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Novel and efficient catalysts for the one-pot synthesis of 3,4-dihydropyrano[*c*]chromene derivatives in aqueous media

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Dedicated to Professor Rolf Gleiter on the occasion of his 70th birthday

Abstract—Diammonium hydrogen phosphate, $(NH_4)_2HPO_4$(DAHP), efficiently catalyzes the one-pot, three-component reaction of an aromatic aldehyde, malononitrile and 4-hydroxycoumarin in aqueous media under mild conditions at room temperature, to afford the corresponding dihydropyrano[*c*]chromenes in high yields. (*S*)-Proline has also been used as another neutral catalyst for this reaction at reflux.

Dihydropyrano[*c*]chromenes and their derivatives are of considerable interest as they possess a wide range of biological properties,[1] such as spasmolytic, diuretic, anticoagulant, anti-cancer, and anti-anaphylactic activity.[2] In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.[3] Also, a number of 2-amino-4*H*-pyrans are useful as photoactive materials.[4] In recent years, the use of water as a solvent medium has been of interest. Compared with organic solvents, water has advantages such as low cost, safety and is environmentally friendly.[5] Diammonium hydrogen phosphate (DAHP) is an inexpensive, water-soluble, non-toxic and commercially available compound that can be used in the laboratory without special precautions.[6] This reagent has been used in important manufacturing processes such as fire-proofing textiles, paper, wood and vegetable fibres.[7] There are a few reports regarding the application of DAHP in the preparation of organic compounds, for example, in the synthesis of dihydropyrimidinones,[8] alkenes,[9] 1,8-dioxo-octahydroxanthenes[10] and tetrahydrobenzo[*b*]pyranes.[11] Thus, continuing our research on new one-pot reactions,[12] we considered DAHP to be ideal for effecting the synthesis of dihydropyrano[*c*]chromenes via a three-component reaction of 4-hydroxycoumarin, aromatic aldehydes and malononitrile. Some of these compounds have already been prepared in this way by heating in a large volume of absolute ethanol in the presence of piperidine.[13] Herein, we describe our very simple, green and efficient route to the synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitriles using a catalytic amount of DAHP in aqueous media at room temperature. Recently, *S*-proline was used as an efficient organocatalyst in some important organic reactions[14] and thus we have also used *S*-proline as a catalyst for this one-pot, three-component reaction in aqueous media at reflux.

The synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3-carbonitrile was achieved by the three-component condensation of an aromatic aldehyde **1**, malononitrile **2**, and 4-hydroxycoumarin **3** in the presence of 10 mol % catalyst. The reaction was carried out in aqueous ethanol (1:1, H_2O–EtOH) at room temperature using DAHP as catalyst or at reflux using

Keywords: Diammonium hydrogen phosphate (DAHP); Dihydropyrano[*c*]chromene; Tandem Knoevenagel–Michael addition.
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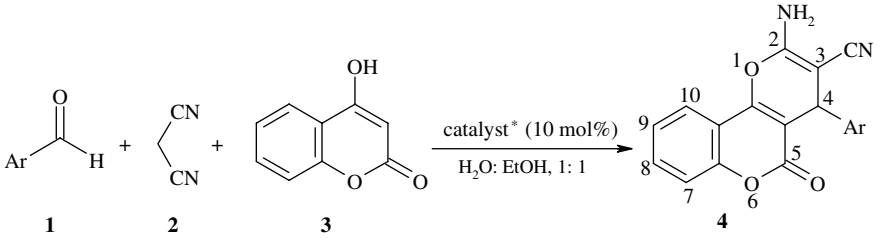

Catalyst: A: 10 mol% diammonium hydrogen phosphate, r.t.

B: 10 mol% (*S*)-proline, reflux.

Scheme 1.

Table 1. Synthesis of 2-amino-4-aryl-3-cyano-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromenes **4a**–**l** in aqueous ethanol using DAHP (method A) and *S*-proline (method B) as catalysts

Product	Ar	Yield[a] (%)	
		Method A	Method B
4a	C_6H_5	81	72
4b	4-BrC_6H_4	82	78
4c	4-ClC_6H_4	85	78
4d	4-NCC_6H_4	87	72
4e	2,3-$Cl_2C_6H_3$	90	80
4f	2,4-$Cl_2C_6H_3$	90	75
4g	2,6-$Cl_2C_6H_3$	89	83
4h	3-HOC_6H_4	90	83
4i	4-HOC_6H_4	92	75
4j	4-$CH_3OC_6H_4$	80	73
4k	3-$O_2NC_6H_4$	93	88
4l	4-$O_2NC_6H_4$	95	82

[a] Yields refer to pure isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Method A: reaction was conducted in H_2O–EtOH (1:1) using DAHP (10%) as catalyst at rt. Method B: reaction was carried out in H_2O–EtOH (1:1) using *S*-proline as catalyst at reflux.

S-proline as catalyst to give products **4a**–**l** in good to high yields (Scheme 1 and Table 1).

In order to optimize the conditions, we used 3-nitrobenzaldehyde, **2** and **3** and tested various amounts of DAHP as catalyst. After 2 h with 5, 10, and 15 mol % of DAHP, yields of 34%, 93%, and 93%, respectively, were obtained. In the absence of DAHP there was no reaction. To show that DAHP is an efficient catalyst rather than just a mild base, we tried the reaction in solution at pH 7–8, but there was no reaction.

Although we have not yet established the mechanism, a possible explanation is given in Scheme 2. We suggest that, DAHP catalyses the formation of iminium ion **5** in a reversible reaction with the aromatic aldehyde. The higher reactivity of the iminium ion compared to the carbonyl species is utilized to facilitate Knoevenagel condensation between aryl aldehyde **1** and malononitrile **2**, via intermediate **6** and after dehydration, olefin **7** is produced. DAHP also catalyzes the generation of proposed enamine intermediate **8**, formed from 4-hydroxycoumarin and diammonium hydrogen phosphate. Enamine intermediate **8** adds to olefin **7** to generate product **4** after proton transfer, tautomerization and hydrolysis of intermediate **9**.

The mechanism proposed for the reaction using *S*-proline as catalyst is also outlined in Scheme 2. Based on this mechanism, *S*-proline is an effective catalyst for the formation of olefin **7**, readily prepared in situ from Knoevenagel condensation of aryl aldehyde **1** and malononitrile **2**, which proceeds via iminium ion **5** and then intermediate **6**. It is proposed that enamine **8** is formed from *S*-proline and 4-hydroxycoumarin **3**, which then reacts with olefin **7** followed by cyclization to give product **4** after hydrolysis.

The results are summarized in Table 1. Substituents on the aromatic ring did not show any electronic effects in terms of yields under these reaction conditions.

The structures of compounds **4a**–**l** were deduced from their high-field ^1H NMR, ^{13}C NMR, and IR spectral data and also by mass spectrometry. All of the products exhibited a singlet in ^1H spectra at about $\delta = 4.34$–5.56 ppm for H-4 and also a distinguishing peak at $\delta = 55.90$–58.86 ppm for C-4 in the ^{13}C NMR spectra. The mass spectra displayed molecular ion peaks at appropriate values. Selected spectroscopic data are reported.[15]

In summary, we have demonstrated that diammonium hydrogen phosphate (DAHP) efficiently catalyzes the one-pot three-component synthesis of dihydropyrano-[*c*]chromene derivatives.

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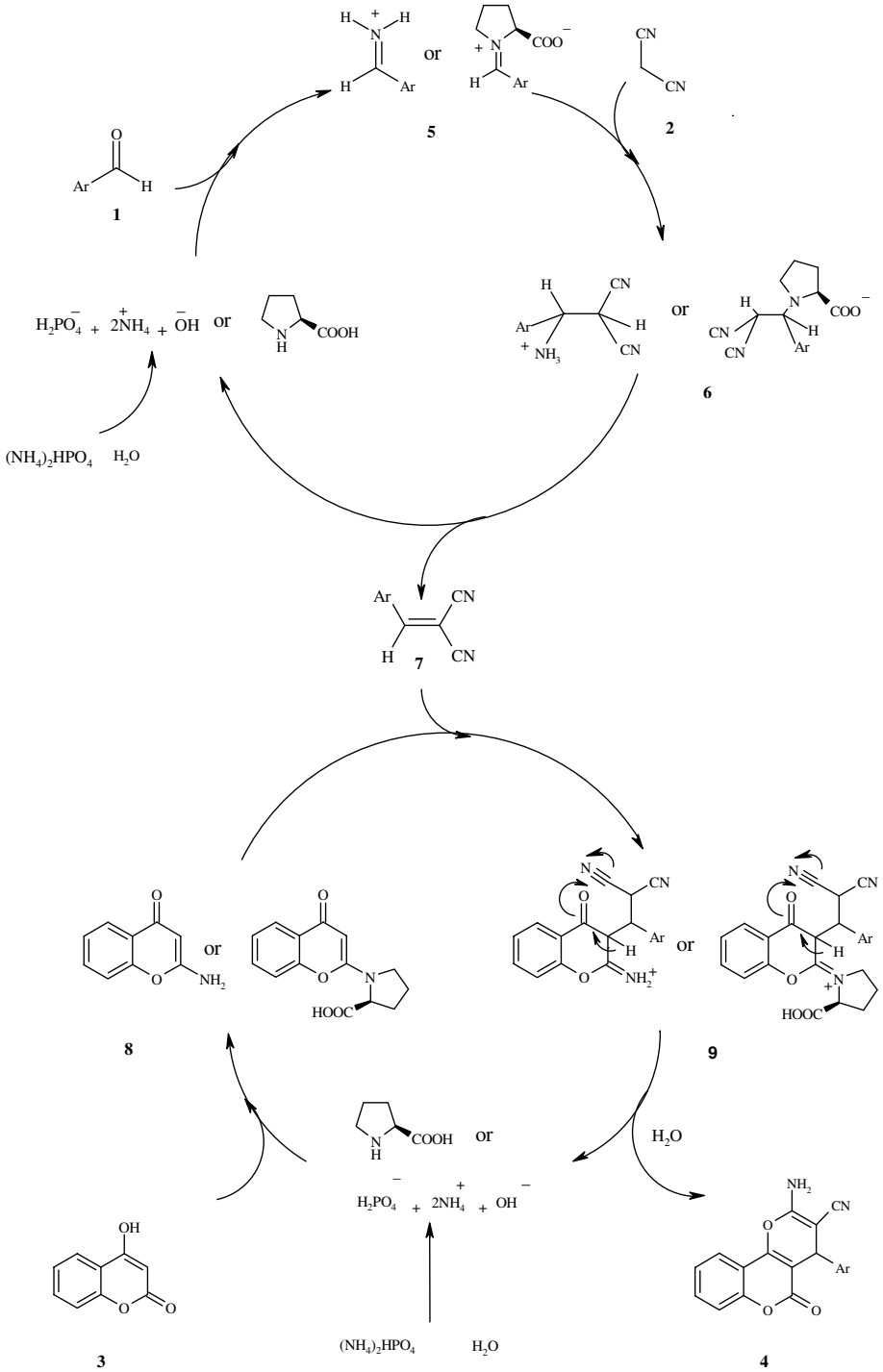

Scheme 2. The proposed mechanism for the synthesis of 3,4-dihydropyrano[*c*]chromenes in aqueous media catalyzed by diammonium hydrogen phosphate (10%) or *S*-proline (10%).

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15. *General procedure for the preparation of compounds* **4a–l**:

Method A: A solution of aromatic aldehyde **1** (1 mmol), malononitrile (**2**, 1.2 mmol), 4-hydroxycoumarin (**3**, 1 mmol), and diammonium hydrogen phosphate (13.2 mg, 10 mol %) in H_2O (10 ml) and EtOH (10 ml) was stirred at room temperature for 4 h. After completion of the reaction, the solid product was collected by filtration and purified by washing with aqueous ethanol.

Method B: A solution of aryl aldehyde, for example, 3-nitrobenzaldehyde **1k** (1 mmol, 151 mg), malononitrile (**2**, 1.2 mmol, 79 mg), 4-hydroxycoumarin (**3**, 1 mmol, 162 mg), and *S*-proline (11.5 mg, 10 mol %) in H_2O (10 ml), and EtOH (10 ml) was stirred at reflux for 3 h. After completion of the reaction, the solid product was collected by filtration and purified by washing with aqueous ethanol to afford **4k** in 88% yield.

Selected data:

Compound **4a**: White solid, mp = 256–258 °C [lit: 258–260 °C].[13] ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.46 (1H, s, H-4), 7.25 (2H, d, $J = 7.8$ Hz, H_{Ar}), 7.28 (1H, br s, H_{Ar}), 7.33 (2H, t, $J = 7.5$ Hz, H_{Ar}), 7.42 (2H, br s, NH_2), 7.45 (1H, d, $J = 8.4$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.71 (1H, t, $J = 7.5$ Hz, H_{Ar}), 7.91 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 58.86, 104.88, 113.84, 117.44, 120.10, 123.34, 125.54, 127.99, 128.50, 129.39, 133.79, 144.21, 153.01, 154.29, 158.86, 160.41 ppm. IR (KBr) ν_{max} 3378, 3286, 3178, 2196, 1709, 1674, 1604 cm^{-1}. MS (EI, 20 eV): *m*/*z* (%) 316.2 (M^+, 23), 249.2 (27), 239.1 (100), 221.2 (5), 121.1 (14), 102.2 (5), 92.1 (9), 66.2 (6). Anal. Calcd for $C_{19}H_{12}N_2O_3$ (316.31) C, 72.15; H, 3.79; N, 8.86. Found: C, 72.19; H, 3.72; N, 8.83.

Compound **4c**: White solid, mp = 263–265 °C [lit: 258–260 °C].[13] ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.50 (1H, s, H-4), 7.31 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.36 (2H, br s, NH_2), 7.38 (2H, br s, H_{Ar}), 7.44 (1H, d, $J = 8.2$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.71 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.92 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 58.65, 104.40, 113.80, 117.34, 119.86, 123.38, 125.42, 129.28, 130.45, 132.65, 133.75, 143.12, 153.06, 154.42, 158.93, 160.34 ppm. IR (KBr) ν_{max} 3383, 3314, 3189, 2194, 1715, 1675, 1607 cm^{-1}. MS (EI, 20 eV): *m*/*z* (%) 352.2 (M^++2, 65), 350.2 (M^+, 24), 315.2 (24), 283.1 (24), 249.2 (49), 239.2 (100), 121.1 (23), 92.1 (10), 66.2 (5). Anal. Calcd for $C_{19}H_{11}N_2O_3Cl$ (350.76) C, 65.05; H, 3.14; N, 7.99. Found: C, 65.17; H, 3.12; N, 7.82%.

Compound **4f**: White solid, mp = 257–259 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.99 (1H, s, H-4), 7.36 (1H, dd, $J = 8.3$, 1.9 Hz, H_{Ar}), 7.40 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.41 (2H, br s, NH_2), 7.46 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.51 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.56 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.73 (1H, t, $J = 8.2$ Hz, H_{Ar}), 7.92 (1H, d, $J = 8.9$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.10, 103.38, 113.71, 117.47, 119.43, 123.42, 125.57, 128.71, 129.73, 132.95, 133.28, 133.96, 134.28, 140.26, 153.14, 155.05, 159.05, 160.23 ppm. IR (KBr) ν_{max} 3463, 3295, 3163, 3070, 2198, 1715, 1674, 1590 cm^{-1}; MS (EI, 20 eV) *m*/*z* (%) 386.2 (M^++2, 19), 384.2 (M^+, 29), 349.2 (74.3), 332.2 (16.1), 321.2 (12), 283.1 (66), 239.2 (100), 121.2 (45), 92.2 (9), 66.2 (3). Anal. Calcd. for $C_{19}H_{10}N_2O_3Cl_2$ (385.20) C, 59.22; H, 2.60; N, 7.27. Found: C, 59.12; H, 2.57; N, 7.13.

Compound **4j**: White solid, mp = 240–242 °C [lit: 232–234 °C].[13] ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 4.40 (1H, s, H-4), 6.87 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.18 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.37 (2H, br s, NH_2), 7.45 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.70 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.89 (1H, d, $J = 7.7$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6):δ 55.90, 59.10, 105.13, 113.84, 114.71, 117.37, 120.18, 123.29, 125.47, 129.64, 133.66, 136.26, 152.94, 153.94, 158.79, 159.20, 160.38 ppm. IR (KBr) ν_{max} 3378, 3314, 3190, 2196, 1709, 1672, 1608 cm^{-1}; MS (EI, 20 eV): *m*/*z* (%) 346.3 (M^+, 80), 331.2 (11), 315.2 (27), 279.2 (63), 249.2 (51), 239.2 (100), 225.2 (5), 185.2 (6), 145.2 (9), 121.2 (16), 92.2 (4), 66.2 (8). Anal. Calcd for $C_{20}H_{14}N_2O_4$ (346.34) C, 69.36; H, 4.05; N, 8.09. Found: C, 69.32; H, 4.03; N, 8.11.

Compound **4k**: White solid, mp = 262–264 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.74 (1H, s, H-4), 7.44 (1H, d, $J = 6.7$ Hz, H_{Ar}), 7.51 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.56 (2H, br s, NH_2), 7.64 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.73 (1H, dt, $J = 7.5$, 1.3 Hz, H_{Ar}), 7.82 (1H, d, $J = 6.8$ Hz, H_{Ar}), 7.92 (1H, dd, $J = 6.8$, 1.2 Hz, H_{Ar}), 8.12 (1H, dd, $J = 8.4$, 1.4 Hz, H_{Ar}), 8.14 (1H, s, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.82, 103.74, 113.81, 117.44, 119.83, 123.13, 123.33, 123.46, 125.54, 130.92, 133.96, 135.63, 146.36, 148.72, 153.13, 154.75, 159.03, 160.46 ppm. IR (KBr) ν_{max} 3404, 3322, 3194, 2202, 1703, 1672, 1531, 1349 cm^{-1}; MS (EI, 20 eV): *m*/*z* (%) 361.2 (M^+, 83), 344.2 (48), 314.2 (22), 294.2 (18), 278.2 (35), 239.2 (100), 121.1 (21), 92 (15), 66.2 (7). Anal. Calcd for $C_{19}H_{11}N_3O_5$ (361.31) C, 63.16; H, 3.05; N, 11.63. Found C, 63.08; H, 3.01; N, 11.57.

Compound **4l**: Pale yellow solid, mp = 258–260 °C [lit: 255–256 °C].[13] ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.68 (1H, s, H-4), 7.47 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.52 (1H, t,

$J = 7.7$ Hz, H_{Ar}), 7.57 (2H, br s, NH_2), 7.60 (2H, d, $J = 8.0$ Hz, H_{Ar}), 7.74 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.91 (1H, d, $J = 7.8$ Hz, H_{Ar}), 8.18 (2H, d, $J = 8.3$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.65, 103.64, 113.74, 117.46, 119.78, 123.43, 124.57, 125.56, 130.04, 133.99, 147.46, 151.61, 153.13, 154.81, 158.93, 160.42 ppm. IR (KBr) ν_{max} 3482, 3432, 3371, 3335, 2195, 1718, 1673, 1607, 1506, 1374,1306 cm^{-1}; MS (EI, 20 eV): m/z (%) 361.2 (M^+, 58), 344.2 (21), 314.2 (11), 294.2 (10), 278.2 (53), 248.2 (55), 239.2 (100), 120.1 (25), 92.2 (17), 66.2 (8). Anal. Calcd for $C_{19}H_{11}N_3O_5$ (361.31) C, 63.16; H, 3.05; N, 11.63. Found: C, 63.19; H, 3.10; N, 11.67.