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ORIGINAL PAPER

Green procedure for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles using saccharose

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Abstract Saccharose was applied as an efficient and homogeneous catalyst for one-pot, four-component synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives from aromatic aldehydes, malononitrile, ethyl acetoacetate and hydrazine monohydrate under thermal solvent-free conditions. This protocol has a considerable number of advantages including mild condition, high yields, operational simplicity, environmentally benign and simple work-up procedures.

Keywords Saccharose · 1,4-dihydropyrano[2,3-*c*]pyrazoles · Solvent-free condition

Introduction

In the past few years, focusing on green chemistry using environmentally benign reagents and conditions is one of the most fascinating developments for the synthesis of widely used organic compounds. Use of natural materials as a promising catalyst in organic reactions has received a considerable attention owing to their green credentials [1]. Organic synthesis using green catalysts offers key advantages including rate enhancement and insolubility of the final products leading to simple isolation of product.

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Nitrogen-containing heterocyclic compounds are widespread in natural products and medicinal agents [2], and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials have increasingly become important [3, 4]. Among them, dihydropyrano[2,3-*c*]pyrazoles are very interesting compounds and have received a noticeable attention as a result of their biological activity and an interesting template for medicinal chemistry. Many of those compounds are known as antimicrobial [5], insecticidal [6] and anti-inflammatory [7]. Furthermore, dihydropyrano[2,3-*c*]pyrazoles showed molluscicidal activity [8, 9] and was identified as a screening hit for Chk1 kinase inhibitor [10]. By the pioneering studies by Otto [11] on the base-catalyzed cyclization of 4-aryliden-5-pyrazolone, there has been growing number of profound research activities on the study of dihydropyrano[2,3-*c*]pyrazoles [12–20]. Recently, Laufer and colleagues [21] performed a library of diverse dihydropyrano[2,3-*c*]pyrazoles in ethanol. However, most of these synthetic methods suffer from drawbacks such as employing toxic reagent, strong basic conditions, expensive and complex catalysts or reagents, too many tedious steps, in most cases low yields of the products and long reaction times which restrict their usage in practical applications. Solvent-free reactions obviously reduce pollution and bring down handling costs due to simplification of experimental procedure, work-up technique and labor-saving [22]. In continuation of our research on multi-component reactions [23, 24], herein we report one-pot four-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives under thermal solvent-free conditions in the presence of saccharose (Fig. 1) as a biodegradable catalyst (Scheme 1).

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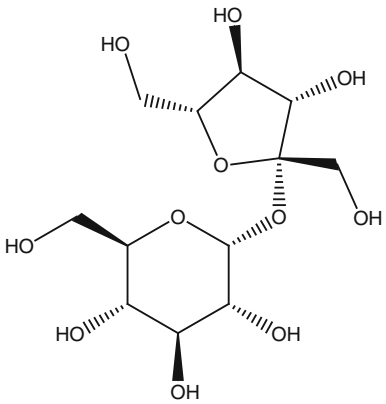


Fig. 1 Structure of saccharose

Experimental

General

Hydrazine monohydrate was purchased from Merk along with other reagents that were purchased from Sigma–Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by the comparison of physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DRX 400 MHz instrument. The spectra were measured in DMSO-d6 relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 accompanied by spectrophotometer. Melting points were determined in open capillaries with an electro thermal 9100 melting point apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. TLC was conducted on silica–gel PolyGram SILG/UV 254 plates.

General procedure for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives

A mixture of hydrazine monohydrate (1 mmol) and ethyl acetoacetate (1 mmol) was stirred at 0 °C until 3-methyl-2-pyrazolin-5-one was precipitated (5 min). The reaction mixture was then left to warm to room temperature. Aryl aldehyde (1 mmol), malononitrile (1 mmol) and saccharose (20 mol%) were then added and the mixture was heated at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and dissolved in water. The precipitated product was filtered off and recrystallized from ethanol to afford the pure pyranopyrazole derivatives.

Selected spectroscopic data of some products

6-amino-1,4-dihydro-3-methyl-4-(2-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 3)

IR (KBr, cm^{-1}): 3,477, 3,228, 3,120, 2,196, 1,651, 1,595, 1,493,1,401, 1,353, 1,107, 744; ^{1}H NMR (400 MHz), (DMSO-d_6): δ (ppm) = 1.78 (3H, CH_3, S), 5.11 (1H, CH, S), 7.04 (2H, NH_2, S), 7.34 (1H, Ar, d, J = 6.8 Hz), 7.50 (1H, Ar, t, J = 7.2 Hz), 7.67 (1H, Ar, t, J = 7.2 Hz), 7.86 (1H, Ar, d, J = 7.6 Hz), 12.22 (1H, NH, S); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 9.9, 31.8, 56.5, 96.8, 120.6, 124.0, 128.7, 131.7, 133.8, 136.1, 138.0, 149.6, 155.4, 161.6. Analysis of $C_{14}H_{11}N_5O_3$ (297.09). Anal.Calcd For $C_{14}H_{11}N_5O_3$: C: 56.56, H: 3.73, N: 23.56 %. Found: C: 56.65, H: 3.58, N: 23.45 %.

6-amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 4)

IR (KBr, cm^{-1}): 3,414, 3,374, 3,316, 3,175, 2,186, 1,654, 1,598, 1,529, 1,492, 1,412, 1,350, 1,072, 872, 791; ^{1}H NMR (400 MHz), (DMSO-d_6): δ (ppm) = 1.82 (3H, CH_3, S), 4.84 (1H, CH, S), 7.06 (2H, NH_2, S),7.48 (2H, Ar, d, J = 8.4 Hz), 8.22 (2H, Ar, d, J = 8.4 Hz), 12.22 (1H, NH, S); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 10.2, 31.1, 56.4, 97.0, 120.9, 124.3, 129.3, 136.3, 146.8, 152.5, 155.1, 161.6. Anal.Calcd For $C_{14}H_{11}N_5O_3$: C: 56.56, H: 3.73, N: 23.56 %. Found: C: 56.68, H: 3.68, N: 23.55 %.

6-amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, Entry 6)

IR (KBr, cm^{-1}): 3,391, 3,357, 3,314, 3,169, 2,190,1,609, 1,489, 1,408, 1,350, 1,052, 763; ^{1}H NMR (400 MHz), (DMSO-d_6): δ (ppm) = 1.78 (3H, CH_3, S), 5.08 (1H, CH,

Scheme 1 Synthesis of 1, 4-dihydropyrano [2,3-*c*]pyrazoles under thermal solvent-free conditions in the presence of saccharose as biodegradable catalysts

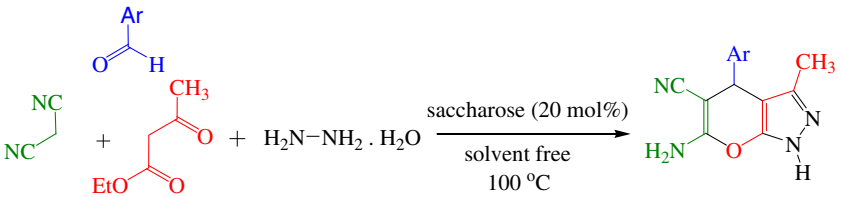


Table 1 Optimization of temperature in synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles under thermal solvent-free conditions

Entry	Temperatures (°C)	Yield (%)[a]
1	Room temperature	–
2	40	45
3	60	50
4	70	60
5	80	65
6	90	70
7	**100**	**75**
8	110	75

Bold values indicate the optimized conditions

[a] Yields refer to pure isolated product

Table 2 Optimization of amount of catalyst in synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles under thermal solvent-free conditions

Entry	Catalyst (g)	Time (min)	Yield (%)[a]
1	0.03	25	55
2	0.05	20	65
3	**0.06**	**10**	**75**
4	0.15	10	75

Bold values indicate the optimized conditions

[a] Yields refer to pure isolated product

Table 3 Different catalytic systems and catalytic activity evaluation for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles under thermal solvent-free conditions

Entry	Catalyst	Mol%	Time (min)	Yield (%)[a]
1	Maltose	20	10	98
2	Saccharose	20	10	75
3	Glucose	20	20	70

[a] Yields refer to pure isolated product

S), 6.96 (2H, NH_2, S), 7.19–7.54 (4H, Ar, m), 12.14 (1H, NH, S); ^{13}C NMR (100 MHz, DMSO-d_6): 10.0, 33.9, 56.2, 97.3, 120.9, 128.2, 129.0, 129.9, 131.2, 132.4, 135.8, 141.4, 155.4, 161.7. Anal.Calcd For $C_{14}H_{11}ClN_4O$: C: 58.65, H: 3.87, N: 19.54 %. Found: C: 57.68, H: 3.78, N: 20.15 %.

Results and discussion

We tried to optimize the amount of catalyst and temperature for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles using benzaldehyde derivatives, malononitrile, ethyl acetoacetate and hydrazine monohydrate. As can be seen in Table 1, it was found that the best reaction conditions could be obtained at 100 °C, in the presence of 0.06 g (20 mol%) of saccharose (Table 2). It should be noted that the reaction was conducted in water as solvent but no better results obtained. Also, we used maltose [20] and glucose as catalyst under the optimized reaction conditions, the results are summarized in Table 3.

Table 4 Four component synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives

Entry	Ar	Time (min)	Yield (%)	Found M.P. (°C)/ [Lit.M.P. (°C)][Ref.]
1	C_6H_5	10	75	243–245 (244–246) [12, 14]
2	4-$N(CH_3)_2C_6H_4$	15	75	165–168 (167–169) [12, 14]
3	2-$NO_2C_6H_4$	15	73	218–220 (220–222) [12, 14]
4	4-$NO_2C_6H_4$	15	72	247–249 (249–252) [12, 14]
5	3-$NO_2C_6H_4$	19	65	190–192 (193–195) [12, 14]
6	2-ClC_6H_4	17	75	143–145 (145–147) [12, 14]
7	4-ClC_6H_4	18	73	233–235 (234–236) [12, 14]
8	2,5-$(CH_3O)_2C_6H_3$	25	65	209–211 (210–212) [12, 14]
9	2,4-$Cl_2C_6H_3$	15	75	237–182 (235–237) [12, 14]
10	4-MeC_6H_4	20	70	204–206 (206–208) [12, 14]
11	*n*-heptanal	24 h	Trace	–

[a] Yields refer to pure isolated product

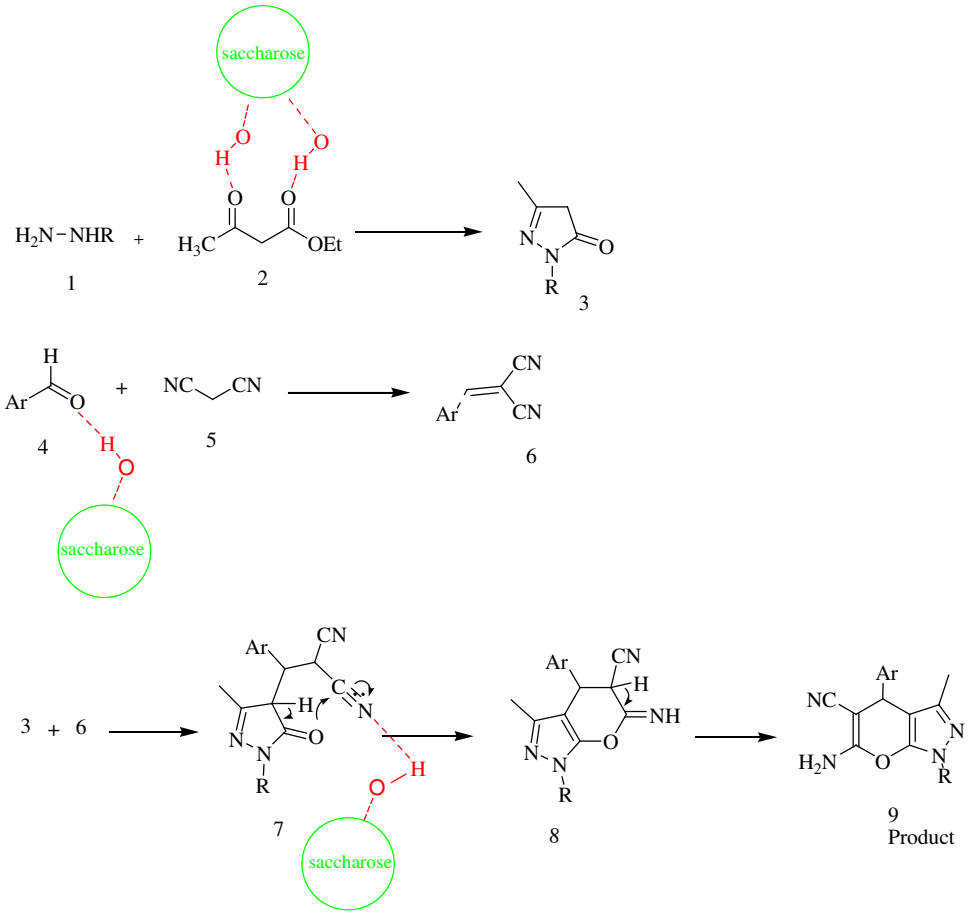
Using these optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 1,4-dihydropyrano[2,3-*c*]pyrazoles using hydrazine monohydrate, ethyl acetoacetate, aryl aldehydes and malononitrile. The results have been summarized in Table 4.

Interestingly, a variety of aryl aldehydes including electron withdrawing or releasing substituents (*ortho*-, *meta*-, and *para*-substituted) participated well in this reaction and gave the 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in good to excellent yield.

The proposed mechanism has been shown in Scheme 2. First, pyrazolone **3** was formed by the reaction of **1** and **2**. Then, Knoevenagal condensation of **4** and **5** led to the formation of 2-benzylidenemalononitrile **6**. Finally, Michael addition of **3–6**, followed by cyclization and tautomerization which afforded the corresponding product 9 (Scheme 2).

Conclusion

A highly efficient method has been developed based on thermal solvent-free conditions for the synthesis of 1,4-



Scheme 2 Proposed mechanism for the synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazoles in the presence of saccharose as catalyst

dihydro pyrano[2,3-*c*]pyrazoles using saccharose as catalyst. This procedure has many advantages including high yields, operational simplicity, non-hazardous catalyst and solvent, short reaction time and minimum environmental pollution.

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