An efficient one-pot synthesis of dihydropyrano[c]chromenes and amino-2-chromenes under solvent-free conditions

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1,8-Diazabicyclo[5.4.0]-undec-7-en-8-ium acetate, a basic ionic liquid, showed excellent catalytic activity in the three-component condensation reaction of aldehydes and malononitrile with α- or β-naphthol or 4-hydroxycoumarin. The products, amino-4*H*-chromenes and dihyropyrano[c]chromenes respectively, were obtained under mild conditions without any additional organic solvents in good to excellent yields and short reaction times. The catalyst could be recycled several times with only slight loss of activity.

Keywords: ionic liquid, chromenes, multi-component reaction, solvent-free reaction, green chemistry

The principles of green chemistry have been introduced to eliminate or at least to reduce the use of hazardous materials in chemical processes. Since one of the key areas of green chemistry is the replacement of hazardous solvents with environmentally benign ones or the elimination of solvents altogether,[1,2] development of new solid phase (solvent-free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest.

Ionic liquids (ILs) are salt-like compounds, which are liquids at room temperature and possess low vapour pressures. ILs are considered as "green solvents" since unlike the conventional solvents which are volatile, they do not evaporate and are not harmful to the environment.[3–7] These compounds are known as environmentally benign solvents or catalysts and much attention has currently been focused on the organic reactions with ILs as catalysts or solvents and many organic reactions were performed in ILs with high performance.[8,9]

Modern synthesis needs access to fast and very efficient methods to avoid isolation during the reaction. This feature is perfectly exemplifieded by multi-component reactions (MCRs).[10–12] The first MCR was initiated by Strecker in 1850 for the synthesis of amino acids.[13]

Since 2-amino-2-chromenes and dihydropyrano[c]chromen es are known as spasmolytic, diuretic, anticancer, anti-coagulant and anti-HIV agents, much research has been done on them recently.[14]

Benzochromenes are widely used as pigments and agrochemicals and exhibit interesting biological activities.[15] Also, they are cognitive enhancers for the treatment of neurodegenerative diseases including Parkinson's disease, Down's syndrome, schizophrenia, Alzheimer's disease and AIDS associated dementia.[16]

Recently, relatively benign catalysts such as KF/Al_2O_3,[17] basic alumina,[18] triethylamine,[19] tetrabutylammonium bromide (TBAB) and sodium dodecyl sulfate were employed for their synthesis. However, some of these procedures are limited due to the use of toxic organic solvents, expensive catalysts and tedious workup. Thus, here we report an efficient method for the synthesis of different chromenes using 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate (DBU[Ac]), an ionic liquid.

Results and discussion

The reaction of 4-chlorobenzaldehyde (1.0 mmol) and malononitrile (1.2 mmol) with β- or α- naphthol (1.0 mmol) or 4-hydroxycoumarin (1.0 mmol) in the presence of DBU[Ac] at 80 °C was selected as a model to optimise the reaction conditions and it wasfound that the best yield was obtained with 10 mol% of the catalyst (Table 1). When these reactions were carried out at room temperature or in the absence of the catalyst, the yield was very low.

Amino-4*H*-benzo[h]chromenes (**2a–h** and **3a–h**) and 3,4-di hydropyrano[c]chromenes (**4a–h**) were synthesised through the three-component one-pot condensation reaction of aldehydes, malononitrile and β-naphthol/α-naphthol or 4-hydroxycoumarin in the presence of DBU[Ac] under mild conditions without any additional organic solvents in good to excellent yields and short reaction times (Scheme 1, Table 2). All the synthesised compounds are known and were characterised by comparison of their melting points and spectral data with those reported in literature.

Aromatic aldehydes with electron-withdrawing groups such as nitro or halogen (Table 2, entries 3–4, 6–9, 12–14 and 18–22), reacted faster, while those containing the electron-releasing groups such as methyl or methoxy needed longer reaction times (Table 2, entries 2, 5, 11, 15 and 23–24). Electron-withdrawing groups decrease the electron density of the carbon of the carbonyl group, so facilitating the nucleophilic attack on it, while the electron-releasing groups act in the opposite way. Additionally, 4-dimethylaminobenzaldehyde (Table 2, entry 16) failed to give the corresponding product. This may be due to the strong electron-releasing character of the dimethylamino group.

The catalyst was recovered from the aqueous medium, dried under vacuum and reused for consecutive four runs. The yields obtained were sequentially 94, 93, 91 and 89%, which shows that the catalyst may be reused without significant loss of activity.

In Table 3, the capability of the DBU[Ac] catalyst was compared with other literature catalytic systems in the synthesis of chromenes. It is clear that the ionic liquid catalyst is quicker than the others and, moreover is solvent-free.

Table 1 Effect upon the yields of different amounts of DBU[Ac] catalyst on the three-component model reaction of 4-chlorobenzaldehyde (1.0 mmol) and malononitrile (1.2 mmol) and α- or β-naphthol or 4-hydroxycoumarin (1.0 mmol) at 80 °C

Entry	Catalyst/mol%	Time/min	Yield % with β-naphthol[a]	Yield/% with α-naphthol[a]	Yield % with 4-hydroxycoumarin[a]
1	None	240	Trace	Trace	Trace
2	1	30	70	67	60
3	5	30	82	80	75
4	10	5	95	94	93

[a] Isolated yields.

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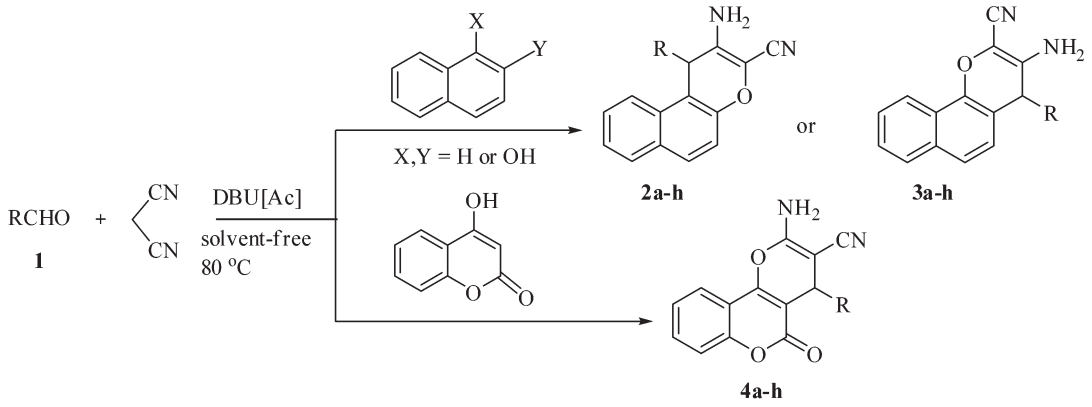

Scheme 1

Table 2 Synthesis from β- or α-naphthol of variously subsituted aminochromenes (**2a–h** or **3a–h**) and from 4-hydroxycoumarin of dihydropyranochromenes (**4a–h**) by a three-component reaction with araldehydes (ArCHO) and malononitrile in the presence of DBU[Ac] at 80 °C

Entry	R-CHO	Hydroxy compound	Product	Time/min	Yield[a]/%	M.p./°C	
						Found	Reported
1	C_6H_4	β-Naphthol	**2a**	4	96	287–290	288–289[21]
2	4-Me-C_6H_4	β-Naphthol	**2b**	15	85	269–271	270–272[22]
3	4-Cl-C_6H_4	β-Naphthol	**2c**	2	93	208–210	207–208.5[23]
4	2-Cl-C_6H_4	β-Naphthol	**2d**	2	95	270–273	272–273[21]
5	4MeO-C_6H_4	β-Naphthol	**2e**	10	89	188–191	190–191.5[23]
6	4-F-C_6H_4	β-Naphthol	**2f**	2	91	231–232	232–233[22]
7	2,4Cl_2-C_6H_3	β-Naphthol	**2g**	2	95	221–223	222–224[21]
8	3NO_2-C_6H_4	β-Naphthol	**2h**	2	95	186–188	188–189[24]
9	4-Cl-C_6H_4	α-Naphthol	**3a**	2	94	230–232	231–232.5[23]
10	C_6H_5	α-Naphthol	**3b**	3	93	210–212	218–219[21]
11	4MeO-C_6H_4	α-Naphthol	**3c**	7	88	192–194	195–196[21]
12	2-Cl-C_6H_4	α-Naphthol	**3d**	2	92	252–254	250–251[21]
13	2,4-Cl_2-C_6H_3	α-Naphthol	**3e**	1	95	214–215	214–216[24]
14	3NO_2-C_6H_4	α-Naphthol	**3f**	1	95	240–243	214.5–216[25]
15	4-Me-C_6H_4	α-Naphthol	**3g**	5	86	205–208	205–207[26]
16	4-Me_2N-C_6H_4	α-Naphthol	–	–	–	–	–
17	3-Br-C_6H_4	4-Hydroxycoumarin	**4a**	5	85	200–202	198–196[27]
18	4-Cl-C_6H_4	4-Hydroxycoumarin	**4b**	5	93	214–215	212–209[28]
19	C_6H_5	4-Hydroxycoumarin	**4c**	7	91	257–259	258–260[28]
20	4-F-C_6H_4	4-Hydroxycoumarin	**4d**	5	90	262–260	260–262[29]
21	3NO_2-C_6H_4	4-Hydroxycoumarin	**4e**	4	91	257–260	262–264[30]
22	4NO_2-C_6H_4	4-Hydroxycoumarin	**4f**	6	93	237–235	255–256[28]
23	4-OMe-C_6H_5	4-Hydroxycoumarin	**4g**	10	85	234–236	232–234[31]
24	3,4-$(OMe)_2C_6H_3$	4-Hydroxycoumarin	**4h**	15	82	230–233	228–230[29]

[a] Isolated yield.

Table 3 Comparison of the DBU[Ac] with other literature catalysts in the in the synthesis of chromenes

Entry	Catalyst/mol%	Conditions	Time	Yield/%
1	Et_3N (10)	CH_3CN, room temperature	24 h	80[32]
2	CuO nanoparticle (15)	H_2O, reflux	5 min	93[33]
3	TEBA (10)	Solvent-free, 80 °C	3.5 h	93[34]
4	Triethyamine (10)	Ethanol/reflux	3 h	82[35]
5	DBU[Ac] (10)	Solvent-free, 80 °C	4 min	82–96 (Present work)

Conclusions

We report an efficient procedure for the synthesis of 2-amino-4*H*-chromenes (**2a–h** and **3a–h**) and 3,4-dihyropyrano[c]-chromenes (**4a–h**) through the three-component condensation reaction of aldehydes, malononitrile and β-naphthol/α-naphthol or 4-hydroxycoumarin in the presence of DBU[Ac] as a reusable, nontoxic and inexpensive catalyst at 80 °C. The major advantage of this method is the ease of the work-up; so the products can be isolated without chromatography. The method also offers some other advantages such as clean reaction, simple synthesis of catalyst, high yields of products and very short reaction times, which make it a useful and attractive strategy for the synthesis of different chromenes.

Experimental

All chemicals were purchased from Aldrich or Merck with high-grade quality, and used without further purification. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. NMR spectra were recorded in DMSO-d_6 on a Bruker 300 MHz spectrometer. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. DBU[Ac] was prepared as a weak basic ionic liquid catalyst according to the reported procedure.[20]

Synthesis of chromenes; general procedure

The aldehyde (1.0 mmol), malononitrile (1.2 mmol) and β-naphthol/α-naphthol or 4-hydroxycoumarin (1.0 mmol) and DBU[Ac] (10% mol) were heated at 80 °C in solvent-free conditions for a certain time (monitored by TLC) during which the contents of the flask solidified. The reaction mixture was cooled to room temperature and water added. The solids were filtered off, washed with H_2O and the crude products purified by recrystallisation from ethanol/water (70:30). The catalyst-containing aqueous filtrate was freed of water and reused in subsequent runs without further purification.

2h: IR ν_{max}: 3464, 3356, 2191, 1659, 1590, 1529, 1302 cm^{-1}; ^1H NMR: δ 5.6 (s, 1H, CH), 7.1 (s, 2H, NH_2), 7.4–7.7 (m, 5H, ArH), 7.34 (d, *J* = 8.7 Hz, 1H, ArH), 7.42–7.47 (m, 3H, ArH), 8.09 (s, 1H, ArH); ^{13}C NMR: 37.8, 57.4, 115.2, 117.4, 120.4, 121.9, 122.3, 123.9, 125.6, 127.8, 129.0, 130.4, 130.5, 130.9 , 131.3, 134.7 , 147.7, 148.4, 148.5, 160.5.

2g: IR ν_{max}: 3462, 3323, 2200, 1661, 1588, 1557, 1288 cm^{-1}; ^1H NMR: δ 4.90 (s, 1H, CH), 6.6–7.10 (m, 1H, ArH, and 2H, NH_2), 7.21–7.62 (m, 6H, ArH), 7.9–8.1 (m, 2H, ArH); ^{13}C NMR: 35.3, 56.2, 114.2, 117.2, 120.2, 123.0, 125.3, 128.0, 129.2, 129.4, 129.6, 130.4, 130.5, 131.3, 132.4, 132.6, 142.2, 147.4, 160.4.

3g: IR: ν_{max}: 3416, 3322, 2194, 1677, 1605, 1507, 1379 cm^{-1}; ^1H NMR: δ 2.61 (s, 3H, CH_3), 4.88 (s, 1H, CH), 7.01 (s, 2H, NH_2), 7.07 (d, *J* = 8.7 Hz, 1H, Ar), 7.17–7.32 (m, 5H, Ar), 7.42–7.53 (m, 2H, Ar), 7.89 (d, *J* = 7.2 Hz, 1H, Ar); 8.26 (d, *J* = 8.1 Hz, 1H, Ar); ^{13}C NMR: δ 32.3, 54.4, 57.9, 112.2, 116.3, 117.8, 120.9, 121.5, 125.3, 127.6, 128.4, 128.9, 129.0, 129.6, 130.1, 131.4, 134.9, 147.5, 159.1, 160.7.

4a: IR: ν_{max} 3382, 3300, 2210, 1715, 1668, 1600, 1498, 1382 cm^{-1}; ^1H NMR: δ 4.45 (s, 1H, H_4), 6.88–7.98 (m, 9H, ArH, and 2H, NH_2); ^{13}C NMR: δ 34.5, 58.7, 104.6, 112.9, 115.1, 116.5, 119.0, 123.5, 129.6, 132.9, 140.1, 151.1, 153.4, 158.9, 159.5, 160.2.

4b: IR: ν_{max} 3378, 3292, 2194, 1716, 1677, 1605, 1507, 1379 cm^{-1}; ^1H NMR: δ 5.1 (s, 1H, H_4), 7.01–8.03 (m, 10H, ArH, and 2H, NH_2); ^{13}C NMR: δ 36.3, 57.9, 103.8, 112.9, 115.0, 116.6, 119.1, 123.0, 130.0, 133.0, 139.5, 152.1, 153.4, 157.9, 159.5, 160.2, 162.2.

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