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Reaction of Amino Acids with Alkyl *p*-Toluenesulfonates

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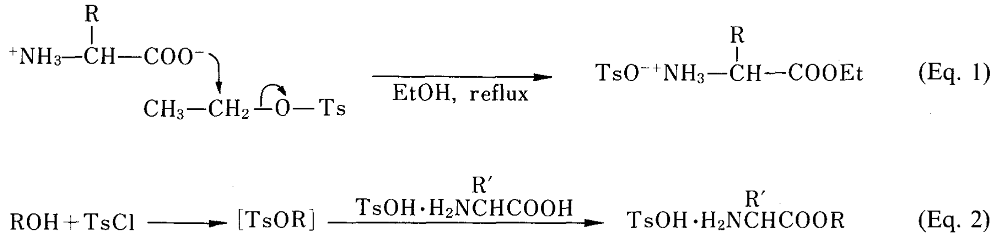
Recently, it has been reported that the treatment of amino acids with alkyl *p*-toluenesulfonates in alcohol affords the *p*-toluenesulfonates of the corresponding alkyl esters in high yields. The results of our examination of this reaction indicated that the reaction proceeds predominantly through the general acid-catalyzed esterification of carboxylic acid by alcohol, and the involvement of transesterification is minor.

Keywords——transesterification; ethyl *p*-toluenesulfonate; amino acid ester; *p*-toluenesulfonic acid; alcoholysis; methionine; phenylalanine; acid-catalyzed esterification

Recently, two papers have appeared describing the esterification of amino acids by alkyl *p*-toluenesulfonates (TsOR), as shown in Chart 1. Ueda[1] obtained the *p*-toluenesulfonates of amino acid ethyl esters in high yields by an esterification procedure that involves refluxing a suspension of the amino acid and 1.1 eq of ethyl *p*-toluenesulfonate (TsOEt) in absolute ethanol for 24—30 h. Arai *et al.*[2] also used an esterification reaction of amino acids; when a mixture of amino acid *p*-toluenesulfonate and *p*-toluenesulfonyl chloride in an alcohol was heated for 1—2 h, the esterification was achieved by transesterification between amino acids and TsOR formed by the reaction of *p*-toluenesulfonyl chloride with alcohol, and the products were isolated as the *p*-toluenesulfonates in excellent yields.



$$\overset{+}{N}H_3\text{—}\overset{\overset{\large R}{|}}{C}H\text{—}COO^- + CH_3\text{—}CH_2\text{—}O\text{—}Ts \xrightarrow[\text{EtOH, reflux}]{} TsO^{-}\,{}^{+}NH_3\text{—}\overset{\overset{\large R}{|}}{C}H\text{—}COOEt \qquad \text{(Eq. 1)}$$

$$ROH + TsCl \longrightarrow [TsOR] \xrightarrow{TsOH\cdot H_2N\overset{R'}{C}HCOOH} TsOH\cdot H_2N\overset{R'}{C}HCOOR \qquad \text{(Eq. 2)}$$

Chart 1

We reported in the previous paper[3] a novel method for the esterification of organic sulfonic acids by using carboxylic acid esters. Our results cast considerable doubt upon their proposed mechanism of transesterification between amino acids and TsOR. The transesterification (Eq. 2) seems to be incompatible with our finding that the reaction of carboxylic acid esters with *p*-toluenesulfonic acid (TsOH) is irreversible. Thus, we felt it important to investigate in some detail their proposal. We now wish to report these results.

First, we examined the reaction of amino acid *p*-toluenesulfonates with TsOEt. Thus, when a mixture of L-phenylalanine *p*-toluenesulfonate with 1.1 eq of TsOEt in dry toluene instead of ethanol was heated at reflux for 24 h, L-phenylalanine ethyl ester *p*-toluenesulfonate was not obtained, while TsOEt was recovered quantitatively. This result is consistent with our finding that the transesterification of carboxylic acid esters into sulfonic acids is an irreversible reaction. Therefore, it seems likely that their procedure for esterification of amino acids can be explained as a general acid-catalyzed reaction of carboxylic acid with alcohol, catalyzed by hydrogen chloride generated *in situ*.The participation of TsOR is not considered in the reaction mechanism proposed by Arai *et al.* We also re-examined the reaction of carboxylic acids with TsOEt in order to further confirm its irreversibility, as only one reaction example was reported in the previous paper.[3b)] The results listed in Table I re-confirm that our reaction is irreversible.

Next, we examined the reaction of free amino acids with TsOEt by the general procedure of Ueda. As examples of amino acids, L-methionine and L-phenylalanine were used. The results are summarized in Table II. As pure *p*-toluenesulfonates of amino acid esters could not be readily obtained, the crude *p*-toluenesulfonates were converted into pure free amino acid esters which exhibited a single spot on TLC. As shown in Table II (runs 7 and 8), ethyl esters of amino acids were not obtained in high yields. However, the reaction of amino acids with 1.1 eq of TsOH in refluxing absolute ethanol for 24 h formed the desired esters in excellent yields (runs 1 and 5), while the use of an equimolar amount of TsOH caused the yields to be decreased (runs 2 and 6).

It has been reported[4)] that when a mixture of amino acid and alcohol in benzene or chloroform was refluxed in the presence of 1.1 eq of TsOH, the amino acid ester *p*-toluenesulfonate was obtained in high yield. Accordingly, when 1.1 eq of TsOEt was used, the

TABLE I. Reaction of Carboxylic Acids with Ethyl *p*-Toluenesulfonate

Run	Carboxylic acids	Recovery of TsOEt (%)
1	$C_6H_{11}COOH$	100
2	$(CH_3)_3CCOOH$	96
3	C_6H_5COOH	96
4	Cl_3CCOOH	98
5	L-$C_6H_5CH_2CH(NH_2)COOH \cdot TsOH$	98

a) The reactions were carried out in refluxing toluene for 24 h.

TABLE II. Reaction of Amino Acids with Alkyl *p*-Toluenesulfonates in Refluxing Ethanol

$$H_2NCHRCOOH + TsOR' \xrightarrow[\text{reflux}]{\text{EtOH}} \underset{\mathbf{1}}{TsOH \cdot H_2NCHRCOOEt} + \underset{\mathbf{2}}{TsOH \cdot H_2NCHRCOOR'}$$

Run	R	R′ (Mol eq of TsOR′)		Time (h)	Yield (%)		Recovery (%) TsOR′
					1[a)]	**2**[a)]	
1	$CH_3S(CH_2)_2$	H	(1.1)	24	94	—	—
2		H	(1.0)	24	25	—	—
3		Et	(1.1)	24	45[b)]		3
4		Et	(1.0)	24	25[b)]		2
5	$C_6H_5CH_2$	H	(1.1)	24	100	—	—
6		H	(1.0)	24	43	—	—
7		Et	(1.1)	24	66[b)]		4
8		Et	(1.1)	30	78[b)]		1
9		Et	(1.0)	24	32[b)]		2
10		Et	(2.0)	24	100[b)]		4
11	$CH_3S(CH_2)_2$	*n*-Bu	(1.1)	24	63	21	4

a) **1** and **2** were converted into the free bases to determine the yields by GC. *b*) In this case, **1** and **2** are the same compound (R′ = Et).

Table III. Reaction of Alkyl *p*-Toluenesulfonates with Alcohols

$$\mathrm{TsOR + ROH \longrightarrow TsOH + R_2O}$$

Run	R	Reaction conditions	Yield (%) TsOH	Yield (%) R_2O[a]	Recovery (%) TsOR
1	Et	Reflux, 24 h	94	275	3
2[b]		Reflux, 24 h	—	91	4
3	*n*-Bu	80 °C, 90 h	84	127	10
4		Reflux, 24 h	92	208	2

a) Yields were based on TsOR. *b*) 0.91 eq of L-phenylalanine was added.

lower yield was probably due to incomplete alcoholysis of TsOEt. Ueda[1] did not consider the reaction of TsOEt with ethanol. Interestingly, the reaction of L-phenylalanine with 2.0 eq of TsOEt in refluxing ethanol for 24 h led to the desired ester in excellent yield (run 10) owing to the formation of sufficient TsOH.

Alcoholysis of TsOEt has been reported by Hückel[5] and Laughton.[6] Thus, our attention was next directed to the reaction of TsOR with alcohols and we examined the amounts of ether compounds and TsOH formed under reflux.[7] As shown in Table III, the ether compounds and TsOH were produced in high yields, respectively, with the recovery of small amounts of TsOR. In run 2, L-phenylalanine was further added to investigate the formation of ether under the conditions of run 7 of Table II. The ether was formed in good yield. In this case, TsOH formed was scavenged by the amino acid and its ester to prevent the further formation of ether by the reaction of TsOH with alcohol.[8] Thus, it appears that the use of 1.1 eq of TsOR led to unsatisfactory formation of the desired products due to the inadequate amounts of TsOH.

However, whether the participation of TsOR in the reaction mechanism proposed by the author[1] does occur remains to be determined. Thus, in order to examine this problem, the reaction of methionine with TsOBu^n in refluxing ethanol was carried out, and it was found that this reaction afforded both ethyl and *n*-butyl esters of methionine in 63 and 21% yields, respectively (Table II, run 11). It is clear that the *n*-butyl ester was formed by the reaction mechanism shown in Chart 1 (Eq. 1). However, the conversion of the *n*-butyl ester formed *in situ* into the ethyl ester, resulting in the low yield of the *n*-butyl ester and the relatively high yield of the ethyl ester, may be able to occur under the conditions described above. Thus, in order to examine the conversion, methionine *n*-butyl ester *p*-toluenesulfonate was treated with ethanol under reflux for 24 h. A mixture of the *n*-butyl and ethyl esters in the ratio of 12 : 1 was obtained: the *n*-butyl ester was negligibly converted to the ethyl ester. Consequently, it was found that the transesterification reaction was minor. These results also demonstrate that the reaction reported by Ueda involves as a major pathway the general reaction of carboxylic acid with ethanol in the presence of an acidic catalyst, *i.e.*, TsOH which was produced by the reaction of TsOEt with ethanol.

The reaction scheme, as shown in Chart 1 (Eq. 1), is based on the fact that the reaction of a 3β-steroidal tosylate with tetrabutylammonium acetate in acetone gives 3α-acetates in good yields[9] and the tosylate is a very good leaving group. Indeed, it is known that the reaction of trialkylammonium salts of amino acids with sulfonic acid esters leads to the formation of amino acid esters.[10] Finally, we examined the reaction of monoalkylammonium salt of cyclohexanecarboxylic acid with TsOEt in acetone in order to study the effect of primary amines on the esterification. The results are presented in Table IV. In going from tertiary amines to primary amines, the yield of ethyl cyclohexanecarboxylate was depressed. Thus, the efficacy of primary amines in the transesterification is less than that of tertiary amines. The

TABLE IV. Reaction of Cyclohexanecarboxylic Acid with Ethyl *p*-Toluenesulfonate in the Presence of Amines

Run	Amine	Solvent	Reaction conditions	Yield (%)[a] $C_6H_{11}CO_2Et$	Recovery (%)[a] TsOEt
1	Et_3N	Benzene	Reflux, 24 h	58	16
2		Acetone	Reflux, 24 h	42	26
3	$H_2NCH_2CH_2OH$	Acetone	Reflux, 24 h	22	2[b]
4	*tert*-$BuNH_2$	Acetone	Reflux, 24 h	10	80

a) Yields were determined by GC. *b*) Low recovery seems to be due to the alcoholysis of TsOEt with β-aminoethanol.

low yield of the transesterification product can be explained in terms of this result.

On the basis of the above argument, we conclude that the transesterification may proceed *via* a nucleophilic bimolecular displacement by carboxylate ion to some extent, but the major process is the acid-catalyzed esterification of carboxylic acid.

Experimental

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in chloroform-*d* solution on a JEOL JNH-MH-100 spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained on a JASCO IR-2 spectrophotometer. Gas chromatography (GC) was carried out on a Shimadzu GC-8A apparatus.

General procedures for the reactions shown in Table I—IV are as follows.

Attempted Reaction of Carboxylic Acids with Ethyl *p*-Toluenesulfonate——A mixture of a carboxylic acid (10 mmol) and TsOEt (10 mmol) in dry toluene (30 ml) was refluxed for 24 h. No formation of the corresponding ethyl ester was detected by GC. The reaction mixture was diluted with benzene (50 ml) and washed with 2 N NaOH solution (30 ml × 2). The solvent layer was washed with water, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give TsOEt, the yield of which was determined by GC. The aqueous layer was acidified with conc. HCl and extracted with benzene (50 ml × 3). The benzene solution was dried with anhydrous sodium sulfate and evaporated to give unchanged carboxylic as a colorless oil or solid.

Reaction of Amino Acids with Ethyl *p*-Toluenesulfonate——A mixture of an amino acid (10 mmol) and TsOEt (1.1 or 1.0 mmol) in absolute ethanol (40 ml) was refluxed for 24—30 h while being stirred, according to the literature procedure.[1] After removal of the solvent, the residual material was treated with ether (50 ml), and then extracted with water (100 ml). The aqueous layer was made alkaline with $NaHCO_3$ and extracted with several portions of $CHCl_3$. The combined chloroform extracts were dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left the free amino acid ethyl ester as a pale yellow oil, which was proved to be pure by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR).

The reaction with anhydrous TsOH instead of TsOEt was carried out by a similar procedure.

Alcoholysis of Alkyl *p*-Toluenesulfonates by Alcohols——A solution of TsOR (10 mmol) and alcohol (40 ml) was refluxed for 24 h. Atmospheric pressure or vacuum (*ca.* 100 mmHg) distillation of the reaction mixture provided the ether compound and the residual material. The yield of the ether compound was determined by GC. The residual material was extracted with benzene (50 ml) and water (50 ml). Unchanged TsOR and TsOH was recovered from the benzene layer and the aqueous layer by the usual work-up, respectively.

Reaction of Cyclohexanecarboxylic Acid with Ethyl *p*-Toluenesulfonate in the Presence of Amines——A mixture of cyclohexanecarboxylic acid (10 mmol), an amine (10 mmol) and TsOEt (11 mmol) in benzene (40 ml) was refluxed for 24 h. The reaction mixture was made alkaline with sodium bicarbonate, and then washed with 2 N HCl to remove the acidic and basic components. The organic layer was washed with water and dried with anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the yields of ethyl cyclohexanecarboxylate and TsOEt in the residual oil were determined by GC.

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