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EXPERIMENTAL PAPER

Facile Protocol for the Synthesis of 2-Amino-4H-Chromene Derivatives using Choline Chloride/Urea

Behrooz Maleki[a], Reza Tayebee[a], Ali Khoshsima[b], and Farshid Ahmadpoor[a]

[a]Department of Chemistry, Hakim Sabzevari University, Sabzevar, Iran; [b]School of Petroleum and Chemical Engineering, Hakim Sabzevari University, Sabzevar, Iran

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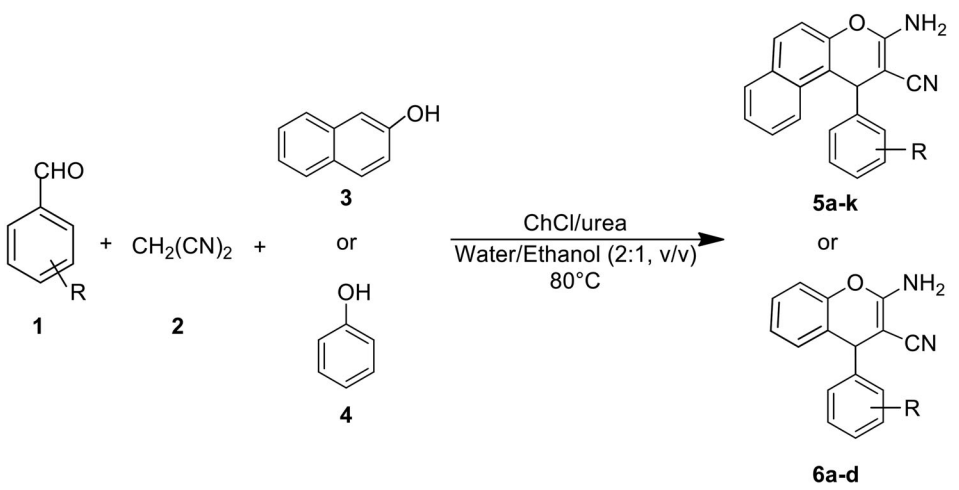
Deep eutectic solvents (DESs) have recently obtained attention as environmentally friendly alternative solvents to replace volatile organic compounds (VOCs). Most DESs are biodegradable, biocompatible and non-toxic.[1] Therefore, compared to the traditional solvents, DESs are considered both promising and versatile.[2–3] Low vapor pressure (nonvolatility), a wide range for the liquid state, thermal and chemical stability, low flammability, high solvation capability, and inertness towards reactions with water qualify them as a good extractants. Due to self-association through intermolecular hydrogen bond interactions, DESs have lower lattice energies and therefore lower melting points than those of their single components. Compared to ionic liquids (ILs), DESs are easier to prepare, cheaper in cost, and more environmentally friendly, while maintaining their task-specific character.[4] In comparison to ILs, which consist of a cation and a complex anion, DESs comprise a cation, an anion and a complexing agent. DESs are obtained by the simple mixing and heating of one or more hydrogen bond donors (HBDs) with one or more hydrogen bond acceptors (HBAs) to form a eutectic mixture.[5] The purity of the prepared mixture is only dependent on the purity of the individual components.

Multicomponent reactions (MCRs) comprise an attractive strategy within synthetic organic chemistry due to their minimal workup requirements, suitability for one-pot synthesis, molecular economy, and ease of processing.[6–9]

The chromene ring system is a widely-used scaffold for pharmaceutical applications, and chromenes have a variety of divergent biological activities, acting as anti-inflammatories,[10] antitubercular agents,[11] antitumor agents,[12] enzyme inhibitors,[13] and potassium channel activators.[14] Generally, 2-amino-4H-chromenes and their derivatives have been synthesized using MCR with malononitrile, aldehydes, and phenols. Catalytic procedures have been reported using methanesulfonic acid (CH_3SO_3H),[15] silica tungstic acid (STA),[16] potassium phthalimide (POPI),[17] $CuSO_4{\cdot}5H_2O$,[18] disodium hydrogen phosphate (Na_2HPO_4),[19] $Fe(HSO_4)_3$,[20] tetrabutylammonium chloride (TBAC),[21] lipase AS (that is, lipase from *Aspergillus niger*),[22] Fe_3O_4/SiO_2/Propyl-Pip,[23] potassium fluoride,[24] triethanolamine,[25] ilmenite ($FeTiO_3$),[26] banana peel ash,[27] lemon fruit shell ash (WELFSA),[28] aspartic acid,[29] molecular sieves under microwave-irradiation,[30] and K_2CO_3/cyanuric acid.[31] Despite their usefulness in many applications, some of the latter

CONTACT Behrooz Maleki b.maleki@hsu.ac.ir; malekibehrooz@gmail.com Department of Chemistry, Hakim Sabzevari University, Sabzevar, Iran



Scheme 1. Synthesis of 2-amino-4H-chromenes using choline chloride/urea.

approaches call for the use of drastic conditions (acidic or basic), multiple steps, complicated synthetic operations or lengthy work-up procedures.

Choline chloride/urea (ChCl/urea) is one of the most commonly used DESs in organic synthesis. The most commonly employed is the 1:2 molar mixture of choline chloride and urea which affords a viscous liquid at room temperature. Advantages of this solvent are several-fold: it is relatively inexpensive (being comparable in price to conventional organic solvents such as acetonitrile and DMF), it is non-toxic, exhibits no detectable vapor pressure under ambient conditions, and is based on biorenewable materials.[32–34] Further to our own interest in green chemistry,[35–50] we considered ChCl/urea as a catalyst for three-component coupling of 2-naphthol or phenol, aromatic aldehydes, and malononitrile in water/ethanol at 80 °C to obtain 2-amino-4H-chromene derivatives (Scheme 1).

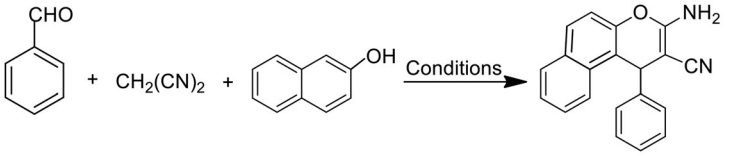
To optimize the reaction conditions, the one-pot reaction of 2-naphthol and benzaldehyde with malononitrile was examined in ChCl/urea as a model reaction. Among the various tested conditions, the best results were given with ChCl/urea in water/ethanol (2:1, *v*/*v*)/80 °C (92% within 15 min (Table 1, entry 3).

In order to explore the versatility of the synergistic effect of ChCl/urea, we examined different substrates. As shown in Table 2, all of them gave the desired products in very good to excellent yields (89-93%). Electron-withdrawing and electron-donating substituents were generally well tolerated, affording the desired products **5a-k**. To further extend the reaction scope, we then studied the reaction of phenol with various aldehydes and malononitrile under the optimal conditions (Table 2, entries **6a-d**).

Finally, to access the efficiency and generality of this methodology, we compared this method with previously reported catalysts in the synthesis of representative 2-amino-4H-chromene derivatives **5a** and **5h** (Table 3). The data show that ChCl/urea is the most efficient catalyst with respect to reaction times, temperature and the avoidance of drastic conditions (acidic or basic).

In summary, a very simple approach towards the one-pot multi-component synthesis of 2-amino-4H-chromene derivatives was developed using biocompatible ChCl/urea.

Table 1. Optimization of reaction conditions for **5a**.[a]



1 **2** **3** **5a**

Entry	Catalyst (ml or g)	Conditions	Time (min)	Yield (%)
1	ChCl/urea (0.1 ml)	Water/80 °C	15	58
2	ChCl/urea (0.1 ml)	Ethanol/80 °C	15	76
3	ChCl/urea (0.1 ml)	Water/Ethanol (2:1, *v/v*)/80 °C	15	92
4	ChCl/urea (0.1 ml)	Solvent-free/80 °C	15	60
5	ChCl/urea (0.1 ml)	Water/Ethanol (2:1, *v/v*)/70 °C	15	82
6	ChCl/urea (0.1 ml)	Water/Ethanol (2:1, *v/v*)/rt	15	45
7	ChCl/urea (0.2 ml)	Water/Ethanol (2:1, *v/v*)/80 °C	15	84
8	ChCl/urea (0.05 ml)	Water/Ethanol (2:1, *v/v*)/80 °C	15	80
9	ChCl (0.04 g)	Water/Ethanol (2:1, *v/v*)/80 °C	15	20
10	Urea (0.01 g)	Water/Ethanol (2:1, *v/v*)/80 °C	15	32
11	–[b]	Water/Ethanol (2:1, *v/v*)/80 °C	30	–[c]

[a]Reaction conditions: benzaldehyde (1 mmol), malononitrile (1.2 mmol) and 2-naphthol (1 mmol) in 0.1 ml water/ethanol (2:1, *v/v*).
[b]This reaction was carried out in the absence of ChCl/urea.
[c]No product **5a** observed.

Advantages of this procedure include all of the merits of using a DES: short reaction times, simple operation, easy handling, low cost, and high yields. The procedure completely avoids strongly basic or acidic conditions and toxic solvents.

Experimental section

All starting materials and DES components were commercially available and purchased from Merck. Melting points were determined on Electrothermal 9200 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer using $CDCl_3$ or DMSO-d_6, and shifts are given in ppm downfield from tetramethylsilane (TMS) as an internal standard. All the reactions were monitored with thin layer chromatography (silica gel, eluting solvent: n-hexane/ethyl acetate (4/1)) and UV light as detecting agent.

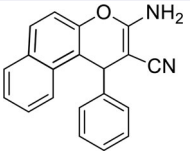
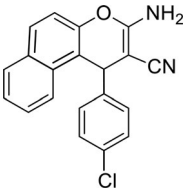
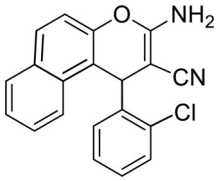
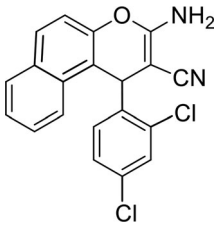
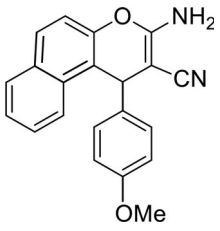
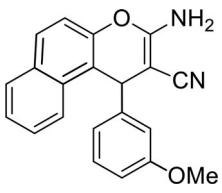
Preparation of ChCl/urea

The ChCl/urea was prepared according to the procedures reported in literature[32] simply by heating a mixture of choline chloride and urea with a molar ratio of 1:2 at 80 °C until a homogeneous liquid was formed.

General procedure for the synthesis of 2-amino-4H-chromene derivatives (5a-k or 6a-d)

A mixture of aldehyde (1 mmol), malononitrile (1.2 mmol) and 2-naphthol or phenol (1 mmol) in the presence of 0.1 ml of ChCl/urea in water/ethanol (2:1, *v/v*, 0.1 ml) was

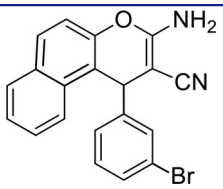
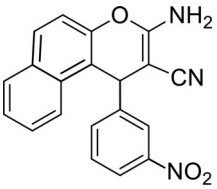
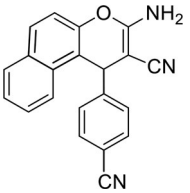
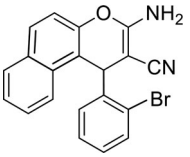
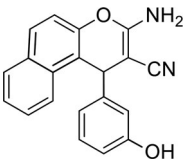
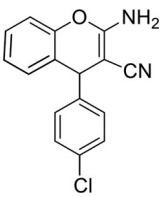
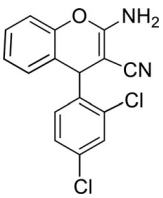
Table 2. One-pot synthesis of 2-Amino-4H-chromene derivatives using ChCl/urea.

				mp (^{0}C)	
Entry	Products	Yield (%)	Time (min)	Found	Lit.[ref]
5a		92	15	278-280	278-279[18]
5b		91	20	205-207	205-206[16]
5c		89	25	254-256	256-258[17]
5d		90	25	218-220	220-222[26]
5e		90	25	184-186	182-183[15]
5f		90	25	252-254	248-250[21]

(*continued*)

placed in a round-bottomed flask (10 ml) fitted with a condenser. The flask was placed in an oil bath and heated to 80 °C. The reaction process was monitored by TLC (silica gel, n-hexane/ethyl acetate (4/1)). After completion of the reaction, 5 mL water was

Table 2. Continued.

Entry	Products	Yield (%)	Time (min)	mp (^{0}C) Found	mp (^{0}C) Lit.[ref]
5g		93	20	242-244	242-244[27]
5h		93	20	188-190	188-189[15]
5i		92	20	286-288	284-286[19]
5j		89	25	180-182	181-183[16]
5k		90	25	280-282	280-282[18]
6a		92	15	163-165	162-164[31]
6b		90	20	193-195	192-194[31]

(*continued*)

Table 2. Continued.

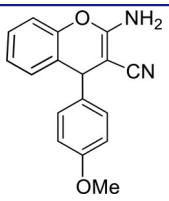
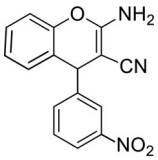
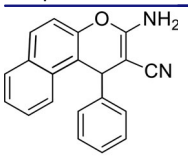
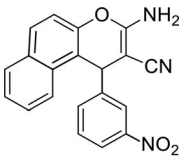
Entry	Products	Yield (%)	Time (min)	mp (^{0}C) Found	mp (^{0}C) Lit.[ref]
6c		90	15	166-168	162-164[31]
6d		94	15	198-200	200-202[31]

Table 3. Comparison of methods for the synthesis of 2-amino-4h-chromene derivatives.

Compounds	**Conditions**[ref]	Time (min)	Yield (%)
 **5a**	ChCl/urea/H_2O/EtOH/(2:1, *v/v*)/80 °C (present work)	15	92
	CH_3SO_3H/CH_3CN/reflux[15]	180	91
	Silica tungstic acid (STA)/solvent-free/120°C[16]	180	90
	$CuSO_4{\cdot}5H_2O$/H_2O/reflux[18]	60	95
	Na_2HPO_4/solvent-free/120°C[19]	60	89
	$Fe(HSO_4)_3$/CH_3CN/reflux[20]	2700	86
	Tetrabutylammonium chloride (TBAC)/water/100°C[21]	120	80
	Lipase AS (*Aspergillus niger*)/CH_3CN/100°C[22]	5760	36
 **5h**	Fe_3O_4/SiO_2/Propyl-Pip/solvent-free/120°C[23]	40	95
	Aspartic acid/solvent-free/100°C[29]	30	92
	ChCl/urea/H_2O/EtOH/(2:1, *v/v*)/80 °C (present work)	20	93
	CH_3SO_3H/CH_3CN/reflux[15]	240	91
	Silica tungstic acid (STA)/solvent-free/120°C[16]	120	80
	Tetrabutylammonium chloride (TBAC)/water/100°C[21]	60	93
	Lipase AS(*Aspergillus niger*)/CH_3CN/100°C[22]	5760	84
	Fe_3O_4/SiO_2/Propyl-Pip/solvent-free/120°C[23]	50	83
	FeTiO3/H_2O/reflux[26]	50	94

added to the reaction mixture and the solid was filtered. The products were recrystallized from ethanol (96%) to give pure compounds **5a-l** or **6a-e**. The known compounds were identified by matching their melting points with those reported in the literature cited in Table 2. For the sake of completeness, characterization data for the representative compound **5h** are provided below.

2-Amino-4-(3-nitrophenyl)-4H-benzo[f]chromene-3-carbonitrile (5h)

^{1}HNMR (300 MHz, DMSO-d_6); 5.81 (s, 1H), 7.27 (s, 2H, exchangeable with D_2O), 7.32–7.40 (m, 4H), 7.79–8.16 (m, 6H); ^{13}CNMR (75 MHz, DMSO-d_6); 39.38, 57.14,

115.53, 118.01, 118.54, 122.86, 123.93, 124.92, 125.67, 128.08, 128.96, 129.44, 129.56, 130.35, 131.06, 131.97, 132.62, 144.16, 148.21, 166.24; IR (KBr, cm^{-1}): 3468, 3350, 3224, 3070, 2890, 2201, 1658, 1580, 1530, 1418, 1370, 1224, 1157, 1092, 1030, 810.

ORCID

Reza Tayebee http://orcid.org/0000-0003-1211-1472
Ali Khoshsima http://orcid.org/0000-0002-3210-7203

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