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Water–SDS–[BMIm]Br composite system for one-pot multicomponent synthesis of pyrano[2,3-*c*] pyrazole derivatives and their structural assessment by NMR, X-ray, and DFT studies†

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Here, we report a simple, efficient, and green protocol for the one-pot synthesis of pyrano[2,3-*c*]pyrazole derivatives *via* a sequential three-component strategy using aromatic aldehydes, malononitrile and pyrazolin-5-one in a water–SDS–ionic liquid system. This is a base and volatile organic solvent-free approach that could be applicable to a wide substrate scope. The key advantages of the method over other established protocols are very high yield, eco-friendly conditions, chromatography-free purification and recyclability of the reaction medium. Our study revealed that the *N*-substituent present in pyrazolinone controls the selectivity of the process. *N*-unsubstituted pyrazolinone favours the formation of 2,4-dihydro pyrano[2,3-*c*]pyrazoles whereas under identical conditions *N*-phenyl substituent pyrazolinone favours the formation 1,4-dihydro pyrano[2,3-*c*]pyrazoles. Structures of the synthesized products were established by NMR and X-ray diffraction techniques. Energy optimized structures and energy gaps between the HOMO-LUMO of some selected compounds were estimated using density functional theory to explain the extra stability of the 2,4-dihydro pyrano[2,3-*c*]pyrazoles over 1,4-dihydro pyrano[2,3-*c*]pyrazoles.

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Introduction

In the present day context, organic synthesis *via* multicomponent reactions (MCRs) becomes a very important method of choice to save time, solvent, energy and for executing the process in a cost effective manner. MCRs provide easy access to wide range of novel functional molecules with high efficiency in terms of yield and selectivity.[1] The heterocyclic compounds are widely spread in nature and play an important role in life processes and therefore they are well recognized in biological and therapeutic arenas.[2] Consequently, synthesis of novel functionally diversified compounds specially heterocyclic compounds by MCR approach has attracted tremendous attention not only to organic synthetic chemists but also pharmaceutical and medicinal chemistry researchers across the globe. Amongst them, pyrano[2,3-*c*]pyrazoles (Fig. 1, **1** or **1′**) is a fused heterocycle comprised of pyrazole and pyran rings which are known as the sub-structural units of several biologically active compounds[3] and widely used as medicinal intermediates due to their biological and pharmacological properties such as analgesic and anti-inflammatory,[4a,b] anti-cancer,[5a,b] anti-oxidant,[6a–c] anticholine-sterase,[7] anti-HIV,[8] anti-microbial activity,[9a–d] human checkpoint kinase 1 (Chk1) inhibitor,[10] fungicidal,[11] bactericidal[12] and vasodilatory[13] activity. They are also used as biodegradable agro-chemicals due to their fungicidal, bactericidal, and herbicidal properties[14] and pharmaceutical ingredients.[15] Some 2-amino-4*H*-pyrans can be used as photoactive materials[16] as they can undergoes dimerization upon UV irradiation, therefore they can act as UV absorbers.[17] Furthermore, these compounds are used as cosmetics and pigments.[18] Fig. 2 displayed structures of some of the important pyranopyrazoles with their possible applications.[4–13,19a–f]

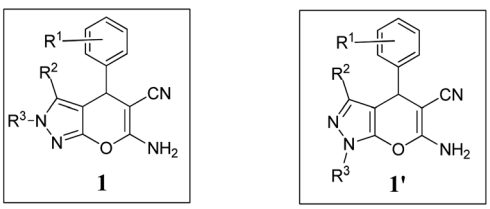

Fig. 1 Structure of 2,4-dihydropyrano-[2,3-*c*]pyrazole (**1**) and 1,4-dihydropyrano[2,3-*c*]pyrazole (**1′**).

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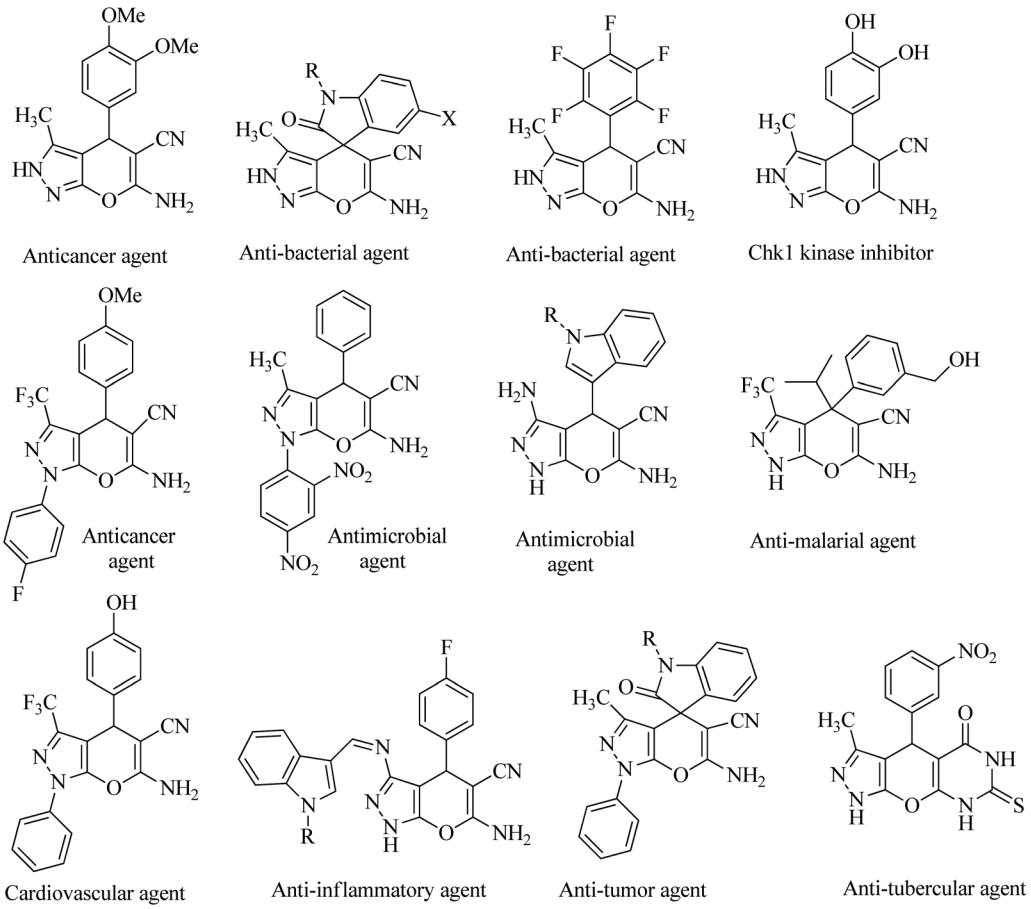
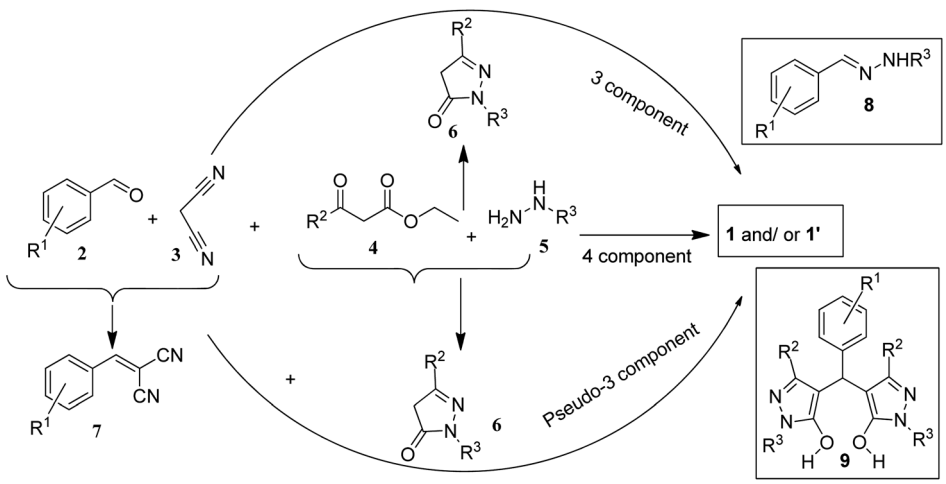


Fig. 2 Structures and applications of some biologically active pyranopyrazoles

Thus, the synthesis of the heterocyclic compounds containing the pyranopyrazole moiety is of great importance and fascinated by research community as an interesting synthetic target since 19th century after its first report from Otto *et al.*[20] Several procedures for the synthesis of pyranopyrazoles (**1** or **1′**) were reported,[21a–c] and documented by Mamaghani and co-workers in the recent review.[21d] Literature survey indicated that most of the synthesis of pyranopyrazoles are revolve around – (i) four component assembly of aldehydes (**2**), malononitrile (**3**) and β-ketoester (**4**) with hydrazine or its derivatives (**5**) using catalytic systems such as imidazole,[22a] [DSim]$AlCl_4$,[22b] poly(4-vinylpyridine),[22c] Fe_3O_4 nanoparticles,[22d] DABCO,[22e] thiamine



Scheme 1 Various strategies for the synthesis of pyranopyrazoles

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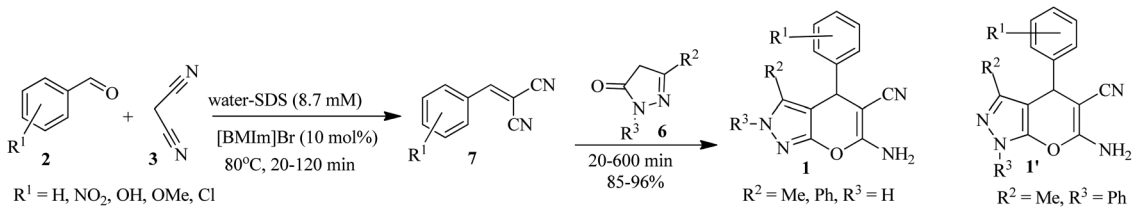
hydrochloride,[22f] thiourea dioxide,[22g] ZrO_2 nanoparticles,[22h] ball milling process,[22i] electro-chemical procedures,[22j] zwitterionic sulfamic acid functionalized nanoclay,[22k] Nano-SiO_2 catalyst,[22l] NMO/Ag_2O,[22m] Fe_3O_4@chitosan-tannic acid nanocatalyst,[22n] BF_3/MNPs,[22o] (ii) pseudo three-component condensation[23a–d] of aromatic aldehydes (**2**), malononitrile (**3**) and pyrazolinone derivatives (**6**) and (iii) pseudo two component assembly,[24a–d] by synthesizing some of its pre-combined constituents like benzylidenemalononitriles (**7**) and pyrazolone derivatives (**6**) (Scheme 1). Four component assembly involving aromatic aldehydes, Meldrum's acid, hydrazine hydrate or its derivatives, and ethyl acetoacetate are also known for pyranopyrazole synthesis.[25] Rapid four-component assembly in the presence of base in aqueous medium for the synthesis of 2,4-dihydropyranopyrazole analogues were also reported.[26] Although the reported methods are effective with their own advantages, however many of the existing methodologies suffer from several drawbacks such as use of toxic bases, tedious catalyst preparation and use of organic solvents rather than aqueous medium, environmental compatibility using toxic and expensive catalysts, lack of recyclability, and co-occurrence of side products. In addition, the ultrasound or microwave assisted synthesis are very fast but requires additional use of sonicator or microwave reactor and may not be suitable for large-scale synthesis. So despite of the available literature for the synthesis of pyranopyrazoles, simple, efficient, and environmentally benign approaches are still demanding. Interestingly, all the four components method started with similar starting materials and worthy to mention that they produced varying product just by changing the catalyst. As example, synthesis of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitriles (**1**) were achieved[27–29] by using ionic liquid, Amberlyst A21 or L-cysteine in water under refluxing condition whereas alternative catalysts such as starch solution, silica-coated cobalt oxide nanostructure-catalyst or taurine generates 6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives (**1′**).[30–32] Till the date no report on such a selectivity with respect to a specific catalyst are available and details of establishment of the structure was yet to report.

With the growing concern over environment pollution and related societal health problems, green chemistry concept is emerging as one of the important tools in the development of environmentally benign chemical processes and clean technologies including generation of solvent-free protocols along with replacement of volatile organic solvents by water as a green reaction medium. Water is non-hazardous, inexpensive, abundant, and eco-friendly in nature having high boiling point. Reactions in aqueous medium not only possess negative activation volume but also help in controlling exothermic reactions. Hence organic synthesis in aqueous medium is preferred from environmental as well as economical point of view.[33]

However; poor solubility of organic compounds in water remains a major issue of the success of any organic reaction in water. One of the possible ways to improve the solubility of organic substrates is the use of surface-active agents that can form micelles or vesicular structures. The micellar and vesicle-forming surfactants form hydrophobic cavity in where organic substrates and reagents assembled and undergoes reaction.[34]

Catalysis has been playing a pivotal role in pollution prevention from fine chemical processes, pharmaceutical industries by activation of functional groups thus by lowering the reaction temperature, reaction time and increased the chemical yield. While choosing the catalyst it is important to think about its water compatibility because water shows some commendable chemical and physical properties which are unrealizable with any other organic solvents. In this respect, ionic liquids plays a larger and more diversified role in catalysis,[35] which is reflected by the fact that the number of literature reports on this subject increases annually with many other advantages. To overcome the poor solubility issue of organic compounds in water and enhances the reactivity of functional group, various strategy have been reported in different occasion. In recent studies it was found that imidazolium based ionic liquids with long hydrophobic chains can reduce the CMCs of SDS greatly in water by ionic interaction as well as hydrophobic–hydrophobic interactions between alkyl chains of IL and SDS surfactant.[36] Motivated with the recent report on developing the multicomponent reaction for the synthesis of pyranopyrazoles and in continuation of our on-going efforts towards the development of environmentally benign protocols for organic transformations,[37a–d] we reported herein a methodology for the synthesis of pyranopyrazole by sequential addition of aromatic aldehyde and active methylene compound (Knoevenagel condensation) followed by the addition of pyrazolone (**6**) derivatives in a one pot fashion at 80 °C in an essentially neutral condition comprising water–SDS–ionic liquid combo system (Scheme 2).

Our method has distinct advantages in comparison to other existing methodology for the same synthesis and these includes – (i) volatile organic solvent and chromatography free procedure (ii) high yield and short reaction time (iii) avoidance of undesirable side reactions, (iv) complete recyclability of the reaction



Scheme 2 One pot sequential MCR strategy for the synthesis of pyranopyrazoles in aqueous medium.

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medium which can be used for subsequent cycles without loss of its activity (v) scale up of the protocol with same level of efficiency and (vi) selectivity. Structures of the synthesised compounds were established by ^{1}H, ^{13}C NMR and ^{1}H–^{1}H COSY and XRD studies. In addition, to find out the energetically favourable optimized structure between 2,4-dihydropyranopyrazoles and 1,4-dihydropyaranopyrazoles and to explain the reason for preferential formation of former from un-substituted pyrazolinone we have performed the density functional theory (DFT) calculations of the tautomers at B3LYP/6311G** level in the gas phase by using the computational program Gaussian 09W.

Results and discussions

In spite of some success of MCR involving four component assembly of pyranopyrazole synthesis it is matter of concern to subside competitive side reaction between reactive aldehydes with hydrazine/substituted hydrazine to form corresponding hydrazone derivatives (**8**) of the aldehydes or the formation bispyrazolone (**9**) from the condensation between aldehyde (**2**) and pyrazolone (**6**) formed as intermediates. Three component strategy is also suffering from some drawbacks such as formation of bis-pyrazoles (**9**) side product (Scheme 1). Based on our recent report[37a] on a versatile "base free" true "on water" strategy by mobilizing SDS as surfactant and neutral ionic liquid ([BMIm]Br) as activator for Knoevenagel condensation to synthesize arylidenemalononitrile derivatives (**7**) which is also an important piece of orchestra for the pyranopyrazoles synthesis, initially we began with 4-nitrobenzaldehyde (**2a**) as a model aromatic aldehyde, malononitrile (**3**), ethylacetoacetate (**4a**) and phenylhydrazine (**5a**). All these components were allowed to react at 80 °C in water–SDS–[BMIm]Br system under the condition established previously for arylidenemalonitrile **7a**. Unfortunately, such attempt resulted pyranopyrazole (**1a′**: R^1 = *p*-NO_2, R^2 = Me and R^3 = Ph) in 43% after 20 min along with the formation of phenylhydrazone derivative (**8a**, 20%) and bis-pyrazolol derivative (**9a**, 32%). Lessoned from these results and to suppress the cross reaction possibilities we drop down the approach to a three component variant by synthesizing intermediate 3-methyl-1-phenyl-5-pyrazolone (**6a**) separately from ethyl acetoacetate (**4a**) and phenylhydrazine (**5a**) and then assembling it with 4-nitrobenzaldehyde (**2a**) and malononitrile (**3**). This attempt definitely shows improvements in yields of **1a′** (65%) but still bis-pyrazolol (**9a**, 26%) was formed due to a tandem Knoevenagel–Michael addition between aromatic aldehyde (**2a**) and pyrazolone (**6a**). To improve further the yield of pyranopyrazole, we then decided to study the reaction in a sequential manner. In this approach initially only aldehyde (**2a**) and malononitrile (**3**) were allowed to react to form benzylidenemalononitrile (**4a**) in the presence of 10 mol% of [BMIm]Br in SDS-water (8.7 mM) and then pyrazolone derivative (**5a**) was added. We were happy to notice that this sequential approach works well and expected 6-amino-4-nitrophenyl-1, 4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**1a′**) was produced in 96% yield without any side reactions (Table 1). Among the two possible pyranopyrazoles **1a** and **1a′** only later one is expected and formed as the substituent's R^2 and R^3 located in 1,3-position. This preliminary result prompted us to investigate the scope and generality of the new protocol for various aldehydes under optimized conditions. Various structurally diverse aromatic aldehydes were considered to establish the generality and functional group tolerance capability of the present methodology towards the synthesis of highly functionalized pyranopyrazole derivatives. Our studies revealed that aromatic aldehydes bearing –NO_2, –OH, –OMe, –Cl *etc.* All underwent facile condensation (with malononitrile) – addition – cyclization with 1-phenyl-3-methyl-5-pyrazolone (**5a**) or 3-methyl-5-pyrazolone (**5b**) to give pyranopyrazole derivatives.

Table 1 Optimization of strategy employed for the synthesis of **1a′**

Entry	Strategy[a]	Time (min)	**1a′**[b]	**8a**[b]	**9a**[b]
1	Four component (**2a** +**3a** + **4a** +**5a**)	20	43	20	32
2	Three component, non-sequential (**2a** +**3a** +**6a**)	20	65	—	26
3	Three component, sequential (**2a**+ **3a** → **7a** then **6a**)	20 + 20	96	—	—

[a] Reactions were carried out with SDS (3.5 mol%, 10 mg) and [BMIm]Br (10 mol%, 20 mg) in H_2O (4 mL) at 80 °C. [b] Isolated yields.

Aldehydes such as *m*-nitro, *m*-hydroxy, *p*-hydroxy and 4-methoxy benzaldehydes, all underwent smooth transformation under the same condition to 6-amino-4-substituted-1-phenyl-1, 4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile derivatives (**1b′**–**e′**) in excellent yield (Table 2, entries 2–5) as 4-nitrobenzaldehyde does (Table 2, entry 1). Here again, no 6-amino-4-substituted 2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives (**1b–e**) were detected in any case. However, benzaldehyde and other substituted benzaldehydes upon similar treatment with malononitrile followed by the addition of 3-methyl-5-pyrazolone (**6b**: R^3 = H) produced 6-amino-4-substituted 2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives (**1f–l**) as sole product (78–96% isolated yield) as revealed by NMR (Table 2, entries 6–12). Other aldehydes, thiophene-2-carboxaldehyde (**2h**), anthracene-9-carboxaldehyde (**2i**) or carbazole-3-carboxaldehyde (**2j**) also underwent similar transformation to 2,4-dihydro pyranopyrazoles **1m–o** in good yields but took unexceptionally longer reaction time (up to 12 h, Table 2, entries 13–15). The 3-phenyl-5-pyrazolone (**6c**: R^3 = H) which was synthesised from ethyl benzoylacetate also produced pyranopyrazoles **1p–r** in excellent yield (Table 2, entries 16–18). Unfortunately when we used salicylaldehyde as aldehyde for the synthesis of concerned pyranopyrazole derivatives it produced a complex mixture of products due to the presence of additional –OH group possibly occurring of cyclization product from intermediate 7 (ref. 42) as well as two more cyclization products after nucleophilic addition of pyrazolinone (**6b**) to the intermediate 7.[26b,43] We also tested our methodology for aliphatic aldehydes such as *n*-butanal, *n*-hexanal or *n*-heptanal, however such attempts did not produced any expected products. Perhaps this is may be due to the presence of enolizable hydrogen in the intermediate active dicyano alkene that reduces its

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Table 2 One pot multicomponent synthesis of pyrano[2,3-*c*]pyrazoles by sequential addition strategy using aldehydes, malononitrile and pyarazolinones in water–SDS–[BMIm]Br system

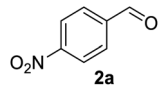
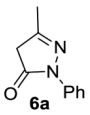
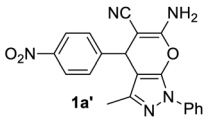
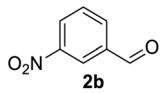
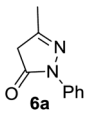
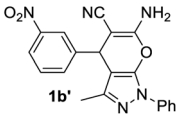
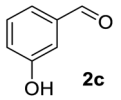
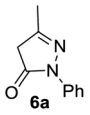
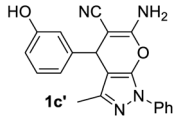
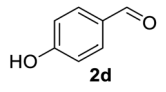
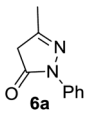
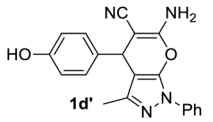
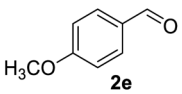
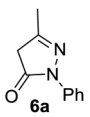
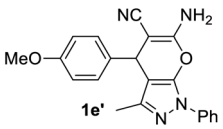
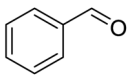
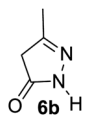
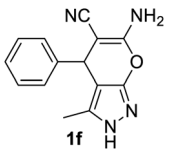
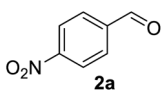
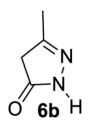
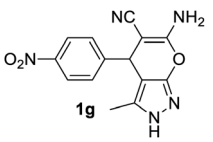
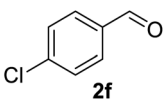
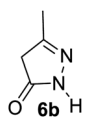
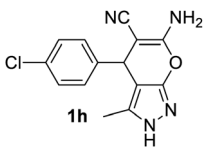
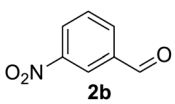
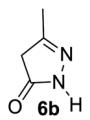
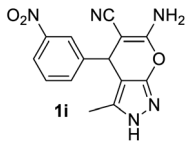
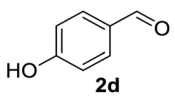
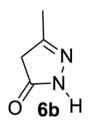
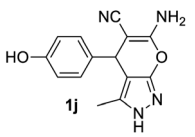
Entry	Aldehyde	Active methylene	Pyrazolone	Product	Time (mins)	Yield (%)
1	 2a		 6a	 1a'	40	96 (ref. 22*c*)
2	 2b		 6a	 1b'	50	95 (ref. 22*c*)
3	 2c		 6a	 1c'	50	94 (ref. 38)
4	 2d		 6a	 1d'	70	94 (ref. 22*c*)
5	 2e		 6a	 1e'	70	95 (ref. 22*c*)
6			 6b	 1f	60	78 (ref. 27)
7	 2a		 6b	 1g	40	96 (ref. 27)
8	 2f		 6b	 1h	50	94 (ref. 27)
9	 2b		 6b	 1i	50	94 (ref. 39)
10	 2d		 6b	 1j	60	94 (ref. 27)
11	2e		6b	1k	70	94 (ref. 27)

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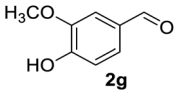
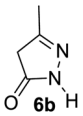
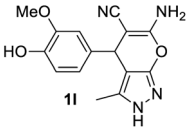
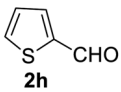
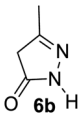
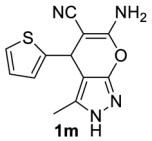
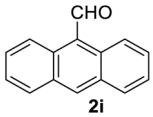
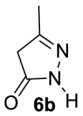
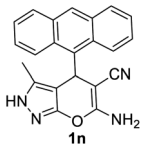
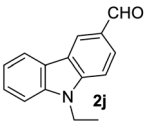
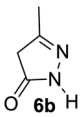
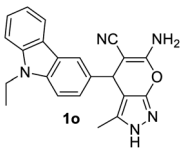
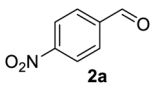
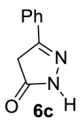
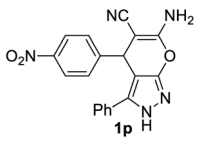
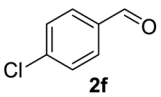
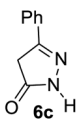
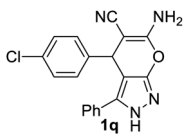
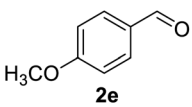
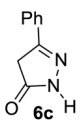
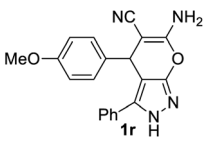
Table 2 (*Contd.*)

Entry	Aldehyde	Active methylene	Pyrazolone	Product	Time (mins)	Yield (%)
12	 2g		 6b	 1l	60	93 (ref. 27)
13	 2h		 6b	 1m	120	92 (ref. 39)
14	 2i		 6b	 1n	720	87[new]
15	 2j		 6b	 1o	720	85[new]
16	 2a		 6c	 1p	60	95 (ref. 40)
17	 2f		 6c	 1q	60	94 (ref. 41)
18	 2e		 6c	 1r	80	93 (ref. 40)

nucleophilicity. To check the selectivity, we have studied a control reaction using butanal (1 mmol), 4-hydroxy benzaldehyde (1 mmol) and malononitrile (2 mmol) under water–SDS–ionic liquid system at 80 °C. After consumption of aldehydes, 1 mmol of pyrazolone (**5b**) was added and heating was continued for 60 min. Only pyranopyrazole (**1j**) was isolated in 90% yield, no pyranopyrazole having aliphatic residue was detected. This experiment indicated that our protocol is highly selective for aromatic aldehydes. All the synthesized products were fully characterized by their IR, NMR and mass spectral data and are strongly resembled with the data those are reported earlier except two new compounds **1n** and **1o**.

The structure of 2,4-dihydropyrano[2,3-*c*]pyrazoles were confirmed by ^{1}H–^{1}H COSY in where correlation was found between H–N and protons of methyl group suggesting that they are located at the adjacent position (see ESI†). Aiming to get single crystal of the newly synthesised compounds **1n** and **1o**, suitable crystals for XRD studies were grown from ethanol-water system. The crystal structure of both **1n** and **1o** are shown in Fig. 3. The crystallographic data were deposited to Cambridge Crystallographic Data Centre (CCDC no. for **1n** and **1o** are

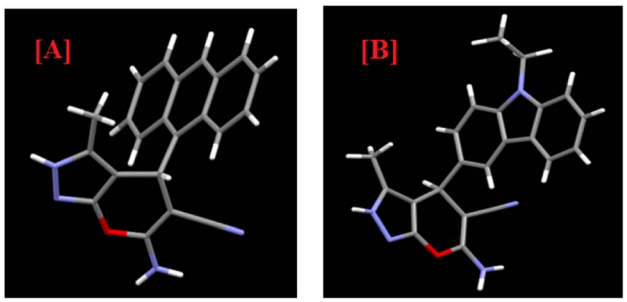


Fig. 3 Single crystal structures of **1n** (A) and **1o** (B).

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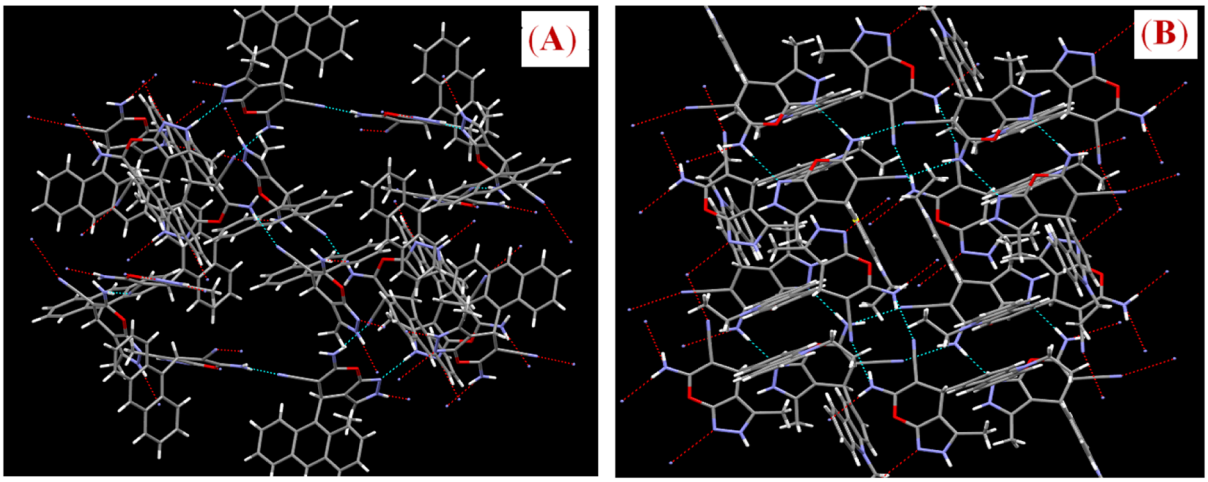

Fig. 4 Crystal packing of (A) **1n** and (B) **1o** showing the intermolecular hydrogen bonding involving pryazole N/NH and of pyran NH_2.

Table 3 Crystallographic experimental details of **1n** and **1o**

Crystallographic parameters	Compound **1n**	Compound **1o**
Crystal data deposition no.	CCDC no. 2203408	CCDC no. 2203466
Chemical formula	$C_{22}H_{16}N_4O$	$C_{22}H_{19}N_5O$
Molecular weight	352.39 g mol^{-1}	369.42 g mol^{-1}
Crystal system, space group	Tetragonal, $I4_1/a$	Tetragonal, $I4_1/a$
Temperature (K)	100	101
a, b, c (Å)	28.496(2), 28.496(2), 10.1953(2)	22.861(2), 22.861(2), 14.185(2)
α, β, γ (°)	90, 90, 90	90, 90, 90
V (Å^3)	8279.0 (17)	7413.4(17)
Z	16	16
Radiation type	Cu Kα (λ = 1.54178)	Cu Kα (λ = 1.54178)
μ (mm^{-1})	0.577	0.682
Crystal size (mm)	0.45 × 0.35 × 0.2	0.18 × 0.12 × 0.12
D_{calc} (g cm^{-3})	1.131	1.324
Diffractometer	Bruker Apex III CCD	Bruker Apex III CCD
Absorption correction	Multiscan (SADABS; Bruker)	Multiscan (SADABS; Bruker)
T_{min}, T_{max}	0.630, 0.753	0.607,0.753
2θ range for data collection/°	9.212 to 136.642	7.334 to 136.68
Reflections collected	126 607	76 619
Independent reflections	3782	3383
R_{int}, R_{sigma}	0.0660, 0.0196	0.0823, 0.0235
$R[F^2 > 2\sigma(F^2)]$, w$R(F^2)$]	0.0639, 0.1999	0.0466, 0.1229
Data completeness	0.994	0.994
θ (theta)$_{max}$	68.321	68.340
Goodness-of-fit on F^2 (S)	1.075	1.084

2203408 and 2203466 respectively). Single crystal X-ray diffraction study of the these synthesized compounds confirms the identity of **1n** or **1o** as 2,4-dihydropyranopyrazoles. The crystal packing indicated presence of intermolecular hydrogen bonding interactions (blue dashed lines) between NH_2 group of one with either nitrogen of pyrazole or –CN group of second molecule (Fig. 4). Crystal data, data collection and structure refinement details are summarized in Table 3. The structures of **1p–r** (R^2 = phenyl) were also confirmed as 2,4-dihydropyranopyrrazole by comparing with reported data as well NOESY spectra of **1r**. In NOESY spectrum of **1r** very nice interaction was seen between –NH and one of the *ortho* proton of phenyl group at the position 3 of pyrazole ring (ESI†). Based on the experimental results, spectroscopic and crystallographic data we concluded that the present pseudo three component strategy favours 1,4-dihydropyranopyrazoles when *N*-substituted (R^3 = Ph) pyrazolone (**6a**) is used whereas *N*-un-substituted (R^3 = H) pyrazolone produced 2,4-dihydropyrano-pyrazoles. To establish the higher stability of 2,4-dihydro pyranopyrazoles than the 1,4-dihydropyranopyrazoles, quantum mechanical calculations using Density Functional Theory (DFT)[44] with B3LYP/6311G (d,p) in Gauss 09w software[45] were performed initially for **1f** and **1f′** as model. The optimized structures shown in Fig. 5 were verified by performing the frequency calculation at the same level of theory and found no imaginary frequency. Based on the calculated

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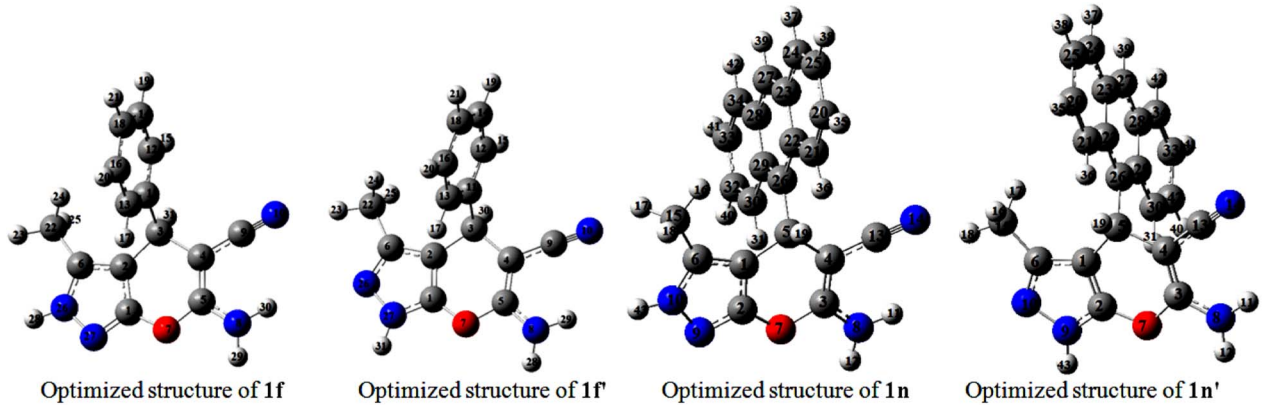

Fig. 5 DFT (B3LYP/6-311G**) computed optimized structure of **1f**, **1f′**, **1n** and **1n′**

energy, **1f** was found to be more stable than **1f′** by 3.47 kcal mol^{-1}.

To assess a possible reason of the stability of **1f** over tautomer **1f′**, the HOMO-LUMO analysis of these structure were performed at the B3LYP/6-311G (d,p) level. Observed HOMO-LUMO energy gap of **1f** (5.1230 eV) and **1f′** (5.3509 eV) is demonstrative of greater delocalization of the pi electrons in **1f** and so it's extra stability. Similar quantum mechanical

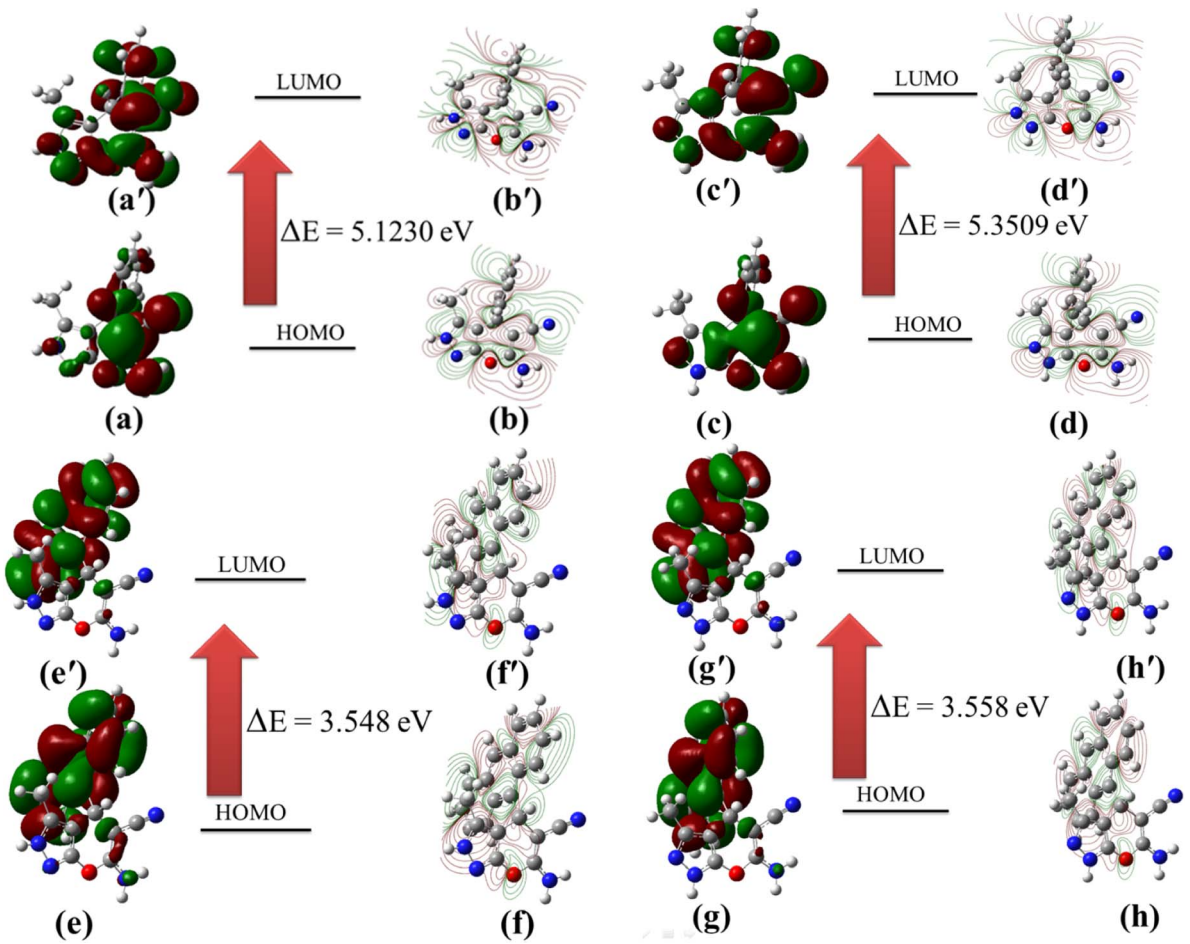

Fig. 6 (a) Contour plot of HOMO of **1f**; (b) transparent surface view of HOMO of **1f**; (a′) contour plot of LUMO of **1f**; (b′) transparent surface view of LUMO of **1f**; (c) contour plot of HOMO of **1f′**; (b) transparent surface view of HOMO of **1f′**; (c′) contour plot of LUMO of **1f′**; (d′) transparent surface view of LUMO of **1f′**; (e) contour plot of HOMO of **1n**; (f) transparent surface view of HOMO of **1n**; (e′) contour plot of LUMO of **1n**; (f′) transparent surface view of LUMO of **1n**; (g) contour plot of HOMO of **1n′**; (h) transparent surface view of HOMO of **1n′**; (g′) contour plot of LUMO of **1n′**; (h′) transparent surface view of LUMO of **1n′**

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Table 4 Calculated bond angles and bond distances of optimized structure of **1f**/**1f′** and **1n**/**1n′** (only fused ring part is given)

Bond angles (°) about various centres of optimized structure			Bond lengths (Å) about various centres of optimized structure			Bond angles (°) about various centres of optimized structure			Bond lengths (Å) about various centres of optimized structure		
Centres (C)	**1f**	**1f′**	Centres(C)	**1f**	**1f′**	Centres (C)	**1n**	**1n′**	Centres(C)	**1n**	**1n′**
C2–C1–C27	114.6734	109.0376	C1–C2	1.4029	1.3664	C2–C1–C5	122.6790	121.7823	C1–C2	1.4075	1.3706
C1–C2–C3	123.0121	121.6485	C1–C7	1.3692	1.3609	C1–C2–C7	124.6190	127.5686	C1–C5	1.5097	1.5091
C1–C2–C6	103.5541	103.5163	C2–C6	1.3872	1.4251	C7–C3–C4	123.8036	123.1996	C1–C6	1.3905	1.4277
C2–C3–C4	106.9077	106.8861	C2–C3	1.5020	1.5014	C3–C4–C5	124.2446	124.5625	C2–C7	1.3914	1.3866
C4–C3–C11	112.3937	111.9773	C3–C4	1.5325	1.5376	C3–C4–C13	117.5447	117.1809	C2–C9	1.3298	1.3540
C3–C4–C5	124.3957	124.7251	C3–C11	1.5319	1.5316	C1–C5–C4	108.4460	108.3026	C3–C7	1.3948	1.4071
C5–C4–C9	117.1141	116.7170	C4–C5	1.3688	1.3651	C1–C5–C26	115.0176	115.1381	C3–C4	1.3698	1.3673
C4–C5–C7	124.4341	123.6470	C4–C9	1.4140	1.4156	C4-C5-26	113.5236	113.6170	C3–C8	1.3599	1.3602
C4–C5–C8	125.5914	126.4661	C5–C7	1.3602	1.3725	C19–C5–C26	106.6745	106.6107	C4–C5	1.5430	1.5471
C2–C6–C26	105.4214	111.3308	C5–C8	1.3631	1.3644	C1–C6–C10	105.5625	111.0949	C4–C13	1.4143	1.4157
C2–C6–C22	131.6480	128.1029	C6–C26	1.3611	1.3298	C1–C6–C15	131.9322	128.8578	C5–C26	1.5434	1.5430
C1–C7–C5	115.7246	114.1018	C6–C22	1.4932	1.4949	C10–C6–C15	122.5053	120.0452	C6–C10	1.3748	1.3508
C6–C26–C27	114.2294	105.3770	C9–C10	1.1599	1.1593	C6–C10–C9	113.6359	104.9480	C6–C15	1.4941	1.4928
C26–C27–C1	102.1212	110.7381	C26–C27	1.3566	1.3566	C2–C9–C10	101.8039	110.2306	C9–C10	1.3862	1.3929

calculations were also done for **1n** (2,4-dihydro) and its 1,4-dihydro form (**1n′**) using the same basis set. In this case HOMO-LUMO gap estimated as 3.548 eV (**1n**) and 3.558 eV (**1n′**) respectively (Fig. 6). Thus, the outcome of the DFT studies reliably in favour of the structure **1f** and **1n** as established by X-ray and NMR studies. The optimized bond lengths and bond angles of all the tautomers are collected and given in Table 4. The DFT study further indicated that 6-amino-4-(*p*-chlorophenyl)-3-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**1q**) is more stable than 6-amino-4-(*p*-chlorophenyl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**1q′**) by 4.60 kcal mole^{-1} (details not given).

The experimental observations and our previous experiences on SDS–IL–water combo catalytic system, the following mechanistic rationale is proposed. It is perceived that SDS form hydrophobic vesicle in water of size about 190 nm which was established by DLS study and the size of this vesicle is enhanced further with the interionic attraction between imidazolium cation which forms a stern layer, resulting in an increase in mean effective diameter of the cavity.[46] The resultant hydrophobic cavity eventually helps the potent transport of all reactants into the nano sized reactor for reaction and efficient formation of highly reactive benzylidenemalononitrile derivative **7**. After the sequential addition of pyrazolone (**6**, 3rd component) a Michael addition reaction took place to form a dicyano intermediate (**A**) which quickly converted the enols depending upon the nature of R^3. When R^3 is phenyl, enol **B** is form which undergoes Pinner type cyclisation to give another intermediate **C** followed by proton shift afforded **1′** (1,4-dihydro). If R^3 is H, enol **D** is formed due to the relatively weaker N–H bond than C–H bond, which than followed similar type of cyclisation and proton shift due to imine-enamine tautomerization gave produced **1** (Scheme 3). Pinner type cyclisation reaction involving enol –OH to the nitrile group which is extensively influenced and activated by the imidazolium cation resulted in the formation of pyran moiety.

To assess the recycling credibility of reaction "waste" (filtrate containing SDS, ionic liquid and water), 4-nitro benzaldehyde and malononitrile were taken in water (4 mL) containing SDS (10 mg) and butyl methyl imidazolium bromide (20 mg). The

Scheme 3 Probable mechanism for pyranopyrazole synthesis.

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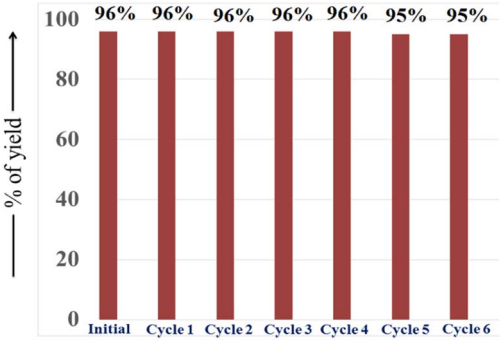

Fig. 7 Recyclability test of the reaction waste containing water–SDS–BMImBr.

mixture was stirred vigorously at 80 °C for 15 min, then 1-phenyl-3-methyl-5-pyrazolone was added to the reaction mixture. After completion of reaction (as revealed by TLC) the precipitate so formed was filtered and washed with small amount of water. The combined filtrate was concentrated to total volume of 4 mL, if exceed and used for next cycle. The recovered medium containing water, SDS and ionic liquid (BMImBr) was used six times without notable loss of yield of **1a′** (Fig. 7). The yields of the initial and subsequent four runs were 96% and last two runs were 95% (Fig. 6). Thus, the SDS–IL–water catalytic media is proved to be recyclable without noticeable alteration of its catalytic activity.

Conclusion

In conclusion, we have developed a base and metal free protocol for the selective synthesis of pyrano[2,3-*c*]pyrazole derivatives *via* sequential pseudo three component strategy using aromatic aldehydes, malononitrile and pyrazolin-5-one in water–SDS–ionic liquid system. The reaction was conducted under an eco-friendly medium which is completely recyclable including the catalyst. The key advantages of the method over other established protocols are very high yield, eco-friendly condition, chromatography free purification and selectivity. Our study revealed that *N*-phenyl pyarazolinone favours the formation 1,4-dihydro pyrano[2,3-*c*]pyrazoles and whereas under identical condition 2,4-dihydro pyrano[2,3-*c*]pyrazoles were formed when nitrogen is un-substituted. Structures of the synthesized products were established by NMR and X-ray diffraction techniques. The preferential formation of 2,4-dihydro pyrano[2,3-*c*]pyrazoles was ascertained based on the energy optimization and estimation of HOMO-LUMO energy gap using density functional theory which explain the extra stability of 2,4-dihydro pyrano[2,3-*c*]pyrazoles over 1,4-dihydro pyrano[2,3-*c*]pyrazoles.

Experimental section

The starting aldehydes (aromatic, aliphatic, heterocyclic *etc.*), malononitrile, ethyl acetoacetate, hydrazine, phenyl hydrazine, SDS were purchased either from Sigma Aldrich chemical Co., USA or Acros Organics or SRL India and were used as received. Ionic liquid butyl methyl imidazolium bromide ([BMIm]Br) was prepared in the laboratory using standard protocol. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using Bruker Ascend 400 MHz spectrometers (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts were reported in parts per million from the tetramethylsilane internal reference, and coupling constants were reported in Hertz. Proton multiplicities were represented as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). FTIR spectra were recorded on Bruker Alpha FTIR spectrometer on Neat or KBr pellets. Mass spectra (HRMS) were obtained from XEVO G2-XS QTOF (Waters) using 70 eV in positive ion mode. The single-crystal X-ray diffraction (XRD) data were collected on a Bruker D8 Venture system with a microfocus optics using Cu Kα radiation. The data were analysed and processed with Bruker Apex III software suite 61 incorporated with multiple tools such as cell_now and RLATT for the determination of the unit cell, SAINT-plus for data reduction, and SADABS for absorption correction. The structure solutions were performed with SHELXT and the full-matrix least-squares refinements were performed with SHELXL suite of programs incorporated in Olex 2.6. For the optimization of geometry of represented compounds the structures were drawn in Gauss view with Gaussian-09W-Gaussview-6 program to obtain the energy minimized structure. The density functional theory (DFT) with the B3LYP correlation function as basis set of calculations have been employed imposing 6-311G(d,p) as additional constraints. Frequency calculations were carried out with the DFT optimized structures using the same basis set to confirm the correctness of optimization and found no imaginary frequency.

Experimental procedure for the synthesis of 1a′–e′ and 1f–o

To a mixture of SDS (10 mg, 3.5 mol%), ionic liquid [BMIm]Br (20 mg, 10 mol%), aromatic aldehydes (**2**, 1 mmol), malononitrile (73 mg, 1.1 mmol) in H_2O (4 mL) were stirred at 80 °C until the disappearance of aldehydes (TLC, usually 20–40 min). Then pyrazolones (**6**, 1 mmol) was added in the reaction mixture and continued heating at the same temperature till the complete consumption of pyrazolones (Table 2). After the completion of reaction as indicated by TLC, the reaction mixture is cooled to 40 °C, the solid obtained was filtered, washed with water and recrystallized from ethanol–water (~1 : 1) mixture. Synthesized products were characterized by melting point, IR data, NMR, mass spectral analysis and compared with the reported one.

Physical and spectral data of new compounds

6-Amino-4-(anthracen-9-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (1n). Yield: 87%, yellowish solid, mp 190–192 °C; IR (KBr) ν_{max} 3394, 3297, 3171, 2888, 2188, 1719, 1636, 1541, 1391, 1155, 1046, 1012, 878, 832, 775, 716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.02 (s, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.70 (s, 1H), 8.15–8.05 (m, 3H), 7.61–7.54 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.96 (s, 2H), 6.40 (s, 1H), 1.19 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.1, 155.1, 135.7, 133.4, 132.1, 131.2, 131.1, 130.1, 129.8, 129.5,

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128.4, 127.1, 125.5, 125.1, 124.5, 124.0, 120.8, 99.1, 58.1, 29.8, 9.8; HRMS calcd for ($C_{22}H_{16}N_4O + H^+$) 353.1402 found 353.1402.

6-Amino-4-(9-ethyl-9*H*-carbazol-3-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (1o). Yield: 85%, yellowish white solid, mp 200–202 °C; IR (KBr) ν_{max} 3352, 3177, 2970, 2192, 1652, 1600, 1482, 1392, 1332, 1223, 1150, 1103, 1039, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 7.59–7.53 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.86 (s, 2H), 4.77 (s, 1H), 4.41 (d, J = 8.0 Hz, 2H), 1.76 (s, 3H), 1.32 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) d 161.1, 155.2, 140.3, 139.0, 136.1, 135.6, 126.1, 126.0, 122.5, 122.3, 121.5, 120.8, 119.5, 119.1, 109.6, 109.5, 98.9, 58.7, 37.5, 36.9, 14.3, 10.3. HRMS calcd ($C_{22}H_{19}N_5O + H^+$) 370.1668 found 370.1668.

Author contributions

S. M. designed the work. S. C. performed all experiments. U. C. D. performed DFT study. B. P. and R. N. performed XRD studies and processing of X-ray data. S. M. and S. C. analyzed the spectral data and wrote the manuscript with input from other authors.

Conflicts of interest

There are no conflicts to declare.

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