Conversion of Amino Acid Benzyl Ester *p*-Toluene Sulfonates to Their Hydrochloride Salts by using Tetramethylguanidine

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Summary

The effective conversion of *p*-tosylate of glycine benzyl ester to its hydrochloride (**1**) can be attained by using tetramethyl guanidine instead of triethyl amine. This procedure is applicable also to the other amino acid benzyl ester *p*-tosylates.

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In the course of the synthetic study of the glycine containing oligopeptides we tried to convert *p*-toluenesulfonic acid salt of glycine benzyl ester to its hydrochloride (**1**) by treating the tosylate with triethylamine according to the procedure described by Miller and Waelsh[1] in analogous to the cases of other amino acids[2], but we failed to obtain **1**. We found that the liberation of glycine benzyl ester could only partly proceed with triethyl amine, and recognized that this procedure was applicable only to its benzene sulfonate[1,3] in the case of glycine benzyl ester as described in the literature[1].

It is desirable to prepare **1** from *p*-tosylate of glycine benzyl ester, because it can be easily prepared as well as in the cases of the other amino acids[2]. Recently a simple procedure of this conversion has been reported by F. M. F. Chen et al[4]. According to it, liberation of benzyl ester from *p*-tosylate and the following formation of its hydrochloride are performed in aqueous solution.

We report here another process of obtaining benzyl ester hydrochloride of glycine almost quantitatively in the organic solvent system. The procedure is similar to that of Miller and Waelsh[1]. However the more basic reagent, tetramethylguanidine is used instead of triethylamine : glycine benzyl ester *p*-tosylate was treated with tetramethyl guanidine (1.0 eq) in chloroform and tetramethylguanidine *p*-tosylate was quantitatively precipitated by adding ether. The filtrate was evaporated to dryness to give free benzyl ester, which can be converted to the hydrochloride with methanolic hydrochloride. This procedure is also applicable to the other amino acid benzyl ester *p*-tosylates.

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Experimental

All melting points (mps) are uncorrected. NMR spectra were recorded with a Bruker AC250 (250 MHz for H) using TMS as an internal standard. Optical rotation was measured with an automatic polarimeter MP 1-T (Applied Electric Lab.).

Glycine benzyl ester hydrochloride from its p-tosylate. To the stirred suspension of glycine benzyl ester *p*-toluene sulfonate salt (0.02 M) in chloroform (20-50 ml) was added tetramethylguanidine (1.00 eq) dropwise at 0°C. After stirring for 0.5 h dry diethyl ether (100 ml) was added and precipitated tetramethylguanidine *p*-tosylate was removed by filtration. The filtrate was evaporated to dryness and the residual oily product (free benzyl ester) was dissolved in methanolic hydrochloride solution (5%, 100 ml). The solvent was evaporated to dryness to give the crystalline product. After recrystallization from methanol/diethyl ether pure product was obtained (3.92g, yield, 97%, mp 126-127°). If the filtrate was concentrated to about one third volume and methanolic HCl was added, the pure product was directly obtained, mp 139° (71%). (Lit.[3] 130.5-132°, crystallized from methyl cellosolve acetate, Lit.[4] 140-141°, Lit.[7] 140°). ^{1}H-NMR($CDCl_3$) δ: 3.65 (s,

Table 1. Benzyl Ester Hydrochlorides of Other Amino Acids

Benzyl ester hydrochloride of	Mp °C	Yield[a] %	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
L-Alanine	138-141[b]	97	$C_{10}H_{14}O_2NCl$	55.69	6.54	54.90	6.58
DL-Alanine	oil						
L-Valine[c]	136-141[d]	95.5, 90*	$C_{12}H_{18}O_2NCl$	59.13	7.44	59.05	7.46
DL-Valine	111	91, 82*	〃	〃	〃	58.96	7.54
L-Leucine	134-136[e]	91, 77*	$C_{13}H_{20}O_2NCl$	60.58	7.82	59.98	7.94
DL-Leucine	141-144	86, 72*	〃	〃	〃	60.35	7.81
L-Isoleucine	oil						
DL-Isoleucine	oil						
L-Phenylalanine[f]	199-200[g]	74*	$C_{16}H_{18}O_2NCl$	65.86	6.22	65.61	6.33
DL-Phenylalanine	182-184[h]	92	〃	〃	〃	65.96	6.13

a. * Yield after recrystallization from methanol/diethyl ether.
b. Mp 140°C in Lit.[5,7]
c. $[\alpha]_D^{20}$ −11.4±1 (c=0.5, 0.1N HCl).
d. Mp 142-143°C in Lit.[4]; 138-139°C in Lit.[6]; 139-141°C in Lit.[8]
e. Mp 135°C in Lit.[4]; 128°C in Lit.[7]
f. $[\alpha]_D^{20}$ −23.2±3 (c=1, 0.1N HCl). $[\alpha]_D^{20}$ −22.5 (c=1. 01, 0.1N HCl) in Lit.[7]
g. Mp 203°C in Lit.[7]
h. Mp 196°C in Lit.[7]

2H, CH_2-G), 5.23 (s, 2H, CH_2-Ph), 7.26-7.54 (m, 5H, Ph), 8.63 (bs, NH_3). ^{13}C-NMR ($CDCl_3$) δ : 39.6 (C-G), 66.80 (CHPh), 128.20, 128.35, 128.50 and 135.28 (C_{arom}-Ph), 167.53 (CO). Found : C, 53.41 ; H, 6.10. Calcd. for $C_9H_{12}O_2NCl$ (201.7) : C, 53.61 ; 6.00%.

Conversion of other amino acid benzyl ester p-tosylates to their hydrochlorides by the same procedure. The results were summarized in Table 1.

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アミノ酸ベンジルエステルの *p*-トシレートから塩酸塩を調製するための改良法

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遊離のグリシンベンジルエステル，あるいはその塩酸塩は，それのフェニルスルホン酸塩からトリエチルアミンで処理することによって得られるが[1]，*p*-トシレートからはこの方法ではほとんど得られない。しかし，グリシンベンジルエステル・*p*-トシレートの方が容易に[2]かつ安価に得られるので，このものから遊離化できる簡便な方法があればより好都合であると考えられる。最近 Benoiton ら[4]は，同じくグリシン及び他の2，3のアミノ酸について，それらの *p*-トシレートから対応する塩酸塩を調製するための改良簡便法を報告した。それによると，中和反応は水溶液中で行われるのであるが，収率は必ずしも好ましくはない。そこで我々は上記の方法[1]で，トリエチルアミンの代りに，より塩基性の強いテトラメチルグアニジンを用いて行ったところ，グリシンベンジルエステルの *p*-トシレートがほぼ定量的に塩酸塩に変換されうることを認めた。なお，他のアミノ酸についても *p*-トシレートは容易に得られるのであるが[2]，これからも同様テトラメチルグアニジンにより簡便に相当するアミノ酸ベンジルエステルの塩酸塩に変換できることを示した。