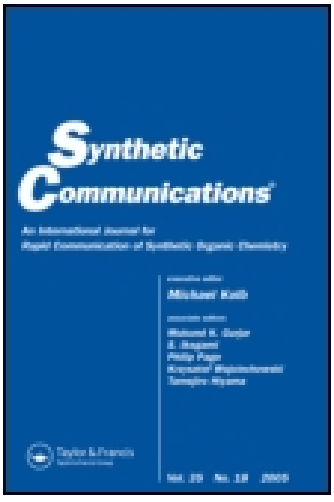

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Clean, One-Pot Synthesis of Naphthopyran Derivatives in Aqueous Media

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Clean, One-Pot Synthesis of Naphthopyran Derivatives in Aqueous Media

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Abstract: A general and practical one-pot synthesis of naphthopyran derivatives using hexadecyltrimethylammonium bromide (HTMAB) as catalyst (10 mol%) is described. This method provides several advantages such as neutral conditions, high yields and simple workup procedure. The catalyst is low cost, facile, active, environmentally friendly, and reusable. In addition, water is chosen as a green solvent.

Keywords: Aqueous media, hexadecyltrimethylammonium bromide, naphthopyran, synthesis

INTRODUCTION

Most chemical reactions of organic substances conducted in the laboratory as well as in industry need organic solvents as reaction media, although water is safe, benign, environmentally friendly, and cheap compared with organic solvents. Around 1980, Breslow et al. discovered that the Diels–Alder reaction performed in water can be subject to huge accelerations.[1] The observation led to increased interest from synthetic organic chemists in organic reactions in water. Soon it was discovered that other organic reactions, such as the Claisen rearrangement,[2] the aldol condensation,[3] Diels–Alder

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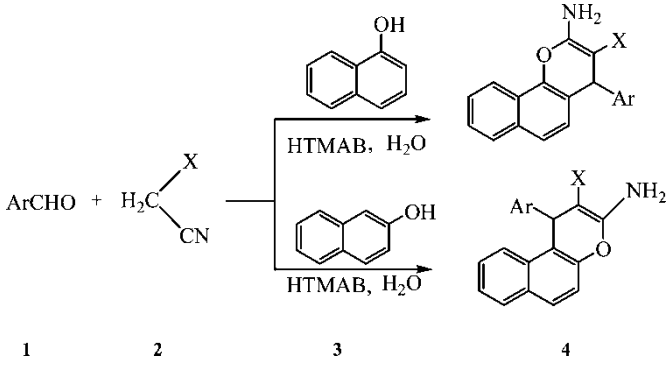
reaction,[4] the benzoin condensation,[5] Mannich reaction,[6] and Michael reaction[7] exhibit rate enhancements in water. To date, many more organic transformations have been carried out in water.[8]

Naphthopyrans are polyfunctionalized benzopyran derivatives. Recently, benzopyran derivatives have attracted strong interest because of their useful biological and pharmacological activities, such as anticoagulant, spasmolytic, diuretic, anticancer, and antianaphylactin activities.[9] Some of them can also be employed as cosmetics and pigments[10] and utilized as potential biodegradable agrochemicals.[11] In addition, polysubstitued benzopyran constitutes a structural unit of a series of versatile synthesis.[12] Several conventional synthesis of these polyfunctionalized benzopynans begins with natural products[13] and involves the condensation of malononitrile with an aldehyde and an activated phenol using base or amide as catalysts.[14] Each of these methods has its own merit, but some of these methods are plagued by poor yields, difficult workup, and effluent pollution.

In this work, we report the synthesis of naphthopyran derivatives catalyzed by hexadecyltrimethylammonium bromide (HTMAB) in the aqueous media. This method provides several advantages such as neutral conditions, high yield, and simple workup procedure (Scheme 1).

To study the generality of this process, several examples illustrating this method for the synthesis of naphthopyran derivatives were studied. The results are summarized in Table 1. The effect of electrons and the nature of substituents on the aromatic ring did not show obvious effects in terms of yields under this reaction condition. The reaction proceeded smoothly under refluxing water to give the corresponding products **4** in high yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxy group, alkoxyl group) were employed and reacted well to give the corresponding naphthopyran derivatives in good to excellent yields.



1 2 3 4

Scheme 1.

Table 1. Synthesis of naphthopyran derivatives **4** catalyzed by HTMAB in aqueous media

Entry	Ar	X	Phenol	Time (h)	Yield[a] (%)	Mp (°C) Found	Mp (°C) Reported
1	C_6H_5 **1a**	CN	1-Naphthol	4	93	214–216	
2	2-ClC_6H_4 **1b**	CN	1-Naphthol	4	95	244–246	
3	3-ClC_6H_4 **1c**	CN	1-Naphthol	4	95	228–230	231–232.5[14e]
4	4-ClC_6H_4 **1d**	CN	1-Naphthol	4	93	235–236	232[14b]
5	2,4-$Cl_2C_6H_3$ **1e**	CN	1-Naphthol	4	91	222–224	
6	3-$NO_2C_6H_4$ **1f**	CN	1-Naphthol	4	94	210–211	214.5–216[14c]
7	4-$NO_2C_6H_4$ **1 g**	CN	1-Naphthol	4	95	240–241	239–241[14e]
8	4-$CH_3OC_6H_4$ **1 h**	CN	1-Naphthol	4	92	184–185	182[14d]
9	3,4-$OCH_2OC_6H_3$ **1i**	CN	1-Naphthol	4	89	240–242	
10	4-OHC_6H_4 **1j**	CN	1-Naphthol	4	92	255–257	252[14b]
11	4-ClC_6H_4 **1 k**	CN	2-Naphthol	6	82	210–211	208[14b]
12	2-ClC_6H_4 **1l**	CN	2-Naphthol	6	81	265–267	261–263[14b]
13	3,4-$OCH_2OC_6H_3$ **1 m**	CN	2-Naphthol	6	85	258–260	
14	4-$CH_3OC_6H_4$ **1n**	CN	2-Naphthol	6	78	194–196	192[14d]
15	4-ClC_6H_4 **1o**	CO_2Et	2-Naphthol	12	69	190–192	
16	2,4-$Cl_2C_6H_3$ **1p**	CO_2Et	2-Naphthol	12	68	195–197	

[a]Isolated yields based on aromatic aldehyde.

The reaction of acromatic aldehyde with malononitrile or ethyl cyanoacetate and 1-naphthol or 2-naphthol gave different experimental results. From Table 1 we know that malononitrile gives better results and needs shorter reaction time than ethyl cyanoacetate. For instance, 4-chlorobenzaldehyde (**1k**) reacted with malononitrile or ethyl cyanoacetate and 2-naphthol in the refluxing water and gave yields of **4k** (82%) and **4o** (69%) in 6 or 12 h, respectively. And the yield of the reaction of acromatic aldehyde with malononitrile and 1-naphthol was much better than that of 2-naphthol. For instance, 4-chlorobenzaldehyde (**1d**) and 2-chlorobenzaldehyde (**1b**) were treated with malononitrile and 1-naphthol; in 4 h, they gave the isolated yields of the corresponding compounds **4d** (93%) and **4b** (95%). When 4-chlorobenzaldehyde (**1k**) and 2-chlorobenzaldehyde (**1l**) were treated with malononitrile and 2-naphthol for 6 h, the yields of **4k** (82%) and **4l** (81%) were only obtained. We conclude that malononitrile and 1-naphthol exhibit higher reactivity than ethyl cyanoacetate and 2-naphthol.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, 4-chlorobenzaldehyde reacted with malononitrile (ethyl cyanoacetate) and 1-naphthol in the presence of 1 mol% HTMAB to give the product **4b** in modest yield (55%) in refluxing water after 4 h of reaction time. Increasing the catalyst to 5, 10, and 15 mol% results in accelerating the reaction yields to 86%, 93%, and 93% respectively. Use of just 10 mol% HTMAB in refluxing water is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Thus, 10 mol% HTMAB was chosen as a quantitative catalyst for these reactions.

The catalyst could be reused six times for the synthesis of **4b** without significant loss of activity. The results are summarized in Table 2. In addition, it must be pointed out that all of these reactions were carried out in water and those products were characterized by melting point, IR, ^{1}H NMR, and elemental analyses.

In conclusion, we have described a general and highly efficient procedure for the preparation of naphthopyran derivatives catalyzed by HTMAB under refluxing water. In addition, it is possible to apply the tenets of green

Table 2. Reuse of the catalyst for syntheses of **4b**

Entry	Yield (%)
1	95
2	94
3	93
4	91
5	90
6	89

chemistry to the generation of interesting products using aqueous media methods that are less expensive and less toxic than those with organic solvents. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reactions, and minimal environmental impact, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

The new compounds prepared were characterized by ^{1}H NMR, IR, and element analyses and are described in this section. Liquid aldehydes were purified by distillation before use. IR spectra were recorded on a Bio-rad FIS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on an Avance-400 spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Elemental analysis measured on a Heraeus (CHN, Rapid) analyzer.

General Procedure for Synthesis of Naphthopyran Derivatives in Aqueous Media

A mixture of an aromatic aldehyde (1.0 mmol) with 1-naphthol (2- naphthol) (1.0 mmol), malononitrile (ethyl cyanoacetate) (1.0 mmol), and HTMAB (10 mol%) in water (20 mL) was stirred at reflux for a period of time summarized in Table 1. The progress of the reaction was monitored by TLC. After completion of the reactions, the mixture was cooled to room temperature, solid was filtered off and washed with H_2O (40 mL), and the crude products were obtained. The crude products were purified by recrystallization from ethanol (95%).

Data of Some Compounds

4a. IR (KBr) ν (cm^{-1}) 3456, 3320, 3018, 2932, 2205, 1662, 1572, 1450, 1372, 1267, 1100, 811, 744; ^{1}H NMR δ (ppm) 4.90 (s, 1H, H-4), 7.10 (s, 2H, NH_2), 7.07–7.12 (m, 6H, H-5, and ArH), 7.56–7.66 (m, 3H, H-6, 7,8), 7.94 (d, 1H, $J = 8.4$, H-9 or H-10), 8.23 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. calcd. for $C_{20}H_{14}N_2O$: C, 80.54; H, 4.70; N, 9.39. Found: C, 80.42; H, 4.78; N, 9.35.

4b. IR (KBr) ν (cm^{-1}) 3475, 3318, 2917, 2195, 1670, 1600, 1410, 1360, 1275, 1180, 1040, 805, 750; ^{1}H NMR δ (ppm) 5.41 (s, 1H, CH), 7.20 (s, 2H, NH_2), 7.01 (d, 1H, $J = 8.4$, H-5), 7.25–7.31 (m, 3H, ArH), 7.45 (d, 1H, $J = 8.4$, ArH), 7.56–7.67 (m, 3H, H-6, 7, 8), 7.89 (d, 1H, $J = 8.4$, H-9 or H-10), 8.24 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. Calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.10; H, 4.02; N, 8.35.

4c. IR (KBr) ν (cm^{-1}) 3459, 3343, 3025, 2935, 2210, 1650, 1600, 1580, 1470, 1378, 1030, 750, 700; ^{1}H NMR δ (ppm) 4.98 (s, 1H, H-4), 7.24

(s, 2H, NH_2), 7.12–7.38 (m, 4H, ArH), 7.23 (s, 1H, ArH-2′), 7.56–7.66 (m, 3H, H-6, 7, 8), 7.89 (d, 1H, $J = 8.4$, H-9 or H-10), 8.26 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.09; H, 4.05; N, 8.44.

4e. IR (KBr) ν (cm^{-1}) 3459, 3333, 3035, 2186, 1663, 1600, 1575, 1466, 1378, 1200, 1050, 860, 755; ^1H NMR δ (ppm) 5.47 (s, 1H, H-4), 7.30 (s, 2H, NH_2), 6.98 (d, 1H, $J = 8.4$, ArH-6′), 7.60 (s, 1H, ArH-3′), 7.39–7.59 (m, 2H, H-5 and ArH-5′), 7.69–7.89 (m, 3H, H-6, 7, 8), 8.03 (d, 1H, $J = 8.4$, H-9 or H-10), 8.25 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. calcd. for $C_{20}H_{12}Cl_2N_2O$: C, 65.39; H, 3.27; N, 7.63. Found: C, 65.26; H, 3.23; N, 7.61.

4g. IR (KBr) ν (cm^{-1}) 3460, 3335, 2196, 1665, 1600, 1575, 1536, 1500, 1346, 1270, 1195, 1100, 770; ^1H NMR δ (ppm) 5.12 (s, 1H, H-4), 7.29 (s, 2H, NH_2), 7.05 (d, 1H, $J = 8.4$, H-5), 7.51–7.72 (m, 3H, H-6, 7, 8), 7.52 (d, 2H, ArH-2′, 6′), 7.90 (d, 1H, $J = 8.4$, H-9 or H-10), 8.15 (d, 2H, ArH-3′, 5′), 8.27 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. calcd. for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.79; N, 12.24. Found: C, 70.05; H, 3.92; N, 12.16.

4i. IR (KBr) ν (cm^{-1}) 3438, 3324, 2907, 2196, 1673, 1605, 1575, 1490, 1405, 1380, 1190, 1040, 770; ^1H NMR δ (ppm) 4.88 (s, 1H, H-4), 5.92 (s, 2H, OCH_2O), 6.74–6.85 (m, 3H, ArH), 7.13 (s, 2H, NH_2), 7.55–7.65 (m, 3H, H-6, 7, 8), 7.88 (d, 1H, $J = 8.4$, H-9 or H-10), 8.22 (d, 1H, $J = 8.4$, H-10 or H-9). Anal. calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09; N, 8.19. Found: C, 73.74; H, 4.03; N, 8.26.

4m. IR (KBr) ν (cm^{-1}) 3443, 3340, 3045, 2886, 2195, 1657, 1600, 1580, 1500, 1400, 1234, 1040, 743; ^1H NMR δ (ppm) 5.25 (s, 1H, H-4), 5.91 (s, 2H, -OCH_2O-), 6.95(s, 2H, NH_2), 6.66–6.80 (m, 3H, ArH), 7.86–7.95 (m, 2H, H-5 or H-8), 7.91 (d, 1H, $J = 8.0$, H-9 or H-10), 7.20–7.49 (m, 3H, H-6, 7, 10). Anal. calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09; N, 8.19. Found: C, 73.75; H, 3.97; N, 8.08.

4o. IR (KBr) ν (cm^{-1}) 3475, 3325, 1675, 1630, 1505, 1460, 1400, 1305, 1215, 1070, 825; ^1H NMR δ (ppm) 1.26 (t, $J = 7.2$ Hz, 3H, CH_3), 4.09 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.51 (s, 1H, CH), 7.23–7.53 (m, 7H, Naph-H), 7.65 (s, 2H, NH_2), 7.92 (d, $J = 8$ Hz, 2H, ArH), 7.99 (d, $J = 8$ Hz, 1H, ArH). Anal. calcd. for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69. Found: C, 69.48; H, 4.74; N, 3.82.

4p. IR (KBr) ν (cm^{-1}) 3395, 3290, 1610, 1525, 1465, 1395, 1370, 1310, 1257, 1100, 1075, 1030, 745; ^1H NMR δ (ppm) 1.19 (t, $J = 7.2$ Hz, 3H, CH_3), 4.07 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.81 (s, 2H, NH_2), 7.23–7.53 (m, 7H, Naph-H), 7.92 (d, $J = 8.8$ Hz, 2H, ArH), 8.14 (d, $J = 8.8$ Hz, 1H, ArH). Anal. calcd. for $C_{22}H_{17}C_{l2}NO_3$: C, 63.78; H, 4.14; N, 3.38. Found: C, 63.90; H, 4.09; N, 3.29.

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