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Solid-phase synthesis of benzimidazole *N*-oxides on SynPhase™ Lanterns

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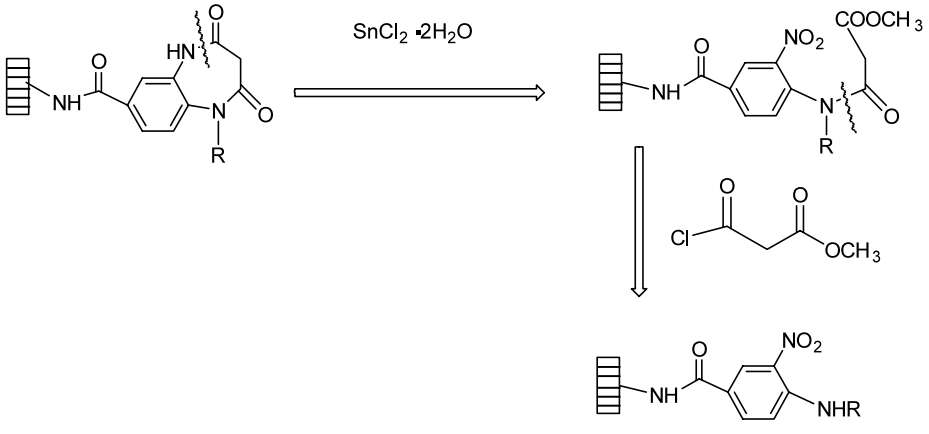
Abstract—A solid-phase synthesis of benzimidazole *N*-oxides was developed while attempting to synthesize 1,5-benzodiazepine-2,4-diones. The key step of the synthesis involves the reduction of an arylnitro to a hydroxyamino intermediate which subsequently condenses with an internal carbonyl group to give a benzimidazole *N*-oxide. A library of nine benzimidazole *N*-oxides was prepared on SynPhase™ Lanterns using this reduction–cyclization methodology.

Benzimidazole *N*-oxides are a group of compounds with an interesting history. Although benzimidazole *N*-oxides were discovered as early as 1887, as a by-product from the reduction of *N*-acyl-*o*-nitroanilines with tin/hydrochloric acid or with ammonium sulfide, research on benzimidazole *N*-oxide chemistry was dormant for several decades and was only revived in the 1960s.[1] Benzimidazole *N*-oxides have been reported as useful synthetic intermediates for preparation of benzimidazoles with antihistaminic activities,[2–5] and have been used in chemically modified rubber compositions.[6] While there have been numerous established solution phase synthetic methods to prepare benzimidazole *N*-oxides,[1] no solid-phase syntheses have been reported. Herein, we report a solid-phase synthesis of benzimidazole *N*-oxides, which was discovered incidentally while attempting to synthesize 1,5-benzodiazepine-2,4-diones on SynPhase™ Lanterns.

Recently, we reported the solid-phase synthesis of tetrahydro-1,4-benzodiazepine-2-ones on SynPhase™ Lanterns by reduction–cyclization of the arylnitro methyl esters.[7] We envisaged that the strategy of reduction–cyclization of the arylnitro methyl esters could be used to prepare 1,5-benzodiazepine-2,4-diones, which are compounds of great pharmaceutical interest.[8] As shown in the retrosynthesis of 1,5-benzodiazepine-2,4-diones (Scheme 1), the 1,5-benzodiazepine-2,4-dione



Scheme 1. Retrosynthesis of 1,5-benzodiazepine-2,4-diones.

Keywords: solid-phase synthesis; benzimidazole *N*-oxide; SynPhase™ Lantern.

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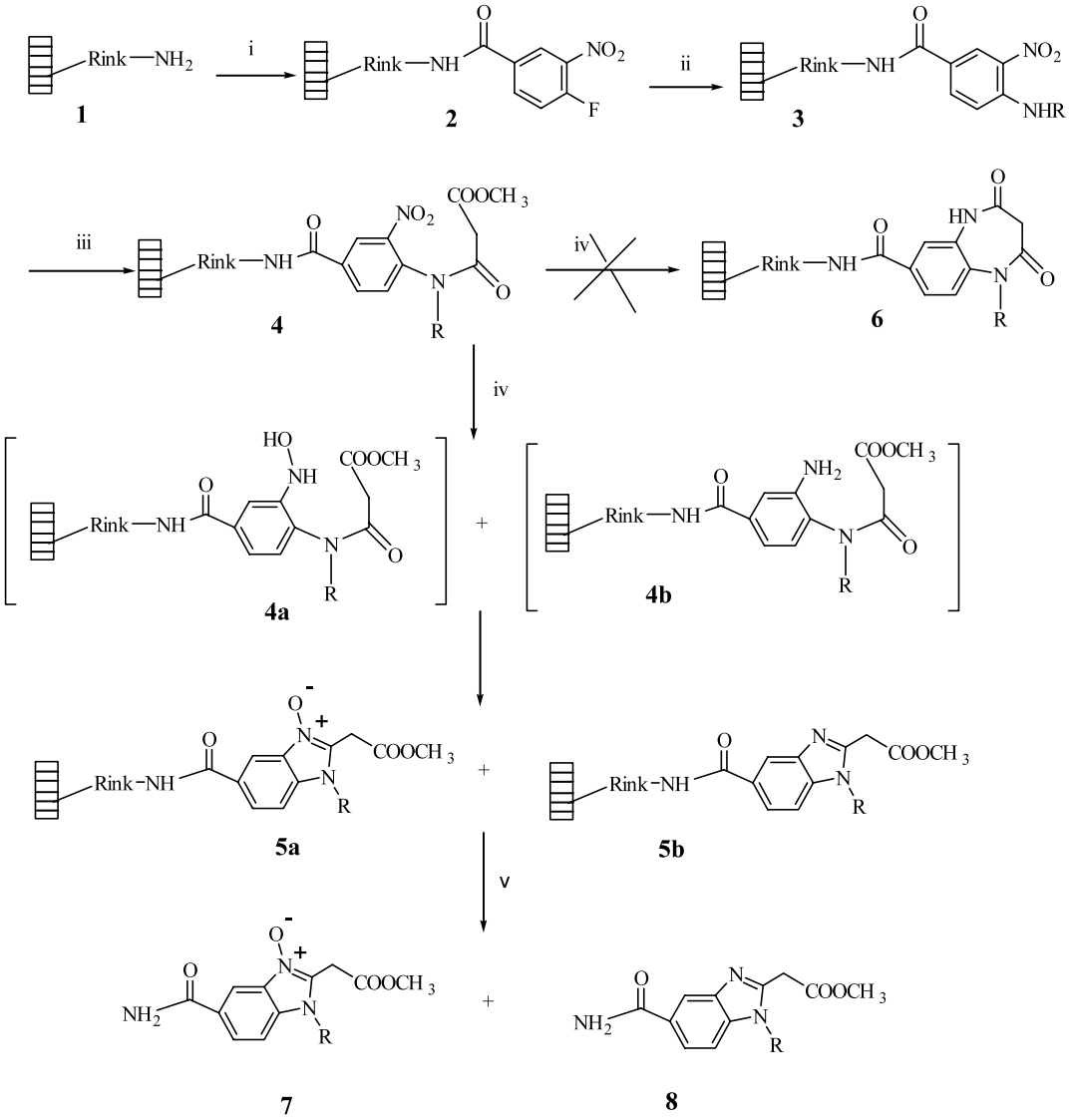
template was expected to be derived from reduction–cyclization of the arylnitro β-keto methyl ester, which itself can be assembled by acylation of an easily accessible *N*-substituted *o*-nitroaniline with methyl malonyl chloride. Thus, *N*-propyl *o*-nitroaniline **3** (R = propyl) was prepared in two steps from polystyrene SynPhase™ Rink Lanterns using the procedure reported previously (Scheme 2).[9] Subsequent acylation of the *o*-nitroaniline **3** with methyl malonyl chloride in DCM in the presence of DIEA at 40°C for 24 h was however incomplete, but after repeating the acylation, the arylnitro β-keto methyl ester **4** was obtained in 90% purity. Treatment of the arylnitro β-keto methyl ester **4** with 2.0 M tin(II) chloride dihydrate in NMP at room temperature for 16 h followed by TFA cleavage gave a major product (85%) along with a minor product (8%) as shown by HPLC. The molecular weights obtained by LC–MS indicated that the minor product was likely to be the benzimidazole **8** (R = propyl) which was presumably derived from reduction of the arylnitro to the arylaniline **4b** with subsequent cyclization to the amide carbonyl, instead of the expected ester carbonyl of the β-keto methyl ester. The fact that the major product had a molecular weight 16 greater than that of **8** implied that it could be the benzimidazole *N*-oxide **7**. The ^{1}H NMR[10] of the major product indicated the presence of a methyl ester (3.83 ppm, singlet) and a methylene next to the ester carbonyl (2.91 ppm, singlet), which was consistent with the structure of the benzimidazole *N*-oxide **7**. Furthermore, the methyl ester was hydrolyzed by LiOH to the corresponding carboxylic acid, as confirmed by ^{1}H NMR and LC–MS. The benzimidazole *N*-oxide **7** was believed to be formed via the hydroxyamino intermediate **4a**. Although benzimidazole *N*-oxides were formed merely as the *by-products* of reduction of *N*-acyl-*o*-nitroanilines in solution phase via the hydroxyamino intermedi-

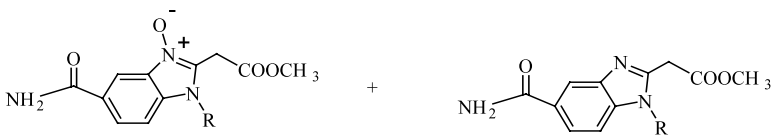


Scheme 2. *Reagents and conditions*: (i) 4-fluoro-3-nitrobenzoic acid, DIC, HOBt, DMF, rt, 16 h; (ii) RNH_2, 5% DIEA/NMP, 60°C, 6 h; (iii) methyl malonyl chloride, DIEA, DCM, 40°C, 2×24 h; (iv) $SnCl_2{\cdot}2H_2O$, NMP, rt, 5 h; (v) 20% TFA/DCM, rt, 1 h.

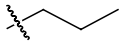
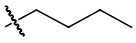
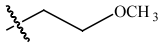
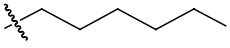
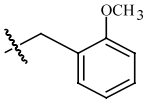
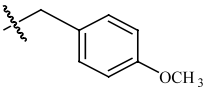
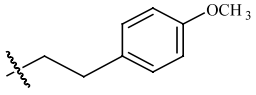
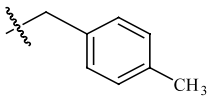
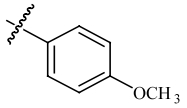
ate,[1] the current method presents the first example of a practical solid-phase synthesis of benzimidazole *N*-oxides. It is also worth noting that the entropically favored five-membered-ring benzimidazole (and oxide) was formed so predominantly that no trace of the expected seven-membered-ring 1,5-benzodiazepine-2,4-dione **6** was detected by LC–MS.

In an attempt to eliminate the minor product (benzimidazole **8**), the reduction–cyclization was optimized by varying reaction solvent, concentration of tin(II) chloride dihydrate and reaction time. Although formation of the benzimidazole **8** could not be completely eliminated, the reduction–cyclization was achieved in a shorter reaction time (5 h) and lower reaction concentration (0.5 M tin(II) chloride dihydrate). Further attempts to oxidize the benzimidazole to the oxide using in situ oxidants such as DDQ, urea hydrogen peroxide addition compound and oxygen (constant bubbling) were not successful.

Table 1. Analytical results of the benzimidazole *N*-oxides (**7a**–**i**)



7 **8**

entry	R in benzimidazole oxides (7a-j)	HPLC purity %*	Yield %	(M) (calculated)	(M+H) (found)
a		85 (8)	88	291	292
b		84 (13)	73	305	306
c		73 (14)	53	307	308
d		84 (11)	77	333	334
e		77 (17)	80	369	370
f		72 (8)	66	369	370
g		81 (12)	73	383	384
h		82 (7)	67	353	354
i		59 (14)	52	355	356

* Notes: (1) figures in parenthesis indicate percentage of benzimidazole by-product **8**.
(2) all benzimidazole by-products **8** were confirmed by LC-MS characterization.
(3) crude yields are based on weights of cleaved compounds.

To demonstrate that the above-mentioned reduction–cyclization strategy can be used as a general method for the preparation of benzimidazole *N*-oxides on solid supports, a small library was prepared on SynPhase™ Lanterns. Nine primary amines including an aniline were used to vary R. As expected, all benzimidazole *N*-oxides **7** were obtained as the major products in good purity along with the corresponding benzimidazoles **8** as the minor by-products.[11] The purity of benzimidazole *N*-oxides ranged from 59 to 85% while the average yield of the library was about 70%, as summarized in Table 1 All compounds were characterized by LC–MS and selected members of the library gave satisfactory ^{1}H NMR spectra.[10]

In summary, a solid-phase synthesis of benzimidazole *N*-oxides was discovered while attempting to synthesize 1,5-benzodiazepine-2,4-diones by tin(II) promoted reduction–cyclization of an arylnitro β-keto methyl ester. Although the benzimidazole *N*-oxides were generally contaminated by a small amount of benzimidazole, it presents the first example of a practical solid-phase synthesis of benzimidazole *N*-oxides.

Acknowledgements

The authors wish to acknowledge the helpful discussions with Dr. Andrew M. Bray and the assistance of Heather Patsiouras and Petro van Poppel in obtaining analytical data.

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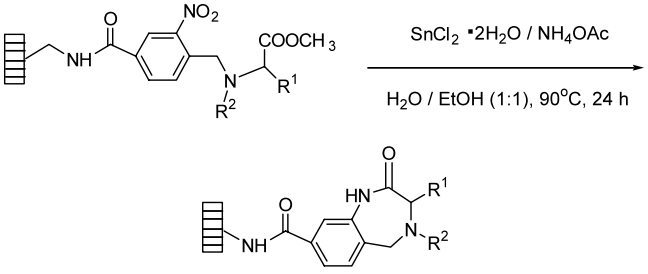

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9. Wu, Z.; Ede, N. J. *Tetrahedron Lett*. **2001**, *42*, 8115–8118.
10. ^{1}H NMR data for **7a** (R = propyl) (400 MHz, $CDCl_3$): δ 8.52, (s, 1H), 8.21 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 4.33 (t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 2.91 (s, 2H), 1.97 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H); **7b** (R = butyl) (400 MHz, $CDCl_3$): δ 8.50, (s, 1H), 8.16 (dd, J = 1.6 Hz, 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 4.32 (q or overlapping t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 2.91 (s, 2H), 1.88 (m, 2H), 1.44 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H) (minor peaks due to the corresponding benzimidazole are not quoted).
11. A typical procedure for the preparation of the benzimidazole *N*-oxides **7** (R = propyl) from *o*-nitroaniline **3** is as follows: Each *o*-nitroaniline D-Series Lantern **3** was suspended in 0.5 mL of a solution of 0.5 M DIEA in DCM and carefully treated with methyl malonyl chloride (0.5 M). After heating the reaction mixture at 40°C for 24 h, the reaction solution was decanted and the acylation repeated. Lanterns were washed with DMF (3×3 min), DCM (2×3 min) to give the *N*-acylated Lanterns **4**. Each of the *N*-acylated Lanterns **4** was treated with 0.5 mL of a solution of 0.5 M tin(II) chloride dihydrate in NMP at rt for 5 h. The reagent solution was decanted. The Lanterns were washed with DMF (2×3 min), 20% H_2O/THF (60°C, 3×10 min), MeOH (2×3 min), and DCM (2×3 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 to yield **7a** (9.5 mg, yield 88%). The residue was dissolved in 90% CH_3CN/H_2O for HPLC and LC–MS analysis.