Tetrahedron Letters,Vol.23,No.41,pp 4259-4262,1982 0040-4039/82/414259-04$03.00/0
Printed in Great Britain

α-METHYL AMINO ACIDS BY CATALYTIC PHASE-TRANSFER ALKYLATIONS[1]

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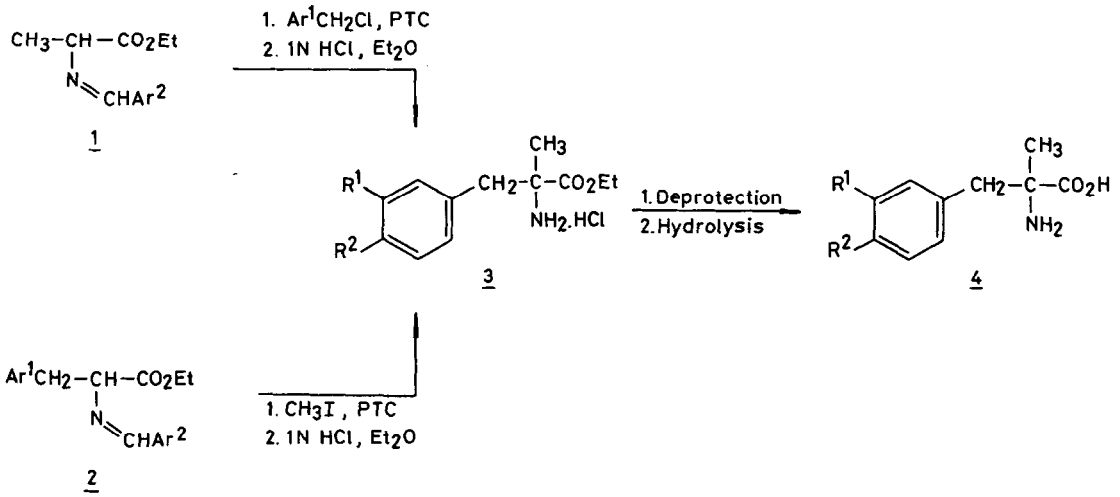
Abstract : The α-methyl amino acids, α-methyl p-chlorophenylalanine, α-methyl p-tyrosine, α-methyl m-tyrosine and α-methyl DOPA have been prepared in good yields from amino ester hydrochlorides. The key step in the method is the catalytic phase-transfer alkylation of Schiff base derivatives of monoalkyl amino acids.

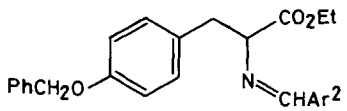
We have recently reported the general synthesis of higher amino acids from glycine derivatives by the novel use of phase-transfer alkylations.[2] This procedure has now be extended to the preparation of α-methyl amino acids[3] using readily prepared Schiff base derivatives (1 or 2) of aromatic aldehydes and higher amino esters as substrates for the phase-transfer alkylations. The alkylation step can be accomplished either by an ion-pair extraction (IPE) procedure[2a] with a full equivalent of $nBu_4N^+HSO_4^-$ as the phase-transfer reagent and a two-phase solvent system (CH_2Cl_2/10% aq. NaOH) or by catalytic phase-transfer (PTC or CTP) alkylation in a solid-liquid two-phase system (KOH/CH_2Cl_2 or CH_3CN).[2c] The alkylated Schiff base product is generally not isolated but is hydrolyzed under mild conditions to the amino ester hydrochloride (3) which can then be converted to the amino acid (4) by ester hydrolysis. Using the PTC procedure, α-methyl p-chlorophenylalanine 4d was prepared in 58% overall yield based on alanine ethyl ester hydrochloride. An overall yield of 63% was achieved by the IPE method.[2a]

The biologically interesting amino acids α-methyl p-tyrosine 4a, α-methyl m-tyrosine 4b and α-methyl DOPA 4c were chosen as synthetic targets for further application of this procedure. In order to make the syntheses as general and versatile as possible, we have investigated preparations of these amino acids from either alanine ethyl ester hydrochloride by a benzylation route (1→3), or from the appropriate higher amino ester hydrochloride by a methylation route (2→3).

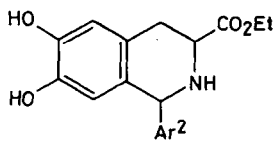


1 2 3 4

The alanine Schiff base 1 was synthesized by the procedure used previously for the corresponding glycine imine.[2c] The O-benzyl protected tyrosine derivative 2a (Ar^2=4-ClC_6H_4) was prepared in 73% yield by first condensing p-chlorobenzaldehyde with Tyr-OEt·HCl (Et_3N, CH_2Cl_2, $MgSO_4$) and then protecting the phenol ($PhCH_2Br$, K_2CO_3, acetone). Application of this procedure to DOPA-OEt·HCl resulted in isolation of 5 (Ar^2=4-ClC_6H_4) following the initial condensation step.



2a



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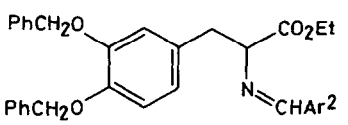

2b

The tetrahydroisoquinoline 5 is formed by a Pictet-Spengler cyclization[4] of the initially formed imine. This undesirable result can be prevented by using a sterically demanding aldehyde, such as mesitaldehyde, to form the Schiff base which is then dibenzylated to give 2b (Ar^2=2,4,6-$Me_3C_6H_2$) in 71% yield.

A typical alkylation is accomplished using a solid-liquid catalytic phase-transfer alkylation procedure:[2c] the Schiff base 1 or 2 and alkyl halide (Ar^1CH_2Cl or MeI) in methylene chloride or acetonitrile were added dropwise with stirring to a mixture of finely powdered potassium hydroxide and a catalytic amount (0.1 eq) of the phase-transfer reagent in the same solvent at 0°C. Following addition, the mixture was stirred at 10-15°C until starting material had been consumed (generally 1-5 hours, monitored by HPLC). An aqueous workup was followed by mild acid hydrolysis (1N HCl, Et_2O, 0°C, 1-3 hours) of the crude alkylated Schiff base to yield the α-methyl amino ester hydrochloride 3. Following this general procedure, the products 3a-3c

were obtained in 55-93% yield (see Table).

Following deprotection and hydrolysis, the overall yields of the three target α-methyl amino acids by the benzylation (5 steps) and methylation (6 steps) routes were : α-methyl p-tyrosine, 54%, 44%; α-methyl m-tyrosine, 53%, --[5]; α-methyl DOPA, 47%, 26%. The described procedure provides a convenient and versatile method for the preparation of α-methyl amino acid derivatives.

Table : α-Methyl Amino Acids and Derivatives Prepared by PTC Alkylation

Cmpd.[a]	R^1	R^2	Method[b]	Yield
3a·HCl	H	$PhCH_2O$	A	84%
3a·HCl	H	$PhCH_2O$	B	86%
3b·HCl	$PhCH_2O$	H	A	93%
3c·HCl	$PhCH_2O$	$PhCH_2O$	A	79%
3c·HCl	$PhCH_2O$	$PhCH_2O$	B	55%
4a	H	HO	C	70%
4b	HO	H	C	63%
4c	HO	HO	C	66%
4d	H	Cl	D	58%

[a] All new products gave satisfactory elemental analyses as well as NMR and IR spectra consistent with the assigned structures. In addition, the amino acids 4a-4c showed one spot on TLC identical with a commercial sample.

[b] Method A : Ar^1CH_2Cl, $PhCH_2\overset{+}{N}Et_3\ Cl^-$, CH_2Cl_2; alkylation in the case of 3b·HCl was accomplished with $nBu_4N^+Br^-$, CH_2Cl_2. Method B : MeI, $nBu_4N^+I^-$, CH_3CN. Method C : Catalytic hydrogenation (H_2, 10% Pd/C, EtOH) followed by ester hydrolysis (6N HCl). Method D : Alkylation by Method A followed by ester saponification (LiOH, MeOH).

Acknowledgements. We (M.J.O.) are grateful for support from the National Institutes of Health (GM 28193). We (L.G.) would also like to thank I.R.S.I.A. and UCB for financial aid. Our collaboration was made possible by the North Atlantic Treaty Organization (RG 1613).

References

1. Presented in part at the 183rd National American Chemical Society Meeting, Las Vegas, Nevada, April 1, 1982, ORGN 198.

2. a) M. J. O'Donnell, J. M. Boniece and S. E. Earp, Tetrahedron Lett., 2641 (1978); b) M. J. O'Donnell and T. M. Eckrich, ibid, 4625; c) L. Ghosez, J. P. Antoine, E. Deffense, M. Navarro, V. Libert, M. J. O'Donnell, W. A. Bruder, K. Willey, K. Wojciechowski, ibid, see preceeding paper.

3. For some recent preparations of α-alkyl amino acid by alkylation routes, see : a) U. Schöllkopf, U. Groth, K. O. Westphalen and C. Deng, Synthesis, 969 (1981); b) I. Hoppe and U. Schöllkopf, ibid, 646; c) U. Schöllkopf, H. H. Hausberg, M. Segal, U. Reiter, I. Hoppe, W. Saenger and K. Lindner, Liebigs Ann. Chem. 439 (1981); d) H. H. Lau and U. Schöllkopf, ibid, 1378; e) B. Kübel, P. Gruber, R. Hurnaus and W. Steglich, Chem. Ber., 112, 128 (1979); f) D. Hoppe and L. Beckmann, Liebigs Ann. Chem., 2066 (1979); g) P. Bey, J. P. Vevert, V. Van Dorsselaer and M. Kolb, J. Org. Chem., 44, 2732 (1979); h) M. Kolb and J. Barth, Tetrahedron Lett., 2999 (1979).

4. E. C. Weinbach and W. H. Hartung, J. Org. Chem., 15, 676 (1950).

5. The methylation is not practical in this case because of the cost of m-tyrosine.

(Received in France 30 July 1982)