A Facile, One-Pot, Green Synthesis of Polysubstituted 4*H*-Pyrans via Piperidine-Catalyzed Three-Component Condensation in Aqueous Medium

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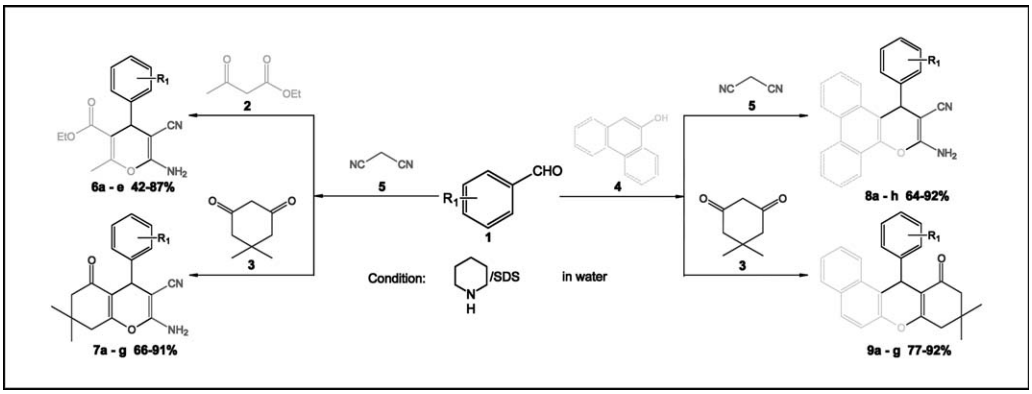

An efficient, one-pot method was described for the synthesis of various polysubstituted 4*H*-pyrans via piperidine catalyzed three-component condensation in aqueous medium. The reaction could be promoted effectively by adding sodium dodecyl sulfate to aqueous medium.

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INTRODUCTION

The chemical industry is one of the major contributors to environment pollution, owing to the use of hazardous chemicals and, in particular, large amounts of flammable, volatile, and toxic organic solvents. Therefore, green chemistry that emphasizes on the development of environmentally benign chemical processes and technologies has attracted much attention in recent years [1,2]. On one hand, designing organic reactions in aqueous medium is one of the most attractive areas in green chemistry [3–6]. Water as an abundant and environmentally benign solvent offers several benefits including simple work-up procedure, unique reactivity and selectivity, and so on.

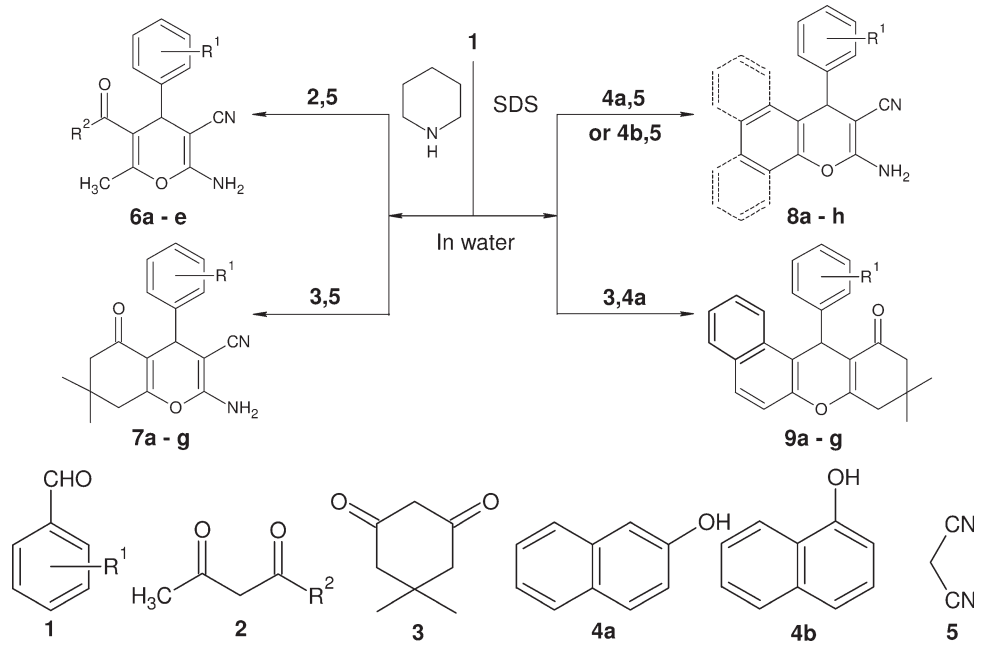
On the other hand, the multicomponent reaction has become popular in the synthesis of heterocyclic components due to its simple experimentations and atom economy [7,8]. Polysubstituted 4*H*-pyrans as an important class of heterocyclic components present in many natural or synthetic compounds with important biological or pharmacological activities such as antibacterial [9], anticancer [10], and antiallergic [11]. Many methods such as ionic liquid [12], solid base [13], Lewis acid [14,15], and electrochemistry [16] have been used to synthesize polysubstituted 4*H*-pyrans, but a lot of methods use volatile and toxic organic solvents, which are the major pollution source in chemical industry.

To replace organic solvent with nontoxic and cheap water, many efforts have been made to synthesize polysubstituted 4*H*-pyrans [17–22]; however, most of procedures have merits, including long reaction time, harsh conditions, tedious work-up procedures, cost of catalysts, and so on. In an attempt to design a facile, pronounced protocol to synthesize polysubstituted 4*H*-pyrans in water, we have found piperidine to be an effective catalyst for the synthesis of these compounds in aqueous medium via a one-pot, three-component reaction (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of benzaldehyde, malononitrile, and ethylacetoacetate was selected as a model reaction to optimize the reaction conditions (Table 1). When the reaction was carried out in water with different catalysts (Table 1, entries 1–5), it was found that piperidine was more effective than other catalysts and a moderate yield of 77% could be obtained after 1 h (Table 1, entry 5). With the aim of improving the unsatisfactory reaction yields, surfactants were added to the reaction. Remarkably, when sodium dodecyl sulfate (SDS) was subjected to form a ensure adequate mixing by stirring for 5 min, and then piperidine was added, a good yield of 85% was obtained after 10 min (Table 1, entry 7), indicating that

Scheme 1. The synthesis of polysubstituted 4*H*-pyrans catalyzed by piperidine in aqueous medium.

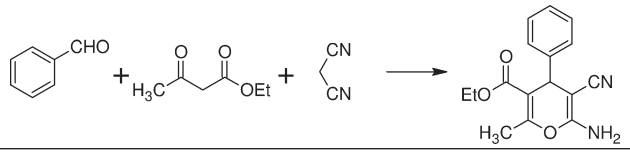


SDS could promote the reaction in water due to lower mass transfer resistance and enlargement of the interfacial area [23–25]. By changing the amount of piperidine from 10 to 5 mol %, the reaction yield was decreased to 72% and only trace product was obtained in the absence of piperidine (Table 1, entries 7–9), so 10 mol % of piperidine was selected as catalyst in further studies. To show the possibility for large-scale operation, we also scaled up the reaction to 40 mmol and the reaction proceeded well with 82% yield of the desired product (Table 1, entry 10).

With the optimized conditions in hand, various substituted benzaldehydes were used to explore the generality and scope of this protocol (Table 2, entries 1–5). For benzaldehydes with electron-withdrawing groups, the

Table 1

Optimization of the reaction conditions.[a]



Entry	Time	Catalyst (10 mol %)	Additive (0.1 g)	Yield (%)[b]
1	5 h	KF/Al_2O_3	–	Trace
2	5 h	MgO	–	40
3	5 h	L-proline	–	Trace
4	5 h	$I_2/KI/K_2CO_3$	–	Trace
5	1 h	Piperidine	–	77
6	1 h	Piperidine	TX10	58
7	10 min	Piperidine	SDS	85
8	12 h	–	SDS	Trace
9[c]	10 min	Piperidine	SDS	72
10[d]	10 min	Piperidine	SDS	82

[a] Reaction condition: benzaldehyde (2 mmol), malononitrile (2 mmol), ethylacetoacetate (2 mmol), catalyst (0.2 mmol), H_2O (3 mL), 100°C.
[b] Isolated yield of product.
[c] 5 mol % of piperidine was used.
[d] The reaction was performed with 40 mmol benzaldehyde, 40 mmol malononitrile, 40 mmol ethylacetoacetate, 4 mmol piperidine, 2 g SDS, 60 mL H_2O, 100°C.

Table 2

Synthesis of various 2-amino-4*H*-pyrans and tetrahydro-4*H*-chromenes in aqueous medium.[a]

Entry	Time (min)	Temperature (°C)	Diketone	R^1	Product	Yield (%)[b]	Mp (°C)/(lit)
1	10	100	**2**	H	**6a**	85	192–194 (195–196) [9]
2	10	100	**2**	4-O_2N	**6b**	87	180–182 (180–183) [9]
3	10	100	**2**	4-Cl	**6c**	74	172–174 (172–174) [9]
4	10	100	**2**	4-Br	**6d**	72	172–174
5	60	100	**2**	4-MeO	**6e**	42	140–142 (142–144) [9]
6	5	80	**3**	H	**7a**	90	228–230 (229–231) [22]
7	5	80	**3**	4-Cl	**7b**	91	208–210 (208–210) [22]
8	5	80	**3**	4-MeO	**7c**	87	198–200 (199–201) [22]
9	5	80	**3**	4-O_2N	**7d**	84	176–178 (177–178) [22]
10	5	80	**3**	4-OH	**7e**	74	212–214 (214–215) [22]
11	5	80	**3**	4-$(CH_3)_2N$	**7f**	66	218–220 (220–222) [22]
12	5	80	**3**	2-Cl	**7g**	90	216–218 (217–218) [22]

[a] Reaction condition: **1** (2 mmol), **5** (2 mmol), **2** or **3** (2 mmol), piperidine (0.2 mmol), SDS (0.1 g), H_2O (3 mL).
[b] Isolated yield of product.

reactions were processed smoothly, but for benzaldehydes containing electron-donating groups such as methoxyl group, only a moderate yield of 42% could be gained even after longer reaction time (Table 2, entry 5), because the electron-donating group decreases the activity of intermediate (arylidenemalononitrile), which does not favor the following reaction to form the corresponding 4*H*-pyran.

In an effort to expand the scope of the method, the synthesis of diverse 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes was undertaken (Table 2, entries 6–12). Because **3** is a more reactive methylene component compared with ethylacetoacetate, various benzaldehydes with electron-withdrawing or electron-donating groups were used and reacted well to give the corresponding 4*H*-pyrans in good yields after 5 min at lower temperature (Table 2, entries 6–11). The ortho-substituted benzaldehyde could also provide a satisfactory yield (Table 2, entry 12).

The remarkable results obtained with the protocol promoted us to use naphthols instead of ethylacetoacetate to synthesize polysubstituted 4*H*-pyrans (Table 3). Both 2-naphthol and 1-naphthol could react with various benzaldehydes and give the desired products. Generally, a prolonged reaction time was needed when benzaldehydes with electron-donating groups were used (Table 3, entries 3 and 8).

The scope of the protocol was also expanded to the synthesis of various tetrahydrobenzo[*a*]xanthene-11-ones successfully (Table 4). A test reaction using 2-naphthol, compound **3**, benzaldehyde in the presence of piperidine/SDS in aqueous medium at 100°C was performed. To our delight, an excellent yield of 91% could be obtained by simply prolonging the reaction time to 2 h (Table 4, entry 1). The further investigations proved that the reaction was not affected obviously by the characteristic of the substituent group on benzaldehyde, when 2-naphthol was used. However, 1-naphthol failed to give the desired product even after 24 h (Table 4, entry 8).

In conclusion, we have developed a facile, green, and effective method for the synthesis of polysubstituted 4*H*-pyrans catalyzed by piperidine in aqueous medium. The procedure could be applied easily for large-scale operation, owing to its simple operation, clear reaction

Table 3

Synthesis of various 2-amino-2-chromenes in aqueous medium.[a]

Entry	Time (min)	Naphthol	R^1	Product	Yield (%)[b]	Mp (°C)/(lit)
1	5	**4a**	H	**8a**	87	>270
2	5	**4a**	4-Cl	**8b**	89	206–208 (206–208) [19]
3	30	**4a**	4-MeO	**8c**	74	188–190 (190–191) [19]
4	5	**4b**	H	**8d**	92	204–206 (206–207) [19]
5	5	**4b**	4-O_2N	**8e**	83	238–240 (239–241) [19]
6	5	**4b**	4-Cl	**8f**	89	230–232 (231–233) [19]
7	5	**4b**	4-MeO	**8g**	90	180–182 (182–183) [19]
8	30	**4b**	4-$(CH_3)_2N$	**8h**	64	202–204 (203–205) [19]

[a] Reaction condition: **1** (2 mmol), **5** (2 mmol), **4a** or **4b** (2 mmol), piperidine (0.2 mmol), SDS (0.1 g), H_2O (3 mL), 100°C.
[b] Isolated yield of product.

Table 4

Synthesis of various tetrahydrobenzo[*a*]xanthene-11-ones in aqueous medium.[a]

Entry	Time (h)	R^1	Product	Yield (%)[b]	Mp (°C)/(lit)
1	2	H	**9a**	91	150–152 (151–153) [26]
2	1.5	4-Cl	**9b**	92	178–180 (180–182) [26]
3	1.5	4-O_2N	**9c**	85	176–178 (178–180) [26]
4	3	4-MeO	**9d**	89	202–204 (204–205) [26]
5	2	4-$(CH_3)_2N$	**9e**	77	200–202
6	6	4-OH	**9f**	88	222–224 (223–225) [26]
7	1.5	2-Cl	**9g**	90	178–180 (179–180) [26]
8[c]	24	H	–	NR[d]	–

[a] Reaction condition: **1** (2 mmol), **3** (2 mmol), **4a** (2 mmol), piperidine (0.2 mmol), SDS (0.1 g), H_2O (3 mL), 100°C.
[b] Isolated yield of product.
[c] 1-Naphthol instead of 2-naphthol was used.
[d] No reaction.

profile, short reaction time, and high yields. In addition, the reaction system could be successfully applied to a variety of substrates to synthesize a wide variety of polysubstituted 4*H*-pyrans in good to excellent yields.

EXPERIMENTAL

All reagents were obtained from commercial suppliers and used without further purification. All melting points are determined uncorrected. Mass spectra were taken on a Agilent Liquid chromatography-mass spectrometry (LC-MS) 1100 series instrument in the electrospray ionization [positive electrospray ionization (ESI)] mode. ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively, in DMSO-d_6, and chemical shifts were reported in ppm from internal trimethylsilyl (TMS) (δ). All products were identified by comparing of their spectral data and m.p. with those reported in the literature. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

General procedure for the synthesis of polysubstituted 4*H*-pyrans catalyzed by piperidine in aqueous medium. Benzaldehyde (2 mmol), malononitrile (2 mmol), ethylacetacetate (2 mmol), SDS (0.1 g), and distilled water (3 mL) were added to a 25-mL round-bottom flask. The mixture was stirred for 5 min at 100°C, followed by adding piperidine (0.4 mmol) and stirring under reflux for 10 min. After completion, the reaction mixture was cooled to room temperature. The precipitated solid was collected by filtration, washed by water, dried, and recrystallized from ethanol to afford the pure product in 85% isolated yield. The reactions for other substrates to synthesize corresponding polysubstituted 4*H*-pyrans were performed in the similar procedures. Sometimes, the products were recrystallized from EtOH/H_2O (1:1 v/v) instead of ethanol.

Selected spectroscopic data for some of compounds.

Compound 6a, ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (Table 2, entry 1). Recrystallized from EtOH. White solid; m.p. 192–194°C; 98% pure by LC-MS; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.02–1.07 (m, 3H, —CH_3), 2.33 (s, 3H, —CH_3), 3.98–4.00 (m, 2H, —CH_2—), 4.31 (s, 1H, —CH(C) —), 6.95 (s, 2H, —NH_2), 7.16–7.33 (m, 5H, aromatic); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.08, 18.49, 39.15, 57.53, 60.53, 107.58, 120.10, 127.20, 127.56, 127.57, 128.81, 128.82, 145.25, 156.97, 158.78, 165.81; MS (ES^+) *m/z* 285 (M + H). Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; N, 9.85; H, 5.67. Found: C, 67.49; N, 9.89; H, 5.87.

Compound 7a, 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, entry 6). Recrystallized from EtOH. Light yellow solid; m.p. 228–230°C; 99% pure by LC-MS; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.98 (s, 3H, —CH_3), 1.06 (s, 3H, —CH_3), 2.12 (d, 1H, *J* = 16.1 Hz, —CH(H)—), 2.28 (d, 1H, *J* = 16.1 Hz, —CH(H)—), 2.52 (m, 2H, —(CH_2)—), 4.19 (s, —CH(C)—), 7.05 (s, —NH_2), 7.15–7.23 (m, 3H, aromatic), 7.29–7.34 (m, 2H, aromatic); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 26.96, 28.54, 31.92, 35.74, 39.86, 50.15, 58.53, 112.93, 119.83, 126.69, 127.29, 127.30, 128.45, 128.45, 144.88, 158.65, 162.60, 195.73; MS (ES^+) *m/z* 295 (M + H). Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; N, 9.52; H, 6.16. Found: C, 73.67; N, 9.55; H, 6.01.

Compound 8f, 2-amino-4-(4-chlorophenyl)-4H-benzo[h]-chromene-3-carbonitrile (Table 3, entry 6). Recrystallized from EtOH. White solid; m.p. 230–232°C; 99% pure by LC-MS; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 4.98 (s, 1H, —CH(C)—), 7.12 (d, 1H, *J* = 8.5 Hz, aromatic), 7.25 (s, 2H, —NH_2), 7.30 (d, 2H, *J* = 8.4 Hz, aromatic), 7.41 (d, 2H, *J* = 8.4 Hz, aromatic); 7.58–7.70 (m, 3H, aromatic), 7.92 (d, 1H, *J* = 7.9 Hz, aromatic), 8.26 (d, 1H, *J* = 8.1 Hz, aromatic); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 40.37, 56.09, 117.54, 120.46, 120.86, 122.90, 124.14, 126.19, 126.85, 126.99, 127.82, 128.82, 128.83, 129.70, 129.71, 131.70, 132.91, 142.9, 144.78, 160.32; MS (ES^+) *m/z* 333 (M + H). Anal. Calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; N, 8.42; H, 3.94. Found: C, 72.27; N, 8.23; H, 3.84.

Compound 9e, 12-(4-dimethylaminophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (Table 4, entry 5). Recrystallized from EtOH/H_2O (1/1, v/v). White solid; m.p. 200–202°C; 98% pure by LC-MS; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.94 (s, 3H, —CH_3), 1.09 (s, 3H, —CH_3), 2.14 (d, 1H, *J* = 16.3 Hz, —CH(H)—), 2.35 (d, 1H, *J* = 16.2 Hz, —CH(H)—), 2.60 (m, 2H, —CH_2—), 2.78 (s, 6H, —$N(CH_3)_2$), 5.46 (s, 1H, —CH(C)—), 6.54 (d, 2H, *J* = 8.5 Hz, aromatic), 7.09 (d, 2H, *J* = 8.5 Hz, aromatic), 7.41–7.54 (m, 3H, aromatic), 7.88–7.93 (m, 2H, aromatic), 8.06 (d, 1H, *J* = 8.3 Hz, aromatic); MS (ES^+) *m/z* 398 (M + H). Anal. Calcd. for $C_{27}H_{27}NO_2$: C, 81.58; N, 3.52; H, 6.85. Found: C, 81.47; N, 3.43; H, 6.82.

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