Four-Component Synthesis of pyrano[2,3-c]pyrazoles Catalyzed by Triphenylphosphine in Aqueous Medium

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Abstract:

Background: The pyrano[2,3-c]pyrazoles have various biological properties such as anti-inflammatory, anti-cancer, antifongical, analgesics and have a potential inhibitor for human ChK1 kinase. For these reasons several synthetic methods are reported. For our part we want to propose a method which respects the environment.

Method: To achieve our study we used as a model the condensation reaction of hydrazine hydrate, ethyl acetoacetate, benzaldehyde and malononitrile in the respective proportions of 1/1/1/1 and in the presence of Triphenylphosphine in various concentrations and different solvents.

Results: We found that the optimal conditions for this reaction are 10 mol% of catalyst in refluxed H_2O. Given these results and to show the generality of the procedure, we applied the optimized reaction conditions for the synthesis of various dihydropyrano[2,3-c]pyrazoles from a range of substituted aromatic and heteroaromatic aldehydes. We have also applied these conditions by changing hydrazine by phenylhydrazine. The desired products are obtained in good to excellent yields.

Conclusion: We describe a simple, efficient and benign method for the dihydropyrano[2,3-c]pyrazoles synthesis by a four-component condensation between hydrazine (or phenylhydrazine), ethyl acetoacetate, malononitrile and a variety of aromatic and heteroaromatic aldehydes, catalyzed by Triphenylphosphine.

Keywords: Aqueous medium, multicomponent reaction, pyrano[2,3-c]pyrazoles, triphenylphosphine.

INTRODUCTION

The pyrano[2,3-c]pyrazoles have various biological properties; they are, for example, antibacterial [1], anti-inflammatory [2], anti-cancer [3], antifongical [4], analgesics [5] and have a potential inhibitor for human ChK1 kinase [6]. For these reasons they have attracted the researcher's interest and this is reflected in the large number of the synthetic methods of this class of compounds reported in the literature. The first described pyranopyrazoles syntheses are the two-component reactions of 3-methyl-1-phenylpyrazolon-5-one and tetracyanoethylene in refluxing ethanol [7] or between 4-arylidene-3-methyl-2-pyrazoline-5-one and malononitrile in the presence of triethylamine [8] or of arylidenemalononitriles and 3-methyl-1-phenylpyrazolon-5-one catalyzed also by triethylamine [9]. Thereafter were proposed the three-component approaches of pyrazol-5-one derivatives, aromatic aldehydes and malononitrile catalyzed by triethylbenzylammonium chloride in H_2O [10], hexadecyltrimethylammonium bromide [11], nanoparticles $La_{0.7}Sr_{0.3}MnO_3$ [12] and Palladium(0) [13], ionic liquids [14, 15], *p*-toluenesulfonic acid [16] and Cesium fluoride [17].

Another three-component method from methyl acetyldicarboxylate, an isonitrile and 3-methyl-1-phenylpyrazolon-5-one without catalyst in refluxed acetonitrile was also described [18].

However the majority of described methods during recent years are four-component reactions of hydrazine (and its derivatives), ethyl acetoacetate, malononitrile and diverse aldehydes catalyzed by piperazine in water at room temperature [19], triethylamine in ethanol [20], β-cyclodextrin without solvent [21], imidazole in H_2O at 80°C [22], *L*-proline in aqueous medium [23], γ-alumina in reflux water [24], $Ba(OH)_2$ in also reflux water [25], sodium bisulfate under ultrasonic irradition without solvent [26].

Pyrano[2,3-c]pyrazoles four-component synthesis was also successfully performed under influence of catalysts such as iodine [27], sodium benzoate [28], silica [29], ionic liquids [30], nanoparticles [31], heteropolyacids [32], and *Aspergillus Niger lipase* [33].

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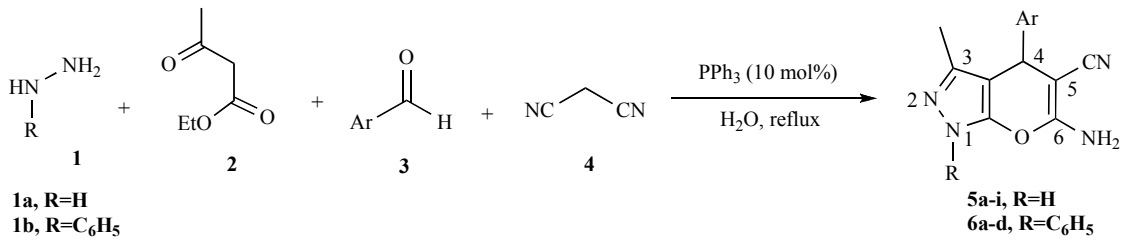


Scheme 1. Dihydropyrano[2,3-c]pyrazoles synthesis.

Table 1. Synthesis of dihydropyrano[2,3-c]pyrazoles (5a) catalyzed by PPh_3[a]: Effect of the solvent and the temperature.

Entry	Solvent	Catalyst (mol %)	Time (h)	Temperature (°C)	Yield (%)
1	H_2O	10	5	Ambient	48
2	H_2O	10	2	50	61
3	H_2O	10	1	Reflux	82
4	EtOH	10	1	Reflux	76
5	EtOH/H_2O	10	1	Reflux	67
6	CH_2Cl_2	10	1	Reflux	8
7	CH_3CN	10	1	Reflux	27
8	-	10	1	8O°C	79

[a] Reactions conditions: benzaldehyde (2 mmol), hydrazine (2 mmol), ethyl acetoacetate (2 mmol), malononitrile (2 mmol), PPh_3 (0.1 mmol), solvent (5 ml). [b] Isolated yields of pure products.

Particular reaction of aromatic aldehydes, hydrazine, malononitrile and methyl acetylenedicarboxylate in water and without catalyst for the preparation of a series of 3-methylcarboxylate pyrano[2,3-c]pyrazoles was reported [34].

The literature review shows also some enantioselective syntheses in the presence of *L*-proline [35] or more complexes organic catalysts [36].

Triphenylphosphine (PPh_3) was used as catalyst in a number of chemical transformations [37]. For our part, we successfully applied this catalyst in Biginelli [38] and Hantzsch [39] multicomponent reactions and also in the tetrahydrobenzo[b]pyrans synthesis [40].

In continuation of our research of new, efficient, inexpensive and environmentally friendly procedures [41-43], we report here the use of triphenylphosphine as an effective catalyst in the preparation of dihydropyrano[2,3-c]pyrazoles in aqueous medium (Scheme **1**).

RESULTS AND DISCUSSION

To achieve our study we used as a model the condensation reaction of hydrazine hydrate (**1a**), ethyl acetoacetate (**2**), benzaldehyde (**3a**) and malononitrile (**4**) in the respective proportions of 1/1/1/1 and in the presence of 10 mol% of our catalyst.

First, we examined the reaction in various solvents such as H_2O, EtOH, EtOH/H_2O (1/1), CH_3CN and CH_2Cl_2 at different temperatures: ambient, 50°C and at reflux. The reaction without solvent at 80°C was also performed. The results reported in Table **1** show that the desired product (**5a**) is obtained with yields ranging between 8 and 79%. However, the reaction in H_2O at reflux gave a better result with a yield of 82% (Table **1**, entry **3**).

In a second step, we conducted several manipulations in order to determine the effect of the catalyst and its optimum amount by carrying out the above condensation in refluxed water with various amounts of catalyst increasing from 5, 20, 30 to 50 mol%. The results summarized in Table **2** show that condensations with 5, 20 and 30 mol% of triphenylphosphine provide yields of 51, 72 and 64% respectively. However, an amount of 10 mol% previously gave significantly higher yield (82%) (Table **1**, entry **3**).

Therefore the optimal conditions for this reaction are 10 mol% of catalyst in refluxed H_2O.

Given these results and to show the generality of the procedure, we applied the optimized reaction conditions for the synthesis of various dihydropyrano[2,3-c]pyrazoles from a range of substituted aromatic and heteroaromatic aldehydes. We have also applied these conditions by changing hydrazine by phenylhydrazine. The obtained results are summarized in Table **3**.

Table **3** shows that aldehydes bearing electron donating or electron-withdrawing groups gave the desired products in good yields (entries **1-9**). Moreover, wherever the position of substituents (*o*, *m*, *p*), yields are also comparables (entries **2**, **3**, **4**). In addition, the reactions with phenylhydrazine give excellent yields but with longer reaction times (entries **10-13**). Good yield is observed with heteroaromatic aldehyde (entry **8**).

Table 2. Synthesis of dihydropyrano[2,3-c]pyrazoles (5a) catalyzed by PPh_3[a]: Amount of catalyst.

Entry	Solvent	Catalyst (mol%)	Time (h)	Temperature (°C)	Yield (%)
1	H_2O	0	1	Reflux	59
2	H_2O	5	1	Reflux	69
3	H_2O	10	1	Reflux	82
4	H_2O	20	1	Reflux	76
5	H_2O	30	1	Reflux	71
6	H_2O	50	1	Reflux	67

[a] Reactions conditions: benzaldehyde (2 mmol), hydrazine (2 mmol), ethyl acetoacetate (2 mmol), malononitrile (2 mmol), PPh_3 (different amounts) in H_2O (5 ml) at reflux. [b] Isolated yields of pure products.

Table 3. Synthesis of dihydropyrano[2,3-c]pyrazoles (5a-i; 6a-d) catalyzed by PPh_3[a].

Entry	Product	Ar	R	Time (h)	Yield (%)[b]	Mp (°C)[Ref]
1	**5a**	C_6H_5	H	1	82	242-244[28]
2	**5b**	2-$O_2NC_6H_4$	H	0.5	87	244-246[28]
3	**5c**	3-$O_2NC_6H_4$	H	0.5	84	188-190[33]
4	**5d**	4-$O_2NC_6H_4$	H	0.5	82	244-246[28]
5	**5e**	4-$(CH_3)_2NC_6H_4$	H	0.5	67	168-170[24]
6	**5f**	4-$H_5C_2C_6H_4$	H	2	63	220-222
7	**5g**	2-SC_4H_3	H	0.5	79	236-238[26]
8	**5h**	4-HOC_6H_4	H	1	73	222-224[28]
9	**5i**	4-$CH_3C_6H_4$	H	1	88	206-210[33]
10	**6a**	C_6H_5	C_6H_5	2	87	168-170[28]
11	**6b**	4-$O_2NC_6H_4$	C_6H_5	2	86	198-200[12]
12	**6c**	4-HOC_6H_4	C_6H_5	2	92	210-212[28]
13	**6d**	4-$H_5C_2C_6H_4$	C_6H_5	2	89	182-184

[a]Reaction conditions: Aldehyde (2 mmol), hydrazine or phenylhydrazine (2 mmol), ethyl acetoacetate (2 mmol), malononitrile (2 mmol), PPh_3 (0.1 mmol) in water (5 ml) at reflux. [b] Isolated yields of pure products.

In Scheme **2** we propose a plausible mechanism [44, 45] for the formation of dihydropyrano[2,3-c]pyrazoles based on the nucleophilic character of PPh_3 which is able to attack electrophilic carbons and thus facilitate the reaction in its different stages. This mechanism is characterized by the formation of two key intermediates **1** and **2**. The first one is the result of the Knoevenagel reaction of aromatic aldehyde and malononitrile. The formation of benzylidene **1** is facilitated by the nucleophilic character of PPh_3 which allows the formation of entities capable to extract protons and thus create the ideal conditions for the Knoevenagel reaction. In the other hand, intermediate **2** provides from the classic reaction of hydrazine (or its derivatives) with carbonyls. After enolisation favoured by the medium, **2** reacts with **1** in a Michael-type condensation. The resulting intermediate **3**, after intramolecular cyclization and tautomerization, yields the expected products **5** or **6**.

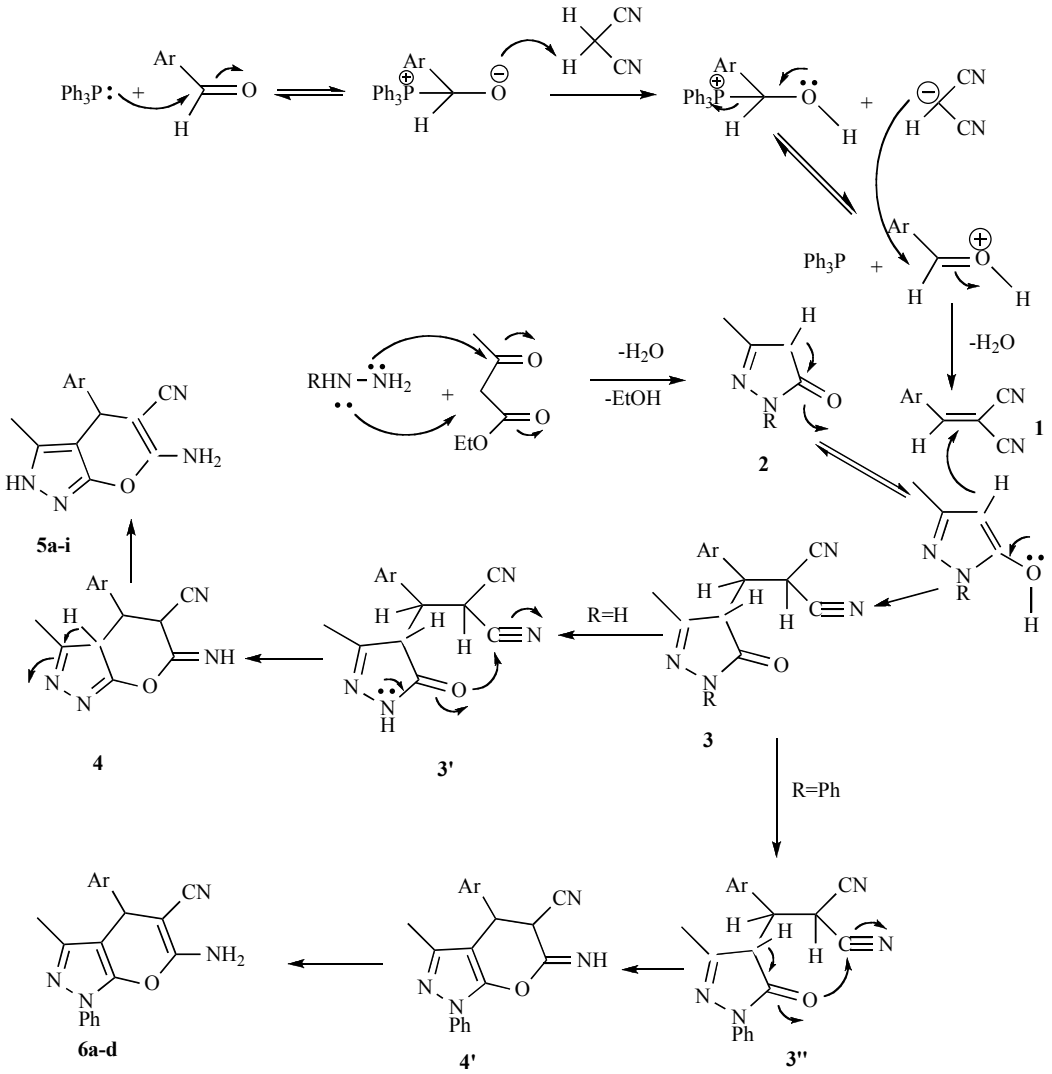
CONCLUSION

In this work, we have proposed a new procedure for the synthesis of dihydropyrano[2,3-c]pyrazoles, an important class of compounds for their various applications in medicine, pharmacy and agriculture. This new method is based on a four-component condensation of aldehydes, ethyl acetoacetate, hydrazine or phenylhydrazine and malononitrile using, for the first time, triphenylphosphine, a provided molecule, cheap and somewhat dangerous, as catalyst.

EXPERIMENTAL

General Procedure for the pyrano[2,3-c]pyrazoles 5 Synthesis

A 50 ml flask equipped with magnetic stirrer was charged with hydrazine hydrate **1a** (2 mmol, 0.1 g) or phen-



Scheme 2. Plausible mechanism for the formation of pyrano[2,3-c]pyrazoles **5** and **6**.

ylhydrazine **1b** (2 mmol, 0.236 g), ethyl acetoacetate **2** (2 mmol, 0.260 g), aldehyde **3** (2 mmol, **3a**=**3j**=0.212 g, **3b**=**3c**=**3d**=**3k**=0.302 g, **3e**=0.298 g, **3f**=**3m**=0.268 g, **3g**=0.224 g, **3h**=**3l**=0.244 g, **3i**=0.240 g, **3j**=0.212 g), malononitrile **4** (2 mmol, 0.132 g), triphenylphosphine (10 mol%, 0.052 g) in 5 ml of H_2O. The mixture is brought to reflux with continuous stirring until the reaction is finished (the progress of reaction is monitoring by TLC). After cooling, the mixture is poured onto ice water and the obtained solid is filtered. The products were purified by crystallization from ethanol.

Spectral Data for Selected pyrano[2,3-c]pyrazoles

6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (5a): IR (KBr): ν_{max} = 3367; 3170; 2191; 1647; 1600; 1400; 1041 cm^{-1}. ^1H NMR (DMSO, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.6 (s, 1H, C4-H); 6.90 (s, 2H, NH_2); 7.14-7.42 (m, 5H, ArH); 12.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.87 (CH_3); 36.37 (C4); 57.31 (C-CN); 97.77 (C-pyran); 120.98 (CN); 126.88 (C4'); 127.60 (C3', C5'); 128.57 (C2', C6'); 135.78 (C1'); 144.51 (C3); 154.89 (C-O); 161.01 (C-NH_2).

6-amino-3-methyl-4-(2-nitrophenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5b): IR (KBr): ν_{max} = 3413; 3313; 2187; 1651; 1600; 1527; 1407; 1218 cm^{-1}. ^1H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.6 (s, 1H, C4-H); 7.08 (s, 2H, NH_2); 7.32 (d, 1H, *J* = 7.7, Ar-H); 7.47 (t, 1H, *J* = 7.5, Ar-H); 7.54 (t, 1H, *J* = 7.5, Ar-H); 7.83 (d, 1H, *J* = 7.4, Ar-H); 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.63 (CH_3); 31.57 (C4); 56.16 (C-CN); 96.50 (C-pyran); 120.46 (CN); 123.37 (C5'); 124.91 (C4'); 127.99 (C2'); 132.25 (C1'); 134.07 (C3'); 135.93 (C3); 148.24 (C6'); 155.09 (C-O); 161.33 (C-NH_2).

6-amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5c): (KBr): ν_{max} = 3472; 3117; 2970; 2885; 2195; 1651; 1601; 1528; 1404; 1350. ^1H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.7 (s, 1H); 6.6 (s, 2H, NH_2); 7.49 (m, 2H, Ar-H); 8.0 (m, 2H, Ar-H); 12.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.82 (CH_3); 36.19 (C4); 56.81 (C-CN); 96.18 (C-pyran); 120.4 (CN); 121.71 (C4'); 121.95 (C3'); 129.47 (C6'); 133.94 (C2'); 135.83 (C1'); 146.16 (C3); 147.98 (C5'); 154.75 (C-O); 160.97 (C-NH_2).

6-amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5d): IR (KBr): ν_{max} = 3475; 3229; 3113; 2195; 1651; 1597; 1520; 1404; 1350. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.8 (s, 1H, C4-H); 6.8 (s, 2H, NH_2); 7.43 (d, 2H, J = 8.6, Ar-H); 8.16 (d, 2H, J = 8.6, Ar-H); 12.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.75 (CH_3); 36.16 (C4); 56.02 (C-CN); 96.25 (C-pyran); 119.0 (CN); 120.39 (C3', C5'); 123.61 (C2', C6'); 128.62 (C3); 135.68 (C1'); 146.33 (C4'); 151.77 (C-O); 161.07 (C-NH_2).

6-amino-4-(4-dimethylaminophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e): IR (KBr): ν_{max} = 3391; 3163; 2932; 2854; 1620; 1477; 1392; 1064. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.79 (s, 3H, CH_3); 2.87 (s, 6H, N-$(CH_3)_2$); 4.40 (s, 1H, C4-H); 6.42 (s, 2H, NH_2); 6.60 (d, 2H, J = 8.63, Ar-H); 6.96 (d, 2H, J = 8.63, Ar-H); 11.79 (s, 1H, NH).). ^{13}C NMR (DMSO-d_6, δppm): 9.72 (CH_3); 35.43 (C4); 58.70 (C-CN); 97.78 (C-pyran); 111.98 (CN); 120.82(C3', C5'); 127.83 (C1'); 131.54 (C2', C6'); 135.45 (C3); 148.96 (C4'); 154.76 (C-O); 160.32 (C-NH_2).

6-amino-4-(4-ethylphenyl)-3-methyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5f): IR (KBr): ν_{max} = 3463;; 3128; 2966; 2927; 2191; 1651; 1600; 1400; 1049 cm^{-1}. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.3 (t, H, *J* = 7.4, CH_3); 1.8 (s, 3H, CH_3); 2.57 (q, 2H, *J* = 7.4, CH_2); 4,6 (s, 1H, C4-H); 6,90 (s, 2H, NH_2); 7,09 (d, 2H, *J*=8, Ar-H); 7.15 (d, 2H, *J* =8.0, Ar-H) 12.17 (s,1H). ^{13}C NMR (DMSO-d_6, δppm): 9.92 (C3-$\underline{C}H_3$); 15.59 (CH_3); 27.94 (CH_2); 36.04 (C4); 57.57 (C-CN); 97.95 (C-pyran); 121.10 (CN); 127.54 (C2', C6'); 127.95 (C3', C5'); 135.79 (C1'); 141.66 (C3); 142.22 (C4')); 154.98 (C-O); 161.03 (C-NH_2). HRMS calcd for $C_{16}H_{16}N_4O$ [M^+] 280.1324, found 280.1305.

6-amino-3-methyl-4-(thiophen-2-yl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5g): IR (KBr): ν_{max} = 3355; 3170; 2187; 1647; 1600; 1400; 1041cm^{-1}. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 2.0 (s, 3H, CH_3); 5 (s, 1H, C4-H); 7.20 (s, 2H, NH_2); 6.9-7.1 (m, 3H, thiophene-H); 12.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.85 (CH_3); 31.48 (C4); 57.65 (C-CN); 97.65 (C-pyran); 120.76 (CN); 124.50 (C5'); 125.11 (C3'); 126.63 (C4'); 136.20 (C3); 149.61 (C2'); 154.37 (C-O); 160.74 (C-NH_2).

6-amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h): IR (KBr): ν_{max} = 3390.64; 3300.69; 3141.44; 2176.32; 1646.50; 1599.76; 1408.55 cm^{-1}. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.4 (s, 1H, C4-H); 6.7 (d, 2H, J = 8.2; Ar-H); 6.8 s, 2H, NH_2); 6.9 (d, 2H, J = 8.2; Ar-H); 9.30 (s, 1H, NH); 12 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, δppm): 10.2 (CH_3); 35.91 (C4); 58.22 (C-CN); 98.5 (C-pyran); 115.55 (C3', C5'); 121.35 (CN); 128.88 (C1'); 135.20 (C2', C6'); 135.97 (C3); 155.19 (C4'); 156.45 (C-O); 161.07 (C-NH_2).

6-amino-4-(4-methylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5i): ν_{max} = 3406; 3193; 2191; 1643; 1600; 1400; 1045. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.79 (s, 3H, CH_3); 2.25 (s, 3H, CH_3); 4.55 (s, 1H, C4-H); 6.85 (s, 2H, NH_2); 6.95-7.06 (m, 4H, Ar-H); 12.11 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δppm): 9.90 (CH_3); 20.84 (Ar-CH_3); 36.26 (C4); 58.99 (C-CN); 98.03 (C-pyran); 120.14 (CN); 121.35 (C1'); 128.05 (C3', C5'); 129.61 (C2', C6'); 136.73 (C4'); 141.50 (C3); 155.82 (C-O); 161.59 (C-NH_2).

6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6a): IR (KBr): ν_{max} = 3467; 3321; 2194; 1969; 1648; 1589; 1446 cm^{-1}. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4,7 (s, 1H, C4-H); 7.25-7.39 (m, 8H, Ar-H and NH_2); 7.51(t, 2H, J = 7.7, Ar-H); 7.80 (d, 2H, J = 7.7, Ar-H). ^{13}C NMR (DMSO-d_6, δppm): 12.65 (CH_3); 36.81 (C4); 58.21 (C-CN); 98.72 (C-pyran); 120.03 (C2', C6'); 126.26 (C4', C4''); 127.15 (C3'', C5''); 127.87 (C2'', C6''); 128.62 (C3', C5'); 137.60 (C1''); 143.69 (C1'); 143.94 (C3); 145.36 (C-O); 159.51 (C-NH_2).

6-amino-4-(4-nitrophenyl)-3-methyl--1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6b): IR (KBr): ν_{max} = 3440; 3328; 2194; 1658; 1593; 1446; 1064. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.9 (s, 1H, C4-H); 7.4-7.6 (m, 7H, Ar-H, NH_2); 8.25 (d, 2H, J = 8.64, Ar-H); 7.85 (d, 2H, J = 7.96, Ar-H). ^{13}C NMR (DMSO-d_6, δppm): 12.63 (CH_3); 36.46 (C4); 56.91 (C-CN); 97.65 C-pyran); 119.84 (CN); 120.15 (C2', C5'); 123.98 (C3'', C5''); 126.40 (C4'); 129.28 (C3', C5'); 129.34 (C2'', C6''); 137.48 (C1'); 137.64 (C1''); 144.06 (C4''); 145.24 (C3); 151.24(C-O); 159.79 (C-NH_2).

6-amino-4-(4-hydroxyophenyl)-3-methyl--1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6c): IR (KBr): ν_{max} = 3417; 3317; 2179; 1658; 1589; 1446; 1068 cm^{-1}. ^{1}H NMR (DMSO-d_6, δppm, *J* Hz): 1.8 (s, 3H, CH_3); 4.6 (s, 1H, C4-H); 6.74 (d, 2H, J = 7.50, Ar-H); 7.05 (d, 2H, J = 7.50, Ar-H); 7.16 (s, IH, NH_2); 7.32 (t, 2H, J = 7.50, Ar-H); 7.50 (t, 2H, J = 7.50, Ar-H); 7.79 (d, 2H, J = 7.50, Ar-H). ^{13}C NMR (DMSO-d_6, δppm): 12.68 (CH_3); 36.07 (C4); 58.81 (C-CN); 99.12 (C-pyran); 115.29 (CN); 119.96 (C3'', C5''); 120.25 (C2', C6'); 126.19 (C4'); 128.87 (C3', C5'); 129.43 (C3); 134.02 (C2'', C6''); 137.64 (C1'); 143.64 (C1''); 145.46 (C-O); 156.35 (C-OH); 159.27 (C-NH_2).

6-amino-4-(4-ethylphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6d): IR (KBr): ν_{max} = 3386; 3332; 2966; 2869; 2187; 1658; 1593; 1446; 1088 cm^{-1}. ^{1}H NMR (DMSO, δppm, *J* Hz): 1.2 (t, 3H, *J* = 7.4, CH_3); 1.75(s, 3H, CH_3); 2.6 (q, 2H, *J* = 7.4, CH_2); 4.6 (s, 1H, C4-H); 7.17-7.21 (m, 5H, Ar-H and NH_2); 7.32 (t, 2H, J = 7.50, Ar-H); 7.50 (t, 2H, J = 7.50, Ar-H); 7.80 (d, 2H, J = 7.50, Ar-H). ^{13}C NMR (DMSO-d_6, δppm): 12.70 (CH_3); 15.56 (CH_3); 27.87 (CH_2); 36.48 (C4); 58.41(C-CN); 98.87 (C-pyran); 120.22 (C2', C6'); 126.25 (C3'', C5''); 127.77 (C2'', C6''); 127.99 (C3', C5'); 129.45 (C3); 137.63 (C1''); 141.00 (C1'); 142.49 (C4''); 145.42 (C-O); 159.49 (C-NH_2). HRMS calcd for $C_{22}H_{20}N_4O$ [M^+] 356.1637, found 356.1629.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Zhu, J., Bienaymé, H. *Multicomponent Reactions*; Eds.; Wiley-VCH: Weinheim, Germany, **2005**.

[2] Mandour, A.H.; El-sawy, E.R.; Ebaid, M.S.; Hassan, M.S. Synthesis and potential biological activity of some novel 3-[N-substitutesindol-3-yl)methyleneamino]-6-amino-4-aryl-pyran(2,3-c)pyrazole-5-carbonitriles and 3,6-diamino-4-(N-substitutesindole-3-yl)pyrano(2,3-c)pyrazole-5-carbonitrile. *Acta Pharma.*, **2012**, *62*, 15-30.

[3] Wang, J.L.; Liu, D.; Zheng, Z.J.; Shan, S.; Han, X.; Srinivasula, S.M.; Croce, C.M.; Alnemri, E.S.; Huang, Z. Structure-based discovery of an organic compounds that bind Bc1-2 protein and induces apoptosis of tumor cells. *Proc. Natl. Acad. Sci. USA.*, **2009**, *97*, 7124-7129.

[4] Ramiz, M.M.; Abdel Hafiz, I.S.; Abdel Reheim, M.A.M.; Gaber, H.M. Pyrazolones as building blocks in heterocyclic synthesis: synthesis of new pyrazolopyran, pyrazolopyridazine and pyrazole derivatives of expected antifongical activity. *J. Chin. Chem. Soc.*, **2012**, *59*, 72-80.

[5] Kuo, S.C.; Huang, L.J.; Nakamura, H. Studies on heterocyclic compounds. 6. Synthesis and analgesic and antiinflammatory activities of 3,4-dimethyl-pyrano[2,3-c]pyrazol-6-one derivatives. *J. Med. Chem.*, **1984**, *27*, 539-544.

[6] Follope, N.; Fisher, L.M.; Howes, R.; Potter, A.; Robertson, A.G.S.; Surgenor, A. E. Idendification of chemically diverse Chk1 inhibitors by receptor-based virtual screening. *Bioorg. Med. Chem.*, **2006**, *14*, 4792-4802.

[7] Junek, H.; Igner, H. Synthesen mit nitrilen, XXXV: Reaktionen von Tetracyanäthylen mit Heterocyclen. *Chem. Ber.*, **1973**, *106*, 914-921.

[8] Otto, H.H. Synthesis of some *4H*-pyrano[2,3,-c]pyrazoles. *Arch. Pharm.*, **1974**, 444-447.

[9] Shestopalov, A.M.; Yakubov, A.P.; Tsyganov, D.V.; Emel'yanova, Y.M.; Nesterov, V.N. Synthesis of 6-amino-4-aryl-5-cyano-2H,4H-pyrano[2,3-c]pyrazoles. Crystal and molecular structure of 6-amino-3-methyl-4-(2',4',6'-triethylphenyl)-2H,4H-pyrano[2,3-c]pyrazole. *Chem. Heterocycl. Compd.*, **2002**, *38*, 1180-1189.

[10] Shi, D.; Mou, J.; Q. Zhuang, Q.; Niu, L.; Wu, N.; Wang, X. Three component one-pot synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives in aqueous media. *Synth. Commun.*, **2004**, *34*, 4557-4563.

[11] Jin, T-S.; Wang, A-Q.; Cheng, Z-L.; Zhang, J-S.; Li, T-S. A clean and simple synthesis of 6-amino-4-aryl-5cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole in water. *Synth. Commun.*, **2005**, *35*, 137-143.

[12] Azarifar, A.; Nejat-Yami, R.; Al Kobaisi, M.; Ararifar, D. Magnetic $L_{a0.7}S_{r0.3}Mn_{O3}$ nanoparticules: recycable and efficient catalyst for ultrasound-accelerated synthesis of *4H*-chromenes, and *4H*-pyrano[2,3-c]pyrazoles. *J. Iran Chem. Soc.*, **2013**, *10*, 439-446.

[13] Saha, M.; Pal, A.K. Palladium (0) nanoparticules: a novel and reusable catalyst for the synthesis of various pyran derivatives. *ANP*, **2012**, *1*, 61-70.

[14] Khurana, J.M.; Chaudhary, A. Efficient and green synthesis of *4H*-pyrans and *4H*-pyrano[2,3-c]pyrazoles catalyzed by task-specific ionic liquid [bmim]OH under solvent-free conditions. *Green Chem. Lett. Rev.*, **2012**, *5*, 633-638.

[15] Niknam, K.; Piran, A. Silica-grafted ionic liquids as reusable catalysts for the synthesis of 3,4-dihydrochromenes and pyrano[2,3-c]pyrazoles. *GSC*, **2013**, *3*, 1-8.

[16] Jin, T.-S.; Zhao, R.-Q.; Li, T.-S. An one-pot three-component process for the synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles in aqueous media," *Arkivoc*, **2006**, *11*, 176-182.

[17] Bhosale, V.N.; Angulwar, J.A.; Khansole, G.S.; Waghmare, G.S. One-pot three-component condensationfor the synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles using cesiumfluoride as an efficient catalyst. *J. Chem. Pharm. Res.*, **2014**, *6*, 733-737.

[18] Shaabani, A.; Sarvary, A.; Resayan, A.H.; Keshipour, S. Synthesis of fully substituted pyrano[2,3-c]pyrazole derivatives *via* a multicomponent reaction of isocyanides. *Tetrahedron*, **2009**, *65*, 3492-3495.

[19] Vasuki, G.; Kumaravel, K. Rapid four-component reactions in water: synthesis of pyranopyrazoles. *Tetradedron Lett.*, **2008**, *49*, 5636-5638.

[20] El-Assaly, S.A. A simple and clean method for four-component synthesis of pyrano[2,3-c]pyrazole derivatives. *Der Pharma Chem.*, **2011**, *3*, 81-86.

[21] Kanagarj, K.; Pitchumani, K. Solvent-free multicomponent synthesis of pyranopyrazoles: per-6-amino-b-cyclodextrin as a remarkable catalyst and host. *Tetrahedron Lett.*, **2010**, *51*, 3312-3316.

[22] Siddekha, A.; Nizam, A.; Pasha, M.A. An efficient and simple approach for the synthesis of pyranopyrazoles using imidazole (catalytic) in aqueous medium, and the vibrational spectroscopic studies on 6-amin-4-(4-methoxyphenyl)-5-methyl-1-phenyl-2,4-dihydropyrrano[2,3-c]pyrazole using density functional theory. *Spectrochim. Acta A.*, **2011**, *81*, 431-440.

[23] Elnagdi, N.M.H.; Al-hokbani, N.S. Orgaocatalyst in synthesis: L-proline as an enantioselective catalyst in the synthesisof pyrans and thiopyrans. *Molecules*, **2012**, *17*, 4300-4312.

[24] Mecadon, H.; Rohman, Md. R.; Rajbangshi, M.; Myrboh, B. g-Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles in aqueous medium. *Tetrahedron Lett.*, **2011**, *52*, 2523-2525.

[25] Azzam, S.H.S.; Pasha, M.A. Simple and efficient protocol for the synthesis of novel dihydro-1H-pyrano[2,3-c]pyrazol-6ones *via* a one-pot four-component reaction. *Tetrahedron Lett.*, **2012**, *53*, 6834-6837.

[26] Darandale, S.; Sngshetti, J.S.; Shinde, D.B. Ultrasound, sodium bisulfate catalyzed, solvent free synthesis of 6-amino-3-methyl-4-substituted-2,4-dihydropyrano[2,4-c]pyrazole-5-carbonitrile. *J. Korean Chem. Soc.*, **2012**, *56*, 328-333.

[27] Reddy, M.B.M.; Pasha, M.A. One-pot multicomponent synthesis of *4H*-pyrano[2,3-c]pyrazole in water at 25°C. *Indian J. Chem., Sect B*, **2012**, *51B*, 537-541.

[28] Kiyani, H.; Samimi, H.A.; Ghorbani, F.; Esmaieli, S. One-pot, four-component synthesis of pyrano[2,3-c]pyrazoles catalyzed by sodium benzoate in aqueous medium. *Cur. Chem. Lett.*, **2013**, *2*, 1-10.

[29] Shinde, P.V.; Gujar, J.B.; Shingate, B.B.; Shingare, M.S. Silica in water: a potential valuable medium for the synthesis of pyrano[2,3-c]pyrazoles. *Bull. Korean Chem. Soc.*, **2012**, *33*, 1345-1348.

[30] Ebrahimi, J.; Mohammadi, A.; Pakjoo, V.; Bahramzade, E; Habibi, A. Highly efficient solvent-free synthesis of pyranopyrazoles by a Brönsted-acidic ionic liquid as a green and reusable catalyst. *J. Chem. Sci.*, **2012**, *124*, 1013-1017.

[31] Babaie, M.; Sheibani, H. Nanosized magnesium oxide as a highly effective heterogeneous catalyst for the rapid synthesis of pyranopyrazoles *via* a tandem four-component reaction. *Arabian J. Chem.*, **2011**, *4*, 159-162.

[32] Chavan H.V.; Babar, S.B.; Hoval, R.U.; Bandgar, B.P. Rapid one-pot, four component synthesis of pyranopyrazoles using heteropolyacid under solvent-free condition. *Bull. Korean Chem. Soc.*, **2011**, *32*, 3963-3966.

[33] Bora, P.P.; Bihani, M.; Bez, G. Multicomponent synthesis of dihydropyrano[2,3-c]pyrazoles catalyzed by lipase from *Aspergillus niger*. *J. Mol. Catal. B: Enzym.*, **2013**, *92*, 24-33.

[34] Zonouz, A.M.; Eskandari, I.; Khavasi, H.R. A green and convenient approach for the synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-c]pyrazole-4-carboxylates *via* a one-pot, multicomponent reaction in water. *Tetrahedron Lett.*, **2012**, *53*, 5519-5522.

[35] (a) Muramulla, S.; Zha, C-G. A new catalytic mode of the modularly designed organocatalysts (MDOs): enantioselective synthesis of dihydropyrano[2,3-c]pyrazoles. *Tetrahedron Lett.*, **2011**, *52*, 3905-3908. (b) Elnagdi, N.M.H.; Al-hokbani, N.S. Orgaocatalyst in synthesis: L-proline as an enantioselective catalyst in the synthesisof pyrans and thiopyrans. *Molecules*, **2012**, *17*, 4300-4312.

[36] (a) Gogoi, S.; Zhao, C-G. Organocatalyzed enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-c]pyrazoles. *Tetrahedron Lett.*, **2009**, *50*, 2252-2255. (b) Zhang, H-F.; Ye, Z-Q.; Zhao, G. Enantoselective synthesis of funtionalized fluorinated dihydro[2,3-c]pyrazoles catalyzed by a simple bifunctional diaminocyclohexane-thiourea. *Chin. Chem. Lett.*, **2014**, *25*, 535-540.

[37] (a) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Manas, M. Michael additions catalyzed by phosphines. An overlooked synthetic method. *Tetrahedron* 2005, *61*, 8598-8605. (b) Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Surech Reddy, Ch.; Narsaiah, A.V. Triphenylphosphine: An efficient catalyst for transesterification of b-ketoesters. *J. Mol. Catal.* 2007, *261*, 93-97. (c) Nicolas, L.: Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S. *Tetrahedron Lett.* 2014, *55*, 849-852. (d) Bai, L.; Zhang, L.; Liu, Y.; Pan, X.; Cheng, Z.; Zhu, X. Triphenylphosphine as phosphorus catalyst for

reversible chain-transfer catalyzed polymerization (RTCP). *Polym. Chem.* 2013, *4*, 3069-3076.

[38] Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones by triphenymphosphine as Lawis base. *Tetrahedron Lett.*, **2008**, *49*, 6119-6121.

[39] Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. An efficient one-step synthesis of 1,4-dihydropyridines *via* a triphenylphosphine-catalyzed three-component Hantzsch reaction under mild conditions. *Tetrahedron Lett.*, **2009**, *50*, 5248-5250.

[40] Ghalem, W.; Sedrati, R.H.; Benloucif, N.; Berrée, F.; Boumoud, B.; Debache, A. Triphenylphosphine-catalyzed one-pot three comoponent synthesis of tetrahydrobenzo[b]pyrans in aqueous media. *Lett. Org. Chem.*, **2013**, *10*, 150-154.

[41] Amine Khodja, I.; Ghalem, W.; Dehimat, Z.; Boulcina, R.; Carboni, B.; Debache, A. Solvent-free Synthesis of Dihydropyridines and Acridinediones *Via* a Salicylic Acid-catalyzed Hantzsch Multicomponent Reraction, *Synth. Commun.*, **2014**, *44*, 959-967.

[42] Amine Khodja, I.; Boulcina, R.; Debache, A.. Novel one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones and 3,4,7,8-tetrahydroquinazoline-2,5-diones using pyridinium *p*-toluenesufonate as catalyst. *Lett. Org. Chem.*, **2015**, *12*, 77-84.

[43] Boukezzoula, F.; Boumoud, T.; Boumoud, B.; Debache, A. Multicompnent reaction, Ionic Liquid and Aqua Mediated: A Perfect Synergy for Eco-compatible Heterocyclic Synthesis. *Chem. Sci. Trans*., **2015**, *4*, 611-619.

[44] Riyaz, S.; Naidu, A.; Dubey, P.K. Triphenylphosphine Catalyzed One-Pot, Multicompnent Synthesis of Spirooxindoles. *Lett. Org. Chem.*, **2012**, *9,* 101-105.

[45] Vasuky, G.; Kumaravel, K. Rapid four-component reactions in water: synthesis of pyranopyrazoles. *Tetrahedron Lett.*, **2008**, *49*, 5636-5638.