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A novel synthesis of amino acid derivatives of phospholene oxides

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Abstract—A convenient synthetic approach is established to prepare a new class of 1-L-α-amino acid derivatives of phospholene oxides by amination of (±)-1-chloro-2-phospholene-1-oxides with several optically pure L-α-amino acid esters. All compounds obtained as a diastereomeric mixture in good to high yields. The two diastereomers were successfully separated by column chromatography and structurally identified by their spectral analyses.

Isolation of 2-amino ethyl phosphonic acid from several organisms and human beings has clearly shown that amino phosphonic acids are biologically an important class of compounds.[1] Jacobsen and Barlett et al. evaluated phosphinic and phosphonic acid peptide derivatives as inhibitors of aspartic proteases, pepsin, pencillopepsin,[2] carboxy peptidase A[3] as exemplified in Figure 1.

In recent years, we have been involved in the preparation and evaluation of bioactivity of phospha sugar derivatives. The term 'phospha sugar' belongs to the class of hetero sugar, and in the area of phospha sugars, it has meant the replacement of hemiacetal oxygen of normal sugar by phosphorus moiety. Hetero sugars are inherently interesting substances because of the ubiquity of carbohydrates in living systems. Phospha sugars, have never been found in naturally occurring products and information about their expected bioactivity[4] has hitherto been sparse, since the amounts and kinds of phospha sugars obtained were very small. Previous methods, for the preparation of phospha sugars, sugars as starting materials required many and tedious synthetic steps,[5,6] and resulted in low overall yields. Hence, development of general methods for easy preparation of such compounds would undoubtedly spur on more detailed studies of their chemistry, synthetic and biological utility. Therefore, during our continuing efforts on development and synthesis of new phospholene and phospholane oxide derivatives, we have reported a variety of tetrofuranose analogs of phospholane oxides in high yields via simple reaction methods.[7] More recently, we also reported the successful preparation of a new class of phospha sugar–sugar disaccharides using (±)-2-bromo-3-methoxy-1-phenylphospholane oxide as glycosyl donor.[8]

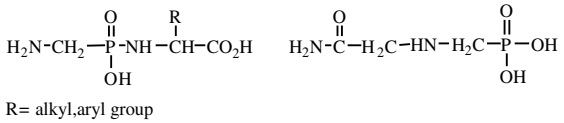

Figure 1. General structures of amino acid derivatives linked with phosphates and exhibiting potential biological activity.

However, amino acid derivatives of phospholene oxides are a new class of compounds, and expected to be possessing of potential biological activities. To our knowledge such a synthesis is unprecedented and has not yet been reported. Therefore, it was of our interest to synthesize these compounds and in further evaluate their biological activity. Hence, herein we describe the first successful preparation and structural analysis of amino acid derivatives of phospholene oxides in high yields.

Addition of phosphorus trihalides or phosphonus dihalides to 1,3-alkadienes is known to produce cyclic

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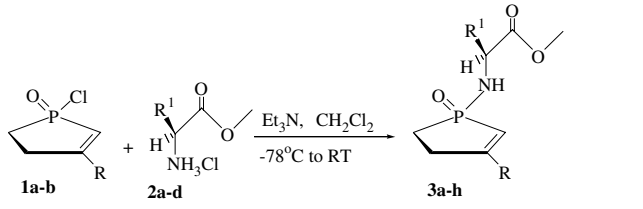
unsaturated phosphorus compounds, that is, phospholene oxides.[9,10] These phospholene oxides are key intermediates to synthesize several new class of phospholene and phospholane oxide derivatives.

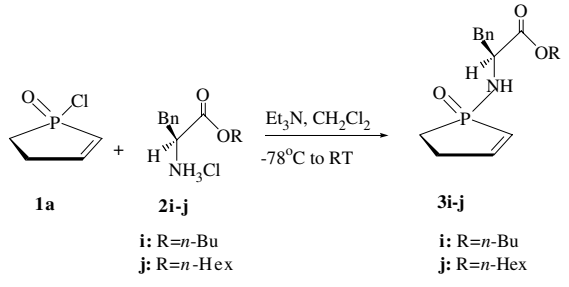
A pure compound of 1-chloro-2-phospholene-1-oxide **1a**–**b** was prepared from the corresponding 1-methoxy-2-phospholene-1-oxide precursors by treatment with excess of thionylchloride at room temperature for 24 h, followed by subsequent fractional distillation under reduced pressure afforded pure compounds of **1a**–**b**. To a prepared solution of amino acid esters **2a**–**d** and triethylamine in dichloromethane was added slowly compounds **1a**–**b** in dichloromethane at −78 °C, and stirred for 24 h at room temperature resulted in the formation of new amino acid derived 2-phospholene oxides **3a**–**h** in 61–70% yields,[11] shown in Scheme 1.

Having established the synthetic route with L-alanine, we decided to use L-leucine, L-valine, and L-phenylalanine as precursors of chiral amino acids and methyl, butyl, and hexyl amino acid ester hydrochlorides, which were prepared using corresponding alcohols in the presence of thionyl chloride, whereas in case of hexyl ester, *para*-toluene sulfonic acid monohydrate was used.

Encouraged by the results in Scheme 1, we next tried to use two different esters of L-phenylalanine, that is, butyl and hexyl esters. Therefore, by applying the similar reaction conditions in Scheme 1, compounds **3i**,**j** were obtained in 68% and 65% isolated yields as oily liquids (Scheme 2). It is worth stressing that hexyl ester was less reactive than butyl and methyl esters and it is reasoned due to steric hindrance caused by hexyl group. The maximum yield was up to 70% because of the formation



Scheme 1.



Scheme 2.

Table 1

Entry	Substrate	Product	Isolated yield (%)
1	**1a**, **2a**	**3a**:**3a′**	34:36
2	**1a**, **2b**	**3b**:**3b′**	32.5:33.5
3	**1a**, **2c**	**3c**:**3c′**	32:32
4	**1a**, **2d**	**3d**:**3d′**	33:34
5	**1b**, **2a**	**3e**:**3e′**	36:32
6	**1b**, **2b**	**3f**:**3f′**	31:32
7	**1b**, **2c**	**3g**:**3g′**	30:31
8	**1b**, **2d**	**3h**:**3h′**	33:32
9	**1a**, **2i**	**3i**:**3i′**	34:34
10	**1a**, **2j**	**3j**:**3j′**	31:34

of side products (P–Cl was converting to P–OH) being the chloro phospholenes are very unstable and moisture sensitive. However, the obtained products **3a**–**h** are found to be very stable and can be stored at room temperature. Initially, we conducted the reactions at 0 °C but the desired products were not obtained. Therefore, the optimum reaction conditions are achieved by maintaining purely dry reaction conditions and lower reaction temperature that is, at −78 °C.

All compounds, shown in Table 1 are obtained as diastereomeric mixtures. Preliminary TLC and HPLC analyses showed that each compound consists of two diastereomers. Hence, the diastereomeric ratio of **3a**–**j** was determined by ^{31}P NMR spectral data. In all the cases, the diastereomeric ratio was found to be ~1:1 (Table 1). Further purification of all compounds by column chromatography on silica gel using chloroform and ethanol (97:3) as eluent, gave diastereomerically pure form of desired compounds as light yellow color oily liquids.

The structural assignment of all compounds was carried out by thorough investigation of ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral analyses.[12] Interestingly, in proton NMR spectra of all compounds, the proton on nitrogen attached to phosphorus atom resonated as a complex multiplet due to the existence of P–N–H and C–1–H coupling, while H-1 on phospholene ring was resonated as a complex triplets due to coupling with P–N–H and C–2–H, whereas the same proton resonated as a pair of triplets in the corresponding starting compound, that is, 1-chloro-2-phospholene-1-oxide **1a**. The disappearance of NH_2 peak at ~8.3 ppm strongly supported the formation of final compounds **3a**–**j**. It is also confirmed from ^{31}P NMR spectra that all final compounds were shifted to higher field by 10–12 ppm from the starting 1-chloro-2-phospholene oxides **1a**–**b**.

The configuration at P atom of two diastereomers was ascertained from their ^{1}H NMR spectroscopy (recorded on 300 MHz). The *C–H proton (on amino ester) of one isomer was clearly shifted to down field (by 0.07 ppm) from the other isomer, because the *C–H is deshielded due to the shielding effect exerted by P=O[13] and thus it represents C–H and P=O are coplanar and possessing anti relationship between P=O and C–NH (i.e., *C–H is *syn* to P=O), whereas the other isomer has the opposite relationship.[12]

In conclusion, we have successfully prepared different types of amino acid derivatives of 2-phospholene oxides in good yields, for the first time. All reactions underwent smoothly, the work up of all the reactions is very simple. The bioassay results and further synthesis of amino acid derivatives of phospholane oxides will be reported in due course.

Acknowledgements

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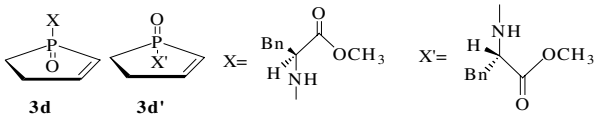
11. Preparation of amino acid derivatives of 1-chloro-2-phospholenes from amino acid ester hydrochlorides (**3a–i**): Triethylamine (0.53 mL, 3.8 mmol) was added dropwise to a suspension of the amino acid ester hydrochloride (3.0 mmol) in dry methylene chloride (40 mL). The reaction mixture was cooled to −78 °C and 1-chloro-2-phospholene 1-oxide (3.4 mmol) was added slowly in dropwise manner. Stirring was continued for 24 h at room temperature. The precipitate of triethylamine hydrochloride was filtered off, and the methylene dichloride was removed from rotary evaporator. The crude reaction mixture was purified by column chromatography on silica gel using 97:3 chloroform–ethanol eluent.
Preparation of amino acid derivatives of 1-chloro-2-phospholenes from amino acid hexyl esters (**3j**): The amino acid hexyl ester (3.0 mmol) was dissolved in methylene chloride (40 mL). Subsequently, triethylamine (0.55 mL, 3.8 mmol) was added and the mixture was cooled to −78 °C. The 1-chloro-2-phospholene (3.4 mmol) was added slowly dropwise. Stirring was continued for 24 h at room temperature. The work up was identical as in the above procedure.
12. All compounds were structurally characterized by spectral ^{1}H NMR (JEOL JNM-300 at 300.40 MHz), ^{13}C NMR (JEOL JNM-300 at 75.0 MHz), ^{31}P NMR (JEOL JNM EX-90 at 36.18 MHz), mass (Kompact MALDI-TOF MS using α-cyano-4-hydroxycinnamic acid as a matrix, reflectron flight path and 100 profiles per sample)analyses.
Compound **3d**: ^{1}H NMR ($CDCl_3$): δ 2.37–2.62 (m, 4H, H-3,3′, 4,4′), 2.94–3.11 (m, 2H, CH_2–Ph), 3.72 (s, 3H, OCH_3), 4.03 (m, 1H, CH–CO_2), 5.89–5.98 (m, 1H, NH), 6.14–6.25 (ddt, 1H, $^{3}J_{PH}$ = 23.6 Hz, J_{HH} = 8.6, 2.1 Hz, H-2), 6.96–7.09 (m, 1H, H-1), 7.18 (m, 2H, Ph), 7.28 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.86, 27.62, 40.69, 52.23, 54.62, 124.35, 126.26, 128.51, 129.47, 136.36, 152.28, 176.41; ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 66.31. MS (*m*/*z*): 279.14 (M^+) for $C_{14}H_{18}NO_3P$.
Compound **3d′**: ^{1}H NMR ($CDCl_3$): δ 2.33–2.58 (m, 4H, H-3,3′, 4,4′), 2.91–3.05 (m, 2H, CH_2–Ph), 3.74 (s, 3H, OCH_3), 3.96 (m, 1H, CH–CO_2), 5.86–5.88 (m, 1H, NH), 6.11–6.25 (ddt, 1H, $^{3}J_{PH}$ = 22.1 Hz, J_{HH} = 8.1, 1.9 Hz, H-2), 6.85–6.99 (m, 1H, H-1), 7.08 (m, 2H, Ph), 7.18 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.66, 25.22, 41.65, 52.33, 53.72, 124.14, 126.11, 128.23, 129.12, 136.56, 152.61, 176.34; ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 64.65. MS (*m*/*z*): 279.17 (M^+) for $C_{14}H_{18}NO_3P$.



3d 3d'

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