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Sodium ascorbate as an expedient catalyst for green synthesis of polysubstituted 5-aminopyrazole-4-carbonitriles and 6-amino-1,4-dihyd ropyrano[2,3-*c*]pyrazole-5-carbonitriles

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Abstract Sodium ascorbate (SA) was used as a safe catalyst for the synthesis of 5-aminopyrazole-4-carbonitriles from the one-pot three-component cyclocondensation (3-CC) of aldehydes, phenylhydrazine, and malononitrile at 50 °C. This 3-CC proceeds in a mixture of ethanol–water as a green reaction medium to give the desired densely functionalized pyrazoles in good to high yields. 6-Amino-1,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitriles were also synthesized in the presence of SA via an eco-friendly and simple four-component cyclocondensation (4-CC). This 4-CC performed in refluxing water as a green medium and dihydropyrano-[2,3-c] pyrazole products were obtained in excellent yields and relatively shorter reaction times. These environmentally friendly multicomponent cyclocondensations offer some interesting advantages, including time-saving, easily available starting materials, mild conditions, minimizing the amount of waste, good atom efficiency, avoiding hazardous organic solvents or catalysts, and the ease of the work-up.

Keywords 5-Aminopyrazole-4-carbonitrile · 6-Amino-1,4-dihydropyrano-[2,3-c] pyrazole-5-carbonitrile · Green · Phenylhydrazine · Hydrazine · Sodium ascorbate

Introduction

A pyrazole unit possessing two adjacent nitrogen atoms in a five-membered heteroaromatic ring is a compound which shows a wide range of interesting biological activities, such as antimicrobial, anti-inflammatory, analgesic, antiviral, antibacterial, anticancer, anticonvulsant, cardiovascular, antihypertensive, antipyretic,

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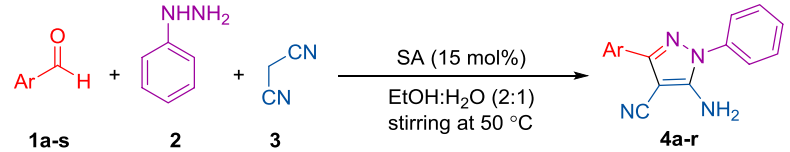
cytotoxic, and antitubercular activities [1–9]. Pyrazoles are also known as key building blocks and structural motifs in the synthesis of pesticides, UV stabilizers, cosmetic colorings, insecticides, fungicides, and ligands in coordination chemistry, as well as antimalarial and antileishmanial agents [10–12]. Aminopyrazole as a type of pyrazole has a widespread distribution in organic synthesis for the construction of compounds with promising biological activity and as drug candidates [13–16]. Given such medicinal significance of these heterocycles, the methods developed for the synthesis of polysubstituted pyrazoles employ different catalysts. Some of these include the use of ionic liquids [17], molecular iodine [18–20], piperidinium acetate [21], $Cu(OAc)_2$ [22], [Cp*$RhCl_2$] and NaOAc [23], graphene oxide-TiO_2 (GO-TiO_2) [24], oxone [25], CuO/ZrO_2 [26], piperidine [27], eosin Y under atmospheric oxygen [28], 1-methylimidazolium trinitromethanide {[HMIM]$C(NO_2)_3$} [29], cerium (IV) ammonium nitrate [30], silica chloride [31], alum [32], $Yb(PFO)_3$ [33], palladium and copper [34], CuBr-bpy [35], and AgOTf [36]. Moreover, PEG-400 and water using ultrasound waves [37] is another synthetic method for the construction of these significant heterocyclic scaffolds.

On the other hand, 1,4-dihydropyrano[2,3-*c*]pyrazole and its derivatives are another important fused heterocyclic frameworks that have many applications in pharmaceutical chemistry. In many reports, 1,4-dihydropyrano[2,3-*c*]pyrazoles are introduced as compounds that have attractive biological properties, such as antimicrobial, anti-inflammatory, analgesic, anticancer, vasodilator, human Chk1 kinase inhibitor, and molluscicidal activities. In addition to using them in pharmaceutical chemistry, 1,4-dihydropyrano[2,3-*c*]pyrazoles are recognized as antifungal agents [38–40].

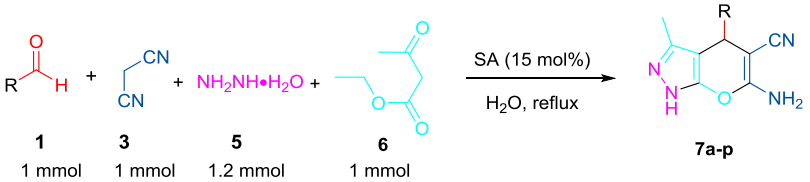
The most well-known method for the synthesis of the pyrano[2,3-*c*]pyrazole scaffold is the four-component cyclocondensation (4-CC) of aldehydes, hydrazine derivatives, ethyl acetoacetate, and malononitrile. Up to now, the above-mentioned 4-CC has been catalyzed by various catalysts, including *β*-cyclodextrin (*β*-CD) [41], cocamidopropyl betaine (CAPB) [42], lipase [43], urea [44], ZrO_2 nanoparticles [45], cetyltrimethylammonium chloride (CTACl) [46], NaOH [47], poly(4-vinylpyridine) [48], meglumine [49], tetraethylammonium bromide (TEABr) [50], silica-bonded *N*-propylpiperazine sodium *n*-propionate (SBPPSP) [51], nickel nanoparticles [52], *β*-cyclodextrin-SO_3H [53], silica sodium carbonate (SSC) [54], NaOAc [55], methyltriphenylpho-sphonium bromide [56], iodine [57], tungstate sulfuric acid [58], molecular sieves [59], isonicotinic acid [60], 1,4-diazabicyclo[2.2.2] octane (DABCO) [61], phase transfer catalyst [62], thiourea dioxide (TUD) [63], *p*-toluenesulfonic acid (*p*-TsOH) [64], phenylboronic acid [65], starch-sulfuric acid (SSA) [66], sodium benzoate [67], and the juice of *Citrus limon* [68].

Multistep one-pot processes in organic synthetic chemistry that generate a single product from more than two substrates are called multicomponent reactions (MCRs) [69, 70]. MCRs have a special place in modern organic chemistry due to high efficacy, the rapid achievement of high levels of complexity and diversity of molecules, time-saving operation, mild conditions, simplicity, environmental friendliness, elimination of waste production, atom economy, energy efficiency, fewer side reactions, costly purification processes, the avoidance of changing the conditions during the implementation of the reaction, and excellent functional group compatibility.



Ar: C_6H_5 (**1a**), 4-Me-C_6H_4 (**1b**), 4-MeO-C_6H_4 (**1c**), 4-HO-C_6H_4 (**1d**), 4-Me_2N-C_6H_4 (**1e**), 4-NO_2-C_6H_4 (**1f**), 4-Cl-C_6H_4 (**1g**), 4-Br-C_6H_4 (**1h**), 4-F-C_6H_4 (**1i**), 4-HO-3-MeO-C_6H_3 (**1j**), 3,4-diMeO-C_6H_3 (**1k**) 3-NO_2-C_6H_3 (**1l**), 2-Cl-C_6H_3 (**1m**), 2-HO-C_6H_3 (**1n**), 2-MeO-C_6H_3 (**1o**) 2-NO_2-C_6H_3 (**1p**), 2-thienyl (**1q**), 3-indolyl (**1r**)

Scheme 1 Reaction of aldehydes (**1a**–**s**) with phenylhydrazine (**2**) and malononitrile (**3**) for the synthesis of highly functionalized 5-aminopyrazole-4-carbonitriles (**4a**–**r**) in the presence of sodium ascorbate (SA)



R: C_6H_5 (**1a, 7a**), 4-Me-C_6H_4 (**1b, 7b**), 4-MeO-C_6H_4 (**1c, 7c**), 4-HO-C_6H_4 (**1d, 7d**), 4-Me_2N-C_6H_4 (**1e, 7e**), 4-NO_2-C_6H_4 (**1f, 7f**), 4-Cl-C_6H_4 (**1g, 7g**), 4-HO-3-MeO-C_6H_3 (**1j, 7h**), 3,4-diMeO-C_6H_3 (**1k, 7i**), 3-NO_2-C_6H_3 (**1l, 7j**), 2-Cl-C_6H_3 (**1n, 7k**), 2-NO_2-C_6H_3 (**1q, 7l**), 2-thienyl (**1r, 7m**), 2,4-diCl-C_6H_3 (**1t, 7n**), butyraldehyde (**1u, 7o**), isobutyraldehyde (**1v, 7p**)

Scheme 2 Four-component synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles (**7a**–**p**) catalyzed by SA

Also, carrying out of a MCR with a fuscous to avoid hazardous solvents and catalysts has also received considerable attention [71–80]. Thus, according to the points mentioned above, the development of efficient and facile methods for the synthesis of aminopyrazoles and 1,4-dihydropyrano[2,3-*c*]pyrazoles is still a challenge in organic synthesis. Due to a variety of applications of the described heterocycles, and in continuation of our previous work to develop green chemistry [71–75], in this contribution, the catalytic performance of sodium ascorbate (SA) as the basic organocatalyst has been explored in the rapid and efficient synthesis of highly functionalized 5-aminopyrazole-4-carbonitriles (Scheme 1) and 1,4-dihydropyrano[2,3-*c*]pyrazole heterocyclic compounds (Scheme 2) in green solvents through MCRs. To our knowledge, SA has not been used as the catalyst in the synthesis of 5-aminopyrazole-4-carbonitriles and 1,4-dihydropyrano[2,3-*c*]pyrazoles under aqueous conditions.

SA is a well-known anti-oxidant, which is often added to meat products and is capable of reducing a variety of oxidative compounds, especially free radicals [81–84]. Furthermore, SA as a safe, green, and effective organocatalyst has been used for the Knoevenagel condensation of aldehydes with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum′s acid) [85], the synthesis of triazole ring by “click reaction”

strategy [86–88], and the synthesis of isoxazoles [89, 90]. It has also been applied as a reducing agent in the synthesis of copper nanoparticles [91–93].

Experimental

General

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, except liquid aldehydes, which were distilled before use. All the solvents were freshly dried and distilled before use. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. Melting points of the products were measured on a Buchi 510 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were acquired with a Bruker Avance DRX-400 at 400 MHz in the appropriate solvent ($CDCl_3$ or DMSO-d_6) at room temperature (rt). FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. The development of the reactions and purity of the products were monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure for the 3-C synthesis of polysubstituted 5-aminopyrazole-4-carbonitriles (4a–r)

A mixture of equimolar quantities of aryl/heteroaryl aldehyde (**1**, 1 mmol), phenylhydrazine (**2**, 1 mmol), malononitrile (**3**, 1 mmol), and 15 mol% SA in a mixture of ethanol:water (2:1, 5 mL) was stirred at 50 °C. After completion of the reaction (monitored by TLC analysis), the reaction mixture was cooled to rt and poured into water. The filtered and the residue was taken in hot EtOH and filtered again to separate the product as filtrate from the catalyst. The product was formed by cooling the filtrate or evaporation of the solvent. If necessary, further purification was performed by recrystallization from hot ethanol to give desired compounds in good to high yields. NMR data for some target compounds are as follows:

5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile **(4a)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (*t*, *J* = 8.0 Hz, 1H), 7.02 (*d*, *J* = 7.9 Hz, 2H), 7.14 (*d*, *J* = 7.8 Hz, 2H), 7.19 (*t*, *J* = 7.9 Hz, 1H), 7.42 (*t*, *J* = 7.6 Hz, 2H), 7.68 (*d*, *J* = 8.5 Hz, 2H), 7.81 (*s*, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.8, 113.4, 120.4, 126.5, 127.9, 128.1, 129.7, 135.8, 137.9, 146.2, 150.4, 156.4.

4-Amino-3-(4-(dimethylamino)phenyl)-1-phenyl-1H-pyrazole-5-carbonitrile **(4e)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (*s*, 6H), 7.16 (*s*, 2H), 7.24–7.28 (*m*, 2H), 7.63 (*s*, 1H), 7.66–7.81 (*m*, 2H), 7.79–7.82 (*m*, 4H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 41.2, 108.4, 113.5, 115.4, 123.2, 125.5, 127.9, 128.2, 128.6, 129.5, 137.3, 144.1, 151.2.

5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile **(4f)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (*s*, 1H), 7.21–7.32 (*m*, 2H), 7.75–7.78 (*m*, 3H), 7.81 (*d*, *J* = 7.6 Hz, 2H), 8.02 (*s*, 1H), 8.25 (*d*, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.4, 113.5, 123.4, 122.8, 129.9, 130.8, 131.6, 135.3, 138.8, 146.4, 149.7, 156.5.

5-Amino-3-(4-hydroxy-3-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile **(4j)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.92 (*s*, 3H), 6.85–6.93 (*m*, 2H), 7.07 (*d*, *J* = 7.1 Hz, 1H), 7.12 (*d*, *J* = 8.2 Hz, 2H), 7.32 (*d*, *J* = 7.4 Hz, 2H), 7.41 (*s*, 1H), 7.62 (*s*, 1H), 9.91 (*s*, 1H), 10.81 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 113.5, 114.6, 118.9, 119.0, 119.4, 120.5, 131.8, 131.9, 133.0, 133.3, 138.7, 140.3, 150.5, 157.6.

5-Amino-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile **(4l)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (*t*, *J* = 7.2 Hz, 1H), 7.20 (*d*, *J* = 8.4 Hz, 2H), 7.36 (*t*, *J* = 7.5 Hz, 2H), 7.54 (*t*, *J* = 7.9 Hz, 1H), 7.76 (*s*, 1H), 7.89 (*s*, 1H), 8.02 (*d*, *J* = 7.5 Hz, 1H), 8.15 (*d*, *J* = 8.0 Hz, 1H), 8.46 (*s*, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.2, 113.5, 121.2, 121.5, 123.1, 129.8, 130.0, 131.9, 134.1, 137.8, 144.5,149.3, 156.3.

5-Amino-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-4-carbonitrile **(4q)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (*t*, *J* = 7.3 Hz, 1H), 7.05 (dd, *J* = 3.6, 4.9 Hz, 1H), 7.12 (*t*, *J* = 7.4 Hz, 2H), 7.31 (*d*, *J* = 5.0 Hz, 1H), 7.42 (*d*, *J* = 7.4 Hz, 2H), 7.51 (*d*, *J* = 4.8 Hz, 1H), 7.56 (*s*, 1H), 7.84 (*s*, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.2, 114.2, 122.4, 120.6, 126.9,127.8, 128.7, 129.8, 132.7, 140.9, 142.9, 155.1.

General procedure for the 4-C synthesis of 6-amino-1,4-dihydropyrano-[2,3-c] pyrazole-5-carbonitriles (7a-p)

A mixture of aryl/heteroaryl aldehyde (**1**, 1 mmol), malononitrile (**3**, 1 mmol), hydrazine hydrate (**5**, 1 mmol), ethyl acetoacetate (**6**, 1 mmol), and 15 mol% SA in water (5 mL) was stirred under the refluxing condition. After completion of the reaction as indicated by TLC analysis, the reaction mixture was cooled to rt and the precipitated products were formed. The precipitated products were filtered off and then were taken in hot EtOH or chloroform and filtered again to separate the products as filtrate from the catalyst (SA insoluble in chloroform and very slightly soluble in water). The product was formed by cooling the filtrate or evaporation of solvent. The

solid products were further purified through recrystallization in ethanol. NMR data for some 6-amino-1,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitriles are as follows:

*6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile***(7a)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.78 (*s*, 3H), 4.57 (*s*, 1H), 6.87 (*s*, 2H), 7.17–7.24 (*m*, 3H), 7.27–7.31 (*m*, 2H), 12.06 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.7, 36.2, 57.2, 97.7, 126.7, 127.6, 127.8, 128.8, 135.7, 144.6, 154.8, 160.8.

6-Amino-4-(4-methylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7b)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 2.34 (*s*, 3H), 4.63 (*s*, 1H), 6.84 (*s*, 2H), 7.14 (*d*, *J* = 8.4 Hz, 2H), 7.34 (*d*, *J* = 8.4 Hz, 2H), 12.18 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.1, 22.5, 35.5, 56.5, 113.2, 118.0, 125.3, 128.2, 132.4, 135.8, 139.2, 155.6, 161.9.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7c)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 3.74 (*s*, 3H), 4.50 (*s*, 1H), 6.86 (*s*, 2H), 7.31 (*d*, *J* = 8.3 Hz, 2H), 7.77 (*d*, *J* = 8.3 Hz, 2H), 12.09 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.6, 37.6, 55.4, 58.4, 98.2, 114.3, 121.3, 129.7, 145.5, 147.9, 155.4, 159.7, 162.6.

6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7d)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 4.47 (*s*, 1H), 6.68 (*d*, *J* = 8.4 Hz, 2H), 6.74 (*s*, 2H), 7.94 (*d*, *J* = 8.4 Hz, 2H), 9.26 (*s*, 1H), 12.03 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.7, 35.5, 57.8, 98.0, 115.1, 120.8, 128.4, 134.7, 135.5, 154.7, 156.0, 160.6.

6-Amino-4-(4-(dimethylamino)phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole5-carbonitrile **(7e)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 2.85 (*s*, 6H), 4.45 (*s*, 1H), 6.66 (*d*, *J* = 8.6 Hz, 2H), 6.74 (*s*, 2H), 6.96 (*d*, *J* = 8.6 Hz, 2H), 12.02 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.7, 35.3, 58.0, 98.2, 112.3, 120.9, 127.9, 129.5, 132.0, 135.4, 149.2, 154.8, 160.5.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7f)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.81 (*s*, 3H), 4.83 (*s*, 1H), 7.05 (*s*, br, 2H), 7.46 (*d*, 2H, *J* = 8.4 Hz), 8.23 (*d*, 2H, *J* = 8.4 Hz), 12.14 (*s*, 1H); ^{13}C NMR (100 MHz,

DMSO-d_6): δ = 10.3, 34.2, 60.5, 98.4, 120.8, 124.0, 129.3, 136.0, 146.5, 149.3, 151.8, 161.5.

6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7g)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 4.62 (*s*, 1H), 6.93 (*s*, 2H), 7.19 (*d*, *J* = 8.0 Hz, 2H), 7.36 (*d*, *J* = 8.0 Hz, 2H), 12.11 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.7, 35.7, 56.8, 97.0, 120.5, 128.2, 129.2, 131.3, 135.6, 143.2, 154.7, 160.8.

6-Amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole5-carbonitrile **(7h)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.82 (*s*, 3H), 3.71 (*s*, 3H), 4.48 (*s*, 1H), 6.54 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.73 (*t*, *J* = 8.8 Hz, 2H), 6.77 (*s*, 2H), 8.82 (*s*, 1H), 12.03 (*s*, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.8, 35.8, 55.6, 57.6, 97.9, 111.6, 115.4, 119.7, 135.4, 135.6, 145.2, 147.3, 160.7

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7i)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.83 (*s*, 3H), 3.70 (*s*, 3H), 3.84 (*s*, 3H), 4.55 (*s*, 1H), 6.70 (dd, *J* = 2.0, 7.5 Hz, 1H), 6.76 (*d*, *J* = 2.0 Hz, 1H), 6.81 (*s*, 2H), 6.88 (*d*, *J* = 8.3 Hz, 1H), 12.07 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.8, 35.8, 55.4, 57.3, 97.7, 111.2, 111.6, 119.6, 120.8, 135.6, 136.9, 147.5, 148.5, 154.8, 160.7.

6-Amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7j)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.82 (*s*, 3H), 4.88 (*s*, 1H), 7.06 (*s*, 2H), 7.63–7.69 (*m*, 2H), 8.03 (*s*, 1H), 8.14 (*m*, 1H), 12.22 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.2, 36.0, 56.6, 97.2, 120.9, 122.3, 122.5, 130.8, 134.8, 136.2, 147.3, 148.4, 155.1, 161.6.

6-Amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7k)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.80 (*s*, 3H), 5.17 (*s*, 1H), 7.06 (*s*, 2H), 7.26 (*d*, *J* = 7.3 Hz, 1H), 7.32–7.44 (*m*, 2H), 7.49 (dd, *J* = 1.3, 7.8 Hz, 1H), 12.23 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.5, 33.2, 55.6, 96.8, 120.4, 127.8, 128.6, 129.5, 130.7, 131.9, 135.4, 141.1, 154.8, 161.3.

6-Amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7l)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (*s*, 3H), 5.21 (*s*, 1H), 7.06 (*s*, 2H), 7.35 (*d*, *J* = 8.0 Hz, 1H), 7.48 (*t*, *J* = 7.4 Hz, 1H), 7.65 (*t*, *J* = 7.6 Hz, 1H), 7.84 (*d*, *J* = 8.0 Hz, 1H), 12.02 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.2, 29.2, 57.2, 118.1, 120.3, 126.8, 129.5, 132.5, 134.5, 136.7, 138.6, 150.3, 155.6, 165.2.

6-Amino-3-methyl-4-(thiophen-2-yl)-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **(7m)**

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.88 (*s*, 3H), 4.94 (*s*, 1H), 6.84–6.91 (*m*, 4H), 7.29–7.32 (*m*, 1H), 12.06 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.9, 30.5, 57.5, 97.8, 121.0, 124.6, 125.0, 126.8, 136.4, 149.6, 153.8, 161.1.

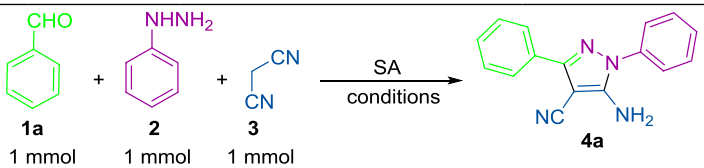
Results and discussion

Our initial test reaction was run by the treatment of benzaldehyde (**1a**) with phenylhydrazine (**2**) and malononitrile (**3**) without any catalyst in a mixture of ethanol–water (2:1, v:v) at rt and 50 °C for 30 min. The reaction did not occur in these tests (Table 1, entries 1 and 2). When catalytic amounts of SA was added to the same reaction mixture at 50 °C, the desired product (**4a**) was isolated with moderate yield (70%) after 30 min (Table 1, entry 3). After achieving this encouraging result, the reaction conditions were then screened with the aim of optimizing the yield of **4a**. It was observed that **4a** could be obtained in 98% yield when SA (15 mol%) was subjected to the reaction in refluxing ethanol–water for 10 min (Table 1, entry 5). Further increase of the amount of SA had no significant beneficial effect on the reaction (Table 1, entry 6). There were no satisfactory results from the reactions at other temperatures (Table 1, entries 7–11). The same reaction had no significant development in other solvents such as water, ethanol, dichloromethane (DCM), dimethylformamide (DMF) and ethyl acetate (Table 1, entries 12–16). Also, running the reaction in solvent-free conditions did not improve in yield (Table 1, entry 17).

Having established the optimal conditions for the synthesis of **4a**, to extend the catalyst performance, a range of available aldehydes (**1a**–**r**) were reacted with phenylhydrazine (**2**), and malononitrile (**3**) under optimized reaction condition. The results are summarized in Table 2. Both electron-deficient, electron-rich, and heteroaromatic aldehydes were similarly viable, affording the products (**4a**–**r**) in good to high yields.

After the success of SA in the synthesis of functionalized pyrazoles (**4a**–**r**), we decided to explore the catalytic activity of SA in the preparation of 1,4-dihydropyrano[2,3-*c*]pyrazoles. In this regard, we tried to achieve the best reaction conditions. For this purpose, 4-CC of vanillin (**2j**), malononitrile (**3**), hydrazine monohydrate (**5**), and ethyl acetoacetate (**6**) was selected as a model reaction (Table 3). Excellent conversions of the starting compoundswere achieved and 98% yield of 6-amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]

Table 1 Optimization of the reaction conditions for the three-component synthesis of 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile (**4a**)



Entry	Catalyst loading/mol%	Solvent	Temp./°C	Isolated yields/%	Time/min.
1	–	EtOH:H_2O (2:1)	rt	Trace	30
2	–	EtOH:H_2O (2:1)	50	Trace	30
3	5	EtOH:H_2O (2:1)	50	70	30
4	10	EtOH:H_2O (2:1)	50	75	16
5	**15**	**EtOH:H_2O (2:1)**	**50**	**98**	**10**
6	20	EtOH:H_2O (2:1)	50	99	9
7	15	EtOH:H_2O (2:1)	60	96	10
8	15	EtOH:H_2O (2:1)	70	95	19
9	15	EtOH:H_2O (2:1)	25	90	120
10	15	EtOH:H_2O (2:1)	30	92	120
11	15	EtOH:H_2O (2:1)	40	93	80
12	15	H_2O	50	86	10
13	15	EtOH	50	90	10
14	15	DCM	50	50	10
15	15	DMF	50	57	10
16	15	EtOAc	50	32	10
17	15	–	50	25	10

Optimized conditions are shown in bold

pyrazole-5-carbonitrile (**7h**) was obtained when the reaction was carried out in refluxing water in the presence of 15 mol% SA in 4 min (entry 5).

Under the optimal conditions, namely SA (15 mol%) as the catalyst, water as a solvent, and reflux, various substituted aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents and aliphatic aldehydes (**1u**–**v**) were converted into the expected 1,4-dihydropyrano[2,3-*c*]pyrazoles (**7a**–**p**) in good to excellent yields. The results are summarized in Table 4. Benzaldehydes with electron-donating and electron-withdrawing substitutions, heteroaryl aldehydes, and aliphatic aldehydes worked well in this 4-CC. All the products synthesized in this 4-CC are precipitated in the reaction vessel after cooling. The targeted compounds were then obtained in high yield without any chromatographic purification methods.

The possible formation mechanism of densely functionalized pyrazoles is suggested in Scheme 3. During the reaction, the aldehydes are activated, and the Knoevenagel products (**10**) are formed via reaction of anion **8** with activated aldehydes

Table 2 Sodium ascorbate (SA) promoted three-component synthesis of highly functionalized pyrazole derivatives (**4a–r**) via Scheme 1

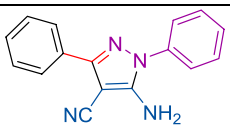
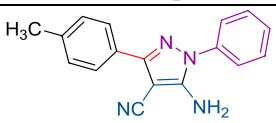
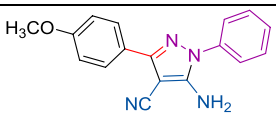
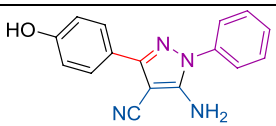
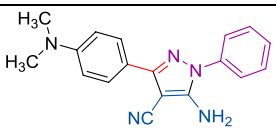
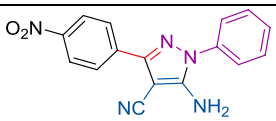
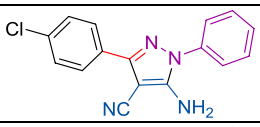
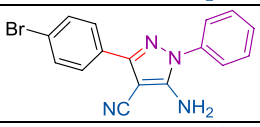
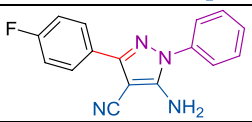
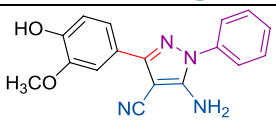
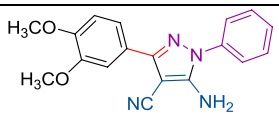
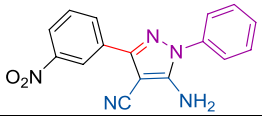
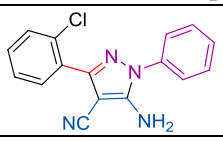
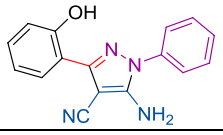
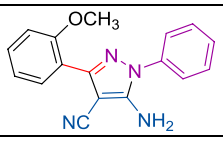
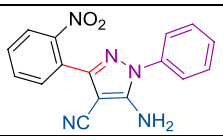
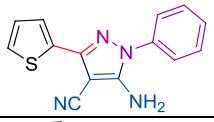
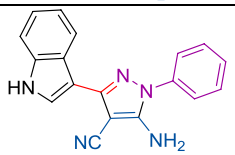
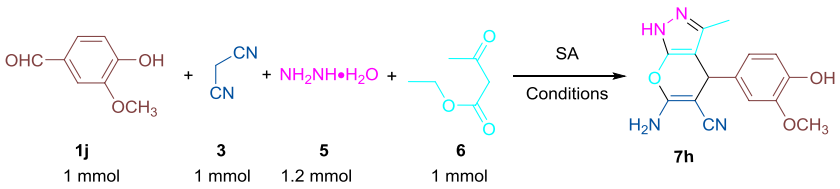
Comp. no	Structure of pyrazole derivatives	Time/min.	Isolated yields/%	m.p. /°C	
				Found	Lit. [17, 18, 29, 74]
4a		10	98	157–159	159–160
4b		13	95	117–118	118–120
4c		8	97	107–108	106–108
4d		12	95	208–210	209–211
4e		11	88	104	105–107
4f		10	90	156	164–166
4g		14	98	128	128–130
4h		15	96	164–165	163–165
4i		15	92	Oil	Oil
4j		10	98	120–121	120–121

Table 2 (continued)

Comp. no	Structure of pyrazole derivatives	Time/min.	Isolated yields/%	m.p. /°C	
				Found	Lit. [17, 18, 29, 74]
4k		13	95	120–122	120–123
4l		20	86	127–129	128–130
4m		15	92	Semi-solid	Semi-solid
4n		18	92	161–162	160–161
40		18	93	130–131	129–130
4p		20	88	159–161	160–162
4q		10	93	137–139	138–140
4r		14	91	224–225	223–225

(**6**). In the next step, the Michael addition occurred between **10** and **11** in the presence of SA, which gave intermediate **12**. After intramolecular cyclization and oxidation, final products (**4a**–**r**) were formed.

Table 3 Optimization of the reaction conditions for the four-component synthesis of 6-amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**7h**)



1j 1 mmol | **3** 1 mmol | **5** 1.2 mmol | **6** 1 mmol | **7h**

Entry	Catalyst loading/mol%	Solvent	Temp./°C	Isolated yields/%	Time/min.
1	–	EtOH	rt[a]	Trace	60
2	–	H_2O	Reflux	Trace	60
3	5	H_2O	Reflux	50	3
4	10	H_2O	Reflux	55	3
5	**15**	**H_2O**	Reflux	**98**	**4**
6	20	H_2O	Reflux	91	3
7	15	EtOH	Reflux	88	6
8	15	EtOH:H_2O (2:1)	Reflux	40	9
9	15	DCM	Reflux	72	12
10	15	DMF	Reflux	30	10
11	15	–	100 °C	53	50
12	15	H_2O	25 °C	50	40
13	15	H_2O	50 °C	67	15
14	15	H_2O	75 °C	70	10

Optimized conditions shown in bold

[a]The reaction was checked at r.t., 50, 80, 100, and 120 °C and the product did not form

Conclusions

In summary, SA has been found to be an efficient and environmentally benign catalyst for the synthesis of highly functionalized pyrazoles from aldehydes, phenylhydrazine, and malononitrile as well as 6-amino-1,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile derivatives from aldehydes, hydrazine, malononitrile, and ethyl acetoacetate in good to excellent product yields. The reactions proceed efficiently for the synthesis of highly substituted pyrazoles in an ethanol–water solvent system at 50 °C. Pyrano-[2,3-*c*]pyrazoles have also been synthesized in refluxing water as a friendly reaction medium. These protocols are a promising methodology from ecological and practical chemistry points of view. The simplicity of experimental procedures, the ready availability of reactants and catalyst, green reaction media, and safety of the catalyst makes this approach potentially useful for the synthesis of four-substituted pyrazoles and dihydropyrano-[2,3-*c*]pyrazoles.

Table 4 The SA catalyzed synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles (**7a–p**) via Scheme 2

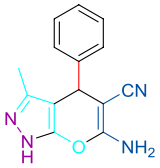
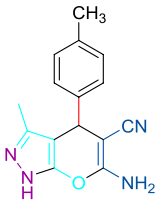
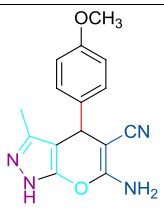
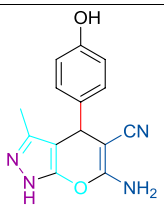
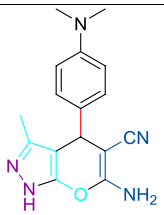
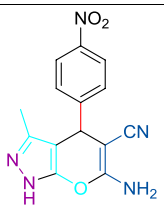
Comp. no	Structure of 1,4-dihydropyrano[2,3-c]pyrazole derivatives	Time/min	Isolated yields/%	m.p. /°C	
				Found	Lit. [42, 59, 60, 62, 75]
7a		9	88	242–244	244–246
7b		2	95	208–209	205–208
7c		3	90	211–213	208–211
7d		8	97	226–225	225–226
7e		3	86	217–219	217–219
7f		5	88	249–250	248–250

Table 4 (continued)

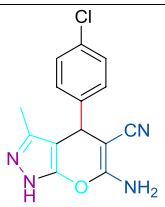
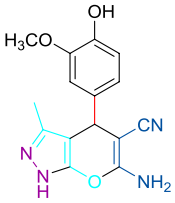
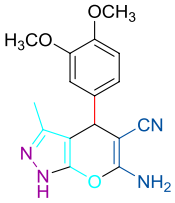
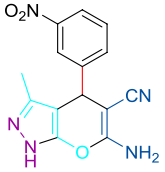
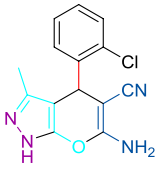
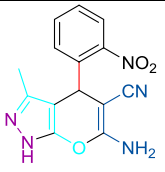
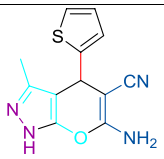
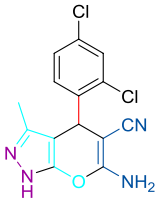
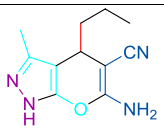
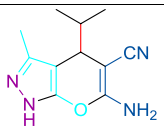
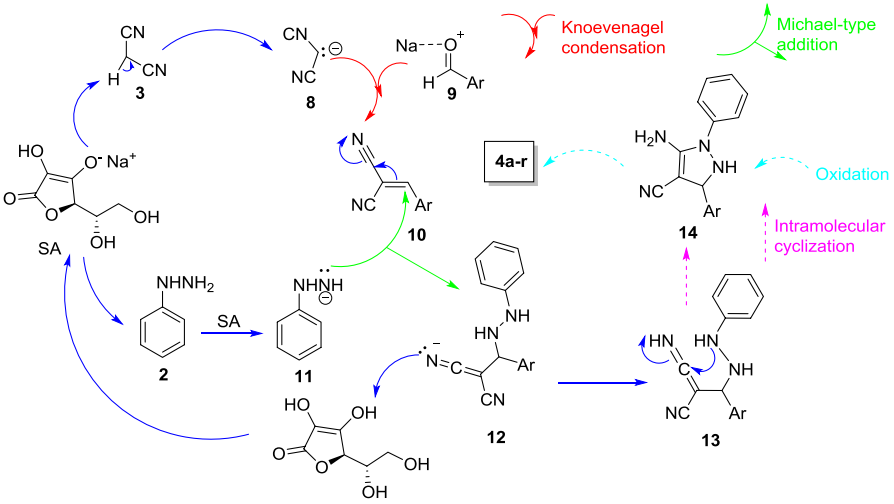
Comp. no	Structure of 1,4-dihydropyrano[2,3-c]pyrazole derivatives	Time/min	Isolated yields/%	m.p. /°C	
				Found	Lit. [42, 59, 60, 62, 75]
7g		8	85	230–232	234–236
7h		4	98	238–239	235–238
7i		8	92	189–191	188–191
7j		3	84	234–236	235–236
7k		8	80	247–248	246–248
7l		6	80	224–225	221–225

Table 4 (continued)

Comp. no	Structure of 1,4-dihydropyrano[2,3-c]pyrazole derivatives	Time/min	Isolated yields/%	m.p. /°C	
				Found	Lit. [42, 59, 60, 62, 75]
7m		12	88	192–194	192–194
7n		15	82	237–238	237–238
7o		25	81	144–145	143–144
7p		25	82	181–183	182–183



Scheme 3 A proposed reaction mechanism for SA-catalyzed synthesis of functionalized 5-aminopyrazole-4-carbonitriles (**4a**–**r**)

Acknowledgements The Damghan University is acknowledged for the provision of facilities.

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