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Hydroxy-(2-chlorophenyl)methyl Polystyrene Resin: Studies on the Immobilization and Cleavage of Acids and Alcohols

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Abstract: The utility of hydroxy-(2-chlorophenyl)methyl polystyrene resin in solid phase synthesis is demonstrated. Methods are given for the immobilization and cleavage of acids and phenols.

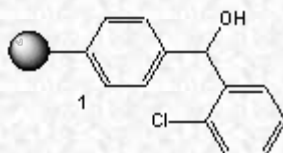
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Introduction

Benzhydrol-based supports, such as hydroxy-(2-chlorophenyl)methyl polystyrene **1**, were first introduced by Barlos, *et al.* [\[1\]](#) for use in solid phase peptide synthesis. Esters derived from resins of this type exhibit an acid sensitivity intermediate between those derived from the very acid labile Rink Acid resin [\[2\]](#) and the more acid stable Wang resin [\[3\]](#). To determine the optimum conditions for the use of hydroxy-(2-chlorophenyl)methyl polystyrene in peptide as well as organic chemistry, various methods for the immobilization and subsequent cleavage of acids and phenols were examined, and the results of these studies are presented here.



Results and Discussion

Loading Studies-Acylation

Hydroxy-(2-chlorophenyl)methyl polystyrene resin 1 (substitution 1.18 mmol/g, as determined by chlorine analysis, Calbiochem-Novabiochem, Product No. 01-64-0345) was loaded with Fmoc-Leu-OH using diisopropylcarbodiimide (DIC) and 1-methylimidazole (1-Melm) activation in DMF, as outlined in Scheme 1, to afford resin 2a. The loading of the resin was determined to be 0.75 mmol/g by the Fmoc UV assay, which represents a coupling yield of 85%. Following Fmoc removal, this material was then used to prepare resins 3 (yield 96%, determined by Fmoc UV assay) and 4 (quantitative two step reaction, determined by bromine combustion), as described in Scheme 1.

Loading Studies - Mitsunobu reaction

The results of investigations into the loading of 1 with various phenols and acids under Mitsunobu conditions are summarized in Table 1. The reactions were carried out overnight in dry THF, using varying excesses of acidic component, DEAD and Ph₃P (Scheme 2). The attachment yield of p-hydroxybenzaldehyde was found to vary considerably with the excess of reagents used: 3 eq., 51%; 2 eq., 25.4 %.

Cleavage Studies

To determine optimal cleavage conditions, the resins prepared above were treated 4 times with 1 - 23% TFA in DCM for 30 minutes. TLC analysis of the cleavage filtrates indicated that generally after the third TFA treatment no further product was released from the resin. After the final TFA treatment, the resins were washed three times with DCM, and the filtrates pooled, concentrated and the residues dried *in vacuo*. The cleavage yields are given in Table 2.

Tables

Table 1: Immobilization of acids and alcohols.

Immobilized compound	Method/Yield		
	DIC/1-Melm (4 eq.)	Mitsunobu (3 eq.)	Mitsunobu (2 eq.)
Fmoc Leu- OH 2b	93% / 85% ^a	67% ^a	-
Fmoc Leu- OH to Wang resin	-	-	62% ^a
Fmoc Rink Linker 8	-	44% ^a	-
p-Hydroxybenzaldehyde 9	-	51% ^b	25% ^b
p-Nitrophenol 7	-	-	80% ^c

^aLoading determined by Fmoc UV assay [4].

^bLoading determined by derivatization with tosyl hydrazine then sulfur combustion analysis.

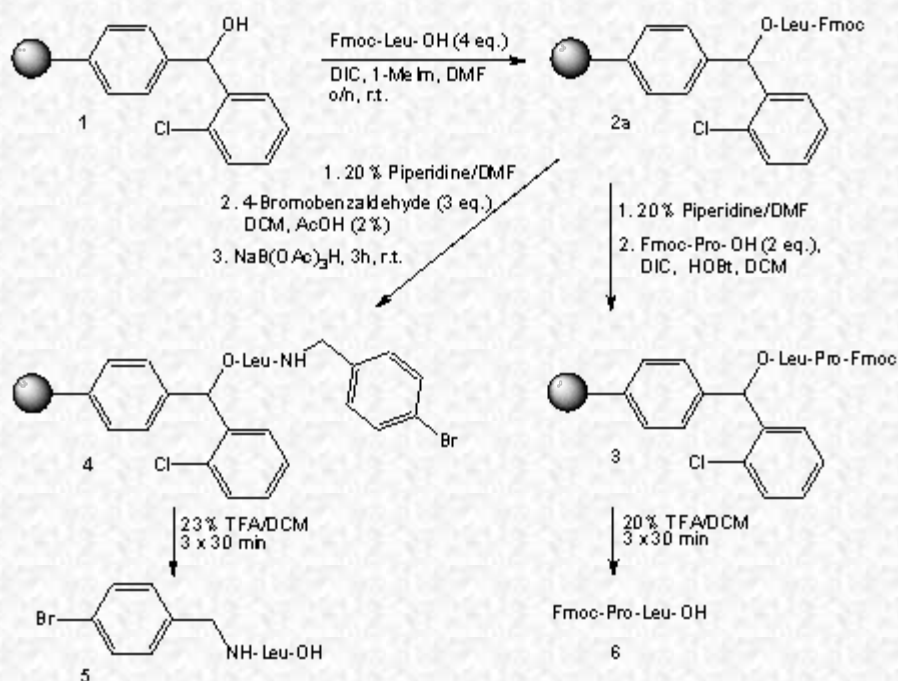
^cLoading determined by nitrogen combustion analysis.

Table 2: Cleavage yields obtained after treatment of the resins with different concentrations of TFA/DCM.

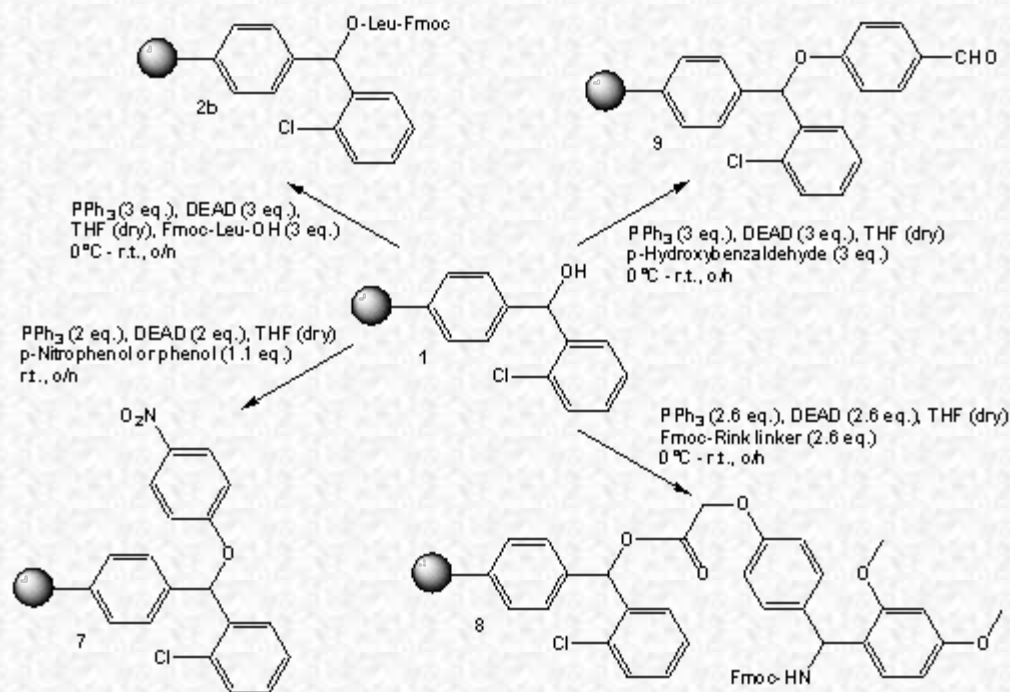
Product	Cleavage conditions: % TFA in DCM/Yield					
	1	5	10	15	20	23
Fmoc-Leu-OH	70%	quant.	quant.	-	96%	-
p-Nitrophenol	55%	67%	76%	83%	85%	-
Fmoc-Pro-Leu-OH 6	-	-	-	-	66% ^a	-
4-Bromobenzyl-Leu-OH 5	-	-	-	-	-	73% ^a

^aCleavage was performed three times for 30 minutes.

Schemes



Scheme 1: Loading of resin 1 by acylation with Fmoc-Leu-OH and derivatization of resin 2a.



Scheme 2: Loading of resin 1 using Mitsunobu conditions.

Conclusion

Acylation is more efficient for loading of the hydroxy-(2-chlorophenyl)methyl polystyrene resin than the use of Mitsunobu

conditions. Since coupling yields of Fmoc-Leu-OH using Mitsunobu conditions are comparable for Wang resin and resin 1, the sterically demanding structure of resin 1 might not have an important influence on the immobilization. Cleavage from hydroxy-(2-chlorophenyl)methyl polystyrene is best performed using 5% TFA in DCM for acids and 20% TFA for phenols. Thus, the resin can be used as an alternative to bromo- or chloro-(4-methoxyphenyl)methyl polystyrene resins [5] (Calbiochem-Novabiochem, Product No. 01-64-0253) which have to be loaded using basic conditions.

References

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