Convenient two-step one-pot synthesis of benzimidazoles using 2-nitroanilines and thiourea dioxide

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A new convenient method for the conversion of 2-nitroanilines into benzimidazoles by two-step one-pot procedure is reported. The procedure involves the reduction of nitro group followed by the intramolecular cyclisation of the corresponding o-phenylenediamines utilising thiourea dioxide and sodium hydroxide at 70 °C in mixed solvents of H_2O and EtOH (v/v, 3/1). The yields are good to excellent and the workup is simple.

Keywords: 2-nitroanilines, benzimidazoles, thiourea dioxide, reduction, cyclisation reaction

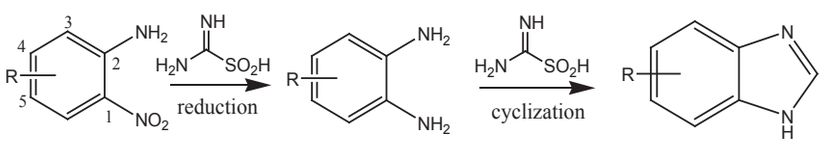
Benzimidazole derivatives are important intermediates in the synthesis of pharmaceutical compounds, and heterocycles with benzimidazole structures are ubiquitous in bioactive compounds.[1,2] In particular, benzimidazoles are used as anti-viral, anti-tumour, anti-fungal, and anti-phlogosis agents.[3–5] Some of these compounds also possess neuroleptic, spasmolytic and hypotensive action.[6–8] Therefore, preparation of benzimidazole derivatives has been important in organic synthesis.

The conventional methods to access benzimidazoles are based upon the condensation reactions of *o*-phenylenediamines with cyclising agents, such as aldehydes, formic acid or its derivatives (imidates, esters, orthoesters, or nitriles) under strong acidic conditions at high temperature.[9] Recently, benzimidazoles have been reported to be synthesised *via* one-pot method from 2-nitroanilines and orthoesters in the presence of reducing agents and metal catalysts (*e.g.*, ytterbium[10], indium[11] and Raney nickel[12]). Although much progress has been made in the synthesis of benzimidazoles, it is still desirable to develop convenient and environmental methods to prepare benzimidazoles.

Interested in the synthesis of benzimidazoles, we found a new method of preparing of benzimidazoles from 2-nitroanilines and thiourea dioxide (TUD)[13] at 70 °C in mixed solvents of H_2O and EtOH (v/v, 3/1). TUD which is easily prepared by the oxidation of thiourea with hydrogen peroxide has been known as an powerful reducing agent capable of reducing many kinds organic compounds[14]. Very interestingly, we found that TUD could spontaneously condense with *o*-phenylenediamines to produce benzimidazoles in water at 70 °C. Earlier researches have established that TUD can efficiently reduce aromatic nitro, azoxy, azo, hydrazo compounds to amines at 70 °C in NaOH aqueous solutions.[15,16] For the purpose of exploring a convenient method for the synthesis of benzimidazoles, we employed TUD to reduce 2-nitroaniline followed by the intramolecular cyclisation of newly generated intermediate *o*-phenylenediamine with TUD. In the synthetic process, TUD functioned as reducing agent and cyclising agent (Scheme 1). In the present work, we proposed a mild and catalyst-free one-pot process to prepare benzimidazoles from 2-nitroanilines and TUD at 70 °C in mixed solvents of H_2O and EtOH (v/v, 3/1). Compared with traditional methods, this synthetic strategy has the following advantages: (1) the operation of experiments is simple and convenient because of using TUD as the reducing agent and cyclising agent; (2) the reaction can proceed in water which represents an eco-friendly alternative to many existing procedures; and (3) the workup is simple and only needs simple filtration.

Results and discussion

First, the reaction of 2-nitroaniline (**1a**) with TUD was chosen as the model reaction to explore the optimised reaction conditions. The effects of solvents and quantity of reactants upon the synthesis of **2a** were investigated. As shown in Table 1, an unsatisfactory yield of 33% was obtained when only H_2O served as the solvent. The yield was greatly improved when using mixed solvents of H_2O and EtOH (v/v, 3/1) under similar conditions. To better understand the importance of each reactant, the ratio between TUD and **1a** was also explored. As a preliminary reaction, we tested the conversion of compound **1a** to **2a** varying the number of equivalents of TUD in the presence of 1 equiv. of **1a** and 3 equiv. of NaOH. The yield of **2a** increased with increasing the amounts of TUD from 4 to 5 equiv. No substantial improvement in the yield was found with a further increase of TUD. As a result, the optimised ratio between TUD and **1a** was 5 : 1. The impact of the amount of NaOH upon the reaction was also investigated at a reactant ratio of 5 : 1 (TUD/**1a**). An improvement of yield was observed with increasing the amount of NaOH from 3 to 4 equiv. Further increasing the amount of NaOH to 4.5 equiv., a relatively poor yield of 45% was obtained.



1a-h **2a-h**

a R = H **b** R = 5-CH_3
c R = 3-CH_3 **d** R = 5-OCH_3
e R = 5-F **f** R = 5-Cl
g R = 5-Br **h** R = 3,5-dibromo

Scheme 1 Synthetic route of benzimidazoles **2a–h.**

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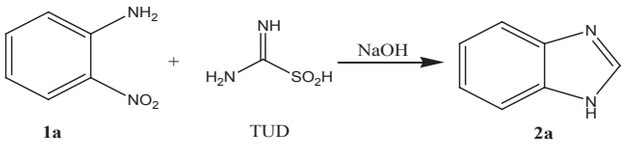
Table 1 Optimisation of reaction condition in the synthesis of **2a**[a]



1a TUD **2a**

Entry	Solvent	NaOH/equiv.	TUD/equiv.	Yield/%[b]
1	H_2O	4	5	33
2	H_2O+EtOH	3	4	40
3	H_2O+EtOH	3	5	50
4	H_2O+EtOH	3	6	48
5	H_2O+EtOH	3.5	5	55
6	H_2O+EtOH	4	5	65
7	H_2O+EtOH	4.5	5	45

[a]Conditions: reactions were performed with compound **1a** (0.69 g, 1 equiv.) at 70 °C.
[b]Isolated yield.

Having established the optimised reaction conditions, we then successfully synthesised a variety of benzimidazoles **2a**–**h** by treatment of 1 equiv. of 2-nitroanilines, 4 equiv. of NaOH and 5 equiv. of TUD in mixed solvents of H_2O/EtOH (v/v, 3/1) at 70 °C (Table 2). Purification of benzimidazoles **2a–h** was performed by recrystallisation from H_2O. All products were characterised by ^{1}H NMR, ^{13}C NMR, IR and HR-MS. Data of compounds **2a–h** were in accordance with previous reports.[17–20]

In conclusion, a new two-step one-pot synthesis of a series of substituted benzimidazoles had been reported. Compared with earlier methods, this procedure has several advantages including catalyst-free reaction, simplicity in experiments and work-up, and use of water as solvent. Furthermore, it was unnecessary to isolate the intermediate aromatic diamines which were unstable during the separation process. This reaction applies to a relatively wide range of substituted 2-nitroanilines which are stable under basic conditions. The reagent TUD as cyclisation agent was first used in the synthesis of benzimidazoles, and was inexpensively available compared with reported cyclisation agents. Undoubtedly, all these advantages are a useful improvement to the present methodologies for the benzimidazoles synthesis.

Experimental

Melting points were measured by a XRC-1 melting point apparatus without being corrected. IR spectra were obtained on 1700 Perkin-Elmer FT-IR using KBr disks. NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ were given in ppm relative to tetramethylsilane in DMSO-d_6 for ^{1}H NMR and ^{13}C NMR. Mass spectra were determined on a Waters Q-TOF Premier using the electrospray ionisation (ESI) method. All reagents were of commercial quality or purified by standard procedures.

Synthesis of **2a–h***; general procedure*

TUD (20 mmol) was added in batches to a solution of substituted 2-nitroanilines (5 mmol) and NaOH (20 mmol) in H_2O (15 mL) and EtOH (5 mL) at 70 °C. The reaction mixture was stirred for a certain period of time as required to complete the reaction (monitored by TLC). After cooling, 10% NaOH solutions were added until pH = 9–10, the precipitated solid was filtered off and washed with water to obtain crude product. The crude product was recrystallised from water to give a white solid. The physical and spectra data of the compounds **2a–h** were as follows.

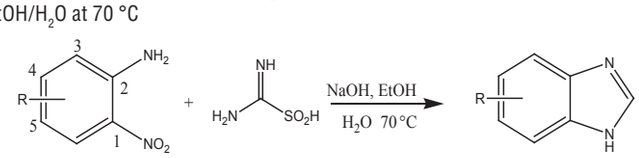
1H-Benzoimidazole (**2a**): Off-white solid, m.p. 171–172 °C; yield 65%. FT-IR (KBr)(cm^{-1}): 3390, 3115, 1767, 1589, 1248, 956, 746; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.17–7.22 (m, 2H, ArH), 7.58–7.61 (m, 2H, ArH), 8.22 (s, 1H, N=CH), 12.44 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 115.75, 122.19, 138.70 (Ar), 142.43 (N=CH); HR-MS (ESI): calcd for $C_7H_7N_2$ $[M+H]^+$: 119.0609; found 119.0602.

5-Methyl-1H-benzoimidazole (**2b**): White solid, m.p. 108–110 °C; yield 60%. FT-IR (KBr)(cm^{-1}): 3426, 3088, 3026, 1615, 1257, 959; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.41 (s, 3H, CH_3), 7.01 (d, J = 8.0 Hz, 1H, ArH), 7.37 (s, 1H, ArH), 7.46 (d, J = 8.4 Hz, 1H, ArH), 8.12 (s, 1H, N=CH), 12.29 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm) = 21.67 (CH_3), 115.06, 115.77, 123.70, 131.38, 137.27, 138.30 (Ar), 142.06 (N=CH); HR-MS (ESI): calcd for $C_8H_9N_2$ $[M+H]^+$: 133.0766; found 133.0755.

4-Methyl-1H-benzoimidazole (**2c**): Brown solid, m.p. 140–142 °C; yield 57%. FT-IR (KBr)(cm^{-1}): 3423, 3062, 2990, 1592, 1295, 948; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.52 (s, 3H, CH_3), 6.98 (d, J = 7.2 Hz, 1H, ArH), 7.08 (t, J = 7.6 Hz, 1H, ArH), 7.39 (d, J = 8.0 Hz, 1H, ArH), 8.18 (s, 1H, N=CH), 12.45 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 17.26 (CH_3), 113.12, 122.20, 122.49, 125.45, 129.06, 138.17 (Ar), 141.79 (N=CH); HR-MS (ESI): calcd for $C_8H_9N_2$ $[M+H]^+$: 133.0766; found 133.0761.

5-Methoxy-1H-benzoimidazole (**2d**): Brown solid, m.p. 123–126 °C; yield 59%. FT-IR(KBr)(cm^{-1}): 3420, 3097, 1627, 1385, 1021, 814; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.78 (s, 3H, OCH_3), 6.82 (dd, J = 8.8, 2.4 Hz, 1H, ArH); 7.08 (d, J = 2.4 Hz, 1H, ArH), 7.47 (d, J = 8.8 Hz, 1H, ArH), 8.09 (s, 1H, N=CH), 12.27 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 55.83 (OCH_3), 97.87, 111.87, 116.79, 133.87, 138.35 (Ar), 141.92 (N=CH), 156.08 (Ar); HR-MS (ESI): calcd for $C_8H_9N_2O$ $[M+H]^+$: 149.0715; found 149.0705.

Table 2 One-pot synthesis of benzimidazoles using 2-nitroanilines (5 mmol) and TUD (5 equiv.) in the presence of NaOH (4 equiv.) in EtOH/H_2O at 70 °C



Entry	R	Product	Reaction time/h	Yield/%[a]	M.p.[lit.]/°C
1	H	**2a**	1	65	171–172 [173][17]
2	5-CH_3	**2b**	2	60	108–110 [112–114][18]
3	3-CH_3	**2c**	2	57	140–142 [145–146][19]
4	5-OCH_3	**2d**	1.5	59	123–126[118–120][20]
5	5-F	**2e**	1	62	114–116
6	5-Cl	**2f**	1	64	119–121[122–123][17]
7	5-Br	**2g**	1.5	68	124–126
8	3,5-Dibromo	**2h**	3	50	220–222

[a]Isolated yield.

5-Fluoro-1H-benzoimidazole (**2e**): Pale solid, m.p. 114–116 °C; yield 62%. FT-IR(KBr)(cm^{-1}): 3429, 3044, 1624, 1293, 953, 808; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.05 (td, J = 9.6, 2.0 Hz, 1H, ArH), 7.39 (dd, J = 9.6, 2.4 Hz, 1H, ArH), 7.57–7.61 (m, 1H, ArH), 8.25 (s, 1H, N=CH), 12.53 (brs, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 101.68 (d, $J_{C,F}$ = 24.0 Hz, Ar), 110.35 (d, $J_{C,F}$ = 25.0 Hz, Ar), 116.47 (Ar), 135.17 (Ar), 138.89 (Ar), 143.80 (N=CH), 158.95 (d, $J_{C,F}$ = 233.1, C-F); HR-MS (ESI): calcd for $C_7H_6FN_2$ $[M+H]^+$: 137.0515; found 137.0504.

5-Chloro-1H-benzoimidazole (**2f**)**:** Tan solid, m.p. 119–121 °C; yield 64%. FT-IR(KBr)(cm^{-1}): 3432, 3109, 1624, 1284, 953, 793; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.22 (dd, J = 8.8, 2.0 Hz, 1H, ArH), 7.60 (d, J = 8.8 Hz, 1H, ArH), 7.65 (d, J = 1.6 Hz, 1H, ArH), 8.28 (s, 1H, N=CH), 12.61 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 115.67, 116.83, 122.48, 126.66, 137.09, 139.74 (Ar), 143.88 (N=CH); HR-MS (ESI): calcd for $C_7H_6ClN_2$ $[M+H]^+$:153.0220; found 153.0210.

5-Bromo-1H-benzoimidazole (**2g**): White solid, m.p. 124–126 °C; yield 68%. FT-IR(KBr)(cm^{-1}): 3423, 3088, 1617, 1287, 963, 808; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm) = 7.33 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.56 (d, J = 8.4 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 8.26 (s, 1H, N=CH), 12.61 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 114.53, 117.30, 118.66, 125.09, 137.35, 140.41 (Ar), 143.74 (N=CH); HR-MS (ESI): calcd for $C_7H_6BrN_2$ $[M+H]^+$: 196.9714; found 196.9705.

5,7-Dibromo-1H-benzoimidazole (**2h**): Pale solid, m.p. 220–222 °C; yield 50%. FT-IR(KBr)(cm^{-1}): 3425, 3088, 1622, 1282, 968, 827; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.59 (s, 1H, ArH), 7.77 (s, 1H, ArH), 8.35 (s, 1H, N=CH), 12.90 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm) = 114.73, 126.91, 135.23, 135.96, 140.53, 141.60 (Ar), 144.37 (N=CH); HR-MS (ESI): calcd for $C_7H_5Br_2N_2$ $[M+H]^+$: 274.8819; found 274.8809.

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