ChemistrySelect

Review
doi.org/10.1002/slct.202400028

Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

Recent Synthesis of Mono- & Bis-Pyranopyrazole Derivatives

Saba Farooq*[a] and Zainab Ngaini*[a]

Pyranopyrazole is an important structural unit in heterocyclic chemistry and is useful in pharmaceutical and agrochemical industries. The pyranopyrazole-based compounds are known in the agricultural industry as herbicides, fungicides, and insecticide agents and in medicinal fields as antimicrobial, anticancer, and antiHIV agents. Despite its wide range of applications, the synthesis of pyranopyrazole has several limitations such as the cost of reagents, potential environmental risks, harsh reaction conditions, longer reaction times, laborious workup procedures, and unsatisfactory yields. However, many studies have been recently reported on the synthesis of pyranopyrazoles using mild, green, and environmentally friendly methods that also give higher yields. Different catalysts and conditions have been reported for the synthesis of pyranopyrazole using four, three, and two components. Among these, four-component synthesis is commonly reported by using benzaldehyde, hydrazine derivatives, ethyl acetoacetate and malononitrile due to the commercial availability and stability of the reagents. This review summarized the recent synthesis of pyranopyrazole *i.e.*, *mono*- and *bis*-pyranopyrazole derivatives *via* four-, three- and two-component-based reactions. *Mono*- and *bis*-pyranopyrazole derivatives varied due to the number of pyranopyrazole units that contributed to play an important role in increasing the binding interaction and biological activities beneficial for pharmaceutical industries.

Introduction

Pyranopyrazole is a heterocyclic structural unit possessing a fused pyran with a pyrazole ring.[1,2] It has two isomeric structures with common names of 1,4-dihydropyrano[2,3-c]pyrazole (**1**) and 2,4-dihydropyrano-[2,3-c]pyrazole (**2**) (Figure 1).[3,4]. Among these, compound (**1**) is the most stable isomer.[5,6] It has other alternative names such as pyrano[2,3-c]pyrazoles, 4H-pyrano[2,3-c]pyrazoles and also 1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanides.[7,8] Pyranopyrazole is a bioactive moiety[9] that has numerous applications in pharmaceuticals and agrochemicals, herbicide, fungicide,[10] insecticide,[11] larvicidal,[12] and biological activities *i.e.*, antibacterial,[13–15] antimicrobial,[16] anticancer,[17–20] antitubercular,[21] antiallergenic,[22] antioxidant,[23,24] antineoplastic,[25], anti-inflammatory,[26] and human Chk1 kinase inhibitor activities (Figure 2).[3,27–29] The stability of pyranopyrazoles depends on substituent rings and intermolecular hydrogen bonding interactions between the molecules. Pyranopyrazoles have high stability and low reactivity due to resonance or conjugation.[1] Several approaches for the synthesis of these compounds have been reported using various catalysts such as 1,4-diazabicyclo[2.2.2] octane (DABCO),[30] nano-SiO_2/DABCO, ZrO_2 NPs, isonicotinic, choline chloride/urea deep, L-proline/KF-alumina, CAPB, TPSPPTNM, [HMIM]C$(NO_2)_3$, CTACl, bovine serum albumin, lipase, morpholine triflate,[31] [Dabco-H][AcO],[32] sodium ascorbate,[33] Fe_3O_4@SiO_2@piperidinium benzene-1,3-disulfonate[34] and nano-SiO_2.[35,36] Despite numerous applications, the synthesis of pyranopyrazoles has many limitations such as expensive reagents, environmental hazards, harsh reaction circumstances, metal catalyst, long reaction time, monotonous workup process, tedious catalyst recycling process and unacceptable yield.[37,38] Many recent studies reported methods on the synthesis of pyranopyrazoles in an eco-friendly, mild, and green strategies with better yields.[31]

The synthesis of dihydropyrano[2,3-c]pyrazole has received great interest among researchers.[39] Otto initiated the first approach for the synthesis of these substances via cyclization of base-catalyzed 4-aryliden-5-pyrazolone.[40] In an altered method, malononitrile was used to treat 3-methyl-3-pyrazolin-5-ones in a weak basic medium.[41–43]. Further research leads to the current methods for the synthesis of pyranopyrazoles which employ solvent-free conditions,[44] ionic liquid[32] (*i.e.*, [Et_3NH][HSO_4],[45] [Bmim][BF_4],[46] dihydrogen 4,4′-trimethylenedipiperidine phosphate [H_2-TMDP][HPO_4],[47] Fe_3O_4@CTC@[BisPy][HC_2O_2],[48] TEA–Im-IL–Cu[49]), aqueous media,[50] and microwave (MW) irradiation.[4]

The general mechanism for the synthesis of pyranopyrazole derivative involves the activation of methylene nitrile *via* deprotonation before conversion into malonate carbanion (Scheme 1). The carbanion acted as a nucleophile[51] and reacted with an aldehyde *via* Knoevenagel condensation to form 2-arylidenemalononitrile intermediate as a Knoevenagel adduct. Furthermore, the reaction of ethyl acetoacetate and hydrazine hydrate formed the corresponding pyrazolone, which underwent Michael addition with Knoevenagel adduct to produce an acyclic Michael adduct that further cyclized to yield pyranopyrazole (**1**).[52]

[a] *Dr. S. Farooq, Prof. Dr. Z. Ngaini*
Faculty of Resource Science and Technology
Universiti Malaysia Sarawak
94300 Kota Samarahan, Sarawak, Malaysia
E-mail: sabafarooq61@yahoo.com
nzainab@unimas.my