ORGANIC LETTERS

2009
Vol. 11, No. 16
3558−3561

Solid-Phase Synthesis of Amino- and Carboxyl-Functionalized Unnatural α-Amino Acid Amides

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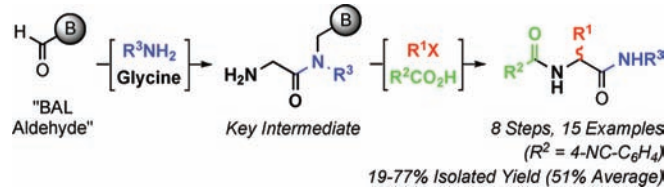
Received June 8, 2009

ABSTRACT



A new solid-phase synthesis efficiently incorporates three different substituents (from R^1-X, R^2-CO_2H, and R^3-NH_2) into a glycine-based peptidomimetic scaffold. The synthetic sequence is general and is typically accomplished in >50% overall isolated yield. Alkylating agents with a range of reactivities and normal and branched primary amines give good results. Utility was demonstrated by the synthesis of a series of protected phosphotyrosine mimetics.

The Distributed Drug Discovery (D^3) project[1,2] develops methodology for the simple, economical synthesis of structural scaffolds commonly found in biologically active molecules. The goal of D^3 is to expedite the discovery of drug leads for neglected diseases. It relies on solid-phase chemistry, a critical component of which is the nature of the linker used to join the substrate molecule to the solid support.[3] D^3 has utilized various linkers to enable the solid-phase synthesis of many derivatized scaffolds based on α-monosubstituted and α,α-disubstituted resin-bound unnatural amino acid intermediates.

Regardless of the linker, D^3-type syntheses based on derivatives of α-monosubstituted resin-bound unnatural amino acids start from resin-bound glycine **1** and utilize an activated benzophenone imine derivative **2**. This proceeds, depending on the linker, to acid **3** (from Wang),[1b] ester **4** (from Merrifield or Wang),[2a,1c] amide **5** (from Rink),[4] or ketone/aldehyde **6** (from Weinreb)[5] (Scheme 1).

BAL (Backbone Amide Linker) resins[3c,6] were developed for peptide synthesis (Scheme 2). When amino acid amides **7** are made by conventional BAL chemistry, the naturally occurring amino acids used are obtained commercially and then attached to the BAL resin (**9** to **10**).

Our goal is to apply BAL methodology to the synthesis of the fundamental peptidomimetic scaffold **7**, now with the

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(2) For lead references concerning the solid-phase synthesis of unnatural α-amino acids, peptides, and peptidomimetics from the authors' laboratory, see: (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070–6071. (b) Scott, W. L.; Martynow, J. G.; Huffman, J. C.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7077–7088.

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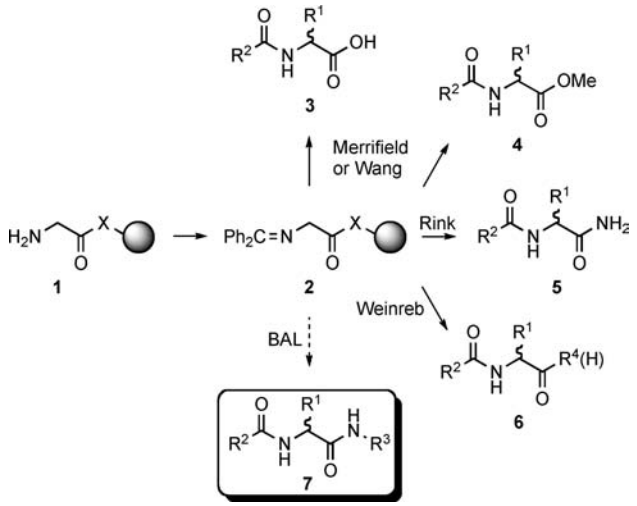
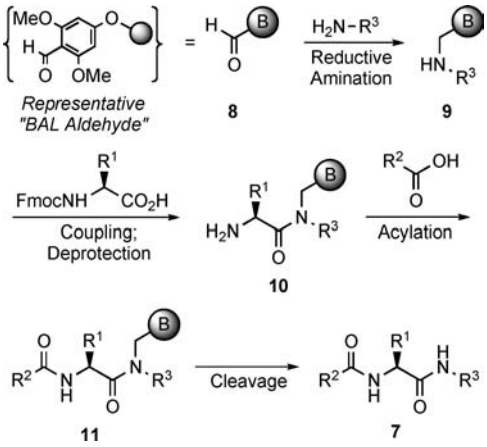
10.1021/ol901279v CCC: $40.75
Published on Web 07/22/2009

Scheme 1. Synthesis of Unnatural α-Amino Acid Derivatives from Resin-Bound Glycine **1**



Scheme 2. Synthesis of Targets **7** by Conventional BAL Chemistry

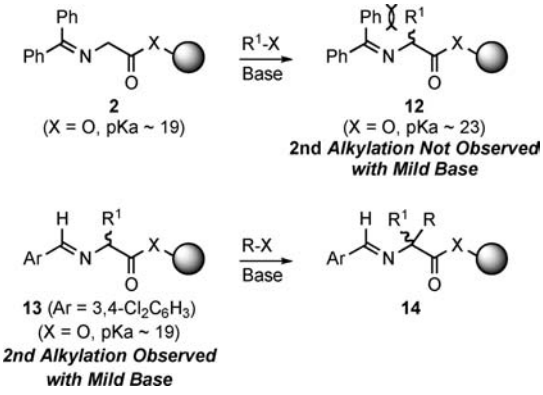


potential to contain multiple variations of unnatural amino acids. This paper reports a continuous solid-phase BAL-based route that incorporates amines and the *on-resin synthesis of these unnatural amino acids*. It requires an alternative activated intermediate to the benzophenone imine **2** shown in Scheme 1. Subsequent acylation with carboxylic acids and final cleavage provides the N-acylated unnatural amino acid amides **7**.

A key premise in our solid-phase alkylation chemistry is the ability to selectively monoalkylate the benzophenone imines of glycine derivatives **2** to lead to products **3**−**6** (Scheme 1). This is based on our earlier solution-phase studies,[7] which predict that monoalkylation products **12** should be ~10^4 less acidic than **2** as a result of $A_{1,3}$ strain in such products (Scheme 3). When α,α-dialkylation is required, the ketimine in **2** is replaced with an aldimine (**13**),[8] which is not subject to the acid-weakening effect observed in **12**.

On the basis of this extensive solution- and solid-phase

Scheme 3. Role of Imine Activating Group in Controlling Mono- or Dialkylation Chemistry



precedence, we expected that initial model studies with imines **15** and **16a** would give the desired products **7** and **17**, respectively (Scheme 4). Pilot alkylations of **15** with benzyl bromide gave **7a** (95% crude purity by LC/MS). However, incomplete alkylation was observed with the less reactive 1-iodooctane, which yielded **7g** (28% crude purity by LC/MS), and alkylation of the aldimine **16a** with benzyl bromide gave no dialkylated product **17** (R^2 = 4-NC-C_6H_4). This lack of reactivity was unanticipated. The increased steric environment imposed by the BAL linker likely alters the acidity of **15** and **16a** and/or the reactivity of the anion obtained upon their deprotonation.

These preliminary studies suggested, however, that the glycine aldimine **19** (Ar = 3,4-$Cl_2C_6H_3$) might provide the required activation for complete monoalkylation to **16** without further undesired dialkylation (Scheme 5).

Alkylation of **19** with benzyl bromide and the base BTPP[9] followed by acylation and cleavage provided clean monoalkylation to **7a** (Scheme 5, Figure 1). No dialkylated product was observed. As in the majority of our previous solid-phase syntheses, the current products are racemic.[10]

To demonstrate the variety of substitutions possible at the two more challenging scaffold positions, R^1 and R^3, twelve products **7** were prepared exploring these variables with a constant N-acylating agent (R^2-CO_2H = 4-cyanobenzoic acid) (Figure 1). Resin-bound **18** was prepared by reductive amination of the aldehyde resin **8** with primary amines R^3-NH_2 followed by coupling with FmocGly and deprotection. **18** was reacted with 3,4-dichlorobenzaldehyde to form **19**.

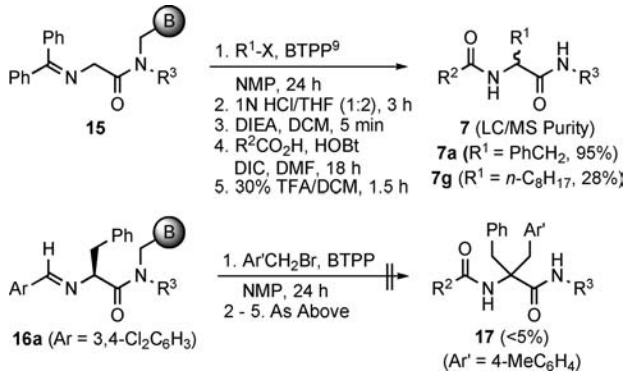
(7) pK_a (DMSO) of the ethyl ester starting materials and monomethylated product: $Ph_2C{=}NCH_2CO_2Et$, 18.7; $Ph_2C{=}NCH(Me)CO_2Et$, 22.8; 4-$ClC_6H_4CH{=}NCH(Me)CO_2Et$, 19.2. See: (a) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520–8525. (b) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775–8778.

(8) (a) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695–3698. (b) Ten different aldehydes were previously studied for the aldimine activating step.[8a] Since the 3,4-dichlorobenzaldehyde imine gave the best results in this earlier case, this variable was not explored in the current BAL imine-based work.

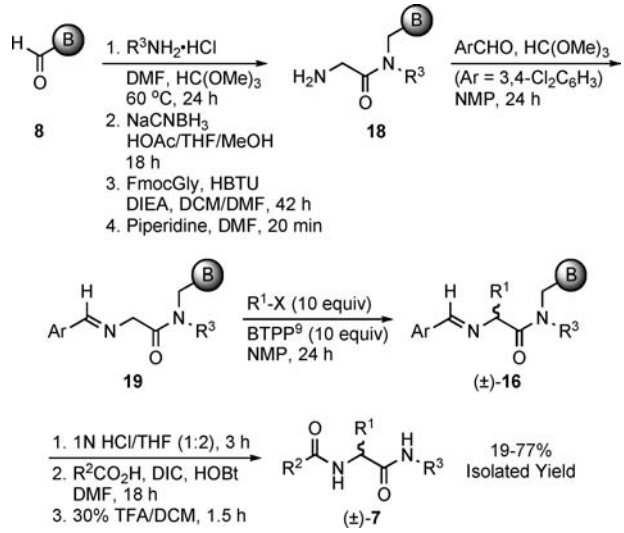
(9) BTPP = *tert*-butylimino-tri(pyrrolidino)phosphorane.

(10) For a discussion, see footnotes 32−35 in ref 1b and associated text.

Scheme 4. Pilot BAL-Based Alkylations to Mono- and Disubstituted Derivatives



Scheme 5. Synthetic Route to Secondary N-Acylated Unnatural α-Amino Acid Amides



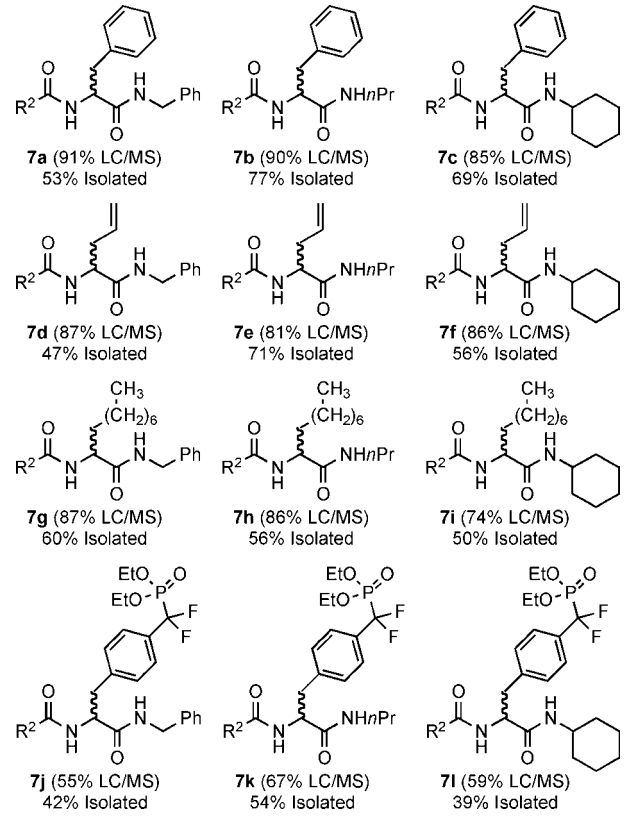


Figure 1. Survey of alkylating agents and amines for the preparation of products **7**. R^2 = 4-NC-C_6H_4. Yields of final products, after chromatographic purification, were calculated on the basis of the initial loading of the starting resin and are the overall yields for all reaction steps starting from these resins.

The key alkylation of **19** to **16** was conducted at room temperature with 10 equiv each of the alkylating agent and the base BTPP. Hydrolysis, acylation, and resin cleavage to **7** followed standard procedures.[1,2]

Alkylating agents (R^1-X) were used to represent an active benzylic and allylic halide (benzyl bromide and allyl bromide, respectively) as well as a less reactive halide (1-iodooctane).[11] The success with the latter halide is in marked contrast with the poor conversion obtained in the earlier pilot scale alkylation of **15** with 1-iodooctane to yield **7g**. In addition, a benzylic difluorophosphonate was used to prepare products **7j**−**7l** and demonstrate the syntheses of stable, protected phosphotyrosine-containing peptidomimetics.[12,13] In turn, the three primary amines R^3-NH_2 (benzylamine, *n*-propyl amine, and cyclohexylamine) illustrate compatibility of this new procedure with normal and branched alkyl amines.

As noted above (Scheme 4), initial pilot studies had indicated reduced reactivity for BAL-based Schiff bases. To probe the limitations this might impose with the new activation procedure, more hindered benzylic alkylating agents were examined (Figure 2, R^1X = 2-methylbenzyl bromide, 2,6-dimethylbenzyl bromide, benzhydryl bromide, and 9-bromofluorene). Ortho substitution, leading to **7m** and **7n**, did not appear to adversely affect reactivity. However, the secondary halide benzhydryl bromide gave poor yields of **7o** and the more rigid and sterically demanding 9-bromofluorene was problematic, yielding only trace amounts (∼5% by LC/MS) of the crude product **7p**.

The all-solid-phase synthetic procedure reported here incorporates three different substituents (from R^1-X, R^2-

(11) For routes to a variety of α-side-chain functionalized α-amino acid derivatives [-$(CH_2)_n$-G where G = CN, OAc, SR, N_3, NHR, NR_2, NHAr, alkyne, nitrogen heterocycle] via Schiff base derivatives of α-amino esters and related compounds, see :(a) Scott, W. L.; O'Donnell, M. J.; Delgado, F.; Alsina, J. *J. Org. Chem.* **2002**, *67*, 2960–2969. (b) Table 5 in ref 1b.

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(13) Use of diethyl ((4-α-bromomethyl)phenyldifluoromethyl)phosphonate to prepare protein tyrosine phosphatase (PTP) inhibitors:(a) Solas, D.; Hale, R. L.; Patel, D. V. *J. Org. Chem.* **1996**, *61*, 1537–1539. (b) Liu, W.-Q.; Roques, B. P.; Garbay, C. *Tetrahedron Lett.* **1997**, *38*, 1389–1392. (c) Liu, W.-Q.; Vidal, M.; Olszowy, C.; Million, E.; Lenoir, C.; Dhôtel, H.; Garbay, C. *J. Med. Chem.* **2004**, *47*, 1223–1233.

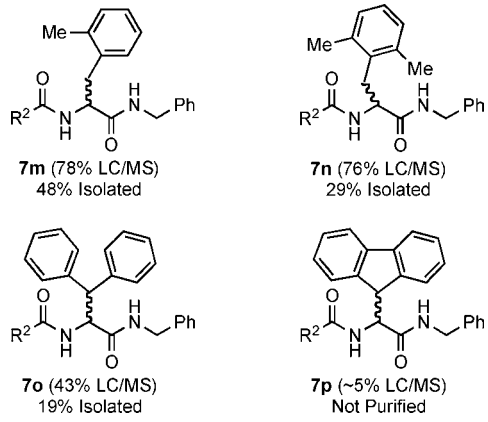

Figure 2. Products **7m**−**7p** from sterically demanding benzylic halides. R^2 = 4-NC-C_6H_4.

CO_2H, and R^3-NH_2) into the glycine-based peptidomimetic scaffold **7**. Utilizing simple Bill-Board solid-phase equipment[1] the 8-step sequence can typically be accomplished in >50% overall isolated yield, providing a very efficient new method to a wide variety of unnatural α-amino acid amides. The reduced reactivity of benzophenone imine activated intermediate **2** was overcome by utilizing aldimine activation (e.g., **19**) for the alkylation step. Clean monoalkylation was observed at this critical stage. The scope and limitation of the complete sequence was examined with a variety of alkylating agents R^1-X and amines R^3-NH_2. Both reactive and less reactive alkylating agents gave good results. Because initial pilot studies indicated reduced reactivity for BAL-based Schiff bases, more hindered alkylating agents were probed. Some hindrance is tolerated, but bulky alkylating agents were more problematic, with the sterically crowded 9-bromofluorene giving only a trace amount of product. Both normal and branched primary amines are compatible with the procedure. The syntheses of **7j**, **7k**, and **7l** demonstrate the ability to use this procedure to incorporate a stable protected phosphotyrosine mimetic into a peptidomimetic series.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (R01 GM028193), The National Science Foundation (MRI CHE-0619254), and The Camile and Henry Dreyfus Foundation for their financial support. We thank Profs. J. R. McCarthy (IUPUI) and Z.-Y. Zhang (Indiana University School of Medicine) for helpful discussions.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901279V