Pergamon

Tetrahedron Letters 41 (2000) 6619–6622

TETRAHEDRON LETTERS

Lewis acid-catalyzed cleavage of carbamate and carbonate resins

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Received 2 June 2000; revised 27 June 2000; accepted 30 June 2000

Abstract

A procedure for the preparation of amides and esters on a Merrifield resin-bound benzyloxycarbonyl equivalent has been developed. Polymer-supported carbamates react cleanly with zinc bromide and the appropriate acyl halide in the presence of triethylamine to provide their corresponding amides in high yields and purities. Cleavage of resin-bound carbonates was carried out using the similar reagent systems in the absence of triethylamine to give acetates or benzoates.

Combinatorial solid-phase synthesis has become the focus of intense interest as a tool for lead discovery and optimization of new drugs,[1–6] catalysts and materials.[7–9] The linker strategy plays an important part in the designing of a combinatorial library.[10] This necessitates the development of new sets of linkers that possess different chemical stability and their cleavage methods in order to apply various combinations of reaction conditions.

As we were particularly interested in the combinatorial solid-phase synthesis of radiosumin libraries, trypsin inhibitors,[11,12] we needed a linker that would be stable to dilute trifluoroacetic acid treatment and allow for transformation of amines to acetates. Only a few works on carbamate linkers[13–26] and Merrifield resin based amine linkages[27,28] were reported in the literature and their cleavage methods did not look suitable to us. Therefore, we decided to develop a Merrifield resin-bound linker and its cleavage method by a modification of previously developed methodology by our group for the synthesis of salmisteine derivatives.[29] The linker described in this paper is based on the benzyloxycarbonyl protection group. Benzyl carbamates are more resistant to acid and oxidizing agent than are *p*-methoxybenzyl carbamates.[30] Therefore, the benzyl type of Merrifield resin-bound carbamates should show greater stability under acidic and oxidative conditions than those linked to Wang resin due to the absence of the electron-donating effect of the *p*-benzyloxy group.

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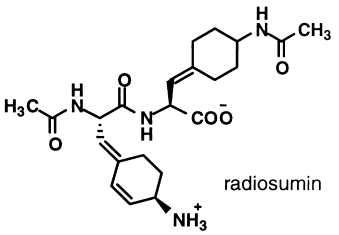
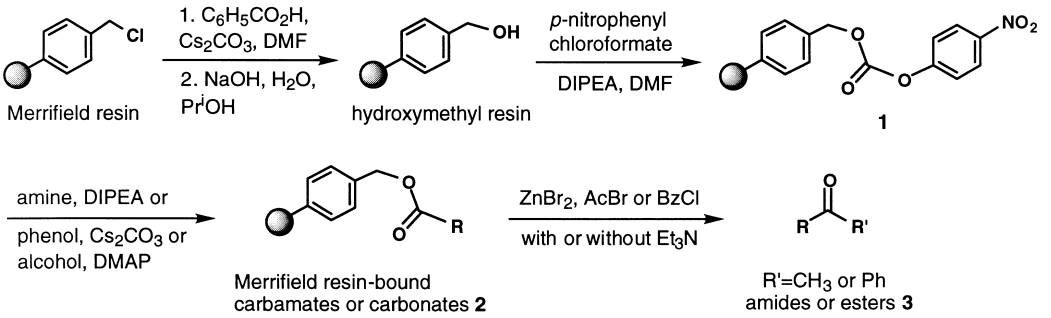
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01131-X



The Merrifield resin-bound benzyloxycarbonyl linkages were prepared and cleaved according to Scheme 1 and the results are summarized in Table 1. Various types of carbamates and carbonates were linked to solid support, all leading to a mild and efficient one-pot cleavage of resins into the amides or esters in good yields. In Table 1, benzamides for the most part were obtained in better yields. Faster cleavage occurred with acetyl bromide as compared to benzoyl chloride. It should be noted that benzyl esters (entries 2, 3 and 5) were stable under cleavage conditions. No epimerization was observed when the cleavage of resin-bound carbamates was conducted with $ZnBr_2$/AcBr or BzCl/Et_3N reagent systems. It is noteworthy that the triethylamine was not necessary to drive the reaction to completion when the resin-bound carbonates were cleaved (entries 7–9). In view of the high purity of the crude products and the simplicity of the procedure, this reaction sequence is suitable for the combinatorial synthesis of a large number of amides and esters on solid support.

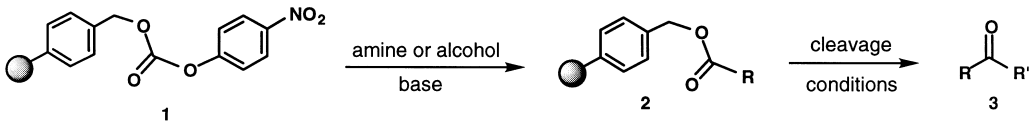


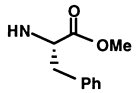
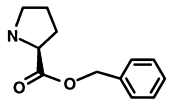
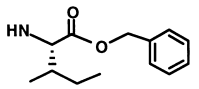
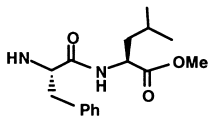
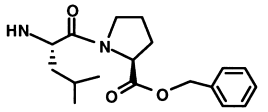
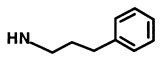
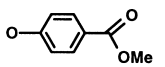
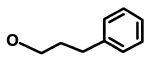
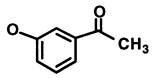
Scheme 1.

General procedure for the attachment to *p*-nitrophenyl carbonate resin **1**: (A) Amines: The *p*-nitrophenyl carbonate resin (300 mg, 0.48 mmol) in DMF (1.9 mL) was added to the desired substrate hydrochloride amine salt (1.44 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL, 2.88 mmol) and left to shake at room temperature for 6 h. The resin was then washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3); (B) Phenols: Same as condition A, except DIPEA was changed to Cs_2CO_3 and the mixture was agitated for 24 h; (C) Aliphatic alcohol: Same as condition B, except Cs_2CO_3 was changed to DMAP.

General procedure for the cleavage of resin-bound carbamates **2**: The carbamate resin (200 mg, 0.32 mmol) was swelled with CH_2Cl_2 (1.6 mL) and treated with dry zinc(II) bromide (36 mg, 0.16 mmol) and acetyl bromide or benzoyl chloride (0.07 mL, 0.96 mmol) under an argon atmosphere. The mixture was agitated for 24 h at room temperature, then a solution of triethylamine (0.07 mL, 0.48 mmol) in 0.38 mL CH_2Cl_2 was added dropwise. After the reaction was completed, the resin was collected by filtration. The filtrate was washed with 5% $NaHCO_3$, 5% HCl and

Table 1
Synthesis of amides and esters by Lewis acid-assisted cleavage of resin-bound carbamates and carbonates **2**



Entry	Resin **2**: R Group =	Base Used	Cleavage Conditions[a]	Product **3**: R' Group	Overall Yields[b] (%)
1		DIPEA	A	R' = CH_3	81
		DIPEA	B	R' = Ph	86
2		DIPEA	A	R' = CH_3	77
		DIPEA	B	R' = Ph	80
3		DIPEA	A	R' = CH_3	72
		DIPEA	B	R' = Ph	74
4		DIPEA	A	R' = CH_3	72
		DIPEA	B	R' = Ph	78
5		DIPEA	A	R' = CH_3	70
		DIPEA	B	R' = Ph	75
6[c]		DIPEA	A	R' = CH_3	61
7		Cs_2CO_3	C	R' = CH_3	93
		Cs_2CO_3	D	R' = Ph	97
		DMAP	C	R' = CH_3	97
8		DBU	C	R' = CH_3	40
		NaH	C	R' = CH_3	10
9		Cs_2CO_3	C	R' = CH_3	75

[a]Cleavage Conditions: A. $ZnBr_2$/AcBr/Et_3N; B. $ZnBr_2$/BzCl/Et_3N; C. $ZnBr_2$/AcBr; D. $ZnBr_2$/BzCl. [b]Overall isolated yields are calculated based on the loading level of the hydroxymethyl resin.[31] Products were synthesized using the described procedure and characterized by NMR, IR and mass spectroscopy. [c]Technical grade 3-phenyl-1-propylamine was used.

saturated NaCl solutions. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed on silica gel to yield the desired amides **3**.

In conclusion, we have successfully developed a new cleavage strategy for Merrifield resin-bound benzyloxycarbonyl linkers. This new one-pot release protocol has proven to be a general reaction for the cleavage of carbamate and carbonate resins. The carbamate and carbonate

linkers are suitable for the anchoring of amines, phenols and alcohols, allowing the construction of both peptide and organic combinatorial libraries in a bi-directional fashion. The strategy should expand the utility of Merrifield resin and increase the sophistication of solid-phase synthesis. Currently, we are in the process of using this protocol in the combinatorial synthesis of radiosumin libraries and those results will be reported in due course.

Acknowledgements

The authors are grateful to the National Science Council, ROC, for the financial support (NSC 88-2113-M-008-005) of this work.

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