

A ONE-POT SYNTHESIS OF PYRIDO[2,3-*d*]- AND QUINOLINO[2,3-*d*] PYRIMIDINES

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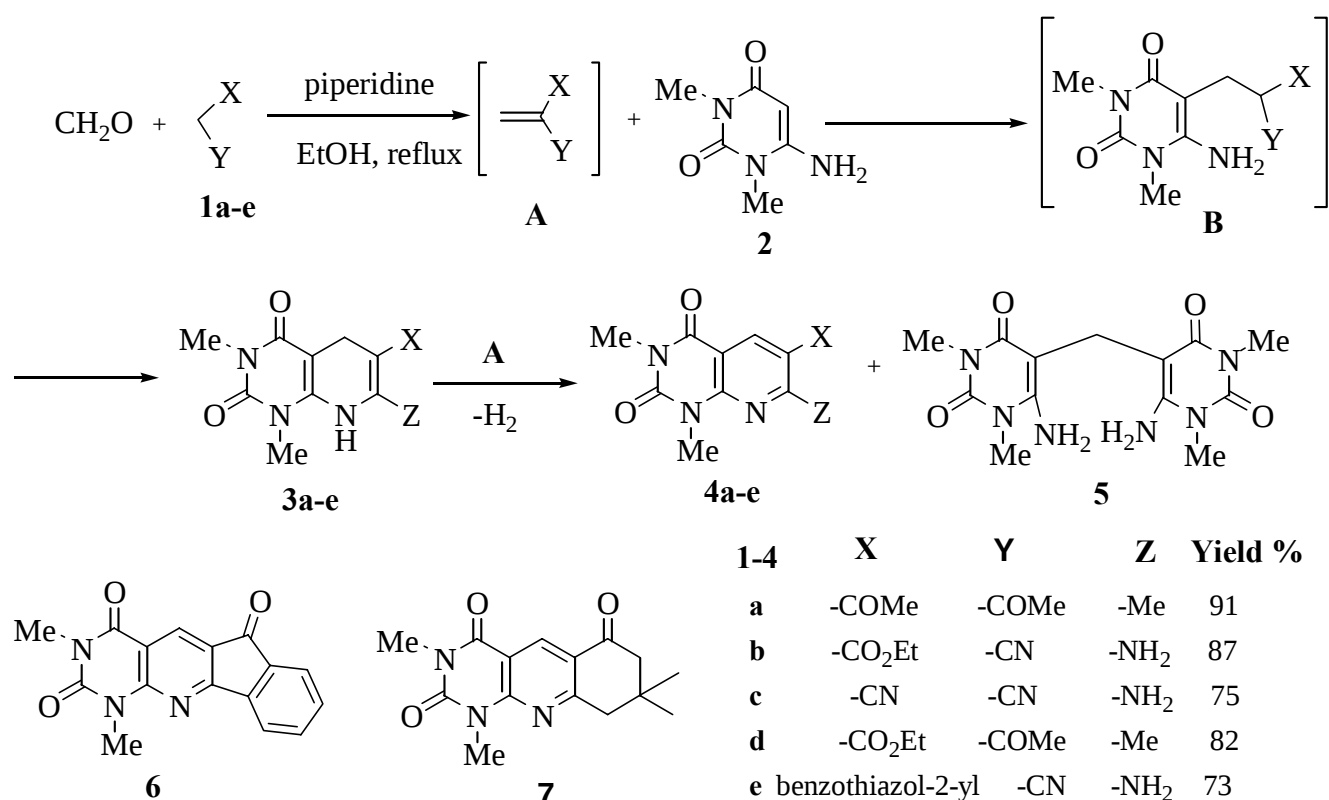
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Abstract—The *in situ* formed methylene derivatives of 1,3-dicarbonyl compounds; ethyl cyanoacetate; malononitrile and ketones; react with 6-amino-1,3-dimethyluracil as activated alkenyl derivatives, affording Michael adducts. The adducts simultaneously undergo cyclization to furnish pyrido[2,3-*d*]- or quinolino[2,3-*d*]pyrimidine derivatives in high yield.

Uracil and its annelated substrates occupy a unique place in the field of medicinal chemistry as useful anticancer and antiviral drugs.¹⁻³ Besides, the discoveries of many pyrido[2,3-*d*]pyrimidine derivatives with potential antitumor,^{4,5} anti-inflammatory and CNS depressant activities,⁶ have stimulated considerable interest in the synthesis of pyrido[2,3-*d*]pyrimidines *via* new and efficient routes. Many strategies have been developed for the preparation of these compounds. One of the major routes involves the reaction of 6-aminouracil with cyanolefins.⁷ An alternative route involves the condensation of 6-amino-1,3-dimethyluracil-5-carboxaldehyde with active methylene compounds.⁸ Herein we wish to disclose a simple straightforward, three-component heteroannulation reaction that converts 6-aminouracil into pyrido[2,3-*d*]- or quinolino[2,3-*d*]pyrimidines in high yield.

The reaction of active methylene compounds with formaldehyde has been reported⁹ to afford *in situ* the corresponding ylidene derivatives and thus can be considered as synthetic equivalent of these intermediates. The reaction of these reactive synthons with heterocyclic enamines has not been reported. 6-Aminouracils have been reported to behave as heterocyclic enamines and undergo Michael addition with different activated olefins and acetylenes, followed by cyclization to afford annelated heterocycles.^{10,11} We have found that a 2: 2: 1 mixture of active methylene compounds (**1a-e**); formaldehyde and 6-amino-1,3-dimethyluracil (**2**), reacts in refluxing ethanol containing a catalytic amount of piperidine to give the annelated pyrimidine derivatives (**4a-e**) in 91-73 % yield. However, bis(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimid-5-yl)methane (**5**) was detected in a minute amount and was separated easily by fractional crystallization (lit.,^{12,13} mp > 300 °C). Moreover, the reaction tolerates cyclic active methylene compounds. Thus, the reaction of indane-1,3-dione or dimedone with formaldehyde and **2** affords the indenopyridopyrimidine derivative (**6**) and quinolinopyrimidine derivative (**7**) in 69% and 81% yields, respectively.



Scheme 1

The desired compounds (**4a-e**) are assumed to be formed *via* in situ formation of methylene derivatives (**A**), which then reacts with **2** to yield the Michael adduct (**B**) that spontaneously cyclizes into the dihydropyridine intermediates (**3**), which subsequently undergoes oxidation, in presence of intermediate (**A**), to the pyrido[2,3-*d*]pyrimidines (**4a-e**). This mechanism finds support from the observation that the yield of the reaction was decreased considerably when equimolar amounts of a mixture of **2**, formaldehyde and active methylene compounds were allowed to react under the same conditions. The oxidation of dihydropyridines into the corresponding pyridines has been reported previously.¹⁴ The structures of **4a-e**, **6**, and **7** were determined from spectral data and elemental analyses. The ¹H NMR of compound (**4e**), showed a 1:1 mixture of the two hydrogen-bonding structures, Figure 1.

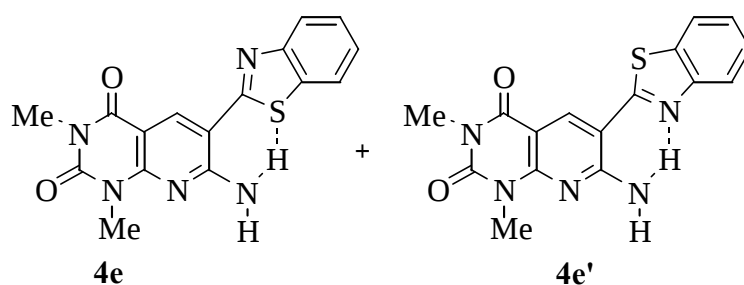


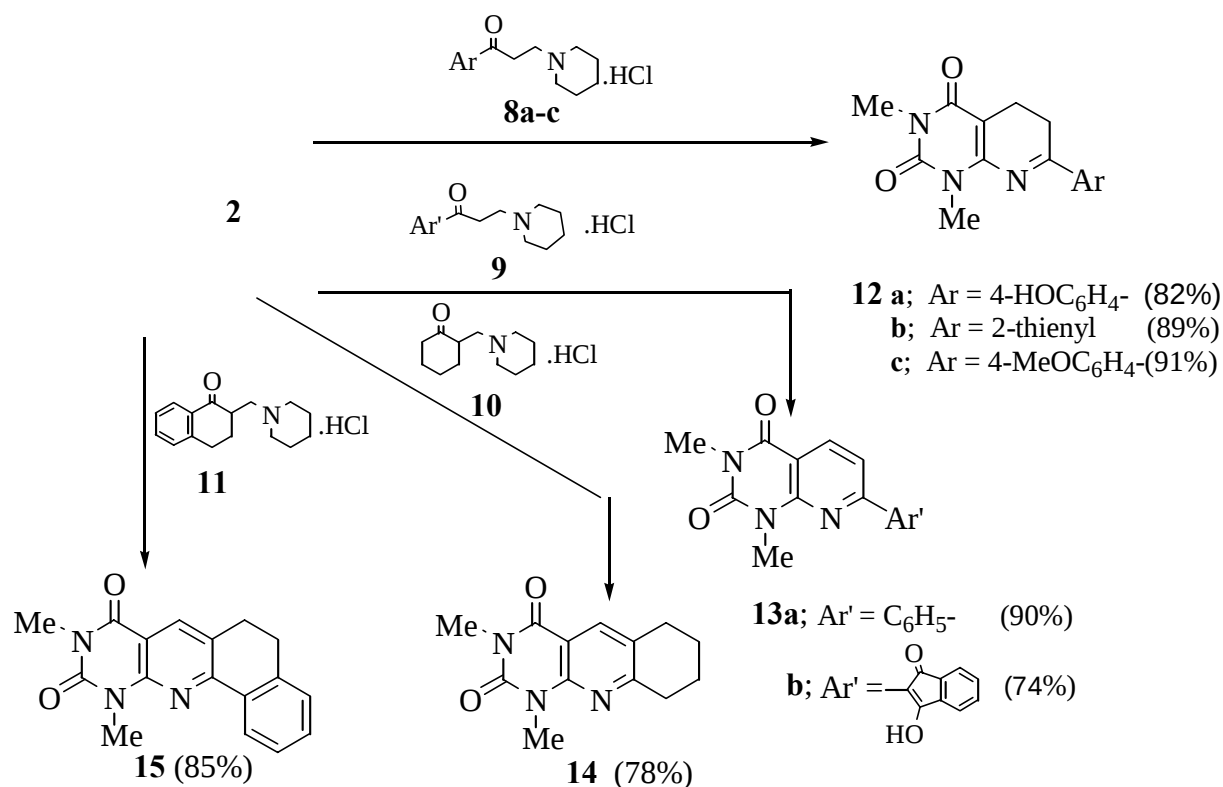
Figure 1

On the other hand, use of ketones or nitroalkanes, as active methylene components, was unsuccessful: the stepwise addition of ketone to formaldehyde and stirring 2 h followed by the addition of **2** gave only the

undesired compound (**5**). This can be explained in terms of that ketones or nitroalkanes were not incorporated to form active methylene species in this reaction. However, we came upon a solution to this problem based on the fact that ketonic Mannich bases hydrochloride are good sources of methylene derivatives of ketones. Consequently, the reaction of aminouracil (**2**) with ketonic Mannich bases hydrochloride (**8-11**), in refluxing ethanol furnished pyrido[2,3-*d*]- and quinolino[2,3-*d*]pyrimidines (**12a-c**, **13**, **14**, **15**) in 91- 74 % yield (Scheme 2).

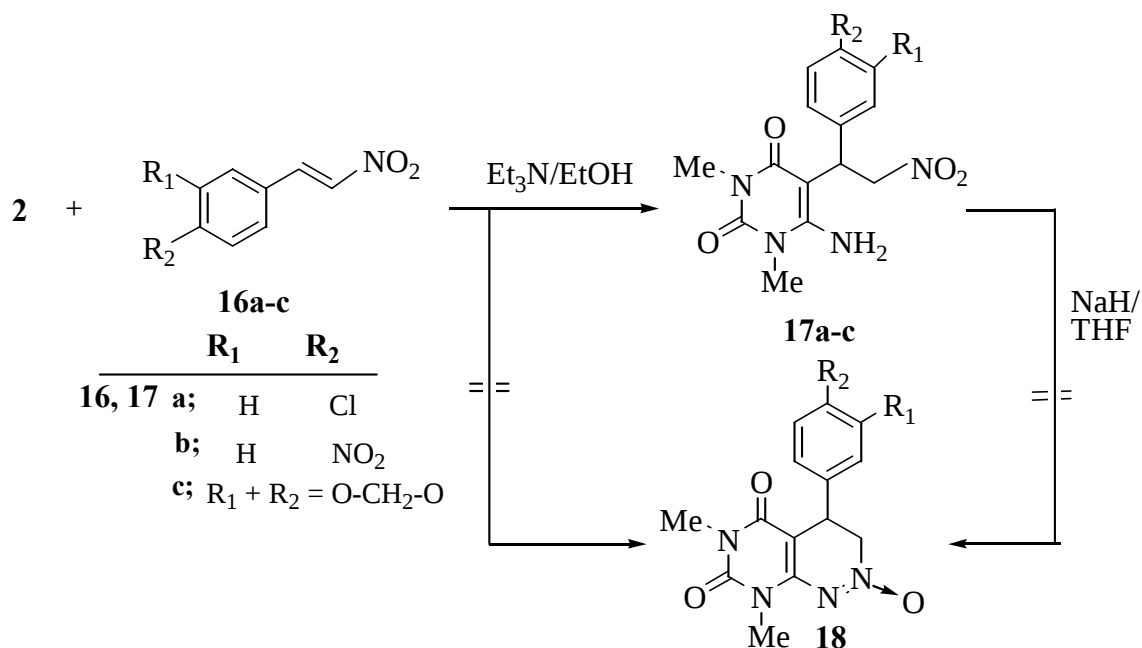
In contrast to the facile aromatization during formation of **13-15**, the ring system of **12a-c** is stable under the same condition. These different outcomes can be attributed to the presence of electron-rich groups, e.g., 2-thienyl, *para*-hydroxyphenyl, *para*-methoxyphenyl, which stabilize the azadiene ring system of **12a-c**.

The structures of compounds (**12a-c**, **13-15**) were assigned unambiguously by analysis of the ^1H NMR spectral data. Thus, the compound (**12c**) gave two triplets for the two methylene groups (δ 2.70, 2.89). By contrast, compounds (**14**) and **15** showed the presence of one-proton singlet (aromatic H-5) at δ 8.08 and 8.22, respectively.



Scheme 2

While the reaction of nitroalkanes, formaldehyde and (**2**) afforded only compound (**5**), the reaction of nitroolefins (**16a-c**) with **2** in refluxing ethanol containing a catalytic amount of Et₃N furnished the Michael adduct (**17a-c**) in excellent yield and the cyclized pyridazine *N*-oxide (**18**) were not detected under this condition. Several attempts to enhance the ring closure of **17a-c** to **18** were unsuccessful.



Scheme 3

EXPERIMENTAL

Melting points (Pyrex capillary) are not corrected. ^1H NMR spectra were obtained on a Varian-Gemini 200 MHz, 270 MHz and 300 MHz instruments. Unless otherwise indicated the NMR spectra were taken in deuteriochloroform at 25 °C, with TMS as an internal standard. IR spectra were recorded using KBr wafer technique. Mass spectra were recorded on GC-MS GP-1000 EX. Shimadzu machine.

General procedure for the preparation of pyrido[2,3-*d*]pyrimidines (4a-e): A suspension of 6-amino-1,3-dimethyluracil (**2**) (1.55 g, 10 mmol), active methylene compounds (**1a-e**) (20 mmol) and paraformaldehyde (0.06 g, 20 mmol) in ethanol (50 mL) was treated with few drops of piperidine. The reaction mixture was refluxed for 6 h. After cooling the reaction mixture, the formed precipitate was filtered off, and the desired products (**4a-e**) were separated from the by-product (**5**) by fractional crystallization.

6-Acetyl-1,3,7-trimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (4a): yield 91%; mp 155 °C (EtOH, lit.,¹⁵ mp 151°C).

Ethyl-7-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate (4b): yield 87%; mp 210-212 °C (EtOH, lit.,⁸ mp 211-212 °C, lit.,¹⁵ mp 220 °C).

7-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4c): yield 75%; mp 354 °C (AcOH, lit.,⁸ 354-356 °C, lit.,¹⁶ 354 °C).

Ethyl 1,3,7-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate (4d): yield 82%; mp 135-136 °C (EtOH, lit.,¹⁵ mp 123 °C).

7-Amino-6-(2-benzthiazolyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine

(4e): yield 73%, mp >300 °C; IR cm^{-1} 3439, 3263, 1717, 1674, 1607, 1588, 1527, 1466. ^1H NMR (DMSO- d_6) δ 2.76 (s, 3H), 2.91 (s, 3H), 3.25 (s, 3H), 3.49 (s, 3H), 7.44 (m, 2H), 7.98 (m, 2H), 8.21 (s, 1H), 8.38 (s, 1H), 8.41 (br s, 1H, NH), 8.8 (br s, 2H, NH₂), 10.8 (bs, 1H, NH). *Anal.* Calcd for C₁₆H₁₃N₅O₂S: C, 56.63; H, 3.86; N, 20.64. Found: C, 56.32; H, 3.95; N, 20.78.

1,3-Dimethyl-2,3,4,6-tetrahydro-1*H*-inden-[2',1':5,6]-pyrido[2,3-*d*]pyrimidine-2,4,6-trione (6): yield 69%, mp >300 °C (AcOH); MS (m/z, rel.int.) 293 (80, M⁺), 181 (100). IR cm^{-1} 1709, 1654, 1616, 1595. ^1H NMR (DMSO- d_6) δ 3.7 (s, 3H), 3.9 (s, 3H), 7.4 (m, 1H), 7.6 (m, 3H), 8.55 (s, 1H). *Anal.* Calcd for C₁₆H₁₁N₃O₃: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.35; H, 3.54; N, 14.15.

1,3,8,8-Tetramethyl-1,2,3,4,6,7,8,9-octahydropyrimidino[4,5-*b*]quinoline-2,4,6-trione (7): yield 81%; mp 179-180 °C (EtOH); IR cm^{-1} 2960, 1716, 1688, 1665, 1597, 1501, 1474, 1413, 1361. ^1H NMR δ 1.12 (s, 6H), 2.56 (s, 2H), 3.04 (s, 2H), 3.47 (s, 3H), 3.73 (s, 3H), 8.99 (s, 1H). *Anal.* Calcd for C₁₅H₁₇N₃O₃: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.42; H, 6.21; N, 14.85.

General procedure for the preparation of pyrido- and quinolino[2,3-*d*]pyrimidines (12a-c, 13-15).

A mixture of 6-amino-1,3-dimethyluracil (**2**) (1.55 g, 10 mmol) and Mannich base hydrochlorides (**8a-c**, **9**, **10**, **11**, 10 mmol) in ethanol (40 mL) was refluxed for 6 h. The reaction mixture was left to stand overnight, the formed precipitate was filtered off, dried and crystallized from the appropriate solvent to give the desired products.

7-(4-Hydroxyphenyl)-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (12a): yield 82%; mp 340 °C (DMF); MS (m/z, rel. int.) 285 (70, M⁺), 284 (100), 192 (17), 81 (35). IR cm^{-1} 3113, 3025, 2955, 1687, 1624, 1598, 1542, 1511, 1375. *Anal.* Calcd for C₁₅H₁₅N₃O₃: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.45; H, 5.19; N, 14.56.

1,3-Dimethyl-7-(2-thienyl)-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-2,4-dione (12b): yield 89%, mp 188-190 °C (EtOH); IR cm^{-1} 3084, 1690, 1636, 1548, 1474, 1416. ^1H NMR δ 2.70 (t, J = 8.4 Hz, 2H), 2.89 (t, J = 8.4 Hz, 2H), 3.41 (s, 3H), 3.60 (s, 3H), 7.18 (m, 1H), 7.69 (m, 2H). *Anal.* Calcd. for C₁₃H₁₃N₃O₂S: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.52; H, 4.44; N, 15.53.

7-(4-Methoxyphenyl)-1,3-dimethyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-2,4-dione (12c): yield 91%; mp 184-185 °C (EtOH); IR cm^{-1} 2953, 1688, 1639, 1617, 1582, 1547. ^1H NMR δ 2.66 (t, J = 8.2 Hz, 2H), 2.86 (t, J = 8.2 Hz, 2H), 3.41 (s, 3H), 3.64 (s, 3H), 3.89 (s, 3H), 6.98 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H). *Anal.* Calcd for C₁₆H₁₇N₃O₃: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.60; H, 5.95; N, 14.34.

1,3-Dimethyl-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (13a): yield 90%; mp 189-190 °C (EtOH, lit.,¹⁶ mp 188°).

7-(1,3-Dioxo-2,3-dihydro-1H-2-indenyl)-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (13b): yield 74%; mp 302-304 °C (DMF); ^1H NMR (DMSO- d_6) δ 3.34 (s, 3H overlapped with the water peak of solvent), 3.69 (s, 3H), 5.61 (d, $J=9\text{Hz}$, 1H), 6.12 (d, $J=9$, 1H), 7.55 (m, 2H), 7.71 (m, 1H), 7.92 (m, 1H), 8.41 (s, 1H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.55; H, 4.02; N, 12.75.

1,3-Dimethyl-6,7,8,9-tetrahydroquinolino[2,3-d]pyrimidine-2,4-(1H,3H)-dione (14): yield 78%, mp 135-136 °C (EtOH-Et $_2$ O, lit.,¹⁷ mp 132-133 °C).

9,11-Dimethyl-5,6,8,9,10,11-hexahydrobenzo[h]pyrimido[4,5-b]quinoline-8,10-dione (15): yield 85%; mp 265-267 °C (EtOH); IR cm^{-1} 2946, 2922, 1701, 1653, 1601, 1500, 1466, 1441. ^1H NMR δ 2.99 (s, 4H), 3.47 (s, 3H), 3.80 (s, 3H), 7.26 (m, 1H), 7.40 (m, 2H), 8.22 (s, 1H), 8.34 (m, 1H).. *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.85; H, 5.01; N, 14.62.

Reaction of 6-amino-1,3-dimethyluracil with β -nitrostyrenes. Formation of 6-amino-5-[1-aryl-5-yl]-2-nitroethyl]-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-diones (17a-c). A suspension of 6-amino-1,3-dimethyluracil (**2**) (1.55 g, 10 mmol) and β -nitrostyrenes (**16**) (10 mmol) in ethanol (40 mL) was treated with Et $_3$ N (0.3 mL, 2 mmol). The reaction mixture was refluxed for 12 h. After cooling, the formed precipitate was filtered off, dried, crystallized from the appropriate solvent to give the desired products (**17a-c**).

6-Amino-5-[1-(4-chlorophenyl)-2-nitroethyl]-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (17a): yield 86%, mp 180-182 °C (EtOH); IR cm^{-1} 3463-3232, 1695, 1656, 1603, 1533. ^1H NMR δ 3.35 (s, 3H), 3.50 (s, 3H), 4.7 (dd, $J_1=9\text{ Hz}$, $J_2=13\text{ Hz}$, 1H), 4.8 (br s, 2H, NH $_2$), 5.3 (dd, $J_1 = 6.05\text{ Hz}$, $J_2 = 13.4\text{ Hz}$, 1H), 5.6 (dd, $J_1 = 6\text{ Hz}$, $J_2 = 9$, 1H), 7.25 (d, $J = 8\text{ Hz}$, 2H), 7.4 (d, $J = 8\text{ Hz}$, 2H). *Anal.* Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_4\text{Cl}$: C, 49.64; H, 4.46; N, 16.54. Found: C, 49.82; H, 4.26; N, 16.21.

6-Amino-1,3-dimethyl-5-[2-nitro-1-(4-nitrophenyl)ethyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (17b): yield 75%, mp 188-189 °C (EtOH); IR cm^{-1} 3465-3227, 1692, 1654, 1613, 1590. ^1H NMR δ 3.48 (s, 3H), 3.62 (s, 3H), 4.75 (dd, $J_1=9.2\text{ Hz}$, $J_2=13.5\text{ Hz}$, 1H), 5.25 (br s, 2H, NH $_2$), 5.43 (dd, $J_1 = 6.50\text{ Hz}$, $J_2 = 13.51\text{ Hz}$, 1H), 5.82 (dd, $J_1 = 6.2\text{ Hz}$, $J_2 = 9.2\text{ Hz}$, 1H), 7.45 (d, $J = 8\text{ Hz}$, 2H), 8.2 (d, $J = 8\text{ Hz}$, 2H). *Anal.* Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_6$: C, 48.14; H, 4.33; N, 20.05. Found: C, 48.38; H, 4.25; N, 19.98.

6-Amino-5-[1-(1,3-benzodioxol-5-yl)-2-nitroethyl]-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (17c): yield 83%; mp 139-141°C (H $_2$ O/EtOH, 1:1); ^1H NMR δ 3.30 (s, 3H), 3.50 (s, 3H), 4.60 (m, 1H), 4.75 (br s, 2H), 5.10 (dd, $J_1 = 8.1\text{ Hz}$, $J_2 = 13.2\text{ Hz}$, 1H), 5.40 (dd, $J_1 = 8.4\text{ Hz}$, $J_2 = 13.2$, 1H), 6.0 (s, 4H), 6.75-6.90 (m, 2H), 7.25 (s, 1H). IR cm^{-1} 3410-3252, 1683, 1649, 1600, 1500. *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_6$: C, 51.72; H, 4.63; N, 16.09. Found: C, 51.97; H, 4.53; N, 15.95.

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