Tetrahedron Letters,Vol.29,No.35,pp 4465-4466,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Press plc

FACILE SYNTHESIS OF α-PHOSPHORYLATED α-AMINO ACIDS

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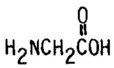
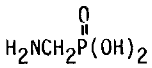
Summary : Various α-phosphorylated α-amino acid derivatives were synthesized conveniently by the reaction of methyl α-methoxyhippurate and methyl α-methoxy-N-benzyloxycarbonylglycinate with phosphites under the Lewis acid. Hydrolysis of (12) with TMSI gave 2-phosphonoglycine in quantitative yield.

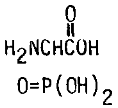
Compared with the broad chemistry of glycine(1)[1] and α-carbon substituted α-amino acids, a few derivatives of α-heteroatom substituted α-amino acids[2], for example, α-methoxy, α-amino α-mercapto and α-halo α-amino acids as the unisolated intermediates have been prepared. Aminomethylphosphoric acid (2, AMPA)[3] and its alkyl derivatives[4,5], which are known to increase the yield of sugar cane and to have antibacterial activity against several microoganisms have received much attention in recent years. 2-Phosphonoglycine (3)[6] which has the structural feature of the combined molecular moiety of (1) and (2) is of a considerable interest to us. As a part of synthetic approaches to α-heteroatom substituted α-amino acids, we describe efficient synthesis of some α-phosphorylated α-amino acids.[7]


$\mathrm{H_2NCH_2\overset{\overset{O}{\|}}{C}OH}$

1

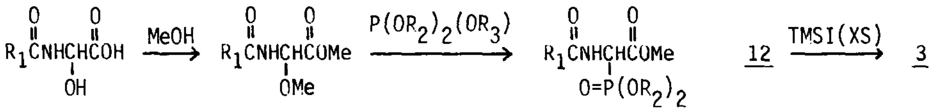

$\mathrm{H_2NCH_2\overset{\overset{O}{\|}}{P}(OH)_2}$

2


$\mathrm{H_2N\underset{O=P(OH)_2}{CH}\overset{\overset{O}{\|}}{C}OH}$

3

Thus, methyl α-methoxyhippurate (6)[8] and methyl α-methoxy-N-benzyloxycarbonylglycinate (7), readily prepared from α-hydroxyhippuric acid (4) and α-hydroxy-N-benzyloxycarbonyl glycine (5) with methanolic sulfuric acid were phosphorylated with phosphites under the Lewis acid to give various α-phosphono-α-amino acid derivatives (8-12). (Scheme I)



4; R_1=Ph
5; R_1=$PhCH_2O$

6; R_1=Ph
7; R_2=$PhCH_2O$

8; R_1=Ph, R_2=Me
9; K_1=Ph, R_2=Et
10; R_1=Ph, R_2i-Pr

11; R_1=R_2=Ph
12; R_1=$PhCH_2O$, R_2=Et

Scheme I

The procedure for the phosphorylation is as follows; To a stirred solution of (6, 1mmol) or (7, 1mmol) and phosphites (1.1mmol) (A) in CH_2Cl_2 was added dropwise $BF_3 \cdot OEt_2$ (1.1mmol) at -10°C followed by warming up to rt (B) in THF was added dropwise $BF_3 \cdot OEt_2$ (1.1mmol) at -10°C and stirred for 5 min. TBAF (1mmol) was added dropwise, then the solution was warmed up to rt. Usual aqueous workup gave the crude products. Pure samples were obtained by SiO_2 column

Table I. Reaction of (6) and (7) with phosphites

Run	Substrate	Phosphite	Product[11] (Yield %)	m.p(^{o}C)	^{31}P nmr(δ in ppm)
1	6	$P(OMe)_3$	8 (78)[a]	108-109	19.380
2	6	$P(OMe)_2(OSiMe_3)$	8 (95)[b]		
3	6	$P(OEt)_3$	9 (72)[a]	110-112	16.799
4	6	$P(OEt)_2(OSiMe_3)$	9 (96)[b]		
5	6	$P(OPr\text{-}i)_3$	10 (70)[a]	115-116	14.712
6	6	$P(Opr\text{-}i)_2(OSiMe_3)$	10 (42)[a]		
7	6	$P(OPh)_3$	11 (36)[a]	oil	
8	7	$P(OEt)_3$	12 (88)[a]	79-81	16.554
9	7	$P(OEt)_2(OSiMe_3)$	12 (41)[a]		
10	7	$P(OEt)_2(OSiMe_2Bu\text{-}t)$	12 (86)[b]		

a; Procedure (A) b; Procedure (B) employed. See text.

chromatography (EtOAc/n-Hex) and recrystallization (EtOH). The results were summarized in Table I. $BF_3 \cdot OEt_2$ was the Lewis acid of choice, since other acids (H_2SO_4, $AlCl_3$, $TiCl_4$, $SnCl_4$) gave the product but in lower yield. Dialkyl trimethylsilyl phosphites[9] were employed to obtain the better results using procedure (B) compared with the less reactive trialkylphosphites. Hydrolysis of (12) with TMSI (5 eqiv.)[10] at rt in $CHCl_3$ gave the 2-phosphonoglycine (3, m.p (^{o}C); 128-130, lit.; 130-132)[6] in quantitative yield.

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11. Characterization of 8-12; 8; ^{1}H nmr ($CDCl_3$, δ in ppm); 7.26(m,5H), 7.04(d,1H), 5.46(dd, J(Hz)=22,9,1H), 3.85(d,3H), 3.82(s,3H), MS(EI, 70ev) 3.01(M), 105(100%), 9; ^{1}H nmr; 7.53(m,5H), 5.46(dd,J=23,8,1H), 4.23(m,4H), 3.79(s,3H), 1.36(t,6H), MS; 329(M), 105(100%), 10; ^{1}H nmr; 7.52(m,6H), 5.20 (dd,J=22,8,1H), 4.61(m,2H), 3.61(s,3H), 1.14(d,12H), MS; 357(M), 105(100%), 11; ^{1}H nmr; 7.30(m, 16H), 5.21(dd,J=22,9,1H), 3.81(s,3H), 12; ^{1}H nmr; 7.29(m,5H), 5.73(dd,J=22,9,1H), 5.09(s,2H), 4.88(dd,1H), 4.10(m,4H), 3.76(s,3H), 1.25(t,6H), MS; 359(M), 100(100%).

(Received in Japan 27 June 1988)