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A Convenient Method of Preparing *p*-Toluenesulfonates of Ethyl Esters of Amino Acids Using Ethyl *p*-Toluenesulfonate

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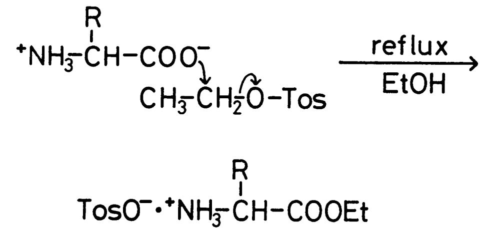
Synopsis. The treatment of amino acids with ethyl *p*-toluenesulfonate affords the *p*-toluenesulfonates of the ethyl esters in good yields. Tryptophan ethyl-ester *p*-toluenesulfonate was also prepared in an 81% yield.

In the peptide synthesis, the *p*-toluenesulfonates of ethyl esters of amino acids are of importance as starting materials.[1)]

The *p*-toluenesulfonates of the ethyl esters of amino acids have previously been prepared by the use of *p*-toluenesulfonic acid as a catalyst; the synthesis involved the azeotropic distillation of a mixture of amino acid, *p*-toluenesulfonic acid, ethanol, and carbon tetrachloride.[2)]

We have now found that amino acids are easily converted to the *p*-toluenesulfonates of the ethyl esters in good yields by treatment with ethyl *p*-toluenesulfonate. The results thus obtained are summarized in Table 1. The method was very convenient and required neither special apparatus nor complicated manipulation: the ethanolic suspension of amino acid was refluxed while being stirred for 24—30 h in the presence of ethyl *p*-toluenesulfonate. We have not observed any *N*-ethylation or *N*-tosylation of the amino acids under these conditions. Tryptophan ethyl-ester *p*-toluenesulfonate has not been synthesized previously, probably because of its instability to *p*-toluenesulfonic acid. However, we succeeded in synthesizing this compound in an 81% yield by the use of our method.

It has previously been reported that the reaction of 3β-steroidal tosylates with tetrabutylammonium acetate in acetone gives 3α-acetates in good yields and appears to be a nucleophilic bimolecular S_N2 displacement by acetate.[3)] Taking into account the fact that the tosylate is a very good leaving group,[3—5)] the esterification may be explained as is shown in the following reaction scheme.



Experimental

All the melting points were uncorrected. The TLC was carried out on a silica-gel 60 F_{254} pre-coated plate (Merck and Co.) with the following solvent systems: $R_{f,1}$ $CHCl_3$–MeOH (5: 1, v/v); $R_{f,2}$ *n*-BuOH–AcOH–pyridine–H_2O (15: 3: 10: 12, v/v). The optical rotations were measured on an Atago polarimeter Polax. The IR spectra were recorded on a Hitachi EPI-2 spectrometer. Ethyl *p*-toluenesulfonate was purified by distillation under reduced pressure, a fraction with a bp of 121 °C/2 mmHg being used. All the amino acids used in this experiment, except glycine and 4-aminobutyric acid (4-Abu), had an L-configuration.

General Esterification Procedure. A suspension of the amino acid (10 mmol) and ethyl *p*-toluenesulfonate (11 mmol) in absolute ethanol (40 ml) was refluxed while being stirred for 24—30 h, during which dissolution occurred. After the evaporation of the solvent, the residual material was treated with ether. The precipitate filtered off was recrystallized from hot ethanol–ether.

L-*Tryptophan Ethyl-ester* p-*Toluenesulfonate.* This was prepared from Trp (2.04 g, 10 mmol) and ethyl *p*-toluenesulfonate (2.20 g, 11 mmol) as has been described above. Yield 3.28 g (81%); mp 139—140 °C; $[\alpha]_D^{30}$ +15.4° (*c* 4, EtOH); IR (Nujol) 3370 (indole NH) and 1730 cm^{-1} (C=O); $R_{f,1}$ 0.49, $R_{f,2}$ 0.81. Found: C, 59.38; H, 6.09; N, 6.67%. Calcd for $C_{20}H_{24}O_5N_2S$: C, 59.39; H, 5.98; N, 6.92%.

TABLE 1. *p*-TOLUENESULFONATES OF ETHYL ESTERS OF AMINO ACIDS

Amino acid	Yield[a)] (%)	Mp (°C)		$[\alpha]_D^t$ (°)	
		Obsd	Lit[2)]	Obsd (*c*, solvent, *t* °C)	Lit[2)] (*c* 2, DMF, 20 °C)
Gly	100[b)]	oil	oil		
4-Abu	86	82—84	83		
Val	87	147—149	143—144	+12.5 (4 DMF 20)	+10.2
Leu	92	153—154	158	+6.0 (4 DMF 18)	+ 7.8
Phe	89	153.5—154	153	+14.9 (2 DMF 17)	+15.5
Tyr	93	190—190.5	193	+12.3 (4 DMF 21)	+12.6
Met	86	128—129	127	+6.9 (4 DMF 22)	+ 6.5
Trp	81	139—140		+15.4 (4 EtOH 30)	
Pro	100[b)]	oil	oil		

a) Yields were of recrystallized products. b) Yield was estimated by TLC.

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