Mono- and Bis-2-amino-4*H*-pyrans: Alum Catalyzed Three- or Pseudo Five-Component Reaction of 4-Hydroxycoumarin, Malononitrile and Aldehydes

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Abstracts: An efficient method for the three- or pseudo five-component synthesis of mono- and bis-2-amino-4*H*-pyrans in excellent yields using Alum ($KAl(SO_4)_2.12H_2O$) as recyclable catalyst is described. The present methodology offers several advantages such as excellent yields, simple procedures, shorter reaction times, milder conditions and the catalysts exhibited remarkable reusable activity.

Keywords: Alum ($KAl(SO_4)_2.12H_2O$), 2-Amino-4*H*-pyrans, 4-Hydroxycoumarin.

INTRODUCTION

4*H*-pyran is a privileged heterocyclic ring system because many of its derivatives possess useful pharmacological activities [1]. 2-Amino-4*H*-pyran derivatives represent an important class of compounds. They are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals [2]. Polyfunctionalized 4*H*-pyrans also constitute a structural unit of many natural products [3] and biologically interesting compounds which possess various pharmacological activities [1], such as antiallergic [3], antitumor [1] antibacterial [4]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [5] which are structurally similar to biologically active 1,4-dihydropyridines.

Recently, 2-amino-4*H*-pyrans were synthesized by three-component condensation reaction of aldehyde, malononitrile or ethyl 2-cyanoacetate and β-dicarbonyl compounds such as dimedone, barbituric acid or hydroxycoumarin in the presence of base such as piperidine [6], morpholine, pyridine [7] triethylamine [8], sodium methoxide [9] or 1,1,3,3-tetramethylguanidine [10]. Recently, it was found that chemical bases could be replaced with an electrogenerated base to promote reactions [11]. Also this condensation has been catalyzed by variety of reagents such as: HMTAB [12], TEBA [13], $RE(PFO)_3$ [14], NaBr [15], (S)-proline [16], the use of microwave irradiation [17], KF-basic alumina under ultrasound irradiation [18], DAHP [19], Na_2SeO_4 [20], Mg/La mixed oxide catalyst [21], TMG-[bmim][X] and [2-aemim][PF_6] [22], morpholine [23], CTACl (cetyltrimethyl-ammonium chloride) [24], TBAB [25] and aminoalcohol [26].

Thus, each of the known procedures for the synthesis of corresponding 2-amino-4*H*-pyrans has its merits; however, further studies are still necessary for the essence of facile, environmental and economical multicomponent methodology. Due to the biological activity of 4*H*-pyrans and our interest in the synthesis of heterocyclic compounds [27], herein, we report a simple and efficient method for the preparation of mono- and bis-2-amino-4*H*-pyran derivatives using Alum as the catalyst in the multi-component reaction of 4-hydroxycoumarin, malononitrile and aldehydes.

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RESULTS AND DISCUSSION

Alum is an inexpensive, water-soluble, non-toxic and commercially available compound that can be used in the laboratory without special precautions. Alum, well known for its traditional role in water treatments (coagulation and clarification) has recently been reported as a reusable, cheap and excellent catalyst for the preparation of organic compounds, for example, in the transesterification of palm oil [28], synthesis of α-aminophosphonates [29], 2,3-dihydroquinazolin-4(1*H*)-ones [30], 1,3,4-Oxadiazoles [31], di-hydropyrimidinones [32], *cis*-isoquinolonic acids [33], pyrroles [34] and coumarins [35]. Thus, continuing our research on new one-pot reactions, we considered Alum to be ideal for affecting the synthesis of mono- and bis-2-amino-4*H*-pyrans *via* a three- or pseudo five-component reaction of 4-hydroxycoumarin, malononitrile and aldehydes in ethanol/water media at room temperature.

The synthesis of mono-2-amino-4*H*-pyran derivatives **4a-i** were achieved by the three-component condensation of aldehydes **1a-i**, malononitrile **2** and 4-hydroxycoumarin **3** in the presence of 10 or 15 mol % catalyst. The reaction was carried out in aqueous ethanol using Alum as catalyst at room temperature to give products **4a–i** in good to high yields (Scheme **1**). Bis-2-amino-4*H*-pyran derivatives **4j-k** were obtained by pseudo five-component reaction of isophthalaldehyde **1j** or terephthalaldehyde **1k** (1 mmol), malononitrile **2** (2.2 mmol) and 4-hydroxycoumarin **3** (2 mmol).

Firstly, 3-chlorobenzaldehyde **1a**, 4-nitrobenzaldehyde **1b** and propionaldehyde **1i** were chosen as models for the

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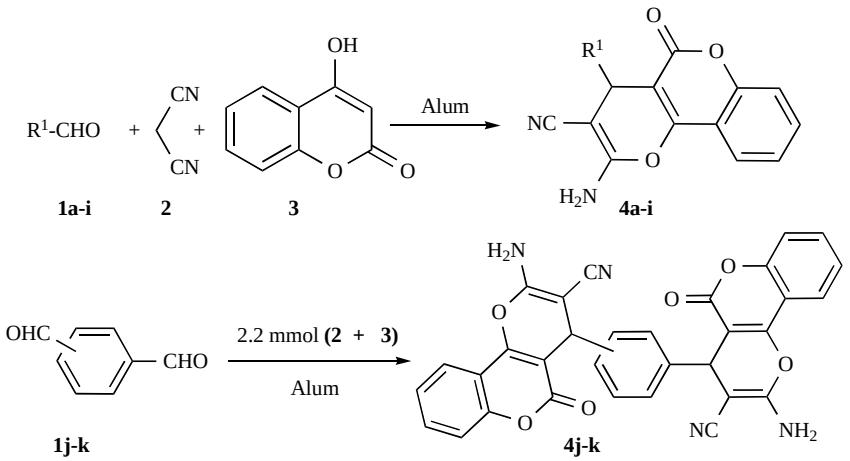


Scheme 1. Three or pseudo five-component synthesis of mono- and bis-2-amino-4*H*-pyrans **4a-k.**

Table 1. Optimization of Reaction

Entry	Aldehyde	Catalyst[a]	Solvent	Yield[a]
1	3-chlorobenzaldehyde **1a**[b]	Alum 5%	EtOH:H_2O (4:1)	68%
2	3-chlorobenzaldehyde **1a**[b]	Alum 10%	EtOH:H_2O (4:1)	81%
3	3-chlorobenzaldehyde **1a**[b]	Alum 15%	EtOH:H_2O (4:1)	90%
4	3-chlorobenzaldehyde **1a**[b]	-	EtOH:H_2O (4:1)	30%
5	3-nitrobenzaldehyde **1b**[b]	Alum 5%	EtOH:H_2O (4:1)	73%
6	3-nitrobenzaldehyde **1b**[b]	Alum 10%	EtOH:H_2O (4:1)	86%
7	3-nitrobenzaldehyde **1b**[b]	Alum 15%	EtOH:H_2O (4:1)	95%
8	propionaldehyde **1i**[c]	Alum 5%	EtOH:H_2O (4:1)	73%
9	propionaldehyde **1i**[c]	Alum 10%	EtOH:H_2O (4:1)	80%
10	propionaldehyde **1i**[c]	Alum 15%	EtOH:H_2O (4:1)	70%
11	3-chlorobenzaldehyde **1a**[b]	Alum 15%	EtOH	83%
12	3-chlorobenzaldehyde **1a**[b]	Alum 15%	CH_3CN:H_20 (4:1)	55%
13	3-chlorobenzaldehyde **1a**[b]	Alum 15%	THF	40%
14	3-chlorobenzaldehyde **1a**[b]	Alum 15%	CH_3CN	31%
15	3-chlorobenzaldehyde **1a**[b]	Alum 15%	CH_2Cl_2	20%
16	3-chlorobenzaldehyde **1a**[b]	Alum 15%	Toluene	10%

[a]yields refer to isolated products (25 ºC). [b]reaction time: 4h. [c]reaction time: 9h.

reaction with malononitrile **2** and 4-hydroxycoumarin **3**. Our investigation began with the evaluation of amounts of Alum as a catalyst in the reaction of 3-chlorobenzaldehyde **1a** or 4-nitrobenzaldehyde **1b** (1 equiv), malononitrile **2** and 4-hydroxycoumarin **3** (1 equiv) at 25 ºC. After 4 h with 5, 10 and 15 mol% of Alum, yields of 68%, 81% and 90%, respectively for **1a**, and 73%, 86% and 95%, respectively for **1b** were obtained (Table **1**, entries 1-3 and 5-7). However, the results indicated that the yield was decreased using 15 mol% of Alum by comparison with 10 mol% loading on the formation of **4i** (Table **1**, entries 9 and 10). In the absence of Alum there were low yield of the products (Table **1**, entry 4).

The choice of reaction solvent was crucial. Changing the solvent from EtOH/H_2O to ethanol was not beneficial as the yield was reduced to 83% (Table **1**, entry 11). The use of CH_3CN, THF, CH_3CN:H_2O (4:1) and CH_2Cl_2 as solvents furnished poor yields (Table **1**, entries 12-15). Side products were obtained when CH_3CN:H_2O (4:1) and CH_2Cl_2 was used as solvent. The results indicated that the yield gradually decreased as we moved from highly polar to less polar solvents. Other solvents, such as toluene were ineffective for this transformation (Table **1**, entry 16). Hence, the conditions of entries 3 and 9, shown in Table **1**, were the optimized reaction conditions for aromatic and aliphatic aldehydes, respectively. We next examined a wide variety of aldehydes (both aromatic and aliphatic) and dialdehydes to establish the scope of this catalytic transformation (Table **2**).

Although we have not yet established the mechanism, a possible explanation is given in Scheme **2**. Aldehyde **1** first condenses with malononitrile **2** to afford arylidene

Table 2. Synthesis of 4a-k Catalyzed by Alum

4a-k	Aldehyde	Yield	Time	M.p. (°C)	Lit. M.p. (°C)
4a	3-chlorobenzaldehyde	90%[a]	4h	253-256	-
4b	4-nitrobenzaldehyde	95%[a]	2h	278-280	258-260 [19]
4c	2,4-dichlorobenzaldehyde	92%[a]	4h	311-313	257-259 [19]
4d	3-nitrobenzaldehyde	87%[a]	4h	264-266	262-264 [19]
4e	benzaldehyde	82%[a]	4h	254-256	256-258 [19]
4f	4-fluorobenzaldehyde	81%[a]	4h	256-258	-
4g	cinnamaldehyde	85%[a]	6h	211-215	
4h	acetaldehyde	79%[b]	9h	229-232	-
4i	propionaldehyde	80%[b]	9h	249-251	-
4j	terphthalaldehyde	78%[c]	2.5h	307 dec.	-
4k	isoterphthalaldehyde	79%[c]	2.5h	296 dec.	-

[a]Yields refer to isolated products (reaction temperature: 25 ºC); Alum: 15 mol%.
[b]25 ºC; Alum: 10 mol%. [c](0.5h : 25 ºC and then 2h : 70 ºC); Alum: 15 mol%.

malononitrile **5** in the presence of Alum. This step was regarded as a fast Knoevenagel condensation. Then, **5** is attacked *via* Michael addition of 4-hydroxycoumarin **3** to give the intermediate **6** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **4** (Scheme **2**).

We found that the catalyst showed high catalytic activity and could be recovered and recycled several times without significant loss of activity.

EXPERIMENTAL

Mps were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Unicom Galaxy Series FTIR 5000 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker Avance 300 MHz spectrometer. Elemental analyses were performed using a Vario EL III elemental analyzer.

General Procedure for Preparation of 6a-f, 7a-c and 8a-d

A mixture of aldehyde **1a-i** or **1j-k** (1 mmol), malononitrile **2** (1 mmol for **1a-i** or 2.2 mmol for **1j-k**), 4-hydroxycoumarin (1 mmol for **1a-i** or 2.2 mmol for **1j-k**), and Alum (15 mol% for aromatic aldehydes or 10 mol% for aliphatic aldehydes) in 5 mL EtOH:H_2O (4:1) was stirred at room temperature or 70 ºC for several hours (Table **2**). Upon completion, monitored by TLC (n-hexane/ethyl acetate: 2/1), the solid was filtered off and washed with water and cool ethanol to give the desired products. The crude products were recrystallized from EtOH or EtOH:H_2O to yield mono- and bis-2-amino-4*H*-pyrans **4a-i** and **4j-k**.

The products **4a-g** are known compounds and their structures were deduced by comparison of their physical and spectroscopic data (IR and ^{1}H NMR) with those of previously reported. The new products **4h-k** were characterized on the basis of their elemental analysis and IR, ^{1}H NMR and ^{13}C NMR spectra.

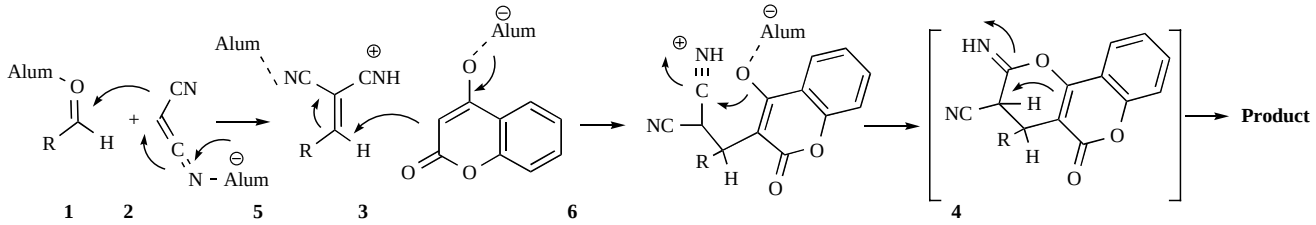
Spectral Data

2-Amino-4-(3-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4a)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3383, 3325, 3196, 2928, 2206, 1697, 1668, 1608, 1383, 760. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.51(1H , s, CH), 7.23–7.35 (4H, m, H_{arom}), 7.48 (2H, bs, NH_2), 7.46–7.53 (2H, m, H_{arom}), 7.72 (1H, dt, *J*=8.1 and 1.6 Hz, H_{arom}), 7.90 (1H, dd, *J*=7.9 and 1.4 Hz, H_{arom}) ppm.

2-Amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4b)

Pale yellow solid. IR (KBr) (ν_{max}, cm^{-1}): 3481, 3433, 3369, 3200, 2195, 1716, 1672, 1606, 1506, 1373, 1346, 765. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.67 (1H, s, CH), 7.46–7.61 (4H, m, H_{arom}), 7.58 (2H, bs, NH_2), 7.73 (1H, t, *J*= 8.0 Hz, H_{arom}), 7.91 (1H, d, *J*=7.8 Hz, H_{arom}), 8.18 (2H, d, *J*= 8.4 Hz, H_{arom}) ppm.



Scheme 2. Plausible mechanism of the Alum-catalyzed synthesis of 2-amino-4*H*-pyrans.

2-Amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4c)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3416, 3279, 3173, 2200, 1707, 1672, 1599, 1379, 758. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.53 (1H, s, H_{arom}), 7.29–7.39 (3H, m, H_{arom}), 7.46–7.52 (2H, m, H_{arom}), 7.54 (2H, s, NH_2), 7.72 (1H, t, *J*=8.1 Hz, H_{arom}), 7.88 (1H, d, *J*=7.8 Hz, H_{arom}) ppm.

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4d)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3398, 3323, 3211, 3088, 2876, 2195, 1699, 1674, 1602, 1531, 1456, 1379, 1062. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.73 (1H, s, CH), 7.45–7.65 (3H, m, H_{arom}), 7.56 (2H, bs, NH_2), 7.70– 7.82 (2H, m, H_{arom}), 7.91 (1H, dd, *J*=7.9 and 1.4 Hz, H_{arom}), 8.10–8.14 (2H, m, H_{arom}) ppm.

2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4e)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3373, 3284, 3180, 2198, 1709, 1674, 1604. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.44 (1H, s, H_{arom}), 7.26 (2H, d, *J*=7.6, H_{arom}), 7.28-7.34 (3H, m, H_{arom}), 7.41 (2H, bs, NH_2), 7.45-7.50 (2H, m, H_{arom}), 7.72 (1H, t, *J*=7.6, H_{arom}), 7.92 (1H, d, *J*=7.8, H_{arom}) ppm.

2-Amino-4-(4-fluorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4f)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3379, 3310, 3192, 3074, 2195, 1716, 1676, 1604, 1560, 1506, 765. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.54 (1H, s, CH), 7.34–7.60 (4H, m, H_{arom}), 7.50 (2H, bs, NH_2), 7.71 (2H, t, *J*= 7.9 Hz, H_{arom}), 7.89-8.07 (2H, m, H_{arom}) ppm. Anal. Calcd for $C_{19}H_{11}FN_2O_3$: C, 68.26; H, 3.32; N, 8.38. Found: C, 68.45; H, 3.28; N, 8.55.

2-Amino-5-oxo-4-styryl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4g)

Pale Yellow solid. IR (KBr) (ν_{max}, cm^{-1}): 3383, 3323, 3200, 2191, 1716, 1674, 1606, 1377. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.04 (1H, d, *J*=7.9 Hz, CH), 6.23 (1H, dd, *J*=15.7 and 7.9 Hz, H_{alkene}), 6.54 (1H, d, *J*=15.7, H_{alkene}), 7.20–7.33 (3H, m, H_{arom}), 7.37–7.49 (6H, m, NH_2 and H_{arom}), 7.70 (1H, t, *J*=7.2 Hz, H_{arom}), 7.85 (1H, d, *J*=7.9 Hz, H_{arom}) ppm.

2-Amino-4-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4h)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3394, 3317, 3211, 2962, 2195, 1707, 1672, 1608, 1456, 1386, 761. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.29 (3H, d, *J*= 6.5 Hz, CH_3), 3.37 (1H, q, *J*=6.5 Hz, CH), 7.28 (2H, bs, NH_2), 7.43–7.48 (2H, m, H_{arom}), 7.70 (1H, t, *J*=7.8 Hz, H_{arom}), 7.80 (1H, d, *J*=7.9 Hz, H_{arom}) ppm. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 65.95; H, 3.88; N, 10.92.

2-Amino-4-ethyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4i)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3396, 3315, 3192, 2958, 2193, 1707, 1670, 1606, 1392. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.77 (3H, d, *J*=7.4 Hz, CH_3), 1.58 and 1.79 (2H, m, CH_2), 3.43 (1H , dd, *J*=3.8 and 4.5 Hz, CH), 7.34 (2H, bs, NH_2), 7.44–7.49 (2H, m, H_{arom}), 7.70 (1H, t, *J*=7.2 Hz, H_{arom}), 7.80 (1H, d, *J*=7.9 Hz, H_{arom}) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 8.99, 26.47, 32.21, 54.89, 103.97, 113.31, 116.95, 120.04, 122.55, 125.00, 133.16, 152.48, 154.77, 159.98, 160.35 ppm. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.97; H, 4.70; N, 10.62.

4,4'-(1,4-phenylene)-bis-(2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile) (4j)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 34.68, 3393, 3325, 3192, 2198, 1709, 1674, 1606, 1379, 760. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.43 (1H, s, CH), 7.20–7.50 (12H, m, NH_2 and H_{arom}), 7.69 (2H, m, H_{arom}), 7.87–7.90 (2H, m, H_{arom}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 37.00, 58.32, 104.42, 113.35, 115.88, 116.99, 119.75, 122.90, 125.10, 128.21, 131.38, 133.37, 142.55, 152.54, 153.92, 158.58, 160.05 ppm. Anal. Calcd for $C_{32}H_{18}N_4O_6$: C, 69.31; H, 3.27; N, 10.10. Found: C, 69.88; H, 3.34; N, 10.27.

4,4'-(1,3-phenylene)-bis-(2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile) (4k)

White solid. IR (KBr) (ν_{max}, cm^{-1}): 3408, 3321, 3192, 2193, 1714, 1672, 1606, 1379, 760. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.43 (1H, s, CH), 7.10–7.13 (1H, m, H_{arom}), 7.18–7.27 (1H, m, H_{arom}), 7.39–7.49 (5H, m, NH_2 and H_{arom}), 7.70 (1H, m, H_{arom}), 7.86 (1H, t, *J*=7.6 Hz, H_{arom}) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 37.13, 57.96, 58.32, 104.16, 104.55, 113.33, 117.03, 119.66, 122.87, 125.15, 126.39, 126.72, 127.40, 129.36, 133.36, 143.67, 143.88, 152.55, 153.80, 154.11, 158.40, 158.77, 159.87 ppm. Anal. Calcd for $C_{32}H_{18}N_4O_6$: C, 69.31; H, 3.27; N, 10.10. Found: C, 69.93; H, 3.21; N, 10.21.

CONCLUSION

In conclusion, we have described an efficient, one-pot, and three- or pseudo five-component method for the synthesis of mono- and bis-2-amino-4*H*-pyrans catalyzed by Alum. Short reaction times, high yields and easy workup are the advantages of this protocol.

ACKNOWLEGMENT

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