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p-(Aminomethyl)phenoxymethyl Polymer for Solid Phase Synthesis of Protected Peptide Amides[1]

Piergiorgio Pietta* and Oreste Brenna

Istituto di Chimica Organica dell'Università, 20133 Milano, Italy

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We have previously[2] reported on the use of *p*-methoxybenzyl (pmb) as an amido protecting group and on the synthesis of a related *p*-alkoxybenzylamine support for the preparation of C-terminal peptide amides. Attempts to prepare peptide amides using this polymer as a substitute of the benzhydryl amino polymer[3] showed that the anchoring bond between the first amino acid and the polymer is not stable in the conditions normally associated with the removal of *N-tert*-butyloxycarbonyl (Boc). Thus, when the Boc-Ala-*p*-alkoxybenzylamine resin, Boc-Ala-NH-resin, was treated with 50% (v/v) trifluoroacetic acid in methylene chloride or 1 *N* HCl–acetic acid to remove the Boc group, alanine amide was released in 80% yield. A similar result has been obtained by the use of Boc-Val-NH-resin and Boc-Gly-NH-resin. This experimental finding led us to use this support for the preparation of small protected peptide amides suitable for conventional peptide synthesis. This approach has been already described[4] and is very important, since the two most necessary requirements for the successful synthesis of pure long peptide chains by the solid phase peptide technique, i.e., nearly 100% stepwise yields and careful choice of protecting groups, are often difficult to meet.

This paper describes the preparation of the *p*-(aminomethyl)phenoxymethyl polymer (*p*-alkoxybenzylamine polymer) and its application to the synthesis of three protected peptide amides using for amino protection the very acid labile 2-phenylisopropyloxycarbonyl group (Ppoc).[5]

Two synthetic routes to this support are outlined in Scheme I.

Initial preparation was carried out by reaction of the Merrifield resin (IV) with *p*-cyanophenol followed by reduction with $LiAlH_4$ in presence of ammonia. A second procedure involved the treatment of the *p*-alkoxybenzyl alcohol resin[6] with HBr in methylene chloride to give the *p*-alkoxybenzyl bromide polymer, which was converted to the desired amine derivative by reaction with ammonia in methylene chloride.

The first method required accurately controlled conditions because of the possible concurrent formation of the *p*-alkoxybenzyl alcohol polymer. To overcome this drawback the cyano polymer, obtained by treating the Merrifield resin with a large excess of *p*-cyanophenol for short reaction times, was reduced in a stream of dry ammonia. This difficulty did not occur in the preparation of the *p*-alkoxybenzylamine polymer starting from the *p*-alkoxybenzyl alcohol support. However, this route was discarded since the sequence of reactions, i.e., preparation of the *p*-alkoxybenzyl alcohol polymer, conversion to the corresponding bromide derivative, and final amination, was long and tedious. For this reason the synthesis of our models was carried out on the polymer prepared by the first procedure. Ppoc-amino acids were attached to the amine support via DCC. The degree of substitution was 0.4–0.5 mequiv/g; the remaining free amino groups were blocked by acylation. The Ppoc group was removed by 30-min exposure to 1% (v/v) trifluoroacetic acid in methylene chloride.[5] During this time there was hardly any free amide released from the resin, indicating that the anchoring bond was largely stable under these conditions.

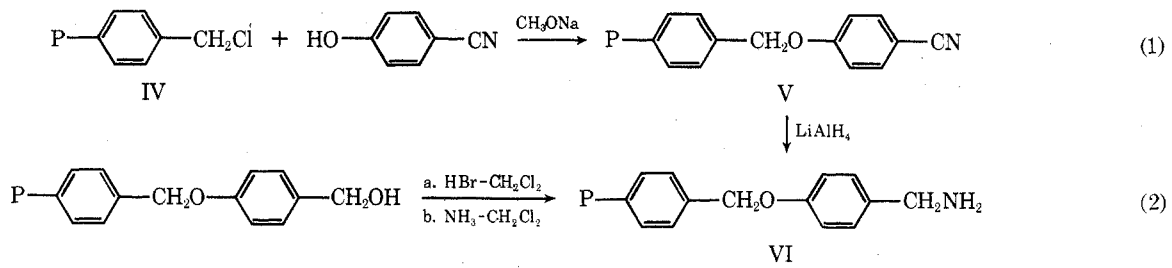
The following protected peptide amides were prepared on the *p*-alkoxybenzylamine support: Z-Pro-Leu-Gly-NH_2 (I), Z-Ala-Phe-Gly-Leu-Met-NH_2 (II), and Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). The protected peptides were released from the resin by 50% (v/v) trifluoroacetic acid in methylene chloride after 30 min and were purified by crystallization.

The products proved to be homogeneous by thin layer chromatography and gave the expected amino acid analysis after acid hydrolysis.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer IR-257 with KBr pellets. Amino acid analyses were carried out on a Beckman Model 120 B amino acid analyzer. Thin

Scheme I



layer chromatography was run on precoated silica gel plates (Merck, GF_{254}) using the following systems: A, benzene–ethyl acetate–acetic acid–water (10:10:2:1, v/v); B, 1-butanol–acetic acid–water (4:1:1, v/v); C, chloroform–methanol–acetic acid (85:10:31, v/v).

The Merrifield resin (IV) (chloromethylated copolystyrene, 1% divinylbenzene, 0.9 mequiv/g, 200–400 mesh) was purchased from Bio-Rad Laboratories.

p-Cyanophenyl Resin (V). Merrifield resin (IV, 20 g, 18 mmol) in 200 ml of dry diglyme was treated with 14.28 g (120 mmol) of *p*-cyanophenol and 6.48 g (120 mmol) of $NaOCH_3$ at 60° for 2 hr. The resin was collected and washed with DMF, dioxane, CH_2Cl_2, and methanol to give 21.4 g of V. The resin absorbed strongly at 2250 cm^{-1}.

p-Alkoxybenzylamine Resin (VI). A solution of 2.28 g (60 mmol) of $LiAlH_4$ in 60 ml of dry ether was placed in a three-necked flask. A suspension of the *p*-cyanophenyl resin (20 g) in 100 ml of dry ether was added from a dropping funnel. The mixture was then stirred for 6 hr under dry ammonia stream. The resin was then filtered and washed with ethyl acetate, methanol, and CH_2Cl_2 to give a grayish product. The colored matter was removed by stirring in 500 ml of a 1:1 mixture of acetic acid and 1 *N* HCl for 15 min. The product was washed with 10% (v/v) triethylamine in $CHCl_3$ to convert the hydrochloride to the free amine, $CHCl_3$, and CH_2Cl_2, and dried under vacuum at 30° to give 18.4 g of the *p*-alkoxybenzylamine resin (VI). The ir showed a broad absorption at 3500–3100 cm^{-1} and no cyano band. The capacity, determined by the Esko procedure,[7] was in the range of 0.6 mequiv of NH_2/g of polymer.

Ppoc-Glycyl-p-alkoxybenzylamine Resin (VII). The amino resin VI (10 g, 6 mmol) was washed several times with ethanol and methylene chloride and then treated with 2.84 g (12 mmol) of Ppoc-Gly and 2.48 g (12 mmol) of DCC for 120 min. After washings with CH_2Cl_2, $CHCl_3$–MeOH (1:1 v/v), and CH_2Cl_2, the resin was suspended in 100 ml of CH_2Cl_2 and then allowed to react with acetic anhydride (2 ml) for 30 min in the presence of a catalytic amount of 4-dimethylaminopyridine.[8] After washings with CH_2Cl_2, 11.2 g of resin was obtained; it contained no detectable amount of free amino group. Amino acid analysis indicated that there was 0.42 mmol of glycine/g of resin.

Ppoc-Met Resin (VIII) and Ppoc-Val Resin (IX). The amino resin VI was treated with Ppoc-Met or Ppoc-Val in the same manner as above yielding respectively Ppoc-Met resin (VIII) and Ppoc-Val resin (IX).

The resin VIII was found to have 0.47 mmol/g of methionine; the resin IX was found to have 0.39 mmol/g of valine.

Stability of the p-Alkoxybenzylamide Anchoring Bond. Several samples of resin VII (150 mg) were placed in test tubes and suspended in 1% TFA in CH_2Cl_2 (5 ml). The tubes were stoppered and the reaction was allowed to proceed for the desired time at 23°. Then the samples were taken, filtered, and washed with 2 ml of CH_2Cl_2. The liberated glycine amide was separated by thin layer chromatography on silica gel using the system B; the spots were detected with ninhydrin–cadmium acetate (0.2% v/v)[9] and evaluated by densitometry.[10]

Results of such experiments showed that there was 8% loss of the anchoring bond in 12 hr. In the case of polymers VIII and IX a loss of 7.7 and 7.2 was found in 12 hr.

Cleavage Experiments. Small samples of the resins VII, VIII, and IX were treated with 50% v/v TFA in methylene chloride for 30 min. The filtrates were concentrated and chromatographed. Gly-NH_2, Phe-NH_2, and Met-NH_2 were found in presence of traces of the free amino acids.

The results confirmed that the conversion of the amino resin VI into resins VII, VIII, and IX had proceeded satisfactorily.

Z-Pro-Leu-Gly-NH_2 (I). Solid phase synthesis was carried out on 5 g (2.1 mmol) of resin VII with a threefold excess of amino acid derivatives and DCC in each cycle. The tripeptide released (720 mg) was twice crystallized from methanol, yield 491 mg (56%), mp 161–162° (lit.[11] mp 162–163°).

Z-Ala-Phe-Gly-Leu-Met-NH_2 (II). Solid phase synthesis of this protected amide was carried out similarly starting from resin VIII, yield 32%, mp 222–223° from methanol, $[\alpha]^{25}D$ −29.54° (*c* 1, DMF). It gave corrected amino acid analysis upon acid hydrolysis: $Ala_{1.02}Gly_{1.00}Leu_{1.03}Met_{0.92}Phe_{1.06}$.

Anal. Calcd for $C_{33}H_{46}N_6O_7S$ (670.8): C, 59.03; H, 6.85; N, 16.69. Found: C, 59.51; H, 6.92; N, 16.58.

Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). Resin IX (5 g, 1.95 mmol) was placed in the peptide synthesis flask and the synthesis was carried out with fourfold excess of amino acid derivatives and DCC in each cycle. Ppoc-Leu (2.28 g), Ppoc-Gly (1.84 g), and Z-Gln(Dmb) [*N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine] (4.76 g) were sequentially coupled to the resin to give 6.2 g of the protected tetrapeptide polymer. The peptide was then released from the polymer by stirring in 100 ml of 50% (v/v) trifluoroacetic acid in methylene chloride for 30 min. After filtration and evaporation, the residue was treated with ethyl acetate–petroleum ether. The solid obtained (0.920 g) was crystallized from ethyl acetate: yield 0.734 g (54%); mp 246–248°; $[\alpha]^{25}D$ +62.07° (*c* 1.5, DMF). On acid hydrolysis, the compound gave the correct amino acid analysis: $Gly_{1.04}Glu_{1.02}Leu_{1.02}Val_{0.97}$.

Anal. Calcd for $C_{35}H_{50}N_6O_9$ (698.6): C, 60.12; H, 7.22; N, 12.02. Found: C, 59.87; H, 7.35; N, 12.12.

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Registry No.—I, 14485-80-4; II, 56195-91-6; III, 56195-92-7.

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Condensations of Phthalaldehydic and *o*-Acetylbenzoic Acids with Naphthalenes[1]

Melvin S. Newman,* S. Venkateswaran,[2] and V. Sankaran[3]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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The acid-catalyzed condensation of phthaldehydic acid (**1**) with benzene and halogenated benzenes to produce 3-phenylphthalides[4] **2**, and of *o*-acetylbenzoic acid (**3**) with 1,2-dimethoxynaphthalene[5] have been reported. Because of the utility of this type of reaction in the synthesis of benz[*a*]anthracenes of interest in the field of cancer research we report herein on the condensations of phthaldehydic and *o*-acetylbenzoic acids with substituted naphthalenes.

In the condensation of **1** with benzene and halogenated benzenes, Floutz used concentrated sulfuric acid, or 20% oleum, at room temperature to obtain almost quantitative yields of 3-phenylphthalides,[4] **2**. However, we have found that such strong acid is not advisable for the condensation of **1** or **3** with naphthalene derivatives because sulfonation and/or oxidation occurs. In studies with naphthalenes and **1**, 90–100% methanesulfonic acid[6] proved superior as no sulfonation or oxidation occurred in 20–24 hr at room temperature and almost quantitative yields of 3-(4-X-1-naphthyl)phthalides, **2**, were attained. With the more reactive 1-methoxynaphthalene, the reaction was complete in 3 hr. In this case 90% methanesulfonic acid was preferable to 100% acid because the latter caused some demethylation.

When *o*-acetylbenzoic acid (**3**) (see Experimental Section for an improved synthesis of **3**) was used in place of **1** a different technique was required because of the tendence of **3**