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Aluminum Acetylacetonate as a Recyclable Organometallic Catalyst for One-Pot Four-Component Synthesis of Pyranopyrazoles

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ABSTRACT

*Multicomponent reactions exhibit higher atom economy and selectivity and generally produce fewer by-products compared to classical multistep syntheses, thus multicomponent reactions play an important role in modern organic chemistry. In this context, we report herein, an environmentally benign four-component reaction in aqueous medium at reflux temperature for the synthesis of 6-amino-5-cyano-3-methyl-4-aryl/heteroaryl-2H,4H-dihydropyrano[2,3-***c***]pyrazoles in the presence of aluminum acetylacetonate as a recycled organometallic catalyst.*

Keywords: Pyranopyrazole, aluminuim acetylacetonate, Al(acac)$_3$, organometallic catalyst, multicomponent reactions, aqueous medium.

INTRODUCTION

1,4-Dihydropyrano[2,3-c]pyrazole derivatives are known since early 19th century. These compounds are widely used as anticancer [1], cytotoxic[2], pesticide [3], antibacterial and antifungal, analgesic, antioxidant, anti-inflammatory, antiplatelet, Chk1 kinase inhibitory, molluscicidal, biodegradable agrochemcials like insectidials, vasodilating and hypoglycemic and anti-microbial agents [4]. They also possess ulcerogenic, antitubercular, antimalarial, antitumor, antiproliferative, antihypertensive and hypnotic properties [5]. Owing to these significant biological properties, several synthetic approaches for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives were reported among which we can cite the simple approach involving the four component condensation of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate in the presence of different catalysts such as [Bmim]OH [6], nano ZnO [7], L-proline, and γ-alumina [8], glycine [9], silica in water [10], Ba(OH)$_2$ in water at reflux [11], acetyltrimethylammonium bromide [12] and citric acid [13] under different conditions such as microwave irradiation [14]

On the other hand, it is well known that water can be used as green solvent in organic synthesis due to its abundant, nontoxic, non-corrosive and non-flammable nature, thus, the combination of multi-component reactions and water as a green solvent has become a promising frontier field of research in organic, medicinal, and combinatorial chemistry.

Given the importance of 1,4-dihydropyrano[2,3-c]pyrazole derivatives and as a part of ongoing program in search of novel catalysts and multicomponent methodologies [15], in this study, we investigate the catalytic effect of Aluminum acetylacetonate [Al(acac)$_3$] in the synthesis of pyranopyrazole derivatives via four component reaction of carbonyl compound **1**, hydrazine hydrate **2,** malononitrile **3**, and β-ketoester **4** in aqueous medium (Scheme 1).

MATERIALS AND METHODS

Apparatus and analysis

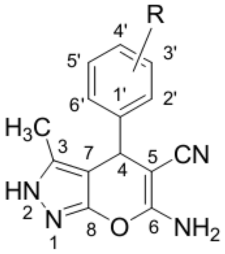
Unless otherwise specified all solvents and reagents were of reagent grade and used without further purification.

Melting points were determined on Banc Kofler apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC), visualizing with ultraviolet. ^{1}H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 and chemical shifts are reported in parts per million (ppm) on a BRUKER AVANCE DPX spectrometer at 250 and 62.9 MHz respectively using TMS as internal standard. Spectral patterns are designated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constants are reported in hertz (Hz). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer.

General procedure for the synthesis of [2,4-dihydropyrano[2,3-c]pyrazole] derivatives (5a-k)

A mixture of hydrazine hydrate (0.05 g, 1.0 mmol), β-ketoester (0.130 g, 1.0 mmol), benzaldehyde (0.106 g, 1.0 mmol) and malononitrile (0.066 g, 1.0 mmol) in the presence of aluminum acetylacetonate (5 mol%) in water (5ml) was stirred at reflux for appropriate time of period (course of the reaction was monitored by TLC). After completion of the reaction, the mixture was poured onto ice-cold water and obtained solid product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to afford the desired product.

The structures of all the prepared products were clearly established on the basis of their spectral analysis (IR, ^{1}H&^{13}C NMR) and melting points.



6-Amino-4-(2-nitrophenyl)-3-methyl-2, 4-dihydropyrano [2, 3-c] pyrazole-5-carbonitrile (5m)

Blackish powder; yield: 90%; mp. 246-247 °C; IR cm-^{1}: 3413, 3263 (NH_2), 2191 (CN), 1600 (Ar), 1523 (C-NO_2); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 12. 06 (s, 1H, NH), 7.80 (1H, d, *J* = 6.5 Hz, CH aromatic), 7.61 (1H, t, *J* = 6.0 Hz, CH aromatic), 7.41 (1H, t, *J* = 6.0 Hz, CH aromatic), 7.30 (d, *J* = 6.5 Hz, CH aromatic), 6.80 (s, 2H, NH_2), 5.12 (1H, s, 1H, C4-H), 1.8 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 159.80 (C6), 150.31 (C3), 134.50 (C8), 153.50, 145.11, 127.30 and 122.32 (C aromatic), 119.10 (CN), 94.91 (C7), 55.10 (C5), 35.10 (C4), 8.51 (CH_3).

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

Yellow crystal; yield: 90%; mp 219-220 °C; IR cm^{-1}: 3401, 3190 (NH_2), 2187 (CN), 1636 (C=N), 1604 (Ar); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 12.11 (1H, s, NH), 7.12 (2H, d, *J* = 7.0 Hz, CH aromatic), 7.05 (2H, d, *J* = 7.0 Hz, CH aromatic), 6.89 (2H, s, NH_2), 4.55 (1H, s, C4-H), 2.27 (3H, s, CH_3), 1.79 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 160.80 (C6), 154.71 (C3), 135.81 (C8), 141.50, 129.01, 127.31 and 121.01 (C aromatic), 119.40 (CN), 97.90 (C7), 57.3 (C5), 35.91 (C4), 20.71 (CH_3), 9.80 (CH_3).

RESULTS AND DISCUSSION

Initially, we carried out the model reaction of benzaldehyde **1a** (1.0 mmol), hydrazine hydrate **2** (1.0 mmol), malononitrile **3** (1.0 mmol) and ethyl acetoacetate **4** (1.0 mmol) in the presence of Al(acac)$_3$ (5mol %) as catalyst at different temperatures and in different solvents

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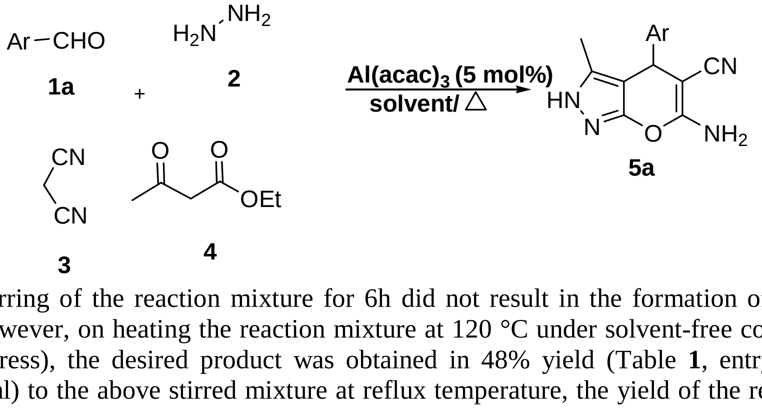


Room temperature stirring of the reaction mixture for 6h did not result in the formation of the expected product (Table **1**, entry 1). However, on heating the reaction mixture at 120 °C under solvent-free conditions for 3 h (using TLC to monitor progress), the desired product was obtained in 48% yield (Table **1**, entry 2). Surprisingly, the addition of water (5 ml) to the above stirred mixture at reflux temperature, the yield of the reaction jumped to 90% within 30 minutes (Table **1**, entry 3), so, in order to seek the optimal solvent, the model reaction was explored using different solvents such as water, ethanol, acetonitrile and a mixture of water/ethanol (1:1) at reflux temperature (Table **1**, entries 4-7). The results, summarized in Table **1**, show that acetonitrile or ethanol as well as the mixture EtOH/H_2O are less effective than water (Table **1**, entries 5-7) and the best yield is obtained with water (Table **1**, entry 4).

Table 1 Optimization of the appropriate solvent and temperature.[a]

Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%) [b]
1	none	none	Rt	6.0	--
2	none	5	120	--	48
3	H_2O	none	120	4.0	70
4	H_2O	5	reflux	1/2	90
5	AcCN	5	reflux	4.0	27
6	EtOH/H_2O	5	reflux	1.0	56
7	EtOH	5	reflux	1.1/2	71
8	H_2O	10	reflux	1/2	67
9	H_2O	15	reflux	1/2	64
10	H_2O	20	reflux	1/2	58

[a]*Reaction condition: hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol) and malononitrile (1.0 mmol) and Al(acac)$_3$ (5 mol%) stirred at reflux temperature;* [b] *Isolated yields.*

Beside the solvent and temperature, the amount of the catalyst plays a crucial role in terms of rate of the reaction, thus, the model reaction was performed with different amounts of catalyst at reflux temperature of water during 30 min (Table **1**, entries 8-10). For this condensation, the optimal amount of aluminum acetylacetonate was found to be 5 mol% (regarding to benzaldehyde).

To explore the scope of the methodology, a range of different substituted groups on aromatic aldehydes involving electron-withdrawing groups such as 3-nitro, 4-nitro, and electron-donating groups such as 4-chloro and 4-dimethylaminobenzaldehyde reacted under optimized conditions into corresponding **5c-f** in 94%, 94%, 95% and 91% yield respectively after 30 min heating at reflux temperature (Table **2**, entries 3-6).

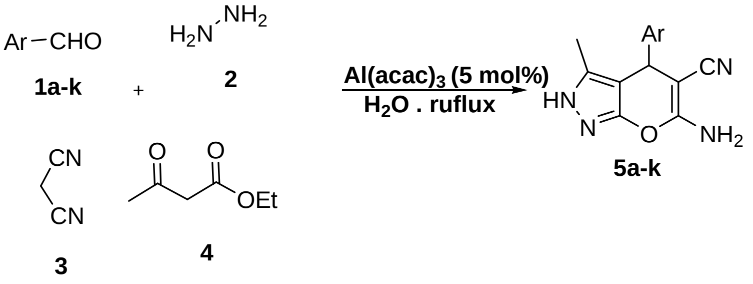
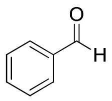
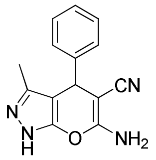
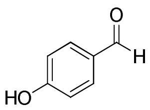
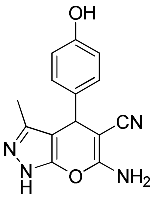
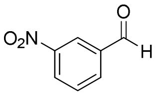
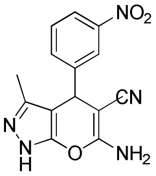
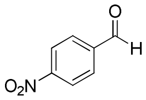
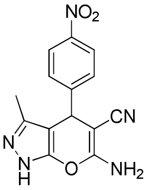
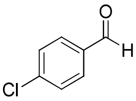
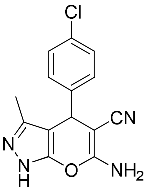
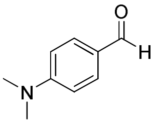
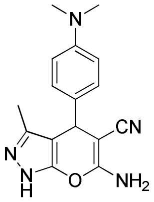
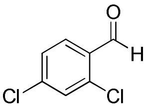
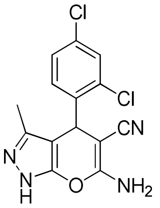
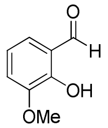
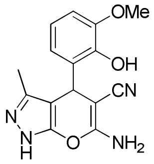
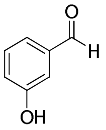
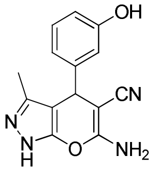
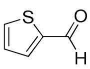
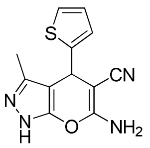
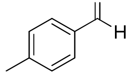
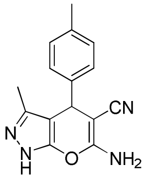
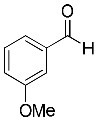
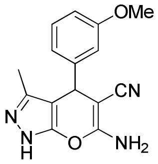
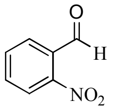
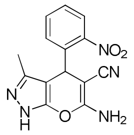
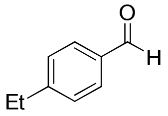
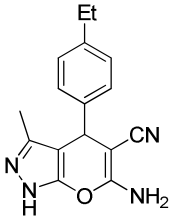


Table 2. **One-pot synthesis of pyranopyrazoles catalyzed by Al(acac)$_3$**[a]

Entry	Substrate	Product	Time (min)	Yield[b] (%)	M.p. (°C)	
					Measured	Reported[ref]
1		 **5a**	30	82	245-246	243-245[16]
2		 **5b**	35	91	229-230	225-227[17]

3		 **5c**	30	94	214-215	214-216[18]
4		 **5d**	30	94	249-250	249-252[16]
5		 **5e**	30	95,88,79,65[c]	239-240	248-249[17]
6		 **5f**	30	91	219-222	220-222[18]
7		 **5g**	15	91	196-198	198-205[19]
8		 **5h**	20	90	221-222	-
9		 **5i**	25	82	248-249	233-235[16]
10		 **5j**	40	95	226-228	224-226[3]
11			35	90	219-220	206-207[17]

		5k				
12		 **5l**	25	90	225-226	---
13		 **5m**	25	90	246-247	245-2473
14		 **5n**	45	96	248-249	---

[a] *Reactions were performed on a 1.0 mmol scale of all reactants with 5 mol % of Al(acac)$_3$ in refluxed water (5 ml;* [b] *Melting points were matched with authentic samples and literature data;* [c]*The recovered catalyst was used .*

The possibility of recycling the catalyst was examined using the reaction of malononitrile, 4-chlorobenzaldehyde, hydrazine and ethyl acetoacetate and under the optimized conditions. Upon completion, the reaction mixture was washed with cold ethanol (3 × 30 ml), the solvent was evaporated and the recovered catalyst was dried and reused for subsequent runs. The recycled catalyst was reused fourth times without any additional treatment. Appreciable loss in the catalytic activity of recovered Al(acac)$_3$ was observed (Table **2**, entry 5).

CONCLUSION

In conclusion, we reported the synthesis of dihydropyrano[2,3-c]-pyrazoles via four component reaction of various benzaldehydes, ethyl acetoacetate, hydrazine hydrate and malononitrile in the presence of aluminum acetylacetonate as an organometallic catalyst in aqueous medium. We examined a wide variety of benzaldehydes with various substituents to establish the catalytic importance of this catalyst for this reaction. The easy purification of products by simple crystallization, and the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.

Acknowledgements

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