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Propane-1,2,3-triyl tris(hydrogen sulfate): An alternative, eco-friendly catalyst for synthesis of substituted pyrimidinones

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ABSTRACT

Propane-1,2,3-triyl tris(hydrogen sulfate) catalyzed simple, one pot, solvent-free and environmentally benign process for synthesis of substituted pyrimidinones via Biginelli reaction is described. It was found that the catalyst is reusable and exhibited remarkable activity.

KEYWORDS

Propane-1,2,3-triyl tris (hydrogen sulfate); Solvent-free conditions; Substituted pyrimidinone derivatives.

INTRODUCTION

Glycerol is usually produced as a byproduct of the transesterification of a triglyceride in the production of natural fatty acid derivatives. These derivatives are utilized in many areas from pharmaceuticals and food industry to alternative fuels, e.g., biodiesel, and thus as the production of glycerol raises its price decreases. In addition, glycerol has also promising physical and chemical properties. It has a very high boiling point and negligible vapor pressure; it is compatible with most organic and inorganic compounds, and does not require special handling or storage. Glycerol, as other polar organic solvents such as DMSO and DMF, allows the dissolution of inorganic salts, acids, and bases, as well as enzymes and transition metal complexes (TMCs), but it also dissolves organic compounds that are poorly miscible in water and is non-hazardous. Different hydrophobic solvents such as ethers and hydrocarbons which are immiscible in glycerol allow removing the products by simple extraction. Distillation of products is also feasible due to the high boiling point of glycerol[1]. Chemically modified glycerols are generally made by treating glycerol with agents that can react with hydroxyl groups. Such glycerols have physicochemical properties that differ significantly from the parent glycerol, thus widening their usefulness in many applications such as in biodiesel industriesand other industrial processes, so some reviews have appeared recently dealing with the use ofglycerol as a source of commodity chemicals[2].

Biginelli reaction, a more than a century old reaction came into prominence after the discovery and development of dihydropyridinesbased calcium channel modulator drugs such as nifedipine used in cardiovascular diseases[3].The pyrimidinone skeleton is an integral part of many natural or synthetic bioactive materials[4]. Pyrimidinones containing specific functional groups exhibitspecific biological properties. Fused pyrimidinones containing an arylidene skeleton behave as potential antitumor agents. A new series of 3,5-bis(arylidene)-4-piperidones, as chalcone analogs carrying a variety of aryl and heteroaryl groups, pyrazolo[4,3-c]pyridines, pyrido[4,3-d]pyrimidines and pyrido[3,2-c]pyridines, carrying an arylidene moiety, and a series of pyrano[3,2-c]pyridines, as flavone and

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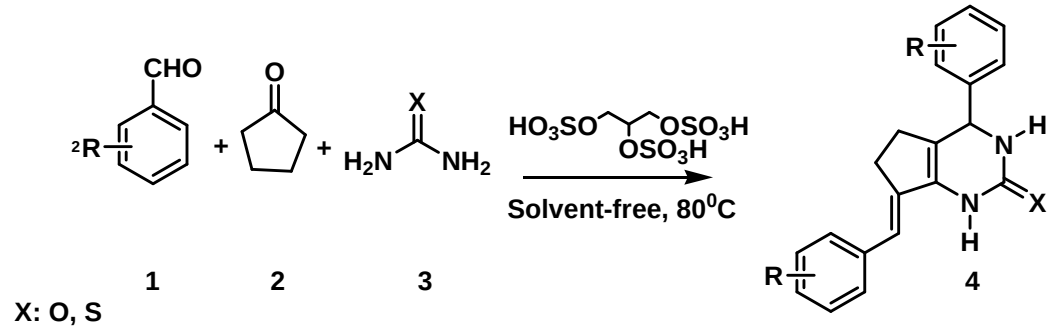
coumarinisosteres, were synthesized and screened for their in vitro antiviral and antitumor activities at the National Cancer Institute (NCI)[5].

Very few cases of earlier instances for the synthesis of pyrimidinone derivatives exist where Biginelli-type condensation was done by the reaction of α,α'-bis(arylidene)cycloalkanones with urea or thiourea. In majority of the cases, either a strong Brønsted acid such as HCl[6] or strong Brønsted base such as KOH or sodium alkoxide[7] has been used for the reaction. Recently, the some methodologies have been developed using stoichiometric amount of TMSCl in dimethylformamide (DMF)/MeCN as solvent[8,9], yterbium chloride as catalyst[10], and boric acid and glycerol in aqueous medium[11]. Even then, some drawbacks exist in these systems such as use of strong acids, which leads to cleavage of sensitive functional groups, toxicsolvents, and moisture-sensitive reagents. As a result, the search for a new catalyst for this Biginelli-type reaction is still actively pursued. Therefore, we report here an efficient, mild, highly convenient, and smooth procedure for the synthesis of substituted pyrimidinone derivatives by three-component coupling of aromatic aldehydes, cyclopentanone, and urea or thiourea using propane-1,2,3-triyl tris(hydrogen sulfate) (PTTH) under solvent-free conditions.(Scheme 1).



Scheme 1 : Synthesis of dihydropyrimidinone derivatives with propane-1,2,3-triyl tris(hydrogen sulfate) under solvent-free conditions

EXPERIMENTAL

General

All chemicals and analytical grade solvents were purchased from Merck or Fluka chemical company. Melting points of all products were determined in open glass capillaries on Mettler 9100 melting point apparatus. Infrared (IR) spectra were recorded using a 4300 Shimadzu FT-IR spectrometer. ^{1}HNMR spectra were recorded on a Bruker 400MHz spectrometer. All products were characterized by comparison of their melting points IR and ^{1}HNMR spectra with those of authentic samples.

Preparation of propane-1,2,3-triyl tris(hydrogen sulfate)

A 250 ml suction flask charged with glycerol (8.30 g, 90.22 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution *i.e.* water. Chlorosulfonic acid (~20.0 ml, ~300 mmol) was added in small portions over a period of 30 min at 0 °C. HCl gas evolved from the reaction vessel immediately (Scheme 2). After completion of the addition of chlorosulfonic acid, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. Then, the mixture was concentrated under vacuum, and washed with ether (10 ml) three times and dried under vacuum. PTTH (26.40) was obtained as yellow oil, which was stored in a capped bottle. IR: 3374, 2944, 1657, 1510, 1110, 1043 cm^{-1}. According to the results, the efficiency of the coupling of glycerol was estimated to ~88% via spectrophotometric analysis. Also, according to the Boehm back-titration analysis, the percentage of three sulfur atom presented in the Propane-1,2,3-triyl tris(hydrogen sulfate), as the proposed catalyst synthesized according to the recommended procedure was estimated to quantity of 87.67%.

General procedure for the synthesis of pyrimidinone derivatives

To a stirred slurry of aromatic aldehyde (2 mmol),

cyclopentanone (1 mmol), and urea (thiourea) (1 mmol) was added PTTH (0.1 g, 0.03 mol %) and heated at 80 °C.Progress of the reaction was monitored by TLC for the specified time period (TABLE 2).After completion of the reaction, the reaction mixture was cooledto room temperatureand diluted with water (5 mL).Then the crude product (solid) was washed with 5 mL water for removal of additional PTTHthat might be adhering to the product. The crude product was then directly recrystallized from EtOH.

Compound 4a

M.p. 232–234 °C. IR (KBr) 3420, 3215, 1900, 1708, 1565, 1480, 1071, 820 cm^{-1};^{1}H NMR: δ= 8.75 (s, 1 H), 7.30–7.15 (m, 9 H), 6.65 (s, 1 H), 5.17 (s, 1 H), 2.85–2.70 (m, 2 H), 2.50 (m, 1 H), 2.12–1.97 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 303.

Compound 4b

M.p. 254–256 °C.IR (KBr): 2943, 1677, 1496, 1215, 1040 cm^{-1}; ^{1}H NMR: δ= 8.75 (s, 1 H), 7.33–7.10 (m, 4 H), 7.01–7.85 (m, 5 H), 6.70 (s, 1 H), 5.49 (s, 1 H), 3.79(s, 3 H), 3.75 (s, 3 H), 2.77–2.66 (m, 2 H), 2.35–2.30 (m, 1 H), 1.99–1.90 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$363.

Compound 4c

M.p. 240–242 °C.IR (KBr) 3419, 3318, 1676, 1599, 1506, 1460, 850 cm^{-1}; ^{1}H NMR: δ= 8.75 (s, 1 H), 7.26–7.14 (m, 9 H), 6.58 (s, 1 H), 5.10 (s, 1 H), 2.80–2.71 (m, 2 H), 2.39–2.30 (m, 1 H), 2.25 (s, 6 H), 2.00–1.96 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$331.

Compound 4d

M.p.250–252 °C. IR (KBr) 3400, 3210, 1890, 1715, 1550, 1485, 1060, 835 cm^{-1};^{1}H NMR: δ= 8.85 (s, 1 H), 7.45–7.25 (m, 9 H), 6.62 (s, 1 H), 5.16 (s, 1 H), 2.85–2.70 (m, 2 H), 2.45–2.36 (m, 1 H), 2.05–1.96 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 371.

Compound 4e

M.p.220–222°C. IR (KBr) 3418, 3320, 2235, 1675, 1605, 1520, 1455, 850 cm^{-1}; ^{1}H NMR: δ= 8.90 (s, 1 H), 7.90–7.45 (m, 9 H), 6.75 (s, 1 H), 5.35 (s, 1 H), 2.85–2.70 (m, 2 H), 2.48–2.40 (m, 1 H), 2.05–1.95 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 352.

Compound 4f

M.p. 230–232 °C. IR (KBr) 3390, 3215, 1875, 1720, 1550, 1485, 1356, 1085, 855 cm^{-1}, ^{1}H NMR: δ= 8.85 (s, 1 H), 8.27–8.02 (m, 4 H), 7.88–7.45 (m, 5 H), 6.81 (s, 1 H), 5.50 (s, 1 H), 2.97–2.80 (m, 2 H), 2.53–2.45 (m, 1 H), 2.10–2.03 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 393.

Compound 4g

M.p. 218–220 °C.IR (KBr) 3395, 1688, 1560, 1506, 1460, 852 cm^{-1},^{1}H NMR: δ= 10.30 (s, 1 H), 9.18 (s, 1 H), 8.29–8.27 (d, J= 8.7 Hz, 2 H), 8.19–8.17 (d, J= 8.8 Hz,2 H), 7.54 (m, 4 H), 7.09 (s, 1 H), 2.93–2.86 (m, 2 H), 2.52–2.49 (m, 1 H), 2.13–2.08 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 409.

Compound 4h

M.p. 294–296 °C. IR (KBr) 3380, 1670, 1545, 1525, 1475, 850 cm^{-1},^{1}H NMR: δ= 9.34 (s, 1 H), 8.63 (s, 1 H), 8.60 (s, 1 H), 8.51 (s, 1 H), 7.49–7.30 (m, 8 H), 5.39 (d, J= 3.6 Hz, 1 H), 4.08 (d, J= 11.3 Hz, 1 H), 2.71–2.67 (m, 2 H), 1.56–1.52 (m, 1 H), 1.41–1.36 (m, 1 H), 1.15–1.09 (m, 1 H), 1.09–1.02 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 463.

Compound 4i

M.p. 208–210 °C. IR (KBr) 3375, 1685, 1555, 1515, 1465, 1365, 845 cm^{-1},^{1}H NMR: δ= 8.85 (s, 1 H), 7.39–7.32 (m, 4 H), 7.20–7.14 (m, 5 H), 6.68 (s, 1 H), 5.22 (s, 1 H), 2.88–2.70 (m, 2 H), 2.44–2.37 (m, 1 H), 2.12–1.95 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 339.

Compound 4j

M.p. 280–283 °C. IR (KBr) 3380, 1675, 1550, 1510, 1460, 1370, 830 cm^{-1},^{1}H NMR: δ= 10.5 (s, 1 H), 8.85 (s, 1 H), 7.65–7.15 (m, 9 H), 6.98 (s, 1 H), 5.45 (s, 1 H), 2.85–2.64 (m, 2 H), 2.49–2.40 (m, 1 H), 2.10 (m, 1 H) ppm. MS (ESI) $[M+ H]^+$ 431.

RESULTS AND DISCUSSION

PTTH was readily prepared by addition of chlorosulfonic acid to glycerol while keeping the temperature at 0 °C. The reaction is easy and clean, and needs no special work-up procedure because HCl gas is evolved from the reaction vessel immediately. This liquid catalyst is safe and easy to handle (Scheme 2).

To evaluate the feasibility of PTTH forBiginelli-type condensation reaction a model reaction (Scheme 1) with

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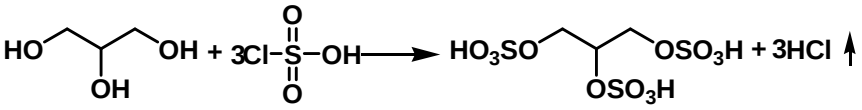


Scheme 2 : Synthesis of propane-1,2,3-triyl tris(hydrogen sulfate)

TABLE 1 : Biginelli-type reaction of benzaldehyde (2.0 mmol), cyclopentanone (1.0 mmol), urea (1.0 mmol), over PTTH under different conditions

Entry	Solvent	T (°C)	Catalyst (g)	Time (min)	Yield (%)
1	Solvent-free	80	-	180	30
2	Solvent-free	80	0.05	15	50
3	Solvent-free	80	0.1	15	90
4	Solvent-free	50	0.1	120	60
5	Solvent-free	25	0.1	120	35
6	Acetonitrile	Reflux	0.1	360	55
7	THF	Reflux	0.1	360	40
8	Ethanol	Reflux	0.1	360	75
9	Water	Reflux	0.1	360	70

a building block ratio of 2:1:1 of benzaldehyde,cyclopentanone, and urea respectively to give(E)-7-benzylidene-4-phenyl-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4a), was conducted under different conditions.

When attempts were made to carry out the model reaction in absence of catalyst, we found that only 30% yield of the product was obtained even after heating at 80 °C for 3 h with recovery of starting material (entry 1, TABLE 1).

The yield of pyrimidinone derivative increased with increasing the amounts of the catalyst from 0.05 to 0.1 g. Higheramounts of the catalyst did not improved the yield(entry 2- 3, TABLE 1).Also, the yield increased from 35% to 90% by increasing the temperature from 25 °C to 80 °C(entry 3- 5, TABLE 1).The reaction was also examined in solvents such as acetonitrile, THF, ethanol, and water(entry 6- 9, TABLE 1). In the presence of solvents reaction was sluggish.All further studies were carried out under solvent-free conditions with 0.1 g catalyst at 80 °C.

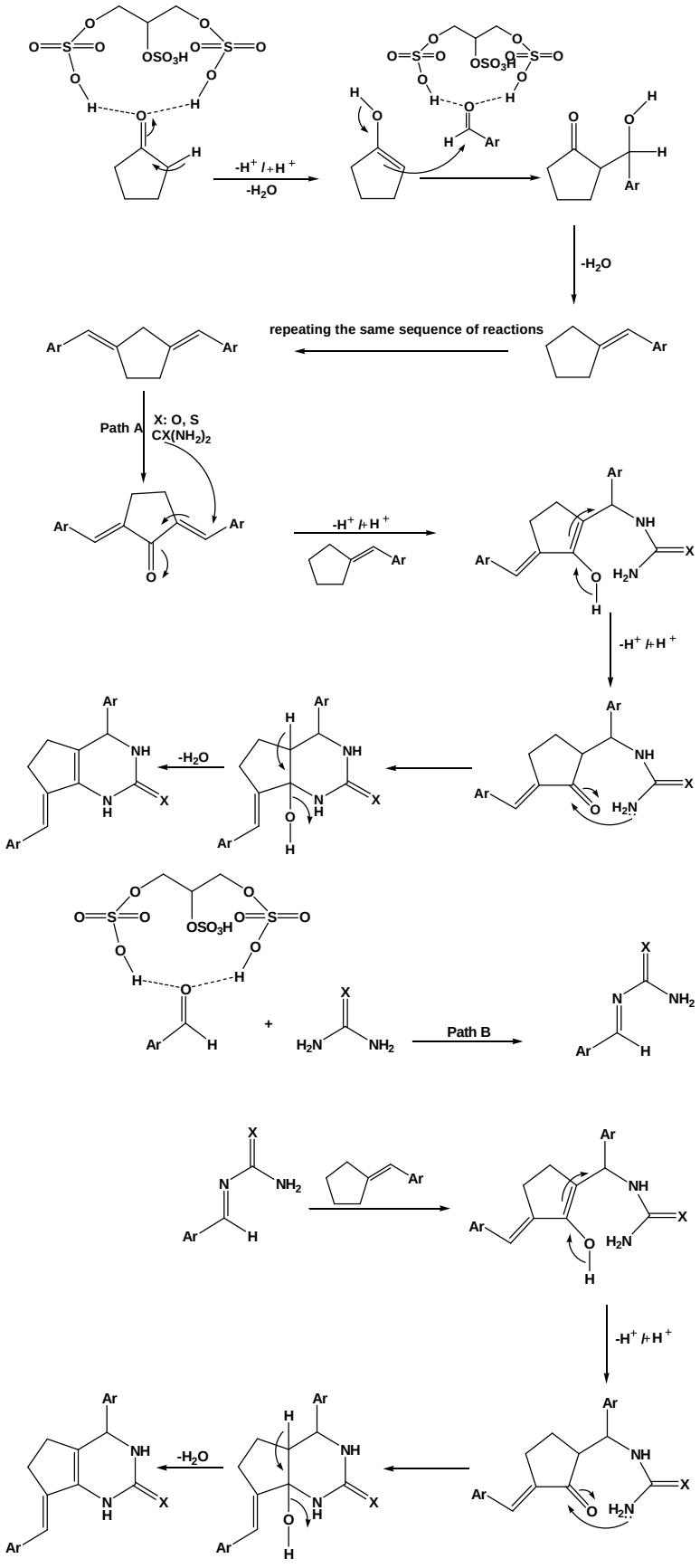
Scope and generality of this protocol were demonstrated by subjecting a broad range of building block combinations such as aromatic aldehydes carrying both electron-donating or electron-withdrawing substituent, and urea/thiourea. All the building block combination reacted very well, giving moderate-to-excellent yields of the desired products under optimized reaction conditions.

The structural variations in the aldehydes had no significant effect on the yield and with aldehydes bearing sensitive functional groups like OCH_3, Cl and NO_2 the reaction proceeded smoothly to afford the corresponding products in excellent yields (entries 2, 4, 6, 8, and 9, TABLE 2). The reaction proceeded comparatively faster with aldehyde conatining p-methoxy group and required only 10 min to give correspondingsubstituted pyrimidinones in excellent yields (entry 2, TABLE 2).Thiourea has been also used with success to provide the corresponding products in low yields(entries 7-10, TABLE 2).

TABLE 2 : Solvent-free Biginelli reactions over PTTH

Entry	Substrate		Product	Yield (%)	Time (min)	References
	R	X				
1	H	O	4a	90	15	9
2	4-OMe	O	4b	95	10	9
3	4-Me	O	4c	92	15	9
4	4-Cl	O	4d	90	20	9
5	4-CN	O	4e	85	20	11
6	3-NO_2	O	4f	83	20	9
7	H	S	4g	85	20	9
8	2-Cl	S	4h	80	20	9
9	4-NO_2	S	4i	75	30	9
10	2-F	S	4j	85	30	9

There are two possible mechanisms for this reaction, path A and path B (Scheme 3). In path A, initially a crossed aldol condensation takes place between cyclopentanone and aldehyde, followed by Michael addition of urea, to ultimately form pyrimidinone derivatives. In path B, the aryl aldehydes react with urea or thiourea to form the aryl-imine intermediates, which then react with arylidene cyclopentanone to give the final product.The highly solving action of PTTH on the reactants makes them readily available to interact, and the carbonyl carbon of the aldehyde will be activated because of the intermolecular hydrogen bonding with the hydroxyl groups of PTTH. In addition, the formed intermediates could be stabilized by several types of



Scheme 3 : Plausible mechanism for catalytic effect of PTTH in Biginelli-type reaction

complexations and hydrogen bonding with the hydroxyl groups of PTTH (Scheme 3).

TABLE 3 : Reusability study

Run no	Yield(%)
Fresh	90
First recycle	89
Second recycle	86
Third recycle	83
Fourth recycle	80

In order to recover the catalyst totally,after washing of the reaction mixture with water, the separated aqueous layercontaining the catalyst was washed with diethyl ether (3×5 ml) and concentrated under vacuum conditions.For reusability experiments recovered catalyst was used and results are given in Table 4. The results indicate that the catalyst was reusable four times without any significant loss of activity.

CONCLUSION

We have developed an efficient and environmentally benign strategy for the synthesis of substituted pyrimidinones using PTTH as a catalyst. This method offers several advantages including high yield of products, short reaction time, low cost, cleaner reaction profile and ease of preparation of catalyst and ease of product isolation. Also the catalyst was successfully recovered and recycled at least for three runs without significant loss in activity.

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