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Basic ionic liquid-catalyzed multicomponent synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[*c*]chromenes

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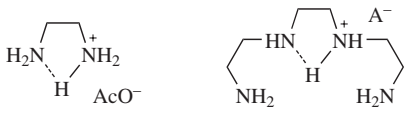
Triethylenetetraammonium trifluoroacetate-catalyzed condensation of benzaldehydes, malononitrile and cyclic 1,3-dioxo compounds in aqueous medium affords the corresponding fused 2-amino-4-aryl-3-cyanopyrans.

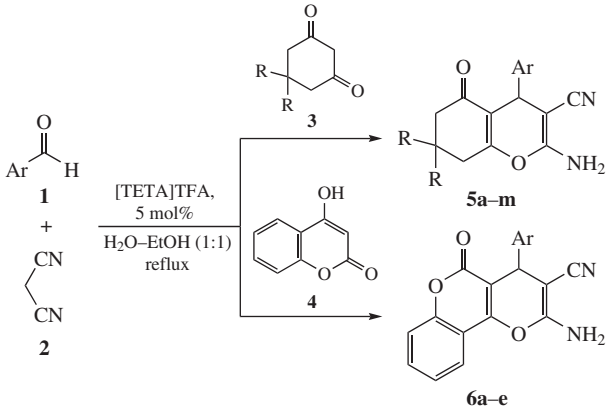
Recently, tetrahydrobenzo[*b*]pyran and pyrano[*c*]chromene derivatives have attracted increasing interest due to their wide range of biological properties.[1] A variety of technologies including the use of microwave[2] and ultrasonic[3] irradiation, as well as catalysis by tetrabutylammonium bromide (TBAB),[4] fluoride anion,[5] rare earth perfluorooctanoate,[6] acidic ionic liquids (ILs),[7] Na_2SeO_4,[8] high surface area MgO,[9] [bmim]OH[10] *etc*. were found to be efficient to promote them. In spite of the merits of these procedures, each of them suffers at least from one of the following limitations: low yields, unavailability of the catalyst, long reaction times, effluent pollution, harsh reaction conditions, and tedious work-up.

As environmental friendly reaction media or designable catalysts, ILs are receiving considerable global attention[11] and used widely in organic reactions.[12] In view of the merits of ILs such as environmental benignity, reusability and easy handling, we are interested in use of ILs as catalysts in the synthesis of important biologically active compounds through multicomponent reaction (MCR) concept. We herein report the preparation of a series of new Lewis basic task-specific ILs (Scheme 1)† and their use as catalysts in environmentally benign MCR approach for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[*c*]chromene derivatives (Scheme 2).‡

We initially studied the catalytic activities of the five as-prepared ILs using the model reaction between 4-chlorobenzaldehyde **1a**, malononitrile **2** and dimedone **3** (Table 1, entries 1–5). [TETA]TFA proved to have the best catalytic activity under the optimal conditions (Table 1, entry 7).



Scheme 1 Novel functionalized basic ILs.



Scheme 2

Table 1 Optimization of conditions of the reaction between **1**, **2** and **3**.[a]

Entry	Solvent	Catalyst (IL)	*T*/°C	Time/min	Yield of **5a** (%)[b]
1	H_2O	[EDA]OAc	80	60	42
2	H_2O	[TETA]OAc	80	40	70
3	H_2O	[TETA]PTS	80	40	65
4	H_2O	[TETA]BF_4	80	40	57
5	H_2O	[TETA]TFA	80	30	77
6	EtOH	[TETA]TFA	reflux	30	93
7	H_2O–EtOH (1:1)	[TETA]TFA	reflux	10	95
8	H_2O–EtOH (1:1)	[TETA]TFA	room temperature	120	41
9	H_2O–EtOH (1:1)	[TETA]TFA	60	60	74
10[c]	H_2O–EtOH (1:1)	[TETA]TFA	reflux	45	92
11[d]	H_2O–EtOH (1:1)	[TETA]TFA	reflux	10	95

[a] *Reaction conditions*: 4-chlorobenzaldehyde (2.0 mmol), malononitrile (2.0 mmol), dimedone (2.0 mmol), ionic liquid (0.1 mmol), solvent (5.0 ml). [b] Isolated yield. [c] 1 mol% of catalyst was used. [d] 10 mol% of catalyst was used.

† *Catalyst preparation.* A Brønsted acid (0.05 mol, dissolved in 10.0 ml ethanol) was added dropwise with vigorous stirring to a solution of triethylenetetramine or ethylenediamine (0.05 mol) in ethanol (10.0 ml) cooled in an ice–water bath. Then the reaction mixture was stirred for additional 24 h. After evaporating ethanol, the crude product was washed three times with diethyl ether, and then dried *in vacuo* at 60 °C to afford the desired product. All target ILs were characterized by IR, ^{1}H NMR and ^{13}C NMR (see Online Supplementary Materials).

‡ *Synthesis of 2-amino-4-aryl-3-cyano-7,7-dimethyl-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran-5-ones* **5a**–**m** *and 2-amino-4-aryl-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-ones* **6a**–**e** *(typical procedure).* An equimolar (2.0 mmol) mixture of an aromatic aldehyde **1**, malononitrile **2** and dimedone **3** or hydroxycoumarin **4** were dissolved in H_2O–EtOH (1:1, 5.0 ml). Then triethylenetetraammonium trifluoroacetate ([TETA]TFA) (5 mol%) was added to a flask, and the mixture was vigorously stirred at reflux for 10–240 min (TLC monitoring). After completion, water (15.0 ml) was added to quench the reaction and to precipitate the crude product. The crude product was collected by filtration and further purified by recrystallization from methanol.

For **5a**: IR (KBr, ν/cm^{-1}): 3381, 3184, 2959, 2188, 1674, 1635, 1604, 1365, 1216. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.93 (s, 3H), 1.02 (s, 3H), 2.10 (d, 1H, *J* 16.1 Hz), 2.21 (d, 1H, *J* 16.1 Hz), 2.50 (s, 2H), 4.19 (s, 1H), 7.05 (s, 2H), 7.18 (d, 2H, *J* 8.3 Hz), 7.33 (d, 2H, *J* 8.3 Hz).

For spectral characteristics of compounds **5d**,**f**,**h**,**l** and **6a**,**b**, see Online Supplementary Materials.

Table 2 [TETA]TFA catalyzed synthesis of tetrahydrobenzo[*b*]pyrans **5a–m** in aqueous media.[a]

Entry	Ar	R	Product	Time/ min	Yield (%)[b]	Mp/°C
1	4-ClC_6H_4	Me	**5a**	10	94	211–213[4(a)]
2	2,4-$Cl_2C_6H_3$	Me	**5b**	30	94	114–116[6]
3	4-BrC_6H_4	Me	**5c**	5	92	193–195[3]
4	4-$O_2NC_6H_4$	Me	**5d**	30	87	183–185[7]
5	3-$O_2NC_6H_4$	Me	**5e**	25	91	202–204[6]
6	Ph	Me	**5f**	20	85	213–216[13]
7	4-HOC_6H_4	Me	**5g**	240	50	205–207[8]
8	4-$MeOC_6H_4$	Me	**5h**	50	88	197–199[7]
9	4-MeC_6H_4	Me	**5i**	15	89	208–210[4(a)]
10	4-$Me_2NC_6H_4$	Me	**5j**	25	83	214–215[8]
11	2-Furyl	Me	**5k**	90	73	228–230[5]
12	Ph	H	**5l**	10	69	220–222[9]
13	4-$MeOC_6H_4$	H	**5m**	30	75	186–189[7]

[a] *Reaction conditions*: aldehyde (2.0 mmol), malononitrile (2.0 mmol), dimedone (or cyclohexane-1,3-dione) (2.0 mmol), [TETA]TFA (0.1 mmol), H_2O–EtOH (1:1, 5.0 ml), reflux. [b] Isolated yield.

Subsequently, we demonstrated the scope and generality of the present method by the reaction of various benzaldehydes **1** with malononitrile **2** and cyclohexane-1,3-diones **3** catalyzed by [TETA]TFA under the optimal conditions (Table 2). Benzaldehyde and the aromatic aldehydes bearing electron-withdrawing groups (such as nitro group, halogen) (Table 2, entries 1–6) required a shorter reaction time and gave higher yields than those bearing electron-donating groups (such as *N*,*N*-dimethylamino, hydroxy, methoxy and methyl) (Table 2, entries 7–10). Note that no O-protection was required for 4-hydroxybenzaldehyde (Table 2, entry 7).

Encouraged by these results, we extended the scope of this method towards the synthesis of pyrano[*c*]chromenes **6** from 4-hydroxycoumarin **4** (Scheme 2, Table 3). 3-Nitrobenzaldehyde bearing nitro group in *meta*-position in the aromatic ring has lower reactivity and required longer reaction time (Table 3, entry 5) than *p*-nitro-substituted benzaldehyde (entry 1). Other benzaldehydes provided good yields in short time (Table 3, entries 2–4).

In view of green chemistry, reuse of the catalyst is highly preferable. The reusability of the catalyst was exemplified on reaction between 4-chlorobenzaldehyde, dimedone and malononitrile. After the separation of products, the IL catalyst was easily recovered and recycled by removal of the filtrate after filtering off the products. The product was obtained in 94, 94, 95, 93, 94, 93, 91 and 90% yield in consecutive 1 to 8 runs, respectively, which indicated that the catalyst could be reused for at least 8 runs without loss of its activity. In comparison with the reported IL [bmim]OH[10] and [bmim]PF_6[17] systems, our IL catalytic system shows comparative yields and excellent reusabilities.

Table 3 [TETA]TFA catalyzed synthesis of pyrano[*c*]chromenes **6a–e** in aqueous media.[a]

Entry	Ar	Product	Time/min	Yield (%)[b]	Mp/°C
1	4-$O_2NC_6H_4$	**6a**	10	94	249–251[14]
2	Ph	**6b**	20	86	253–255[14]
3	4-$MeOC_6H_4$	**6c**	50	85	238–240[15]
4	4-MeC_6H_4	**6d**	20	88	245–247[16]
5	3-$O_2NC_6H_4$	**6e**	120	75	246–248[16]

[a] *Reaction conditions*: aldehyde (2.0 mmol), malononitrile (2.0 mmol), 4-hydroxycoumarin (2.0 mmol), [TETA]TFA (0.1 mmol), H_2O–EtOH (1:1, 5.0 ml), reflux. [b] Isolated yield.

In summary, we have prepared a series of new basic task-specific ionic liquids and used them as catalysts for the synthesis of pyran-annulated heterocyclic systems. This novel catalytic system demonstrates the advantages of environmentally benign character, mild reaction conditions, short reaction times, high yields, easy handling as well as good reusability.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.09.017.

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