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A facile synthesis of 6-amino-2*H*, 4*H*-pyrano[2,3-c]pyrazole-5-carbonitriles in deep eutectic solvent

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ABSTRACT

A convenient synthesis of 6-amino-2*H*,4*H*-pyrano[2,3-c]pyrazole-5-carbonitriles has been accomplished by one pot four-component cyclocondensation of aromatic aldehydes (**1a-o**) malanonitrile (**2**), ethyl acetoacetate (**3**), and hydrazine hydrate (**4**) in freshly prepared deep eutectic solvent, DES (choline chloride:urea). This protocol has afforded corresponding pyrano[2,3-c]pyrazoles in shorter reaction time with high yields, and it avoids the use of typical toxic catalysts and solvents.

1. Introduction

The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their use as scaffolds in the design of therapeutically active new compounds [1]. Polyfunctionalized pyran and their derivatives are very important heterocyclic compounds which frequently exhibit a variety of biological activities [2,3]. 4*H*-Pyran is an important and common structural unit both in natural and synthetic heterocyclic molecules [4,5]. The dihydropyrano[2,3-c]pyrazole represents a fascinating template in the pharmaceutical field and is responsible for a wide spectrum of biological activities in molecules containing this significant unit [6]. Such compounds are exhibiting biological activities like antimicrobial [7], anticancer [8], anti-inflammatory [9] and inhibition of human Chk1 kinase [10] activities. Consequently, there has been continuous interest in the development of facile synthetic protocols for the construction of dihydropyrano[2,3-c]pyrazoles.

A one pot four component cyclocondensations of aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate was reported for obtaining dihydropyrano[2,3-c]pyrazoles [11]. This cyclocondensation has been accelerated by incorporating various catalysts *viz*; per-6-amino-β-cyclodextrin [12], glycine [13], γ-alumina [14], L-proline [15], nanosized magnesium oxide [16], Mg/Al hydrotalcite [17], *N*-methylmorpholine [18], heteropolyacids [19], sodium benzoate [20], and amberlyst A21 [21] and obtained good to moderate yields of dihydropyrano[2,3-c] pyrazoles. One pot three component cyclocondensations have also been reported for dihydropyrano[2,3-c]pyrazoles, in which pyrazolone derived from condensation of ethyl acetoacetate and hydrazine hydrate is cyclocondensed with *in situ* intermediates generated from the interaction of aldehydes and malononitrile. The latter route has also been accelerated by various organic and inorganic bases [22]. The reported methods still have certain inadequacies, such as long reaction time, toxic and expensive catalysts, excess heating, and tedious work-up procedure. Therefore, an exploration of a more general, efficient, and greener approach is highly desirable.

Green technology actively seeks new, safer, alternative solvents to replace common widely used organic solvents that present inherent toxicity and high volatility, leading to evaporation of volatile organics to the atmosphere [23]. In performing the majority of organic transformations, solvents play a critical role in making the reaction homogeneous and hence facilitating molecular interactions [24]. Over the last two decades more attention has been directed on the use of non-volatile organic media like ionic liquids, PEGs, glycerine, water *etc.* for carrying value added transformations. Ionic liquids (ILs) are quaternary

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salts/PTCs/inorganic salts having melting points less than 100 °C. It has been reported that most of the ILs less biodegradable, more toxic, and more expensive than hoped. Because of this, ILs are now becoming less popular as media. Recently, chemists have been paying more attention on the use of deep eutectic solvents (DESs) for carrying various chemical transformations safely and rapidly. A DES is generally composed of two or three cheap and safe components which are capable of keeping association with each other through hydrogen bond interactions to form a eutectic mixture. The resulting DES is characterized by its melting point, which is lower than that of the individual components. Generally, DESs are characterized by very large depression of freezing point, and most are liquid at room temperature [25].

Choline chloride (ChCl), or 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium chloride, has been widely used as an organic salt to produce eutectic mixtures when blended with cheap and safe hydrogen bond donors like urea, polyols, and carboxylic acids [26]. Urea is cheap readily available and has better self association with ChCl. Therefore, it is widely used in generating DES by blending with ChCl. Novel solvent properties of ChCl:urea mixtures have been reported by Abbott et al., who concluded that a blend of ChCl:urea with ratio 1:2 has the best self association through hydrogen bond interactions and forms appropriate eutectic mixture [25c]. Such DESs are attracting researchers as they exhibit similar physicochemical properties to traditional ionic liquids, and are thus found to be more advantageous in organic syntheses. DESs are lower in cost, more biodegradable, and less toxic than the traditional ionic liquids and therefore are replacing the traditional ionic liquids while carrying value added organic transformations *viz.* Knoevenagel condensation [27], Diels–Alder reactions [28], Fischer indole annulations [29], Perkin reaction [30], selective acylation of primary hydroxyl groups in cellulose [31], fluorination of acetophenone [32], bromination of substituted 1-aminoanthra-9,10-quinone, and benzylation of phenols [33].

Considering the advantages of these deep eutectic solvents and in continuation of our efforts to develop environmentally benign protocols for various chemical transformations [34], here an attempt has been made to develop a modified protocol by optimizing the reaction conditions for carrying the cyclocondensation of aromatic aldehydes, malanonitrile, ethyl acetoacetate, and hydrazine hydrate in DES for obtaining polyfunctional pyranopyrazoles in a cost effective and rapid way.

2. Experimental

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz using DMSO-d_6 solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz on Jeol. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent, and visualization was accomplished by iodine/ultraviolet light.

2.1. Synthesis of deep eutectic solvent

A mixture of choline chloride (70 mmol) and urea (140 mmol) *i.e.* in the ratio of 1:2 was heated at 80 °C with stirring for 30 min. The resulting eutectic solvent was then allowed to cool to room temperature and was used for the synthesis of pyranopyrazoles (**5a-o**) without further purification.

2.2. Synthesis of 6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (*5a*)

A mixture of 4-methoxy benzaldehyde (**1a**) (3 mmol), malononitrile (**2**) (3 mmol), hydrazine hydrate (**3**) (3 mmol), and ethyl acetoacetate (**4**) (3 mmol) was added in DES (5 mL) and then the reaction mass was stirred at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane 1:9). After 20 min of stirring, the reaction mixture was cooled to room temperature. Then, it was extracted using ethylacetate. The ethyl acetate phase was separated from undissolved DES and the organic layer was separated, dried, filtered, and concentrated in vacuo. The crude solid residue that remained was then crystallized from ethanol.

Similarly, the other compounds (**5b-o**) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 2.

6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**5a**): IR (KBr, υ cm^{-1}): 3425 (N–H stretching), 3128 (Ar–H stretching), 2928 (C–H stretching), 2200 (CN stretching), 1597 (C=N stretching), 1153 and 1203 (C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (s, 3*H*, –CH_3), 3.78 (s, 3*H*, –OCH_3), 4.45 (s, 1*H*, –CH–), 6.81 (s, 2*H*, –NH_2), 6.87 (d, 2*H*, *J* = 8.0 Hz), 7.23 (d, 2*H*, *J* = 8.0 Hz) and 12.08 (s, 1*H*, –NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.82, 34.74, 53.77, 57.75, 94.70, 96.54, 112.46, 119.71, 127.38, 134.69, 134.85, 153.85, 157.02 and 159.50; MS (ESI): *m/z*: 283.2 [M$^+$]; Elemental analysis: Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85; found C, 63.37; H, 5.67; and N, 19.65

6-Amino-1,4-dihydro-4-(4-phenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**5b**): IR (KBr, υ cm^{-1}): 3427 (N–H stretching), 3119 (Ar–H stretching), 2934 (C–H stretching), 2200 (CN stretching), 1595 (C=N stretching), 1149 and 1211 (C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 3*H*, –CH_3), 4.51 (s, 1*H*, –CH–), 6.79 (s, 2*H*, –NH_2), 6.99–7.76 (m, 5*H*, Ar–H) and 12.04 (s, 1*H*, –NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.85, 34.69, 57.67, 94.69, 96.48, 112.57, 119.69, 127.35, 134.73, 134.79, 153.84, 157.23 and 159.45; MS (ESI): *m/z*: 253 [M$^+$]; Elemental analysis: Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; found C, 66.67; H, 4.75; and N, 22.21

2.3. Recycling of DES, choline chloride:urea

A mixture of 4-methoxy benzaldehyde (**1a** 3 mmol), malononitrile (**2** 3 mmol), hydrazine hydrate (**3** 3 mmol), and ethyl acetoacetate (**4** 3 mmol) was added in DES (5 mL), and then the reaction mass was stirred at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane 1:9). After 20 min of stirring, reaction mixture was cooled to room temperature. Then it was extracted using ethylacetate. Thus obtained undissolved DES was further extracted with ethyl acetate (10 mL), and the undissolved viscous liquid was separated and recycled for reuse for future cycles.

3. Results and discussion

An efficient protocol has been developed for pyranopyrazoles (**5a-o**) by one pot cyclocondensation of aromatic aldehydes (**1a-o**),

Table 1
Screening of reaction media for the synthesis of compound **5a**.[a]

Entry	Solvents	Yield (%)[b]
1	PEG-400	72
2	Dicationic ionic liquid	65
3	Ionic liquid (*N*-methylpyridinium tosylate)	62
4	DES (40, 60, 80, 100 °C)	78, 85, 91, 92

[a] Reaction conditions: All the reactions were carried at 80 °C for 20 min.
[b] Isolated yields, DES: choline chloride:urea.

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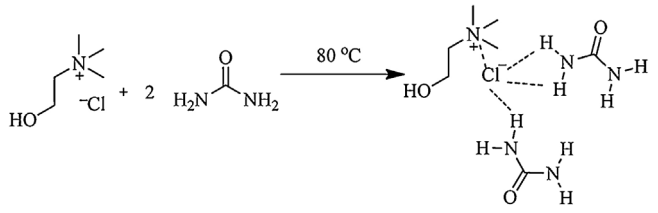
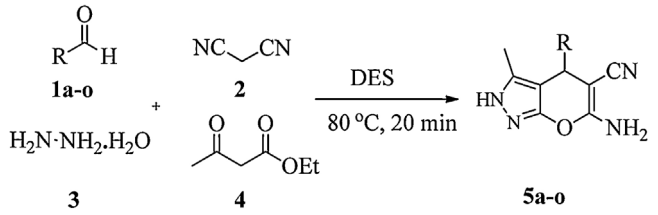


Scheme 1. Schematic presentation of synthesis of DES based on choline chloride and urea.



Scheme 2. 6-Amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (**5a-o**).

Table 2
Physical data of 6-amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (**5a-o**).[a]

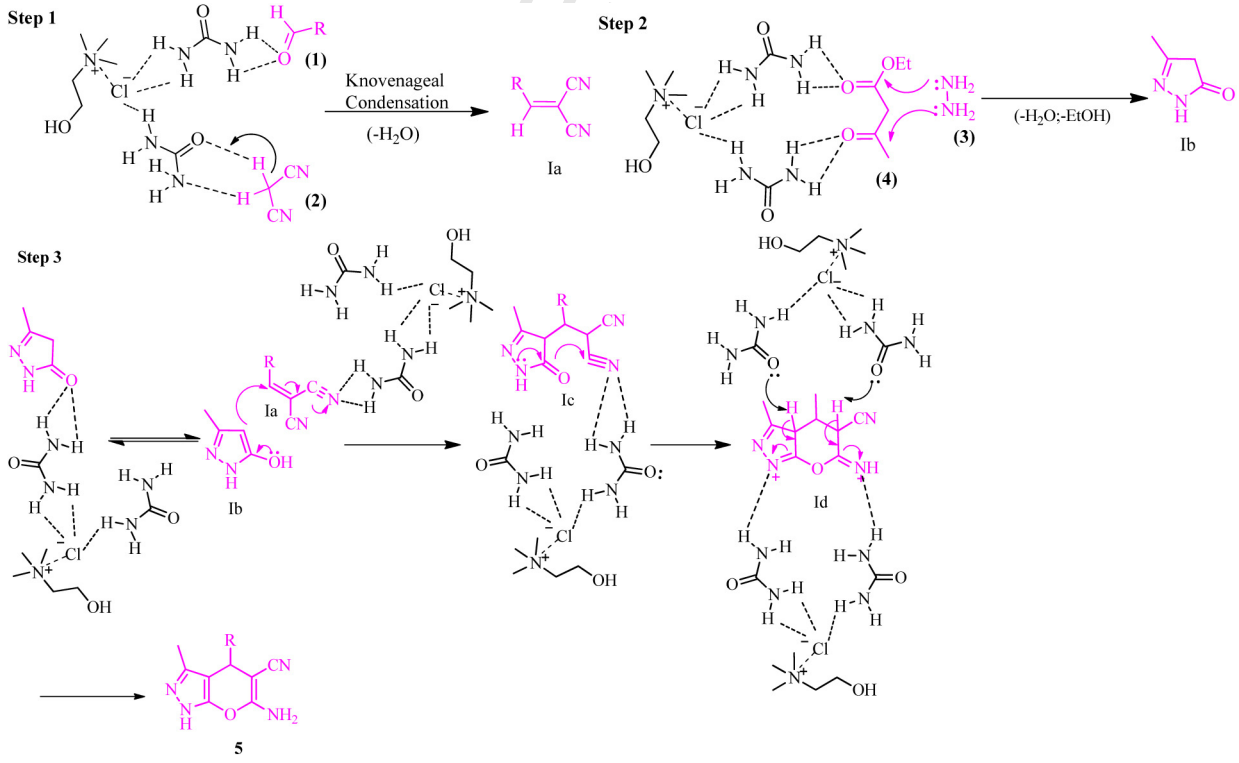
Compound	*R*	Yield (%)[b]	Mp[c] (°C)
5a	4-OCH_3-Ph	91	209–211
5b	-Ph	92	243–244
5c	4-Cl-Ph	89	230–232
5d	4-CH_3-Ph	91	174–175
5e	4-F-Ph	87	171–172
5f	3-Br-Ph	81	223–224
5g	4-NO_2-Ph	85	254–256
5h	4-OH-Ph	90	221–223
5i	2-Cl-Ph	79	244–245
5j	3-NO_2-Ph	87	190–192
5k	3,4-$(OMe)_2$-Ph	84	189–190
5l	4-OH-3-OMe-Ph	82	235–237
5m	2-furyl	69	240–242
5n	2-thiophenyl	72	224–224
5o	4-pyridyl	71	214–216

[a] Reaction conditions: aldehydes (**1a-o**) (3 mmol), malononitrile (**2**) (3 mmol), hydrazine hydrate (**3**) (3 mmol) and ethyl acetoacetate (**4**) (3 mmol) in DES (5 mL) was stirred at 80 °C for 20 min.
[b] Isolated Yields.
[c] Melting points are in good agreement with those reported in the literature [35].

malononitrile (**2**), ethyl acetoacetate (**3**), and hydrazine hydrate (**4**) in freshly prepared deep eutectic solvent choline chloride:urea (Scheme 1) at 80 °C (Scheme 2).

To examine the choice of solvents, an investigation was initiated in to the optimization of four component one pot condensation of 4-methoxy benzaldehyde (**1a**), malononitrile (**2**), hydrazine hydrate (**3**), and ethyl acetoacetate (**4**) to afford pyranopyrazole (**5a**) as a model reaction. Initially, the reaction was run in the absence of a catalyst and a solvent by varying temperature (30–100 °C). It was observed that after prolonged heating, the cyclocondensation did not run satisfactorily. Considering the significance of green chemistry efforts were directed towards the use of green reaction media. Hence, the above model reaction was performed separately in various green solvents, like PEG-400. Ionic liquids at 80 °C gave the desired pyranopyrazole with moderate to better yields (Table 1, entries 1–3). Considering the above results and the importance of DES, model reaction was then carried out in DES, derived from a mixture with 1:2 composition of choline chloride:urea, and 91% yield of the pyranopyrazole (**5a**) was obtained.

In preliminary studies, the model reaction was performed by condensing 2-(4-methoxybenzylidene) malononitrile (obtained by Knoevenagel condensation of 4-methoxy benzaldehyde and malononitrile) and pyrazolin-5-one (prepared by condensation of hydrazine hydrate and ethyl acetoacetate) in DES at 80 °C and the expected product **5a** was obtained with 82% yield. After obtaining these results, one pot four component reaction of **1a**, malononitrile (**2**), hydrazine hydrate (**3**), and ethyl acetoacetate (**4**)



Scheme 3. Plausible mechanism for the synthesis of pyranopyrazoles (**5a-o**).

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was carried out at 80 °C. It successfully yielded **5a** with high yields without the need of prior isolation of the intermediates. From these results, it was confirmed that DES promotes the formation of the intermediates and their successive condensation to the desired title product **5a**.

During the study, the model reaction was performed using DES as a reaction medium at different temperatures. Model reaction in DES at 80 °C was found to proceed with excellent yield (91%) of **5a** in 20 min (Table 1). It was also noted that under similar reaction conditions there was no condensation at room temperature. As temperature increased (40, 60, 80, 100 °C) the yield of the product also increased (78%, 85%, 91%, 92%). There was no significant change in the product yield when reaction was kept above 80 °C.

The recyclability/reuse of the DES has also been confirmed for the model reaction and it was noticed that even after three successive cycles, DES was found to effectively as medium and catalyst. The details of recovery and reuse of DES is given in the experimental section.

The generality of this protocol was tested using various aldehydes with electron donating and withdrawing groups in order to determine the scope of the DES as medium and catalyst. A variety of aldehydes (**1a-o**) have been found to undergo cyclocondensation smoothly to offer the respective pyranopyrazoles (**5a-o**) in good to excellent yields at 80 °C within 20 min (Table 2).

The rate acceleration of this one pot four component cyclocondensation leading to pyranopyrazoles is attributed to the unique use of DES as a medium, as it has the capacity to dissolve various organic/inorganic solutes readily. This might be responsible for maintaining high concentrations of the reactants in the beginning of the reaction and during its progression. High to saturated solutions of the reactants in the reaction mass would be responsible for rate acceleration of the cyclocondensation.

Stronger hydrogen-bonding capabilities of DES might enhance the electrophilic character of carbonyl carbons of the reactants, *viz*; aldehydes and intermediate. It might also be increasing the rate of *in situ* formation of carbanion from malononitrile. A plausible mechanism, supporting the role of the DES in rate enhancement is presented in Scheme 3.

4. Conclusion

We have been able to introduce a facile and environmentally friendly approach for the synthesis of biologically active substituted pyranopyrazoles *via* one pot cyclocondensation of various aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate, and malononitrile in a safe to use deep eutectic solvent, choline chloride:urea. High yields, easy work-up, cost effectiveness, and the reusability of the medium are the key advantages of this approach. Therefore, DES is found to have wide scope for rapidly making value added organics *via* multicomponent cyclocondensations.

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