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A NEW PREPARATION OF 4-(BOC-AMINOACYLOXYMETHYL)PHENYLACETIC ACIDS FOR SOLID-PHASE PEPTIDE SYNTHESIS

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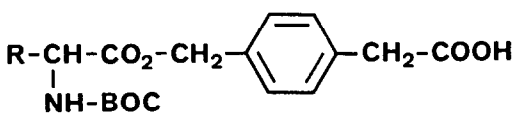
Summary : *A new preparation of 4-(BOC-aminoacyloxymethyl)phenylacetic acids 1, consisting of an esterification of the corresponding BOC-amino acids 2 with 4-(bromomethyl)phenethyl alcohol 3, followed by a Collins oxidation and an oxidation with sodium chlorite is described. The overall yields range from 58 to 69 %.*

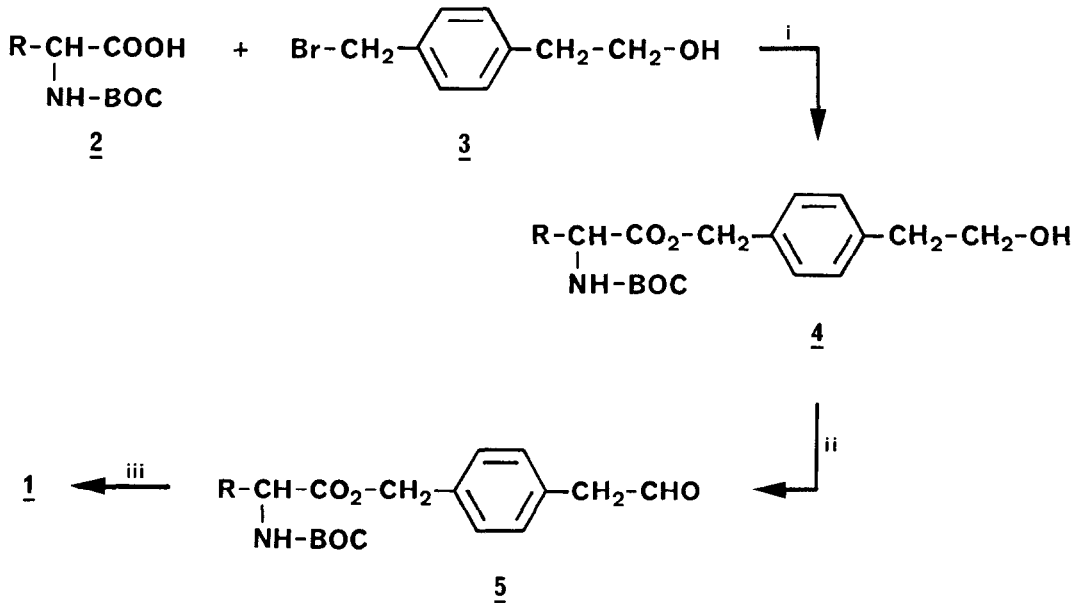
In recent years, the 4-(aminoacyloxymethyl)phenylacetamidomethyl-resins (PAM-resins) have become widely used in solid-phase peptide synthesis. These PAM-resins are prepared from 4-(BOC-aminoacyloxymethyl)phenylacetic acids 1 and aminomethyl-resin [1]. Therefore, ready access to the acids 1 is of prime importance.



1 (BOC = CO_2-t-Bu)

The compounds 1 are currently synthesized by esterification of a BOC-amino acid salt with a protected 4-(bromomethyl)phenylacetic acid, followed by deprotection of the phenylacetic acid carboxyl [2, 3]. This method has several drawbacks. One of them is the difficult removal of the acetic acid when the deprotection step is performed with zinc/acetic acid. Early attempts to perform the esterification with unprotected 4-(halomethyl)phenylacetic acids resulted in low yields of impure phenylacetic acids 1, due to competition between the BOC-amino acid salt and the 4-(halomethyl)phenylacetic acid salt in the esterification reaction [2].

In this letter, we wish to describe a new and convenient way to the title compounds 1, consisting of an esterification of the BOC-amino acids 2 with 4-(bromomethyl)phenethyl alcohol 3, and an oxidation of the resulting phenethyl alcohols 4 into the phenylacetic acids 1 (Scheme).



Scheme : *i) i-Pr$_2$NEt, ethyl acetate, reflux ; ii) CrO$_3$-py$_2$, CH$_2$Cl$_2$; iii) NaClO$_2$, Me$_2$C=CHMe, NaH$_2$PO$_4$, t-BuOH, water.*

Thus, by treatment for 24 hours, of 4-(bromomethyl)phenethyl alcohol 3 with 2 molar equivalents of BOC-phenylalanine and 3 molar equivalents of N,N-diisopropylethylamine in refluxing ethyl acetate, followed by removal of the reagents in excess by washing with the appropriate buffers, phenethyl alcohol 4 (R=CH$_2$Ph) was obtained as an almost TLC pure oil. Oxidation of the latter alcohol was then attempted with pyridinium dichromate[4] in N,N-dimethylformamide. This reaction led essentially to an aldehyde which was not 5 but which we suspect to derive from 5 by benzylic oxidation. Other chromium based oxidations [5] were tested and gave the same result. However, by submitting the alcohol 4 to a Collins oxidation (CrO$_3$-py$_2$,CH$_2$Cl$_2$) [6] for five minutes and by filtering the reaction medium under pressure on a silica gel short-column, a 9:1 mixture (determined by ^{1}H-NMR) of aldehyde 5 (R=CH$_2$Ph) and of unwanted aldehyde could be obtained. This mixture was then dissolved in t-butanol and oxidized with an aqueous solution of sodium chlorite [7,8] in the presence of 2-methyl-2-butene and sodium dihydrogenophosphate. The resulting crude phenylacetic acid 1 (R=CH$_2$Ph) could be purified by crystallization from an ether-hexane mixture.

Four other BOC-amino acids were afterwards submitted to the same reaction sequence and gave the corresponding 4-(BOC-aminoacyloxymethyl)phenylacetic acids 1 as shown in the Table.

Table : Preparation of 4-(BOC-aminoacyloxymethyl)-phenylacetic acids 1[§]

Phenylacetic acid 1 (R)	Starting BOC-amino acid 2	Yield based on 3[+]	mp °C (literature mp)[3]
1a (Ph-CH_2-)	Phe	69 %	94.5-97.5 (92-96)
1b* (Me_2CH-)	Val	65 %	121.5-123.5 (117-119)
1c* (C_6H_{11}-O-CO-$(CH_2)_2$-)	Glu(cHx)	60 %	132.5-134.5
1d (o-Br-C_6H_4-CH_2-O-CO_2-C_6H_4-CH_2-)	Tyr(Br-Z)	65 %	99-103
1e* (o-Cl-C_6H_4-CH_2-O-CO-NH-$(CH_2)_4$-)	Lys(Cl-Z)	58 %	55-60 (dec)

§ The acids 1 were TLC pure, gave satisfactory analyses (± 0.3 % for C, H and N ; exception 1d: C -0.5 %) or had melting points in agreement with the literature data, and had the expected 200 MHz ^{1}H-NMR spectra[10].

+ Because compound 3 is not commercially available, it is used as the limiting reagent. BOC-amino acids were used in a two-fold excess. The possibility of reducing this excess was not investigated.

* Dicyclohexylammonium salt.

This method allows routinely the preparation of phenylacetic acids 1 from 20 mmoles of BOC-amino acid 2 and 10 mmoles of 4-(bromomethyl)phenethyl alcohol 3 within two days. The overall yields, though not optimized, compare favorably with those of other published procedures.

4-(Bromomethyl)phenethyl alcohol 3 (mp 87-87.5 °C) was obtained quantitatively by reduction of the corresponding acid [2] with borane-methyl sulfide complex [9] in a 1:1 mixture of toluene and tetrahydrofuran.

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References and notes

1) A.R. Mitchell, B.W. Erickson, M.N. Ryabtsev, R.S. Hodges and R.B. Merrifield, **J. Am. Chem. Soc.** (1976) 98, 7357

2) A.R. Mitchell, S.B.H. Kent, M. Engelhard and R.B. Merrifield, **J. Org. Chem.** (1978) 43, 2845

3) J.P. Tam, S.B.H. Kent, Tai Wai Wong and R.B. Merrifield, **Synthesis** (1979) 955 ; F.S. Tjoeng and G.A. Heavner, **Synthesis** (1981) 897

4) E.J. Corey and G. Schmidt, **Tetrahedron Lett.** (1979) 399