

Novel Approach Towards the Synthesis of Poly Heterocyclic Compounds: Total Synthesis of 12-Oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene

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A simple and facile synthesis of the hexahydrochrysene derivative, 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene has been reported through the use of conventional and green methodologies. The key steps are, microwave assisted O-alkylation of a bromophenol ether, synthesis of halosynthon, 1,4-dihydro-1,4-epoxynaphthalenyl methyl *o*-bromophenyl ether *via* reaction with benzyne formed *in situ* followed by its subsequent 6-exo-*trig* cyclization towards the synthesis of the polycyclic ring system in good yield.

Keywords: Halosynthon, Microwaves, Radical cyclization, Hexahydrochrysene derivative.

INTRODUCTION

Heterocyclic compounds are widely distributed in nature and their functions are often of fundamental importance to living systems [1]. Amongst the various classes of natural products which possess a heterocyclic ring are saponins [2], polyketides [3], steroids [4], alkaloids [5], terpenes [6] and antibiotics such as penicillin, sulphur containing drugs [7] and cephalosporin [8,9]. Many modern synthetic drugs contain a heterocyclic ring as one of its important molecular unit [10-12]. One such a group of heterocyclic compounds are the hexahydro-chrysenes and hexahydropyrenes. Substituted hexahydro-chrysenes are known to show biological activity and estrogenic potency [13]. Literature reports the synthesis of substituted chrysenes [14] and hexahydrochrysenes [15,16]. In these syntheses, various routes have been adopted to produce functional groups in a highly stereoselective manner.



In continuation to our interest in the use of halosynthons or synthetic units that contain a halogen atom as one of the reactive sites, we reported herein a novel and simple synthesis of a polyheterocyclic system, 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene (**6**). And towards our ongoing endeavor for the utilization of greener technologies [17-21] for assisting organic synthesis one of the synthetic steps employs the use of microwave energy.

EXPERIMENTAL

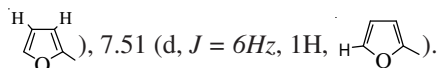
¹H NMR spectra were recorded on Bruker AC 300F, 300 MHz spectrometer. Chemical shift values are expressed as δ value (ppm) downfield from tetramethylsilane, used as the

internal standard. The infrared spectra were recorded using a Perkin-Elmer Model 1430 spectrophotometer and signals are expressed in cm^{-1} . Mass spectra were recorded at 70 eV using VG Analytical 11-250-J705 spectrometer. The elemental analysis (C, H, N) was carried out using Perkin-Elmer 2400 elemental analyzer. Column chromatography was performed using silica gel (Acme's Synthetic Chemicals, 100-200 mesh). Reactions assisted by microwave energy were carried out in a BPL BMO 700T (640 W) microwave oven. Most of the reactions were carried out in oven-dried glassware under a dry N_2 atmosphere. During work ups all organic solvents with density less than water were dried over anhydrous Na_2SO_4 and those with density more than water with CaCl_2 .



2-Furfuryl alcohol (2): To a stirred suspension of NaBH_4 (0.79 g, 24.76 mmol) in dry THF (10 mL) taken in a 100 cm^3 two-necked round bottomed flask, fitted with a pressure equalizer, was added a solution of furfural (2.0 g, 20.63 mmol) in dry THF (15 mL). The reaction mixture was cooled in an ice-bath and to it was added a solution of I_2 (1.27 g, 5 mmol) in dry THF (15 mL) over a period of 30 min. Stirring was continued, till TLC monitoring showed completion of reaction. The reaction mixture was quenched with 3 N HCl (2 \times 5 mL) followed by extraction with diethyl ether (3 \times 10 mL). The combined organic extracts were washed with 3 N NaOH (3 \times 5 mL), brine and dried. Evaporation of solvent under vacuum furnished the pure alcohol **2** (1.82 g, 91 %).

¹H NMR (CCl_4): δ 3.5 (bs, 1H, $-\text{OH}$, D_2O exchangeable), 4.51 (s, 2H, $-\text{CH}_2\text{OH}$), 6.1 (m, 2H, , 7.1 (d, $J = 6\text{ Hz}$, 1H, ).

2-Furfuryl bromide (3): To a stirred solution of **2** (1.8 g, 18.36 mmol) and dry pyridine (3.61 g, 45.69 mmol) in anhydrous ether (25 mL) at 0 °C was added drop wise phosphorus tribromide (1.98 g, 7.3 mmol) in 5 mL of anhydrous ether. The contents were stirred for 4 h at 0 °C. The reaction mixture was extracted with ether (50 mL) and washed with water (2 × 20 mL) and brine (10 mL). The ethereal layer was dried and a small portion was evaporated for analysis. Carbon tetrachloride was immediately added to this portion to run the ¹H NMR spectrum. DMF (3 mL) was added to the remaining portion and ether was evaporated under vacuum to furnish **3** as 2-furfuryl bromide is highly unstable and decomposes almost immediately. ¹H NMR (CCl₄): δ 4.51 (s, 2H, -CH₂Br), 6.42 (m, 2H,



***o*-Bromophenyl-2-furanylmethyl ether (4):** To a solution of **3** (2.0 g, 12.4 mmol) in dry DMF (6 mL) was added anhydrous potassium carbonate (4.28 g, 31.0 mmol) and *o*-bromophenol (2.57 g, 14.8 mmol) in a 100 mL beaker covered with a watch glass. The reaction mixture was first irradiated at 640 W for 2 min and then another 1 min in the microwave oven. The contents were allowed to cool and then extracted with ether (2 × 50 mL). The organic extracts were washed successively with aqueous NaOH solution (20 mL), water (3 × 25 mL) and brine (20 mL). The organic layer was dried and evaporated to give pure **4** (2.1 g, 66.8 %). m.f. C₁₁H₉O₂Br; Elemental analysis found (%): C, 52.17; H, 3.55; calculated : C, 52.13; H, 3.57. R_f: 0.66 (petroleum ether:ethyl acetate:: 9.5:0.5); IR (neat)/ν_{max}: 1680, 1230 and 720 cm⁻¹; ¹H NMR

(CCl₄): δ 5.11 (s, 2H, -OCH₂), 6.40 (m, 2H, , 6.89-7.73 (m, 5H, Ar-H & ).

1,4-Dihydro-1,4-epoxynaphthalenylmethyl *o*-bromophenyl ether (5): To a well stirred and mildly refluxing solution of **4** (1.0 g, 3.95 mmol) and freshly prepared *n*-pentyl nitrite (0.55 g, 4.7 mmol) in dry THF (15 mL) was added drop wise a solution of anthranilic acid (0.64 g, 4.67 mmol) in dry THF (5 mL) over a period of 30 min. A deep red coloured solution was obtained which was further refluxed for 2 h. The reaction mixture was cooled and extracted with ether (2 × 50 mL). The combined organic layers were washed successively with aqueous KOH (2 × 20 mL), water (3 × 20 mL) and brine (10 mL). The organic extract was dried and solvent removed under vacuum to give a thick oil which was purified by column chromatography over silica gel to afford pure compound **5** (0.9 g, 69.2 %). m.f. C₁₇H₁₃O₂Br; Elemental analysis found (%): C, 62.05; H, 3.92; calculated (%): C, 62.00; H, 3.95. R_f: 0.41 (petroleum ether:ethyl acetate::9.5:0.5); IR (CCl₄)/ν_{max}: 1230, 1090 and 740 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 4.75 (dd, *J* = 21.5, 10.1 Hz, 2H, -OCH₂-), 5.8 (d, *J* = 1.7 Hz 1H, bridgehead proton), 6.9-7.6 (m, 10H, Ar-H, HC=CH); ¹³C NMR (CDCl₃, 300 MHz): δ 67.4, 82.4, 90.8, 112.6, 113.9, 120.1 (2C), 122.7, 125.2 (2C), 128.6, 133.5, 142.7, 144.1, 148.7, 149.9, 155.1; MS *m/z* (relative intensity): 330 (10.1), 328 (10.1), 249 (8.1), 221 (17.4), 191 (16.8), 187 (15.5), 185 (15.5), 174 (14.3), 172 (14.6), 131 (43.5), 130 (15.0), 129 (100.0), 115 (29.2), 85 (27.9), 77 (21.9).

12-Oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene (6): To a flamed dried 100 mL three necked round bottomed flask equipped with a dropping funnel, reflux condenser and a septum cap was added a solution of **5** (0.4 g, 1.21 mmol) in dry benzene (30 mL). The mixture was thoroughly purged with nitrogen gas for about 15 min and then refluxed for a few minutes. A solution of *n*-Bu₃SnH (0.42 g, 1.44 mmol) and catalytic amount of AIBN in dry benzene (30 mL) was added very slowly over a period of 2 h and further refluxed for 6 h. Evaporation of the solvent followed by column chromatography over silica gel gave pure compound **6** (0.25 g, 82.5 %). m.f.: C₁₇H₁₄O₂; Elemental analysis found (%): C, 81.8; H, 5.3; calculated (%): C, 81.6; H, 5.6; R_f: 0.45 (petroleum ether:ethyl acetate::9.5:0.5); IR (Nujol)/ν_{max}: 3100, 1200, 1180 and 740 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 2.2 (m, 2H, C-O-C-CH₂), 3.0 (m, 1H, methine), 4.6 (d, *J* = 3.4 Hz, 2H, -OCH₂-), 5.5 (d, *J* = 4.6 Hz 1H, bridge head proton), 6.9-7.3 (m, 8H, Ar-H). ¹³C NMR (CDCl₃, 300 MHz): δ 38.1, 39.2, 64.0, 79.3, 83.9, 117.3, 117.4, 119.5, 121.7, 126.0, 126.8, 127.3 (2C), 130.1, 144.4, 146.4, 152.5; MS *m/z* (relative intensity): 250 (20.1), 199 (4.5), 177 (5.4), 175 (4.3), 149 (4.4), 132 (13.9), 131 (100.0), 129 (5.7), 128 (6.1), 103 (16.6).

RESULTS AND DISCUSSION

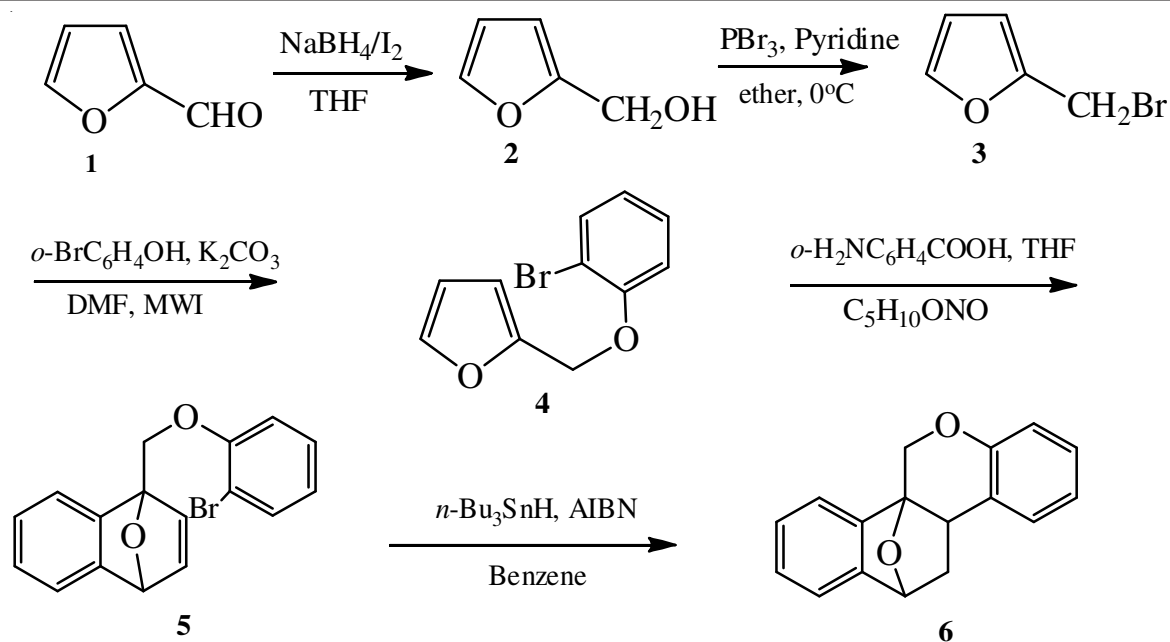
Furfural (**1**) on reduction with sodium borohydride and iodine in dry THF at 0 °C yielded 2-furfuryl alcohol [22] (**2**). It was subjected to bromination with PBr₃ in the presence of two equivalents of dry pyridine to furnish 2-furfuryl bromide (**3**), which due to its instability was used as its solution in DMF in subsequent reactions. A mixture of this solution, *o*-bromophenol and anhydrous K₂CO₃ was exposed to microwave radiations at 640 W to result in the formation of the O-alkylated product [23] (**4**). The structure of **4** was confirmed on the basis of spectral data and elemental analysis. The ¹H NMR of **4** showed a sharp singlet at δ 5.1 corresponding to -OCH₂-protons. This compound was then reacted with benzyne [24] formed *in situ* by the reaction of anthranilic acid and *n*-pentyl nitrite, to give the halosynthon **5**. This was then subjected to 6-exo-*trig* cyclization [25] with *n*-Bu₃SnH and AIBN in refluxing benzene [26] to yield the target molecule 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene (**6**). The schematic representation employed is given in **Scheme-I**.

The mass spectrum of compound **5** showed the molecular ion peak at *m/z* 328 and 330 (10.1) and other prominent peaks at 221 (17.4), 191 (16.8), 187, 185 (15.5), 129 (100.0), 115 (29.2) can be explained on the basis of the fragmentation pattern shown in **Scheme-II**.

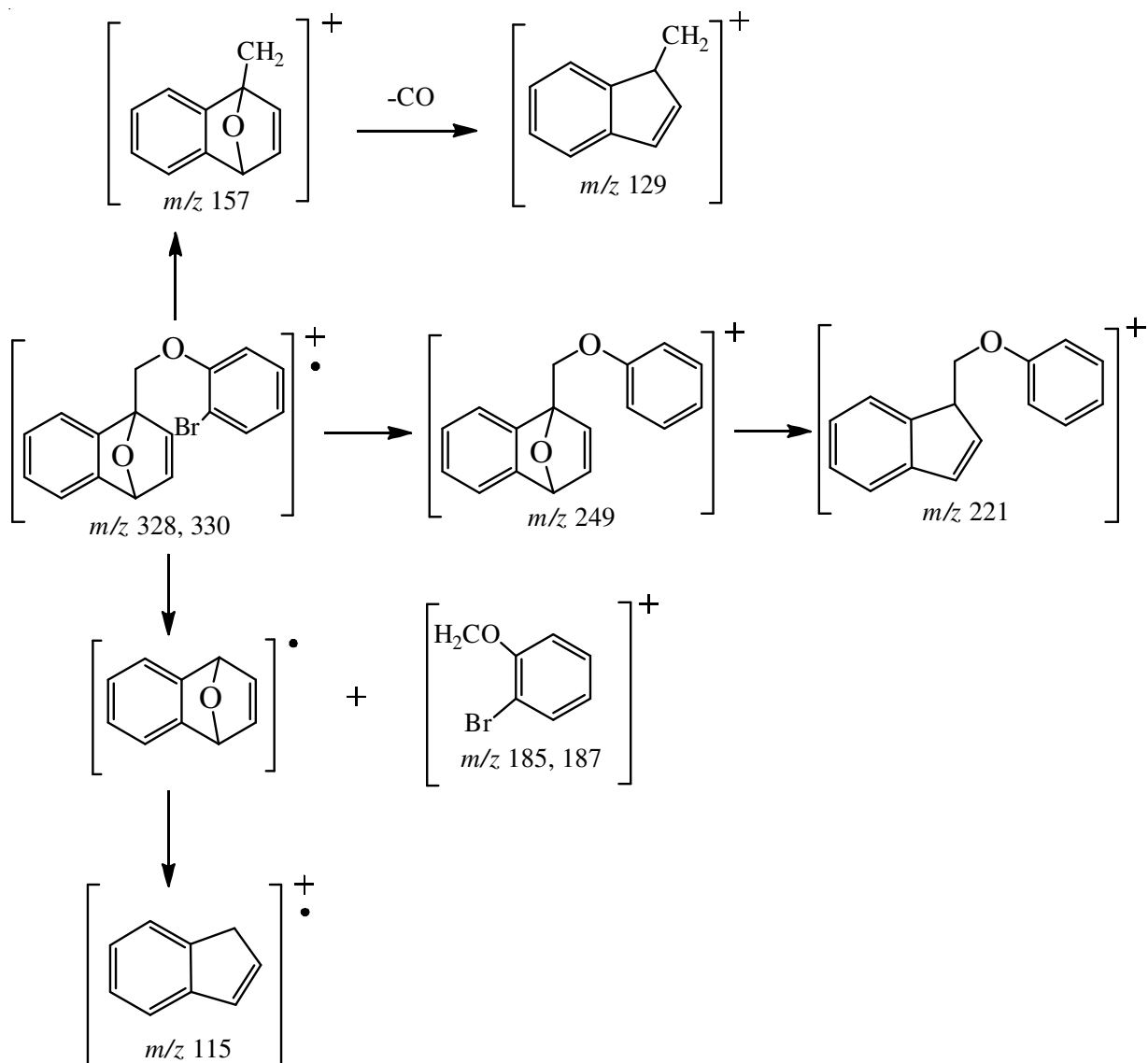
The structure of **6** was confirmed on the basis of its spectral data and mass spectrum. Its mass spectrum showed the molecular ion peak at *m/z* 250 (20.1) and other prominent peaks at 132 (13.9), 131 (100.0), 129 (5.7), 128 (6.1), 103 (16.6) can be explained on the basis of the following fragmentation pattern (**Scheme-III**).

Conclusion

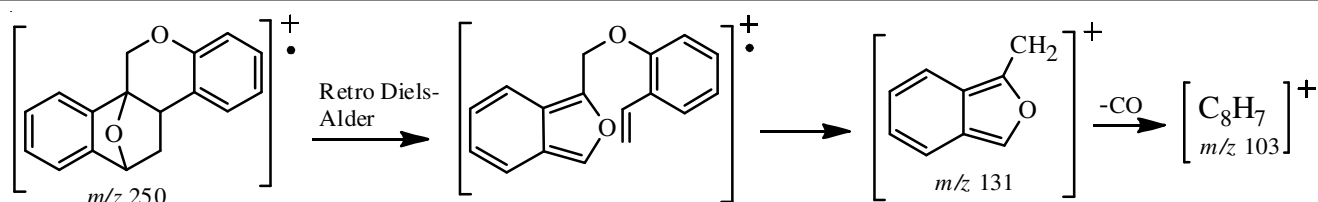
A simple and effective total synthesis of a hexahydrochrysene derivative has been reported starting from furfural. Its reduction and subsequent bromination followed by



Scheme-I: Schematic representation employed for the total synthesis of 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene (6)



Scheme-II: Mass fragmentation pattern obtained for 1,4-dihydro-1,4-epoxynaphthalenyl methyl *o*-bromophenyl ether (5)



Scheme-III: Mass fragmentation pattern obtained for 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene (**6**)

microwave assisted reaction with a bromophenol resulted in the formation of the corresponding O-alkylation product. Its reaction with *in situ* generated benzyne furnished the halosynthon **5** which was made to undergo tandem free radical cyclization using tributyltin hydride as the radical source, leading to the synthesis of 12-oxa-6,10b-epoxy-4b,5,6,10b,11,12-hexahydrochrysene **6** in 82 % yield.

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