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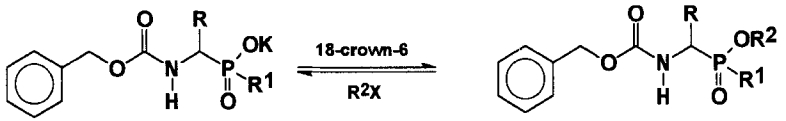
ALKYLATION OF POTASSIUM 1-(N-BENZYLOXYCARBONYL-AMINO)ALKYLPHOSPHONATES AND PHOSPHINATES IN THE PRESENCE OF 18-CROWN-6

Mariusz Skwarczyński and Paweł Kafarski*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wrocław, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, POLAND

During past several years we have been engaged in the synthesis of phosphono peptides, peptide analogues with phosphonic acid replacing C-terminal or N-terminal carboxylate moiety. These compounds are of interest not only because of their promise of direct practical applications[1,2] but also as a source of information about mechanisms of enzymatic reactions.[1,3-5] Esters of N-blocked 1-aminoalkylphosphonic and phosphinic acids are popularly used as starting substrates in multistep syntheses of phosphono peptides.[6-9] Although several methods for their preparation have been described [6,10-13] the search for the new and useful methods of their synthesis is still in progress. In this paper we report that the use of complexes of potassium 1-(N-benzyloxycarbonylamino)alkylphosphonates and phosphinates with 18-crown-6 as nucleophiles in the reaction with alkyl halides afforded the desired esters in good yields.



1 2

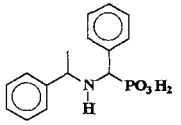
Good solubility of complexes of salts (1) with 18-crown-6 in benzene and toluene was the main factor of their choice as substrates in this reaction. As seen from Tables 1 and 2

Table 1. Alkyl 1-(N-benzyloxycarbonylamino)alkylphosphinates

Product			Halide	Substrate-crown ether-alkyl halide molar ratio	Reaction time[a] (h)	Yield (%)
R	R^2	R^1	X			
$(CH_3)_2CHCH_2$	CH_3	CH_3	I	1:1:1	6	59
				1:1:5	-[b]	48
					1.5	73[c]
					4.5	73
				1:1:10	1.5	67
				1:catalytic:5	11	79
					10.5	50[c]
$(CH_3)_2CHCH_2$	CH_3CH_2	CH_3	I	1:1:1	2	64
$(CH_3)_2CHCH_2$	$CH_3CH_2CH_2$	CH_3	I	1:1:1	3	88
$(CH_3)_2CHCH_2$	$CH_3(CH_2)_3$-	CH_3	I	1:1:1	2	17
				1:1:5	7	83
$(CH_3)_2CHCH_2$	$CH_3(CH_2)_8$-	CH_3	I	1:1:1	1	10
$(CH_3)_2CHCH_2$	$CH_2CH=CH_2$	CH_3	Br	1:catalytic:5	7.5	31
				1:1:1	2	95
$(CH_3)_2CHCH_2$	CH_2COOEt	CH_3	Cl	1:catalytic:5	7.5	8
				1:1:1	-[b]	39
				1:1:5	5.5	83
$(CH_3)_2CHCH_2$	CH_3	Ph	I	1:1:5	5.5	0[d]
$(CH_3)_2CHCH_2$	$CH_2CH=CH_2$	Ph	Br	1:1:5	5.5	0[d]
$(CH_3)_2CHCH_2$	$CH_2C_6H_5$	CH_3	Cl	1:1:1	2	0

[a] reaction was carried out in boiling benzene
[b] reaction was carried out at room temperature
[c] reaction was carried out in boiling toluene
[d] decomposition of the substrate was observed

Table 2. Products of esterification of 1-(N-benzyloxycarbonylamino)alkylphosphonic acids (**1**, R^1=OH)

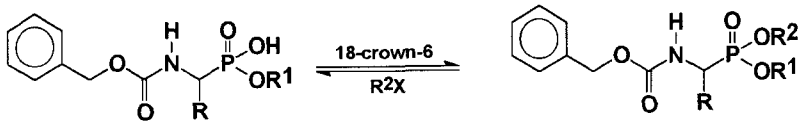
Substrate R	Halide R^2X	Substrate-crown ether-alkyl halide molar ratio	Reaction time[a] (h)	Yield of monoester (%)	Yield of diester (%)
$(CH_3)_2CHCH_2$	CH_3I	1:1:5	-[b]	38	3
		1:2:10	2	9	64
$(CH_3)_2CHCH_2$	CH_3CH_2I	1:2:2	2	18	16
$(CH_3)_2CHCH_2$	CH_2=$CHCH_2Br$	1:2:2	2	22	16
		1:2:10	7	6	68
		1:2:10	8	4	94
		1:1:5	8	11	43
CH_3CH_2	CH_2=$CHCH_2Br$	1:2:10	6	3	73
	CH_3	1:1:10	8	0	74

[a] reaction was carried out in boiling benzene
[b] reaction was carried out at room temperature

only halides easily undergoing nucleophilic substitutions of S_N2 type and allyl bromide gave satisfactory results. Thus, primary chloro- and bromoalkanes appear to be less reactive than the corresponding iodoalkanes. Moreover, the secondary and tertiary alkanes appeared to be totally unreactive.

The reaction of 1-(N-benzyloxycarbonylamino)alkylphosphonic acids (Table 2) appeared to be more complicated and, despite of the conditions used, afforded the mixtures of monoesters (**2**, R^1= OH) and diesters (**2**, R^1= OR^2). Fortunately these products were easily separable by simple extraction. It is also worth to notify that the use of N-alkylated aminoalkylphosphonate (last entry to Table 2) gave only the corresponding diester with quite high yield.

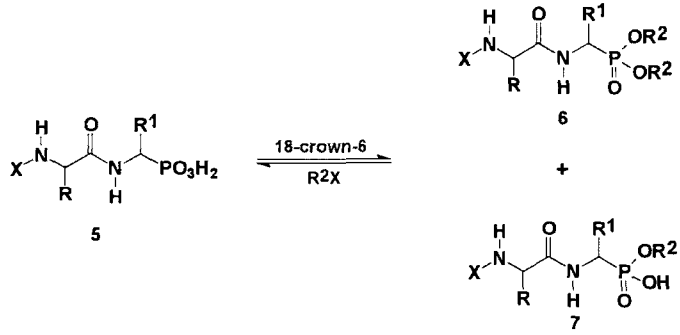
The presented in this paper method also gives an opportunity for the preparation of mixed diesters (**4**) of N-blocked aminoalkylphosphonic acids:



3 4

As seen from Table 3 also in this case the reaction follows the same pattern as this observed when N-blocked aminoalkylphosphinic acids were used as substrates. Thus, the best results were obtained if methyl iodide was used as a substrate. Generally, the mixed esters were obtained with moderate or good yields.

Finally, we have used this method for the esterification of N-blocked phosphono peptides (5) and achieved the desired products with satisfactory yields (Table 4).



5 6 7

Also in this case the mixtures of monoesters (6) and diesters (7) were obtained (Table 4). When N-phtaloyl derivatives were used as substrates unexpected decomposition of the phtaloyl moiety was observed.

Experimental

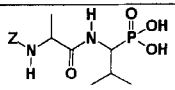
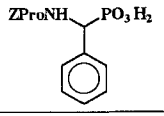
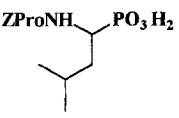
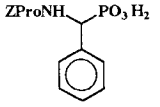
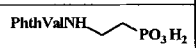
General comments

All the reagents were of analytical purity and were used without additional purification. The structures of all the synthesized compounds were supported by their ^{1}H-n.m.r., ^{31}P-n.m.r. (Bruker 300 mHz) and i.r. spectra (Perkin Elmer 377 spectrometer).

Table 3. Mixed esters of N-blocked 1-aminoalkylphosphonic acids.

Substrate		Halide	Substrate-crown ether-alkyl halide	Reaction time	Yield
R	R^1	R^2X	molar ratio	(h)	(%)
$(CH_3)_2CHCH_2$ *R-isomer*[a] *S-isomer*[b]	CH_3CH_2	CH_3I	1:1:5	8	83
$(CH_3)_2CHCH_2$	CH_3	$CH_2=CHCH_2Br$	1:1:1	4	44
$(CH_3)_2CHCH_2$	CH_3CH_2	$CH_2=CHCH_2Br$	1:1:1	2	53
$(CH_3)_2CHCH_2$	CH_3	$ClCH_2COOEt$	1:1:1	4	8
$(CH_3)_2CHCH_2$	CH_3	$CH_3CH_2CH_2CH_2I$	1:1:5	8	52
$(CH_3)_2CHCH_2$	Ph	CH_3I	1:1:5	8	32

Table 4. Esters of phosphono peptides

Peptide	Halide R^2X	Substrate-crown ether-alkyl halide molar ratio	Reaction time (h)	Yield of mono-ester (%)	Yield of diester (%)
	$CH_2=CHCH_2Br$	1:2:5	6	2	25
	CH_3I	1:2:10	5	21	49
	CH_3I	11:1:1	10	0	25
	$CH_2=CHCH_2Br$	1:2:10	6	9	61
	$CH_2=CHCH_2Br$	1:2:10	5.5	0	2

General procedure for the esterification of N-blocked aminoalkylphosphinic acids and alkyl aminoalkylphosphonates

N-blocked aminoalkylphosphinic acid or alkyl aminoalkylphosphonate (3 mmole) was dissolved in 0.5 M methanolic solution of potassium hydroxide (6.64 ml, 0.003 mmol). Then the methanol was removed by evaporation and the oily residue was suspended in toluene (100 ml). This solvent was also removed under reduced pressure to remove any traces of methanol. The residue was then suspended in benzene (100 ml) and 18-crown-6 (0.88 g; 0.03 mmol) was added. To the resulting solution excess of alkyl halide (see Tables 1 and 3) was added and the mixture refluxed 2-8 hr (depending on the kind of the halide used). The benzene solution was then extracted with water (100 ml, upon acidification of this fraction unreacted substrate was recovered), and washed successively with 5% hydrochloric acid (100 ml), water (100 ml), saturated sodium bicarbonate (100 ml) and water. Benzene solution was then dried over anhydrous magnesium sulphate. Removal of the drying agent and evaporation of benzene gave analytically pure oily products.

General procedure for the esterification of N-blocked aminoalkylphosphonic acids and phosphono peptides

Reaction was carried out analogously as described above using two-molar equivalents of potassium hydroxide and over two-molar excess of halide. The monoester was recovered from first aqueous extract of the reaction mixture.

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