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Solid-phase synthesis of indolines via palladium-catalyzed cyclization

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Abstract—The solid-phase synthesis of indolines from resin-bound 2-bromophenylacetylated amino acids is described. The exhaustive reduction of solid-support bound amides with borane afforded the requisite secondary amines that, following the palladium-catalyzed intramolecular cyclization and cleavage, provided the corresponding disubstituted indolines.

The rapid synthesis of large organic compound collections by combinatorial methods using solid-phase approaches is a promising strategy for the discovery of new pharmaceutical lead compounds.[1] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents.[2] As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds recently have been prepared using solid-phase methodology.[3–6] This approach permits the rapid synthesis of large numbers of individual compounds, as well as mixture-based combinatorial libraries in a short time period and facilitates their use in high-throughput screening.[7] Indolines are found in many biologically active naturally occurring compounds and medicinal agents.[8] As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule and heterocyclic compounds using amino acids and peptides as starting materials,[9] we report here an efficient strategy for the synthesis disubstituted indolines from resin-bound acylated amino acids.

The parallel solid-phase synthesis of indolines was carried out on the solid-phase using the 'tea-bag' methodology.[1b] The reaction sequence is illustrated in Scheme 1. Starting from *p*-methylbenzhydrylamine (MBHA) resin, a Boc-L-amino acid (Boc-AA(R_1)-OH) was coupled to the resin. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resulting primary amine was acylated with a variety of 2-bromophenyl acetic acid derivatives to provide the resin-bound acylated amino acid **3**. The generated resin-bound diamide was treated with borane in THF, resulting in the exhaustive reduction of the two amides to yield resin-bound diamine **4**. The palladium-catalyzed intramolecular and intermolecular coupling of aryl halides with amines has been shown to be an efficient method for the synthesis of a variety of aniline derivative.[10] Following optimization of the reaction conditions, we found the resin-bound indoline **5** could be obtained by treatment of **4** with NaO*t*-Bu (5 equiv.), $Pd_2(dba)_3$ (0.1 equiv.) and (±)-BINAP (0.2 equiv.) in toluene at 100°C for 48 h in good yield and purity. The desired product was obtained following cleavage from the resin using HF/anisole (95/5) for 7 h at 0°C (Table 1).[11] The product was characterized by electrospray LC-MS, ^1H and ^{13}C NMR. Figure 1 illustrates a typical LC–MS spectra of indoline **6b** derived from phenylalanine and 2-bromo-5-chlorophenylacetic acid. The possibility of racemization was determined. (2*S*)-2-(2,3-Dihydro-1*H*-indol-1-yl)-3-methylbutan-1-amine **6k** starting from L-valine and (2*R*)-2-(2,3-dihydro-1*H*-indol-1-yl)-3-methylbutan-1-amine starting from D-valine were synthesized. Baseline separation of the enantiomers by chiral HPLC demonstrated negligible racemization occurred during either exhaustive reduction or palladium-catalyzed intramolecular cyclization.[12]

In summary, this approach is a continuation of our efforts directed toward the synthesis of acyclic and heterocyclic

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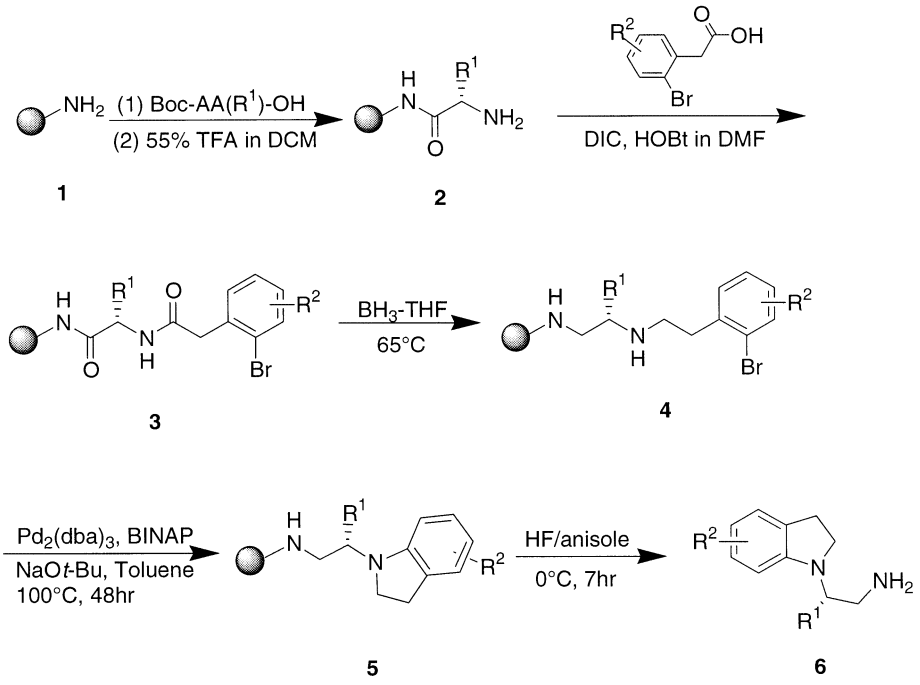
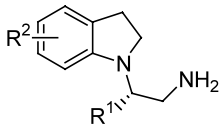


Scheme 1. Solid-phase synthesis of indolines.

Table 1. Individual indolines **6**



Entry	R^1	R^2	Yield[a]	Purity[b]	MW (found)[c]
6a	$C_6H_5CH_2$	H	78	83	252.2 ($[M+H]^+$)
6b	$C_6H_5CH_2$	5-Cl	73	72	286.1 ($[M+H]^+$)
6c	H	5-Cl	78	72	196.1 ($[M+H]^+$)
6d	$(CH_3)_2CH$	5-Cl	81	69	238.1 ($[M+H]^+$)
6e	CH_3	H	78	73	176.1 ($[M+H]^+$)
6f	CH_3	5-Cl	67	65	210.1 ($[M+H]^+$)
6g	$(CH_3)_2CH$	5,6-Di-CH_3O	73	76	264.2 ($[M+H]^+$)
6h	$(CH_3)_2CHCH_2$	5,6-Di-CH_3O	73	72	278.2 ($[M+H]^+$)
6i	$C_6H_5CH_2$	5,6-Di-CH_3O	68	74	312.2 ($[M+H]^+$)
6j	$(CH_3)_2CHCH_2$	5-Cl	84	63	252.1 ($[M+H]^+$)
6k	$(CH_3)_2CH$	H	66	78	205.1 ($[M+H]^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated from analytical RP-HPLC traces at $\lambda = 214$ nm.
[c] Confirmed by mass spectra (ESI).

compounds from amino acids and short peptides. Using the 'libraries from libraries' concept,[13] we have demonstrated the feasibility of the synthesis of indolines from the acylated amino acids on the solid-phase via palladium-catalyzed intramolecular cyclizaton reaction.

Acknowledgements

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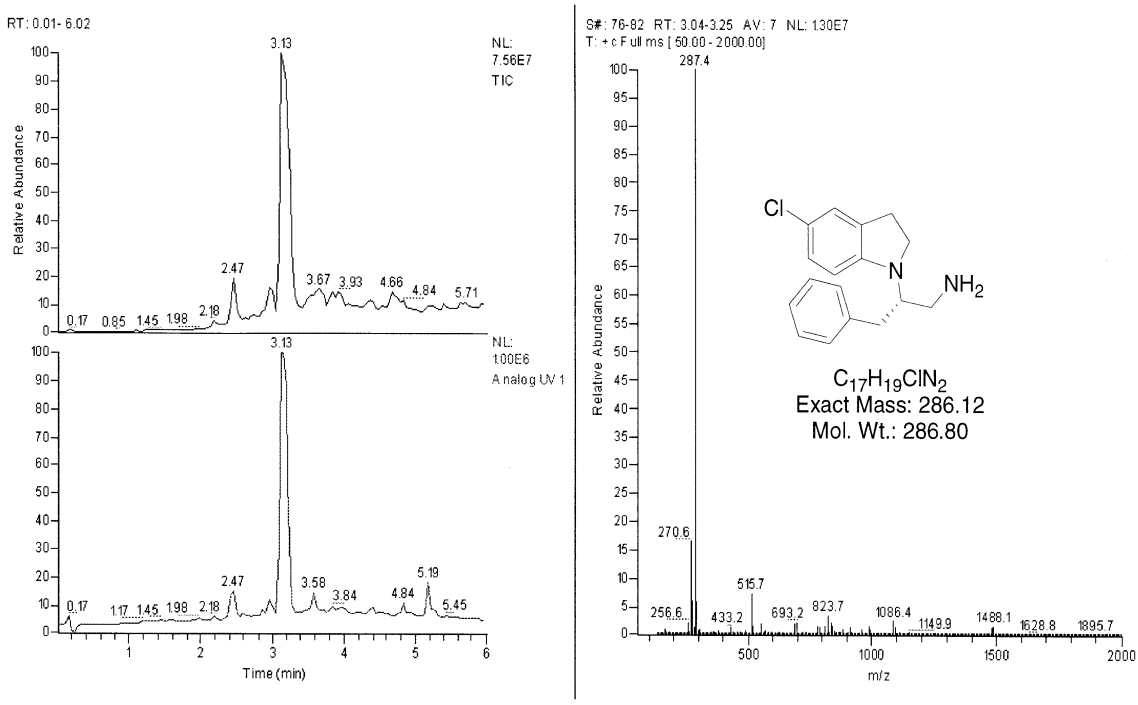

Figure 1. LC–MS of crude indoline **6b**.

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11. Typical procedure for the synthesis of indoline **6**: 100 mg of MBHA resin was contained in a polypropylene mesh packet.[1b] Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. The first Boc L-amino acid (6 equiv., 0.1 M) was coupled using hydroxybenzotriazole (HOBt, 6 equiv., 0.1 M) and diisopropylcarbodiimide (DICI, 6 equiv., 0.1 M) for 2 h. Upon removal of the Boc group with 55% TFA in DCM (30 min), the packet was washed, neutralized with a solution of 5% DIEA in DCM. The resin-bound amine was acylated with a 2-bromophenyl acetic acid derivative (10 equiv., 0.1 M) in DMF using DICI and HOBt as coupling reagents overnight. The exhaustive reduction of the resin-bound amides was carried out in 50 ml glass conical tubes under nitrogen. To each tube was added the resin packet, boric acid (12 equiv.) and trimethyl borate (12 equiv.), followed by the slow addition of borane–THF complex (40 equiv.). After cessation of hydrogen evolution, the capped tubes were heated at 65°C for 72 h in a heating block followed by decantation of the reaction solution and quenching with MeOH. The resin packet was then washed with

DMF and MeOH. The resin was treated with piperidine at 65°C overnight to disproportionate the borane complex. Following decantation of the piperidine–borane solution, the resin packet was washed with DMF, DCM, MeOH and dried. The cyclization reaction was performed under nitrogen. To each tube was added the resin packet, NaO*t*-Bu (5 equiv.), $Pd_2(dba)_3$ (0.1 equiv.) and (±)-BINAP (0.2 equiv.), followed by 10 ml of toluene. The reaction mixture was heated at 100°C for 48 h. Following washes with DMF (three times), MeOH (three times), DCM (three times), the resin was cleaved with HF/anisole (95/5) at 0°C for 7 h. The desired product was extracted with acetic acid/water (95/5), and lyophilized. The product was characterized by electrospray LC–MS under ESI conditions, ^1H and ^{13}C NMR. Compound **6a**: MS(ESI) m/z 252.3 ($M+H^+$). ^1H NMR (500 MHz, DMSO) δ 0.89 (3H, t, $J=7.1$), 2.68–2.80 (4H, m), 2.89–2.94 (2H, m), 3.47–3.52 (2H, m), 3.95–3.98 (1H, m), 6.56–6.60 (2H, m), 7.01–7.05 (2H, m), 7.20–7.33 (3H, m), 7.75 (2H, brs). ^{13}C NMR (DMSO, 125 MHz): δ 27.6, 33.1, 45.7, 52.3, 54.9, 106.9, 117.4, 124.4, 126.3, 127.1, 128.5, 129.0, 130.0, 138.2, 150.4.

12. Analytical chiral HPLC was performed on a LiChroCART250-4 ChiraDex column. Eluent: methanol/water+0.1% triethylamine (pH 4.1) from 5/95 to 95/5 V/V. Flow rate: 0.8 ml/min. Detection: UV 260 nm. Retention time of *R* isomer was 7.5 min. Retention time of *S* isomer was 8.1 min.
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