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Synthesis of 4-(5',6',7', 8'-tetrahydro-naphthalene)-1-tetralone

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ABSTRACT

A new one-pot synthesis of 4-aryltetralone was discovered. This tandem process includes condensation of alpha-naphthol with tetralin in presence of Lewis acids, most preferably by aluminium chloride followed by its hydrolysis yields 4-aryltetralone in fairy good yield under Friedel-Crafts conditions. The primarily advantage of present protocol is use of tetralin as a solvent as well as reactant. The structure of newly synthesized compounds were characterized by advanced spectral (IR, ^{1}H-NMR, ^{13}C-NMR and LC/MS) and analytical (elemental analysis and melting point) techniques. The synthesized compound was subjected to powder X-ray diffraction shows its crystalline nature. The operational simplicity and easily scalable process are major benefits.

Keywords: tetralone, Lewis acid, aluminium chloride.

INTRODUCTION

Substituted tetralones have played an important role in organic synthesis as a result of their high reactivity and suitability as starting material for a wide range of synthetic heterocyclic compounds [1, 2], pharmaceuticals [3] with biological activities and other useful properties as well as precursors of several natural products and their derivatives [4, 5]. Among the various tetralones compounds, 1-tetralones are relatively inexpensive to make, easy to prepare and are of readily available. Several derivatives of 1-tetralone especially those with a hydroxyl or methoxy functionalized aromatic rings, are building blocks that have been employed in the synthesis of bio-medicinally active compounds such as some antidepressants [6], acetyl cholinesterase inhibitors effective in the treatment of Alzheimer's disease [7], alkaloids bearing antitumor activity [8] and antibiotics [9]. 7-aryl tetralones have been used in the synthesis of CCR5 antagonists such as anti-HIV-1 agents [10]. These were generally prepared by multistep sequence consisting of an intra-molecular Friedal Craft cyclization [11- 16]. Similarly 6-aryl tetralones [17] were also prepared by Friedal Craft reaction [18-20].

As a part of the study aimed at expanding the synthetic utility of 1-tetralone thus we proposed a simple and convenient method for preparation of 4-aryl-1-tetralone.

MATERIALS AND METHODS

All materials were purchased from commercial suppliers and used without further purification. All NMR spectra were recorded on a 500MHz Avance III Bruker spectrophotometer. Mass were recorded on Waters Q-TOF (w) premier spectrometer. IR spectra were recorded in KBr on a SHIMADZU 400-50 infrared spectrophotometer. Elemental analysis of compound was determined by PERKIN ELMER elemental analysis. X-Ray Diffraction pattern was recorded on X'Pert PRO PANalytical Diffractometer. The X-ray generator was operated at 40 mA and 45 kv, using the K-alpha line of copper at 1.54060A^{o} as the radiation source. It was scanned in the diffraction range of 4.0^{o} to 30.9^{o} 2Θ at a scan rate of 0.020^{o} 2Θ. Commercially available isopropyl alcohol and ethyl acetate were used as such without purification.

Preparation of 4-(5',6',7',8'-tetrahydro-naphthalene)-1-tetralone (Compound I) : 6.93g (0.05mol) of Aluminium chloride and 18.33g (0.13mol) of tetralin and 5.0g (0.03 mol) of alpha naphthol was heated to 100°-110° C for 15minutes. As the reaction mixture becomes thick yellowish-green in color added again 18.33g (0.13mol) of tetralin and maintain for another 15minutes at 100°-110° C. The reaction mass was then cooled, added 200ml of purified water dropwise. Extract the compound in ethyl acetate, washed with water and concentrated completely under vacuum at 90° C to an oily residue. This oily residue was purified by column chromatography using hexane: ethyl acetate as mobile phase followed by recrystallization in isopropyl alcohol which afforded 5.9g of the title product as a white crystalline powder.

Melting Point: 92.9° C. Yield: 62%. **Anal. Calcd**. for $C_{20}H_{20}O$: C, 86.86; H, 7.23. Found: C, 86.82; H, 7.21; **IR υ_{max} (KBr) cm^{-1}**: 3058 (Ar-H), 2932 (Alip-H), 1674(C=O of ring), 1595 (C=C stretching of aromatic ring), 1434 (C-H bending), 1044 (C-O stretching); **^{1}H-NMR (500MHz, $CDCl_3$, δ / ppm)**: 1.77 (4H, *m*, -CH_2 of naphthyl ring), 2.29 (1H, *m*, -CH_2 of alip. tetralone ring), 2.44 (1H, *m*, -CH_2 of alip. tetralone ring), 2.63 (2H, *m*, -CH_2 of naphthyl ring), 2.73 (2H, *m*), 4.20 (1H, *m*, -CH of alip. tetralone ring), 6.82-8.13 (7H, *m*, aromatic); **^{13}C-NMR (125.76MHz, $CDCl_3$, δ / ppm)**: 23.16 (C_2, -CH_2), 23.21(C_3, -CH_2), 29.04 (C_{15}, -CH_2), 29.45(C_{16}, -CH2), 31.87(C_{17}, -CH2), 36.83(C_{18}, -CH2), 44.98(C_4, -CH), 125.71, 126.92, 127.02, 129.29, 129.37, 129.65, 132.77, 133.58, 135.68, 137.39, 140.73, 146.65 (-C, aromatic rings), 197.80 (C_1, -C=O); **ESI-MS** (*m/z*,(relative abundance, %)): 299 (M+, 23) 277, 74.11.

Preparation of Racemic mixture of 1-hydroxy-4(5',6',7',8'-tetrahydro-naphthalene)-1-tetralin (Compound II):

Compound (I) **(**2.0g, 0.007mol) dissolved in a mixture of 20ml of methanol and 5ml of dichloromethane. The reaction mixture was stirred at ambient temperature and then 0.068g (0.0018 mol) of sodium borohydride was added, stirred the reaction mass for 12-14 hrs .The reaction mass was concentrated completely under reduced pressure to get an oily residue. To the oily residue added dichloromethane and water, separate the layers, wash the organic layer with water, dried over sodium sulphate, concentrated to an oil which was recrystallised in diethyl ether to afforded 1.2g of tittle compound as a white powder.

Melting Point: 109° C. Yield; 60%. **Anal. Calcd**. for $C_{20}H_{22}O$: C, 86.23; H, 7.96. Found: C, 86.20; H, 7.90; **IR υ_{max} (KBr) cm^{-1}**: 3334 (-OH streching), 3062 (C-H aromatic stretching); 2929 (C-H aliphatic stretching); 1500, 1488 (C=C aromatic stretching); 1435 (C-H bending), 1052 (C-O stretching); **^{1}H-NMR (500MHz, $CDCl_3$, δ / ppm):** 1.86 (4H, *m*, -CH_2 of naphthyl ring), 2.08 (1H, *m*, -CH_2 of naphthyl ring), 2.16 (1H, *m*, -CH_2 of tetralone ring), 2.72 (2H, *m*, -CH_2 of tetralone ring), 3.80, 4.11 (1H, *m*, -CH of tetralone ring), 4.86, 4.91(1H, *s*, racemic -OH), 6.73-7.56 (7H, *m*, aromatic); **^{13}C-NMR (125.76MHz, $CDCl_3$, δ / ppm):** 23.22-36.83(-CH_2 of ring), 44.97, 45.50 (C_4, -CH of ring), 68.23, 68.59 (C_1, C-OH), 125.83-143.62 (-C, aromatic ring); **ESI-MS** (*m/z*,(relative abundance, %)): 301(M+, 23) 261.18, 175.12, 102.13, 74.10.

Preparation of Racemic mixture of 1-(2,2-dimethyl-butanoate)-4-(5',6',7',8'-tetra-hydronaphthalene)-1-tetralin (Compound III):

Compound (II) (2.0g, 0.007mol), dimethylamino-pyridine (0.061g, 0.0005mol) and imidazole (1.17g, 0.017mol) were dissolved in 50ml toluene. The reaction mixture stirred for 15 minutes and then 2,2dimethyl-butyrylchloride (2.32g, 0.017mol) was dropwise added .Reflux the reaction mixture for 8 hrs at 108° -110° C .The reaction was quenched with water (20ml) and washed the organic layer with 10ml of 0.1N hydrochloric acid solution followed by 10ml of 5% sodium bicarbonate solution. Dried the organic layer over sodium sulphate and concentrate completely under reduced pressure at 50° C. 1.8g of dark colored oily residue was obtained.

Boiling Point: 115° C. Yield: 66.6%. **Anal. Calcd**. for $C_{26}H_{32}O$: C, 82.86; H, 7.96. Found: C, 82.82; H, 7.90; **IR υ_{max} (KBr) cm^{-1}**: 3051 (-C-H aromatic stretching), 2959 (-C-H aliphatic stretching), 1724, 1698(-C=O stretching of -COO), 1534 (-C=C stretching), 1459 (-C-H bending), 1045 (-C-O stretching); **^{1}H-NMR (500MHz, $CDCl_3$, δ / ppm):** 0.83(3H, *t*, terminal -CH_3 of butyryl gp), 1.12 (3H, *s*, -CH_3 of (CH_3)2), 1.15(3H, *s*,-CH_3 of (CH_3)2), 2.02 (m, 2H), 2.63 (2H, *m*, -CH_2), 4.20 (1H, *m*, -CH), 7.07-7.21 (7H, *m*, aromatic ring); **^{13}C-NMR (125.76MHz, $CDCl_3$, δ / ppm):** 9.27, 9.29 (C_{23},C_{24}, (-CH_3)$_2$ dimethyl carbon of butyryl gp), 23.20, 23.22 (C_{26}, -CH_3 terminal carbon), 24.74, 24.66 (C_{25}, -CH_2 of butyryl gp) 24.46-33.35 (-CH_2, of ring), 42.43, 42.73 (C_{22}, -CH(CH_3)$_2$ gp), 44.58-45.26 (C_4,-C H of ring), 69.71,70.00 (C_1, C-O), 125.85-143.35 (C, aromatic ring), 177.54 (C=O); **ESI-MS** (*m/z*,(relative abundance, %)): 399 (M+, 23) 329, 238, 237, 74.10.

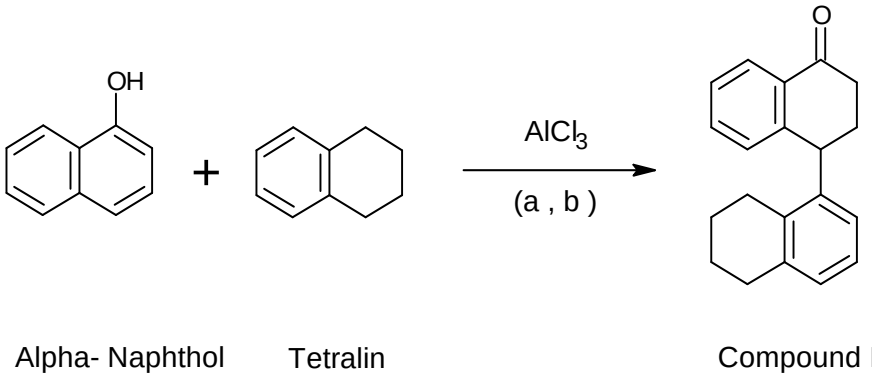
RESULTS AND DISCUSSION

For synthesizing novel 4-aryltetralone represented by general formula **I** was designed as the target compound. The synthesis of the compounds **I** as depicted in scheme 1 was initiated by reacting the key starting material alpha-

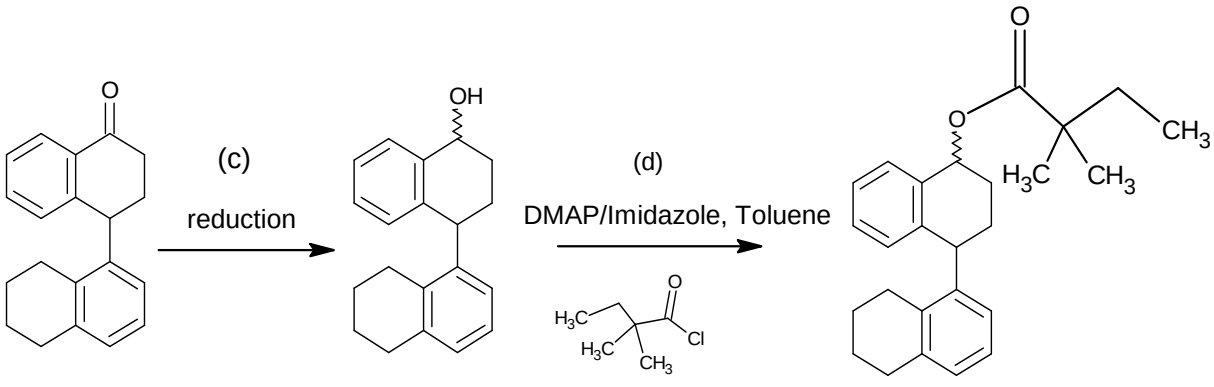
naphthol with tetralin in the presence of Lewis acid especially by $AlCl_3$ followed by water hydrolysis afforded the compound **I** in 62% yield. The optimal temperature for the reaction is 100-110^o C. In this approach the isolated compound was purified via column chromatography followed by its recrystallization in isopropyl alcohol. In our attempt the compound **I** was prepared, isolated and characterized successfully. The highest yield was obtained when $AlCl_3$ was used (entry 1, Table 1). As expected, it is due to strong Lewis acidity of $AlCl_3$. The reactions using $SnCl_4$, $ZnCl_4$ and $TiCl_4$ does not initiated even after several hours. This concluded that reaction takes place only with relatively strong Lewis acids as catalysts. No reaction was observed with weak Lewis acids such as $SnCl_4$, $TiCl_4$ and BF_3 (entry 2, 5, 6 in Table 1). It was preferable that tetralin to be used in excess with respect to alpha- naphthol, the best yields being obtained when tetralin was used at the ratio of 8-10 molar equivalent with respect to alpha-naphthol. This indicates that excess tetralin, may play the role of solvent too. The reaction is generally completed after 30minutes. However this time varies depending on the amount of acid agent used. Compound **I** shows a sharp endothermic peak in differential scanning calorimeter. The X-ray powder diffractogram was obtained using X'Pert-PRO PANalytical Diffractometer shows crystalline nature of compound **I**. The X-ray generator was operated at 40 mA and 45 kv, using the K-alpha line of copper at 1.54060 A^o as the radiation source. It was scanned in the diffraction range of 4.0^o to 30.9^o 2Θ at a scan rate of 0.020^o 2Θ. ^{1}H-NMR spectra showed a multiplet at δ 6.82-8.13 for seven protons which accounted for aromatic protons of ring. A multiplet at δ 4.23 was observed, corresponding to single proton of –CH group. Two multiplets were observed at δ 2.29 and δ 2.44 corresponds to each single proton of $-CH_2$ group of C2. A sharp multiplet observed at δ 1.77, attributed to four protons of two $-CH_2$ groups.

Table 1. Preparation of compound I in the presence of different Lewis Acid

Entry No	Lewis acid	Equiv.	Reaction Time (hrs)	Yield% (compound I)
1	$AlCl_3$	1.5	0.5	62
2	$SnCl_4$	1.5	5.0	--
3	$FeCl_3$	1.0	1.0	42
4	$ZnCl_2$	1.5	5.0	--
5	$TiCl_4$	1.5	8.0	--
6	BF_3	1.5	5.0	--
7	$AlCl_3$	1.0	1.5	58



Alpha- Naphthol Tetralin Compound I



Compound I compound II compound III

Scheme 1. Reagents and conditions: (a) Aluminium chloride, 100^o-110^o C, 30minutes. (b) Ethyl acetate, Isopropyl alcohol 0^o-5^o C (c) Methanol, sodium borohydride, room temperature (d) Dimethylaminopyridine, imidazole, 2,2 dimethylbutyryl chloride, toluene, 100^o-110^o C, 8hrs.

CONCLUSION

In conclusion we have developed a simple and convenient method to synthesize compound **I** in a quantitative yield using $AlCl_3$. The simple procedure, fairy good yield generality render this method a valuable addition to tetralone chemistry.

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