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## Aromatic C-acylation of Phenols by using Acid and Acid Anhydride in Presence of Lewis Acid Catalyst

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### ABSTRACT

Ring acylations of aromatic substances are very difficult to achieve to a great extent. Nencki reaction has attempted on mono to poly hydroxy and substituted phenols have good results. Reactions are using solely acetic acid, acetic anhydride and adipic acid or mixture of acid and anhydride resulting complete consumption of phenols. The use Lewis acid freshly fused  $ZnCl_2$  is best suitable catalyst compare to others. The essential data on phenols acylation has been studied and described as below.

**Keywords:** Nencki reaction, Phenols, Acetic acid, Acetic anhydride, Adipic acid, Freshly fused  $ZnCl_2$

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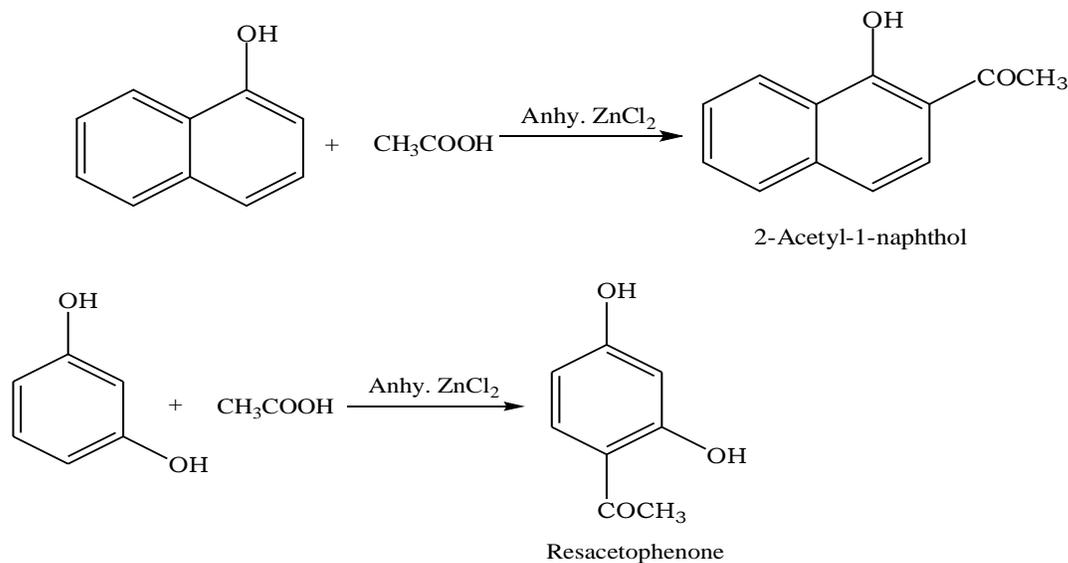
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## INTRODUCTION

Direct C-acylation of phenol reaction was first reported by Nencki *et al.* in 1881<sup>1-3</sup>. An acyl phenol derivative prepared from anhydrous zinc chloride activated acylation between a phenol & carboxylic acid or anhydride is generally known as the Nencki reaction<sup>4-13</sup>.

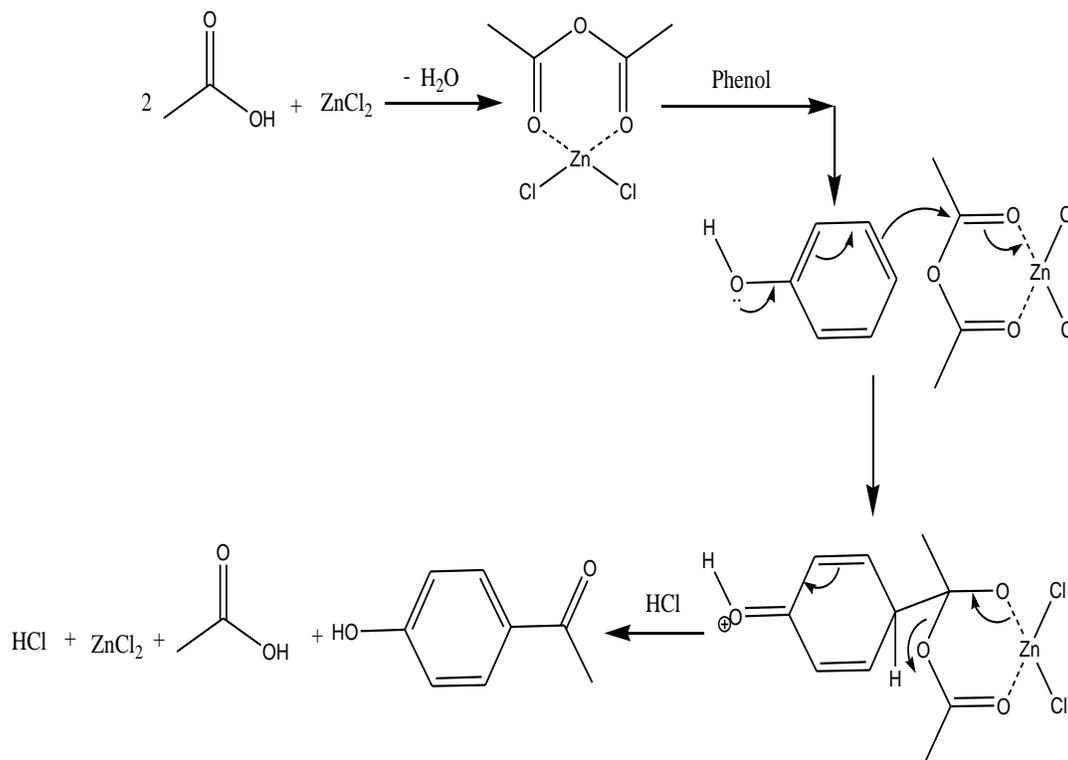
Nencki & Sieber were the first to prepare 2-acetyl-1-naphthol & 4-acetyl-resorcinol by condensing  $\alpha$ -naphthol & resorcinol respectively with acetic acid in presence of fused zinc chloride. The synthesis of 4-acetyl-resorcinol (Resacetophenone) was then modified by Robinson & Shah<sup>14</sup> & the yield of 2-acetyl-1-naphthol was later improved by Witt & Braun<sup>15</sup>



With the help of this reaction many other hydroxyl ketones such as respropiofenone, resbutyrophenone<sup>16</sup> 4-stearyl, 4-palmityl, 4-lauryl resorcinols & pyrogallols<sup>17</sup> & 2-propionyl, 2-butyryl & 2-isobutyryl-1-naphthols have been prepared.

The condensation of cresols with acetic, propionic and butyric acids was tried under conditions of Nencki's reaction employing anhydrous zinc chloride as the condensing agent. Only *o*-cresol gave rise to both the *ortho*- and *para*-substituted derivatives, while the *m*- and the *p*-cresols produced only the *ortho*-substituted products. The yields varied with the duration of heating<sup>18</sup> to reaction mass.

### Flow of reaction mechanism:



The regioselectivity of the reaction in para-acylation depends on the size of the acylating reagent. Therefore we have studied yield effect by addition of anhydride<sup>19</sup> with a carboxylic acid.

It is a simplest method of phenol and naphthol acylation. Initially we have tried acetic acid and acetic anhydride solely as an acylating agent on a resorcinol and freshly fused  $\text{ZnCl}_2$  as a catalyst; which have further modified by use of acetic acid and acetic anhydride mixture for the improvement in yield. Catalyst freshly fused  $\text{ZnCl}_2$  is suitable during solely use of acid to study its solubility. With different phenol and naphthol we have studied and standardized the effects of different mole ratios of acetic anhydride and acetic acid in a reaction. To study the acylation of phenolic ketones by Nencki method has been tried on resacetophenone which did not work.

It has been found that the regioselectivity in preference of para-acylation decreases when the size of the acylating reagent increases<sup>20</sup>.

We have tried adipic acid first time as a acylating agent on a resorcinol using  $\text{ZnCl}_2$  catalyst in a carbon tetrachloride media to which hydroquinone and chatechol does not support.

Free hydroxyl groups of phenolic compounds confirmation has been done by derivatization using acetic anhydride.

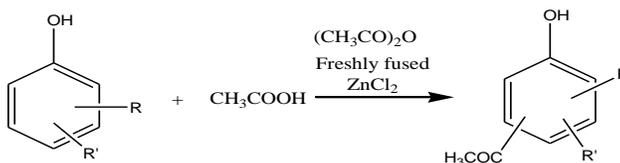
## MATERIALS AND METHOD

All chemicals Phenols, Naphthols, Acetic acid, Acetic anhydride, Adipic acid and Zinc chloride are used of LR grade quality. Phenols and Naphthols are purified if and when required.

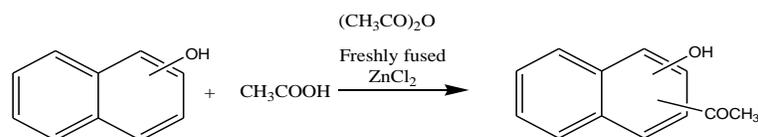
## Methods

Nencki Reaction of mono, di and trihydric phenols using  $ZnCl_2$  catalyst.

### Scheme-I:

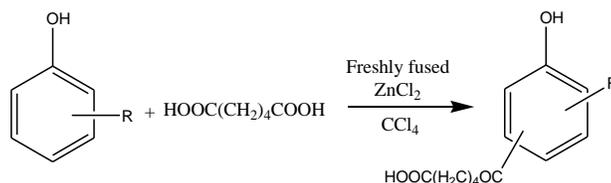


R=ortho OH, R'= H	No product
R=meta OH, R'= H	2,4 Dihydroxy acetophenone
R=para OH, R'= H	2,5 Dihydroxy acetophenone
R=meta $NO_2$ , R'= H	No product
R=ortho OH, R'=meta OH	2,3,4 Trihydroxy acetophenone
R=meta OH, R'=meta OH	2,4,6 Trihydroxy acetophenone



$\alpha$ -Naphthol	1-Hydroxy 2-Acetonaphthone
$\beta$ -Naphthol	2-Hydroxy 3-Acetonaphthone

### Scheme-II:



R=ortho OH	No product
R=meta OH	6-(2,4-dihydroxyphenyl)-6-oxohexanoic acid
R=para OH, R'= H	No product

## Experimental

### Scheme-I (Using Acetic acid)

In a clean and dry 250ml glass beaker taken acetic acid and freshly fused  $ZnCl_2$ . Resulting mixture is heated to dissolve  $ZnCl_2$  in acetic acid till continuous removal of vapors of moisture. In a 100ml RBF charge substituted phenol and  $ZnCl_2$ -acetic acid solution and heated it to 150-180°C for 1hrs. After reaction maintaining it is cool to room temp. and add 1:1 HCl soln. To precipitate out

product completely stir it for 1hrs at room temp. Filter off product and wash it thoroughly with water. Suck dry and dry product in air oven.

#### Scheme-I (Combination of Acetic acid & Acetic anhydride)

To a clean and dry 100ml single neck RB flask substituted Phenol, acetic acid, acetic anhydride and freshly fused ZnCl<sub>2</sub> are charged in single lot. Resulting mixture is stirred and heated to 150°C to 180°C. After reaction maintaining it at same condition for 1hrs it is then cool to room temp. and add 1:1 HCl soln. To precipitate out product completely stir it for 1hrs at room temp. Filter off product and wash it thoroughly with water. Suck dry and dry product in air oven.

#### Scheme-II (Reaction using Adipic acid)

Arranged clean and dry 250ml single neck RBF under reflux set up. Charged substituted phenol, adipic acid, freshly fused ZnCl<sub>2</sub> and CCl<sub>4</sub> in RBF to heat on gentle burner flame for 3 to 4hrs. Cool resulting reaction mass to room temp. decanted CCl<sub>4</sub> and kept reaction mass as such for overnight. To the sticky yellow orange colored reaction mass add 1:1 HCl gives solid precipitation. Filter off product and wash it thoroughly with water. Suck dry and dry product in air oven.

#### **Analysis**

The spectral data of compound from:

Compound-**2**: 2, 4-Dihydroxyacetophenone: recrystallization from a water

Mel. Pt.: 138-142°C

IR.(KBr)/v (cm<sup>-1</sup>):3300, 1610, 1375, 1180, 457

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz, ppm) δ: 2.5(s, 3H), 4.2(bs, OH), 6.1-6.3(t, 1H), 7.3-7.5(d, 2H)

Compound-**3**: 2, 5-Dihydroxyacetophenone: recrystallization from a EtOH+ water

Mel. Pt.: 203-205°C

IR.: (KBr)/v (cm<sup>-1</sup>):3300, 1610, 1375, 1180, 457

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz, ppm) δ: 2.2(s, 3H), 3.8(bs, OH), 6.2-6.4(d, 2H), 7.0-7.2(d, 2H)

Compound-**4**: 2, 3, 4-Trihydroxyacetophenone: recrystallization from a EtOH+ water

Mel. Pt.: 170-172°C

IR.: (KBr)/v (cm<sup>-1</sup>):3370, 3150, 1650, 1080, 560

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz, ppm) δ: 2.8(s, 3H), 5.1(d, OH), 5.3-5.5(t, OH), 6.1(s, 1H), 6.3(s, 1H)

Compound-**6**: 2,4,6-Trihydroxyacetophenone: recrystallization from a water

Mel. Pt.: 220-222°C

IR.: (KBr)/v (cm<sup>-1</sup>):3403, 3305, 1627, 1340, 1124, 409

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz, ppm) δ: 2.5(s, 3H), 5.0(s, OH), 5.8(d, 2H)

Compound-**7**: 2-Acetyl-1-naphthol

recrystallization from a EtOH+water

Mel. Pt.: 98-102°C

IR.(KBr)/v (cm<sup>-1</sup>):3200-3400, 1635, 1600, 455

<sup>1</sup>HNMR(CDCl<sub>3</sub> 400MHz,ppm) δ: 2.6(s, 3H), 3.4(s, OH), 6.8-7.6(m, 6H)

Compound-**8**: 1-Acetyl-2-naphthol

recrystallization from a EtOH+water

Mel. Pt.: 61-63°C

IR. (KBr)/v (cm<sup>-1</sup>): 3000-3500, 1670, 1540, 550

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz,ppm) δ: 2.7(s, 3H), 3.25(s, OH), 6.6-7.6(m, 6H)

Compound-**10**: 6-(2,4-dihydroxyphenyl)-6-oxohexanoic acid

recrystallization from a water

Mel. Pt.: 193-195°C

UV: 276nm

IR.(KBr)/v (cm<sup>-1</sup>):3300, 2900, 1715, 1630, 1410, 1200, 960, 750, 455

<sup>1</sup>H NMR(CDCl<sub>3</sub> 400MHz,ppm) δ: 1.4-2.5(m, 8H), 4.4(bs, OH), 6.1(t, 1H), 6.3(t, 1H), 7.5(d, 1H), 12.2(s, OH)

## RESULTS AND DISCUSSION

Acetic acid is a weak monoprotic acid and commonly uses a reagent as well as solvent. It's application as an acylating agent in a combination of acetic acid and acetic anhydride benefits in terms of good yields. The ketones obtained from acetic acid without acetic anhydride was dark-coloured and required tedious purification. Solely use of acetic acid leads to troublesome process and acetic anhydride gives hard tarry reaction mass containing diacetyl impurities. This can be resolve by use of combination of acetic acid and dehydrating agent acetic anhydride. To give reaction anhydrous condition ZnCl<sub>2</sub> freshly fused is prepared and used for each experiment.

We have found in this reactions good ortho regioselectivity on phenols. This selectivity can be related to chelating the phenolic OH with zinc chloride accomplished with carboxylic acid for the formation of acylium ion

Optimum mole ratios of acetic acid, acetic anhydride and ZnCl<sub>2</sub> are identified by isolated ketones yields and melting points.

The use of dibasic acid as an acylating agent giving phenolic ketoacid with a average yield. C-acylated product of resorcinol is prepared by using adipic acid and catalyst freshly fused ZnCl<sub>2</sub> in a solvent Carbon tetrachloride. Heterogeneous reaction mass after separating CCl<sub>4</sub> turns into light

yellow orange sticky mass. Resulting product is water soluble acid which obtained from resorcinol but does not obtained from catechol and hydroquinone. We have developed the direct ortho-acylation of phenol by using adipic acid with solvent.

The reaction is regioselective; in that ortho-acylated products are obtained in the most cases. Once the ortho position occupied by acyl group no further acyl substituted product was obtained.

**Table-1 Study of temperature effect on yields by using Acetic acid solely or combination with Acetic anhydride.**

For Scheme-I:

Comp. No.	Phenols(1eq.each)	Ac-OH (eq.)	With Ac <sub>2</sub> O (eq.)	F.F. ZnCl <sub>2</sub> (eq.)	% Yields at Reaction Conditions	
					150°C	180°C
1.	Catechol	2.1	1.2	1.5	---	---
		3.2	---	2.2	---	---
2.	Resorcinol	2.1	1.3	0.7	73	64*
		2.95	---	1.21	78	61*
3.	Hydroquinone	2.5	1.05	0.9	---	30
		3.0	---	2.2	---	---
4.	meta-Nitro phenol	2.1	1.2	1.5	---	---
		4.3	---	2.2	---	---
5.	Pyrogallol	1.7	0.8	2.4	56	41
		3.2	---	1.6	38	22
6.	Phloroglucinol	1.7	0.8	2.4	70	62
		3.3	---	1.6	55	50
7.	$\alpha$ -Naphthol	1.4	1.0	0.5	74	82
		5.8	---	1.1	78	80
8.	$\beta$ -Naphthol	1.4	1.0	0.5	76	65
		5.8	---	1.1	79	85

\*Diacyl impurities reduces yield.

---Product not obtained.

**Table-2 Acylation of substituted phenol using adipic acid acylating agent.**

For Scheme-II:

Comp. No.	Substituted Phenols(1eq.each)	Adipic acid (eq.)	F.F. ZnCl <sub>2</sub> (eq.)	Remark & % Yield
9.	Catechol	1.0	1.85	No product
10.	Resorcinol	1.0	1.62	46%
11.	Hydroquinone	1.0	1.85	No product

## CONCLUSIONS

As per Table-1 results for combination of acetic acid and acetic anhydride yields are much improved along with ease in operation of practical handling. Using this combination good region selectivity has achieved to get direct para acylation.

We have concluded that dibasic acid can be use as a acylating agent to get carboxylic acid of phenolic ketone. Resorcinol which is having more reactivity compared to hydroquinone and catachol; therefore adipic acid acyl substitution is feasible.

The ketone group always occupied the 4-position in the phenol and 2-position in naphthol nucleous. Mono or Poly hydroxy phenols readily undergo acylation while substitution of electron withdrawing group acylation by this Nencki method is not feasible.

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