## **Ionic Liquid Promoted Knoevenagel and Michael Reactions**

Xuesen Fan,<sup>A,C</sup> Xueyuan Hu,<sup>A,B</sup> Xinying Zhang,<sup>A</sup> and Jianji Wang<sup>A</sup>

<sup>A</sup> School of Chemical and Environmental Sciences, Henan Key Laboratory for Environmental

Pollution Control, Henan Normal University, Xinxiang, Henan 453007, China.

<sup>B</sup> Chongqing University of Medical Sciences, Chongqing 400016, China.

<sup>C</sup> Corresponding author. Email: fanxs88@263.net

The utilization of the ionic liquid [bmim][BF<sub>4</sub>] as both reaction medium and promoter for the Knoevenagel condensation and Michael addition reactions is described in this paper. Through these reactions, several useful electrophilic alkenes and chromene derivatives are obtained in high yields. The advantages of these two novel procedures include their environmentally benign nature, atom economy, simple operation process, and mild reaction conditions.

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### Introduction

The development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. From both economical and environmental points of view, the use of non-volatile solvents and non-metallic catalysts is very promising. In the last few years roomtemperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidaxolium cations,<sup>[1]</sup> have been recognized as a possible environmentally benign alternative to chemical volatile solvents because, in contrast with the conventional organic solvents, they are non-volatile, recyclable, nonexplosive, easy to handle, and thermally robust.<sup>[2]</sup> Furthermore, in many cases, the products are weakly soluble in the ionic phase so that they can be easily separated by simple filtration or extraction with ether.<sup>[3]</sup> On the other hand, because of the great potential of RTILs as novel reaction media for catalytic processes, much attention has also been currently focussed on organic reactions promoted by ionic liquids.

Knoevenagel condensations of aldehydes with active methylene compounds, and Michael additions of active methylene compounds to  $\alpha,\beta$ -unsaturated compounds are of great importance in the construction of new carbon–carbon bonds. Usually, they are carried out in the presence of either base or acid catalysts in volatile organic solvents and thus create much waste.<sup>[4,5]</sup> Recently, there are several reports on the new versions of Knoevenagel condensations in ionic liquids; for example, Salunkhe and coworkers reported a Knoevenagel condensation involving the use of Lewis acidic ionic liquids [bmim]Cl·xAlCl<sub>3</sub> and [bpy]Cl·xAlCl<sub>3</sub>.<sup>[6]</sup> Although the experimental procedure is simple, the ionic liquids are sensitive to moisture and air. Therefore, the reaction must be carried out in an inert-atmosphere glove box and the ionic liquid used cannot be recycled. In another case, Forbes

and coworkers reported a glycine-promoted Knoevenagel condensation of benzaldehyde with malononitrile in ionic liquid, but only one example was examined.<sup>[7]</sup> As an alternative, Chen and coworkers reported that this classical reaction can also be well realised in ionic liquids by using ethylenediammonium diacetate (EDDA) as a catalyst.<sup>[8a]</sup> Very recently, two greener processes for the Knoevenagel reaction have also been realized efficiently in water or in the absence of solvent.<sup>[8b,8c]</sup> However, to our knowledge, there are no precedents in terms of using ionic liquids as both reaction media and promoter in Knoevenagel condensation and Michael addition reactions. As continuation of our interest in the area of green synthesis,<sup>[9]</sup> we then checked the improvement that can be expected if these reactions can be carried out in ionic liquid without any such added catalysts as mentioned above. Herein we report our preliminary results on the using of an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF<sub>4</sub>]), as a recyclable alternative to classical molecular solvents and a promoter for Knoevenagel condensation and Michael addition reactions.

#### **Results and Discussion**

We began our work by examining the Knoevenagel condensation between benzaldehyde 1a and malononitrile 2 in [bmim][BF<sub>4</sub>] (Scheme 1).

Though almost all the Knoevenagel condensation procedures in ionic liquids mentioned above necessitated the use of additional catalysts, we found that this reaction did occur in the presence of [bmim][BF<sub>4</sub>] alone and afforded the corresponding product **3a** with considerably high yields under optimized reaction conditions. As shown in Table 1, when the mixture of **2** and **1a** was stirred in [bmim][BF<sub>4</sub>] for just 1 h at room temperature, the yield of **3a** is disappointingly low





Scheme 3.

(Table 1, entry 1). However, with a higher reaction temperature along with longer reaction time, the yield of **3a** can be improved considerably. In fact, it turned out that **3a** can be obtained with a yield as high as 85% when the reaction was conducted at 80°C for 4 h (Table 1, entry 7). This result is well comparable to the yields reported in the literature involving additional catalysts.

With the above results in hand, we then turned our attention to the condensation of other structurally varied aldehydes with malononitrile or ethyl cyanoacetate by using [bmim][BF<sub>4</sub>] as both reaction medium and promoter (Scheme 2, Table 2). As can be seen in Table 2, the reactions were found to be general. Aldehydes with various substituents, such as chloro, bromo, fluoro, nitro, or methoxy groups, all gave the corresponding products in fairly good results. It should be noted that with ethyl cyanoacetate, a prolonged reaction time was needed to give reasonably high yields because of its lower nucleophilic activity compared with malononitrile.

Considering that the electron-poor alkenes **3** are good Michael addition receptors, we then started to check the possibility of performing the 1,4-addition of dimedone **4** to **3** in the presence of ionic liquids (Scheme 3), which has been used as an efficient method to prepare the chromene derivatives **5** (Scheme 3). When the mixture of **3a** and **4** was stirred in [bmim][BF<sub>4</sub>] at 40°C for 4 h without any additional catalyst, the corresponding product was formed almost quantitatively. In addition, the separation process of the final product is quite simple, just through adding a little amount of H<sub>2</sub>O to the mixture and then subsequent suction to collect the product crystals. Moreover, this simple process is also applicable to other electron-poor alkenes and they all give the chromene derivatives in good yields under mild conditions (shown in Table 3).

Table	1. Knoever	Knoevenagel	condensation	between	1a	and	2	in
			[bmim][BF <sub>4</sub> ]					

Reaction conditions: 1 mL [bmim][BF4], 0.5 mmol benzaldehyde, 0.5 mmol malononitrile

Entry	Reaction temp. [°C]	Reaction time [h]	Isolated yield [%] <b>3a</b>
1	Room temp.	1	5
2	40	1	11
3	40	2	28
4	40	4	42
5	60	4	65
6	80	2	62
7	80	4	85

Table 2. Knoevenagel condensation of aldehydes with malononitrile or ethyl cyanoacetate in [bmim][BF4] at 80°C

Entry	Ar	R	Reaction time [h]	Products	Isolated yield [%]
1	C <sub>6</sub> H <sub>5</sub>	CN	4	3a	85
2	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	2	3b	95
3	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	4	3c	83
4	p-ClC <sub>6</sub> H <sub>4</sub>	CN	3	3d	91
5	p-BrC <sub>6</sub> H <sub>4</sub>	CN	3	3e	92
6	p-FC <sub>6</sub> H <sub>4</sub>	CN	2	3f	89
7	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CN	4	3g	78
8	o-BrC <sub>6</sub> H <sub>4</sub>	CN	4	3h	85
9	o-ClC <sub>6</sub> H <sub>4</sub>	CN	4	3i	88
10	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	3	3j	86
11	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	5	3k	78
12	p-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	5	31	68
13	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	$CO_2Et$	5	3m	70
14	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	6	3n	58
15	o-ClC <sub>6</sub> H <sub>4</sub>	$CO_2Et$	6	30	60

 
 Table 3. Michael addition reactions of 3 and 4 in [bmim][BF4] at 40°C

Entry	Ar	R	Reaction time [h]	Products	Isolated yield [%]
1	C <sub>6</sub> H <sub>5</sub>	CN	4	5a	88
2	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CN	4	5b	85
3	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	2	5c	96
4	p-ClC <sub>6</sub> H <sub>4</sub>	CN	3	5d	95
5	o-ClC <sub>6</sub> H <sub>4</sub>	CN	4	5e	83
6	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	4	5f	84
7	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	3	5g	90
8	$p-FC_6H_4$	CN	2	5h	95
9	m-BrC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	4	5i	79
10	o-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	4	5j	86
11	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	3	5k	89
12	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	3	51	86
13	p-FC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	3	5m	93
14	p-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	3	5n	91
15	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	5	50	82
16	C <sub>6</sub> H <sub>5</sub>	$CO_2Et$	5	5p	83

By thoroughly referenced screening, we found that this kind of reaction is frequently performed in solution or solvent-free under base catalysis,<sup>[10,11]</sup> or under acid<sup>[12]</sup> or Lewis acid<sup>[13]</sup> catalysis, and required chromatographic



Table 4. Three-component coupling reaction of 1, 2 and 4 in [bmim][BF4] at 40°C

Reaction conditions: 1 mL [bmim][BF4], 0.5 mmol aldehyde, 0.5 mmol malononitrile, 0.5 mmol dimedone

Entry	Ar	R	Reaction time [h]	Products	Isolated yield [%]
1	C <sub>6</sub> H <sub>5</sub>	CN	5	5a	84
2	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	3	5c	90
3	p-ClC <sub>6</sub> H <sub>4</sub>	CN	4	5d	88
4	o-ClC <sub>6</sub> H <sub>4</sub>	CN	4	5e	80
5	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	5	5f	82
6	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	3	5g	85
7	p-FC <sub>6</sub> H <sub>4</sub>	CN	3	5h	87

purification techniques to give the pure products. Other methods such as dry solid supports and microwave heating were also applied, but the situation did not improve significantly.<sup>[14]</sup> With the process presented in this paper, the Michael addition and the subsequent rearrangement and cyclization of the Michael adducts to give the corresponding chromene derivatives were achieved efficiently without any conventional solvents, base or acid catalyst, or microwave irradiation conditions.

Currently, the art of performing efficient chemical transformations, coupling three or more components in a single operation by a catalytic process and avoiding stoichiometric toxic reagents, large amounts of solvents, and costly purification procedures represents a fundamental target of modern organic synthesis. It has been reported that RTILs are able to efficiently catalyze the three-component coupling reactions of aldehydes, amines, and homophthalic anhydrides to give the corresponding cis-isoquinolonic acids in excellent yields.<sup>[15]</sup> This result promoted us to study the potential role of RTILs in promoting the three-component coupling reaction of aldehyde 1, malononitrile or ethyl cyanoacetate 2, and dimedone 4 to afford the corresponding chromenes 5 in a one-pot reaction. To our delight, treatment of benzaldehyde, malononitrile, and dimedone in [bmim][BF<sub>4</sub>] at 40°C afforded the corresponding chromene derivative 5 in 84% yield (Scheme 4).

Similarly, several other aryl aldehydes also reacted smoothly with malononitrile and dimedone to give the corresponding chromenes in reasonably high yields (Table 4).

However, when benzaldehyde and ethyl cyanoacetate were treated with dimedone in  $[bmim][BF_4]$  at ambient temperature, no chromene derivative was obtained. Instead, almost quantitative formation of **6**, a condensation product of benzaldehyde and dimedone occurred (Scheme 5). It is probably attributable to the much weaker nuleophilic activity of cyanoacetate compared with dimedone, which can





react with benzaldehyde before cyanoacetate and afforded the corresponding product **6** exclusively.

One important feature of the use of ionic liquids as reaction medium is the possibility of its recyclability and reuse for the same, as well as for different, types of reactions. We found that the recyclability and reuse of [bmim][BF4] is feasible in all the above procedures. At completion of the reactions, the products were isolated by filtration and the filtered solution was heated in an oven with reduced pressure to remove water. The residue was then reloaded with the initial reagents and this solution was re-submitted to the usual reaction conditions. No decrease in the efficiency of the reused ionic liquid was observed after several rounds.

In summary, we have demonstrated that the ionic liquid [bmim][BF<sub>4</sub>] can be used as both reaction medium and promoter for the Knoevenagel condensation and Michael addition reactions, which usually involve the use of additional catalyst when they are carried out in conventional organic solvents. In addition, it has also been demonstrated that [bmim][BF<sub>4</sub>] is a useful medium for the three-component coupling reaction of aldehydes, malononitrile, and dimedone to give chromene derivatives in high yields. Compared with the reported methods, the notable features of the above procedures are atom economy, mild conditions, cleaner reaction profiles, and simple operational process, together with convenient and efficient recovery and reuse of this novel reaction medium.

#### **Experimental**

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption values quoted in cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were determined on a Bruker AC 400 spectrometer as CDCl<sub>3</sub> solutions. Chemical shifts ( $\delta$ ) were expressed in ppm downfield from the internal standard tetramethylsilane, and coupling constants *J* were given in Hz. <sup>13</sup>C NMR spectra were recorded on a Bruker AC 100 spectrometer as CDCl<sub>3</sub> solutions. Mass spectra were recorded on a HP5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

#### General Procedure for the Knoevenagel Condensation in [bmim] [BF<sub>4</sub>]

The aromatic aldehyde 1 (0.5 mmol) and active methylene compound 2 (0.5 mmol) were added to a round bottom flask containing 1 mL of [bmim][BF<sub>4</sub>]. The mixture was stirred at 80°C for a certain time to complete the reaction (monitored by TLC). At completion, water was added. The precipitates in the reaction mixture were then collected and further purified by recrystallization with 95% ethanol to give the pure

products **3**. The aqueous solution of ionic liquid was concentrated at reduced pressure to recover the ionic liquid for subsequent use.

# General Procedure for the Michael Addition Reactions in [bmim][BF<sub>4</sub>]

The alkene **3** (0.5 mmol) and dimedone **4** (0.5 mmol) were added to a round bottom flask containing 1 mL of [bmim][BF<sub>4</sub>]. The mixture was stirred at  $40^{\circ}$ C for a certain time to complete the reaction (monitored by TLC). At completion, water was added. The precipitates in the reaction mixture were then collected and further purified by recrystallization with 95% ethanol to give the pure chromenes **5**. The aqueous solution of ionic liquid was concentrated at reduced pressure to recover the ionic liquid for subsequent use.

#### General Procedure for the Three-Component Coupling Reactions in [bmim] [BF<sub>4</sub>]

Aldehyde 1 (0.5 mmol), malononitrile 2 (0.5 mmol), and dimedone 4 (0.5 mmol) were added to a round bottom flask containing 1 mL of [bmim][BF4]. The mixture was stirred at 40°C for a certain time to complete the reaction (monitored by TLC). At completion, water was added. The precipitates in the reaction mixture were then collected and further purified by recrystallization with 95% ethanol to give the pure chromenes 5. The aqueous solution of ionic liquid was concentrated at reduced pressure to recover the ionic liquid for subsequent use.

**3a**, mp 78–80°C (lit.<sup>[16]</sup> 84°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.50–7.73 (3H, m, ArH), 7.90 (1H, s, HC=C), 8.13 (2H, d, J 5.6, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3020, 2250, 1592, 1081.

**3b**, mp 161–163°C (lit.<sup>[16]</sup> 159°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.83 (1H, s, HC=C), 8.12 (2H, d, *J* 7.2, ArH), 8.34 (2H, d, *J* 7.2, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3020, 2245, 1595, 1528.

**3c**, mp 111–113°C (lit.<sup>[16]</sup> 114°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 3.87 (3H, s, OCH<sub>3</sub>), 6.89 (2H, d, *J* 9.2, ArH), 7.58 (1H, s, HC=C), 7.84 (2H, d, *J* 9.2, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3021, 2245, 1590.

**3d**, mp 161–163°C (lit.<sup>[17]</sup> 161–162°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.53 (2H, d, *J* 9.0, ArH), 7.69 (1H, s, HC=C), 7.86 (2H, d, *J* 9.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3012, 2225, 1563.

**3e**, mp 160–162°C (lit.<sup>[17]</sup> 159–160°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.50 (2H, d, *J* 9.0, ArH), 7.65 (1H, s, HC=C), 7.79 (2H, d, *J* 9.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3011, 2228, 1563.

**3f**, mp 124–125°C (lit.<sup>[18]</sup> 126.8–127.2°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.60 (2H, d, *J* 8.0, ArH), 7.70 (1H, s, HC=C), 7.98 (2H, d, *J* 8.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3010, 2230, 1542.

**3g**, mp 130–133°C (lit.<sup>[16]</sup> 135°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 2.33 (3H, s, CH<sub>3</sub>), 7.20 (2H, d, *J* 8.2, ArH), 7.61 (1H, s, HC=C), 7.62 (2H, d, *J* 8.2, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3022, 2245, 1593. **3h**, mp 83–85°C (lit.<sup>[18]</sup> 90.5–91.0°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz)

**3h**, mp 83–85°C (lit.<sup>[18]</sup> 90.5–91.0°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.31–8.03 (4H, m, ArH), 8.15 (1H, s, HC=C).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3030, 2245, 1581.

**3i**, mp 85–86°C (lit.<sup>[17]</sup> 93–94°C). δ<sub>H</sub> (CDCl<sub>3</sub>, 400 MHz) 7.38–8.11 (4H, m, ArH), 8.23 (1H, s, HC=C). ν<sub>max</sub> (KBr/cm<sup>-1</sup>) 3032, 2245, 1583.

**3j**, mp 99–100°C (lit.<sup>[16]</sup> 100°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 7.58 (1H, t, *J* 8.0, ArH), 7.80 (1H, s, HC=C), 8.24 (1H, d, *J* 8.0, ArH), 8.39 (1H, d, *J* 8.0, ArH), 8.64 (1H, s, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3018, 2235, 1583.

**3k**, mp 168–170°C (lit.<sup>[4a]</sup> 170°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.49 (3H, t, *J* 7.2, CH<sub>3</sub>), 4.38 (2H, q, *J* 7.2, OCH<sub>2</sub>), 8.12 (2H, d, *J* 8.8, ArH), 8.30 (1H, s, HC=C), 8.34 (2H, d, *J* 8.8, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3017, 2241, 1728, 1595, 1528, 1348.

**3**, mp 85–87°C (lit.<sup>[4a]</sup> 87°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.45 (3H, t, J 7.2, CH<sub>3</sub>), 4.32 (2H, q, J 7.2, OCH<sub>2</sub>), 7.46 (2H, d, J 8.8, ArH), 7.95 (2H, d, J 8.8, ArH), 8.17 (1H, s, HC=C).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3019, 2227, 1728, 1591, 1532, 1250.

**3m**, mp 131–133°C (Found: C 58.4, H 4.1, N 11.4.  $C_{12}H_{10}N_2O_4$  requires C 58.5, H 4.1, N 11.4%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 1.44 (3H, t, *J* 7.2, CH<sub>3</sub>), 4.44 (2H, q, *J* 7.2, OCH<sub>2</sub>), 7.74–7.81 (1H, m, ArH), 7.91 (1H, s, HC=C), 8.33–8.41 (2H, m, ArH), 8.72 (1H, s, ArH).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 162.01, 152.31, 149.22, 135.21, 133.48, 132.58, 131.51, 128.74, 113.13, 107.32, 63.81, 14.65.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3018, 2245, 1730, 1600, 1352. *m/z* (70 eV) 246 (M<sup>+</sup>).

**3n**, mp 81–83°C (lit.<sup>[4*a*]</sup> 86°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.40 (3H, t, *J* 7.2, CH<sub>3</sub>), 3.88 (3H, s, OCH<sub>3</sub>), 4.28 (2H, q, *J* 7.2, OCH<sub>2</sub>), 6.97 (2H, d, *J* 8.8, ArH), 7.99 (2H, d, *J* 8.8, ArH), 8.12 (1H, s, HC=C).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3019, 2240, 1738, 1605, 1310.

**30**, mp 46–48°C (Found: C 61.1, H 4.4, N 5.9.  $C_{12}H_{10}CINO_2$  requires C 61.2, H 4.3, N 5.9%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 1.43 (3H, t, *J* 7.2, CH<sub>3</sub>), 4.42 (2H, q, *J* 7.2, OCH<sub>2</sub>), 7.41–7.54 (3H, m, ArH), 8.25 (1H, dd, *J* 8.0, 1.2, ArH), 8.71 (1H, s, HC=C).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 162.35, 151.65, 136.98, 134.18, 130.88, 130.49, 130.41, 128.01, 115.32, 106.83, 63.48, 14.67.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3032, 2245, 1728, 1583. *m/z* (70 eV) 235 (M<sup>+</sup>).

**5a**, mp 222–224°C (lit.<sup>[19]</sup> 226–228°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.05 (3H, s, CH<sub>3</sub>), 1.10 (3H, s, CH<sub>3</sub>), 2.19 (2H, s, CH<sub>2</sub>), 2.49 (2H, s, CH<sub>2</sub>), 4.31 (1H, s, CH), 4.57 (2H, br s, NH<sub>2</sub>), 6.89 (2H, d, *J* 6.8, ArH), 7.25 (3H, m, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3330, 3247, 3040, 2985, 2963, 2145, 1650, 1608, 1461.

**5b**, mp 207–209°C (lit.<sup>[19]</sup> 208–210°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.00 (3H, s, CH<sub>3</sub>), 1.07 (3H, s, CH<sub>3</sub>), 2.21 (5H, m, CH<sub>2</sub>, CH<sub>3</sub>), 2.37 (2H, s, CH<sub>2</sub>), 4.28 (1H, s, CH), 4.53 (2H, br s, NH<sub>2</sub>), 6.86 (2H, d, *J* 6.8, ArH), 7.19 (2H, d, *J* 6.8, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3325, 3241, 3040, 2985, 2963, 2194, 1680, 1606, 1510, 1463.

**5c**, mp 124–126°C (lit.<sup>[19]</sup> 130–132°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.09 (3H, s, CH<sub>3</sub>), 1.15 (3H, s, CH<sub>3</sub>), 2.24 (2H, s, CH<sub>2</sub>), 2.49 (2H, s, CH<sub>2</sub>), 4.80 (1H, s, CH), 6.27 (2H, br s, NH<sub>2</sub>), 7.47 (2H, d, *J* 8.0, ArH), 8.12 (2H, d, *J* 8.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3370, 3186, 2961, 2194, 1680, 1600, 1510.

**5d**, mp 201–203°C (lit.<sup>[19]</sup> 207–209°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.08 (3H, s, CH<sub>3</sub>), 1.13 (3H, s, CH<sub>3</sub>), 2.21 (2H, s, CH<sub>2</sub>), 2.46 (2H, s, CH<sub>2</sub>), 4.53 (1H, s, CH), 6.26 (2H, br s, NH<sub>2</sub>), 7.41 (2H, d, *J* 8.0, ArH), 7.99 (2H, d, *J* 8.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3367, 3191, 2969, 2194, 1687, 1658, 1606, 1510, 1490.

 $\mathbf{5e},$  mp 206–208°C (lit.<sup>[19]</sup> 200–202°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.08 (3H, s, CH<sub>3</sub>), 1.14 (3H, s, CH<sub>3</sub>), 2.19 (2H, s, CH<sub>2</sub>), 2.42 (2H, s, CH<sub>2</sub>), 4.60 (1H, s, CH), 6.26 (2H, br s, NH<sub>2</sub>), 7.39 (1H, m, ArH), 7.65 (2H, m, ArH), 8.09 (1H, d, J 7.4, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3367, 3191, 2963, 2194, 1680, 1658, 1600, 1502, 1451.

**5f**, mp 193–195°C (lit.<sup>[19]</sup> 198–200°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.05 (3H, s, CH<sub>3</sub>), 1.20 (3H, s, CH<sub>3</sub>), 2.23 (2H, s, CH<sub>2</sub>), 2.45 (2H, s, CH<sub>2</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 4.38 (1H, s, CH), 4.53 (2H, br s, NH<sub>2</sub>), 6.83 (2H, d, J 6.8, ArH), 7.16 (2H, d, J 6.8, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3377, 3186, 2963, 2194, 1680, 1658, 1606, 1510, 1463.

**5g**, mp 208–210°C (Found: C 63.6, H 5.0, N 12.3.  $C_{18}H_{17}N_3O_4$  requires C 63.7, H 5.1, N 12.4%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 1.05 (3H, s, CH<sub>3</sub>), 1.13 (3H, s, CH<sub>3</sub>), 2.25 (2H, s, CH<sub>2</sub>), 2.53 (2H, s, CH<sub>2</sub>), 4.53 (1H, s, CH), 4.81 (2H, br s, NH<sub>2</sub>), 7.49 (1H, t, *J* 8.0, ArH), 7.68 (1H, d, *J* 8.0, ArH), 8.07 (1H, d, *J* 8.0, ArH), 8.10 (1H, s, ArH).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 196.32, 162.87, 158.40, 149.19, 145.98, 134.93, 130.02, 122.89, 113.55, 62.54, 51.12, 41.23, 36.20, 32.78, 29.37, 28.17.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3429, 3336, 3202, 3103, 2957, 2875, 2187, 1681, 1600, 1532, 1427, 1418, 1375. *m/z* (70 eV) 339 (M<sup>+</sup>).

**5h**, mp 184–186°C (Found: C 69.1, H 5.4, N 9.0.  $C_{18}H_{17}FN_2O_2$  requires C 69.2, H 5.5, N 9.0%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 1.04 (3H, s, CH<sub>3</sub>), 1.13 (3H, s, CH<sub>3</sub>), 2.23 (2H, s, CH<sub>2</sub>), 2.45 (2H, s, CH<sub>2</sub>), 4.46 (1H, s, CH), 6.88 (2H, br s, NH<sub>2</sub>), 6.99 (2H, d, *J* 8.0, ArH), 7.11 (2H, d, *J* 8.0, ArH).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 196.34, 161.93, 161.62, 157.86, 129.78, 129.70, 128.83, 116.08, 115.86, 51.28, 51.22, 41.26, 35.49, 32.72, 29.43, 28.25.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3392, 3326, 3214, 2951, 2875, 2193, 1683, 1656, 1607, 1514, 1369. *m/z* (70 eV) 312 (M<sup>+</sup>).

**5i**, mp 133–135°C (Found: C 5.70, H 5.2, N 3.3.  $C_{20}H_{22}BrNO_4$  requires C 57.2, H 5.3, N 3.3%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 1.00 (3H, s, CH<sub>3</sub>), 1.11 (3H, s, CH<sub>3</sub>), 1.18 (t, 3H, *J* 8.0, CH<sub>3</sub>), 2.22 (2H, s, CH<sub>2</sub>), 2.45 (2H, s, CH<sub>2</sub>), 4.05 (q, 2H, *J* 8.0, OCH<sub>2</sub>), 4.67 (1H, s, CH), 6.23 (2H, br s, NH<sub>2</sub>), 7.09 (1H, t, *J* 8.0, ArH), 7.22 (1H, d, *J* 8.0, ArH), 7.24 (1H, d, *J* 8.0, ArH), 7.39 (1H, s, ArH).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 196.72, 169.42, 162.14, 158.86, 148.72, 131.93, 129.86, 129.72, 127.62, 122.42, 116.72, 80.79, 60.32, 51.25, 41.23, 34.39, 32.81, 29.57, 28.01, 14.74.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3410, 3298, 2959, 2928, 1695, 1658, 1622, 1525, 1471, 1369. *m/z* (70 eV) 419 (M<sup>+</sup>).

**5j**, mp 179–181°C (lit.<sup>[19]</sup> 181–183°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 1.00 (3H, s, CH<sub>3</sub>), 1.14 (3H, s, CH<sub>3</sub>), 1.19 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.19 (2H, s, CH<sub>2</sub>), 2.42 (2H, s, CH<sub>2</sub>), 4.03 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.60 (1H, s, CH), 6.26 (2H, br s, NH<sub>2</sub>), 7.39 (1H, m, ArH), 7.65 (2H, m, ArH), 8.09 (1H, d, *J* 7.4, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3367, 3191, 2963, 2194, 1680, 1658, 1600, 1502, 1451.

**5k**, mp 180–182°C (lit.<sup>[20]</sup> 172–174°C) (Found: C 62.1, H 5.7, N 7.2. C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub> requires C 62.2, H 5.7, N 7.3%).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 0.99 (3H, s, CH<sub>3</sub>), 1.12 (3H, s, CH<sub>3</sub>), 1.16 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.22 (2H, s, CH<sub>2</sub>), 2.49 (2H, s, CH<sub>2</sub>), 4.04 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.80 (1H, s, CH), 6.27 (2H, br s, NH<sub>2</sub>), 7.39 (1H, t, *J* 8.0, ArH), 7.67 (1H, d, *J* 8.0, ArH), 8.00 (1H, d, *J* 8.0, ArH), 8.11 (1H, s, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3442, 3302, 2986, 2956, 2903, 1693, 1673, 1623, 1523, 1475.

**51**, mp 185–187°C (Found: C 62.1, H 5.7, N 7.2.  $C_{20}H_{22}N_2O_6$  requires C 62.2, H 5.7, N 7.3%).  $\delta_H$  (CDCl<sub>3</sub>, 400 MHz) 0.97 (3H, s, CH<sub>3</sub>), 1.12 (3H, s, CH<sub>3</sub>), 1.14 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.21 (2H, s, CH<sub>2</sub>), 2.46 (2H, s, CH<sub>2</sub>), 4.03 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.80 (1H, s, CH), 6.27 (2H, br s, NH<sub>2</sub>), 7.44 (2H, d, *J* 8.0, ArH), 8.09 (2H, d, *J* 8.0, ArH).  $\delta_C$  (CDCl<sub>3</sub>, 100 MHz) 196.69, 169.13, 162.47, 158.97, 153.97, 146.93, 129.74, 123.73, 116.18, 80.00, 60.43, 51.17, 41.24, 34.85, 32.79, 29.60, 27.88, 14.75.  $\nu_{max}$  (KBr/cm<sup>-1</sup>) 3377, 3186, 2963, 2194, 1680, 1658, 1606, 1510, 1463, 1369. *m/z* (70 eV) 386 (M<sup>+</sup>).

**5m**, mp 152–155°C (Found: C 66.7, H 6.1, N 3.8. C<sub>20</sub>H<sub>22</sub>FNO<sub>4</sub> requires C 66.8, H 6.2, N 3.9%).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 0.98 (3H, s, CH<sub>3</sub>), 1.11 (3H, s, CH<sub>3</sub>), 1.16 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.20 (2H, s, CH<sub>2</sub>), 2.43 (2H, s, CH<sub>2</sub>), 4.04 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.69 (1H, s, CH), 6.20 (2H, br s, NH<sub>2</sub>), 6.89 (2H, d, *J* 8.0, ArH), 7.23 (2H, d, *J* 8.0, ArH).  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 100 MHz) 196.87, 169.54, 163.02, 161.83, 160.60, 158.86, 142.19, 130.22, 117.23, 115.13, 114.92, 81.21, 60.23, 51.28, 41.22, 33.81, 32.76, 29.61, 27.90, 14.75.  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3402, 3289, 2998, 2964, 2940, 2914, 1693, 1614, 1527, 1479, 1371, 1287, 1203. *m/z* (70 eV) 359 (M<sup>+</sup>).

**5n**, mp 152–154°C (lit.<sup>[19]</sup> 150–152°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 0.97 (3H, s, CH<sub>3</sub>), 1.10 (3H, s, CH<sub>3</sub>), 1.14 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.14 (2H, s, CH<sub>2</sub>), 2.42 (2H, s, CH<sub>2</sub>), 4.03 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.61 (1H, s, CH), 6.20 (2H, br s, NH<sub>2</sub>), 6.80 (2H, d, *J* 8.0, ArH), 7.16 (2H, d, *J* 8.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3400, 3280, 2991, 1680, 1658, 1513, 1474.

**50**, mp 160–162°C (lit.<sup>[19]</sup> 156–157°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 0.96 (3H, s, CH<sub>3</sub>), 1.05 (3H, s, CH<sub>3</sub>), 1.10 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.12 (2H, s, CH<sub>2</sub>), 2.30 (3H, s, CH<sub>3</sub>), 2.40 (2H, s, CH<sub>2</sub>), 4.01 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.59 (1H, s, CH), 6.20 (2H, br s, NH<sub>2</sub>), 6.80 (2H, d, *J* 8.0, ArH), 7.12 (2H, d, *J* 8.0, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3370, 3175, 2969, 2194, 1682, 1658, 1600, 1511, 1463.

**5p**, mp 154–156°C (lit.<sup>[19]</sup> 158–156°C).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 400 MHz) 0.96 (3H, s, CH<sub>3</sub>), 1.08 (3H, s, CH<sub>3</sub>), 1.12 (3H, t, *J* 8.0, CH<sub>3</sub>), 2.12 (2H, s, CH<sub>2</sub>), 2.42 (2H, s, CH<sub>2</sub>), 4.01 (2H, q, *J* 8.0, OCH<sub>2</sub>), 4.38 (1H, s, CH), 4.53 (2H, br s, NH<sub>2</sub>), 6.85 (2H, d, *J* 6.8, ArH), 7.21 (3H, m, ArH).  $\nu_{\rm max}$  (KBr/cm<sup>-1</sup>) 3365, 3171, 2963, 2194, 1680, 1610, 1510, 1460.

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