Aqueous [bmim][BF$_4$] as green solvent in microwave-assisted organic reactions: clean synthesis of 1*H*-benzo[*f*]chromene derivatives

Xin-Min Wen*, Hui-Yun Wang and Shu-Ling Li

Department of Medicinal Chemistry, Jining Medical College, Rizhao 276826, China

The mixture of hydrophilic [bmim][BF$_4$] and water has been found to be a green and safe reaction medium in the synthesis of ethyl 3-amino-1-aryl-1*H*-benzo[*f*]chromene derivatives using domestic microwave oven.

Keywords: microwave, ionic liquids, aqueous synthesis, 1*H*-benzo[*f*]chromene, catalyst

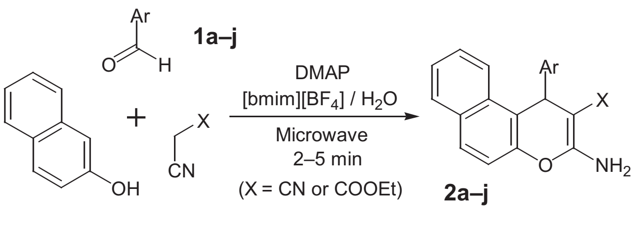
The general areas of investigation in green chemistry include selections of reagents, solvents, reaction conditions, catalysts and the design of safer chemicals.[1] As a result, water[2] and ionic liquids[3] have been recognised and are attracting attention as new alternative solvents for organic synthesis. While the use of water as solvent is probably the most desirable approach, this is often not possible due to the hydrophobic nature of the reactants. Room-temperature ionic liquids are currently exploited as potentially green and recyclable alternative solvents for a large variety of chemical reactions. In contrast to traditional solvents, ionic liquids do not produce volatile organic compounds due to their negligible vapor pressure. On the other hand, despite the many applications of ionic liquids in synthetic processes, less attention has been paid on the use of water–ionic liquid mixed solvents. Only several systems, [bmim][BF$_4$]–H$_2$O,[4] [bmim][Cl]–H$_2$O,[5] [omim][BF$_4$]–H$_2$O[6] have been employed as reaction medium in organic synthesis.

Microwave heating through dielectric losses has been used in synthetic organic chemistry, as it allows the transformations to be performed very safely and with a low energy input.[7] However, the development of green solvent systems acceptable for dielectric heating has lagged behind the rapid advance of microwave-assisted organic synthesis. It has been demonstrated that the ionic character of ionic liquids provides excellent coupling capability with microwave[8] and, therefore, small amounts of an ionic liquid could be employed as additives in order to increase the dielectric constant of an otherwise nonpolar organic solvents.[9] To combine the advantages of microwave technique (rapid reactions) and ionic liquids (green solvents), several reactions, such as olefin metathesis,[10] Heck reaction,[11] Kabachnik–Fields reaction,[12] catalytic transfer hydrogenation,[13] and rapid synthesis of alkyl halides from alcohols and nitriles from aryl halides,[14] have been carried out by using ionic liquid as solvent under microwave irradiation. Nevertheless overheating is a problem, with organic reactions performed in ionic liquids, due to the non-volatile nature (nearly zero vapor pressure) of such solvents. Side reactions may occur at elevated temperature and give erratic results; especially when the reactant or product is thermosensitive. Indeed, this problem could be settled by using complicated microwave reactors, in which the temperature threshold is restricted by computer-aided control of dielectric heating.[11,14]

Table 1 Effect of heating mode and various ratio of water to ionic liquid on model reactions

Entry	Water/IL/ % wt	Heating mode	Time/min	Yield/%^{a}
1	0/100	Oil bath	60	86
2	0/100	MW	2	—
3	20/80	Oil bath	70	85
4	20/80	MW	2	84
5	30/70	Oil bath	70	81
6	30/70	MW	2	89
7	40/60	MW	7	79
8	50/50	MW	10	73

^{a}Isolated yields.



Scheme 1

On the other hand, 2-aminochromenes are biologically interesting compounds which possess various pharmacological activities. For example, ethyl 2-amino-4-(3-nitrophenyl)-4*H*-benzo[*h*]chromene-3-carboxylate, LY 290375, was found as an inhibitor of MCM-induced neutral protease activity.[15] Generally, these compounds were prepared from ethyl α-cyanocinnamates and 2-naphthol catalysed by an organic base in alcoholic solution.[16]

Considering the great synthetic potentiality of the microwave-induced organic reactions in ionic liquids and the potential biological activities of 2-aminochromenes, we report here the synthesis of ethyl 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carboxylates **2a–j** using aqueous [bmim][BF$_4$] as green solvent using a domestic microwave oven (Scheme 1). In aqueous [bmim][BF$_4$], the microwave-mediated three-component cyclisation occurred smoothly and gave products in excellent yields.

As a starting point to develop our methodology, we initially chose the condensation of benzaldehyde **1a** with malononitrile and 2-naphthol in the presence of DMAP (4-dimethylaminopyridine) (10%mol) as a model for optimising reaction conditions. In a typical experiment, a mixture of **1a** and 1 equiv of malononitrile and 2-naphthol in certain solvent was heated in a preheated oil bath (110°C) or microwaved. The results are summarised in Table 1. In the case using neat [bmim][BF$_4$], model reaction performed smoothly under conventional heating and gave desired product in high yield (Table 1, entry 1), while the reaction system was very complicated under microwave irradiation, while large quantities of tarry by-products were obtained due to side reactions at elevated temperature (Table 1, entry 2). In contrast to those in entries 1 and 2, reactions in H$_2$O-[bmim][PF$_4$] (20/80%wt.) gave desired product in good yields under either conventional or dielectric heating (Table 1, entries 3 and 4). Note that the reaction rates and yields were diminished with the increase of water content in the mixed solvent (Table 1, entries 7 and 8). From the synthetic and economical points of view, H$_2$O–[bmim][PF$_4$] (30/70%wt) was chosen in follow-up reactions.

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* Correspondent. E-mail: xinmwen@yahoo.com.cn

Table 2 Microwave-assisted synthesis of ethyl 3-amino-1-aryl-1*H*-benzo[f]chromene derivatives in aqueous [bmim][BF_4]

Entry	Ar	X	Time/min	Yield/%^{a}	M.p. (Obs.)/°C	M.p. (Lit.)/°C
a	C_6H_5	CN	2	89	280–281	277[17]
b	4-ClC_6H_4	CN	2	93	219–220	218[17]
c	2,4-$Cl_2C_6H_3$	CN	2	91	255–256	258–260[18]
d	4-$MeOC_6H_4$	CN	2	92	197–198	192[19]
e	4-MeC_6H_4	CN	2	87	275–277	270[17]
f	C_6H_5	COOEt	5	88	202–204	195[19]
g	4-ClC_6H_4	COOEt	4	91	171–172	168[20]
h	2,4-$Cl_2C_6H_3$	COOEt	4	95	195–196	199–200[21]
l	4-$MeOC_6H_4$	COOEt	5	85	168–169	168[19]
j	4-MeC_6H_4	COOEt	5	90	209–210	204[21]

^{a}All yields refer to isolated products characterised by m.p. data, ^{1}H NMR and IR spectral analysis.

By using dedicated instruments, with characteristics such as direct temperature control with the aid of IR sensors, and software that enables on-line temperature control by modulating the microwave output, reactions in ionic liquids can be carried out under nearly steady temperature because the lost control of microwave heating would be avoided by temperature feedback power control device. In our method, the upper limit of reaction temperature was restricted through steady refluxing of water, by which the use of complicated instruments could be avoided.

To generalise the feasibility of this new protocol, a range of aromatic aldehydes **1a–j** were treated with 2-naphthol and malononitrile or ethyl cyanoacetate under microwave irradiation by using H_2O-[bmim][BF_4] (30/70%wt) as solvent, and the results are summarised in Table 2. Both electron-rich and electron-deficient aldehydes provide the desired products in good to excellent yields in short reaction periods (°<5 min).

The recycling of DMAP-[bmim][BF_4]-H_2O was investigated using the synthesis of **2f**. After initial experiment, the precipitated product was collected by filtration and the catalyst-containing filtrate was subjected to subsequent run of the reaction by recharging with the same substrates. As shown in the stick plot (Fig. 1), some undulation in chemical yield is observed using recovered aqueous ionic liquid. This reaction was repeated for seven times using the same batch of solvent, and the yields remain around 85–90%. It is noted that, in the seventh run, a yield as high as 89% was still observed.

There are some other advantages in using aqueous ionic liquids. Firstly, ionic liquid is a good alternative to volatile, flammable, and/or toxic co-solvents in reacting hydrophilic reagent with hydrophobic substrates in water. Secondly, the solvency of this mixed solvent could be tuned by varying its composition to get an optimised balance between hydrophobic and hydrophilic substrates. Thirdly, many of the organic products can be separated by simple filtration or decantation from resulting mixture. In contrast, the reaction using neat [bmim][BF_4] often necessitates a tedious distillation, or extraction with volatile organic solvents such as ether and hydrocarbons.

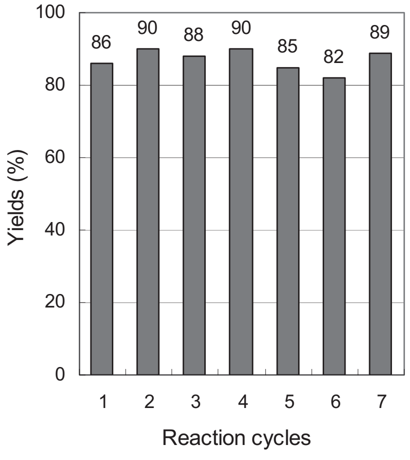

Fig. 1 Recyling of DMAP-[bmim][BF_4]–H_2O.

In summary, aqueous [bmim][BF_4] was employed successfully as a safer and cleaner polar solvent for microwave-assisted synthesis. The operational simplicity, reusable catalyst–solvent system as well as good yields in short reaction time make this procedure an economically valuable and environmentally friendly alternative to the currently available methods for the synthesis of title compounds.

Experimental

The commercially available reagents and solvents were used as received. Ionic liquid [bmim][BF_4] was prepared by standard method. Microwave-induced reactions were conducted using a domestic microwave oven (Granz WD-700S, frequency: 2450 MHz, full power level: 700W). Products obtained are all known compounds and were identified by comparing of their physical and spectra data with those reported in the literature. IR spectra were recorded on a Nicolet Nexus 470 spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on Bruker AC 200 spectrometer in DMSO-d_6 with TMS as an internal standard.

General procedure

A mixture of aromatic aldehyde (5 mmol), malononitrile or ethyl cyanoacetate (5 mmol), 2-naphthol (0.72 g, 5 mmol), DMAP (0.06 g, 0.5 mmol) and 10 ml of aqueous [bmim][BF_4] (water: IL: 30/70%wt) was placed in a 400 ml beaker and was subjected to microwave irradiation (200W) for an optimised period listed in Table 2. On completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The crude product thus precipitated was collected by filtration, washed with H_2O, air dried, and recrystallised from EtOH-DMF (3 : 1 v/v) to afford pure products.

Spectral data of selected compounds

Ethyl3-amino-4-(4-methylphenyl)-4H-benzo[f]chromene-2-carboxylate (**2j**): ^{1}H NMR (DMSO-d_6): δ_H 1.16 (t, J = 7.2 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 4.00 (q, J = 7.2 Hz, 2H, CH_2O), 4.83 (s, 1H, 4-H), 6.97 (s, 2H, NH_2), 7.06–7.09 (m, 4H, ArH), 7.32 (d, J = 8.8 Hz, 1H, ArH), 7.42–7.45 (m, 2H, ArH), 7.85–7.94 (m, 3H, ArH) ppm. IR (KBr): v 3389, 3290, 1690, 1610, 1530, 1460, 1395, 1370, 1310, 1230, 1100, 1030, 810, 750 cm^{-1}.

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