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SODIUM GLUCONATE: AN EFFICIENT ORGANOCATALYST FOR THE SYNTHESIS OF DIHYDROPYRANO[2,3-C]PYRAZOLE DERIVATIVES

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ABSTRACT. Sodium gluconate presented as a category of biomolecule found to be a proficient and recyclable organocatalyst for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives via one-pot multicomponent reaction of aryl aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate in water as a solvent. The catalyst is non-toxic in nature, commercially available, biodegradable and easily separated from the reaction mixture. Present protocol avoids the use of the heavy metal catalyst, harsh reaction condition and the reusability of catalyst, broad substrate scope, simple work-up procedure and excellent yield of products make this protocol greener.

KEY WORDS: Pyrano[2,3-c]pyrazole, Sodium gluconate, Multicomponent reaction (MCR), Knovenagel condensation, Bio-based organocatalyst

INTRODUCTION

Advances in one pot multicomponent reactions (MCRs) become one of the powerful ways of synthesizing medicinally important fused heterocycles. This area of MCRs has much attention towards the eco-compatibility, energy minimization, waste minimization and increased atom economy in one pot single step which becomes an effectual and fascinating method for organic synthesis [1-3].

The increased attention on the use of novel catalyst and newer techniques *via* one pot multi component reactions led to the integration of a variety of novelty in their line of investigation [4-7]. The developments of newer catalyst which are in accordance with the principle of green chemistry are mostly used in one pot synthesis of heterocyclic compounds [8-9]. The direct use of commercially available biomolecules as a catalyst makes the processes simple and efficient and gains the significance over the conventional catalytic system, since their biocompatibility and known inclusive data about non-toxic nature allow them to enter into the category of catalyst and accepted as an environmentally suitable methodology. In this regard, great efforts have been performed to use different biomolecules like chitosan [10], β-cyclodextrin-monosulphonic acid [11], meglumine [12], starch [13], cellulose [14], and sodium alginates [15] as catalytic systems.

These catalysts have different active sites and the wide range of pH, promote the reactants to achieve the activation energy for product formation and make an alternative to the catalysts like heavy metal catalyst, nanocatalyst, ionic liquids, etc. However, the use of such molecules in pure form without post modification, as catalysts is of great importance since they are easily available, eliminate toxic metals, cost effective, biodegradable and eco-compatible. In this context, sodium gluconate can play a major role as a natural and biodegradable salt.

Sodium salt of gluconic acid is commercially available in the form of white crystalline powder having admirable solubility in water and partial solubility in alcoholic solutions. It has carboxylate ion and three hydroxyl groups with chelating ability and resistance to oxidation and reduction in aqueous media [16]. Sodium gluconate used in pharmaceutical and food industries as cleaners and sizing agents. It also dissolves the mineral deposit in alkaline solution. Especially this salt is characterized by many hydroxyl groups, which makes this species highly

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hydrophilic and immiscible with non-polar organic solvents and, consequently, makes the product separation easy by extraction and follows the recovery of the catalyst. These features persuade us to admit it as a catalyst for the one pot synthesis of dihydropyrano[2,3-c]pyrazole derivatives.

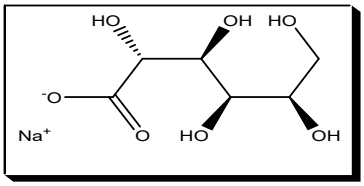


Figure 1. Structure of sodium gluconate.

Pyranopyrazole heterocycle is one of the resourceful beginning destinations of biologically vital molecules. Since the biological activity of the pyran ring is closely linked to the core structure substitution pattern and attachment of other ring motifs into the pyran frame could significantly add to the parent molecule's biological activity [17]. It is composed of fused five-member pyrazole ring join to six-member pyran ring which participate in different biological activities including anticancer [18], anti-inflammatory [19], antimicrobial, and antioxidant activity [20]. However, they also act as Chk1 kinase inhibitor and show vasodilatory and molluscicidal activity [21], and antimicrobial activity [29]. Agriculturally their pronounced effect has been observed as herbicide [22].

Recently, several amendments have been done for the synthesis of dihydropyrano[2,3-c] pyrazole which involve the use of morpholine triflate [23], β-cyclodextrin [24], meglumine [25], L-proline [26], Fe_3O_4 nanoparticles [27], green cellulose-based nanocomposite catalyst [28], lactic acid [29], isonicotinic acid [30], sodium dodecyl sulfate [31], molecular sieve [32], DABCO [33], lipase [34], bovine serum albumin [35], deep eutectic solvent [36], Ag/TiO_2 nano-thin films [37], $Ba(OH)_2$ [38], polyphosphoric acid supported nanoparticles [39], $[Yb(OTf)_3]$ ytterbium triflate [40], and micellar medium [41].

By detailing the criteria for all these reported one pot synthesis, the insight and concepts presented are projected to complete the reaction efficiently. Herein, we proposed a novel target relevant method in terms of greenness for the synthesis of dihydropyrano[2,3-c]pyrazole by using sodium gluconate as catalyst.

EXPERIMENTAL

General experimental procedure for the synthesis of dihydropyrano[2,3-c]pyrazole

To the mixture of ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), 15 mL of water and 10 mol% of sodium gluconate was added and stirred for 5-10 min then aldehyde (1 mmol) and malononitrile (1 mmol) was added to the same reaction mass and was refluxed for the time specified in (Table 3). Progress of reaction was monitored on TLC. After the completion of reaction, the reaction mass cooled to room temperature and the obtained precipitate was filtered, washed with aqueous ethanol and recrystallized to get the desired product. In order to recover the catalyst, the filtrate was dried under reduced pressure and recovered catalyst was washed with diethyl ether and reused for next reaction.

Spectral data for representative compound

6-Amino-3-methyl-4-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile ***(5a)***. FT-IR (KBr) ν_{max} (cm^{-1}): 3373, 3312, 3173, 2194, 1650, 1612, 1045, 764. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77 (s, 3H, CH_3), 4.59 (s, 1H, C-H), 6.88 (s, 2H, NH_2), 7.15-7.33 (m, 5H, Ar-H), 12.11 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.77, 36.28, 57.20, 97.96, 120.84, 126.80, 127.51, 128.49, 135.67, 144.47, 154.81, 160.91 ppm.

6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile ***(5f)***. FT- IR (KBr) ν_{max} (cm^{-1}): 3410, 3309, 3178, 2918, 2189, 1645, 1601, 1401, 1279, 859; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (s, 3H, CH_3), 4.65 (s, 1H, C-H), 6.94 (s, 2H, NH_2), 7.19-7.23 (m, 2H, Ar-H), 7.3-7.4 (m, 2H, Ar-H), 12.15 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.2, 36.0, 57.2, 97.6, 121.1, 128.9, 129.8, 131.7, 136.1, 143.9, 155.1, 161.3 ppm.

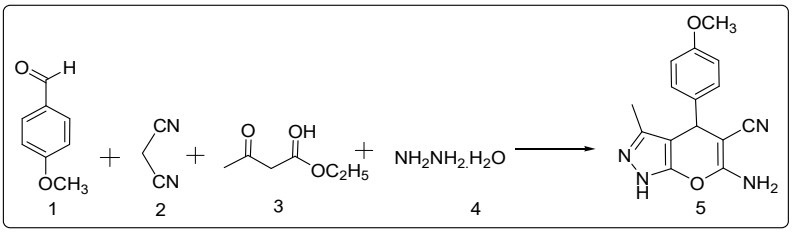
6-Amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile ***(5m)***. FT-IR (KBr) ν_{max} (cm^{-1}): 3337, 3224, 3117, 2195, 1652, 1525, 1491, 1400, 1349, 805, 733; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80 (s, 3H, CH_3), 4.65 (s, 1H, C-H), 6.94 (s, 2H, NH_2), 7.13-7.24 (m, 2H, Ar-H), 7.15-7.23 (m, 2H, Ar-H), 12.13 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.2, 35.9, 57.5, 97.9, 115.5, 121.2, 129.7, 136.1, 141.1, 155.1, 160.2, 161.3, 162.6 ppm.

6-Amino-4-(4-bromophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile ***(5g)***. FT-IR (KBr) ν_{max} (cm^{-1}): 3397, 3309, 3183, 2190, 1644, 1599, 1402, 1073, 798; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (s, 3H, CH_3), 4.63 (s, 1H, C-H), 6.95 (s, 2H, NH_2), 7.13-7.17 (m, 2H, Ar-H), 7.51-7.54 (m, 2H, Ar-H), 12.15 (s ,1H,NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.2, 36.1, 57.1, 97.6, 120.2, 121.1, 130.2, 131.8, 136.1 ,144.3, 155.1, 161.4 ppm.

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, C-H), 6.82 (s, 2H, -NH2), 7.04 (m, 2H, Ar-H), 7.12 (m, 2H, Ar-H), 12.06 (s, 1H, -NH) ppm; ^{13}C NMR (DMSO-d_6, 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

To optimize the reaction condition 4-methoxy benzaldehyde, malononitrile, ethyl acetoacetate and hydrazine was chosen as model reaction substrate (Scheme 1). Initially, reaction was carried out without any catalyst in aqueous media and it observed that only Knovengel product was formed in lesser amount which proves the need of catalyst for the reaction. In order to evaluate the effect of catalyst, various type of naturally occurring acids and their salts was incorporated as a catalyst.



Scheme 1. Model reaction.

Table 1. The effects of various catalysts for the synthesis of dihydroprano-[2,3-*c*]-pyrazoles[a].

Entry	Catalyst	Solvent	Yield (%)[b]
1	Without catalyst	Water	NR[c]
2	Tannic acid	Water	40
3	Tartaric acid	Water	45
4	Sodium tartarate	Water	58
5	Sodium citrate	Water	65
6	Sodium lactate	Water	70
7	Sodium ascorbate	Water	NR
8	Sodium succinate	Water	35
9	Sodium chloride	Water	60
10	Sodium gluconate	Water	92
11	Glucinic acid (50%)	Water	75
12	Sodium gluconate	Ethanol	78
13	Sodium gluconate	Methanol	60
14	Sodium gluconate	DMF	50
15	Sodium gluconate	Acetonitrile	45
16	Sodium gluconate	n-hexane	22
17	Sodium gluconate	Toulene	26

[a]Reaction conditions: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol), ctalyst (15 mol%), in respective solvent (10 mL) at reflux temperature for 2 h**.** [b]Isolated yields. [c]NR = No reaction.

It observed that the use of tannic acid (Table 1, entry 2) as catalyst, gives a very less yield. However tartaric acid and its sodium salt give the yields 45% and 58%, respectively (Table 1, entry 3, 4). In case of sodium citrate and sodium lactate the yield was found to be moderate (65% and 70%) in compared to sodium succinate (35%) and sodium ascorbate (0%) (Table 1, entry 7 and 8). It was found that reaction seems to precede smoothly sodium chloride. (Table 1, entry 9) When Sodium gluconate was used as a catalyst, the reaction was completed in a shorter time with excellent yield of desired product. The reported work on gluconic acid aqueous solution (GAAS) [42-44] encouraged us to check the catalytic role of GAAS for the synthesis of dihydropyrano[2,3-c]pyrazole. The use of (GAAS 50%) revealed that sodium gluconate give better yield than gluconic acid solution.

As the selection of an appropriate reaction medium is of crucial importance for the success of the reaction so, the model reaction was screened by various solvents in the presence of sodium gluconate at same reaction condition. The results show the effectiveness of solvents on the product yield. The use of n-hexane and toluene, gave poor yield (Table 1, entries, 16, 17**)**. Polar protic solvents like ethanol, methanol gave a moderate yield as compare to polar aprotic solvents (DMF, acetonitrile) (Table 1, entries, 12-15). It may possible that the slight solubility of sodium gluconate in ethanol and methanol affects the catalytic activity and polar protic solvents favour the formation of Knovenagel condensation and cyclization type of reactions. The best conversion was observed when the reaction was performed in water (Table 1, entry 10) due to the complete solubility of catalyst in water. Based on these results; water selected as the medium for the further analysis.

It is observed that the low temperature was not favourable to complete the reaction. The yield of reaction was obtained as 70% after 6 h at room temperature (Table 2, entry 1). Increase of temperature up to reflux level reveals that reflux condition was suitable to get proficient yield in short time. To evaluate the exact amount of catalyst under the same reaction condition, the reaction was carried out in 10 mol% and 5 mol%, it observed that reaction proceeds rapidly at 15 mol% catalyst in 20 min in excellent yield; decrease amount of catalyst up to 10 mol% has also given the same result but at 5 mol% yield decreased up to 80 % in one hour. So, 10 mol% of catalyst was taken as an optimum catalyst concentration.

Table 2. Impact of temperature and amount of catalyst[a].

Entry	Catalyst (mol %)	Temperature (°C)	Time (min/h)	Yield[b] (%)
1.	15	RT	6hr	70
2.	15	40	3hr	78
3.	15	60	2hr	80
4.	15	80	40 min	86
5.	15	Reflux	20 min	92
6.	10	Reflux	20 min	92
7.	05	Reflux	1 hr	80

[a]Reaction condition: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), ethylacetoacetate (1 mmol), sodium gluconate as catalyst in water (10 mL). [b]Isolated yield.

It can be hypothesized that the solubility of sodium gluconate in water balances the reaction in support of product formation by enhancing the rate of reaction to deliver the desired product in short reaction time.

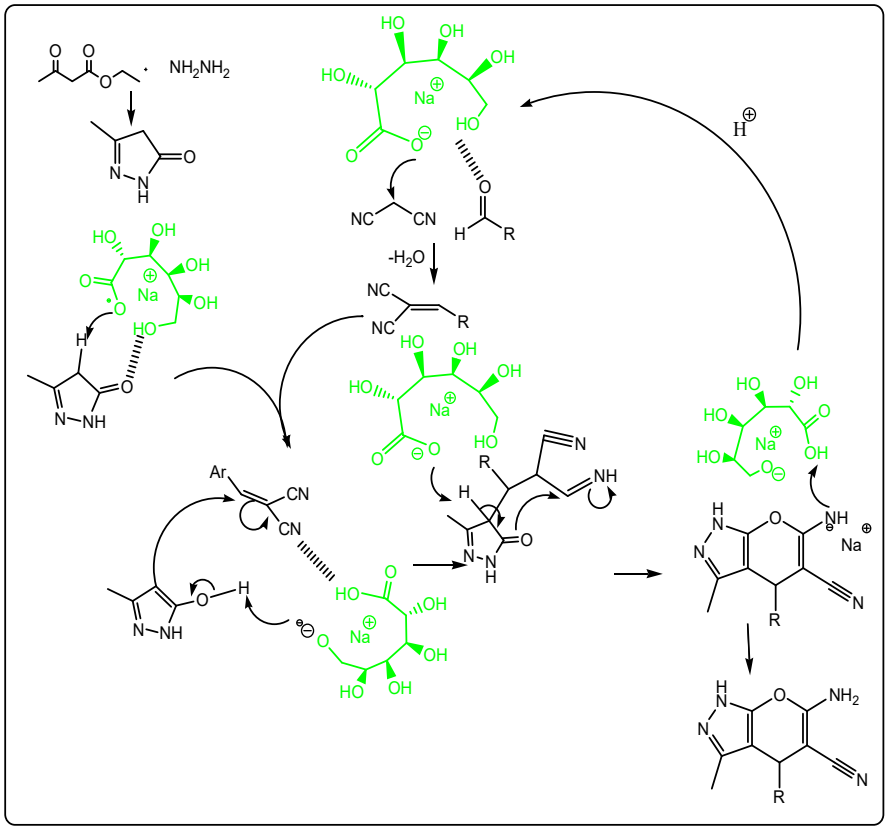
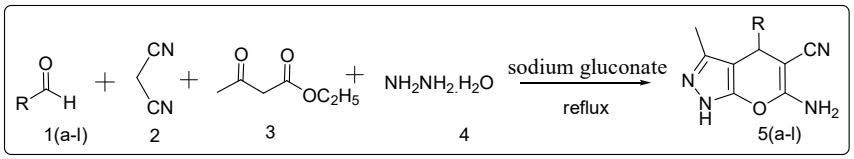


Figure 2. Possible mechanism for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives.

As a part of green chemistry the reusability is a vital aspect, thus in order to recover the catalyst the water was evaporated and the recycled catalyst was used for the next run and

showed that it was able to carry out the same reaction up to three runs without loss of its efficiency which reflects the good turnover number, i.e. maximum use that can be made of a catalyst for a special reaction under defined conditions by a number of molecular reactions or reaction cycles.

Table 3. Synthesis of dihydropyrano [2, 3-*c*]pyrazole in the presence of sodium gluconate in water at reflux temperature[a].



Entry	R	Time (min)	Yield (%)[b]	Mp (°C) [Ref.]
5a	Ph	15	90	240-245 (243-245) [25]
5b	4-OCH_3-Ph	20	92	208-210 (210-212) [25]
5c	Thiophene	30	82	222-224 (216-217) [25]
5d	4-N,N-dimethyl-Ph	40	85	162-166 (168-170) [23]
5e	3-methoxy,4-hydroxy-Ph	45	85	238-240 (238-240) [23]
5f	4-Cl-Ph	20	91	233-236 (236-238) [23]
5g	4-Br-Ph	25	90	180-182 (178-180) [23]
5h	4-Me-Ph	20	88	204-206 (206-208) [23]
5i	2-Cl-Ph	15	85	242-244 (245-246) [25]
5j	Aceatldehyde	45	82	158-160 (155-157) [32]
5k	2-methoxy-Ph	20	85	250-252 (249-250) [25]
5l	4-OH-Ph	20	88	220-222 (220-223) [32]
5m	4-F-Ph	25	90	246-248 (244-246) [32]

[a]Reaction condition*:* aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol), sodium gluconate (10 mol%) as a a catalyst in 10 mL of water at reflux temperature.[b]Isolated yield.

Table 4. Various reports for the synthesis of dihydropyrano[2,3-*c*]pyrazole.

S. No.	Catalyst	Reaction condition	Time (min)	Yield (%)	Ref.
1	Glycerol	80-100 °C	100	91	45
2	(TBD)-anchored mesoporous silica nanoparticle	Reflux	35	90	46
3	Morpholine triflate	Reflux	420	85	23
4	TUD	80	45	95	47
5	Lactic acid	RT	25	95	29
6	[Hmim]HSO4	50	40	87	48
7	β-cyclodextrin	80	20	86	49
8	Cocamidopropyl betaine (CAPB)	50-60	9	88	50
9	Trichloroacetic acid	100	9	91	51
10	Sodium Gluconate	Reflux	20	92	This work

The importance and relationship of obtained activity of sodium gluconate can be explained with the concept of Brønsted acids and base. In continuation of our study on green catalyst we have contended the catalytic activity of sodium gluconate as Brønsted base. There are number of reports are available which demonstrated the salt of acid as a Brønsted base to serve as active

catalysts for a variety of synthetically useful reactions in organic chemistry. However, no combination of sodium gluconate with other reactant in water at reflux temperature up to 5 hours has provided any side products.

An acceptable mechanism is shown in Figure 2. According to this mechanism the carboxylate ion of gluconic acid species remove the hydrogen of malononitrile species and 3-methyl-1H-pyrazol-5(4H)-one to get the enol form which will further cyclize with arylidinemalononitrile, produces the desired product.

After optimization of reaction condition, the practical applicability and scope of reaction was checked to large scale for different aldehydes by carrying out the reaction at multiple of milligram level of reagents. The desired products were obtained in good yield. The scalability, suitability and easy commercial availability of catalyst make this approach as flexible and alternative to the best of other reported procedures. The obtained products were characterized by spectral data and compared (MS, NMR) with authentic sample. In order to recover the catalyst, the filtrate was dried under reduced pressure and recovered catalyst was washed with diethyl ether and reused for next reaction. Degradation of sodium gluconate was not observed during recycling for three cycles of reactions.

In order to clarify the use of sodium gluconate instead of gluconic acid, an explanation can be done by targeting the features of gluconic acid which is normally existing in aqueous solution, which is a compilation of an equilibrium mixture of acid and the γ and δ-lactones, can be formed by concentration and temperature parameters by exact mode of reaction can't be predicted for the said reaction. In addition to these criteria as we are going towards the usage of eco friendly strategy and avoidance of organic solvent, the present methodology eliminates the process of extraction in isolating the product, which is occurred during the use of Gluconic acid aqueous solution. To show the advatages of our method here we have compared the recent reports in the literature on the synthetic methodologies of the aim products, which mainly have used as the same strategy of one pot four component reactions, are given in Table 4.

CONCLUSION

Finally, we report a simple, efficient and eco-friendly alternative way to synthesize dihydropyrano[2,3-c]pyrazole by using sodium gluconate as a catalyst in aqueous media. The capability of catalyst to be applicable over wide range of substrate with respect to structure and quantity is most important in the greener catalytic protocol of reaction. This technique of applying readily available bio-based catalyst offers many advantages like simple procedure, easy isolation of product without any separation technique, shorter reaction time with excellent yield of products. The use of sodium gluconate as non-toxic, biodegradable and easily available catalyst makes this method green.

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