HETEROCYCLES, Vol. 55, No. 7, 2001, pp. 1315 - 1321, Received, 21st March, 2001

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

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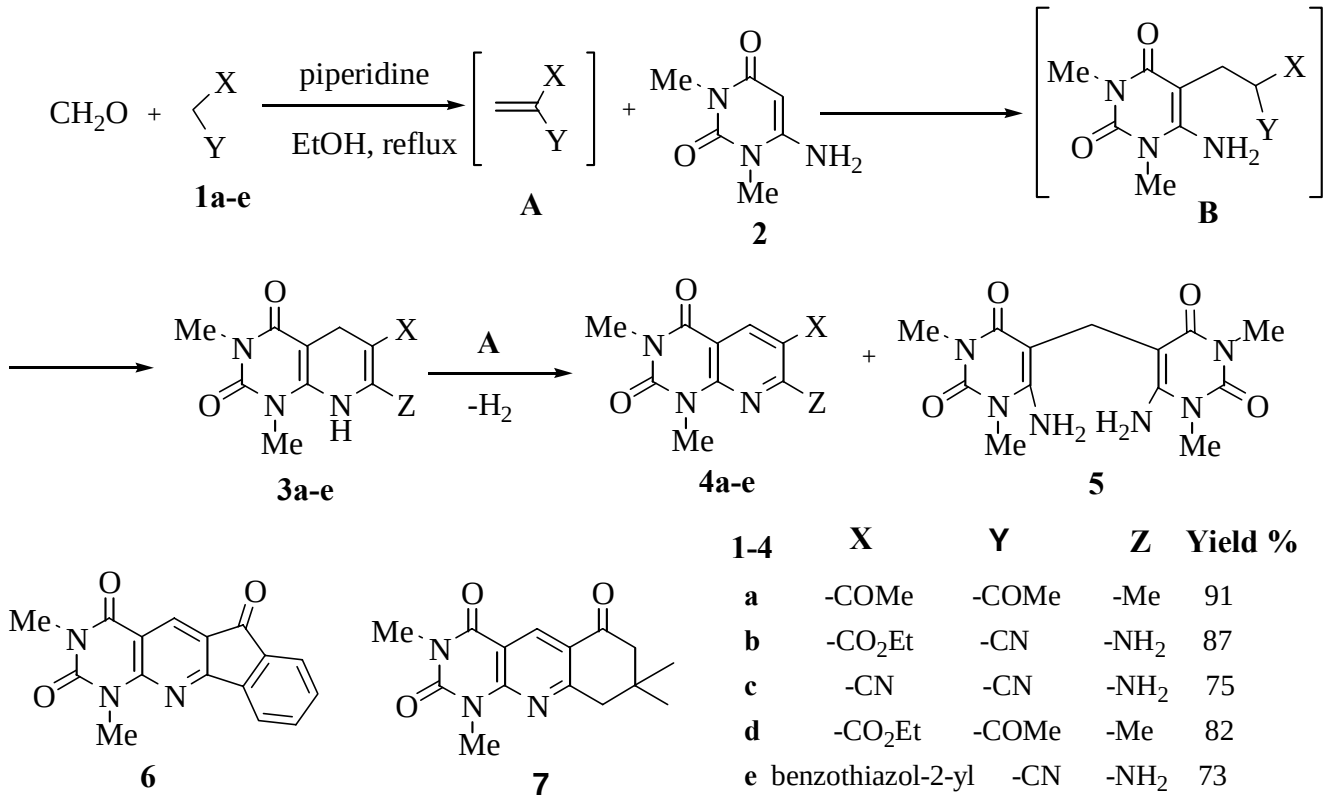
Abstract—The in *situ* formed methylene derivatives of 1,3-dicarbonyl compounds; ethyl cyanoacetate; malononitrile and ketones; react with 6-amino-1,3-dimethyluracil as activated alkenyl derivatives, affording Michael adducts. The adduts simultaneously undergo cyclization to furnish pyrido[2,3-*d*]- 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 reported[9] 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 ^{o}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.



1-4	X	Y	Z	Yield %
a	-COMe	-COMe	-Me	91
b	$-CO_2Et$	-CN	$-NH_2$	87
c	-CN	-CN	$-NH_2$	75
d	$-CO_2Et$	-COMe	-Me	82
e	benzothiazol-2-yl	-CN	$-NH_2$	73

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 dihyropyridines 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 ^{1}H NMR of compound (**4e)**, showed a 1:1 mixture of the two hydrogen-bonding structures, Figure 1.

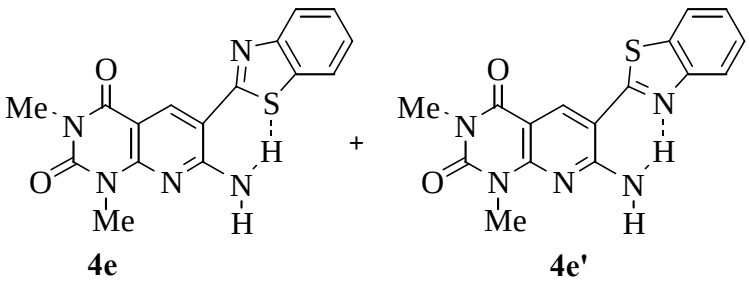


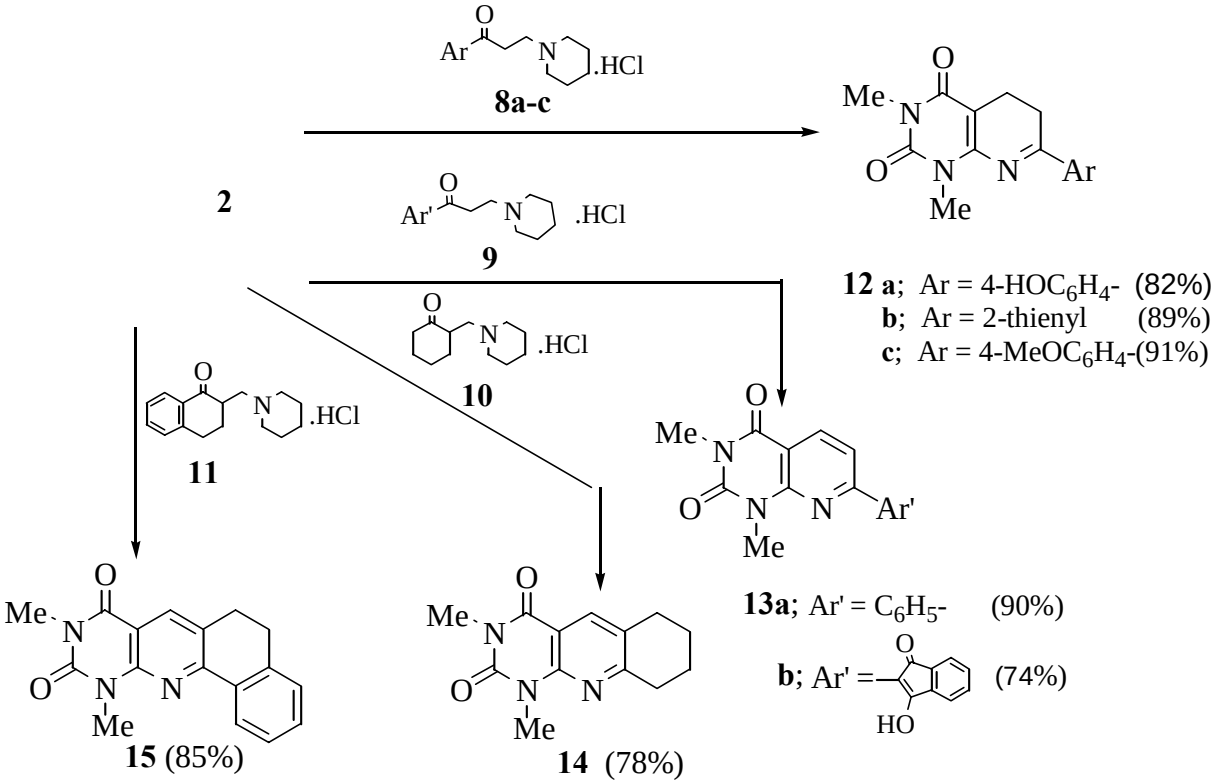
Figure 1

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).

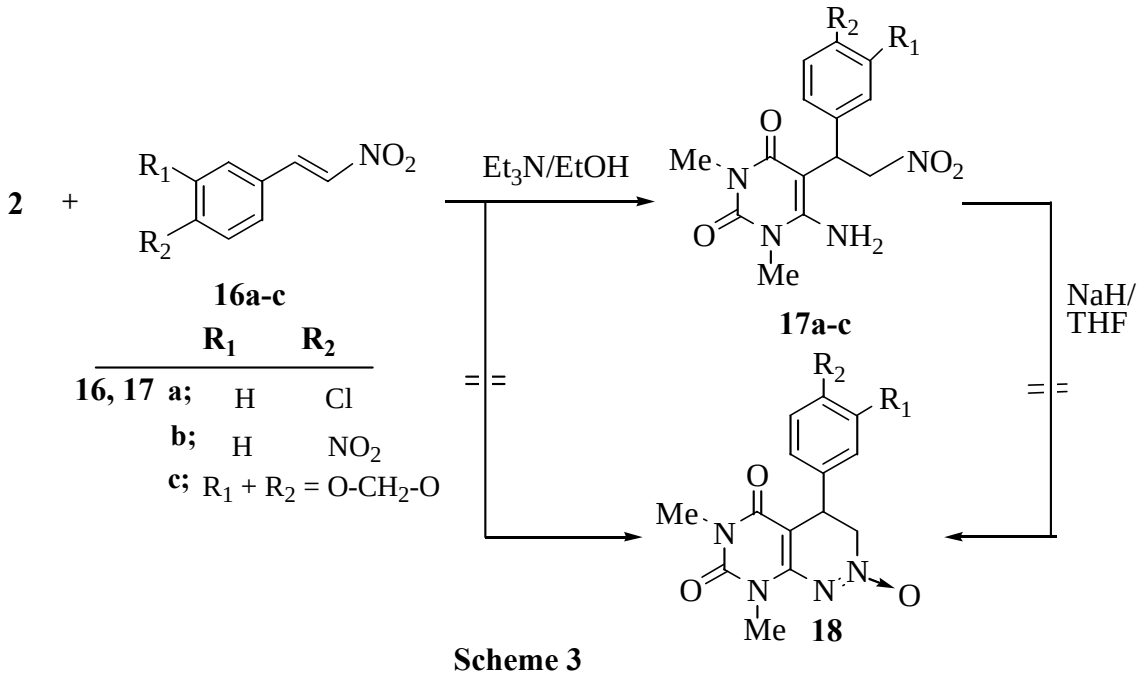
In contrast to the facile aromatization during formation of **13-15**, the ring system of **12a-c** is stable under the same condition. These different outcomes can be attributed to the presence of electron-rich groups, e.g., 2-thienyl, *para*-hydroxyphenyl, *para*-methoxyphenyl, which stabilize the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

The structures of compounds **(12a-c**, **13-15)** were assigned unambiguously by analysis of the ^{1}H 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 Et_3N 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. ^{1}H 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 ºC, 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 ºC (EtOH, lit.,[15] mp 151ºC).

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 ºC (EtOH, lit.,[8] mp 211-212 ºC, lit.,[15] mp 220 ºC).

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

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 ºC (EtOH, lit.,[15] mp 123 ºC).

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 ºC; IR cm^{-1} 3439, 3263, 1717, 1674, 1607, 1588, 1527, 1466. ^{1}H 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, NH_2), 10.8 (bs, 1H, NH). *Anal*. Calcd for $C_{16}H_{13}N_5O_2S$: 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 ºC (AcOH); MS (m/z, rel.int.) 293 (80, M^+), 181 (100). IR cm^{-1} 1709, 1654, 1616, 1595. ^{1}H 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 $C_{16}H_{11}N_3O_3$: 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 ºC (EtOH); IR cm^{-1} 2960, 1716, 1688, 1665, 1597, 1501, 1474, 1413, 1361. ^{1}H 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 $C_{15}H_{17}N_3O_3$: 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 ºC (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 $C_{15}H_{15}N_3O_3$: 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 ºC (EtOH); IR cm^{-1} 3084, 1690, 1636, 1548, 1474, 1416. ^{1}H 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 $C_{13}H_{13}N_3O_2S$: 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 ºC (EtOH); IR cm^{-1} 2953, 1688, 1639, 1617, 1582, 1547.^{1}H 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 $C_{16}H_{17}N_3O_3$: 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 ºC (EtOH, lit.,[16] mp 188º).

7-(1,3-Dioxo-2,3-dihydro-1*H*-2-indenyl)-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (13b): yield 74%; mp 302-304 ºC (DMF); ^{1}H NMR (DMSO-d_6) δ 3.34 (s, 3H overlapped with the water peak of solvent), 3.69 (s, 3H), 5.61 (d, J=9Hz, 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 $C_{18}H_{13}N_3O_4$: 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-(1*H*,3*H*)-dione (14): yield 78%, mp 135-136 ºC (EtOH-Et_2O, lit.,[17] mp 132-133 ºC).

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 ºC (EtOH); IR cm^{-1} 2946, 2922, 1701, 1653, 1601, 1500, 1466, 1441. ^{1}H 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 $C_{17}H_{15}N_3O_2$: 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_3N (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 ºC (EtOH); IR cm^{-1} 3463-3232, 1695, 1656, 1603, 1533. ^{1}H NMR δ 3.35 (s, 3H), 3.50 (s, 3H), 4.7 (dd, J_1=9 Hz, J_2=13 Hz, 1H), 4.8 (br s, 2H, NH_2), 5.3 (dd, J_1 = 6.05 Hz, J_2 = 13.4 Hz, 1H), 5.6 (dd, J_1 = 6 Hz, J_2 = 9, 1H), 7.25 (d, J = 8 Hz, 2H), 7.4 (d, J = 8 Hz, 2H). *Anal*. Calcd for $C_{14}H_{15}N_4O_4Cl$: 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 ºC (EtOH); IR cm^{-1} 3465-3227, 1692, 1654, 1613, 1590. ^{1}H NMR δ 3.48 (s, 3H), 3.62 (s, 3H), 4.75 (dd, J_1=9.2 Hz, J_2=13.5 Hz, 1H), 5.25 (br s, 2H, NH_2), 5.43 (dd, J_1 = 6.50 Hz, J_2 = 13.51 Hz, 1H), 5.82 (dd, J_1 = 6.2 Hz, J_2 = 9.2 1H), 7.45 (d, J = 8 Hz, 2H), 8.2 (d, J = 8 Hz, 2H). *Anal*. Calcd for $C_{14}H_{15}N_5O_6$: 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 139-141ºC (H_2O/EtOH, 1:1); ^{1}H 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 Hz, J_2 = 13.2 Hz, 1H), 5.40 (dd, J_1 = 8.4 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 $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63; N, 16.09. Found: C, 51.97; H, 4.53; N, 15.95.

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