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FULL-LENGTH PAPER

Unexpected deviation from diene behaviour of uracil amidine: towards synthesis of some pyrido[2,3-*d*]pyrimidine derivatives

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Abstract Condensation products obtained from the treatment of uracil amidine with preformed or in situ generated suitably substituted olefins unexpectedly undergo intramolecular cyclisation during silica gel chromatography to generate pyrido[2,3-*d*]pyrimidines. Various reaction conditions are studied and the altered nature of the uracil amidine molecule is further explored by reacting it with different suitably substituted alkenes.

Keywords Cycloaddition reaction · Heterocycles · Silica gel · Pyridopyrimidines

Introduction

Synthesis of nitrogen containing heteroaromatic species of biological significance is an ever interesting field of research, as these entities are prevalent as substructures in living systems and constitutes the core structure of numerous pharmaceuticals. The exhibition of exciting biological properties and their role as pharmacophores of historical importance has generated considerable interests among synthetic chemists for developing new methodologies for synthesizing these nitrogen containing heterocycles. Favourable exploitation of the 5,6-double bond of uracil for synthesizing fused pyrimidines is a challenging area [1–3]. Synthesis of a library of fused pyrimidines such as pyrimidopyrimidines [4], pyrazolopyrimidines [5] and pyridopyrimidines [6] can be designed by its synthetic manipulation. The synthesis of pyridine containing molecules has attracted much attention as this structural motif appears in a large number of pharmaceutical agents and natural products [7]. Pyrido[2,3-*d*]pyrimidine is known to act as potent inhibitor of dihydrofolate reductase (DHFR) [8,9], which is an important target site in most of the parasitic diseases. Pyrimidine derivatives have also shown remarkable activity as bronchodilators, vasodilators, antiallergic, antihypertensive and anticancer agents [10–15].

The behaviour of 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **1** as a reactive diene was first demonstrated by Wamhoff and coworkers about two decades ago [16]. The diene system of the 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil molecule is very reactive for [4+2] cycloaddition reactions and diverse range of potential products can be obtained by its synthetic exploitation. A literature survey revealed that this molecule behaves as an excellent diene in Diels–Alder reactions. Our group has continuously been exploiting the diene nature of this molecule and its reaction with electron deficient olefins and a variety of polarised double bonds to generate libraries of novel and interesting pyrimido fused heterocycles [17–20]. Inspired by these results, we became interested to investigate the reaction of uracil amidine **1** with polarised alkenes. We initially envisioned that reaction of 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **1** with suitably polarised alkenes could afford [4+2] cycloaddition products. However, to our surprise, we observed, for the first time, that **1** deviated from its established diene behaviour and yielded a [3+3] cycloaddition product via an addition–cyclisation process. The unexpected behaviour of uracil amidine was thoroughly studied and the results of this effort are presented herein. Quite fortunately, literature reports are available to compare and confirm our end products which are discussed in this report [21–23]. Our present study reveals that reaction of **1** with olefins can be switched from [4+2] to a formal [3+3]

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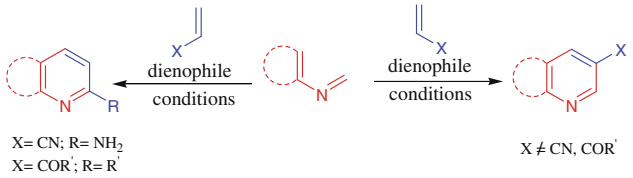


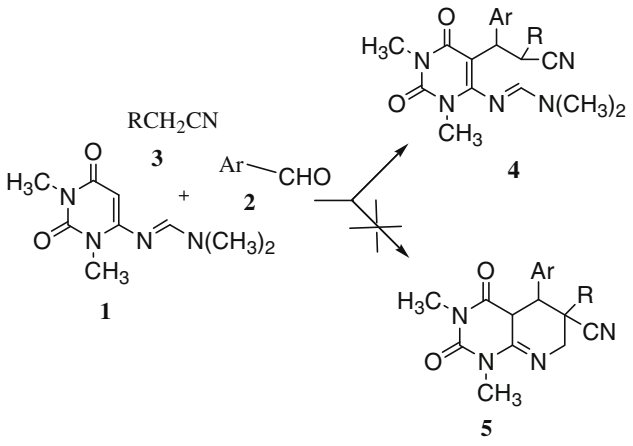
Scheme 1 Concept of [4+2] and [3+3] cycloaddition reactions in the synthesis of pyridopyrimidines

reaction by suitably tuning the substituent moieties in the olefin (Scheme 1).

Results and discussion

Our synthetic strategy involved condensation of polarised alkenes generated in situ from an aromatic aldehyde and an active methylene compound with uracil amidine **1** to afford regiospecific one-pot synthesis of pyrido[2,3-*d*]pyrimidines. Subsequent treatment of 6-[(dimethylamino)methylene] amino-1,3-dimethyl uracil **1** with an aromatic aldehyde **2** and active methylene cyano compound **3** yielded compound **4** instead of our expected [4+2] cycloaddition product **5** (Scheme 2).

Our initial effort was to develop an appropriate solvent system and reaction condition to perform the proposed reaction. The results of this study are summarised in Table 1. We observed that the three component reaction of **1**, *p*-nitro-benzaldehyde **2a** and malononitrile **3a** led to the recovery of starting materials in most of the organic solvents (Table 1, entries 1–7). However, compound **4** was unexpectedly formed in 60% yield when the reaction was carried out under refluxing acetonitrile for 20 h (Table 1, entry 8). The use of PEG-400 as solvent in presence of 10 mol% of K_2CO_3 increased the yield of the product to 70% under much reduced time (Table 1, entry 13). The reaction did not yield any



Scheme 2 Synthesis of compound **4** from uracil amidine **1**

Table 1 Optimisation of reaction conditions for synthesis of compound **4a**

Entry	Solvent	Time (h)	Reaction condition	Yield (%)[a]
1	$PhNO_2$	12	Reflux	No reaction
2	Dioxane	15	Reflux	No reaction
3	THF	15	Reflux	No reaction
4	DMF	12	Reflux	No reaction
5	DCM	14	Reflux	No reaction
6	EtOH	14	Reflux	No reaction
7	Toluene	16	Reflux	No reaction
8	Acetonitrile	20	Reflux	60
9	H_2O	18	stirring, 80 °C	No reaction
10	[hmim]PF_6	20	Stirring, r.t.	No reaction
11	[bmim]PF_6	18	Stirring, r.t.	No reaction
12	[bmim]BF_4	20	Stirring, r.t.	No reaction
13	PEG-400/K_2CO_3	10	Stirring, r.t.	70

[a] Isolated yield

product when ionic liquids were employed as solvent (Table 1, entries 10–12).

The structure of compound **4a** was confirmed by NMR, IR and mass spectrometric analysis. The ^{1}H NMR spectrum showed the presence of two tertiary protons as doublets at δ 4.43 and 5.90 and other peaks at δ 8.20 (d, J = 8.6 Hz, 2H, arom.), 7.64 (d, J = 8.6 Hz, 2H, arom.), 7.27 (s, 1H, C*H*=N–), 3.31 (s, 3H, NCH_3), 3.28 (s, 3H, NCH_3), 3.18 (s, 3H, CHNCH_3), 3.10 (s, 3H, CHNCH_3). The ^{13}C NMR spectrum showed 17 peaks at δ 162.9, 159.8, 153.6, 151.1, 147.6, 145.2, 129.1, 124.0, 112.9, 112.7, 94.4, 45.2, 40.6, 34.6, 31.5, 28.0 and 25.6. The IR spectrum showed absorptions at 2254.3 and 2217.2 cm^{-1} due to the two CN groups. The mass spectrum of **4a** revealed a strong molecular ion peak at m/z 408 (M^+, 100). Similarly, other products **4b–m** were prepared and characterised (Table 2).

The PEG-400/K_2CO_3 system provides a suitable, operation friendly and green route to synthesise compounds **4**. PEGs are able to form complexes with alkaline and alkaline earth cations in protic and aprotic solvents and can be regarded as open chain crown ethers [24,25]. A possibility is that in the PEG/K_2CO_3 media, the CO_3^{2-} anion could be brought into solution through coordination of the cationic centre of K_2CO_3 with the oxygen atom of PEG. The CO_3^{2-} anions present in the solution thereby promotes the reaction by enhancing the reactivity of the C-5 atom of uracil amidine **1** for [4+2] cycloaddition towards electron deficient alkenes, which are generated in situ in the reaction media. The specific role of PEG-400 in the reaction, however, is not yet clear at this stage and further studies are being carried out in this direction.

Interestingly, while separating compound **4** by column chromatography, we were excited to note that a very fast

Table 2 Substrate study for synthesis of compound **4**

Entry	Ar	R	Product	Yield (%)[a]
1	*p*-NO_2–C_6H_4–	CN	**4a**	70
2	*p*-F–C_6H_4–	CN	**4b**	66
3	*p*-Cl–C_6H_4–	CN	**4c**	65
4	C_6H_5–	CN	**4d**	63
5	2-Thienyl	CN	**4e**	60
6	3-Br–C_6H_4–	CN	**4f**	67
7	3-Br–C_6H_4–	COOEt	**4g**	50
8	*p*-N0$_2$–C_6H_4–	COOEt	**4h**	40
9	*p*-Cl–C_6H_4–	COOEt	**4i**	42
10	2-Thienyl	COOEt	**4j**	40
11	3-Br–C_6H_4–	$CONH_2$	**4k**	42
12	*p*-NO_2–C_6H_4–	$CONH_2$,	**4l**	45
13	C_6H_5–	$CONH_2$	**4m**	46

Reaction conditions: Uracil amidine (1 equiv.), aromatic aldehyde (1 equiv.), active methylene compound (1 equiv.) was stirred in PEG-400 at r.t. in presence of 10 mol% of K_2CO_3 until the reaction is complete
[a] Isolated yield

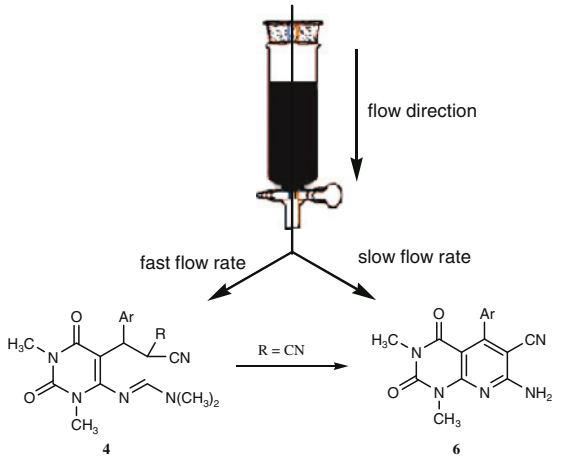


Fig. 1 Conversion of compound **4** into pyridopyrimidine derivatives **6** inside a chromatographic column

column chromatographic purification resulted in the separation of **4**, but a slow column run yielded a new compound with R_f value much lower than that of **4**. Subsequent analysis of this compound showed that it is neither the [4+2] cycloadduct **5** nor the adduct **4**, but a pyrido[2,3-*d*]pyrimidine derivative of type **6** (Fig. 1).

This type of organic transformations inside a chromatographic column promoted by silica gel used for column chromatography is rare and there are very few literature reports available. Matsushima and Kino [26] reported one such reaction during their total synthesis of *N*-Bz-D-daunosamine and *N*-Bz-D-ristosamine. The structure of product **6** as a pyrido[2,3-*d*]pyrimidine derivative was assigned on the basis of its elemental and spectral analyses. The ^{1}H NMR spectrum showed the absence of the H-5 proton of the uracil **1** and the presence of two methyl groups from the cycloadduct **6a** at δ 3.28 (s, 3H, NCH_3) and at 3.65 (s, 3H, NCH_3), and other peaks at 8.38 (d, J= 8.6 Hz, 2H, *arom.*), 7.45 (d, J = 8.6 Hz, 2H, arom.), and 5.78 (s, 2H, NH_2). The ^{13}C NMR spectrum showed peaks at δ 166.1, 164.9, 162.5, 157.8, 156.7, 148.8, 143.7, 127.3, 123.1, 113.2, 98.4, 84.2, 36.8 and 28.7. The mass spectrum of **6a** revealed a strong molecular ion peak at m/z 353 (M^+, 100). The formation of the products **6** were further confirmed by comparing with literature values [21,22]. Similarly, other pyrido [2,3-*d*]pyrimidines **6a–f** were prepared in 90–95% yields and fully characterised (Table 3). Further investigation showed that the formation of **6** depends on the rate of flow of the eluent through the column. A fast elution of **4** through the column did not yield any **6**, a slow elution resulted in conversion of all **4** to **6**, while a moderately fast column resulted in mixture of **4** and **6.**

Table 3 Substrate study for the cylisation step

Entry	Ar	R	Product	Yield (%)[a]
1	*p*-NO_2–C_6H_4–	CN	**6a**	90
2	*p*-F–C_6H_4–	CN	**6b**	92
3	*p*-Cl–C_6H_4–	CN	**6c**	95
4	C_6H_5–	CN	**6d**	90
5	2-Thienyl	CN	**6e**	93
6	3-Br–C_6H_4–	CN	**6f**	93

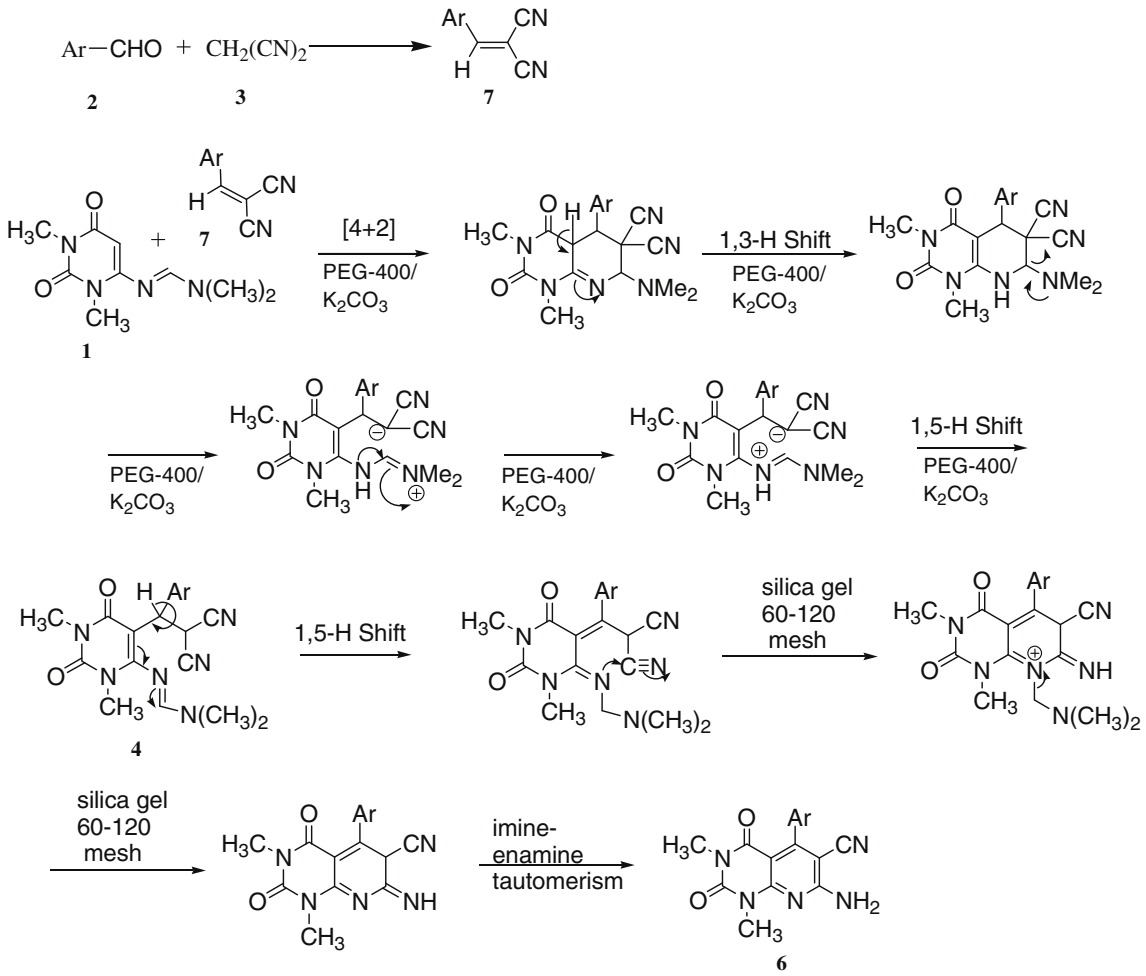
[a] Isolated yield

Encouraged by this observation, we set out to study the scope and limitation of the transformation of **4** to **6** under different reaction conditions and the results are summarised in Table 4. The reaction did not proceed at all in organic solvents (Table 4, entries 1–5). Further, silica gel failed to catalyse the reaction under microwave condition (Table 4, entry 6). Trace amount of product formation was observed when the reactants were irradiated under MW after adsorption on acidic Al_2O_3 (Table 4, entry 7). These results led us to the conclusion that the transformation of **4** to **6** is promoted by the silica gel used for column chromatography. Quite interestingly, however, no formation of **6** was observed when one of the CN moiety of the alkene was substituted by COOEt or $CONH_2$. Thus, it can be remarked that the silica gel specifically catalyses cycloaddition of 1,1-dicyano-substituted olefins only. Silica gel itself or in combination with variety of other co-reagents [27–29] have been known to mediate various organic transformations. A reasonable mechanism for the formation of pyrido[2,3-*d*]pyrimidines from the three component reaction is outlined in Scheme 3. The sequence starts with the formation of Knoevenagel product **7** from **2** and **3**, which then undergoes [4+2] cycloaddition followed by rearrangement to give compound **4**. The cyclisation of **4** to **6** proceeds via an initial 1,5-hydrogen shift followed by elimination of trimethylamine from 1:1 cycloadduct.

Table 4 Optimisation of reaction conditions for the cyclisation step

Entry	Solvent	Time	Reaction condition	Yield (%)[a]
1	CH_3CN	11 h	Reflux	No reaction
2	EtOH	16 h	Reflux	No reaction
3	Toluene	12 h	Reflux	No reaction
4	THF	15 h	Reflux	No reaction
5	Nitrobenzene	20 h	Reflux	No reaction
6	Adsorb on silica	30 min	MW	No reaction
7	Adsorb on $A1_2O_3$ (acidic)	20 min	MW	Trace
8	Eluted through silica gel 60–120 mesh	16 h	1:1 Hexane:ethyl acetate as eluent	90–95

[a] Isolated yield



Scheme 3 Mechanistic rationale for the formation of pyrido[2,3-*d*]pyrimidine derivative **6**

Finally, an imine-enamine tautomerism leads to the formation of pyrido[2,3-*d*]pyrimidine derivative.

We then confirmed the mechanism by performing the reaction in two steps. First we synthesised the ylidine malononitrile **7a** by the Knoevenagel condensation of malononitrile with aromatic aldehydes. It was then reacted with 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **1** in PEG-400 in presence of 10 mol% of K_2CO_3 at room

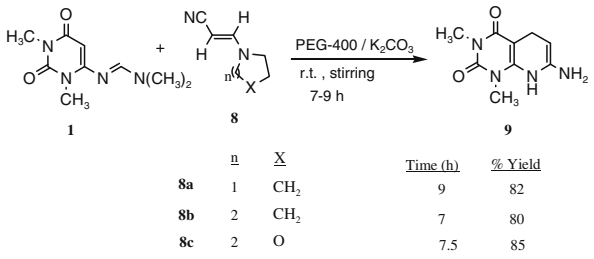
temperature. We observed that the reaction proceeds smoothly and isolated the product **4** in yields comparable to the three component reaction.

We further investigated the scope of the reaction by reacting **1** with 2-amino-substituted acrylonitriles **8** under the same reaction conditions. Thus, when equimolar amount of the two reactants were stirred in PEG-400 in presence of 10 mol% of K_2CO_3 at room temperature, to our delight, 5,8-dihydropyrido[2,3-*d*]pyrimidine **9** formed directly without formation of any intermediate (Scheme 4). The structure of product **9** was assigned on the basis of its elemental and spectral analyses. The ^{1}H NMR spectrum showed the presence of two N-methyl groups at δ 3.16 and 3.33 as singlets, and other peaks at 3.53 (t, J = 7.2 Hz, 1H, CH), 3.63 (d, J = 7.2 Hz, 2H CH_2), 4.68 (s, 1H, NH), 6.87 (s, 2H, NH_2). The ^{13}C NMR spectrum showed peaks at δ 21.91, 27.49, 29.73, 70.23, 75.36, 79.63, 152.72, 155.35 and 161.88. The mass spectrum of **9** revealed a strong molecular ion peak at m/z 209 ([M+1]$^+$, 100). The IR spectrum showed peaks at 3231.2 cm^{-1} for the NH group and at 3355.7 and 3397.3 cm^{-1} for the NH_2 group. Further D_2O exchange spectrum was recorded and it did not show the peaks at δ 4.68 and δ 6.87 which confirms the presence of the labile hydrogen of NH and NH_2 groups.

We tried to generalise the reaction by taking different amine substituents in **8** and observed that cyclic secondary amines like morpholine, piperidine and pyrrolidine leads to generation of the same product after elimination of the amine moiety. However, when *N*,*N*-diphenyl amine was taken as the substituent, the reaction did not proceed at all despite long reaction time and the reactants were quantitatively recovered. This could be due to the large steric hindrance offered by the phenyl groups that renders the initial step sterically unfavourable.

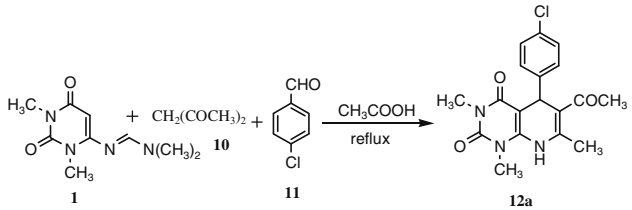
During the course of the reaction, we became interested to see how the uracil amidine molecule **1** would behave if the cyano group is substituted with a carbonyl group. We postulated that like a cyano group, the carbonyl group also provides a potential site for the nucleophilic N atom of **1** to attack and thus should undergo the same reaction pathway. We initially selected 1,3-diketones as potential active methylene candidates for this reaction. Subsequently, we carried out a three component reaction between uracil amidine **1**, an aldehyde and acetyl acetone **10** in PEG-400 but failed to obtain the desired product. The reaction was unsuccessful despite elevating the reaction temperature and starting materials were recovered quantitatively. Encouraged by the fact that silica gel, which is slightly acidic, promoted the cyclisation of acyclic intermediate **4** to pyrido[2,3-*d*]pyrimidines (Scheme 3), we tried this reaction under acidic medium, and the results that we obtained quite fascinated us.

Equimolar mixture of uracil amidine **1**, acetyl acetone **10** and 4-chloro benzaldehyde **11** when refluxed in acetic acid



	n	X	Time (h)	% Yield
8a	1	CH_2	9	82
8b	2	CH_2	7	80
8c	2	O	7.5	85

Scheme 4 Synthesis of dihydropyrido [2,3-d] pyrimidine **9**



Scheme 5 Synthesis of pyridopyrimidine derivative **12a**

for an appropriate amount of time, yielded, to our expectation, pyrido[2,3-*d*]pyrimidine derivative **12a** (Scheme 5) [23].

The structure of the compound **12a** was assigned from its spectral analysis. The ^{1}H NMR spectrum showed the CH_3 and $COCH_3$ peaks at δ 2.14 and 2.30 and other peaks at 3.29 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 5.26 (s, 1H, NH), 5.95 (s, 1H, CH), 7.45–7.52 (m, 4H, arom.). Finally, the structure of **12a** was confirmed by single crystal X-ray diffraction study (Fig. 2).[1] It clearly shows the methyl group α- to the NH group and thereby confirms that the N atom has attacked one of the carbonyl groups of acetyl acetone. The choice of the reagents in the transformation is quite interesting as uracil amidine is found to behave as an excellent diene in presence of acetic acid with different reactants [30].

The generality of the reaction scheme was checked by altering different aromatic aldehydes and acyclic and cyclic 1,3-dicarbonyl compounds. In all cases, the reaction occurred smoothly and good to excellent yields of the products were obtained. Further, the reaction was clean and formation of no side products was observed. The results obtained are summarised in Table 5.

In summary, we have reported the first deviation from diene behaviour of uracil amidine molecule, which leads to generation of some biologically important pyrido[2,3-*d*]pyrimidine derivatives. The procedure presented here employs, in the first step, PEG-400 as both solvent and promoter for the addition of uracil amidine to acrylonitriles.

[1] CCDC-775735 and CCDC-787459 contains the supplemtary crystallographic data for compound 12a and 12k. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

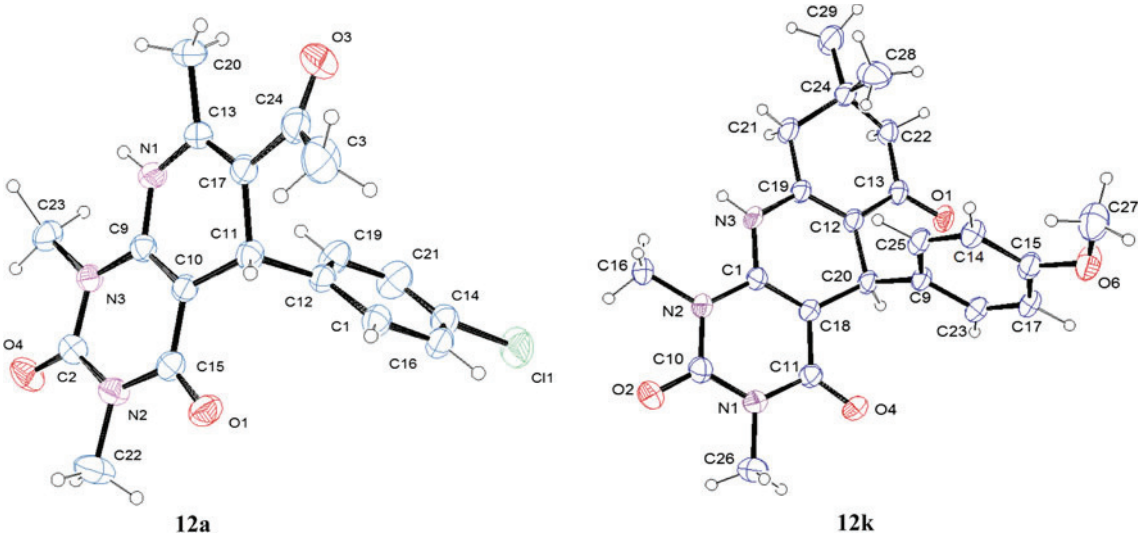


Fig. 2 Ortep diagram of compound **12a** and **12k** drawn with 30% probability ellipsoid

The second step involves silica gel promoted cyclisation of the intermediate adduct to pyrido[2,3-*d*]pyrimidine inside a chromatographic column in excellent yields. The deviation from diene nature of uracil amidine is further explored by reacting it with 2-amino-substituted acrylonitriles and other 2-carbonyl-substituted acrylonitriles under various conditions. In all cases formation of pyridopyrimidines was observed in excellent yields. This is quite significant in view of understanding cycloaddition reaction strategies and it can pave new ways for exploitation of other –C=C–N=C– type of diene systems.

Experimental

All reactions were carried out under air. All the commercially available reagents were used as received. Melting points were measured with a Buchi B-540 melting point apparatus and uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400 instrument. ^{1}H NMR spectra were recorded on an Advance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given from TMS (0 ppm) and coupling constants are expressed in Hertz (Hz). ^{13}C NMR spectra were recorded on an Advance DPX 75 MHz FT-NMR spectrometer and chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm). Mass spectra were recorded on an ESQUIRE 3000 mass spectrometer. Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate: hexane as eluent.

General procedure for synthesis of compounds **4a–m**

1 mmol each of uracil amidine **1**, aromatic aldehyde **2** and the active methylene compound **3** were taken in a 50 mL round bottomed flask and to this 2 mL of PEG-400 and K_2CO_3 (10 mol%, 0.1 mmol, 0.014 g) were added and the reaction mixture was stirred at room temperature for 10–12 h. After completion, as indicated by TLC, the reaction mixture was poured into ice cold water, whereby crude product precipitated out. It was filtered and purified by fast column chromatography using 1:1 ethyl acetate:hexane as the eluent to get pure product **4**.

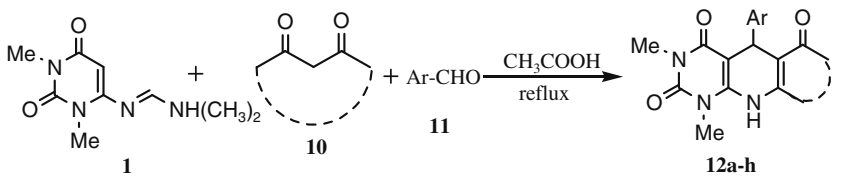
General procedure for synthesis of pyrido[2,3-*d*]pyrimidine derivatives **6a–f**

The product pyrido[2,3-*d*]pyrimidine **6** was obtained when the intermediate **4** was very slowly eluted in a chromatographic column using 1:1 ethyl acetate:hexane as the eluent over a period of 16–18 h. Alternatively, product **6** can be directly obtained from the crude reaction mixture by eluting it very slowly through the chromatographic column over a period of 20–22 h without obtaining the intermediate **4**. A moderately fast elution of the crude product yields mixtures of **4** and **6**.

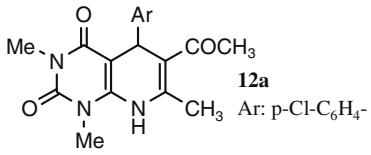
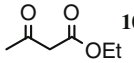
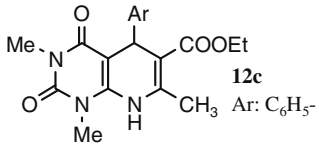
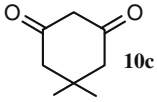
General procedure for synthesis of 5,8-dihydropyrido[2,3-*d*]pyrimidine **9**

7-amino-1,3-dimethyl-5,8-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione **9** was obtained by mixing equimolar amounts (1 mmol) of uracil amidine **1** and 2-amino-substituted ylidine nitrile **8** in 2 mL of PEG-400 and K_2CO_3 (10 mol%, 0.1 mmol, 0.014 g) and then subjecting to stirring at room temperature for 7–9 h. After the reaction is complete (as indicated by TLC), the reaction mixture is

Table 5 Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **12**



1 **10** **11** **12a-h**

Entry	Active methylene compound **10**	Aldehyde **11**	Product	Yield(%)[b]
1	 **10a**	p-Cl-C_6H_4-	 **12a** Ar: p-Cl-C_6H_4-	75
2	**10a**	p-NO_2-C_6H_4-	**12b** Ar: p-NO_2-C_6H_4-	92
3	 **10b**	C_6H_5-	 **12c** Ar: C_6H_5-	80
4	**10b**	p-CH_3-C_6H_4-	**12d** Ar: p-CH_3-C_6H_5-	82
5	**10b**	p-OCH_3-C_6H_4-	**12e** Ar: p-OCH_3-C_6H_5-	78
6	**10b**	p-Cl-C_6H_4-	**12f** Ar: p-Cl-C_6H_5-	75
7	**10b**	p-Br-C_6H_4-	**12g** Ar: p-Br-C_6H_5-	80
8	**10b**	C_4H_3S-	**12h** Ar: C_4H_3S-	75
9	 **10c**	p-CH_3-C_6H_4-	**12i** Ar: p-CH_3-C_6H_5-	90
10	**10c**	p-Cl-C_6H_4-	**12j** Ar: p-Cl-C_6H_5-	92
11	**10c**	p-OCH_3-C_6H_4-	**12k** Ar: p-OCH_3-C_6H_5-	90
12	**10c**	C_3H_7-	**12l** Ar: C_4H_9-	77

Reaction conditions: Uracil amidine (1 equiv.), active methylene compound (1 equiv.) and aldehyde (1 equiv.), CH_3COOH (5 mL), reflux, 5–8 h
[a] Isolated yield

poured into ice cold water, whereby crude product precipitated out. It was filtered and purified by column chromatography using 1:1 ethyl acetate:hexane as the eluent to get pure 7-amino-1,3-dimethyl-5,8-dihydro-1H-pyrido[2,3-*d*]pyrimidine-2,4-dione **9**.

General procedure for synthesis of pyrido[2,3-*d*]pyrimidine derivatives **12a–l**

Equimolar amounts (1 mmol) of uracil amidine **1**, aromatic aldehyde **11** and the active methylene compound **10** were

taken in a round bottomed flask and to this 10 mL of acetic acid was added and the reaction mixture was refluxed until the reaction goes to completion. After completion, as indicated by TLC, the reaction mixture was poured into water, whereby crude product precipitated out. It was filtered, washed thoroughly with water, dried and purified by column chromatography using 3:7 ethyl acetate:hexane as the eluent to get pure products **12a–l**.

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