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AN EFFICIENT SYNTHESIS OF BENZIMIDAZOLE DERIVATIVESUSING OXALIC ACID DIHYDRATE AND PROLINE BASED LOW TRANSITION TEMPERATURE MIXTURE

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ABSTRACT: We have disclosed an efficient green protocol, one pot multi-components strategy for the synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrilederivatives from simple precursors like 2 amino benzimidazole, aryl aldehyde and malononitrile in the presence of Low Transition Temperature Mixtures (LTTMs) (Oxalic acid dihydrate: L-Proline) medium to sustain eco-friendly strategy. LTTMs found to be greener, faster, recyclable and efficient solvents/catalyst for the synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole- 3-carbonitrile derivatives. Short reaction time, high yield, easy work up procedure and environmentally benign method are the main merits of the present protocol.

Keywords: Low transition temperature mixtures (LTTMs); 2 amino benzimidazole; aryl aldehydes; malononitrole; atom economy.

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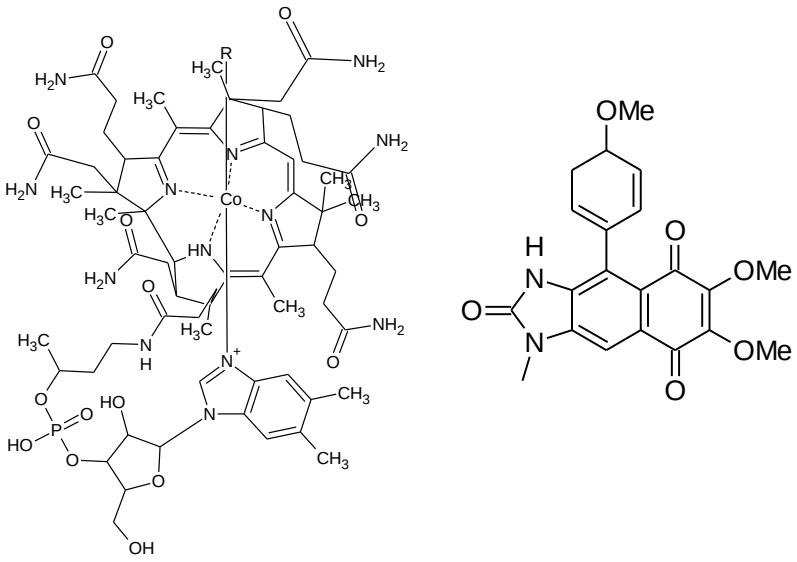
1. INTRODUCTION

Under the umbrella of green chemistry, the development of drug like molecule from simple preliminary materials is one of the growing areas in organic transformations. Benzimidazole is an important class of nitrogen containing heterocyclic compounds having higher biological potentials. Along with fused benzimidazol derivatives are one of the most significant sub class of benzimidazole because of it has been exhibit a wide range of biological activities such as antifungal [1-5], antibacterial [6], anti-tuberculosis, antiviral, anticancer, anti hypertensive, anti-inflammatory, [7-9], anti-helmentic[10-12], proton pump inhibitors [13], tyrosine kinase inhibitors [14], molluscicidal activities [15], etc. They have been also found in many natural products such as Vitamin B12 [16], Kealiquinine etc. [17][Figure 1]. In view of occurrence in medicinal applications of this class of heterocycles, the synthesis of benzimidazole is an attractive domain in organic chemistry. Due to these versatile applications, the quest for new synthetic methodologies for the development of benzimidazole scaffold is common goal in front of synthetic chemists.



(a) (b)

Figure 1 Some representative biological active Benzimidazole derivatives.
(a) Vitamin B12, (b) Kealiquinine

Traditional method for the synthesis of benzimidazole a range of catalysts and solvents have been employed such as p-toluenesulfonic acid [18], Microporous zeolite [19], water [20], ethanol [21], microwave assisted [22] and Ceric ammonium nitrate [23] etc. However, most of the methods abide with its own merits and demerits. Hence, there is still need to develop an efficient, cost effective, eco-friendly methodology. That could overcome the traditional drawback in protocol. In this circumstance, a Low Transition Temperature Mixtures (LTTMs) plays an important role in the development of eco-friendly, sustainable procedure for the synthesis of new drug like molecules. [24-28] LTTMs have been referred as designer solvent, presented by Abbott and co-workers. [29] The unanimous properties like low vapor pressure, thermal stability and reusability make it

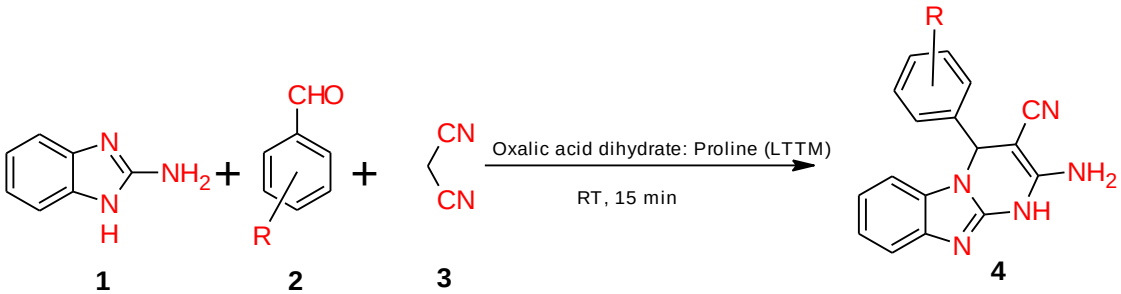
extremely necessary in modern organic transformation, which is depicted by the successful synthesis of Benzimidazole.

2. MATERIALS AND METHODS

All chemicals were used commercially available and purchased from Sigma Aldrich. Melting points were taken on a melting point apparatus and are uncorrected. The reactions were monitored by thin layer chromatography (TLC). Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz/ 75 MHz frequencies, respectively using DMSO d_6 as a solvent and Tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a JASCO, FTIR 4600 spectrophotometer.

3. RESULTS AND DISCUSSION

As discussed in introduction, synthesis of Benzimidazole motif by numerous acidic and basic catalysts. Herein, we have been reported synthesis of Benzimidazole skeleton using multi-component reaction using LTTM solvent depicted in scheme 1.



Scheme 1. Methods for the synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives.

In continuation of our work, we examined the reaction of 2 aminobenzimidazole (1), aldehydes (2) and malononitrile (3) in a without solvent at RT up to 700-750 min (Table 1, Entry 1). Then after, we tried an aqueous medium at RT as well as at reflux condition up to 600 – 700 min (Table 1, Entry 2, 3). To attain the desired compound, we have been screened the reaction using various solvents like ethanol, acetonitrile, water:ethanol (1:1) mixture and some of LTTMs (Table1, Entry 4-11) then screened up to 15 -700 min. at RT as well as reflux conditions. After that efforts were made for carrying out the reaction in basic catalyst such as NaOH and piperidine (Table 2, Entry 1, 2). Then we turned to optimize this reaction using acidic catalysts such as AcOH, p-TSA $FeCl_3$ and $ZnCl_2$ however we got inferior results (Table 2, Entry 3-6) for this reaction condition. It has been observed that in non-polar and polar solvents as well as acidic and basic catalytic condition, the yield of the product is poor but we observed that LTTMs as an excellent solvent for this reaction with respect to reaction time and reaction yield as compared to other solvents and catalysts. Inspire from this results, we employed this reaction at room temperature in other LTTMs like Oxalic acid dihydrate: L-proline, Choline chloride: Oxalic acid, Choline Chloride: Urea and Guanidine Hydrochloride: Urea (Table 1, Entry 8-11). After the study of effect of catalysts and solvents, it is clear from table, the desired

product of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives was achieved an excellent yield in Oxalic acid dihydrate: L-proline(LTTM) (Table 1, Entry 9). The results depicted in Tables 1 and 2 indicate that oxalic acid dihydrate: L-proline(1:1) LTTM can act as appropriate, eco-friendly encouraging reaction medium for the synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives. Subsequently, the same reaction was performed by sequential and domino MCRs techniques. Along with this Domino MCR technique afforded a low yield of targeted compound while, at sequential MCR technique gives good results with respect to time and yield of compound. In sequential addition reaction 5mL (LTTM) Oxalic acid dihydrate: L-Proline, malononitrile (1 mmol) and benzaldehyde (1 mmol) was added in flask to Knoevenagel condensation product formed within 5 minutes then 2 aminobenzimidazole (1 mmol) Michel donor was further added in same reaction mixture. The reaction was completed by addition of third compound within 15-25 min. which was monitored by using TLC.

Table 1. Comparative study of various solvents and LTTMs with respect to time and yields of desire products

Sr. No.	**Solvent**	**Temperature condition**	**Reaction time[a] (min.)**	**Yield[b] (%)**
1	Without solvent	RT	700-750	---
2	Water	RT	600-700	35
3	Water	Reflux	600-660	50 [20]
4	Ethanol	RT	580-600	45
5	Ethanol	Reflux	420-500	65
6	Acetonitrile	Reflux	560-600	40
7	Water: Ethanol (1:1)	Reflux	300-340	62
8	Choline chloride: oxalic acid	RT	25-30	72
9	**Oxalic acid dihydrate: L-proline**	**RT**	**15-25**	**95**
10	Choline Chloride: Urea	RT	25-30	70
11	Guanidine Hydrochloride: Urea	RT	30-50	65

Highest yield in shortest reaction time shown in bold,

[a] Reaction of 2-aminobenzimidazole, 4-Cynobenzaldehyde and malononitrile,

[b]Yields refer to pure isolated products

Table 2. Comparative study of Oxalic acid dihydrate:L-proline (LTTM) over different catalyst on yields of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3 carbonitrile derivatives (4b)

Sr. No.	Catalyst	Catalyst Load (mol %)	Solvent/Reaction Condition	Reaction time [a] (min.)	Yield[b] (%)
1	NaOH	20	Water/Reflux	150	60
2	Piperidine	20	Water/Reflux	60	81
3	AcOH	20	Water/Reflux	180	55
4	FeCl3	20	Water/Reflux	320	50
5	$ZnCl_2$	20	Water/Reflux	360	52
6	PTSA	20	Water/Reflux	170	75[18]
7	**Oxalic acid dihydrate: L-proline**	**-**	**RT**	**15-25**	**95**

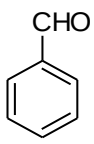
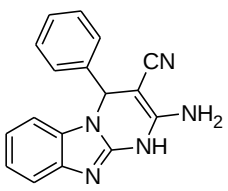
Highest yield in shortest reaction time shown in bold,

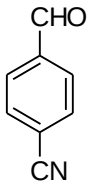
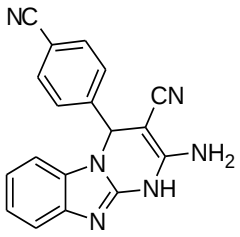
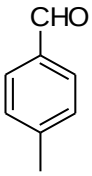
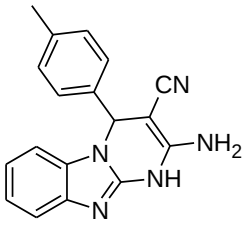
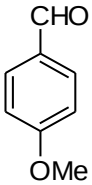
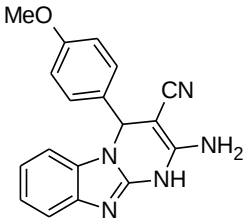
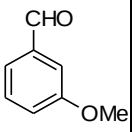
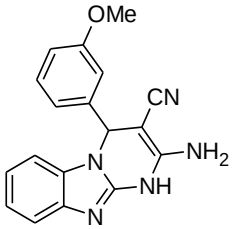
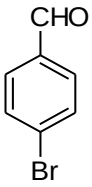
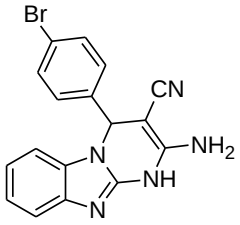
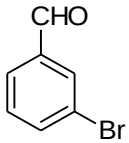
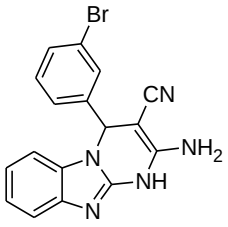
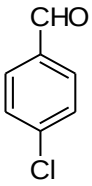
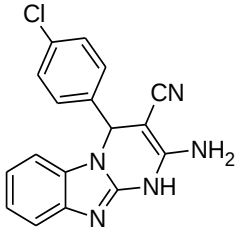
[a] Reaction of 2-aminobenzimidazole, 4-Cynobenzaldehyde and malononitrile,

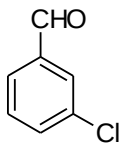
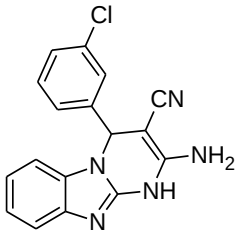
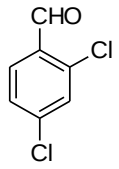
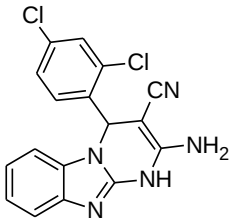
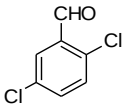
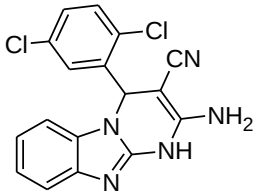
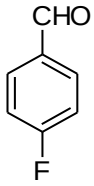
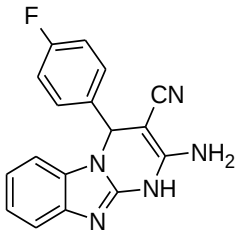
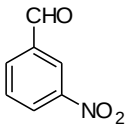
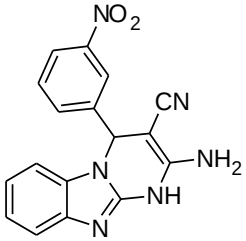
[b] Isolated yield heated at 100°C in 5 mL of aqueous medium

Promoting by this results, we turn to investigate the diversity of reaction procedure by using various functional groups electorn withdrawing and electron dinating associated with aromatic aldehydes were subjected to study with malononitrile and 2 amino benzimidazole, under mentioned optimized condition. Interestingly, all the aldehydes contributed well in the reaction and no subsequent effect of the any substituent's on reaction yield of compound, purity, time of reaction along with this our procedure has been found to be best for this reaction. (Table 3)

Table 3: Synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3 carbonitrile derivatives usingOxalic acid dihydrate: L-proline (1:1) LTTMs solvent

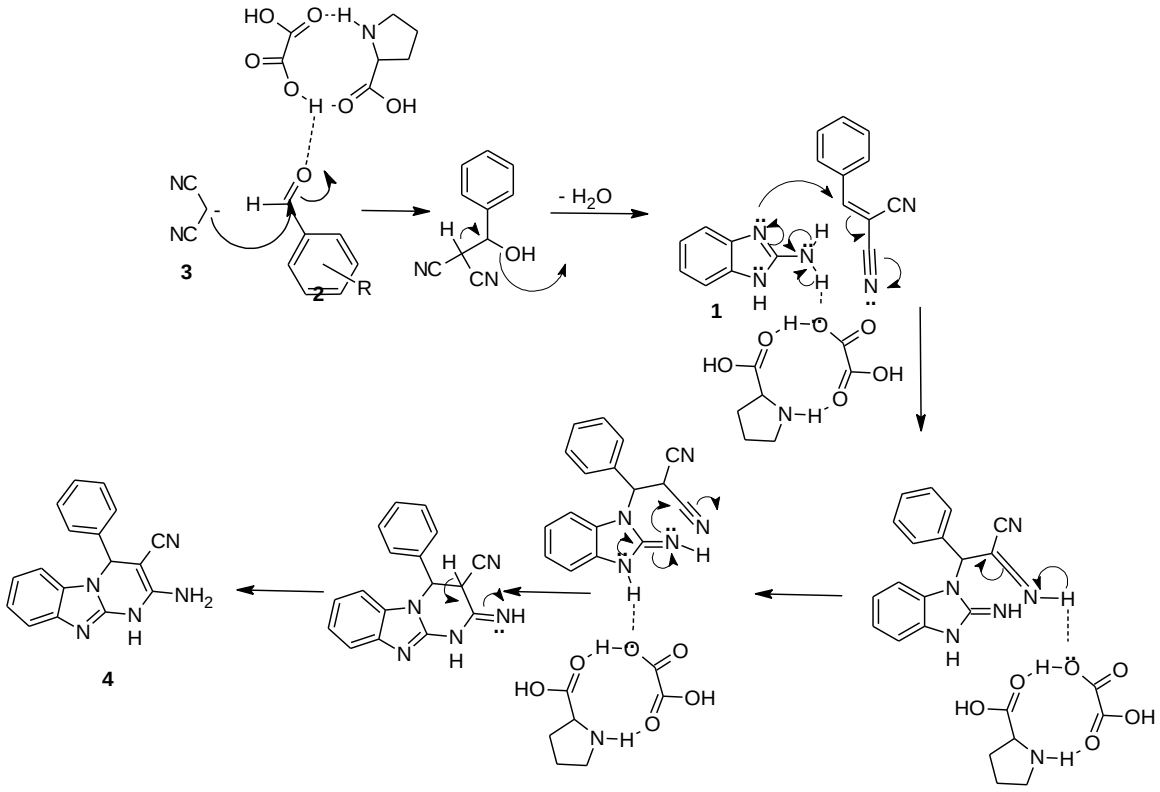
Sr. No.	-R	Product		Reaction Time (min.)	Yield[b] (%)	Atom Economy[c]	M. P. ° C Obs. (Lit.)
1.			4a	25	92	84.5	236-238

2.			4b	15	95	89.22	279-280
3.			4c	20	90	85.02	231-233
4.			4d	16	88	84.12	266-268
5.			4e	20	87	83.44	224-226
6.			4f	20	90	84.9	>300 (Dec.) (317-319)[18]
7.			4g	22	91	86.02	239-241 (240) [18]
8.			4h	18	95	88.95	239-242 (236) [18]

9.			4i	22	90	86.07	226-228
10.			4j	12	92	85.15	268-270
11.			4k	15	88	83.34	247-250
12.			4l	15	86	82.1	268-270 (270) [18,15]
13.			4m	15	91	85.78	237-239 (236) [18]

[a] Reaction of 2-aminobenzimidazole, aryl aldehyde and malononitrile optimized condition, [b] Isolated yield, [c] Atom economy =(molecular mass of desired product / molecular mass of all reactants) × 100

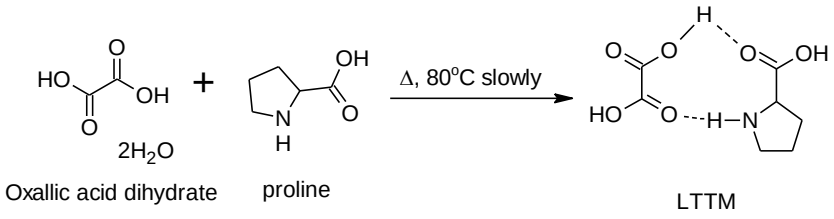
The plausible mechanism of the product formation is depicted in Scheme 2. In LTTM, Oxalic acid dihydrate and L-prolinemake proton acceptance and proton donor sites, creating hydrogen bonding network. This characteristic nature of LTTM may be create electrophilic activation of aldehyde (2) and subsequent attack of malononitrile(3) gives the Knovenagel intermediate which promote the nucleophilic attack of another molecule of 2 aminobenzimidazole (1) followed by succeeding cyclization afforded a series of targeted compounds.



Scheme 2: Plausible mechanism of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile

Typical procedure for preparation of a LTTM

The LTTM was synthesized according to the reported method in the literature.[24, 29]The mixture of L-proline (50 mmol) and oxalic acid dihydrate (50 mmol) in a ratio of 1:1 and heated slowly at 80°C for 1 hrs to get a yellowish viscous liquid (i.e., LTTM) with 100 % atom economy (Scheme 3).



Scheme 3: Preparation of Oxalic acid dihydrate:L-proline (LTTM)

In addition, the reusability of the LTTMs/DES taking into consideration for the profitable point of view, was scrutinized by using 2 aminobenzimidazole (1 mmol) and malononitrile (1 mmol) with various aromatic aldehydes (1 mmol) as substrates and Oxalic acid dihydrate: L-prolineLTTM (5 ml) at optimized condition. Completion of the reaction was monitored by using TLC, and then about 5 mL of water is added in reaction mixture to separate out the desired compound, which was then filtered and reused. The LTTMs/DES was soluble in water and recovered in good yield by evaporating the water under reduced pressure below 60°C. The recycled LTTM was dried under vacuum and reused for the next two successive reactions (Table 4 and figure 2).

Table 4: Reusability of LTTMs/DES

Run	Fresh	Frist	Second	Third
LTTM Reusability (%)	-	90	84	78
Yield of Product (%)	95	92	85	80

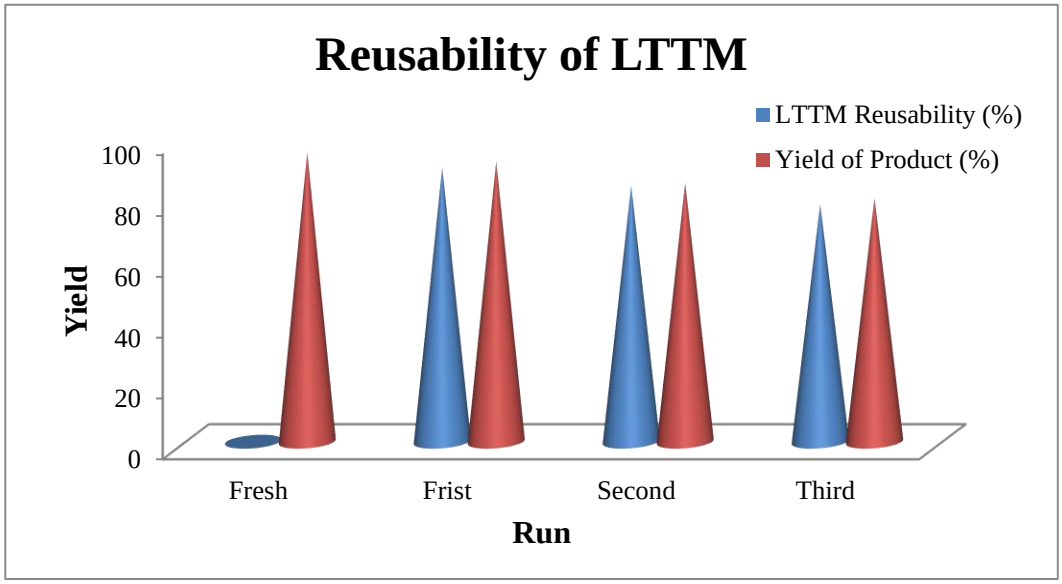


Figure 2 Reusability of Oxalic acid dihydrate: L-proline(LTTM)

From these results, it is observed that the LTTM (Oxalic acid dihydrate: L-Proline) verified to be significantly reused and resourceful solvent with insignificant loss of the activity.

After these successes, we excessively worked out an atom economy and the results are summarized in Table 2 (Fig. 3). It was observed that atom economy of the reaction is good to excellent which indicates that maximum amount of all the reactants finished up in the product and a minimum amount of waste was formed.

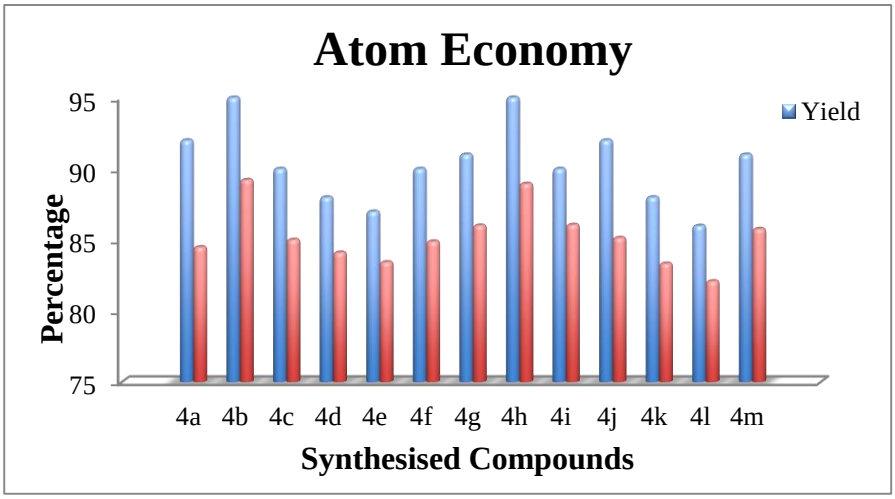


Figure 3 Atom economy of the synthesized Benzimidazole derivatives.

General procedure for the syntheses of compounds [4a-m]

Aryl aldehyde (1 mmol) and malononitrile (1 mmol) added in to a round bottom flask (RBF) containing 5mL of (LTTM) Oxalic acid dihydrate:L-proline (1:1). Then reaction mixture stirred at room temperature for about 5 min. After that added 2 aminobenzimidazole (1mmol) and reaction mixture stirred again at room temperature for about 10-20 min. precipitate is observed in RBF. Completion of the reaction monitor by TLC, 5 mL water was added to the reaction mixture to separate out the product it was filtered and recrystallized. Removal of extra water from the filtrate under reduced pressure recovered the LTTM (90 %), which was reused for three times (Table 4).

Physical and spectral data of synthesized compounds

2-Amino-4-(4-cyanophenyl)-1,4-dihydropyrimido[1,2-*a*]benzimidazole -3-carbonitrile (4b)

White Coloured powder; yield 95 %; mp 279-280°C; IR (ν max): 3424.96, 3315.03, 2233.16, 2192.67, 1680.66 cm $^{-1}$;^{1}H NMR (DMSO$_{d6}$, 300 MHz): δ, 5.371 (s, 1H), 6.960 (s, 2H), 7.002-7.054 (t, 1H, *J* = 7.8 Hz), 7.111-7.162 (t, 1H, *J* = 7.7 Hz), 7.232-7.258 (d, 1H, *J* = 7.8 Hz), 7.437-7.464 (d, 2H, *J* = 8.1 Hz), 7.570-7.596 (d, 1H, *J* = 7.8 Hz), 7.773-7.800(d, 2H, *J* = 8.1 Hz), 7.988 (s, 1H) ppm; ; ^{1}H NMR (DMSO$_{d6}$, D-Exchange, 300 MHz): δ, 5.336 (s, 1H), 7.002-7.054 (t, 1H, *J* = 7.8 Hz), 7.111-7.162 (t, 1H, *J* = 7.7 Hz), 7.232-7.258 (d, 1H, *J* = 7.8 Hz), 7.437-7.464 (d, 2H, *J* = 8.1 Hz), 7.570-7.596 (d, 1H, *J* = 7.8 Hz), 7.773-7.800(d, 2H, *J* = 8.1 Hz) ppm; ^{13}C NMR(DMSO$_{d6}$, 75 MHz): δ, 53.50, 61.11, 111.34, 112.56, 116.68, 118.60, 119.20, 120.63, 123.79, 127.24, 129.56, 129.80, 132.30, 132.47, 143.84, 148.81, 149.86, 151.77 ppm.

4. CONCLUSION

We have successfully demonstrated the use of LTTMs as solvent as well as catalyst system for synthesis of 2-amino-4-phenyl-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives. The present protocol provides an excellent and suitable method for the preparation of Benzimidazole derivatives. The products obtained have pure and are isolated with simple procedure. Moreover, easy work-up procedure with high yield, rapid reactions with high atom economy, solvents reusability are the beautiful features of the procedure. LTTM are readily prepared, greener solvent as well as catalyst, which will provide new opportunities to follows rules of greener organic transformations.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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