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Convenient Preparation of Pyrano Benzopyranes in Aqueous Media

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Abstract: The three-component reaction of aldehyde, malononitrile, and 4-hydroxy coumarin has been efficiently performed in aqueous K_2CO_3 using a simple, clean, environmentally benign, novel procedure employing microwave irradiation. The observed yields and enhancement in reaction rates can be attributed to the uniform heating effect of microwave. The microwave-accelerated reaction technique not only eliminates the use of external base and organic solvents but also requires only water in both the reaction step and workup, thus rendering the whole procedure into a truly ecofriendly protocol.

Keywords: Aqueous K_2CO_3, environmentally benign, microwave irradiation, pyrano[3,2-c]benzopyran

The environmentally benign synthesis[1,2] of organic compounds has come several steps closer in recent years to the removal of organic solvents from the synthetic procedure. To reduce the employment of ecologically suspected solvents, it is most advantageous to carry out reactions in an aqueous medium. Indeed, water is recognized as an attractive medium for many organic reactions because it is the cheapest abundantly available solvent. The use of water as the reaction medium represents a remarkable benefit because this green solvent is highly polar and therefore immiscible with most organic compounds. Moreover the water-soluble catalyst resides and operates in the aqueous phase, and separation of organic materials is thus easy. Also, dramatic rate enhancements can be achieved in water in many organic reactions such as the Claisen rearrangement, aldol condensation,

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and Diels–Alder cycloaddition reaction.[3,4] Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple to handle, comparatively cheaper to operate, and especially important in industry. Further, coupling of this solvent-free synthesis[5,6] with microwave irradiation has associated benefits of shorter reaction times, uniform heating, higher yields, enhanced selectivity, and associated ease of manipulation.[7] In addition, multicomponent reactions (MCRs) are becoming increasingly prevalent because of their improved efficiency, reduced waste, and rapid access to structural diversity.[8,9]

4-Hydroxy coumarin constitutes the structural nucleus of many natural products, drugs, and pesticides.[10–12] It is the key intermediate for various widely used oral anticoagulants and rodenticides.[13] It has been reported that pyran derivatives also exhibit antimicrobial,[14] antitumor,[15] antifungal, antidepressant,[16] and platelet aggregation activity.[17] With this in mind and in continuation of our ongoing endeavour[18–20] aimed at developing new selective and green methodologies for the synthesis of bioactive compounds, it was thought worthwhile to synthesize pyrano[3,2-c]benzopyran by a simple, one-pot, environmentally benign method using aqueous K_2CO_3 under microwave irradiation (MWI).

A literature[21,22] survey revealed that the reaction of 4-hydroxy coumarin with malononitrile and substituted aldehydes proceeds in ethanolic piperidine to form pyrano[3,2-c]benzopyran derivatives. This classical procedure employs piperidine as a hazardous organic base, refluxing for long hours in organic solvents (ethanol, acetonitrile), and gives low yields of products. To study the role of base used and to greenify the classical method to an efficient, clean, economical method utilizing MWI under solvent-free conditions, the reaction was attempted in K_2CO_3. Different experimental trials were carried out to standardize the reaction under MWI. As a test case, a saturated solution of K_2CO_3 in water was added to the reaction mixture containing equimolar amounts of aldehyde (**1a–f**), malononitrile, and 4-hydroxy coumarin and was subjected to MWI at low power (560 W). On completion of reaction as monitored by TLC, the reaction mixture was cooled and the solid obtained was triturated with few milliliters of water to give the required product in excellent yields within just few minutes of MWI. These encouraging results inspired us to synthesize some novel pyrano benzopyran derivatives using heterocyclic aldehydes.

Under conventional heating, keeping similar reaction conditions, the reaction gave impure products even after long hours of heating and in certain cases led to charring. Direct heating of the reactants with solid K_2CO_3 in the absence of water led to charring. Also, an attempted neat reaction in the absence of K_2CO_3 and water yielded no product even after several minutes of MWI. This can be attributed to the requirement of basic conditions for the nucleophilic attack of the OH group to the cyano nitrogen in the acyclic intermediate (**III**) formed by the addition of α-H of 4-hydroxy coumarin to the electrophilic C=C bond of benzylidenemalononitrile

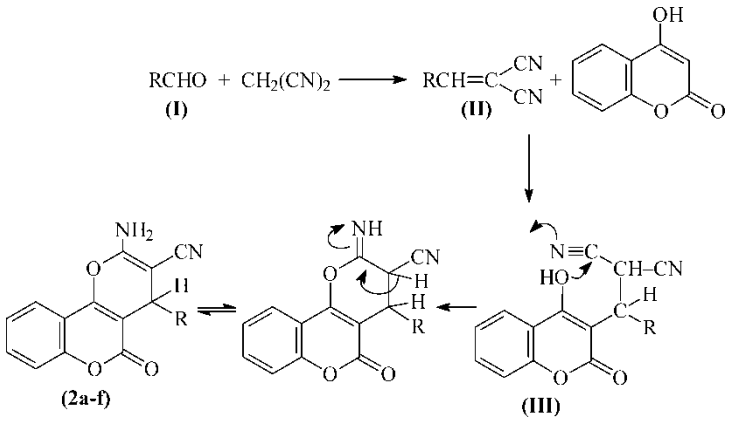


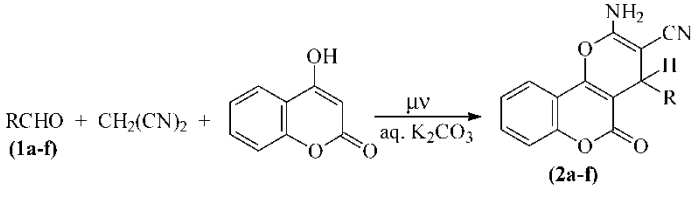
Figure 1. Probable reaction pathway for the formation of (**2a**–**f**).

intermediate (**II**), which was formed initially by the Knoevengel addition of aldehyde with malononitrile (Fig. 1).

In conclusion, we have developed an easier, practically convenient, novel, ecologically safe method for the synthesis of pyrano[3,2-c]benzopyran using a green chemistry protocol. The use of aqueous K_2CO_3 as a green catalyst under MWI not only gave good yields in less reaction time but also provided a procedure that does not the use organic solvents and corrosive organic bases (Scheme 1).

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance 300 Spectrospin (300-MHz) instrument using TMS as an internal standard and $CDCl_3$ as a solvent. Microwave irradiation was carried



R = phenyl, 4-chlorophenyl, 2-furyl, 3-indolyl, piperonyl, 2-chloro-3-quinolyl

Scheme 1. K_2CO_3-mediated synthesis of pyrano[3,2-c]benzopyran in aqueous media.

Table 1. Reaction time and yield for compounds (**2a–f**)

Compound no.	R	Time (min)[a]	Yield (%)
2a	Phenyl	2.6	91
2b	4-Chlorophenyl	2.8	89
2c	2-Furyl	2.0	92
2d	3-Indolyl	2.2	93
2e	Piperonyl	2.5	88
2f	2-Chloro-3-quinolyl	1.8	87

[a]Microwave heating (560 W, 2450 MHz, 110–120 °C, 30 s).

out in a Kenstar microwave oven, model no. OM9925E (2450 MHz, 800 W). The reaction was monitored through TLC, using silica-gel-coated Al plates (Merck). The reaction temperature was measured through AZ, Mini Gun Type Non-Contact IR thermometer (model no. 8868). 2-Chloro-3-quinoline aldehyde was prepared according to the literature method.[23]

General Procedure for the Synthesis of 2-Amino-3-cyano-4-aryl-4H,5H-pyrano[3,2-c] [1] benzopyran-5-one (2a–f)

A mixture of neat reactants, 4-hydroxy coumarin (0.01 mol), aldehydes **(1a–f)** (0.01 mol) and malononitrile (0.01 mol) was put into an Erlenmeyer flask, and 10-mL of a saturated solution of K_2CO_3 in water was added to it. The reaction mixture was subjected to MWI for a specific time (Table 1) at low power (560 W). The progress of the reaction was monitored by TLC examination at an interval of every 30 s. On completion of the reaction, the reaction mixture was cooled and was triturated with 2–3 mL of ice-cold water to get the solid product **(2a–f)**, leaving behind K_2CO_3 dissolved in water. The product obtained was filtered, washed with cold water, dried, and recrystallized from ethanol.

Data

2a: mp 257–258 °C[21]; IR (KBr): 3385 (NH_2), 2223 (C≡N), 1715 (CO δ lactone), 1677 (C=C vinylnitrile), 1596 (C=C aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.95 (s, 1H, pyran CH), 7.22 (brs, 2H, NH), 7.30–7.48 (m, 9H, Ar-H). Anal. calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.79; N, 8.86. Found: C, 72.22; H, 3.70; N, 8.77.

2b: mp 261–262 °C[21]; IR (KBr): 3369 (NH_2), 2231 (C≡N), 1708 (CO δ lactone), 1674 (C=C vinylnitrile), 1604 (C=C aromatic) cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ: 4.40 (s, 1H, pyran CH), 7.26 (brs, 2H, NH), 7.33–7.82 (m, 8H, Ar-H). Anal. calcd. for $C_{19}H_{11}ClN_2O_3$: C, 65.04; H, 3.13; N, 7.98. Found: C, 65.12; H, 3.18; N, 7.89.

2c: mp 252–253 °C[24]; IR (KBr): 3354 (NH_2), 2212 (C≡N), 1710 (CO δ lactone), 1655 (C=C vinylnitrile), 1570 (C=C aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.61 (s, 1H, pyran CH), 6.25–6.37 (m, 2H, furan), 7.24 (brs, 2H, NH), 7.46–7.90 (m, 5H, Ar-H + furan). Anal. calcd. for $C_{17}H_{10}N_2O_4$: C, 66.66; H, 3.26; N, 9.15. Found: C, 66.54; H, 3.18; N, 9.19.

2d: mp 215–217 °C; IR (KBr): 3370 (NH_2), 2218 (C≡N), 1718 (CO δ lactone), 1667 (C=C vinylnitrile), 1581 (C=C aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.62 (s, 1H, pyran CH), 7.20 (brs, 2H, NH), 7.31–8.52 (m, 9H, Ar-H), 10.2 (s, 1H, NH indole). Anal. calcd. for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.79; N, 12.24. Found: C, 69.90; H, 3.72; N, 12.31.

2e: mp 180–181 °C; IR (KBr): 3365 (NH_2), 2237 (C≡N), 1710 (CO δ lactone), 1671 (C=C vinylnitrile), 1592 cm^{-1} (C=C aromatic); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.36 (s, 1H, pyran CH), 6.14 (s, 2H, OCH_2 piperonyl), 7.12 (brs, 2H, NH), 7.24–7.74 (m, 7H, Ar-H). Anal. calcd. for $C_{20}H_{12}N_2O_5$: C, 66.66; H, 3.33; N, 7.77. Found: C, 66.57; H, 3.39; N, 7.68.

2f: mp 305–308 °C; IR (KBr): 3380 (NH_2), 2218 (C≡N), 1717 (CO δ lactone), 1672 (C=C vinylnitrile), 1608 (C=C aromatic) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.12 (s, 1H, pyran CH), 7.20 (brs, 2H, NH), 7.44–8.12 (m, 9H, Ar-H). Anal. calcd. for $C_{22}H_{12}ClN_3O_3$: C, 65.75; H, 2.98; N, 10.46. Found: C, 65.68; H, 2.91; N, 10.51.

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