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Investigation of efficient synthesis of 1,8-dioxo-octahydroxanthene derivatives under solvent-free grinding method

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ABSTRACT

In these studies, we had observed polyaniline (PANI) supported *p*-toluene sulfonic acid (TsOH) and FeCl₃(PANI-TsOH, PANI-FeCl₃) as excellent reusable solid acid catalysts for the synthesis of 1, 8-dioxo-octahydroxanthene derivatives **4(a-g)** under solvent-free grinding method at mild conditions. Additionally, in the same optimized condition ferric nitrate nonahydrate also acted as (non-reusable) very reactive inexpensive Lewis acid catalyst. The ferric nitrate nonahydrate lost its activity in the form of Clayfen (Clay-supported ferric nitrate) catalyst.

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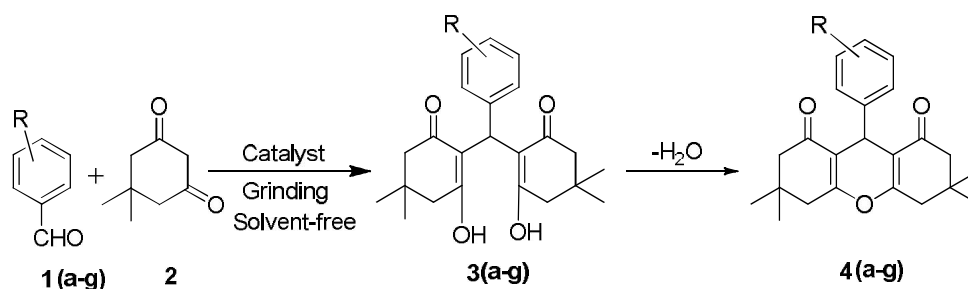
1. Introduction

The combined application of solvent-free mechanochemical process¹ and reusable solid acid catalyst in organic synthesis will reduce pollution and cost, simplify the work-up steps, and eliminate excessive and wasteful heating. The flexibility in choice of all types of reagent pairs at room temperature is an important aspect of mechanochemical processes. The potential use of reusable supported solid acid catalysts^{2,3} in organic synthesis make reaction methods more convenient, economic and environmentally benign, since the product purification is simple due to easy separation of insoluble support from the reaction medium^{4,5}.

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The syntheses of xanthene derivatives are important in medicinal chemistry as antibacterials, antioxidant, antifungal, antiviral and anti-inflammatory agents⁶, photodynamic therapy and antagonists for the paralyzing action of zoxazolamine.⁷ In material science, they are applied as leuco dye⁸ in laser technologies, and as pH sensitive fluorescence materials for visualization of biomolecules.⁹ Some xanthene derivatives are presented in natural products with different biological activities, e.g. strong and selective inhibition of MAO-A, antitumor activity.^{10,11} For 1,8-dioxo-octahydroxanthene derivatives, the inherent reactivity of pyran ring¹² makes them building block of several natural products. In literature, a number of synthetic approaches^{13,14} have been developed for the preparation of 1,8-dioxo-octahydroxanthenes involving acid or base catalyzed condensation of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione (**Scheme 1**) in solvent-free condition, ionic liquid and aqueous medium. Each of these methods have their own merits but also suffers from one or more drawbacks such as longer reaction time, high temperature, tedious work-up processes, low yield and non-recycling of catalysts. Therefore, the synthesis of 1,8-dioxo-octahydroxanthene derivatives require the investigation of novel routes with efficient recyclable catalyst at mild condition, short reaction time and simple work-up procedure for isolation of product.



Scheme 1: Synthesis of xanthenedione derivatives

In this view point, we were interested to study the activities of *p*-toluene sulfonic acid (TsOH), FeCl₃ and ferric nitrate nonahydrate as reusable supported solid acid catalysts (PANI-TsOH, PANI-FeCl₃, Clayfen) for the synthesis of 1,8-dioxo-octahydroxanthene derivatives from aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione (**Scheme 1**) in mild conditions using polyaniline and K-10 Montmorillonite as inert supports.

2. Results and Discussion

In continuation¹⁵⁻¹⁷ of our development of environmentally benign syntheses, we examined the catalytic activity of supported acids (PANI-TsOH, PANI-FeCl₃, Clayfen) and conventional Brønsted or Lewis acid (TsOH, FeCl₃, Fe(NO₃)₃·9H₂O) catalysts in the synthesis of xanthenedione derivatives from aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione in solution under reflux and solvent-free grinding condition at ambient temperature. In this context, to study the activity of various catalysts in solution and solvent-free grinding conditions we selected the reactions of *p*-chlorobenzaldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) which led to xanthenedione derivative **4**. The results are shown in **Table 1**.

Table 1. Optimization of conditions of the reaction of 4-chlorobenzaldehyde and 5,5-dimethyl 1,3-cyclohexanedione in chloroform under reflux and solvent-free grinding.

| Entry | Catalysts | Amount (mmol) | Time (min) | Method ^a | Product yields (%) | | Total conversion (%) |
|-------|--|---------------|------------|---------------------|--------------------|-----------------|----------------------|
| | | | | | Diol 3b | Dione 4b | |
| 1 | TsOH/FeCl ₃ /Fe(NO ₃) ₃ ·9H ₂ O | 0.1 | 3h/3h/30 | A | 20/25/58 | -/-/42 | 20/25/100 |
| 2 | PANI-TsOH/PANI-FeCl ₃ /Clayfen | 0.1 | 45/45/20 | A | 54/60/65 | 46/40/35 | 100/100/100 |
| 3 | TsOH/FeCl ₃ /Fe(NO ₃) ₃ ·9H ₂ O | 0.1 | 55/20/10 | B | 30/28/10 | 70/72/90 | 100/100/100 |
| 4 | PANI-TsOH/PANI-FeCl ₃ /Clayfen | 0.1 | 25/15/60 | B | 15/10/43 | 85/90/57 | 100/100/100 |
| 5 | TsOH/FeCl ₃ /Fe(NO ₃) ₃ ·9H ₂ O | 0.05 | 90/70/15 | B | 10/10/5 | 45/53/70 | 55/63/75 |
| 6 | Fe(NO ₃) ₃ ·9H ₂ O | 0.2 | 10 | B | 8 | 92 | 100 |
| 7 | -- | -- | 40 | B | 90 ¹⁴ | -- | 90 |

^a Method A : Using 3 ml of chloroform under reflux condition ; Method B : Solvent-free grinding method.

We have observed that with all catalysts (**Table 1**, Entries 3-4) the product selectivity for **4b** in solvent-free grinding method increases as compared to reactions (Entries 1, 2) in chloroform. The above reaction was also observed in other polar (ethanol, acetone, THF) and non-polar solvents (dichloromethane, toluene) in presence of 0.1 mmol of catalysts. We observed less reactive or non selective nature of the supported/traditional form of TsOH, FeCl₃ and ferric nitrate nonahydrate in solution. The catalysts TsOH and FeCl₃ transformed into more reactive and selective catalysts on PANI support (**Table 1**, entries 4) under solvent-free medium for the formation of product **4b** as compared to Clayfen(Claysupported ferric nitrate) catalyst. It was observed that ferric nitrate nonahydrate lost its activity and selectivity in the form of Clayfen catalyst. The optimized condition utilized 0.1 mmol of polyaniline supported acids (TsOH, FeCl₃) and Fe(NO₃)₃.9H₂O catalysts in solvent-free grinding method (entries 3-4). We observed incompleteness of the reactions with 0.05 mmol of unsupported TsOH, FeCl₃ and Fe(NO₃)₃.9H₂O catalysts (**Table 1**, Entry 5).

To see the feasibility of the reaction in solvent-free method we had extended the above standard condition with other aromatic aldehydes containing both electron withdrawing and donating groups using supported acid (PANI-TsOH, PANI-FeCl₃) and unsupported acid (TsOH, FeCl₃, Fe(NO₃)₃.9H₂O) catalysts. All these results are summarized in **Table 2**.

Table 2. Substituent effect of aromatic aldehydes for the synthesis of 1,8-dioxo-octahydroxanthene derivatives **4** in solvent-free grinding method.

| Entry | Catalysts ^a | Substrate | Time (min) | Product yields (%) ^b Mp (reported) ^{19,14,18b} | |
|-------|------------------------|---|-------------------|--|---------------------------------|
| | | | | Diol 3(a-g) | Dione 4(a-g) |
| 1 | C/D/E/F/G | C ₆ H ₅ - | 45/25/25/15/10 | 55/20/52/17/15; 195(193-195) | 45/80/48/83/85; 204(205) |
| 2 | C/D/E/F/G/H | 4-ClC ₆ H ₄ | 55/20/20/15/10/60 | 30/15/28/16/10/43;141(140-142) | 70/85/72/84/90/57;231 (228-230) |
| 3 | C/D/E/F/G | 4-NO ₂ C ₆ H ₄ | 40/30/60/30/12 | 47/8/32/13/14; 187 (188-190) | 53/92/68/87/86; 219 (216-218) |
| 4 | C/D/E/F/G | 3-NO ₂ C ₆ H ₄ | 60/25/30/15/10 | 27/12/46/9/11; 196 (198-199) | 73/88/54/91/89; 171 (170-173) |
| 5 | C/D/E/F/G | 4-OHC ₆ H ₄ | 45/60/60/55/60 | 25/12/17/9/18; 191 (190-192) | 75/89/83/91/82; 250 (249-251) |
| 6 | C/D/E/F/G | 4-OMeC ₆ H ₄ | 10/10/15/10/10 | ----- | 94/96/95/97/98; 243 (241-243) |
| 7 | C/D/E/F/G | 2-ClC ₆ H ₄ | 20/15/20/10/15 | 46/16/7/-/-; 203 (203-204) | 54/84/93/97/95;229 (229-230) |

^a Where C/D/E/F/G/H indicate TsOH/PANI-TsOH/FeCl₃/PANI-FeCl₃/Fe(NO₃)₃.9H₂O/Clayfen catalysts.

^b Isolated yields. All products were characterized by ¹HNMR and also their TLC comparison with authentic sample prepared by reported method

The results in **Table 2** indicated that the PANI supported TsOH and FeCl₃ catalysts are superior regarding the time of reaction and product selectivity with all aromatic aldehydes (**Table 2**) as compared to unsupported catalysts. The activity of the PANI supported acid catalyst depends on the strength of non-bonding interaction between the -NH group of support and acid catalyst by the donation of lone pair of electron on the nitrogen atom. The strong interaction of ferric ion with the Montmorillonite clay decreases the reactivity of ferric nitrate nonahydrate in the supported form (Entry 2). The three supported catalysts were found to be inactive with pentanal. Furaldehyde forms polymeric product with these catalysts.

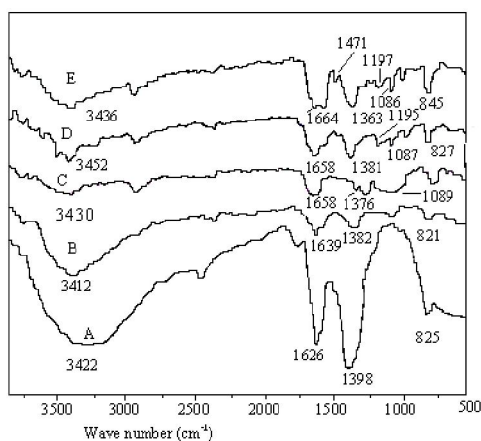


Fig. 1 FT-IR monitoring on the progress of reaction .A: Spectra of Fe(NO₃)₃.9H₂O catalyst; B: Initial reaction mixture without grinding; C: Reaction mixture after 5 min of grinding; D: Reaction mixture after 10 min of grinding; E: Spectra of pure product

The FT-IR studied the progress of reaction between *p*-chlorobenzaldehyde and 5, 5-dimethyl-1, 3-cyclohexanedione (**Fig. 1**) under the optimized condition with ferric nitrate nonahydrate as catalyst at different time intervals from the beginning. The spectra B-D did not show any prominent signal for the catalyst $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ during the course of reaction, which may be due to the lower concentration of catalyst and its interaction with the reaction mixture.

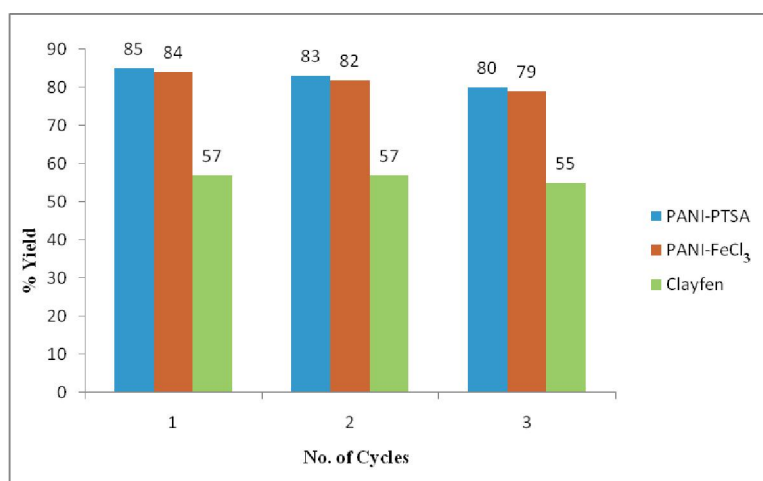


Fig. 2. Histogram of reusability of supported catalysts

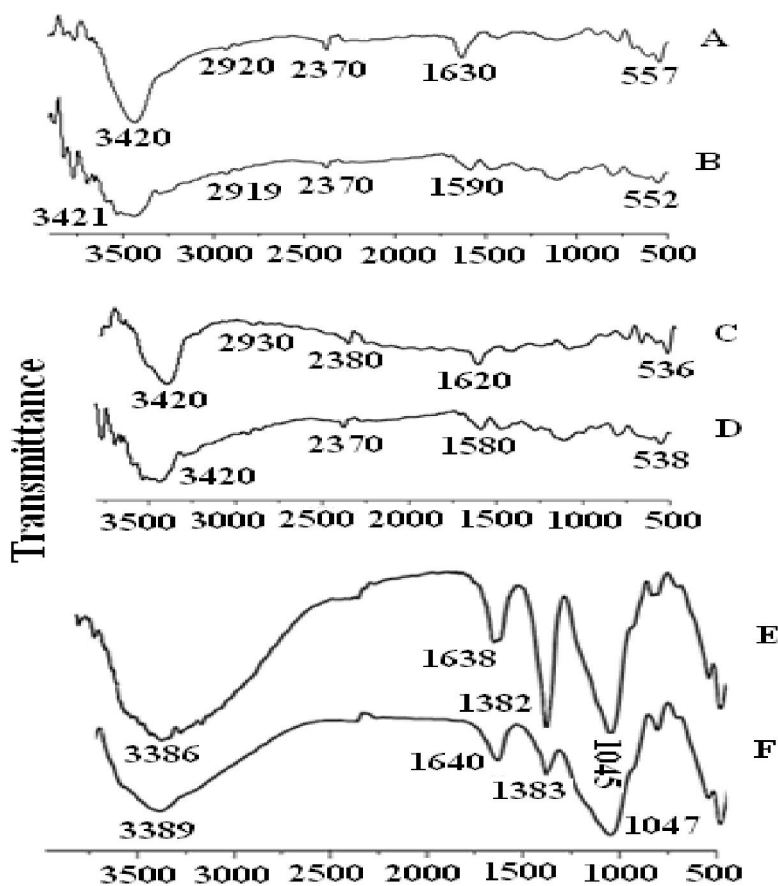


Fig. 3 FT-IR spectra of fresh and 3rd recyclable catalyst. A : PANI-TsOH(fresh); B: PANI-TsOH (3rd); C: PANI- FeCl₃;(fresh); D: PANI-FeCl₃ (3rd); E: Clayfen (fresh); F: Clayfen (3rd)

The reusability of the three supported catalysts (PANI-TsOH, PANI-FeCl₃, Clayfen) were investigated for three times (**Fig. 2**) with the reaction of *p*-chlorobenzaldehyde and dimedone in solvent-free method which were further supported by FT-IR spectra of reused catalyst up to 3rd cycles (**Fig. 3**). The reusability of Fe(NO₃)₃·9H₂O catalyst in organic solvents was studied by dissolving the reaction mixtures in chloroform, dichloromethane, ethanol, ethyl acetate and diethyl ether after completion. The hygroscopic nature of the catalyst changed its state from solid to liquid in these solvents and made it very difficult to filter as solid residue from the solution for recycling.

3. Conclusion

This article investigates the activities of three reusable supported acid catalysts PANI-TsOH, PANI-FeCl₃ and Clayfen for the synthesis of xanthenedione derivatives in mild conditions with different aromatic aldehydes and dimedone under solvent-free grinding method. The ferric nitrate nonahydrate was found as an efficient and selective catalyst for this reaction in absence of support. The advantage of this protocol lies in the avoidance of organic solvent, high yield, energy efficiency, variation of substrates, and use of inexpensive reusable catalyst.

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4. Experimental

4.1. Materials and Methods

All chemicals are commercially available and were used without further purification. The products were identified by comparison of their FT-IR, ¹H NMR and ¹³C NMR spectroscopic data with those of authentic compounds (prepared by known method) and literature reported data.^{13, 14, 18-20} The polyaniline supported and Clayfen catalysts were prepared using already reported method.^{21, 22}

4.2. Methods for the preparation of polyaniline supported acid catalysts:

Three steps were involved for the synthesis of polyaniline supported TsOH and FeCl₃ catalysts.

(i) Preparation of polyaniline salt.

A solution of 15 mL of sulphuric acid in 350 mL of water was prepared in a 500 mL round bottom flask with stirring. To the stirring solution, 5 mL of aniline was added at 5–10 °C and allowed to continue for stirring in presence of 130 mL aqueous solution of sodium persulfate (12 g) for 4 h at the same temperature. The polyaniline powder was precipitated, filtered and washed with 2 L distilled water followed by 200 mL acetone. The polyaniline salt powder was dried at 100 °C till a constant weight (3.5 g).

(ii) Synthesis of polyaniline base.

In this step, 3.5 g of polyaniline salt powder was kept in a 500 mL round bottom flask and stirred in 300 mL aqueous sodium hydroxide solution (1.0 M) for 8 h at ambient temperature. Polyaniline base was precipitated, filtered and washed with water and then with acetone. The base was dried at 100 °C till a constant weight (2.5 g).

(iii) Redoped polyaniline salt.

Firstly, 50 mL of 1.0 M two standard solution of TsOH and FeCl₃ in acetone were prepared separately. To each of the above solutions, 0.5 g of polyaniline base was added and kept under

constant stirring at ambient temperature for 4 h. The supported catalyst was isolated through filtration, washed with acetone and dried at 100°C till a constant weight. Amount of acid group present in the polymeric chain was calculated based on the weight of redoped polyaniline salt obtained and the weight of polyaniline base used. Amount of dopant present in PANI-TsOH and PANI-FeCl₃ were found to be 40.2% and 27.1% respectively.

4.3. General procedure for the Synthesis of 1,8-dioxo-octahydroxanthene Derivatives **4** in Organic Solvent and solvent-free grinding method :

A mixture of 0.5 mmol of 4-chlorobenzaldehyde and 1 mmol of 5, 5-dimethyl-1, 3-cyclohexanedione in organic solvent (3 mL) is taken in a 25 mL round bottom flask containing 0.1 mmol of acid catalyst. For solvent-free method, the above mixture is grinded continuously with the help of mortar and pestle. The progress of the reaction in both conditions is monitored with the help of TLC technique. After completion, the reaction mixture is diluted with ethyl acetate and filtered to get the catalysts as residue. During the work-up step, the filtrate is diluted with aqueous sodium bicarbonate (NaHCO₃) solution and the organic part is extracted with ethyl acetate. The organic extract is dried over anhydrous sodium sulfate. The solvent ethyl acetate is distilled under reduced pressure to get the crude product. Recrystallization of crude product from ethanol yielded the pure product. The used catalyst is dried at 100°C and made ready for reuse.

4.4. Spectral Data of Selected Compounds

4.4.1. 9-Phenyl-3, 3, 6, 6-tetramethyl-1, 8-dioxo-octahydroxanthene **4a** (Table- 2, Entry- 1)²³

¹H NMR (400 MHz, CDCl₃) δ ppm: 0.95 (s, 6H), 1.06 (s, 6H), 2.15-2.26 (m, 4H), 2.43 (s, 4H), 4.71 (s, 1H), 7.06-7.24 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 196.4, 162.1, 144.1, 128.4, 128.07, 126.4, 115.7, 52.9, 50.8, 41.1, 32.2, 31.8, 29.3, 28.0, 27.4; IR (KBr) : 3439, 2954, 1663, 1458, 1362, 1198, 1146, 1004, 697 cm⁻¹.

4.4.2. 9-(4-nitrophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene **4c** (Table-2, Entry-3)²⁴

¹H NMR (CDCl₃, 400 MHz) δ ppm: 1.00(s, 6H), 1.13(s, 6H), 2.16-2.29 (m, 4H), 2.51(s, 4H), 4.84(s, 1H), 7.48 (d, *J*= 8.2 Hz, 2H), 8.10 (d, *J*= 8.7 2H); ¹³C NMR (100 MHz, CDCl₃) δ ppm : 195.8, 169.8, 148.7, 147.9, 145.8, 141.4, 129.4, 127.3, 123.8, 123.7, 110.7, 93.4, 50.6, 41.7, 32.7, 32.5, 29.6, 29.1, 27.8; IR (KBr): 3431, 2956, 1660, 1515, 1355, 1199, 1138, 1005, 869, 828 cm⁻¹.

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