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MEGLUMINE AS A BIODEGRADABLE CATALYST FOR THE ONE-POT SYNTHESIS OF DIHYDROPYRANO [2,3-*c*]PYRAZOLE DERIVATIVES

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ABSTRACT

A series of dihydropyrano[2,3-c]-pyrazole was efficiently synthesized via one-pot, four component reaction of aldehydes, malononitrile, ethylacetoacetate, hydrazine hydrate in the presence of catalytic amount of meglumine under EtOH-H_2O (1:1) at reflux conditions. The present protocol offers the advantages of clean reaction, short reaction time, high yield, easy purification and economic availability of the catalyst.

KEYWORDS: Dihydropyrano[2,3-c]-pyrazole; Meglumine; Multicomponent reaction; One-pot synthesis

1. INTRODUCTION

The realization of simple and green synthetic procedures constitutes an important goal in organic synthesis. To combat the harmful effect of volatile organic solvents frequently used in large quantities for organic transformations, many green solvent systems have been recently introduced as alternative reaction media [1]. Among all the green solvents developed so far, water and ionic liquids have gained most of the interests of chemists. Because many remarkable results have been achieved in recent years, work on the replacement of conventional organic solvents with a green solvent system has become one of the most important topics of green chemistry [2].

Multicomponent reactions (MCRs) are known as a powerful synthetic strategy in recent years for the construction of novel and structurally complex molecules in a one pot ensuring high atom-economy, high selectivity, energy saving, shorter reaction times and avoidance of expensive purification processes. MCRs are very attractive tools to obtain complex molecules from one-pot procedures. These reactions save both energy and raw materials and reduce the time. In the recent years, being focused on green chemistry using

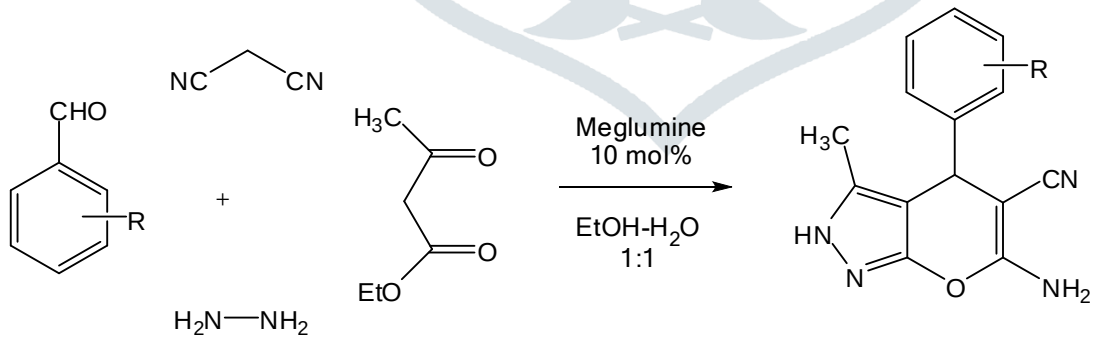
environmentally benign reagents and conditions is one of the most fascinating developments in synthesis of widely used organic compounds [3-5].

Dihydropyrano[2,3-*c*]pyrazole is one of the most important classes of bioactive heterocycles among pyranopyrazoles possessing a unique 4*H*-pyran ring fused with pyrazole, which are well known for their medicinal importance and applications in myriad agrochemicals and pharmaceutical ingredients [6]. In view of the pharmaceutical ingredients, several drug candidates containing the dihydropyrano[2,3-c]pyrazole skeleton display an extremely wide range of biological activities such as antibacterial [7], antimicrobial [8], antianaphylactin [9], antiallergenic [10], antiproliferative [11], antitumor [12], cytotoxic [13], mutagenic [14], sex pheromonal [15], anti-inflammatory [16], hypoglycaemic [17] and analgesic [18].

Generally, pyranopyrazoles have been synthesized from aldehydes, malononitrile, ethyl acetoacetate, and hydrazine derivatives through multicomponent reactions, which was one of the effective methods applied. Several protocols have been reported for using various catalysts such as Fe_3O_4@THAM-SO_3H as a highly reusable nanocatalyst [19], silica-coated cobalt oxide nanostructures [20], β-CD on Fe_3O_4@Ag core-shell nanoparticles [21], nano-SiO_2 [22] and Amberlyst A21 [23].

Following the increasing environmental and economic considerations, the search for enviro-economic synthetic methods for organic reactions has received overwhelming attention. In this regard, efforts are being made to replace the expensive and hazardous catalysts with biodegradable materials, which are safe, inexpensive, harmless, and environmentally benign. Recently meglumine has been reported as a promoting catalyst for the multicomponent synthesis of functionalized 2-amino-4*H*-pyrans [24]. Meglumine is an amino sugar derived from sorbitol with molecular formula $C_7H_{17}NO_5$. Meglumine possesses environmentally benign properties such as biodegradability and physiological inertness.

Considering the above facts we wish to report a facile, one-pot, four-component process for the synthesis of functionalized dihydropyrano[2,3-c]-pyrazole derivatives from the reaction of aldehydes, malononitrile, ethylacatoacetate and hydrazine in the presence of meglumine in EtOH-H_2O (Scheme 1).



Scheme – 1 Synthesis of dihydropyrano[2,3-c]-pyrazole derivatives from different substituted aldehydes using Meglumine as a catalyst

2. EXPERIMENTAL

2.1 Apparatus and analysis

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using Bruker DRX- 500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer.

2.2 General procedure for the synthesis of dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5a–e)

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol) and meglumine (10 mol %) in water (5 mL) was taken in a 50 ml round-bottomed flask. The resulting mixture was stirred at room temperature for a period as indicated in Table 1. After completion of the reaction (monitored by TLC), the solid obtained was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethanol to afford the desired product. The products (5a-e) were confirmed by comparing the physical and spectral data with those of the reported compounds.

2.3 Spectral data for the synthesized compounds (5a-e)

2.3.1 6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5a):

Yellow solid, IR (KBr): 3455, 3320, 2225, 1661, 1587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.89 (s, 3H, CH_3); 4.86 (s, 1H, CH); 6.79 (s, br, 2H, NH_2); 7.10-7.65 (m, 5H, *J*= 7.5-8 Hz, Ar-H); 12.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6,100 MHz) δ 11.2, 11.9, 23.3, 36.9, 55.0, 66.3, 97.4, 118.7, 121.3, 128.9, 136.0, 138.8, 157.2, 157.9, 166.1 ppm;.

2.3.2 6-Amino-3-methyl-4-(3-chlorophenyl)-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5b):

White solid, IR (KBr): 3430, 3025, 2975, 1627, 1575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.90 (s, 3H, CH_3); 5.20 (s, 1H, CH); 6.91 (s, br, 2H, NH_2); 7.15-7.70 (m, 4H, *J* = 7.3-7.9 Hz, Ar-H); 12.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6,100 MHz) δ 11.8, 12.1, 24.3, 32.9, 52.0, 64.3, 97.4, 118.7, 123.3, 126.9, 134.0, 138.8, 157.2, 157.9, 162.1 ppm;.

2.3.3 6-Amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5c):

Yellowish solid; IR (KBr): 3475, 3186, 2190, 1651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.97 (s, 3H, CH_3), 4.77 (s, 1H, CH), 6.21 (s, 2H, NH_2), 7.53 (d, 2H, *J* = 7.6 Hz, Ar-H), 8.04 (d,2H, *J* = 8 Hz, Ar-H), 12.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6,100 MHz) δ 10.8, 11.3, 23.3, 31.9, 59.0, 69.3, 98.4, 118.7, 125.3, 128.9, 136.0, 138.8, 157.2, 159.9, 166.1 ppm;.

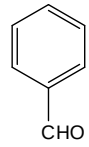
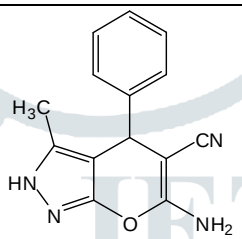
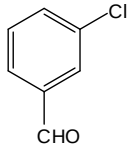
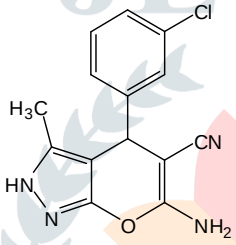
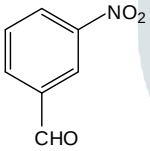
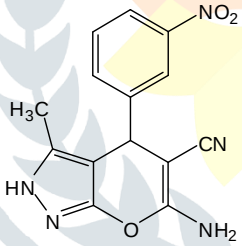
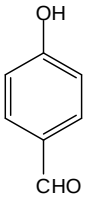
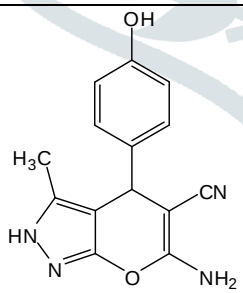
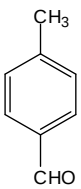
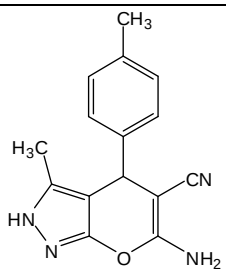
2.3.4 6-Amino-3-methyl-4-(4-hydroxyphenyl)-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5d):

white solid, IR (KBr): 3390, 3239, 3145, 2971, 2195, 1644, 1603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.81 (s, 3H, CH_3), 4.49 (s, 1H, CH), 6.71(d, *J* = 8.4 Hz, 2H, Ar-H), 6.76 (s, 2H, NH_2), 6.93 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.27 (s, 1H, OH), 12.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6,100 MHz) δ 11.4, 11.7, 23.4, 31.9, 54.0, 65.3, 94.4, 114.7, 124.3, 128.9, 133.0, 138.8, 157.2, 158.9, 169.1 ppm;.

2.3.5 6-Amino-3-methyl-4-(4-methylphenyl)-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5e):

White solid, IR (KBr): 3370, 3050, 2785, 1600 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): 1.85 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 4.52 (s, 1H, CH), 6.72 (s, 2H, NH_2), 7.04–7.13 (m, 4H, Ar-H), 12.10 (s, 1H); ^{13}C NMR (DMSO-d_6,100 MHz) δ 10.4, 10.7, 22.4, 35.9, 55.0, 65.3, 97.4, 115.7, 122.3, 128.9, 134.0, 137.8, 155.2, 156.9, 160.1 ppm;.

Table 1 Synthesis of dihydropyrano[2,3-c]-pyrazole from different substituted aldehydes Meglumine as a catalyst[a]

Entry	Aldehyde	Product	Time min	Yield (%)[b]	M pt (°C)
1			40	93	243-245
2			40	89	234-236
3			50	87	248-250
4			50	90	212-214
5			40	88	206-208

[a]Reaction conditions: Aldehyde (1 mmol), malononitrile (1 mmol), ethylacetoacetate (1 mmol) and hydrazine (1 mmol) in the presence of meglumine (10 mol %) in EtOH-H_2O (1 : 1).

[b]Isolated yield.

3. RESULTS AND DISCUSSION

In order to optimize the reaction conditions, initially we carried out the reaction between benzaldehyde 1**a** (1 mmol) and malononitrile **2** (1 mmol) ethyl acetoacetate **3** (1 mmol), hydrazine hydrate **4** (1 mmol) as a model reaction. In the beginning, the model reaction was carried out in the absence of catalyst, it was found that only a low yield of product was obtained even after 90 min. Therefore to improve the yield, it was thought that intervention of catalyst is necessary. Hence, we tried a various catalysts like K_2CO_3, imidazole, Al_2O_3, L-proline and meglumine to promote this transformation at room temperature. To our delight, reaction proceeds smoothly in the presence of meglumine affording higher yield (93%) within 40 min. Therefore, considering the effective catalytic activity, meglumine was preferred as a catalyst of choice for subsequent optimization studies.

Having established optimum experimental conditions in hand, next we examined the scope and generality of this method using a variety of substituted aromatic aldehydes for synthesizing dihydropyrano[2,3-*c*]pyrazoles. Under the optimized conditions, irrespective of the substituent present on the aromatic ring of the aldehyde, the corresponding products were obtained in high to excellent yields (Table - 1). Formation of the desired product was confirmed by comparing their physical constants, FTIR, ^1H and ^{13}C NMR data with those of reported compounds.

Recyclability of catalysts is an important aspect of a reaction from an economical and environmental point of view, and has attracted much attention in recent years. Thus the recovery and reusability of Meglumine was investigated. After completion of the reaction, the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the Meglumine was filtered off. The recycled catalyst has been examined in the next run. The Meglumine catalyst could be reused four times without any loss of its activity and yields ranged from 93 to 88 %.

4. CONCLUSION

In conclusion, we have achieved the synthesis of dihydropyrano[2,3-*c*] pyrazole derivatives in excellent yields by a simple and efficient procedure in the presence of meglumine as a biodegradable catalyst. The important features of this protocol are the very short reaction time, high yields and simple workup. This procedure could be classified within green chemistry.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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