



OPEN

# [18-C-6H<sub>3</sub>O<sup>+</sup>]: an in-situ generated macrocyclic complex and an efficient, novel catalyst for synthesis of pyrano[2,3-c]pyrazole derivatives

Manisha Mishra, K. J. Jomon, V. R. Sriram Krishnan &amp; Aatika Nizam

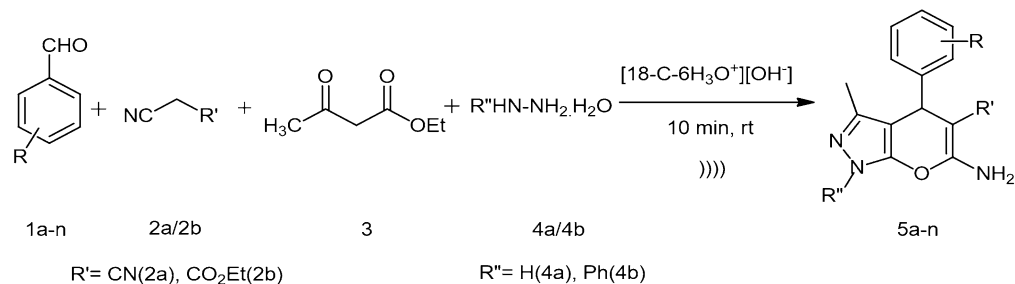
Synthesis of small aromatic heterocycles is of greater importance in the organic chemistry due to their vibrant applications in pharmaceuticals, agrochemicals and veterinary products. Pyranopyrazoles are one such class of heterocycles associated with numerous applications. Hence herein we report a multicomponent crown ether catalyzed, ultrasound irradiated methodology to make different functionalized pyranopyrazoles in a single step. This technique involves the in-situ generation of [18-C-6H<sub>3</sub>O<sup>+</sup>][OH<sup>-</sup>] complex, which in turn activates the aromatic aldehyde and aids in the facile nucleophilic addition.

The physical properties of pyranopyrazoles (pypys) have rendered them as highly efficient pharmacophores, for the treatment of cancer, diabetic, pyretic, HIV, etc<sup>1</sup>. The existing synthetic methods for the generation of pypys requires long reaction time, tedious purification and tough conditions<sup>2–11</sup>, therefore the development of a straightforward method is sought for. Among macrocycles, crown ethers are of great value in synthetic chemistry field as phase transfer catalyst. The ionic-liquid type behaviour of crown ethers by forming complexes with metals and molecular cations opened a new door to the catalysis world. The importance of crown ether cation complexed ionic-liquids (CECILs) was known from the past but the real application in organic synthesis was explored by Jing et al. in 2011<sup>12</sup>. Later in 2017 Abaszadeh and Mohammad synthesized 1,4-dihydropyridines and tetrahydro-4*H*-chromenes using some CECILs<sup>13</sup>. In continuation of our work on the development of new and simple catalyst for the synthesis of bioactive compounds<sup>14–17</sup>, also taking inspiration from K Nikoofar's work on the preparation of Spiro[indoline-3,2'-quinoline] substrates using [DB-18-C-6K<sup>+</sup>][OH<sup>-</sup>]nIL<sup>18</sup> and noting the fact that very little is explored in this, herein we report the in-situ generation of crown ether hydronium ion complex ([18-C-6H<sub>3</sub>O<sup>+</sup>][OH<sup>-</sup>]) and its catalytic activity in four-component synthesis of pypys under sonication (Fig. 1). The key to the success of this method is the synthesis of bis-pypys, which was also established using the developed catalytic system (Fig. 2).

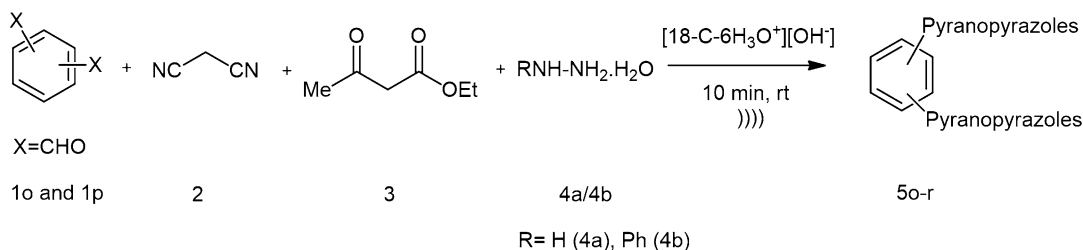
## Results and discussion

We began our investigation by performing a model reaction using benzaldehyde (**1a**), **2a**, **3** and **4a** as substrates, and 2 mol% of 18-crown-[6]-ether/H<sub>2</sub>O in methanol under ultrasound irradiation for 10 min. We were encouraged by the formation of **5a** in 52% yield. Further sonication did not show any changes in the product yield. In order to confirm the influence of the catalytic system few control experiments were carried out. First, the reaction was conducted without crown ether/H<sub>2</sub>O, trace amount of product was formed after 25 min. About 35% of the product was obtained when the reaction was carried out only with water, and 20% yield was obtained when only crown ether was used (Table 1, entries 1–4). This observation led us to suggest the in-situ generation of [18-C-6H<sub>3</sub>O<sup>+</sup>][OH<sup>-</sup>] complex and its catalytic activity towards this transformation. The literature provided strong support to our suggestion<sup>19–23</sup>. Normally hydronium ions have a very short lifetime, ~ 10<sup>-12</sup> s<sup>24</sup> but by the addition of crown ether, the short-living hydronium ions get stabilized by forming a complex with it and stays

Department of Chemistry, CHRIST (Deemed to be University), Hosur Road, Bangalore 560029, India. email: aatika.nizam@christuniversity.in



**Figure 1.** Schematic representation for the synthesis of pyrano[2,3-*c*]pyrazoles.

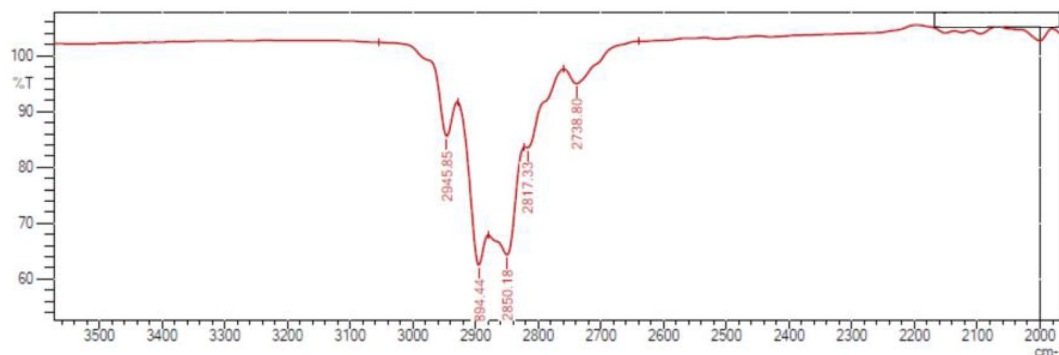


**Figure 2.** Synthesis of bis-pyrano[2,3-*c*]pyrazoles.

Entry	Solvent	Catalyst (mol %)	Time (min)	Reaction condition	Yield (%)
1	MeOH	2	10	rt/)))))	52
2	MeOH	–	25	rt/)))))	Trace
3	MeOH	Water only	10	rt/)))))	35
4	MeOH	18-C-6 only	10	rt/)))))	20
5	CH <sub>3</sub> CN	2	10	rt/)))))	52
6	CH <sub>2</sub> Cl <sub>2</sub>	2	10	rt/)))))	55
7	Toluene	2	10	rt/)))))	60
8	DMSO	2	10	rt/)))))	66
9	DMF	2	10	rt/)))))	63
10	H <sub>2</sub> O	2	10	rt/)))))	71
11	H <sub>2</sub> O	4	10	rt/)))))	80
12	H <sub>2</sub> O	6	10	rt/)))))	83
13	H <sub>2</sub> O	8	10	rt/)))))	88
14	<b>H<sub>2</sub>O</b>	<b>10</b>	<b>10</b>	<b>rt/)))))</b>	<b>92*</b>
15	H <sub>2</sub> O	12	10	rt/)))))	90
16	H <sub>2</sub> O	14	10	rt/)))))	90
17	H <sub>2</sub> O	10	40	Reflux	50

**Table 1.** Catalyst loading and solvent screening for pyrano[2,3-*c*]pyrazole synthesis. \*Reaction condition- Benzaldehyde (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), hydrazine hydrate (2 mmol) and 18-Crown-[6]-ether (10 mol%) in 10 ml of water at RT under ultrasonication.

indefinitely long at room temperature<sup>19,24</sup>. To confirm the formation of [18-C-6H<sub>3</sub>O<sup>+</sup>][OH<sup>-</sup>] complex we recovered the catalyst from the filtrate and subjected for FTIR analysis. The strong band at the 2,850 cm<sup>-1</sup> showed the presence of H<sub>3</sub>O<sup>+</sup> in the crown ether. This was compared with the results published by Robert Chenevert and



**Figure 3.** FTIR spectrum of  $[18\text{-C-}6\text{H}_3\text{O}^+][\text{OH}^-]$  high frequency region.

Andre Rodrigue to establish the presence of  $\text{H}_3\text{O}^+$  ion in the 18-crown-6- $\text{H}_3\text{O}^+\text{-BF}_4$  complex<sup>24</sup> and was found to be in good agreement (Fig. 3).

A series of reactions were carried out in order to find a suitable solvent for this reaction and concluded that water itself is the best medium, which made our methodology more eco-friendly and greener (Table 1, entries 5–10). After choosing the catalyst and solvent the reaction progress was checked with different quantities of 18-crown-[6]-ether and found that the reaction profile improved considerably from 2 to 10 mol%, but further increase did not make any effect on the yield (Table 1, entries 10–16). Finally, it was concluded that 10 mol% of the catalyst is required on 2 mmol scale reaction. To confirm the effect of ultrasound waves on the reaction kinetics one reaction under reflux condition was conducted, desired product formation was observed after 40 min by checking TLC (Table 1, entry 17).

Intrigued by the formation of desired product **5a**, we examined the generality of the reaction with various substrates using the optimized conditions. Aldehydes bearing electron-donating groups and electron-withdrawing groups (**1b–1j**) were examined and gratifyingly all were well tolerated to furnish good yield of products (**5b–5j**) (Fig. 4). Moreover, heteroaryl aldehyde (**1k**) and cinnamaldehyde (**1l**) also provided the corresponding pypys (**5k** and **5l** respectively) in good yield.

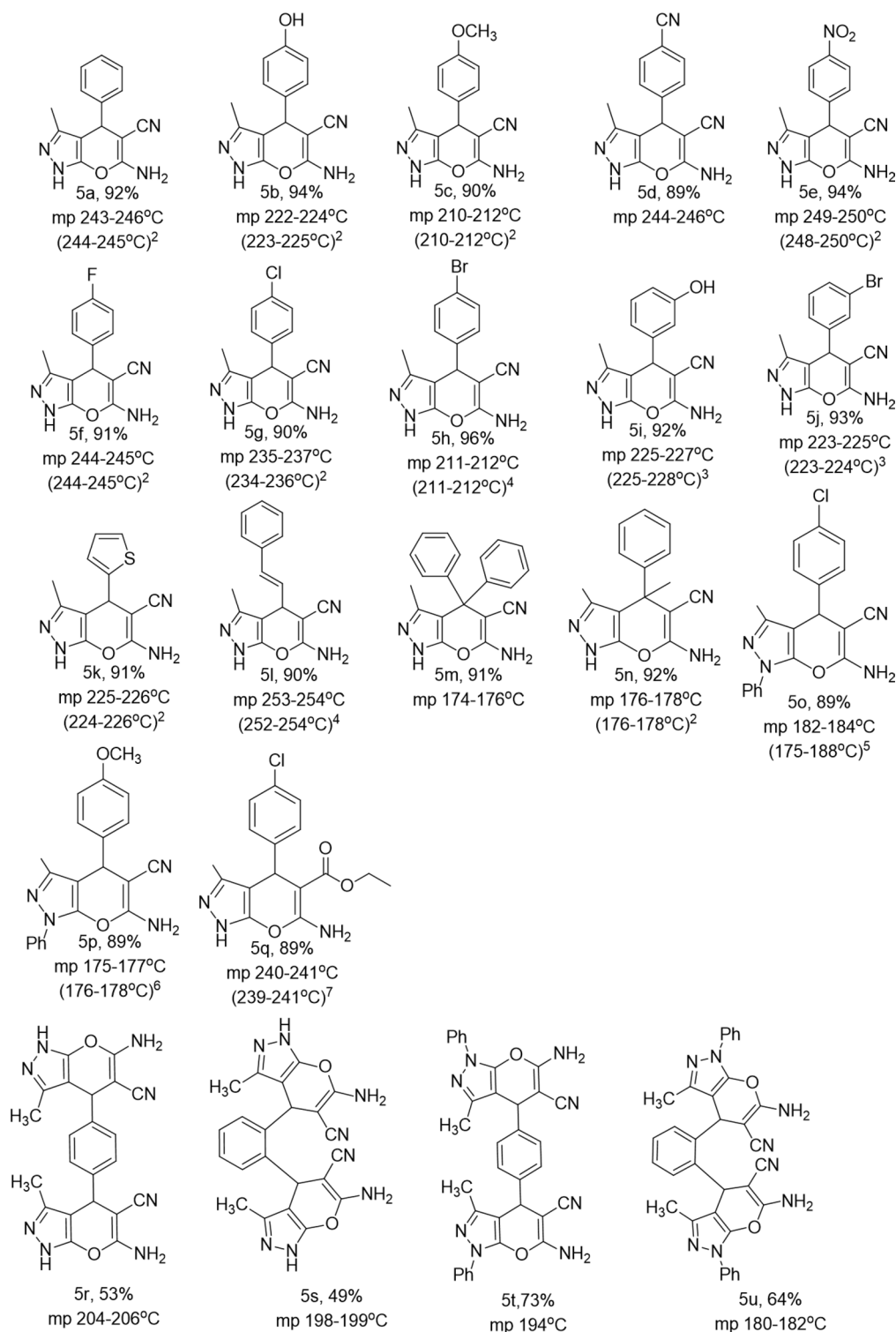
Furthermore, employing ketones (**1m**, **1n**) in place of aldehyde resulted in the formation of a quaternary carbon center at the pyran ring in the product (**5m**, **5n**), which made our method much more interesting. After the successful demonstration of the feasibility of aromatic aldehydes and ketones for this strategy. We employed phenyl hydrazine (**4b**) and ethyl cyanoacetate (**2b**) in the reaction (Fig. 1). The results were satisfying giving good yield of the products (**5o–5q**). The formation of products (**5o–5q**) were confirmed by comparing their melting points with reported melting points<sup>5–7</sup>. Next, we were interested in the synthesis of *bis*-pypys with the established conditions by using *bis*-aldehyde functionalities (Fig. 2). For that terephthalaldehyde (**1o**) and phthalaldehyde (**1p**) were chosen and furnished the respective *bis*-pypys (**5r**, **5s**) in moderate yield. The study was further extended to synthesize *N*-arylated pypys using phenyl hydrazine (**4b**) instead of hydrazine hydrate (**4a**) under the same conditions and to our delight, the formation of **5t** was observed in 73% and **5u** in 64% yield.

Based on the observations and literature reports, we propose a pathway, that first involves the C-H activation of malononitrile by Lewis basic water molecule and activation of aromatic aldehyde by the  $[18\text{-C-}6\text{H}_3\text{O}^+][\text{OH}^-]$  complex, which resulted in the formation of Knoevenagel adduct (**I**). Further  $[18\text{-C-}6\text{H}_3\text{O}^+][\text{OH}^-]$  activates the ethyl acetoacetate and speeds up the formation of pyrazolone (**II**). Michael addition of pyrazolone (**II**) with Knoevenagel adduct (**I**) and finally cyclization and tautomerization gives the final product (Fig. 5).

In order to elaborate the synthetic application of our strategy, a 10g-scale synthesis of **5a** was demonstrated and delightfully the yield was reproduced which clearly indicates that there is a substantial potential for industrial application. All the products were confirmed by comparing their physical and spectroscopic data with reported data.

## Conclusion

We have successfully developed a simple, expeditious and green method for the synthesis of various pyrano[2,3-*c*]pyrazoles and *bis*-pyrano[2,3-*c*]pyrazoles by using 18-Crown-[6]-ether under ultrasonication condition in the aqueous medium. The catalyst generated within the reaction medium boosted up the reaction rate and yield. The crown ether hydronium ion complex are known but the catalytic activity of these complex for the synthesis of pyranopyrazoles was found to be new and understudied in current literature.

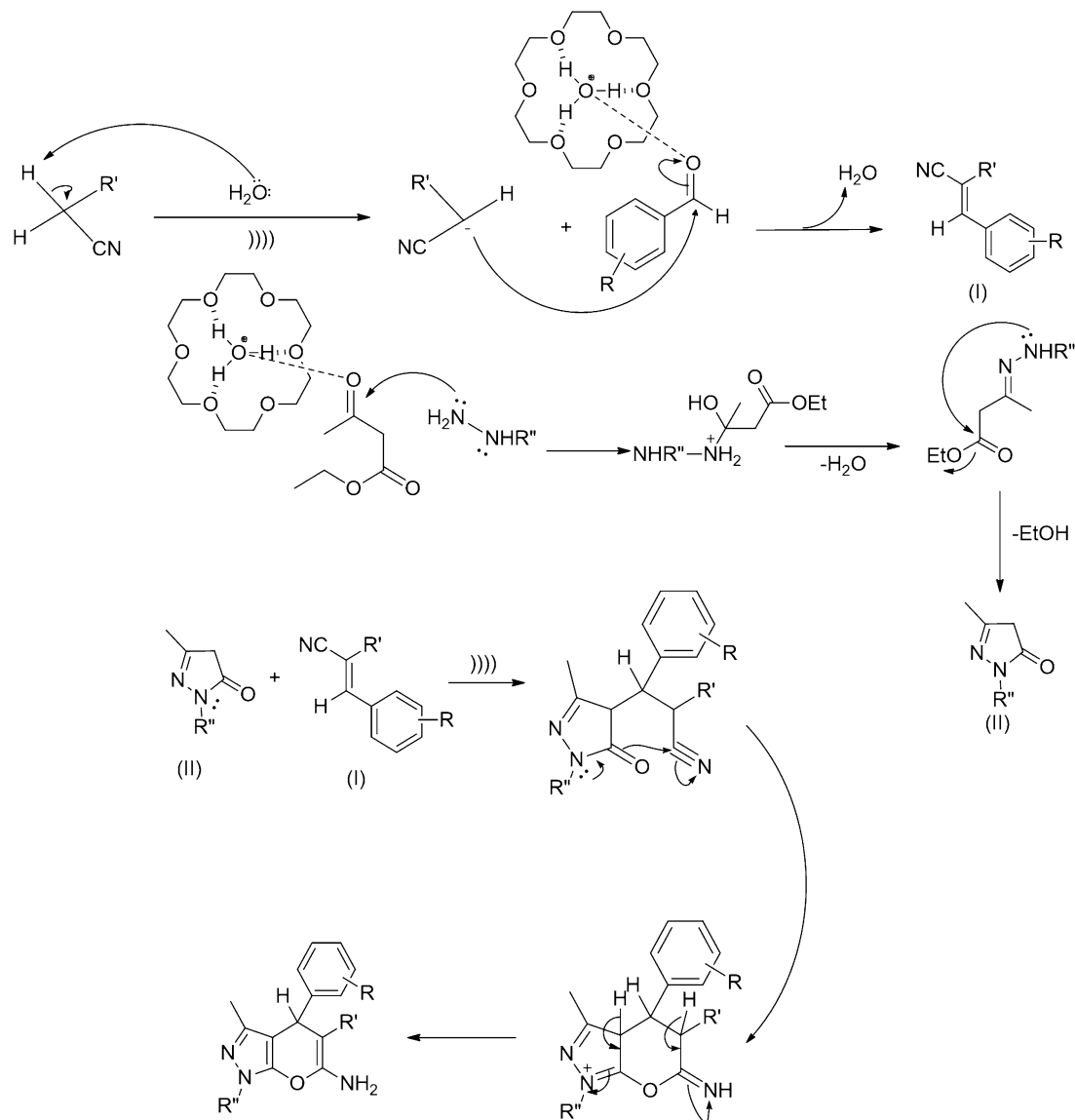


**Figure 4.** Substrate scope for pyrano[2,3-c]pyrazoles synthesis catalyzed by  $[18\text{-C-6H}_3\text{O}^+][\text{OH}^-]$  under ultrasonic irradiation.

## Experimental section

### Methods and apparatus.

All the chemicals and crown ether were commercially purchased and used without further purification. Melting points were recorded using Electronics india 935 Digital Melting Point Apparatus. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR were recorded using BRUKER 400 MHz and 100 MHz instruments respectively using TMS as reference. The IR spectra were recorded on a SHIMADZU FT-IR-84000 s spectrophotometer.



**Figure 5.** Plausible mechanism for the formation of pyrano[2,3-*c*]pyrazoles catalyzed by [18-C-6H<sub>3</sub>O<sup>+</sup>][OH<sup>-</sup>].

**General procedure for the synthesis of pyrano[2,3-*c*]pyrazoles using crown ether as a catalyst.** To a mixture of aromatic aldehyde **1a-p** (2 mmol), **2** (2 mmol), **3** (2 mmol), **4a/4b** (2 mmol) in water (10 mL) taken in a 50 mL RB flask, crown ether 10 mol% was added. The reaction mixture was subjected to sonication for 10 min at room temperature. The completion of reaction was confirmed using TLC. The solid product was filtered and recrystallized from aqueous ethanol to get the pure products.

Received: 1 October 2019; Accepted: 14 July 2020  
Published online: 31 August 2020

## References

1. Chauhan, P., Mahajan, S. & Enders, D. Asymmetric synthesis of pyrazoles and pyrazolones employing the reactivity of pyrazolin-5-one derivatives. *Chem. Commun.* **51**, 12890–12907 (2015).
2. Guo, R. Y. *et al.* Meglumine promoted one-pot, four-component synthesis of pyranopyrazole derivatives. *Tetrahedron* **69**, 9931–9938 (2013).
3. Tamaddon, F. & Alizadeh, M. A four-component synthesis of dihydropyrano[2,3-*c*]pyrazoles in a new water-based worm-like micellar medium. *Tetrahedron Lett.* **55**, 3588–3591 (2014).
4. Avudaiappan, G., Unnimaya, T. J., Asha, P., Unnikrishnan, V. & Sreekumar, K. Green synthesis of pyrazolopyranopyrimidinone and pyranopyrazole derivatives using porphyrin-initiated amine-functionalized PolyBCMO dendritic polymer as sonocatalyst. *J. Heterocycl. Chem.* **57**, 197–209 (2020).
5. Azarifar, D., Nejat-yami, R., Sameri, F. & Akrami, Z. Ultrasonic-promoted one-pot synthesis of 4 H-chromenes, pyrano [2, 3-*d*] pyrimidines, and 4 H-pyrano [2, 3-*c*] pyrazoles. **98**, 435–439 (2012).
6. Basak, P., Dey, S. & Ghosh, P. Sulfonated graphene-oxide as metal-free efficient carbocatalyst for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones and substituted pyrazole. *ChemistrySelect* **5**, 626–636 (2020).

7. Beerappa, M. & Shivashankar, K. Four component synthesis of highly functionalized pyrano[2,3-*c*]pyrazoles from benzyl halides. *Synth. Commun.* **48**, 146–154 (2018).
8. Mecadon, H. *et al.* L-Proline as an efficient catalyst for the multi-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in water. *Tetrahedron Lett.* **52**, 3228–3231 (2011).
9. Figure, S. Gfp-rab, M. P. & Gfp-rab, Q. L. 4 h 4 h. *Optimem* **55**, 4–5 (2019).
10. Vasuki, G. & Kumaravel, K. Rapid four-component reactions in water: Synthesis of pyranopyrazoles. *Tetrahedron Lett.* **49**, 5636–5638 (2008).
11. Ambethkar, S., Padmini, V. & Bhuvanesh, N. A green and efficient protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives via a one-pot, four component reaction by grinding method. *J. Adv. Res.* **6**, 975–985 (2014).
12. Song, Y., Jing, H., Li, B. & Bai, D. Crown ether complex cation ionic liquids: Preparation and applications in organic reactions. *Chem. A Eur. J.* **17**, 8731–8738 (2011).
13. Abaszadeh, M. & Seifi, M. Crown ether complex cation ionic liquids: Synthesis and catalytic applications for the synthesis of tetrahydro-4H-chromene and 1,4-dihydropyridine derivatives. *J. Sulfur Chem.* **38**, 440–449 (2017).
14. Nizam, A. & Pasha, M. A. Iodine-catalyzed, rapid and efficient, one-pot synthesis of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones under solvent-free conditions. *Synth. Commun.* **40**, 2864–2868 (2010).
15. Pasha, M. A. & Nizam, A. Amberlite IR-120 catalyzed, microwave-assisted rapid synthesis of 2-aryl-benzimidazoles. *J. Saudi Chem. Soc.* **16**, 237–240 (2012).
16. Hamood, S., Azzam, S., Siddekha, A., Nizam, A. & Pasha, M. A. SiO<sub>2</sub>-NaHSO<sub>4</sub> as an efficient reusable heterogeneous catalyst for the one-pot three-component synthesis of octahydro-quinazolin-2, 5-diones in water. *Chin. J. Catal.* **33**, 677–680 (2012).
17. Mishra, M., Nizam, A., Jomon, K. J. & Tadaparthi, K. A new facile ultrasound-assisted magnetic of pyrano [2,3-*c*] pyrazoles. **55**, 1925–1928 (2019).
18. Nikoofar, K. & Khani, S. New crown ether-based nano ionic liquid ([DB-18-C-6K+][OH<sup>-</sup>] nIL): A versatile nanocatalyst for the synthesis of spiro[indoline-3,2'-quinoline] derivatives via the cascade four-component reaction of arylamines, dialkylacetylenedicarboxylates, isatins and dimedone. *Catal. Lett.* **148**, 1651–1658 (2018).
19. Gaikwad, A. G., Noguchi, H. & Yoshio, M. Stability constants of crown ether complexes with aqueous hydronium ion. *Anal. Sci.* **3**, 217–220 (1987).
20. Takeoka, S., Kitada, A., Fukami, K. & Murase, K. An ionic liquid consisting of crown ether - Coordinated hydronium cation and amide anion. *ECS Trans.* **75**, 239–244 (2016).
21. Marin, T. W., Shkrob, I. A. & Dietz, M. L. Hydrogen-bonding interactions and protic equilibria in room-temperature ionic liquids containing crown ethers. *J. Phys. Chem. B* **115**, 3912–3918 (2011).
22. Hurtado, P. *et al.* Crown ether complexes with H<sub>3</sub>O<sup>+</sup> and NH<sub>4</sub><sup>+</sup>: Proton localization and proton bridge formation. *J. Phys. Chem. A* **115**, 7275–7282 (2011).
23. Junk, P. C. Crown ethers as stabilising ligands for oxonium ions. *New J. Chem.* **32**, 762–773 (2008).
24. Chênevert, R. & Rodrigue, A. Preparation of a stoichiometric complex of hydronium tetrafluoroborate and 18-crown-6 by phase transfer. *J. Chem. Educ.* **61**, 465–466 (1984).

### Author contributions

The authors A.N. and M.M. of the manuscript titled “[18-C-6H<sub>3</sub>O<sup>+</sup>]: an in-situ generated macrocyclic complex and an efficient, novel catalyst for synthesis of pyrano[2,3-*c*]pyrazole derivatives” have contributed towards conceptualization of idea. M.M., J.K.J. and S.K.V.R. carried out the experimental work. Further the authors A.N., M.M. and J.K.J. wrote the manuscript and prepared the figures. All the authors have read the final draft and approved.

### Competing interests

The authors declare no competing interests.

### Additional information

**Correspondence** and requests for materials should be addressed to A.N.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2020