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Constructing the 2-(thiobenzyl)ethyl carbamate linker via thiyl radical addition

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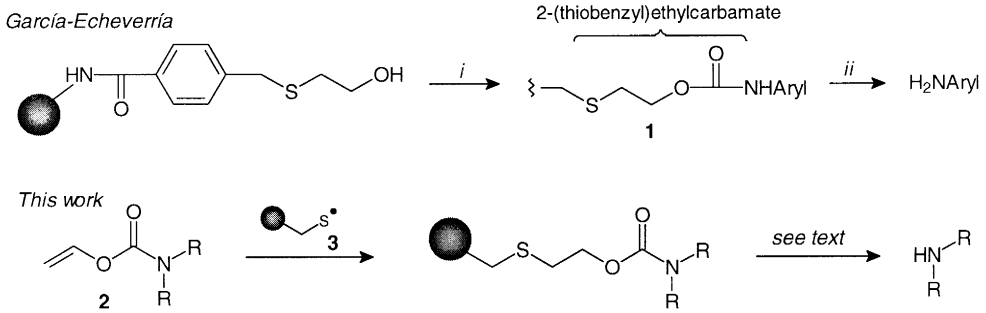
Abstract

N-Vinyloxycarbonyl derivatives of secondary amines undergo efficient addition of thiyl radical and, using Merrifield SH resin, this reaction provides a new entry to resin-bound 2-(thiobenzyl)ethyl carbamates.

A variety of methods exist for linking amines to resin supports for use in solid phase synthesis.[1–5] Many of these methods are based on protocols developed in the area of peptide chemistry, and limitations of the linkers used become apparent with less traditional amine substrates. As a consequence, alternative linkers have been developed and recently García-Echeverría described the use of 2-(thiobenzyl)ethyl carbamate **1** as a base labile traceless linker.[6] The carbamate unit is established via alcohol addition to an isocyanate, and cleavage of the desired primary amine from **1** is achieved using an oxidation/elimination sequence (Scheme 1).[7]



Scheme 1. Reagents: (i) ArylNCO; (ii) (following chemical modification of the aryl moiety) 4 equiv. *m*CPBA, then 10% NH_4OH in 2,2,2-trifluoroethanol

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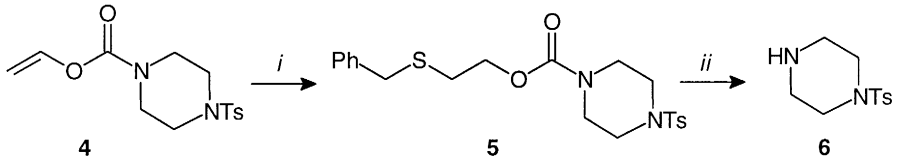
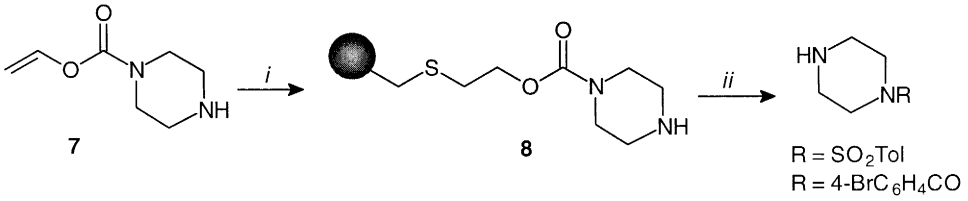
In this paper we describe an alternative method for constructing the 2-(thiobenzyl)ethyl carbamate unit based on the ability of an *N*-vinyloxycarbonyl (VOC) derivative **2** to undergo addition of a benzylic thiyl radical **3**.[8] This methodology provides a method for attaching secondary amines (and thereby complements the isocyanate method outlined in Scheme 1) and serves to extend the synthetic utility of this flexible traceless linker. While we have used García-Echeverría's oxidation/elimination sequence to release the product amine, we also suggest an improvement to this original protocol which has given higher yields of final products, together with an alternative method for cleavage of the linker based on *S*-alkylation.

The underlying efficiency of the thiyl radical addition step was evaluated in solution, and the process has also been applied to solid phase using simple piperazines as model substrates. Under solution conditions, radical addition of benzylmercaptan to *N*-VOC **4** (Ts=SO_2Tol) was best accomplished under strictly O_2-free conditions to give **5** in 87% isolated yield. Using a modification of García-Echeverría's original conditions, oxidation of **5** followed by treatment of the corresponding sulfone with either DBU or *N*,*N*,*N*′,*N*′-tetramethylguanidine in CH_2Cl_2 gave amine **6** in 81% yield (Scheme 2).[9]



Scheme 2. Reagents: (i) $PhCH_2SH$, AIBN, DMF, 80°C (87%); (ii) *m*CPBA (5 equiv.), CH_2Cl_2, then DBU, CH_2Cl_2, rt, 2 h (81%)

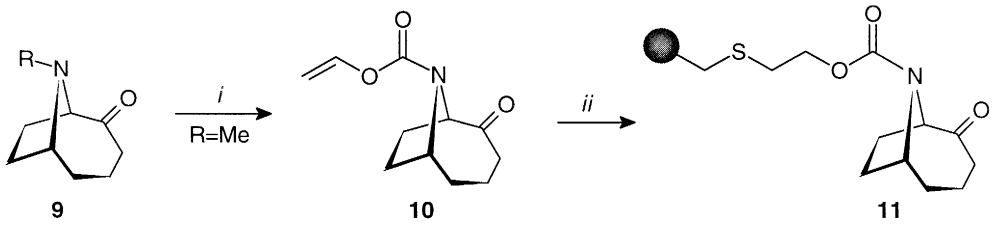
For the application of this methodology to solid phase we have focused on the Merrifield SH resin as the source of thiyl radicals, although a number of alternative thiol resins are commercially available. Merrifield SH resin[14] must be primed before use by reduction with 1,4-dithiothreitol (DTT) to cleave disulfides and release reactive thiol sites. The monoacylated *N*-VOC piperazine **7** was then incorporated onto the resin under radical conditions (AIBN, DMF, 80°C) and, based on microanalytical data, the thiyl addition process proceeded with high efficiency (Scheme 3). The resulting resin **8** was then derivatised with either toluenesulfonyl chloride or 4-bromobenzoyl bromide. The corresponding monosubstituted piperazine products were released using the modified oxidation/elimination procedure in 47% and 50% overall yield (>90% purity based on HPLC analysis using an internal standard and authentic materials), respectively.[14]



Scheme 3. Reagents: (i) Merrifield SH resin, AIBN, DMF, 80°C; (ii) $TolSO_2Cl$/py or 4-BrC_6H_4COBr/py; (iii) *m*CPBA (5 equiv.), CH_2Cl_2, then DBU (47% and 50% overall yield from **7** based on a loading level of 0.31 mmol gm^{-1} of thiol)

Any synthetic process is enhanced when a choice of more than one preparative protocol is available, but an ability to construct the 2-(thiobenzyl)ethyl carbamate by exploiting a pre-existing carbamate moiety does have other advantages particularly when substrates containing amine-sensitive functionality, for example aminoketones, are involved (Scheme 4). We have already employed azabicycloketones, such as **9**, as an entry to novel and potent nicotinic agonists,[15] and while the *N*-methyl variants (**9**, R=Me) are readily accessible, the corresponding free secondary amines (**9**, R=H) are prone to rapid degradation.

Vinyl chloroformate serves to effect a facile *N*-demethylation of (**9**, R=Me) and concomitant *N*-protection to give the *N*-VOC derivative **10** in excellent yield, which underwent thiyl radical addition (using the primed Merrifield SH resin under the conditions described above) to give **11**.



Scheme 4. Reagents: (i) vinyl chloroformate, K_2CO_3, CH_2Cl_2 (96%); (ii) Merrifield SH resin, AIBN, DMF, 80°C

To demonstrate the basic feasibility of this strategy, we have carried out a simple reduction of the resin bound aminoketone **11** (using $NaBH_4$) and released the corresponding alcohol (as a mixture of diastereoisomers) using the oxidation/elimination procedure.[16] Studies are now underway to assess the compatibility of **11** (and related derivatives) towards a wider range of synthetically useful transformations, including metal-mediated cross coupling reactions, to determine the broader utility of the sulfur-containing 2-(thiobenzyl)ethyl carbamate linker.

In summary, vinyloxycarbonyl derivatives of secondary amines undergo efficient thiyl radical addition which provides an alternative and complementary method for constructing the traceless 2-(thiobenzyl)ethyl carbamate linker.

Acknowledgements

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