An Efficient and Convenient Approach to the Synthesis of Benzopyrans by a Three-Component Coupling of One-Pot Reaction

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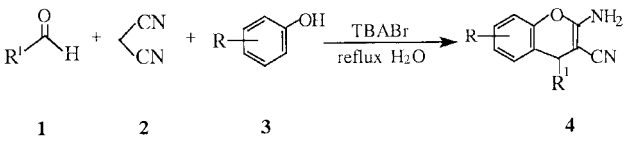
Abstract: A general and practical chemistry route to the synthesis of polyfunctionlized benzopyrans using tetrabutylammonium bromide (TBABr) as the catalyst (10 mol%) is described. This method provides several advantages such as neutral conditions, high yields and simple work-up procedure. In addition, water was chosen as a green solvent.

Key words: benzopyrans, tetrabutylammonium bromide, synthesis

At the beginning of the new century, with the increasing environmental concerns and the regulatory constrains faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.[1] Recently Wender defined the 'ideal synthesis' as one in which the target components is produced in one step, in quantitative yield from readily available and inexpensive starting materials in resource-effective and environmentally acceptable process.[2] The one-pot multicomponent condensations represent a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibilities of building-up complex molecules with maximum simplicity and brevity.[3]

In recent years, polyfunctionalized benzopyrans and their derivatives have attracted strong interest due to their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, diuretic, antianaphylactin, anticancer.[4] In addition, they also constitute a structural unit of a series of natural products[5] and because of the inherent reactivity of the inbuilt pyran ring are versatile synthesis.[6] Furthermore, these compounds can be employed as cosmetics, pigments[7] and utilized as potential biodegradable agrochemicals.[8] Thus, synthesis of the heterocyclic nucleus is of much current importance. The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents and expensive purification techniques represents a fundamental target of the modern organic synthesis.[9] Several conventional synthesis of these polyfunctionalized benzopyrans involves three-component, one-pot condensation of malononitrile with an aldehyde and an activated phenol using base or amide as catalysts.[10] Each of the above methods has its own merit, while some of these methods are plagued by the limitation of poor yields, difficult work-up and effluent pollution. Consequently, there is scope for further renovation toward mild conditions, increased of variation of the substituents in the components and better yields.

As a good phase transfer catalyst, tetrabutylammonium bromide has been used in a number of organic reactions. However, the use of TBABr as a catalyst in the synthesis of these polyfunctionalized benzopyrans has not been reported. In this manuscript, we wish to report a general and highly efficient route for the synthesis of benzopyrans using an inexpensive and commercially available TBABr as catalyst. This is an one-pot combination using water as a green solvent that not only preserves the simplicity but also consistently gives the corresponding products in good to excellent yields (Scheme 1).



1 2 3 4

Scheme 1

In a typical general experimental procedure, a solution of malononitrile, an aromatic aldehyde and an activated phenol in water was heated under reflux water in the presence of a catalytic amount of TBABr (10 mol%) for a certain period of time required to complete the reaction, resulting in the formation of benzopyrans, the reaction mixture was extracted with ether or ethyl acetate. After drying over anhydrous sodium sulfate, the solid product was purified by recrystallization from ethanol.

To study the generality of this process, several examples illustrating this method for the synthesis those polyfunctionalized benzopyrans were studied. The results are summarized in Table 1. The effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under this reaction conditions. The three-component cyclocondensation reaction proceeded smoothly under refluxing water to give the corresponding products **4** in high yields. Benzoaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro groups, halides) or electron-donating groups (such as hydroxy group, alkoxyl group,

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Table 1 Tetrabutylammonium Bromide-Catalyzed Synthesis of Benzopyrans

Entry	R^1	Phenol	Product	Yields[a,b] (%)	Mp (°C)	
					Found	Reported[10]
1	C_6H_5 **1a**	1-Naphthol	**4a**	89	206–207	
2	4-ClC_6H_4 **1b**	1-Naphthol	**4b**	95	231–232	232
3	3-ClC_6H_4 **1c**	1-Naphthol	**4c**	93	216–218	
4	2-ClC_6H_4 **1d**	1-Naphthol	**4d**	87	236–237	
5	2,4-$Cl_2C_6H_3$ **1e**	1-Naphthol	**4e**	88	213–215	
6	4-$NO_2C_6H_4$ **1f**	1-Naphthol	**4f**	85	239–241	
7	3-$NO_2C_6H_4$ **1g**	1-Naphthol	**4g**	84	214–216	214.5–216
8	3,4-$OCH_2OC_6H_3$ **1h**	1-Naphthol	**4h**	88	242–244	
9	4-OHC_6H_4 **1i**	1-Naphthol	**4i**	92	249–251	252
10	4-$CH_3OC_6H_4$ **1j**	1-Naphthol	**4j**	91	182–183	182
11	4-$Me_2NC_6H_4$ **1k**	1-Naphthol	**4k**	89	203–205	
12	4-ClC_6H_4 **1l**	2-Naphthol	**4l**	79	206–208	208
13	2-ClC_6H_4 **1m**	2-Naphthol	**4m**	75	259–261	261–263
14	4-$NO_2C_6H_4$ **1n**	2-Naphthol	**4n**	77	185–186	
15	3,4-$OCH_2OC_6H_3$ **1o**	2-Naphthol	**4o**	82	250–252	
16	4-$CH_3OC_6H_4$ **1p**	2-Naphthol	**4p**	75	190–191	192

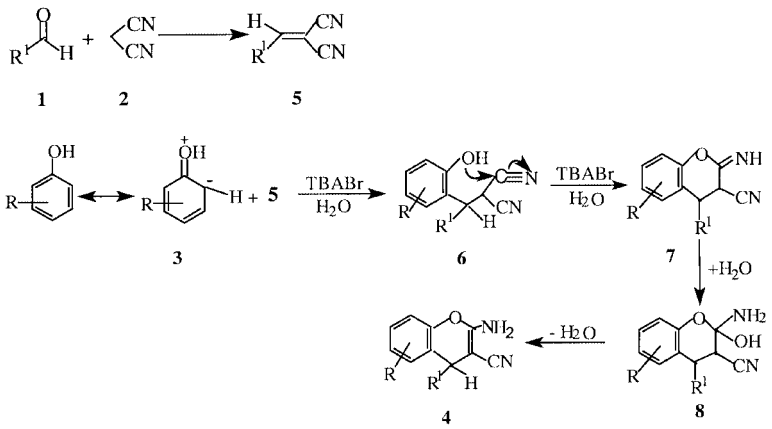
[a] Isolated yields.
[b] Reaction conditions.[11]

dimethylamino group) were employed and reacted well to give the corresponding benzopyrans in good to excellent yields.

The reaction of 1-naphthol or 2-naphthol with an aromatic aldehyde and malononitrile gave different experimental results. For instance, 4-chlorobenzoaldehyde reacted with malononitrile and 1-naphthol or 2-naphthol under the refluxing water and gave yields of 2-amino-2-chromenes **4b** (95%) and **4l** (79%), respectively. When 4-nitrobenzaldehyde was treated with malononitrile and 1-naphthol or 2-naphthol under the same conditions, the isolated yields of corresponding compounds were **4f** (85%) and **4n** (77%). We conclude that 1-naphthol exhibits higher reactivity than 2-naphthol does.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, 4-chlorobenzoaldehyde reacted with malononitrile and 1-naphthol in the presence of 1 mol% TBABr to give the product **4b** in quantitative yield (67%) at refluxing water after six hours of reaction time. Increasing of the catalyst to 5 mol% and 10 mol% results in accelerating the reaction yields to 85% and 95% respectively. Use of just 10 mol% TBABr in refluxing water is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. The yields are, in general, very high regardless of the structural variations in aromatic aldehyde. The reaction could be carried out in the absence of TBABr at different time intervals (3 h, 6 h, 12 h) when the same reaction mixture (**1b**, malononitrile and 1-naphthol) was subjected to heating in refluxing water. The yields of these runs were 19%, 37%, 42%, respectively. Under the identical condition, the rate of the reaction was affected by the presence of TBABr and the yields were 72% and 95% after different time intervals (3 h, 6 h). Thus, 10 mol% TBABr was chosen as a quantitative catalyst for these reactions. In addition, it must be pointed out that all of these reactions were carried out in water and those products were characterized by ^{1}H NMR, IR and elemental analyses.

We propose the possible following mechanism to account for the reaction.[10] An aromatic aldehyde **1** was firstly condensed with malononitrile **2** to afford α-cyanocinnamonitrile derivative **5**. The step (**1** + **2**→**5**) can be regarded as a fast knoevenagel addition. With a model reaction, the knoevenagel reaction of malononitrile and aromatic aldehydes can be carried out in water without any catalyst. Thus we think that the second step requires the presence of TBABr probably. The phenol ortho C-alkylation by reaction with the electrophilic C=C double bond giving the intermediate **6**. Then the intermediate **6** was cyclized by the nucleophilic attack of OH group on the cyano (CN) moiety and gave the intermediate **7**. Finally the expected



Scheme 2

products **4** were afforded by addition and elimination of water (**7**→**8**→**4**) (Scheme 2). In this process, TBABr as an emulsifying agent makes the mixture more even, which contributes to promote these reactions.

In conclusion, we have described a general and highly efficient procedure for the preparation of polyfunctionalized benzopyrans by TBABr-catalyzed, three component condensation under the refluxing water. In addition, it is possible to apply the tenets of green chemistry to the generation of biologically interesting products using aqueous media approaches, which are less expensive and less toxic than those with organic solvents. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reactions, minimal environmental impact which makes it a useful and attractive process for the synthesis of these compounds.

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(11) **General Procedure for the Preparation of Benzopyrans:** A mixture of an aromatic aldehyde (1 mmol), malononitrile (1 mmol), phenol (1 mmol) and TBABr (10 mol%) in H_2O (20 mL) was stirred at refluxing for 6 h. The progress of the reaction was monitored by thin layer chromatograph. After completion of the reactions, the mixture was cooled to r.t. and extracted by Et_2O and EtOAc. The organic phase was collected and dried over anhyd Na_2SO_4. Then evaporate the solvent under reduced pressure and get the crude products. The crude products were purified by recrystallization by EtOH. Data of some compounds are shown below: **Compound 4a, 2-Amino-3-cyano-4-(phenyl)-4*H*-benzochromene.** Mp 210–211 °C (from EtOH): IR (KBr): ν_{max} = 3454, 3318, 3020, 2932, 2205, 1656, 1600, 1572, 1450, 1372, 1267, 1100, 1022, 811, 744 cm^{-1}. ^1H NMR: δ = 4.90 (s, 1 H, H-4), 7.10 (s 2 H, NH_2), 7.07–7.12 (m, 6 H, H-5, H-2′, H-3′, H-4′, H-5′, H-6′), 7.56–7.66 (m, 3 H, H-6, H-8, H-9), 7.94 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.23 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.54; H, 4.70; N, 9.39. Found: C, 80.40; H, 4.75; N, 9.37. **Compound 4c, 2-Amino-3-cyano-4-(3-chlorophenyl)-4*H*-benzo-chromene.** Mp 216–218 °C (from EtOH). IR (KBr): ν_{max} = 3455, 3340, 3023, 2930, 2210, 1645, 1600, 1580, 1470, 1378, 1266, 1030, 816, 750, 700 cm^{-1}. ^1H NMR: δ = 4.98 (s, 1 H, H-4), 7.24 (s, 2 H, NH_2), 7.12–7.38 (m, 4 H, H-4′, H-5′, H-6′, H-5), 7.23 (s, 1 H, H-2′), 7.56–7.66 (m, 3 H, H-6, H-8, H-9), 7.89 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.26 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.11; H, 4.01; N, 8.40.

Compound 4d, 2-Amino-3-cyano-4-(2-chlorophenyl)-4*H*-benzo-chromene. Mp 236–237 °C (from EtOH). IR (KBr): ν_{max} = 3476, 3320, 2915, 2195, 1664, 1600, 1410, 1360, 1275, 1180, 1040, 805, 750 cm^{-1}. ^1H NMR: δ = 5.41 (s, 1 H, CH), 7.20 (s, 2 H, NH_2), 7.01 (d, 1 H, *J* = 8.4 Hz, H-5), 7.25–7.31 (m, 3 H, H-4′, H-5′, H-6′), 7.45 (d, 1 H, *J* = 8.4 Hz, H-3′), 7.56–7.67 (m, 3 H, H-6, H-8, H-9), 7.89 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.24 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.11; H, 4.00; N, 8.39.

Compound 4e, 2-Amino-3-cyano-4-(2,4-dichlorophenyl)-4*H*-benzo-chromene. Mp 213–215 °C (from EzOH). IR (KBr): ν_{max} = 3454, 3336, 3030, 2186, 1667, 1600, 1572, 1466, 1378, 1200, 1050, 860, 811, 755 cm^{-1}. ^1H NMR δ = 5.47 (s, 1 H, H-4), 7.30 (s, 2 H, NH_2), 6.98 (d, 1 H, *J* = 8.4 Hz, H-6′), 7.60 (s, 1 H, H-3′), 7.39–7.59 (m, 2 H, H-5, H-5′), 7.69–7.89 (m, 3 H, H-6, H-8, H-9), 8.03 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.25 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{20}H_{12}Cl_2N_2O$: C, 65.39; H, 3.27; N, 7.63. Found: C, 65.23; H, 3.25; N, 7.60.

Compound 4f, 2-Amino-3-cyano-4-(4-nitrophenyl)-4*H*-benzo-chromene. Mp 239–241 °C (from EtOH). IR (KBr): ν_{max} = 3460, 3335, 2196, 1665, 1600, 1575, 1536, 1500, 1346, 1270, 1195, 1100, 805, 770 cm^{-1}. ^1H NMR δ = 5.12 (s, 1 H, H-4), 7.29 (s, 2 H, NH_2), 7.05 (d, 1 H, *J* = 8.4 Hz, H-5), 7.51–7.72 (m, 3 H, H-6, H-8, H-9), 7.52 (d, 2 H, H-2′, H-6′), 7.90 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.15 (d, 2 H, H-3′, H-5′), 8.27 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.79; N, 12.24. Found: C, 70.09; H, 3.99; N, 12.12.

Compound 4h, 2-Amino-3-cyano-4-(3,4-dioxymethyl-enephenyl)-4*H*-benzo-chromene. Mp 242–244 °C (from EtOH). IR (KBr): ν_{max} = 3434, 3320, 2905, 2196, 1670, 1605, 1575, 1490, 1405, 1380, 1225, 1190, 1040, 790, 770 cm^{-1}. ^1H NMR δ = 4.88 (s, 1 H, H-4), 5.92 (s, 2 H, CH_2), 6.74–6.85 (m, 3 H, H-2′, H-5′, H-6′), 7.10–7.13 (m, 3 H, NH_2 + H-5), 7.55–7.65 (m, 3 H, H-6, H-8, H-9), 7.88 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.22 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09; N, 8.19. Found: C, 73.70; H, 4.00; N, 8.25.

Compound 4k, 2-Amino-3-cyano-4-(4-dimethylamino-phenyl)-4*H*-benzo-chromene. Mp 203–205 °C (from EtOH). IR (KBr): ν_{max} = 3465, 3340, 3090, 2955, 2863, 2806, 2193, 1662, 1605, 1570, 1522, 1400, 1380, 1342, 1262, 1190, 1100, 800, 750 cm^{-1}. ^1H NMR δ = 2.84 [s, 6 H, $N(CH_3)_2$], 4.75 (s, 1 H, H-4), 7.03–7.10 (m, 3 H, H-5 or NH_2), 6.65 (d, 2 H, *J* = 8.4 Hz, H-2′, H-6′ or H-3′, H-5′), 7.06 (d, 2 H, *J* = 8.4 Hz, H-3′, H-5′ or H-2′, H-6′), 7.53–7.64 (m, 3 H, H-6, H-8, H-9), 7.88 (d, 1 H, *J* = 8.4 Hz, H-7 or H-10), 8.24 (d, 1 H, *J* = 8.4 Hz, H-10 or H-7). Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.42; H, 5.57; N, 12.32. Found: C, 77.36; H, 5.60; N, 12.23.

Compound 4n, 3-Amino-2-cyano-1-(4-nitrophenyl)-1*H*-benzo-chromene. Mp 185–186 °C (from EtOH). IR (KBr): ν_{max} = 3430, 3325, 2190, 1650, 1610, 1582, 1540, 1502, 1340, 1244, 1200, 1070, 810 cm^{-1}. ^1H NMR δ = 5.45 (s, 1 H, H-4), 7.20 (s, 2 H, NH_2), 7.36–7.52 (m, 3 H, H-6, H-7, H-9 or H-10), 7.69–8.03 (m, 2 H, H-5 and H-8), 7.98 (d, 1 H, *J* = 9.2 Hz, H-10 or H-9), 7.44 (d, 2 H, H-2′ and H-6′), 8.15 (d, 2 H, H-3′ and H-5′). Anal. Calcd for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.79; N, 12.24. Found: C, 70.10; H, 3.88; N, 12.08.

Compound 4o, 2-Amino-3-cyano-4-(dioxymethylene-phenyl)-4*H*-benzo-chromene. Mp 250–252 °C (from EtOH). IR (KBr): ν_{max} = 3443, 3340, 3045, 2886, 2195, 1657, 1600, 1580, 1500, 1454, 1400, 1234, 1195, 1040, 811, 743 cm^{-1}. ^1H NMR δ = 5.25 (s, 1 H, H-4), 5.91 (s, 2 H, -OCH_2O-), 6.95 (s, 2 H, NH_2), 6.66–6.80 (m, 3 H, H-2′, H-5′, H-6′), 7.86–7.95 (m, 2 H, H-5 or H-8), 7.91 (d, 1 H, *J* = 8.0 Hz, H-9 or H-10), 7.20–7.49 (m, 3 H, H-6, H-7, H-10). Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09; N, 8.19; Found: C, 73.72; H, 3.99; N, 8.06.