RESEARCH ARTICLE Am. J. PharmTech Res. 2016; 6(6) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Urea: A Highly Efficient Recyclable Organocatalyst For Synthesis of Bioactive Annulated Pyrimidine via Knoevenagel-Michael Addition Pathway In Aqueous Ethanol

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ABSTRACT

A highly efficient synthetic procedure were developed for the synthesis of bioactive pyrido [2,3-d] pyrimidines by one-pot three component reaction of 6-amino 1,3-dimethyluracil, active methylene compounds and substituted aromatic aldehydes catalyzed using urea catalyst in aqueous media at room temperature. Mild reaction conditions, excellent yields, operational simplicity, no tedious separation procedures and clean reaction profiles are the key advantages of the present method. The bioactive synthesized derivatives showed no significant effect of electron donating or withdrawing moieties of the reacting aromatic aldehydes. This protocol produced the desired products in high yields (85-95 %) and short reaction times (45-75min) with reusability of reaction medium. Synthesized compounds were characterized by IR, ^{1}HNMR & ^{13}C NMR and mass spectral data.

Keywords: Pyrido[2,3-d] pyrimidines, Malononitrile, Aromatic aldehydes, Aqueous ethanol, Urea.

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Received 12 November 2016, Accepted 20 November 2016

Please cite this article as: Dongre RS *et al.*, Urea: A Highly Efficient Recyclable Organocatalyst For Synthesis of Bioactive Annulated Pyrimidine via Knoevenagel-Michael Addition Pathway In Aqueous Ethanol. American Journal of PharmTech Research 2016.

INTRODUCTION

Heterocycle containing molecules are widely studied for their synthesis and their applications in medicinal chemistry as variety of biological activities. The 6-Amino-uracil represents vital functionalized class of nitrogen heterocycles. These bioactive uracils find wide utility as substrates to synthesis the number of fused uracil derivatives viz; pyrano-, pyrido-, pyrazolo-, pyrimido-, pyridazino-pyrimidines. Among these synthesized bioactive drugs, pyrido pyrimidines have a wide range of biological activities such as antibacterial and antifungal activity [1], antihypertensive [2], antimicrobial[3], cardiotonic[4], tyrosine kinase[5] ,anti-inflammatory[6],and analgesic[7]calcium channel antagonists[8]tuberculostatic[9] antilieshmanial activity[10]. Therefore, for the preparation of these fused molecules great efforts have been directed toward the synthetic manipulation of annulated pyrido [2,3-*d*]pyrimidine derivatives based on diverse procedures such as Knoevenagel condensation, Michael addition followed by cyclodehydration strategy and finally heterocyclization.

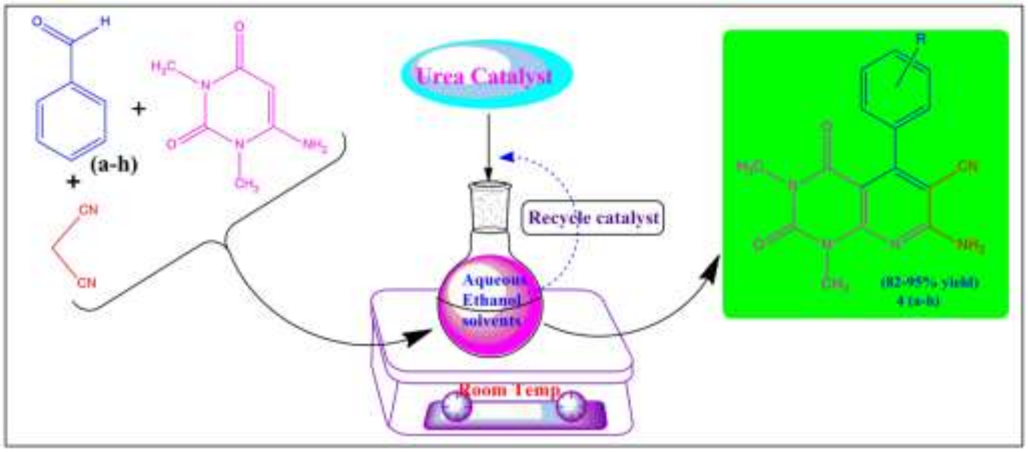
Literature reported on pyrido [2,3-*d*]pyrimidine derivatives uses catalytic *L*-proline[11],diammonium hydrogen phosphate (DHAP)[12], palladium-catalysed oxidative coupling[13],nucleophilic-induced ring transformation [14], KF-Al_2O_3 [15], and some are without catalyst [16,17] . All these reported methodologies appeared in the literature usually needs forcing reaction conditions, pro-longed reaction time, create solid-wastes, complex synthetic pathway and low yields. Excellent yields, operational simplicity, short reaction time, reusability of the reaction medium and use of environmentally benign catalyst are the key advantages of the reported protocol.

MATERIALS AND METHOD

All chemicals were obtained from Aldrich Chemical Co. and S. D. Fine chem Co. and used as such without further purification. The melting points of all the products were determined by open capillary method and were found to be uncorrected. All the ^{1}H-NMR spectra of products were obtained on a BRUKER instrument (300 MHz). FTIR spectra of products were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet and all ^{13}C-NMR (100 MHz) spectra of products were recorded in DMSO-d_6 as solvent with TMS as internal standard. Corresponding characteristics chemical shifts in all types of NMR spectra are reported in ppm and the mass spectra were measured using high resolution GC–MS (DFS) thermo spectrometers with EI (70 EV). All the reactions were monitored frequently with every fifteen minutes time span by thin layer chromatography (TLC) on 0.2-mm pre-coated plates of silica gel G60 F254 (Merck).

General procedure for the preparation of pyrido[2,3-*d*]pyrimidines:

Substituted aromatic aldehydes **1** (1 mmol), Malononitrile **2** (1 mmol), 6-amino 1, 3-dimethyl uracil **3** (1 mmol) and urea (10 mol%) as organo catalyst were taken in an R.B. flask with solvent aqueous ethanol (1:1 ratio, 14 ml) and stirred for 45–75 min at room temperature. The reaction was monitored by thin layer chromatography using eluent petroleum ether and ethyl acetate 7:3. The solid compound was filtered, washed with cold water several times and recrystallization from ethanol to obtain pure product pyrido [2, 3-*d*] pyrimidine derivatives. (Scheme 1).



Scheme 1: General synthesis of substituted pyrido [2, 3-*d*] pyrimidine derivatives.

Spectral data for synthesized pyrido[2,3-d]pyrimidine products.

7-amino-5-(4-methyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4a).

IR (KBr, cm^{-1}): 3394($-NH_2$), 2218(-CN), 1699(-C=O), 1615(-C=O);^{1}H NMR (300MHz, DMSO-d_6, ppm): 2.36(s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 7.12(d, 2H, H_{Ar}), 7.20(d, 2H, H_{Ar}), 7.60(br s, 2H, NH_2), ppm; ^{13}C NMR (100MHz, DMSO-d_6, ppm): 160.8, 159.9, 155.5, 150.1, 137.4, 129.7, 128.2, 125.4, 114.1, 98.3, 88.7, 57.3, 31.2, 29.5, 20.9ppm; EI-MS (m/z) = 322 (M^+)

7-am1ino-5-(phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4b).

IR (KBr, cm^{-1}): 3403($-NH_2$),2224(-CN),1707(-C=O), 1623(-C=O);^{1}H NMR(300MHz, DMSO-d_6, ppm): 3.3(s, 3H, CH_3),3.65 (s,3H,CH_3),7.24(d,2H,H_{Ar}), 7.40 (t, 3H, H_{Ar}), 7.59 (br s, 2H, NH_2)ppm; ^{13}C NMR(100MHz, DMSO-d_6, ppm):160.9 160.1, 159.0, 158.3, 150.7, 134.2, 127.9, 127.7, 116.7, 115.1, 88.8, 40.1, 35.0, 24.1, ppm; EI-MS(m/z)= 308 (M^{+1})

7-amino-5- (4-methoxyphenyl)-1,3-dimethy l-2, 4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4c).

IR (KBr, cm^{-1}): 3404($-NH_2$), 2219(-CN), 1760(-C=O), 1625(-C=O); ^{1}H NMR (300MHz, DMSO-d_6, ppm): 3.1(s, 3H, CH_3), 3.4 (s, 3H, CH_3), 4 (s, 3H, OCH_3), 7(d, 2H, H_{Ar}), 7.25(br s, 1H, NH_2), 7.9(d, 2H, H_{Ar}), ppm;^{13}C NMR (100MHz, DMSO-d_6, ppm): 160.8, 160.0, 159.9, 158.8, 155.5, 150.1, 129.5, 128.6, 115.7, 112.9, 98.3, 88.8, 62.5, 23.4, 28.3 ppm; EI-MS (m/z) = 338 (M^+)

7-amino-5- (4-hydroxyphenyl)-1,3-dimethyl-2, 4-dioxo-1,2,3,4-tetrahydropyrido [2,3 *d*] pyrimidine-6-carbonitrile (4d).

IR (KBr, cm^{-1}): 3391(-NH_2), 2237(-CN), 1786(-C=O), 1624(-C=O); ^{1}H NMR (300MHz, DMSO-d_6, ppm):3.1(s, 3H, CH_3), 3.3 (s, 3H, CH_3), 6.59(s, 1H, H_{Ar}), 6.62(d, 1H, H_{Ar}),6.78(d,1H,H_{Ar}), 7.18(t, 1H, H_{Ar}), 7.58 (br s, 2H, NH_2), 9.46(s, 1H, OH)ppm;^{13}C NMR (100MHz, DMSO-d_6, ppm):160.8, 159.8, 155.4, 150.2, 130.9, 121.8, 118.1, 115.4, 115.2, 98.3, 88.5, 28.3, 26.4ppm.;EI-MS (m/z) = 324(M^+)

7-amino-5- (4-chlorophenyl)-1,3- dimethyl-2,4-dioxo-1,2,3,4- tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4e).

IR (KBr, cm^{-1}): 3377(-NH_2), 2206(-CN), 1759(-C=O), 1618(-C=O); ^{1}H NMR (300MHz, DMSO-d_6, ppm):3.2(s, 3H, CH_3), 3.55 (s, 3H, CH_3), 7.34(d, 1H, H_{Ar}), 7.50 (d, 1H, H_{Ar}), 7.72 (br s, 1H, H_{Ar}),7.81 (br s, 2H, NH_2) ppm; ^{13}C NMR (100MHz, DMSO-d_6,ppm): 170, 165, 155.4, 154.6, 150.1, 135.0, 133.7, 131.7, 70, 55, 28, 25.ppm; EI-MS (m/z) = 341 (M^{+1})

7-amino-5- (4-nitrophenyl)-1,3-dimethyl- 2,4-dioxo- 1,2,3,4- tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4f).

IR (KBr, cm^{-1}): 3297(-NH_2), 2222(-CN),, 1758(-C=O), 1624(-C=O) ;^{1}H NMR (300MHz, DMSO-d_6, ppm): 3.3(s, 3H, CH_3), 3.7 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 7.45(d, 2H, H_{Ar}), 8.38(d, 2H, H_{Ar}) ppm; ^{13}C NMR (100MHz, DMSO-d_6, ppm): 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. ppm; EI-MS (m/z) = 353 (M^+)

7-amino-5- (3-nitrophenyl)- 1,3- dimethy l-2,4-dioxo- 1,2,3,4- tetrahydropyrido [2,3-*d*] pyrimidine-6- carbonitrile (4g).

IR (KBr, cm^{-1}): 3384(-NH_2), 2216(-CN), 1768(-C=O), 1622(-C=O);^{1}H NMR (300MHz, DMSO-d_6, ppm): 3.3(s, 3H, CH_3), 3.7 (s, 3H, CH_3), 7.75(m, 2H, H_{Ar}), 7.77(br s, 2H, NH_2), 8.19(s, 1H, H_{Ar}), 8.29(qd, 1H, H_{Ar}),ppm;^{13}C NMR (100MHz, DMSO-d_6, ppm): 160.8, 160.2, 156.1, 159.0, 155.5, 150.1, 147.1, 138.4, 129.4, 134.8, 98.3, 88.3, 25.4, 29.3ppm; EI-MS (m/z) = 353 (M^+)

7-amino-5- (2-nitrophenyl)- 1,3-dimethy l-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4h)

.IR(KBr,cm-1): 3403(-NH_2), 2225(-CN) , 1707(-C=O), 1613(-C=O); ^{1}H NMR(300MHz, DMSO-d_6,ppm): 3.3 (s, 3H, CH_3), 3.7(s, 3H, CH_3), 7.75(s, 2H, NH_2), 7.51(d,1H,H_{Ar}), 7.43(dt, 1H, H_{Ar}), 7.38 (t, 1H, H_{Ar}), 7.28(dd, 1H, H_{Ar}) ppm;^{13}C NMR(100MHz,DMSO-d_6,ppm), 167.50, 173.50, 158.15, 156.02, 130.63, 129.53, 128.70, 128.37, 126.65, 114.50, 75, 53.3 ,29.49, 27.56ppm; EI-MS (m/z) = 353 (M^+)

RESULTS AND DISCUSSION

Herein, we report a synthesis of annulated pyrido [2, 3-*d*] pyrimidines (4a-**h)** using equimolar amount of Aromatic aldehydes **1,** Malononitrile **2** and 6-amino 1, 3-dimethyl uracil **3** in the presence of a catalytic amount of urea (10 mol%) using ethanol: water (1:1 ratio) as green solvent (Scheme 1). The formation of pyrido[2,3-d]pyrimidines proceeds tandem one-pot via Knoevenagel–cyclocondensation of aldehydes, malononitrile, in the presence of urea as a novel organo-catalyst and subsequent Michal addition of 6-amino 1,3 dimethyl uracil in aqueous ethanol at room temperature. Initial studies were focused on the reaction of 4-nitrobenzaldehyde (1mmol), malononitrile (1 mmol), and 6-amino 1,3 dimethyl uracil (1mmol) using aqueous ethanol solvent in presence of urea at room temperature**.** By using different catalytic amount of urea (5 mole %, 10 mole %, 15 mole %, 20 mole %, 30 mole **%**) the reactions were conducted at room temperature in aqueous ethanol.(Table 2) The best result obtained using 10 mol % of urea catalyst in terms of time and product yield. In the absence of the catalyst, the reaction was rather sluggish and resulted in poor yield (46%) even after 2.5 h time under same reaction conditions thus confirming role of urea as an efficient catalyst.

Table 1: Synthesis of pyrido[2,3-d]pyrimidine derivatives.

Product	Ar	Time	Yield	mp(in ^{0}C)	mp (Lit)
4a	4-Methyl	50	85	>300	>300 [12]
4b	Phenyl	45	90	>300	>300 [12]
4c	4-Methoxy	55	93	>300	>300 [12]
4d	4-hydroxyl	55	91	>300	___
4e	4-Chloro	55	92	>300	>300 [18]
4f	4-Nitro	55	95	>300	>300 [12]
4g	3-Nitro	65	86	>300	>300 [12]
4h	2-Nitro	75	89	>300	___

Table 2: Optimization of Mole % of Urea during the synthesis for model product 4f.

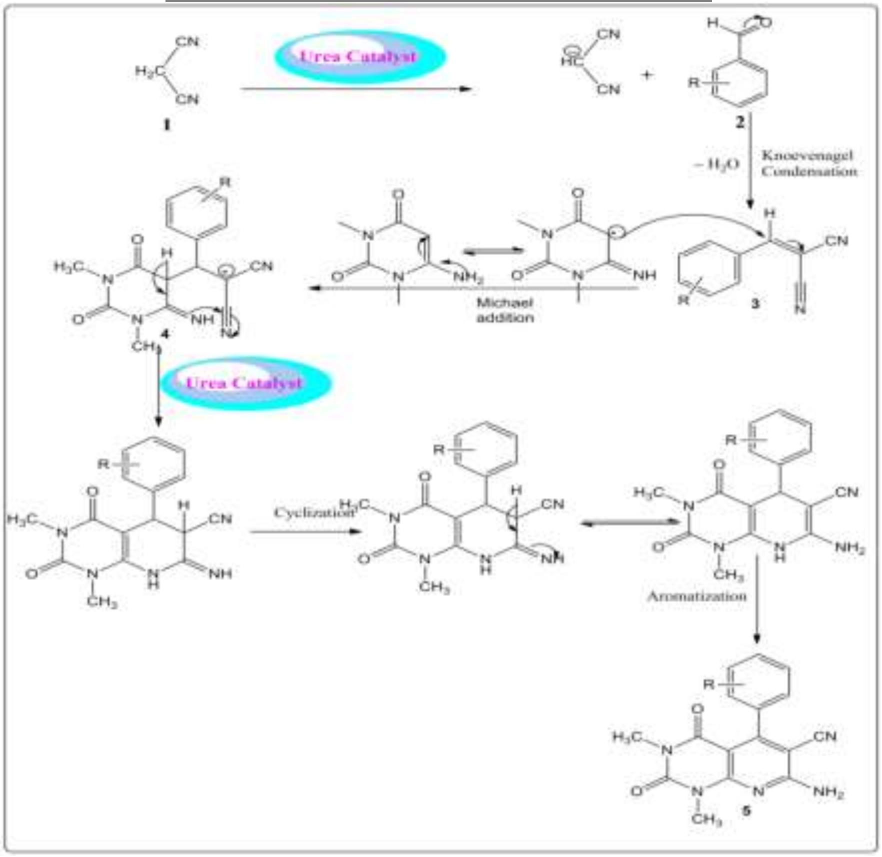
Entry	Mole% of urea	Time ^{a}(min)	Yield^b(%)
1	5	50	80
2	10	55	95
3	15	45	73
4	20	40	62
5	30	40	54
6	No catalyst	2.5hr	45

^{a}Reaction condition:- 4-Nitrobenzaldehyde, malononitrile (1mmol), 6 amino 1,3-dimethyl uracil(1mmol), in presence and absence of urea.

[b]Isolated yield.

Table 3: Synthesis of model product 4f with recycled urea catalyst.

No. of cycles	Time (min)	Yield (%)
1st run	55	95
2nd run	64	83
3rd run	76	67
No catalyst	150	45



Scheme 2: Plausible mechanism for the formation of pyrido[2,3-d]pyrimidine derivatives.

Herein, urea catalyst acts as a base which facilitates proton removal from active methylene compounds thereby increases reaction rate and yields of annulated pyrido[2,3-*d*]pyrimidines facilitating Knoevenagel condensation between aromatic aldehydes and active methylene compounds, proceeds via intermediate, undergoes dehydration and finally heterocyclization to produce annulated pyrido[2,3-*d*]pyramidine derivatives.(Scheme 2) All the isolated products were pure by washing with cold chromatographic purification was needed. Catalyst gets easily removed by aqueous washing due to its solubility in water; hence no need of further neutralization and work-up is accomplished by simple filtration. The organocatalyst urea and solvent obtained upon filtration of the reaction mixture after completion of the reaction can be reused up to third run.

Reactants added directly into the filtrate without adding further catalyst and solvent resulted in the formation of desired product with slight loss of catalytic activity at least up to third run. (Table 3). The structure of model compound **4f** was confirmed by IR, ^{1}H NMR,^{13}C NMR and mass spectrometric analysis. The ^{1}H NMR spectrum showed the presence three protons (CH_3) as singlet at δ δ 3.3and 3.7 other peaks at 5.78 (s, 2H, NH_2), 7.45(d, 2H, H_{Ar}), 8.38(d, 2H, H_{Ar}) The ^{13}C NMR spectrum showed 16 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. ppm. The mass spectrum of **4f** revealed a strong molecular ion peak at *m*/*z* 399 (M^+) in agreement with molecular weight of compound.

CONCLUSION

In conclusion, we have developed a very simple, facile and conveniently practical method for synthesis of annulated pyrimidines in the presence of urea as a novel organocatalyst. Mild reaction conditions, excellent yields, operational simplicity, no tedious separation procedures, clean reaction profiles, energy-efficiency and high atom-economy as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method. Therefore the synthetic method is simple as no special apparatus for work up are required and the compound formed is filtered and purified just by simple crystallization.

ACKNOWLEDGEMENT

Authors are thankful to SAIF-Chandigarh for providing spectral data and also thankful to head, department of Chemistry, RTM Nagpur University, Nagpur for providing laboratory facilities.

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