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CONVERSION OF α-AMINOCARBOXYLIC ACIDS TO α-AMINOPHOSPHONIC ACIDS

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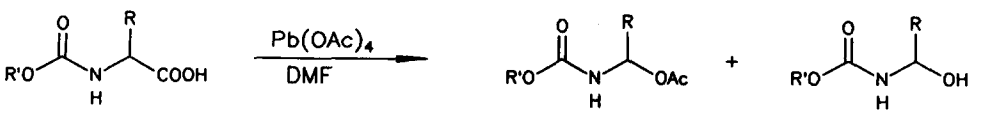
Summary: *Naturally occurring α-amino acids may be converted to their phosphonate analogues in good yield by oxidative decarboxylation with lead tetraacetate, followed by reaction with $(MeO)_3P$ and $TiCl_4$.*

Phosphonate analogs of α-amino acids have proved to be very effective components for the synthesis of transition state analog inhibitors for peptidases.[1] These α-amino phosphonates may be synthesized in a number of different ways, but the most common routes involve the addition of phosphites to imines which are either preformed or generated *in situ* from an aldehyde and an amine.[2] A variation of the latter strategy has involved the reaction of O-methyl-N-carbomethoxy-[3] or O-methyl-N-acyl-N,O-acetals[4] with trimethyl phosphite in the presence of a Lewis acid. The requisite N,O-acetals for these approachs are produced by the electrochemical oxidation of urethanes or by the electrochemical oxidative decarboxylation of N-acyl α-amino acids, respectively.

When we recently had need of phosphonate analogues of some dipeptides the route of Seebach and coworkers[4] appeared particularly attractive, as it allows the use of natural α-aminocarboxylic acids and dipeptides as substrates. However, we lacked access to the necessary electrochemical apparatus for carrying out the oxidative decarboxylation of our dipeptide substrates. This lack inspired us to develop an alternative method for accomplishing the overall conversion of α-aminocarboxylic acids to α-aminophosphonic acids.

The key to our route to α-aminophosphonic acids is the oxidative decarboxylation of α-aminocarboxylic acids with lead tetraacetate. Depending on the reaction conditions and substrate structure, treatment of α-amino acids and their derivatives with lead tetraacetate may yield N-acyl imines,[5] N-acyl enamines,[6] aldehydes and amines,[6,7] and O-acetyl-N,O-acetals.[8] In the case of the latter class of compounds — desired for the present study — oxidative decarboxylation with lead tetraacetate has only been successfully applied to N-acyl[8a] and N-aroylglycines;[8b] N-aroyl derivatives of other amino acids were reported to give none of the O-acetyl-N,O-acetals. We thought it likely that the failure to produce N,O-acetals from amino acids other than glycine was due to the harsh reaction conditions employed ($Pb(OAc)_4$ in AcOH at 60°C),[8b] or due to decomposition during the work-up of the reaction.[6]

We find that treatment of N-acylated α-amino acids with lead tetraacetate in dry dimethylformamide (DMF), followed by a mildly basic aqueous work-up, results in good yields of the desired O-acetyl-N,O-acetals.



1 2 3

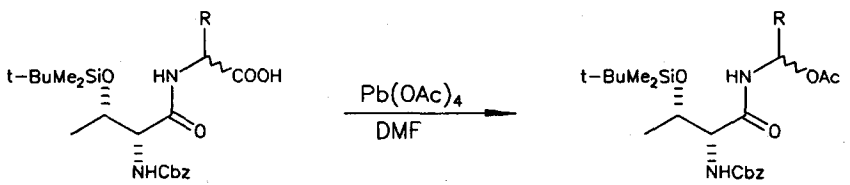
Table 1: Oxidative Decarboxylation of Protected Amino Acids

Substrate	R'	R	2 : 3	Yield
1 a	$-CH_2Ph$	$-CH_2CH(CH_3)_2$	1 : 1	91
b	$-CH_2Ph$	$-CH_2Ph$	1 : 1	90
c	$-CH_2Ph$	$-CH(OSi\Sigma)CH_3$@	2c only*	86
d	$-CH_3$	$-CH(OSi\Sigma)CH_3$@	2d only*	70

*Formed as a 1 : 1 mixture of diastereomers.
@$Si\Sigma$ = $SiMe_2t$-Bu

The reaction may be applied to simple α-amino acids (Table 1) as well as to dipeptides (Table 2). The isolated products are generally quite pure, with the sole contaminant being the non-acetylated N,O-acetal 3.[9] The corresponding aldehyde is not observed, providing the sample is analyzed soon after the reaction is worked-up.[10] The amount of the simple hydroxy N,O-acetal formed depends on the quality of the lead tetraacetate employed,[11] as well on the substrate structure.[12] None of the non-acetylated N,O-acetal is observed in the reactions of dipeptides 4.

Table 2: Oxidative Decarboxylation of Dipeptides



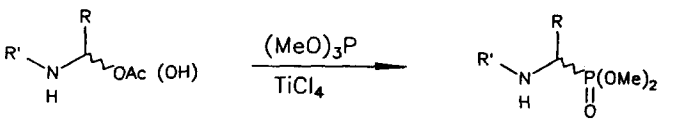
4 5

Substrate	R	Yield of 5*
4 a	$-CH_3$	76%
b	$-CH_2CH(CH_3)_2$	74
c	$-CH_2Ph$	75
d	$-CH_2OSi\Sigma$	83

*Formed as a mixture of diastereomers.

Treatment of the crude[13] products 2/3[14] or 5 with trimethylphosphite and titanium tetrachloride according to the procedure of Seebach *et al.*[4] results in the formation of the the dimethyl esters of the corresponding α-aminophosphonic acids in good yield (Table 3).

Table 3: Synthesis of Phosphorus Amino Acids



(2 + 3) or 5 6

Substrate	R'	R	Yield
(2a + 3a)	-C(O)OCH$_2$Ph	-CH$_2$CH(CH$_3$)$_2$	84
(2b + 3b)		-CH$_2$Ph	75
2e		-CH(OSiΣ)CH$_3$	81*
2f	-C(O)OCH$_3$	-CH(OSiΣ)CH$_3$	98*
4a	O-SiΣ-N-Cbz-threonyl	-CH$_3$	71*
4b		-CH$_2$CH(CH$_3$)$_2$	54*
4c		-CH$_2$Ph	90*
4d		-CH$_2$OSiΣ	69*

*Formed as a mixture of diastereomers

The route described above for the synthesis of phosphorus analogues of α-aminoacids has several advantages over other methods. It employs natural α-amino carboxylic acids as substrates, obviating the need for exotic starting materials. The reaction series may be applied to substrates of diverse structural types, including protected dipeptides. Finally, the simple chemical oxidative decarboxylation avoids the necessity of using electrochemical apparatus which may not be readily available.

Typical Procedure For Oxidative Decarboxylation: A solution of 1d (0.103g, 0.35 mmol) in dry dimethylformamide (0.4 mL) was added to a cold (ice/water), stirred suspension of Pb(OAc)$_4$ (0.181, 0.41 mmol) in dry dimethylformamide (0.4 mL). The cooling bath was removed after 30 minutes, and the mixture stirred an additional 3.5 hours, at which point the reaction was quenched by the addition of saturated aqueous NaHCO$_4$ (4 mL) and immediately extracted with ethyl acetate (4 x 3 mL). The combined organic extracts were washed with saturated aqueous NaHCO$_3$ and brine, then dried (Na$_2$SO$_4$), filtered, and evaporated at ambient temperature to yield 2d (0.0756 g, 70%).[15] This crude product was treated with (MeO)$_3$P and TiCl$_4$ under the reaction conditions which Seebach *et. al.* have applied to the corresponding O-methoxy-N,O-acetal.[4] The resulting phosphonate, obtained in 98% yield, had spectroscopic properties in accord with those reported by Seebach for the same compound.

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9. Compounds 2 and 3 may be readily distinguished from one another on the basis of ^{1}H NMR; the chemical shift of the N,O-acetal methine hydrogen differs substantially for the two compounds (e.g., δ6.23 and δ5.22 in 2a and 3a, respectively), and compounds 3 lacks the acetyl methyl resonance of 2 (δ1.97 in 2a).

10. Decomposition to the aldehyde occurs slowly at room temperature for both 2 and 3, although the rate is substantially more rapid for the latter.

11. Different lots of $Pb(OAc)_4$ from the same supplier gave quite different ratios of 2 and 3. The best results were obtained by using $Pb(OAc)_4$ which had been recrystallized from 2% acetic anhydride/acetic acid, filtered under nitrogen and dried overnight at 0.2 torr.

12. For example, N-acetyl derivatives of amino acids gave only the simple non-O-acetylated N,O-acetals, and in low yield (ca. 25%).

13. Attempts to purify these compounds by column chromatography (silica gel or alumina) were unsuccessful.

14. A comparison of the results of the first two entries of Table 3 with subsequent entries indicates that both the O-acetyl compound 2 and the simple hydroxy acetal 3 must react with comparable efficiency to yield the phosphonate product.

15. Formed as a ca. 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6 H, t-Bu(CH_3)$_2$SiO), 0.87 (s, 9 H, (CH_3)$_3$Me$_2$SiO-), 1.12 (3 H, d, 6.3 Hz, CH_3CH(OSiΣ)-), 2.01 & 2.03 (3 H, s, CH_3C(O)-), 3.66 & 3.69 (3 H, s, CH_3OC(O)-), 4.00 (1 H, m, CH_3CH(OSiΣ)-), 5.6 & 5.74 (1 H, bs & bd, 10 Hz, NH), 6.02 & 6.12(1 H, bd (10 Hz) & dd (10 Hz, 4.2 Hz, MeOOCNHCH(OAc)-).
   ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.00/-4.95 & -4.88/-4.50 (t-Bu(CH_3)$_2$SiO-), 17.94 ((CH_3)CMe$_2$SiO-), 18.64 & 19.90 (CH_3CH(OSiΣ)-), 20.97 & 21.20 (CH_3C(O)-), 25.65 ((CH_3)$_3$Me$_2$SiO-), 52.43 (CH_3OC(O)-), 68.48 & 68.79 (CH_3CH(OSiΣ)-), 78.89 & 80.37 (MeOOCNHCH(OAc)-), 155.46 & 155.88 (MeOC(O)NH-), 169.78 & 169.93 (CH_3C(O)O-).
   IR (film): 3447, 3333 (br), 2956, 2938, 2860, 1750, 1728, 1504, 1377, 1250, 1224, 1018, 838, 785 cm^{-1}.

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