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

Hiroshi Tanaka,[†] Hiroshi Ohno,[‡] Kuniaki Kawamura,[‡] Atsushi Ohtake,[‡] Hiroshi Nagase,[‡] and Takashi Takahashi*[,†]

Department of Applied Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152-8552, Japan, and Department of Medicinal Chemistry, Pharmaceutical Research Laboratory, Toray Industries, Inc., 1111 Tebiro, Kamakura, Kanagawa 248-8555, Japan

ttakashi@o.cc.titech.ac.jp

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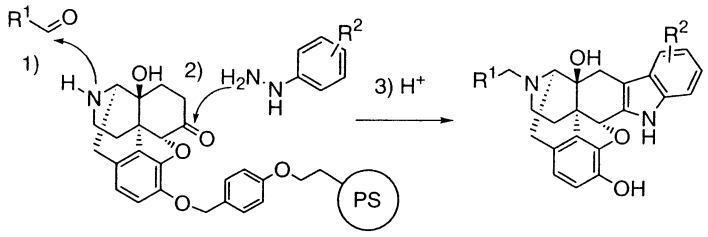
ABSTRACT



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 D_3, 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 phase[4] but also on a solid phase.[5] Fischer indole synthesis is one of the most common and effective reactions for the

* Phone: +81-3-5734-2120. Fax +81-3-5734-2884.
[†] Tokyo Institute of Techonolgy.
[‡] Toray Industries, Inc.

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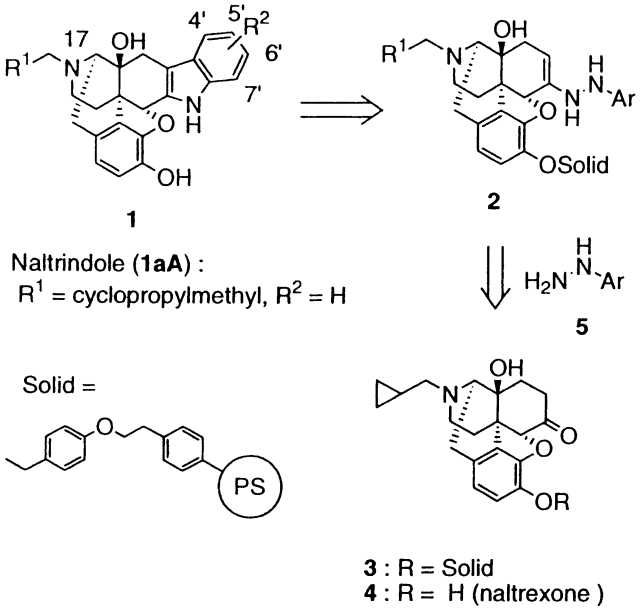
synthesis of substituted indoles from a ketone and an arylhydrazine via cyclization of a hydrazone intermediate under strongly acidic conditions.[6] There are few reports of the solid-phase synthesis of simple indole derivatives using ester-type linkers or a benzyloxy carbonyl linker, which are stable 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

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*-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 PPh_3 in THF. The loading yield was determined by cleavage of **3**

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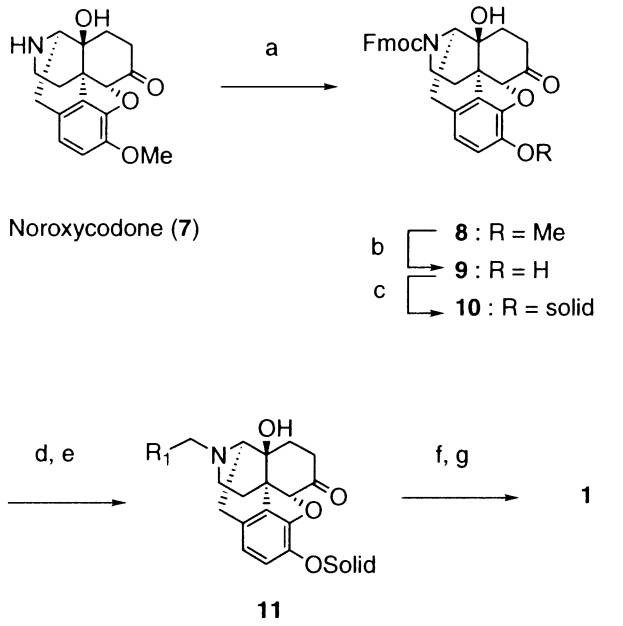
under acidic conditions, followed by measurement of mass recovery of naltrexone (**4**), which was 92% on the basis of the resin. Fischer indole synthesis using solid-linked naltrexone **3** was examined next. Hydrazone formation of

Scheme 2[a]



[a] Reagents and conditions: (a) FmocCl, Na_2CO_3 aqueous THF, rt, 88%; (b) BBr_3, CH_2Cl_2, 0 °C, 56%; (c) hydroxymethylphenoxyethyl polystyrene resin, DEAD, PPh_3, 1 h, rt; (d) 20% piperidine in CH_2Cl_2, rt; (e) **6**, $NaBH_3CN$, DMF−AcOH (100:1); (f) **5** ,4 Å MS, AcOH−CH_2Cl_2 (1:1), rt.; (g) 10%TFA /CH_2Cl_2, rt.

naltrexone **3** was achieved by treatment with an excess of phenylhydrazine (**5a**) under mildly acidic conditions (CH_2Cl_2/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 CH_2Cl_2 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 naltrindole 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 PPh_3 (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 CH_2Cl_2 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 CH_2Cl_2−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 CH_2Cl_2. The resulting resins were treated with 10% TFA/CH_2Cl_2 (1 mL) for 30 min at room temperature, filtered, and then washed with CH_2Cl_2. 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.

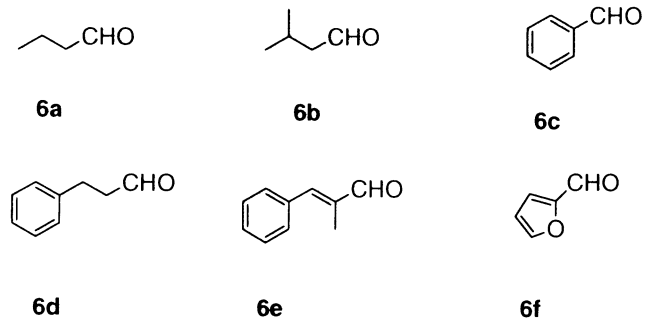


Figure 1. Aldehydes for a building block.

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 Naltrindole 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 $NaBH_3CN$ 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 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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(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-hydroxylbenzyl moiety. These results indicate that the acid-stable base polymer is essential for the solid-phase indole formation.

(13) Column: HYPERSIL ODS 3 μm, 4.6 × 75 mm; flow rate 1 mL/min. Mobile phase: 0.1% HCOOH in H_2O:0.1% HCOOH in MeCN = 95:5 (0 min) and then 0:100 (8 min). UV: 254 nm.