

Facile Synthesis and Characterization of Substituted Pyrimidin-2(1*H*)-ones and their Chalcone Precursors

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Abstract. A new and efficient method has been developed for the quantitative transformation of chalcones to pyrimidine frame work *via* solid support catalysis. Silica supported sulphuric acid (SSA) efficiently catalyzed the reaction of α - β -unsaturated carbonyl, chalcones (1-10) with urea to afford substituted pyrimidin-2(1*H*)-ones (11-20) in good to excellent yield. The interesting behaviour of SSA lies in the fact that it can be re-used after simple washing with chloroform thereby rendering this procedure more economical. The chemical structures were confirmed by analytical data as well as spectroscopic means.

Keywords: catalyst, spectroscopic means, chalcones, 4-phenylbut-3-en-2-one

Introduction

The pyrimidine moiety is one of the most widespread heterocycles in biologically occurring compounds, such as nucleic acid components (uracil, thymine and cytosine) and vitamin B₁, and is an important constituent of numerous drug molecules in many therapeutic areas (Kakiya *et al.*, 2002). In the light of the recent findings concerning the role of apoptosis and of tumour cell enzymes in cancer chemotherapy (Rich *et al.*, 2004), the interest in pyrimidine derivatives has greatly increased (Kaufmann and Earnshaw, 2000). Pyrimidine templates have been reported to possess, among others, antimicrobial (Behalo, 2009; Moustafa, *et al.*, 2008; Habib *et al.*, 2007; Vaghasia and Shah, 2007), anticancer (Xie *et al.*, 2009; Singh and Paul, 2006), anticoagulant (Saif, 2008; Ries and Priepke, 2000), antitubercular, (Trivedi *et al.*, 2008; Virsodia *et al.*, 2008; Alksnis *et al.*, 2001), anti-HIV (Al-Masoudi *et al.*, 2008; Muruges *et al.*, 2008; Balzarini *et al.*, 2007; Miyashita *et al.*, 2003), analgesic (Hafez *et al.*, 2008; Sondhi *et al.*, 2005), anti-inflammatory (Pandas and Chowdary, 2008), anticonvulsant (Paronikyan *et al.*, 2007; Jain *et al.*, 2006), antiplatelet (Husted, 2007; Leoncini *et al.*, 2004), antiviral (Korkach *et al.*, 2007; Holy *et al.*, 2002), antimalarial (Rodenko *et al.*, 2007; Katritzky *et al.*, 2006) antifungal (Youssef *et al.*, 2006), antibacterial (Sriharsha *et al.*, 2006), antitumoural (Grigoryan *et al.*, 2005) and antileukemic (Liu *et al.*, 2003) activities.

Although various procedures for the synthesis of pyrimidine derivatives have been developed, it is convenient to synthesize substituted pyrimidines by the reaction of amidine or guanidine derivatives with a variety of 1,3-dielectrophilic three-carbon units such as α , β -unsaturated carbonyl compounds (chalcones). Some series of pyrimido[3,2-*a*]pyrimidine derivatives have also been designed as targeted structures with modest activity against gram-positive bacterial strains (Al-Thebeiti, 2001).

In a similar manner, many attempts on the synthetic manipulation of chalcones have always been very productive because of biological relevance of this frame work. In fact, all the pyrimidinone derivatives synthesized in the work herein were obtained from the chemical transformation of α , β -unsaturated carbonyl in the presence of urea under acidic condition. Chalcones and pyrimidine derivatives are classes of heterocycles that are of considerable interest because of the diverse range of their biological properties.

Due to high biological diversity of chalcone reported above, among other things, some of these chalcones have been synthesized earlier by using various approaches (McConville *et al.*, 2009; Kreher *et al.*, 2003; Hayakawa *et al.*, 1984; Lyle and Paradis, 1955). However, chemical transformation of these templates to pyrimidinone derivatives using re-usable silical sulphuric acid (SSA) has not been explored to the best of our knowledge. Thus, it is conceivable to develop a

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series of pyrimidinones using SSA catalyst technique and also compare it with the traditional method of conventional heating in concentrated HCl. Therefore, it was envisaged that the synthetic manipulation of chalcones by incorporating pyrimidine moieties therein might lead to the discovery of more pharmaceutically useful compounds.

Materials and Methods

General condition. Melting points were determined in open capillary tubes on a Stuart melting point apparatus and were uncorrected. Infrared spectra were recorded on a Shimadzu spectrometer. The ultraviolet spectra were run on a Genesys spectrometer using acetone solvent. ^1H and ^{13}C NMR were run on JEOL-JNM-GX 300-MHz spectrometer (in δ ppm relative to Me_4Si) using deuteriated chloroform. Mass spectra were run on Finnigan MAT 312 machine. All compounds were routinely checked by TLC on silical gel G plates using $\text{CHCl}_3:\text{CH}_3\text{OH}$ (9:1, v/v) solvent system and the developed plates were visualized by UV light. The elemental analysis (C, H, N) of compounds were performed using a Carlo Erba-1108 elemental analyzer.

General procedure for the synthesis of aromatic chalcones (1-7). To a solution of sodium hydroxide (2.5 g) in water (20 mL), was added ethanol (10 mL) with continuous stirring until it cools down to room temperature. To this solution was added a mixture of appropriate ketone (14.15 mmol) and benzaldehyde (14.15 mmol or 28.30 mmol) drop-wise with continuous stirring at room temperature for 30 min. The resulting solution formed coloured precipitate which was filtered by suction, washed and recrystallized from ethanol to afford 1-7.

4-Phenylbut-3-en-2-one (1). Yield 90.3%; mp. 38-40 °C {Lit. mp. 39-41 °C, McConville *et al.*, 2009}. UV-VIS $\{\lambda_{\text{max}}(\log \epsilon)\}$: 331 (1.83), 253 (4.18), 232 (3.30), 205 (3.76). IR [ν , cm^{-1} , KBr]: 2928 (CH aliphatic), 1690 (C=O), 1615 (C=C), 1190 (CH aromatic), 1040 (CH_3). ^1H NMR (300 Hz, δ ppm, CDCl_3): 7.60 (d, 1H, CO-C=CH, $J = 15$ Hz), 7.33-7.60 (m, 3H, Ar-H), 6.69 (d, 1H, CO-CH=C, $J = 15$ Hz), 2.27 (s, 3H, CH_3). ^{13}C NMR (300 Hz, δ ppm, CDCl_3): 197.7 (C=O), 142.7, 135.2, 128.6, 128.6, 128.5, 128.5, 127.9, 127.2, 27.4. MS m/z : 146 [M^+ , 25%], 131 [$\text{M} - \text{CH}_3$, 100%], 69 [$\text{M} - \text{Ph}$, 80%]. R_f (TLC): 0.52. Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}$ (146): C, 82.2; H, 6.8. Found: C, 82.4; H, 6.9.

1-(4-Ethylphenyl)-3-phenylprop-2-en-1-one (2). Yield 95.0%; mp. 58-60 °C {Lit mp. 59-61 °C, (Lyle and

Paradis, 1955)}. UV-VIS $\{\lambda_{\text{max}}(\log \epsilon)\}$: 325 (3.22), 244 (3.15), 226 (3.29), 208 (4.19). IR [ν , cm^{-1} , KBr]: 3010 (CH aliphatic), 1690 (C=O), 1600 (C=C), 1040 (CH_3). ^1H NMR (300 Hz, δ ppm, CDCl_3): 8.06 (d, 1H, CO-C=CH, $J = 15$ Hz), 7.59 (d, 1H, CO-CH=C, $J = 15$ Hz), 7.01-8.04 (m, 9H, Ar-H), 2.60 (q, 2H, CH_2 , $J = 8$ Hz), 1.25 (t, 3H, CH_3 , $J = 8$ Hz). ^{13}C NMR (300 Hz, δ ppm, CDCl_3): 189.7 (C=O), 150.1, 145.1, 135.2, 135.1, 129.8, 129.8, 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 127.9, 121.3, 28.2 (CH_2), 14.5 (CH_3). R_f (TLC): 0.61. Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}$ (236): C, 86.4; H, 6.8. Found: C, 86.6; H 6.7.

2-Benzylidenecyclopentanone (3). Yield 73.66%; mp. 55-58 °C {Lit mp. 54-57 °C, (Kreher *et al.*, 2003). UV-VIS $\{\lambda_{\text{max}}(\log \epsilon)\}$: 346 (4.35), 205 (3.47). IR [ν , cm^{-1} , KBr]: 2928 (CH aliphatic), 1695 (C=O), 1604 (C=C). ^1H NMR (300 Hz, δ ppm, CDCl_3): 7.60 (d, 2H, Ar-H), 7.33-7.40 (m, 3H, Ar-H), 7.25 (s, 1H, Ar-CH=C), 2.94 (t, 2H, CH_2 , $J = 7.2$ Hz), 1.96 (t, 2H, CH_2 , $J = 7.2$ Hz), 1.44 (quin., 2H, CH_2 , $J = 7.2$ Hz). ^{13}C NMR (300 Hz, δ ppm, CDCl_3): 168.4 (C=O), 153.1, 144.9, 140.5, 133.2, 133.2, 124.7, 124.7, 112.4, 35.8, 22.5, 19.7 (CH_2). MS m/z : 172 [M^+ , 50%], 95 [$\text{M} - \text{Ph}$, 100%]. R_f (TLC): 0.69. Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}$ (172): C, 83.7; H, 7.0. Found: C, 83.4; H, 6.9.

2,5-Dibenzylidenecyclopentanone (4). Yield 69.92%; mp. 192-194 °C. UV-VIS $\{\lambda_{\text{max}}(\log \epsilon)\}$: 346 (4.01), 274 (3.30), 253 (3.31), 205 (3.69). IR [ν , cm^{-1} , KBr]: 3000 (CH aliphatic), 1690 (C=O), 1600 (C=C), 1250 (CH aromatic). ^1H NMR (300 Hz, δ ppm, CDCl_3): 7.60 (m, 4H, Ar-H), 7.37 (s, 2H, $2 \times \text{Cp}=\text{CH}$), 7.33-7.40 (m, 6H, Ar-H), 3.02 (s, 4H, $2 \times \text{CH}_2$, $J = 7.1$ Hz). ^{13}C NMR (300 Hz, δ ppm, CDCl_3): 196.6 (C=O), 143.6, 143.6, 135.2, 135.2, 132.8, 132.8, 128.6 (four times), 128.5 (four times), 127.9, 127.9, 29.4 (CH_2), 29.4 (CH_2). R_f (TLC): 0.59. Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{O}$ (258): C, 88.4; H, 5.4. Found: C, 88.7; H 5.6.

2,5-Bis(3-methoxybenzylidene)cyclopentanone (5). Yield 71.78%; mp. 144-147 °C. UV-VIS $\{\lambda_{\text{max}}(\log \epsilon)\}$: 358 (3.19), 328 (3.28), 241 (3.06), 208 (3.55). IR [ν , cm^{-1} , KBr]: 2928 (CH aliphatic), 1690 (C=O), 1605 (C=C), 1450 (OCH_3), 1250 (CH aromatic). ^1H NMR (300 Hz, δ ppm, CDCl_3): 7.37 (s, 2H, $2 \times \text{Cp}=\text{CH}$), 6.87-7.59 (m, 8H, Ar-H), 3.83 (s, 6H, $2 \times \text{OCH}_3$), 3.02 (s, 4H, $2 \times \text{CH}_2$, $J = 7.1$ Hz). ^{13}C NMR (300 Hz, δ ppm, CDCl_3): 196.6 (C=O), 160.5, 160.5, 143.6, 143.6, 134.8, 134.8, 132.8, 132.8, 129.6, 129.6, 120.8, 120.8, 113.5, 113.5, 113.2, 55.8, 55.8, 29.4, 29.4 (CH_2).

R_f (TLC): 0.54. Anal. Calcd. for C₂₁H₁₈O (286): C, 88.1; H, 6.3. Found: C, 88.3; H, 6.5.

2-Benzylidenecyclohexanone (6). Yield 76.43%; mp. 56-57 °C {Lit mp. 53-55 °C, (Kreher *et al.*, 2003)}. UV-VIS{λ_{max}(log ε)}: 348 (3.98), 265 (4.01), 220 (3.87). IR [ν, cm⁻¹, KBr]: 1685 (C=O), 1612 (C=C). ¹H NMR (300 Hz, δ ppm, CDCl₃): 7.33-7.60 (m, 5H, Ar-H), 7.25 (s, 1H, Cp=CH), 3.16 (t, 2H, CH₂), 2.81 (t, 2H, CH₂, *J* = 7.1 Hz), 1.67-1.74 (m, 4H, 2×CH₂, *J* = 7.1 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 202.1 (C=O), 143.8, 135.6, 135.2, 128.6, 128.6, 128.5, 128.5, 127.9, 39.0 (CH₂), 27.2 (CH₂), 26.1 (CH₂), 22.8 (CH₂). R_f (TLC): 0.66. Anal. Calcd. for C₁₃H₁₄O (186): C, 83.9; H, 7.5. Found: C, 83.7; H, 7.4.

2,6-Dibenzylidenecyclohexanone (7). Yield 79.12%; mp. 121-123 °C. UV-VIS{λ_{max}(log ε)}: 328 (4.17), 274 (3.15), 247 (3.15), 208 (3.93). IR [ν, cm⁻¹, KBr]: 2980 (CH aliphatic), 1690 (C=O), 1610 (C=C), 1310 (CH aromatic). ¹H NMR (300 Hz, δ ppm, CDCl₃): 7.60-7.61 (m, 4H, Ar-H), 7.33-7.40 (m, 6H, Ar-H), 7.37 (s, 2H, 2×CH=CH), 2.81 (t, 4H, 2×CH₂, *J* = 7.1 Hz), 1.60 (quin., 2H, CH₂, *J* = 7.1 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 190.4 (C=O), 137.1, 137.1, 135.2, 135.2, 132.2, 132.2, 128.6 (four times), 128.5 (four times), 127.9, 127.9, 26.1 (CH₂), 26.1 (CH₂), 25.1 (CH₂). R_f (TLC): 0.68. Anal. Calcd. for C₂₀H₁₈O (274): C, 87.6; H, 6.6. Found C, 87.7; H, 6.3.

General procedure for the synthesis of heteroaromatic chalcones (8-10). Sodium hydroxide (2.98 g) was dissolved in a mixture of water (20 mL) and methylated spirit (10 mL) in an ice bath with continuous stirring until a clear solution is obtained. To the clear solution, a mixture of furfural (1.95 mL, 23.57 mmol) and appropriate ketone (23.57 mmol) was added with continuous stirring for 2 h under ice bath. A clear solution was obtained. The reaction mixture was neutralized with dilute sulphuric acid and a crystalline product was formed immediately, filtered by suction and recrystallized from aqueous ethanol (1:1) to afford the product 8-10.

4-(Furan-2-yl)but-3-en-2-one (8). Yield 51.20%; mp. 34-36 °C {Lit. mp. 33-34 °C, (Hayakawa *et al.*, 1984)}
VIS{λ_{max}(log ε)}: 348 (3.47), 272 (3.86), 220 (4.11). IR [ν, cm⁻¹, KBr]: 1685 (C=O), 1612 (C=C). ¹H NMR (300 Hz, δ ppm, CDCl₃): 8.17 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.65 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.54 (d, 1H, CO-C=CH, *J* = 15 Hz), 6.91 (d, 1H, CO-CH=C, *J* = 15 Hz), 6.87 (m, 1H, Fr-H, *J* = 7.5 Hz), 2.27 (s, 3H, CH₃).

¹³C NMR (300 Hz, δ ppm, CDCl₃): 197.7 (C=O), 151.6, 143.8, 129.1, 123.1, 113.6, 112.7, 26.8 (CH₃). R_f (TLC): 0.70. Anal. Calcd. for C₈H₈O₂ (136): C, 70.6; H, 5.9. Found: C, 70.7; H 5.7.

2-(Furan-2-ylmethylene)cyclopentanone (9). Yield 35.90%; mp. 58-61 °C. UV-VIS{λ_{max}(log ε)}: 348 (3.44), 304 (3.77), 216 (4.09). IR [ν, cm⁻¹, KBr]: 2928 (CH aliphatic), 1685 (C=O), 1612 (C=C), 1375 (C-O, epoxy). ¹H NMR (300 Hz, δ ppm, CDCl₃): 8.17 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.65 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.27 (s, 1H, Cp=CH), 6.87 (t, 1H, Fr-H, *J* = 7.5 Hz), 2.94 (t, 2H, CH₂, *J* = 7.0 Hz), 1.95 (t, 2H, CH₂, *J* = 7.0 Hz), 1.44 (quin., 2H, CH₂, *J* = 7.0 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 208.5 (C=O), 151.5, 147.4, 143.7, 119.4, 112.7, 109.6, 38.5 (CH₂), 21.4 (CH₂), 19.8 (CH₂). R_f (TLC): 0.69. Anal. Calcd. for C₁₀H₁₀O₂ (162): C, 74.1; H, 6.2. Found: C, 74.4; H, 6.5.

2-(Furan-2-ylmethylene)cyclohexanone (10). Yield 41.20%; mp. 45-47 °C. UV-VIS{λ_{max}(log ε)}: 368 (3.89), 340 (3.78), 220 (4.11). IR [ν, cm⁻¹, KBr]: 1685 (C=O), 1610 (C=C). ¹H NMR (300 Hz, δ ppm, CDCl₃): 8.17 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.66 (d, 1H, Fr-H, *J* = 7.5 Hz), 7.27 (s, 1H, Cp=CH), 6.86 (t, 1H, Fr-H, *J* = 7.5 Hz), 3.16 (t, 2H, CH₂, *J* = 7.0 Hz), 2.82 (t, 2H, CH₂, *J* = 7.0 Hz), 1.68-1.75 (m, 4H, 2×CH₂, *J* = 7.0 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 201.9 (C=O), 151.5, 149.8, 143.7, 119.5, 112.7, 109.4, 38.4 (CH₂), 25.5 (CH₂), 24.8 (CH₂), 22.8 (CH₂). R_f (TLC): 0.57. Anal. Calcd. for C₁₁H₁₂O₂ (176): C, 75.0; H, 6.8. Found C, 74.8; H, 6.5.

General procedure for synthesis of pyrimidinone derivatives (11-20). *Method I.* A mixture of any of chalcones 1-10 (10 mmol) and urea (1.30 g, 21 mmol) was ground in mortar and quantitatively transferred to a 250 mL quick fit flask containing ethanol (30 mL). Later, concentrated hydrochloric acid (10 mL) was added drop-wise with continuous stirring and the reaction mixture was reflux for appropriate time and reduced by evaporation to half of the original volume. It was then cooled to room temperature and neutralized with 30% sodium hydroxide and left in the freezer chest over night. The solid product obtained was recrystallized from ethanol to afford the corresponding pyrimidinone 11-20 in moderate to good yield.

Method II. To a mixture of any of chalcones 1-10 (10 mmol), urea (1.30 g, 21 mmol) and ethanol (20 mL), a catalytic amount of SSA (100 mg, 0.26 mmol) was added and the reaction mixture was refluxed for

appropriate time. The SSA catalyst was extracted with chloroform (20 mL) and removed from the entire solution. The remaining solution was reduced to half of its volume and cooled to room temperature. It was neutralized with 30% sodium hydroxide and left in the freezer chest over night. The solid product obtained was recrystallized from ethanol to afford the corresponding pyrimidinone **11-20** in good to excellent yield.

4-Methyl-6-phenyl-5,6-dihydropyrimidin-2(1H)-one (11). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 325 (3.96), 274 (3.33), 244 (3.78), 226 (3.44), 202 (3.13). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3241 (N-H), 2928 (CH aliphatic), 1685 (C=O), 1612 (C=C), 1575 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 7.26-7.40 (m, 5H, Ar-H), 4.90 (t, 1H, CH, $J = 7.0$ Hz), 1.94 (s, 3H, CH_3), 1.91-1.66 (m, 2H, CH_2 , $J = 7.0$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 180.1 (C=O), 160.2, 143.5, 128.7, 128.5, 128.5, 126.9, 126.9, 126.7, 47.7, 40.0, 22.1 (CH_3).

4-(4-Ethylphenyl)-6-phenyl-5,6-dihydropyrimidin-2(1H)-one (12). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 310 (3.68), 265 (3.86), 230 (3.97), 215 (3.77). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3133 (N-H), 1685 (C=O), 1570 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 7.27-7.40 (m, 7H, $2 \times \text{Ar-H}$), 7.78 (d, 2H, Ar-H, $J = 7.5$ Hz), 4.90 (t, 1H, CH, $J = 7.0$ Hz), 1.91-1.66 (m, 2H, CH_2 , $J = 7.0$ Hz), 2.60 (q, 2H, CH_2 , $J = 8.0$ Hz), 1.25 (t, 3H, CH_3 , $J = 8.0$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 164.6 (C=O), 160.1, 146.7, 143.5, 137.8, 128.5, 128.5, 127.8, 127.8, 127.0, 127.0, 126.9, 126.9, 126.7, 47.3 (CH), 42.7 (CH_2), 28.2 (CH_2), 14.5 (CH_3).

4-Phenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta [d]pyrimidin-2-one (13). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 328 (4.12), 274 (3.39), 247 (3.41), 208 (4.02). $[\text{IR } \nu, \text{cm}^{-1}, \text{KBr}]$: 3295 (NH), 2928 (CH aliphatic), 1690 (C=O), 1600 (C=C), 1565 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.01 (s, 1H, NH, D_2O exchangeable), 7.25-7.41 (m, 5H, Ar-H), 4.92 (d, 1H, CH), 2.67-2.84 (m, 5H, Cp-H), 1.22-1.41 (m, 4H, $2 \times \text{CH}_2$, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 208.4 (C=O), 150.0, 146.1, 142.9, 135.0, 135.0, 128.1, 128.1, 115.0, 115.0, 39.1 (CH_2), 23.8 (CH_2), 20.4 (CH_2). MS m/z : 214 [M^+ , 12.5%], 137 [$\text{M}^+ - \text{Ph}$, 75%], 109 [$\text{M}^+ - \text{Ph} - \text{CO}$, 100%].

7-Benzylidene-4-phenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (14). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 330 (3.98), 208 (4.14). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3387 (NH), 1685 (C=O), 1612 (C=C), 1575 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchange-

able), 7.27-7.60 (m, 10H, $2 \times \text{Ar-H}$), 6.34 (s, 1H, CH), 4.91 (d, 1H, CH, $J = 7.0$ Hz), 2.69 (t, 1H, CH, $J = 7.0$ Hz), 1.22-2.02 (m, 4H, $2 \times \text{CH}_2$, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 163.0 (C=O), 160.1, 141.5, 137.1, 135.2, 130.8, 128.6, 128.6, 128.5 (four times), 128.1, 128.1, 127.9, 125.9, 49.9, 45.3, 33.6 (CH_2), 31.3 (CH_2).

7-(3-Methoxybenzylidene)-4-(3-methoxyphenyl)-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (15). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 366 (3.98), 345 (3.77), 210 (4.14). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3387 (NH), 1685 (C=O), 1612 (C=C), 1575 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 6.82-7.59 (m, 8H, $2 \times \text{Ar-H}$), 6.35 (s, 1H, CH), 4.90 (d, 1H, CH, $J = 7.0$ Hz), 3.84 (s, 6H, $2 \times \text{CH}_3$, $J = 7.0$ Hz), 1.81-2.32 (m, 5H, Cp-H, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 163.1 (C=O), 160.5, 160.4, 160.1, 141.5, 141.5, 134.8, 133.2, 130.9, 129.6, 129.5, 120.8, 120.3, 113.5, 113.2, 111.5, 55.8 ($2 \times \text{OCH}_3$), 50.3, 45.3, 33.4, 31.2.

4-Phenyl-4,4a,5,6,7,8-hexahydroquinazolin-2(3H)-one (16). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 375 (3.69), 344 (3.87), 210 (4.02). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3387 (NH), 1685 (C=O), 1600 (C=C), 1573 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 7.27-7.41 (m, 5H, Ar-H), 4.91 (d, 1H, CH, $J = 7.0$ Hz), 2.19 (q, 1H, CH, $J = 7.0$ Hz), 1.19-1.41 (m, 8H, $4 \times \text{CH}_2$, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 164.7 (C=O), 160.1, 137.1, 128.5, 128.5, 128.1, 128.1, 125.9, 49.8, 41.9, 33.8, 27.0, 24.8, 24.2.

8-Benzylidene-4-phenyl-4,4a,5,6,7,8-hexahydroquinazolin-2(3H)-one (17). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 378 (3.84), 362 (4.01), 220 (3.91). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3385 (NH), 1684 (C=O), 1612 (C=C), 1573 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 7.60 (d, 2H, Ar-H), 7.28-7.40 (m, 8H, Ar-H), 6.35 (s, 1H, Ph-CH=C), 4.90 (d, 1H, CH, $J = 7.0$ Hz), 2.19 (q, 1H, CH, $J = 7.0$ Hz), 1.97 (t, 2H, CH_2 , $J = 7.1$ Hz), 1.20-1.39 (m, 4H, $2 \times \text{CH}_2$, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (300 Hz, δ ppm, CDCl_3): 164.6 (C=O), 160.1, 137.0, 135.2, 130.1, 128.6, 128.6, 128.5 (five times), 128.1, 128.1, 127.8, 125.9, 50.2, 38.2, 27.4, 24.6, 24.6.

6-(Furan-2-yl)-4-methyl-5,6-dihydropyrimidin-2(1H)-one (18). UV-VIS $\{\lambda_{\max}(\log \epsilon)\}$: 365 (3.66), 335 (3.59), 210 (3.72). IR $[\nu, \text{cm}^{-1}, \text{KBr}]$: 3365 (NH), 1675 (C=O), 1610 (C=C), 1575 (C=N). $^1\text{H NMR}$ (300 Hz, δ ppm, CDCl_3): 8.0 (s, 1H, NH, D_2O exchangeable), 6.30-6.61 (m, 3H, Fr-H), 5.11 (t, 1H, CH, $J = 7.0$ Hz),

1.94 (s, 3H, CH₃, *J* = 7.0 Hz), 1.65-1.91 (d, 2H, CH₂). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 180.1 (C=O), 160.2, 151.0, 141.5, 110.0, 109.3, 48.7, 38.2, 21.5(CH₃).

4-(Furan-2-yl)-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[d] pyrimidin-2-one (19). UV-VIS {λ_{max} (log ε)}: 368 (4.03), 345 (3.87), 210 (4.14). IR [ν, cm⁻¹, KBr]: 3371 (NH), 1690 (C=O), 1612 (C=C), 1572 (C=N). ¹H NMR (300 Hz, δ ppm, CDCl₃): 8.00 (s, 1H, NH, D₂O exchangeable), 7.66 (d, 1H, Fr-H), 6.43-6.47 (t, 2H, Fr-H), 5.10 (d, 1H, CH, *J* = 7.0 Hz), 2.67-2.82 (m, 3H, Cp-H), 1.20-1.41 (m, 4H, 2 × CH₂, *J* = 7.1 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 164.6 (C=O), 160.1, 150.1, 141.6, 110.0, 108.9, 50.8, 45.7, 37.4, 24.7, 22.8.

4-(Furan-2-yl)-4,4a,5,6,7,8-hexahydroquinazolin-2(3H)-one (20). UV-VIS {λ_{max} (log ε)}: 379 (3.92), 365 (3.75), 210 (4.01). IR [ν, cm⁻¹, KBr]: 3272(N-H), 1673(C=O), 1605(C=C), 1575(C=N). ¹H NMR (300 Hz, δ ppm, CDCl₃): 8.00 (s, 1H, NH, D₂O exchangeable), 7.65 (d, 1H, Fr-H), 6.43-6.47 (t, 2H, Fr-H), 5.10 (d, 1H, CH, *J* = 7.0 Hz), 2.19 (q, 1H, CH, *J* = 7.0 Hz), 1.18-1.39 (m, 8H, 4 × CH₂, *J* = 7.1 Hz). ¹³C NMR (300 Hz, δ ppm, CDCl₃): 164.5 (C=O), 160.1, 150.0, 141.5, 110.0, 108.8, 51.0, 40.0, 33.3, 27.0, 24.1, 21.8.

Results and Discussion

In the first part of this study, α,β-unsaturated carbonyls (1-7) were synthesized *via* condensation of benzaldehyde with ketones in basic medium while replacing of benzaldehyde with heteroaromatic aldehyde, furfural, resulted in the formation of α,β-unsaturated carbonyls 8-10 (Scheme 1). Although, compounds 1-7 were formed in good yields *via* a continuous stirring at room temperature, 8-10 violated this reaction protocol at room temperature but were obtained in improved yields *via* continuous stirring in ice bath at a controlled temperature of 0 °C. Later, compounds (1-10) were subsequently reacted with urea under two different conditions to afford pyrimidinone derivatives (11-20). The difference in the condition lied in the nature of the catalyst. Hence, the synthesis of pyrimidinone in the presence of concentrated HCl (Method I) was compared with one using solid support catalyst, silica sulfuric acid (SSA) (Method II). The products of the reactions were monitored through thin layer chromatography (TLC) spotting using chloroform: methanol (9:1, v/v) solvent system. Each of the reactions gave one spot with R_f values varying from 0.40 to 0.85. The main method used to construct the pyrimidine skeleton is the [3+3]cyclocondensation of N-C-N and C-C-C units.

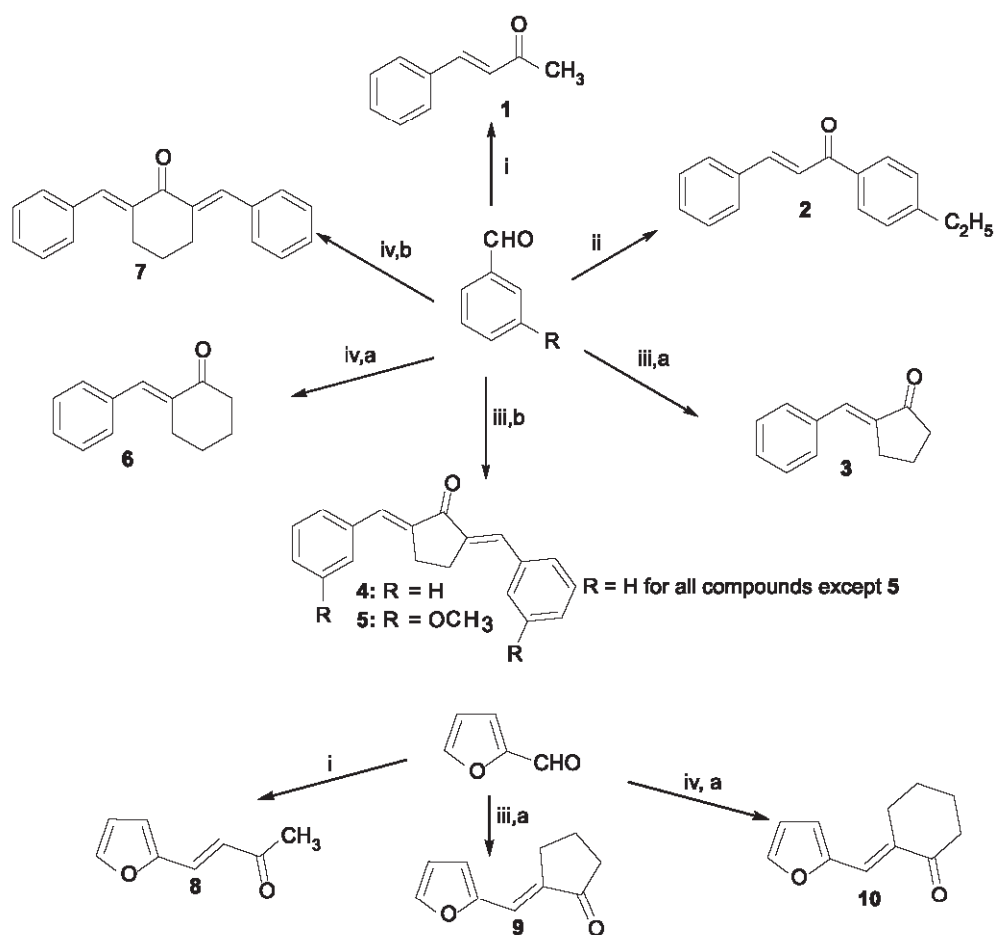
As a case study, condensation of an equimolar mixture of benzaldehyde with cyclopentanone affords 2-benzylidenecyclopentanone (3). The chalcone 3 was subsequently treated with urea in ethanol in the presence of either concentrated hydrochloric acid (Method I) or silica sulphuric acid (Method II) under reflux at 140 °C to afford 4-phenyl-3,4,4a,5,6,7-hexahydro-2*H*-cyclopenta[*d*] pyrimidin-2-one, (13), Scheme 2. This procedure was repeated for the chemical transformation of other chalcones to their corresponding pyrimidinone derivatives. In Method I, upon completion (TLC), the reaction was worked up to afford 13 in moderate yield 51% after refluxing for 9 h. However, in Method II, where conc. HCl was replaced with solid support catalyst SSA, the reaction time did not only reduced drastically to 3 h but also led to the formation of the product (13) at a higher yield, 91% (Table 1). The SSA catalyst was recovered with chloroform (20 mL). The resulting filtrate was reduced to half its volume and cooled. It was neutralized with ammonium hydroxide and filtered by suction to afford 4-phenyl-3,4,4a,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-one, (13). In a nutshell, it was observed that SSA did not only emerge as an efficient catalyst in this study but also afforded the pyrimidinone products in higher yields (75-93%) within smaller reaction time (3-4 h) compared with concentrated hydrochloric acid which gave smaller yields (40-71%) at higher reaction time of 8-9 h (Table 1).

From the spectroscopic studies, using 13 as a typical representative of the pyrimidones, the UV-visible absorption spectrum in chloroform gave rise to wavelength ranging from 208 nm to 328 nm. The peak at λ_{max} = 208 (log ε = 4.02) was as a result of π→π* of benzene nucleus, while the highest one at λ_{max} = 328 (log ε = 4.12) was as a result of n→π* transition due to presence of iminone and additional conjugation. Two shoulders were noticed at 247 nm and 274 nm. The infrared spectrum of 13 showed absorption bands due to the stretching vibrations of N-H and C-H aliphatic at 3295 cm⁻¹ and 2928 cm⁻¹, respectively, while the band at 1690 cm⁻¹ depicted the presence of conjugated C=O. The infrared band of C=C aromatic and C=N of pyrimidine were confirmed at 1600 cm⁻¹ and 1565 cm⁻¹ respectively. The chemical shifts and multiplicity patterns of ¹H and ¹³C NMR correlated well with that of the proposed structures. For instance, the ¹H NMR spectrum of 13 in deuteriated chloroform showed NH signal, which was exchangeable with D₂O, as a singlet down

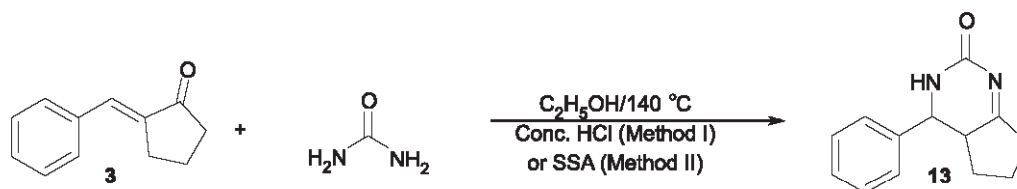
Table 1: Physicochemical properties of synthesized pyrimidinone (11-20)

Comp. code	Molecular formula	Mol. Wt.	M.P. (°C)	R _f *	Colour	Method I		Method II	
						Time** (h)	Yield (%)	Time** (h)	Yield (%)
11	C ₁₁ H ₁₂ N ₂ O	188	124-127	0.77	Yellow	8	45	3	77
12	C ₁₈ H ₁₈ N ₂ O	278	211-213	0.56	White	9	58	3	82
13	C ₁₃ H ₁₄ N ₂ O	214	184-186	0.85	Green	9	51	3	94
14	C ₂₀ H ₁₇ N ₂ O	301	227-229	0.49	Green	8	63	3	89
15	C ₂₂ H ₂₁ N ₂ O ₃	355	240-242	0.69	Green	9	60	4	91
16	C ₁₄ H ₁₆ N ₂ O	228	198-200	0.76	Orange	7	48	3	75
17	C ₂₁ H ₂₀ N ₂ O	316	>320	0.63	Black	8	71	3	95
18	C ₉ H ₁₀ N ₂ O ₂	178	106-108	0.55	Yellow	7	68	3	90
19	C ₁₁ H ₁₂ N ₂ O ₂	204	133-135	0.68	Black	8	71	3	92
20	C ₁₂ H ₁₄ N ₂ O ₂	218	144-147	0.40	Orange	7	40	3	75

* = solvent system: CHCl₃:CH₃OH (9:1, v/v); ** = reaction under reflux at 140 °C.



Scheme 1. (i) acetone (ii) 4-ethyl acetophenone (iii) cyclopentanone, a=1 eq, b=0.5 eq (iv) cyclohexanone, a=1 eq, b=0.5 eq. Reaction conditions for 1-7 = NaOH/EtOH/ H₂O/RT while conditions for 8-10 = NaOH/methylated spirit/H₂O/ice bath at 0 °C.



Scheme 2. Synthesis of 4-phenyl-3, 4, 4a, 5, 6, 7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (13).

field at δ 8.01 while five aromatic protons were observed as a multiplet at δ 7.25-7.41. The only proton on carbon adjacent to NH resonated as a doublet δ 4.92. All the seven protons from cyclopentyl (Cp) group were noticed up field; three of them as a multiplet at δ 2.67-2.84 while the remaining four (2 x CH₂, Cp) were observed as a multiplet at δ 1.22-1.41. In addition, ¹³C NMR spectrum of 13 showed the presence of twelve carbon atoms with the signals ranging from 208.4(C=O) to 20.4 (CH₂) ppm. In the mass spectral data of 13, the molecular ion peak observed at m/z 214 corresponded with its molecular mass while the base peak found at m/z 109 was as a result of the loss of a phenyl radical and a stable ethylene molecule. Loss of a phenyl radical from the molecular ion peak accounted for the daughter fragment with m/z of 137.

Conclusion

Silica sulphuric acid (SSA) was found to be a mild, efficient and reusable solid catalyst for the reaction of α,β -unsaturated carbonyl with urea to furnish the corresponding pyrimidinone derivatives in good to excellent yield. The interesting behaviour of SSA lies in the fact that it can be re-used after simple washing with chloroform thereby rendering this procedure more economical compared with concentrated HCl method. In addition, SSA gave better yields in a reduced reaction time. Thus, the pyrimidinone library synthesized herein could be very useful candidates for further studies in terms of toxicity effect and structural activity relationship (SAR) in order to improve their biological and pharmacological activities.

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