An Approach to Tetrahydrobenz[*b*,*d*]pyrans and Hexahydrophenanthridines by Reaction of Dilithiated Phenol and Aniline with Pulegone

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7,8,9,10-Tetrahydro-6,6,9-trimethyldibenzo[*b*,*d*]pyran and 5,6,7,8,9,10-hexahydro-6,6,9-trimethylphenanthridine have been prepared by reaction of pulegone with lithium *ortho*-lithium phenolate and lithium *ortho*-lithium *N*-trimethylsilylaniline. The cyclization into the annellated systems could be performed under essentially non-acidic conditions.

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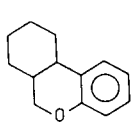
The dibenzo[*b*,*d*]pyran derivative **1** and the isosteric phenanthridine derivative **2** are of importance as parent heterocycles in natural and synthetic cannabinoids *e.g.* tetrahydrocannabinol **3** [4]. As a result of our interest in



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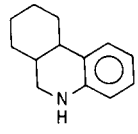

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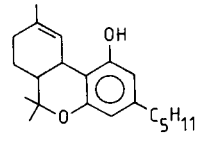

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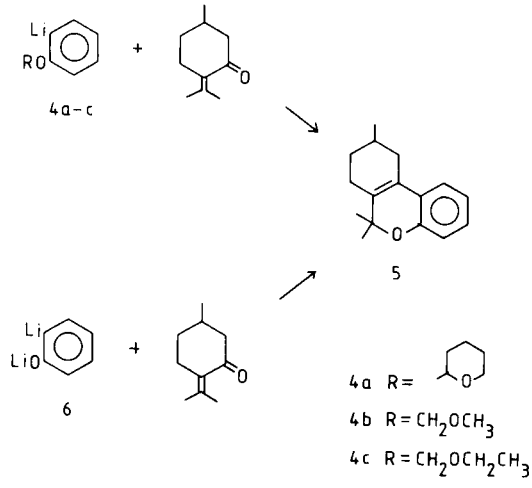
ortho-dilithiated compounds as reactive intermediates [5] it occurred to us that heterocycles **1** and **2** could be generated, in principle, *via* reaction of *ortho*-dilithiated phenols and anilines with α-exomethylene ketones. A possible benefit of such methodology is that acid sensitive functional groups could be tolerated. Most of the known syntheses of such systems require acid catalysis. This communication describes our preliminary efforts in this area.

Initially we investigated the reaction of *ortho*-lithiated aryl ethers with pulegone in order to determine if the desired 1,2-addition could be achieved [6]. Thus, the

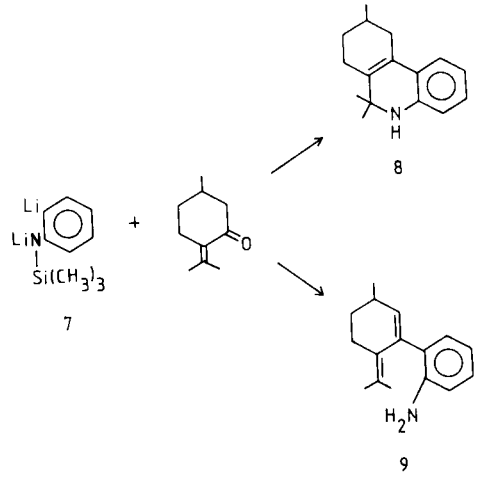
Scheme 1



ortho-lithio aryl ethers **4a**, **4b**, **4c** when treated with pulegone after acidic removal of the protective groups gave 7,8,9,10-tetrahydro-6,6,9-trimethyldibenzo[*b*,*d*]pyran **5** in moderate yield (40-45%). Our next objective was to determine if **5** could be prepared using lithium *ortho*-lithiumphenolates **6** [7] and thereby avoid the manipulation of protective groups. Thus, compound **6** after reaction with pulegone smoothly gave the cyclized products **5** in moderate yields after stirring the presumed allylic alcohol intermediate in a slurry of silica in toluene [8] (Scheme 1).

We then turned our attention to the preparation of the corresponding nitrogen analogue. We chose to utilize lithium *ortho*-lithium-*N*-trimethylsilylanilide **7** [9] which, when reacted with pulegone, gave 5,6,7,8,9,10-hexahydro-6,6,9-trimethylphenanthridine directly upon work-up. It is interesting to note that when the reaction mixture was heated in THF before hydrolysis, the diene **9** was formed and only traces of **8** could be detected (Scheme 2).

Scheme 2



We have thus demonstrated the feasibility of using dilithiated phenols and anilines for constructing tricyclic heterocycles under essentially non-acidic conditions. We suggest that this approach may have broad applicability.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Jeol MH 100 spectrometer and the ir spectra were recorded on a Perkin-Elmer 298 spectrometer. Mass spectra were obtained using a Finnigan 4021 (Data System Incos 2100) gas chromatography-mass spectrometer and were in accordance with the proposed structures. Quantitative gas chromatographic analyses were performed on a Varian 3700 instrument equipped with a 2 m column of 5% NPGS on Chromosorb W. Elemental analyses were performed by Ilse Betz Mikroanalytisches Laboratorium, West Germany. All experiments with organo-lithium reagents were performed in an atmosphere of dry nitrogen.

7,8,9,10-Tetrahydro-6,6,9-trimethyldibenzo[*b*,*d*]pyran (**5**).

To a solution of 3.46 g (20 mmoles) of *ortho*-bromophenol in 150 ml of ether was added, at −70°, 30 ml (43 mmoles) of 1.44 *N* butyllithium in hexane. The temperature was allowed to reach room temperature and after two hours the reaction mixture was again cooled to −70° and 3.0 g (20 mmoles) of pulegone in 20 ml of ether was added over ten minutes. The temperature was allowed to reach room temperature over night and the reaction mixture was hydrolyzed by the addition of aqueous ammonium chloride. Extraction with ether, drying and evaporation gave the alcohol as an oil. This was not further purified but dissolved in 200 ml of toluene and stirred with a catalytic amount of *p*-toluenesulfonic acid for 20 hours. Evaporation of the toluene and distillation gave 1.8 g (8 mmoles, 40%) of the title compound, bp 130-132° at 0.8 mm Hg; nmr (deuteriochloroform): δ 7.2-6.6 (m, 4H, aromatic), 2.5-1.5 (m, 7H, aliphatic), 1.43 (s, 3H, methyl), 1.27 (s, 3H, methyl), 1.03 (d, 3H, methyl, J = 5.0 Hz).

Anal. Calcd. for $C_{16}H_{20}O$ (228.331): C, 84.16; H, 8.83; O, 7.01. Found: C, 83.94; H, 8.95.

Cyclization of the intermediate allylic alcohol could also be effected by stirring the toluene solution with silica (4 g) instead of pts, giving a gc yield of 51% as compared to 52% for pts-induced cyclization. (NPGS, 150-230°). The cyclization could be monitored by tlc (silica, hexane/ethyl acetate 90/10).

Non-preparative Experiments.

Five mmoles of phenol-tetrahydropyranyl ether (0.95 g) [10], -methoxymethyl ether (0.70 g) [11] and -ethoxymethyl ether (0.75 g) [12], respectively, in 20 ml of ether were lithiated with 5.6 mmoles of butyllithium (4 ml of a 1.4 *N* hexane solution) at room temperature for 26 hours. After cooling to −70° 0.75 g (5 mmoles) of pulegone in 5 ml of ether was added. The reaction mixtures were allowed to reach room temperature over night. After hydrolysis with aqueous ammonium chloride, extraction with ether and evaporation the crude products were heated in methanol/hydrochloric acid/water (10/2/8 ml) for 2 hours to remove the protective groups. A minor amount of the cyclized product **5** was formed during this procedure. Extraction with toluene and addition of pts followed by heating of the toluene phase (50°) for 3 hours gave the cyclized title compound in 44, 37 and 35% yield, respectively (gc).

2-(6-Isopropylidene-3-methyl-1-cyclohexenyl)aniline (**9**).

To a solution of 1.22 g (5 mmoles) of *N*-trimethylsilyl-*ortho*-bromoaniline in 50 ml of THF was added at −70° 8 ml (11.5 mmoles) of 1.44 *N* butyllithium in hexane. The temperature was allowed to reach room temperature and after a total time of two hours the solution was cooled again to −50°, whereafter 0.85 ml (0.75 g, 5.0 mmoles) of pulegone in THF was added dropwise. After stirring over night (room temperature) the reaction mixture was heated to 60° for one hour whereafter the THF was evaporated. Water and ether was added, the ether phase was dried and evaporated and the crude product chromatograped (silica-toluene/ethyl acetate, 95/5) to give 0.52 g (2.3 mmoles, 46%) of the title compound as a slightly yellow oil; ir: 3460 and 3370 cm^{-1} (NH_2); nmr (deuteriochloroform): δ 7.2-6.6 (m, 4H, aromatic), 5.62 (d, 1H, vinylic, J = 3.3 Hz), 3.70 (bs, 2H, NH_2), 2.5-1.7 (m, 5H, aliphatic), 1.77 (s, 3H, allylic methyl), 1.30 (s, 3H, allylic methyl), 1.07 (d, 3H, aliphatic methyl, J = 7.7 Hz).

Anal. Calcd. for $C_{16}H_{21}N$ (227.35): C, 84.53; H, 9.31. Found: C, 84.20; H, 9.25.

5,6,7,8,9,10-Hexahydro-6,6,9-trimethylphenanthridine (**8**).

The reaction was carried out as above for compound **9** but the temperature of the reaction mixture was kept below 0° until it was hydrolyzed by the addition of water followed by neutralization with dilute hydrochloric acid. Ether was added and the ether phase treated with dilute hydrogen chloride. The acidic aqueous phase was then extracted with methylene chloride which was then washed with dilute sodium hydroxide solution, dried and evaporated giving the title product as an oil. Chromatography gave, from 5 mmoles of the aniline, 0.48 g (42%) of the title compound as a solid, mp 62-65°; ir: 3450 cm^{-1} (NH); nmr (dueteriochloroform): δ 7.2-6.4 (m, 4H, aromatic), 3.50 (bs, 1H, NH), 2.3-1.7 (m, 7H, aliphatic), 1.27 (s, 3H, methyl), 1.17 (s, 3H, methyl), 1.03 (d, 3H, methyl, J = 5.0 Hz).

Anal. Calcd. for $C_{16}H_{21}N$ (227.35): C, 84.53; H, 9.31. Found: C, 84.22; H, 9.21.

The title compound **8** could also be prepared in comparable yield by the following working-up procedure: The reaction mixture was added to a water and ether mixture, whereupon the organic phase was stirred with silica. Compound **8** was isolated after evaporation and chromatography. Alternatively, compound **8** was isolated after evaporation at room temperature of the organic phase and subsequent treatment with pts in toluene.

If the reaction mixture was not neutralized after addition of water thin-layer chromatography indicated the absence of the cyclized product and instead the presence of another compound with much lower rf value assumed to be the allylic alcohol. However, on a preparative plate this alcohol cyclized to the title compound. Compounds **9** and **8** separate well on a tlc plate, compound **9** having the lowest rf value. Compound **8** gives a dark blue spot upon treatment of the plate with iodine whereas **9** gives only a faint colouring.

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