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AN EXPEDITIOUS SYNTHESIS OF PYRROLO[3,4-*d*] - PYRIMIDINE -2,4-DIONE FROM URACIL

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Abstract - An efficient, practical and cost effective synthesis of the title compound has been realized from uracil. The key step is the construction of the pyrrole ring using tosylmethylisocyanide (TosMIC) methodology. The structure of uracil, reaction intermediates and the final product were investigated using density functional calculations.

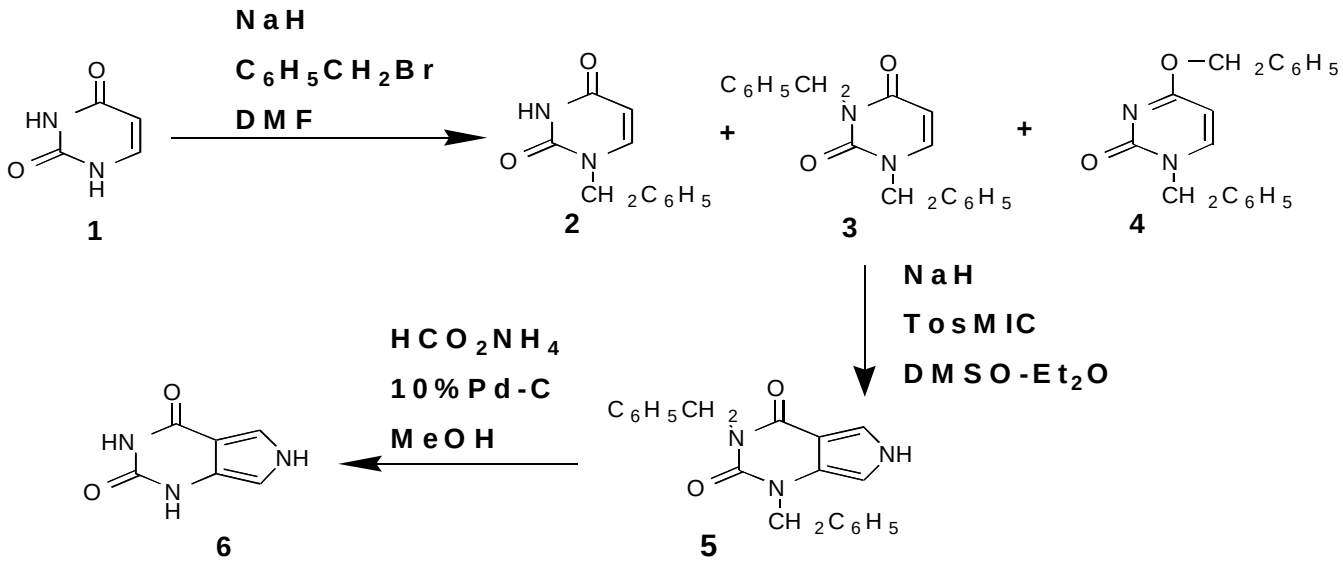
INTRODUCTION

Several pyrrolopyrimidine derivatives have been shown to be potent inhibitors of the purine nucleoside phosphorylase (PNP) salvage enzyme and a few of these are currently in clinical trials for the treatment of T cell cancers, psoriasis and AIDS.[1] Since pyrimidine based molecules offer significant structural diversity, they are important targets for analogue preparation and process development activities. A recent report[2] on the synthesis of similar structures prompted us to report the results of our investigation in this area which utilizes construction of a pyrrole ring system, *in one step*, from a substituted uracil using tosylmethylisocyanide (TosMIC) methodology.

RESULTS AND DISCUSSION

The *N*-alkylation of uracils has been the subject matter of a number of reports.[3] Our synthesis begins with commercially available uracil **(1).**

Scheme



The reaction of uracil with benzyl bromide using potassium carbonate as the base, as described by Kundu *et al.*,[3] gave us very low yields of alkylated products. This observation, in conjunction with the recent isolation of an *O*-alkylated product during *N*-alkylation of thymine,[4] led us to investigate the alkylation of uracil in more detail. Alkylation of uracil was carried out with varying amounts of sodium hydride and benzyl bromide; the results are summarized in Table 1.

Table 1

				Yield (%)		
Entry	Heating Time (h)	NaH (eq)	$C_6H_5CH_2Br$(eq)	**2**	**3**	**4**
1	48	2	23	29	25	9.5
2	24	2	23	25.8	32	15.2
3	48	3	2.3	3	89	3
4	24	3	2.3	26	38.7	10

Three products were isolated from the reaction and characterized by spectral data (IR, NMR and MS spectra). To our knowledge this represents the first report of the isolation of an *O*-alkylated product during the *N*-alkylation of uracil. Good yields (89%) of dibenzylated uracil **(3)** were realized using 3 equivalents of NaH and 2.3 equivalents of benzyl bromide in dimethylformamide for 48 h. It is worth noting that reaction of uracil with benzyl bromide using hexamethyldisilazine (HMDS) in the presence of a catalytic amount of ammonium sulfate[5] gave very low yields of both mono- and dialkylated uracil.

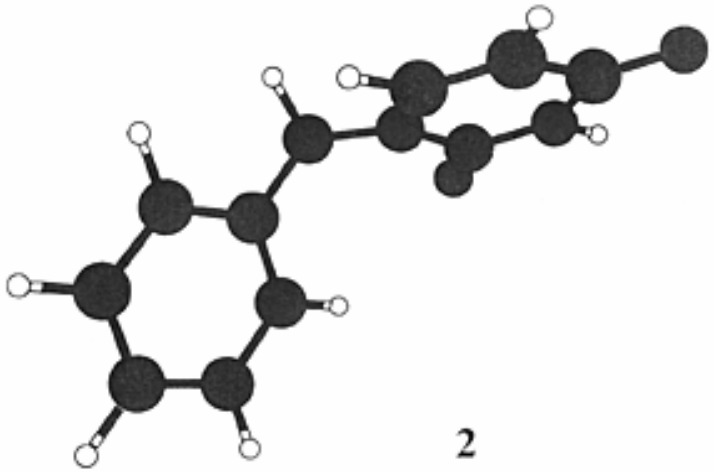
The structures of the monobenzyl **(2)**, dibenzyl **(3)** and *O*-benzyl **(4)** products were investigated using density functional methods (DFT) at the BP/DN** computational level, as implemented in Spartan 5.0.[6] In each case several different conformers were optimized. For the lowest energy conformers of both structures **(3)** and (**4)** the benzene rings are found to be in *anti* orientations relative to the pyrimidine ring (Figure 1) but the *anti* form of **3** is only 1.1 kcal/mol lower in energy than the *syn* form. It is interesting to note that the energy difference between uracil **(1)** and its enol form is 11.5 kcal/mol whereas the energy difference between structures **(3)** and (**4)** is significantly larger, 19.0 kcal/mol. In Table 2, we compare the calculated bond lengths in the pyrimidine ring of **3** with those of the parent uracil compound. It is evident that the introduction of the two phenyl rings does not significantly alter the uracil ring structure. Furthermore, the dipole moments of these two molecules are also in close agreement, (Table 2).

Table 2

COMPARISON OF BOND LENGTH ($A^{\bullet}$) IN PYRIMIDINE RING IN URACIL DERIVATIVES

Structure	N_1C_2	C_2N_3	N_3C_4	C_4C_5	C_5C_6	C_6N_1	Dipole Moment
1	1.400	1.389	1.423	1.456	1.357	1.378	4.43
*eno*1	1.432	1.383	1.313	1.427	1.368	1.358	4.85
Syn 3	1.405	1.396	1.429	1.447	1.355	1.373	4.32
Anti 3	1.405	1.396	1.428	1.445	1.356	1.375	4.37
Syn 5	1.390	1.412	1.422	1.445	1.425	1.388	6.03
Anti 5	1.396	1.417	1.423	1.445	1.424	1.388	6.03
6	1.386	1.404	1.416	1.452	1.430	1.392	6.68

The second step in the synthetic sequence involves the construction of the pyrrole ring system using the procedure developed by Van Leusen *et al.*[7] and subsequently employed by others.[8] Reaction of **3** with TosMIC was carried out using varying amounts of sodium hydride and the results are summarized in Table 3.



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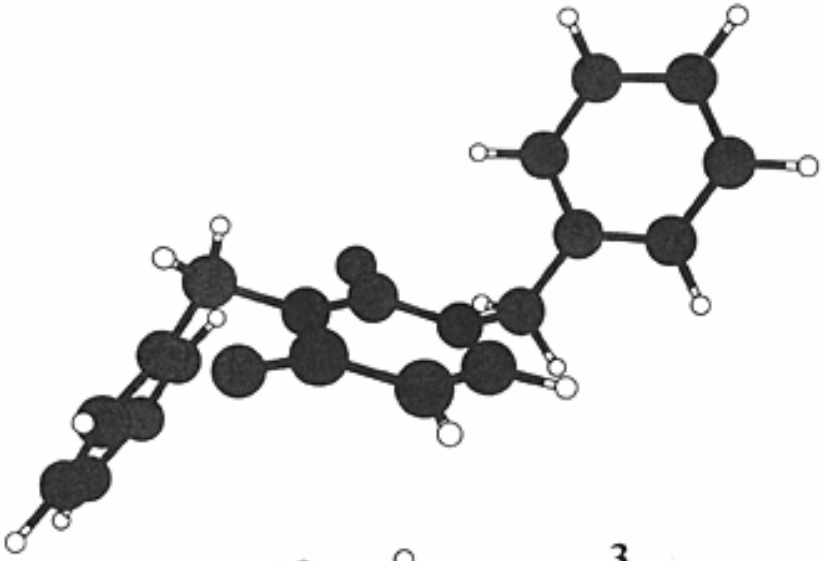

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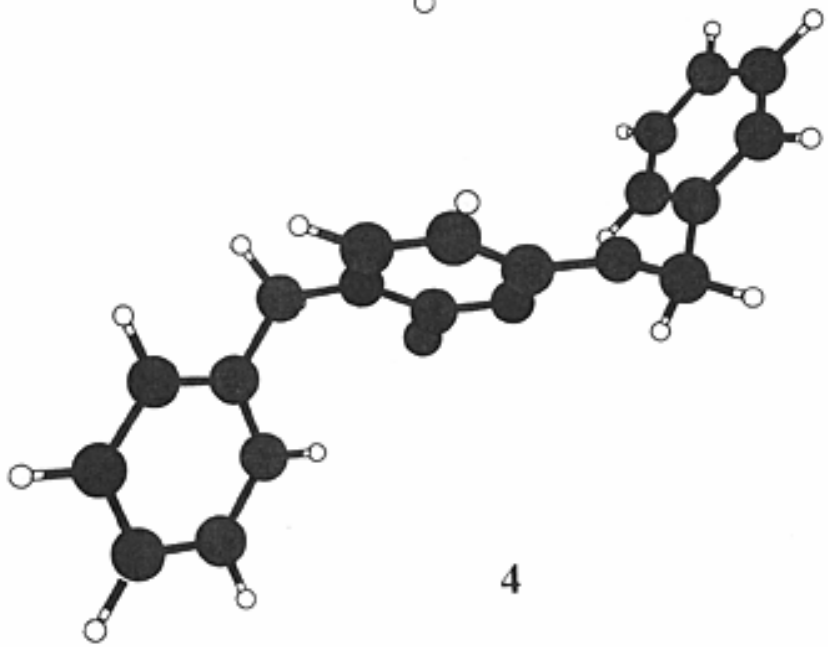

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Figure 1

Table 3

						Yield (%)
Entry	Stirring Time (h)	NaH (eq)	TosMIC(eq)	mL ether/g **3**	mL DMSO/g **3**	of **5**
1	5	2	1.5	30	5	21
2	5	3	1.5	30	5	47
3	15	2.5	2.5	30	5mL acetone	0.02
4	15	3	1.5	40	10	91

Treatment of **3** with 3 equivalents of NaH and 1.5 equivalents of TosMIC generated the pyrrolopyrimidine derivative **(5)** in 91% yield. It should be noted that the use of HMDS as the base in this reaction gave almost no yield of **5**. Our procedure for the construction of the pyrrole ring system, *in a single step*, is clearly more efficient to the multistep procedure used by Majumdar *et al*.[9] for the synthesis of pyrrolopyridimine derivatives.

Two conformers of structure **(5)** were also optimized at the BP/DN** level (Figure 2). Interestingly at this computational level the *syn* form is found to be 2.8 kcal/mol lower in energy than the *anti* form; semiempirical AMI calculations find these two conformers to have nearly the same heat of formation.[10] The values of the bond lengths around the uracil ring in **5** (Table 2), clearly show the loss of the C_5 - C_6 double bond in **3**. There is also a dramatic increase in the calculated dipole moment.

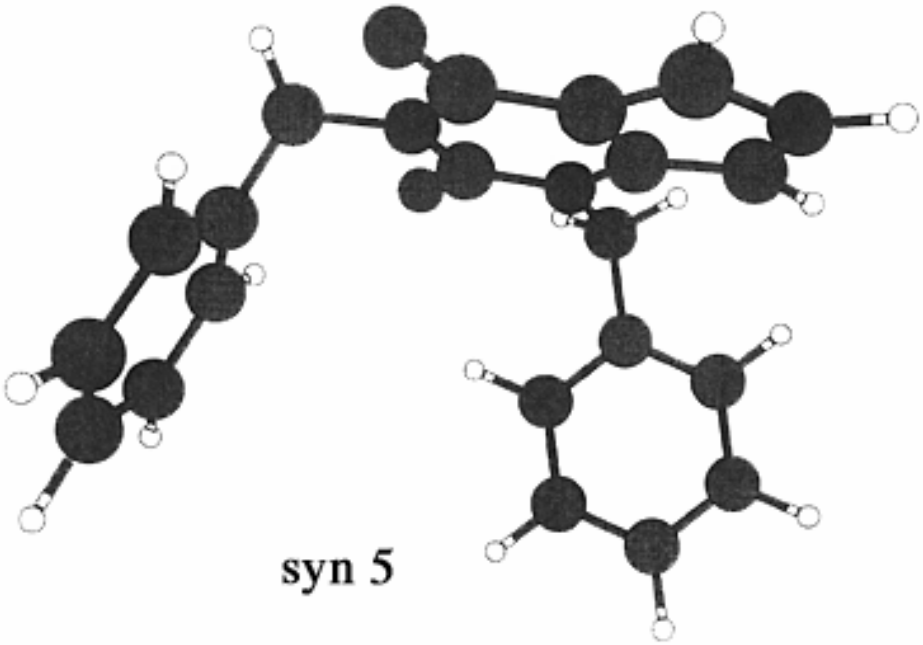
We investigated various conditions for the removal of the benzyl groups in **5**. Treatment of 5 with boron tribromide[11]in refluxing benzene or xylene for different periods of time led either to the recovery of starting material or to an intractable mixture from which no deprotected compound could be isolated. Treatment of **5** with 10% palladium on charcoal and ammonium formate in methanol[12] gave **6** in 66% yield.

The BP/DN* optimized structure of **6** is planar (Figure 2). The small bond length changes in the pyrimidine ring in going from **5** to **6** (removal of phenyl groups) are similar in magnitude but opposite in direction to the changes observed in going from **1** to **2** (introduction of phenyl groups). The same pattern is observed for the calculated dipole moments as well.

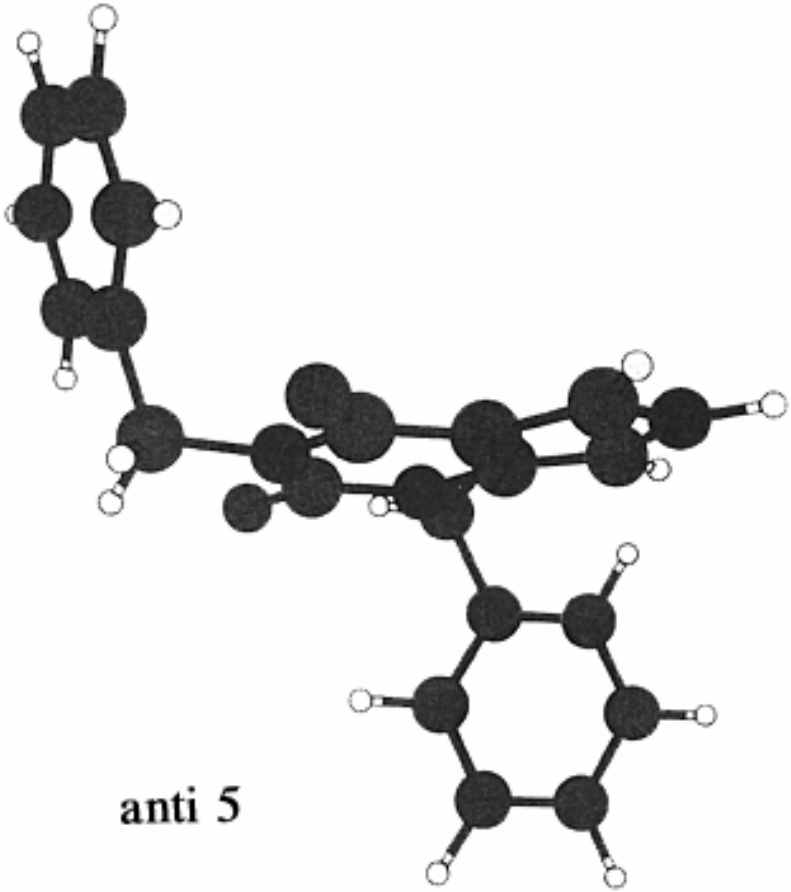
We have developed a convergent synthesis of pyrrolo[3,4-*d*]pyrimidine-2,4-dione from commercially available uracil. This molecule represents the parent structure containing the basic pyrroloprimidine skeleton. The extension of this methodology to other uracil related bases such as cytosine will lead to substituted pyrrolopyrimidine derivatives, some of which have the potential of being immunosuppressive and/or anti-inflammatory agents.

EXPERIMENTAL

GENERAL METHODS. All reactions were carried out under a nitrogen atmosphere. Glassware was oven dried and cooled to rt under a nitrogen atmosphere. Ether was distilled from sodium benzophenone ketyl. DMF and DMSO were distilled under reduced pressure and stored over 4□ molecular sieves. Benzyl bromide was washed with concentrated sulfuric acid, water, 10% sodium carbonate, dried over $MgSO_4$ and distilled in the dark under reduced pressure prior to use. The melting points reported are uncorrected. ^{1}H NMR spectra were measured at 60 and 500 MHz using acetone-d_6 as solvent. TLC was performed on 0.25 mm precoated silica plates (60F-254); the plates were initially examined under UV light and spots were then visualized with iodine and 7% solution of phosphomolybdic acid in ethanol. Silica gel (70-230 mesh) was used for column chromatography.



syn 5



anti 5

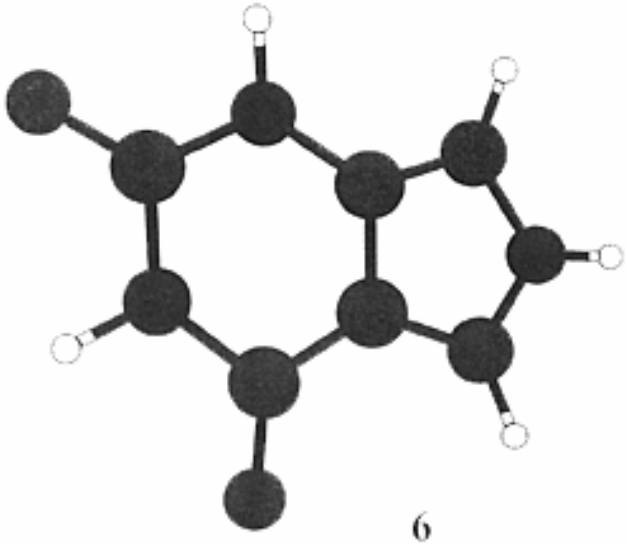


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Figure 2

Computational Methods. All optimizations were performed using the highly efficient Becke-Perdew (BP)density functional method with the numerical DN** basis set, as implemented in Spartan 5.0.[6] This non local (gradient corrected) BP/DN** method[13] incorporates the effects of electron correlation into the optimization and the DN** basis set includes *d*-type polarization functions on all the heavy atoms and *p*-type polarization functions on all the hydrogen atoms. No symmetry constraints were employed during the optimizations.

***N*[1], *N*[3] – Dibenzyluracil (3)**- To sodium hydride (2.135 g, 53.4 mmol) in 60% mineral oil was added pentane (15 mL). After stirring for five min the pentane was decanted off. To the dry sodium hydride under a nitrogen atmosphere was added uracil (2.0 g, 17.8 mmol) in DMF (50 mL). The mixture was subsequently stirred at 100°C for 4 h, then cooled to rt and benzyl bromide (4.86 mL, 40.94 mmol) was added. The reaction mixture was stirred at rt for an additional 2 h and then at 100°C for 48 h. It was then cooled to rt and quenched with water (7 mL). DMF and water were removed under reduced pressure. The crude residue was partitioned between water and ethyl acetate. The ethyl acetate layer was dried ($MgSO_4$) and evaporated to yield a viscous yellow oil. Cooling this oil (0°C) gave a solid (0.107 g, 3%) characterized as compound **(2)**, mp166-167°C (lit.,[3] mp 169-170°C); IR 1701 and 1667; ^{1}HNMR δ 4.96 (2H, s),5.55(1H, d, J = 8 Hz), 7.27(5H, s), 7.62(1H, d, J = 8 Hz) and 9.88(1H, s). Flash chromatography of the mother liquor using hexane-ethyl acetate (2:1) as solvent for elution gave initially compound **(4)** (0.148 g, 3%) as oil, IR 3333.6, 3030, 1736, 1663.7, 1208.3; ^{1}HNMR(DMSO-d_6) δ 4.52 (4H, s), 5.09 (1H, d, J = 10 Hz), 7.32 (5H, s), 7.53 (5H, m), 10.19 (1H, s). Further elution gave **3**, (4.64 g, 89%), mp 67-68°C (lit.,[3]mp 61-62°C); ^{1}H NMR δ 4.98 (2H, s), 5.06 (2H, s), 5.67 (1H, d, J = 10 Hz), 7.39 (10H, m), 7.6 (1H, d, J = 10 Hz), ^{13}C NMR (acetone-d_6); 44.5, 52.6, 101.8, 127.9, 128.6, 128.7, 129.0, 129.1, 129.5, 137.6, 138.5, 144.2, 152.5, 163.2. HRMS Calcd for $C_{18}H_{16}N_2O_2$ $[M + Na]^+$ 315.1109, found 315.1121.

***N*[1], *N*[3] – Dibenzylpyrrolo [3,4-*d*]pyrimidine - 2, 4-dione (5)**

Pentane (10 mL) was added to sodium hydride (0.816 g, 20.4 mmol) in 60% mineral oil. After stirring for 5 min the pentane was decanted off. To the dry sodium hydride was added ether (30 mL) to form a slurry. After 5 min, compound **(3)** (2 g, 6.8 mmol) was added to the slurry and cooled to O°C. A solution of TosMIC (1.99 g, 10.2 mmol) in ether:DMSO (4:1, 50 mL) was added dropwise. When the addition was complete the resulting solution was stirred at rt for 15 h. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) and extracted with ether (1 x 20 mL) and ethyl acetate (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue was purified by column chromatography. Elution with hexane-ethyl acetate (1.5:1) gave **5** (2.12g, 91%),^{1}HNMR δ 5.03 (2H, s), 5.15 (2H, s), 6.61 (1H, s), 7.15 (6H, m), 7.32 (2H, m), 7.38 (3H, m), 10.89 (1H, s); ^{13}C NMR 44.4, 49.2, 101.6, 106.6, 119.1, 127.7,128.1, 128.2, 128.8, 128.9, 129.0, 129.3, 137.9, 139.7, 152.7, 160.3. HRMS Calcd for $C_{20}H_{17}N_3O_2$ $[M + Na]^+$ 354.1218, found 354.1232. Anal. Calcd for $C_{20}H_{27}N_3O_2$: C,72.49; H, 5.17; N, 12.68. Found: C, 72.56; H, 5.21; N, 12.73.

Pyrrolo[3, 4-*d*]pyrimidine - 2, 4 –dione (6)

To compound **(5)** (0.2 g,0.6 mol) were added ammonium formate (20 mL, 0.4 N in dry methanol) and 10% palladium on charcoal catalyst (0.6 g). The mixture was allowed to reflux for 72 h. It was then cooled to rt and passed through celite washing extensively with methanol. Removal of methanol and purification by column chromatography using chloroform-methanol (9:1) as solvent for elution afforded **6** (0.06 g, 66%) as oil. ^{1}HNMR δ 10.05 (1H, s), 8.10 (1H, s), 7.82 (1H, s), 5.19 (1H, s), 5.56 (1H, s). HRMS Calcd for $C_6H_5N_3O_2$ $[M + 1]^+$ 152.0459, found 152.0462. Anal. Calcd for $C_6H_5N_3O_2$: C,47.69; H, 3.33; N, 27.80. Found: C,47.75; H, 3.36; N, 27.77.

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