


Research Article

Biginelli Synthesis of Novel Dihydropyrimidinone Derivatives Containing Phthalimide Moiety

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A new series of novel Biginelli compounds, 5-benzoyl-substituted phenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (**1–10**), were synthesized from enaminone, 2-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]phenyl}-1H-isoindole-1,3(2H)-dione (**IV**), which was synthesized by refluxing 2-(4-acetylphenyl)-1H-isoindole-1,3(2H)-dione (**III**), with dimethylformamide-dimethylacetate (DMF-DMA) without solvent for 12 h. The compound 2-(4-acetylphenyl)-1H-isoindole-1,3(2H)-dione (**III**) was obtained by reacting phthalic anhydride (**I**) with para-aminoacetophenone (**II**) in glacial acetic acid for 2 h. The dihydropyrimidinone derivatives containing phthalimide moiety (**1–10**) were obtained by reacting enaminone, 2-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]phenyl}-1H-isoindole-1,3(2H)-dione (**IV**), with urea and different substituted benzaldehydes in the presence of glacial acetic acid for 3 h. Simple and efficient method was employed to synthesize the dihydropyrimidinone derivatives containing phthalimide moiety. Structures of all the synthesized compounds were characterized by spectroscopic methods.

1. Introduction

Pyrimidines have played a vital role in the field of pharmaceutical chemistry [1]. Pyrimidines are important moiety because of their various pharmacological activities. Nifedipine, 4-aryl-1,4-dihydropyridines, was the first antihypertensive agent into the clinical medicine. For the treatment of various cardiovascular diseases, dihydropyridines are the most potent calcium channel modulators [2, 3].

Substituted dihydropyrimidinone compounds show interesting biological properties, e.g., calcium channel blockers and antihypertensive agents [4, 5]. These compounds display a broad spectrum of biological activities such as anti-inflammatory, antitumor, antiviral, and antibacterial ones [6, 7]. Dihydropyrimidinone compounds were first synthesized by Pietro Biginelli. The type of compounds is known as Biginelli

compounds. The synthesis of this type of compounds involves the reacting of numerous aldehydes with urea and a beta-keto ester to give a tetrahydropyrimidinone.

Phthalimide analogues have been reported with large range of pharmacological activities that are anticonvulsant, anti-inflammatory, analgesic, and hypolipidemic [8–11]. Phthalimide analogues have been synthesized as tumor necrosis factor- α (TNF- α) inhibitors [12]. TNF- α plays an important role in certain physiological immune systems. It stimulates the inflammatory response leading to autoimmune disorders including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis, and refractory asthma [13]. Extensive research on the phthalimide analogues has been reported in the literature [14–17].

The hybrid compounds containing these two important moieties (dihydropyrimidinone and phthalimide) may have

a substantial therapeutic potential. In continuation of our work on dihydropyrimidinones, a series of novel phthalimide dihydropyrimidinone hybrids were synthesized by simple method and fully characterized by elemental analysis and spectral data [18, 19].

2. Experiment

2.1. Chemistry. Solvents were procured from Merck, New Jersey, USA. Thin layer chromatography (TLC) was performed on Silica gel 60F₂₅₄ coated plates (Merck, Millipore, Billerica, MA, USA) to check the purity of compounds. For performing FT-IR, PerkinElmer FT-IR spectrophotometer (PerkinElmer Inc., Waltham, MA, USA) was used. Melting points were determined by Gallenkamp melting point apparatus. ¹H and ¹³C NMR were recorded in Bruker NMR 500/700 MHz and 125/176 MHz spectrophotometer (Bruker Corporation, Billerica, MA, USA). The samples were dissolved in DMSO-*d*₆ with tetramethylsilane (TMS) as an internal standard. The molecular masses of compounds were determined by Agilent triple quadrupole 6410 TQ GC/MS equipped with ESI (electrospray ionization) source (5301 Stevens Creek Blvd, Santa Clara, CA 95051, USA). The CHN (Elementar Analysensysteme GmbH, Langenselbold, Germany) was used for elemental analysis of the compounds.

Scheme 1 depicts a reaction by which the dihydropyrimidinone derivatives of phthalimide were prepared. The dihydropyrimidinone derivatives (**1–10**) were synthesized by refluxing phthalic anhydride (**I**) (0.01 mol) and para-aminoacetophenone (**II**) (0.01 mol) in glacial acetic acid for 2 h. The reaction mixture was added to the ice cold water. The white product was precipitated and was filtered by vacuum filtration. The washing of the product was performed by ice cold water. The compound 2-(4-acetylphenyl)-1H-isindole-1,3(2H)-dione (**III**) was obtained, which was recrystallized by ethanol. A mixture of (**III**) (0.02 mol) and dimethylformamide-dimethylacetal (DMF-DMA) (0.023 mol) was refluxed for 12 h without solvent on a heating mantle. After the completion of reaction, the reaction mixture was cooled to room temperature. Diethyl ether was added to precipitate the reaction mixture and vacuum filtration was performed. The obtained product enamionone, 2-{4-[3-(dimethylamino) prop-2-enoyl] phenyl}-1H-isindole-1,3(2H)-dione (**IV**), was recrystallized from absolute ethanol.

2.2. Synthesis of the Dihydropyrimidinone Derivatives (1–10). A mixture of enamionone, 2-{4-[3-(dimethylamino) prop-2-enoyl] phenyl}-1H-isindole-1,3(2H)-dione (**IV**) (0.01 mol), differently substituted benzaldehyde (0.01 mol), urea (0.01 mol), and glacial acetic acid (10 mL), was refluxed for 3 h. The precipitates (**1–10**) were obtained by adding ice cold water to the reaction mixture. The products were obtained by filtration under vacuum. The products were washed several times with water. The products were purified by recrystallization from glacial acetic acid and ethanol mixture. The physicochemical properties of compounds (**1–10**) are given in Table 1.

2.2.1. 5-Benzoyl-3,4-dimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (1). m.p.: 150–152°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.74 (3H, s, -OCH₃), 3.76 (3H, s, OCH₃), 5.43 (1H, s, H-4), 6.88–8.00 (12H, m, Ar-H), 9.39 (1H, s, CONH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 53.3, 55.9, 65.4, 110.9, 112.1, 112.7, 118.6, 124.0, 127.5, 129.1, 131.9, 134.5, 135.3, 136.8, 138.3, 142.5, 148.6, 151.6, 167.2, 191.3; MS: *m/z* = 483.47 [M]⁺; Analysis: for C₂₇H₂₁N₃O₆ calcd. C 67.07, H 4.38, N 8.69%; Found C 67.27, H 4.37, N 8.67%.

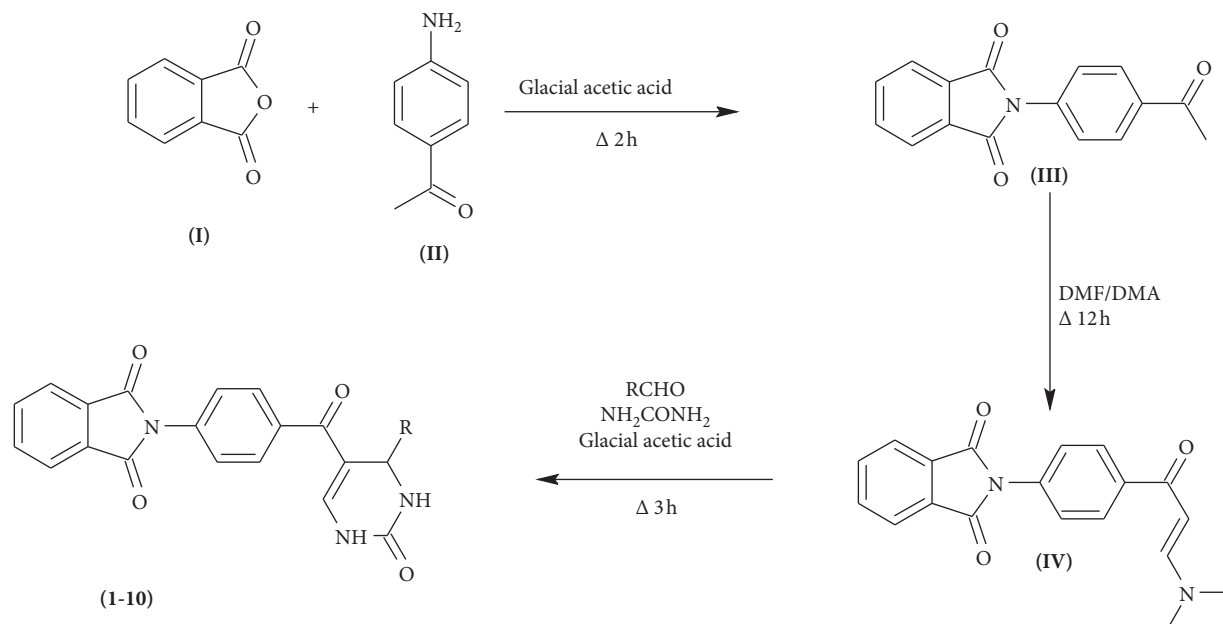
2.2.2. 5-Benzoyl-4-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (2). m.p.: 175–177°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 5.62 (1H, s, H-4), 7.20–8.41 (13H, m, Ar-H), 9.60 (1H, s, CONH, D₂O exch.), 10.16 (1H, s, NH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 111.7, 123.9, 124.7, 128.4, 129.1, 131.0, 131.9, 134.6, 135.2, 138.0, 140.5, 143.3, 147.2, 151.5, 167.2, 191.1, 192.7, 207.0; MS: *m/z* = 468.41 [M]⁺; Analysis: for C₂₅H₁₆N₄O₆ calcd. C 64.10, H 3.44, N 11.96%; Found C 64.28, H 3.45, N 11.98%.

2.2.3. 5-Benzoyl-3-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (3). m.p.: 240–242°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 5.64 (1H, s, H-4), 7.22–8.22 (13H, m, Ar-H), 9.60 (1H, s, CONH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 111.6, 121.7, 123.0, 124.0, 127.4, 129.1, 130.7, 131.9, 133.7, 134.6, 135.2, 138.0, 146.5, 148.3, 151.3, 167.2, 191.2; MS: *m/z* = 468.41 [M]⁺; Analysis: for C₂₅H₁₆N₄O₆ calcd. C 64.10, H 3.44, N 11.96%; Found C 64.27, H 3.46, N 11.94%.

2.2.4. 5-Benzoyl-2-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (4). m.p.: 170–172°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 6.17 (1H, s, H-4), 7.22–7.98 (13H, m, Ar-H), 9.62 (1H, s, CONH, D₂O exch.), 10.30 (1H, s, NH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 111.6, 123.9, 124.5, 127.3, 129.3, 130.0, 131.9, 134.5, 135.2, 137.7, 138.5, 143.3, 148.3, 150.9, 167.1, 191.0; MS: *m/z* = 468.41 [M]⁺; Analysis: for C₁₀H₁₀N₂O₂ calcd. C₂₅H₁₆N₄O₆ calcd. C 64.10, H 3.44, N 11.96%; Found C 64.26, H 3.43, N 11.97%.

2.2.5. 5-Benzoyl-2,3-dimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (5). m.p.: 190–192°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.81 (3H, s, -OCH₃), 3.89 (3H, s, OCH₃), 5.76 (1H, s, H-4), 6.94–7.99 (12H, m, Ar-H), 9.36 (1H, s, CONH, D₂O exch.), 10.31 (1H, s, NH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 49.8, 56.5, 56.5, 60.6, 62.4, 65.4, 112.3, 112.6, 118.7, 120.2, 123.9, 124.4, 127.4, 129.0, 131.9, 134.4, 135.2, 137.3, 138.4, 146.6, 146.6, 151.4, 152.9, 167.2, 190.4, 191.1; MS: *m/z* = 483.47 [M]⁺; Analysis: for C₂₇H₂₁N₃O₆ calcd. C 67.07, H 4.38, N 8.69%; Found C 67.26, H 4.39, N 8.71%.

2.2.6. 5-Benzoyl-2,4,5-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isindole-1,3(2H)-dione (6). m.p.: 180–182°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.69 (3H, s, -OCH₃), 3.79 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 5.60 (1H, s, H-4), 6.73–8.00



SCHEME 1: Reaction scheme for the synthesis of dihydropyrimidinone derivatives (1–10).

TABLE 1: Physicochemical properties of compounds (1–10).

Compd.	R	% yield
1	3,4-(OCH ₃) ₂ -C ₆ H ₃	70
2	4-NO ₂ -C ₆ H ₄	75
3	3-NO ₂ -C ₆ H ₄	72
4	2-NO ₂ -C ₆ H ₄	74
5	2,3-(OCH ₃) ₂ -C ₆ H ₃	68
6	2,4,5-(OCH ₃) ₃ -C ₆ H ₂	80
7	3,4,5-(OCH ₃) ₃ -C ₆ H ₂	82
8	2,3,4-(OCH ₃) ₃ -C ₆ H ₂	80
9	2,4,6-(OCH ₃) ₃ -C ₆ H ₂	75
10	2,4-(OCH ₃) ₂ -C ₆ H ₃	70

(11H, m, Ar-H), 9.33 (1H, s, CONH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 49.5, 56.2, 56.5, 56.9, 65.4, 99.2, 111.5, 113.1, 123.0, 124.0, 127.5, 129.0, 131.0, 131.9, 134.4, 135.2, 135.4, 138.5, 142.8, 149.7, 151.7, 152.0, 167.2, 191.6; MS: *m/z* = 513.49 [M]⁺; Analysis: for C₂₈H₂₃N₃O₇ calcd. C 65.49, H 4.51, N 8.18%; Found C 65.47, H 4.50, N 8.20%.

2.2.7. 5-Benzoyl-3,4,5-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (7). m.p.: 195–197°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.66 (3H, s, -OCH₃), 3.79 (6H, s, OCH₃), 5.45 (1H, s, H-4), 6.67–7.99 (11H, m, Ar-H), 9.44 (1H, s, CONH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 53.7, 56.3, 56.5, 60.4, 65.4, 104.0, 112.1, 124.0, 127.5, 129.1, 131.9, 134.5, 135.2, 137.2, 138.3, 139.8, 151.5, 153.3, 167.2, 191.3; MS: *m/z* = 513.49 [M]⁺; Analysis: for C₂₈H₂₃N₃O₇ calcd. C 65.49, H 4.51, N 8.18%; Found C 65.46, H 4.52, N 8.16%.

2.2.8. 5-Benzoyl-2,3,4-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (8). m.p.: 165–167°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.78 (3H, s, -OCH₃), 3.79 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 5.65 (1H, s, H-4),

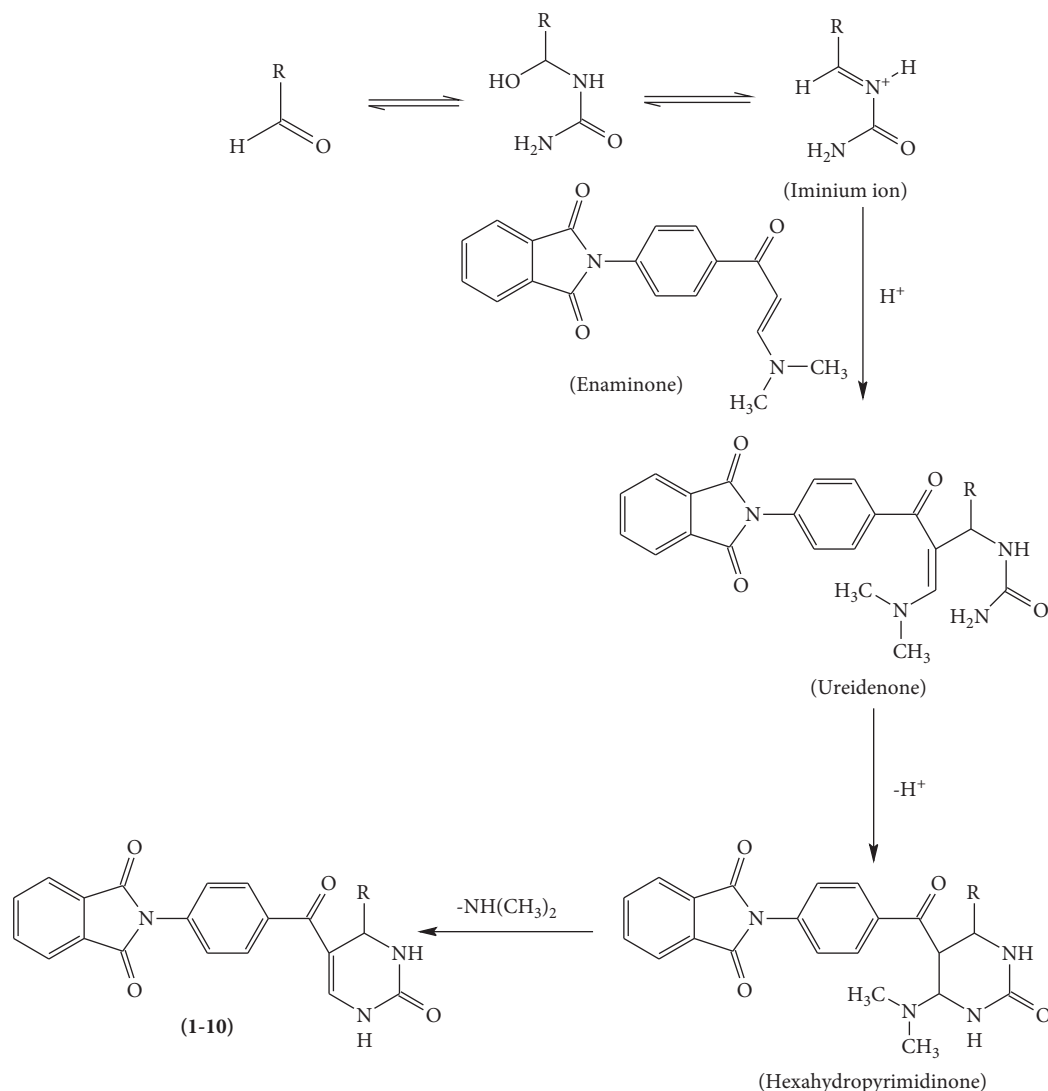
6.77–7.99 (11H, m, Ar-H), 9.36 (1H, s, CONH, D₂O exch.), 10.12 (1H, s, NH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 45.0, 55.5, 56.3, 56.5, 65.0, 91.1, 91.6, 93.2, 111.5, 112.9, 123.9, 131.1, 139.1, 142.2, 152.0, 159.6, 160.6, 161.6, 163.8, 167.1, 186.1, 191.2; MS: *m/z* = 513.49 [M]⁺; Analysis: for C₂₈H₂₃N₃O₇ calcd. C 65.49, H 4.51, N 8.18%; Found C 65.36, H 4.49, N 8.16%.

2.2.9. 5-Benzoyl-2,4,6-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (9). m.p.: 155–157°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.69 (3H, s, -OCH₃), 3.70 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 5.65 (1H, s, H-4), 6.77–7.99 (11H, m, Ar-H), 9.36 (1H, s, CONH, D₂O exch.), 10.12 (1H, s, NH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 45.2, 55.5, 56.3, 56.5, 65.4, 91.1, 91.6, 93.2, 111.5, 112.9, 123.9, 127.2, 128.9, 131.9, 135.2, 139.1, 142.2, 152.0, 159.6, 160.6, 161.6, 167.2, 186.1, 191.2; MS: *m/z* = 513.49 [M]⁺; Analysis: for C₂₈H₂₃N₃O₇ calcd. C 65.49, H 4.51, N 8.18%; Found C 65.59, H 4.50, N 8.20%.

2.2.10. 5-Benzoyl-2,4-dimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (10). m.p.: 168–170°C; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 3.75 (3H, s, -OCH₃), 3.84 (3H, s, OCH₃), 5.66 (1H, s, H-4), 6.59–8.00 (12H, m, Ar-H), 9.33 (1H, s, CONH, D₂O exch.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 49.1, 55.6, 56.0, 65.4, 99.1, 104.9, 111.5, 123.8, 124.0, 127.4, 127.5, 128.7, 129.1, 131.0, 131.9, 134.4, 135.2, 138.5, 142.9, 151.8, 158.4, 160.5, 167.0, 191.0; MS: *m/z* = 483.47 [M]⁺; Analysis: for C₂₇H₂₁N₃O₆ calcd. C 67.07, H 4.38, N 8.69%; Found C 66.82, H 4.39, N 8.70%.

3. Results and Discussion

As shown in Scheme 1, enaminone, 2-[4-[(2E)-3-(dimethylamino)prop-2-enyl]phenyl]-1H-isoindole-1,3(2H)-dione (IV), was synthesized by refluxing 2-(4-acetylphenyl)-1H-



SCHEME 2: The possible mechanism for the synthesis of dihydropyrimidinone derivatives containing phthalimide (1-10).

isoindole-1,3(2H)-dione (III) with dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free conditions for 12 h. To prepare the final dihydropyrimidinone derivatives, a mixture of substituted benzaldehyde (0.01 mol), enaminone (IV) (0.01 mol), urea (0.01 mol), and glacial acetic acid (10 mL) was heated under reflux for 3 h. The ethylenic protons indicate that the enaminone existed in the *E*-configuration [20]. Compounds presented the D_2O exchangeable broad singlet at δ 9.33–9.62 ppm and δ 10.12–10.31 ppm corresponding to the two NH protons. The H-4 protons of dihydropyrimidinone moiety and aromatic protons were observed at δ 5.43–6.17 and δ 6.59–8.41 ppm, respectively [21]. ^{13}C NMR spectra confirmed all the carbon atoms for compounds (1-10). Molecular weights of the compounds were confirmed by mass spectral data. Molecular ion peaks were observed in all compounds respective to their molecular weights. The composition of the synthesized compounds (1-10) was confirmed by spectral and elemental data. The possible reaction mechanism involves the acid catalyzed formation of iminium ion intermediate from the substituted aryl aldehydes and urea. Reaction of phthalimide

enaminone by iminium ion yields ureidenone, which forms hexahydropyrimidine by cyclization. Final dihydropyrimidinone derivatives (1-10) were obtained by elimination of $\text{NH(CH}_3)_2$ group from hexahydropyrimidine in presence of glacial acetic acid (Scheme 2).

4. Conclusion

In conclusion, a series of novel dihydropyrimidinone derivatives containing phthalimide moiety were synthesized in good yield, at high level of purity, and in efficient manner from the enaminone, which was derived from phthalimide by simple and solvent-free method. The enaminone existed in the *E*-configuration. All the compounds were characterized and confirmed by different spectroscopic methods and elemental analysis.

Data Availability

Samples of the compounds (1-10) in pure form are available from the authors upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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