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A Green and Efficient Sythesis of Pyranopyrazole Derivatives Catalyzed by Copper(II) triflate in Aqueous Medium

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Asian Journal of Organic & Medicinal Chemistry

Volume: 6 Year: 2021
Issue: 4 Month: October–December
pp: 322–326
DOI: https://doi.org/10.14233/ajomc.2021.AJOMC-P409

Received: 16 December 2021
Accepted: 28 December 2021
Published: 31 December 2021

ABSTRACT

A sustainable, multi-component reaction has been established for the synthesis of pyranopyrazole in an aqueous medium utilizing $Cu(OTf)_2$ as catalyst. This eco-friendly synthesis process utilizes aromatic aldehydes, malonitrile, hydrazine hydrate and ethyl acetoacetate as substrates to obtain pyranopyrazole derivatives. The method is characterized by its mild reaction conditions, cost-effectiveness, high efficiency, energy savings and functional group tolerance, producing the target compounds in good to excellent yields. Copper(II) triflate [$Cu(OTf)_2$] demonstrates high catalytic efficacy without generating side products and can be easily recovered post-reaction without complex procedures. The structure of the synthesized pyranopyrazole derivatives were confirmed using spectroscopic analysis.

KEYWORDS

Pyranopyrazoles, Copper(II) triflate, Aromatic aldehyde, Malonitrile, Ethyl acetoacetate, hydrazine hydrate.

INTRODUCTION

Heterocyclic chemistry is a crucial sub-discipline of organic synthesis, as it encompasses million of known heterocyclic derivatives, with new ones being synthesized frequently [1,2]. Heterocycles are fundamental to a wide range of natural and synthetic compounds with significant biological and pharmaceutical activities. A major challenge in this field is the preparation of practical methods, reaction media and conditions based on the philosophy of green chemistry [3,4]. The idea of "Green Chemistry" has made a scope on guiding principle for environmental gracious synthesis, with organic chemists increasingly adopting eco-friendly and sustainable approaches in current years [5]. The key goal of green synthesis is to lessen or eliminate harmful substances and processes, thereby minimizing pollution and dipping the environmental footprint of chemical production [6].

In aqueous media, the organic reactions benefit from the hydrophobic effect, which lowers activation energies and accelerates reactions. This feature makes water an attractive solvent for many organic reactions, offering a more sustainable alternative to toxic solvents commonly used in traditional organic chemistry [7]. Efforts have focused on minimizing or eliminating toxic solvents and reagents, which can lead to severe environ-

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mental and health risks. Reducing the reliance on such substances is essential for ensuring safer chemical processes. Pyranopyrazole heterocycles, in particular, hold significant value in both synthetic and therapeutic chemistry due to their extensive range of biological behaviour. These derivatives are instigate in synthetic products and numerous natural products exhibiting a broad variety of biological activity including potent inhibitor of human Chk1 kinase [8], anticancer [9], anti-inflammatory [10], antimicrobial [11], analgesic [12], insecticidal [13], antifungal property [14]. These diverse biological activities have made pyranopyrazole derivatives a valuable class of compounds in drug discovery and the development of therapeutic agents.

Multicomponent reactions (MCRs) offer a rapid and elegant method for constructing complex structure from simple building blocks in a one synthetic operation, thus improving reaction efficiency while reducing waste and the need for multiple steps. These reactions are well-known for their high atom economy and high selectivity, making them a promising approach for sustainable chemical synthesis [15-18]. In the context of green chemistry, MCRs are especially useful because they minimize the number of reagents and solvents required, which is beneficial for both economic and environmental reasons. However, the choice of catalyst remains a key issue, as the catalyst must not only facilitate the reaction but also be recyclable and environmentally benign [19].

Recent studies have proposed several synthetic methods for pyranopyrazoles including a four-component, one-pot synthesis using ethyl acetate, malononitrile, aromatic aldehydes and hydrazine hydrates. This method is particularly suitable due to its simplicity and the ability to generate pyranopyrazoles efficiently in a single step. While several catalysts have been explored for this reaction, some of the commonly used catalysts take account of DABCO [20], cinchona alkaloids and organocatalysts. Despite their efficiency, these approaches frequently suffer from limitations such as the use of hazardous catalysts, lengthy workup procedures, and insufficient yields. Therefore, the search for more resourceful, green and recyclable catalysts for the preparation of pyranopyrazoles remains an central area of research.

EXPERIMENTAL

All chemicals and reagents utilized were procured from reputed commercial suppliers and used with no additional distillation. The melting points of the synthesized compounds were measured using Gallenkamp (Electronic) melting-point apparatus and the values are uncorrected. The IR spectra were recorded on a Bruker Tensor II bench-top spectrometer between 4000 and 600 cm^{-1}, while ^1H NMR data were obtained on a Bruker Spectrspin spectrometer operating at 300 MHz, with TMS serving the same as the inner set.

General synthesis procedure: To a stirred dilute hydrazine hydrates and ethyl acetoacetate, substituted benzaldehyde, malononitrile (all taken in equimolar amount) and a little quantity of $Cu(OTf)_2$ as catalyst were mixed. The composition reaction mixture was heated for a specific duration until completion as monitored periodically by TLC. Completed, the composition was taken out to isolate the solid rough product, which was subsequently purified by recrystallization from hot ethyl alcohol (**Scheme-I**). The $Cu(OTf)_2$ was collected through simple refining, dehydrated below void and reused in subsequent reactions without significant loss of activity.

6-Amino-4-(4-methoxy phenyl)-3-methyl pyranopyrazole: IR (KBr, ν_{max}, cm^{-1}): 3489, 3250, 3112, 2835, 2195, 1640, 1498; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.74 (3H, $-CH_3$), 4.65 (3H, $-OCH_3$), 5.53 (1H, -CH), 5.94 (2H, $-NH_2$), 6.85-7.18 (2H, Ar-H), 7.09-7.12 (2H, Ar-H), 11.09 (1H, -NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 8.79, 34.42, 58.90, 59.89, 97.86, 118.72, 120.80, 128.55, 135.51, 136.52, 154.73, 157.54, 160.77; Mass: *m/z* 284 (M^+).

6-Amino-4-(4-methyl phenyl)-3-methyl pyranopyrazole: IR (KBr, ν_{max}, cm^{-1}): 3243, 3047, 2922, 2350, 1686, 1286; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.75(3H, $-CH_3$), 2.26 (3H, $-CH_3$), 4.62(1H, -CH), 5.87(2H, $-NH_2$), 7.02-7.09 (2H, Ar-H), 7.07-7.17 (2H, Ar-H),12.08(1H, -NH); Mass: *m/z*-268 (M^+).

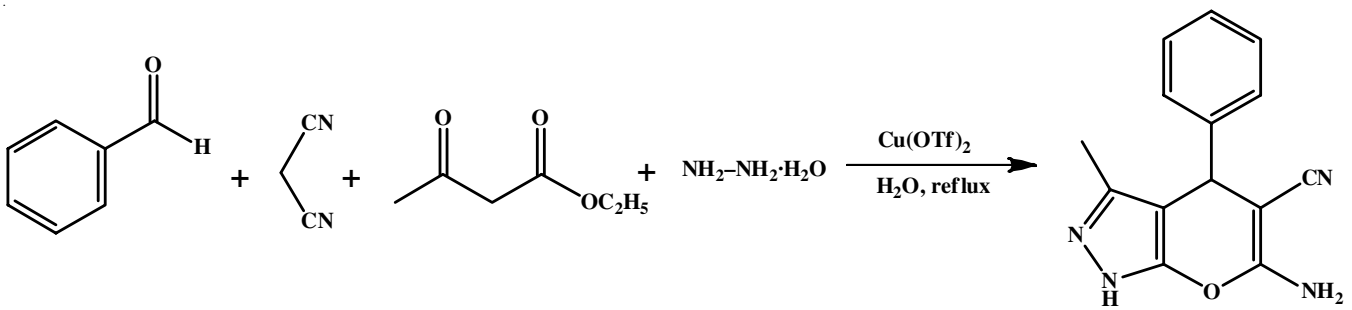
6-Amino-4-(4-chloro phenyl)-3-methyl pyranopyrazole: IR (KBr, ν_{max}, cm^{-1}): 3408, 3306, 3176, 2185, 1678; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.77 (3H, CH_3), 4.63 (1H, -CH), 6.85 (2H, $-NH_2$), 6.99-7.26 (2H, Ar-H), 7.36-7.43 (2H, Ar-H), 11.18 (1H, -NH); Mass: *m/z* 288 ($M^{+\bullet}$).

6-Amino-4-(2,4-dichloro phenyl)-3-pyranopyrazole: IR (KBr, ν_{max}, cm^{-1}): 3475, 3246, 3119, 2174, 1640, 1583; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.78 (3H, $-CH_3$), 4.74 (1H, -CH), 7.09 (1H, ArH), 7.13 (2H, $-NH_2$), 7.16 (2H, ArH), 7.79 (2H, ArH), 11.88 (1H, NH); Mass: *m/z* 322($M^{+\bullet}$).

6-Amino-4-(4-hydroxy-3-methoxy phenyl)-3-methyl pyranopyrazole: ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65 (s, $-CH_3$), 3.79 (s, $-OCH_3$), 5.46 (s, 1H, -CH), 6.64 (d, 1H, OH), 6.77 (t, $-CH_2$), 6.77 (s, $-CH_2$), 8.92 (s, -H), 12.07 (s, -NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 9.8, 35.5, 58.6, 57.8, 96.9, 111.9, 115.4, 118.7, 135.9, 135.3, 145.7, 147.3, 160.5.

RESULTS AND DISCUSSION

To evaluate the catalytic activity of $Cu(OTf)_2$ for synthesizing pyranopyrazole, a series of reactions involving benzal-



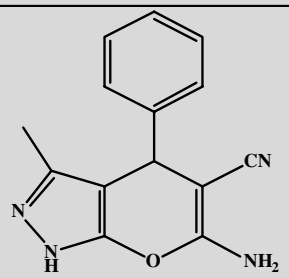
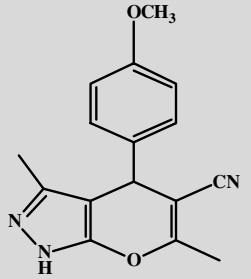
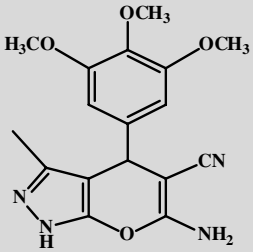
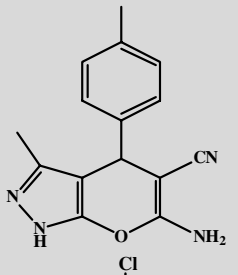
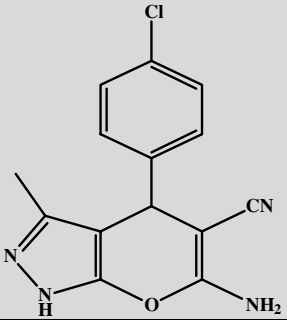
Scheme-I

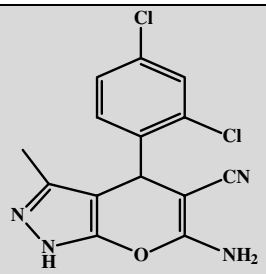
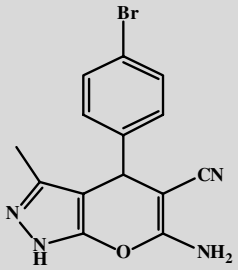
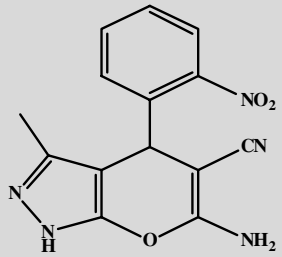
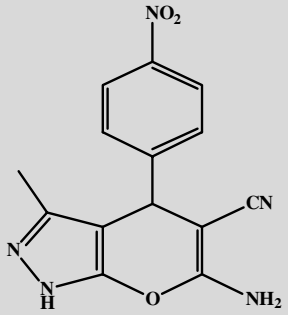
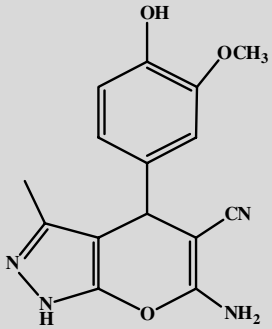
dehydes, malononitrile, ethyl acetoacetate and phenylhydrazine were performed under optimized conditions as summarized in Table-1.

Initially, benzaldehyde was reacted with malononitrile, ethyl acetoacetate and phenylhydrazine under reflux, leading to cyclization and producing the pyranopyrazole derivative with an 82% yield in 3 h (Table-1, entry 1). Subsequently, the influence of electron-donating groups (EDGs) on the reaction was investigated using 4-methoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde and 4-methylbenzaldehyde. The reactions were conducted at 60 ºC with the same substrates, yielding 78%, 80% and 76% of the respective pyranopyrazole derivatives in 3.5, 3 and 4 h, respectively (entries 2, 3 and 4). These results suggest that the occurrence of EDGs on the aromatic aldehyde reduces the reaction rate and yield.

In contrast, reactions involving the electron-withdrawing group (EWG) substituted aldehydes such as 4-chlorobenzaldehyde, 2,4-dichlorobenzaldehyde and 4-bromobenzaldehyde, displayed improved performance. Yields of 84%, 88% and 89% were obtained in 3, 2 and 2 h, respectively (entries 5, 6 and 7). Furthermore, the impact of strong EWGs was also assessed using 2-nitrobenzaldehyde and 4-nitrobenzaldehyde. Significantly, these reactions produced yields of 94% and 92% in just 1.5 h each (entries 8 and 9). These findings evidently

TABLE-1
PREPARATION OF DIVERSE PYRANOPYRAZOLE THROUGH $Cu(OTf)_2$ UNDER OPTIMIZED REACTION

Entry	Products	Time (h)	Yield (%)[P]
1		3.0	82
2		3.5	78
3		3.0	80
4		4.0	76
5		3.0	84

6		2.0	88
7		2.0	89
8		1.5	94
9		1.5	92
10		3.0	76

[a]Process carried out with similar quantity of reactant; [b]p indicates to an lonely yields.

demonstrate that EWG substituents significantly enhance the reaction rate and yield, while electron-donating substituents have the opposite effect, confirming the influence of electronic effects on the cyclocondensation process for pyranopyrazole synthesis.

Conclusion

An eco-friendly method for synthesizing pyranopyrazole derivatives in aqueous medium has been developed. This multi component condensation reaction employs different aromatic aldehyde, malononitrile, ethyl acetoacetate and phenylhydrazine under aqueous reflux conditions. The reaction was catalyzed by $Cu(OTf)_2$, which exhibits excellent catalytic activity and recyclability. This method offers several advantages, including excellent yields, less reaction time and simplified work-up procedures. The sustainability of this move toward aligns well with the green synthesis principles.

ACKNOWLEDGEMENTS

The authors are grateful to the Department of Chemistry, Shaheed Veer Narayan Singh Government College and

Department of Botany, D.P. Vipra Post Graduate College, for the continual support of this work. The authors also express their gratitude to Instrumentation Facility, CSMCRI-CSIR, Bhavnagar, and Guru Ghasidas Central University Bilaspur, India for providing the spectral data.

REFERENCES

1. L.D. Quin and J.A. Tyrell, Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals, Wiley (2010).
2. R. Dua, S. Shrivastava, S.K. Sonwane and S.K. Srivastava, Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review, *Adv. Biol. Res*., **5**, 120 (2011).
3. P.T. Anastas and E.S. Beach, Green Chemistry: The Emergence of a Transformative Framework, *Green Chem. Lett. Rev*., **1**, 9 (2007); https://doi.org/10.1080/17518250701882441
4. W.M. Nelson, Green Solvents for Chemistry: Perspectives and Practice, Oxford University Press (2003).
5. G.J. Ruiz-Mercado, A. Carvalho and H. Cabezas, Using Green Chemistry and Engineering Principles to Design, Assess and Retrofit Chemical Processes for Sustainability, *ACS Sustain. Chem. Eng*., **4**, 6208 (2016); https://doi.org/10.1021/acssuschemeng.6b02200
6. J. Song and B. Han, Green Chemistry: A Tool for the Sustainable Development of the Chemical Industry *Natl. Sci. Rev.*, **2**, 255 (2015); https://doi.org/10.1093/nsr/nwu076
7. M. Bihani, P.P. Bora, G. Bez and H. Askari, Amberlyst A21 Catalyzed Chromatography-Free Method for Multicomponent Synthesis of Dihydropyrano[2,3-*c*]pyrazoles in Ethanol, *ACS Sustain. Chem. Eng.*, **1**, 440 (2013); https://doi.org/10.1021/sc300173z
8. D.S. Fischer, G.M. Allan, C. Bubert, N. Vicker, A. Smith, H.J. Tutill, A. Purohit, L. Wood, G. Packham and M.F. Maho, E-Ring Modified Steroids as Novel Potent Inhibitors of 17ß-Hydroxysteroid Dehydrogenase Type 1, *J. Med. Chem*., **48**, 5749 (2005); https://doi.org/10.1021/jm050348a
9. J.L. Wang, D. Liu, Z.J. Zhang, S. Shan, X. Han, S.M. Srinivasula, C.M. Croce, E.S. Alnemri and Z. Huang, Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells, *Proc. Natl. Acad. Sci.*, **97**, 7124 (2000); https://doi.org/10.1073/pnas.97.13.7124
10. M.M.F. Ismail, N.M. Khalifa, H.H. Fahmy, E.S. Nossier and M.M. Abdulla, Design, Docking, and Synthesis of Some New Pyrazoline and Pyranopyrazole Derivatives as Anti-inflammatory Agents, *J. Heterocycl. Chem*., **51**, 450 (2014); https://doi.org/10.1002/jhet.1757
11. G.M. Reddy, J.R. Garcia, G.V. Zyryanov, G. Sravya and N.B. Reddy, Pyranopyrazoles as Efficient Antimicrobial Agents: Green, One Pot and Multicomponent Approach, *Bioorg. Chem*., **82**, 324 (2019); https://doi.org/10.1016/j.bioorg.2018.09.035
12. A. Kumar, P. Lohan, D.K. Aneja, G.K. Gupta, D. Kaushik and O. Prakash, Design, Synthesis, Computational and Biological Evaluation of Some New Hydrazino Derivatives of DHA and Pyranopyrazoles, *Eur. J. Med. Chem*., **50**, 81 (2012); https://doi.org/10.1016/j.ejmech.2012.01.042
13. S.A.M. Abdelgaleil and Y.M. Badawy, Herbicidal, Insecticidal and Structure-Activity Relationship Studies on Pyranopyrazole and Oxinobispyrazole Derivatives, *Alexand. Sci. Exchange J.*, **37**, 572 (2016); https://doi.org/10.21608/asejaiqjsae.2016.2594
14. G.M. Reddy, A.K. Kumari, V.H. Reddy and J.R. Garcia, Novel pyranopyrazole Derivatives Comprising a Benzoxazole Core as Antimicrobial Inhibitors: Design, Synthesis, Microbial Resistance and Machine Aided Results, *Bioorg. Chem.*, **100**, 103908 (2020); https://doi.org/10.1016/j.bioorg.2020.103908
15. D.M. D'Souza and T.J.J. Müller, Multi-Component Syntheses of Heterocycles by Transition-metal Catalysis, *Chem. Soc. Rev*., **36**, 1095 (2007); https://doi.org/10.1039/B608235C
16. P.V.G. Reddy, B.R.P. Reddy, M.V.K. Reddy, K.R. Reddy, N.P. Shetti, T.A. Saleh and T.M. Aminabhavi, A Review on Multicomponent Reactions Catalysed by Zero-Dimensional/One-Dimensional Titanium Dioxide (TiO_2) Nanomaterials: Promising Green Methodologies in Organic Chemistry, *J. Environ. Manag.*, **279**, 111603 (2021); https://doi.org/10.1016/j.jenvman.2020.111603
17. G. Bosica, K. Baldacchino, R. Abdilla and R. De Nittis, Green Organic Synthesis via Multicomponent Reactions, *Xjenza Online, Sci. J. Malta Chamber Scient*., **9 (Special issue)**, 173 (2021); https://doi.org/10.7423/XJENZA.2021.3.10
18. O. Ghashghaei, F. Seghetti and R. Lavilla, Selectivity in Multiple Multicomponent Reactions: Types and Synthetic Applications, *Beilstein J. Org. Chem.*, **15**, 521 (2019); https://doi.org/10.3762/bjoc.15.46
19. R.A. Sheldon, Atom Efficiency and Catalysis in Organic Synthesis, *Pure Appl. Chem.*, **72**, 1233 (2000); https://doi.org/10.1351/pac200072071233
20. A. Shaabani, A.H. Sarvary, S. Rezayan and S. Keshipour, Synthesis of Fully Substituted Pyrano[2,3-*c*]pyrazole Derivatives *via* a Multi-component Reaction of Isocyanides, *Tetrahedron*, **65**, 3492 (2009); https://doi.org/10.1016/j.tet.2009.02.035