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Choline chloride.$ZnCl_2$: green, effective and reusable ionic liquid for synthesis of 7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1*H*-pyrano [2, 3-*d*] pyrimidine-6-carbonitrile derivative

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Abstract
Pyrano [2, 3-*d*] pyrimidines could be synthesized using Lewis acid ionic liquid Choline chloride.$ZnCl_2$ and triethanolamine as catalyst, as well as aromatic aldehydes, malononitrile and barbituric acid or 2-thiobarbituric acid as substrates. The ionic liquid showed good catalytic activity and reusable performance under mild conditions. The reaction proceeds smoothly under ultrasonic irradiation at 75 °C. This method provides several advantages such as being environmentally friendly, using a simple workup procedure, shorter reaction time and affording good yields.

Key words: Green chemistry; Multicomponent reactions; Ultrasound technique; Ionic liquids; Pyrano [2, 3-*d*] pyrimidines.

1.Introduction
Multicomponent reactions (MCRs) are significant in producing great level of diversity, as they allow more than two building units to be combined in practical synthesis, time-saving one pot operations, generate complex structures by formation of two or more bonds [1]. Recently, various literature mentioned the application of ultrasound irradiation in chemical synthesis [2-5] and designing MCRs under ultrasonic irradiation is another attractive area in synthetic organic chemistry. From the past few years, ultrasound technique has increasingly been used in organic synthesis. The usefulness of ultrasound irradiation plays an important role in process chemistry; especially in cases where classical methods required drastic conditions or prolonged reaction times [6]. The ultrasound assisted organic transformation provides simple experimental procedure, environmental friendliness, good yields and shorter reaction times.

Condensed uracils are an important structural type in synthetic heterocyclic compounds of pharmaceutical interests. Pyrano [2, 3-*d*] pyrimidine is a condensed uracil, which has attracted considerable interest in recent times because of their wide utility in pharmaceutics [7]. Thus, synthesis of this heterocyclic nucleus is of much current importance. Other recent methods for the synthesis of pyrano [2, 3-*d*] pyrimidines have been reported [7-9]. However, the use of expensive and excess amount of catalysts and longer reaction times are some of the disadvantages encountered in reported literature. Therefore, there is need for a versatile and eco-friendly synthetic protocol to obtain these valuable compounds in good yields.

Acidic ionic liquids have been used in some reactions due to their unique properties such as vapourless and reusability [10]. However, imidazolium, pyrazolium and pyridinium based ionic liquids suffer expensive cost. Some ionic liquids give unwanted side products and release some undesired acids due to their moisture sensitivity. Recently, choline chloride.$ZnCl_2$, an inexpensive and moisture stable ionic liquid, has been developed for the protection of carbonyls [11]. Choline chloride.$ZnCl_2$ is easily accessible and has mild and simple protocol for our synthesis of substituted pyrano [2, 3-*d*] pyrimidines. Choline chloride.$ZnCl_2$ can provide better solvation effect for the reactants used in our reaction and thereby enhance the yield of the product.

In our present study, we describe the synthesis of a substituted pyrano [2,3-*d*] pyrimidines via one-pot three-component condensation of aromatic aldehydes, malononitrile and barbituric acid or 2-thiobarbituric acid using trace amounts of ionic liquid (choline chloride.$ZnCl_2$) and triethanolamine at 75°C with stirring and under ultrasound irradiation. This is one of the most prominent existing procedure used for the synthesis of 7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1*H*-pyrano [2, 3 *d*] pyrimidine-6-carbonitriles derivatives.

2. Materials and methods
Infra red (IR) spectra were recorded on KBr discs by using Perkin Elmer (Spectrum100) Fourier transform (FT-IR) spectrophotometer. ^{1}H NMR (300 MHz) spectra were obtained by JEOL AL 300 FT-NMR in $CDCl_3$ using TMS as internal standard. The SiliaPlate™ TLC Plates - Aluminum (Al) Silica were used for thin layer chromatography. Melting points were determined in open capillaries and are uncorrected. Reagents were obtained from commercial resources and were used without further purification.

3. Results and discussion

We hereby report a green and efficient method for the condensation of various aromatic aldehydes (**1**) with malononitrile (**2**) and barbituric acid (**3**) or 2-thiobarbituric acid. When the reaction was carried out in the absence of catalyst the product formed in very trace amount. Thereafter, the reaction of benzaldehyde, malononitrile and barbituric acid was selected as a model to examine the effect of amine bases such as dimethylamine, ethanolamine, triethanolamine, piperidine and dibutylamine (Table 1).

Table 1: Effect of bases[a]

Entry	Base	Time (min)	Yield (%)
1	Dimethyl amine	10	81
2	Ethanolamine	12	80
3	Triethanolamine	8	85
4	Piperidine	5	83
5	Dibutylamine	10	78

[a]Reaction conditions: Aromatic aldehyde (2 mmol), malononitrile (2mmol), barbituric acid (2 mmol), ethanol (1ml) with stirring

In comparison with these triethanolamine proved to be slightly better and very cost effective. Thereafter, we have examined the effect of ionic liquid (choline chloride.$ZnCl_2$) in catalytic amount in above mentioned reaction condition. In the absence of ionic liquid, the reaction takes longer time for completion and leads normal yield of the product due to the less solubility of substrates in the reaction medium which may cause them to react slowly. In the presence of ionic liquid the reaction was completed in shorter time and the yield of the products were increased. Hence we decided to employ the ionic liquid which increases the concentration of the substrates in reaction medium. To determine the appropriate concentration of the triethanolamine, we have investigated the model reaction at different concentrations of triethanolamine such as 0.01, 0.05 and 0.1 mol %. The product was formed in 67%, 78% and 85% yields, respectively (Table 2).

Table 2: Effect of concentration of a base[a]

Entry	Triethanolamine (mol %)	Yield (%)
1	0.01	67
2	0.05	78
3	0.1	85

[a]Reaction conditions: Aromatic aldehyde (2 mmol), malononitrile (2mmol), barbituric acid (2mmol), ethanol (1ml) and triethanolamine with stirring

This indicates that 0.1 mol % of triethanolamine is sufficient to carry out the reaction smoothly. To examine the effect of concentration of ionic liquid in above mentioned reaction condition, we have performed the reaction at various concentrations of ionic liquid such as 0.1, 0.3, 0.5 and 1 mmol (Table 3).

Table 3: Effect of concentration of a ionic liquid (choline chloride.$ZnCl_2$)[a]

Entry	Choline chloride.$ZnCl_2$ (mmol)	Yield (%)
1	0.1	85
2	0.3	89
3	0.5	94
4	1.0	94

[a]Reaction conditions: Aromatic aldehyde (2 mmol), malononitrile (2mmol), barbituric acid (2mmol), ethanol (1ml) and triethanolamine (0.1 mol %) with stirring

The obtained percentage yields were 85, 89, 94 and 94. In order to evaluate the effect of solvent DD (double distilled) water, EtOH, DMSO, MeCN, CH_2Cl_2 and $CHCl_3$ were used for model the reation (Table 4).

Table 4: Screening of solvent[a]

Entry	Solvent	Time (min.)	Yield (%)
1	Double distilled water	15	35
2	Ethanol	1	97
3	DMSO	30	–
4	CH_3CN	25	34
5	CH_2Cl_2	25	–
6	$CHCl_3$	20	Trace

[a]Reaction conditions: Aromatic aldehyde (2 mmol), malononitrile (2mmol), barbituric acid (2mmol), triethanolamine (0.1 mol %) and Choline chloride.$ZnCl_2$ (0.5mmol) in solvent (1ml)

Reaction in MeCN and DD water resulted in moderate yields 34% and 35%. Reactions in presence of DMSO and CH_2Cl_2 were not taken place (TLC monitored). Very insignificant yield obtained in presence of $CHCl_3$. The best result was obtained when the reaction was carried out in the presence of 0.1 mol % of triethanolamine and 0.5 mmol of choline chloride.$ZnCl_2$ in small amount of ethanol at 75 ˚C. The model reation was further investigated under ultrasound irradiation with a view to

explore either the reaction could be accelerated or yield could be enhanced. In this case, better improvement in the product yield was observed, but the reaction time enormously reduced to few seconds when compared to conventional method (in several minutes in reported literatures). In both methods, the temperature of 75°C was chosen as optimum temperature. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 75°C did slow down the reaction rate.

In conclusion, we have demonstrated the condensation of aromatic aldehydes, malononitrile and barbituric acid or 2-thiobarbituric acid in the presence of triethanolamine (0.1 mol %) and choline chloride.$ZnCl_2$ (0.5mmol) in small amount of ethanol at 75 °C under ultrasound irradiation (Figure 1).

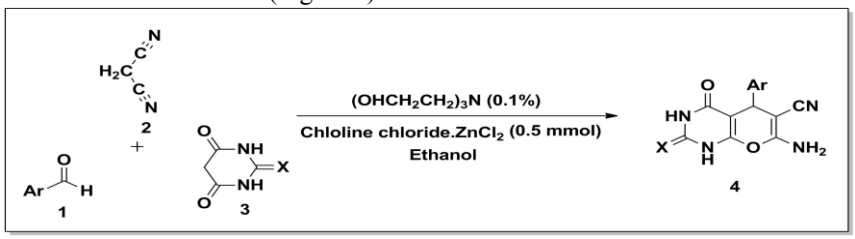

Figure 1: Synthetic route of pyranopyrimidines

The present method has various advantages over the methods reported in literature due to simplicity of reaction work up, ease of product isolation (by simple filtration), cost effective catalyst, good yields, environmentally benign condition and above all very short reaction times (Table 5).

Table 5: Synthesized 7-amino-6-carbonitrile-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1*H*-pyrano [2, 3-*d*] pyrimidine derivatives

Entry	Compound	Ar	X	Conventional		Ultrasound		Mp (°C)
				Time (Sec.)	Yield (%)	Time (Sec.)	Yield (%)	
1	a	Ph	O	300	96	80	98	205-207[a]
2	b	4-Me-Ph	O	240	97	70	97	160-163
3	c	4-Me_2N-Ph	O	120	94	40	95	182-184
4	d	4-NO_2-Ph	O	180	64	92	67	230-234[a]
5	e	3-NO_2-Ph	O	182	51	81	54	258-260[a]
6	f	2-Cl-Ph	O	305	70	120	70	208-211[a]
7	g	3-Cl-Ph	O	480	69	180	71	239-242[a]
8	h	4-Cl-Ph	O	120	82	65	85	231-232[a]
9	i	4-MeO-Ph	O	60	94	30	98	279-280[a]
10	j	4-MeO-Ph	S	75	93	33	96	116-118
11	k	CH=CH-Ph	S	90	87	45	87	228-229
12	l	4-NO_2-Ph	S	420	41	240	42	232-235[a]
13	m	3-NO_2-Ph	S	300	54	160	54	230-233[a]
14	n	3-Cl-Ph	S	480	52	120	53	234-237[a]

[a]Melting points match with literature (Ref. 7-9)

The plausible mechanism for the formation of pyrano [2, 3-*d*] pyrimidines is demonstrated (Figure 2).

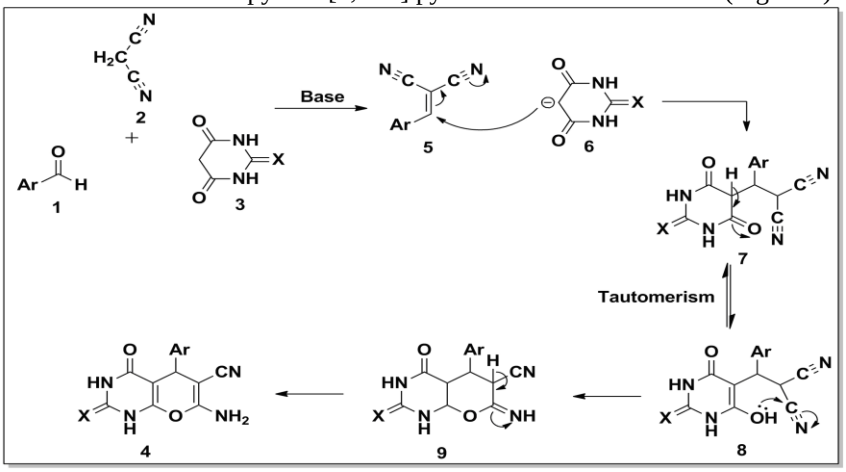

Figure 2: Plausible mechanism of the reaction

Firstly, the malononitrile (2) condense with aromatic aldehyde (1) (through Knoevenagel condensation) to give electrophilic olefin (5). A nucleophilic barbiturate (6), generated from the barbituric acid (proton abstraction) by the base, attack on

electrophilic olefin to give (7) which then tautomerize to give (8). The intermediate (8) by intramolecular nucleophilic addition gives (9) which then converted to final product (4) by intramolecular Thorpe-Zeigler reaction.

3.1. Synthetic procedure

7-amino-2, 4-dioxo-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (Ultrasound method)

Aromatic aldehyde (2 mmol), malononitrile (0.119 g, 2mmol), barbituric acid (0.256 g, 2mmol) or 2-thiobarbituric acid (0.288g, 2mmol), choline chloride. $ZnCl_2$ (0. 06 g, 0.5mmol), ethanol (1ml) and triethanolamine (0.1 mol %) in water (1ml) were taken in a 25 ml beaker and were subjected to ultrasound irradiation at 75 °C. Completion of the reaction was checked by TLC (EtOAc: Benzene, 1:9). The reaction mixture was filtered and the precipitate was washed with water. The products were purified by recrystallization from ethanol. The identity of the products was confirmed by comparing their TLC, melting points (Table 5), IR and NMR data.

7-amino-2, 4-dioxo-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (General method)

The reactants were taken as described above into a 25 ml flat beaker. The reaction mixture was stirred for 10-15 min at 75 °C. The progress of the reaction was monitored with TLC. The reaction mixture was filtered and the precipitate was washed with water. Further purification was accomplished by recrystallization from ethanol.

Analytical data of selected compounds:

7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile **(1a)** IR (KBr, cm^{-1}): *v* 3392, 3064, 2223, 1718, 1677, 1565, 676; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (s, 1H) 7.51-7.66 (m, 5H), 7.78 (s, 2H), 7.89 (s, 1H), 7.92 (s, 1H).

7-amino-2, 4-dioxo-5-(4-methylphenyl)-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (2b) IR (KBr, cm^{-1}): *v* 3446, 3034, 2220, 1746, 1655, 1585, 659; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06 (s, 3H), 7.25 (s, 1H), 7.32 (d, 2H J_{HH} = 8.0), 7.35 (d, 2H J_{HH} =8.0), 7.72 (s, 2H), 7.79 (s, 1H), 7.82 (s, 1H)

7-amino-2, 4-dioxo-5-(4-(dimethyamino) phenyl)-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile **(3c)** IR (KBr, cm^{-1}): *v* 3448, 2925, 2206, 1752, 1615, 1565, 599; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.16 (s, 6H), 2.49 (s, 1H), 3.34 (d, 2H J_{HH} = 8.0), 4.73 (d, 2H J_{HH} = 8.0),6.80 (s, 2H), 6.86(s, 1H), 6.96 (s, 1H)

7-amino-5-(4-methoxyphenyl)-4-oxo-2-thioxo-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile **(10j)** IR (KBr, cm^{-1}): *v* 3450, 3190, 2218, 1682, 1605, 1508, 644; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H), 6.0 (s, 1H), 6.99 (d, 2H J_{HH} = 8.0), 7.25 (d, 2H J_{HH} =8.0), 7.65 (s, 2H), 7.89 (s, 1H), 8.92 (s, 1H).

7-amino-4-oxo-5-(4-styrylphenyl)-2-thioxo-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile **(11k)** IR (KBr, cm^{-1}): ν 3402, 3079, 2224, 1753, 1605, 1578, 685; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (s, 1H), 7.25 (d, 1H J_{HH} = 8.0), 7.28 (d, 1H J_{HH} = 8.0), 7.44-7.59 (m, 5H), 7.62 (s, 2H), 7.71 (s, 1H), 8.81 (s, 1H).

Conclusion

In short, we have developed a straightforward and efficient method for the preparation of 7-amino-6-carbonitrile-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1*H*-pyrano [2, 3-*d*] pyrimidine derivatives via one-pot reaction of aldehydes, malononitrile and barbituric acid or 2-thiobarbituric acid catalyzed ionic liquid (Choline chloride.$ZnCl_2$) and triethanolamine under ultrasonic irradiation. This work is the first application of Lewis acid ionic liquid in the preparation of these compounds.

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References

1. Gnanasambandam V., Kandhasamy K., *Tetrahedron Lett.* 39 (2008) 5636.
2. Bazgir A., Ahadi S., Ghahremanzadeh R., Khavasi H. R., Mirzaei P., *Ultrason. Sonochem.* 17 (2010) 447.
3. Khorrami A. R., Faraji F., Bazgir A., *Ultrason. Sonochem.* 17 (2010) 587.
4. Ruiz E., Rodriguez H., Coro J., Salfran E., Suarez M., Alvarez R. M., Martin N., *Ultrason. Sonochem.* 18 (2011) 32.
5. Singh A. K., Shukla S. K., Quraishi M. A., *J. Mater. Environ. Sci.* 2 (2011) 403.
6. Xu H., Liao W. M., Li H. F., *Ultrason. Sonochem.* 14 (2007) 779.
7. Bararjanian M., Balalaie S., Movassagh B., Amani A. M., *J. Iranian Chem. Soc.* 6 (2009) 436.
8. Mashkouri S., Naimi-Jamal M. R., *Molecules* 14 (2009) 474.
9. Shestopalov A.A., Rodinovskaya L.A., Shestopalov A. M., Litvinov V.P., *Russian Chem. Bull., Int. Ed.* 53 (2004) 2342.
10. Li D., Shi F., Peng J., Guo S., Deng Y., *J. Org. Chem.* 69 (2004) 3582.
11. Duan Z., Gu Y., Deng Y., *Catal. Commun.* 7 (2006) 651.