A Highly Efficient Synthesis Route for the Rapid Generation of 1,2,5,6-Tetrasubstituted Benzimidazoles

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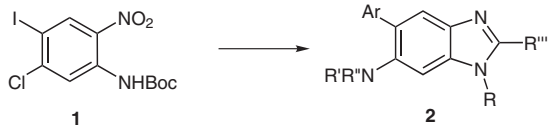
Abstract: Herein we describe the facile generation of novel benzimidazoles starting from 5-chloro-4-iodo-2-nitroaniline. A synthesis protocol was established which allows the parallel synthesis of compound arrays as well as the rapid generation of single representatives thereof.

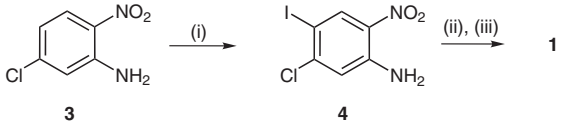
Key words: benzimidazoles, parallel synthesis, medicinal chemistry, palladium coupling, nucleophilic aromatic substitution

Hit discovery and lead generation are key strategies in modern pharmaceutical research. The identification of chemical starting points and the subsequent optimization of those are fundamental activities within medicinal chemistry.[1,2] Besides drug likeness and novelty of a compound class, the chemical tractability is mandatory for rapid success, particularly in the early stage of a drug discovery program. Benzimidazoles are well-known elements in nature and thus appear quite frequently in pharmaceutical products such as astemizole, omeprazole, or candesartan to name but a few. The chemical synthesis of the benzimidazole core is well established and has been reviewed in a number of journals and books.[3] We were looking for a synthesis strategy to generate 1,2,5,6-tetrasubstituted benzimidazoles of type **2** (Scheme 1), based upon diverse sets of readily available building blocks and the ability to generate compound arrays using parallel synthesis technologies. To obtain maximum flexibility for the array design, the introduction of the different residues should be possible at any stage of the reaction protocol. Our contribution herein describes a chemical synthesis route where an orthogonally functionalized benzene ring can be regarded as a core structure for the generation of highly diverse 1,2-phenylenediamines and the resulting benzimidazole derivatives thereof. Building blocks that were used for decorating the core scaffold consisted of alkyl and benzyl halides, primary and secondary amines, boronic acids, and carboxylic acids.

Starting from commercially available 5-chloro-2-nitroaniline (**3**) a further point of diversification can be easily introduced by ICl treatment to generate 5-chloro-4-iodo-2-nitroaniline (**4**, Scheme 2).[4] Treatment of compound **4** with Boc anhydride leads to the bis-Boc-protected compound which undergoes selective single Boc cleavage



Scheme 1 General synthesis route for 1,2,5,6-functionalized benzimidazoles **2** starting from Boc-protected 5-chloro-4-iodo-2-nitroaniline (**1**).

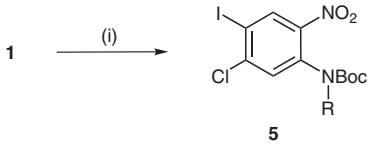


Scheme 2 Synthesis route for Boc-protected 5-chloro-4-iodo-2-nitroaniline (**1**). *Reagents and conditions*: (i) ICl, NaOAc, AcOH, 60 °C, 2 h, 99%; (ii) $(Boc)_2O$ (2 equiv), DMAP, THF, r.t., 16 h, quant.; (iii) TFA (2 equiv), CH_2Cl_2, 0 °C, 3 h, 99%.

when treated with TFA at 0 °C to generate the desired core structure **1** in high yield and purity.[5]

Instead of synthesizing full combinatorial arrays, we were rather looking for reaction protocols that are highly flexible and allow the rapid follow-up synthesis of singletons. Therefore we investigated broadly applicable reaction conditions for the introduction of R, R′R′′N and Ar, always starting from compound **1**.

For the introduction of R an N-alkylation of the Boc-protected anilide nitrogen was envisaged using alkyl and benzyl halides as building blocks. Due to the high acidity of this nitrogen, mild bases such as sodium hydride or cesium carbonate can be used for deprotonation. Addition of the corresponding alkyl or benzyl halides in DMF at room temperature leads in most cases to full conversions (Scheme 3). A catalytic amount of KI was added when using alkyl or benzyl chlorides as starting material.[6]



Scheme 3 Synthesis route for N-alkylation of **1**. *Reagents and conditions*: (i) alkyl or benzyl halide (1 equiv), Cs_2CO_3 (1 equiv), DMF, r.t., 16 h.

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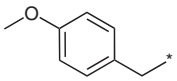
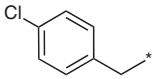
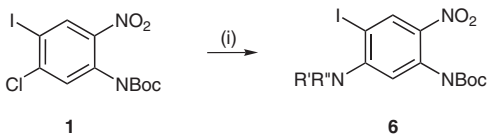
Table 1 Yields for Representative Compounds after N-Alkylation of **1**

Compound	R	Yield (%)
5a		86
5b		98
5c		95

Three representative compounds **5a–c** are depicted in Table 1. The yields reported correspond to products isolated via silica gel chromatography.

For the introduction of N-nucleophiles at position 5 of compound **1** a rapid and high-yielding conversion to intermediate **6** (Scheme 4) is observed when treating compound **1** with an excess of the corresponding amine R′R″NH in DMSO at elevated temperature (80 °C). The conversions observed are usually quantitative. Addition of water results in the precipitation of the products. No further purification is necessary although we crystallized the resulting material from MeOH to be able to report proper yields.[7]

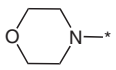
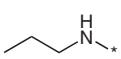


1 6

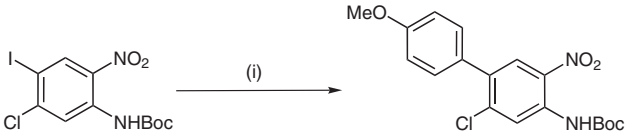
Scheme 4 Synthesis route for nucleophilic displacement of chlorine in **1**. *Reagents and conditions*: (i) primary or secondary amine (5 equiv), DMSO, 80 °C, 3 h.

Table 2 summarizes three representative compounds **6a–c** generated via S_NAr displacement reactions.

Table 2 Yields for Representative Compounds after S_NAr Reaction of **1**

Compound	RN	Yield (%)
6a		87
6b		98
6c		96

Although the chlorine atom is highly activated due to the *para*-nitro group present in the benzene ring system, boronic acid couplings can be achieved selectively when using mildly basic conditions (aq Na_2CO_3 soln). This is exemplified in Scheme 5 were the corresponding Suzuki product was generated successfully in an 88% yield after silica gel chromatography. The reaction was performed in



1 7

Scheme 5 Synthesis route for Suzuki coupling of (**1**). *Reagents and conditions*: (i) 4-methoxyphenylboronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.02 equiv), aq Na_2CO_3 soln, DMF, 80 °C, 16 h.

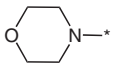
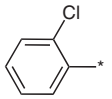
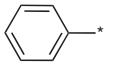
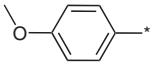
DMF under elevated temperature using tetrakis(triphenylphosphine)palladium as a catalyst.[8] Complete conversion to compound **7** was observed by LC-MS.

Full conversion and satisfactory yields are also observed with the chlorine being substituted with sterically more demanding residues as exemplified in Table 3 (Scheme 6). Here the Suzuki coupling was performed after the introduction of R′R″N. For library production a proper purification is not really necessary. The representative compounds shown in Table 4 were purified though via crystallization to report the corresponding yields.

8

Scheme 6 Synthesis route for 4,5-bis-substituted-2-nitroanilines. *Reagents and conditions*: (i) R′R″H (5 equiv), DMSO, 80 °C 2 h; (ii) $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (0.02 equiv), aq Na_2CO_3 soln, DMF, 80 °C, 16 h.

Table 3 Yields for Representative Compounds after Suzuki Couplings and Crystallization from MeOH or MeCN

Compound	R′R″N	Ar	Yield (%)
8a			78[a]
8b			65[a]
8c			78[b]

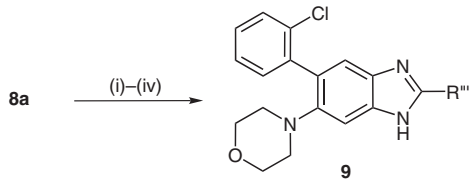
[a] Crystallization from MeOH.
[b] Crystallization from MeOH.

Various procedures have been established for the reduction of nitrobenzenes. For our purposes we felt that the Zn-powder method was most appropriate since it is a high yielding reaction, which tolerates many functional groups and can be handled reasonably well in a parallel synthesis set-up.[9]

Concerning the acylation step we investigated various coupling reagents where HATU was identified to deliver the best results. Besides the rapid reaction kinetics, it can also easily be removed by an additional extraction step.[10]

Boc cleavage with neat TFA leads to clean monoacylated 1,2-phenylenediamines which partially cyclize to the corresponding benzimidazoles. Complete conversion is obtained after TFA evaporation, dissolution in acetic acid and heating to 80 °C for two hours (for library production we extended the reaction time to 16 h).[11]

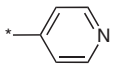
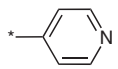
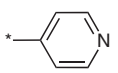
Based on the findings mentioned above various synthesis routes can be envisaged to create the corresponding compound arrays. We generated a sublibrary with R being H since the H-bonding capability of the benzimidazole moiety was required based on the pharmacophore hypothesis available. Therefore a reaction sequence was chosen starting from **1** with S_NAr reactions, followed by Suzuki couplings to generate intermediates of type **8**. Reduction, acylation, and cyclization lead to the corresponding benzimidazoles as shown in Scheme 7.



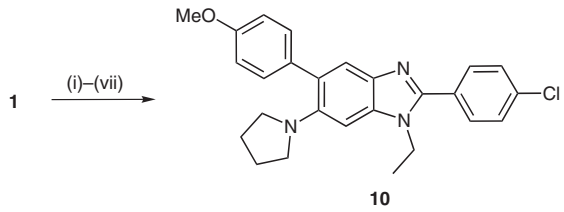
Scheme 7 Synthesis route for 2,5,6-trisubstituted-benzimidazoles. *Reagents and conditions*: (i) Zn powder, sat. NH_4Cl, MeOH, r.t., 16 h; (ii) RCOOH (1.1 equiv), HATU (1.1 equiv), DIPEA (1.1 equiv), DMF, r.t. 1 h; (iii) TFA, 2 h; (iv) AcOH, 80 °C, 16 h.

Table 4 summarizes three representative compounds **9a–c** generated from the corresponding nitroaniline **8a** via nitroreduction, N-acylation, Boc cleavage, and cyclization reactions to their corresponding benzimidazoles. The recoveries mentioned below summarize the last four reaction steps after purification via preparative HPLC. The yields for the single reaction steps are not reported separately since these chemical transformations usually proceed very smoothly under full conversion to the corresponding products.

Table 4 Yields for Representative Compounds after Preparative HPLC

Compound	R‴	Yield (mg/%)	Yield (%)
9a		30	47
9b		52	62
9c		67	76

To exemplify the feasibility for rapid singleton synthesis of such tetrasubstituted benzimidazoles we generated compound **10** in seven steps starting from compound **1** where only the product was isolated properly (Scheme 8). All crude intermediates were recovered from simple filtration after ice-water treatment of the corresponding reaction mixtures. Starting from 1 mmol of **1** we were able to isolate 32% of product **10** after silica gel chromatography (average 85% yield per step).



Scheme 8 Synthesis route for 1,2,5,6-tetrasubstituted-benzimidazoles. *Reagents and conditions*: (i) ethyl iodide (1 equiv), Cs_2CO_3 (1 equiv), DMF, r.t., 16 h; (ii) pyrrolidine (5 equiv), DMSO, 80 °C, 2 h; (iii) 4-methoxyphenylboronic acid (1.1 equiv), $Pd(PPh_3)_4$ (0.02 equiv), aq Na_2CO_3 soln, DMF, 80 °C, 16 h; (iv) Zn powder, sat. NH_4Cl, MeOH, r.t., 16 h; (v) 4-chlorobenzoic acid (1.1 equiv), HATU (1.1 equiv), DIPEA (1.1 equiv), DMF, r.t. 1 h; (vi) TFA, r.t., 2 h; (vii) AcOH, 80 °C, 16 h.

Using the reaction protocols described above, we were not only able to generate highly diverse subsets of compound arrays, but rather respond very quickly to the biological and physicochemical data obtained from the first libraries. Additionally, further benzoannelated heterocycles such as benzimidazolones, 1,4-dihydroquinoxaline-2,3-diones, and 1,3-dihydrobenzodiazepin-2-ones were successfully prepared from the corresponding 1,2-phenylenediamines obtained from **8**. Their detailed chemical syntheses and the corresponding biological activities will be reported in due course.

References and Notes

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(5) (a) Adam, G.; Alanine, A.; Goetschi, E.; Mutel, V.; Woltering, T. J. WO 2001029011, **2001**; *Chem. Abstr.* **2001**, *134*, 311234. (b) Adam, G.; Goetschi, E.; Mutel, V.; Wichmann, J.; Woltering, T. J. WO 2002083652, **2002**; *Chem. Abstr.* **2002**, *137*, 325447.
(6) **General Procedure for N-Alkylation Reactions**
(5-Chloro-4-iodo-2-nitro-phenyl)-carbamic acid *tert*-butyl ester (**1**, 1 mmol) was dissolved in DMF (10 mL) and alkylating agent (1 equiv) and Cs_2CO_3 was added. In case of benzyl chlorides, a catalytic amount of KI was added. The reaction mixture was stirred at r.t. overnight. After evaporation of the solvent, the crude was taken up in EtOAc and extracted with a sat. $NaHCO_3$ solution. The residue could be purified by column chromatography using SiO_2 or used directly in the following step.
(7) **General Procedure for Nucleophilic Displacement Reactions**
(5-Chloro-4-iodo-2-nitro-phenyl)-carbamic acid *tert*-butyl ester (**1**, 10 mmol) was dissolved in DMSO and amine (5 equiv) added. The reaction mixture was stirred at 80 °C for 3 h. After addition of H_2O, the product precipitated from the solution and was filtered off, washed twice with H_2O and dried under vacuum. The residue could be purified by

crystallization from MeOH or used directly in the following step.

(8) **General Procedure for Suzuki Coupling Reactions**
(5-Chloro-4-iodo-2-nitro-phenyl)-carbamic acid *tert*-butyl ester (**1**, 2 mmol) was dissolved in DMF. Then, arylboronic acid (1.1 equiv), tetrakis(triphenylphosphine)-palladium (0.02 equiv), and sat. Na_2CO_3 solution (1.5 mL) were added. The reaction mixture was heated to 80 °C overnight. The crude product was extracted from EtOAc–H_2O. The residue could be purified by crystallization from MeOH or MeCN or used directly in the following step.

(9) **General Procedure for Nitro Reductions**
The corresponding nitroanilines were suspended in a mixture of MeOH and sat. aq NH_4Cl (2:1). An excess of zinc powder was added and the reaction mixture stirred at r.t. overnight. The remaining solid was filtered off. After evaporation of the organic solvent, EtOAc was added and the crude product extracted with H_2O. The residue could be purified by column chromatography using SiO_2 or used directly in the following step.

(10) **General Procedure for Acylation Reactions**
The corresponding anilines were dissolved in DMF and added to a mixture of carboxylate (1 equiv), HATU, and DIPEA. The reaction mixture was stirred at r.t. for 2 h. The solvent was evaporated and the resulting residue taken up in EtOAc and extracted with aq $NaHCO_3$. The crude product was not further purified.

(11) **General Procedure for Cyclization Reactions**
The crude products from the previous step were treated with neat TFA and stirred at r.t. for 2 h. Depending on the residues introduced, partial cyclization to the corresponding benzimidazole was observed. Full conversion was obtained after evaporation of the TFA, dissolution of the mixture in AcOH and heating to 80 °C overnight. All final library products were isolated by preparative HPLC and characterized via LC-MS.