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L-Proline based ionic liquid: A highly efficient and homogenous catalyst for synthesis of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione and pyrano[2,3-d] pyrimidine diones under ultrasonic irradiation

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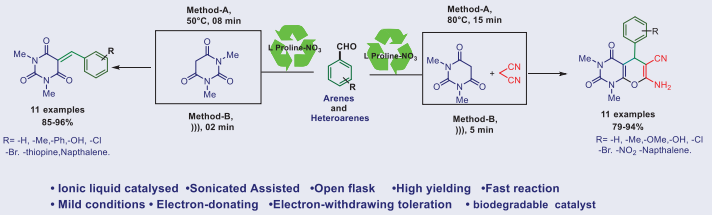
ABSTRACT

A catalytic, practical, efficient procedure for the synthesis of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione and pyrano[2,3-d] pyrimidine diones at room temperature was developed using L-Proline nitrate ionic liquid under ultrasonic irradiation. The L-Proline nitrate is homogeneous and green catalyst easy to prepare by mixing L-Proline and nitric acid possess excellent catalytic activity under standard ultrasonic bath at room temperature for the synthesis of pyrimidine core. This adequate procedure offers some advantages like the use of green solvent H_2O, environmentally green benign procedure, excellent yields, simple procedure, short reaction times, no need for column chromatographic separation and reusability of catalyst for five subsequent reaction.

GRAPHICAL ABSTRACT



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Amino acid ionic liquid; e5-benzylidene-1,3-dimethyl-pyrimidine-2,4,6(1H,3H,5H)-trione; L-Proline nitrate; pyrano[2,3-d] pyrimidine diones; ultrasonic irradiation

Introduction

Ionic liquids (ILs) have attracted extensive interest in organic synthesis, in recent years[1] because of their supreme values in organic synthesis. Basically, ionic liquid exists in synthetic quaternary nitrogen organic salts due to their high selectivity which added green treasure in ongoing organic research.[2] High thermal stability, low volatility, recyclability, non-flammability, negligible vapors pressure, ability to dissolve many organic and inorganic substances and miscibility with water and organic solvents are

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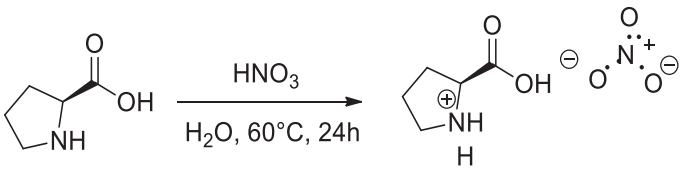


Scheme 1. Synthesize of L-Proline nitrate ionic liquid.

key features of the ionic liquid.[3] L-Proline-NO_3 ionic liquids are an important class of amino acid ionic liquids (AAILs) easily derived from naturally occurring precursors. L-Proline nitrate ILs are green ILs obtained from natural, bio-compatible and nontoxic materials and additionally they can be easily synthesized from commercially available material.[4] Being inspired by these common advantages and demand of AAIL-mediated reactions for synthetic organic chemists for the synthesis of biologically active molecules, we have synthesized L-Proline nitrate ionic liquid with previous reported procedure in our lab (Scheme 1).

5-Benzylidene barbituric acids and their derivatives are pharmacologically important because compounds containing these structural motifs possess, antibacterial, antileprotics,[5] sedative-hypnotic, anticonvulsant, and local anesthetic drugs,[6] antitumor[7] activities. 5-benzylidene barbituric acids and their 2-thio derivatives are seem to be important class of compounds found as intermediate in preparation of heterocyclic compounds,[8] oxathiazolidines,[9] benzyl barbituric derivatives,[10] and unsymmetrical desulfated[11]. 5-benzylidene barbituric acids are easily synthesized *via* Knoevenagel condensation reaction of barbituric acid derivatives with aromatic aldehydes. Literature search displays several described methods for synthesis of various 5-benzylidene barbituric acids derivatives. Such as nickel nanoparticles,[12] nano Fe_3O_4,[13] DABCO-based polymer,[14] piperidine,[15] aq KOH.[16] Pyran frameworks are common structural subunits in natural products such as alkaloids, carbohydrates, polyether antibiotics, pheromones, and iridoids.[17]

Pyrano[2,3-d] pyrimidine is unsaturated six-membered heterocycle which is framed by a combination of pyran and pyrimidine rings together, comprising two nitrogen atoms at position number 1,3 and one oxygen atom present at position number 8. Pyrano[2,3-d] pyrimidine possesses remarkable therapeutic applications and biological activities such as antitumor, anticancer, antifungal, antioxidant, and antihypertensive.[18] Therefore, for the preparation of the important pyrimidine and their derivatives large assays have been occurred. Figure 1 represents some of the bioactive pyrimidine-annulated heterocyclic compounds exhibiting a diverse kind of pharmaceutical potentials.

Between the known procedures for the synthesis of pyrano[2,3-d] pyrimidine diones derivatives, the most simple and straightforward protocol for synthesis of pyrano[2,3-d] pyrimidine diones *via* three-component condensation of 1,3 dimethyl barbituric acid, malononitrile, and aromatic aldehyde. To date, wide variety of catalyst have been reported for the synthesis of pyrano[2,3-d] pyrimidine compounds, such as $(NH_4)_2HPO_4$,[19] SBA-Pr-SO_3H,[20] TMU-16-NH_2,[21] KF,[22] $ZnFe_2O_4$,[23] $\{Fe_3O_4@SiO_2@(CH_2)_3$-Urea-$SO_3H/HCl\}$ magnetic nanoparticle,[24] Et_3N,[25] and ZnO nano powder.[26] However, the methods go through one or more drawbacks, such as

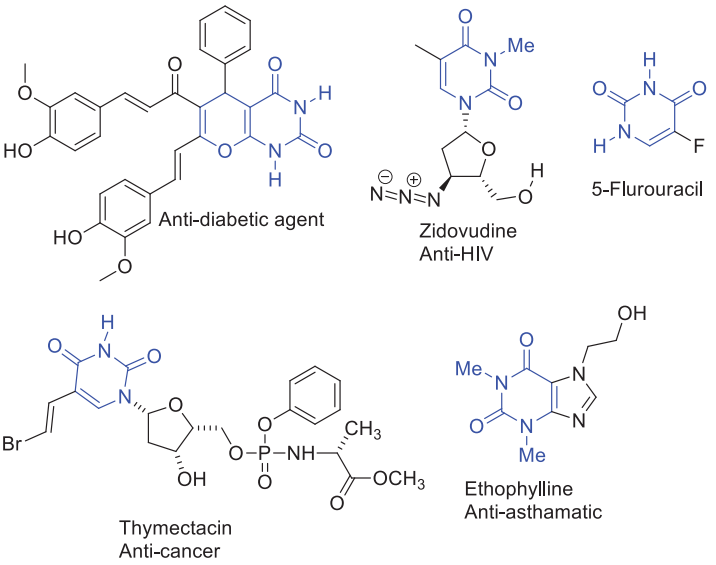


Figure 1. Some bioactive pyrimidine-annulated heterocyclic compounds.

longer reaction time, unsatisfactory yield, harsh reaction condition, expensive reagents, tedious workup, use of toxic, and volatile organic solvents. Therefore, this encourages us to develop efficient clean, high-yielding, and environmentally friendly methodology for the synthesis of pyrimidine.

Thus, the researcher is compelled to search an efficient, environmentally friendly approach for the synthesis of these heterocyclic compounds with impressive yields. In continuation of our previous literature studies, we wish to report the applicability of L-Proline-NO_3 ionic liquid in promoting the synthesis of pyrano[2,3-d] pyrimidine diones. All reaction is carried out in mild reaction condition with high yield and comparatively in short reaction time.

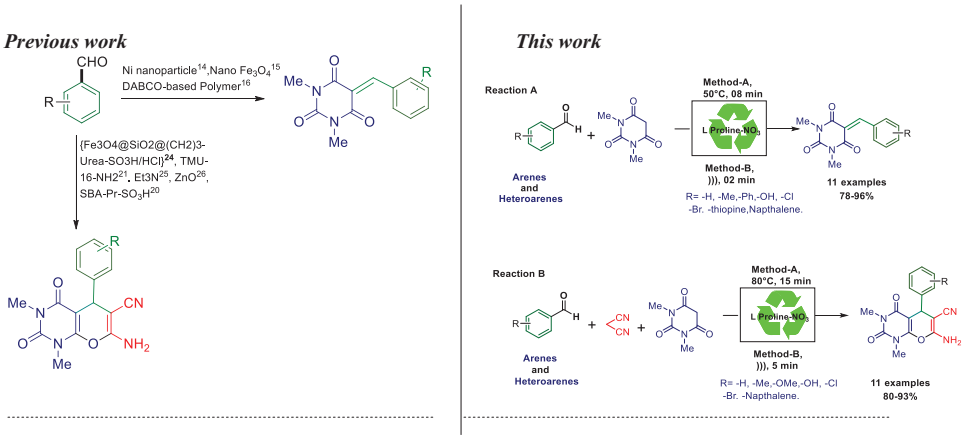
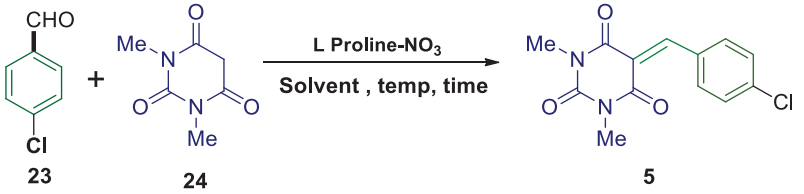


Table 1. Optimization of reaction condition for synthesis of 5-(4-chlorobenzylidene)-1, dimethylpyrimidine-2,4,6(1H,3H,5H)-trione by L-Proline Nitrate[a].



Entry	Catalyst (mole%)	Solvent	Temp. °C	Time (min)	Yield (%)[b]
1	–	Solvent free	RT	6 h	Traces
2	20	Solvent free	RT	2 h	<20
3	20	*n*-Hexane	Reflux	80	60
4	20	CH_2Cl_2	Reflux	80	75
5	20	CH_3CN	Reflux	60	78
6	20	C_2H_5–OH	Reflux	30	86
7	20	H_2O	Reflux	08	94
8	5	H_2O	50	20	80
9	10	H_2O	50	10	86
10[d]	**15**	**H_2O**	**50**	**08**	**94**
11	25	H_2O	50	08	94
12[c]	**15**	**H_2O**	**RT**	**02**	**94**

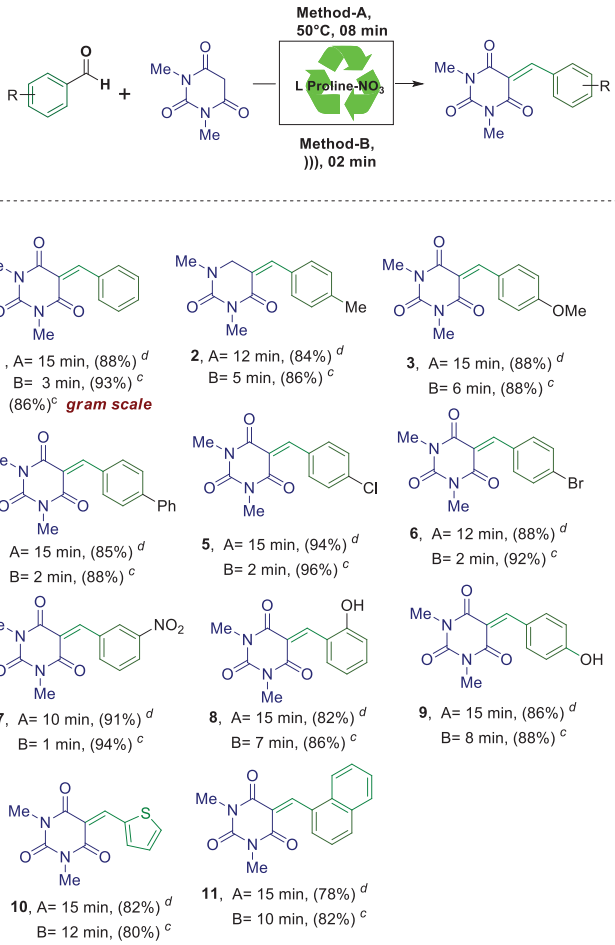
[a]Reaction conditions: 4-chloro benzaldehyde (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), solvent (0.15 *M*), open flask, [d]Method A= conventional method, [c]Method B = ultrasonication, and [b]Isolated yield.
Best yield are shown by bold.

Results and discussion

Recently, our group publish the activation of aromatic aldehyde using Chitosan–SO_3H catalyst.[27] Those results encouraged us also, ILs reports on multicomponent type reaction. We hypothesized that using an ionic liquid, such as L-Proline-NO_3 could give rise to **1**–**11** and **12**–**22** type of compound activating aromatic aldehyde *via* nucleophilic addition of 1,3 dimethyl barbituric acid. In the beginning, we focused our attention for the synthesis of pyrimidine motif to search optimal reaction condition the condensation of 4-chlorobenzaldehyde (1 mmol) with 1,3 dimethyl barbituric acid (1 mmol) was selected as a model reaction and the optimization assay including the method of reaction, amount of catalyst, solvent and temperature were examined, the results of which are tabulated in (Table 1).

We first studied the reaction at room temperature in the and presence of L-Proline-NO_3 catalyst under solvent-free in 6 and 2 h respectively, which gave product **5** in trace and <20% yield, respectively (Entries **1**–**2**). These experiments validated our hypothesis and confirmed that the presence of L-Proline-NO_3 was able to increase yield. These results inspired us for further optimization. In fathered optimization, we carried out the reaction with different nonpolar and polar hexane, CH_2Cl_2, CH_3CN, EtOH, H_2O with 20 mole% of L-Proline-NO_3 catalyst product **5** yields in 60, 75, 78, 86, and 94%, respectively (Entries **3**–**7**).

Next, we decided to decrease the catalyst loading for these purposes, hence analyzed the model reaction in water as solvent at temperature 50 °C in different amount of catalyst at 5 mole%, 10 mole%, 15 mole%, and 25 mole% affording 80, 86, 94, and 94% products yield, respectively (Entries **8**–**11**). Then, further increase in the amount of catalyst



[a]Reaction conditions: aromatic aldehyde (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), Method. [d] Method **A**= Conventional method, [c]Method **B**= Ultra sonication, Isolated yield.

Scheme 2. Synthesis of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione derivatives under optimized conditions.

beyond 15 mole% had no additional effect on the increase in the yield of product **5**. After optimizing catalyst loading and solvent condition, an additional optimization reaction was performed using method B in the presence of ultrasound irradiation. Gratifyingly, the best yields were obtained using method B of 96% and time was reduced to 2 min (Entry **12**). Among the various tested conditions, Entries **10** and **12** show the more appropriate condition for this reaction (Scheme 2).

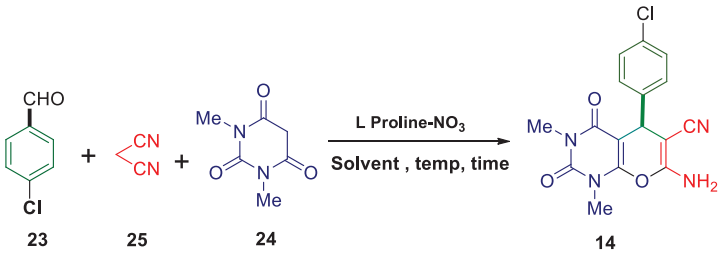
With the optimal reaction condition in hand, we proceeded to explore the scope of this new protocol with respect to changes in the aryl unit with 1,3-dimethyl barbituric acid (Scheme 2). A range of electron-donating and electron-withdrawing aromatic aldehyde substrate was tested as well as some of their heterocyclic derivatives. Thus,

benzaldehyde treated with 1,3-dimethyl barbituric acid in an optimized condition leads to **1** in 93%. Remarkably, gram-scale reactions were achieved providing **1** in 86% this reaction proved scalability and efficiency of our procedure. 4-Methyl benzaldehyde and 4 methoxy benzaldehyde treated with 1,3-dimethyl barbituric acid 86 and 88% yields were obtained for **2** and **3,** respectively. The [1,1′-biphenyl]-4carbaldehyde in the same reaction condition yielded an excellent 88% to get **4**. Encouraged by excellent results of electron-donating aldehyde derivative, in further scope for reaction was tested for electron deactivating aromatic aldehyde derivatives. The 4-chlorobenzaldehyde and 4-bromobenzaldehyde treated with 1,3-dimethyl barbituric acid 96 and 92% yields were obtained for **5** and **6**, respectively. Also, strong electron $-NO_2$ leads to the formation of **7** in 94% yield which revels the excellent efficiency of our protocol toward the strongly electron-withdrawing group. 2 hydroxy benzaldehyde and 4 hydroxy benzaldehyde treated with 1,3-dimethyl barbituric acid yielded 86 and 88% for **8** and **9**, respectively. It shows that free –OH group did not influence for the formation of the corresponding product and allowed reaction to proceed. In the case of heterocyclic aldehyde, substrate thiophene-2-carbaldehyde gave rise to corresponding product **10** in 80% yield, also fused aromatic aldehyde substrate alpha naphthaldehyde gives corresponding product **11** in good yield of 82%. Thus, we denied that heterocyclic aldehyde and fused aromatic aldehyde affect yield. Interestingly, the catalyst also efficiently promoted the reaction of 1,3-dimethyl barbituric acid with various electron-donating, electron-withdrawing and heteroaromatic as well as fused aromatic aldehyde to furnish corresponding product in high to excellent yields and in short reaction times.

After our first successful synthesis of 5-benzylidene-1,3-dimethylpyrimidine 2,4,6 (1H, 3H, and 5H)-trione, we were inspired to achieve an advantage for another reaction synthesis for a synthesis of pyrano[2,3-d] pyrimidinones derivative. We initially require validation of our hypothesis using 4-chlorobenzaldehyde, malononitrile, 1,3 dimethyl barbituric acid using L-Proline-NO_3 selected as a model reaction. The illustrative optimization assays are summarized in Table 2. Initially attempt carried out were performed based on our previously developed conditions for the synthesis of pyrimidine (Table 1) in the absence of catalyst at room temperature under solvent-free condition after 6 h observed that starting material remains unreacted (Entry **1**). Then, we carry out reaction with L-Proline-NO_3 (20 mol%) at room temperature under solvent-free condition to form product **14** in $<$10% (Entry **2**), it shows that our another hypothesis also work using L-Proline-NO_3 catalyst further for optimization solvent were examined under reflux condition. Using different polar and non-polar solvent, such as *n*-Hexane, CH_2Cl_2, CH_3CN, EtOH, H_2O with (20 mole%) catalyst product led product **14** yields in 55, 70, 75, 86, and 92%, respectively (Entries **3**–**7**), it shows moderate to excellent yield.

Also, for the conventional method, we optimized assay in order to check the optimized reaction for varying temperature and catalyst loading; the model reaction was carried at 50 °C in H_2O and 80 °C with (10 mole%), (15 mole%), (20 mole%), and (25 mol%) product **14** yield in 70, 84, 92, and 92%, respectively (Entries **8** and **12**–**14**). After optimizing some entries for a conventional method by variating parameters such as temperature, solvent, and catalyst loading, we moved to optimized reaction assay for method B in the presence of ultrasound irradiation, which led to the formation of **14** in

Table 2. Optimization of reaction condition for the synthesis of 7-amino-5-(4-chlorophenyl)-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-1H-pyrano(2,3-d) pyrimidine-6-carbonitrile catalyzed by L-Proline-NO_3[a].



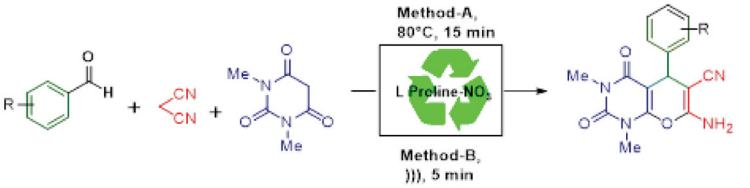
Entry	Catalyst (mole %)	Solvent	Temperature °C	Time (min)	Yield %[b]
1	–	Solvent free	RT	6 h	n. r.
2	20	Solvent free	RT	3 h	<10
3	20	*n*-Hexane	Reflux	90	55
4	20	CH_2Cl_2	Reflux	90	70
5	20	CH_3CN	Reflux	90	75
6	20	C_2H_5-OH	Reflux	25	86
7	20	H_2O	Reflux	15	92
8	20	H_2O	50	60	70
9[c]	10	H_2O	RT	10	84
10[c]	**15**	**H_2O**	**RT**	**04**	**94**
11[c]	20	H_2O	RT	04	94
12[d]	10	H_2O	80	20	84
13[d]	**15**	**H_2O**	**80**	**15**	**92**
14[d]	25	H_2O	80	20	92

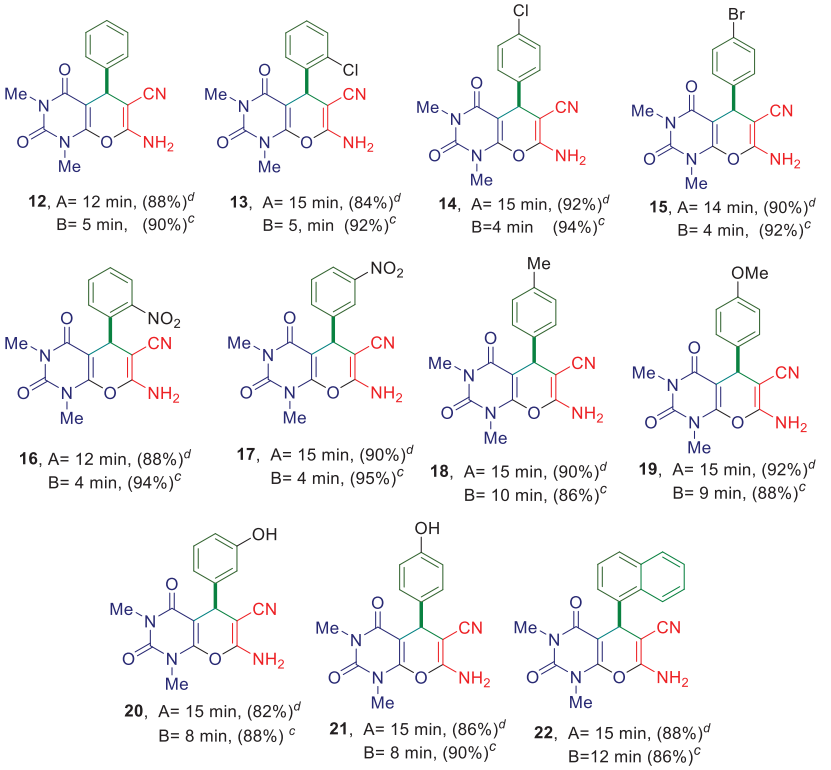
[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol), Malononitrile (1 mmol), 1,3 di methyl barbituric acid (1 mmol), solvent (0.15 *M*), open flask. n.r. = no reaction observed. Method: [d]Method A = Conventional method, [c]Method B = ultrasonication, [b]Isolated yield.

94% and reduced to 4 min (Entry **10**). It is concluded that our hypothesis also works for L-Proline-NO_3 catalyst under ultrasound irradiation with an excellent yield. In further optimization assay, we varied catalyst lodging (20 moles %) (10 moles %), which led to Product **14** yield in 94% and 84%, respectively (Entries **9** and **11**).

Further increase or decrease in the amount of catalyst loading did not significantly change in the yield of Product **14.** After all this optimization assay with various tested conditions, it concludes that Entries 10 and **13** show that the more appropriate condition for this reaction are methods A and B. With the optimal reaction condition in hand, we proceeded to explore the scope (Scheme 3).

After established optimal reaction condition, we developed a broad scope for this protocol with different electronic environment, such as electron rich, electron deficient, and fused aryl aldehyde. Benzaldehyde treated with malononitrile and 1,3-dimethyl barbituric acid in standard optimized condition leads **12** in 90% yield. To examine electronic effect with different electron-withdrawing aldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, and 4-bromobenzaldehyde treated with malononitrile and 1,3-dimethyl barbituric yielded 92, 94, and 92% of **13**, **14,** and **15**, respectively, showing an excellent yield. Also, strong electron-withdrawing group 2-nitrobenzaldehyde and 3-nitrobenzaldehyde, yielded 94% and 95% of products **16** and **17**. The above results conclude that our protocol tolerates the electron-withdrawing substituent leading to an

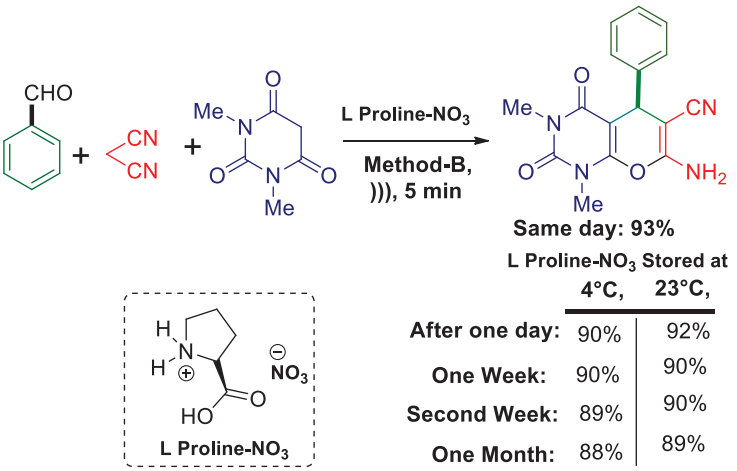




[a]Reaction conditions: aromatic aldehyde (1 mmol), Malanonitrile, (1 mmol) and 1,3 di methyl barbituric acid (1 mmol), [d] Method **A**= Conventional method, [c]Method **B**= Ultra sonication, Open flask. Isolated yield.

Scheme 3. Synthesis of pyrano[2,3-d] pyrimidine diones derivatives under optimized conditions.

excellent yield in the corresponding product. These results clearly clarify that the use of electronically deactivating substituent at ortho, meta, and para positions have no significant effect on the yield. In the further scope some electron-donating aldehyde was treated, with the electron-releasing 4-methylbenzaldehyde and 4-methoxybenzaldehyde 86 and 88% yields were obtained for **18** and **19**, respectively. In general, excellent yields were observed for electron-donating and electron-withdrawing aldehyde, afterwards we tested the scope of this procedure with free –OH and fused aromatic aldehyde. In this protocol, 2-hydroxybenzaldehyde and 4-hydroxybenzaldehyde also produced expected products **20** and **21** in 88 and 90% yields, respectively. The presence of free –OH group in aromatic aldehyde was well tolerated by our procedure. In the case of fused aromatic aldehyde, 1-Napthaldehyde results yielded 86% of Product **22**. They do not have any



Scheme 4. Experimental study on the thermal stability and reactivity of the L-Proline-NO_3 for our developed procedure.

negative impact on the reaction yield, it accomplished that our protocol was also useful for fused aromatic aldehyde. Also, we could not observe any decomposition of the product during reaction and recrystallization of the product.

At this point, it is important to focus on some following points on our protocol: (1) We obtained product using ultrasonication method as well as a conventional method, (2) ionic liquid catalyzed, (3) use of green solvent H_2O, (4) the absence of an inert atmosphere, (5) reusability of catalyst, (6) no need of column purification, (7) easily recrystallized in ethanol, (8) high yielding, and (9) short reaction time. However, we overcame many literature limitations: (1) long reaction time, (2) low yields, (3) hard conditions for the catalyst preparation, and (4) in some cases no or low reusability of catalyst.

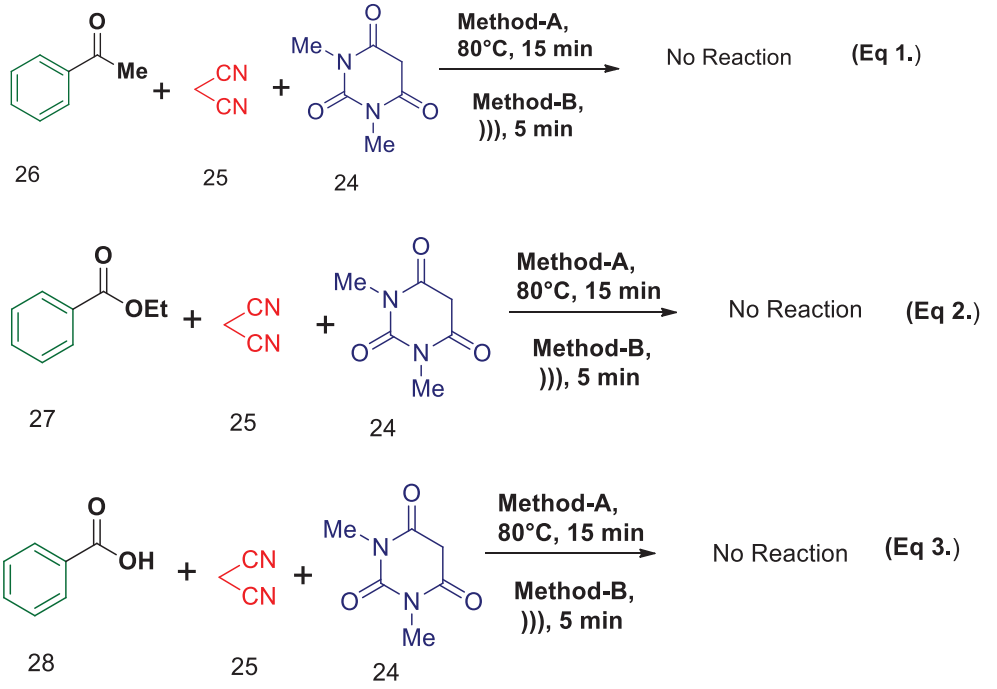
We carried out the synthesis and characterization of ionic liquid catalyst L-Proline-NO_3 in our lab with the reported procedure. Also, to carry out study for the possible thermal and sensitivity of the catalyst, we carried out the synthesis of pyrano[2,3-d] pyrimidine diones over the period of one month by comparing two storage temperature 23 and 4 °C (Scheme 4).

In this study, we used a standard reaction condition for Method B. On the same day, 93% of product 12 was yielded at 23 °C. This reaction was carried out the day after the synthesis of the reagent, which was stored at 4 °C before use. When the reaction was attempted with a reagent stored at 23 °C for one day, we obtained a slightly lower yield (90 and 92%) of product **12**. In general, L-Proline-NO_3 stored at 4 °C gave essentially high yields (90–88%) of product **12** even after one month of storage. In the reactions carried out with the reagent stored at 23 °C, notably diminished but still encouraging yields (90–89%) of Product **12** were observed over a period of one month. All these experimental data conclude that the thermal stability and reactivity of the L-Proline-NO_3 does not change over a period of one month at different temperature conditions. The characterization IR and synthesis of catalyst L-Proline-NO_3 are provided in the Supplementary material.

We also investigated the regeneration and reusability of the catalyst, the reaction between 4-chlorobenzaldehyde, malononitrile and 1,3-dimethyl barbituric acid was studied in standard optimized reaction conditions. After completion of the reaction, the mixture was filtered and catalyst was recovered from the evaporation of solvent under vacuum at 70 °C. The recovered catalyst was washed with diethyl ether and dried under vacuum. The recovered catalyst could be used up to five times without any appreciable loss in activity, as shown in Figure 2. After a deep analysis of previous literature, our protocol provides excellent reusability of catalysts and also thermal stability and reactivity.

To gain more understanding toward the chemoselectivity of our protocol, we decided to carry out the synthesis with ketone, acid, and ester functional group to correspond for the synthesis of pyrano[2,3-d] pyrimidine diones derivatives, as we cannot observe any reaction with standard reaction conditions.

The sets of reactions in Eqs. (1–3) concluded that our protocol has an excellent chemo-selectivity aldehyde functional group.



Plausible mechanism

Here, we propose a plausible mechanistic path for our protocols, which is represented in (Schemes 5 and 6), respectively, According to the mechanism in the formation of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione, L-Proline NO_3 acts as a proton donor which increases the electrophilic character of aldehyde as well as accelerate enolization of 1,3-dimethyl barbituric acid. Next, the enolized 1,3-dimethyl barbituric acid easily leads to Knoevenagel condensation with an aldehyde to form

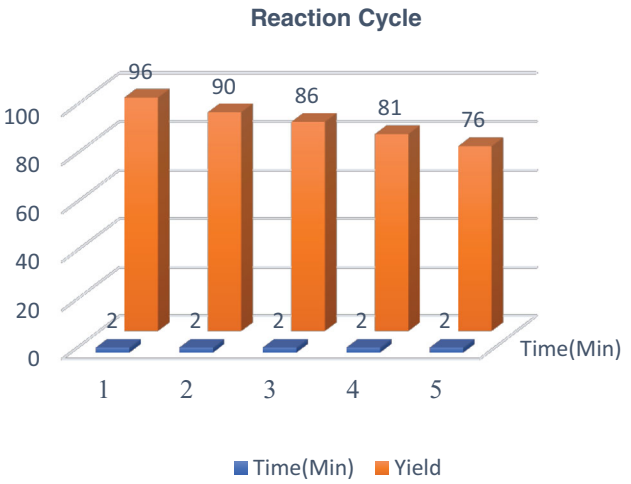
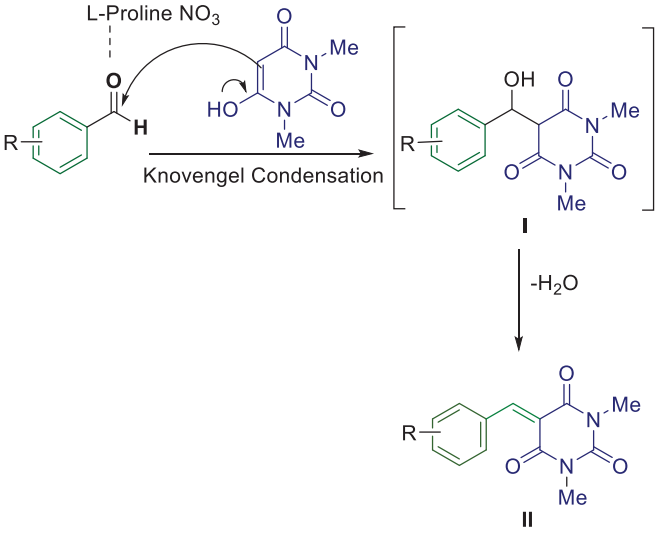


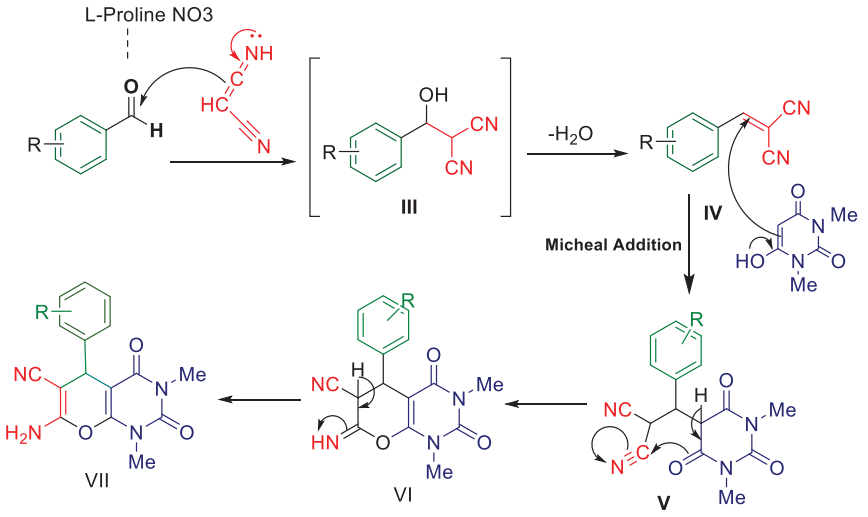
Figure 2. Reusability of catalysts for the synthesis of Product **14**.



Scheme 5. Plausible mechanistic pathway for Scheme 2.

intermediate I followed by the elimination of water molecule, resulting in the formation of Product II.

Also, for the proposed mechanism of the formation of pyrano[2,3-d] pyrimidine diones is shown in Scheme 6. Initially, electrophilic activation of the carbonyl group of aromatic aldehyde takes place in the presence of L-Proline NO_3 which triggered a nucleophilic attack of activated malanonitrile followed by the loss of water molecule in Knoevenagel condensation to form 2-arylidenemalanonitrile (IV). In the next step, the presence of L-Proline NO_3 enolized 1,3-dimethyl barbituric acid undergoes Michael type of addition leading to form V followed by intramolecular cyclization, which further leads to the formation of intermediate VI. In a final step, intermediate VI undergoes an



Scheme 6. Plausible mechanistic pathway for Scheme 3.

Table 3. Comparison of the results obtained from the synthesis of pyrano[2,3-d] pyrimidine diones.

Product	Catalyst	Time	Yield	References
Product **14**	Urea based ionic liquid {Fe_3O_4@SiO_2@$(CH_2)_3$-Urea-SO_3H/HCl}	30 min	97	[24]c
	TMU-16-NH_2. Reflux, H_2O	60 min	90	[21]a
	Et_3N, ultrasonication	25 min	87	[25]a,d
	Tungustophosphoric acid $H_3PW_{12}O_{40}$, EtOH Reflux	40 min	90	[28]a
	ZnO Nanopowder	2.5 h	86	[26]a,b

Literature limitations: [a]long reaction time [b]low yields, [c]hard conditions for the catalyst preparation, and [d]ultrasonication.

imine-enamine tautomerism which resulted in the formation of a desired product VII (Table 3).

Conclusions

In summary, our experiment suggests a new route for a promising synthesis of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione and pyrano[2,3-d] pyrimidine diones using L-Proline-NO_3 catalyst under ultrasonication method. L-Proline-NO_3 was found to be effective and applied to a broad range of different arenas including aromatic, fused aromatic, and heteroaromatic derivatives. Mild reaction condition, operationally simple, eco-friendly catalyst, recyclability of catalyst, good tolerance with electron donating, no need of column chromatography, electron withdrawing aldehyde, and clean reaction profile are key advantages of the present protocol. The above result describes ultrasonication replaces the classical method in terms of short reaction time, simple work up, and high isolated product yield.

Experimental section

General procedure for the preparation of of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1H, 3H, and 5H)-trione

Method A: A 25 mL oven-dried round-bottom flask was filled with a mixture of aromatic aldehyde (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), and L-Proline Nitrate

(15 mol%, 0.15 mmol) in 10 mL water as solvent. The resulting mixture was heated in an oil bath for the appropriate time as mentioned in Table 1. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate in the ratio of 7:3. After the completion of reaction, crude product was filtered off, washed with water and recrystallized from ethanol to give the desired product.

Method B: A 25 mL oven-dried round-bottom flask was filled with a mixture of aromatic aldehyde (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), and L-Proline Nitrate (15 mol%, 0.15 mmol) in 10 mL water as solvent. The resulting mixture was sonicated in an ultrasonic bath at room temperature for the appropriate time as mentioned in Table 1. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate in the ratio of 7:3. After completion of the reaction, crude product was filtered off, washed with water, and recrystallized from ethanol to give the desired product.

General procedure for the preparation of pyrano[2,3-d] pyrimidinones

Method A: A 25 mL oven-dried round-bottom flask was filled with a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), and L-Proline Nitrate (15 mol%, 0.15 mmol) in 10 mL water as solvent. The resulting mixture was heated in an oil bath for the appropriate time as mentioned in Table 2. The progress of reaction was monitored by TLC using n-hexane:ethyl acetate in the ratio of 8:2. After completion of reaction, crude product was filtered off, washed with water, and recrystallized from ethanol to give the desired product.

Method B: A 25 mL oven-dried round-bottom flask was filled with a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), 1,3 dimethyl barbituric acid (1 mmol), and L-Proline Nitrate (15 mol%, 0.15 mmol) in 10 mL water as solvent. The resulting mixture was sonicated in an ultrasonic bath at room temperature for the appropriate time as mentioned in Table 2. The progress of reaction was monitored by TLC using n-hexane:ethyl acetate in the ratio of 8:2. After completion of reaction, crude product was filtered off, washed with water, and recrystallized from ethanol to give the desired product.

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Disclosure statement

The authors declare no competing financial interest.

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References

[1] (a) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. Green Chemistry: Science and Politics of Change. *Science* **2002**, *297*, 807–810. DOI: 10.1126/science.297.5582.807. (b) Kirchner, B.; Clare, B. *Ionic Liquids*. Springer Science & Business Media: Berlin, Germany, 2009.(c) Santra, S.; Majee, A.; Hajra, A. Task-Specific Ionic Liquid-Catalyzed Efficient Couplings of Indoles with 1,3-Dicarbonyl Compounds: An Efficient Synthesis of 3-Alkenylated Indoles. *Tetrahedron Lett.* **2011**, *52*, 3825–3827. DOI: 10.1016/j.tetlet.2011.05.069.

[2] (a) Handy, S. T. Greener Solvents: Room Temperature Ionic Liquids from Biorenewable Sources. *Chem. Eur. J.* **2003**, *9*, 2938–2944. DOI: 10.1002/chem.200304799. (b) List, B. Asymmetric Aminocatalysis. *Synlett* **2001**, *2001*, 1675–1686. DOI: 10.1055/s-2001-18074.

[3] (a) Shirini, F.; Langarudi, M. S. N.; Daneshvar, N.; Jamasbi, N.; Irankhah-Khanghah, M. M. Preparation and Characterization of [H2-DABCO][ClO4]2 as a New Member of DABCO-Based Ionic Liquids for the Synthesis of Pyrimido[4,5-b]-Quinoline and Pyrimido[4,5-d]Pyrimidine Derivatives. *J. Mol. Struct.* **2018**, *1161*, 366–382. DOI: 10.1016/j.molstruc.2018.02.069. (b) Nabinia, N.; Shirini, F.; Tajik, H.; Mashhadinezhad, M.; Langarudi, M. S. N. An Affordable DABCO-Based Ionic Liquid Efficiency in the Synthesis of 3-Amino-1-Aryl-1H-Benzo[f] Chromene-2-Carbonitrile, 1-(Benzothiazolylamino) Phenylmethyl-2-Naphthol, and 1-(Benzoimidazolylamino) Phenylmethyl-2-Naphthol Derivatives. *J. Iran. Chem. Soc.* **2018**, *15*, 2147–2157. DOI: 10.1007/s13738-018-1408-x.(c) Shirini, F.; Langarudi, M. S. N.; Goli-Jolodar, O. Synthesis of 2H-Indazolo[2,1-b]Phthalazine-1,6,11(13H)-Triones Using 1,4-Disulfo-1,4-Diazabicyclo[2.2.2]Octane-1,4-Diium Dihydrogen Sulfate {DABCO(HSO3)2(HSO4)2} as a New Ionic Liquid Catalyst. *Dye. Pigment* **2015**, *123*, 186–195. DOI: 10.1016/j.dyepig.2015.07.036.(d) Das, S.; Santra, S.; Mondal, P.; Majee, A.; Hajra, A. Zwitterionic Imidazolium Salt: Recent Advances in Organocatalysis. *Synthesis* **2016**, *48*, 1269–1285. DOI: 10.1055/s-0035-1561336.

[4] (a) Bahekar, S. P.; Sarode, P. B.; Wadekar, M. P.; Chandak, H. S. Simple and Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-Thiones Utilizing L-Proline Nitrate as a Proficient, Recyclable and Eco-Friendly Catalyst. *J. Saudi Chem. Soc.* **2017**, *21*, 415–419. DOI: 10.1016/j.jscs.2015.09.004. (b) Bahekar, S. P.; Agrawal, N. R.; Sarode, P. B.; Agrawal, A. R.; Chandak, H. S. L-Proline Nitrate: An Amino Acid Ionic Liquid for Green and Efficient Conjugate Addition of Thiols to Sulfonamide Chalcones. *Chem. Select* **2017**, *2*, 9326–9329. DOI: 10.1002/slct.201701891.

[5] Levina, R. Y.; Velichko, F. K. Advances in the Chemistry of Barbituric Acid. *Russ. Chem. Rev.* **1960**, *29*, 437–459. DOI: 10.1070/RC1960v029n08ABEH001245.

[6] Singh, P.; Paul, K. A Simple Synthesis of 5-Spirobarbituric Acids and Transformations of Spirocyclopropanobarbiturates to 5-Substituted Barbiturates. *Indian J. Chem. Sect. B Org. Med. Chem.* **2006**, *45*, 247–251. DOI: 10.1002/chin.200618154.

[7] Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; LeBlanc, B. Anticancer Activity for 4,4′-Dihydroxybenzophenone-2,4-Dinitrophenylhydrazone (A-007) Analogues and Their Abilities to Interact with Lymphoendothelial Cell Surface Markers. *Bioorganic Med. Chem. Lett.* **2002**, *12*, 3407–3411. DOI: 10.1016/S0960-894X(02)00725-4.

[8] Bojarski, J. T.; Mokrosz, J. L.; Bartoń, H. J.; Paluchowska, M. H. Recent Progress in Barbituric Acid Chemistry. *Adv. Heterocycl. Chem.* **1985**, *38*, 229–297. DOI: 10.1016/S0065-2725(08)60921-6.

[9] Figueroa-Villar, J. D.; Cruz, E. R.; Lucia dos Santos, N. Synthesis of Oxadeazaflavines from Barbituric Acid and Aromatic Aldehydes. *Synth. Commun.* **1992**, *22*, 1159–1164. DOI: 10.1080/00397919208021101.

[10] Frangin, Y.; Guimbal, C.; Wissocq, F.; Zamarlink, H. Symthesis of Substituted Barbituric Acids *via* Organozinc Reagents. *Synthesis* **1986**, *12*, 1046–1050.

[11] Tanaka, K.; Chen, X.; Yoneda, F. Oxidation of Thiol with 5-Arylidene-1,3-Dimethylbarbituric Acid: Application to Synthesis of Unsymmetrical Disulfide1. *Tetrahedron* **1988**, *44*, 3241–3249. DOI: 10.1016/S0040-4020(01)85957-3.

[12] Khurana, J. M.; Vij, K. Nickel Nanoparticles Catalyzed Knoevenagel Condensation of Aromatic Aldehydes with Barbituric Acids and 2-Thiobarbituric Acids. *Catal. Lett.* **2010**, *138*, 104–110. DOI: 10.1007/s10562-010-0376-2.

[13] Fattahi, M.; Davoodnia, A.; Pordel, M. Efficient One-Pot Synthesis of Some New Pyrimido[5′,4′:5,6]Pyrido[2,3-d]Pyrimidines Catalyzed by Magnetically Recyclable Fe3O4 Nanoparticles. *Russ. J. Gen. Chem.* **2017**, *87*, 863–867. DOI: 10.1134/S1070363217040326.

[14] Ziyaei Halimehjani, A.; Barati, V.; Karimi, M. Synthesis of a Novel Tetracationic Acidic Organic Salt Based on DABCO and Its Applications as Catalyst in the Knoevenagel Condensation Reactions in Water. *Synth. Commun.* **2019**, *49*, 724–734. DOI: 10.1080/00397911.2019.1570268.

[15] Pałasz, A. Three-Component One-Pot Synthesis of Fused Uracils - Pyrano[2,3-d]-Pyrimidine-2,4-Diones. *Monatsh. Chem.* **2008**, *139*, 1397–1404. DOI: 10.1007/s00706-008-0935-z.

[16] Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. Fe-Catalyzed Allylic C–C-Bond Activation: Vinylcyclopropanes as Versatile A1,A3,D5-Synthons in Traceless Allylic Substitutions and [3 + 2]-Cycloadditions. *J. Am. Chem. Soc.* **2012**, *134*, 5048–5051. DOI: 10.1021/ja300294a.

[17] Tietze, L. F.; Kettschau, G. Hetero Diels-Alder Reactions in Organic Chemistry. In *Stereoselective Heterocyclic Synthesis*, Peter Metz, Ed.; Springer: Berlin, Heidelberg, Germany, 1997; Vol. 189, pp 1–120.

[18] (a) Aly, H. M.; Kamal, M. M. Efficient One-Pot Preparation of Novel Fused Chromeno[2,3-d]Pyrimidine and Pyrano[2,3-d]Pyrimidine Derivatives. *Eur. J. Med. Chem.* **2012**, *47*, 18–23. DOI: 10.1016/j.ejmech.2011.09.040.. . (b) Paliwal, P. K.; Jetti, S. R.; Jain, S. Green Approach towards the Facile Synthesis of Dihydropyrano(c)Chromene and Pyrano[2,3-d]Pyrimidine Derivatives and Their Biological Evaluation. *Med. Chem. Res.* **2013**, *22*, 2984–2990. DOI: 10.1007/s00044-012-0288-3.(c) Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K. A. R.; El-Agrody, A. M. Synthesis and Antimicrobial Activities of Novel Naphtho[2,1-b]Pyran, Pyrano[2,3-d]Pyrimidine and Pyrano[3,2-e][1,2,4]Triazolo[2,3-c]-Pyrimidine Derivatives. *Farmaco* **2001**, *56*, 965–973. DOI: 10.1016/S0014-827X(01)01168-5.(d) Daneshvar, N.; Nasiri, M.; Shirzad, M.; Safarpoor Nikoo Langarudi, M.; Shirini, F.; Tajik, H. The Introduction of Two New Imidazole-Based Bis-Dicationic Brönsted Acidic Ionic Liquids and Comparison of Their Catalytic Activity in the Synthesis of Barbituric Acid Derivatives. *New J. Chem.* **2018**, *42*, 9744–9756. DOI: 10.1039/C8NJ01179F.

[19] Balalaie, S.; Abdolmohammadi, S.; Bijanzadeh, H. R.; Amani, A. M. Diammonium Hydrogen Phosphate as a Versatile and Efficient Catalyst for the One-Pot Synthesis of Pyrano[2,3-d]Pyrimidinone Derivatives in Aqueous Media. *Mol. Divers.* **2008**, *12*, 85–91. DOI: 10.1007/s11030-008-9079-7.

[20] Ziarani, G. M.; Faramarzi, S.; Asadi, S.; Badiei, A.; Bazl, R.; Amanlou, M. Three-Component Synthesis of Pyrano[2,3-d]-Pyrimidine Dione Derivatives Facilitated by Sulfonic Acid Nanoporous Silica (SBA-Pr-SO3H) and Their Docking and Urease Inhibitory Activity. *Daru* **2013**, *21*, 3–13. DOI: 10.1186/2008-2231-21-3.. .

[21] Beheshti, S.; Safarifard, V.; Morsali, A. Isoreticular Interpenetrated Pillared-Layer Microporous Metal-Organic Framework as a Highly Effective Catalyst for Three-Component Synthesis of Pyrano[2,3-d]. *Pyrimidines. Inorg. Chem. Commun.* **2018**, *94*, 80–84. DOI: 10.1016/j.inoche.2018.06.002.

[22] Elinson, M. N.; Ryzhkov, F. V.; Merkulova, V. M.; Ilovaisky, A. I.; Nikishin, G. I. Solvent-Free Multicomponent Assembling of Aldehydes, N,N′-Dialkyl Barbiturates and Malononitrile: Fast and Efficient Approach to Pyrano[2,3-d]Pyrimidines. *Heterocycl. Commun.* **2014**, *20*, 281–284. DOI: 10.1515/hc-2014-0114.

[23] Khazaei, A.; Ranjbaran, A.; Abbasi, F.; Khazaei, M.; Moosavi-Zare, A. R. Synthesis, Characterization and Application of ZnFe2O4 Nanoparticles as a Heterogeneous Ditopic Catalyst for the Synthesis of Pyrano[2,3-d] Pyrimidines. *RSC Adv.* **2015**, *5*, 13643–13647. DOI: 10.1039/C4RA16664G.

[24] Zolfigol, M. A.; Ayazi-Nasrabadi, R.; Baghery, S. The First Urea-Based Ionic Liquid-Stabilized Magnetic Nanoparticles: An Efficient Catalyst for the Synthesis of Bis(Indolyl)Methanes and Pyrano[2,3-d]Pyrimidinone Derivatives. *Appl. Organometal. Chem.* **2016**, *30*, 273–281. DOI: 10.1002/aoc.3428.

[25] Azarifar, D.; Nejat-Yami, R.; Sameri, F.; Akrami, Z. Ultrasonic-Promoted One-Pot Synthesis of 4 H -Chromenes, Pyrano [2, 3- d] Pyrimidines, and 4 H -Pyrano [2, 3-c]. *Lett. Organic Chem.* **2012**, *9*, 435–439. DOI: 10.2174/157017812801322435.

[26] Maleki, N.; Shakarami, Z.; Jamshidian, S.; Nazari, M. Clean Synthesis of Pyrano[2,3-D]Pyrimidines Using ZnO Nano-Powders. *Acta Chem. Iasi.* **2016**, *24*, 20–28. DOI: 10.1515/achi-2016-0002.

[27] Patil, P. G.; Sehlangia, S.; More, D. H. Biodegradable Polymeric Catalyst for the Synthesis Amidoalkyl- β -Naphthol's. *Synth. Commun.* **2020**, *50*, 1696–1711. DOI: 10.1080/00397911.2020.1753078.

[28] Gholipour, S.; Davoodnia, A.; Moghaddam, M. N. 12-Tungstophosphoric Acid (H3PW12O40): an Efficient and Reusable Catalyst for One-Pot Synthesis of Pyrano[2,3-*d*]Pyrimidines. *Der Pharm. Chem.* **2015**, *7*, 368–372.