Synthesis and characterization of \( o \)-hydroxyarylalkylketones by using eco-friendly solvent free catalyst in frie’s rearrangement

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**ABSTRACT

The Fries rearrangement of aromatic esters is usually performed in Lewis acid (\( \text{AlCl}_3 \)), we have optimized this reaction with \( p \)-toluene sulphonic acid (PTSA). It was found to be as efficient new reagent for probing the mechanism of acylation reactions and Fries rearrangement of aromatic esters. PTSA is a strong, stable and biodegradable acid giving high conversion and selectivity (up to 90\% of ortho-isomer and 10\% of para-isomer at 100\% conversion). Further, the conversion was confirmed by elemental and spectral (IR, \(^1\)H NMR Mass) analyses.

**Keywords:** Acylation, Fries arrangement, Eco-Friendly Catalyst, \( o \)-Hydroxyacetophenone.

**INTRODUCTION

The Fries rearrangement of aryl esters, a special case of Friedel-Craft acylation provides an important route for the synthesis of aromatic hydroxyl aryl ketones that find various uses[1]. Lewis acids such as aluminium chloride[2-3], boron trifluoride[3-4], bismuth trifluoride or strong protopic acid such as hydrogen fluoride, methane sulfonic acid[4-9] can be used for this reaction. But these are corrosive and environment unfriendly catalysts. For example aluminium chloride is too powerful a need to be used in reagent quantities because of its ability to strongly complex Lewis base products[10]. Method for separating the aluminium chloride is by destructive water quench leading to large volume of hazardous wastes. Thus the use of aluminium chloride can lead to violations of several principles of green chemistry through the release in the environment of hazardous substances, which pose problem of high toxicity, corrosion and spent acid disposal.

In view of these disadvantages of the use of Lewis acids it was proposed to achieve the migration of aryl esters to corresponding hydroxyketones with compound other than Lewis acid[11-12].
MATERIALS AND METHODS

General: All the chemicals were obtained from E-Merck, India (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. IR spectra were recorded on a Shimadzu DR-8031 instrument. 1H NMR spectra of the synthesized compounds were recorded on a Bruker-Avance (300MHz) and Varian-Gemini (200MHz) spectrophotometer using CDCl3 solvent and TMS as an internal standard.

Synthesis of p-Toluenesulfonic acid (PTSA). A mixture of pure toluene 87g (100ml, 0.95mol) and concentrated sulfuric acid 37g (20ml, 0.35mol) was gently boiled for 1 hour and cooled, the solid p-toluenesulfonic acid was precipitated out. It was filtered and dried, yield 35%, m.p. 105°-106°C.

Synthesis of Phenyl acetates. Phenyl acetate 2a. A mixture of phenol (94g, 1mol) and dry pyridine (10ml) was placed in a 500ml beaker. It was kept in ice bath and acetic anhydride (127ml, 1.25mol) was added slowly with constant stirring. The reaction mixture was poured on a mixture of ice cold water and concentrated hydrochloric acid (50ml) and extracted with carbon tetrachloride (100ml). The extract was washed successively with water, 10% NaOH solution and again with water. It was dried over calcium chloride. The solvent was removed by distillation and phenyl acetate was collected at 195 to 197°C, yield 70%, (Table 2.1).

Synthesis of o-Tolylacetate 2b. A mixture of o-cresol (54g, 1mol) and dry pyridine (5ml) was placed in a 500ml beaker. It was kept in ice bath and acetic anhydride (64ml, 1.25mol) was added slowly with constant stirring. The reaction mixture was poured on a mixture of ice (100g) and concentrated hydrochloric acid (50ml) and extracted with carbon tetrachloride (50ml). The extract was washed successively with water, 10% NaOH solution and again with water. It was dried over calcium chloride. The solvent was removed by distillation and o-tolyl acetate was collected at 175 to 182°C, yield 60%, (Table 2.1).

Synthesis of m-Tolylacetate 2c. A mixture of m-cresol (54g, 1mol) and dry pyridine (5ml) was placed in a 500ml beaker. It was kept in ice bath and acetic anhydride (64ml, 1.25mol) was added slowly with constant stirring. The reaction mixture was poured on a mixture of ice (100g) and concentrated hydrochloric acid (50ml) and extracted with carbon tetrachloride (50ml). The extract was washed successively with water, 10% NaOH solution and again with water. It was dried over calcium chloride. The solvent was removed by distillation and m-tolyl acetate was collected at 180 to 187°C, yield 65.1%, (Table 2.1).

Synthesis of o-Chlorophenylacetate 2d. A mixture of o-chloro phenol (80g, 1mol) and dry pyridine (5ml) was placed in a 500ml beaker. It was kept in ice bath and acetic anhydride (64ml, 1.25mol) was added slowly with constant stirring. The reaction mixture was poured on a mixture of ice (100g) and concentrated hydrochloric acid (50ml) and extracted with carbon tetrachloride (50ml). The extract was washed successively with water, 10% NaOH solution and again with water. It was dried over calcium chloride. The solvent was removed by distillation and o-chlorophenyl acetate was collected at 175 to 182°C, yield 62.38%, (Table 2.1).

Synthesis of p-Chlorophenylacetate 2e. A mixture of p-chloro phenol (80g, 1mol) and dry pyridine (5ml) was placed in a 500ml beaker. It was kept in ice bath and acetic anhydride (64ml, 1.25mol) was added slowly with constant stirring. It was poured on a mixture of ice (100g) and concentrated hydrochloric acid (50ml) and extracted with carbon tetrachloride (50ml). The extract was washed successively with water, 10% NaOH solution and again with water. It
was dried over calcium chloride. The solvent was removed by distillation and p-chloro phenyl acetate was collected at 175 to 182°C, Yield 60%, (Table 2.1).

### Table 2.1 Phenyl acetates 2a-e

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>% Yield</th>
<th>Solubility (NaOH)</th>
<th>B. p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>70</td>
<td>Insoluble</td>
<td>195</td>
</tr>
<tr>
<td>2b</td>
<td>o-CH₃</td>
<td>60</td>
<td>Insoluble</td>
<td>180</td>
</tr>
<tr>
<td>2c</td>
<td>m-CH₃</td>
<td>65</td>
<td>Insoluble</td>
<td>185</td>
</tr>
<tr>
<td>2d</td>
<td>o-Cl</td>
<td>62</td>
<td>Insoluble</td>
<td>175</td>
</tr>
<tr>
<td>2e</td>
<td>p-Cl</td>
<td>60</td>
<td>Insoluble</td>
<td>172</td>
</tr>
</tbody>
</table>

**Fries rearrangement of Phenyl acetate into Hydroxyacetophenone**

**Synthesis of 2-Hydroxyacetophenone 3a.** Phenyl acetate 2a (10g, 0.073mol) was poured in 100 ml round bottom flask containing p-toluene sulphonic acid (7g, 0.042mol). The reaction mixture was heated on an oil bath at 100-110°C for 30 minutes. It was poured on ice cold water with vigorous stirring, a mixture of o-hydroxyacetophenone (liquid) and p-hydroxyacetophenone (solid) was obtained. o-Hydroxyacetophenone was isolated by steam distillation. Yield 60%, b.p.213°C, (Table 2.2). UV: λ max 274 mµ, IR (KBr): 3385 cm\(^{-1}\), br (-OH); 1650 cm\(^{-1}\) str (-CO); 2940 cm\(^{-1}\) str (C-H); 3008 cm\(^{-1}\)(-CH₃) in methyl.

**Synthesis of 2-Hydroxy-3-methylacetophenone 3b.** o-Tolyl acetate 2b (10g, 0.066mol) was poured in 100ml round bottom flask containing p-toluene sulphonic acid (8g, 0.048mol). The reaction mixture was heated on an oil bath at 90-120°C for 30 minutes. It was poured in ice cold water with vigorous stirring, a mixture of 2-hydroxy-3-methylacetophenone (liquid) and 4-hydroxy-3-methylacetophenone (solid) was obtained. O-isomer was isolated by steam distillation. Yield 75%, b.p.237°C, (Table 2.2). UV: λ max 255 mµ, ¹H NMR (CDCl₃) ppm: [12.05 (s, 1H) -OH; [2.24-2.30 (s, 3H) –CH₃]; [2.59-2.63 (s, 3H) –CH₃]; [6.50-8.10 (m, 3H) –Ar-H].

**Synthesis of 2-Hydroxy-4-methylacetophenone 3c.** m-Tolyl acetate 2c (10g, 0.066mol) was poured in 100ml round bottom flask containing p-toluene sulphonic acid (8g, 0.042mol). The reaction mixture was heated on an oil bath at 90-110°C for 30 minutes. It was poured in ice cold water with vigorous stirring, a mixture of 2-hydroxy-4-methylacetophenone (liquid) and 4-hydroxy-2-methyl acetophenone (solid) was obtained. 2-Hydroxy-4-methyl acetophenone isomer was isolated by steam distillation method. Yield 60% b.p.242°C, (Table 2.2). UV: λ max 270 mµ, IR (KBr): 3410 cm\(^{-1}\), br (-OH); 1770 cm\(^{-1}\) str (-CO); 2940 cm\(^{-1}\) str (C-H); 3040 cm\(^{-1}\) (Ar-H); 1450 cm\(^{-1}\) str (C=C). 800 cm\(^{-1}\) str (C-Cl).

**Synthesis of 2-Hydroxy-3-chloroacetophenone 3d.** o-Chlorophenylacetate 2d (10g, 0.091mol) was in 100ml round bottom flask containing p-toluene sulphonic acid (9g, 0.052 mol). The reaction mixture was heated on an oil bath at 80-110°C for 30 minutes. It was poured in ice cold water with vigorous stirring, a mixture of 2-hydroxy-3-chloro acetophenone (liquid) and 4-hydroxy-2-chloro acetophenone (solid) was obtained. 2-Hydroxy-3-chloro acetophenone isomer was isolated by steam distillation. Yield 58% b.p. 92°C (Table 2.2). IR (KBr): 3405 cm\(^{-1}\), br (-OH); 1630 cm\(^{-1}\) str (-CO); 2910 cm\(^{-1}\) str (C-H) str (Ar-H); 3040 cm\(^{-1}\)(Ar-H); 1450 cm\(^{-1}\) str (C=C). 800 cm\(^{-1}\) str (C-Cl).
Synthesis of 2-Hydroxy-5-chloroacetophenone \(3e\). p-Chlorophenyl acetate \(2e\) (10g, 0.091mol) was in 100 ml round bottom flask containing \(p\)-toluenesulphonic acid (9 g, 0.052 mol). It was heated on an oil bath at 90-120\(^\circ\)C for 30 minutes. The reaction mixture was poured in ice cold water with vigorous stirring, a single compound of 5-chloro-2-hydroxyacetophenone (liquid) was obtained. \(o\)-chlorohydroxyacetophenone isomer was isolated by steam distillation. Yield 65%. b.p. 128\(^\circ\)C (Table 2.2) IR (KBr): 3405 cm\(^{-1}\), br (-OH); 1630 cm\(^{-1}\) str (-CO); 2910 cm\(^{-1}\) str – (C-H) str\(\text{in CH}_3\); 3040 cm\(^{-1}\) (Ar-H); 1450 cm\(^{-1}\) str (C=C) 800 cm\(^{-1}\) str-(C-Cl).

<table>
<thead>
<tr>
<th>Compd.</th>
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<th>% Yield</th>
<th>Solubility (NaOH)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>70</td>
<td>213</td>
<td>Violet, Soluble</td>
</tr>
<tr>
<td>3b</td>
<td>mCH(_3)</td>
<td>80</td>
<td>237</td>
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</tr>
<tr>
<td>3c</td>
<td>o-CH(_3)</td>
<td>70</td>
<td>242</td>
<td>Violet, Soluble</td>
</tr>
<tr>
<td>3d</td>
<td>o-Cl</td>
<td>60</td>
<td>92</td>
<td>Violet, Soluble</td>
</tr>
<tr>
<td>3e</td>
<td>p-Cl</td>
<td>70</td>
<td>128</td>
<td>Violet, Soluble</td>
</tr>
</tbody>
</table>

Comparative Chart of formation of Product by Both the Catalyst \(\text{AlCl}_3\) and PTSA.

RESULTS AND DISCUSSION

The Fries rearrangement was performed at 90\(^\circ\)-160\(^\circ\)C without any solvent using catalytic amount of \(p\)-toluenesulfonic acid. The yields of products were obtained near about same as that of withaluminiumchloride (\(\text{AlCl}_3\)). The reaction time was also importance, 98% conversion of phenyl acetates \(2a\) was achieved within 30 min at 90\(^\circ\)-160\(^\circ\)C. The ortho/para ratio \(3a/4a\) was always infavour of the desired compound \(3a\) and decreased during the conversion of phenyl acetates. The reaction may be carried out under optimized temperature, low temperaturefavoursthe formation paraproduct and high temperaturefavours the formation orthoprodust.
synthesized compounds have been confirmed on the basis of elemental analysis and spectral data. It was found to be very important to use an anhydrous p-toluenesulfonic acid, as traces of water hydrolyse phenyl acetate 2a to phenol and acetic acid.

**Scheme 1: Synthesized of Phenyl acetate from Phenol.**

\[
\begin{align*}
\text{phenol} & \quad \xrightarrow{(CH_3CO)_2O/Pyridine} \quad \text{phenyl acetate} \\
1 & \quad \xrightarrow{ \quad \text{(CH}_3\text{CO})_2\text{O/Pyridine} \quad } \quad \text{phenyl acetate}
\end{align*}
\]

**Scheme 2: Fries of Phenyl acetate into Ortho/Para Hydroxyacetophenone.**

\[
\begin{align*}
\text{phenyl acetate} & \quad \xrightarrow{\text{PTSA}} \quad \text{hydroxyacetophenone} \\
2a & \quad \xrightarrow{\text{PTSA}} \quad 3a \quad \text{and} \quad 4a
\end{align*}
\]

**Mechanism of reaction**

\[
\begin{align*}
\text{phenol} + \text{p-toluenesulfonic acid} & \quad \xrightarrow{\text{H}_2\text{C}^+\text{O}^-\text{O}^-\text{SO}_3^-\text{C}_6\text{H}_4\text{CH}_3} \quad \text{hydroxyacetophenone} \\
\end{align*}
\]

**CONCLUSION**

p-Toluenesulfonic acid, a biodegradable white solid, was used in the Fries rearrangement of phenyl acetate to o-hydroxyacetophenone and p-hydroxyacetophenone with very good conversion of around 98% and very good yield of the ortho product. To obtain such performances, a molar ratio of p-toluenesulfonic acid is not necessary. Hydroxyketones were easily separated from the aqueous solution by extraction with organic solvents. p-
Toluenesulfonic acid is a biodegradable and easy to handle. Its performances are similar to aluminium chloride (yield, conversion, selectivity) and has lower impact on the environment.

REFERENCES