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ORIGINAL PAPER

Chemoselective synthesis of 1,2-disubstituted benzimidazoles in lactic acid without additive

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Lactic acid is recognised as a biocompatible medium for the chemoselective synthesis of the 1,2-disubstituted benzimidazole scaffold via a direct one-pot cyclocondensation of *o*-phenylenediamine with aldehydes. Various 1,2-disubstituted benzimidazole derivatives were successfully synthesised with high selectivity with good to excellent yields without any additional catalyst or additive. Most products could be isolated by a simple filtration after completion of the reactions. Satisfactory results were also obtained from multi-gram scale reactions.
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Keywords: chemoselective, 1,2-disubstituted benzimidazoles, lactic acid, green synthesis

Introduction

Benzimidazoles are regarded as favoured structures in the area of medicinal chemistry (Kallashi et al., 2011). 1,2-Disubstituted benzimidazoles and their derivatives as an important branch of this family exhibit valuable pharmacological activities, such as antitumour (Boiani & González, 2005), antiviral (Miller et al., 2010) and antifungal (Chen et al., 2009) applications. In addition, 1,2-disubstituted benzimidazoles are of special interest for their application in polymers and catalysis (Plater et al., 2009; Harkal et al., 2004; Georgiou et al., 2009). These special uses of 1,2-disubstituted benzimidazoles highlight the importance attached to their synthesis (Carvalho et al., 2011).

Substantial effort has been invested in the construction of this scaffold, such as cyclocondensation procedures (Özden et al., 2005; Vourloumis et al., 2003), alkylation or arylation procedures (Porcari et al., 1998; Ezquerra et al., 1997; Zheng & Buchwald, 2007), intramolecular cyclisation procedures (Brain & Steer, 2003; Zhu et al., 2009; Shenvi et al., 2009). In addition, the novel "all water" strategy for the synthesis of 1,2-disubstituted benzimidazoles was devised by Chakraborti (Kommi et al., 2012, 2013).

However, the cyclocondensation of *o*-phenylenediamine with aldehydes encounters a selectivity problem due to the competitive formation of the 1,2-disubstituted, the 2-substituted benzimidazoles and the Schiff base compounds (Fig. 1). Several methods have been reported for the selective synthesis of 1,2-disubstituted benzimidazoles using FeF_3 (Kumar et al., 2012), Me_3SiCl (Wan et al., 2009), ZnO-NPs (Sharma et al., 2015), $HClO_4$–SiO_2 (Kumar et al., 2013) as catalyst or microwave irradiation in acetic acid (Azarifar, 2010), ultrasonic irradiation (Kumar et al., 2014). In addition, Chebolu et al. (2012) reported a metal/Lewis acid-free protocol in which fluorous alcohols with better hydrogen bond donor (HBD) abilities could efficiently promote the selective formation of 1,2-disubstituted benzimidazoles.

The present study reports a "green" and efficient procedure for the synthesis of 1,2-disubstituted benzimidazoles in lactic acid as a biocompatible solvent at ambient temperature and with an easy set-up via a direct one-pot cyclocondensation of *o*-phenylenediamine with aldehydes. In addition, most of the products could be obtained by simply adding water and recrystallisation after completion of the reactions.

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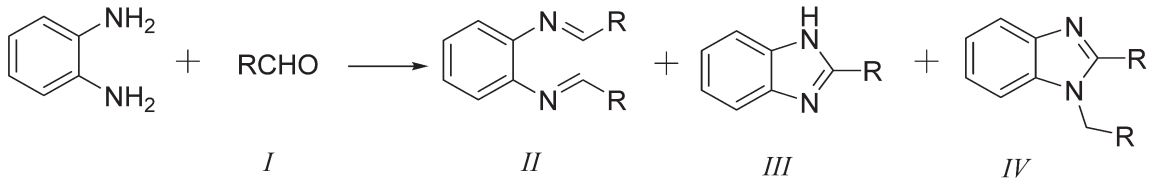

I *II* *III* *IV*

Fig. 1. Cyclocondensation of *o*-phenylenediamine with aldehydes.

Table 1. Formation of *IVa* via condensation of o-phenylenediamine with benzaldehyde[a]

Entry	solvent	T (℃)	t (h)	Yield of *IVa*[b] (%)
1[d]	ethyl lactate	80	12	35
2	lactic acid	80	12	85
3[d]	ethanol	80	12	15
4[d]	furfuryl alcohol	80	12	25
5	lactic acid	60	12	86
6	lactic acid	40	12	84
7	lactic acid	rt	12	83
8	lactic acid	rt	10	84
9	lactic acid	rt	8	82
10	lactic acid	rt	6	85
11	lactic acid	rt	4	84
12	lactic acid	rt	2	70
13[c]	lactic acid	rt	4	95

a) Reaction conditions: *Ia* (1 mmol), *o*-phenylenediamine (1 mmol) in solvent (2 mL); *b*) yield of isolated product in relation to *Ia*; *c*) *Ia* (2 mmol), *o*-phenylenediamine (1 mmol); *d*) determined by GC; rt – ambient temperature.

Experimental

Lactic acid (AR, 85–90 % aqueous solution) and ethyl lactate (purity ≥ 99 %) were purchased from Aladdin (Shanghai, China). Other reagents such as aldehydes, *o*-phenylenediamine and solvents were of analytical grade and used without further purification. Thin-layer chromatography (TLC) was used to monitor the reaction progress. Melting points were recorded in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a BRUKER AVANCE (Germany) 400 MHz spectrophotometer using $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane (TMS) as the internal standard. Mass spectra analysis was performed using GC–MS (Trace1300/ISQ, Thermo Fisher Scientific, USA) analyser and high resolution mass spectrometry (HRMS) spectra analysis was performed by electrospray ionisation (ESI-micro TOF).

Aldehydes (2 mmol), *o*-phenylenediamine (1 mmol) were dissolved in lactic acid (2 mL). The mixture was stirred at ambient temperature for 4–6 h (TLC). After complete consumption of the aldehydes, 15 mL of water was added to the reaction mixture and the solution phase was filtered. The pure products were recrystallised from ethanol.

Results and discussion

At the outset, 2-substituted benzothiazoles could be obtained in ethyl lactate via the aerobic condensation of aminothiophenol with aldehydes (Yu et al., 2015). This result prompted investigation of the construction of 2-substituted benzimidazoles under the same conditions. Accordingly, *o*-phenylenediamine was treated with an equivalent of benzaldehyde (*Ia*) in ethyl lactate at 80 ℃ overnight. However, the yield of 2-phenyl benzimidazole was not good under these conditions, and 1,2-disubstituted benzimidazole (*IVa*) was obtained with a 35 % yield (in relation to *Ia*). In order to increase the yield of 2-phenyl benzimidazole, *o*-phenylenediamine was treated with *Ia* in different protic solvents by using a 1 : 1 mole ratio (Table 1, entries 1–4).

The unexpected results showed that the use of equimolar amounts of *o*-phenylenediamine and benzaldehyde afforded *IVa* as the major product in lactic acid. Hence, the reaction of *o*-phenylenediamine with *Ia* at 1 : 1 mole ratio was adopted as the model reaction. The effects of reaction temperature, time and mole ratio of raw materials were assessed (Table 1, entries 5–13). The results showed that the reaction at ambient temperature gave a similarly high yield of *IVa* as in the elevated temperature. Subsequent examination of the reaction time showed that there was almost no change in the yield of *IV*, even though the reaction time was shortened from 12 h to 4 h (Table 1, entries 7–12), but a reaction time of 2 h was not sufficient for complete conversion as detected by TLC analysis. Hence, the reaction time was selected as 4 h. Finally, the yield of *IVa* was further increased to 95 % with

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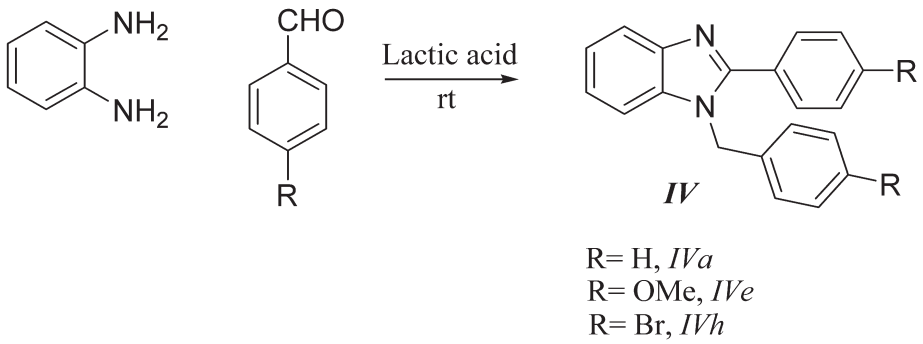

Fig. 2. Multi-gram scale synthesis of 1,2-disubstituted benzimidazoles; conditions: *p*-substituted benzaldehydes (50 mmol), yield for *IVa* (5.8 g, 82 %); *IVe* (7.6 g, 88 %); *IVh* (8.8 g, 80 %).

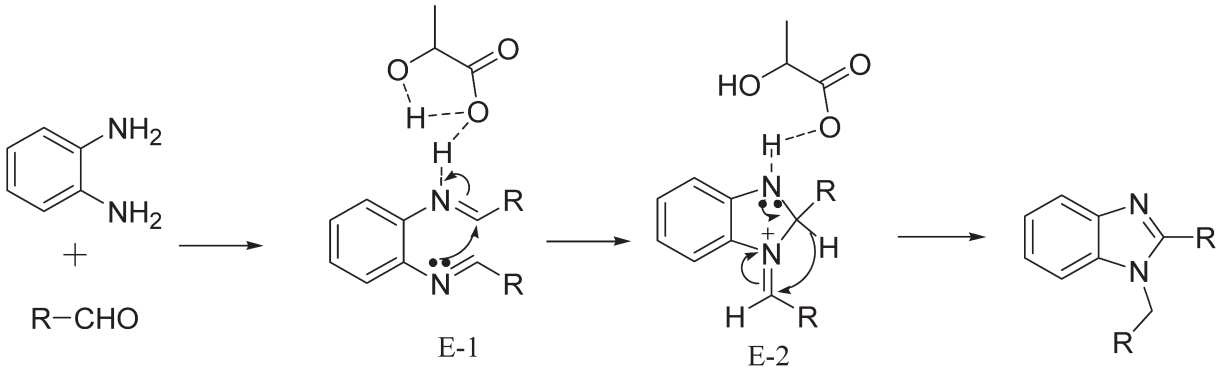

Fig. 3. Plausible mechanism for formation of 1,2-substituted benzimidazole derivatives in lactic acid.

Table 2. Comparison of Brønsted acids with lactic acid in synthesis of 1,2-disubstituted benzimidazoles[a]

Entry	Solvent	*t* (h)	Yield of *IVa*[b] (%)
1	HOAc	4	84
2[c]	oxalic acid	6	68
3[c]	H_2SO_4	6	58
4[c]	glyoxalic acid	4	73
5	lactic acid	4	95

a) Reaction conditions: *Ia* (2 mmol), *o*-phenylenediamine (1 mmol, phenylenediamine is the limiting reagent) in solvent (2 mL) at ambient temperature; *b*) isolated yield; *c*) 30 % aqueous solution.

the 2 : 1 mole ratio of *Ia* to *o*-phenylenediamine.

These results indicated lactic acid to have the ability to drive increase selectivity towards the formation of *IVa*. According to a report in the literature (Chebolu et al., 2012), the better hydrogen bond donor (HBD) abilities of the solvent exhibit better selectivity. In this case, lactic acid may also act as a hydrogen-bond-driven electrophilic activator for the selective formation of 1,2-disubstituted benzimidazoles. This may be attributed to the formation of intramolecular hydrogen bond in lactic acid increasing the HBD ability (Fig. 3). In addition, the performance of lactic acid was compared with the results of other Brønsted acids (Table 2). The superiority of lactic acid was clearly established not only in its good selectivity of 1,2-disubstituted benzimidazoles but also in the "green" and sustainable chemistry.

Subsequently, the general applicability of selective 1,2-disubstituted benzimidazoles was also explored. The reaction of *o*-phenylenediamine with various aromatic aldehydes was further examined (Table 3). It was observed that all aromatic aldehydes and the aliphatic aldehyde (i.e. *n*-butyl aldehyde) could be successfully converted to the corresponding 1,2-disubstituted benzimidazoles and these products could be readily obtained with good to excellent yields by crystallisation. The structures of all products were confirmed by ^{1}H NMR and mass spectrometry and by comparing the melting points with results in the literature (Table 4).

In view of the simplicity of this synthetic method, scale-up experiments were subsequently performed so as to confirm the applicability of this protocol. Accordingly, the direct one-pot cyclocondensation of *o*-phenylenediamine and aldehydes with an electron-withdrawing or electron-donating group was performed on a multi-gram scale (Fig. 2). The satisfactory results from these scale-up experiments further confirmed the advantage of this simple and "green" protocol for its potential in large-scale synthesis.

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Table 3. Lactic acid-promoted 1,2-disubstituted benzimidazoles formation[a]

Entry	R	Product	Yield[b] (%)	m.p. (°C)	m.p.[c] (°C)
1	Ph	*IVa*	95	136–138	130–132
2	4-HOC_6H_4	*IVb*	85	256–258	254–256
3	4-MeC_6H_4	*IVc*	90	125–127	129–130
4	2-$O_2NC_6H_4$	*IVd*	85	165–167	170–172
5	4-$MeOC_6H_4$	*IVe*	91	128–131	130–131
6	3,4-$(MeO)_2C_6H_4$	*IVf*	92	148–150	142–144
7[d]	*n*-butyl	*IVg*	86	125–127	129–130
8	4-BrC_6H_4	*IVh*	85	133–135	139–141
9	thienyl	*IVi*	93	146–148	146–147

a) General conditions: *o*-phenylenediamine (1 mmol) and *Ia* (2 mmol) in lactic acid (2 mL), stirred at ambient temperature for 4–6 h; *b*) yield of isolated product; *c*) values reported in literature (Kumar et al., 2012; Chebolu et al., 2012; Ahmadian et al., 2015); *d*) reaction at 80 °C and purified by silica gel column chromatography.

Table 4. Spectral data of compounds

Compound	Spectral data
IVa	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.90–7.92 (m, 1H), 7.70–7.71 (m, 2H), 7.46–7.50 (m, 3H), 7.31–7.35 (m, 4H), 7.22 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 5.48 (s, 2H); MS m/z $(MH)^+$ calcd.: 285.4, found: 285.1
IVb	^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.97 (s, 1H), 9.41 (s, 1H), 7.65 (d, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 1H), 7.18–7.21 (m, 2H), 6.89 (d, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 2H), 6.65 (d, J = 8 Hz, 2H), 5.42 (s, 2H); HRMS m/z $(MH)^+$ calcd.: 317.1285, found: 317.1305
IVc	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.82 (d, J = 8 Hz, 1H), 7.53–7.55 (m, 2H), 7.25–7.13 (m, 5H), 7.07–7.09 (m, 2H), 6.95–6.97 (m, 2H), 5.38 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H)
IVd	^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.14–8.16 (m, 2H), 7.95–7.98 (m, 1H), 7.86 (d, J = 8 Hz, 1H), 7.67–7.69 (m, 2H), 7.47–7.52 (m, 2H), 7.30–7.37 (m, 2H), 7.15 (d, J = 8 Hz, 1H), 6.94–6.96 (m, 1H), 5.70 (s, 2H); HRMS m/z $(MH)^+$ calcd.: 375.1088, found: 375.1099
IVe	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.96–7.98 (m, 1H), 7.80–7.83 (m, 3H), 7.69 (d, J = 8 Hz, 2H), 7.38–7.43 (m, 3H), 7.20–7.23 (m, 3H), 5.55 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H); HRMS m/z $(MH)^+$ calcd.: 345.1598, found: 345.1576
IVf	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.88 (d, J = 8 Hz, 1H), 7.51–7.57 (m, 1H), 7.27−7.31 (m, 2H), 7.22–7.24 (m, 1H), 7.11–7.13 (m, 1H), 6.92 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 6.66 (m, 1H), 6.64 (d, J = 8 Hz, 1H), 5.41 (s, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H); HRMS m/z $(MH)^+$ calcd.: 405.1809, found: 405.1813
IVg	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.71–7.73 (m, 1H), 7.27–7.30 (m, 1H), 7.20–7.23 (m, 2H), 4.07 (t, J = 8 Hz, 2H), 2.82 (t, J = 8 Hz, 2H), 1.90–1.96 (m, 2H), 1.74–1.78 (m, 2H), 1.37–1.41 (m, 2H), 1.07 (t, J = 8 Hz, 3H) 0.96 (t, J = 8 Hz, 3H); HRMS m/z $(MH)^+$ calcd.: 216.1626, found: 216.1623
IVh	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.82–7.83 (m, 1H), 7.54–7.56 (m, 2H), 7.48–7.50 (m, 2H), 7.41–7.43 (m, 2H), 7.25–7.28 (m, 2H), 7.15–7.17 (m, 1H), 6.93–6.96 (m, 2H), 5.42 (s, 2H); HRMS m/z $(MH)^+$ calcd.: 440.9596, found: 440.9560
IVi	^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.83–7.85 (m, 1H), 7.51–7.53 (m, 1H), 7.47–7.48 (m, 1H), 7.36–7.38 (m, 1H), 7.28–7.31 (m, 2H), 7.23–7.25 (m, 1H), 7.13–7.15 (m, 1H), 6.93–6.95 (m, 1H), 6.86–6.87 (m, 1H), 5.71 (s, 2H); HRMS m/z $(MH)^+$ calcd.: 297.0515, found: 297.0527

From the experimental observations and literature reports on experiments carried out under similar reaction conditions (Chebolu et al., 2012), a plausible reaction mechanism for the selective formation of 1,2-substituted benzimidazoles in lactic acid was proposed (Fig. 3). First, Schiff base bisimine E-1 is formed in lactic acid. Subsequently, lactic acid promotes the formation of immonium E-2 by the intramolecular cyclisation of E-1. Finally, lactic acid mediated the rearrangement of imminium E-2 to afford 1,2-substituted benzimidazole derivatives.

Conclusions

A simple and "green" protocol was developed for the chemoselective synthesis of 1,2-disubstituted benzimidazoles in lactic acid as a biocompatible medium under mild conditions. The α-hydroxy acid structure of lactic acid may gain a better hydrogen bond donor (HBD) ability in the formation of 1,2-disubstituted benzimidazoles. The products of 1,2-disubstituted benzimidazoles could be readily obtained by simply adding water and recrystallisation after completion of the reactions. More notably, the reactions were found to be practical for scale-up synthesis by affording 1,2-disubstituted benzimidazoles in a multi-gram scale reaction.

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