A NEW SYNTHESIS OF 2-METHYL-2,3-DIHYDROBENZO[*B*]FURAN-6,7,8,9-TETRAHYDRO CYCLOHEPTENE-5-ONE

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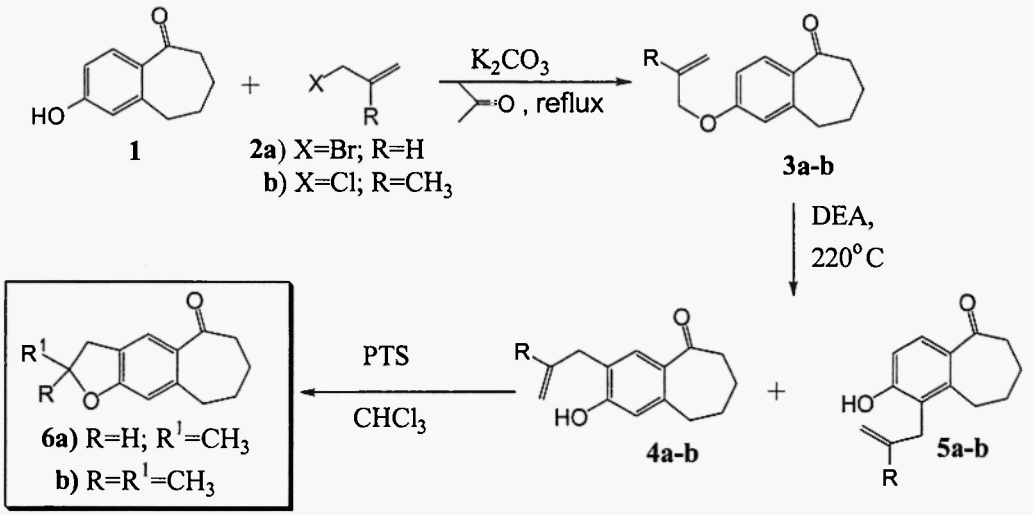
Abstract: 2-Methyl-2,3-dihydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6a**) and 2,3-dimethyl-3-hydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6b**) have been synthesized from 6,7,8,9-tetrahydro-2-hydroxybenzocyclohepten-5-one (**1**) via Claisen rearrangement and PTS, in good yield.

Introduction

Benzosuberone derivatives posses potential anti-inflammatory, antipyrutic, antiulcer, CNS-depressant, CNS-stimulant and anticonvulsant. Some of the derivatives also knew for antitumor activity in murine p388 tests.[1] Because of their wide range of biological importance, various approaches have been reported to construct the benzosuberone skeleton.[2-13] Our involvement in the development of new methodologies promted us to make a simple and sharp rout for the synthesis of 2-Methyl-2,3-dihydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6a**) and 2,3-dimethyl-3-hydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6b**) starting from 6,7,8,9-tetrahydro-2-hydroxybenzocyclohepten-5-one (**1**)[14,15].

Chemistry

Alkylation of 6,7,8,9-tetrahydro-2-hydroxybenzocyclohepten-5-one (**1**) with allyl bromide (**2a**) or methallyl chloride (**2b**) in dry acetone, potassium carbonate medium give the corresponding O-allyl ethers (**3a-b**). This on heating in *N,N'*-diethyl aniline at 200^{0}C gave C-allyl derivatives (**4a-b**). The resulting C-allyl derivatives were then cyclized in good yield to 2-Methyl-2,3-dihydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6a**) and 2,3-dimethyl-3-hydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (**6b**) with PTS in chloroform at reflux temperature for 4-5h. Thus, the allyl ether **2a-b** obtained from the hydroxy benzocycloheptenone **1** by treatment with **2a-b** was rearranged Claisen rearrangement and gave two isomeric products **4a-b** and **5a-b**. These were separated on a neutral alumina column gave a major (more polar) and a minor (less polar)[16] (**Scheme-1**). Their structures were established by ^{1}H NMR, IR and Mass.



Scheme-1

Experimental Section

Melting points were determined in open glass capillaries on a polmon melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts are recorded in δ, ppm); internal standard was TMS and IR spectra were recorded in KBr on a Perkin-Elmer bio-spectrometer.

2-Allyloxy-6,7,8,9-tetrahydrobenzocyclohepten-5-one (3a)

A mixture of the hydroxy ketone (1.2.0 g, 0.011 mole), allyl bromide (2.0 mL), anhydrous potassium carbonate (5.0 g) and dry acetone (100 mL), was refluxed for 6 hrs. After cooling to room temperature the reaction mixture was filtered to remove potassium carbonate ethyl acetate (100 mL) was added to the filtrate and then washed with 0.8% NaOH with brine to neutrality, dried and concentrated. The residue on chromatography over silica gel by eluting with benzene: pet ether (1:9) a liquid (90%)[16].

2-(2-Methyl allyloxy)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (3b)

Liquid (88%). ^{1}H NMR ($CDCl_3$) : δ 1.48-1.66 (m, 4H, 7&8-H), 2.47-2.55 (m, 4H, 6 & 9-H), 1.76 (s, 3H, $-CH_3$), 4.58 (d, 2H, $-OCH_2-$), 4.96-5.01 (dd, 2H, $=CH_2$), 6.76 (d, ArH, 1H, J = 9.6 Hz), 7.10 (d, ArH, 1H, J = 9.8 Hz), 6.82 (s, 1H, ArH).

Claisen rearrangement of 3a-b :

The above O-allyl ether was heated in *N,N'*-diethyl aniline at 200°C in *vacuo* for 3h. After cooling, the solide was dissolved in chloroform and shown to contain two compounds by TLC. These were separated by chromatography over silica gel by eluting with pet.ether. Final purification was achieved by PTLC (chloroform). The first fraction (R_f = 0.27) was 2-hydroxy-(3-allyl)-6,7,8,9-tetrahydrobenzocyclohepten-

5-one (**4a**, 10%), m.p.90.6°C (lit.[16] m.p.90°C). The second fraction (R_f = 0.16) was 2-hydroxy-(1-allyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**5a**, 40%).[16]

2-Hydroxy-3-(2-methyl allyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (4b, 10%)

Liquid. IR (KBr) : λ_{max} 3550 (OH), 2910 (C=C), 1720 (C=O) cm^{-1} ; ^1H NMR ($CDCl_3$) :δ 1.50-1.67 (m, 4H, 7 & 8-H), 2.50-2.59 (m, 4H, 6 & 9-H), 1.81 (s, 3H, $-CH_3$), 3.31(d, 2H, $-CH_2$-), 5.10-5.26 (dd, 2H, $=CH_2$), 6.78 (s, 1H, ArH,), 7.10 (s, 1H, ArH).

2-Hydroxy-1-(2-methyl allyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (5b, 40%)

Liquid. IR (KBr) : λ_{max} 3500 (OH), 2920 (C=C), 1710 (C=O) cm^{-1} ; ^1H NMR ($CDCl_3$) :δ 1.49-1.65 (m, 4H, 7&8-H), 2.40-2.51 (m, 4H, 6 & 9-H), 1.80 (s, 3H, $-CH_3$), 3.28 (d, 2H, $-OCH_2$-), 4.86-5.00 (dd, 2H, $=CH_2$-), 6.77 (d, 1H, ArH, *J* = 9.5 Hz), 7.26 (d, 1H, ArH, *J* = 9.6 Hz), 6.76 (s, 1H, ArH).

2-Methyl-2,3-dihydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (6a)

The mixture of 2-hydroxy-(3-allyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**4a,** 300mg) and PTS (100mg) were dissolved in chloroform (20mL) and refluxed for 4.5 h. After cooling to room temperature poured on crushed ice and extracted with chloroform. The chloroform layer was washed with water (50mL), dried and concentrated. The residue on column chromatography over silica gel, eluting with benzene : EtOAc (8:2) gave the final product (**6a**) in 78% yield. IR(KBr) : λ_{max} 2910 (C=C), 1620 (C=O) cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 1.46-1.67 (m, 4H, 7 & 8-H), 2.55-2.62 (m, 4H, 6 & 9-H), 1.42 (s, 3H, $-CH_3$), 3.00-3.06(dd, 2H, $-CH_2$-), 4.26 (m, 1H, O-CH-), 6.75 (s, 1H, ArH,), 7.32 (s, 1H, ArH).

2,3-dimethyl-3-hydrobenzo[*b*]furan-6,7,8,9-tetrahydro cycloheptene-5-one (6b)

Semi-solide, yield 66%. IR(KBr) : λ_{max} 2900 (C=C), 1610 (C=O) cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 1.42-1.69 (m, 4H, 7 & 8-H), 2.51-2.59 (m, 4H, 6 & 9-H), 1.46 (s, 6H, 2 x CH_3), 2.86(s, 2H, $-CH_2$-), 6.66 (s, 1H, ArH,), 7.53 (s, 1H, ArH). MS : m/z 230 (M^+, 100), 215, 187, 173, 145, 132.

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