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A Novel Synthesis of Some Pyranopyrazoles Derivatives

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ABSTRACT

Synthesis of Non-aqueous biocatalytic synthesis of pyranopyrazoles via one-pot Knoevenagel condensation–Michael-type addition heterocyclization cascade conventional methods like green synthesis. Compounds were synthesized properly. NMR and mass spectroscopy gave good results of the compounds All the compounds were synthesized according to the procedure by varying different aldehydes but we obtained good yield in a nitro substituent when compared to other substituents. All compounds gave promising yields according to the literature.

Keywords: Aldehydes, Hydrazine hydrate, Mass spectroscopy, Aldehydes, NMR

INTRODUCTION

Heterocyclic compounds containing the 4*H*-pyran ring display significant roles in medicinal and synthetic chemistry, and polyfunctionalized 4*H*-pyran has attracted the attentions of many researchers involved in drug discovery process [**1-3**] due to its pharmacological and biological characteristics [**4**]. On the other hand, pyrazole and its derivatives find applications as biodegradable agrochemicals and pharmaceutical ingredients [**5, 6**]. Compounds containing a pyrazole scaffold have been shown to exhibit interleukin (IL)-1 synthesis inhibition and human immunodeficiency virus (HIV)-1 reverse transcriptase [**7**], as well as antibacterial, anti-hyperglycaemic, anti-inflammatory, sedative/hypnotic, analgesic and antipyretic activities [**8**]. Pyranopyrazole compounds, oxygen- and nitrogen-ring fused heterocycles, are important group of heterocyclic compounds with natural and synthetic molecules [**9**]. They showed numerous biological activities such as antibacterial [**10**], antimicrobial [**11, 12**], anticancer [**13**], anti-inflammatory and analgesic [**14**] properties. Pavlik *et al*., have also reported that pyranopyrazoles can form dimers under UV light [**15**] so that, they can act as UV absorbers. In addition, pyranopyrazoles have also a significant role in agrochemical research due to their fungicidal, bactericidal, and herbicidal properties [**16, 17**]. Thus, the synthesis of the heterocyclic compounds containing the pyranopyrazolemoeity, is of great importance. There are four isomeric structures for pyranopyrazole including: pyrano[2,3-*c*]pyrazole (**1**), pyrano[3,2-*c*]pyrazole (**2**), pyrano[3,4-*c*]pyrazole (**3**), and pyrano[4,3-*c*]pyrazole (**4**) (Figure 1), but pyrano[2,3-*c*]pyrazoles (**1**) have so far been the most investigated one. This can be attributed to the biological significance of this isomer. On the other hand, reports on the preparation of other three pepopyrazoles are rare.

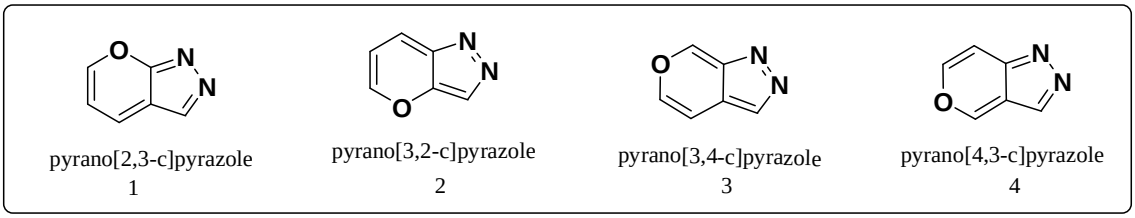


Figure 1. Pyranopyrazole isomers

Pyrano[2,3-*c*]pyrazoles have important activities, such as antitumor [**18**], analgesic, anti-inflammatory [**19, 20**], antimicrobial [**21**] and molluscicidal [**22**] properties. In addition, these compounds are significant precursors for promising drugs in the field of medicinal chemistry [**23, 24**]. They also act as potential inhibitors of human Chk1 kinase (Figure 2) [**25**].

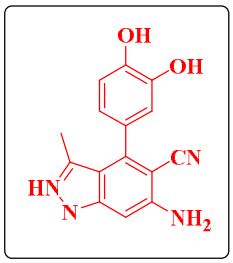


Figure 2. Potential inhibitors of human Chk1 kinase.

Thus, considering the importance of pyranopyrazole, several synthetic routes have been reported to prepare these biologically valuable heterocycles. The synthetic procedure includes single or multi-steps, and two-component or multi-component reactions (three or more compound) to obtain pyranopyrazole. Multi-component reaction is the best reported method for preparation of this biologically active heterocycle. The multi-component reactions (MCRs) are one-pot process in which at least three or more compound react together to form target product without separation and purification of the intermediates, the main advantages of MCRs, in comparison with traditional multistep protocols, are high efficiency, experimental simplicity, low cost, avoidance of large quantities of waste, reducing labor cost, reaction times, and waste production [**26**]. As MCRs are one-pot reaction, they are easier to perform than the multistep reactions. In addition, MCRs are ecofriendly, and often proceed with excellent chemoselectivities [**27-29**]. The design and development of multi-component synthetic strategies based on green principles and using renewable and recyclable materials, using solvent-free condition, green solvents, and green or reusable catalyst, using non-classical conditions such as microwave technologies, ultrasonic irradiations give a possibility to achieve an "ideal synthesis." In addition, the combination of MCRs processes with environmentally benign protocols, such as performing organic reactions in water is a protocol that has become highly interesting for synthetic chemists, "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water" [**30**]. Water has emerged as a versatile solvent for organic reactions recently, because of special effects of water such as abundant, eco-friendly benign, hydrogen bonding in the transition state and high cohesive energy density and also negative activation volume. The use of water as a natural and green solvent is emphasized in green chemical processes [**31, 32**] For these reasons, MCRs in water are of prominent value in green chemistry and organic synthesis [**33, 34**].

This will summarize the reported protocols for the preparation of pyranopyrazole and its spiro conjugated derivatives, but as mentioned, most reports include pyrano[2,3-*c*]pyrazole, so this review covers the preparation of pyrano[2,3-*c*]pyrazole and spiro- pyrano[2,3-c]pyrazole derivatives by multi-component reactions using conventional conditions, MW, and ultrasonic irradiations from 2005 to 2018. The most multi-component reactions (four-component) have been introduced by employing

in situ preparation of pyrazolone ring through the reaction between hydrazine and a *β*-dicarbonyl compounds.

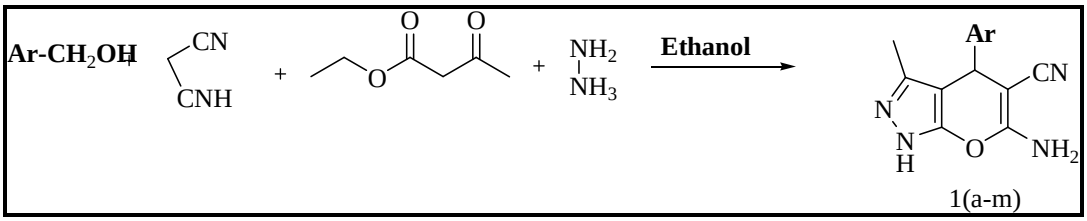
The first approach to synthesize these substances was performed by Otto [35], in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. In a further report, Otto and Schmelz showed that weak bases can also be utilized for a Michael-type cyclization [36]. This work was extended by Klokol et al. who performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base [37].

MATERIALS AND METHODS

Melting points of final products were measured on a Shimadzu-Gallenkamp apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DX instrument (Billerica, USA) (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR); $CDCl_3$ and DMSO-d_6 were used as solvent; chemical shifts are quoted in δ (ppm) from tetramethylsilane. Mass spectra were measured on a GCMS-QP1000EX (EI, 70 eV) mass spectrometer. Starting materials were obtained from Aldrich (Mumbai, India) and used directly.

General procedure for the synthesis of 6-amino-4-(2,5disubstituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (1a-e): In a round-bottom fask (50 mL), a mixture of various disubstituted aromatic aldehydes (5 mmol), malononitrile (5 mmol), hydrazine hydrrate (5 mmol), and ethyl acetoacetate (5 mmol) was taken with ethanol (20 mL) as a solvent, and then baker's yeast (2 g) was added to the reaction mixture. The resulting reaction mass was stirred at room temperature on a magnetic stirrer, and the reaction progress was monitored using thin-layer chromatography (TLC) in an n-hexane/ethyl acetate solvent system (3:1). The reaction mass was filtered under reduced pressure using a silica bed to remove the catalyst and washed with ethanol after 34 h of constant stirring at room temperature (50 mL). The crude products were purified by recrystallization in ethanol and column chromatography

Experimental Section



Scheme 1. Non-aqueous biocatalytic synthesis of pyranopyrazoles via one-pot Knoevenagel condensation–Michael-type addition heterocyclization cascade (1a-m).

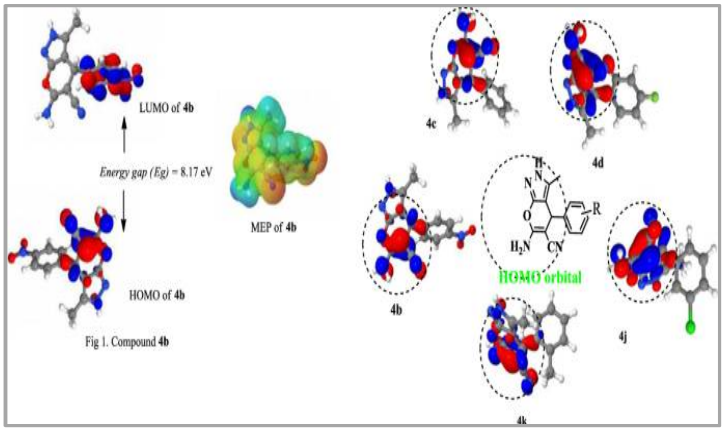
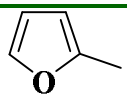
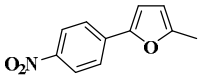
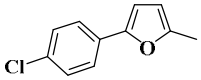
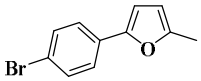
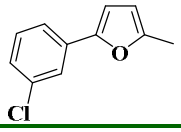


Table 1. Physicochemical data of Pyranopyrazole derivatives

S.No	Ar	Colour and Crystal Form	Melting Point (^{0}C)
1a		Brownish Colour	160
1b		Yellow	162
1c		White	163
1d		Brown	165
1e		Brown	168

Spectral data of Synthesised Compounds

Compound 1a: ^{1}H NMR: δ 2.21 (3H, s), 4.90 (1H, s), 6.12-6.26 (2H, 6.18 (dd, *J* = 3.4, 1.2 Hz), 6.21 (dd, *J* = 3.4, 1.8 Hz)), 7.37 (1H, dd, *J* = 1.8, 1.2 Hz), 8.30 (1H, s). ^{13}C NMR: δ 13.7 (1C, s), 34.5 (1C, s), 107.1 (1C, s), 112.0 (1C, s), 114.1 (1C, s), 127.3 (1C, s), 135.6 (1C, s), 143.2 (1C, s), 143.6 (1C, s), 154.8 (1C, s), 156.3 (1C, s), 159.8 (1C, s).

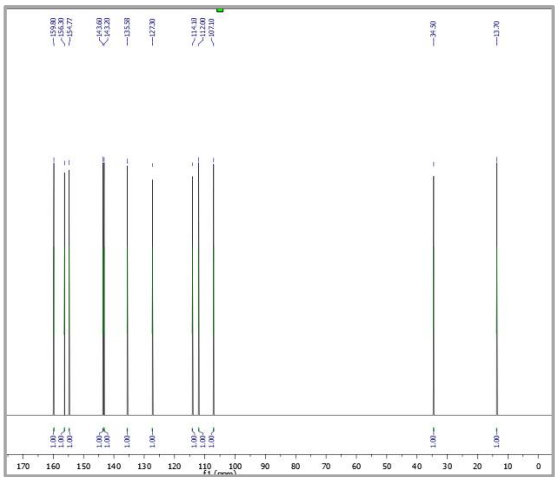


Figure 3. ^{1}H NMR spectrum of Compound 1a.

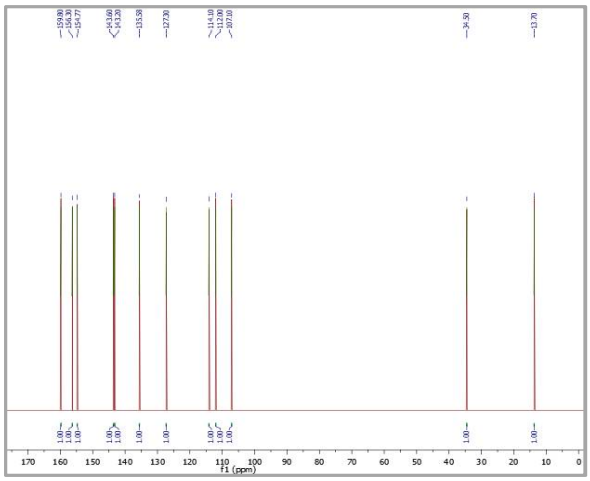


Figure 3(a). ^{13}C NMR spectra of Compound 1a.

Compound 1b: ^{1}H NMR: δ 2.21 (3H, s), 5.09 (1H, s), 6.21-6.40 (2H, 6.26 (d, *J* = 3.4 Hz), 6.34 (d, *J* = 3.4 Hz)), 6.93 (2H, ddd, *J* = 9.0, 1.1, 0.5 Hz), 7.39 (2H, ddd, *J* = 9.0, 1.5, 0.5 Hz), 8.32 (1H, s). ^{13}C NMR: δ 13.7 (1C, s), 34.5 (1C, s), 104.8 (1C, s), 107.9 (1C, s), 114.1 (1C, s), 114.3 (2C, s), 126.0 (2C, s), 127.3 (1C, s), 129.1 (1C, s), 135.6 (1C, s), 143.2 (1C, s), 148.4 (1C, s), 154.8 (1C, s), 155.2 (1C, s), 156.3 (1C, s), 159.8 (1C, s).

RESULT AND DISCUSSION

Developed efficient, one-pot, four-component coupling reaction of aromatic aldehyde, malononitrile, CAN , and hydrazine hydrate in aqueous medium to access substituted pyranopyrazoles in higher yields within short time. The present protocol has several advantages not only in terms of yield but also applicability for large-scale synthesis using water as the green reaction medium in short reaction

time. Operational simplicity, recyclability of the catalyst, and atom economical and environmentally benign nature make it an attractive process. It meets the requirements of clean organic reactions in water as well as the vigorously increasing applications of nanocatalysts in organic synthesis. Thus the present protocol helps in generating molecular complexity and developing diversity through the one-pot four-component reaction.

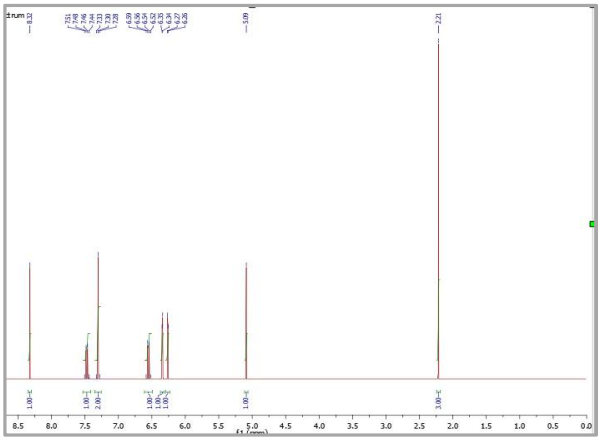


Figure 4. ^{1}H NMR spectrum of Compound 1b

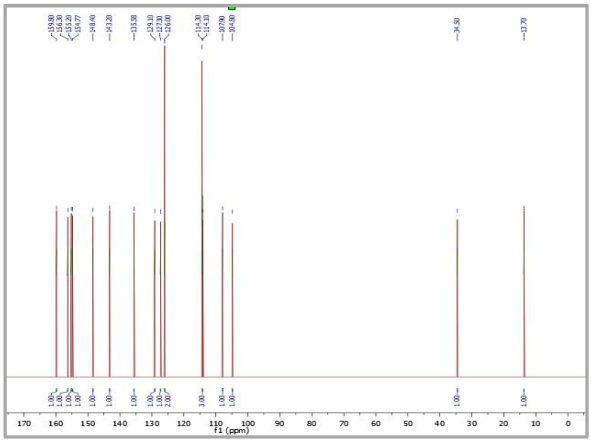


Figure 4(a). ^{13}C NMR spectra of Compound 1b.

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