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Solid Phase Synthesis of Fully Protected Peptide Alcohols

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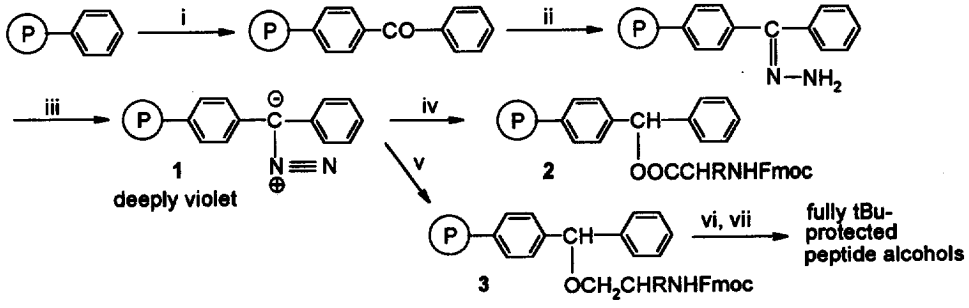
Abstract: A mild and efficient method to obtain fully t-butyl type protected alcohols based on the alkylation of Fmoc amino alcohols with the "polymeric diphenyldiazomethane" **1** followed by standard Fmoc solid phase synthesis is presented. The resulting peptidyl benzhydryl ethers **3** can be cleaved with 1 - 2% trifluoroacetic acid in methylene chloride to yield the protected peptide alcohols.

Peptide alcohols have gained attention not only as naturally occurring peptide antibiotics such as the peptaibols but also as analogs of bioactive peptides of considerable pharmaceutical interest such as the somatostatin analog octreotide. Furthermore, protected peptide alcohols find use as precursors of the rather labile peptide aldehydes, important enzyme inhibitors as well as versatile synthons.

In order to circumvent the cumbersome synthesis of peptide alcohols in solution, a range of methods relying on solid phase peptide synthesis (SPPS) was developed [1]. Here we present a method to obtain rapidly carriers loaded with Fmoc/tButyl protected amino alcohols or with suitable derivatives of hydroxy amino acids based on the well-established etherification of hydroxyls with diazoalkanes catalyzed by Lewis acids [2]. The resin derivatives were devised especially for the large-scale SPPS of precursors of peptide aldehydes and octreotide analogs.

"Polymeric diphenyldiazomethane" (PDDM) **1**, i.e. the diphenyldiazomethyl derivative of crosslinked polystyrene, has been reevaluated recently as an easily accessible polymeric carrier for SPPS [3,4]. The deeply violet colored polymer smoothly alkylates Fmoc amino acids and other carboxylic acids [4]. As expected from the behavior of diphenyldiazomethane, less acidic substrates such as phenols, thiols and alcohols should react with **1** either at elevated temperatures (cf. [5]) or in the presence of a catalytic amount of a Lewis acid such as boron trifluoride etherate. Synthesis and derivatization of **1** are illustrated in Scheme 1.



Scheme 1: i.benzoyl chloride, $AlCl_3$, -10°C. ii. $N_2H_4 \cdot H_2O$, nBuOH, reflux. iii. tetramethylguanidine, CH_3CO_3H, CH_2Cl_2, cat. I_2, -10° → 0°C. iv. FmocNHCHRCOOH, CH_2Cl_2 or CH_2Cl_2/DMF (3:1). v. FmocNHCHRCH$_2$OH, cat. $BF_3 \cdot OEt_2$, CH_2Cl_2. vi. Fmoc/tBu-based SPPS. vii. 1 - 2% CF_3COOH in CH_2Cl_2, 5 min, repeat several times.

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Alkylation of Fmoc amino alcohols and Fmoc-Ser derivatives is simple and straightforward, but a moderate solubility of the substrate in methylene chloride is required as, in contrast to the alkylation of Fmoc amino acids with **1**, the addition of cosolvents such as DMF to improve solubility will inhibit the etherification of alcohols. So the deeply violet **1** is allowed to swell in dry CH_2Cl_2. An excess of Fmoc amino alcohol is added and dissolved to saturation. Subsequently 0.1 - 0.2 equiv. of $BF_3 \cdot Et_2O$ are added slowly causing rapid discoloration and effervescence (N_2). As etherification proceeds more slowly stirring is continued for at least 3 h, then the resin is filtered off and thorougly washed with CH_2Cl_2. After drying in vacuo the load of the resin is determined photometrically [6] and the resin is subjected to standard Fmoc/tBu SPPS. Cleavage of protected peptide alcohols from the resin is achieved by repetitive short treatments (2 - 5 min. each) with 1 - 2% CF_3COOH in CH_2Cl_2. Cleavage with hexafluoroisopropanol/CH_2Cl_2 (1:4) [7] failed. A range of examples for anchoring Fmoc amino alcohols including side-chain etherification is compiled in Table 1.

Employing the Fmoc-Asp(OtBu)-ol benzhydryl ether resin the aldehyde precursor Ac-Leu-Glu(OtBu)-Val-Asp(OtBu)-ol could be synthesized rapidly in excellent yield and purity. The corresponding aldehyde was smoothly obtained by oxidation with $SO_3 \cdot$ pyridine complex / DMSO / Et_3N [8].

In summary we have developed a mild and efficient method to obtain fully protected peptide alcohols based on the readily accessible "polymeric diphenyldiazomethane". The polymer can also be used for side-chain anchoring of hydroxy and mercapto amino acid derivatives. It may as well find application in solid phase organic chemistry (SPOC) / combinatorial chemistry for anchoring and modifying alcohols, thiols and carboxylic acids.

Table 1. Etherification of N-Fmoc amino alcohols and N-Fmoc hydroxy amino acid derivatives at room temperature in CH_2Cl_2. Excess of hydroxy compound: ca. 2 equivalents; 0.05 to 0.1 mol equiv. of $BF_3 \cdot Et_2O$.

Fmoc-alcohol	react.time,hrs	load,meq/g	yield,%	Fmoc-alcohol	react.time,hrs	load,meq/g	yield,%
Gly-ol	5	0.58	81	Ala-ol	4	0.59	80
Asp(OtBu)-ol	5	0.77	83	Thr-ol[a]	3	0.52	90
Met-ol[b]	6	0.50	72	Ile-ol	4	0.57	81
Ser-OMe	2	0.53	73	The-OMe	7	0.30	42
Hyp-OMe	7	0.39	56	Tyr-OMe	6	0.32	48
cysteamine	5	0.54	75				

[a] probably linked via primary OH, conditions of the following SPPS had to be adapted as to avoid O-acylation of secondary OH.
[b] SPPS of TyrDAlaGlyMePheMet(O)ol, oxidation after cleavage from the resin, crude product (HPLC : 91%) coelutes with reference.

References and Notes

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