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Synthesis of 4-Phenyltetralone Derivatives and Reaction Mechanism

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4-(*p*-Chlorophenyl)tetralone (**6**) and 7-chloro-5-(*p*-chlorophenyl)tetralone (**9**) are key intermediates for the development of benzazepinone derivative haftens. These compounds could be synthesized from 4-phenyltetralone derivatives by triflic acid catalyzed Friedel-Crafts reaction. The reaction mechanism of Friedel-Crafts alkylation/acylation with lactones in triflic acid is presented. According to our tentative research, ring opening of protonated lactone (**2**) occurs in alkyl cleavage and the rate of the reaction is not dependent on concentration of triflic acid. So, alkylation of lactone in Friedel-Crafts reaction is presumed to be $A_{AL}1$. In second step, intramolecular acylation of the intermediates **4** to **6**, **4** can be transformed to a triflic acid-carboxylic anhydride and then the cyclization is undergone after leaving of the triflate anion.

Key words: 4-(*p*-Chlorophenyl)tetralone,7-Chloro-4-(*p*-chlorophenyl)tetralone, Benzazepinone derivative haften, Friedel-Crafts reaction mechanism, $A_{AL}1$

INTRODUCTION

The benzazepinone derivative haftens can be used as a component of the reagents for the detecting benzodiazepine drugs which are commonly abused and used in clinics as CNS depressants. 4-(*p*-Chlorophenyl)tetralone (**6**) and 7-chloro-5-(*p*-chlorophenyl)tetralone (**9**) are necessary as a key intermediate for the development of benzazepinone derivative haftens.

It is knwon that 4-phenyltetralone can be synthesized by the Friedel-Crafts reaction of lactone with benzene and aluminum chloride (Truce and Olson,1952). Reaction of 4-phenyltetrahydrofuran-2-one and benzene with aluminum chloride or trifluoromethanesulfonic(triflic) acid provides 4-phenyltetralone. Same method can be applied to the synthesis of **6** and **9**. When triflic acid is applied as a catalyst, high yields of pure phenyltetralone could be obtained (Quallich, 1990).

Lactones are cyclic esters. The reaction mechanism of Friedel-Crafts alkylation with lactones in triflic acid as catalyst does not appear to have been reported previously.

MATERIALS AND METHODS

Melting points were determined using a Fischer-Johns melting apparatus and were not corrected. Infrared spectra were obtained using a Perkin-Elmer FT-IR spectrometer. ^{1}H-NMR spectra were obtained using Jeol JMN-LA 300 MHz and LA 400 MHz spectrometer and chemical shifts were reported as ppm δ units from tetramethylsilane(TMS) as an internal standard. Commercially available chemicals and solvents were used and purchased from Aldrich, Sigma, Merck. Column chromatography was carried out on silica gel 60Å(70-230 mesh, Merck).

5-(*p*-Chlorophenyl)tetrahydrofuran-2-one

A mixture of 3-(p-chlorobenzoyl) propionic acid (21 g, 0.1 mol) and demineralized water (250 ml) was heated to 75-80°C while 1N-NaOH (100 ml) was gradually added in portions. The solution was heated at the same temperature for 2.5 h with the pH of the final solution being 10-11. Sodium borohydride (4.2 g, 0.11 mol) in demineralized water (200 ml) was added gradually to the solution. The reaction mixture was heated at the same temperature for 3 h, acidified with c-HCl (pH 1-2) and heated at 70°C for 1.5 h. After cooling the reaction mixture was extracted twise with ethyl acetate (50 ml).

The combined organic extracts were washed with 1N-NaOH (100 ml), dried over anhydrous magnesium sulfate and concentrated to give yellowish oil residue. The product was crystallized in ethyl acetate.

Yield: 17 g (93 %); mp 52°C ; ^{1}H-NMR (300/400 MHz/$CDCl_3$) δ 2.07-2.13 (m, 1H), 2.58-2.64 (m, 3H), 5.41-5.45 (m,1H), 7.21-7.24 (m, 2H), 7.31-7.33 (m, 2H); IR (KBr) 1,783 (CO), 2,986 (CH), 3,066 (aromatic), 3,530 (OH) cm^{-1}.

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4-(*p*-Chlorophenyl)tetralone

Method A

5-(*p*-Chlorophenyl)tetrahydrofuran-2-one (13.8 g, 0.07 mol) was added to anhydrous benzene (60 ml) under nitrogen atmosphere. To the mixture was added triflic acid (12 g, 0.08 mol) solution in dry benzene (5 ml) gradually through a syringe. The reaction mixture was refluxed for 15 h, and then poured into 70 g of crushed ice. The organic materials were extracted three times with methylene chloride (50 ml). The combined methylene chloride extracts were washed with 4N-NaOH (50 ml), dried over anhydrous magnesium sulfate and evaporate to give a brown sticky oil. The residue was purified by silica gel column chromatography using ethyl acetate-hexane mixture (1:1) eluent. Yield; 7.0 g (45%); oil; ^{1}H-NMR (300/400 MHz/acetone-d_6), δ 2.20-2.38(m, 1H), 2.40-2.45 (m, 1H), 2.58-2.67 (m, 2H), 4.22-4.26 (m, 1H), 6.89-8.00 (m, 8H); IR (KBr) 1,686 (CO), 2,946 (CH), 3,062 (aromatic) cm^{-1}.

Method B

5-Phenyltetrahydrofuran-2-one (11.4 g, 0.07 mol) was added to anhydrous monochlorobenzene (60 ml) under nitrogen atmosphere. To the mixture was added triflic acid (12 g, 0.08 mol) solution in monochlorobenzene (5 ml) through a syringe added gradually. The reaction mixture was refluxed for 10 min. and then poured into 70 g of crushed ice. The organic materials were extracted three times with methylene chloride (50 ml). The following procedure was the same as the method A for 4-(p-chlorophenyl)tetralone. Yield: 6.3 g (5%).

7-Chloro-4-(*p*-chlorophenyl)tetralone

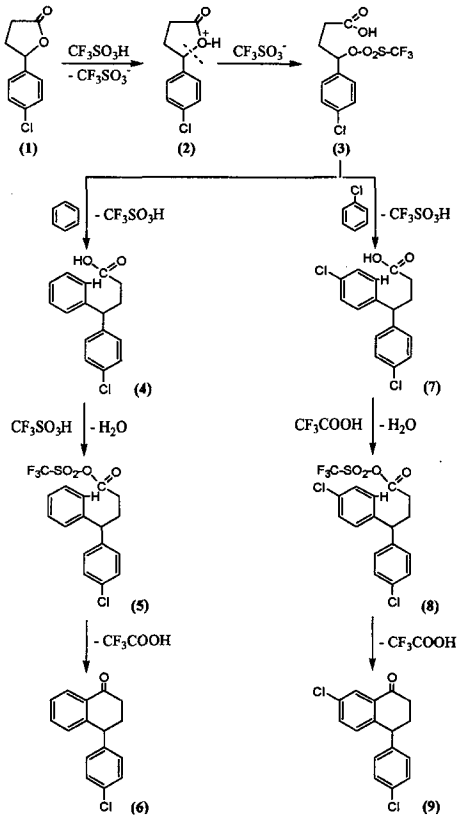
5-(p-Chlorophenyl)tetrahydrofuran-2-one (13.8 g, 0.07 mol) was added to anhydrous monochlorobenzene (60 ml) under nitrogen atmosphere. To the mixture was added triflic acid (12 g, 0.08 mol) solution in monochlorobenzene (5 ml) gradually through a syringe. After stirring for 10 min. at room temperature, the reaction temperature was allowed to rise to 50-60°C and stirred for 5 min. The reaction mixture was poured into 70 g of crushed ice and extracted three times with methylene chloride (50 ml). The following procedure was the same as method A for 4-(*p*-chlorophenyl) tetralone. Yield: 6.1 g (30%); oil; ^{1}H-NMR (300/400 MHz/acetone-d_6) δ 2.20-2.25 (m, 1H), 2.39-2.46 (m, 1H), 2.61-2.70 (m, 2H), 4.20-4.24 (m, 1H), 6.87-6.89 (d, J=7.5 Hz, 1H), 7.00-7.03 (m, 2H), 7.23-739 (m, 3H), 8.04 (s,1H); IR (KBr) 1,689 (CO), 2,948 (CH), 3,061 (aromatic), 3,358 (OH) cm^{-1}.

RESULTS AND DISCUSSION

In the Friedel-Crafts alkylation and acylation, there are several mechanistic pathways depending on substrate and reaction conditions especially the nature of the leaving groups. The triflate anion ($CF_3SO_3^-$) is one of the best leaving groups known to chemists. According to recent investigation, triflic acid as the Friedel-Crafts reaction catalyst in the mixture of acyl chloride and aromatic compounds, is first transformed to an intermediate, triflic-carboxylic anhydride as the active acylating agent (Effenberger and Epple, 1972).

According to the Ingold acid-and base-catalized hydrolysis of ester can theoretically be classified into eight possible mechanims depending on the three criteria such as acid- or base-catalyzed, unimolecular or bimolecular and acyl cleavage or alkyl cleavage(Ingold, 1969). The normal mechanims are those classified as $A_{AC}2$ and $B_{AL}2$; both mechanisms involve a tetrahedral intermediate and essentially an addition-elimination mechanism.

Lactones are cyclic esters and in the Friedel-Crafts alkylation with lactones in triflic acid as catalyst the reaction mechanism can be illustrated by applying Ingold and Effenberger theories. The formation of **6** in the Friedel-Crafts reaction with 4-(*p*-chlorophenyl)tetrahydrofuran-2-one (**1**) is followed by two steps, alkylation and acylation. In the intermolecular electrophilic alkylation to aromatic ring, ring opening of protonated lactone (**2**) after acceptance of a proton by triflic acid can occur in two ways, acyl cleavage or alkyl cleavage, but even though acyl cleavage



Scheme 1. Friedel-Crafts alkylation/acylation mechanism of lactone by triflic acid catalyst

is predominating ($A_{AC}2$) in ester, alkyl cleavage is undergone in this reaction (Scheme 1). If acyl cleavage were undergone, the product were 1-(*p*-chloro-phenyl)-3-benzoyl-1-propanol, but no traces of this product could be detected. The other evidence of alkyl cleavage is that in the same kind of condensation of γ-butyro-lactone with benzene in the presence of aluminum chloride the inter-mediate of this reaction is γ-phenylbutyric acid (Truce and Olson,1952). Wether the alkyl cleavage is unimolecular ($A_{AL}1$) or bimolecular ($A_{AL}2$), it is not precisely investigated, but looks like unimolecular. Because according to our tentative research the rate of the reaction is not dependent on concentration of triflic acid. So alkylation of lactone is presumed to be $A_{AL}1$. Even though the $A_{AL}2$ mechanism has been reported in the acid cleavage of γ-lactone (Moore and Schwab, 1991), $A_{AL}2$ is exceptional and rare. In second step the cyclization of the intermediate, γ-phenyl-γ-(p-chlorophenyl)butyric acid **4** to **6** is a intra-molecular Friedel-Crafts acylation. The cyclization was taken place as expected with the unsubstituted aromatic ring rather than the aromatic ring substituted with chlorine, an electron-withrawing group. It is logical to illustrate that this acylation is performed according to Effenberger. **4** can be tranformed to triflic-carboxylic anhydride **5** (Effenberger, 1972) and then intramolecular acylation is undergone after leaving of the triflate anion. When chloro-benzene was applied in stead of benzene in this reaction, **9** could be obtained through the intermediates **7** and **8** in the same way.

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