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Synthesis, Characterization, Crystal, and Molecular Structure Analysis of 3,4-dihydro-6-(2-hydroxyphenyl)-5-nitro-4-phenylpyrimidin-2(1*H*)-one

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A novel nitro and 2-hydroxyphenyl functionalized pyrimidinone at C5 and C6, respectively, has been synthesized using 1-(2-hydroxyphenyl)-2-nitroethanone, benzaldehyde, urea, and etidronic acid as a catalyst is described. The synthesized compound characterized by spectroscopic techniques and finally confirmed by X-ray diffraction studies. The molecule crystallizes in the monoclinic crystal class in the space group $P2_1/c$ with cell parameters $a = 11.1070(10)$Å, $b = 8.8210(4)$Å, $c = 15.1110(13)$Å, $\beta = 106.193(2)^\circ$, and $Z = 4$. The pyrimidine ring adopts flattened boat conformation.

Keywords Flat boat; hydrogen bonds; multicomponent; nitro-dihydropyrimidine; Polymeric chains

Introduction

Nowadays, there is considerable interest in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives due to their important pharmacological and therapeutic properties such as antihypertensive, antitumor, anti-inflammatory, and behaving as calcium channel blockers [1–3]. The DHPMs structurally related to the dihydropyridine (DHP) compounds, have been known for a long time. Over the past few years, this class of compounds have received considerable attention after their hypotensive and spasmolytic properties were demonstrated [4, 5]. However, usual DHPs and dihydropyrimidinones contain an ester group in the position 5 of the heterocyclic scaffold [6, 7]. They can also allow other functional groups without loss of basic biological activity. The substitution of nitro group for ester group in the dihydropyrimidines may alter their biological action. Some 4-aryl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-ones exhibit an appreciable biological activity, specifically as calcium channel modulators [8]. Moreover, nitro functionalized

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Table 1. Crystallographic characteristics and the X-ray-data collection and structure-refinement parameters for compound **4** ($C_{16}H_{13}N_3O_4$)

System, sp. gr., Z	Monoclinic, $P2_1/c$, 4
a, b, c Å	11.1070(10), 8.8210(4), 15.1110(13)
β, deg	106.193(2)°
V, Å^3	1421.76(2)
D_x g.cm^{-3}	1.454
Radiation, λ, Å	Mo$K_{\alpha,}$ 0.71073
Monochromator	Graphite
μ, mm^{-1}	0.107
T, K	293
Sample size, mm	0.270 × 0.250 × 0.230
Diffractometer	DIPLabo
Absorption correction, T_{min}, T_{max}	None
θ_{max}, deg	25.03
h, k, l ranges	$-13 \leq h \leq 13$, $-9 \leq k \leq 9$, $-17 \leq l \leq 17$
Number of reflections: measured/unique	4,326/2,351 [R(int) = 0.0205]
Refinement method	Full-matrix least-squares on F^2
Number of refined parameters	209
Final R indices [$I > 2$sigma(I)]	$R_1 = 0.0470$, $wR_2 = 0.1344$
R indices (all data)	$R_1 = 0.0526$, $wR_2 = 0.1422$
S	0.045(8)
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	−0.265/0.238
Programs	SHELXS-97 and SHELXL-97

DHPMs were synthesized and found as pyrimidine nucleoside analogues [9]. Numerous lead derivatives of DHPM compounds have been revealed to be superior in potency and duration of antihypertension activity as compared to usual DHP drugs. Recently Shkurko et al. have found, that several 4-aryl-5-nitro-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives show a high antiarrhythmic activity, the stability of the heterocyclic fragment in 1,4(or 3,4)-dihydropyrimidines and structurally related 1,4-DHPs to aromatization is important for their biological activity [10, 11]. Overall, DHPM compounds were found to have pharmacological profile similar to that of classical DHP calcium channel blocking [6, 7].

Among various approaches known for the synthesis of multifunctionalized DHPMs and related heterocyclic compounds [7], three component biginelli reaction [12], is the most common. However, in Biginelli's reaction 1,3 diketone is used as a synthone. The ability of nitro group to enhance biological and therapeutic activities of certain organic compounds has led to widespread interest in the selective introduction of nitro groups into organic compounds [13]. For example, DHPMs are important heterocycles in both natural and synthetic compounds. The synthesis of 5-nitro and 6-phenyl substituted DHPM have been reported using metal salts as a catalyst [14]. Reports reveal that nitro group containing dihydropyrimidines which might have potential biological activities were less studied [15]. These findings make it highly necessary to develop efficient methods for the synthesis of this class of pyrimidines.

As a part of our ongoing research work, the development of useful synthetic methodologies by employing heterogeneous catalysts [16–18], we herein report the

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Table 2. Bond lengths (Å) and bond angles (°)

Atoms	Length (Å)	Atoms	Length (Å)
N1-C2	1.376(2)	C5-C6	1.352(2)
N1-C6	1.382(2)	C5-N15	1.435(2)
C2-O14	1.239(2)	C6-C7	1.477(2)
C2-N3	1.332(2)	C12-O13	1.343(2)
N3-C4	1.460(2)	N15-O17	1.223(2)
C4-C5	1.513(2)	N15-O16	1.229(2)
C4-C18	1.528(2)		
Atoms	Angle (°)	Atoms	Angle (°)
C2-N1-C6	123.67(1)	C8-C9-C10	119.27(2)
O14-C2-N3	123.97(1)	C11-C10-C9	120.69(2)
O14-C2-N1	120.70(1)	C10-C11-C12	120.57(2)
N3-C2-N1	115.32(1)	O13-C12-C1	121.74(2)
C2-N3-C4	122.82(1)	O13-C12-C7	119.25(2)
N3-C4-C5	106.58(1)	C11-C12-C7	118.98(2)
N3-C4-C18	112.46(1)	O17-N15-O16	122.50(1)
C5-C4-C18	113.67(1)	O17-N15-C5	120.23(1)
C6-C5-N15	121.88(1)	O16-N15-C5	117.21(1)
C6-C5-C4	120.65(1)	C23-C18-C19	118.20(2)
N15-C5-C4	117.36(1)	C23-C18-C4	119.40(2)
C5-C6-N1	116.27(1)	C19-C18-C4	122.40(2)
C5-C6-C7	130.54(1)	C20-C19-C18	120.9(2)
N1-C6-C7	113.19(1)	C21-C20-C19	119.9(2)
C8-C7-C12	119.16(2)	C22-C21-C20	119.6(2)
C8-C7-C6	118.23(1)	C21-C22-C23	120.3(2
C12-C7-C6	122.36(1)	C18-C23-C22	121.1(2)
C9-C8-C7	121.31(2)		

synthesis, crystal and molecular structure analysis of 3,4-dihydro-6-(2-hydroxyphenyl)-5-nitro-4-phenylpyrimidin-2(1*H*)-one using 1-(2-hydroxyphenyl)-2-nitroethanone instead of 1,3 diketone with excellent yield.

Experimental

Chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India) and used without purification. The solvents were analytical grade. THF was distilled over sodium/benzophenone prior to use. Analytical thin layer chromatography (TLC) was performed on Silica Gel 60 F_{254} precoated plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO and TMS was used as an internal reference on a Bruker AVANCE II spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer. IR spectra were recorded on KBr discs, using FTIR-8400 spectrophotometer. The syntheses were carried out in a Questron Technologies Corporation QPro-M microwave synthesizer. Melting points were measured in open capillaries and are uncorrected.

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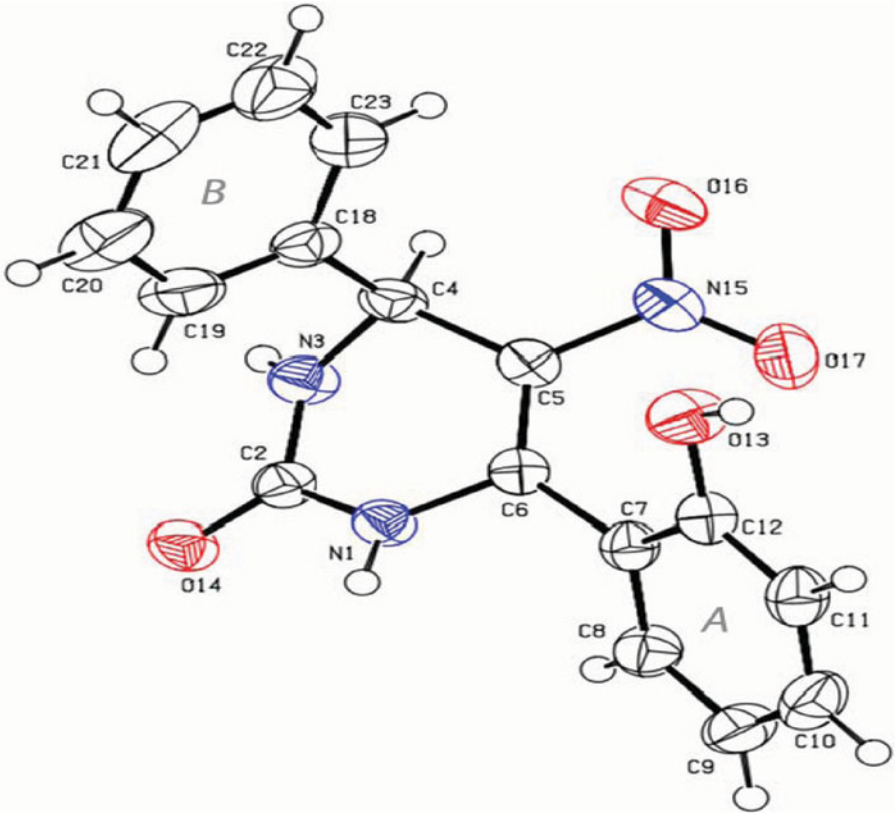

Figure 1. ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

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Spectral Data of 3,4-dihydro-6-(2-hydroxyphenyl)-5-nitro-4-phenylpyrimidin-2(1H)-one 4

Lemon yellow solid; mp 241–243°C; MS *m/z*: 311(M^+); IR (KBr, cm^{-1}): 3624(O–H stretching), 3076(N–H stretching), 1334(C–N stretching), 1674(C=O stretching, ketone), 2927(C−H stretching, Asymmetric), 2833(C–H stretching, Symmetric), 1518(C– NO2); ^{1}H NMR (400 MHz): δ 5.74 (d, 1H, $J = 3.16$ Hz), 6.90-6.94 (t, 2H, Ar-H), 7.24–7.27 (m, 3H, Ar-H), 7.29–7.37 (m, 2H, Ar-H), 7.58 (d, 2H, $J = 7.24$ Hz), 7.68 (s, 1H, NH), 8.97 (s, 1H, NH), 9.64 (s, 1H, OH); ^{13}C NMR (400 MHz): 55.30, 114.54, 116.08, 119.31, 120.38, 126.99, 128.73, 131.61, 142.12, 146.22, 151.53, 166.05; Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50%. Found: C, 61.58; H, 4.08; N, 13.33%.

Procedure for the Development of Single Crystals

The pure, single spot (on TLC) compound was taken in glacial acetic acid and heated with stirring till it dissolved. A small quantity of charcoal was added for decolorizing. The solution was then heated to boiling and immediately filtered while hot in corkable 50 ml conical flask using Whatmann filter paper. The flask was corked and kept for several days. The crystals thus grown by thin film evaporation technique were isolated

Table 3. Hydrogen bonding geometry

Atoms	Length (Å)	Angle(°)	Symmetry codes
N1-H1 . . . O14	2.892(2)	170	*2−x,1−y,−2*
O13-H13 . . . O14	2.799(2)	172	*x,1+y,z*

and washed with chilled methanol. The constitution of 3,4-dihydro-6-(2-hydroxyphenyl)-5-nitro-4-phenylpyrimidin-2(1*H*)-one was supported by IR, ^{1}H and ^{13}C NMR, and mass spectral studies.

Results and Discussions

To a mixture benzaldehyde **2** (10 mmol) and urea **3** (10 mmol) in dry THF (5 ml) was added etidronic acid (0.1 mmol) as a catalyst and stirred it for 5 min at r.t. to this add 1-(2-hydroxyphenyl)-2-nitroethanone **1** (10 mmol) and subjected to microwave irradiation

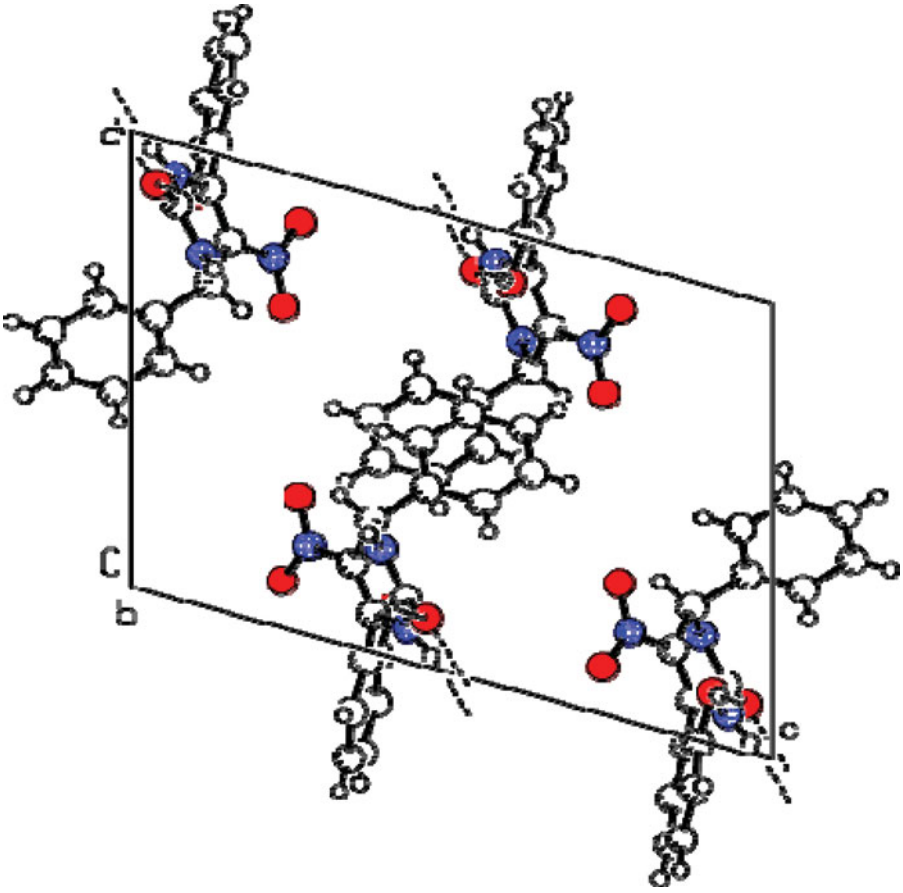

Figure 2. Packing of the molecules when viewed down the *b* axis along *y* direction in bc projection. The dashed lines represent the hydrogen bonds.

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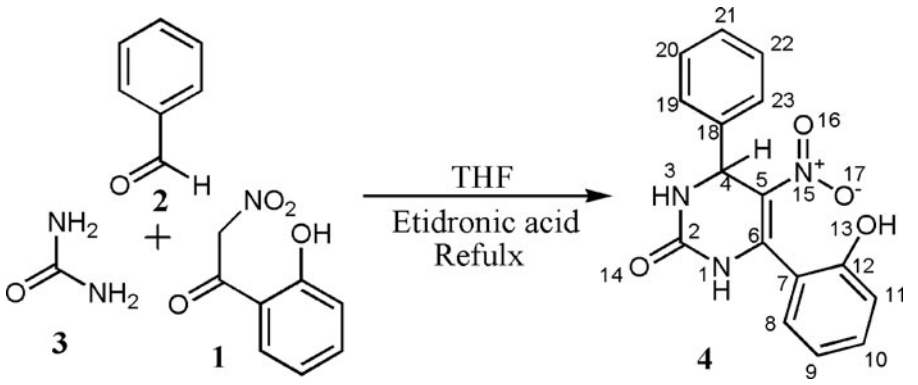

Scheme 1. Synthesis of 5-nitro functionalized dihydropyrimidine.

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at 360 W for 3 min. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The separated solid was washed with water and followed by methanol, filtered, dried, and crystallized from glacial acetic acid to furnish analytically pure lemon yellow product, yield 93%. This indicate that the cyclocondensation reaction of the 1-(2-hydroxyphenyl)-2-nitroethanone **1** with benzaldehyde **2** and urea **3** took place smoothly in the presence of etidronic acid (EDA) in THF resulted in the formation of usual dihydro biginelli product **4** in excellent yield.

A single crystal of suitable size was chosen for X-ray diffraction studies. The data were collected at room temperature on a DIPLabo Image Plate system with graphite monochromated radiation MoK_α. Each exposure of the image plate was set to a period of 400 s. Thirty-six frames of data were collected in the oscillation mode with an oscillation range of 5° and processed using Denzo [19]. The reflections were merged with Scalepack. All the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS-97 [20]. Least-squares refinement using SHELXL-97 [20] with isotropic displacement parameters for all the non-hydrogen atoms converged the residual to 0.1402. Subsequent refinements were carried out with anisotropic thermal parameters for the non-hydrogen atoms. After eight cycles of refinement the residuals converged to 0.0470. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms.

The details of crystal data and refinement are given in Table 1. The bond lengths and bond angles of all the nonhydrogen atoms (Table 2) and are in good agreement with the standard values [21]. Fig. 1 represents the ORTEP [22] diagram of the molecule with thermal ellipsoids drawn at 50% probability. In the title compound $C_{16}H_{13}N_3O_4$, the heterocyclic ring adopts a flattened boat conformation, with a puckering amplitude [23] $Q = 0.3833(2)$Å, $\theta = 106.2(3)^\circ$ and $\Phi = 352.1(3)^\circ$. The phenyl ring ***A*** (C7-C8-C9-C10-C11-C12) has an equatorial orientation with the heterocyclic ring whereas the phenyl ring ***B*** (C18-C19-C20-C21-C22-C23) has an axial orientation.

The nitro group C6-C5-N15-O17 is almost coplanar with the pyrimidine ring as indicated by the torsion angle value of 12.6(3)°. The carbonly group C2 = O14 is indicated by the torsion angle value of 163.58(1)° for C6-N1-C2-O14. The hydroxyl group of phenyl ring ***A*** makes an angle of 121.74(2)° with the C11 and 119.25(2)° with the C7 atoms. The observed bond length of O13 atom of hydroxyl group with C12 was 1.343(2). Further, the hydrogen atom H13 of hydroxyl group make intramolecular hydrogen bond with O14

of heterocyclic ring with the bond length 2.799(2) and bond angle 172. The bond lengths N15-O16, N15-O17, N1-C6, N1-C2, N3-C2, N3-C4 are comparable with other reported compounds [24,25]. The structure exhibits intermolecular hydrogen bonds of the type N-H . . . O and O-H . . . O, which bind the molecules into one-dimensional polymeric chains. The observed hydrogen bonds are listed in Table 3. The packing of the molecules down b axis along the y direction in bc projection is shown in the Fig. 2.

Conclusion

In summary, we have developed a facile method of introducing nitro group into dihydropyrimidine using etidronic acid as an efficient heterogeneous catalyst. This procedure is general and provides nitro functionalized pyrimidine in excellent yield. Further, crystal structures of compound **4** were confirmed by the X-ray single-crystal diffraction analysis. The nitro group appeared almost coplanar with the pyrimidine ring. The resonance-assisted intermolecular hydrogen bond between the carbonyl C2 = O14 and o-hydroxyl group of phenyl ring **A** was examined in crystal structures. The intermolecular hydrogen bonds have vital role in arrangement of molecules into one-dimensional polymeric chains in the observed crystals. Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Center allocated the deposition number CCDC No. 743221.

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