

Solid-Phase Synthesis of Naltrindole Derivatives Using Fischer Indole Synthesis Based on One-Pot Release and Cyclization Methodology

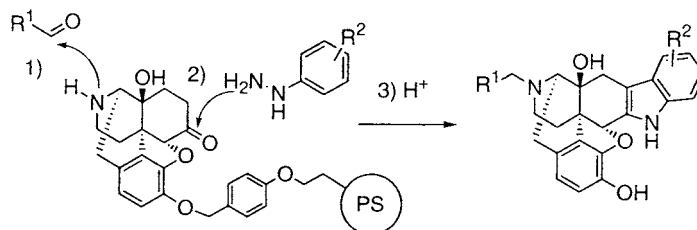
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ABSTRACT



We describe a new approach for the solid-phase synthesis of indoles **1** that involves a one-pot release and cyclization reaction of a solid-supported hydrazone through a Wang-type linker. Using this solid-phase methodology, we accomplished the synthesis of 40 naltrindole derivatives.

Combinatorial chemistry involving solid-phase synthesis has proven to be an important tool for drug discovery.¹ Solid-phase synthesis is especially effective for the high-speed synthesis of the chemical libraries of highly polar compounds because workup and purification can be achieved by only washing and filtration. We have already reported several solid-phase syntheses of small molecule libraries, including Vitamin D₃, glycoconjugates, and morphinan derivatives.² However, loading of the substrates to a solid matrix often reduces their chemical reactivity, thus resulting in low yields

of the desired compounds. Therefore, there is particular interest in developing new linking strategies to maintain the efficiency of the reaction using solid-linked substrates.³

Substituted indoles possess a wide range of biological properties and, as a result, have attracted considerable attention from organic chemists, thus resulting in the development of effective synthetic methodology for the synthesis of indole derivatives not only in the solution phase⁴ but also on a solid phase.⁵ Fischer indole synthesis is one of the most common and effective reactions for the

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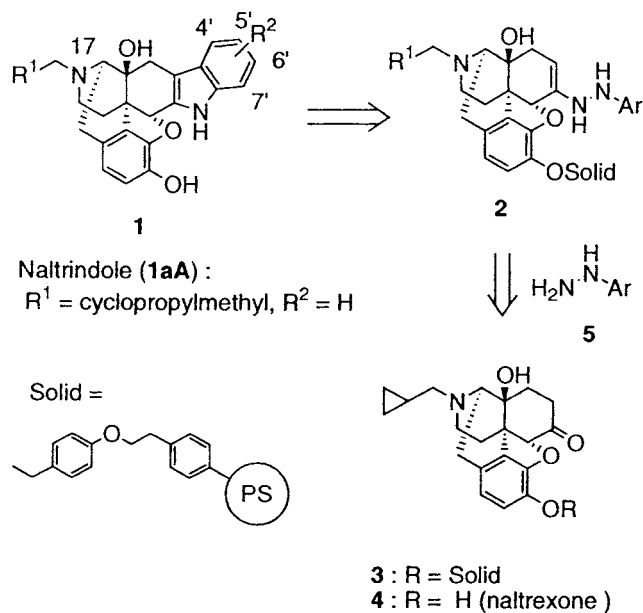
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synthesis of substituted indoles from a ketone and an arylhydrazine via cyclization of a hydrazone intermediate under strongly acidic conditions.⁶ There are few reports of the solid-phase synthesis of simple indole derivatives using ester-type linkers or a benzyloxy carbonyl linker, which are stable to strongly acidic conditions.⁷ If the hydrazone supported on resin through an acid-labile linker is isolable, exposure of the solid-supported hydrazone to the acidic cyclization conditions would result in simultaneous release and cyclization reactions to provide the substituted indole. The released hydrazone intermediate would easily undergo cyclization reaction in comparison to the solid-supported intermediate. Furthermore, this methodology requires no additional manipulation for release of the products from the resin. Herein we describe an effective solid-phase synthesis of indole derivatives by Fischer indole synthesis using a solid-supported ketone through a Wang linker.

Naltrindole (NTI) (**1aA**) is an efficient selective δ -opioid receptor ligand.⁸ The amino substitution at the N-17 position is essential for elicitation of intrinsic activity at the opioid receptor. Its indole moiety causes selective binding to δ -opioid receptors and, in addition, recently has been proposed to be critical in its immunosuppressive activity, which is not mediated via δ -opioid receptors.⁹ Therefore, for elucidation of structure–activity relationships, new, effective, and practical methodologies for the synthesis of naltrindoles **1** varying at the indole moiety and the 17-N-position are required.

Our strategy for the solid-phase synthesis of the NTI derivatives **1** based on the one-pot release and cyclization is illustrated in Scheme 1. The stepwise Fischer indole synthesis of ketones **3** with phenyl hydrazine **5** via hydrazone **2** would release the substituted indole **1**. A Wang linker on a

Scheme 1. Strategy for the Solid-Phase Synthesis of Naltrindoles **1**



hydroxymethylphenoxyethyl resin would be used as the polymer support. The linker could survive under mildly acidic conditions needed for the hydrazone formation and can be cleaved under the cyclization conditions. A phenyl 2-phenylethyl ether would be stable to these reaction conditions.

We first conducted the release and cyclization reaction to give naltrindole (NTI) (**1aA**) using solid-linked naltrexone **3** and phenylhydrazine (**5a**) (entry 1 in Table 1).¹⁰ Preparation

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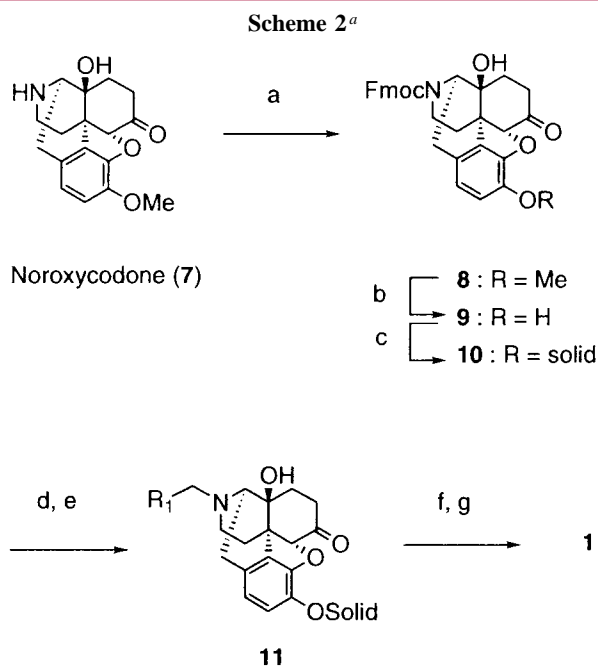
Table 1. Effect of Hydrazine on Solid-Phase Synthesis of Indole **1aA–jA**

entry	hydrazine	Ar	product	yield ^a (%)	purity ^b (%)
1	5a	phenyl	1aA	quant	93
2	5b	4-chlorophenyl	1bA	90	76
3	5c	4- <i>i</i> -propylphenyl	1cA	92	54
4	5d	1-naphthyl	1dA	88	93
5	5e	2-methylphenyl	1eA	95	85
6	5f	4-methylphenyl	1fA	92	68
7	5g	2-chlorophenyl	1gA	82	71
8	5h	4-methoxyphenyl	1hA	90	57
9	5i	2-methoxyphenyl	1iA	90	48
10	5j	3-methylphenyl	1jA	91	93 ^c

^a Yield was estimated by measurement of mass weight. ^b Purity was estimated by HPLC-MS analysis using UV absorption in 254 nm. ^c Mixture of 6'- and 4'-regioisomers in a ratio of 2.5:1.

of the solid-supported naltrexone **3** was achieved by treatment of commercially available naltrexone (**4**) with a hydroxymethylphenoxyethyl resin (0.42 mmol/g)¹¹ in the presence of diethylazodicarboxylate (DEAD) and PPh₃ in THF. The loading yield was determined by cleavage of **3**

under acidic conditions, followed by measurement of mass recovery of naltrexone (**4**), which was 92% on the basis of the resin. Fischer indole synthesis using solid-linked naltrexone **3** was examined next. Hydrazone formation of



^a Reagents and conditions: (a) FmocCl, Na₂CO₃ aqueous THF, rt, 88%; (b) BBr₃, CH₂Cl₂, 0 °C, 56%; (c) hydroxymethylphenoxyethyl polystyrene resin, DEAD, PPh₃, 1 h, rt; (d) 20% piperidine in CH₂Cl₂, rt; (e) **6**, NaBH₃CN, DMF–AcOH (100:1); (f) **5**, 4 Å MS, AcOH–CH₂Cl₂ (1:1), rt.; (g) 10% TFA /CH₂Cl₂, rt.

naltrexone **3** was achieved by treatment with an excess of phenylhydrazine (**5a**) under mildly acidic conditions (CH₂Cl₂/AcOH = 1:1) in the presence of 4 Å MS at room temperature. After removal of the excess phenylhydrazine (**5a**) by washing and filtration, exposure of the hydrazone **2** to 10% TFA in CH₂Cl₂ for 0.5 h released NTI **1aA** in quantitative yield with 93% purity, which was determined by HPLC-MS analysis of the residue on the basis of UV absorption at 254 nm.^{12,13} The applicability of the indole synthesis to other phenyl hydrazines **5b–j** is examined as

(10) Typical procedure for the solid-phase synthesis of naltrexone derivatives **1**: To a mixture of hydroxymethylphenoxyethyl resin (Watanabe; 0.42 mmol/g, 1.00 g, 420 μmol), naltrexone (**4**) (1.02 g, 3 mmol), and PPh₃ (0.45 g, 1.7 mmol) in THF (8 mL) was added DEAD (40% toluene solution, 0.68 mL, 1.5 mmol) in THF (2 mL) slowly at room temperature. After the mixture was shaken for 1 h at the same temperature, the solvents were then removed by filtration. The resulting beads were washed with THF, DMF, MeOH, THF, and CH₂Cl₂ and dried in vacuo to give resin-supported naltrexone **3** (1.05 g). The loading yield was determined by cleavage of **3** under acidic conditions, followed by measurement of mass recovery of naltrexone (**4**), which was 92% on the basis of the resin. To the beads (50 mg) were added 4 Å MS (powder, 60 mg) and the mixture of phenylhydrazine HCl in CH₂Cl₂–AcOH (1:1) (1 mL) at room temperature. After being shaken for 1 h at the same temperature, the mixture was filtered and then washed with DMF, MeOH, THF, and CH₂Cl₂. The resulting resins were treated with 10% TFA/CH₂Cl₂ (1 mL) for 30 min at room temperature, filtered, and then washed with CH₂Cl₂. The combined filtrates were evaporated and dried in vacuo to give 10.4 mg of morphinan compound **1aA** TFA salt with 93% purity determined by reversed-phase HPLC.

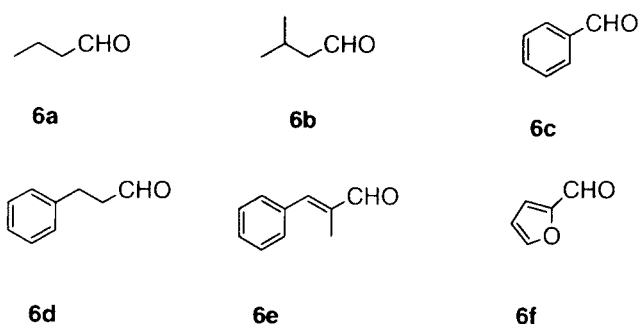


Figure 1. Aldehydes for a building block.

shown in Table 1. Most of the examples proceeded well to give the corresponding indoles **1bA**, **1dA–gA**, and **1jA** in excellent yields with a good purity (95–68%)¹¹ (entries 2, 4–7, and 10, Table 1). Substitution of the phenylhydrazine with an electron-donating group led to reduced purity of the desired indoles (entries 3, 8, and 9). Use of *m*-methylphenylhydrazine resulted in a mixture of two regioisomers **1hA** (6'-: 4'- = 2.5:1).^{8b}

Table 2. Combinatorial Synthesis of Naltrexone Derivatives **1aB–eG**

entry	aldehyde	hydrazine	product	yield (%) ^a	purity (%) ^b
1	11a	5a	1aB	77	81
2	11a	5b	1bB	81	68
3	11a	5c	1cB	76	65
4	11a	5d	1dB	62	81
5	11a	5e	1eB	88	74
6	11b	5a	1aC	76	80
7	11b	5b	1bC	81	79
8	11b	5c	1cC	79	49
9	11b	5d	1dC	59	86
10	11b	5e	1eC	88	86
11	11c	5a	1aD	85	77
12	11c	5b	1bD	90	82
13	11c	5c	1cD	81	64
14	11c	5d	1dD	61	88
15	11c	5e	1eD	94	83
16	11d	5a	1aE	71	72
17	11d	5b	1bE	81	76
18	11d	5c	1cE	79	55
19	11d	5d	1dE	60	89
20	11d	5e	1eE	92	78
21	11e	5a	1aF	71	63
22	11e	5b	1bF	77	72
23	11e	5c	1cF	74	60
24	11e	5d	1dF	56	52
25	11e	5e	1eF	83	66
26	11f	5a	1aG	76	79
27	11f	5b	1bG	91	77
28	11f	5c	1cG	85	48
29	11f	5d	1dG	64	83
30	11f	5e	1eG	91	80

^a Yield was estimated by measurement of mass weight. ^b Purity was estimated by HPLC analysis using UV absorption at 254 nm.

We next achieved a combinatorial synthesis of naltrindole derivatives **1** varying the 17-N-position and the indole ring. (Scheme 2) Six aldehydes **6a–f** for N-substitution and five hydrazines **5a–e** for indole formation were used (Figure 1). Protection of the secondary amine of noroxycodone (**7**) with Fmoc-Cl gave Fmoc derivative **8** (88%). Cleavage of the methyl ether of the phenol with boron tribromide provided phenol **9** in 55% yield. Immobilization of phenol **9** was achieved under Mitsunobu reaction conditions to provide the solid-supported ether **10**. The loading yield was determined by cleavage of **10** under acidic conditions, followed by measurement of mass recovery and HPLC analysis using UV absorption at 254 nm, to be 97% yield with 96.6% purity. Introduction of N-substitution to the Fmoc-protected amine **10** was achieved by removal of the Fmoc group with piperidine in DMF solution, followed by treatment with the six aldehydes **6a–f** and NaBH₃CN in DMF–AcOH (100:1), afforded the corresponding *tert*-amines **11** in good purity (76–89%), as determined by analysis of their cleaved residues using UV absorption at 254 nm. Reduction of the solid-linked ketone to the secondary alcohol was not observed under these conditions. Exposure of ketone **11** to

(11) Hydroxymethylphenoxyethyl resin was supplied by Watanabe Chemical.

(12) Reaction of solid-linked ketone on Wang resin instead of the hydroxymethylphenoxyethyl resin resulted in the reduced purity (79% purity) of **5aA**. HPLC-MS analysis of the mixture showed that it contained NTI derivatives bearing the 4-hydroxybenzyl moiety. These results indicate that the acid-stable base polymer is essential for the solid-phase indole formation.

(13) Column: HYPERSIL ODS 3 μ m, 4.6 \times 75 mm; flow rate 1 mL/min. Mobile phase: 0.1% HCOOH in H₂O:0.1% HCOOH in MeCN = 95:5 (0 min) and then 0:100 (8 min). UV: 254 nm.

stepwise indole-formation conditions with the five phenylhydrazines **5a–e** provided 30 NTI derivatives **1**. Analysis of the obtained crude mixtures using HPLC-MS based on UV absorption at 254 nm revealed 20 compounds with more than 70% purity, which was acceptable for initial biological assay (Table 2). The rest were obtained in moderate purity (70–48%) but can be readily purified.

In conclusion, we have demonstrated a one-pot release and cyclization reaction for the solid-phase synthesis of indole derivatives **1** by Fischer indole synthesis. In this new release strategy, release and cyclization reactions proceeded simultaneously to provide good yields of the corresponding indole derivatives. We applied this methodology to the solid-phase synthesis of naltrindole derivatives **1** to provide 40 indoles in moderate purity. Biological assay of the indole derivatives is currently underway.

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Supporting Information Available: Experimental procedures for syntheses and full characterization of compounds **1aA–jA**, **1aB–eB**, **1aC–eC**, **1aD–eD**, **1aE–eE**, **1aF–eF**, **1aG–eG**, **8**, and **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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