Synthesis of 5-hetaryluracil derivatives *via* 1,3-dipolar cycloaddition reaction

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**This paper is dedicated to Jacek Młochowski – a good colleague and a friend
on the occasion of his 80th birthday**

Abstract

1,3-Dipolar cycloaddition is a convenient method for construction of various heterocyclic systems. We applied this method for the synthesis 5-hetaryluracil derivatives where substituted uracils played the role of 1,3-dipoles or dipolarophiles. Treatment of the nitrile oxide derived from 5-formyluracil and substituted alkenes gave the appropriate 5-(4,5-dihydroisoxazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-diones, which by oxidation with *N*-bromosuccinimide were transformed into appropriate 5-(isoxazol-3-yl)uracils. When 5-cyanouracil was used as a dipolarophile in the reaction with nitrile oxides, generated from aromatic aldoximes, several 5-(1,2,4-oxadiazol-5-yl)uracils were obtained. An alternative reaction of 5-formyluracil with an excess of nitriles in the presence of cerium ammonium nitrate as an oxidant gave 1,2,4-oxadiazol-3-yl derivatives in moderate yields.
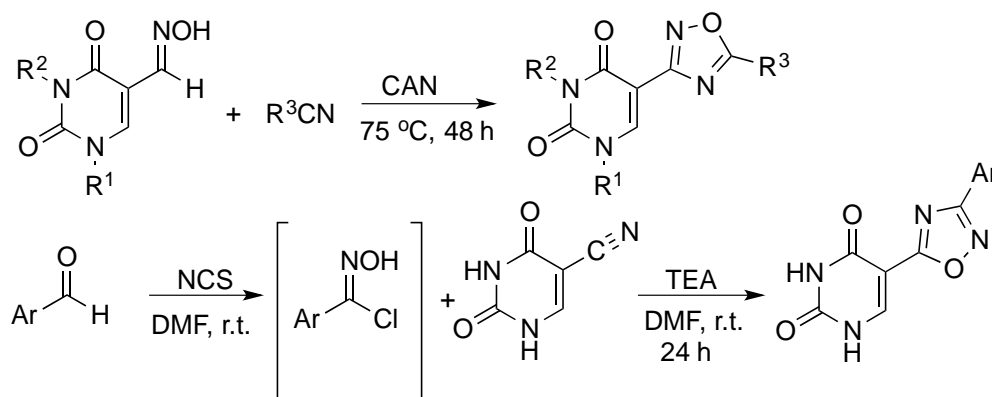
Keywords: Uracil, 1,3-dipolar cycloaddition, 5-cyanouracil, nitrile, nitrile oxides, oxidation

Introduction

5-Substituted uracil derivatives and their nucleosides play an important role in medical treatment. Several uracil derivatives exhibit antitumor, antiparasitic and antifungal activity.[1-3] Promising bioactivity has been observed also in the case of 5-hetaryluracil derivatives. They exhibit anticancer [4-9] and antiviral activity against several DNA and RNA viruses.[10-37] The activity against *Leishmania donovani* promastigotes has also been reported.[38,39] The heterocyclic ring can be bound to a uracil ring using different strategies. One of the first successful syntheses of 5-hetaryluracils was the preparation of 5-(2,5-dimethylpyrrol-1-yl)uracil by condensation of 5-aminouracil hydrochloride with 2,5-hexanedione.[40] The same strategy was applied to obtain 5-pyrrol-1-yl-2'-deoxyuridine[41] or substituted imidazolyl derivatives of uracil. 5-(Imidazol-2-yl)uracil has been obtained in poor yield under Debus-Radziszewski reaction conditions from 5-formyluracil, glyoxal and ammonia.[42] Formamide treated with 5-bromoacetyluracil at elevated temperature produced 5-(imidazol-4-yl)uracil.[41] Similarly 5-bromoacetyluracil reacted with thioamides or thioureas gave 5-(thiazol-4-yl)uracils in yields over 80%.[41,42]

In another approach, cross-coupling reactions in the presence of an organometallic catalyst have been applied in the synthesis of 5-hetaryluracil derivatives. Thus, uracil or uridine containing a halogen atom on C5, usually iodine or bromine, were treated with appropriate organostannanes derived from different heterocycles like furan, thiophene, pyridine in the presence of transition metal complexes producing 5-hetaryl derivatives in satisfactory yields.[43-45] Other types of cross-coupling reaction involving an organometallic catalyst applied in the syntheses of 5-hetaryl derivatives have recently been reviewed.[46] The less explored strategy for the synthesis of 5-hetaryl uracil derivatives involves 1,3-dipolar cycloaddition reactions. Possible manipulation of dipolarophiles (unsaturated compounds like alkenes, alkynes or nitriles) and 1,3-dipoles (i.e. azides, nitrones etc.,) has made this reaction a very powerful tool for the synthesis of 5-membered heterocyclic rings. [46-54]

Several papers have described the formation of 5-(1,2,3-triazol-4-yl)uracil derivatives from 5-ethynyluracil and organic azides in the presence of CuI-sodium ascorbate catalytic system.[46-51] The formation of both possible regioisomers 1,4- and 1,5-disubstituted triazoles, depending on the applied catalyst, has been found. Thus, the use of the copper salt-sodium ascorbate system as a catalyst has led to the formation of 1,4-regioisomers, whereas 1,5-regioisomers were obtained with Cp*RuCl(PPh$_3$)$_2$ employed instead of the standard Cu catalyst.[35] Other 1,3-dipoles have been used less frequently. The addition of nitrile oxides to 2'-deoxy-5-ethynyluridine was used in the construction of 5-(isoxazol-5-yl) derivatives.[52] The nitrile oxide and nitrones derived from 5-formyluracil were applied as 1,3-dipoles in construction of 5-hetaryluracils.[53,54] Other methods like Diels–Alder cycloaddition, cleavage of diazonium salts formed from 5-aminouracil in the presence of azoles have had limited application for single reactions only.[46]

In this paper we report the results of our investigation on the 1,3-dipolar addition reaction where uracil derivatives were used either as dipolarophiles or as 1,3-dipoles. Depending on the reagents used, uracil derivatives bearing a heteroaromatic ring on carbon C5 were obtained directly or the primary forming cycloadduct was oxidized using available oxidants to achieve the desired product.

Results and Discussion

The key substrates 5-formyluracils **3** and **6** were obtained in a sequence of reactions (Scheme 1). To avoid interaction of protons present in the uracil molecule **1** with reactants used in the next steps an uracil derivative was primary alkylated either on both ring N atoms or only on N1. Uracil **1** was alkylated with

dimethyl sulfate under basic conditions and the resulting 1,3-dimethyl uracil **2** was formylated under Vilsmeier-Haack reaction conditions.[55]
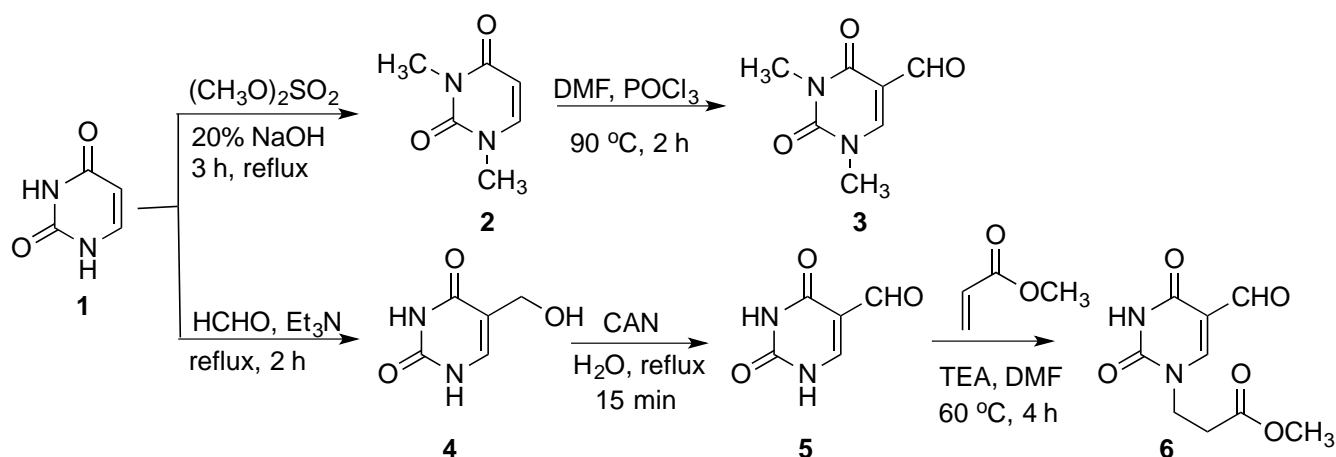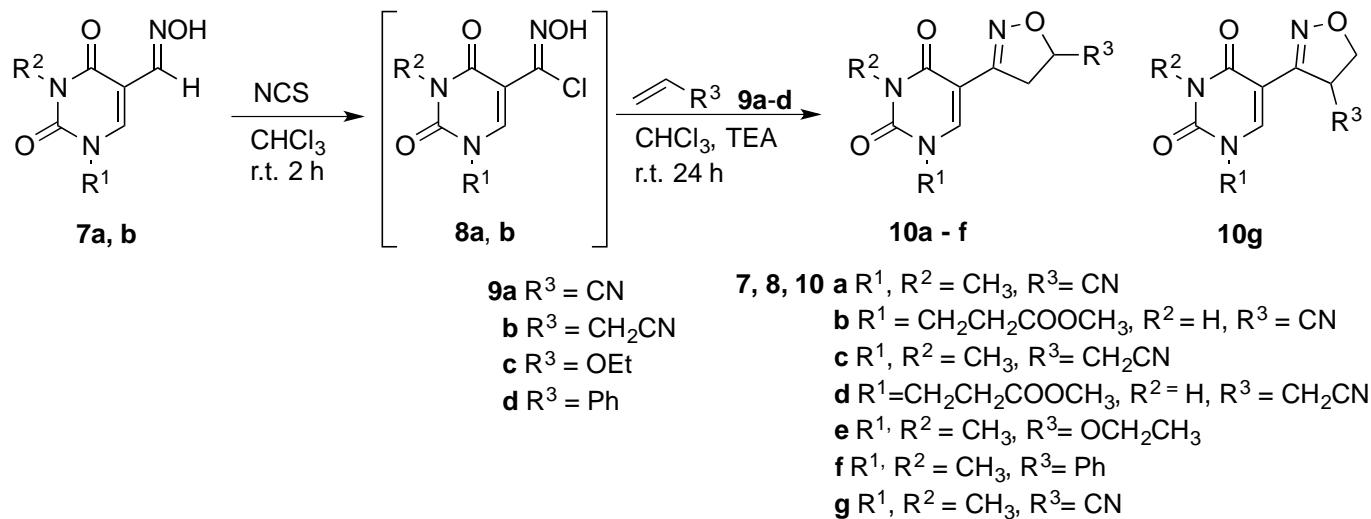

Scheme 1. Synthesis of 5-formyl uracil derivatives.

In a parallel experiment, uracil **1** at first was treated with formaldehyde in the presence of triethylamine and the resulting 5-hydroxymethyluracil **4** was oxidized by ceric ammonium nitrate (CAN)[56] to 5-formyluracil **5**. In both cases the product was obtained in a satisfactory yield exceeding 70% (Scheme 1). Compound **5** was alkylated by methyl acrylate in the presence of triethylamine as a base and product **6** was achieved in 80% yield.[56] Uracil derivatives **3** and **6** were transformed into appropriate oximes **7a**, **b** in the reaction with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol solution (Scheme 2).

3, 7 a R^1, R^2 = CH_3
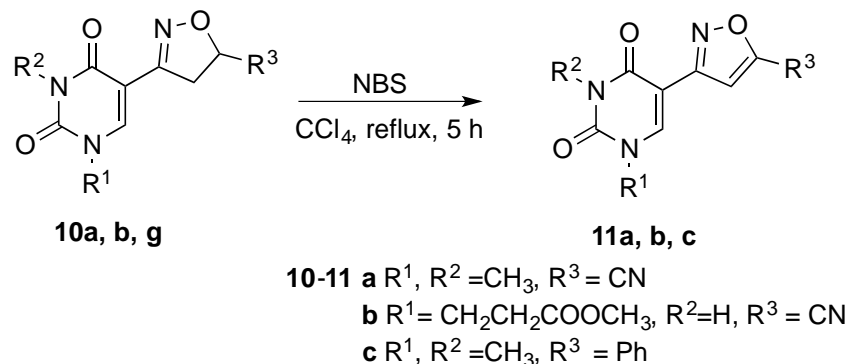**6, 7 b** R^1 = $CH_2CH_2COOCH_3$, R^2 = H
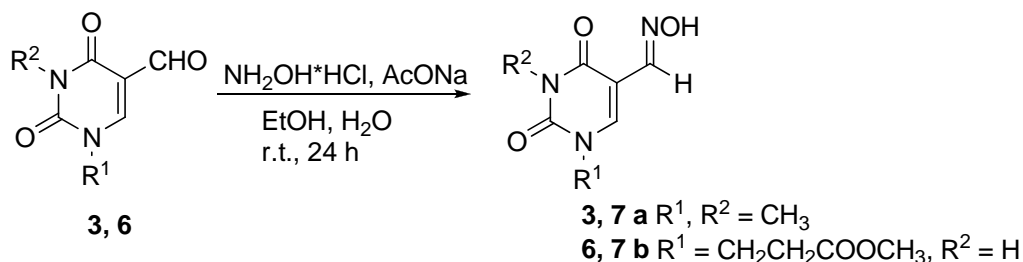
Scheme 2. Synthesis of oximes of 5-formyluracil derivatives.

The oximes **7a** and **7b** were obtained as mixtures of geometrical isomers *E* and *Z*. Separation of the isomers was performed using column chromatography. The ratio of the isomers strongly depended on the reaction time. After 24 hours only isomer *Z* of **7a** was obtained; when the time of reaction was extended to 6 days the isomer equilibrium settled to a ratio of *Z/E* = 58:42 as determined by ^{1}H NMR analysis. In the case of **7b** formation of both isomers was observed from the beginning till the end of the reaction: after 24 h the ratio *Z/E* was 84:16 and after 6 days changed to Z/E = 26:74. Mixtures of stereoisomeric oximes **7a,b** were transformed *in situ* into the corresponding nitrile oxides by a treatment with *N*-chlorosuccinimide (NCS) and triethylamine, these then were directly used in 1,3-dipolar cycloadditions.

9a R^3 = CN
  b R^3 = CH_2CN
  c R^3 = OEt
  d R^3 = Ph

7, 8, 10 a R^1, R^2 = CH_3, R^3= CN
  b R^1 = $CH_2CH_2COOCH_3$, R^2 = H, R^3 = CN
  c R^1, R^2 = CH_3, R^3= CH_2CN
  d R^1=$CH_2CH_2COOCH_3$, R^2 = H, R^3 = CH_2CN
  e R^1, R^2 = CH_3, R^3= OCH_2CH_3
  f R^1, R^2 = CH_3, R^3= Ph
  g R^1, R^2 = CH_3, R^3= CN

Scheme 3. Cycloaddition of nitrile oxides to dipolarophiles **9a–9d**.

To the dipolarophiles (**9a-d**) we applied unsaturated compounds containing different substituents. In the case of nitrile **9a** the double bond is conjugated with a cyano group but it is isolated in **9b**. The cycloaddition occurred in satisfactory yield and in both cases the carbon-carbon double bond participated whereas the nitrile group remained unchanged. We assume that the energy of interacting frontier orbitals of nitrile oxides derived from **8a,b** correlate better with orbitals of the double bond present in dipolarophiles **9a-b** than with HOMO/LUMO orbitals of nitrile group. In the case of acrylonitrile **9a** we observed also traces of a regioisomeric cycloadduct, namely 1,3-dimethyl-5-(4-cyano-4,5-dihydroisoxazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **10g** in the post reaction mixture. The obtained cycloadducts are non-aromatic compounds. Among tested oxidizing agents like 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), iodine and *N*-bromosuccinimide (NBS) only the latter gave desired 5-(5-substituted-isoxazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-diones **11** in 40-45% yield (Scheme 4).

10a, b, g   **11a, b, c**

10-11 a R^1, R^2 =CH_3, R^3 = CN
  b R^1= $CH_2CH_2COOCH_3$, R^2=H, R^3 = CN
 **c** R^1, R^2 =CH_3, R^3 = Ph

Scheme 4. Aromatization of selected cycloadducts by oxidation with NBS.

For the synthesis of 5-(1,2,4-oxadiazol-3-yl)uracil derivatives we explored a synthetic pathway where uracil derived aldoximes were directly treated, in the presence of cerium ammonium nitrate, with an excess of the appropriate nitrile **12**, used as a solvent.[58] The procedure is simplified in comparison to that described above for the synthesis of 5-(isoxazol-3-yl)uracils. Nevertheless, also in this case, yields of isolated products were only moderate (Scheme 5).
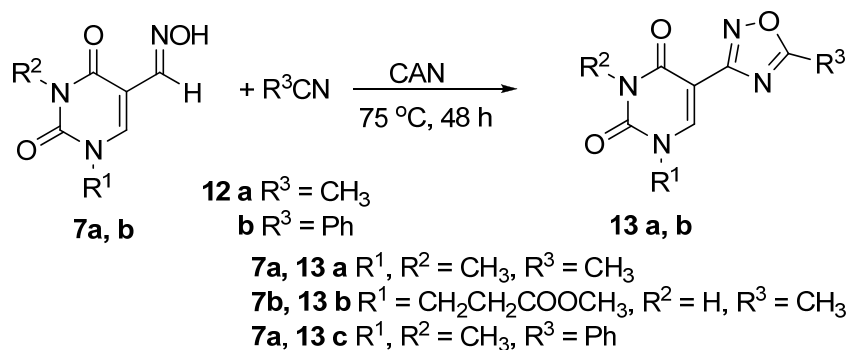
Scheme 5. An alternative approach toward the synthesis of 5-hetaryluracils.

The 1,3-dipolar cycloaddition reaction of nitrile oxides to 5-ethynyl uracils has been described in the chemical literature as a method for the preparation of isoxazoles.[36] We decided to use 5-cyanouracil **16**, a new commercially available dipolarophile (Scheme 6) for a similar purpose. In this case we generated the nitrile oxide from aromatic aldoximes **14**. Application of 5-cyanouracil as a dipolarophile in reactions with aromatic nitrile oxides opened up a new simple route to 5-(1,2,4-oxadiazol-5-yl)uracil derivatives. The cycloaddition reaction was carried out in DMF solution with NCS as the chlorinating agent and triethylamine as a base at room temperature for 24 h. The aldoximes were used in a slight excess in respect to the 5-cyanouracil. Isolation of cycloadducts **17** using column chromatography gave pure products in moderate yields of 44-51%.
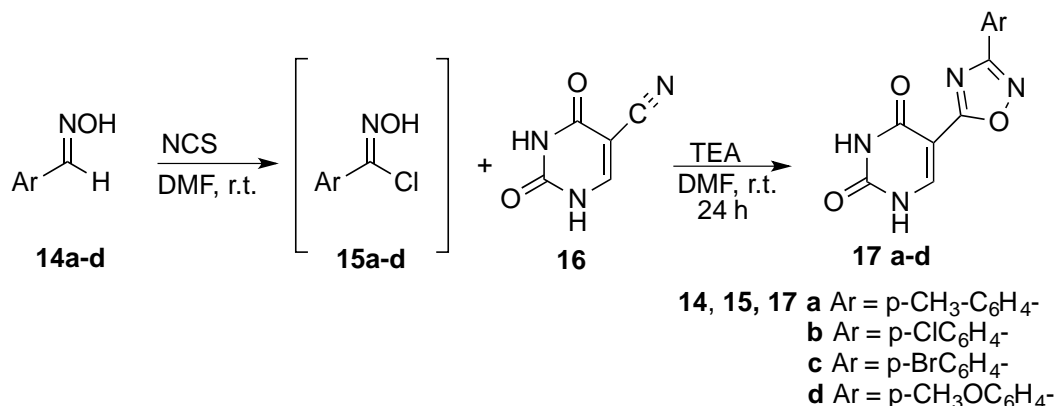
Scheme 6. Synthesis of 5-(1,2,4-oxadiazo-5-yl)uracil derivatives.

Conclusions

We have devised a synthetic pathway for the preparation of various 5-hetaryluracil derivatives using 1,3-dipolar cycloaddition reaction. We showed that the studied uracil derivatives could be used either as a source of 1,3-dipoles or dipolarophiles. Nitrile oxides generated *in situ* from substituted 5-formyluracil oximes treated with alkenes as the dipolarophiles afforded cycloadducts in moderate yields of 40-60%. An oxidation step is necessary to obtain isoxazole derivatives. We also showed that treatment of 5-formyluracil oximes with nitriles in the presence of ceric ammonium nitrate as an oxidizer leads directly to the respective 5-(oxadiazol-3-yl)uracils. 5-Cyanouracil applied as dipolarophile and reacting with aromatic aldoximes gives 5-(oxadiazol-5-yl)uracil derivatives in satisfactory yields. In summary we proved that different types of 5-heteroaryluracil derivatives could be synthesized by manipulation of 1,3-dipole and dipolarophile structures. The cycloadducts

were obtained in moderate yields regardless of the cycloaddition method applied. Traces of unidentified compounds near to the base line of TLC plates were observed. These are probably the products of nitrile oxide dimerization or isomerisation, like furoxanes or isocyanates etc. In our opinion the moderate yields obtained can be attributed mainly to the crystallization used as a final purification method.

Experimental Section

General. All reagents and solvents of analytical grade were purchased from commercial suppliers. Most of them were used without further purification except for CH_2Cl_2, which was distilled prior to use and for DMF purified by distillation and dried over activated 3A molecular sieves. Also anhydrous Et_3N was dried through storage over activated 4A molecular sieves. All reactions were monitored by TLC using silica-gel-coated aluminium plates with a fluorescence indicator (SiO_2 60, F_{254}) and spots were visualized by UV light. Column chromatography was performed using silica gel packed columns (particle size 0.040-0.063 mm, Merck). The purified products were obtained as the colorless solids. ^{1}H NMR spectra were recorded at Varian 600 MHz System or Varian Inova 300 MHz spectrometer. ^{13}C NMR spectra were recorded at 150 MHz or 75 MHz, respectively. Chemical shifts were measured relative to residual non-deuterated solvent signals. Melting points were determined using a Boethius M HMK hot-stage apparatus. IR spectra by ATR (Attenuated Total Reflection) technique were recorded on Nicolet 6700 FT-IR Spectrometer (Thermo Scientific). High-resolution electrospray ionization mass spectroscopy (ESI-MS) experiments were performed using a Waters Xevo G2 QTOF instrument equipped with an injection system (cone voltage 50 V; source 120 °C). 5-Formyl-1,3-dimethyluracil (**3**) was prepared in 72% yield according to reported method.[55] 5-(Hydroxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**)[56] and 2,4-Dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (**5**)[56] were obtained in yield 95% and 73%, respectively. The recorded NMR data for **3**, **4**, and **5** were in accordance with reported data. *N*1-Alkylation of 5-formyluracil using methyl acrylate was performed according to procedure reported earlier.[57]

Methyl 3-(5-formyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (6). To a suspension of 5-formyl uracil **5** (1.4g, 10 mmol) in anhydrous DMF (25 mL) triethylamine (1.01 g, 1.4 mL, 10 mmol) was added and the resulting solution was heated in an oil bath at 60 °C for 0.5 h. Methyl acrylate (0.56 mL, 6 mmol) was added dropwise and the mixture was heated for 2 h, then the next portion of methyl acrylate (6 mmol) was added and the reaction was continued for another 2 h. The volatiles were removed at reduced pressure and the residue was crystallized from EtOAc. Yield 1.81 g (79%), mp. 153-155 °C (EtOAc). FT IR: 3052, 1687, 1667, 1602, 1452, 1207 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.76 (t, 2H, *J* 6.6, CH$_2$), 3.60 (s, 3H, OCH$_3$), 4.04 (t, 2H, *J* 6.6, CH$_2$), 8.47 (s, 1H, H-6), 9.77 (s, 1H, CH=O), 11.76 (s, 1H, N3-H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 32.1, 45.1, 51.1, 109.9, 150.0, 152.4, 162.2, 171.2, 186.2. Anal. Calcd for $C_9H_{10}N_2O_5$ (226.19): C, 47.97; H, 4.46; N, 12.39%. Found: C, 48.21; H, 4. 26; N, 12.16%.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde oximes (7a). A solution of sodium acetate trihydrate (0.41 g, 3 mmol) and $NH_2OH \cdot HCl$ (0.37 g, 2.25 mmola) in H_2O (3 mL) was added to a suspension of uracil **3** (0.34 g, 2 mmol) in EtOH (5 mL) while stirring at room temperature. After a few minutes a white solid started to precipitate and the stirring was continued for 24 h. A progress of the reaction was monitored by TLC (EtOAc : *n*-hexane, 2:1). The solid consisting of a mixture of two isomeric oximes was isolated in yield of 93% (0.34 g). The E/Z isomers were separated on silica gel column using MeOH : CHCl$_3$ (5 : 95, v/v) as an eluent. When the time of synthesis was extended to 48 h *Z*-isomer was obtained exclusively. ***Z*-Isomer**: yield 73% (0.27 g), mp 198-199 °C (MeOH). FT IR: 3289, 1702, 1640, 1614, 1444, 942 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.18 (s, 3H, N1-CH$_3$), 3.38 (s, 3H, N3-CH$_3$), 7.86 (s, 1H, H-6), 8.09 (s, 1H, CH=N), 11.06 (s,

1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.5, 36.7, 104.7, 141.1, 141.4, 150.9, 161.4. Anal. Calcd for $C_7H_9N_3O_3$ (183.16): C, 45.90; H, 4.95; N, 22.94%. Found: C, 45.56; H, 4.90; N, 22.68%. *E*-**Isomer**: yield 27% (0.09 g), mp 140-141 °C. FT IR: 3287, 1700, 1643, 1610, 1442, 943 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.20 (s, 3H, N1-CH$_3$), 3.38 (s, 3H, N3-CH$_3$), 7.34 (s, 1H, H-6), 8.99 (s, 1H, CH=N), 11.83 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 27.7, 37.2, 103.2, 136.6, 147.4, 150.4, 161.8. Anal. Calcd for $C_7H_9N_3O_3$ (183.16): C, 45.90; H, 4.95; N, 22.94%. Found: C, 45.68; H, 4.89; N, 22.66%.

Methyl 3-(5-((hydroxyimino)methyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (7b). A solution of AcONa*3H$_2$O (1.63 g, 12 mmol) and NH$_2$OH*HCl (0.97 g, 14 mmol) in H$_2$O (10 mL) was added while stirring to a suspension of **6** (2.29 g, 10 mmol) in EtOH (20 mL). After a few minutes the suspension disappeared and then white solid started to precipitate from a solution. The stirring was continued for 24 h. The solid was filtered off and purified on silica gel column using a mixture of CHCl$_3$:MeOH (95:5, v/v) as an eluent. The separated isomers were crystallized from MeOH. *Z*-**Isomer**: yield 84% (1.81 g), mp 179-180 °C (MeOH). FT IR: 3296, 1679, 1467, 1208, 948 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.73 (t, 2H, *J* 6.6, CH$_2$), 3.60 (s, 3H, OCH$_3$), 3.97 (t, 2H, *J* 6.6, CH$_2$), 7.81 (s, 1H, H-6), 8.05 (s, 1H, CH=N), 11.07 (s, 1H, OH), 11.57 (s, 1H, N3-H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 32.4, 44.5, 51.5, 105.7, 140.9, 142.4, 150.2, 162.1, 171.3. Anal. Calcd for $C_9H_{11}N_3O_5$ (241.20): C, 44.82; H, 4.60; N, 17.42%. Found: C, 44.58; H, 4.83; N, 17.38%. *E*-**Isomer**: yield 16% (0.34 g), mp 189-190 °C (MeOH). FT IR: 3295, 1677, 1464, 1206, 945 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.77-2.68 (m, 2H, CH$_2$), 3.59 (s, 3H, OCH$_3$), 4.01-3.91 (m, 2H, CH$_2$), 7.28 (s, 1H, H-6), 9.03 (s, 1H, CH=N), 11.64 (s, 1H, OH), 11.82 (s, 1H, N3-H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 32.5, 45.1, 51.6, 104.1, 136.2, 149.1, 149.7, 162.6, 171.2. Anal. Calcd for $C_9H_{11}N_3O_5$ (241.20): C, 44.82; H, 4.60; N, 17.42%. Found: C, 44.60; H, 4.58; N, 17.28%.

General procedure for preparation of 5-(4,5-Dihydroisoxazol-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones (10a-f). To a suspension of oxime **7a** or **7b** (0.77 mmol) in CHCl$_3$ or DMF (3 mL) *N*-chlorosuccinimide (0.11 g, 0.85 mmol) and concentrated hydrochloric acid (1 drop) was added while stirring. An appropriate dipolarophile **9a**-**d** (0.7 mmol) and triethylamine (0.11 mL, 0.77 mmol) were added after 2 h. The stirring was continued for 24 h. The volatiles were removed under reduced pressure and the residue was purified on silica gel column (EtOAc : *n*-hexane, 3:1, v/v).

3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,5-dihydroisoxazole-5-carbonitrile (10a). Yield 65% (0.11 g), mp 177-178 °C (MeOH). FT IR: 2998, 2830, 2250, 1724, 1655, 1594, 1481, 1373 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.20 (s, 3H, N1-CH$_3$), 3.39 (s, 3H, N3-CH$_3$), 3.80-3.73 (m, 2H, H$_A$-4', H$_B$-4'), 5.73 (dd, 1H, *J* 9.0, 6.6, H-5'), 8.35 (s, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 27.7 (N1-CH$_3$), 36.9 (N3-CH$_3$), 41.9 (C-4'), 66.3 (C-5'), 100.4 (C-5), 118.5 (CN), 145.5 (C-6), 150.7 (C-2), 153.3 (C-3'), 160.2 (C-4). Anal. Calcd for $C_{10}H_{10}N_4O_3$ (234.21): C, 51.28; H, 4.30; N, 23.92%. Found: C, 51.08; H, 4.13; N, 23.68%.

Methyl 3-(5-(5-cyano-4,5-dihydroisoxazol-3-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (10b). Yield 56% (0.12 g), mp 162-165 °C (MeOH). FT IR: 3166, 3049, 2823, 2250, 1737, 1683, 1464 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.75 (t, 2H, *J* 6.4, CH$_2$COOCH$_3$), 3.61 (s, 3H, OCH$_3$), 11.71 (s, 1H, N3-H), 3.74 (d, 2H, *J* 7.8, H$_A$-4', H$_B$-4'), 3.99 (t, 2H, *J* 6.4, N1-CH$_2$), 5.70 (t, 1H, *J* 7.8, H-5'), 8.29 (s, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 32.3 (CH$_2$COOCH$_3$), 41.9 (C-4'), 44.5 (N-CH$_2$), 51.6 (OCH$_3$), 66.2 (C-5'), 101.4 (C-5), 118.5 (CN), 147.0 (C-6), 150.0 (C-2), 153.0 (C-3'), 161.0 (C-4), 171.2 (COOCH$_3$). Anal. Calcd for $C_{12}H_{12}N_4O_5$ (292.25): C, 49.32; H, 4.14; N, 19.17%. Found: C, 49.58; H, 4.03; N, 18.95%.

2-(3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,5-dihydroisoxazol-5-yl)acetonitrile (10c). Yield 35% (0.06 g), mp 206-208 °C (EtOH). FT IR: 3059, 2950, 2256, 1694, 1640, 1449, 1343 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.00-2.80 (m, 2H, CH$_2$CN), 3.24-3.13 (m, 4H, H$_B$-4', N1-CH$_3$), 3.39 (s, 3H, N3-CH$_3$), 3.54 (dd, 1H, *J* 18.0, 10.5, H$_A$-4'), 4.94-4.82 (m, 1H, H-5'), 8.25 (s, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm):

22.7 (CH$_2$CN), 27.6 (N1-CH$_3$), 36.8 (N3-CH$_3$), 41.0 (C-4'), 75.0 (C-5'), 101.6 (C-5), 117.9 (CN), 144.3 (C-6), 150.8 (C-2), 152.7 (C-3'), 160.4 (C-4). ESI-MS [M+H]$^+$ calcd. for C$_{11}$H$_{13}$N$_4$O$_3$(249.0989). Found 249.1011. Anal. Calcd for C$_{11}$H$_{12}$N$_4$O$_3$ (248.24): C, 53.22; H, 4.87; N, 22.57%. Found: C, 53.08; H, 4.63; N, 22.35%.

Methyl 3-(5-(5-(cyanomethyl)-4,5-dihydroisoxazol-3-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (10d). Yield 38% (0.08 g), mp 181-183 °C (EtOH). FT IR: 3172, 3051, 2250, 1735, 1708, 1651, 1457, 1204 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ (ppm): 2.74 (t, 2H, *J* 6.6, CH$_2$COOCH$_3$), 2.99-2.81 (m, 2H, CH$_2$CN), 3.17 (dd, 1H, *J* 17.7, 6.9, H$_B$-4'), 3.51 (dd, 1H, *J* 17.7, 10.2, H$_A$-4'), 3.61 (s, 3H, OCH$_3$), 3.99 (t, 2H, *J* 6.6, N1-CH$_2$), 4.93-4.80 (m, 1H, H-5'), 8.19 (s, 1H, H-6), 11.76 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ (ppm): 23.7 (CH$_2$CN), 32.4 (CH$_2$COOCH$_3$), 41.0 (C-4'), 44.5 (N1-CH$_2$), 51.6 (OCH$_3$), 75.0 (C-5'), 102.7 (C-5), 117.9 (CN), 145.8 (C-6), 150.1 (C-2), 152.3 (C-3'), 161.2 (C-4), 171.4 (COOCH$_3$). ESI-MS [M+H]$^+$ calcd. for C$_{13}$H$_{15}$N$_4$O$_5$ (307.1043). Found 307.0998.

5-(5-Ethoxy-4,5-dihydroisoxazol-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (10e). Yield 47% (0.08 g), mp 177-179 °C (EtOH). FT IR: 3067, 2977, 1647, 1457, 1345 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 3.30 (dd, 1H, *J* 18.0, 1.8 Hz, H$_B$-4'), 3.37 (s, 3H, N1-CH$_3$), 3.47 (s, 3H, N3-CH$_3$), 3.56 (dd, 1H, *J* 18.0, 7.2, H$_A$-4'), 3.58 (dq, 1H, *J* 9.6, 7.2, OCH$_{2B}$CH$_3$), 3.86 (dq, 1H, *J* 9.6, 7.2 Hz, OCH$_{2A}$CH$_3$), 5.61 (dd, 1H, *J* 7.2, 1.8, H-5'), 7.96 (s, 1H, H-6). ^{13}C NMR (150 MHz, CDCl$_3$) δ (ppm): 15.0 (OCH$_2$<u>CH$_3$</u>), 28.1 (N1-CH$_3$), 37.5 (N3-CH$_3$), 43.1 (C-4'), 63.8, (O<u>CH$_2$</u>CH$_3$), 103.2 (C-5'), 103.6 (C-5), 145.9 (C-6), 151.2 (C-2), 153.1 (C-3'), 161.1 (C-4). Anal. Calcd for C$_{11}$H$_{15}$N$_3$O$_4$ (253.25): C, 52.17; H, 5.97; N, 16.59%. Found: C, 51.94; H, 5.67; N, 16.36%.

1,3-Dimethyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (10f). Yield 60% (0.14 g), mp 150-152 °C (MeOH). FT IR: 3061, 2952, 1698, 1648, 1447, 1344 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 3.36 (s, 3H, N1-CH$_3$), 3.45 (s, 3H, N3-CH$_3$), 3.49 (dd, 1H, *J* 18.0, 8.4, H$_B$-4'),), 3.90 (dd, 1H, *J* 18.0, 11.4, H$_A$-4'), 5.65 (dd, 1H, *J* 11.4, 8.4, H-5'), 7.33-7.28 (m, 1H, Ar-H), 7.39-7.34 (m, 4H, ArH), 7.95 (s, 1H, H-6). ^{13}C NMR (150 MHz, CDCl$_3$) δ (ppm): 28.1 (N1-CH$_3$), 37.5 (N3-CH$_3$), 44.1 (C-4'), 82.7 (C-5'), 103.8 (C-5), 125.9 (2 x C-Ph), 128.2 (C-4-Ph), 128.7 (2 x C-Ph), 140.6 (C-1-Ph), 142.2 (C-6), 151.2 (C-2), 152.5 (C-3'), 162.2 (C-4). ESI-MS [M+H]$^+$ Calcd for C$_{15}$H$_{16}$N$_3$O$_3$ 286.1192. Found 286.1675.

3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,5-dihydroisoxazole-4-carbonitrile (10g). Yield 2% (0.003 g), mp 175-178 °C. FT IR: 2996, 2248, 1723, 1652, 1592, 1480, 1371 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 3.41 (s, 3H, N1-CH$_3$), 3.52 (s, 3H, N3-CH$_3$), 4.62 (dd, 1H, *J* 11.1, 8.7, H$_A$-5'), 4.71 (dd, 1H, *J* 8.7, 7.2, H-4'), 5.73 (dd, 1H, *J* 11.1, 7.2 Hz, H$_B$-5'), 7.97 (s, 1H, H-6). ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm): 28.4, 37.9, 39.5, 72.7, 100.7, 116.0, 143.9, 148.2, 150.9, 160.0. ESI-MS [M+H]$^+$ Calcd for C$_{10}$H$_{11}$N$_4$O$_3$ (235.2193). Found 235.2084.

General procedure for oxidation of cycloadducts (**10a**-**f**). To the 4,5-dihydroisoxazole derivative **10a** - **f** (0.5 mmol) in CCl$_4$ (4 mL) NBS (0.13 g, 0.74 mmol) was added and the reaction mixture was refluxed and monitored by TLC (MeOH:CHCl$_3$, 5:95, v/v). After disappearance of 4,5-dihydroisoxazole (usually 4-5 h) the reaction mixture was evaporated to dryness and the residue was purified on silica gel column using a mixture of MeOH:CHCl$_3$ (5:95, v/v) as an eluent.

3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)isoxazole-5-carbonitrile (11a). Yield 45% (0.05 g), mp 187-189 °C (MeOH). FT IR: 3186, 3069, 2246, 1702, 1645, 1479, 1350 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ (ppm): 3.43 (s, 3H, N1-CH$_3$), 3.55 (s, 3H, N3-CH$_3$), 7.74 (s, 1H, H-4'), 8.19 (s, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ (ppm): 28.4, 37.9, 96.3, 100.8, 108.3, 113.9, 142.7, 143.1, 157.3, 160.9. Anal. Calcd for C$_{10}$H$_8$N$_4$O$_3$ (232.20): C, 51.73, H, 3.47, N, 24.13%. Found: C, 51.49, H, 3.28; N, 24.05%.

Methyl 3-(5-(5-cyanoisoxazol-3-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (11b). Yield 43% (0.06 g), mp 182-185 °C (MeOH). FT IR: 3180, 2246, 1700, 1650, 1470 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ (ppm): 2.77 (t, 2H, *J* 6.6, N1-CH$_2$), 3.60 (s, 3H, OCH$_3$), 4.04 (t, 2H, *J* 6.6, CH$_2$COOCH$_3$), 7.96 (s, 1H, H-4'), 8.54 (s,

1H, H-6), 11.87 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 32.2, 44.6, 51.5, 79.1, 99.5, 114.6, 141.4, 146.8, 150.0, 157.3, 161.1, 171.1. Anal. Calcd for $C_{12}H_{10}N_4O_5$ (290.23): C, 49.66, H, 3.47, N, 19.30%. Found: C, 49.52, H, 3.27, N, 19.05%.

1,3-Dimethyl-5-(5-phenylisoxazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (11c). Yield 40% (0.06 g), mp 226-227 °C (EtOH). FT IR: 3061, 1699, 1674, 1609, 1515, 1452 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 3.27 (s, 3H, N1-CH$_3$), 3.39 (s, 3H, N3-CH$_3$), 7.37 (s, 1H, H-4'), 7.59-7.50 (m, 3H, ArH), 7.90 (d, 2H, *J* 7.2 ArH), 8.45 (s, 1H, H-6). ^{13}C NMR (150 MHz, CDCl$_3$) δ (ppm): 27.8 (N1-CH$_3$), 36.9 (N3-CH$_3$), 100.2 (C-4'), 100.6 (C-5), 125.6 (2 x C-Ph), 126.8 (C-1-Ph), 129.3 (2 x C-Ph), 130.4 (C-4-Ph), 144.4 (C-6), 150.9 (C-2), 157.5 (C-3'), 160.7 (C-4), 168.7 (C-5'). Anal. Calcd for $C_{15}H_{13}N_3O_3$ (283.28): C, 63.60; H, 4.63; N, 14.83%. Found: C, 63.48; H, 4.38; N, 14.66%.

General procedure for cycloaddition of 7a and 7b to nitriles in the presence of CAN. CAN (0.33 g, 0.6 mmol) was added to a suspension of oxime **7a** or **7b** (0.6 mmol) in acetonitrile (16 mL) and the resulting suspension was stirred in an oil bath at 75 ^{o}C for 48 h. After spot of substrate decay (TLC MeOH:CHCl$_3$, 1:9), the solvent was evaporated and the residue was purified on silica gel column (MeOH:CHCl$_3$, 5:95 or 1:9, v/v).

1,3-Dimethyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (13a). Yield 47% (0.07 g), mp 230-232 °C (MeOH). FT IR: 3040, 1680, 1467, 1270 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.62 (s, 3H, C5'-CH$_3$), 3.44 (s, 3H, N1-CH$_3$), 3.54 (s, 3H, N3-CH$_3$), 8.17 (s, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 12.2, 28.2, 37.6, 102.1, 145.1, 151.0, 159.3, 163.4, 175.6. Anal. Calcd for $C_9H_{10}N_4O_3$ (222.20): C, 48.65; H, 4.54; N, 25.21%. Found: C, 48.54; H, 4.27; N, 24.98%.

Methyl 3-(5-(5-methyl-1,2,4-oxadiazol-3-yl)-2,-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoate (13b). Yield 44% (0.08 g), mp 189-192 °C (EtOH). FT IR: 3038, 1683, 1463, 1261 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.61 (s, 3H, C5'-CH$_3$), 2.76 (t, 2H, *J* 6.6, NCH$_2$), 3.60 (s, 3H, OCH$_3$), 4.06 (t, 2H, *J*= 6.6, CH$_2$COOCH$_3$), 8.48 (s, 1H, H-6), 11.71 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 11.6, 32.2, 44.7, 51.5, 100.8, 148.8, 149.9, 159.6, 163.0, 171.2, 175.5. Anal. Calcd for $C_{11}H_{12}N_4O_5$ (280.24): C, 47.15; H, 4.32; N, 19.99%. Found: C, 47.24; H, 4.15; N, 19.78%.

1,3-Dimethyl-5-(5-phenyl-1,2,4-oxadiazol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (13c). Oxime **7a** (0.6 mmol) and CAN (0.33 g, 0.6 mmol) were heated in benzonitrile (8 mL) at 75 ^{o}C for 48 h. The workup as above gave the product. Yield 38% (0.07 g), mp 207-208 °C (MeOH). FT IR: 3063, 1710, 1657, 1636, 1452, 1327 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 3.45 (s, 3H, N1-CH$_3$), 3.57 (s, 3H, N3-CH$_3$), 7.53 (t, 2H, *J* 7.2, ArH), 7.61 (t, 1H, *J* 7.2, ArH), 8.16 (d, 2H, *J* 7.2, ArH), 8.31 (s, 1H, H-6). ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm): 28.3, 37.7, 102.2, 123.8, 128.1, 129.1, 132.9, 145.5, 151.0, 159.3, 163.8, 172.3, Anal. Calcd for $C_{14}H_{12}N_4O_3$ (284.27): C, 59.15; H, 4.25; N, 19.71%. Found: C, 58.89; H, 4.19; N, 19.58%.

General procedure for preparation of uracils (17a-d). NCS (0.06 g, 0.44 mmol) was added while stirring to a solution of oxime **14a**-**d**[55] (0.4 mmol) in dry DMF (3 mL) at room temperature. The completion of the reaction was indicated by TLC (EtOAc : *n*-hexane, 1:1 v/v). The solution of generated oxymoyl chloride **15a**-**d** was immediately used for the next step without purification. 5-Cyanouracil **16** (0.05 g, 0.35 mmol) was added followed by dropwise addition of triethylamine (0.06 mL, 0.4 mmol). The reaction mixture was stirred for 24 h at room temperature. After that time the solvent was removed under reduced pressure and the residue purified on a silica gel packed column using EtOAc : *n*-hexane (1:1) as an eluent. The products **17a**-**d** were obtained in satisfactory yields.

5-(3-*p*-Tolyl-1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1*H*, 3*H*)-dione (17a). Yield 51% (0.05 g), mp 196-197 °C (MeOH). FT IR: 3152, 3051, 1736, 1675, 1620, 1430, 1299, 1016 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.34 (s, 3H, C4'-CH$_3$), 7.26 (d, 2H, *J* 8.1, ArH), 7.60 (d, 2H, *J* 8.1 Hz, ArH), 8.74 (s, 1H, H-6), 12.31 (s, 1H, N1-H),

12.38 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 20.6, 89.3, 113.5, 125.3, 127.5, 129.1, 140.0, 142.6, 147.3, 153.2, 160.0. Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270.24): C, 57.78; H, 3.73; N, 20.73%. Found: C, 57.65; H, 3.68; N, 20.59%.

5-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1*H***,3***H***)-dione (17b)**. Yield 40% (0.04 g), mp 168-172 °C (EtOH). FT IR: 3180, 3072, 2241, 1732, 1706, 1681, 1309 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.51 (d, 2H, *J* 8.4, ArH), 7.76 (d, 2H, *J* 8.4, ArH), 8.74 (s, 1H, H-6), 12.34 (s, 1H, N1-H), 12.65 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 89.8, 113.7, 127.4, 128.9, 129.6, 135.1, 142.1, 147.6, 153.4, 160.2. Anal. Calcd for $C_{12}H_7ClN_4O_3$ (290.66): C, 49.59; H, 2.43; N, 19.28%. Found: C, 49.37; H, 2.09; N, 19.14%.

5-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1*H***, 3***H***)-dione (17c)**. Yield 33% (0.04 g), mp 169-172 °C (MeOH). FT IR: 3293, 3071, 1768, 1682, 1432, 1297, 1025 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.65 (d, 2H, *J* 9.0 ArH), 7.69 (d, 2H, *J* 9.0, ArH), 8.74 (s, 1H, H-6), 12.34 (s, 1H, N1-H), 12.66 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 89.8, 113.6, 123.8, 127.6, 129.9, 131.8, 142.2, 147.5, 153.3, 160.2. Anal. Calcd for $C_{12}H_7BrN_4O_3$ (335.11): C, 43.01; H, 2.11; N, 16.72%. Found: C, 42.88; H, 1.89; N, 16.68%.

5-(3-(4-Methoxyphenyl)-1, 2, 4-oxadiazol-5-yl)pyrimidine-2, 4(1*H***, 3***H***)-dione (17d)**. Yield 51% (0.05 g), mp 170-174 °C (MeOH). FT IR: 3063, 1710, 1657, 1636, 1451, 1318 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.03 (s, 3H, OCH$_3$), 6.99 (d, 2H, *J* 9.0, ArH), 7.64 (d, 2H, *J* 9.0, ArH), 8.72 (s, 1H, H-6), 12.22 (s, 1H, N1-H), 12.29 (s, 1H, N3-H). ^{13}C NMR (75 MHz, DMSO-d_6 δ (ppm): 55.1, 89.2, 113.4, 114.0, 122.6, 127.0, 147.2, 153.2, 160.0, 160.7. Anal. Calcd for $C_{13}H_{10}N_4O_4$ (286.24): C, 54.55; H, 3.52; N, 19.57%. Found: C, 54.35; H, 3.27; N, 19.35%.

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