Efficient α-Alkylation of α-Amino Acids by Means of a Novel Pyridoxal Model Compound

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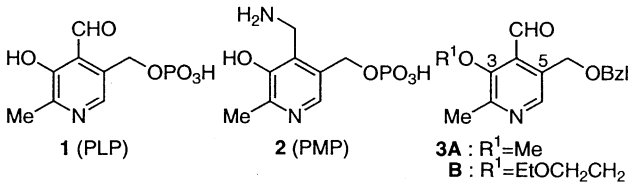
α-Alkyl-α-amino esters were prepared by the alkylation of α-imino esters obtained from α-amino acids and a novel PLP model compound possessing a Li^+ ionophore character.

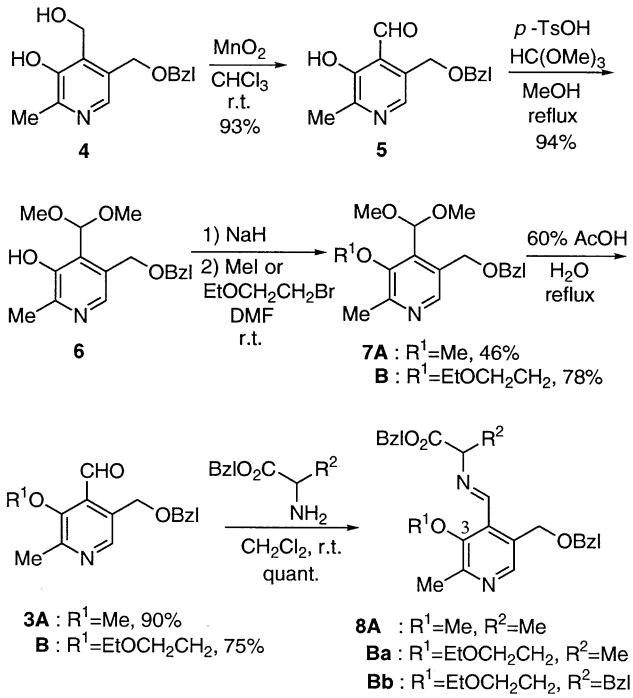
Pyridoxal 5'-phosphate (**1**; PLP) and pyridoxamine 5'-phosphate (**2**; PMP) are very important coenzymes for biosynthesis and metabolism of α-amino acids, such as transamination, α- and β-decarboxylation, aldol reaction, β-substitution reaction, and so on.[1] Much attention of organic chemists has been focussed on development of new PMP (and/or PLP) model compounds, which could be useful for mimicking those enzymatic reactions. Chemical modifications of the coenzymes have been concentrated on the C-5 side chain and little is known about modification of the 3-OH group in the coenzyme itself.[2-4] Now we have designed a novel PLP model compound **3B** possessing a 3-O$(CH_2)_2OCH_2CH_3$ group. This model compound is of interest from the viewpoint of the first example for modification of the 3-OH group in pyridoxal molecule. The ethoxyethoxy function is expected to play an important role on fixing conformation around the imino ester moiety in α-imino esters **8B** by a stable chelate formation with Li^+ ion as illustrated in Scheme 2 (structure **11**) and this feature should be helpful for modeling of the enzymatic reactions.



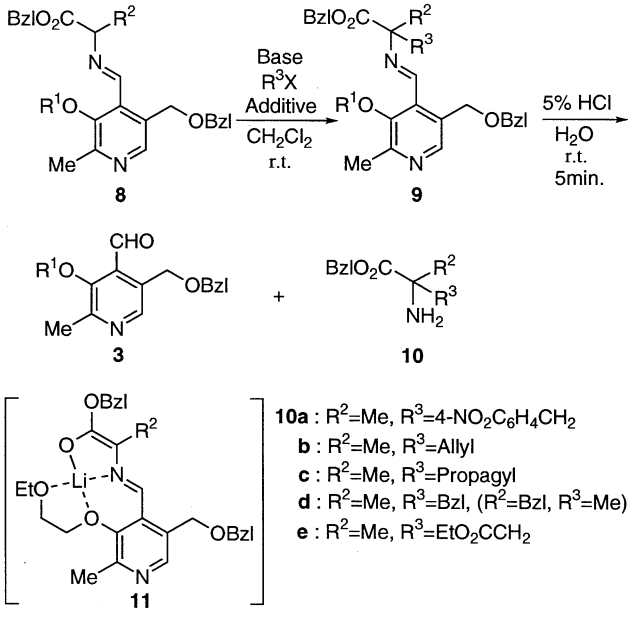
In this paper we wish to describe the preparation and physical properties of the novel PLP model compound **3B**, and also its successful application to synthesis of α-alkyl-α-amino esters *via* α-alkylation of α-imino esters **8B**.

As shown in Scheme 1, 5'-*O*-benzylpyridoxine[5] (**4**) was oxidized to **5**, which was converted into the 3-*O*-methylated and 3-*O*-ethoxyethylated PLP derivatives, **3A** and **3B**, respectively, *via* acetals **6** and **7** in the usual way. These PLP model compounds were found to give quite easily the corresponding imino products **8A** and **8Ba** by reaction with alanine benzyl ester in dichloromethane at room temperature.

First, we examined α-alkylation of α-imino ester **8A** with 4-nitrobenzyl bromide. The alkylation with an alkali hydroxide (LiOH, NaOH or KOH) in dichloromethane was found not to proceed at all and resulted in complete recovery of the starting material **8A** (Runs 1-3 in Table 1). When the alkylation was carried out in the presence of 0.2 equiv. of $BzlN^+Et_3Cl^-$ or 18-crown-6 as a phase-transfer catalyst (PTC), followed by an acidic hydrolysis, the alkylated product **10a** was obtained *via* **9** in good



Scheme 1.



Scheme 2.

Table 1. The alkylation of the imines **8A** and **8Ba** with 4-nitrobenzyl bromide

Run	Reaction conditions [a]				Amino ester **10a**
	Imine	Base (6.0 eq.)	Additive (0.2 eq.)	Time / min.	Isolated yield / %
1	**8Aa**	LiOH	—	90	N.R.
2	**8Aa**	NaOH	—	90	N.R.
3	**8Aa**	KOH	—	90	N.R.
4	**8Aa**	NaOH	$BzlN^+Et_3Cl^-$	15	64 [b]
5	**8Aa**	KOH	18-crown-6	15	58 [b]
6	**8Ba**	LiOH	—	20	66 [b]
7	**8Ba**	NaOH	—	90	56 [b]
8	**8Ba**	KOH	—	90	trace

[a]All runs were carried out at room temperature. [b]PLP model compounds **3A**, **B** were recovered in 73-80% yields.

Table 2. The alkylation of the imines **8Ba** and **8Bb**

Run	Reaction conditions [a]			Amino ester	
	Imine	R^3X	Time / min.	Product	Isolated yield [b] / %
1	**8Ba**	allyl bromide	15	**10b**	70
2	**8Ba**	propagyl bromide	15	**10c**	84
3	**8Ba**	benzyl bromide	30	**10d**	56
4	**8Ba**	ethyl bromoacetate	60	**10e**	58
5	**8Bb**	methyl iodide	30	**10d**	54

[a]All runs were carried out at room temperature. [b]PLP model compound **3B** was recovered in 77-87% yields.

yields (Runs 4, 5). On the other hand, in the case of the ethoxyethoxy analog **8Ba**, α-alkylation took place smoothly without any PTC (Runs 6, 7). The alkylation proceeded most readily with LiOH. Sodium hydroxide was shown to be less effective for the alkylation and the alkylation with KOH hardly occurred (Run 8). Alkylations of **8Ba** or **8Bb** with various alkylating agents and LiOH also gave the alkylated products **10b-e** in moderate yields (Table 2). The same product **10d** was obtainable both by benzylation of **8Ba** and by methylation of **8Bb** (Runs 3, 5). These results indicate that the ethoxyethoxy imino esters **8B** have a strong Li^+-ionophore activity, probably owing to a chelate model **11** which structurally resembles to a Li^+-12-crown-4 complex.

In order to make the ionophore activity of **8B** clear, we evaluated the interaction between Li^+ and the imine **8Ba** by means of the ^{1}H-NMR spectra in CD_3CN (Figure 1). By the addition of $LiClO_4$, the signals for protons on C-3 side-chain and the imino ester moiety moved to *downfield*. Changing of the splitting patterns of some these signals were also recognized [Figure 1-(*a*)]. These observations could be explained in terms of the Li^+-induced conformational change as illustrated in Figure 1-(*a*). Nuclear Overhauser effect (NOE) experiments [Figure 1-(*a*)] and the shift experiments by a continuous addition of $LiClO_4$ (a continuous variation method)[6] [Figure 1-(*b*)] strongly supported the formation of a 1:1 chelate complex between Li^+ and the imino ester **8Ba**.

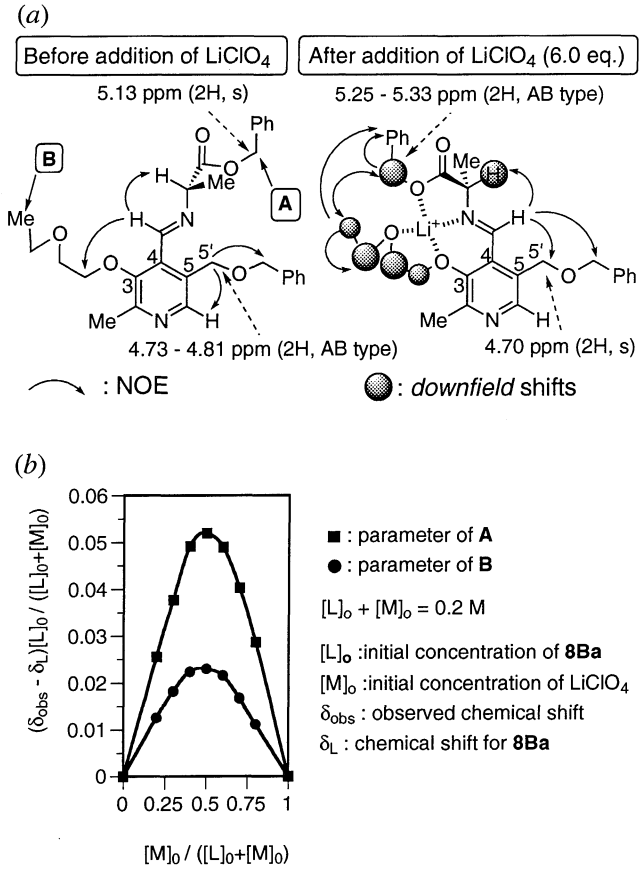


Figure 1. ^{1}H-NMR studies of **8Ba** before and after addition of $LiClO_4$. (*a*) The spectral and conformational change. (*b*) a continuous variation method.

Based on the present results, synthetic studies of various optically active α-amino acids by means of chiral PLP (and PMP) model compounds are now in progress.

References and Notes

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