.65 d (2H).

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