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One-pot synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives using β-cyclodextrin-SO_3H as a reusable catalyst in aqueous medium

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Abstract: We have developed an expedient and highly efficient β-cyclodextrin-SO_3H catalyzed approach for the eco-friendly synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous medium. The reaction proceeded smoothly with a range of functionalities within 15-30 min to produce the dihydropyrano[2,3-*c*]pyrazole scaffolds in good to excellent yields. β-cyclodextrin-SO_3H can be recycled and reused with an insignificant loss of catalytic activity.

Keywords: Dihydropyrano[2,3-*c*]pyrazoles, β-cyclodextrin-SO_3H, Green chemistry.

Introduction

In the community of fused heterocycles, pyranopyrazoles are omnipresent and have been referred as "core structures" in drug discovery. Among these, dihydropyrano[2,3-*c*]pyrazoles displayed a wide range of biological activities such as antitumor [1a], anti-inflammatory [1b], analgesic [1c] and antimicrobial [1d]. Moreover these dihydropyrano[2,3-*c*]pyrazoles act as potential insecticidal and molluscidal agents [2] as well as potential inhibitors of human chk1 kinase [3]. On the other hand compounds bearing 4*H*-pyran motif are of medicinal interest [4].

The most straightforward route for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives involves a four-component coupling of aromatic aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate. The previously reported methods for the construction of this heterocyclic system include catalysts such as tetraethyl ammonium bromide, heteropolyacids, disulphonic acid imidazolium chloroaluminate, piperazine, piperidine, glycine, alumina, sodium benzoate, per-6-amino-β-cyclodextrin and imidazole [5]. Most of these synthetic protocols

reported so far suffer from harsh reaction conditions, prolonged reaction time period, high catalyst loading, expensive methods, poor recyclability and low yields. Despite the advances in synthetic methodologies, development of a new catalytic route towards this direction is still an active area of research.

Organic synthesis is continuously evolving to serve the needs of a changing society. One of such advancements in that direction is implementing green chemistry practices. Multicomponent reactions (MCR) as well as ecofriendly catalysts that bring about organic transformations in operationally simple ways have always been an attractive approach for an organic as well as medicinal chemist. In this regard, biopolymers have attracted researchers as being inexpensive, readily available, biodegradable, renewable and recyclable catalysts [6] and such methodology for the mild synthesis of dihydropyrano[2,3-*c*]pyrazoles is still not explored. Among these biopolymers, cyclodextrins are cyclicoligosaccharides. They are composed of 6 to 8 units of D-glucopyranose in a rigid truncate conic structure. Recently, β-cyclodextrin-SO_3H has emerged as a promising biopolymeric solid support acid catalyst for the synthesis of 3,4-dihydropyrimidine-2(*1H*)-ones, 2,3-dihydroquinazolin-4(*1H*)-ones as well as 3-indolyl-3-hydroxy oxindoles and 3,3-di(indolyl)indolin-2-ones in greener way [7].

Our group has paid special attention to the synthesis of bioactive molecules using MCR which are catalyzed by environment friendly catalysts [8]. Therefore, encouraged by the promising biological activities of the structurally diverse dihydropyrano[2,3-*c*]pyrazoles, herein, we report an efficient and eco-friendly β-cyclodextrin-SO_3H catalyzed approach for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous medium.

Experimental

Materials and methods:

All chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light. Melting points were recorded in open capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz and Bruker DRX 100 MHz spectrometer respectively. Chemical shift values (δ) are expressed in (parts per million) ppm relative to TMS. Mass spectra were recorded on a macro mass spectrometer (waters) by electro-spray (ES) method.

Preparation of β-cyclodextrin-SO_3H

To a well stirred mixture of β-cyclodextrin (10.0 g, 4.5 mmol) in CH_2Cl_2 (50 mL), chlorosulfonic acid (2.00 g, 10 mmol) was added slowly at 0 °C during 3 h. The resulting mixture was stirred for another 2 h to remove HCl from the reaction vessel. Then, the mixture was filtered and washed with methanol (50 mL) and dried at room temperature to obtain sulfonated β-cyclodextrin as white powder (10.56 g). The -SO_3H content was measured by the titration method and it showed 0.52 mequiv. g^{-1} [7].

*General experimental procedure for the synthesis of dihydropyrano[2,3-c]pyrazoles **5(a-p)***

A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), ethyl acetoacetate **3** (2 mmol), hydrazine hydrate **4** (2 mmol) and β-cyclodextrin-SO_3H (10 mol%) in water (8 mL) was stirred vigorously at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane, 2:8). After specified time as given in Table **4**, the reaction mixture was cooled down to RT.Crude product was collected by simple filtration, washed with water and dried. After that it was purified by crystallization from 10% aqueous ethanol.

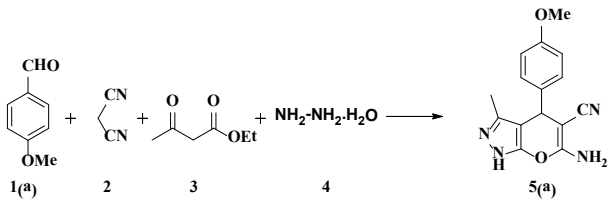
***Spectral data for representative compound*:**

6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5a): ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 1.76 (s, 3H, -CH_3), 3.71 (s, 3H, -OCH_3), 4.51 (s, 1H), 6.79 (s, 2H, -NH_2), 6.84 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 12.04 (s, 1H, -NH); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ 11.1, 24.6, 56.2, 62.0, 114.4, 114.9, 127.5, 128.7, 140.0, 143.4, 152.9, 158.8, 166.3; ES-MS: m/z 283.2 $[M+H]^+$.

6-amino-1,4-dihydro-4-(4-methylphenyl)-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5h): ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 1.78 (s, 3H, -CH_3), 2.26 (s, 3H, -CH_3), 4.54 (s, 1H), 6.82 (s, 2H, -NH_2), 7.04 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 12.06 (s, 1H, -NH); ^{13}C NMR (DMSO-*d6*, 100 MHz): δ 9.80, 20.67, 35.88, 57.37, 97.76, 120.88, 127.40, 129.03, 135.50, 135.75, 141.53, 154.8, 160.81; ES-MS: m/z 265.2 $[M-H]^+$.

Results and Discussion

Initially, p-methoxybenzaldehyde (1a), malononitrile (2), ethylacetoacetate (3) and hydrazine hydrate (4) were chosen as substrates for model reaction (Scheme 1).



Scheme 1. Standard model reaction

As per the requirements of green chemistry and excellent solubility of catalyst in water, we used water as the solvent of our first choice. In the absence of a catalyst, trace amount of product was detected at room temperature and the reaction proceeded at reflux with low yield (35%) in aqueous medium (Table 1, entries 1-2). We screened various catalysts bearing sulphonated functionalities at reflux condition (Table 1). Out of these β-cyclodextrin-SO_3H exhibited the best result giving the desired product **5a** in excellent yield (93%) within 30 min (Table 1, entry 11). It indicated that β-cyclodextrin-SO_3H not only increased the product yield but also accelerated the reaction rate. The other acids proved to be inferior with the overall catalytic activity following the order β-cyclodextrin-SO_3H>PEG-SO_3H>silica-SO_3H>carbon-SO_3H>camphor sulfonic acid (CSA)>p-toluene sulfonic acid (PTSA)>sulphanilic acid~sulphamic acid. Also, we studied the effect of β-cyclodextrin on reaction, but the corresponding product **5a** was obtained in 60% yield (Table 1, entry 10) using 100 mol% of β-cyclodextrin. Therefore, considering the effective catalytic activity of β-cyclodextrin-SO_3H and for exploitation of its applications in organic transformation,β-cyclodextrin-SO_3H was preferred as a catalyst of choice for subsequent optimization studies.

Table 1. Screening of catalysts[a]

Entry	Catalyst	Temperature (°C)	Time (min)	Yield[b] (%)
1	-	RT	200	Trace
2	-	Reflux	30	35
3	PTSA	Reflux	30	43
4	CSA	Reflux	30	48
5	Sulphanilic acid	Reflux	30	40
6	Sulphamic acid	Reflux	30	39
7	Carbon-SO_3H	Reflux	30	64
8	Silica-SO_3H	Reflux	30	69
9	PEG-SO_3H	Reflux	30	80
10	β-cyclodextrin	Reflux	30	60[c]
11	β-cyclodextrin-SO_3H	Reflux	30	93

[a]*Reaction condition*: p-methoxybenzaldehyde (2mmol), malononitrile (2mmol), ethyl acetoacetate (2mmol), hydrazine hydrate (2mmol), catalyst (15 mol%), water (10 ml). [b]Isolated yields. [c]β-cyclodextrin (100 mol%).

To determine the effect of solvents, we

examined our reaction in different solvents as depicted in Table 2. Use of these solvents did not improve the yield (Table 2, entries 1-5). It can be noted that the polar protic solvents such as ethanol and methanol gave better yields (72% and 67%, respectively) than the polar aprotic solvents such as dichloromethane, tetrahydrofuran and acetonitrile which offered only moderate yields of the products (40%, 46% and 55%, respectively). Finally, the reaction was performed without solvent at 100 ^{0}C, but there was decrease in yield (65%) of **5a** (Table 2, entry6). Therefore, water was found to be the most suitable solvent for this reaction (Table 1, entry11). It was established that 8 ml of water is sufficient to carryout reaction excellently by further set of experiments (Table 2, entry 8).

Table 2. Screening of solvents[a]

Entry	Solvent	Amount of solvent (ml)	Temperature (^{o}C)	Time (min)	Yield[b] (%)
1	Ethanol	10	Reflux	30	72
2	Methanol	10	Reflux	30	67
3	DCM	10	Reflux	30	40
4	THF	10	Reflux	30	46
5	Acetonitrile	10	Reflux	30	55
6	Solvent free	-	100	30	65
7	Water	4	Reflux	45	82
8	Water	8	Reflux	30	93

[a]*Reaction condition*: p-methoxybenzaldehyde (2mmol), malononitrile (2mmol), ethyl acetoacetate (2mmol), hydrazine hydrate (2mmol), β-cyclodextrin-SO_3H (15 mol%). [b]Isolated yields.

We further investigated the effect of temperature on the rate of reaction. For this purpose the reaction was carried out at different temperatures (Table 3, entries 1-5). It was observed that the reaction rate enhanced significantly with increased temperature upto 80 ^{o}C. Temperature higher than 80 ^{o}C did affect the product yield (Table 3, entry 5). Therefore, the best reaction temperature was 80 ^{o}C (Table 3, entry 4). Also, the optimal loading of β-cyclodextrin-SO_3H was revealed to be 10 mol% (Table 3, entry 8) as it gave the highest yield (93%). Therefore, the conditions described in Table 3, entry 8 were found to be optimal for the highest conversion into product (**5a**).

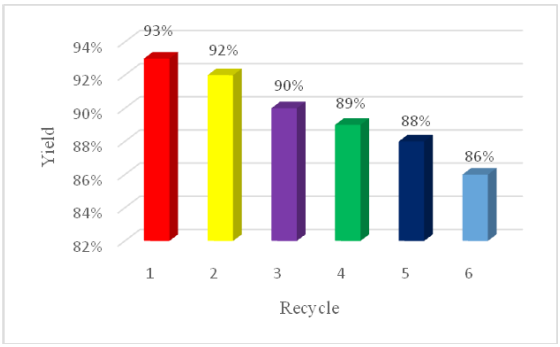
Table 3. Effect of temperature and concentration of catalyst[a]

Entry	Temperature (^{o}C)	Concentration of catalyst (mol%)	Time (min)	Yield[b] (%)
1	RT	15	240	60
2	40	15	150	71
3	60	15	60	86
4	80	15	30	93
5	Reflux	15	30	93
6	80	2	30	77
7	80	6	30	86
8	80	10	30	93

[a]*Reaction condition*: p-methoxybenzaldehyde (2mmol), malononitrile (2mmol), ethylacetoacetate (2mmol), hydrazine hydrate (2mmol), water (8ml). [b]Isolated yields.

To reinforce the advantage of biopolymer based solid acid catalysts, the recyclability of the β-cyclodextrin-SO_3H was investigated on model reaction. After completion of the reaction, the product from aqueous reaction mixture was completely isolated by filtration. The filter aqueous layer still containing catalyst β-cyclodextrin-SO_3H was evaporated under vacuum and the crude catalyst was collected. Recovered crude catalyst was washed with diethyl ether to obtained pure catalyst, which was dried and reused for further reactions. Catalyst was found to be efficient for every cycle without significant loss of activity as shown in **figure 1.** Practically observed fall in yield after successive runs may be due to minute loss of catalyst during each recovery process.

Figure 1. Recycling and reuse of catalyst



A plausible reaction mechanism that accounts for the β-cyclodextrin-SO_3H catalyzed formation of dihydropyrano[2,3-*c*]pyrazoles is depicted in **figure 2.** The β-cyclodextrin-SO_3H activates carbonyl group of aldehyde to form Knoevenagel condensation product **A**, which on protonation gives intermediate **B** and nucleophilic attack of -NH_2 groups of hydrazine on activated carbonyl groups of ethyl acetoacetate leads to pyrazolone **D**. These two initial steps take place simultaneously. The formation of enol **E** of pyrazolone **D** takes place in presence of catalyst, which undergoes Michael type addition with intermediate **B** to afford intermediate **F**. Intermediate **F** on intramolecular cyclization gives the desired product **G**.

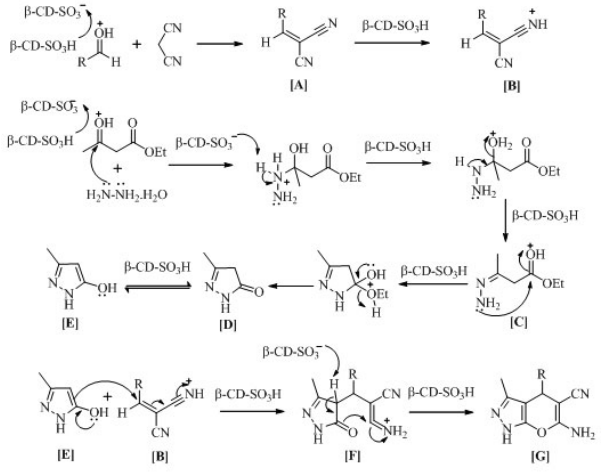


Figure 2. A plausible mechanism of reaction

In order to study scope of the reaction, we used commercially available aromatic aldehydes having electron donating and electron withdrawing substituents to form a series of dihydropyrano[2,3-*c*]pyrazoles (Table 4, entries 5a-5n). All these aromatic aldehydes afforded desired products in good to excellent yield. The electronic effects had no significant impact on reaction rate or else the reaction time in ortho-substituted aldehydes would have been long, reflecting its steric property. Heteroaromatic aldehydes also gave desired products in excellent yield (Table 4, entries 5o-5p). As only few methods are available for the synthesis of these dihydropyrano[2,3-*c*]pyrazoles, our methodology can serve as a useful tool in synthesis of these pharmacologically active scaffolds. Structures of the products were confirmed on the basis of ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

Conclusion

In conclusion, we have demonstrated a most concise, highly efficient, and facile protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives using β-cyclodextrin-SO_3H as an eco-friendly and recyclable catalyst in aqueous medium. This approach features products in good to excellent yields within short reaction time and under relatively mild conditions. Easy accessibility to starting materials, reuse of catalyst as well as the use of environmentally benign water as solvent are the key advantages of this method.

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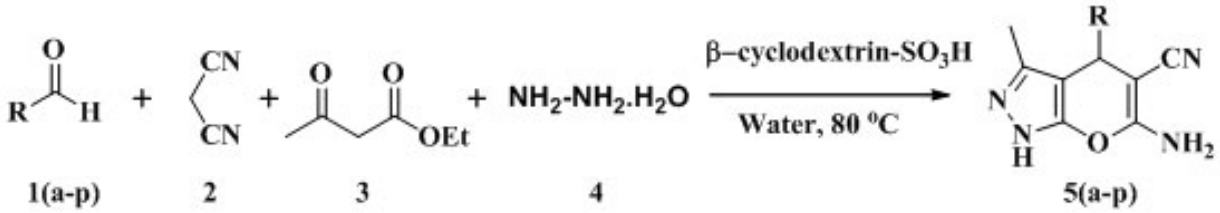
Table 4. Synthesis of dihydropyrano[2,3-*c*]pyrazoles[a]



Product	R	Time (min.)	Yield[b] (%)	M.P.[c] (°C)
5a	4-OMe-Ph	25	93	210-212
5b	Ph	15	95	164-166
5c	4-Cl-Ph	20	94	245–247
5d	3-Cl-Ph	20	91	158-160
5e	2-Cl-Ph	20	90	143–145
5f	4-F-Ph	20	92	170-172
5g	4-Br-Ph	20	87	177–179
5h	4-Me-Ph	25	89	174-176
5i	4-OH-Ph	20	90	221–223
5j	2-OH-Ph	20	85	208-210
5k	3-NO_2-Ph	25	86	191–193
5l	2-NO_2-Ph	25	82	222-224
5m	4-(Me_2N)-Ph	20	90	226–228
5n	3,4-$(OMe)_2$-Ph	25	86	189–191
5o	2-Thienyl	30	88	222–224
5p	2-Furanyl	30	90	175–177

[a]*Reaction condition*: aldehydes (2mmol), malononitrile (2mmol), ethylacetoacetate (2mmol), hydrazine hydrate (2mmol), β-cyclodextrin-SO_3H (10 mol%), water (8ml). [b]Isolated yields. [c]Melting points match with literature values [5].

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