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AN EFFICIENT SYNTHESIS OF γ-AMINO-β-KETOALKYLPHOSPHONATES FROM α-AMINO ACIDS

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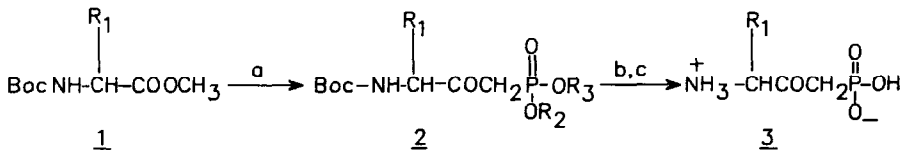
SUMMARY: The reaction of lithium salts of dialkyl methylphosphonates with suitably protected amino acid methyl esters at low temperature, followed by removal of protecting groups in the presence of trimethylsilyl bromide provides an efficient method for the synthesis of the titled compounds.

Recently, a few γ-amino-β-ketoalkylphosphonates[1] have been described as stable methylene analogs of α-amino acylphosphates. The acylphosphates derived from α-amino acids and γ-amino acids have been postulated as active intermediates in various enzyme processes, and stable analogs of such intermediates are of general interest as potential enzyme inhibitors[2,3].

β-Ketophosphonates are useful synthetic intermediates, and several efficient methods[4,5] for the synthesis of a variety of β-ketoalkylphosphonates are available. However, no effective procedure for the synthesis of γ-amino- β-ketoalkylphosphonates has been reported. We have found that the currently available procedure[1] involving Arbuzov reaction of trialkyl phosphites with α-iodomethyl ketones obtained from suitably protected α-amino acids to be cumbersome, and to give the desired product in low yield with partial racemization. In this communication, we describe an efficient, general and racemization-free[8] procedure for the synthesis of γ-amino- β-keto alkylphosphonates 3 (**Scheme**).

The reaction of methyl esters of suitably protected α-amino acids 1 with an excess (6 equivalents) of the lithium salt of dialkylmethylphosphonate[4] at low temperature in THF gives the protected ketophosphonates 2 in excellent yield (**Table**).



1 2 3

a. $LiCH_2PO(OR_2)(OR_3)$ b. $(CH_3)_3SiBr$ c. CH_3OH

Scheme

We have found that the standard acidolytic (HBr or HCl) removal of protecting groups gives the desired products 3 with substantial racemization. This problem was obviated, however, by converting 2 into the corresponding trimethylsilyl derivatives with trimethylsilyl bromide[6], which were then hydrolyzed with methanol to give 3.

In a typical procedure, a solution of N-t-butoxycarbonyl α-amino acid methyl ester 1 (0.025 mol) in dry THF (100 ml) is added dropwise to a cooled (-78°C) solution of the lithium salt of dialkyl methylphosphonate (0.15 mol) in THF (150 ml) under nitrogen. The

reaction mixture is stirred at -78°C (1-2h) and then at -30°C (1h). The reaction is quenched with glacial acetic acid (0.7 ml), and the mixture is poured into saturated aqueous $NaHCO_3$. After the usual extractive work-up and purification of the crude product by flash chromatography[9], the pure product 2 is obtained as a colorless oil in high yield. For deprotection, a solution of 2 (3 mmol) in CH_2Cl_2 (6 ml) is treated with trimethylsilyl bromide (24 mmol) for 18h at 25°C. Removal of excess reagent and hydrolysis of the silyl derivative with methanol (10 ml) gives the product 3, after precipitation with dry ether, in good yield (70-80%)[7,10].

Table

Entry	R_1	R_2	R_3	Yield of 2 (%)[7]
1	CH_3	CH_3	CH_3	87
2	CH_3(S)	CH_3	CH_3	78
3	CH_3(R)	CH_3	$C_6H_5CH_2$	93
4	CH_3CH_2(R)	CH_3	CH_3	86
5	C_6H_{11}(S)	CH_3	CH_3	96
6	H	CH_3	CH_3	68
7	FCH_2(R)	CH_3	CH_3	57
8	CH_3SCH_2(S)	CH_3	CH_3	82
9	$tBuSiMe_2OCH_2$(R)	CH_3	CH_3	79

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7) Isolated yield. All compounds gave satisfactory spectral and analytical data. ^{1}H NMR (δ , Selected peaks): Compound 2 ($R_1 = R_2 = R_3 = CH_3$)($CDCl_3$) : 1.46 (s, 9H), 3.15 (dd, J_1= 14 Hz and J_2= 20 Hz, 1H), 3.24 (dd, J_1=14 Hz and J_2= 20 Hz, 1H), 3.80 (d J=12 Hz, 6H), 4.24-4.38 (m, 1H). Compound 3 ($R_1 = CH_3$)(D_2O): 3.0 (dd J_1= 12 Hz and J_2= 20 Hz, 1H), 3.30 (dd J_1=12 Hz and J_2=20 Hz).

8) The extent of racemization was determined by reverse-phase HPLC analysis of the product formed from the reaction of 3 with R-(+)-α-Methylbenzyl isocyanate. In most of the cases examined, the extent of racemization was found to be less than 5%.

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10) Biological data of selected compounds 3 will be reported elsewhere.

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