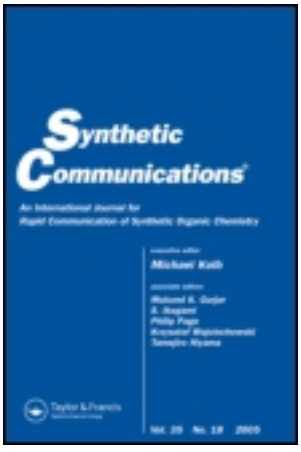

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One-Pot, Three-Component Condensation Reaction in Water: An Efficient and Improved Procedure for the Synthesis of Pyran Annulated Heterocyclic Systems

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One-Pot, Three-Component Condensation Reaction in Water: An Efficient and Improved Procedure for the Synthesis of Pyran Annulated Heterocyclic Systems

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Abstract: Environmentally friendly three-component condensation reactions of an activated C-H acid, an aldehyde, and alkyl nitriles to afford the corresponding pyran annulated heterocyclic systems in water in good yields, avoiding the addition of any catalyst, are reported.

Keywords: 1,3-dimethylbarbituric acid, 4-hydroxycoumarin, 4-hydroxy-6-methyl-pyrone, pyran annulated heterocyclic system, three-component reaction, water

INTRODUCTION

Although synthesis of organic compounds in the nature occurs very efficiently in water, organic chemists have traditionally been taught that water is not generally a good solvent for carrying out synthetic reactions. Nevertheless, in recent years reports have appeared in increasing number describing use of water as a solvent for various organic reactions.[1–3]

An important example of the significant rate enhancements, which sparked much interest in the use of water as a solvent, was the finding by Breslow that the reaction between cyclopentadiene and butanone was more than 700 times faster in water than in many organic solvents.[4] Breslow

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explained his results on the basis of hydrophobic interactions that induce a favorable aggregating of the polar components in the polar water.[5]

Further reasons that make water unique compared to other organic solvents are that it is inexpensive, nonflammable, and naturally occurring; has a high specific heat capacity; and more importantly, is not toxic. Choice of solvent is one of the problems to face to perform eco-efficient processes.

Pyrano[2,3-*d*]-, pyrido[2,3-*d*]pyrimidines, and pyrano[3,2-*c*]benzopyran have attracted much attention owing to their biological activities. A number of methods have been reported for the synthesis of these compounds in the presence of organic bases such as piperidine or pyridine in an organic solvent (i.e., ethanol, methanol, pyridine); however, most of these rely on multistep reactions and complex synthetic pathways, have long reaction times, and have low yields.[6–20]

Recently, the one-pot synthesis of pyran annulated heterocyclic systems from condensation of 4-hydroxycoumarin[18] or 4-hydroxy-6-methylpyrone[18] or 1,3-dimethylbarbituric acid[19] with relatively expensive reagents such as dimethyl acetylenedicarboxylate and isocyanide has been reported in toxic benzene under reflux conditions. In addition, a new method based on a multi-component reaction strategy using microwave heating in the solid state has been presented.[20] Nevertheless, the use of a green solvent such as water, which shows both economical and synthetic advantages, is desirable.

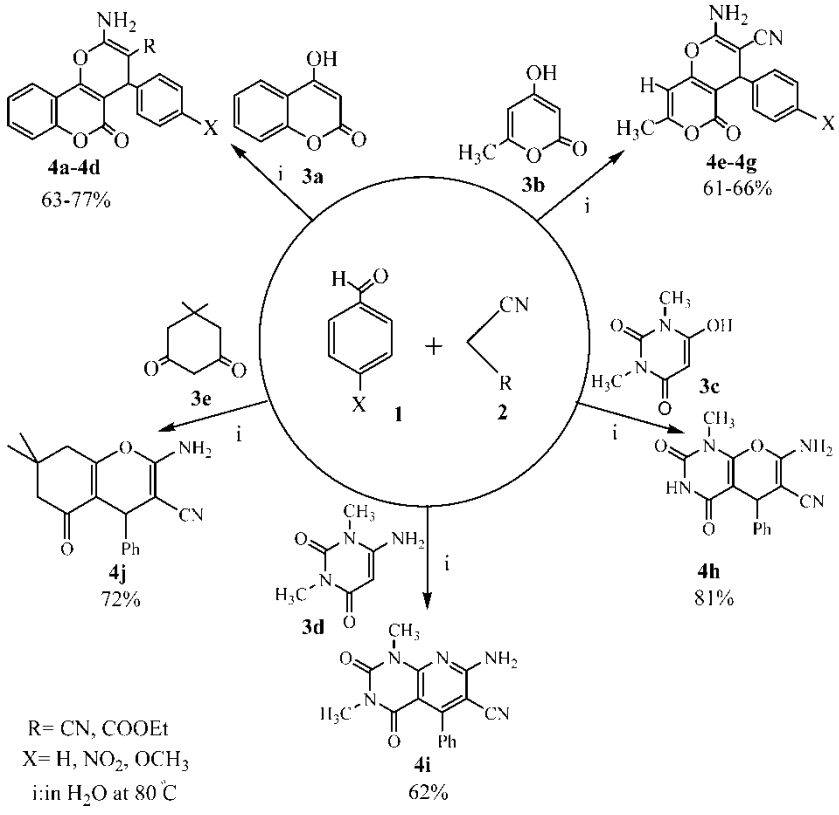
As a part of our research to develop a green chemistry by one-pot uncatalyzed synthesis of target molecules in water alone as the reaction medium,[21–23] we report here the three-component condensation reactions of 4-hydroxycoumarin **3a,** 4-hydroxy-6-methylpyrone **3b,** 1,3-dimethylbarbituric acid **3c,** 1,3-dimethyl-6-amino uracil **3d**, or dimedone **3e** with *p*-substituted benzaldehydes **1** and alkyl nitriles **2** for the preparation of pyran annulated heterocyclic systems without using any catalysts in water at 80°C (Scheme 1).

Because of hydrophobic interaction behavior that generates an internal pressure and promotes the association of the reagents in a solvent cavity during the activation process, water showed an acceleration of the three-component reactions in comparison to organic solvent. The results for various pyran annulated heterocyclic systems are summarized in Table 1.

It is important to note that the separation and purification processes are very simple, as they involve only Buchner funnel filtration and washing with water.

It is interesting that the reaction easily occurs in water although the mechanism involves a net dehydration of the alcoholic intermediates obtained by nucleophilic attack of the active methylene of **2** to the carbonyl group of **1**; the ease of the dehydration process is ascribable to the extent of C═C double bond conjugation in the Knoevenagel condensation product. Other authors have also previously found similar unexpected solvent effects.[24–26]

We have not established a mechanism for the formation of pyran annulated heterocyclic systems, but a reasonable possibility is indicated in Scheme 2.



Scheme 1.

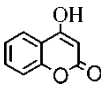
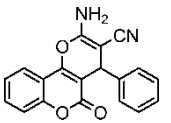
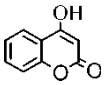
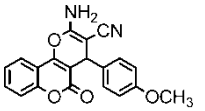
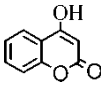
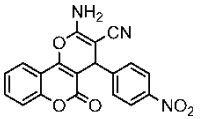
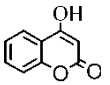
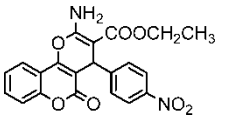
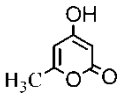
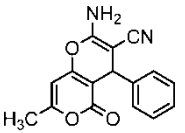
The reaction presumably proceeds in two steps: condensation of aldehyde **1** and alkyl nitrile **2** by standard Knoevenagel reaction produces 3-benzylidene-2,4-pentanedione **5**.[27] Then C-H acid **3e** is reacted with compound **5** through a Michael addition, produces product type **6**, and after cyclization affords pyran annulated heterocyclic system **4j**.[28]

To explore the scope and limitations of this reaction further, we have extended it to various para-substituted benzaldehydes in the presence of active C-H acids. As indicated in Table 1, the reaction proceeds efficiently with benzaldehyde and electron-withdrawing and electron-releasing para-substituted benzaldehydes.

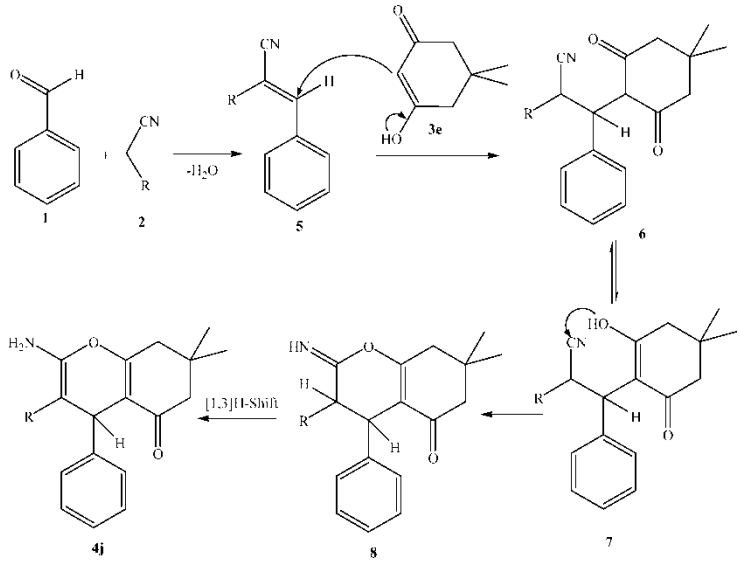
CONCLUSION

In summary, the one-pot, three-component uncatalyzed conversion of activated C-H compounds such as 4-hydroxycoumarin, 4-hydroxy-6-methylpyrone,

Table 1. One-pot synthesis of pyran annulated heterocyclic systems in water at 80°C

Entry	Activated C-H reactant	Product	Yield (%)	Time (h)	MP (°C)	
					Found	Reported
4a			77	9.5	265–267	273–275[6]
4b			70	10	237–239	—
4c			69	7.5	258–260	—
4d			63	10	240–243	—
4e			65	10.5	230–233	236–238[15]

4f			61	11	205–208	205–207[15]
4g			66	9.5	210–213	216–218[15]
4h			81	11	206–208	210–212[20]
4i			62	8.5	290–293	308–309[20]
4j			72	8.5	229–231	233–234[29]



Scheme 2.

1,3-dimethylbarbituric acid, 1,3-dimethyl-6-amino uracil or dimedone, with *p*-substituted benzaldehydes and alkyl nitriles, to pyran annulated heterocyclic systems has been efficiently performed in water as a green solvent. The one-pot nature, the use of water as an ecocompatible reaction solvent, and the easy separation of products make it an interesting alternative to the reported approaches.[18–20]

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d_6. All the products are known compounds (except **4b**, **4c**, and **4d**), which were characterized by IR, ^{1}H NMR, and mass spectral data, and their melting points were compared with literature reports.

Typical Procedure for the Preparation of 4a

The mixture of malononitrile (0.066 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) in 20 ml of distilled water was stirred for 3 h at 80°C. The reaction

mixture was cooled, and 4-hydroxycoumarin (0.162 g, 1 mmol) was added in small portions. Stirring was continued at 80°C for 9.5 h. The progress of reaction was monitored on thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature, and the resulting yellow precipitated was filtered and washed with water (50 ml). The solid residue (yellow crystals) was dried and crystallized from Et_2O or acetone to yield **4a** (0.243 g, 77%).

Data

2-Amino-3-cyano-4-(phenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (4a): Light yellow crystals. Mp 265–267°C. IR (KBr) ν: 3370 (NH_2), 2190 (CN), 1701 (C═O) cm^{-1}. ^1H NMR (acetone-d_6) δ 4.56 (s, CH, 1H), 6.66 (br s, NH_2, 2H), 7.25–8.00 (m, arom. 9H) ppm. MS m/z (%): 316 (M^+, 15), 249 (100), 221 (21), 163 (15), 121 (28), 92 (69).

2-Amino-3-cyano-4-(4′-methoxyphenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (4b): Yellow crystals. Mp 237–239°C. IR (KBr) ν: 3365 (NH_2), 2185 (CN), 1702 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.72 (s, OCH_3, 3H), 4.40 (s, CH, 1H), 6.87–7.90 (m, arom. 8H and NH_2, 2H) ppm. ^{13}C NMR (DMSO-d_6) δ 36.7, 55.5, 58.7, 104.7, 113.5, 114.3, 117.0, 119.8, 122.9, 125.1, 129.2, 133.3, 135.9, 152.5, 153.6, 158.4, 158.8, 160.0 ppm. MS m/z (%): 346 (M^+, 10), 280 (100), 249 (80), 184 (59), 162 (25), 120 (30).

2-Amino-3-cyano-4-(4′-nitrophenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (4c): Yellow crystals. Mp 258–260°C. IR (KBr) ν: 3275 (NH_2), 2180 (CN), 1703 (C═O). ^1H NMR (DMSO-d_6) δ 4.67 (s, CH, 1H), 7.45–8.19 (m, arom. 8H, and NH_2, 2H) ppm; ^{13}C NMR (DMSO-d_6) δ 37.2, 57.2, 103.2, 113.3, 117.1, 119.4, 123.0, 124.2, 125.2, 129.6, 133.6, 147.0, 151.2, 152.7, 154.4, 158.5, 160.0 ppm. MS m/z (%): 362 (M^+, 47), 345 (15), 296 (40), 278 (100), 248 (83), 92 (85).

2-Amino-3-carboethoxy-4-(4′-nitrophenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (4d): Yellow crystals. Mp 240–243°C. IR (KBr) ν: 3430 (NH_2), 1714 (C═O). ^1H NMR ($CDCl_3$): δ 1.16 (t, $^3J = 7.11$ Hz, CH_3, 3H), 4.08 (q, $^3J = 7.11$ Hz, CH_2, 2H), 5.03 (s, CH, 1H), 6.56 (br s, NH_2, 2H), 7.33–8.13 (m, arom. 8H) ppm. ^{13}C NMR ($CDCl_3$) δ 14.2, 35.8, 60.2, 106.4, 113.1, 117.0, 122.3, 123.4, 124.3, 124.6, 129.5, 132.7, 146.7, 151.7, 152.7, 153.6, 158.0, 160.5, 168.2 ppm. MS m/z (%): 408 (M^+, 2), 335 (25), 286 (100), 240 (90), 121 (40), 92 (25).

2-Amino-3-cyano-7-methyl-4-(phenyl)-4*H*-pyrano[4,3-*b*]pyran-5-one (4e): Yellow crystals. Mp 230–233°C. IR (KBr) ν: 3300 (NH_2), 2190 (CN), 1706 (C═O). ^1H NMR (acetone-d_6) δ 2.25 (s, CH_3, 3H), 4.38 (s, CH, 1H), 6.17

(s, C═CH, 1H), 6.40 (br s, NH_2, 2H), 7.23–7.32 (m, arom. 5H) ppm. MS m/z (%): 281 (M + 1, 52), 280 (M^+, 50), 203 (100), 171 (10), 102 (38), 43 (52).

2-Amino-3-cyano-7-methyl-4-(4′-methoxyphenyl)-4*H*-pyrano[4,3-*b*]pyran-5-one (4f): Yellow crystals; Mp 205–208°C. IR (KBr) ν: 3320 (NH_2), 2275 (CN), 1700 (C═O). ^{1}H NMR (DMSO-d_6) δ 2.21 (s, CH_3, 3H), 3.72 (s, OCH_3, 3H), 4.22 (s, CH, 1H), 6.26 (s, C═CH, 1H), 6.84–7.16 (m, arom. 5H and NH_2, 2H) ppm. MS m/z (%): 310 (M^+, 75), 279 (10), 243 (90), 203 (90), 145 (55), 117 (30), 43 (100).

2-Amino-3-cyano-7-methyl-4-(4′-nitrophenyl)-4*H*-pyrano[4,3-*b*]pyran-5-one (4g): Yellow crystals. Mp 210–213°C. IR (KBr) ν: 3390 (NH_2), 2190 (CN), 1701 (C═O). ^{1}H NMR (DMSO-d_6) δ 2.23 (s, CH_3, 3H), 4.51 (s, CH, 1H), 6.32 (s, C═CH, 1H), 7.36 (br s, NH_2, 2H), 7.51 (d, 2H, ^3J = 8.03 Hz, $C_6H_4NO_2$), 8.19 (d, 2H, ^3J = 8.03 Hz, $C_6H_4NO_2$) ppm. MS m/z (%): 325 (M^+, 25), 301 (10), 273 (30), 242 (40), 203 (75), 43 (100).

7-Amino-6-cyano-1,3-dimethyl-5-(phenyl)-1,5-dihydro-pyrano[2,3-*d*] pyrimidine-2,4-dione (4h): White crystals. Mp 206–208°C. IR (KBr) ν: 3300 (NH_2), 2195 (CN), 1710 (C═O). ^{1}H NMR (DMSO-d_6) δ 3.07 (s, CH_3, 3H), 3.36 (s, CH_3, 3H), 4.31 (s, CH, 1H), 7.24–7.34 (m, arom. 5H, and NH_2, 2H) ppm. MS m/z (%): 311 (M^+, 23), 243 (100), 186 (33), 131 (16).

7-Amino-6-cyano-1,3-dimethyl-5-(phenyl)-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione (4i): White crystals. Mp 290–293°C. IR (KBr) ν: 3350 (NH_2), 2195 (CN), 1710 (C═O). ^{1}H NMR (DMSO-d_6) δ 3.06 (s, CH_3, 3H), 3.49 (s, CH_3, 3H), 7.21–7.43 (m, arom. 5H, and NH_2, 2H) ppm. MS m/z (%): 306 (M^+, 100), 249 (16), 222 (10), 194 (52), 165(10), 140 (28).

2-Amino-3-cyano-7,7-dimethyl-4-phenyl-4,6,7,8-tetrahydro-chromen-5-one (4j): White crystals. Mp 229–231°C. IR (KBr) ν: 3390 (NH_2), 2190 (CN), 1675 (C═O). ^{1}H NMR ($CDCl_3$) δ 1.04 (s, CH_3, 3H), 1.12 (s, CH_3, 3H), 2.22 (2 × d, AB system, ^2J = 16.40, CH_AH_B, 2H), 2.45 (s, CH_2, 2H), 4.40 (s, CH, 1H), 4.58 (br s, NH_2, 2H), 7.17–7.32 (m, arom. 5H) ppm. MS m/z (%): 293 (28), 217 (100), 161 (35), 133 (25), 102 (20), 77 (25), 39 (45).

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