A CONVENIENT NEW METHOD FOR 2-HYDROXY-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTEN-5-ONE[†]

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Abstract: A novel approach has been developed for the synthesis of 2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one is reported using 4-carboxybutyl triphenyl phosphonium bromide (Wittig salt) in excellent yield.

Introduction

Benzosuberone derivatives posses potential bacteriostatic antiinflammatory, antipyretic, antiucler, CNS-depressant, CNS-stimulant and anticonvulsant. Some of the derivatives also knew for anti tumor activity in murine p388 tests.[1] Because of their wide range of biological importance, various approaches have been reported to construct the benzosuberone skeleton. The most practicable methods includes either by the Friedel-Crafts acylation[2] of benzene or by the reaction of 3-methoxy benzaldehyde with crotanate[3-13]. Though these methods gave satisfactory yields, the number of steps, longer time and harsh reaction conditions are the main drawbacks of this procedure. Our involvement in the development of new methodologies[14,15] promoted us to make a simple and sharp route for the synthesis of 2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one 4. Herein we wish to report the novel and short approach to construct (**4**).

Chemistry

The reaction of m-phenoxy benzaldehyde 1 with 4-carboxybutyl triphenyl phosphonium bromide in the presence of stoichiometric amount of sodium hydride in DMSO THF gave (*E*)-5-(*m*-phenoxy phenyl)pent-4-enoic acid **2** (yield 89%).

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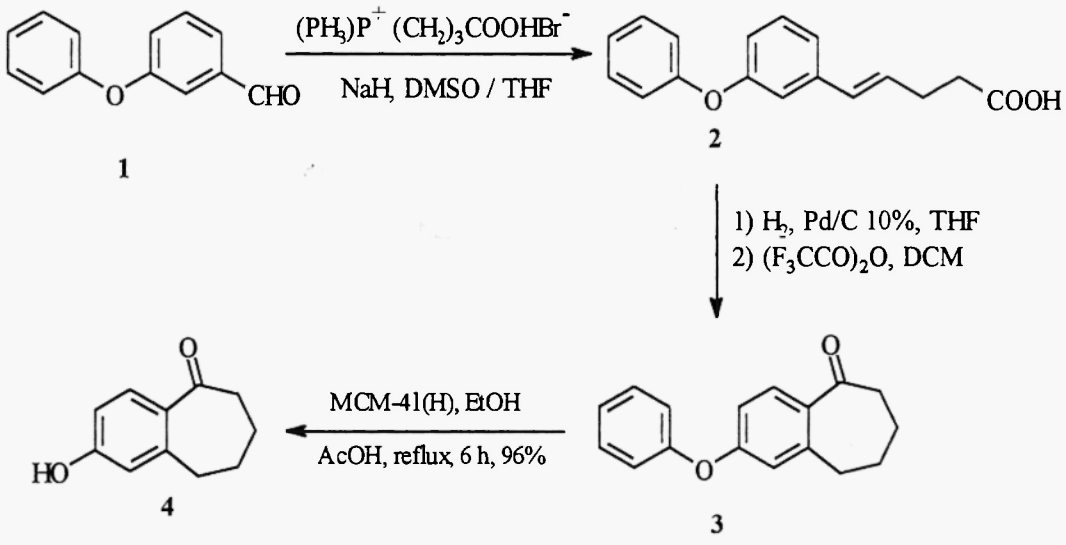

Scheme

Without purification of compound (**2**) was hydrogenated over Pd/C 10% in H_2 atom gave 5-(3-phenoxy phenyl) pentanoic acid, which on subsequent cyclisation with trifluroacetic anhydride in DCM resulted in the 2-phenoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one **3**. The cleavage of phenoxy ether (**3**) with MCM-41(H)[16-18] zeolite in ethanol at reflux temperature gave the title compound **4** in high yield (96%).

However, the m-methoxy substituted ether lower the yield (70%) of compound (**4**) in the similar reaction condition. So, the present method using *m*-phenoxy ether has some advantages over the earlier methods in respect of yield and easy workup.

In conclusion, we have demonstrated practical synthesis of 2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one from *m*-phenoxy benzaldehyde. The present procedure reduces the number of steps and yields are high in each step.

Experimental

M.p.s are uncorrected. ^{13}C and ^{1}H NMR spectra are recorded in $CDCl_3$ on a Gemini (200 MHz) spectrometer with TMS as an internal standard and mass spectra are taken on a VG micromass 7070H mass spectrometer.

A Typical Procedure for (E)-5(m-phenoxy phenyl)pent-4-enoic acid (**2**) : A solution of *m*-phenoxy benzaldehyde (0.1 mol) and 4-carboxybutyl triphenyl phosphonium bromide[19] (0.1 mol) in a 1:1 mixture (40

mL) of dry, freshly distilled THF and DMSO was added dropwise to a slurry of freshly washed (n-pentane) NaH (8.0 g, 60% dispersion in mineral oil, 0.2 mol) in dry THF (50 mL) at 0° C. The mixture was mechanically stirred for 22 hrs. at ambient temperature, and then cautiously quenched with water (26.8 mL) and washed with ether (3 x 13.4 mL). the aqueous mixture was acidified to pH 2 with conc. HCl and extracted with ether (2 x 13.4 mL). The combined organic layers were washed with ether (2 x 13.4 mL), dried ($MgSO_4$) and solvent was removed under reduced pressure. Titration of the residue with hexane gave 2, which was further crystallized from DCM, yield 89%, m.p. 172-73°C. ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.12-2.42 (4H, m, CH_2; J = 15.8 Hz and 7.1 Hz) α -from both (COOH & CH=CH), 5.55-5.69 and 6.12-6.48 (2H, m, HC=CH), 7.08-7.48 (9H, m, CH-Ar) and 11.30 (1H, s, COOH). ^{13}C NMR ($CDCl_3$) : 180 (COOH), 116.2 (CH=CH), 130.5 (CH=CH), 155, 160.1, 155.5, 157.9, 138.6, 130, 129.7, 123.5, 119.06, 119.3, 115.4, 121.8, 33.68 and 28.8 m/z (rel intensity) 268 (M^+ 5%), 251 (100%), 223 (7%), 195 (48%), 103 (20%) [Found : C, 76.00; H, 6.00; $C_{17}H_{16}O_3$ requires C, 76.09; H, 6.01%].

5-(m-Phenoxy phenyl) butanoic acid : An ethyl acetate (3 ml) solution of butenoic acid (0.1 mol) was hydrogenated over 10% palladium on carbon (0.01 mol) for one hr in a Paar hydrogenator at 25°. The catalyst was removed by filtration through a bed of Celite, and the solvent evaporated in vacuo to provide 98% of pure butanoic acid; m.p. 82-83.5°C. ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.36 (2H, t, J = 7.3 Hz, CH_2; α from COOH), 2.58 (2H, t, J = 7.5 Hz, CH_2; α from Ar), 1.62 (2H, m, -CH_2-), 1.45 (2H, m, -CH_2-) and 7.09-7.52 (9H, m, Ar); ^{13}C NMR ($CDCl_3$) : 179.9 (COOH), 154.5, 160, 155.1, 157.8, 144, 138.8, 129.8, 129.7, 123.1, 120, 119.3, 33.8, 35.8, 35.21, 30.9 and 25.5; m/z (rel intensity) 270 (M^+ 14%), 253 (80%), 225 (10%), 133 (100%), 156 (5%). [Found : C, 76.53; H, 6.79; $C_{17}H_{18}O_3$ requires C, 75.52; H, 6.71%].

2-Phenoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one **(3)** : Trifluoro acetic anhydride (0.1 equiv) was added slowly to a stirred solution of 5 (*m*-phenoxy phenyl) butanoic acid (0.2 mole) in dry dichloromethane and refluxed for 1.5 hr. This mixture was subsequently cooled and quenched with water. The organic layer was dried over Na_2SO_4 and the solvent removed to give 3, yield 88%, semi-solid. ^{1}H NMR ($CDCl_3$) : δ 1.88-1.99 (4H, m, 2-CH_2-), 2.78-2.96 (4H, m, -$COCH_2$- & Ar-CH_2-), 6.81-7.66 (8H, m, Ar-H), ^{13}C NMR ($CDCl_3$) : 204.1, 164.5, 154.8, 142.0, 137.6, 131.1, 123.8, 129.0, 119, 40.8, 24.18, 21.15, 21.0; m/z (rel intensity)

252 (M^+ 4%), 224 (80%), 132 (17%), 91 (100%). [Found : C, 80.90; H, 6.40; $C_{17}H_{16}O_2$ requires C, 80.92; H, 6.39%].

***2-Hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one* (4) :** MCM-41(H) (0.1 equiv.) was added to a solution of phenoxy suberone (**3**, 0.1 mole) in dry ethanol (10 mL) and few drops of acetic acid the reaction was heated at reflux temperature. The reaction mixture was allowed to cool to room temperature and filtered. The solvent was evaporated under reduced pressure removed and was purified by column chromatography on silica gel (100-200 mesh, hexane - ethylacetate, 4:1), yield 96%, m.p. 166° (lit.,[5] 164-165°); ^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.86-1.89 (4H, m, 2-CH_2-), 2.80-2.97 (4H, m, -C-CH_2- & Ar-CH_2-), 6.82 (1H, s, 1-H), 7.00 (1H, d, 3-H), 7.48 (1H, d, 4-H), 4.86 (1H, brs, OH); ^{13}C NMR ($CDCl_3$) : 204.8 (C=O), 158.3 (C-OH), 148.1, 135.0, 130.19, 120.9, 118.0, 40.5, 24.3, 22.6, 21.8 [Found : C, 74.95; H, 6.85; $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%].

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