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'One-pot' nitro reduction–cyclisation solid phase route to benzimidazoles

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Abstract

An improved solid phase synthesis of benzimidazoles is described. A polymer-bound *o*-nitroaniline was reacted with aldehydes in DMF in the presence of $SnCl_2 \cdot 2H_2O$ at 60°C for three hours to give benzimidazoles in excellent purity and good yield after TFA cleavage. A library of 25 benzimidazoles was prepared using this 'one-pot' procedure.

Keywords: solid phase synthesis; benzimidazole; SynPhase™ Lantern.

In the course of evaluating our new proprietary products (SynPhase™ Lanterns) for SPOS, we have developed some new chemistry. Herein we wish to report an improved solid phase synthesis of benzimidazoles from readily available amines and aldehydes.

A number of groups have reported solid phase routes to benzimidazoles,[1–9] and the majority of these syntheses involve an *o*-nitroaniline intermediate of the type shown in Scheme 1 (i.e. compound **4**).[1–4,6–9] Smith et al.[9] recently reported a synthesis of 2-arylaminobenzimidazoles on SynPhase™ Crowns, which involved an intermediate like **4**. We, however, intended to use the route reported by Mayer et al.[3] to synthesize 1,2,5-trisubstituted benzimidazoles on our latest solid phase product SynPhase™ Lanterns.

Thus, the Wang linker was attached to chloromethylpolystyrene Lanterns[11a] **1** using a two-step process. The loading of the Wang Lanterns **2** was established by coupling Fmoc-β-Ala-OH and then performing a quantitative Fmoc analysis. Coupling of 4-fluoro-3-nitrobenzoic acid onto the Wang linker was complete in two hours using diisopropylcarbodiimide and 4-dimethylaminopyridine for carboxyl activation. Substitution of the fluorobenzene **3** by *n*-propylamine gave the corresponding *o*-nitroaniline **4** ($R^1 = -CH_2CH_2CH_3$ in Scheme 1) in greater than 95% purity, as judged by HPLC analysis of the cleaved compound. Reduction of the *o*-nitroaniline **4** with tin(II) chloride dihydrate at room temperature, however, gave inconsistent results in our

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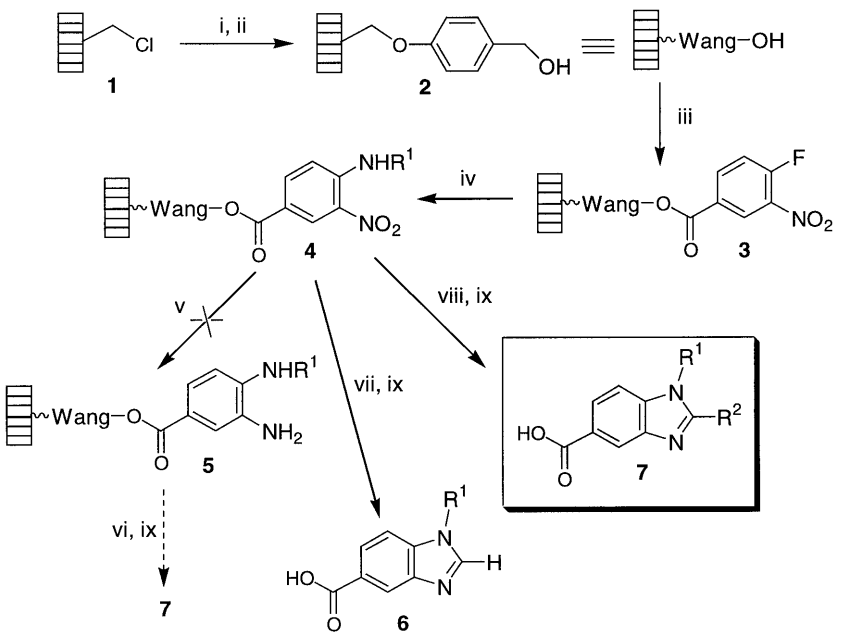
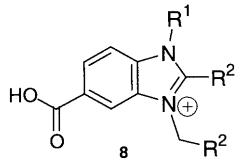


Scheme 1. *Reagents and conditions*: (i) 4-hydroxybenzaldehyde, $^{t}BuO^{-}K^{+}$, DMA, 60°C, 18 h; (ii) $NaBH_4$, EtOH, DMF, rt, 18 h; (iii) 4-fluoro-3-nitrobenzoic acid, DIC, DMAP, DMF, rt, 6 h; (iv) R^1NH_2, 5% DIEA/DMF, rt, 6 h; (v) $SnCl_2{\cdot}2H_2O$, DMF, rt; (vi) R^2CHO, DDQ, DMF; (vii) $SnCl_2{\cdot}2H_2O$, DMF, 60°C, 18 h; (viii) $SnCl_2{\cdot}2H_2O$, R^2CHO, DMF, 60°C, 3 h (ix) 20% TFA/DCM, rt, 1 h

hands. In addition, the use of either $SnCl_2{\cdot}2H_2O$ or $SnCl_2$ in either DMF or NMP as solvent produced only a small amount of the desired product along with other products which were not characterized.

These results are interesting, given that three out of the eight published solid phase routes to benzimidazoles involve tin(II) chloride reduction of an *o*-nitroaniline intermediate using DMF as solvent at room temperature and four out of eight used NMP as solvent at either room temperature or 50°C. Some authors specify that they used the hydrate of tin(II) chloride, but others simply mention $SnCl_2$. Smith et al.[9] did report, however, that they 'occasionally observed incomplete reduction of the nitro group', using 2 M $SnCl_2$ in NMP at room temperature overnight. Phillips and Wei[1] have reported that tin(II) chloride gave inconsistent results, and they subsequently used $NaBH_4$–$Cu(acac)_2$ to carry out the nitro reduction in their benzimidazole synthesis. In a later paper,[12] however, in which they describe the solid phase synthesis of benzimidazolones, Wei and Phillips report that tin(II) chloride (1.0 M $SnCl_2{\cdot}2H_2O$/DMF/30 h) was superior to $NaBH_4$–$Cu(acac)_2$ for *o*-nitroaniline reduction. In Pan and Sun's paper,[13] the reduction of support-bound *o*-nitroanilines has also been an intermediate step in the synthesis of benzopiperazinones. While Lee et al.[14] obtained complete reduction using $SnCl_2{\cdot}2H_2O$ in DMF at room temperature for 24 h, Morales et al.[10] observed incomplete reduction when the reduction was carried out with tin(II) chloride in aqueous DMF at room temperature, even for prolonged periods (2 M aqueous $SnCl_2$/DMF/25°C/overnight to 4 days). However, they managed to achieve complete reduction on Wang resin by heating the *o*-nitroanilines with tin(II) chloride in aqueous DMF at 80°C overnight.

In the present case, treatment of the *o*-nitroaniline 4 ($R^1 = -CH_2CH_2CH_3$) with $SnCl_2 \cdot 2H_2O$ in DMF at 60°C overnight produced exclusively 1-propyl-2(*H*)-benzimidazole **6**. This type of product has been reported previously by Tumelty et al.,[4] and is presumably formed via formylation of the aniline nitrogen,[15] nitro reduction and cyclization. Formylation of the aniline nitrogen is believed to assist nitro reduction, since neither benzimidazole **6** nor any clean reduction product of the *o*-nitroaniline **4** (viz. **5**) was obtained when the reduction was performed in NMP. This prompted us to investigate whether benzimidazoles might be synthesized directly (albeit via a different mechanism) by heating a mixture of the *o*-nitroaniline **4**, aldehyde and $SnCl_2 \cdot 2H_2O$ in DMF. In fact, heating a mixture of the *N*-propylaniline **4** ($R^1 = -CH_2CH_2CH_3$), propionaldehyde ($R^2 = -CH_2CH_3$) and $SnCl_2 \cdot 2H_2O$ in DMF at 60°C overnight led to the desired benzimidazole **7** (42%) along with a side-product (53%) after TFA cleavage. ESMS and ^1H NMR spectra of the side product are consistent with the benzimidazolium species **8** ($R^1 = -CH_2CH_2CH_3$, $R^2 = -CH_2CH_3$).



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After extensive optimization, the desired product **7** ($R^1 = -CH_2CH_2CH_3$, $R^2 = -CH_2CH_3$) was obtained in 74% purity (by HPLC) along with 25% of the side product **8** ($R^1 = -CH_2CH_2CH_3$, $R^2 = -CH_2CH_3$). The optimized conditions[16] for 'one-pot' reduction–cyclisation involved using two molar equivalents of aldehyde (relative to the loading of the Wang linker: 36 μmol/D-series Lantern) and 0.75 M $SnCl_2 \cdot 2H_2O$ (10 molar equivalents) in DMF and heating at 60°C for three hours. The optimum concentration of tin(II) chloride (0.75 M) determined for this reaction is well below that typically used[3,4] (2.0–3.0 M) for the reduction of nitrobenzenes attached to a solid support. Using the optimized method, a library of 25 benzimidazoles was synthesized from five amines ($5 \times R^1NH_2$ in Scheme 1) and five aldehydes ($5 \times R^2CHO$ in Scheme 1). For each amine/aldehyde combination, two products were obtained, the desired benzimidazole **7** and the benzimidazolium side-product **8** (see Table 1). Clearly, this 'one pot' method can provide benzimidazoles of excellent crude purity and in good yield, but it should be noted that the

Table 1
Product distribution and HPLC purities of 5×5 benzimidazole library[a]

R^2 (from aldehydes)	R^1 (from amines)				
	n-Propyl	*n*-Butyl	Benzyl	4-Methoxy-benzyl	4-Trifluoromethylbenzyl
Ethyl	74 (25)	56 (32)	73 (25)	72 (27)	76 (20)
n-Propyl	77 (20)	72 (24)	72 (24)	70 (25)	73 (20)
Phenyl	93 (4)	92 (5)	88 (7)	89 (4)	83 (9)
4-Methoxyphenyl	91 (3)	88 (5)	85 (4)	89 (3)	79 (6)
3-Trifluoromethylphenyl	93 (3)	93 (4)	90 (3)	92 (3)	87 (4)

[a] Notes: (1) HPLC purities are given as area %; (2) all compounds gave the expected molecular ions in positive ion ESMS; (3) minor products (area % shown in parentheses) were characterized by LCMS; (4) selected samples gave satisfactory ^1H NMR spectra;[17] (5) crude yields of benzimidazoles were approximately 85%, based on weights of cleaved compounds.

aliphatic aldehydes used in our study gave rise to a significantly greater proportion of the benzimidazolium side-products compared with the benzaldehydes. The product ratios determined by HPLC and shown in Table 1 are consistent with those observed in the ^{1}H NMR spectra.

In summary, we have demonstrated that benzimidazoles can be efficiently prepared from a support-bound *o*-nitroaniline using a 'one-pot' reduction–cyclisation method. This approach has provided the shortest solid phase synthesis of benzimidazoles to date. Since a wide range of amines and aldehydes are commercially available, a large number of benzimidazoles can be easily prepared using this method. It is worth noting that this 'one-pot' method has also been applied to other Lantern products (e.g. Rink amide[11b] and HMP[11c]) and commercially available Wang resins to produce benzimidazoles in excellent purity.

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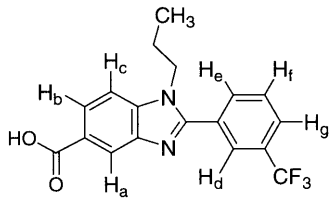
16. A typical procedure is as follows: each *o*-nitroaniline D-series Lantern **4** is treated with 0.5 mL of a solution of aldehyde (0.15 M, 2 molar equivalents) and $SnCl_2{\cdot}2H_2O$ (0.75 M, 10 molar equivalents) in DMF at 60°C for 3 h. The reaction mixture was allowed to cool briefly and the reagent solution decanted. The Lanterns were washed with DMF (3×3 min) and DCM (3×3 min), and air dried. Each Lantern was cleaved in a polypropylene tube with 0.7 mL of 20% TFA/DCM for 1 h. The Lantern was removed and the cleavage solution evaporated. The residue was dissolved in 90% CH_3CN/H_2O for HPLC and MS analysis.
17. For example, compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58, (d, $J=1.2$ Hz, H_a), 8.13 (dd, $J_1=1.2$ Hz, $J_2=8.4$ Hz, H_b), 8.00 (s, H_d), 7.98 (d, $J=8.4$ Hz, H_g), 7.87 (d, $J=8.0$ Hz, H_e), 7.75 (t, $J=8.0$ Hz, H_f), 7.54 (d, $J=8.4$ Hz, H_c), 4.43 (t, $J=7.6$ Hz, $N\underline{CH_2}CH_2CH_3$), 1.90 (m, $NCH_2\underline{CH_2}CH_3$), 0.91 (t, $J=7.6$ Hz, $NCH_2CH_2\underline{CH_3}$).



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