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Supported Heterogeneous Silica Sulphuric Acid: Reusable Catalysts for Synthesis of Barbituric Acid Based Knoevenagel Adducts

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Abstract: The Knovenagel Condensation of various aromatic aldehydes with active methylene compounds such as barbiturates can be achieved in good yields and selectivities by using silica supported silica sulphuric acid (SSA) in the solid-state by grinding under solvent-free condition has been developed. This method provides several advantages including economical, environmental friendliness, short reaction times, high yield adduct and a simple work-up procedure. Moreover, the SSA was successfully reused for four cycles without significant loss of activity. All synthesized compounds were characterized by physical, Spectroscopic and elemental analysis.

Graphical Abstract:

Keywords: Knoevenagel Condensation reaction, Silica sulphuric acid, Grinding, Aldehydes, Barbiturates.

1. Introduction

Organic synthesis takes advantage of the high reactivity of some functional groups that allows the starting reagents to be transformed into the targeted compounds. In fact, the general strategy for forming a new bond requires the presence of a heteroatom or an unsaturation in the carbon backbone of an organic molecule, as clearly stated by Corey and Cheng[1]. In recent years there has been increased interest in the catalysis using solid materials for fine chemicals preparation, since this approach frequently resulted in a less expensive and ecological productive process[2-5]. The grinding method has gained increasing use in organic synthesis. Compared with traditional methods, many organic reactions occur more efficiently in the solid-state than in solution and in many cases even more selectively, because molecules in the crystals are arranged tightly and regularly[6]. Furthermore, solid state reactions have many advantages: little pollution, low cost, and simplicity in progress and handling. A large number of organic reactions can be carried out simply and in high yield under mild conditions by this method. Therefore, we focus on developing a novel procedure involving a solid-state reaction performed by grinding. Knoevenagel condensations are useful and widely employed reactions for carbon-carbon bond formation in organic synthesis. The Knoevenagel condensation reactions are classically catalyzed by base in liquid phase systems; various catalysts are known to effect the reaction with different aldehydes and active methylene groups[7-11]. Barbituric acid of the α-carbon has a reactive hydrogen atom and is quite acidic (pKa = 4.01) even for a diketone species (i.e. dimedone with pKa 5.23 and acetylacetone with pKa 8.95) because of the additional aromatic stabilisation of the carbanion. Using the Knoevenagel condensation reaction, barbituric acid can form a large variety of barbiturate drugs that behave as central nervous system depressants, Barbituric acid is used in synthesis of riboflavin[12]. The medicinal importance of pyrimidine derivatives such as barbituric acid and thiobarbituric acid play vital role among various heterocyclic compounds due to their anti-neoplastic[13-14], antiviral[15], antibiotic[16], and anti-inflammatory[13] activity. The pyrimidine ring system is present in various natural compounds such as nucleic acids, vitamins, coenzymes, uric acid, purines, and some marine microorganisms. (e.g., sponge). Many synthetic d rugs (e.g., barbituric and thiobarbituric acid) derivatives and chemotherapeutic agents (e.g., sulfadiazine)[17]. The diverse biologic activity and

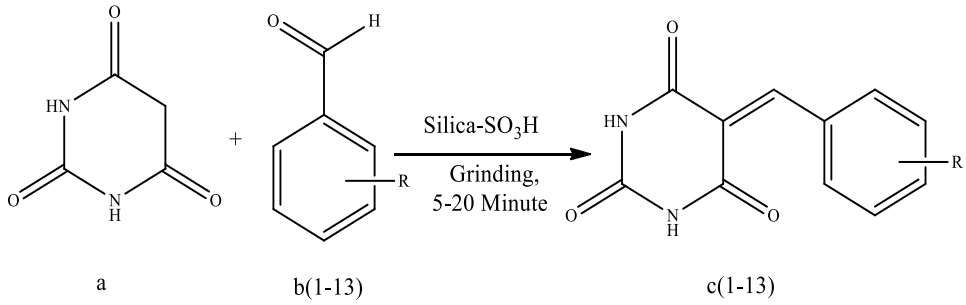
coverage of a broad chemical space make barbituric and thiobarbituric acid derivatives excellent target compounds for organic and medicinal chemists. Owing to their ready availability and various functionalization possibilities, the parent barbituric and thiobarbituric acid are convenient starting materials for the preparation of different fused heterocycles and literature survey also ascribes that 5-substituted derivatives are pharmacologically active compounds[18].

2. Experimental Procedure

Chemicals and solvents were obtained from commercial sources and used as received throughout the investigation. The barbituric acid was synthesized by using diethyl malonate and urea using standard procedure[18] . Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (4000-400 cm^{-1}) of synthesized compounds were recorded on a Perkin Elmer-Spectrum RX-IFTIR spectrophotometer using KBr pellets. Thin layer chromatography was performed on object glass slides (2 x 7.5 cm) coated with silica gel-G and spots were visualized under UV irradiation. ^{1}H NMR, ^{13}C NMR and HMBC spectra were recorded on an Avance-II (Bruker) model using $CDCl_3$ as a solvent and TMS as internal standard with ^{1}H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^{1}H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si). The splitting patterns are designated as follows; s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The preparation of Silica sulphuric acid (SSA) by the dropwise addition of chlorosulfonic acid to Silica-Gel (Merck) suspended in hexane has been carried out as previously described[19].

2.1. General procedure for Knoevenagel condensations: The target compounds were prepared as shown in Scheme 1. An equimolar mixture of active methylene group containing compound i.e. barbituric acid (1 mmol), aromatic aldehydes (1 mmol), and SSA (0.05 g) were ground at room temperature. Silica-sulfuric acid prepared by reported method (Scheme 1).The reactions progresses were monitored by thin layer chromatography (TLC). After completion of reaction, the product was extracted with absolute alcohol (2×20 mL) and the insoluble SSA directly recycled in subsequent runs. The organic layer was washed by brine (2×10 mL), dried over Na_2SO_4 and the solvent removed by rotary evaporation under reduced pressure. The crude product was recrystallized from ethanol to afford pure

corresponding compounds in high yield. The catalyst was recycle by washing the solid reagent remained on the filter by absolute alcohol (20 ml) followed by followed by drying in an oven at 50°C for 2 hrs and can be reusable for another reaction run. Spectral and microanalysis data of selective compounds are summarized below. New compounds were completely characterized based on their spectroscopy data. Derivatives are shown in Table.1.



Reaction Condition: Barbituric acid (1 mol), Aromatic aldehydes (1mol), Silica-H_2SO_4 (0.05g)

Scheme 1

2.2. Spectral Characterization data of synthesized compounds:

2.2.1. 5-(4-hydroxy-3-methoxybenzylidene)pyrimidine 2, 4, 6 (1H, 3H, 5H)-trione (C-1): Yellow Powder, Yield: 91.45 %, M.P. >250 (Decompose)˚C; FT-IR (KBr, cm^{-1}): 1265 (C-O-CH_3), 1665 (C=C, of Aromatic), 1763 (C=O), 2845 (C=CH-Ar, exocyclic), 3440 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 3.87 (3H, s, OCH_3), 5.39 (1H, s, Ar-OH), 6.89-7.75 (3H, m, -CH of Aromatic ring), 8.25 (1H, dd, exocyclic CH) 9.76 (1H, s, barbituric acid NH), 10.15 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 56.1 (C-14), 78.72 (C-5), 110.24 (C-9), 115.18 (C-12), 126.05 (C-13), 128.57 (C-8), 148.02 (C-11) 150.11 (C-10), 152.95 (C-7), 164.91. (C-2), 190.41 (C-4, C-6); M.W=262.22; Anal. Calcd. For $C_{13}H_{12}N_2O_4$: C 60.00, H 4.65, N 10.76 (%). Found: C 60.08, H 4.62, N 10.74 (%).

2.2.2. 5-benzylidenepyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-2): Yellow powder, Yield: 82.32 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1662 (C=C, of Aromatic), 1769 (C=O), 2840 (C=CH-Ar, exocyclic), 3442 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.85-7.60 (5H, m, -CH of Aromatic ring), 8.19 (1H, dd, exocyclic CH) 10.06 (1H, s, barbituric acid NH), 10.68 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 78.39 (C-5), 119.24 (C-7), 127.91 (C-11), 128.50 (C-9, C-13), 128.67 (C-10, C-12),

132.9 (C-8), 150.41. (C-2), 162.31 (C-4, C-6); M.W=216.19; Anal. Calcd. For $C_{11}H_8N_2O_3$: C 61.11, H 3.73, N 12.96 (%). Found: C 61.14, H 3.71, N 12.94 (%).

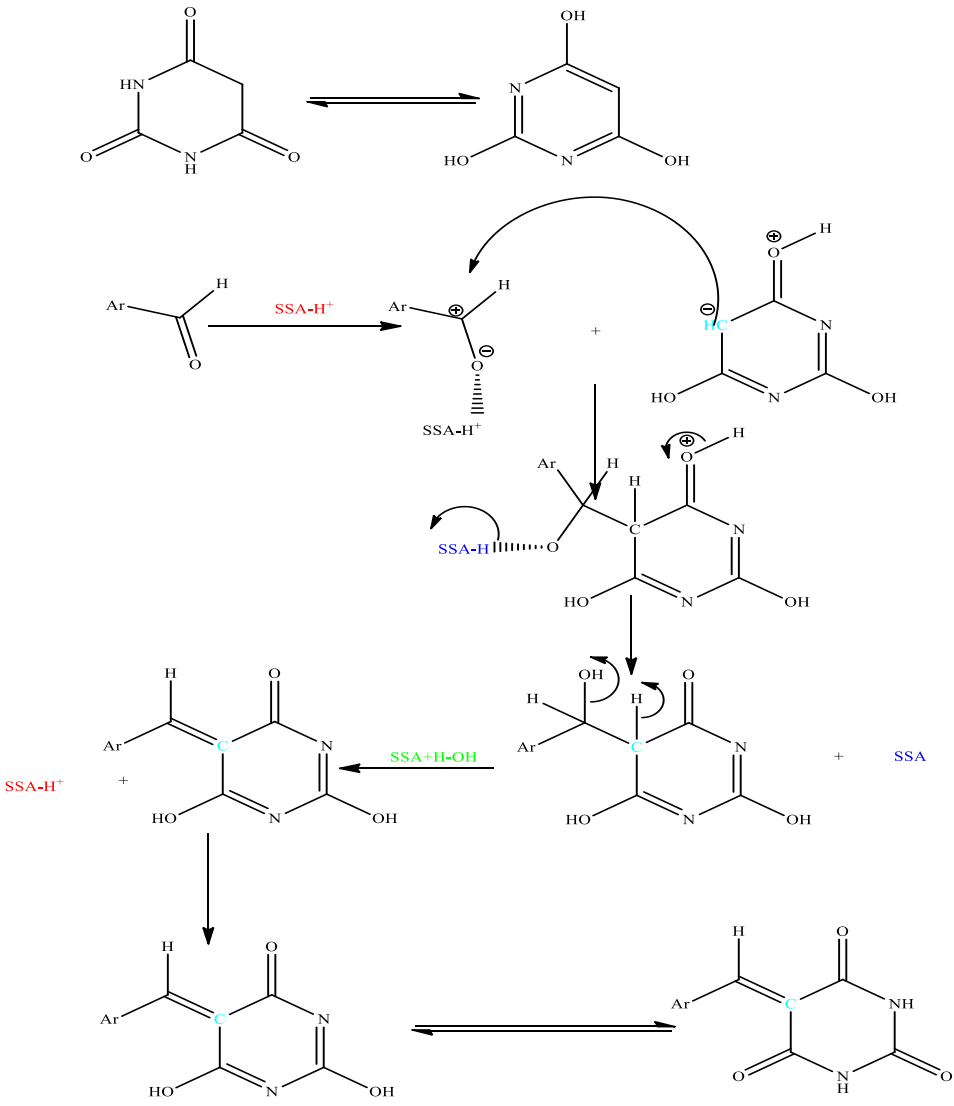


Figure 1. Proposed reaction mechanism (Scheme 2)

2.2.3. 5-(4-methoxybenzylidene)pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-3): Yellow Powder, Yield: 86.53 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1262 (C=O-CH_3), 1658 (C=C, of Aromatic), 1763 (C=O), 2843 (C=C<u>H</u>-Ar, exocyclic), 3439 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 3.83 (3H, s, OC<u>H</u>$_3$), 6.94-7.98 (4H, dd, -C<u>H</u> of Aromatic ring), 8.22 (1H, dd, exocyclic C<u>H</u>) 9.96 (1H, s,

barbituric acid NH), 10.69 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 55.37 (C-14), 79.05 (C-5), 112.24 (C-7), 115.18 (C-10, C-12), 130.05 (C-9, C-13), 128.57 (C-8), 150.41. (C-2), 159.83 (C-11), (C- 162.41 (C-4, C-6); M.W=246.22; Anal. Calcd. For $C_{12}H_{10}N_2O_4$: C 58.54, H 4.09, N 11.38 (%). Found: C 58.51, H 4.13, N 11.41 (%).

2.2.4. 5-(2-hydroxybenzylidene)pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-4): Light Green Powder, Yield: 83.64 %, M.P. 248-250 ˚C; FT-IR (KBr, cm^{-1}): 1660 (C=C, of Aromatic), 1761 (C=O), 2847 (C=CH-Ar, exocyclic), 3446 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm, 5.36 (1H, s, Ar-OH), 6.72-7.70 (4H, m, -CH of Aromatic ring), 8.53 (1H, dd, exocyclic CH) 10.06 (1H, s, barbituric acid NH), 10.72 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 78.50 (C-5), 117.64 (C-10), 120.91 (C-8), 121.2 (C-12), 129.37 (C-11), 132.92 (C-13) 148.56 (C-7), 150.41 (C-2), 152.95 (C-7), 157.12(C-9), 164.91 190.41 (C-4, C-6); M.W=232.19; Anal. Calcd. For $C_{11}H_8N_2O_4$: C 56.90, H 3.47, N 12.06 (%). Found: C 56.92, H 3.51, N 12.09 (%).

2.2.5. 5-(4-hydroxybenzylidene)pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-5): Yellow Powder, Yield: 86.23 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1656 (C=C, of Aromatic), 1771 (C=O), 2843 (C=CH-Ar, exocyclic), 3432 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 5.38 (1H, s, Ar-OH), 6.65-7.56 (4H, m, -CH of Aromatic ring), 8.26 (1H, dd, exocyclic CH) 9.86 (1H, s, barbituric acid NH), 10.57 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 78.95 (C-5), 155.63 (C-10, C-12), 120.36 (C-7), 125.52 (C-8), 130.68 (C-9, C-13), 150.42 (C-2), 157.78 (C-11), 164.91 (C-4, C-6); M.W=232.19; Anal. Calcd. For $C_{11}H_8N_2O_4$: C 56.90, H 3.47, N 12.06 (%). Found: C 56.94, H 3.49, N 12.87 (%).

2.2.6. 5-(furan-2-ylmethylene)pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-6): Brown powder, Yield: 80.12 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1657 (C=C, of Aromatic), 1774 (C=O), 2851 (C=CH-Ar, exocyclic), 3436 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.89-7.42 (3H, m, -CH of Furan ring), 8.11 (1H, dd, exocyclic CH) 10.06 (1H, s, barbituric acid NH), 10.67 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 77.92 (C-5), 109.54 (C-9), 112.78 (C-10), 143.75 (C-11), 147.57 (C-7), 149.42 (C-8) 150.48 (C-2), 166.03 (C-4, C-6); M.W=206.15; Anal. Calcd. For $C_9H_6N_3O_5$: C 52.43, H 2.93, N 13.59 (%). Found: C 52.46, H 2.91, N 13.57 (%).

2.2.7. 5-(2-nitrobenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-7): Yellow Powder, Yield: 89.45 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1345 (C-NO_2), 1657 (C=C, of Aromatic), 1762 (C=O), 2849 (C=CH-Ar, exocyclic), 3438 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm (7.79-8.21) (4H, m, -CH of Aromatic ring), 8.52 (1H, dd, exocyclic CH) 10.16 (1H, s, barbituric acid NH), 10.82 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 79.33 (C-5), 123.82 (C-2), 128.85 (C-11), 130.05 (C-8), 130.46 (C-13), 134.76 (C-12) 147.71 (C-9), 148.45 (C-7), 150.91. (C-2), 163.47 (C-4, C-6); M.W=261.19; Anal. Calcd. For $C_{11}H_7N_3O_5$: C 50.58, H 2.70, N 16.09 (%). Found: C 50.55, H 2.68, N 16.12 (%).

2.2.8. 5-(3-nitrobenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-8): Yellow Powder, Yield: 88.77 %, M.P. 230-234 ˚C; FT-IR (KBr, cm^{-1}): 1347 (C-NO_2), 1652 (C=C, of Aromatic), 1768 (C=O), 2842 (C=CH-Ar, exocyclic), 3441 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 7.66-8.11 (4H, m, -CH of Aromatic ring), 8.37 (1H, dd, exocyclic CH) 9.76 (1H, s, barbituric acid NH), 10.15 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 79.06 (C-5), 123.14 (C-11), 123.68 (C-13), 125.35 (C-9), 129.57 (C-12), 134.32 (C-8) 147.81 (C-10), 150.95 (C-2), 157.61. (C-7), 162.39 (C-4, C-6); M.W=261.19; Anal. Calcd. For $C_{11}H_7N_3O_5$: C 50.58, H 2.70, N 16.09 (%). Found: C 50.59, H 2.73, N 16.11 (%).

2.2.9. 5-(4-nitrobenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-9): Yellow Powder, Yield: 91.12 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1351 (C-NO_2), 1653 (C=C, of Aromatic), 1771 (C=O), 2840 (C=CH-Ar, exocyclic), 3193 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.89-7.66 (4H, dd, -CH of Aromatic ring), 8.21 (1H, dd, exocyclic CH) 9.76 (1H, s, barbituric acid NH), 10.15 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 56.1 (C-14), 78.72 (C-5), 110.24 (C-9), 115.18 (C-12), 126.05 (C-13), 139.00 (C-8), 147.12 (C-11) 150.41 (C-2), 163.65 (C-4, C-6); ^{13}C NMR (DMSO-d_6): δ 78.29 (C-5), 119.04 (C-7), 123.81 (C-10, C-12), 132.25 (C-9, C-13), 128.57 (C-8), 148.02 (C-11) 150.11 (C-10), 152.95 (C-7), 164.91. (C-2), 190.41 (C-4, C-6); M.W=261.19; Anal. Calcd. For $C_{11}H_7N_3O_5$: C 50.58, H 2.70, N 16.09 (%). Found: C 50.53, H 2.69, N 16.12 (%).

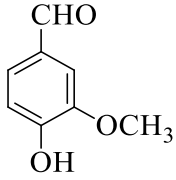
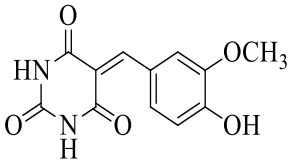
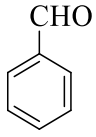
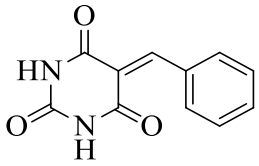
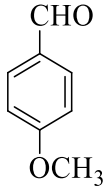
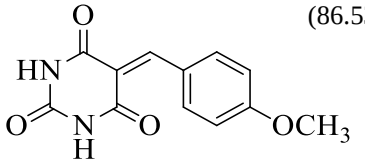
2.2.10. 5-(2, 4-dinitrobenzylidene) pyrimidine-2,4,6(1H,3H, 5H)-trione (C-10): Dark Yellow Powder, Yield: 92.33 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1355 (C-NO_2), 1657 (C=C, of Aromatic), 1761 (C=O), 2849 (C=CH-Ar, exocyclic), 3438 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.90-7.68 (3H, m, -CH of Aromatic ring), 8.25 (1H, dd, exocyclic CH) 10.16 (1H, s, barbituric acid NH), 10.85 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 79.93 (C-5), 119.94 (C-10), 126.18 (C-13), 129.95 (C-12), 136.12 (C-8), 145.92 (C-9) 147.92 (C-7), 148.02 (C-11), 151.25 (C-2), 166.15 (C-4, C-6); M.W=306.19; Anal. Calcd. For $C_{11}H_6N_4O_7$: C 43.15, H 1.98, N 18.30 (%). Found: C 43.12, H 1.96, N 18.36 (%).

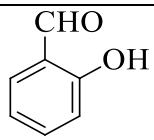
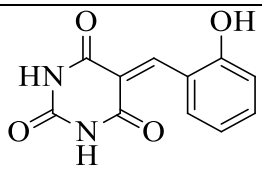
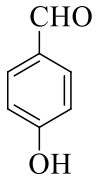
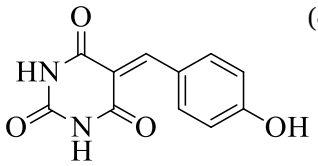
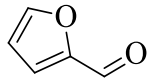
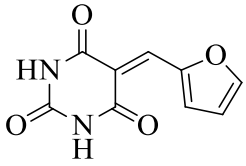
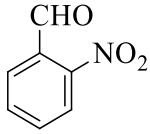
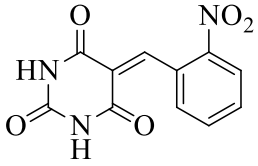
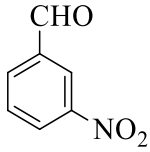
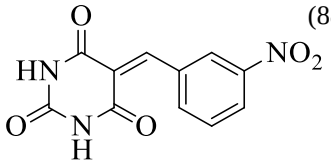
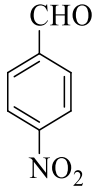
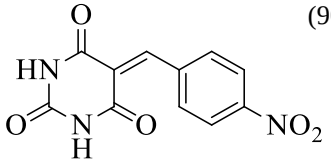
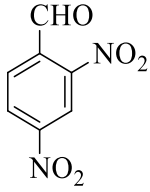
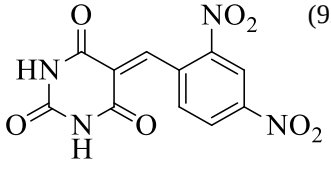
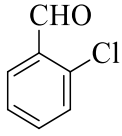
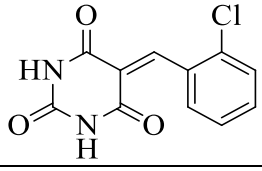
2.2.11 5-(2-chlorobenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-11): Light Yellow Powder, Yield: 82.14 %, M.P. >248-250 ˚C; FT-IR (KBr, cm^{-1}): 827 (C-Cl), 1658 (C=C, of Aromatic), 1763 (C=O), 2840 (C=CH-Ar, exocyclic), 3441 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.95-7.45 (4H, m, -CH of Aromatic ring), 8.23 (1H, dd, exocyclic CH) 10.08 (1H, s, barbituric acid NH), 10.78 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 79.24 (C-5), 126.74 (C-12), 127.80 (C-13), 129.30 (C-11), 129.92 (C-10), 133.02 (C-8), 134.11 (C-9), 148.45 (C-7), 151.13. (C-2), 163.65 (C-4, C-6); M.W=250.64; Anal. Calcd. For $C_{11}H_7ClN_2O_3$: C 52.71, H 2.82, N 11.18 (%). Found: C 52.74, H 2.79, N 11.16 (%).

2.2.12. 5-(4-chlorobenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-12): Light yellow Powder, Yield: 84.09 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 830 (C-Cl), 1660 (C=C, of Aromatic), 1766 (C=O), 2843 (C=CH-Ar, exocyclic), 3445 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 6.89-7.66 (4H, dd, -CH of Aromatic ring), 8.19 (1H, dd, exocyclic CH) 9.96 (1H, s, barbituric acid NH), 10.47 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 78.97 (C-5), 119.24 (C-7), 128.78 (C-10, C-12), 131.05 (C-8), 133.05 (C-11), 134.95 (C-8), 151.45. (C-2), 165.41 (C-4, C-6); M.W=250.64; Anal. Calcd. For $C_{11}H_7ClN_2O_3$: C 52.71, H 2.82, N 11.18 (%). Found: C 52.72, H 2.81, N 11.20 (%).

2.2.13. 5-(4-methylbenzylidene) pyrimidine-2, 4, 6(1H, 3H, 5H)-trione (C-13): Yellow Powder, Yield: 87.39 %, M.P. >250 ˚C; FT-IR (KBr, cm^{-1}): 1665 (C=C, of Aromatic), 1763 (C=O), 2845 (C=CH-Ar, exocyclic), 3445 (N-H of pyrimidine ring); ^{1}H NMR ($CDCl_3$-d_6): δ ppm 2.37 (3H, 1s, CH_3), 6.98-7.59 (4H, dd, -CH of Aromatic ring), 8.26 (1H, dd, exocyclic CH) 10.02 (1H, s, barbituric acid NH), 10.59 (1H, s, barbituric acid NH), ^{13}C NMR ($CDCl_3$-d_6): δ 22.36 (C-14), 78.75 (C-5), 119.24 (C-7), 126.98 (C-10, C-12), 129.9 (C-8), 134.45 (C-9, C-13), 138.57 (C-11) 151.23 (C-2), 163.87 (C-4, C-6); M.W=230.22; Anal. Calcd. For $C_{12}H_{10}N_2O_3$: C 62.60, H 4.38, N 12.17 (%). Found: C 62.58, H 4.36, N 12.19 (%).

Table 1 Silica sulphuric acid catalyzed Knoevenagel reaction by grinding at room temperature 5-Arylidenepyrimidine-2, 4, 6(1H, 3H, 5H)-trione derivatives. (Scheme 1).

Sr. No	Aromatic Aldehydes	5-Arylidenepyrimidine-2,4,6(1H,3H,5H)-trione	Color (Yield %)	M.P (˚C)
C-1			Yellow (91.45)	>250
C-2			(82.32)	>250
C-3			(86.53)	>250

C-4			(83.64)	248-250
C-5			(86.23)	>250
C-6			(80.12)	>250
C-7			(89.45)	>250
C-8			(88.77)	230-234
C-9			(90.12)	>250
C-10			(92.33)	>250
C-11			(82.14)	>248-250

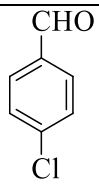
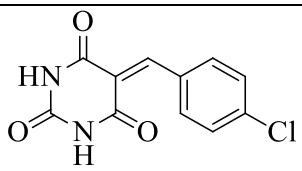
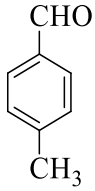
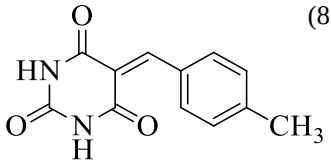
C-12			(84.09)	>250
C-13			(87.39)	>250

Table 2 Effect of proportion of SSA for the synthesis of-(4-hydroxy-3-methoxybenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione from (1 mmol) Barbituric acid and (1 mmol) 4-hydroxy-3-methoxybenzaldehyde by keeping fixed time duration.

Entry	SSA	Time (Minute)	Yield (%)
1	0.01	15	75.26
2	0.02	15	82.15
3	0.03	15	86.79
4	0.04	15	89.13
5	0.05	15	91.45

Table 3 Recycling of SSA for the synthesis of 5-(4-hydroxy-3-methoxybenzylidene) pyrimidine-2,4,6(1H,3H,5H)-trione by keeping fixed time duration (15 minute).

Entry	1st Run	2 nd Run	3rd Run	4th Run	5th Run
Cycle [b]	Fresh	First reuse	Second reuse	Third reuse	Fourth reuse
Yield (%) [c]	91.45	87.87	81.43	78.59	72.14

3. Results and Discussion

The important infrared spectral bands and their tentative assignments for knovenagel adducts were recorded as KBr disks and are presented in experimental section. From FT-IR data of compound (C-1). 1265, 1665, 1763, 2845 and 3189 confirms the C-O-CH_3, C=C, C=O, C=CH-of aromatic and N-H functional groups respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent ^{1}H NMR data of compound

C-1, Compounds shows characteristic peak at 3.87, 5.39, 6.89-7.75. 8.25, 9.76 and 10.15 δ ppm confirms the $OC\underline{H}_3$, Ar-O<u>H</u>, and CH of Aromatic ring, Exocyclic C<u>H</u> and barbituric acid repectively. The ^{13} C-NMR spectra of compounds C-1 showed characteristic peak around 56.1, 78.72, 110.24, 115.18, 126.05, 128.57, 148.02, 150.11, 152.95, 164.91, 190.41 [20]. In continuation of our research work on Knoevenagel condensations and on development of the novel synthetic methodologies[11], herein, we report a simple, efficient and safe methodology for the Knoevenagel condensation in the presence of SSA under grinding condition. The synthetic route is shown in Schemes 1. In order to optimize the reaction conditions, the reaction of Vaniline i.e. 4-hydroxy-3-methoxybenzaldehyde with Barbituric acid was selected as a model to investigate the effect of varying proportions of catalyst on the yield. The best results were obtained by carrying out the reaction with 1:1 mol ratio of aromatic aldehydes: Barbituric acid acid and 0.05 g of SSA under solvent-free conditions by grinding at room temperature. Under these conditions (Table 2, entry 5) was obtained 91.45% yield within 15 min. Encouraged by the results obtained with this model reaction. Different aromatic aldehydes containing electron-withdrawing or electron-donating compounds were reacted with barbituric acid. They all gave the expected products with high yields in short reaction times. To determine the appropriate ratio of the SSA, we investigated the model reaction at different proportions including 0.01, 0.02, 0.03, 0.04 and 0.05 (Table 1). The Knoevenagel product formed in 75.26%, 82.15%, 86.79%, 89.13% and 91.45% yield, respectively, indicating that 0.05 g of SSA is sufficient for the condensation of 1 mmol of each substrate pair (Table 1, entry 5).

We have developed a newer route for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds such as Barbituric acid in presence of SSA under solvent-free condition by grinding at room temperature (Table 2 and 3). All the reactions were carried out at room temperature by grinding, *i.e.*, using mild reaction conditions. In this methodology, condensation reactions were completed in a short reaction time and with excellent yields. Thus, this is an excellent method for the Knoevenagel condensation. Further investigation of the ability to recycle the catalyst is important for potential large-scale and/ or industrial operations. Therefore, the recovery and reusability of SSA was examined. The catalyst can be separated and reused after extracting the desired product. The reusability of the catalyst was investigated in the model reaction. The results illustrated in Table 3 showed that the catalyst could be used at least four times without significant loss of activity.

4. Conclusions

In summary, we have reported a new and effective methodology for the Knoevenagel condensation reaction via the condensation of substituted aromatic aldehydes with active methylene compounds such as barbituric acid and in the presence of SSA under solvent-free conditions by grinding at room temperature. The remarkable merits offered by this methodology are mild reaction conditions, cleaner reactions, short reaction times, simple work-up procedures and excellent yields. Additionally, the SSA was successfully reused for five cycles without significant loss of activity which makes the reaction convenient and environmentally benign.

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