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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Adeleh Moshtaghi Zonouz & Davood Moghani (2015): Green and Highly Efficient Synthesis of Pyranopyrazoles in Choline Chloride/Urea Deep Eutectic Solvent, Synthetic Communications, DOI: 10.1080/00397911.2015.1129668

To link to this article: http://dx.doi.org/10.1080/00397911.2015.1129668

Green and Highly Efficient Synthesis of Pyranopyrazoles in Choline Chloride/Urea Deep Eutectic Solvent

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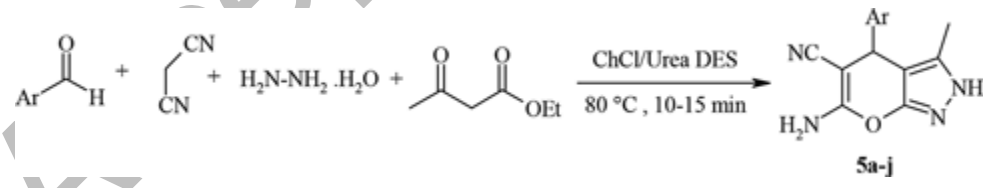
Abstract

A simple and efficient multi-component protocol, using ammonium deep eutectic solvent as a dual catalyst and environmentally benign reaction medium, is developed for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives. This operationally simple protocol does not involve tedious work-up or purification affording the target compounds in short reaction times and excellent yields, and avoiding the use of environmentally hazardous solvents and catalysts.

Graphical Abstract:



5a-j

KEYWORDS: deep eutectic solvent; pyranopyrazole; multi-component reaction; green chemistry

INTRODUCTION

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules.[1] Dihydropyrano[2,3-*c*]pyrazoles play an essential role as biologically active compounds and represent an interesting template for medicinal chemistry. Many of these compounds are known for their antimicrobial,[2] insecticidal[3] and anti-inflammatory activities.[4] Furthermore dihydropyrano[2,3-*c*]pyrazoles show molluscicidal activity[5,6] and are identified as a screening kit for Chk1 kinase inhibitor.[7] They also find applications as pharmaceutical ingredients and biodegradable agrochemicals.[8-10] Several modifications have been developed over the past decade for the synthesis of these biologically important scaffolds. These include using CTACl,[11a] piperazine,[11b] piperidine, [11c] N-methylmorpholine,[11d] L-proline,[11e] heteropolyacids,[11f] alumina,[11g] sodium benzoate, [11h] amberlyst A21, [11i] per-6-amino-cyclodextrin,[11j] imidazole,[11k] I_2,[11l] and glycine[11m] as catalysts. Dihydropyrano [2,3-*c*] pyrazole molecules are also synthesized under ultrasound irradiation using piperidine as catalyst in EtOH.[12] Although, the reported methods are effective, they are confronted with certain drawbacks of environment compatibility by using of toxic or hazardous catalysts and/or solvents.

Within the framework of green chemistry, solvents occupy a strategic place. Green Chemistry aims to replace the hazardous and/or harmful solvents with more environmentally friendly alternatives. One group of solvents that have been investigated for this purpose over recent years is ionic liquids. However, it is now felt that not all ionic liquids can be classified as ‘green’ and that their environmental impact is strongly

dependent on the cation and anion used to make them. A new family of ionic fluids, so-called Deep Eutectic Solvents (DES), exhibit similar physico-chemical properties to the traditionally used ionic liquids, while being much cheaper and environmentally friendlier. Owing to these remarkable advantages, DESs are now of growing interest in many fields of research.[13] A DES is a fluid generally composed of two or three cheap and safe components that are capable of self-association, often through hydrogen bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component. DESs are generally liquid at temperatures lower than 100 °C. The most commonly employed example of DESs is the combination of choline chloride (ChCl) and urea in a 1:2 molar ratio. The combination of these two inexpensive, non-toxic solids results in a mixture that is a viscous liquid at room temperature (mp 12 ºC). The basic nature of ChCl–urea DES and/or hydrogen-bond donor ability of urea are the reasons for the high catalytic activity of this system.[14-16]

As part of our efforts to develop new synthetic methods in heterocyclic chemistry,[17] herein we report a facile, green and efficient four-component synthesis of dihydropyrano[2,3-*c*] pyrazole derivatives from aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate in ChCl–urea DES medium.

RESULTS AND DISCUSSION

The four-component reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethyl acetoacetate(1mmol) in ChCl–urea DES was selected for initial optimization studies, and we were pleased to isolate 96% of

pyranopyrazole **5a** by performing the reaction at 80 °C in 10 min. The optimized conditions were then applied to a range of aldehyde substrates. Both electron-poor and electron-rich aldehydes were well tolerated (Table 1).

The formation of pyranopyrazole derivatives **5a-j** can be rationalized by the following tandem reactions: 1) formation of arylidene malononitrile via Knoevenagel condensation between aldehyde **1** and malononitrile **2**; 2) formation of pyrazolone by reaction of hydrazine hydrate **3** and ethyl acetoacetate **4**; and 3) Michael addition of arylidene malononitrile to pyrazolone, followed by cyclization and tautomerization. It was anticipated that ChCl–Urea DES could serve as a organocatalyst in this reaction.

In summary, we have developed a simple and efficient multi-component protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives using ChCl–Urea deep eutectic solvent as a dual catalyst and environmentally benign reaction medium. The significant advantages offered by this green protocol are short reaction times, operational simplicity, high yields and avoiding the use of environmentally hazardous solvents and catalysts.

EXPERIMENTAL

General: The ^{1}H- and ^{13}C-NMR spectra were taken on Bruker SP-400 AVANCE spectrometers. The IR spectra were recorded on a Bruker PS-15 spectrometer. The melting points were measured on an Electrothermal 9100 apparatus in open capillaries without correction. All the commercial reagents were used without prior purification.

Typical procedure for the preparation of dihydropyrano[2,3-*c*]pyrazoles **5a-j:**

Benzaldehyde (0.5 mmol), malononitrile (0.5 mmol), ethyl acetoacate (0.5 mmol), hydrazine hydrate (0.5 mmol) and choline chloride-urea based DES[14] (1mL) were taken in a test tube. The reaction mixture was stirred at 80 °C till the completion of the reaction as indicated by TLC(10 min). Then water (5 mL) was added and the precipitated solid was filtered, washed with water and recrystallized from ethanol. Compound **5a** (6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) was obtained as white powder in 95% yield.

m.p. 245-246 °C [Lit[18] 244-245]; IR (KBr): 3373, 3310, 3169, 2192, 1649, 1611, 1518, 1401 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.77 (s, 3H, CH_3), 4.59(s, 1H, C(4)-H), 6.88 (s, 2H, NH_2), 7.15–7.33 (m, 5H, Ar-H), 12.11 (s, 1H, NH) ppm; ^{13}C NMR(100 MHz, DMSO-d_6): δ 9.77 (CH_3), 36.28 (CH), 57.20 (C), 97.96 (C), 120.84 (CN), 126.80 (CH), 127.51 (2CH), 128.49 (2CH), 135.67 (C), 144.47 (C), 154.81 (C), 160.91 (C) ppm.

SUPPLEMENTARY DATA

Supporting information associated with this article can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENTS

The authors acknowledge the Research Office of Azarbaijan Shahid Madani University for financial support.

REFERENCES

1. Hailes, H. C. Reaction solvent selection: The potential of water as a solvent for organic transformations. *Org. Process Res. Dev.* **2007**, *11*, 114-120.

2. El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H. Synthesis and biological activity of some pyrazole derivatives. *J. Serb. Chem. Soc.***1999**, *64*, 9-18.

3. Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. Synthesis and insecticidal activity of some new pyranopyrazoles, pyrazolopyranopyrimidines, and pyrazolopyranopyridines. *Egypt J. Biotech.* **2003**, *13*, 73-82.

4. Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. Pyrazolopyranopyrimidines as a class of anti-inflammatory agents. *Z. Naturforsch.* **2006**, *C 61*, 1-5.

5. Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. Synthesis and molluscicidal Aativity of new cinnoline and pyrano[2,3-*c*]pyrazole derivatives. *Arch. Pharm.* **2006**, *339*, 456-460.

6. Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Synthesis and molluscicidal activity of new chromene and pyrano[2,3-c]pyrazole derivatives. *Arch. Pharm.* **2007**, *340*, 543-548.

7. (a) Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor, A. E. Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening. *Bioorg. Med. Chem.* **2006**, *14*, 4792-4802; (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. New series of antiprion compounds: Pyrazolone derivatives have the potent activity of inhibiting protease-resistant prion protein accumulation. *J. Med. Chem.* **2007**, *50*, 5053-5056.

8. Sosnovskikh, V. Y.; Barabanov, M. A.; Usachev, B. I.; Irgashev, R. A.; Moshkin, V. S. Synthesis and some properties of 6-di(tri)fluoromethyl- and 5-di(tri)fluoroacetyl-3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-ones. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2846-2850.

9. El-Assiery, S. A.; Sayed, G. H.; Fouda, A. Synthesis of some new annulated pyrazolo-pyrido (or pyrano) pyrimidine, pyrazolopyridine and pyranopyrazole derivatives. *Acta Pharm.* **2004**, *54*, 143-150.

10. Rodinovskaya, L. A.; Gromova, A. V.; Shestopalov, A. M.; Nesterov, V. N. Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-c]pyrazoles and their hydrogenated analogs. Molecular structure of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 2207-2213.

11. (a) Wu, M.; Feng, Q.; Wan, D.; Ma, J. CTACl as catalyst for four-component one-pot synthesis of pyranopyrazole derivatives in aqueous medium. *Synth. Commun.* **2013**, *43*, 1721-1726; (b) Peng, Y.; Song, G.; Dou, R. Surface cleaning under combined microwave and ultrasound irradiation: Flash synthesis of 4H-pyrano[2,3-*c*]pyrazoles in aqueous media. *Green Chem.* **2006**, *8*, 573-575; (c) Vasuki, G.; Kumaravel, K. Rapid four-component reactions in water: synthesis of pyranopyrazoles.*Tetrahedron Lett.* **2008**, *49*, 5636-5638; (d) Lehmann, F.; Holm Mand Laufer , S. Three-component combinatorial synthesis of novel dihydropyrano[2,3-c]pyrazoles. *J. Comb. Chem.* **2008**, *10*, 364-367; (e) Mecadon, H.; Rohman, Md. R.; Kharbangar, I.; Laloo, B. M.; Kharkongor, I.; Rajbangshi, M.; Myrboh, B. L-Proline as an efficicent 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.* **2011**, *52*, 3228-3231; (f) Heravi, M. M.; Ghods, A.; Derikvand, F.; Bakhtiari, K.; Bammoharram, F.F. *J. Iran. Chem. Soc.* **2010**, *7*, 615-620; (g) Mecadon, H.; Rohman, M. R.; Rajbangshi, M.; Myrboh, B. γ-Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in aqueous medium. *Tetrahedron Lett.* **2011**, *52*, 2523-2525; (h) Kiyania, H.; Samimib, H. A.; Ghorbania, F.; Esmaielia, S. *Curr. Chem. Lett.* **2013**, *2*, 197-206; (i) Bihani, M.; Bora, P. P.; Bez, G.; Askari, H. *ACS Sustainable Chem. Eng.* **2013**, *1*, 440-447; (j) Kanagaraj, K.; Pitchumani, K. Solvent-free multicomponent synthesis of pyranopyrazoles: per-6-amino-β-cyclodextrin as a remarkable catalyst and host. *Tetrahedron Lett.* **2010**, *51*, 3312-3316; (k) Siddekha, A.; Nizam, A.; Pasha, M. A. An efficient and simple approach for the Ssnthesis of pyranopyrazoles using imidazole (catalytic) in aqueous medium, and the vibrational spectroscopic studies on 6-amino-4-(4'methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole using density functional theory. *Spectrochim. Acta A.* **2011**, *81*, 431-440; (l) Madhusudana Reddy, M. B.; Pasha, M. A. One-pot, multicomponent synthesis of 4H-pyrano[2,3-c]pyrazoles in water at 25°C. *Indian J. Chem.*(Sec-B), **2012**, *51*, 537-541; (m) Madhusudana Reddy, M. B.; Jayashan Kara, V. P.; Pasha, M. A. Glycine-catalyzed efficient synthesis of Pyranopyrazoles via one-pot multicomponent reaction. *Synth. Commun.* **2010**, *40*, 2930-2934.

12. Zou , Y.; Hu, Y.; Liu, H.;. Shi, D. Rapid and efficient ultrasound-assisted method for the combinatorial synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives. *ACS Comb. Sci.* **2012**, *14*, 38-43.

13. (a) Zhang, Q.; Vigier, K. D. O.; Royer, S.; Jérôme, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.* **2012**, *41*, 7108–7146; (b) Carriazo, D.; Serrano, M. C.; Gutiérrez, M. C.; Luisa Ferrer, M.; Del Monte, F. Deep eutectic solvents playing multiple roles in the synthesis of polymers and related materials. *Chem. Soc. Rev.* **2012**, *41*, 4996–5014; (c) Abbott, A. P.; Cullis, P. M.; Gibson, M. J.; Harris, R. C.; Raven, E. Novel choline-chloride-based deep-eutectic-solvents with renewable hydrogen bond donors: levulinic acid and sugar based polyols. *Green Chem.* **2007**, *9*, 868–872; (d) Maugeri, Z.; Leitner, W.; Domínguez de María, P. Practical separation of alcohol–ester mixtures using deep eutectic solvents. *Tetrahedron Lett.* **2012**, *53*, 6968–6971; (e) Handy, S.; Lavender, K. Organic synthesis in deep eutectic solvents: Paal–Knorr reactions. *Tetrahedron Lett.* **2013**, *54*, 4377–4379.

14. Abbott, A. P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. *Chem. Commun.* **2003**, 70-71.

15. Sonawane, Y. A.; Phadtare, S. B.; Borse, B. N.; Jagtap A. R.; Shankarling, G. S. Synthesis of diphenylamine-based novel fluorescent styryl colorants by Knoevenagel condensation using a conventional method, biocatalyst, and deep eutectic solvent. *Org. Lett.* **2010**, *12*, 1456–1459.

16. Azizi, N.; Dezfooli, S.; Hashemi, M. Greener synthesis of spirooxindole in deep eutectic solvent. J. Mol. Liq. 2014, 62-67.

17. (a) Moshtaghi Z., A.; Eskandari, I.; Khavasi, H.R. A green and convenient approach for the synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates via a one-pot, multi-component reaction in water. *Tetrahedron Lett.* **2012**, *53*, 5519-5522; (b) Moshtaghi Z., A.; Baradaran H., S. Montmorillonite K10

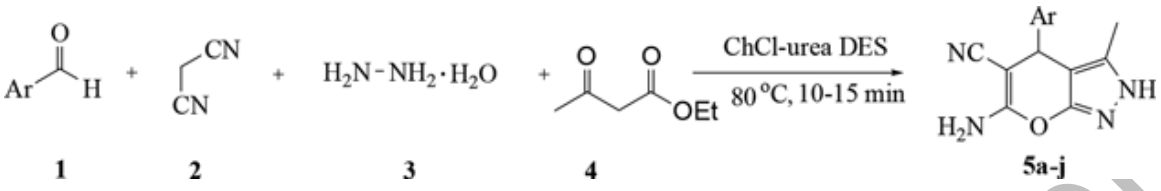
Clay: An efficient catalyst for Hantzsch synthesis of 1,4- dihydropyridine derivatives. *Synth. Commun.* **2008**, *38*, 290-296; (c) Moshtaghi Z., A.; Eskandari, I.; Notash, B. An efficient and green procedure for the synthesis of highly substituted polyhydronaphthalene derivatives via a one-pot, multi-component reaction in aqueous media. *Curr. Chem. Lett.* **2015**, *4*, 85-92.

18. Bez, Gh.; Bora, p.; Bihani, M. Multicomponent synthesis of dihydropyrano[2,3-*c*]pyrazoles catalyzed by lipase from *Aspergillus niger. J. Mol. Cata. B.* **2013**, 92, 24.

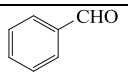
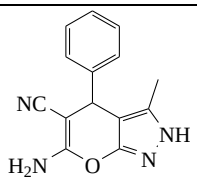
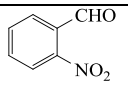
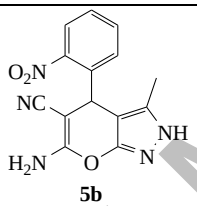
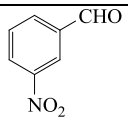
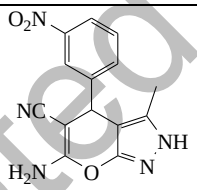
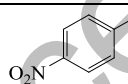
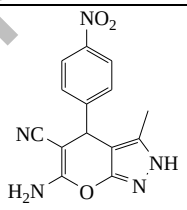
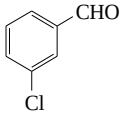
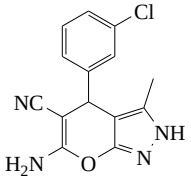
19. El Aleem, M. A.; El-Remaily, A. A. Synthesis of pyranopyrazoles using magnetic Fe_3O_4 nanoparticles as efficient and reusable catalyst. *Tetrahedron* **2014**, *70*, 2971-2975.

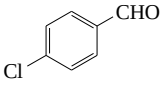
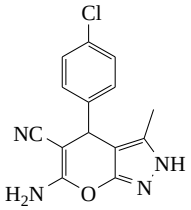
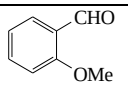
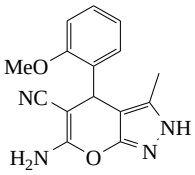
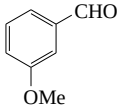
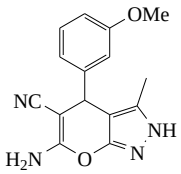
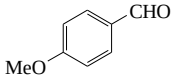
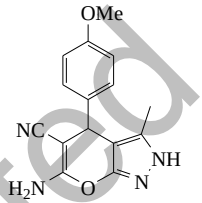
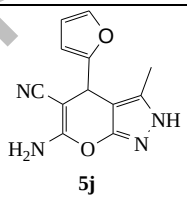
20. Guo, R-Y.; An, Z-M.; Mo, L-P.; Yang, Sh-T.; Liu, H-X.; Wang, Sh-X.; Zhang, Zh-H. Meglumine promoted one-pot, four-component synthesis of pyranopyrazole derivatives. *Tetrahedron* **2013**, *69*, 9931-9938.

Table 1. Synthesis of dihydropyrano[2,3-*c*]pyrazoles via a four-component reaction in ChCl–Urea DES medium



1 **2** **3** **4** **5a-j**

Entry	ArCHO	Product[a]	Time (min)	Yield (%)[b]
1		 **5a**	10	95
2		 **5b**	10	97
3		 **5c**	10	97
4		 **5d**	15	90
5		 **5e**	15	87

6		 **5f**	15	86
7		 **5g**	10	90
8		 **5h**	15	88
9		 **5i**	15	89
10		 **5j**	15	89

[a] All the products are known and were identified by their comparison of their IR and NMR spectra, or by melting points. [18-20] [b] isolated Yields.