A Versatile Method for the Synthesis of Benzimidazoles from *o*-Nitroanilines and Aldehydes in One Step via a Reductive Cyclization

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Abstract: A highly efficient and versatile method for the synthesis of benzimidazoles was achieved in one step via the $Na_2S_2O_4$ reduction of *o*-nitroanilines in the presence of aldehydes. Heating a solution of *o*-nitroaniline (**1c**) and an aldehyde in EtOH or another appropriate solvent, in the presence of aqueous or solid $Na_2S_2O_4$, provided facile access to a series of 2-substituted N-H benzimidazoles **5a**–**m** containing a wide range of functional groups not always compatible with the existing synthetic methods. This methodology has also been applied to the regioselective synthesis of *N*-alkyl and *N*-aryl benzimidazoles **6a**–**f** via the cyclization of the corresponding N-substituted nitroanilines **13a**–**e**, respectively. In addition, the method was applied successfully to the synthesis of other imidazole containing heterocyclic ring systems such as 1*H*-imidazo[4,5-b]pyridines **14a**,**b** and 1*H*-imidazo[4,5-f]quinoline **15**.

Key words: benzimidazoles, reductive cyclization, sodium dithionite, imidazopyridines, imidazoquinolines

Benzimidazole containing structures have been well documented to exhibit a wide range of biological properties. This class of molecules has found commercial applications in several therapeutic areas such as anti-ulcerative, anti-hypertensive, antiviral, antifungal, anti-tumor, and antihistaminic agents as well as antihelminthic agents in veterinarian medicine.[2] Medicinal chemists consider these heterocycles privileged structures. Indeed, the development of new synthetic methods, which could render accessible chemistry space currently not attainable by existing methods, would be of considerable importance to the chemistry community.

The most popular synthetic approaches generally involve the condensation of an arylenediamine with a carbonyl equivalent (Scheme 1).[3] For example, the reaction of arylenediamine **1a** with a carboxylic acid or acid chloride results in intermediate amide **2**. The latter in turn could undergo a cyclodehydration reaction under strong acidic or alternatively under harsh dehydrating conditions, often at elevated temperatures, in order to afford benzimidazole **5** (Scheme 1, route a). Similarly, esters, lactones and anhydrides could generate benzimidazoles via the cyclization of amide **2**, although their scope might be limited given the rather harsh reaction conditions required and the poor diversity profile of the final products. For instance, the reaction of arylenediamines with aliphatic esters and lactones requires the use of strong mineral acids such as hydrochloric acid, sulfuric acid, hot glacial acetic acid or polyphosphoric acid under very high temperatures, conditions not fully compatible with a broad range of functional groups and desirable substrates. Aromatic esters require temperatures of up to 250–300 °C, thus rendering the synthesis of 2-aryl benzimidazoles almost impractical.[4] However, the reaction of aromatic esters with arylenediamines under Weinreb conditions could provide access to 2-aryl benzimidazoles.[5] From the acid anhydrides of monobasic acids, only acetic anhydride has been practically used in the preparation of 2-methyl benzimidazoles. Cyclic anhydrides of dibasic acids have also been utilized in the synthesis of benzimidazoles, although high temperatures and strong acids are usually required to convert the intermediate *N*-(*o*-aminopheny)-imide into the desired benzimidazole.[6] In addition, a mixture of regio-isomeric benzimidazoles could result from the reaction of non-symmetric anhydrides and arylenediamines.

Also, the reaction of diamine **1a** with amides[7] and nitriles[8] at 200–250 °C, in the presence of HCl could afford 2-substituted benzimidazoles with the general structure **5** via the cyclization of intermediate amidine **3a** (Scheme 1, route b). Alternatively, the reaction of diamine **1a** with an imidate could afford benzimidazole **5** as well, upon formation and subsequent cyclization of amidine **3a** under milder conditions.[9] Although the imidate route could provide access to a diverse set of 2-substituted benzimidazoles starting from several commercially available aliphatic and aromatic nitriles, the hydroscopic nature of the intermediate imidates might be of concern, particularly in a high throughput set-up. The palladium catalyzed intramolecular *N*-arylation reaction of *o*-bromophenylamidine precursors of type **3b**, resulting from the assisted $POCl_3$ condensation of bromoaniline **1b** and an amide, has been recently developed providing entry to N-substituted benzimidazoles with general structure **6**.[10] Despite the somewhat harsh conditions required to generate the intermediate amidine precursors, this method successfully addresses the regioselective synthesis of N-substituted benzimidazoles which currently constitutes a limitation of many other approaches.

Aldehydes and, to a lesser extent, ketones can also afford benzimidazoles when they are condensed with arylenediamines (Scheme 1, route c). Although the reaction of ketones with arylenediamine **1a** in the presence of HCl at 250–300 °C can yield benzimidazole **5** by the aromatiza-

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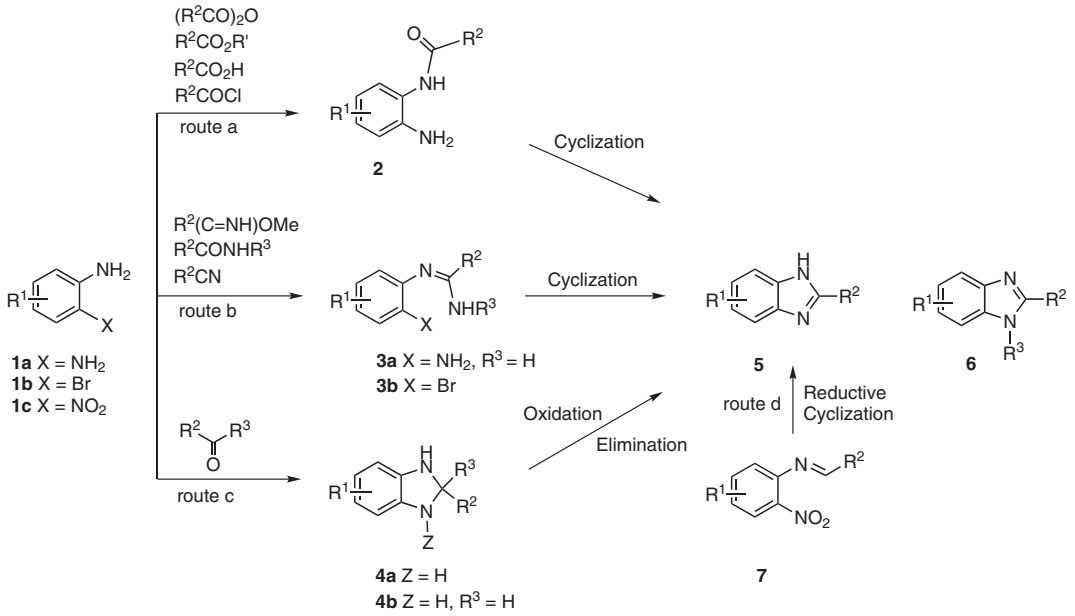


Scheme 1 Common strategies for the synthesis of benzimidazoles

tion of intermediate benzimidazoline **4a**, their use has been rather limited.[3a,11] Furthermore, since aromatization of benzimidazoline **4a** occurs via the elimination of an alkyl group, a mixture of benzimidazoles could result from non-symmetric ketones. Alternatively, aldehydes have been used more extensively in the preparation of 2-substituted benzimidazoles according to Weidenhagen's method.[12] For example, condensation of diamine **1a** with an aldehyde, followed by oxidation of the intermediate benzimidazoline **4b** could afford benzimidazole **5** as well. While the oxidation can proceed spontaneously by disproportionation, this can lead to the occurrence of side products. Oxidative methods usually require heating in nitrobenzene or DMF at elevated temperatures, as well as the use of metal ions, iodine, organic oxidants or inorganic sulfites under heating.[13] However, one mild set of oxidation conditions utilizing oxone® has been recently described for the synthesis of N-substituted and N-H benzimidazoles.[14]

A method which could be a viable alternative to the widely used arylenediamine based synthetic methods, although not studied in depth to date according to our knowledge, employs the reductive cyclization of *N*-benzylidene-2-nitroanilines **7** (R_2 = Ar), prepared from *o*-nitroaniline (**1c**) and benzaldehydes (Scheme 1, route d). Triethylphosphite,[15] triruthenium dodecacarbonyl[16] in the presence of carbon monoxide, and recently, phenylmagnesium chloride[17] have been successfully utilized as the reducing agents for this transformation. The reaction presumably proceeds via an in situ aryl nitro reduction, followed by an intramolecular cyclization,[18] to afford benzimidazole **5** (R_2 = Ar). Even though this strategy could obviate the preparation and isolation of the intermediate arylenediamines, especially those that are known to be water-soluble or prone to air-oxidation, it would still require the preparation and isolation of the corresponding *N*-benzylidene-2-nitroanilines prior to subjecting them to cyclization conditions. Herein, we report the results of our studies describing the development of a versatile method for the synthesis of benzimidazoles in one step, whereby benzimidazoles were directly derived from *o*-nitroanilines and aldehydes, via a reductive cyclization without the need for the preparation or isolation of any intermediate agents.

The synthesis of benzimidazoles from aldehydes and *o*-nitroanilines via the in situ reduction of *o*-nitroanilines was thought to constitute an appealing method, as our premise, with the potential of becoming amenable to high throughput solution phase parallel synthesis, should the appropriate reducing agent be utilized. Although a few methods describing the synthesis of benzimidazoles from *o*-nitroanilines and aldehydes via a transition metal-catalyzed reductive cyclization have been reported in the literature, their scope has been proven to be rather limited.[19] For instance, the synthesis of 2-alkyl benzimidazoles has been reported on the surface of a ZnO or TiO_2 semiconductor, through a reductive cyclization pathway, during the photolysis of a primary alcohol solution of a nitroaniline.[19a] An oxidation-reduction mechanism is postulated where the alcohol is photocatalytically oxidized to the aldehyde, followed by condensation with *o*-nitroaniline (**1c**) to form the corresponding imine **7** (Scheme 2). Subsequent four-electron reduction of the nitro group, which results in hydroxylamine **8**, followed by cyclization to benzimidazoline **4c** and consequent dehydration, could account for the formation of benzimidazole **5**. Although this method leads to the exclusive formation of 2-alkyl benzimidazoles in high yield, it is limited only to the preparation of 2-methyl and 2-ethyl benzimidazoles. When a primary alcohol larger than EtOH or PrOH was used as the solvent during the

photolysis of a nitroaniline, the reaction was found to proceed very slowly. Furthermore, this methodology fails to address the synthesis of 2-aryl benzimidazoles and is not suitable for high throughput synthesis.

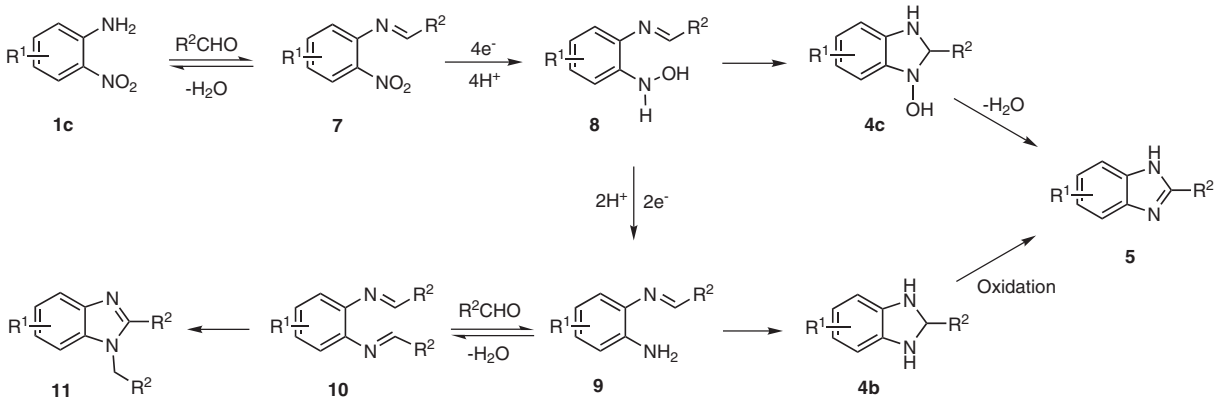
By application of the same strategy (Scheme 2), a mixture of monosubstituted and 1,2-disubstituted benzimidazoles **5** (R_1 = H, R_2 = Ar) and **11** (R_1 = H, R_2 = Ar) respectively, has been synthesized from *o*-nitroaniline and benzaldehydes, in the presence of Zn metal and 2-bromo-2-nitropropane in MeOH–CH_2Cl_2 at room temperature.[19b] Based on GC/MS data, it was proposed that entry to benzimidazole **5** might involve the intermediacy of primary amine **9**, the six-electron reduction product of nitroimine **7**, and subsequently the oxidation of the Weidenhagen benzimidazoline **4b**. Alternatively, access to the disubstituted benzimidazole **11** was rationalized via the cyclization of intermediate diimine **10**,[20] the condensation product of primary amine **9** with another aldehyde molecule. The difficulty in controlling the formation of the undesired 1,2-disubstituted benzimidazoles coupled with the absence of data supporting the use of aliphatic aldehydes has rendered this reducing system less attractive for further investigation.

We surmised that if disubstituted benzimidazole **11** resulted from the formation and cyclization of diimine **10**, then the reduction of hydroxylamine[21] intermediate **8** to **9** should compete with its cyclization to benzimidazoline **4c**, the precursor of **5**. Therefore, by controlling the reduction of nitroimine **7** to hydroxylamine **8** through the appropriate choice of a reducing system, the generation of benzimidazole **5** would be favored thermodynamically via the dehydration of intermediate benzimidazoline **4c**. Sodium dithionite ($Na_2S_2O_4$), a very inexpensive and efficient reducing reagent which acts as a single electron transfer donor, has been reported to reduce aryl nitro groups to aryl amines via hydroxylamines by a six-electron mechanism.[22] This observation coupled with the mild reaction conditions of the method and a demonstrated tolerance for other functional groups such as halogens, aldehydes, ketones, nitriles and olefins, rendered $Na_2S_2O_4$ a prime candidate for our studies.

Our initial results showed that when a solution of a nitroaniline (1 equiv) and an aldehyde (1 equiv) in EtOH was treated with 3 equivalents of a freshly prepared[23] aqueous solution of $Na_2S_2O_4$ at 70 °C for 5 hours, the desired benzimidazoles with general structure **5** were formed in a straightforward manner (Table 1). The products were easily isolated in good yields and high purities by filtration, after cooling and neutralizing the reaction mixture with aqueous ammonia, or by silica gel flash chromatography when the products did not readily precipitate. The chemistry worked well with both aliphatic (entries 1 and 2) and aromatic aldehydes (entries 3–13), including heterocyclic aldehydes (entries 4–6). Substituted *o*-nitroanilines also performed well, under these reaction conditions, providing selective reduction of the nitro group in the presence of a number of other substituents (entries 7–13). The reaction afforded reproducible yields on scales ranging from 200 μmol, typical of high throughput synthesis, to multigram scale, as was illustrated through the synthesis of the benzimidazole **5l** (entry 12) on a 25 g scale.

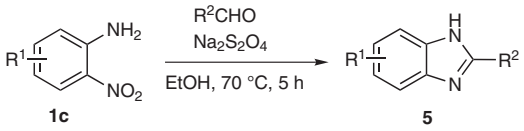
Similarly, N-substituted benzimidazoles with the general structure **6** were efficiently synthesized in one pot from the corresponding N-substituted nitroanilines **13** through the application of this methodology, as shown in Table 2. The requisite *N*-alkyl nitroanilines **13a**,**b** were prepared in situ by heating a mixture of the corresponding 1-fluoro-2-nitrobenzene **12** and a primary amine in DMSO at 80 °C. Subsequent treatment of the DMSO solution of the resulting *N*-alkyl nitroaniline with a solution of an aldehyde in EtOH and solid[24] $Na_2S_2O_4$ at 80 °C for 5 hours afforded the *N*-alkyl benzimidazoles **6a**–**6c** in good yields. Unlike the *N*-alkylation of non-symmetric benzimidazoles, which usually results in a mixture of regioisomers, application of this methodology to substituted *N*-alkyl nitroanilines led to the regioselective formation of *N*-alkylated non-symmetric benzimidazoles (entries 2 and 3).

N-Aryl nitroanilines **13c**–**13e**, prepared similarly by the reaction of the corresponding 1-fluoro-2-nitrobenzene with an aniline in DMSO at 100 °C, also underwent a smooth cyclization under the same conditions, ultimately allowing access to *N*-aryl benzimidazoles **6d**–**6f** (entries 4–6).[10,25]

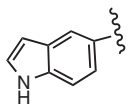
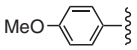
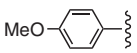
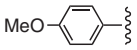
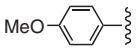
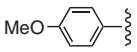


Scheme 2 Benzimidazoles from *o*-nitroanilines and aldehydes via an in situ nitro reduction

Table 1 Synthesis of N-H Benzimidazoles



1c 5

Entry	R^1	R^2	Product	Yield (%)[a]
1	H		**5a**	91
2	H	CH_3CH_2-	**5b**	80
3	H		**5c**	93
4	H		**5d**	95
5	H		**5e**	96
6	H		**5f**	68
7	7-OH[b]		**5g**	80
8	5-CN[b]		**5h**	74
9	5-CO_2H[b]		**5i**	90
10	5-NH_2[b]		**5j**	80
11	5-OH[b]		**5k**	89
12	5-Cl[b]		**5l**	88
13	5-COPh[b]		**5m**	95

[a] Isolated yields. All compounds produced satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra.
[b] Benzimidazole numbering.

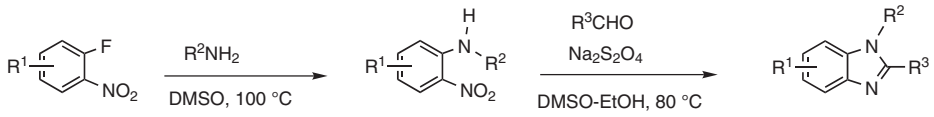
The mild reaction conditions involved in this method allows for the use of reagents, which previously failed to generate the desired products. For example, aldehydes such as pyrrole-2-carboxaldehyde, 2-methoxybenzaldehyde and 4-dimethylaminobenzaldehyde, which failed to yield the desired benzimidazole under a recently reported mild oxidation method,[14] were successfully incorporated using our approach. These results clearly demonstrate the mildness and the versatility of this method, which allows for a wide range of functional groups and substrates to be employed, affording otherwise problematic structures.

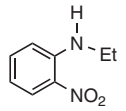
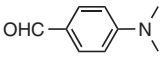
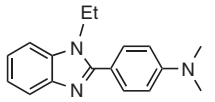
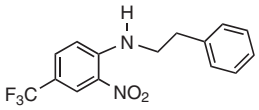
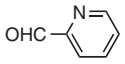
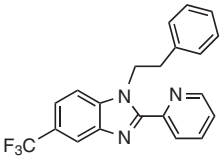
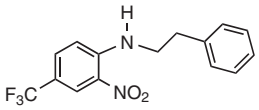
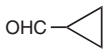
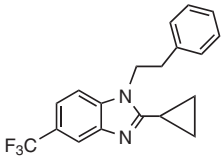
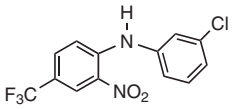
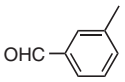
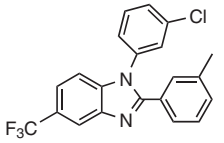
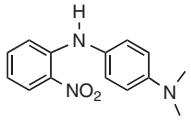
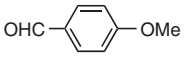
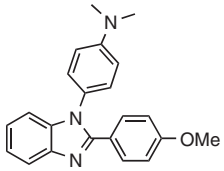
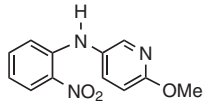
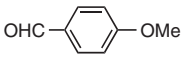
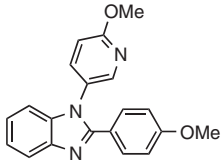
This methodology could be extended successfully to the synthesis of other imidazole containing heterocyclic ring systems such as 1*H*-imidazo-[4,5-b]pyridines **14a**, **14b** and 1*H*-imidazo-[4,5-f]quinoline **15** (Table 3). Slightly longer reaction times (12–24 h) were necessary for these cases in order to drive the reaction to completion. Also, selection of an appropriate solvent was critical in order to dissolve the starting *o*-nitroarylamine. For instance, DMF and DMSO were used as solvents for the synthesis of imidazopyridines (entries 1 and 2) and imidazoquinoline (entry 3), respectively. This indicates that the reaction works in solvents other than EtOH, which constitutes a significant advantage when compared to other methods, given that it is particularly when EtOH is used as the solvent that solubility problems are encountered with polar substrates. Generally, the synthesis of imidazopyridines relies on the preparation of a 2,3-diaminopyridine precursor followed by condensation of the diamine with a carboxylic acid or its equivalent under extensive heating.[26] These approaches are often inefficient and lack regiocontrol. Imidazoquinolines could also be obtained by the Doebner–von Miller quinoline synthesis method which involves the condensation of 5-aminobenzimidazoles and α,β-unsaturated carbonyl compounds or β-ketoesters, followed by a thermal cyclization step at high temperatures.[27] They could also be synthesized by the condensation of quinoline 5,6-diamines with acids or alternatively with aldehydes. In the latter, a mixture of mono- and disubstituted imidazoquinolines is usually observed.[28] On the contrary, our method does not require the synthesis and isolation of the starting diaminopyridines or aminobenzimidazoles, intermediates which sometimes might be difficult to isolate from aqueous media and might be prone to air oxidation depending on the ring substitution. Furthermore, our approach does not require excessively high temperatures, as is usually the case in the Doebner–von Miller quinoline synthesis.

In order to test our initial hypothesis postulating a rather controlled aryl nitro reduction during the reductive cyclization step and in order to explain the observed reaction outcome, we attempted some comparison experiments with two other reducing reagents which have been widely used in the aryl nitro group reduction (Table 4).

For example, when the reaction between *o*-nitroaniline and 4-methoxybenzaldehyde was tried under hydrogenolysis conditions (Pd/HCO_2H) or with $SnCl_2$,[29] a mixture of monosubstituted and 1,2-disubstituted benzimidazoles was formed with the disubstituted analog as the major component (entries 1 and 2). On the contrary, when the same reaction was subjected to the $Na_2S_2O_4$ conditions, the desired monosubstituted benzimidazole was generated as the sole product in high yield (entry 3). The presence of a catalytic amount (0.1 equiv) of methyl viologen chloride, an electron transfer catalyst utilized in the aryl nitro reduction,[22,30] did not alter the reaction outcome. Furthermore, the monosubstituted benzimidazole was maintained as the only product. Exclusive formation of the monosubstituted benzimidazole was also observed even when 6 equivalents of $Na_2S_2O_4$ were utilized with or without methyl viologen chloride. Only a trace amount of the disubstituted benzimidazole could be detected by LC/MS in all cases.

Table 2 Regioselective Synthesis of *N*-Alkyl and *N*-Aryl Benzimidazoles



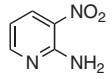
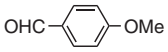
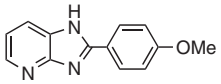
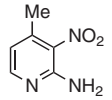
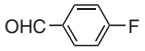
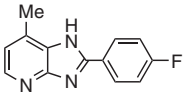
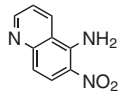
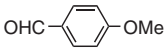
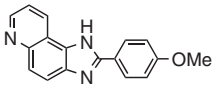
Entry	*o*-Nitroaniline[a]	Aldehyde	Product (Yield, %)[b]
1	 **13a**		 **6a** (88)
2	 **13b**		 **6b** (83)
3	 **13b**		 **6c** (85)
4	 **13c**		 **6d** (90)
5	 **13d**		 **6e** (91)
6	 **13e**		 **6f** (85)

[a] Not isolated. Prepared in situ and used directly in the reductive cyclization step.
[b] Isolated yields. All compounds produced satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra.

However, we found the reaction to be pH dependent. When the reaction was conducted at a basic pH = 8–10, by adding 3 equivalents K_2CO_3, presumably to prevent the decomposition of $Na_2S_2O_4$, only a small amount of the monosubstituted benzimidazole was produced in the same period of time, with no consumption of the starting 4-methoxybenzaldehyde. This suggests that a slightly acidic pH = 4–6, as is the case with our optimum conditions, might be required to catalyze the formation of nitroimine intermediate **7**, thus facilitating the nitro reduction.[31]

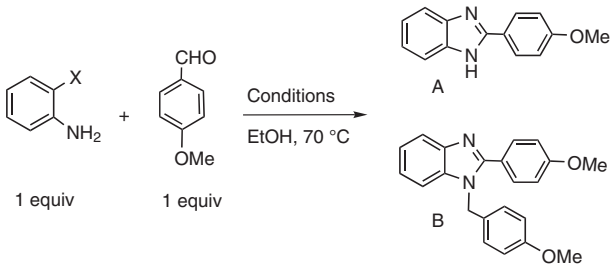
Should the reaction first involve the intermediacy of *o*-phenylenediamine rather than any other intermediate originating from its precursor *o*-nitroaniline, its cyclization with 4-methoxybenzaldehyde would presumably allow the exclusive formation of the monosubstituted benzimidazole as well. However, a mixture of monosubstituted and 1,2-disubstituted benzimidazoles was ob-

Table 3 Entry to Imidazopyridines and Imidazoquinolines

Entry	*o*-Nitroarylamine	Aldehyde	Product (Yield, %)[a]
1			 **14a** (85)
2			 **14b** (89)
3			 **15** (76)

[a] Isolated yields. All compounds produced satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra.

Table 4 Comparison Studies with Other Reducing Reagents



Entry	X	Conditions	A Yield (%)[a]	B Yield (%)[a]
1	NO_2	10 equiv HCO_2H/Pd	13	25
2	NO_2	6 equiv $SnCl_2$	7	30
3	NO_2	3 equiv $Na_2S_2O_4$	90	–
4	NH_2	-	13	25
5	NH_2	3 equiv $NaHSO_3$	–	40
6	NH_2	3 equiv $Na_2S_2O_4$	40	20

[a] Isolated yields.

served after heating *o*-phenylenediamine with 4-methoxybenzaldehyde in EtOH at 70 °C (entry 4). The assumption that sodium bisulfite ($NaHSO_3$), the by-product of the $Na_2S_2O_4$ aryl nitro reduction, could account for the exclusive formation of the monosubstituted benzimidazole by promoting the condensation of the resulting diamine with the aldehyde bisulfite adduct, was also put to the test.[32] When the bisulfite adduct of 4-methoxybenzaldehyde was treated with *o*-phenylenediamine in EtOH at 70 °C, the disubstituted benzimidazole was isolated as the sole product, presumably via the cyclization of an intermediate diimine **10** (entry 5). Also treating *o*-phenylenediamine with 4-methoxybenzaldehyde, in the presence of 3 equivalents of $Na_2S_2O_4$ in EtOH at 70 °C, was conducted to assess whether $Na_2S_2O_4$ by itself or its decomposition by-products would accelerate the formation of the monosubstituted benzimidazole via a rapid oxidation of the intermediate benzimidazoline **4b**. A mixture of mono- and disubstituted benzimidazoles in a 2:1 ratio was observed (entry 6).

Although we were not able to detect any of the putative hydroxylamine or *N*-hydroxy benzimidazoline intermediates during the reductive cyclization of *o*-nitroaniline and 4-methoxybenzaldehyde, by carefully monitoring the reaction by LC/MS, the absence of any disubstituted benzimidazole in conjunction with the exclusive formation of the monosubstituted benzimidazole indicates that the cyclization step might involve the intermediacy of hydroxylamine **8**. This could be the outcome of a controlled reduction of the nitroimine **7** to hydroxylamine **8** with $Na_2S_2O_4$ as the reducing agent.

In summary, we have found an efficient and versatile method for the preparation of a series of benzimidazoles as well of other imidazole containing ring systems, in one step, by the reduction of *o*-nitroarylamines in the presence of aldehydes. This method addresses successfully and uniformly not only the synthesis of N-H benzimidazoles, but the regioselective synthesis of *N*-alkyl and *N*-aryl-benzimidazoles as well, under one set of conditions. The reaction is readily applicable not only to high throughput solution phase parallel synthesis,[33] but also to large scale synthesis. Application of this methodology towards the synthesis of other heterocyclic ring systems is currently under investigation and will be communicated in due course.

^{1}H NMR spectra were recorded on a 300 MHz Varian FT spectrometer. ^{13}C NMR spectra were recorded on a 300 MHz Varian FT (75.4 MHz) spectrometer. Low resolution mass spectra were recorded on a Waters ZQ mass spectrometer with electrospray ionization (ESI). HRMS were recorded on a Micromass LCT mass spectrometer with ESI. TLC was carried out on EM Science precoated silica gel 60F 254 plates. Flash column chromatography was

performed with EM Science silica gel 60 (230–400 mesh). All reagents were purchased from Aldrich and used without further purification.

Method A
This procedure was used for the synthesis of most of the compounds listed in Table 1. A solution of *o*-nitroaniline (1.0 mmol) and aldehyde (1.0 mmol) in EtOH (4 mL) was treated with 1 M aq $Na_2S_2O_4$ (3.0 mmol, 3 mL). After heating the reaction mixture at 70 °C for 5 h, it was cooled to r.t. and treated dropwise with 5 N aq NH_4OH (2 mL). A precipitate was immediately formed which was then filtered, washed with water (2 × 15 mL) and dried under reduced pressure to afford the desired product in satisfactory purity (95% by HPLC: UV 254 nm, ELSD). Precipitated compounds with lower purity were further purified by flash chromatography on silica gel.

Method B
This procedure utilized the addition of solid sodium dithionite. A mixture of *o*-nitroaniline (1.0 mmol) and aldehyde (1.0 mmol) in EtOH (4 mL) was treated with solid $Na_2S_2O_4$ (3.0 mmol) and was then heated at 80 °C for 12 h. After removal of the solvent under reduced pressure, the resulting residue was partitioned between EtOAc (20 mL) and aq NH_4OH (2 N, 5 mL). The organic layer was isolated and the remaining aqueous layer was washed with EtOAc (2 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was then purified by flash chromatography on silica gel.

Method C
This procedure was used for the one-pot synthesis of *N*-alkyl and *N*-aryl benzimidazoles from the corresponding 1-fluoro-2-nitrobenzenes. A solution of 1-fluoro-2-nitrobenzene (1.0 mmol) and amine (1.0 mmol) in DMSO (1 mL) was heated at 100 °C for 10 h. After cooling to r.t., addition of aldehyde (1.0 mmol) in EtOH (4 mL) and solid $Na_2S_2O_4$ (3.0 mmol) followed, and the reaction mixture was heated at 80 °C for 12 h. The crude reaction mixture was then concentrated and treated dropwise with 5 N NH_4OH (2 mL), resulting in the formation of a precipitate which was then filtered, washed with water (2 × 15 mL) and dried under reduced pressure to afford the desired product in satisfactory purity (95% by HPLC: UV 254 nm, ELSD). Precipitated compounds with lower purity were further purified by flash chromatography on silica gel.

Compound 5a
It was prepared according to method A. Registry Number 36947-70-3. Spectral data were consistent with those reported in the literature.[34]

Compound 5b
It was prepared according to method B. Registry Number 1848-84-6. Spectral data were consistent with those reported in the literature.[19a]

Compound 5c
It was prepared according to method A. Registry Number 716-79-0. Spectral data were consistent with those reported in the literature.[35]

Compound 5d
It was prepared according to method A. Registry Number 1137-67-3. Spectral data were consistent with those reported in the literature.[36]

Compound 5e
It was prepared according to method A. Registry Number 166670-56-0. Spectral data were consistent with those reported in the literature.[5]

Compound 5f
It was prepared according to method A. Registry Number 3878-23-7. Spectral data were consistent with those reported in the literature.[37]

2-(4-Methoxyphenyl)-1*H*-benzimidazol-7-ol (5g)
It was prepared according to method A and isolated as a beige solid by flash chromatography on silica gel with EtOAc–hexanes (3:1) as the eluent.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.8 (br s, 1 H), 8.1 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 9.2 Hz, 2 H), 6.95 (q, *J* = 9.2, 8.4 Hz, 2 H), 6.55 (dd, *J* = 1.3, 7.5 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.66, 151.04, 146.52, 139.73, 129.01, 128.25, 123.46, 121.95, 114.26, 107.19, 105.10, 54.73.

HRMS: *m/z* [M + H] calcd for $C_{14}H_{13}N_2O_2$: 241.0977; found: 241.0984.

Compound 5h
It was prepared according to method A. Registry Number 167959-14-0. Spectral data were consistent with those reported in the literature.[38]

Compound 5i
It was prepared according to method A. Registry Number 174422-17-4. Spectral data were consistent with those reported in the literature.[39]

2-(4-Methoxyphenyl)-1*H*-benzimidazol-5-amine (5j)[27a]
It was prepared according to method B and isolated as a brown solid by flash chromatography on silica gel with EtOAc as the eluent. Registry Number 40655-15-0.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.78 (s, 1 H), 6.62 (dd, *J* = 1.2, 8.1 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.01, 151.42, 142.79, 139.05, 134.56, 128.14, 122.84, 116.73, 114.60, 112.83, 99.13, 55.53.

HRMS: *m/z* [M + H] calcd for $C_{14}H_{14}N_3O$: 240.1137; found: 240.1142.

2-(4-Methoxyphenyl)-1*H*-benzimidazol-5-ol (5k)
It was prepared according to method B and isolated as a white solid by flash chromatography on silica gel with EtOAc–hexanes (3:1) as the eluent.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.95 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 8.3 Hz, 2 H), 6.95 (s, 1 H), 6.78 (d, *J* = 8.3 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.59, 154.02, 151.50, 138.67, 133.31, 127.90, 121.99, 115.28, 114.30, 112.22, 98.77, 54.72.

HRMS: *m/z* [M + H] calcd for $C_{14}H_{13}N_2O_2$: 241.0977; found: 241.0980.

5-Chloro-2-(2-methoxyphenyl)-1*H*-benzimidazole (5l)
It was prepared according to method A and isolated as a beige solid. Registry Number 133688-90-1. A large-scale synthesis was carried out as follows:
A solution of 4-chloro-2-nitroaniline (25 g, 0.144 mol) and *o*-anisaldehyde (19.7 g, 0.144 mol) in EtOH (400 mL) was treated with 1 M aq $Na_2S_2O_4$ (0.432 mol, 432 mL) at r.t. After heating the reaction mixture at 70 °C for 5 h, it was cooled to r.t. and treated dropwise with 10 N aq NH_4OH (140 mL). A precipitate was immediately formed which was then filtered, washed with water and dried under reduced pressure to afford pure product (32.7 g, 88%); 95% by HPLC: UV 254 nm, ELSD) as a beige solid.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.66–7.50 (m, 4 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.22 (dd, *J* = 1.7, 8.3 Hz, 1 H), 7.05 (m, 1 H), 3.87 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 160.50, 153.35, 139.88, 137.47, 130.54, 130.05, 128.23, 123.12, 118.86, 116.40, 115.59, 114.53, 111.79, 54.69.

HRMS: *m*/*z* [M + H] calcd for $C_{14}H_{12}ClN_2O$: 259.0638; found: 259.0638.

[2-(2-Chlorophenyl)-1*H*-benzimidazol-5-yl](phenyl)methanone (5m)

It was prepared according to method B and isolated as a white solid by flash chromatography on silica gel with EtOAc–hexanes (1:1) as the eluent.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (m, 1 H), 8.12 (s, 1 H), 7.82 (m, 3 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.60 (m, 1 H), 7.48 (m, 3 H), 7.40 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.98, 151.75, 138.44, 132.87, 132.48, 132.36, 131.70, 131.64, 130.99, 130.24, 128.46, 128.12, 127.83, 125.69.

HRMS: *m*/*z* [M + H] calcd for $C_{20}H_{14}ClN_2O$: 333.0794; found: 333.0788.

4-(1-Ethyl-1*H*-benzimidazol-2-yl)-*N*,*N*-dimethylaniline (6a)

It was prepared according to method A and isolated as a brown solid by flash chromatography on silica gel with EtOAc–hexanes (2:1) as the eluent.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 1 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 7.38 (m, 1 H), 7.25 (m, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 3.00 (s, 6 H), 1.45 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.49, 151.38, 143.40, 135.76, 130.42, 122.26, 119.61, 117.76, 112.04, 109.86, 40.45, 39.85, 15.48.

HRMS: *m*/*z* [M + H] calcd for $C_{17}H_{20}N_3$: 266.1657; found: 266.1655.

1-(2-Phenylethyl)-2-pyridin-2-yl-5-(trifluoromethyl)-1*H*-benzimidazole (6b)

It was prepared according to method C and isolated as a yellow solid by flash chromatography on silica gel with EtAOc–hexanes (1:6) as the eluent.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.8 Hz, 1 H), 8.28 (d, *J* = 7.9 Hz, 1 H), 8.11 (s, 1 H), 7.81 (ddd, *J* = 1.7, 7.9 Hz, 1 H), 7.52 (dd, *J* = 1.3 7.8 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 7.37 (m, 1 H), 7.22 (m, 3 H), 7.10 (m, 2 H), 5.05 (t, *J* = 7.5 Hz, 2 H), 3.18 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.02, 150.20, 148.88, 142.18, 138.52, 138.19, 137.17, 128.98, 128.80, 126.98, 125.46, 125.10, 124.39, 123.27, 120.25, 118.05, 110.66, 47.45, 36.71.

HRMS: *m*/*z* [M + H] calcd for $C_{21}H_{17}F_3N_3$: 368.1374; found: 368.1375.

2-Cyclopropyl-1-(2-phenylethyl)-5-(trifluoromethyl)-1*H*-benzimidazole (6c)

It was prepared according to method C and isolated as a yellow solid by flash chromatography on silica gel with EtOAc–hexanes (1:6) as the eluent.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.02 (s, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.21 (m, 3 H), 7.05 (m, 2 H), 4.90 (t, *J* = 6.6 Hz, 2 H), 3.30 (t, *J* = 6.6 Hz, 2 H), 2.21 (m, 1 H), 1.40 (m, 2 H), 1.25 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.10, 137.73, 135.27, 129.74, 129.19, 127.55, 126.15, 123.45, 121.91, 114.19, 112.28, 79.95, 46.67, 35.06, 11.37, 7.69.

HRMS: *m*/*z* [M + H] calcd for $C_{19}H_{18}F_3N_2$: 331.1422; found: 331.1430.

1-(3-Chlorophenyl)-2-(3-methylphenyl)-5-(trifluoromethyl)-1*H*-benzimidazole (6d)

It was prepared according to method C and isolated as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.59 (dd, *J* = 1.8, 8.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.40–7.15 (m, 7 H), 7.05 (m, 1 H), 2.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.87, 142.76, 137.99, 137.56, 137.13, 135.48, 130.90, 130.88, 130.86, 130.37, 129.20, 128.99, 126.86, 126.17, 125.95, 125.74, 125.03, 120.70, 118.16, 110.94, 20.25.

HRMS: *m*/*z* [M + H] calcd for $C_{21}H_{15}ClF_3N_2$: 387.0876; found: 387.0877.

4-[2-(4-Methoxyphenyl)-1*H*-benzimidazol-1-yl]-*N*,*N*-dimethylaniline (6e)

It was prepared according to method C and isolated as a violet solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.70 (d, *J* = 7.0 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.20 (m, 4 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 3.75 (s, 3 H), 2.96 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.73, 152.60, 150.71, 143.10, 138.52, 131.08, 128.71, 125.30, 123.29, 123.09, 122.90, 119.54, 114.48, 113.27, 111.02, 55.90, 40.62.

HRMS: *m*/*z* [M + H] calcd for $C_{22}H_{22}N_3O$: 344.1763; found: 344.1772.

2-(4-Methoxyphenyl)-1-(6-methoxypyridin-3-yl)-1*H*-benzimidazole (6f)

It was prepared according to method C and isolated as a violet solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.50 (m, 3 H), 7.40–7.12 (m, 3 H), 6.85 (m, 3 H), 4.00 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.86, 160.91, 152.83, 145.67, 143.11, 137.97, 137.58, 131.17, 127.82, 123.49, 123.34, 122.04, 119.90, 114.22, 112.18, 110.20, 55.51, 54.21.

HRMS: *m*/*z* [M + H] calcd for $C_{20}H_{18}N_3O_2$: 332.1399; found 332.1395.

Compound 14a

It was prepared according to method A. Registry Number 63581-47-5. Spectral data were consistent with those reported in the literature.[40]

2-(4-Fluorophenyl)-7-methyl-1*H*-imidazo[4,5-b]pyridine (14b)

It was prepared according to method A and isolated as a yellow solid by flash chromatography on silica gel with EtOAc–hexanes (2:1) as the eluent.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.30 (m, 2 H), 8.17 (d, *J* = 5.3 Hz, 1 H) 7.42 (m, 2 H), 7.05 (d, *J* = 4.8 Hz, 1 H), 2.60 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.28, 162.81, 144.37, 129.79, 129.70, 127.04, 127.01, 119.63, 116.75, 116.53, 16.78.

HRMS: *m*/*z* [M + H] calcd for $C_{13}H_{11}FN_3$: 228.0937; found: 228.0948.

2-(4-Methoxyphenyl)-1*H*-imidazo[4,5-f]quinoline (15)[28b]
It was prepared according to method A. Registry Number 93201-92-4.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.81 (br s, 1 H), 8.68 (dd, *J* = 1.8, 4.4 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 9.2 Hz, 1 H), 7.75 (d, *J* = 9.2 Hz, 1 H), 7.48 (dd, *J* = 4.4, 8.3 Hz, 1 H), 6.97 (d, *J* = 9.2 Hz, 2 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.56, 152.08, 147.47, 145.10, 130.63, 128.02, 123.05, 122.06, 120.95, 114.25, 54.67.

HRMS: *m/z* [M + H] calcd for $C_{17}H_{14}N_3O$: 276.1137; found: 276.1136.

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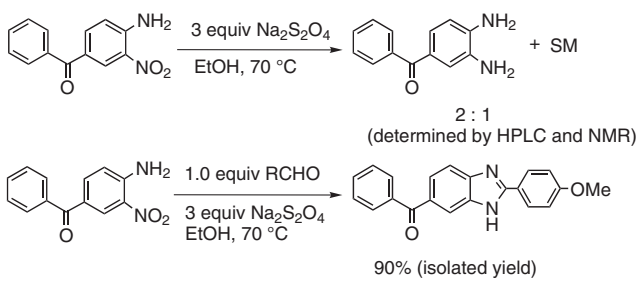

Scheme 3

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