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Novel Solid-Phase Synthesis of 1,2-Dialkoxyindoles†

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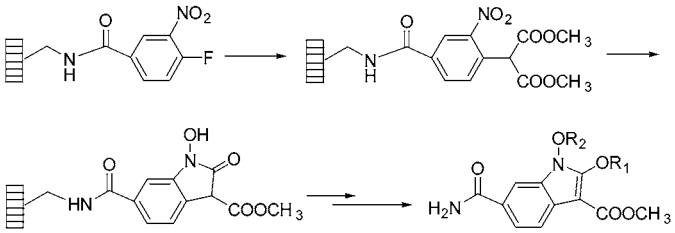
ABSTRACT



A novel solid-phase synthesis of 1,2-dialkoxyindoles on SynPhase lanterns is described. A unique C–C bond formation involving a nucleophilic displacement of a solid-bound aryl fluorine by dimethyl malonate afforded the arylnitro methyl ester, which upon treatment with tin(II) chloride dihydrate gave the *N*-hydroxyindolone. Alkylation of the *N*-hydroxyindolones afforded the corresponding *N*-hydroxy-2-alkoxyindoles, which were further alkylated to give the 1,2-dialkoxyindole. A library of 64 ($8R_1 \times 8R_2$) discrete 1,2-dialkoxyindoles was prepared using a color encoding technique on SynPhase A-series lanterns.

Indole nuclei have been considered to be one of the "privileged" substructures[1] since they are present in a wide range of natural compounds possessing biological activity. As a result, combinatorial solid-phase syntheses of indole libraries have attracted great interest over the past decade. Although numerous reports for solid-phase syntheses of indoles have appeared in the literature,[2−15] the synthetic methodologies are confined to mainly the Fischer indole synthesis,[14] palladium-catalyzed cyclization,[4,5,9−13] intramolecular Wittig or Wittig-like reaction,[3,15] and the Nenitzescu indole synthesis.[7] Among them, the palladium-catalyzed cyclization strategy has dominated the solid-phase syntheses of indoles. Herein we report a novel methodology for solid-phase synthesis of indoles via *N*-hydroxyindolone as the key intermediate.

Recently, we reported the solid-phase synthesis of benzimidazole *N*-oxides on SynPhase lanterns via a tin(II) reduction-promoted intramolecular condensation of an in situ-formed hydroxyamino group with a carbonyl group.[16] We considered using a similar strategy to synthesize *N*-hydroxyindolones and derivatives, which have been reported to be the key moiety of a number of biologically active compounds.[17,18] The retrosynthesis of the *N*-hydroxyindolone **4** is illustrated in Scheme 1. Using the above-mentioned

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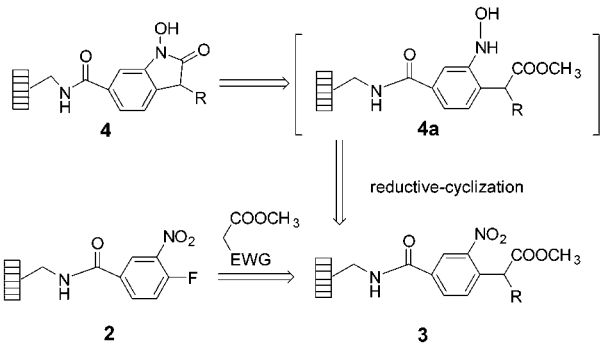
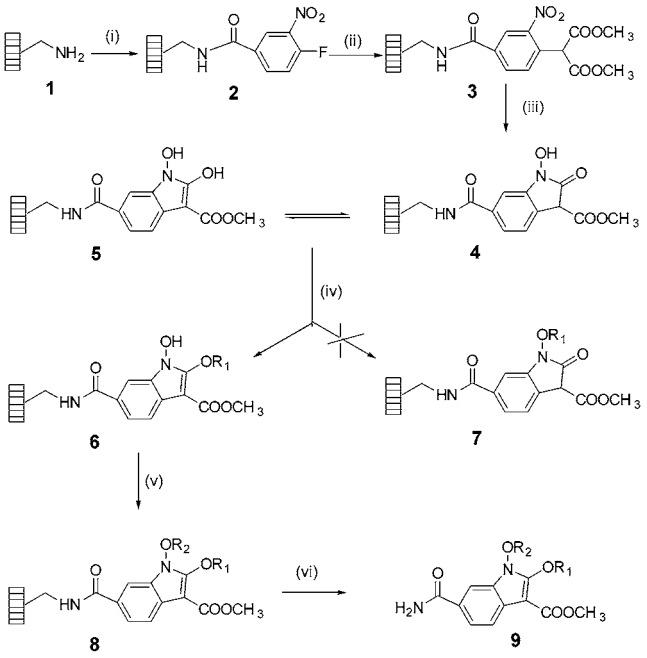
Scheme 1. Retrosynthesis of *N*-Hydroxyindolone on SynPhase Lanterns



Scheme 2. Solid-Phase Synthesis of 1,2-Dialkoxyindoles on SynPhase Lanterns



(i) 4-fluoro-3-nitrobenzoic acid, DIC, HOBt, 20% DMF/DCM, rt, 16 h; (ii) dimethyl malonate, KHMDS, NMP/toluene (1:1), 60°C, 4 h; (iii) tin(II) chloride dihydrate, NMP, rt, 4 h; (iv) R_1X, DMF, 60°C, 18 h; (v) R_2X, DIEA, KI, DMF, 60°C, 18 h; (vi) 20% TFA/DCM, 1 h.

reductive−cyclization strategy, reduction of the arylnitro methyl ester **3** was expected to afford the hydroxyamino intermediate **4a**, followed by an intramolecular cyclization to give the desired *N*-hydroxyindolone **4**.

4-Fluoro-3-nitrobenzoic acid has been extensively used for the solid-phase synthesis of a wide range of heterocycles, typically via an N- or S-involved S_NAr replacement of the fluorine to form a C−X bond.[19] We believed that a similar replacement of the solid-bound fluorine by a carbanion (Scheme 1, R = EWG) should take place, leading to C−C bond formation and thereby easy assembly of the arylnitro methyl ester **3**. In addition, Selvakumar and co-workers[20] and Ruhland et al.[21] have respectively used the S_NAr displacement of fluorine on an *o*-nitrofluorobenzene with activated enolates, including malonates, for the solution-phase syntheses of heterocycles. Thus, for initial reaction optimization, 4-fluoro-3-nitrobenzoic acid was attached to polystyrene Rink amide SynPhase D-series lanterns **1** using a standard coupling procedure (Scheme 2) to give **2**.[22a] Treatment of the lanterns **2** with dimethyl malonate/potassium bis(trimethylsilyl)amide (KHMDS) in NMP/toluene (1:1) at 60 °C for 4 h gave the arylnitro methyl ester **3** in 95% purity. This was confirmed by LC-MS and ^{1}H NMR analysis of the cleaved product.[23] The arylnitro methyl ester **3** was then treated with a solution of 0.5 M tin(II) chloride dihydrate in NMP at room temperature for 4 h to give the *N*-hydroxyindolone **4** in 94% purity. The determination of the structure of the *N*-hydroxyindolone **4**, however, was more complicated than expected. Although the molecular weight 250 as shown by LC-MS (ES) was consistent with the proposed target molecule, the ^{1}H NMR indicated that it appeared to be a mixture of the *N*-hydroxyindolone **4** and its tautomer 1,2-dihydroxyindole **5**. It was hoped that alkylation of the hydroxyl groups would stop the tautomerization, thereby assisting the elucidation of the structure. The solid-bound *N*-hydroxyindolone **4** was thus exposed to a solution of benzyl bromide in DMF at 60 °C for 18 h to give a product in 90% purity. LC-MS analysis clearly indicated that it was an alkylated derivative of **4**. However, its ^{1}H NMR showed that it was not the expected *N*-alkoxyindolone **7**, since there were only two types of aliphatic protons, with three protons (δ = 3.71 ppm) corresponding to the methoxy group and two protons (δ = 3.64 ppm) corresponding to the benzylic methylene group. This confirmed that the alkylated product was the *N*-hydroxy-2-benzyloxyindole **6** rather than the expected *N*-benzyloxyindolone **7** (R_1 = benzyl). It is presumed that the enol-like 2-hydroxy group of the 1,2-dihydroxyindole **5** is more nucleophilic than the *N*-hydroxy group, and the former was preferentially alkylated. Furthermore, it was observed that a partial second alkylation (on the *N*-hydroxy group of **6**) occurred when the reaction was conducted for an extended time and under more forcing conditions (e.g., 80 °C). This observation has opened up a new methodology for the solid-phase synthesis of indoles and in particular 1,2-dialkoxyindoles, which have not been previously reported.

A selection of alkyl halides were reacted with the *N*-hydroxyindolone **4** using the above-mentioned mild alkylating conditions to give the *N*-hydroxy-2-alkoxyindoles **6**. To introduce a second point of diversity into the indole molecule via the *N*-hydroxy group, a variety of stronger alkylating conditions were attempted. For example, bases

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(22) (a) For more information on SynPhase lanterns, please refer to Mimotopes website (http://www.mimotopes.com). (b) SynPhase Technical Note STN 003-1 describing free chemistry transfer between A-, D-, and L-series lanterns is available at Mimotopes website. (c) Colored Spindles and Cogs can be purchased from Mimotopes.
(23) All analytical data were obtained from the cleaved products.

Table 1. Purity and Yield of 1,2-Dialkoxyindoles **9**[a] (Scheme 2)

	R2							
R1	allyl	propyl	benzyl	3-chlorobenzyl	4-*tert*-butylbenzyl	4-fluorobenzyl	3-methoxybenzyl	3-methylbenzyl
allyl	84 (85)	83 (87)	85 (88)	76 (80)	76 (75)	81 (84)	67 (70)	72 (75)
benzyl	73 (80)	71 (80)	79 (83)	76 (81*)	78 (80)	80 (81*)	77 (80*)	73 (75)
4-fluorobenzyl	76 (80*)	80 (83)	75 (80)	64 (70)	74 (75)	80 (85)	78 (79)	54 (60)
3-methoxybenzyl	70 (75)	82 (85)	79 (84)	64 (70)	65 (70)	70 (71*)	73 (75)	73 (77)
4-methylbenzyl	63 (70)	80 (82)	73 (73)	73 (72)	66 (70)	75 (77)	65 (70)	82 (85)
4-bromobenzyl	75 (77)	79 (80)	67 (70)	77 (78)	75 (78)	79 (80)	66 (70)	74 (76)
3-chlorobenzyl	69 (70)	77 (81)	64 (70)	66 (72)	70 (73)	69 (70)	66 (65)	70 (70)
3,5-difluorobenzyl	59 (66)	67 (70)	56 (65)	55 (65)	51 (55)	59 (60)	53 (55)	77 (75)

[a] Notes: (1) HPLC purities are given as area %; (2) all compounds gave the expected molecular ions in positive ion ESMS; (3) selected samples gave satisfactory ^{1}H and ^{13}C NMR spectra; (4) crude yields given in parentheses were based on the weight of dried samples and were consistent with the ^{1}H NMR quantitation results of selected samples* using 1,1,1-trichloroethane as an internal standard.

such as $NaOCH_3$, NaH, KHMDS, DBU, or DIEA were used to deprotonate the *N*-hydroxy group, while KI was added to facilitate the nucleophilic displacement. After some experimentation, the *N*-hydroxy-2-benzyloxyindole **6** (R_1 = benzyl) upon treatment with 3-methoxybenzyl bromide in the presence of KI and DIEA in DMF at 60 °C for 18 h was cleanly converted to the 1,2-dialkoxyindole **9** (R_1 = benzyl, R_2 = 3-methoxybenzyl) in good purity (77%). The structure of the 1,2-dialkoxyindole **9** was confirmed by LC-MS, ^{1}H NMR, and ^{13}C NMR. Using the above-mentioned alkylating conditions afforded 1,2-dialkoxyindoles **9** when a variety of R_2X were reacted with the *N*-hydroxy-2-benzyloxyindole **6**.

To demonstrate the application of this new methodology for the solid-phase synthesis of 1,2-dialkoxyindoles, we synthesized a library of 64 ($8R_1 \times 8R_2$) 1,2-dialkoxyindoles on SynPhase A-series lanterns,[22a] which have approximately twice the loading of D-series lanterns (75 vs 35 μmol). It should be pointed out that since the chemical reactions can be freely transferred between SynPhase A-, D-, and L-series lanterns, no reoptimization was required for the library synthesis.[22b] To facilitate the library synthesis, a color encoding directed split-and-pool technique was employed. Thus, 64 lanterns **4** were divided into 8 groups of 8 lanterns and each group of lanterns were attached to colored Spindles[22c] (for R_1, 8 colors in total), as shown in Figure 1. To each of the Spindle-attached lanterns was loaded a colored Cog (for R_2, 8 colors in total, Figure 1). For the first combinatorial step, the lanterns **4** with the same color Spindles were pooled together to react with one of $8 \times R_1X$ (8 reactions in total). After the reaction, all lanterns were combined for washing to give the lantern-bound *N*-hydroxy-2-alkoxyindoles **6**. For the second combinatorial step, the lanterns **6** with the same color Cogs were pooled together to react with one of $8 \times R_2X$ (8 reactions in total). All lanterns were then combined for washing to give 64 discrete lantern-bound 1,2-dialkoxyindoles **9**. Each lantern-bound 1,2-dialkoxyindole can be simply identified by the color of the attached Spindle (for R_1) and Cog (for R_2). Upon TFA cleavage, 1,2-dialkoxyindoles **9** were obtained typically in 75% purity and in 80% yield based on the initial loading of lanterns (Table 1). The whole library was analyzed by LC and LC-MS, and selected samples were characterized by ^{1}H and ^{13}C NMR (see Supporting Information).

In conclusion, a novel methodology for an efficient and convenient solid-phase synthesis of indoles was developed on SynPhase D-series lanterns, which involves the formation

Figure 1. Color encoding directed split-and-pool library synthesis on SynPhase lanterns.

(24) Typical procedure for the synthesis of 1,2-dialkoxyindole **9** from lantern-bound 4-fluoro-3-nitrobenzoic acid **2**: Each A-series lantern **2** was treated with 1.0 mL of a solution of 0.25 M dimethyl malonate and 0.25 M potassium bis(trimethylsilyl)amide in NMP/toluene (1:1) at 60 °C for 4 h. The reagent solution was decanted, and the lanterns were washed with DMF (3×3 min) and DCM (3×2 min) and air-dried to give **3**. Each lantern **3** was treated with 1.0 mL of a solution of 0.5 M tin(II) chloride dihydrate in NMP at room temperature for 4 h. The reagent solution was decanted, and the lanterns were washed with DMF (3×3 min), 20% H_2O/THF (60 °C, 4×10 min), MeOH (2×3 min) and DCM (3×2 min) and air-dried to give **4**. Each lantern **4** was treated with 1.0 mL of a solution of 0.5 M alkyl halide (R_1Br) in DMF at 60 °C for 18 h. The reagent solution was decanted, and the lanterns were washed with DMF (3×3 min) and DCM (3×2 min) and air-dried to give **6**. Each lantern **6** was treated with 1.0 mL of a solution of 1.0 M alkyl halide (R_2Br), 1.0 M DIEA, and 1.0 M KI in anhydrous DMF at 60 °C for 18 h. The reagent solution was decanted, and the lanterns were washed with DMF (5×3 min), MeOH (60 °C, 4×10 min), DCM (3×2 min) and air-dried to give **8**. Each lantern **8** placed in a well of a Beckmann tray was treated with 1.2 mL of 20% TFA/DCM for 1 h. The lanterns were removed, and the cleavage solution was evaporated in a SpeedVac to give the final product **9**, which was dissolved in 10% H_2O/CH_3CN for LC and LC-MS analysis.

of the key intermediate *N*-hydroxyindolone and subsequent conversion to 1,2-dialkoxyindoles by consecutive alkylations. This methodology has been used to synthesize a library of 64 discrete 1,2-dialkoxyindoles on SynPhase A-series lanterns.[24,25]

(25) Representative analytical data of 1,2-dialkoxyindole **9** (R_1 = benzyl, R_2 = 3-methoxybenzyl): brown oil, 28 mg, yield 77% ("purified yield" 62%, as determined by ^{1}H NMR quantitation); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (dd, AB system, J = 13.6 Hz, 2 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.53 (d, J = 10.8 Hz, 1 H), 4.89 (d, J = 10.8 Hz, 1 H), 6.66 (d, J = 7.2 Hz, 1 H), 6.78 (s, 1 H), 6.90−6.86 (m, 4 H), 7.19−7.07 (m, 4 H), 7.44 (d, J = 8 Hz, 1 H), 7.56 (d, J = 8 Hz, 1 H); ^{13}C NMR δ 39.61, 53.55, 55.33, 59.44, 78.75, 106.82, 114.97, 115.45, 122.26, 122.86, 124.42, 127.51, 128.05, 128.19, 129.72, 130.11, 132.86, 133.30, 135.37, 141.58, 159.79, 160.09, 160.49, 168.19, 168.36, 171.09; LC-MS (ES) t_R 8.11 min, m/z = 461 (M + H); HPLC t_R 8.34 min, 77% (214 nm). For more analytical data of library members, see Supporting Information.

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Supporting Information Available: Analytical data of LC, LC-MS, and NMR for the selected 1,2-dialkoxyindoles.[3] This material is available free of charge via the Internet at http://pubs.acs.org.

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