A Convenient One Pot Synthesis of Substituted 4-Aminobenzopyrano[3,4-*c*]pyridinones

D. W. Rangnekar* and S. V. Dhamnaskar

Dyes Research Laboratory, Department of Chemical Technology, University of Bombey, Matunga, Bombay 400 019, India

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A new synthesis of substituted 4-aminobenzopyrano[3,4-*c*]pyridinones was achieved in one pot by the condensation of an *o*-hydroxyaraldehyde and a cyclic or acylic methyl ketone in the presence of ammonium acetate in refluxing ethanol followed by the treatment of malononitrile and subsequent hydrolysis with hydrochloric acid *in situ*.

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Natural and synthetic coumarin derivatives with 3,4-fused heterocycles possessing biological activities have been of great interest to chemists and pharmacologists [1,2]. Also, several coumarin derivatives have been commercially exploited as useful fluorescent dyes and brighteners [3,4].

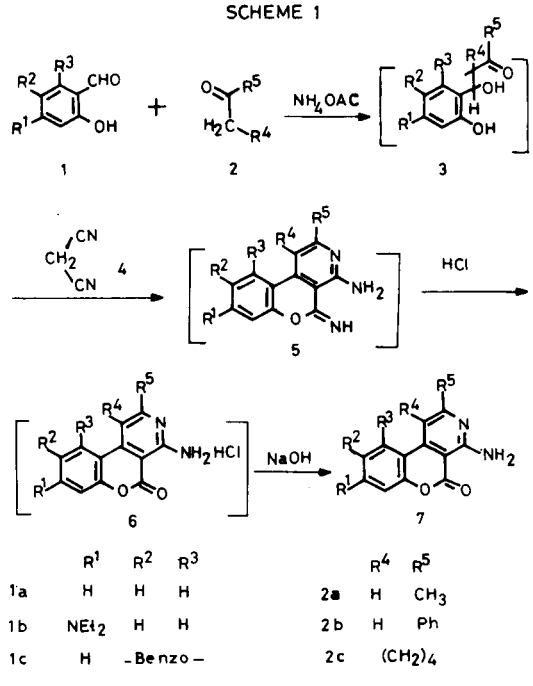
Although a number of routes are known for the synthesis of 3,4-heterocyclic fused coumarins, no facile method for the synthesis of 4-aminobenzopyrano[3,4-*c*]-pyridinones has been reported. An earlier report [5] of the formation of benzopyrano[3,4-*c*]pyridine derivatives by the reaction of malononitrile, salicylaldehydes and aryl methyl ketones in equimolar ratio suffer from very low yields (less than 10%) due to substantial formation of side products.

In the interest of synthesising new fused heterocyclic coumarin ring systems for the possible applicability as biologically active compounds we have synthesised a variety of benzopyrano[3,4-*c*]pyridine derivatives. We wish to report in this communication a facile single pot synthesis of 4-aminobenzopyrano[3,4-*c*]pyridinones in moderate yields (31-53%).

The sequence involved in the present synthesis consists of the condensation of one mole of *o*-hydroxyaraldehyde **1** and one and half mole of aliphatic, aromatic or alicyclic methyl ketones **2** in the presence of two moles of ammonium acetate used as a condensing agent in refluxing ethanol, cooling of the reaction mixture, addition of one mole of malononitrile in the cold *in situ*, continuation of the reaction at reflux temperature and subsequent treatment with hydrochloric acid at room temperature *in situ*. The products were isolated by the neutralization with aqueous sodium hydroxide solution.

Although no intermediate products of the reaction were isolated or trapped to investigate the exact course of the reaction, we presume that the following course of the reaction sequence is involved: a) Reaction of *o*-hydroxyaraldehyde **1** and aliphatic, aromatic or alicyclic methyl ketone **2** leads to initial formation of cross aldol condensation product **3**. b) The cross aldol condensation product **3** undergoes nucleophilic attack with malononitrile **4** anion

SCHEME 1

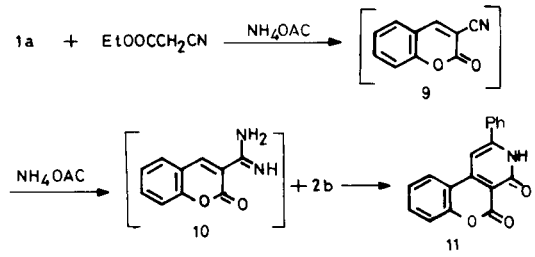


	R^1	R^2	R^3		R^4	R^5
1a	H	H	H	2a	H	CH_3
1b	NEt_2	H	H	2b	H	Ph
1c	H	-Benzo-		2c	$(CH_2)_4$	

at the secondary alcohol carbon atom which follows dehydration and aromatisation in the presence of excess ammonium acetate with the formation of 4-amino-5-iminobenzopyrano[3,4-*c*]pyridinones **5**. c) The action of hydrochloric acid hydrolyses the imino group and converts the amino group to an amino hydrochloride **6**. d) Neutralization of the amino hydrochloride wth sodium hydroxide gave 4-aminobenzopyrano[3,4-*c*]pyridinones **7**.

In the earlier report [6], an interesting observation was made when the sequence of addition of the components used in the above reaction was different. In this report, salicylaldehyde **1a** and ethyl cyanoacetate **8** were first reacted in the presence of ammonium acetate, followed by the addition of acetophenone **2b** which afforded 2-phenyl-5-oxo-6-benz[*f*]-1(2*H*)-isoquinolone **11**. The reaction sequence probably took place as given in the following Scheme 2, with the initial formation of 3-cyanocoumarin **9** and 3-acetamidinocoumarin **10**.

SCHEME 2



The structure of various 4-aminobenzopyrano[3,4-*c*]-pyridinones **7a-7h** were confirmed by their infrared spectra in Nujol and their ^{1}H nmr in dimethylsulfoxide-d_6 and trifluoroacetic acid. Thus, the infrared spectra showed two characteristic peaks at 3320-3350 cm^{-1} and 3175-3260 cm^{-1} indicating the presence of a primary amino group and a peak at 1690-1710 cm^{-1} characteristic of the coumarin carbonyl stretching band. The structures were supported by the ^{1}H nmr as detailed in the Experimental. Thus for example, the ^{1}H nmr spectra of **7e** in dimethylsulfoxide-d_6 showed a deuterium oxide exchangeable singlet at δ 7.3 ppm due to two protons of the amino group.

EXPERIMENTAL

4-Amino-2-methylbenzopyrano[3,4-*c*]pyridin-5-one (**7a**).

A mixture of 3.66 g (0.03 mole) of salicyladehyde (**1a**), 2.61 g (0.045 mole) of acetone (**2a**) and 4.62 g (0.06 mole) of ammonium acetate in 30 ml ethanol was refluxed in a water-bath for 3 hours. The reaction mixture was allowed to cool to 25° and further cooled to 0-5°. With vigorous stirring 1.98 g (0.03 mole) of malononitrile (**4**) was added in three to four portions in about 20 minutes. The temperature of the reaction mixture was gradually raised to gentle reflux and maintained at reflux for the next 4 hours. The reaction mixture was cooled to room temperature, poured in 80 ml of 5*N* hydrochloric acid and digested over a water-bath for 5 hours. The mixture was filtered and carefully neutralized with 10% sodium hydroxide solution. The separated solid was filtered, washed with water and dried. Recrystallization from dimethylformamide gave 3.59 g, 53% of **7a** as white crystals, mp 238-239°; ir (nujol): 3330, 3180, 1710 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.5 (s, 3H, CH_3), 7.1 (s, 1H, H-1), 7.2-7.7 (m, 5H, H-8, H-9, H-10 and 2H of NH_2), 8.1 (d, J = 10 Hz, 2 Hz, 1H, H-7).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.42; N, 12.38. Found: C, 68.85; H, 4.23; N, 11.89.

4-Amino-2-methyl-8-*N,N*-diethylaminobenzopyrano[3,4-*c*]pyridin-5-one (**7b**).

The same procedure described for **7a** was applied except 4-(*N,N*-diethylamino)salicylaldehyde (**1b**) was used in place of **1a** to yield **7b**, recrystallized from ethanol as brown crystals, 45% yield, mp 310-312°; ir (Nujol): 3330, 3175, 1690 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.68; H, 6.39; N, 14.14. Found: C, 68.50; H, 6.28; N, 13.93.

4-Amino-2-methylnaphtho[1,2-*e*]pyrano[3,4-*c*]pyridin-5-one (**7c**).

The same procedure as in **7a** was applied except 2-hydroxynaphthalene-1-carboxaldehyde (**1c**) was used in place of **1a** to yield **7c**, recrystallized from dimethylformamide as pale brown crystals, 47% yield, mp >350°; ir (Nujol): 3340, 3220, 1710 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.91; H, 4.34; N, 10.14. Found: C, 74.13; H, 4.27; N, 10.13.

4-Amino-2-phenylbenzopyrano[3,4-*c*]pyridin-5-one (**7d**).

The same procedure as in **7a** was applied except phenyl methyl ketone (**2b**) was used in place of **2a** to yield **7d**, recrystallized from dimethylformamide as pale yellow crystals, 55% yield, mp >350°; ir (Nujol): 3330, 3210, 1700 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 7.3 (s, 1H, H-1), 7.5-8.1 (m, 8H, H-8, H-9, H-10 and H-2, H-3, H-4, H-5, H-6 of 2-phenyl), 8.3 (m, 1H, H-7).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 75.00; H, 4.16; N, 9.72. Found: C, 74.88; H, 4.03; N, 9.60.

4-Amino-2-phenyl-8-*N,N*-diethylaminobenzopyrano[3,4-*c*]pyridin-8-one (**7e**).

The same procedure as in **7a** was followed except phenyl methyl ketone (**2b**) was used in place of **2a** and 4-(*N,N*-diethylamino)salicylaldehyde (**1b**) was used in place of **1a** to yield **7e**, recrystallized from dimethylformamide as deep yellow crystals, 43% yield, mp 326-327°; ir (Nujol): 3320, 3180, 1690 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.2 (t, 6H, $2CH_3$ of 8-*N,N*-diethylamino), 3.4 (q, 4H, 2 -CH_2- of 8-*N,N*-diethylamino), 6.5 (d, J = 2 Hz, 1H, H-7), 6.7 (d, J = 10 Hz, 2 Hz, 1H, H-9), 7.3 (s, 2H, deuterium oxide exchangeable NH_2), 7.5-8.5 (m, 7H, H-1, H-10 and H-2, H-3, H-4, H-5, H-6 of 2-phenyl).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.53; H, 5.84; N, 11.69. Found: C, 73.28; H, 5.67; N, 11.87.

4-Amino-2-phenylnaphtho[1,2-*e*]pyrano[3,4-*c*]pyridin-5-one (**7f**).

The same procedure as in **7a** was followed except phenyl methyl ketone (**2b**) was used in place of **2a** and 2-hydroxynaphthalene-1-carboxaldehyde (**1c**) was used in place of **1a** to yield **7f**, recrystallized from dimethylformamide as yellow crystals, 31% yield, mp 315-316° dec; ir (Nujol): 3350, 3260, 1700 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 7.5 (s, 1H, H-1), 8-8.5 (m, 11H, H-7, H-8, H-9, H-10, H-11, H-12 of naphthopyranopyridine and H-2, H-3, H-4, H-5, H-6 of 2-phenyl).

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.10; H, 4.14; N, 8.18. Found: C, 78.11; H, 4.05; N, 8.16.

6-Aminobenzopyrano[3,4-*c*]-1,2,3,4-tetrahydroquinoline (**7g**).

The same procedure as in **7a** was followed except cyclohexanone (**2c**) was used in place of **2a** to yield **7g**, recrystallized from DMF as bright yellow crystals, 39%, mp 278°; ir (Nujol): 3330, 3250, 1710 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 2-2.4 (br, 4H, 2 H-2 and 2 H-3 of benzopyranotetrahydroquinoline, 3.1-3.5 (br, 4H, 2 H-1 and 2 H-4 benzopyranotetrahydroquinoline), 7.5 (t, 2H, H-10, H-11), 8.2 (t, 2H, H-9, H-12).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C, 71.88; H, 5.05; N, 10.17.

6-Aminonaphtho[1,2-*e*]pyrano[3,4-*c*]-1,2,3,4-tetrahydroquinoline (**7h**).

The same procedure as in **7a** was used except cyclohexanone (**2c**) was used in place of **2a** and 2-hydroxynaphthalene-1-carboxaldehyde (**1c**) was used in place of **1a** to yield **7h**, recrystallized from dimethylformamide as pale yellow crystals, 33% yield, mp 185-186°; ir (Nujol): 3340, 3240, 1690 cm^{-1}.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.94; H, 5.06; N, 8.86. Found: C, 75.67; H, 4.97; N, 8.45.

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