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ORIGINAL PAPER

Aspirin: an efficient catalyst for synthesis of bis (pyrazol-5-ols), dihydropyrano[2,3-*c*]pyrazoles and spiropyranopyrazoles in an environmentally benign manner

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Abstract This article aimed to present two facile and environmental friendly routes for the rapid assembly of biologically active compounds including pyrazol core using aspirin as a novel and green catalyst. The synthesis of bis(pyrazol-5-ol) derivatives was developed via one-pot, pseudo-five-component condensation, and the target dihydropyrano[2,3-*c*]pyrazoles and spiropyranopyrazoles were prepared by one-pot, four-component reaction. These reactions can be performed in tandem from readily available starting materials. The main merits of the present methods are operational simplicity, no need for column chromatography, inexpensive materials, avoidance of harmless and corrosive acid catalysts, short reaction times, good yields of the products, and utilization of aspirin as a non-toxic, cheap, commercially available, and efficient catalyst.

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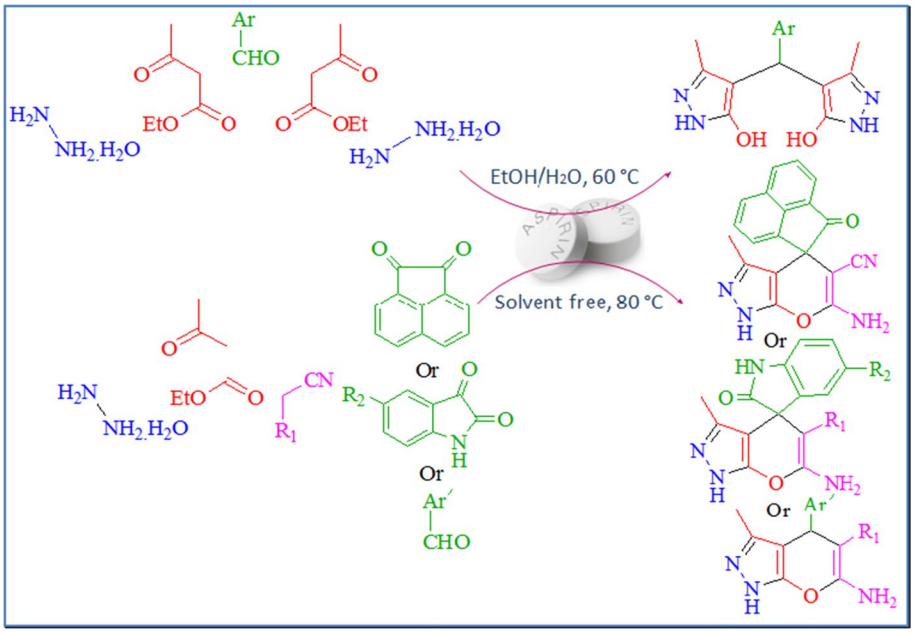
Graphical abstract



Keywords Aspirin · Novel catalyst · One-pot · Bis(pyrazol-5-ols) · Dihydropyrano[2,3-*c*]pyrazoles · Spiropyranopyrazoles

Introduction

In recent years, one of enduring challenges facing chemists is protection of our environment as an endowment of nature. Thus, shifting to the extension of methods that decrease the consumption of hazardous materials has an utmost priority. Solvent and type of catalyst along with notable parameters such as atom and step economy of process as well as nature of by-products are the main aspects in designing green synthetic routes for the synthesis of prominent heterocyclic architectures of medicinal connection. In this context, multicomponent reactions (MCRs) have served as pivotal synthetic procedures toward preparation of assemble libraries of various drug-like chemical entities [1–6].

Pyrazoles and pyranopyrazoles as *N*-fused heterocyclic compounds have exhibited a situation of prominence with a broad spectrum of biological and pharmacological activities such as anti-pyretic [7] analgesic [8], anti-microbial [9], anti-fungal [10], anti-inflammatory [11], anti-anxiety [12], anti-proliferative, and anti-tumor [13, 14]. Some compounds such as celecoxib a NSAIDs (anti-inflammatory and analgesic agent) [15], ENMD-2076 and R1530 (anti-angiogenic) [16], PNU-32945 (HIV-1 non-nucleoside reverse transcriptase inhibitor) [17], and sulfaphenazole (anti-bacterial) [18] have been manufactured as commercial drugs (Fig. 1). 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) as anti-viral agents restrain the peste des petits ruminants virus (PPRV) [19]. Recently, the α-glucosidase inhibitory activity of dihydropyrano[2,3-*c*]pyrazoles has been reported as a useful factor to reduce post-prandial hyperglycemia in diabetic individuals [20]. Also, these classes of compounds have served as valuable synthetic intermediates [21].

Not surprisingly, due to existence of these precious scaffolds in biologically functional molecules, considerable efforts have been documented toward the synthesis of these heterocyclic motifs using various methodologies. In the literature, synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) has occurred in the presence of catalysts namely pyridine trifluoroacetate [22], $ZnAl_2O_4$ NPs [23], sodium dodecyl sulfate [24], and *N*-methylimidazolium perchlorate [25]. On the other hand, some approaches for synthesis of dihydropyrano [2,3-*c*] pyrazoles involve the use of catalysts such as [MNP-PIm-SO_3H]Cl [26], Fe_3-x$Ti_x O_4$@SO_3H MNPs [27], β-cyclodextrin [28], lemon juice [29], morpholine triflate [30], triphenylphosphine [31], γ-alumina [32], imidazole [33], [ChCl][$ZnCl_2$]$_2$ [34], and cerium ammonium nitrate (CAN) [35].

Over the last decade, organocatalytic methods have been extensively employed in medicinal chemistry for designing multicomponent and cascade reactions due to the need for convenience, generality, and robustness catalysts for the synthesis of complex molecular motifs without the presence of any metal atoms. Therefore, the development of new and versatile catalysts is beneficial for chemists [36]. Acetylsalicylic acid or aspirin is a simple chemical

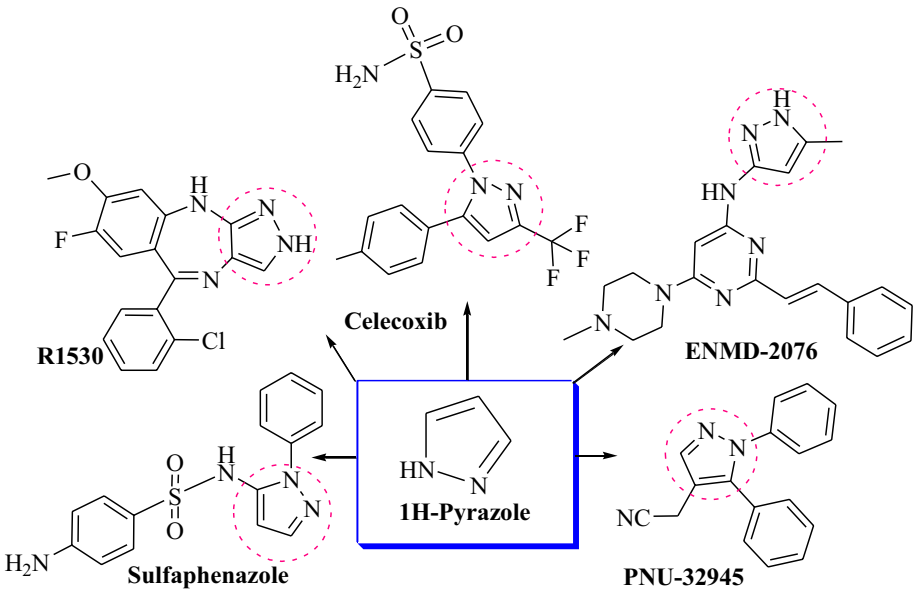


Fig. 1 Some pyrazoles containing drugs

compound which was produced by Hoffmann. Pharmacological effects of aspirin include analgetic, anti-pyretic, anti-tumor, anti-inflammatory [37], anti-platelet [38], anti-thrombotic [39], and anti-oxidan [40]. Aspirin as a non-steroidal anti-inflammatory drug (NSAIDs) has earned remarkable position in the prevention of myocardial infarction, stroke, dementia, and schizophrenia [41].

In a continuation of our endeavors toward the development of green catalytic fashion for important organic conversions, [42–46] herein, we wish to report an efficient one-pot, pseudo-five-component strategy for the rapid synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) from reaction between ethyl acetoacetate **1**, hydrazine monohydrate **2,** and aldehydes **3** and also an efficient one-pot, four-component strategy for effective synthesis of dihydropyrano[2,3-*c*]pyrazole, and spiroindoline-pyranopyrazole derivatives by condensation of hydrazine monohydrate **1**, ethyl acetoacetate **2**, malononitrile derivatives **5**, and arylaldehydes **3** or isatins in the presence of aspirin as a catalyst in an environmentally benign conditions (Scheme 1).

The combination of readily available substrates with a non-toxic, cheap, commercially available, and efficient catalyst features would offer an attractive gateway to assemble a library of heterocyclic with pyrazole motifs.

Experimental

General

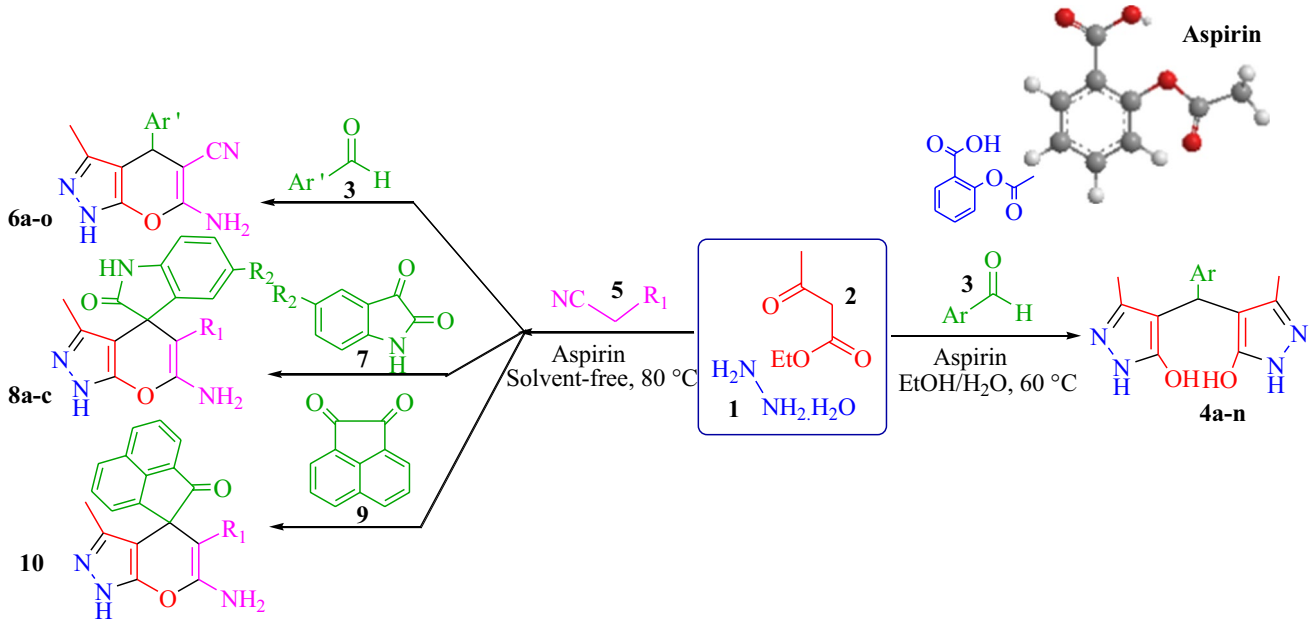
Melting points and IR spectra of all compounds were determined using an Electro thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. The ^{1}H and ^{13}C NMR spectra of known compounds were recorded on a Bruker DRX-300 and 400 Avance instrument in DMSO at 300, 400, and 75 MHz. All chemicals were provided from the chemical producer Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification. Aspirin was prepared by procedure reported by Palleros [51].

General procedure for the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)derivatives

A mixture of ethyl acetoacetate (2.0 mmol), hydrazine hydrate (2.0 mmol), and aspirin (15 mol%) as catalyst was stirred in EtOH/H_2O (3 mL). After 5 min, aromatic aldehyde (1.0 mmol) was added, and the mixture was stirred at 60 °C for the appropriate time. The completion of the reaction was monitored through thin layer chromatography (TLC). Finally, the reaction mixture was cooled to room temperature, and then ethanol (5 mL) was added to the mixture of reaction, and filtered to separate the product. Finally, the crude product was recrystallized from ethanol to afford the pure product.

General procedure for the synthesis of dihydropyrano[2,3-*c*]pyrazole and spiroindoline-pyranopyrazole derivatives

A mixture of hydrazine hydrate (1.0 mmol) and ethyl acetoacetate (1.0 mmol) was stirred for 5 min until 3-methyl-2-pyrazolin-5-one was precipitated. Aromatic aldehydes (1.0 mmol) or isains (1.0 mmol), malononitrile derivatives (1.0 mmol), and aspirin (20 mol%) were then added, and the mixture was heated to 80 °C under



Scheme 1 Aspirin catalyzed one-pot synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) and dihydropyrano[2,3-*c*]pyrazoles and spiroindoline-pyranopyrazoles

solvent-free conditions. The progress of the reaction was monitored by TLC. Then, the reaction mixture was cooled to room temperature. The mixture was washed with EtOH for separating the product. Finally, the crude product was recrystallized from ethanol to afford the pure pyranopyrazole derivatives.

Spectral data for the selected compounds

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-nitrophenyl) methyl)-3-methyl-1H-pyrazol-5-ol ***(4b)*** Yield: (93%). White powder, mp: 269–271 °C; IR (KBr) (νmax, cm^{-1}): 3428, 3145, 2928, 1597, 1518; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.10 (s, 6H, $2CH_3$), 3.35 (2OH exchanged with water of DMSO-d6), 4.99 (s, 1H, CH), 7.39 (d, *J* = 8.4 Hz, 2H, H-Ar), 8.13 (d, *J* = 8.8 Hz, 2H, H-Ar), 11.36 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(3-nitrophenyl) methyl)-3-methyl-1H-pyrazol-5-ol ***(4c)*** Yield: (89%). White powder, mp: 254–257 °C; IR (KBr) (νmax, cm^{-1}): 3405, 3095, 2979, 1600, 1528; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.11 (s, 6H, $2CH_3$), 3.39 (2OH exchanged with water of DMSO-d6), 4.99 (s, 1H, CH), 7.02–7.23 (m, 4H, H-Ar), 11.34 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-chlorophenyl) methyl)-3-methyl-1H-pyrazol-5-ol ***(4e)*** Yield: (92%). White powder, mp: 215–217 °C; IR (KBr) (νmax, cm^{-1}): 3392, 3180, 2925, 1601, 1521, 1488; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.08 (s, 6H, $2CH_3$), 3.39 (2OH exchanged with water of DMSO-d6), 4.81 (s, 1H, CH), 7.12 (d, *J* = 8.4 Hz, 2H, H-Ar), 7.26 (d, *J* = 8.4 Hz, 2H, H-Ar), 9.07 (s, 1H, OH), 11.28 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(p-tolyl)) methyl)-3-methyl-1H-pyrazol-5-ol ***(4h)*** Yield: (89%). Pale orange powder, mp: 197–198 °C; IR (KBr) (νmax, cm^{-1}): 3301, 3104.77, 2924, 1607, 1512; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.06 (s, 6H, $2CH_3$), 2.22 (s, 3H, CH_3), 3.36 (2OH exchanged with water of DMSO-d6), 4.76 (s, 1H, CH), 7.00 (s, 4H, H-Ar), 11.30 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(o-tolyl)) methyl)-3-methyl-1H-pyrazol-5-ol (4i) Yield: (77%). Pale orange powder, mp: 281–283 °C; IR (KBr) (νmax, cm^{-1}): 3432, 3092, 2926, 1604.58, 1525.05; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 1.81 (s, 6H, $2CH_3$), 2.11 (s, 3H, CH_3), 3.38 (2OH exchanged with water of DMSO-d6), 4.92 (s, 1H, CH), 7.02–7.23 (m, 4H, H-Ar), 10.66 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-hydroxyphenyl)methyl)-3-methyl-1H-pyrazol-5-ol ***(4j)*** Yield: (82%). White powder, mp: 255–257 °C; IR (KBr) (νmax, cm^{-1}): 3415, 3268, 3107, 2928, 1600, 1514; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.05 (s, 6H, $2CH_3$), 3.37 (2OH exchanged with water of DMSO-d6), 4.70 (s, 1H, CH), 6.59 (d, *J* = 8.8 Hz, 2H, H-Ar), 6.90 (d, *J* = 8.4, 2H, H-Ar), 9.07 (s, 1H, OH), 11.27 (brs, 2H, 2NH).

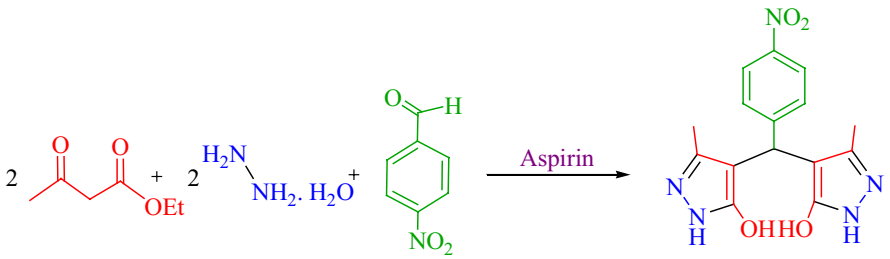
4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(thiophen-2-yl))methyl)-3-methyl-1H-pyrazol-5-ol ***(4l)*** Yield: (78%). White powder, mp: 239–241 °C; IR (KBr) (νmax, cm^{-1}): 3582, 3112, 2926, 1606, 1483; ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) = 2.09 (s, 6H, $2CH_3$), 3.38 (2OH exchanged with water of DMSO-d6), 4.97 (s, 1H, CH), 6.84-6.86 (m, 1H, H-Ar), 6.59–6.60 (m, 1H, H-Ar), 7.27 (d, *J* = 5.2 Hz, 2H, H-Ar), 11.36 (brs, 2H, 2NH).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(pyridin-3-yl)methyl)-3-methyl-1H-pyrazol-5-ol ***(4m)*** Yield: (82%). White powder, mp: 295–298 °C; IR (KBr) (νmax, cm^{-1}): 3193, 3055, 2926, 1596, 1530; ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm) = 2.12 (s, 6H, $2CH_3$), 4.92 (s, 1H, CH), 7.26 (dd, *J* = 7.8 Hz, 1H, H-Ar), 7.54 (d, *J* = 7.8 Hz, 1H, H-Ar), 8.34-8.35 (m, 2H, H-Ar), 11.10 (brs, 4H, 2NH, 2OH). ^{13}C NMR (75 MHz, DMSO-d6): δ (ppm) = 10.7 (CH_3), 31.1 (CH), 103.8, 123.3, 135.5, 139.1, 140.1, 147.0, 149.5, 161.4 (C-Ar).

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-hydroxy-3-methoxyphenyl)methyl)-3-methyl-1H-pyrazol-5-ol ***(4n)*** Yield: (87%). White powder, mp: 254–257 °C; IR (KBr) (νmax, cm^{-1}): 3373, 3193, 2959, 1609, 1485; ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm) = 2.07 (s, 6H, $2CH_3$), 3.65 (s, 3H, OCH_3), 4.75 (s, 1H, CH), 6.55 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H, H-Ar), 6.63 (d, *J* = 8.1 Hz, 1H, H-Ar), 6.76 (d, *J* = 1.5 Hz, 1H, H-Ar), 11.30 (brs, 5H, 2NH, 3OH). ^{13}C NMR (75 MHz, DMSO-d6): δ (ppm) = 10.9 (CH_3), 32.8 (CH), 56.0 (OCH_3), 105.0, 112.7, 115.3, 120.4, 134.8, 140.0, 144.9, 147.4, 161.4 (C-Ar).

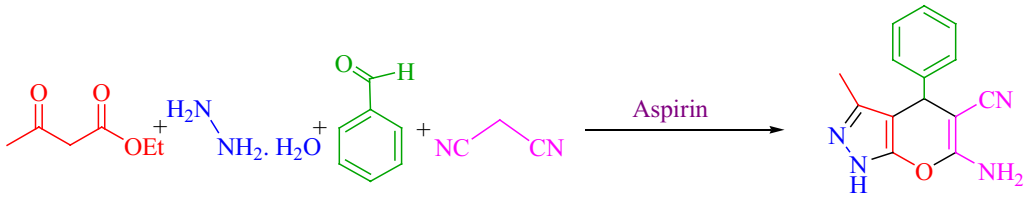
6-amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile ***(6f)*** Yield: (86%). White powder, mp: 231–233 °C; IR (KBr) (νmax, cm^{-1}): 3391, 3357, 3314, 3169, 2190,1609, 1489, 1408, 1350, 1052, 763; ^{1}H NMR (400 MHz, DMSO-d6): 1.77 (s, 3H, CH_3), 5.08 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.18–7.43 (m, 4H, Ar), 12.16 (s, 1H, NH).

Table 1 Optimization of reaction conditions for synthesis of bis(pyrazol-5-ols)



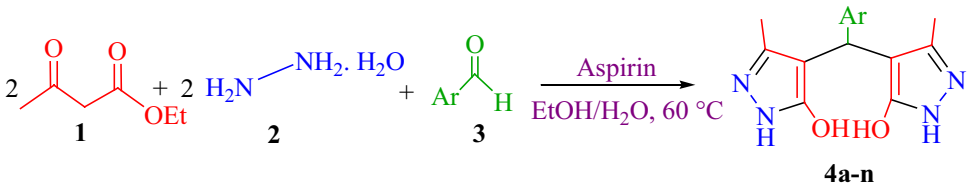
Entry	Temperature (°C)	Solvent	Catalyst (mol%)	Time (min)	Isolated yield (%)
1	60	EtOH	5	35	81
2	60	EtOH	10	30	80
3	60	EtOH	15	25	91
4	60	EtOH	20	25	90
5	60	EtOH:H_2O (1:1)	15	30	90
6	60	EtOH:H_2O (2:1)	15	20	93
7	60	H2O	15	30	87
8	r.t	EtOH:H_2O (2:1)	15	24 (h)	45
9	50	EtOH:H_2O (2:1)	15	240	76
10	70	EtOH:H_2O (2:1)	15	20	90
11	60	EtOH:H_2O (2:1)	–	24 (h)	35

Table 2 Optimization of reaction condition for synthesis of dihydropyrano[2,3-c]pyrazoles



Entry	Temperature (°C)	Catalyst (mol%)	Time (min)	Isolated yield (%)
1	70	5	40	76
2	70	10	35	81
3	70	15	30	86
4	70	20	25	85
5	60	15	180	45
6	80	15	25	91
7	90	15	25	90
8	100	15	20	90
9	80	–	24 (h)	30

Table 3 Synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols)



Entry	Ar	Product	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported [Refs]
1	C_6H_5	**4a**	25	91	207–208	206–207 [23]
2	4-NO_2 C_6H_4	**4b**	20	93	269–271	271–273 [47]
3	3-NO_2 C_6H_4	**4c**	40	89	254–257	253–255 [47]
4	2-NO_2 C_6H_4	**4d**	50	83	240–241	237–240 [22]
5	4-Cl C_6H_4	**4e**	30	92	215–217	214–216 [23]
6	2-Cl C_6H_4	**4f**	40	85	259–261	265–268 [23]
7	2,4-diCl C_6H_3	**4g**	55	79	265–267	267–270 [22]
8	4-Me C_6H_4	**4h**	40	89	197–198	194–196 [47]
9	2-Me C_6H_4	**4i**	50	77	281–283	278–280 [23]
10	4-OH C_6H_4	**4j**	50	82	255–257	267–270 [22]
11	3-OH C_6H_4	**4k**	55	76	209–211	209–211 [23]
12	Thiophene-2-	**4l**	45	78	239–241	200–202 [47]
13	Pyridine-3-	**4m**	45	82	295–298	This work
14	4-OH-3-OMeC_6H_3	**4n**	50	87	254–257	This work

Table 4 Synthesis of dihydropyrano[2,3-*c*] pyrazoles and spiroindoline-pyranopyrazoles

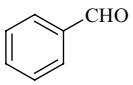
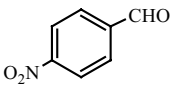
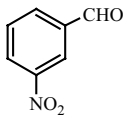
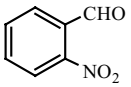
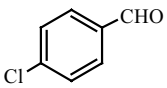
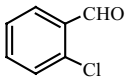
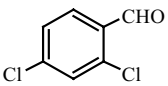
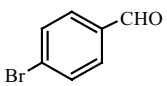
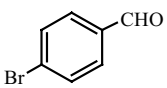
Entry	Substrate	R	Product	Time (min)	Yield (%)	Mp (°C)	
						Found	Reported [Refs]
1		CN	**6a**	25	91	253–255	247–248 [30]
2		CN	**6b**	15	93	221–223	226–228 [26]
3		CO_2Et	**6c**	35	88	179–181	180–182 [53]
4		CN	**6d**	30	87	198–200	204–205 [26]
5		CN	**6e**	15	93	233–235	238–240 [26]
6		CN	**6f**	25	86	231–233	226–227 [26]
7		CN	**6g**	40	84	235–238	235–237 [42]
8		CN	**6h**	20	92	238–240	239–241 [26]
9		CO_2Et	**6i**	30	89	183–185	182–184 [53]

Table 4 continued

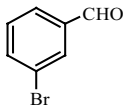
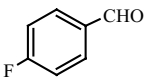
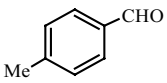
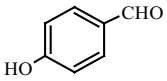
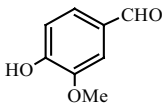
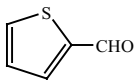
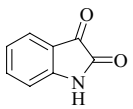
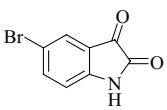
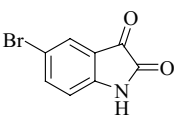
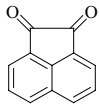
Entry	Substrate	R	Product	Time (min)	Yield (%)	Mp (°C)	
						Found	Reported [Refs]
10		CN	**6j**	30	87	224–226	220–222 [48]
11		CN	**6k**	15	86	231–233	233–234 [26]
12		CN	**6l**	30	87	205–208	208–209 [30]
13		CN	**6m**	35	82	225–226	219–221 [49]
14		CN	**6n**	40	83	237–239	235–237 [32]
15		CN	**6o**	40	81	216–218	208–210 [50]
16		CN	**8a**	30	89	285–287	279–280 [52]
17		CN	**8b**	25	91	283–285	282–283 [52]
18		CO_2Et	**8c**	30	85	250–254	>250 [53]

Table 4 continued

Entry	Substrate	R	Product	Time (min)	Yield (%)	Mp (°C)	
						Found	Reported [Refs]
19		CN	**10**	150	87	278–282	>300 [54]

*6-Amino-1,4-dihydro-3-methyl-4-(4-bromophenyl) pyrano[2,3-c]pyrazole-5-carbonitrile (**6h**)* Yield: (92%). White powder, mp: 254–257 °C; IR (KBr) (νmax, cm^{-1}): 3470, 3227, 3120, 2195, 1651, 1595, 1560, 1401, 1353, 1107, 883, 810, 744, 543; ^{1}H NMR (400 MHz, DMSO-d6): 1.80 (s, 3H, CH_3), 4.63 (s, 1H, CH), 6.96 (s, 2H, NH_2), 7.15 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 12.16 (s, 1H, NH).

Results and discussion

At first, we centralized our attention to the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) and the reaction between ethyl acetoacetate (2.0 mmol), hydrazine hydrate (2.0 mmol), and 4-nitrobenzaldehyde (1.0 mmol) was chosen as a model reaction for preliminary experiments. The effect of catalyst loading was envisaged, and the results were summarized in Table 1. At a catalyst loading of 15 mol%, the highest yield of product was obtained in EtOH (Table 1, entry 3). Further increases to the catalyst loading did not considerably influence the reaction progress. Next, the effects of solvents, water, ethanol, and aqueous ethanol were evaluated and it was found that the rate 2:1 EtOH/Water is better than other rates. Finally, to optimize the reaction temperature, the model reaction was carried out using 15 mol% of the catalyst at different temperatures. It was found that 60 °C is an efficient temperature in terms of reaction time and yield obtained (Table 1, entry 6). As shown in (Table 1, entry 11), a test reaction was accomplished in the absence of catalyst at the optimum condition and offered only 30% yield of the expected product.

In another study for the synthesis of dihydropyrano[2,3-*c*], pyrazoles, we selected reaction of ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), malononitrile (1.0 mmol), and benzaldehyde (1.0 mmol) as model under solvent-free conditions and the effect of amount of catalyst and temperature was envisaged. As shown in (Table 2, entry 6), optimization of the reaction conditions demonstrated that the best results were gained when the reaction was performed at 80 °C in the presence of aspirin (15 mol%) under solvent-free conditions.

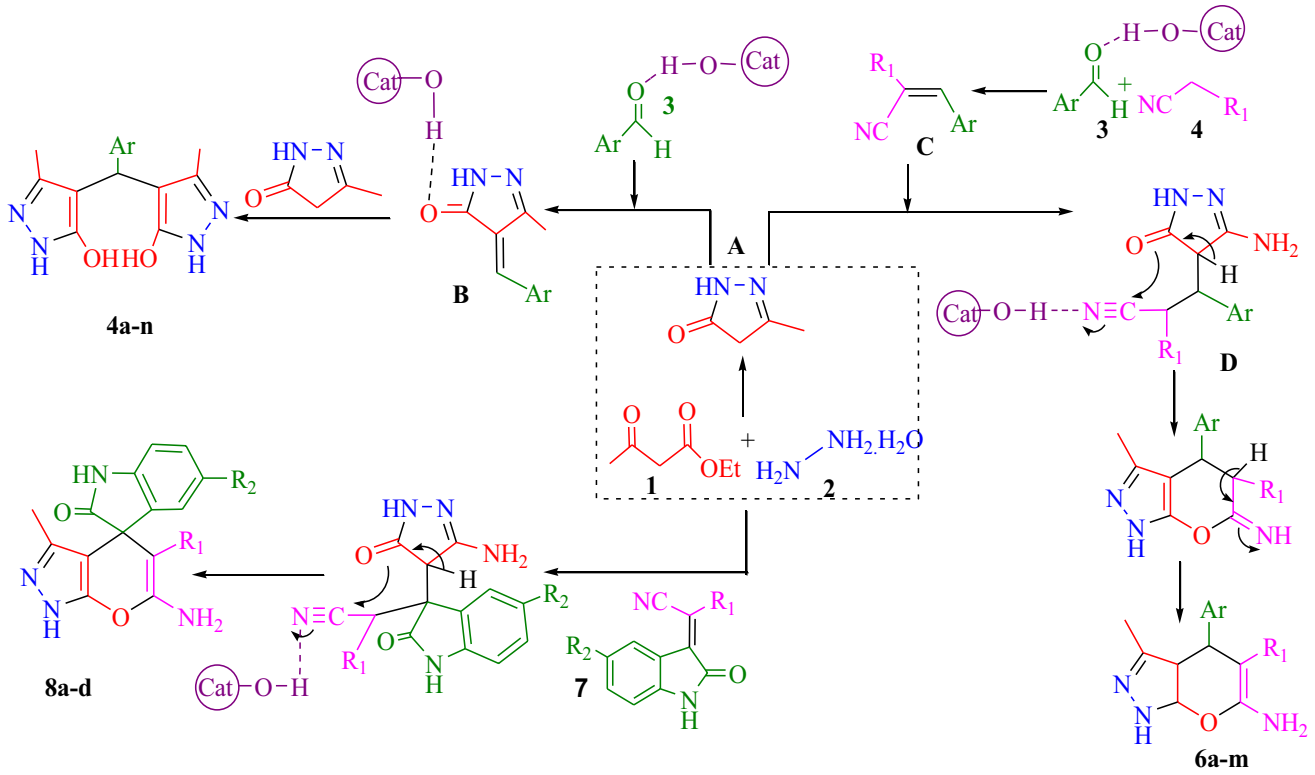
After optimizing the reaction conditions, we evaluated the range and feasibility of reactions using a various aryl aldehydes. As shown in Tables 3 and 4, it was shown that the two reactions tolerated both electron-withdrawing and electron-donating groups on the aldehyde aromatic rings including *ortho-, meta-,* and *para*-substituted with the corresponding products in satisfied yields. In synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols), substitution of NO_2 group in the 4th position of aromatic aldehyde led to a relatively faster rate and higher yield than the substitution of other groups in various positions of aromatic ring.

Then, we investigated the utilization of acenaphthylene-1,2-dione or isatins as a substrate to react with the hydrazine hydrate, ethyl acetoacetate, and malononitrile under the optimized conditions. As expected, the reaction developed well to afford spiro[indoline-3,4′-pyrano[2,3-*c*] pyrazole] derivatives (**8a**–**c**) and spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazole (**10**) in good yields.

A suggested mechanism, illustrating the role of aspirin in the tandem synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol), dihydropyrano[2,3-*c*]pyrazole derivative, and spiroindoline-pyranopyrazole was suggested in Scheme 4. At first, pyrazolone **A** would be formed from the reaction between ethyl acetoacetate **1** and hydrazine hydrate **2**. For the synthesis of 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ol), the activated carbonyl group of the aldehydes **3** by aspirin via Knoevenagel condensation with pyrazolone to create the intermediated **B** where through Michael addition to another pyrazolone to give desirable products (**4a**–**n**).

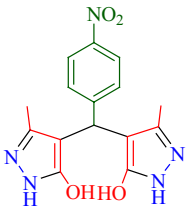
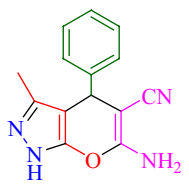
For the synthesis of dihydropyrano[2,3-*c*]pyrazoles is proposed the arylidene malononitrile **C** to generate in situ via Knoevenagel condensation active aldehyes **3** and malononitrile **4**. Michael addition of **A** and **C** gives the acyclic adduct products **D**, which undergoes intramolecular cyclization and tautomerization to afford the corresponding products (**6a**–**o**) (Scheme 2).

In order to appraise the privileged features of our procedure, we compared our results for the synthesis of



Scheme 2 The suggested mechanism for the synthesis 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols), dihydropyrano[2,3-c]pyrazoles, and spiroindoline-pyranopyrazoles

Table 5 Comparison of the results afforded from the synthesis of **4b** and **6a** in the presence of aspirin with those obtained via other catalysts

Product	Catalyst	Reaction conditions	Time	Yield (%) References
	Pyridine trifluoroacetate	H_2O, 70 °C	12 h	85 [22]
	$ZnAl_2O_4$ Nps	H_2O, 60 °C	14 min	92 [23]
	Sodium Dodecyl Sulfate	H_2O, reflux	1 h	88 [24]
	–	H_2O, reflux	6 h	85 [47]
	N-Methylimidazolium perchlorate	50 °C, solvent-free	20 min	90 [25]
	Aspirin	H_2O/EtOH, 60 °C	20 min	93 (This work)
	$NiFe_2O_4$@SiO_2–$H_3PW_{12}O_{40}$ (NFS–PWA)	EtOH, reflux	5 min	84 [49]
	Fe_3-xTixO4@SO_3H MNPs	105 °C, solvent-free	90 min	90 [27]
	β-Cyclodextrin	H_2O/EtOH, 80 °C	15 min	90 [28]
	Lemon juice	H_2O/EtOH, 90 °C	50 min	96 [29]
	Morpholine triflate	EtOH, reflux/H_2O	9 h	92 [30]
	Triphenylphosphine	H_2O, reflux	1 h	84 [31]
	γ-Alumina	H_2O, 100 °C	50 min	80 [32]
	Imidazole	H_2O, 80 °C	25 min	89 [33]
	Aspirin	80 °C, solvent-free	25 min	91 (This work)

bis(pyrazol-5-ols) and dihydropyrano[2,3-*c*]pyrazoles with other results reported in the literature, as shown in Table 5. Compounds including pyrazol core have extensively been used in the synthesis of drugs and pharmaceuticals. Thus, the elimination of residual metal species plays a pivotal role when a metal-containing catalyst was applied [12]. So, this method, compared to the existing ones, uses aspirin as an efficient, non-toxic, inexpensive, and commercially available organocatalyst along with merits including high yields and short reaction time.

The reusability of aspirin was examined in the synthesis of **4b** as an example. It was observed that the yield of product reduced in the 3rd and 4th runs.

Conclusions

In compendium, we expanded an efficient strategy for one-pot synthesis of biologically 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ol), dihydropyrano[2,3-*c*]pyrazole, and spiropyranopyrazole derivatives in the presence of aspirin as a commercially available, and eco-compatibility catalyst under environmental benign conditions. Good to excellent yields, simplicity of operation, comfortable purification, and high atom-economy are the noteworthy advantages of the present method.

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References

1. S. Karamthulla, S. Pal, M.N. Khan, L.H. Choudhury, RSC Adv. **4**, 37889–37899 (2014)
2. P.T. Anastas, T.C. Williamson (eds.), *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes* (Oxford University Press, Oxford, 1998)
3. G.M. Ziarani, S. Faramarzi, N. Lashgari, A. Badiei, J. Iran. Chem. Soc. **11**, 701–709 (2014)
4. P.T. Anastas, M.M. Kirchhoff, Acc. Chem. Res. **35**, 686–694 (2002)
5. E. Ruijter, R. Scheffelaar, R.V.A. Orru, Angew. Chem. Int. Ed. **50**, 6234–6246 (2011)
6. J.L. Tucker, Org. Process Res. Dev. **10**, 315–319 (2006)
7. O.A. Attanasi, D. Spinelli, Soc. Chim. Italiana, Roma. **4**, 105–137 (2000)
8. M.M.F. Ismail, Y.A. Ammar, H.S.A. EI-Zahaby, S.I. Eisa, S.E. Barakat, Arch. Pharm. Chem. Life Sci. **340**, 476–479 (2007)
9. S.P. Prajapati, D.P. Patel, P.S. Patel, J. Chem. Pharm. Res. **4**, 2652–2655 (2012)
10. Y. Liu, G. He, C. Kai, Y. Li, H. Zhu, J. Heterocycl. Chem. **19**, 1370–1375 (2012)
11. G. Mariappan, B.P. Saha, L. Sutharson, A. Singh, S. Garg, L. Pandey, D. Kumar, Saudi Pharm. J. **19**, 115–122 (2011)
12. C.E. Rosiere, M.I. Grossman, Science **131**, 651 (1951)
13. M.G. LaPorte, Z. Wang, R. Colombo, A. Garzan, V.A. Peshkov, M. Liang, P.A. Johnston, M.E. Schurdak, M. Sen, D.P. Camarco, Y. Hua, Bioorg. Med. Chem. Lett. **26**, 3581–3588 (2016)
14. J.L. Wang, D. Liu, Z.J. Zheng, S. Shan, X. Han, S.M. Srinivasula, C.M. Croce, E.S., Z. Huang. Proc. Natl. Acad. Sci. **97**, 7124–7129 (2009)
15. B.P. Bandgar, H.V. Chavan, L.K. Adsul, V.N. Thakare, S.N. Shringare, R. Shaikh, R.N. Gacche, Bioorg. Med. Chem. Lett. **23**, 912–916 (2013)
16. K.M. Kasiotis, E.N. Tzanetou, S.A. Haroutounian, Front. Chem. **2**, 1–7 (2014)
17. M.J. Genin, C. Biles, B.J. Keiser, S.M. Poppe, S.M. Swaney, W.G. Tarpley, Y. Yagi, D.L. Romero, J. Med. Chem. **43**, 1034–1040 (2000)
18. F. Abrigach, R. Touzani, Med. Chem. (Los Angeles) **6**, 292–298 (2016)
19. K. Sujatha, G. Shanthi, N.P. Selvam, S. Manoharan, P.T. Perumal, M. Rajendran, Bioorg. Med. Chem. Lett. **19**, 4501–4503 (2009)
20. H. Kashtoh, M.T. Muhammad, J.J. Khan, S. Rasheed, A. Khan, S. Perveen, K. Javaid, K.M. Khan, M.I. Choudhary, Bioorg. Chem. **65**, 61–72 (2016)
21. A.V. Stachulski, N.G. Berry, A.C.L. Low, S.L. Moores, E. Row, D.C. Warhurst, I.S. Adagu, J.F. Rossignol, J. Med. Chem. **49**, 1450–1454 (2006)
22. E. Soleimani, S. Ghorbani, M. Taran, A. Sarvary, C. R. Chim. **15**, 955–961 (2012)
23. J. Safaei-Ghomi, B. Khojastehbakht-Koopaei, H. Shahbazi-Alavi, RSC Adv. **4**, 46106–46113 (2014)
24. W. Wang, S.X. Wang, X.Y. Qin, J.T. Li, Synth. Commun. **35**, 1263–1269 (2005)
25. N.G. Khaligh, S.B.A. Hamid, S.J. Titinchi, Chin. Chem. Lett. **27**, 104–108 (2016)
26. M.A. Zolfigol, R. Ayazi-Nasrabadi, S. Baghery, V. Khakyzadeh, S. Azizian, J. Mol. Catal. A-Chem. **418–419**, 54–67 (2016)
27. D. Azarifar, Y. Abbasi, Synth. Commun. **46**, 745–758 (2016)
28. Y.A. Tayade, S.A. Padvi, Y.B. Wagh, D.S. Dalal, Tetrahedron Lett. **56**, 2441–2447 (2015)
29. R.H. Vekariya, K.D. Patel, H.D. Patel, Res. Chem. Intermed. **42**, 7559–7579 (2016)
30. C.F. Zhou, J.J. Li, W.K. Su, Chin. Chem. Lett. **27**, 1686–1690 (2016)
31. A.K. Imene, F. Amina, L. Oumeima, B. Raouf, B. Boudjemaa, D. Abdelmadjid, Lett. Org. Chem. **13**, 85–91 (2016)
32. H. Mecadon, M.R. Rohman, M. Rajbangshi, B. Myrboh, Tetrahedron Lett. **52**, 2523–2525 (2011)
33. A. Siddekha, A. Nizam, M.A. Pasha, Spectrochim. Acta A. **81**, 431–440 (2011)
34. A.R. Hajipour, M. Karimzadeh, H. Tavallaei, J. Iran. Chem. Soc. **12**, 987–991 (2015)
35. K. Ablajan, W. Liju, Y. Kelimu, F. Jun, Mol. Divers. **17**, 693–700 (2013)
36. D.W.C. MacMillan, Nature **455**, 304–308 (2008)
37. C.M. Ulrich, J. Bigler, J.D. Potter, Nat. Rev. Cancer **6**, 130–140 (2006)
38. C. Cena, M.L. Lolli, L. Lazzarato, E. Guaita, G. Morini, G. Coruzzi, S.P. McElroy, I.L. Megson, R. Fruttero, A. Gasco, J. Med. Chem. **46**, 747–754 (2003)
39. A. Undas, K.E. Brummel-Ziedins, K.G. Mann, Blood **109**, 2285–2592 (2007)
40. X. Shi, M. Ding, Z. Dong, F. Chen, J. Ye, S. Wan, S.S. Leonard, V. Castronova, V. Vallyathan, Mol. Cell. Biochem. **199**, 93–102 (1999)
41. T. Roberts, F. Shokraneh, S. Nur, Cochrane Libr (2016). doi:10.1002/14651858.CD012116

42. M. Fatahpour, F. Noori Sadeh, N. Hazeri, M.T. Maghsoodlou, M. Lashkari, Res. Appl. Chem. **6**, 1569–1572 (2016)
43. M. Kangani, N. Hazeri, M.T. Mghsoodlou, K. Khandan-Barani, M. Kheyrollahi, F. Nezhadshahrokhabadi, J. Iran. Chem. Soc. **12**, 47–50 (2015)
44. M. Fatahpour, N. Hazeri, M.T. Maghsoodlou, M. Lashkari, Iran. J. Sci. Technol. Trans. A Sci. (2016). doi:10.1007/s40995-016-0064-1
45. F. Mohamadpour, M.T. Maghsoodlou, R. Heydari, M. Lashkari, J. Iran. Chem. Soc. **13**, 1549–1560 (2016)
46. M.T. Maghsoodlou, M. Karima, M. Lashkari, B. Adrom, J. Aboonajmi, J. Iran. Chem. Soc. **14**, 329–335 (2017)
47. J. Xu-dong, D. Hai-feng, L. Ying-jie, C. Jun-gang, L. Da-peng, W. Mao-cheng, Chem. Res. Chin. Univ. **28**, 999–1002 (2012)
48. M. Babaie, H. Sheibani, Arab. J. Chem. **11**, 159–162 (2011)
49. Y. Zou, H. Wub, Y. Hua, H. Liu, X. Zhao, H. Ji, D. Shi, Ultrason. Sonochem. **18**, 708–712 (2011)
50. B. Maleki, H. Eshghi, M. Barghamadi, N. Nasiri, A. Khojastehnezhad, S. Sedigh Ashrafi, O. Pourshiani, Res. Chem. Intermed. **42**, 3071–3093 (2016)
51. D.R. Palleros, *Experimental Organic Chemistry* (Wiley, Hoboken, 2000), p. 494
52. Y. Zou, Y. Hu, H. Liu, D. Shi, ACS comb. Sci. **14**, 38–43 (2011)
53. S. Paul, K. Pradhan, S. Ghosh, S.K. De, A.R. Das, Tetrahedron **70**, 6088–6099 (2014)
54. M.N. Elinson, A.I. Ilovaisky, V.M. Merkulova, P.A. Belyakov, F. Barba, B. Batanero, Tetrahedron **68**, 5833–5837 (2012)