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Solid-phase synthesis of N_α-benzyl-N_α-cinnamyl lysine and glutamic acid derivatives

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Abstract

Several variations of a solid-phase strategy for the synthesis of N_α-benzyl-N_α-cinnamyl lysine and glutamic acid derivatives are presented. Starting from the corresponding N_α-Fmoc amino acids on Wang resin, reductive alkylation using nitrocinnamaldehyde or a substituted benzaldehyde was followed by nucleophilic displacement of a substituted benzyl halide or nitrocinnamyl bromide to provide resin-bound intermediates. Diversity was added by reduction of the nitro group and derivatization of the resulting aminocinnamyl moiety with a variety of acylating or sulfonylating reagents. Using an orthogonal protecting group strategy, N_ε-Dde-protected lysine derivatives were further functionalized at the side-chain amino group prior to cleavage from resin. This method allows for the preparation of analog libraries having up to four points of diversity.

Over the past decade, solid-phase organic chemistry has become a valuable tool for the rapid preparation of small molecules.[1,2] In the pharmaceutical industry, solid phase synthesis provides the medicinal chemist with the means to quickly generate analogs for structure–activity relationship (SAR) studies and more efficiently optimize biological activity. Using both combinatorial and parallel techniques, many groups have constructed large diverse libraries or small- to medium-sized targeted libraries for evaluation in biological assays. One convenient source of solid-supported starting materials for the construction of libraries is the collection of commercially available resin-bound protected amino acids. While this 'chiral pool' has been used in peptide synthesis for more than 35 years,[3] it has more recently been employed in the construction of heterocycles and other non-peptidic molecules of biological interest.[4,5] In our laboratory, work directed toward the discovery of small molecule mimics of protein–protein interactions led to a series of *N*,*N*-disubstituted amino acids having micromolar affinity for the erythropoietin receptor, which we were interested in expanding via solid phase parallel synthesis techniques.[6] A common characteristic of the highest affinity analogs was the presence of phenoxy or benzyloxy substituents on the two

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phenyl rings of core structure **1** (Fig. 1). Although synthesis of phenyl ethers on solid support using the Mitsunobu reaction has been reported, we decided to approach the problem differently by preparing amide analogs of the original benzyl ether leads.[7–9] In this way, we could take advantage of readily available carboxylic and sulfonic acid derivatives for use as coupling partners with a primary amino group at R^3 or R^4 of the core structure.

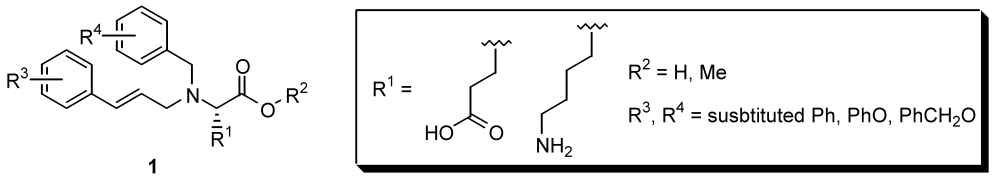
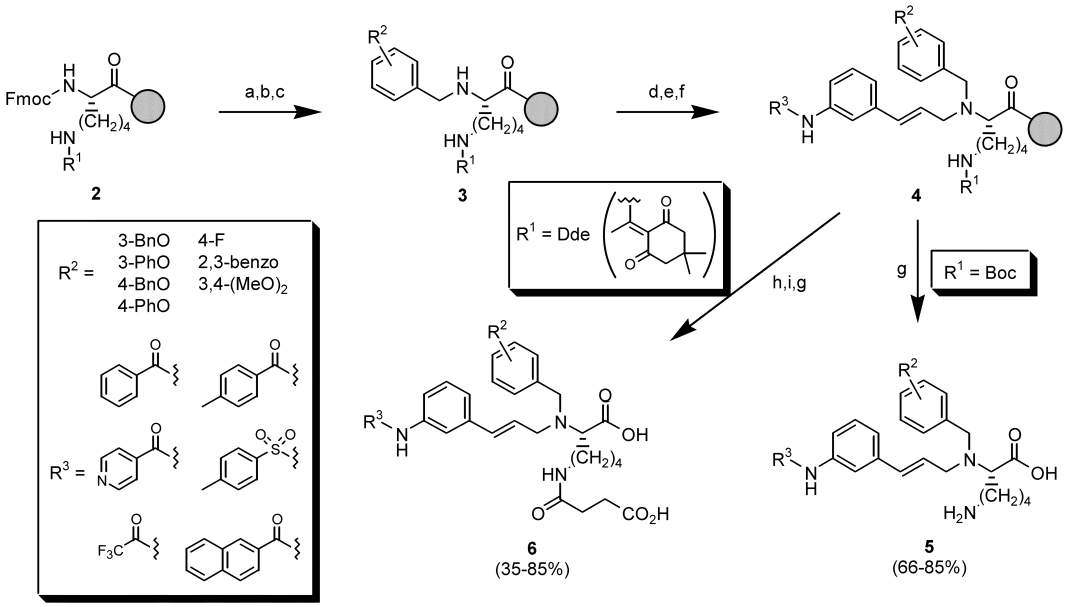


Figure 1.

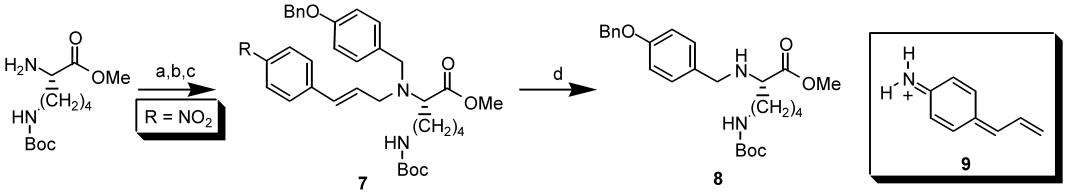
The synthesis of N_α-benzyl-N_α-cinnamyl lysine derivatives was carried out according to the following procedure (Scheme 1). Commercially available Wang resin-bound N_α-Fmoc-N_ε-Boc lysine (**2**, R^1 = Boc) was deprotected with 40% piperidine/DMF and subjected to reductive alkylation with a substituted benzaldehyde using $(MeO)_3CH$ (overnight imine formation) followed by $NaBH(OAc)_3$ in CH_2Cl_2.[10,11] The resulting secondary amine (**3**, R^1 = Boc) was reacted with 3-nitrocinnamyl bromide and diisopropylethylamine (DIEA) in DMF; subsequent nitro reduction using $SnCl_2$ in DMF afforded the corresponding 3-aminocinnamyl derivative.[12,13] Treatment with various sulfonyl chlorides, carboxylic acids, or carboxylic anhydrides in pyridine/CH_2Cl_2



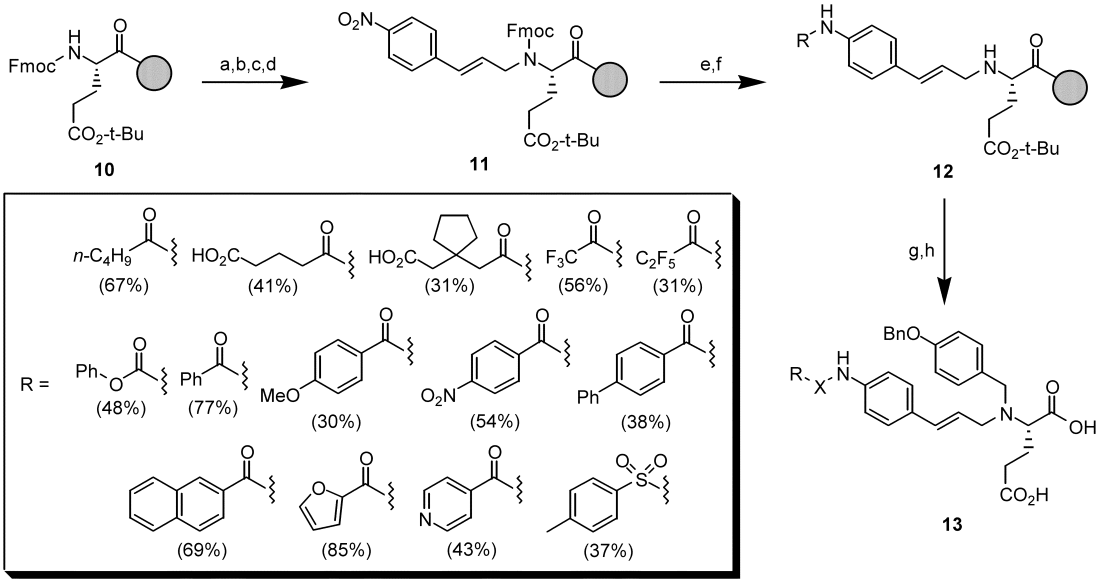
Scheme 1. (a) 40% piperidine/DMF; (b) $R^2C_6H_4CHO$, $(MeO)_3CH$; (c) $NaBH(OAc)_3$, CH_2Cl_2; (d) 3-$NO_2C_6H_4CH{=}CHCH_2Br$, DIEA, DMF; (e) $SnCl_2{\cdot}2H_2O$, DMF; (f) R^3-X, pyridine; (g) 50% TFA/CH_2Cl_2; (h) 2% N_2H_4/DMF; (i) succinic anhydride, pyridine, DMF

provided protected targets **4** (R^1 = Boc) which were cleaved from resin (50% TFA/CH_2Cl_2) to give N_ε-unsubstituted lysine derivatives **5**. In order to prepare analogs having functionality on the ε-amino group, N_ε-Dde-protected lysine (Dde = 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl) was used in place of N_ε-Boc-lysine.[14] To begin, commercially available Fmoc-Lys(Dde)OH was coupled to Wang resin using the standard Sieber technique.[15] The resulting resin (**2**, R^1 = Dde) was treated in the same manner as the N_ε-Boc-lysine resin until just prior to the cleavage step. At this point, the N_ε-protected derivative **4** (R^1 = Dde) was shaken with 2% hydrazine in DMF to remove the Dde group. The resin-bound free amine **4** (R^1 = H) was acylated with succinic anhydride and cleaved from resin with TFA/CH_2Cl_2 to give the target *N*-benzyl-*N*-cinnamyl lysine derivatives **6**.[16] Using this protocol, we generated a 17-member library incorporating four points of diversity in 35–85% yield.[17]

A variation of the lysine route was used to synthesize *N*-benzyl-*N*-cinnamyl glutamic acid analogs bearing substitution at the 4-position of the cinnamyl phenyl ring. Interestingly, when we first applied the 3-nitrocinnamyl methodology to a 4-nitrocinnamyl system, we observed complications in the nitro reduction step (Scheme 2). Specifically, attempted reduction of amine **7** (R = NO_2) with $SnCl_2$ in MeOH did not provide the expected 4-aminocinnamyl derivative, resulting instead in loss of the 4-nitrocinnamyl group and recovery of secondary amine **8**. This unexpected result was accompanied by the appearance of an intense maroon color in the reaction mixture, consistent with the presence of 1-imino-4-methylene-2,5-cyclohexadiene **9**, possibly formed by decomposition of 4-aminocinnamyl product **7** (R = NH_2).[18] Similar behavior has been observed in the Sn^{IV}-mediated cleavage of *p*-nitrobenzyl ethers, esters, and carbamates.[19] We postulated that protonation of the alpha nitrogen of **7** (R = NH_2) under the acidic $SnCl_2$ reduction conditions favors solvolysis of the 4-aminocinnamyl moiety, and that elimination of the positive charge on N_α (by acylation, for example) would minimize the cleavage reaction. Therefore, we redesigned the solid-phase reaction scheme to include Fmoc reprotection at N_α (Scheme 3). Toward that end, commercially available Wang resin-bound *N*-Fmoc glutamic acid (**10**) was deprotected and reductively alkylated with 4-nitrocinnamaldehyde using the conditions described above, giving the expected resin-bound secondary amine. After *N*-protection using Fmoc-Cl/pyridine, $SnCl_2$ reduction of *N*-Fmoc intermediate **11** proceeded cleanly without *N*-dealkylation to provide the desired 4-aminocinnamyl compound. Next, the aniline nitrogen was derivatized with various carboxylic anhydrides, acid chlorides, or sulfonyl chlorides. After removal of the Fmoc protecting group with 40% piperidine/DMF, N_α-alkylation of the resulting secondary amine **12** was carried out using 4-benzyloxybenzyl chloride, NaI, and DIEA. Finally, cleavage from resin using 50% TFA/CH_2Cl_2 provided the target *N*-benzyl-*N*-cinnamyl glutamic acids **13** in yields ranging from 30–85%.



Scheme 2. (a) 4-$NO_2C_6H_4CH$=$CHCHO$, $(MeO)_3CH$; (b) $NaBH(OAc)_3$, CH_2Cl_2; (c) 4-$BnOC_6H_4CH_2Cl$, NaI, DIEA, DMF; (d) $SnCl_2 \cdot 2H_2O$, DMF



Scheme 3. (a) 40% piperidine/DMF; (b) 4-$NO_2C_6H_4CH{=}CHCHO$, $(MeO)_3CH$; (c) $NaBH(OAc)_3$, CH_2Cl_2; (d) Fmoc-Cl, pyridine; (e) $SnCl_2{\cdot}2H_2O$, DMF; (f) R-X, pyridine; (g) 4-BnO-$C_6H_4CH_2Cl$, NaI, DIEA, DMF; (h) 50% TFA/CH_2Cl_2

In conclusion, solid phase techniques have been employed in a straightforward and convenient synthesis of a series of biologically interesting N_α-benzyl-N_α-cinnamyl amino acids. Using a sequence of reductive alkylation followed by nucleophilic displacement, core structure **1** ($R^3 = NO_2$) was easily prepared. Subsequent elaboration of the nitrocinnamyl group and, in the case of N_ε-Dde-protected lysine, the side chain amino group provided two small libraries (**5**, **6**, and **13**) incorporating up to four points of diversity.

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