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An efficient synthesis of pyrano pyrimidine derivatives by using glyoxylic acid:L-Proline deep eutectic solvent as a novel designer reaction promoter

Vishram Karande[a], Priyanka Mohire[a], Shubham Deshmukh[f], Ajinkya Patravale [b,c], Vikram Desai [b,e], Dattatray Chandam[b,d], Sandeep Sankpal [b]& Madhukar Deshmukh[a,b,*]

[a] Department of Agrochemicals and Pest Management, Shivaji University, Kolhapur, Maharastra, India

[b] Department of Chemistry, Shivaji University, Kolhapur, Maharastra, India

[c] Department of Chemistry, Vivekanand College, Kolhapur, Maharastra, India

[d] Department of Chemistry, Bhogawati Mahavidyalaya, Kolhapur, Maharastra, India

[e] Smt. Kasturbai Walchand College, Sangli, M.S., India

[f] Dr B R Ambedkar National Institute of Technology, Jalandar, Punjab., India

*E-mail: shubhlaxmi111@gmail.com

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As part of green chemistry, we designed a novel deep eutectic solvent (DES) by using glyoxylic acid: L-proline (1:1) and efficiency of novel DES has been studied for the synthesis of pyrimidine core derivatives *via* multicomponent reaction. It is an efficient solvent/catalyst to develop a series of 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives. The pyrano pyrimidine derivatives have been synthesized through a one-pot three component reaction of barbutric acid/thiobarbutric acid, aryl aldehydes and malononitrile through Knoevenagel condensation followed by Michael addition and subsequent cyclization. The thermogravimetric analysis and differential scanning calorimetry have been used to identify thermal stability and working temperature range of novel DES. The reusability of the glyoxylic acid:L-proline (1:1) has been tested and the results revealed that the recovered catalyst can be reused at least four additional times in subsequent reactions without significant decrease in product yield. The use of solvent glyoxylic acid: L-proline (1:1) DES to yield vital pyrimidine molecules provide this protocol to cope with the current need for efficient, cost-effective, cleaner reaction profiles, effortless work phase with high yield of product, and with short reaction time and eco-friendly methodology. IR, ^{1}H NMR and MS and alternative methods, whenever available, have verified the chemical structures of the targeted compounds.

Keywords: Barbutric acid, Thiobarbituric acid, Aldehydes; Malononitrile, Glyoxylic acid: L-Proline deep eutectic solvent

Green chemistry focuses on studies aimed at improving safe and environmentally friendly chemical procedures for the design of biologically active and industry-leading molecules in synthetic organic chemistry[1-2]. Green chemistry offers a number of options for carrying out organic transformations in an environmentally friendly manner, including the use of fewer solvents, high nuclear economies and selectivity, the elimination of hazardous wastes, the use of climate, easy methods for chemical separation and purification, and the use of renewable energy sources[3-8]. To solve the disadvantages of ionic liquids (ILs), deep eutectic solvent (DES) were introduced as an alternative. Some researchers classify them as a subset of ILs, and they use the words interchangeably at times. On the other hand, other reports, stressed that, despite their many similarities, they are fundamentally different classes of substances[9-11]. DESs have a high atom economy and a low E-factor[12], an effective synthesis of heterocyclic scaffold has been documented in green chemistry over the last decade. DESs have been used to build heterocyclic skeleton as both an environmentally friendly solvent and a catalyst. Greener solvents support several multi-component reactions to establish biological motif's and complexity in agricultural and pharmaceutical areas in the modern period, with benefits such as environmental friendliness, high yield in less time, operational simplicity of goods, high atom economy, and superficial implementation[13-16].

DES was introduced by Abott *et al.*[17-18]. To produce bio-solvents, the DES is made by combining hydrogen bond acceptor and hydrogen bond donor molecules[19]. It functions as a catalyst and a solvent due to certain physical properties such as low vapour pressure, non-inflammability, biocompatibility, biodegradability and cost efficiency[20-22].

Pyrimidine is a very important class of nitrogen containing heterocyclic compound. Pyrimidine motifs are found in several theoretic and in medicines like antiinflametry and anticancer[23], antitumor[24], kinase inhibitor[25-26] etc. In concern with recent literature, it has been found that the reaction of barbituric acid/thio barbituric acid (1 mmole), aldehyde (1 mmole) and malononitrile (1 mmole) to form targeted molecule was achieved by utilizing various critical methodologies and conditions such as solvent free[27], microwave irradiation[28], magnetic nano partical Fe_3O_4,[29] Al_2O_3[30], Zn[(L) L-Proline[31], montmorolonite[32], ionic Liquids[33], N-methylmorpholine[34], triethyl amine[35], piperidine[36] etc. Despite the available synthetic methods, more efficient procedures that enable the complete synthesis of pyrimidine motifs are still required. As part of our ongoing efforts to establish novel synthetic methodologies for the development of bioactive scaffolds, in this article we are presenting a simple method for synthesizing pyrimidine derivatives.

Experimental Details

Sigma Aldrich, Alfa Aser and Spectrochem provided all of the chemicals, which were used without purification. TLC was used to control the reaction. The melting points were calculated using the open glass capillary method and uncorrected. IR, ^{1}H NMR and ^{13}C NMR were used to confirm the synthesized compounds. The IR spectra were captured using a JASCO FT-IR 4600 spectrophotometer, and the values are expressed in υ_{max} cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Spectrospin Avance II-500 Hz, 300 MHz and 75 MHz spectrophotometer, respectively, with DMSO d_6 as a solvent and TMS as an internal standard. An AB Sciex LC-MS/MS 3200 mass spectrometer was used to capture the mass spectra and the compounds were tested in both +ve and –ve polarity modes.

General procedure for the syntheses of compounds Glyoxylic acid: L-Proline (1:1) (DES)

In a 25 mL of round bottom flask added Glyoxylic acid (100 mmol, 7.403 g) and L-proline (100 mmol, 1.153 g) in a 1:1 proportion mixture. It was heated at 100°C with continuous stirring for 15 min. The resultant DES form red colour liquid with an excellent yield was allowed to cool at room temperature The schematic is shown Scheme 1.

General procedure for the syntheses of compounds (3a-3k and 4a-k)

Thio-barbituric acid/barbituric acid **1** (1 mmol) taken in a 25 mL round-bottom flask to which, aryl aldehyde **2** (1 mmol) and malononitrile **3** (1 mmol) in a 2-5 mL Glyoxylic acid:L-Proline (1:1) DES was added. Then the reaction mixture stirred at 80℃ temperature for 20-30 min till the dense precipitate was observed. This was followed by the addition of 5 mL of ethanol to the reaction mixture, and then filtered. Removal of extra ethanol from the filtrate was achieved under reduced pressure to recover the DES (92%), which was reused four times. The schematic is shown Scheme 2.

Spectroscopic data of the synthesized compounds

7-amino-5-(4-nitrophenyl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carbonitrile (4g): Yellow colour powder; yield 95%; mp >300°C, IR (υ_{max}, cm^{-1}): 3439.42, 3318.89, 2208.09, 1668.12, 1579.41; ^{1}H NMR (DMSO - d_6): δ, 4.418 (s, 1H), 7.258 (s 2H), 7.510-7.539 (d, 2H, *J*= *8.7* Hz), 8.145-8.174 (d, 2H, *J*= *8.7* Hz), 11.102 (s, 1H), 12.159 (s, 1H) ppm; D-Exchange NMR (DMSO- d_6): δ, 4.409 (s, 1H), 7.490-7.519 (d, 2H, *J*= 8.7 Hz), 8.139-8.168 (d, 2H, *J*= 8.7 Hz) ppm; Mass (m/z) at +ve polarity, 344.0844 and –ve polarity, 342.1950

7-amino-5-(4-chlorophenyl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carbonitrile (4c): White colour powder; yield 94%; mp >300°C, IR (υ_{max}, cm^{-1}): 3300.57, 3004.55, 2768.31, 2210.99, 1700.91, 1635.34, 1608.34; ^{1}H NMR (DMSO - d_6): δ, 4.243 (s, 1H), 7.143 (s 2H), 7.223-7.251 (d, 2H, *J*= *8.4* Hz), 7.328-7.356 (d, 2H, *J*= 8.4 Hz), 11.061 (s, 1H), 12.074 (s, 1H) ppm; D-Exchange NMR (DMSO - d_6): δ, 4.234(s, 1H), 7.202-7.230 (d, 2H, *J*= 8.4 Hz), 7.319-7.347 (d, 2H, *J*= 8.4 Hz) ppm; Mass (m/z) at -Ve polarity, 331.1853, 333.1257.

7-amino-5-(4-cyanophenyl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carbonitrile (4b):White colour powder; yield 95%; mp >300°C, IR (ν max): 3431.71, 3316.96, 3193.54, 2233.16, 2196.52, 1714.41, 1673.91 cm-1; ^{1}H NMR (DMSO - d_6): δ, 4.344 (s, 1H), 7.220 (s 2H), 7.424-7.452 (d, 2H, *J*= 8.4 Hz), 7.748-7.776 (d, 2H, *J*= 8.4 Hz), 11.083 (s, 1H), 12.126 (s, 1H) ppm; D-Exchange NMR (DMSO - d_6): δ, 4.336(s, 1H), 7.402-7.429 (d, 2H, *J*= 8.1 Hz), 7.731-7.758 (d, 2H, *J*= 8.1 Hz) ppm.

Results and Discussion

Using glyoxylic acid and L-proline in a 1:1 ratio, we developed a novel DES. A hydrogen bond donor motif

and a hydrogen bond acceptor motif are needed for the preparation of the DES. We used Glyoxylic acid as a hydrogen bond donor motif and L-proline as a hydrogen bond acceptor in this protocol. The preparation of novel DES, glyoxylic acid (100 mmol, 7.403 g) and L-proline (100 mmol, 1.153 g) were in a 1:1 ratio heated at 100°C for 15 min with continuous stirring. The resulting DES, which is a red color viscous liquid, was allowed to cool at room temperature before being used to synthesize pyrano pyrimidine derivatives as shown in Scheme 1. The characterization plots thermal and spectral) are given in Supplementary Information.

As we all know, in organic synthesis, DES acted as both a catalyst and a solvent. These characteristics increase the applicability of DES in multi-component reactions. The complete thermal and physical data of the novel DES have been examined. TGA analysis of glyoxylic acid:L-proline (1:1) DES examined by thermal decomposition process is influenced under a nitrogen setting, glyoxylic acid: L-proline (1:1) DES was heated to 350°C. The graph showed four main weight loss regions. The first weight loss is about 1.216%, in the 25-100°C temperature range. Then the second weight loss region is about 7.095% in the 100-160°C temperature range. Furthermore, the third weight loss region observed at 17.31% in the 160-210°C temperature range may be due to the loss of physically adsorbed and bound water in the DES. This temperature range is efficient to promote and catalyze organic synthesis. The fourth weight loss region observed at 72.34% in the 210-300°C temperature range corresponds to thermal decomposing/degradation of glyoxylic acid: L-proline scaffolds. We may infer from the data that the DES acts as a solvent and remains intact under reaction conditions.

Differential scanning calorimetry (DSC) analysis of glyoxylic acid: L-proline (1:1) DES showed a broad endothermic peak at 199.02°C. This has to do with the interaction between water content and DES, which causes the exothermic phase to begin at about 249.62°C and 299.09°C, which is linked to DES degradation.

The form of interaction and the atoms involved in interactions in the specified ratio of components in the DES were investigated using FT-IR, NMR, and mass spectral analysis. The FT-IR spectra of DES were recorded at room temperature. The stretching vibration band of -OH group is observed at υ_{max} 3351.036 cm^{-1} for -OH, 2981.651 cm^{-1} for NH bond and 2760.639 cm^{-1} for C-H band stretching vibration. The acidic C=O band stretching vibration band is observed at 1720.094 cm^{-1}. The ^1H NMR showed a multiplet at δ, 1.773-1.852 ppm due to (4H) protons and δ, 1.940-1.967 (q, 2H); δ, 2.091-2.138 (q, 2H); δ, 3.055-3.100 (m, 1H); δ, 3.199-3.249 (m, 1H); δ, 3.907-3.937 (t, 1H) represents L-proline and glyoxylic acid in the mixture. The mass spectral data revealed m/z at -ve [M-1] polarity at 72.9717 and 114.195, which are found to be perfectly correlated with glyoxylic acid and L-proline, respectively, to form the preferred DES.

Our current emphasis has been on the synthesis of 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and 7-amino-4-oxo-5-phenyl-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile in compliance with green chemistry principles. We first focused at how different reaction conditions affected the reaction of thio-barbutric acid (1) [1 mmol], benzaldehyde (2) [1 mmol] and malononitrile (3) [1 mmol]. We have tried this reaction initially at room temperature for 120-180 min without using any solvent (Table 1, Entry 1). After that, we tried an aqueous medium at room temperature as well as at reflux for 120-180 min (Table 1, Entry 2, 3).

We screened the reaction using various solvents such as ethanol, acetonitrile, water: ethanol (1:1) mixture (Table1, Entry 4-7), and some DES (Table1, Entry 7-11) to obtain the desired compound, then screened for 120-180 min at RT and reflux conditions. The reaction was then carried out using acidic catalysts such as AcOH, oxalic acid, p-TSA, $FeCl_3$, $ZnCl_2$, Fe_3O_4 and Al_2O_3 (Table 2, Entry 1-7). Then we tried using simple catalysts like NaOH, KOH, Et_3N and piperidine to improve the reaction, but we got poor results (Table 2, Entry 8-11).

In order to improve the reaction conditions, Table 1 shows the effect of solvent on reaction effects, and Table 2 shows the quest for a favourable, effective catalyst for this reaction. We compare the yield of glyoxylic acid: L-proline (1:1) to the yield of other solvents used in this reaction, such as water, ethanol, water: ethanol (1:1), methanol and acetonitrile, oxalic acid dihydrate: L-proline, glycerol: L-proline, and guanidine hydrochloride: L-proline (Table 1, Entry 8-12). When glyoxylic acid: L-proline (1:1) is used as a catalyst, the reaction proceeds quickly and efficiently with a high yield, compared to the other catalysts.

We investigated the reaction using various functional groups with electron withdrawing and electron donating associated with aromatic aldehydes

under optimized conditions to verify the generality and functional feasibility of the same protocol. Surprisingly, both of the aldehydes contributed well to the reaction, with no impact on product purity, reaction yield, or reaction time as a result of any substituent. In addition, our protocol has been found to be the most effective for the proposed reaction (Table 3). The melting point all the products are less than 300℃.

The plausible mechanism of the product formation, proton acceptance and donor sites, as well as the establishment of a hydrogen bonding network in Glyoxylic acid and L-Proline DES are depicted in Scheme 3. This distinctive nature of DES may create electrophilic activation of aryl aldehyde (2) and subsequent attack of malononitrile (3) gives the Knoevenagel intermediate which further upon the nucleophilic attack of another molecule of thio-barbutric acid/barbutric acid (1) followed by subsequent cyclization affords a series of desired molecules.

Furthermore, the reusability of the DES was investigated from a commercial standpoint. The reusability of the DES was tested in this study using thio-barbutaric acid (1 mmol), aromatic aldehydes (1 mmol) and malononitrile (1 mmol) as substrates and DES (2-5 mL) at optimal conditions. The reaction was monitored by using TLC. The reaction was then given 5 to 10 mL of ethanol, and the resulting product was filtered and reused. The DES was soluble in ethanol and could be extracted in large quantities by evaporating the ethanol at low pressure below 60°C. The DES was discovered to be reusable four times with a slight decline in activity: 92, 88, 82, and 78 % (Fig. 1). Based on these findings, it can be concluded that the DES can be substantially reused as a resourceful solvent with insignificant loss of the activity.

Following these accomplishments, we meticulously devised an atom economy, the results of which are summarized in Fig. 2. It was found that the reaction's atom economy is good to excellent, implying that the maximum amount of all reactants is converted into the product with the least amount of waste.

Conclusion

The current protocol allows for the successful development of novel Glyoxylic acid:L-Proline (1:1) (DES), characterization and check its application in synthesis of Pyrano pyrimidine derivatives. The reaction is efficiently conducted at 80℃ with better reusability by using a Glyoxylic acid: L-Proline (1:1) (DES) solvent/catalyst method. The novel DES is environmentally benign solvent and recyclable to facilitate a number of organic alterations. Green, effective protocol with high yields, cleaner reactions, operational simplicity, high purity, low environmental effect, column chromatography-free technique, and convenient protocol for the synthesis of 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and 7-amino-4-oxo-5-aryl-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives. The simple organic transformations to produce bioactive molecules with structural diversity and molecular complexity, the current methodology will be convenient, and provides green alternative pathway for organic transformations.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

References

1 Sayeda A R, Gomha S M, El-lateefa H M A & Abolib T Z, *Green Chem Lett Rev*, 14 (2021) 179.
2 Kiyani H & Ghorbani F, *Res. Chem. Intermed*, 42 (2016**)** 6831.
3 Brahmachari G & Banerjee B, *ACS Sustain Chem Eng*, 2 (2014) 411.
4 Gomha S M, Abdelaziz M R, Abdel-aziz H M & Hassan S A, *Mini-Review in Med. Chem*, 17 (2017) 805.
5 Karhale S, Survase D, Bhat R, Ubale P & Helavi V, *Res Chem Intermed*, 43 (2017**)** 3915.
6 Gomha S M, Badrey M G & Arafa W A A, *Heterocycles*, 92 (2016) 1450.
7 Khalil K D, Riyadh S M, Gomha S M & Ali I, *Inter J Biolog Macromolecules*, 130 (2019) 928.
8 Sharma N, Sharma U, Kumar R & Sinha A R, *RSC Adv*, 2 (**2012)** 10648.
9 Wasylka J P, Guardia M, Andruch V & Vilkov M, *Microchemical Journal*, 159 (2020**)** 105539.
10 Smith E L, Abbott A P & Ryder K S, *Chem Rev*, 114 (2014) 11060.
11 Yao X H, Zhang D Y, Duan M H, Cui Q, Xu W J, Luo M, Li

C Y, Zu Y G & Fu Y J, *Sep Purif Technol*, 149 (2015**)** 116.
12 A V Dolzhenko & A V Dolzhenko, Green Synthetic Approaches for Biologically Relevant Heterocycles, Ed. 1st,(Elsevier, Amsterdam Netherlands) 2015, p. 101.
13 Biggs-Houck J E, Younai A & Shaw J T, *Curr Opin Chemi Bio*, 14 (2010) 371.
14 Mohire P P, Patil R B, Chandam D R, Jadhav S J, Patravale A A, Kumbhar D R, Ghosh J S & Deshmukh M B, *Res Chem Intermed*, 43 (2017) 7013.
15 Patravale A A, Gore A H, Patil D R, Kolekar G B, Deshmukh M B, Choudhari P B, Bhatia M S & Anbhule P V, *Res Chem Intermed*, 42 (**2016)** 2919.
16 Mohire P P, Chandam D R, Patil R B, Patravale A A, Ghosh J S & Deshmukh M B, *J Mol Liq*, 283 (2019) 69.
17 Abbott A P, Capper G, Davies D L, Rasheed R K & Tambyrajah V, *Chem Commun*, 1 (2003) 70.
18 Abbott A P, Boothby D, Capper G, Davies D L & Rasheed R K, *J Am Chem Soc*, 126 (2004) 9142.
19 Francisco M, Bruinhorst A V D & Kroon M C, *Angew Chem Int Ed*, 52 (2013) 3074.
20 Liu P, Hao J, Mo L & Zhang Z, *RSC Adv*, 5 (2015) 48675.
21 Harifi-Mood A R & Buchner R, *J Mol Liq*, 225 (2017) 689.
22 Lobo H R, Singh B S & Shankarling G S, *Catal Lett*, 142 (2012) 11369.
23 Naik N S, Shastri L A, Chougala B M, Holiyachi S M, Joshi S D & Sunagar V, *Chemical Data Collections*, 30 (2020) 100550.
24 Zhang J, Xiong H, Yang F, He J, Chen T, Fu D, Zheng P & Tang Q, *Bioorg Med Chem Lett*, 33 (2021) 127740.
25 Munikrishnappa C S, Kumar S G V, Bhandare R R & Shaik A B, *Arabian J Chem*, 14 (2021) 103054.
26 Sun Y, Fu R, Lin S, Zhang J, Ji M, Zhang Y, Wu D, Zhang K, Tian H, Zhang M, Sheng L, Yan L, Jin J, Chen X & Xu H, *Bioorg Med Chem.* 29 (2020) 115890.
27 Mashkauru S, Jurnal N & Reza M, *Molecules*, 14 (2009) 474.
28 Gao Y, Tu S, Li T, Zhanga X, Zhu S, Fang F & Shi D, *Syn Comm*, 34 (2004) 1295.
29 Kidwai M, Jain A & Bhardwaj S, *Mole Divers*, 16 (2012) 121.
30 Goyal K M & Singhal R K, *Indian J Chem Sec- B*, 46 B (2007) 1159.
31 Heravi M M, Ghods A, Bakhtiari K & Derikvand F, *Syn Comm*, 40 (2010) 1927.
32 Shinde S V, Jadhav W N, Tale R H & Karade N N, *Org Chem*, 5 (2009) 14.
33 Yu J & Wang H, *Syn Comm*, 35 (2005) 3133.
34 Shestopalov A A, Rodinovskaya L A, Shestopalov A M & Litvinov V P, *Rus Chem Bull*, 53 (2004) 2342.
35 Devi I, Kumar B S D & Bhuyan P J, *Tetra Lett*, 44 (2003) 8307.
36 Ibrahim M & Ahmed K, *Indian J Chem Sec B*, 26B (1987) 216.

Table 1 — Comparative study of various solvents and DES with respect to time and yields of desired products[a]

Sr. No.	Solvent	Temperature condition	Reaction time (min.)	Yield[b] (%)
1	Without solvent	RT	120-180	45
2	Water	RT	120-180	50
3	Water	Reflux	120-180	52
4	Ethanol	RT	120-180	55
5	Ethanol	Reflux	120-180	60
6	Acetonitrile	Reflux	120-180	55
7	Water: Ethanol (1:1)	Reflux	120-180	58
8	Choline chloride: Oxalic acid	80ºC	90-120	72
9	Oxalic acid dihydrate: L-Proline	80ºC	90-120	75
10	Glycerol: L-Proline	80ºC	90-120	80
11	Glyoxylic acid: L-Proline	80ºC	20-30	94
12	Guanidine Hydrochloride: L-Proline	80ºC	90-120	70

The highest yield in shortest reaction time is shown in bold.
[a] Reaction of Thio-barbutric acid, benzaldehyde and malononitrile
[b] Yields refer to pure isolated products

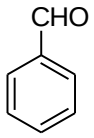
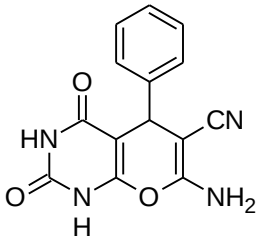
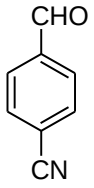
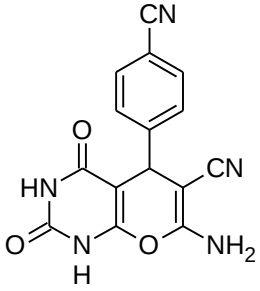
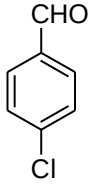
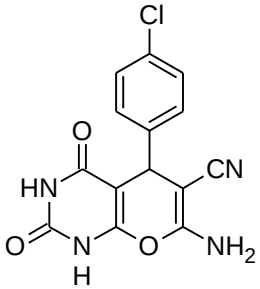
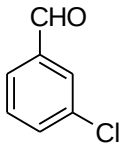
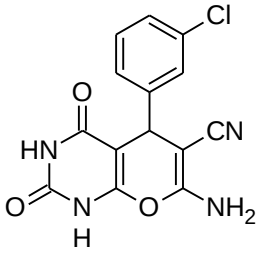
Table 2 — Comparative study of various catalysts and DES with respect to time and yields of desired products

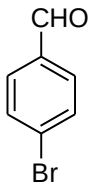
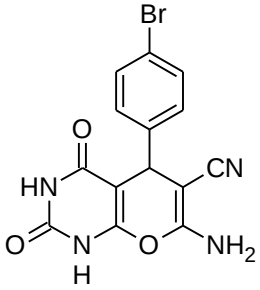
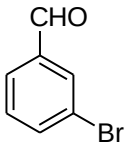
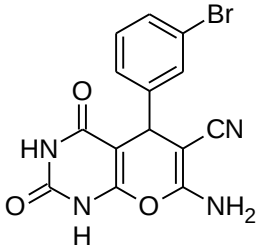
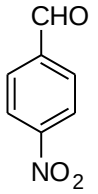
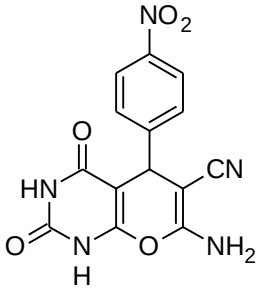
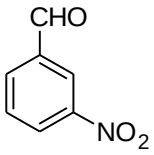
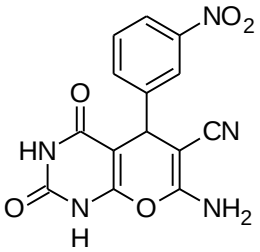
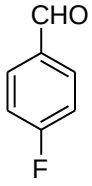
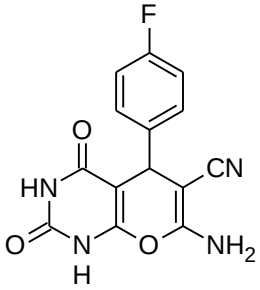
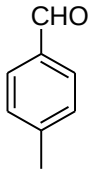
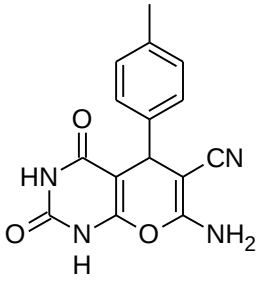
Sr. No.	Catalyst	Catalyst Load (mole %)	Temperature condition	Reaction time[a] (min.)	Yield[b] (%)
1	Acetic acid	20	80 ° C	120-180	45

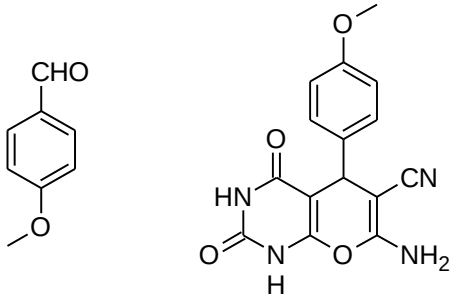
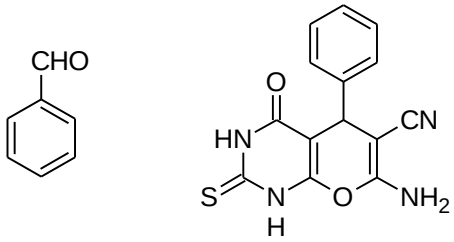
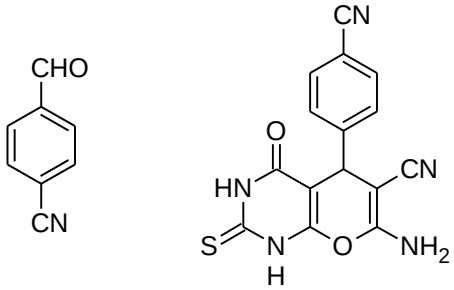
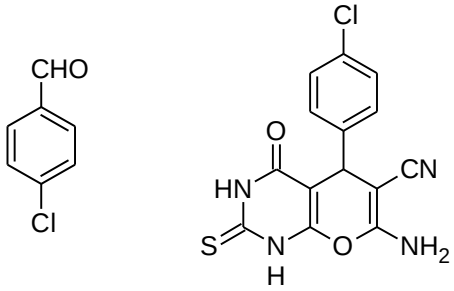
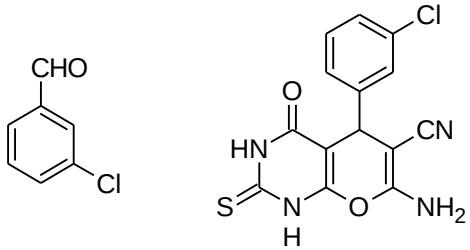
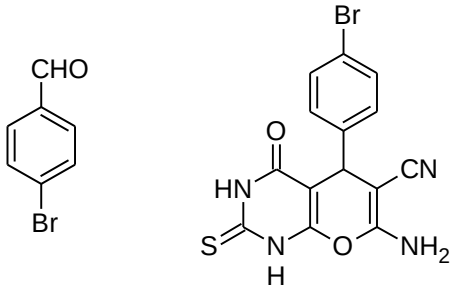
2	P-TSA	20	80 ° C	120-180	50
3	Oxalic acid	20	80 ° C	120-180	45
4	$ZnCl_2$	20	80 ° C	120-180	50
5	$FeCl_3$	20	80 ° C	120-180	55
6	Fe_3O_4	20	80 ° C	120-180	45
7	Al_2O_3	20	80 ° C	120-180	52
8	NaOH	20	80 ° C	120-180	60
9	KOH	20	80 ° C	120-180	58
10	Et_3N	20	80 ° C	120-180	60
11	Pipridine	20	80 ° C	120-180	65
12	Glyoxylic acid: L-Proline	---	80 ° C	20-30	94

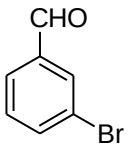
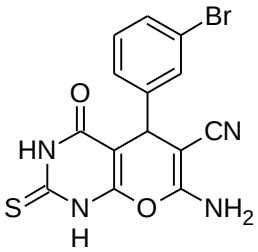
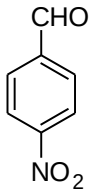
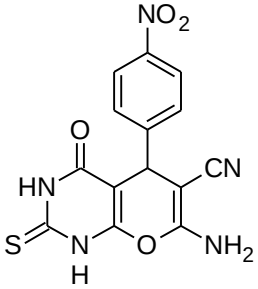
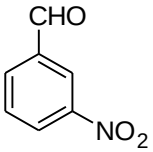
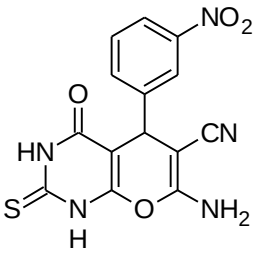
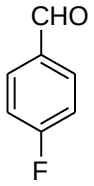
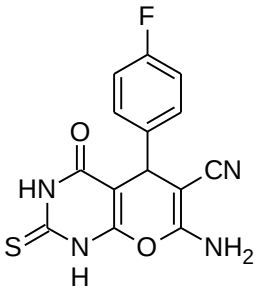
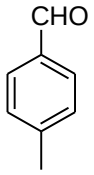
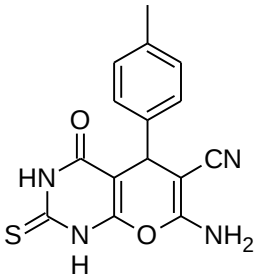
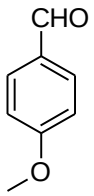
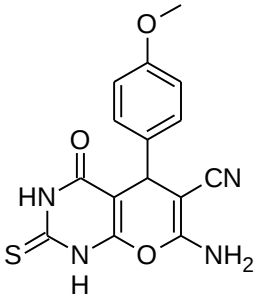
Highest yield in shortest reaction time shown in bold,
[a] Reaction of Thio-barbutric acid, benzaldehyde and malononitrile
[b] Yields refer to pure isolated products

Table 3 — Physical data of title compound [3a-3k and 4a-4k] (7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives)[a]

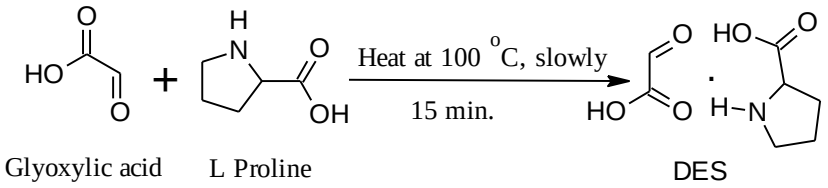
Entry no.	Aldehydes	Products	Reaction Time (min.)	Yield[b] (%)	Atom economy (%)
3a			30	92	91.10
3b			20	94	92.26
3c			20	92	90.40
3d			25	90	88.90

3e			22	95	93.16
3f			25	92	91.28
3g			20	95	93.94
3h			22	92	90.84
3i			20	94	93.04
3j			30	90	88.20

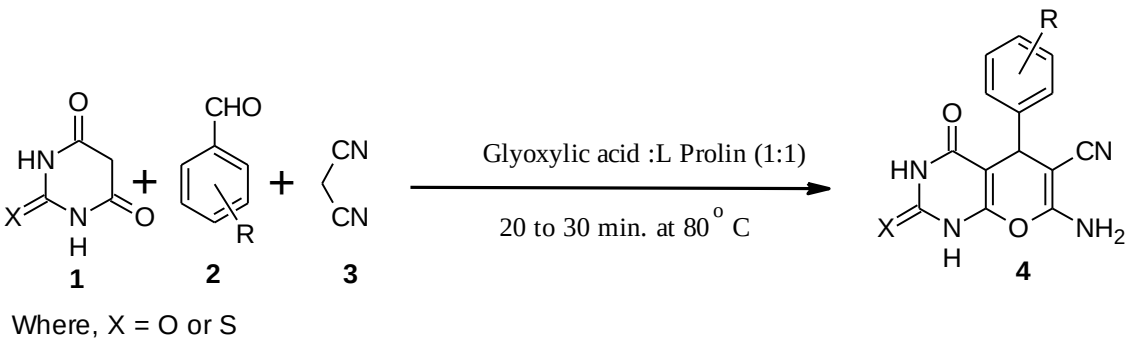
3k		35	88	78.22
4a		30	94	92.96
4b		20	95	94.02
4c		20	94	92.78
4d		30	93	91.20
4e		25	95	93.66

4f			30	94	92.98
4g			20	95	94.12
4h			25	90	89.38
4i			20	94	93.88
4j			30	90	88.94
4k			40	92	90.44

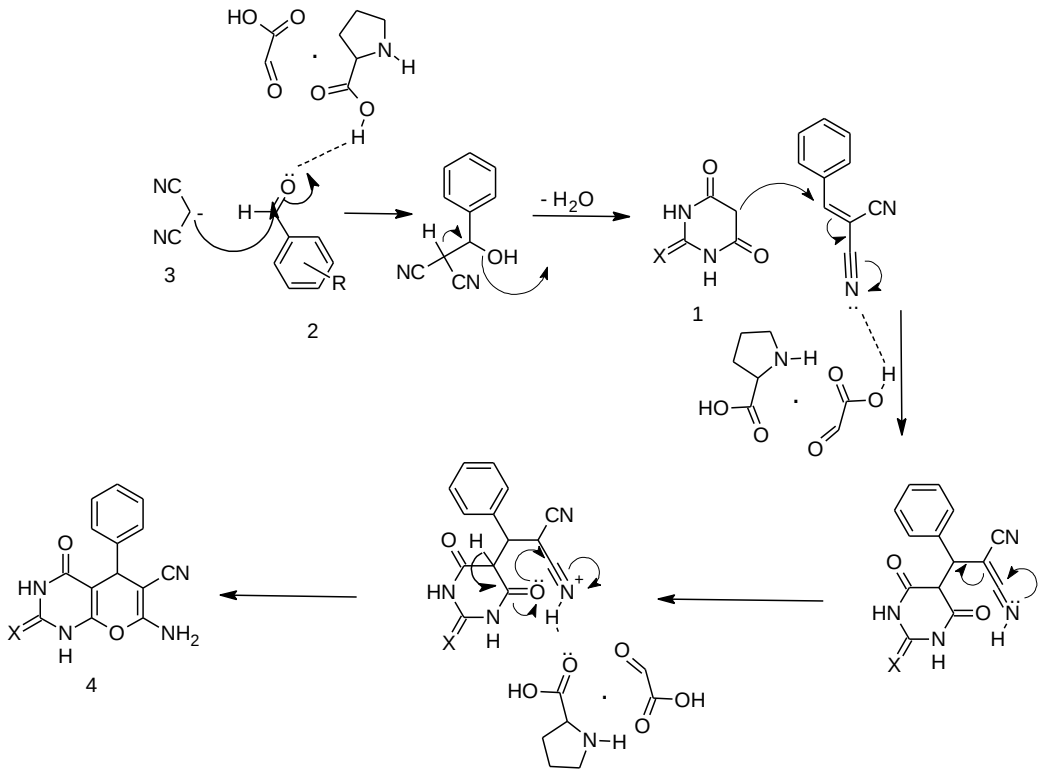
Scheme 1 — Preparation of Glyoxylic acid: L-Proline (1:1) (DES)
Scheme 2 — Methods for the synthesis Pyrano-Pyrimidine derivatives
Scheme 3 — Plausible mechanism of 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives
Fig. 1 — Reusability of Glyoxylic acid: L-Proline (1:1) (DES)
Fig. 2 — Atom economy of the synthesized 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives



Scheme 1: Double column



Scheme 2. Double column



Scheme 3

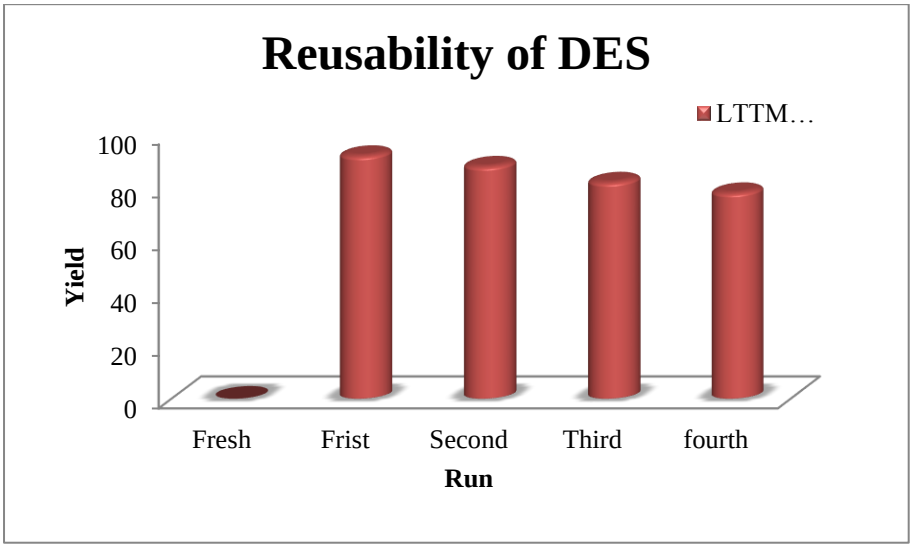


Fig 1

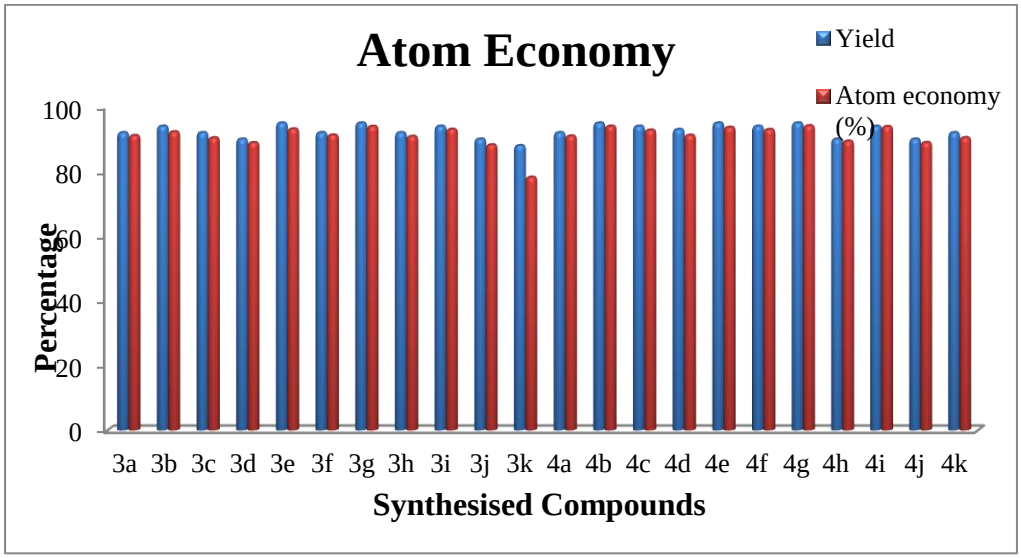

Atom Economy
Yield
Atom economy (%)
Percentage
100
80
60
40
20
0
3a 3b 3c 3d 3e 3f 3g 3h 3i 3j 3k 4a 4b 4c 4d 4e 4f 4g 4h 4i 4j 4k
Synthesised Compounds

Fig- 2