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Organocatalyzed One-Pot Three Component synthesis of 3,4,5,6-tetrahydro-4,5-bis(phenyl)pyrimido[4,5-d]pyrimidine-2,7(1H,8H)-dione/thione

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Abstract: A series of 3,4,5,6-tetrahydro-4,5-bis(phenyl)pyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione/thione (6a-l) were obtained by multi-component reaction of aromatic aldehyde, urea/thiourea and formaldehyde at 80 °C using organocatalyst in ethanol as solvent. The excellent yields, mild reaction condition, and simple experimental work-up are some of the advantages of this method, which makes it a useful protocol for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives.

Keywords: Hydrogen bonding; organocatalyst; pyrimido[4,5-d]pyrimidine; urea, thiourea.

Introduction

The pyrimidine nucleus is present in a wide range of bioactive natural products. In addition, the pharmacological and biological activities of pyrimidine derivatives are well documented [1-2], such as antiviral, antibacterial, antitumor, anti-inflammatory, antifungal, and anti-leishmanial agents [3]. Several documents have been reported for the preparation of these fused heterocycles, derivatives of which are useful as bronchodilators [4], vasodilators [5], anti-allergic [6], anti-hypertensive [7] and anti-cancer agents [4]. The presence of a pyrimidine system in thymine, cytosine, and uracil are the essential building blocks of nucleic acids and one possible reason for the activity [8]. Fused derivatives of pyrimidine with thiazole are bioactive. These derivatives are used as potent and selective inhibitors of acetyl-CoA carboxylase 2 [9] and VEGF receptors I and II [10]. They have also shown potent and selective human adenosine A 3 receptor [11-12] and vanilloid receptor I TRPVI antagonism [13].

One pot multi- component reactions are gaining more importance now days because of environmentally implication [14]. MCRs

are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. Due to these advantages these reactions are perfectly suited for combinatorial library synthesis, and thus are finding increasing use in the discovery process for new drugs and agrochemicals [15-16].

Most of the MCRs are based on condensation of carbonyl group [17]. The Biginelli reaction has been employed for the synthesis of pyrimido[4,5-*d*]pyrimidine [18] by the one-pot condensation of acetophenone, urea and aldehydes. And most of the methods involve modification of the Biginelli reaction by condensation of aldehydes, urea and alkyl arylketones in acetic acid using catalytic amounts of $KHSO_4$ [19]. Although Biginelli reaction is oftenly employed for the synthesis of pyrimido[4,5-*d*]pyrimidine by the use of base [20] and microwave assisted [21] synthesis.

The other promising methods for the synthesis of pyrimido[4,5-*d*]pyrimidines involve multistep syntheses starting from 1,3-disubstituted cyanouracils [22], polymer bound aminopyrimidine derivatives [23], aza-Wittig-type reactions [24] and reacting aminouracils with various heterocumulenes [25]. Synthetic alternatives are many, varied and have resorted to harsh conditions, *e. g.* the use of PTSA (*p*-toluenesulfonic acid) as catalyst, using $POCl_3$ with DMF as a solvent [26]. Additionally, reagents for these procedures are not readily or commercially available.

Considering all above facts and importance of pyrimido[4,5-*d*]pyrimidine derivatives, it is considered worthwhile to find out new methodology for synthesizing these compounds utilizing green chemistry protocol like using eco-friendly reagents and catalysts, solvent free or reaction in non-hazardous solvent, because it offers enhanced chemical process economics concomitant with a reduced environmental burden.

Experimental

General details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F_{254}, Merck grade was used for thin layer chromatography to determine progress of reaction. The column chromatography was carried out over silica gel (80–120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on an Avance 300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

General procedure for the synthesis of tetrahydropyrimido [4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione (6).

To a mixture of formaldehyde (1.2 mmol), aldehyde (1.0 mmol), and urea / thiourea (1.0 mmol) in solvent ethanol (20 mL) 12 mole % of organocatalyst (*S*)-*N*-(4-fluorophenyl)-1-tosylpyrrolidine-2-carboxamide was added. The reaction mixture was heated and stirred at 80 °C for the stipulated period of time till the full consumption of the starting materials (monitored by TLC). After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid obtained was filtered and washed with water to get the crude product they were crystallized from hot ethanol. Crude product may be purified by column chromatography to give pure desired product molecules.

Characterization of some representative compounds

4,5-bis(4-hydroxyphenyl)-3,4,5,6-tetrahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione (6a). White solid; **M.P. (°C):** 220-230.; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.89 (s, 2H, NH), 9.48 (s, 2H, OH), 8.72 (s, 2H, NH), 7.56-7.71 (m, 4H), 6.83-7.19 (m, 4H), 5.71(s, 2H); **^{13}C-NMR (300 MHz, $CDCl_3$):** δ 161.09, 145.55, 136.05, 130.30, 125.42, 118.80, 97.59, 55.13; **GC-MS:** *m*/*z* 352.33 (M^+); **Elemental Analysis:** $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90; O, 18.16; Found C, 61.38; H, 4.60; N, 15.88 O, 18.17.

4,5-bis(4-methoxyphenyl)-3,4,5,6-tetrahydropyrimido[4,5-*d*] pyrimidine-2,7(1*H*,8*H*)-dione (6c) Blackish solid; **M.P. (°C):** 183-185.; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.66 (s, 2H, NH), 7.10-7.28 (m, 4H), 6.82-6.97 (m, 4H), 4.37(s, 2H), 3.49 (s, 6H) 2.41 (s, 2H, NH); **^{13}C-NMR (300 MHz, $CDCl_3$):** δ 182.80, 160.17, 152.33, 138.79, 125.89, 116.00, 83.78, 63.20, 56.61; **GC-MS:** *m*/*z* 380.39 (M^+); **Elemental Analysis:** $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73; O, 16.82; Found C, 63.17; H, 5.27; N, 14.71; O, 16.80.

4,5-bis(4-hydroxyphenyl)-3,4,5,6-tetrahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dithione (6g)
Blackish solid; **M.P. (°C):** 183-185; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.89 (s, 2H, NH), 8.24 (s, 2H, OH), 7.56-5.61-7.18 (m, 8H), 3.90 (s, 2H), 2.22 (s, 2H, NH); **^{13}C-NMR (300 MHz, $CDCl_3$):** δ 173.00, 156.61, 148.21, 132.18, 117.04, 97.04, 52.77; **GC-MS:** *m*/*z* 384.47 (M^+); **Elemental Analysis:** $C_{18}H_{16}N_4O_2S_2$: C, 56.23; H, 4.19; N, 14.57; O, 8.32; S, 16.68; Found C, 56.23; H, 4.19; N, 14.55; O, 8.34; S, 16.67.

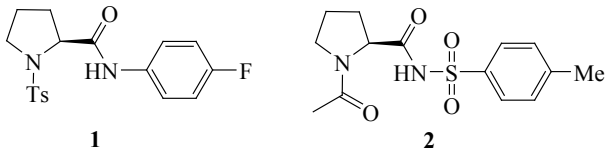
Characterization data for 4,5-bis(4-methoxyphenyl)-3,4,5,6-tetrahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dithione (6i)

Brownish solid; **M.P. (°C):** 183-185; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.38 (s, 2H, NH), 6.82-7.16 (m, 8H), 4.77 (s, 2H), 3.79 (s, 6H) 2.18 (s, 2H, NH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 178.90, 1566.88, 148.20, 135.33, 123.01, 116.48, 93.19, 58.51, 56.58; **GC-MS:** *m*/*z* 412.54 (M^+); **Elemental Analysis:** $C_{20}H_{20}N_4O_2S_2$: C, 58.23; H, 4.89; N, 13.58; O, 7.76; S, 15.55; Found C, 58.20; H, 4.90; N, 13.59; O, 7.77; S, 15.56.

Result and discussion

Continuing our interest in organocatalysis [27], synthesis of bioactive molecules [28] and on the basis of the success of our previous results on hydrogen bonding organocatalysis by neutral chiral pyrrolidine compounds (**Figure 1**) and escalating our research in organocatalysis, we sought to study the synthesis of pyrimido[4,5-*d*] pyrimidine by these pyrrolidine based organocatalysts (**1 and 2**), exclusively *via* hydrogen-bonding interaction.

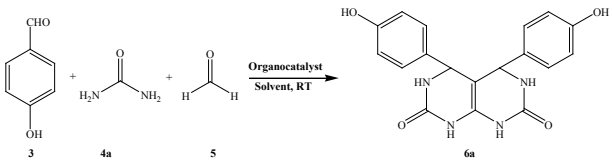
Figure 1. *L*-Proline based organocatalysts.



1 **2**

We started our investigation with the synthesis of 4,5-bis(4-hydroxyphenyl)-3,4,5,6-tetrahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione (**6a)** by stirring equimolar quantity of p-hydroxybenzaldehyde (**3a**), urea (**4a**), formaldehyde (**5)** and 10 mol % of organocatalyst using ethanol as solvent. The reaction was studied using different concentration of both synthesized organocatalyst and optimized using various solvent and varying temperature conditions.

Scheme 1. The synthesis of 3,4,5,6-tetrahydro-4,5-bis(4-hydroxyphenyl)pyrimido[4,5-*d*] pyrimidine-2,7(1*H*,8*H*)-dione (**6a**)



Although reaction completed with both the catalyst at room temperature conditions, results obtained were not satisfactory. When compound **1** was used as catalyst, it required 18 hours for completion to offer poor 58% yield. The reaction performed using organocatalyst **2,** the reaction required 24 hours for completion and yield obtained was 47% (Table 1, entries 1 and 2).

Our next attempt was to find optimum condition for reaction in terms of catalytic loading and solvent. We tried various solvent and different concentration of catalyst; obtained results are given in Table 1. The favorable conditions in ethanol were obtained at 12 mol% of catalyst **1,** the reaction was completed in 15 hours and yield obtained was 67 % (Table 1, entry 3). When organocatalyst **2** was used in 12 mol% reaction rate did not show significant effect but yield of the product was decreased to 45 % (Table 1, entry 4). At the higher catalytic loading (15 mol%) of catalyst **1** drop in reaction rate (20 h) and yield 56 % was observed (Table 1, entry 5).

Further, we screened various solvents using 12 mol% organocatalyst 1. When the reaction was carried out in methanol it offered yield 55 % in 16 h (Table 1, entry 6). By replacing alcoholic solvents with water the reaction time offered very poor 32 % yield even with extended (24 h) reaction time (Table 1, entry 7). To study effect of aprotic polar solvents we used acetonitrile, *N*, *N*-dimethylformamide and dimethyl sulfoxied as solvent. Notably polarity showed insignificant effect on the reaction. In these solvents product yields were less than 40 % and reaction rate was also very slow (Table 1, entries 8-10). Further non polar solvents dichloromethane and chloroform showed more adverse effect on the reaction. In dichloromethane the reaction was more sluggish to offer very poor 28% yield whereas chloroform as solvent gave traces yield (Table 1, entries 11 and 12).

Table 1: Effect of solvent and catalyst concentration on the synthesis of tetrahydropyrimido [4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione reaction.

Entry	Solvent	Catalyst	Conc. mol %	Time (h)	Yield[a](%)
1	Ethanol	1	10	18.00	58
2	Ethanol	2	10	24.00	47
3	Ethanol	1	12	15.00	67
4	Ethanol	2	12	24.00	45
5	Ethanol	1	15	20.00	56
6	Methanol	1	12	16.00	55
7	Water	1	12	24.00	32
8	Acetonitrile	1	12	20.00	39
9	N, N'-Dimethyle formide	1	12	24.00	30
10	Dimethyl sulphoxide	1	12	26.00	28
11	Dichloromethane	1	12	30.00	28
12	Chloroform	1	12	30.00	Trace

[a] Isolated yields

Table 2: Effect of solvent and temperature on synthesis of tetrahydropyrimido[4,5-d] pyrimidine-2,7(1H,8H)-dione

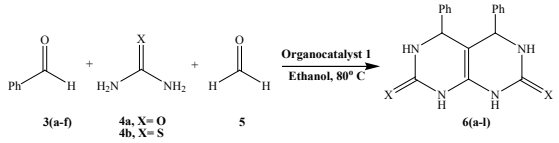
Entry	Solvent	Temperature °C	Time (h)	Yield[a] %
1	Ethanol	40	15.00	75
2	Ethanol	60	12.30	81
3	Ethanol	80	08.00	89
4	Ethanol	100	10.00	83

[a] Isolated yields

To achieve best optimum conditions reaction was further tested at elevated temperatures using organocatalyst **1** in ethanol. When reaction was carried out at slight higher temperature yield of the product was enhanced (75%) and reaction rate showed no effect (Table 2, entry 1). At further elevated temperature of 60 °C reaction time was reduced to 12.30 hours to obtain yield 81 % for product **6a** (Table 5, entry 2). As temperature was raised to 80 °C best optimized conditions were achieved. The reaction completed in 8 h and gave **6a** in excellent yield 89 % (Table 5, entry 3). Further increase in temperature failed to improve performance of the reaction (Table 5, entry 4).

The scope of the reaction was extended to other aldehydes using urea and thiourea. We found that reaction proceeds smoothly for all aldehydes with urea and thiourea. Aromatic ring bearing electron donating groups were more reactive to obtain high yields with less reaction time. Nitro aldehydes gave moderate yield with long reaction time relatively. Amongst urea and thiourea; urea was more reactive however yield obtained for both derivatives were analogous.

Table 3. Exploration of the substrate scope for the synthesis of tetrahydropyrimido [4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione.



Entry	Ar	X	Time (h)	Product	Yield[a] %	MP °C
1	4-OH	O	08.00	6a	89	229-230
2	2-OH	O	08.30	6b	88	210-211
3	4-OCH_3	O	08.00	6c	90	183-185
4	H	O	10.30	6d	80	190-192
5	4-NO_2	O	12.00	6e	78	233-235
6	3-NO_2	O	12.30	6f	79	218-220
7	4-OH	S	10.00	6g	85	165-166
8	2-OH	S	10.00	6h	87	175-177
9	4-OCH_3	S	09.30	6i	88	183-185
10	H	S	12.00	6j	79	155-150
11	4-NO_2	S	13.30	6k	77	177-178
12	3-NO_2	S	13.00	6l	75	180-181

[a] Isolated yields

Figure **3**, represents mechanism for the synthesis of tetrahydropyrimido[4,5-d] pyrimidine-2,7(1H,8H)-dione. Organocatalyst activate substrate through hydrogen bonding, it forms transition state **I** which prevent formation of imine and give intermediate **II**. On reaction with formaldehyde this intermediate undergoes Michael addition to give intermediate **III**. Being unstable it reacts with aldehydes subsequently to give final intermediate **VI** which rearranges to form desire product.

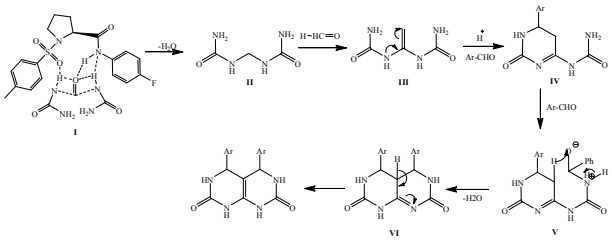


Figure 1. Mechanism for the synthesis of tetrahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,8*H*)-dione derivatives.

Mechanism illustrate the obtained result, in polar solvent reaction proceeds through imine (urea and formaldehyde) formation thus forming undesirable products leading to less yield of product. In water solvent aldehyde was not soluble, water also interrupt hydrogen

bonding so fails to give satisfactory results. In solvent ethanol and methanol almost comparable results were obtain with ethanol as superior to methanol; ethanol is green solvent so we continued our studies with ethanol. In non polar solvent urea and thiourea are insoluble so reaction did not proceed in these solvents. At higher degrees of temperature substrate gets more activated to give excellent results.

Conclusion:

In conclusion, we have developed new facile method for asymmetric synthesis of functionalized piperidines. Reaction was studied using various organocatalysts**1** and **2**. The organocatalyst (*S*)-*N*-(4-fluorophenyl)-1-tosylpyrrolidine-2-carboxamide **1** was proved to be the best organocatalyst in ethanol to yield product **6a** up to 89%. Catalyst plays a crucial role by providing strong hydrogen bonding to substrate. The present method was studied for broad range of aromatic aldehydes. The yields obtained of products were good for all type of substituent on the aromatic ring. Mild reaction condition, eco-friendly solvent system, and high yield with a wide range of substrates are some striking features of reaction.

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Reference:

1. H. Numazl, Y. R. Mirzeni, H. Azamat, J. Heterocycl. Chem., **2001**, 38, 1051.
2. C. O. Kappe, Eur. J. Med. Chem., **2000**, 35, 1043.
3. (a) M. B. Deshmukh, S. M. Salunkhe, D. R. Patil, P. V. Anbhule, Eur. J. Med. Chem., **2009**, 44, 2651; (b) M. J. Aliaga, D. J. Ramon, M. Yus, Org. Biomol. Chem., **2010**, 8, 43.
4. W. J. Coates, European Patent 351058, 1990; Chem. Abstr. **1990**, 113, 40711.
5. J. D. Figueroa-Villar, C. L. Carneiro, E. R. Cruz, Heterocycles, **1992**, 34, 891.
6. N. Kitamura, A. Onishi, European Patent 163599, 1984; Chem. Abstr. **1984**, 104, 186439.
7. R. Gupta, A. Jain, R. Joshi, M. Jain, Bull. Korean Chem. Soc., **2011**, 32, 899.
8. A. Amir, S. A. Javed, H. Kumar, Indian J. Pharm. Sci., **2007**, 69, 337.
9. F. R. Clark, T. Zhang, X. Wang, R. Wang, X. Zhang, S. H. Camp, B. A. Beutel, H. L. Sham, G. Y. Gu, Med. Chem. Lett., **2007**, 17, 1961.
10. A. S. Kiselyov, E. Piatanitski, M. Semenova, V. V. Semenov, Bioorg. Med. Chem. Lett., **2006**, 16, 602.
11. Y. K. Jung, K. S. Kim, G. Z. Geo, A. S. Gross, N. Melman, K. A. Jacobson, C. Y. Kim, Bioorgan. Med. Chem., **2004**, 12, 613.
12. P. Bhattacharya, T. J. Leonard, K. Roy, Bioorgan. Med. Chem., **2005**, 13, 1159.
13. N. Xi, Y. Bo, E. M. Doherty, C. Fotsch, N. R. Gawa, N. Han, R. W. Hungate, L. Klionsky, Q. Liu, R. Tamir, Bioorg. Med. Chem. Lett., **2005**, 15, 5211.
14. C. C. A. Cariou, G. J. Clarkson, M. Shipman, J. Org. Chem., **2008**, 73, 9762.
15. A. Domling, I. Ugi, Angew. Chem. Int. Ed., **2000**, 39, 3168.
16. (a) I. Ugi, A. Domling, Endeavour **1994**, 18, 115; (b) S. Heck, A. Domling, Synlett **2000**, 424.
17. A. Bazgira, M. M. Khanaposhtani, A. A. Soorki, Bioorg. Med. Chem. Lett., **2008**, 18, 5800;
18. (a) V. F. Sedova, O. P. Shkurko, Chem. Heterocycl. Compd. (Engl. Transl.) **2004**, 40, 194; (b) R. L. Magar, P. B. Thorat, P. B. Thorat, V. V. Thorat, B. R. Patil, R. P. Pawar, Chin. Chem. Lett., **2013**, 24, 1070.
19. F. Shi, R. Jia, X. Zhang, S. Tu, S. Yan, Y. Zhang, B. Jiang, J. Zhang, C. Yao, Synthesis, **2007**, 2782.
20. N. Sharma, V. Rane, K. Gurram, Biorg. Med. Chem. Lett., **2004**, 14, 4185.
21. H. Dabiri, H. Arvin-Nezhad, R. Khavasi, A. Bazgir, J. Heterocyclic chem., **2007**, 44, 1009.
22. K. Hirota, Y. Kitade, H. Sajiki, Y. Maki, J. Chem. Soc., Perkin Trans., 1 **1990**, 123.
23. S. K. Srivastava, W. Haq, P. M. S. Chauhan, Bioorg. Med. Chem. Lett., **1999**, 9, 965.
24. H. Wamhoff, J. Muhr, Synthesis, **1998**, 919.
25. D. Prajapati, A. J. Thakur, Tetrahedron Lett., **2005**, 46, 1433.
26. K. Hirota, Y. Kitade, H. Sajiki, Y. Maki, Synthesis, **1984**, 589.
27. (a) P. B. Thorat, S. V. Goswami, B. C. Khade, S. R. Bhusare, Tetrahedron Lett., **2012**, 53, 6083;(b) P. B. Thorat, S. V. Goswami, B. C. Khade, S. R. Bhusare, Tetrahedron: Asymmetry, **2012**, 23, 1320
28. (a) S. V. Goswami, P. B. Thorat, S. R. Bhusare, Tetrahedron Lett., **2012,** 53, 6771; (b) S. V. Goswami, P. B. Thorat, S. R. Bhusare, Heterocycl. Commun., **2012**, 18, 245.