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Solid-Phase Synthesis via N-Terminal Attachment to the 2-Chlorotrityl Resin

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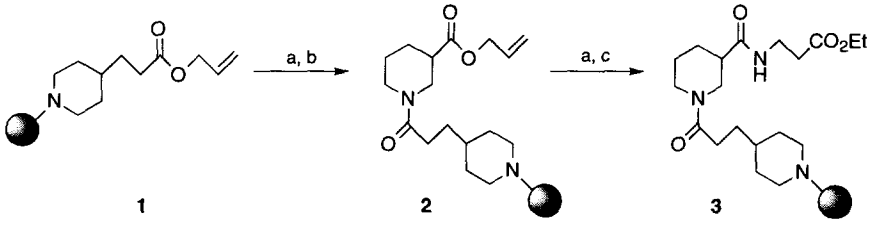
Abstract: Connection of a secondary amine to the 2-chlorotrityl resin followed by iterative saponification/coupling sequences provided a basis for generating focused peptidomimetic mini-libraries. © 1997 Elsevier Science Ltd.

The 2-chlorotrityl resin has become a valuable solid support for high-throughput synthesis of oxygen-linked substrates.[1] High loading and ease of acid-mediated cleavage are two of its more advantageous properties (ca. 1.5 mmol/g; dilute trifluoroacetic acid). Examples have appeared where molecules were constructed starting with an N-terminal junction to a trityl-type resin. Because chiral integrity can be compromised in peptide synthesis by using this approach, applications usually are limited to side chain attachment[2,3] or to nonpeptide systems. For example, Bradley and co-workers reported 2-chlorotrityl resin attachment to putresine, followed by 4-carboxybenzaldehyde amidation and then Wittig olefination.[4] A suitable alternative to a trityl resin for such applications is the acid-labile Wang resin, which involves carbonyl linkage to nitrogen.[5] In this letter, we report N-terminal attachment/ester saponification methodology employing the 2-chlorotrityl resin to provide focused mini-libraries of secondary amine-based peptidomimetics in a rapid, reliable fashion.



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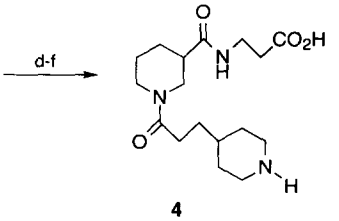


= 2-Chlorotrityl resin

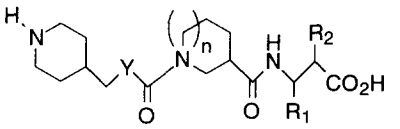
(a) $(Ph_3P)_4Pd$, Me_3SiN_3, DCE. (b) H-Nip-Oallyl•HCl, DIC, DIEA, HOBt.
(c) DIC, DIEA, HOBt, $H_2NCH_2CH_2CO_2Et$•HCl. (d) $KOSiMe_3$, THF.
(e) AcOH/THF (1:2). (f) TFA/CH_2Cl_2 (1:1).

Peptidomimetics based on the γ-chain of fibrinogen,[6,7] exemplified by **4**, were selected for rapid parallel synthesis and biological evaluation. A focused parallel synthesis program was desired to optimize analogue activity. Although all three components of nipecotamide **4** (two amide bond disconnections) were targeted for synthetic variation, the primary point of the structure-activity relationship study, by a variant availability rationale alone, was the β-amino acid component (Eq. 1). N-Terminal and C-terminal resin-anchored strategies were considered. As indicated previously, a C-terminal strategy has much precedent in peptide synthesis. However, there was a concern about the availability of N-protected β-amino acids, vis-a-vis their corresponding β-amino esters, required for N-terminal attachment. Because the latter are readily available either commercially or synthetically, and could be incorporated in a combination of different ester forms (Me, Et, Bn, *t*-Bu, allyl) for a given solid-phase matrix, N-terminal attachment was selected for a synthetic feasibility study. Additionally, this approach would allow resin splitting for incorporation of β-amino ester variants after two-thirds of a particular molecular system has been assembled in a common reaction vessel.

A reliable, high-yielding method for the synthesis and isolation of more than 250 single-entity targets involved initial attachment of the piperidine N-terminus to the 2-chlorotrityl resin, as shown for the nipecotamide **4** (Eq. 1). All reactions were run at ambient conditions under nitrogen. Typically, the resin was washed with aqueous DMF, DMF, THF, and CH_2Cl_2 between transformations. The N-terminal two-thirds of the molecules were assembled in a single reaction vessel, agitated by nitrogen, on a 4-mmol scale. Reaction of 2-chlorotrityl chloride resin with allyl (or methyl) 4-piperidinepropionate hydrochloride in DIEA/DMF over 4-6 hours gave intermediate **2**. Similarly, 4-piperidinemethanol or 4-piperidinemethylphthalimide were affixed to the resin for incipient preparation of tertiary amide isosteric urethanes or ureas, respectively.[8,9] Allyl esters were cleaved using $(Ph_3P)_4Pd/TMSN_3$[10] in 1,2-dichloroethane. Because alkyl esters (Me, Et, Bn) could not be cleaved using standard aqueous hydroxide conditions, as a result of resin contraction, KOTMS in THF was implemented instead.[11] The non-aqueous medium swelled the resin to allow complete, reproducible generation of the desired potassium carboxylate products. Interestingly, unlike as reported for solution phase saponifications,[11] this transformation failed in a Et_2O medium with our resin-bound substrates.

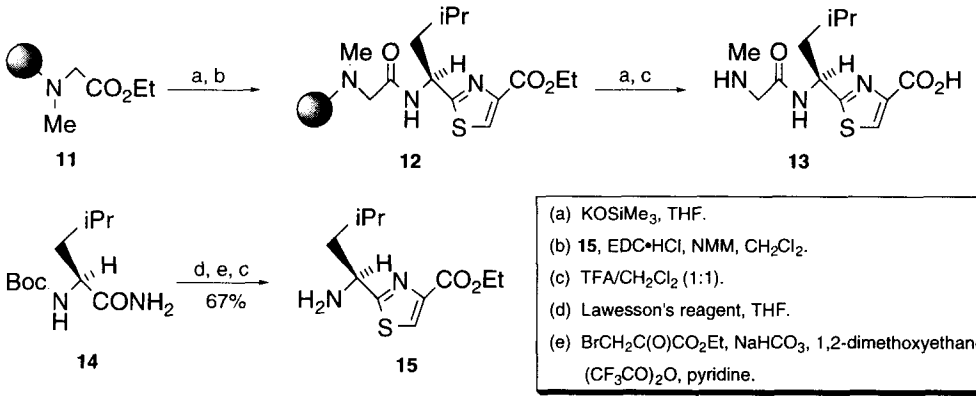
The resin-bound piperidinepropionic acid (or potassium salt) intermediates were coupled with racemic allyl nipecotate hydrochloride by using a standard DIC/HOBt protocol to give **2**, and the allyl ester cleaved with $(Ph_3P)_4Pd/Me_3SiN_3$. Reaction matrices employing either *R*- or *S*-nipecotic acid ethyl ester exhibited 10-15% epimerization. At this point, the resin was divided and β-amino ester variants[12] were coupled to give products such as **3**. Ester products were cleaved with KOTMS, and acidified with AcOH on solid support to reduce salt content of products. Products were isolated by resin cleavage with TFA/CH_2Cl_2 (*tert*-butyl esters removed concurrently) in acceptable yields (53-90%) and purities (80-95%). Subsequent treatment of TFA-washed resin with aqueous THF (1:1) typically afforded an additional 50% of these polar products. Examples **4**-**10** in the table are representatives of over 250 analogues prepared with this methodology.[9]

Peptidomimetics that contain a thiazole-constrained Leu-Xxx core unit[14] (**15**) have been synthesized starting from an N-terminal sarcosine/2-chlorotrityl resin attachment (Eq. 2). Dipeptide surrogate **15** was obtained by a modified Hantzsch procedure by using a thioamide-bromopyruvate annulation.[15,16] Saponification



Cmpd	n	Y	R_1	R_2	FAB (MH^+)	Yield	Purity[13]
4	1	CH_2	H	H	340.5	59%	85%
5	1	CH_2	Ph	H	416.3	70%	90%
6	1	NH	H	Me	355.4	79%	90%
7	0	CH_2	4-Me-C_6H_4	H	416.4	68%	95%
8	1	CH_2	H	OH	356.3	67%	85%
9	1	CH_2	2-thiophene	H	422.5	53%	90%
10	1	CH_2	$(CH_2)_2CO_2H$	H	412.4	54%	90%

of solid-supported thiazole **12** and then resin cleavage with TFA/CH_2Cl_2 rendered, for example, a rigidified pseudotripeptide acid **13** in good yield (88%, HPLC purity >78%). Compound **12** has been a suitable intermediate for the preparation of C-terminal homologues as well. A thorough discussion of this chemistry and related biological results will be published separately.



(2)

Abbreviations. TFA = trifluoroacetic acid; EDC = ethyl 3-dimethylaminopropylcarbodiimide; DIEA = diisopropylethylamine; NMM = *N*-methylmorpholine; DIC = diisopropylcarbodiimide; Nip = 3-nipecotoyl; DCE = 1,2-dichloroethane; HOBt = 1-hydroxybenzotriazole.

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