



# Synthesis of benzimidazoles in high-temperature water†‡

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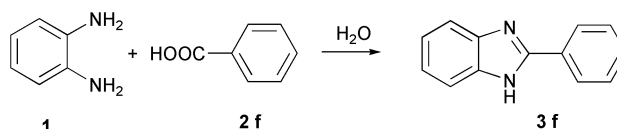
The objective of this research was to conduct constructive organic chemistry in water and to achieve yields that were comparable to, or better than, those in conventional media. The synthesis of 2-phenylbenzimidazole from 1,2-phenylenediamine and benzoic acid was chosen as a benchmark reaction. The reaction parameters, such as temperature, density and reaction time, have been systematically studied to understand whether the solvent properties of high-temperature water can have a positive effect on the chemistry. The reaction was performed in a new design of batch-type autoclave and was also monitored *in situ* by UV-vis spectroscopy. By tuning the parameters, the yield has been optimised to around 90%. The optimised conditions were then applied to related benzimidazoles, some of which crystallised from solution *in situ* to yield single crystals that were sufficiently pure to be analysed directly by X-ray diffraction, without any further purification.

## Introduction

The benzimidazole moiety is an important heterocyclic nucleus which has been used extensively in medicinal chemistry. Current clinical examples include the antihistamine Astemizole,<sup>1</sup> the anti-ulcerative Esomeprazole<sup>2</sup> and Albendazole,<sup>3</sup> which is used to treat parasitic diseases. Benzimidazoles are a component of vitamin B<sub>12</sub> and are related to the DNA base purine and the stimulant caffeine. Bisbenzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity<sup>4</sup> and can act as ligands to transition metals for modelling biological systems.<sup>5</sup>

Conventional synthesis of benzimidazoles involves heating the reactants in refluxing aqueous hydrochloric acid for 30 minutes<sup>6</sup> or in a slurry of the dehydrating agent polyphosphoric acid at 250 °C for 4 hours.<sup>7</sup> The reaction mixture must then be

neutralised with a base, such as aqueous ammonia, thereby generating aqueous waste. The pure product is obtained after recrystallisation from an organic solvent. Clearly, there is a strong opportunity for devising a cleaner route to benzimidazoles. Solid phase synthesis<sup>8</sup> and microwave irradiation using silica gel as a solid acid,<sup>9</sup> are two approaches that have been reported. This work describes the preparation of 2-phenylbenzimidazole (**3f**) from 1,2-phenylenediamine (**1**) and benzoic acid (**2f**) (Scheme 1) using near and supercritical water as an alternative, environmentally benign solvent.



**Scheme 1** Double dehydration and intramolecular cyclisation reaction between 1,2-phenylenediamine and benzoic acid to yield 2-phenylbenzimidazole.

Water is an abundant and cheap solvent, the use of which is limited by its high polarity and consequent poor solubility of organic molecules. As water approaches its critical point ( $T_c =$



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‡ Electronic supplementary information (ESI) available: analytical data for compounds **3a–f** and **5g–j**. See <http://www.rsc.org/suppdata/gc/b2/b212394k/>

## Green Context

Water is an obvious candidate as an environmentally benign replacement for VOC solvents. However the incompatibility of many organics with water restrict its use as a solvent for organic synthesis. Here we see how high temperature water can help overcome this limitation by being better able to solvate organic molecules and by enabling their reaction chemistry. Thus 2-phenylbenzimidazole, a useful compound in medicinal chemistry, can be synthesised effectively in high temperature water. Careful control of the reaction parameters enables high product yields to be obtained. The change in solvation properties of water can be further exploited by allowing the product to crystallise out from the water on cooling.

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374 °C,  $P_c = 22.1$  MPa,  $\rho_c = 0.317$  g cm<sup>-3</sup>), the physical and chemical properties of the fluid change.<sup>10</sup> As the temperature is increased, at a fixed pressure of 20.0 MPa, the dielectric constant ( $\epsilon$ ) decreases from 80 (25 °C) to 36 (200 °C), 21 (300 °C), 14 (350 °C) and 2 (400 °C).<sup>11</sup> These dielectric constants are comparable to those for methanol (33), ethanol (24), acetone (14), and hexane (2) at ambient temperature and pressure.<sup>12</sup> A further change occurs as a result of the breakdown in hydrogen bonding as the temperature is increased; the ionic product ( $K_w$ ) increases with increased local concentration of H<sub>3</sub>O<sup>+</sup> and OH<sup>-</sup> ions, which reaches a maximum at around 250 °C and 25 MPa and then decreases sharply at the critical temperature.<sup>13</sup> This property has allowed acid- and base-catalysed reactions to be performed at this near-critical temperature without adding an acid or base, e.g. in the acid-catalysed Beckmann and pinacol rearrangements<sup>14</sup> and dehydration of alcohols<sup>15,16</sup> and in the base-catalysed aldehyde disproportionation<sup>17</sup> and ester hydrolysis.<sup>18</sup>

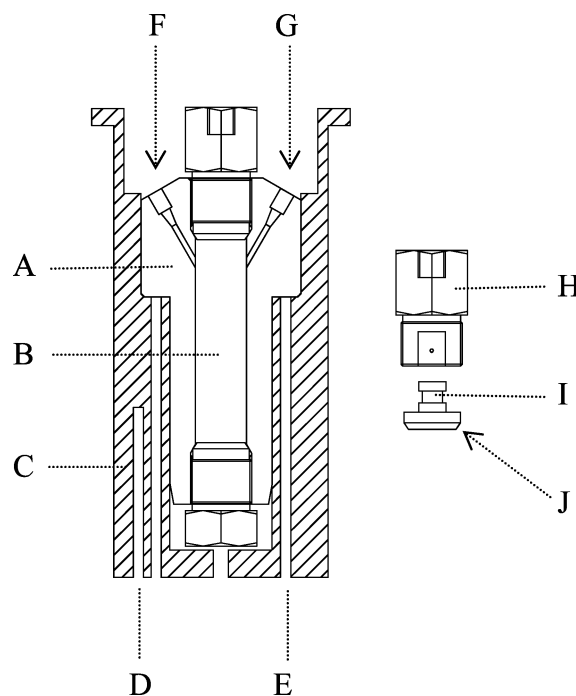
The majority of constructive organic chemistry in hot water has been conducted at near-critical temperatures<sup>19</sup> where the ionic product is favourable, the dielectric constant comparable to organic solvents and the rate of decomposition of organic molecules less than at even harsher conditions. Our group has reported the hydrolysis of esters,<sup>20</sup> the reduction of nitroarenes<sup>21</sup> and subsequent cyclisation to quinolines,<sup>22</sup> the partial oxidation of *p*-xylene to terephthalic acid<sup>23</sup> and the use of water as a reactant in hydrogen exchange reactions.<sup>24</sup>

## Experimental

**Safety warning:** these reactions involve high pressures and must only be carried out in an apparatus with the appropriate pressure rating at the reaction temperature. A trip switch must be used to stop the heating when the pressure nears the limit of the reaction vessel. The maximum amount of water which could be safely loaded without over pressure was calculated from steam tables.<sup>25</sup> A drawing and description of the mini autoclave, which was built in Nottingham, is given in Fig. 1. The vessel was leak tested using CO<sub>2</sub> and hydrostatically tested before commissioning. All chemicals were used as received (Aldrich) and water used was HPLC grade triply distilled (BDH). Water (typically 5.4 mL) and a 1 : 2 molar ratio of 1,2-phenylenediamine (typically 0.20 g, 1.8 mmol) and benzoic acid (typically 0.44 g, 3.6 mmol) were charged to the 10 mL high-pressure mini autoclave. The water density was defined as the mass of water (g) in the vessel (cm<sup>3</sup>) to  $\pm 0.01$  g cm<sup>-3</sup>. The concentration of 1,2-phenylenediamine in water was constant to within experimental error ( $\pm 0.03$  M). Reaction times did not include the time taken to heat the contents. When the vessel had been cooled, the shut-off valve was opened to allow excess pressure to be released. The vessel was opened and the contents, including the water, were dissolved in methanol and transferred to a 50 mL volumetric flask and analysed by HPLC.<sup>26</sup>

## Results and discussion

A systematic study of the reaction parameters in the synthesis of 2-phenylbenzimidazole (**3f**) was conducted in order to tune the solvent properties of water and optimise the yield. Such a study should provide some understanding of the rôle of water as solvent and possible catalyst. Obviously such a route would be impracticable if the product were unstable under the reaction conditions. Therefore, a commercial sample of **3f** was heated in H<sub>2</sub>O for 4 hours at 350 °C in the mini autoclave. The HPLC analysis showed that **3f** was highly stable; 99% of the initial sample was recovered. Regarding the stability of the reactants, **1** gave 70% recovery while only 10% of **2f** was recovered.<sup>27</sup>



**Fig. 1** Drawing of the 10 mL high-pressure mini autoclave (316 SS) in an aluminium holder, showing detail of cap and sealing face. (A) stainless steel autoclave; (B) autoclave cavity of 10 mL volume; (C) aluminium holder surrounded by heating jacket or cooling pipe; (D) well for thermocouple controlling heating jacket; (E) vents to release air during heat-up; (F) high-pressure fitting for tubing to pressure transducer and shut-off valve; (G) high-pressure fitting for securing thermocouple into autoclave cavity; (H) top cap with screw-thread for tool to transfer from hot to cold holder; (I) rotating insert held into top cap by screw; (J) sealing face of cap. The maximum pressure rating is 60 MPa at 400 °C. The autoclave is closed with caps at both ends (sealed to a torque of 50 Nm). 1/16 inch tubing (Swagelok, maximum pressure rating 67 MPa) is held in place by SSI fittings in the top of the autoclave and links a pressure transducer (RDP Electronics, maximum pressure rating 68 MPa) and shut-off valve (HIP) in series. A chromal/alumel thermocouple is positioned at the centre of the autoclave and sealed in place using SSI fittings. The apparatus consisted of two similar aluminium holders for the autoclave, one surrounded by a heating jacket (850 W, Watlow) and the other surrounded by a copper tubing coil for cooling water. Heat up time is between 5 and 10 min and cooling down takes 15 min, though the temperature is halved in the first two minutes.

Thus, for the reaction to be successful, the rate of formation of product must be faster than the rate of decomposition of the reagents.

A set of experiments was performed to assess the effect of temperature over the range 100 to 400 °C. The yields were calculated from HPLC analysis by comparison with standards of commercially available **3f**.<sup>26</sup> As it is shown in Table 1, the

**Table 1** Yield of **3f** at different temperatures and pressures

| Entry          | Time/h | Temp/°C          | Pressure/MPa | Yield (%) <sup>a</sup> |
|----------------|--------|------------------|--------------|------------------------|
| 1              | 2      | 100 <sup>b</sup> | 0.1          | 0                      |
| 2              | 2      | 200              | 1.7          | 18                     |
| 3              | 2      | 250              | 4.5          | 28                     |
| 4              | 2      | 300              | 8.5          | 43                     |
| 5 <sup>c</sup> | 2      | 350              | 17.8         | 71                     |
| 6              | 4      | 350              | 21.7         | 89                     |
| 7              | 14     | 350              | 20.9         | 91                     |
| 8              | 2      | 400              | 57.4         | 74                     |

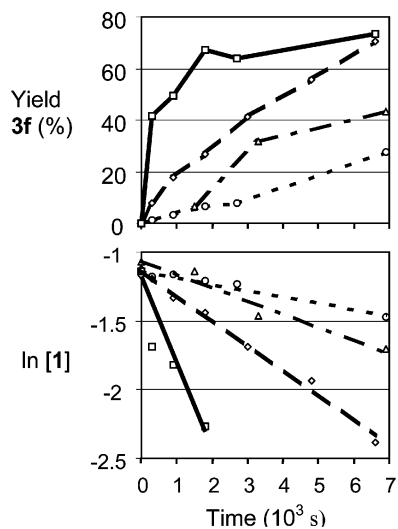
<sup>a</sup> Yield based on HPLC analysis. <sup>b</sup> Reaction was carried out in a round-bottomed flask with reflux condenser. <sup>c</sup> The experiment was repeated to assess the reproducibility of the reaction. The yield was reproducible to  $\pm 1\%$  and the pressure was accurate to  $\pm 0.6\%$ . Reaction conditions: concentration =  $0.3 \pm 0.03$  M; water density =  $0.54 \pm 0.01$  g cm<sup>-3</sup>.

yield increased with increasing temperature from 0% at 100 °C (entry 1) to 71% at 350 °C (entry 5). The highest yield of 89%

was seen at 350 °C after 4 hours and remained constant after 14 hours (Entries 6 and 7 respectively). A further increase in temperature did not lead to any significant improvement in yield *e.g.* 74% at 400 °C (entry 8). The pressure observed in the vessel was almost identical to the vapour pressure of pure water at the same temperature, and increased greatly around the critical temperature as the liquid water was compressed in the vessel. Using the temperature and pressure measured in our reactions, the dielectric constant of water can be estimated to be 35 (200 °C), 27 (250 °C), 20 (300 °C), 14 (350 °C) and 13 (400 °C).<sup>11</sup> The water becomes less polar with increasing temperature, becoming comparable to room temperature dichloromethane.<sup>12</sup> The high pressure observed for the reaction at 400 °C gives rise to high densities, thus the dielectric constants of the water at 350 and 400 °C are similar; this may be an explanation for the similar yields recorded at the two temperatures.

As stated above, high-temperature water can act as both an acid and base catalyst due to the increased ionic product from around  $-14$  to  $-11$  ( $\log K_w$ ) at 25 and 300 °C, respectively (at 400 °C,  $\log K_w$  is around  $-20$ ).<sup>13</sup> A one-fold molar excess of **2f** was used in all experiments. The dissociation constant of **2f** decreases at high temperatures from around  $-4$  to  $-7$  ( $\log K$ ) at 25 and 400 °C, respectively,<sup>28</sup> in a similar way to  $\beta$ -naphthoic acid.<sup>29</sup>

The effect of the temperature on the initial rate of the reaction was also investigated (Fig. 2). The concentration profiles can be

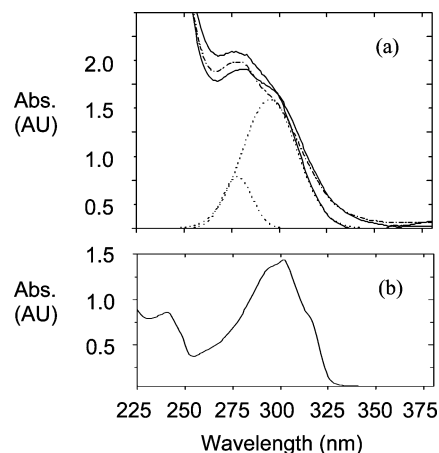


**Fig. 2** Plots of the yield of **3f** (upper) and logarithm of concentration of **1** (lower) against reaction time for temperatures of 250 (dotted line), 300 (dot-dash line), 350 (dashed line) and 400 °C (solid line). Pressures obtained were approximately 4 MPa (250 °C), 9 MPa (300 °C), 17 MPa (350 °C) and from 34 to 57 MPa (400 °C).

approximated, within experimental error, to pseudo-first-order reaction kinetics with reference to 1,2-phenylenediamine (**1**). The reaction rates were strongly influenced by temperature, showing a two-fold increase between 250 and 300 °C and a four-fold increase between 250 and 350 °C. The most dramatic change occurred under supercritical conditions, at 400 °C, where the increase was 12-fold. At 400 °C, the yield increased sharply with reaction time and reached 67% after 1800 s and a further increase in time did not lead to a substantial improvement in yield, *e.g.* 74% after 6600 s. Therefore, the initial rate for the reaction at 400 °C was calculated using data from the first 1800 s of the reaction, while the rates for the lower temperatures were calculated from the first 6900 s of the reaction. The limiting factor in the reaction at 400 °C was likely to be the decomposition of reactants. Indeed the pressure was seen to increase over the 2 hour reaction time, which may have been due to such decomposition. At 400 °C, a small residual pressure of 0.4 MPa was seen on cooling the vessel and the gas

was analysed by GC and found to contain 3.5% carbon monoxide in air for the reaction after 2700 s at 50 MPa. It is likely that carbon dioxide evolved reacts with the  $H_2O$  to form carbonic acid, which may play a part in catalysing the reaction.

This rate effect is also reflected in the *in situ* UV-vis spectra of the reactions at 350 °C, see Fig. 3. The band at around 300 nm



**Fig. 3** (a) UV-vis spectrum of reaction forming **3f** recorded after 120 s (top solid line), 1200 s (dot-dash line) and 8880 s (bottom solid line). The deconvolution procedure was applied to the spectrum at 8880 s; the contour was approximated to the sum of  $n$  Gaussian peaks, where  $n$  is the number of inflection points. The experimental conditions were 350 °C, 25.0 MPa,  $0.534 \times 10^{-3}$  M of **1** and  $1.064 \times 10^{-3}$  M of **2f**. (b) Absorption spectrum of a pure sample of **3f**.

corresponds to **3f**. Clearly, the band at 280 nm decreased with time while the band at 300 nm increased with time. By contrast, the spectrum recorded at 300 °C showed no band at 300 nm being formed over a similar period of time. The concentration of reactants was necessarily very low because of the low solubility of the reactants at lower temperatures and this is the likely explanation for the reaction rate, which is slow compared to the batch experiments. The experiments were carried out in a stopped flow mode in a new high-pressure, high-temperature UV-vis cell.<sup>30</sup>

**Table 2** Yield of **3f** at different solution concentrations

| Entry | Concentration/M <sup>a</sup> | Pressure/MPa   | Yield (%) <sup>b</sup> |
|-------|------------------------------|----------------|------------------------|
| 1     | 0.003                        | — <sup>c</sup> | 4                      |
| 2     | 0.030                        | 14.0           | 5                      |
| 3     | 0.096                        | 15.3           | 19                     |
| 4     | 0.158                        | 15.1           | 35                     |
| 5     | 0.312                        | 17.8           | 71                     |
| 6     | 0.766                        | 16.4           | 82                     |

<sup>a</sup> Concentration of **1**  $\pm 0.009$  M. <sup>b</sup> Yield based on HPLC analysis. <sup>c</sup> Pressure not recorded. *Reaction conditions:* temperature = 350 °C; reaction time = 2 h (chosen as the yield at 4 h had already been found around 89%, hence a change in yield should be more pronounced at 2 h); water density =  $0.60 - 0.47 \pm 0.01$  g cm<sup>-3</sup>.

Table 2 summarizes the effect of the concentration of **1** on the yield of **3f**. The yield increased linearly with concentration from 0.003 to 0.31 M (4–71% yield). Further increase in the concentration did not lead to a significant increase in the yield (0.77 M, 82% yield). These concentrations were equivalent to 0.1 to 27% weight/volume of reactants in the vessel. This increase is consistent with a bimolecular reaction.

Under supercritical conditions, increased density has been shown to increase the product yields of cyclohexanol dehydration due to the increased ionic product.<sup>16</sup> The reaction mechanism to form **3f** is also an acid catalysed dehydration so

the effect of density was investigated at 410 °C, well above the critical point of water. However, we did not find a strong variation in yield (45–67%) over a five-fold increase in density (Table 3). The increase is likely to be due to the presence of

**Table 3** Yield of **3f** at different water densities

| Entry | Water density/ $\pm 0.01$<br>g cm <sup>-3</sup> | Pressure/MPa | Yield (%) <sup>a</sup> |
|-------|---|--------------|------------------------|
| 1     | 0.09  | 20.9         | 45                     |
| 2     | 0.18  | 29.3         | 55                     |
| 3     | 0.36  | 30.5         | 56                     |
| 4     | 0.54  | 45.1         | 67                     |

<sup>a</sup> Yield based on HPLC analysis. *Reaction conditions:* temperature = 410 °C; reaction time = 4 h; concentration =  $0.3 \pm 0.03$  M.

more H<sub>2</sub>O, which can dissociate to form H<sub>3</sub>O<sup>+</sup> ions and catalyse the reaction.

The effect of different solvents at near and supercritical conditions (Table 4) was studied to establish whether water with

**Table 4** Yield of **3f** in different solvents

| Entry          | Solvent                            | Pressure/MPa | Yield (%) <sup>a</sup> |
|----------------|------------------------------------|--------------|------------------------|
| 1              | Ethanol                            | 8.9          | 4                      |
| 2              | Acetone                            | 8.0          | 8                      |
| 3              | Hexane                             | 5.7          | 42                     |
| 4              | <i>p</i> -Xylene and water (1 : 1) | 15.0         | 45                     |
| 5              | <i>i</i> -Propanol                 | 10.7         | 64                     |
| 6              | Water                              | 16.6         | 69                     |
| 7              | <i>p</i> -Xylene                   | 8.1          | 79                     |
| 8 <sup>b</sup> | Water                              | 16.4         | 82                     |

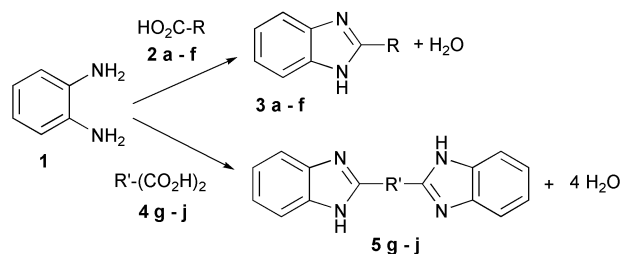
<sup>a</sup> Yield based on HPLC analysis. <sup>b</sup> Reaction time = 4 h. *Reaction conditions:* temperature = 350 °C; reaction time = 2 h; concentration =  $0.3 \pm 0.03$  M; water density =  $0.18 \pm 0.01$  g cm<sup>-3</sup> (pressure generated by larger volumes of some organic solvents under these conditions exceeds the maximum pressure rating of our vessel).

its favourable solvent properties (*e.g.* dielectric constant and ionic product) was playing a key role in the reaction or if the success of the reaction was largely due to the high temperature and pressure. Ethanol ( $T_c = 241$  °C and  $P_c = 6.1$  MPa)<sup>31</sup> and *i*-propanol ( $T_c = 235$  °C and  $P_c = 4.8$  MPa)<sup>12</sup> were chosen because they are polar, protic solvents; ethanol becomes nearly non-polar as its critical temperature is approached.<sup>31</sup> Acetone ( $T_c = 236$  °C and  $P_c = 4.8$  MPa) was chosen as a polar, aprotic solvent. By contrast, *n*-hexane ( $T_c = 234$  °C and  $P_c = 3.0$  MPa), and *p*-xylene ( $T_c = 345$  °C and  $P_c = 3.4$  MPa)<sup>12</sup> are non-polar solvents. In the event, ethanol (entry 1) appeared to react with the benzoic acid to form ethylbenzoate, and the only solvent where the yield was higher than in water was *p*-xylene (entry 7; *i.e.* 79%, 10% higher than that for H<sub>2</sub>O). Combining *p*-xylene and water in a 1 : 1 ratio might be expected to give an intermediate result or even have a synergic effect. However, the mixed solvents gave a lower yield (entry 4) than for water alone (entry 6), possibly due to poor mixing in the vessel. For comparison, *p*-xylene was then used as the solvent for the reaction in a conventional reflux apparatus at 230 °C; even after 4 hours, the yield was only 3%. Although *p*-xylene is a more effective solvent than H<sub>2</sub>O at high pressure and/or high temperature, it is obviously environmentally less benign. This result is surprising and warrants further study. Perhaps **2f** acts differently in water and *p*-xylene. When the reaction in H<sub>2</sub>O was repeated with double the reaction time (entry 8), the yield exceeded that for *p*-xylene suggesting that although the reaction in H<sub>2</sub>O is slower than in *p*-xylene, H<sub>2</sub>O works quite as well as environmentally less acceptable solvents.

The yields for H<sub>2</sub>O and *i*-propanol were better than for acetone and hexane; possibly the acidity of the dissociated

solvent enhances the yield. A solid acid was added to the water to study the effect of acid on the reaction. We used 5% of the solid Brønsted acid catalyst, Deloxan<sup>®</sup> ASP II, a macroporous polysiloxane with alkylsulfonic acid groups, which has previously been used for reactions in supercritical water.<sup>24</sup> The conditions were identical to those given in Table 4. The yield was 70% as compared to 68% in water without catalyst. Therefore, additional acid is not catalysing the reaction significantly under these conditions.

Various substituted benzimidazole and bisbenzimidazole compounds were prepared (Scheme 2) to demonstrate that our



a. R = H b. R = CH<sub>3</sub> c. R = CH(CH<sub>3</sub>)<sub>2</sub> d. R = C(CH<sub>3</sub>)<sub>3</sub> e. R = C<sub>6</sub>H<sub>5</sub>  
f. R = C<sub>6</sub>H<sub>5</sub> g. R' = - h. R' = (CH<sub>2</sub>)<sub>2</sub> i. R' = *p*-C<sub>6</sub>H<sub>4</sub> j. R' = *o*-C<sub>6</sub>H<sub>4</sub>

**Scheme 2** Synthesis of substituted benzimidazoles and bisbenzimidazoles.

method is not unique to the preparation of 2-phenylbenzimidazole. For compounds **3a–f**, the reaction conditions were those optimised in the study above except for **3a**, where the temperature was lowered to 210 °C because formic acid decomposed at higher temperatures.<sup>32</sup> The products were washed from the vessel with methanol; the methanol and water were then removed under vacuum and the product recrystallised and analysed by NMR (see ESI<sup>†</sup>). Table 5 (entries 1–6) shows

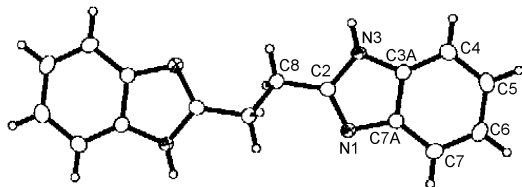
**Table 5** Results of substituted benzimidazoles and bisbenzimidazoles

| Entry           | Product number | Yield (%) <sup>a</sup> |
|-----------------|----------------|------------------------|
| 1 <sup>b</sup>  | <b>3a</b>      | 79                     |
| 2 <sup>c</sup>  | <b>3b</b>      | 42                     |
| 3 <sup>c</sup>  | <b>3c</b>      | 72                     |
| 4 <sup>c</sup>  | <b>3d</b>      | 31                     |
| 5 <sup>c</sup>  | <b>3e</b>      | 92                     |
| 6 <sup>c</sup>  | <b>3f</b>      | 90                     |
| 7 <sup>d</sup>  | <b>5g</b>      | 30                     |
| 8 <sup>e</sup>  | <b>5h</b>      | 68                     |
| 9 <sup>e</sup>  | <b>5i</b>      | 70                     |
| 10 <sup>e</sup> | <b>5j</b>      | 62                     |

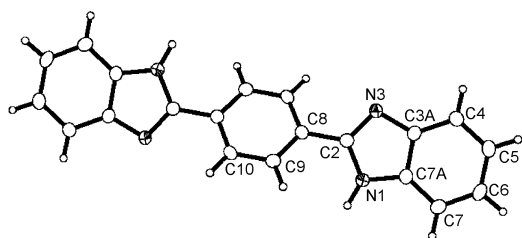
<sup>a</sup> Yields obtained gravimetrically. <sup>b</sup> *Reaction conditions:* temperature = 210 °C; reaction time = 4 h; concentration =  $0.3 \pm 0.03$  M; water density =  $0.54 \pm 0.01$  g cm<sup>-3</sup>. <sup>c</sup> Reaction temperature = 350 °C. <sup>d</sup> Temperature = 300 °C; reaction time = 1 h; concentration  $0.4 \pm 0.03$  M. <sup>e</sup> Temperature = 350 °C; reaction time = 2 h; concentration =  $0.8 \pm 0.03$  M.

that good yields were obtained without further optimisation for a wide range of acids.

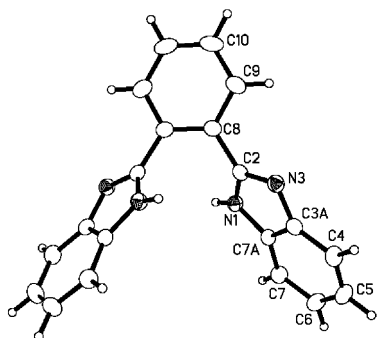
In addition, various bisbenzimidazoles (Scheme 2) were prepared from diacids in a 2 : 1 molar ratio of 1,2-phenylenediamine to diacid (Table 5, entries 7–10). When the autoclave was allowed to cool slowly, crystals were formed which were used directly for single crystal X-ray diffraction studies<sup>33</sup> without any further purification. The unit cell parameters were determined for a single crystal of **5g** and matched those published.<sup>34</sup> The structure of **5h** obtained from collected diffraction data<sup>35</sup> is shown in Fig. 4. The unit cell<sup>36</sup> of **5i** (Fig. 5) is different from the previously published structure.<sup>37</sup> The structure reported here for **5j**<sup>38</sup> (Fig. 6) crystallises in a different form to that previously reported,<sup>37</sup> although the overall structure is very similar. Interestingly the previous sample was



**Fig. 4** Crystal structure of product **5h**, 2,2'-(1,2-ethanediy)bis-1H-benzimidazole. **5h** crystallises around an inversion centre such that the asymmetric unit contains half the molecule with the other half inversion related. The two benzimidazole rings are coplanar and lie at an angle of  $\sim 133^\circ$  to the central C–C bond.



**Fig. 5** Crystal structure of product **5i**, 2,2'-(1,4-phenylene)bis-1H-benzimidazole. **5i** also crystallises around an inversion centre, again with half the molecule in the asymmetric unit. The benzimidazole rings are planar, (mean deviation from planarity 0.033 Å), and lie at an angle of  $\sim 32^\circ$  to the central phenyl ring. In both structures the molecules are linked by NH $\cdots$ N hydrogen bonds to form layers approximately perpendicular to the *a*-axis.



**Fig. 6** Crystal structure of product **5j**, 2,2'-(1,2-phenylene)bis-1H-benzimidazole. **5j** crystallises with half the molecule in the asymmetric unit with the other half generated by a two-fold rotation. The angle between the benzimidazole rings and the central phenyl ring is  $49^\circ$  and in this case the two benzimidazole rings are not coplanar but lie at an angle of  $67.2^\circ$  to one another. The hydrogen bonding arrangement also differs for this compound with the NH $\cdots$ N hydrogen bonds forming a chain in the [001] direction.

red in colour whereas this current form is colourless. See ESI† for full details.

The yields for the above benzimidazoles are often comparable with those obtained using conventional synthetic methods, although in these forcing conditions, some functional groups are more susceptible to decomposition. Therefore less forcing conditions would be needed to optimise the yields.

## Conclusions

This example of green chemistry includes replacement of volatile organic solvents with water and the elimination of acidic media and subsequent neutralisation. Some of the compounds have crystallised *in situ*, when the solvating power of water for organic compounds was lost on cooling, thereby eliminating the need to purify with environmentally less benign

solvents. By varying the reaction parameters, such as temperature, reaction time and concentration, the yield of the desired benzimidazole compound has been successfully optimised. If we are to convince chemists to embrace new solvents, it is vital that we show how we can control the chemistry reproducibly. This work has begun to address this challenge.

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- HPLC was used to determine the concentration of the 1,2-phenylenediamine, benzoic acid and 2-phenylbenzimidazole in the solution by comparison with calibrated standards of these compounds in CH<sub>3</sub>OH. A gradient elution with solvents CH<sub>3</sub>CN (16.7%) and buffer (83.3% to 60% and back to 83.3%) was used. The stock buffer solution was prepared by dissolving 15 g anhydrous CH<sub>3</sub>CO<sub>2</sub>Na in

- 250 mL deionised water, before adding CH<sub>3</sub>CO<sub>2</sub>H (50%, 100 mL). The pH was adjusted to 3.9 ± 0.01 with 5% CH<sub>3</sub>CO<sub>2</sub>H, before diluting to 500 mL. The dilute buffer was prepared by diluting 30 mL of the stock buffer solution to 500 mL with deionised water. The injection volume with needle wash was 1 µL. A Waters Xterra reverse phase C18 column, maintained at 40 °C was used (flow rate 0.7 mL min<sup>-1</sup>, run time 14 min; UV detection at 254 nm). The retention times were 1.8 min (1,2-phenylenediamine), 4.5 min (benzoic acid) and 6.9 min (2-phenylbenzimidazole).
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  - 36 A colourless, tablet crystal, 0.52 × 0.24 × 0.10 mm was mounted in perfluoropolyether oil. C<sub>20</sub>H<sub>14</sub>N<sub>4</sub>,  $M = 310.35$ , monoclinic,  $a = 7.5866(11)$ ,  $b = 10.366(2)$ ,  $c = 9.728(2)$  Å,  $\beta = 107.895(2)^\circ$ ,  $U = 728.0(3)$  Å<sup>3</sup>,  $T = 150$  K, space group *P2<sub>1</sub>/c* (no. 14),  $Z = 2$ ,  $\mu(\text{Mo-K}\alpha) = 0.09$  mm<sup>-1</sup>, 5627 reflections measured, 1738 unique ( $R_{\text{int}} = 0.0407$ ). The final  $wR(F^2)$  was 0.0977 for 1642 data,  $R_1(F)$  was 0.0419 for 1194 observed data where  $I > 2\sigma(I)$ . NH was refined freely. CCDC reference number 200135.
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