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## Simple and Inexpensive Nucleophilic Acyl Substitution of Phenols using Thiol Acetic Acid and Base Catalyst.

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### ABSTRACT

The thiol acetic acid and acetic anhydride both has been used for nucleophilic acyl substitution of phenols in two different methods. Both methods are simple and inexpensive by using aqueous NaOH base with acetic anhydride and no catalyst required for thiol acetic acid reaction. This can be a key method for identification of phenolic functional groups.

**Keyword:** Phenols, Thiol acetic acid, Acetic anhydride, aqueous Sodium hydroxide

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## INTRODUCTION

The prevalence of phenol and its ester or ketone functionalities in drugs, pharmaceuticals, flavones, charcons and perfumery makes the protection or characterization of the structure giving prime importance.

An esterification is a key and fundamental step to protect hydroxyl group during functional transformation in various organic synthesis. There are various methods for protection and the deprotection of hydroxyl group of phenol and naphthols. However the most common acylating reagents used are acetic anhydride and acetyl chloride. Apart from them acetic acid and thioacetic acid also can be used. Albeit many reactions are conveniently carried out in homogeneous solutions, with or without solvent, reaction occurring between two phases can present several advantages.

Organic esters represent an important family of intermediates widely employed in the synthesis of fine chemicals, drugs, plasticizers, perfumes, food preservatives, pharmaceuticals and chiral auxiliaries. Acylation has been reported with different bases such as tertiary amines like Et<sub>3</sub>N and pyridine (1-2), DMAP, tributylphosphine. On the other hand acidic catalysts (3-11) are Amberlyst-15, PTSA, metal chlorides, metal oxides such as ZnO, metal perchlorates, sulfamic acid, perchloric acid adsorbed on silica gel, silica-sulfuric acid, Naflon-H, ZrOCl<sub>2</sub>.8H<sub>2</sub>O, silica embedded-triflate catalysts, Indium trihalides, bis(cyclopentadienyl) zirconium dichloride, and heteropolyacid catalyst.

However, some of the reported methods suffer from one or more of the following disadvantages also:

- a) Harsh reaction conditions
- b) Use of hazardous & expensive materials
- c) Use of excess of acylating agent
- d) Long reaction time, or tedious work-up procedure

To overcome these concerns we have used catalyst aqueous NaOH (12) solution for salt preparation and solvent water as a greener effect. While phenols are deprotonated by base catalyst increases their nucleophilicity. The acidic phenols will not react with anhydride to give esters but their phenate metal salt will. Carboxylic acid derivatives of phenolic ketones undergo phenolic acetylation rather than formation of mixed anhydride with acid. We have first to introduce thioacetic acid as an acylating agent for dihydric phenols. And by general method of base catalyzed phenol or phenolic ketones acetylation through using acetic anhydride; study we have reported.

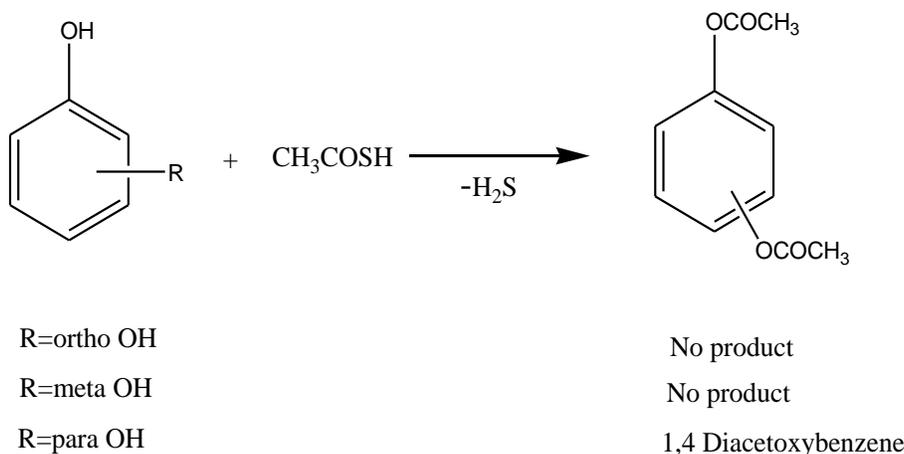
## MATERIALS AND METHOD

Mono, di hydric phenols are taken as a ready source and Phenolic ketones are synthesized. Thiol acetic acid has procured from Spectrochem as a LR material.

Acetic anhydride of Loba chemie has utilized for trials. LR grade Sodium hydroxide fresh solution always are prepared and used for trials.

### Experimental Methods

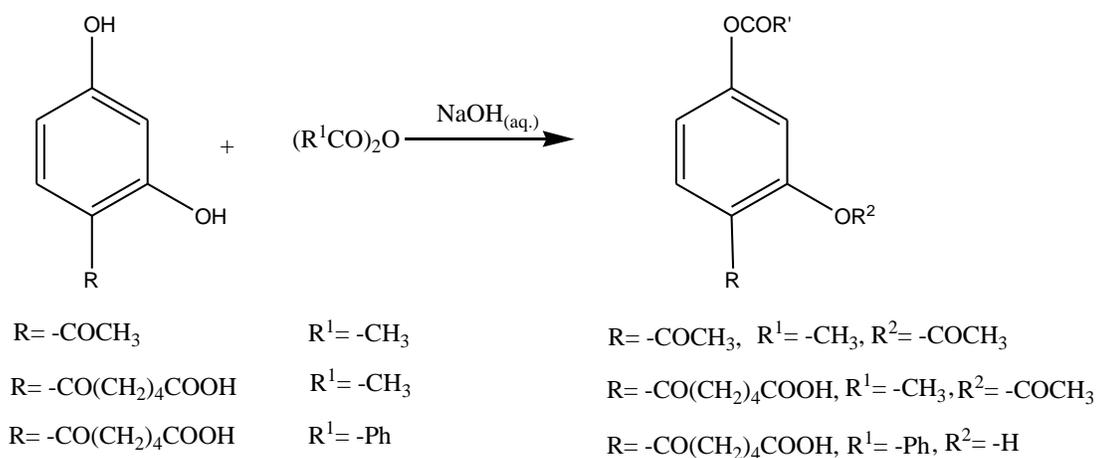
#### Scheme-I



#### Using Thiolacetic acid

In a clean and dry 100ml round bottom flask is taken dihydric phenols 1mmol with thiolacetic acid 2.75mmol. Resulting mass is stirred and heated to 130-140°C for 4hrs. Reaction is monitored by TLC till absence of phenol. Reaction mass is cooled to room temp. added acetone 4 times and stirred for 2hrs. Filter off resulting solid and wash it with water. Dried wet product and purified in ethanol water to get 30-35% yield.

#### Scheme-II



#### Using Acetic anhydride/NaOH catalyst

Phenolic ketone or its carboxylic acid dissolved in equimolar 20% aq. NaOH solution. It is cooled in ice-bath and stirred for 30min. Add corresponding anhydride 1-2mmol slowly in 60min. maintain it for 60min and monitored by TLC. Separated out organic layer or filtered off solid to get desired product with 65 to 85% yield.

### Analysis

The spectral data of compound from:

Compound-3: 1,4-Phenylene diacetate: recrystallization from a acetone

Mel. Pt.: 123-125°C

IR.:(KBr)/v (cm<sup>-1</sup>):3100, 1780, 1500, 1220, 1180

<sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz, ppm) δ: 2.3(s, 3H), 7.2(s, 2H)

Compound-4: 2, 4-Phenylene diacetate acetophenone: recrystallization from a EtOH+water

Mel. Pt.: 38-41°C

IR.:(KBr)/v (cm<sup>-1</sup>):3150, 1795, 1640, 1122, 950

<sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz, ppm) δ: 2.3(s, 3H), 2.5(s, 3H), 6.0(s, 1H), 7.3-7.5(d, 2H)

Compound-5: 6-(2, 4-Phenylene diacetate)-6-oxohexanoic acid

Boil. Pt.: 218-223°C

IR.(KBr)/v (cm<sup>-1</sup>):3300-2500, 3000, 1750, 1710, 1050, 620, 500

<sup>1</sup>H NMR(CDCl<sub>3</sub> 700MHz, ppm) δ: 1.4-2.5(m, 10H), 6.3(s, 1H), 6.5(s, 1H),

7.5(s, 1H), 11.1(s, OH)

Compound-6: 6-(2-Hydroxy, 4-benzoate)-6-oxohexanoic acid

Mel. Pt.: 218-223°C

IR.(KBr)/v (cm<sup>-1</sup>):3300, 2870, 1790, 1680, 1500, 1160, 445

<sup>1</sup>H NMR(CDCl<sub>3</sub> 700MHz, ppm) δ: 1.3-2.7(m, 8H), 6.1(d, 1H), 6.3(d, 1H),

7.2(d, 1H), 7.4-8.1(m, 6H) 11.9(s, OH)

## RESULTS AND DISCUSSION

Acylation of phenol and phenolic ketones has carried out using acetic anhydride and thiolacetic acid. Similarly we have tried O-acetylations using thiolacetic acid as an acetylating agent on hydroquinone without catalyst where resorcinol and catechol does not react. Use of solely thiolacetic acid for acylation resulting phenylene diacetate obtained with adequate yield. During reaction evolution of H<sub>2</sub>S gas is observed. Reactions has carried out with lower moles of thiolacetic acid giving unreacted phenols therefore excess use impact on good dissolution and complete starting material conversion. At higher reaction conditions with lesser mole of thiolacetic

acid leads to very hard reaction mass. We have optimized reaction time which will give complete conversion. We have tried O-acetylations using thiolacetic acid on hydroquinone without catalyst where resorcinol and catechol does not react.

O-Acylation of phenols using expensive catalyst and toxic solvents are arises plenty of disadvantages. To overcome these concerns we have used catalyst aqueous NaOH solution for phenolic salt preparation and water solvent to get a greener effect. This is general derivatization method of phenols characterization; we have reported as follows.

### **Scheme-I**

<b>Comp. No.</b>	<b>Dihydric phenol (1eq. each)</b>	<b>Thiolacetic acid (eq.)</b>	<b>Remark &amp; % Yield</b>
1.	Catechol	2.75	No product
2.	Resorcinol	2.75	No product
3.	Hydroquinone	2.75	35% (light yellow solid)

<b>Comp. No.</b>	<b>Para Substituted dihydric phenol (1eq. each)</b>	<b>Acetic or Benzoic anhydride (eq.)</b>	<b>Remark &amp; % Yield</b>
4.	R=-COCH <sub>3</sub>	acetic	75% (Off white solid)
5.	R=-CO(CH <sub>2</sub> ) <sub>4</sub> COOH	acetic	66% (dark brown oil)
6.	R=-CO(CH <sub>2</sub> ) <sub>4</sub> COOH	benzoic	78% (light yellow solid)

### **CONCLUSION**

In conclusion, on dihydric substituted phenol; their free -OH group confirmation has been done by mono or diacetylations. The use of aqueous media is an efficient, versatile, ecofriendly, inexpensive, nontoxic, heterogeneous and green catalyst. The following are the attractive features of present method:

it's have simplicity, clean, efficient, rapid and mild reaction conditions, the protocol is very general and it works well with variety of phenols affording good to excellent yields, reaction is carried out at greener media as well as in absence of expensive reagent or catalyst, used strong dehydrating agent anhydrides as an acylating agent giving rapid reaction, the process will have ease in operation and remaining MLR can send for sodium acetate recovery. So it have commercial exploitation. First time we have used thiolacetic acid as an acylating agent.

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