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PEPTIDE SYNTHESIS BY A COMBINATION OF SOLID-PHASE AND SOLUTION METHODS III[1)]

RESIN DERIVATIVES ALLOWING MINIMUM-RACEMIZATION COUPLING OF N^{α}-PROTECTED AMINO ACIDS

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SUMMARY

The conversion of 4-alkoxy benzyl alcohol resin and 2-methoxy-4-alkoxy benzyl alcohol resin (SASRIN) into the corresponding halides is described. To these, N^{α}- protected amino acids can be coupled with minimal racemization.

Partial racemization often observed in coupling of N^{α}-protected amino acids to 4-alkoxybenzyl alcohol resin (Wang's resin)[2)] or 2-methoxy-4-alkoxybenzyl alcohol resin (SASRIN)[3)] still is an unsolved problem in solid-phase peptide synthesis.

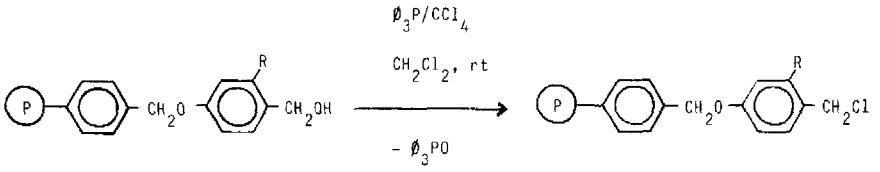
The extent of racemization varies with the amino acid derivative. Cys and His derivatives especially are prone to racemization if the esterification to the resin is performed by carboxyl activation (e.g. with dicyclohexyl carbodiimide and 4-dimethylaminopyridine as catalyst, or via active esters[3),4),5)]).

On the other hand salts of N^{α}-protected amino acids can be treated with alkyl halides to yield esters without noticeable racemization[6)].

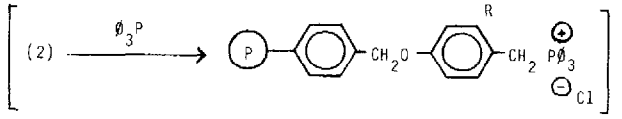
In Merrifield's original solid-phase peptide synthesis protocol C-terminal amino acids were coupled as their triethylammonium salts to chloromethyl polystyrene[7)]. Since then many approaches to increase alkylation rates and yields have been published[7b),8)]. To follow this route Wang's and SASRIN benzyl alcohol resin have to be converted first into halides, an operation requiring special conditions in view of the acid lability of starting materials and products.

The combination triphenylphosphine-carbon tetrachloride converts alcohols into alkyl chlorides under mild conditions in excellent yields[9)].

The reaction proceeds smoothly in less polar solvents such as methylene chloride[9b]. Since the polymer-bound benzyl alcohols swell considerably in this solvent a smooth conversion of (1) to the chlorides (2) according to eq. 1 could be expected.



(1) R = H, OCH_3 (2)

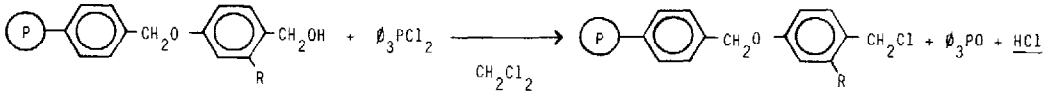


(3) (eq. 1)

The reaction proceeds readily indeed, but unfortunately (2) alkylates unreacted triphenylphosphine leading to an ill-defined polymer containing phosphonium chloride moieties (3) (a model compound of (1), 2-methoxy-4-benzyloxy-benzyl alcohol[14], reacted analogously).

Because of the high reactivity of (2) towards nucleophiles triphenylphosphine must not be used for the halogenation of (1).

We have found triphenylphosphine dichloride to be the reagent of choice for the intended conversion (see eq. 2), although this system will turn acidic. The reagent can be prepared from triphenylphosphine and chlorine[10] or preferentially in situ from the phosphine and carbon tetrachloride (equimolar amounts)[9b].



R = H, OCH_3 (eq. 2)

Some results are listed in table 1.

The 2-methoxy group enhances the replacement rate.

Table 1. Synthesis of Sasrin chloride and Wang's resin chloride with triphenylphosphine dichloride prepared in situ at r.t.

Resin	eq. $\emptyset_3P$	solvent	reaction time (hr)	conversion[a] (%)
Sasrin	5.6	CH_2Cl_2/toluene (3:1)	24	100
Sasrin	1.4	DMF	48	78
Sasrin	5.2	CH_2Cl_2	20	98
Sasrin	5.2	CH_2Cl_2/toluene (3:1)	13	94
Sasrin	5.6	DMF/toluene (3:1)	48	90[b]
Wang's	5	CH_2Cl_2	28	82-88

a) based on chlorine content

b) contains ionic chloride

The best results were obtained in methylene chloride.

The chlorine bound to these resins could be completely replaced by carboxylates (details concerning this reaction are given in the following paper).

Triphenylphosphine dibromide (from $\emptyset_3P$ und Br_2, also commercially available) reacts analogously[12], but the reagent itself and the HBr liberated during reaction cause benzyl ether cleavage[11),13].

Since the reactivity of the resin chlorides turned out to be sufficient further investigations centered on these better-defined derivatives[13].

The following paper will illustrate the use of these in solid-phase peptide synthesis.

Literature and remarks Part III

1) presented in part at the 20th European Peptide Symposium Tübingen, FRG, September 1988.

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12) The $\emptyset_3P/CBr_4$ system is less suitable (it reacts faster, but it seems to produce more inactive side products)

13) Under optimized alkylation conditions even the less reactive p-chloromethyl polystyrene is converted with a somewhat lower yield.

14) 2-methoxy-4-benzyloxy benzyl alcohol: mp 46-48° C, very acid-sensitive

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