An efficient and environmental benign synthesis of 2-benzimidazoles and 2-benzothiazoles using $CeCl_3$-NaI as catalyst

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A one-pot condensation of an aldehyde with 1,2-phenylenediamine or 2-aminothiophenol in dimethyl carbonate at 100 °C under O_2 in the presence of catalytic amounts of $CeCl_3$–NaI gave an imine intermediate, which cyclised and dehydrogenated to give 2-arylbenzimidazoles or 2-arylbenzothiazoles in good yields.

Keywords: 2- benzimidazoles, 2-benzothiazoles, aldehydes, cerium(III) chloride

Benzimidazoles, benzoxazoles and benzothiazoles are important heterocyclic compounds that have many applications in pharmaceutical and biological chemistry.[1] For example, benzimidazole and derivatives are commonly encountered in natural products and agrochemicals, and in pharmaceuticals[2] such as anti-ulcer agents, anti-tumour agents and antiviral agents.[3] This widespread interest in benzimidazole-containing structures has promoted extensive studies of their synthesis.

A conventional method for the synthesis of benzimidazole and derivatives is the reaction of 1,2-phenylenediamine with carboxylic acid derivatives in the presence of strong acid under harsh conditions,[4] sometimes in combination with microwave irradiation.[5] Another method for the preparation of benzimidazoles is oxidative cyclisation of the imine intermediate, which is generated from condensation of an amine with an aldehyde.[6] However, an excessive amount of an oxidant such as DDQ,[7] MnO_2,[8] $PhI(OAc)_2$,[9] I_2,[10] and $Na_2S_2O_5$ is usually required for this oxidation.[11]

Moreover, volatile organic solvents such as toluene and xylene are used in the traditional procedures. Environmental pressures have been forcing chemists to search for more efficient ways of performing chemical reactions using green solvents and green catalysts.

Recently, some methods have also been reported for constructing the benzimidazole framework by using a catalyst containing iridium,[12] copper,[13] nickel,[14] palladium,[15] cobalt[16] iron,[17] and activated carbon.[18] In continuation of our previous studies on the application of cerium(III) chloride as a Lewis acid in organic chemistry,[19,20] we now report a simple, inexpensive and green method for the cerium(III) chloride-catalysed synthesis of 2-alkyl- and 2-aryl-benzimidazoles and 2-alkyl- and 2-aryl-benzothiazoles using O_2 as oxidant in dimethyl carbonate.

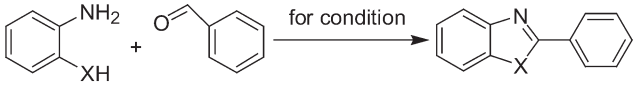
Results and discussion

Initial experiments were carried out with benzaldehyde (1 equiv.) and 2-phenylenediamine (1 equiv.) or 2-aminothiophenol (1 equiv.) as model substrates. Solvent effects were examined in the presence of 10 mol% of $CeCl_3$ and NaI, respectively (Table 1). Moderate yields (50–70%) of the corresponding heterocycles were obtained in refluxing THF or CH_3CN or in dioxane at 100 °C (Table1, entries 1, 3, 4, 6, 8 and 9). When the reaction was carried out in dimethyl carbonate or toluene at 100 °C for 12 h excellent yields (80–90%) were obtained (Table 1, entries 2, 5, 7 and 10). As a control experiment, the same reaction was carried out in the absence of $CeCl_3$–NaI and only 5% of benzothiazole was obtained (Table 1, entry 11).

With the initial results in hand, the scope and limitations of the procedure were then tested. Various aliphatic and aromatic aldehydes (1 mmol) were allowed to react with 2-phenylenediamine (1 mmol) or 2-aminothiophenol (1 mmol) in the presence of 10 mol% of $CeCl_3$ and NaI at 100 °C. As can be seen in Table 2, both aliphatic aldehydes and aromatic aldehydes react with 2-phenylenediamine or 2-aminothiophenol to form the corresponding 2-substituted benzimidazoles or benzothiazoles. Aromatic aldehydes having electron-withdrawing 4-substituents such as nitro, chloro or bromo, were converted into the corresponding benzimidazole in good yields (Table 2, entries 3, 4, 5, 11 and 12). Reactions with aromatic aldehydes having electron-donating group such as methoxy on the benzene ring reduce the yield of the corresponding benzimidazole (Table 2, entry 7 and 13). Heterocyclic aldehydes such as 2-furyl and 2-thiophene carboxaldehyde also gave moderate yields of the corresponding benzimidazole (Table 2, entries 8 and 9). To our delight, aliphatic aldehydes also reacted with 2-phenylenediamine or 2-aminothiophenol smoothly to give the corresponding 2-substituted benzimidazole or benzothiazole in moderate to good yields (Table 1, entries 1, 2, 15 and 16).

A possible mechanism was proposed by Khalil and Sardaria[23] and is shown in Scheme 1. Initially, halogen exchange between $CeCl_3$ and NaI gives a mixed cerium salt CeI_nCl_{3-n}. As a good Lewis acid, CeI_nCl_{3-n} catalyses the reaction of aldehydes with 2-phenylenediamine or 2-aminothiophenol to form an imine

Table 1 Optimisation of the synthesis of 2-phenylbenzimidazoles and 2-phenylbenzothiazoles[a]



1a X=NH, 1b X=S — 2a — 3a X=NH, 3b X=S

Entry	Reagent	Solvent	Temp. /°C	Catalyst/mol %	Yield/ %[b]
1	**1a**	Dioxane	100	$CeCl_3$–NaI (10–10)	50
2	**1a**	Toluene	100	$CeCl_3$–NaI (10–10)	81
3	**1a**	THF	Reflux	$CeCl_3$–NaI (10–10)	60
4	**1a**	Acetonitrile	Reflux	$CeCl_3$–NaI (10–10)	51
5	**1a**	Dimethyl carbonate	100	$CeCl_3$–NaI (10–10)	81
6	**1b**	Dioxane	100	$CeCl_3$–NaI (10–10)	60
7	**1b**	Toluene	100	$CeCl_3$–NaI (10–10)	91
8	**1b**	THF	Reflux	$CeCl_3$–NaI (10–10)	70
9	**1b**	Acetonitrile	Reflux	$CeCl_3$–NaI (10–10)	63
10	**1b**	Dimethyl carbonate	100	$CeCl_3$–NaI (10–10)	90
11	**1b**	Dimethyl carbonate	100	None	<5

[a]Reaction conditions: 2-phenylenediamine (1 mmol) or 2-aminothiophenol (1 mmol) ; aldehyde (1 mmol); $CeCl_3$-NaI (10–10 mol%); solvent (5 mL); 12 h; under O_2.
[b]GC-MS yield.

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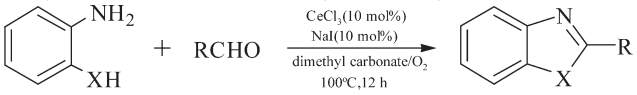
Table 2 $CeCl_3$–NaI catalysed synthesis of 2-alkyl- and 2-aryl-benzimidazoles and 2-alkyl- and 2-aryl-benzothiazoles[a]



1a X=NH
1b X=S

3a X=NH
3b X=S

Entry	X	R	Yield/% [b]
1	NH	H	61
2	NH	$CH_3(CH_2)_3$	67
3	NH	4-$NO_2C_6H_4$	89
4	NH	4-ClC_6H_4	88
5	NH	4-BrC_6H_4	85
6	NH	C_6H_5	81
7	NH	4-$CH_3OC_6H_4$	65
8	NH	2-C_4H_3S	63
9	NH	2-C_4H_3O	61
10	S	C_6H_5	90
11	S	4-ClC_6H_4	92
12	S	4-$NO_2C_6H_4$	92
13	S	4-$CH_3OC_6H_4$	75
14	S	4-$CH_3C_6H_4$	82
15	S	$CH_3(CH_2)_2$	85
16	S	$CH_3(CH_2)_3$	79

[a] Reaction conditions: 2-phenylenediamine (1 mmol) or 2-aminothiophenol (1 mmol) ; aldehyde (1 mmol); $CeCl_3$–NaI (10 mol%-10 mol%); dimethyl carbonate (5 mL); 12 h; under O_2.
[b] Isolated yield.

intermediate. CeI_nCl_{3-n} then promotes cyclisation to a bicyclic intermediate, dehydrogenation of which gives the final product. According to this mechanism, aromatic aldehydes bearing an electron withdrawing group would be highly reactive since they possess a more electrophilic carbonyl carbon which is beneficial for the attack of the amino group to form the imine intermediate which is itself very reactive towards the subsequent attack of the amino or hydroxyl group to form, after dehydrogenation, the final product.

In conclusion, a new method for the synthesis of 2-alkyl- or 2-aryl-benzimidazoles and 2-alkyl- or 2-aryl-benzothiazoles from aldehydes and 2-phenylenediamine or 2-aminothiophenol in the presence of 10% $CeCl_3$–NaI is reported. The one-pot synthesis was carried out in dimethyl carbonate at 100 °C using O_2 as the oxidant. The procedure is suitable for the synthesis of 2-substituted benzimidazoles and benzothiazoles from aliphatic, aromatic or heteroaromatic aldehydes.

Experimental

All chemicals (AR grade) were obtained from commercial resources and used without further purification. Gas chromatography analysis was performed on an Agilent GC-6820 chromatograph equipped with a 30m×0.32mm×0.5μm HP-Innowax capillary column and a flame ionisation detector. GC-MS spectra were recorded on Thermo Trace DSQ GC-MS spectrometer using TRB-5MS (30 m × 0.25 mm × 0.25 μm) column. Melting points were determined using a XT-4 apparatus and are not corrected. The ^{1}H NMR spectra were obtained on a Bruker DRX500 (500 MHz) spectrometer using $CDCl_3$ or DMSO-*d6* as solvent with TMS as internal standard. Progress of the reactions was followed by TLC using silica-gel polygrams SIL G/UV 254 plates. Column chromatography was performed using Silicycle (40–60 mm) silica gel. All products are known compounds and were characterised by comparison of their physical and spectral properties with literature data.

General experimental procedure

2-Phenylenediamine (1 mmol) or 2- aminothiophenol (1 mmol), and benzaldehyde (1 mmol) in dimethyl carbonate (5 mL), were stirred for 20 min at RT, $CeCl_3$ (0.0246 g, 0.1 mmol) and NaI (0.0150 g, 0.1 mmol) were then added and the mixture was stirred at 100 °C under O_2 for 12h. The reaction mixture after cooling was poured into water and the aqueous solution was extracted with ethyl acetate (3 × 8 mL). Evaporation of the solvent gave a crude product which was purified on a small silica gel column with EtOAc: petroleum ether (1:8) as eluent, prior to recrystallisation.

Benzimidazole: M.p. 170–172 °C (EtOH) (lit.[9] 174 °C); ^{1}H NMR (DMSO-*d6*): δ 12.47 (s, 1H), 8.22 (s, 1H), 7.60 (s, 2H), 7.19 (d, *J* = 4.0 Hz, 2H).

2-(4-Nitro-phenyl)-benzimidazole: M.p. 315–317 °C (EtOH) (lit.[21] 316 °C); ^{1}H NMR (DMSO-*d6*): δ 8.34 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 8.5 Hz, 2H), 7.23–7.25 (m, 1H), 7.00–7.03 (m, 1H), 6.74–6.76 (m, 1H), 6.55–6.59 (m, 1H).

2-(4-Chloro-phenyl)-benzimidazole: M.p. 292–294 °C (EtOH) (lit.[21] 294 °C); ^{1}H NMR (DMSO-*d6*): δ 12.99 (s, 1H), 8.19 (m, 2H), 7.54–7.65 (m, 4H), 7.22 (s, 2H).

2-(4-Bromo-phenyl)-benzimidazole: M.p. 298–299 °C (EtOH) (lit.[9] 299–300 °C); ^{1}H NMR (DMSO-*d6*): δ 12.99 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 6.5 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.22 (s, 2H).

2-Phenyl-benzimidazole: M.p. 289–291 °C (EtOH) (lit.[21] 292 °C); ^{1}H NMR (DMSO-*d6*): δ = 12.90 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 2H), 7.50–7.57 (m, 5H), 7.21–7.22 (m, 2H).

2-(4-Methoxy-phenyl)- benzimidazole: M.p. 224–226 °C (EtOH) (lit.[21] 226 °C); ^{1}H NMR (DMSO-*d6*): δ 12.79 (s, 1H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.55 (s, 2H), 7.11–7.18 (m, 4H), 3.84 (s, 3H).

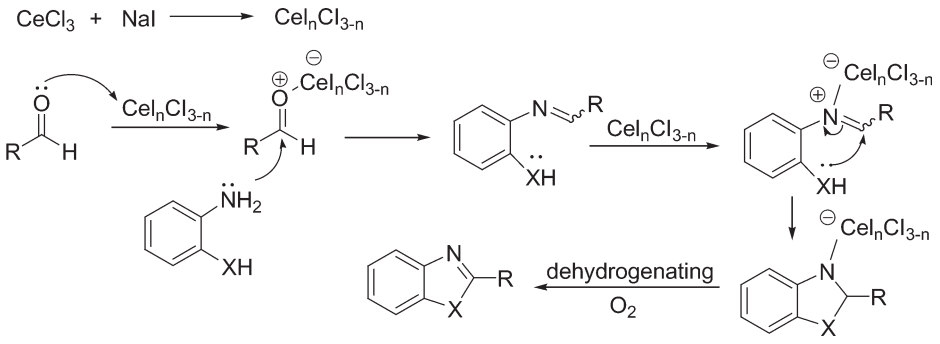
2-(2-Furyl)-1H-benzimidazole: M.p. 287–288 °C (EtOH) (lit.[21] 288 °C); ^{1}H NMR (DMSO-*d6*): δ 12.92 (s, 1H), 7.95 (s, 1H), 7.50–7.62 (m, 2H), 7.19–7.20 (m, 3H), 6.73–6.74 (m, 1H).

2-(2-Thienyl)-1H-benzimidazole: M.p. 329–331 °C (EtOH) (lit.[10] 330 °C); ^{1}H NMR (DMSO-*d6*): δ 12.93 (s, 1H), 7.83 (d, *J* = 3.0 Hz, 1H), 7.73 (d, *J* = 5.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.16–7.24 (m, 3H);

2-Phenyl-benzothiazole: M.p. 113–114 °C (EtOH) (lit.[22] 112–114 °C); ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.52 (m, 3H), 7.34 (d, 1H, *J* = 8.5 Hz), 7.23 (t, 1H, *J* = 8.5 Hz), 7.05 (d, 1H, *J* = 8.5 Hz), 6.94 (t, 1H, *J* = 8.5 Hz); MS (EI) *m/z* 210.94 (M^+).

2-(4-Chloro-phenyl)-benzothiazole: M.p. 116–118 °C (EtOH) (lit.[22] 116–117 °C); ^{1}H NMR ($CDCl_3$) δ = 8.02 (d, 2H, *J* = 8.0 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 7.58 (t, 1H, *J* = 8.0 Hz), 7.49 (d, 2H, *J* = 8. Hz), 7.43 (t, 1H, *J* = 8.5 Hz), 7.20 (d, 1H, *J* = 8.5 Hz).

2-(4-Nitro-phenyl)-benzothiazole: M.p. 226–228 °C (EtOH) (lit.[22] 226–228 °C); ^{1}H NMR ($CDCl_3$) δ 8.37 (d, 2H, *J* = 8.5 Hz), 8.11 (d,



Scheme 1 Possible mechanism and tentative intermediates in the synthesis of 2-arylbenzimidazoles (X=NH) and 2-arylbenzothiazoles (X=S).[23]

2H, *J* = 8.5 Hz), 7.92 (t, 1H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 8.5 Hz), 7.30 (t, 1H, *J* = 8.0 Hz), 7.19 (d, 1H, *J* = 8.5 Hz).

2-(4-Methoxy-phenyl)-benzothiazole: M.p. 111–113 °C (EtOH) (lit.[22] 112–113 °C); ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 2H, *J* = 8.5 Hz), 8.06 (d, 1H, *J* = 8.5 Hz), 7.86 (m, 1H), 7.47–7.54 (m, 2H), 7.08 (d, 2H, *J* = 8.5 Hz), 3.92 (s, 3H).

2-(4-Methyl-phenyl)-benzothiazole: M.p. 86–88 °C (EtOH) (lit.[22] 85–87 °C); ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 2H, *J* = 8.5 Hz), 7.90 (d, 2H, *J* = 8.5 Hz), 7.55 (t, 2H, *J* = 8.5 Hz), 7.44 (d, 2H, *J* = 8.5 Hz), 2.38 (s, 3H).

2-Propyl -benzothiazole: Oil (lit.[24] oil); ^{1}H NMR ($CDCl_3$): δ 7.69 (m, 1H), 7.38 (t, 1H, *J* = 8.5 Hz), 7.26 (d, 1H, *J* = 8.5 Hz), 7.10 (d, 1H, *J* = 8.5 Hz), 2.93 (t, 2H, *J* = 7.5 Hz), 1.84 (m, 2H), 1.00 (t, 3H, *J* = 7.5 Hz); MS (EI) *m/z* 177 (M^+).

2-Butyl-benzothiazole: Oil (lit.[25] oil); ^{1}H NMR ($CDCl_3$): δ 7.69 (m, 1H), 7.38 (t, 1H, *J* = 8.5 Hz), 7.26 (d, 1H, *J* = 8.5 Hz), 7.10 (d, 1H, *J* = 8.5 Hz), 2.93 (t, 2H, *J* = 7.5 Hz), 1.95 (m, 2H), 1.84 (m, 2H), 1.00 (t, 3H, *J* = 7.5 Hz).

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