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Solid-Phase Synthesis of Dehydroalanine Derivatives

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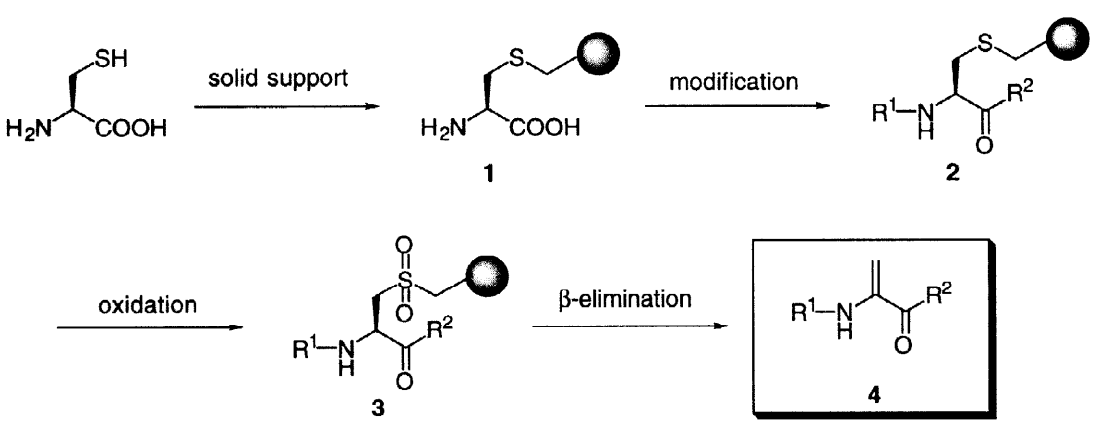
Abstract: A novel solid-phase synthetic method for dehydroalanines and dehydropeptides has been developed. Elimination of the sulfone part with concomitant release from the solid support afforded the desired dehydroalanine derivatives. The products were given in good yields and excellent purities. © 1997 Elsevier Science Ltd. All rights reserved.

Combinatorial organic synthesis of peptides and small organic compounds are well recognized as a powerful tool for drug lead generation.[1] Solid-phase organic synthesis has been used widely for preparation of a large number of structurally diverse compounds for combinatorial libraries.[2] The dehydroamino acid derivatives have attracted considerable attention because of their unique conformational features and various biological activities.[3] However, few synthetic approaches on solid-support have appeared for the preparation of dehydroalanine.[4] In this paper we wish to report a new efficient solid-phase synthesis of dehydroalanine derivatives for combinatorial library.

Scheme 1



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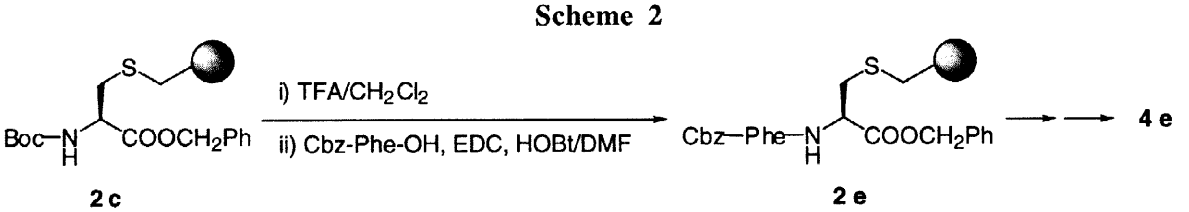
We envisioned the following strategy for the synthesis of dehydroalanine derivatives as shown in Scheme 1. A side-chain linked unprotected cysteine **1**[5] was selected as a starting material, since (i) both the *N*– and *C*–terminus remain available for modification, (ii) the connection between cysteine and the solid support is sufficiently robust to withstand most reaction conditions, and (iii) the sulfide is easily converted to the sulfone which is the desired leaving group in β-elimination.[6] The central feature of our synthetic strategy is a base-promoted β-elimination of the sulfone group to form and simultaneously release the dehydroalanine. This ensures that only the desired α,β-unsaturated compound is released from polymer support.

A typical procedure is outlined as followed. Cysteine was attached to the Merrifield resin[7] by means of the procedure reported by Delaet and Tsuchida to afford the polymer-bound cysteine **1**.[5] Coupling **1** with succinimide esters (Cbz–ONSu, Cbz–Phe–ONSu) in DMF at 25 ℃ for 5 hours or treating **1** with di *tert*-butyl dicarbonate (Boc_2O) in THF at 25 ℃ overnight, followed by esterification with alkyl halide (MeI, $PhCH_2Br$) in the presence of K_2CO_3 in DMF at 25 ℃ for 5 hours[8] afforded the ester type derivatives (**2a–e**) attached to the resin. Treating **1** with Boc_2O and successively coupling with amine ($PhCH_2NH_2$) or amino acid ester (H-Phe-OEt) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) – 1-hydroxybenzotriazole hydrate (HOBt) in DMF at 25℃ for 5 hours provided the amide type derivatives (**2f** and **2g**) attached to the resin, respectively. Oxidation of sulfides **2** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 gave the desired sulfone derivatives **3** attached to the resin.[9] A number of elimination conditions were evaluated, and optimal results were obtained by treating the resin **3** in CH_2Cl_2 with an equimolar of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 25℃ for 5 minutes.[6] Conventional workup procedure provided dehydroalanine derivatives **4**.[10]

For assessing acid-stability of the linkage, we attempted to synthesize the dehydropeptide **4e** by stepwise coupling method (Scheme 2). After removal of Boc group from **2c** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 25℃ for 1 hour, the resulting amine was coupled with Cbz–Phe–OH using EDC–HOBt in DMF to afford **2e**, which was converted to **4e**. This result indicated that the linkage between cysteine and polymer is stable to acidic conditions, making it possible to synthesize dehydropeptides utilizing Boc chemistry.

Scheme 2



2c **2e**

The given compounds **4a–g** were characterized by ^1H NMR and mass spectra,[11] and their analytical data of **4** by HPLC are shown in Table 1. The ester type derivatives (**4a-e**) could be isolated in good yields (75-86%) and purities (95-98%) so that no further purification was necessary. In the case of amide derivatives, the purities of the given products were also reasonable (**4f**: 84%, **4g**: 90%), but the yields (**4f**: 31%, **4g**: 45%) were inferior to those of the ester type derivatives. We are now investigating other suitable elimination conditions for the amide type derivatives, and the result will be reported in due course.

Table 1

product	R^1	R^2	conditions (1→2)[a]	yield (%)[b]	purity (%)[c]
4a	Cbz	OMe	1) Cbz-ONSu[d]/DMF 2) MeI, K_2CO_3/DMF	86	96
4b	Boc	OMe	1) Boc_2O/THF 2) MeI, K_2CO_3/DMF	75	95
4c	Boc	OCH_2Ph	1) Boc_2O/THF 2) $PhCH_2Br$, K_2CO_3/DMF	75	97
4d	1-Nap-CO[d]	OCH_2Ph	1) 1-Nap-COOH, EDC, HOBt/DMF 2) $PhCH_2Br$, K_2CO_3/DMF	76	98
4e	Cbz–Phe[d]	OCH_2Ph	1) Cbz–Phe–ONSu[d]/DMF 2) $PhCH_2Br$, K_2CO_3/DMF	77	98
			1) Boc_2O/THF 2) $PhCH_2Br$, K_2CO_3/DMF 3) TFA/CH_2Cl_2 4) Cbz-Phe-OH, EDC, HOBt/DMF	76	98
4f	Boc	$NHCH_2Ph$	1) Boc_2O/THF 2) $PhCH_2NH_2$, EDC, HOBt/DMF	31	84
4g	Boc	Phe-OEt[d]	1) Boc_2O/THF 2) H-Phe-OEt, EDC, HOBt/DMF	45	90

[a] 2.5 eq. of the reagents based on **1** were used for each reaction.
[b] Based on the initial loading level of $-CH_2Cl_2$ on Merrifield resin.
[c] Analysis was performed using a YMC-Pack R-ODS-5-A (250 x 4.6 mm, S-5 μm) column eluting with a linear gradient of 0-80% CH_3CN in H_2O over 45 minutes at 1 ml/min by area integration at 220 nm.
Retention time (min) **4a**: 32.1, **4b**: 32.5, **4c**: 31.9, **4d**: 31.6, **4e**: 31.2, **4f**: 26.7, **4g**: 29.5.
[d] 1-Nap: 1-Naphthyl, Cbz-ONSu: *N*-(Benzyloxycarbonyloxy)succinimide, Cbz-Phe: *N*-Benzyloxycarbonyl-L-phenylalanyl, Cbz-Phe-ONSu: *N*-Benzyloxycarbonyl-L-phenylalanine *N*-hydroxysuccinimide ester, Phe-OEt: L-Phenylalanine ethyl ester.

In summary, we have developed a novel method for the solid-phase synthesis of dehydroalanine derivatives from polymer-bound cysteine **1**. It is noteworthy that the eliminative release feature of this approach results in a significant enhancement of the purity of the final compounds. This convenient method is applicable for the combinatorial synthesis of structurally diverse dehydroalanine derivatives.

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   This reaction should be carried out under Ar or N_2 atmosphere to avoid oxidation of cysteine.
6. Construction of dehydroalanine moiety *via* β-elimination of sulfone group has been reported.
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7. Merrifield resin (1.0 mmol of CH_2Cl/g : Polystyrene 1% divinylbenzene copolymer) was purchased from Watanabe Chemical Industries, Ltd.
8. A trace of β-elimination product from the resin *via* *S*-alkylation was detected by TLC for each case.
9. In the IR spectrum of **3**, the characteristic absorptions of sulfone were detected. (**3a**: 1120, 1350 cm^{-1} **3b**: 1107, 1320 cm^{-1} **3c**: 1114, 1325 cm^{-1} **3d**: 1117, 1315 cm^{-1} **3e**: 1165, 1320 cm^{-1} **3f**: 1117, 1321 cm^{-1} **3g**: 1131, 1315 cm^{-1})
10. Typical procedures for oxidation and β-elimination are as followed. To a suspension of **2b** (1.46 g, 1.0 mmol) in CH_2Cl_2 (20 ml) was added *m*-CPBA (647 mg, 3 mmol) in one portion at 25 °C. After agitation by N_2 bubbling at 25 °C for 1 hour, the resin was washed successively with CH_2Cl_2 (20 ml x 3), MeOH (20 ml x 5) and Et_2O (20 ml x 3) to provide **3b**. Then, DBU (151 μl, 1 mmol) was added to the suspension of **3b** in CH_2Cl_2 (20 ml) at 25 °C. After agitation at 25 °C for 5 minutes, the resin was filtrated and washed with CH_2Cl_2 (20 ml x 3). The collected CH_2Cl_2 layer was washed with 5% $KHSO_4$ (50 ml), sat. $NaHCO_3$ (50 ml) and brine (50 ml). Drying over $MgSO_4$ and concentration under reduced pressure provided **4b** (Table 1).
11. **4a**: colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 (3H, s), 5.16 (2H, s), 5.79 (1H, s), 6.25 (1H, s), 7.25 (1H, brs), 7.37 (5H,s); MS (SIMS) m/z 236 $[M+H]^+$.
    4b: colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (9H, s), 5.26 (2H, s), 5.79 (1H, d, *J* = 1.5Hz), 6.18 (1H, s), 7.03 (1H, brs), 7.36 (5H, s); MS (SIMS) m/z 278 $[M+H]^+$
    4c: colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.49 (9H, s), 3.83 (3H, s), 5.73 (1H, d, *J* = 1.5 Hz), 6.16 (1H, s), 7.02 (1H, brs); MS (SIMS) m/z 250 $[M+H]^+$.
    4d: mp 74−76 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 5.28 (2H, s), 6.12 (1H,d, *J* = 1.4 Hz), 6.92 (1H, s), 7.30−8.45 (12H, m); MS (SIMS) m/z 332 $[M+H]^+$.
    4e: mp 92−94 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.11 (2H, d, *J* = 6.8 Hz), 4.40−4.60 (1H, m), 5.08 (2H, dd, *J* = 12.6, 12.6 Hz), 5.21 (2H, s), 5.27−5.40 (1H, m), 8.07 (1H, brs), 5.95 (1H, d, *J* = 1.3 Hz), 6.61 (1H, s), 7.19−7.56 (15H, m); MS (SIMS) m/z 383 $[M+H]^+$.
    4f: mp 67−68 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (9H, s), 4.30−4.67 (2H, m), 5.02 (1H, dd, *J* = 1.6, 1.6 Hz), 6.00 (1H, d, *J* = 1.7 Hz), 5.72 (1H, brs), 7.06 (1H, brs); MS (SIMS) m/z 277 $[M+H]^+$.
    4g: colorless powder; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.1 Hz), 1.48 (9H, s), 3.17 (2H, d, *J* = 5.6 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 4.87 (1H, dt, *J* = 5.6, 7.6 Hz), 4.99 (1H, s), 6.00 (1H, d, *J* = 1.7 Hz), 6.53 (1H, d, *J* = 7.1 Hz), 7.03−7.54 (6H, m); MS (SIMS) m/z 363 $[M+H]^+$.