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ON ESTERS OF *p*-TOLUENESULFONIC ACID

R. STUART TIPSON

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During the past few years the esters of *p*-toluenesulfonic acid have achieved considerable practical importance as alkylating agents. They are particularly useful for the alkylation of phenolic substances containing one or more tertiary nitrogen atoms, since they react preferentially with the phenolic hydroxyl group and effect very little alkylation of the tertiary nitrogen atoms.

A satisfactory method for the preparation of these esters in high yield would therefore have great practical value. Unfortunately, however, although a number of methods for their synthesis have been evolved, most of them are unsatisfactory, for reasons to be discussed.

The various ways in which arylsulfonic esters have been synthesized fall into two main groups. The first of these consists in the action of an alkyl halide (or sulfate) on a metallic salt of the sulfonic acid (1, 2, 3).

$$(RSO_2O)_2Pb + 2EtI \rightarrow 2\ RSO_2OEt + PbI_2 \qquad (I)$$

$$2\ RSO_2ONa + Me_2SO_4 \rightarrow 2\ RSO_2OMe + Na_2SO_4 \qquad (II)$$

The applicability of this procedure is obviously limited by such factors as the reactivity, availability, and expense of the alkyl halide or sulfate.

The second method involves the action of the alcohol (or phenol) on the sulfonyl halide (4, 5), as follows.

$$RSO_2Cl + EtOH \rightarrow RSO_2OEt + HCl \qquad (III)$$

This method, in the simple form given, can only be employed successfully provided that three conditions are satisfied. The first is that excess of the alcohol (or phenol) shall be readily removable at the end of the reaction; for example, by evaporation, by extraction with a suitable solvent, or by steam-distillation.

The second requirement is that the rate of reaction between the ester produced and the hydroxylic starting material shall be so low that very little or none of the corresponding ether can be formed by the following type of reaction (6, 7).

$$RSO_2OEt + EtOH = RSO_3H + Et_2O \qquad (IV)$$

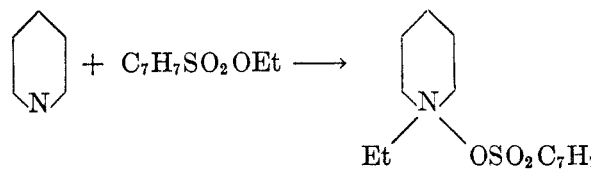
If there is a tendency for ether-formation to occur it can be reduced to the minimum by employing a large excess of the hydroxylic substance and conducting the reaction at room temperature (8). The disadvantages of this modification are the length of time required for the reaction to approach completion and the large excess of the hydroxylic substance which must be employed. The method is, therefore, not feasible for rare alcohols or phenols; nor if the sulfonyl chloride has a very low solubility in the cold hydroxylic substance (9).

The third condition to be met is that the hydrogen halide evolved in the reaction shall have little or no action on either the hydroxylic substance to be

esterified or on the desired ester. To minimize this difficulty Slotta and Franke (10) introduced the modification of aspirating dry air through the hot reaction-mixture, thereby removing hydrogen halide as fast as it is formed. Employing this procedure they were able to prepare *n*-propyl *p*-toluenesulfonate in a yield of 74% of the theoretical.

A better modification, however, consists in the introduction of a substance which will neutralize the hydrogen halide as fast as it is formed. For this purpose, inorganic and organic bases have been employed. Inorganic substances used include sodium hydroxide (11), and sodium carbonate (10, 12). A similar procedure is to allow the sulfonyl halide to react with a sodium alkoxide in the alcohol (2, 13), in dry ether (14), or dry benzene (15). The method is obviously of little or no value for such substances as partially acylated sugars, unsaturated alcohols, or halohydrins which are difficult or impossible to obtain as alcoholates.

Organic bases which have been employed include diethylaniline (12), and pyridine (16). In the preparation of esters of *p*-toluenesulfonic acid by the action of *p*-toluenesulfonyl ("tosyl") chloride upon the alcohol in the presence of pyridine, three different undesired side-reactions can take place. One of these is ether formation (17) (as in equation IV). The second is formation of the pyridinium quaternary salt (17) as in equation V.



(V)

However, Sekera and Marvel (18) stated that this by-reaction usually proceeds to only a minor extent if the reaction is performed at 0°.

The third type of side-reaction is that of chlorination; it has been encountered on attempting to tosylate phenols (19, 20), simple alcohols (21, 22), and such polyhydroxy compounds as sugars (23, 24), sugar alcohols (25), and their derivatives. A simple illustration is the chlorination of phenoxyethanol (21):

$$C_6H_5OCH_2CH_2OH \rightarrow C_6H_5OCH_2CH_2Cl \qquad \text{(VI)}$$

Although these and other examples of this chlorination reaction are to be found in the literature, it seems that it was not until 1935 that the mechanism of the reaction was revealed by Hess and Stenzel (24). However, their work was confined to sugar derivatives and, as far as is known, their theory has never been applied to other chlorinations occurring on treatment with tosyl chloride in pyridine. They discovered that the chlorination takes place *after* tosylation has occurred, according to equation VII, and that chlorination is increased by raising the temperature.

$$ROSO_2C_7H_7 + C_5H_5N \cdot HCl = RCl + C_5H_5N \cdot C_7H_7SO_3H \qquad \text{(VII)}$$

On treating β-methyl glucoside with tosyl chloride in pyridine they were able to obtain at will, by varying the temperature from one experiment to another,

tetratosyl β-methyl glucoside, monochloro-tritosyl β-methyl glucoside, or dichloro-ditosyl β-methyl glucoside.

In the present study, attention has been confined to the use of pyridine as the neutralizing agent. Of the many precautions advocated in the literature as being advisable, it is now found that only two are necessary. First, since *p*-toluenesulfonyl chloride is rapidly hydrolyzed by slightly moist pyridine, it is essential that the pyridine employed be dry and that the reaction be performed with exclusion of atmospheric moisture. Secondly, in some but not all cases to be discussed, the temperature of the reaction mixture should be kept at or somewhat below 0°. The time during which the reaction is permitted to proceed has been reduced considerably and, for convenience, the proportions of solvent and reactants have been standardized. Hence, the method now described is a simplification of the excellent one of Sekera and Marvel (18), and represents, in some respects, a return to the original method of Patterson and Frew (16).

DISCUSSION OF RESULTS

It is found that, if the substance to be esterified is first dissolved in pyridine and the resulting solution then thoroughly cooled, there is very little rise in temperature on adding all the tosyl chloride in one lot. Hence, nothing is to be gained by adding either of the reactants in portions (except in large-scale experiments).

Gentle swirling by hand, during the short period of time required for all of the tosyl chloride to dissolve, is ample to keep the temperature uniform throughout the reaction mixture. Since the mixture then becomes a homogeneous solution and remains so until the crystallization of pyridine hydrochloride (and, in some cases, of ester) commences, mechanical stirring is unnecessary.

Some hydroxylic substances are not very soluble in pyridine; if addition of a non-polar solvent helps to dissolve the material, its use is advantageous but otherwise it serves no useful purpose. Finally, the use of specially purified *p*-toluenesulfonyl chloride is unnecessary. In the following experiments, a ten per cent excess of the commercial reagent has been consistently employed.

The behavior of a number of hydroxylic substances has been studied under these conditions. Only those esters which are new, or which have been found to have properties different from those previously reported, are described in Table I. In no case was the formation of a chloro compound detected and in most instances the yield of *p*-toluenesulfonyl ester was over 75% of the theoretical, showing that the formation of ether or pyridinium salt, or both, was not large.

As examples of substances which are known to undergo chlorination in the presence of tosyl chloride and warm (or hot) pyridine or diethylaniline, we chose for study phenoxyethanol (21) and 2,4-dinitrophenol (19). Under the conditions now described, neither compound gives rise to any chloro derivative. However, the tosyl ester of 2,4-dinitrophenol, as is well known (19, 26), readily reacts with cold pyridine to give the quaternary pyridinium salt. Consequently, the yield of this ester amounted to only 26% of the theoretical.

This led us to study the formation of three tosyl esters (of ethanol, benzyl

alcohol, and 2,4-dinitrophenol, respectively) which, it is alleged, cannot be prepared in the presence of pyridine owing to the formation of their pyridinium salts. However, by the simple procedure of neutralizing the excess pyridine as soon as formation of the ester was judged to have approached the maximum, we have prepared the ethyl, benzyl, and 2,4-dinitrophenyl esters in yields of 72%, 38%, and 90%, respectively. The yield of benzyl ester is inferior to that obtained by Gilman and Beaber (27) by another method but, unlike their product, the ester obtained was quite stable (28) at room temperature, presumably (17) owing to complete elimination of traces of free benzyl alcohol.

It should be mentioned that apocupreine, which has both a phenolic and an alcoholic hydroxyl group, gives rise to a *mono*-tosyl ester only. Thus, in this respect, its alcoholic hydroxyl group seems to behave more like a tertiary than a secondary hydroxyl. As far as is known, the preparation of tosyl esters of tertiary alcohols has not yet been recorded. However, the fact that *tert.*-butyl alcohol gives (22) the chloride, on treatment with tosyl chloride in pyridine at 100°, indicates that its tosyl ester may be capable of existence, at least as a transitory intermediate.

EXPERIMENTAL

General method for preparation of p-toluenesulfonyl esters. The pyridine employed was reagent grade; it was dried over barium oxide and filtered immediately before use.

The appropriate alcohol (10 g.) was dissolved in 100 cc. of dry pyridine and the solution cooled to −5° in an ice-salt bath. *p*-Toluenesulfonyl chloride (1.1 equivalents) was now added in one portion and the flask closed by a rubber stopper through which a thermometer was inserted. The suspension was gently swirled by hand, with cooling in ice-salt, until all the tosyl chloride had dissolved. After keeping at 0° during a further 2 hours, water (10 cc.) was added in portions (1 + 1 + 1 + 2 + 5 cc.) at intervals of 5 minutes, with swirling and cooling so that the temperature did not rise above +5°. The solution was then diluted with 100 cc. of water. (In some cases, the ester crystallized out at this point; in this event, the ester was filtered off, washed with water until free from pyridine, and dried.) The aqueous pyridine solution was now extracted with three 100-cc. portions of chloroform, and the united chloroform extracts washed successively with ice-cold dilute sulfuric acid, water, and sodium bicarbonate solution. The chloroform solution was dried with anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness under diminished pressure. The resulting product was purified by distillation under high vacuum or by recrystallization. In every case, the *crude* ester was free from chloro compound.

All the compounds described in Table I were prepared by the above procedure. However, in the tosylation of many sugar derivatives, and of phenol (16), borneol (17), and apocupreine, the tendency for chlorination or pyridinium salt formation to take place is so low that external cooling is unnecessary.

Bornyl p-toluenesulfonate. On adding the tosyl chloride to the solution of borneol in pyridine at room temperature (21°) the temperature of the mixture fell to 18°. After standing overnight at room temperature, water was added as above, but without cooling; yield, 85%; m.p. 67°. The product was devoid of chlorine.

Tosyl apocupreine. Apocupreine [purified (29), and dried at 110°] was dissolved in dry pyridine and treated with tosyl chloride by the above general method but the product was isolated as follows. After portionwise addition of water to the reaction mixture, sodium bicarbonate powder was added until effervescence ceased. The solution was then evaporated under diminished pressure, with occasional addition of water, until no odor of pyridine remained. The product was dissolved in chloroform plus water, the chloroform layer separated and the tosyl ester isolated from it in the usual manner.

Treatment of apocupreine with 1.1 molar proportions of tosyl chloride gave a product containing unchanged apocupreine, as shown by analysis for sulfur and nitrogen, and by its negative specific rotation, $[\alpha]_D^{24}$ −55.5° in absolute ethanol, c = 1. Treatment with either 2.2 or 3.3 molar proportions of tosyl chloride (in the refrigerator or at room temperature) resulted in a quantitative yield of a colorless, amorphous product having $[\alpha]_D^{24}$ +14.8° (in absolute ethanol, c = 1) and the composition[1] of a *mono*-tosyl ester (30).

Anal. Calc'd for $C_{26}H_{28}N_2O_4S$: N, 6.03; S, 6.91.

Found: N, 6.09; S, 6.97.

Modified method of esterification. In those experiments in which it was desired to form an estimate of the speed of reaction from the rate of deposition of pyridine hydrochloride, the ratio of tosyl chloride to pyridine was held constant and the following standard proportions of reactants were employed: 22 g. of tosyl chloride, 88 cc. of dry pyridine, and the amount of hydroxylic substance equivalent to 20 g. of tosyl chloride. These were mixed under the conditions given above. 2,4-Dinitrophenol is not sufficiently soluble in dry pyridine to permit use of the above proportion of pyridine; its quantity was accordingly increased.

TABLE I

REFRACTIVE INDICES, MELTING POINTS AND ANALYSES OF SOME ESTERS OF *p*-TOLUENESULFONIC ACID

ESTER	YIELD, %	n_D^{25}	M.P., °C.	B.P., °C.	FORMULA	ANALYSES, %S	
						CALCULATED	FOUND
Methoxyethyl	82	1.5085	10	141/0.2 mm.	$C_{10}H_{14}O_4S$	13.93	14.07
Ethoxyethyl	92[a]	1.5026	18.5	122/0.1 mm.	$C_{11}H_{16}O_4S$	13.13	13.31
n-Propoxyethyl	93	1.5004	8	140/0.1 mm.	$C_{12}H_{18}O_4S$	12.42	12.71
n-Butoxyethyl	92[b]	1.4960		142[b]/0.1 mm.	$C_{13}H_{20}O_4S$	11.78	11.92
Phenoxyethyl	92[b]		80–81[c]		$C_{15}H_{16}O_4S$	10.97	11.08
Diethylcarbinyl	75		43–44[d]		$C_{12}H_{18}O_3S$	13.24	13.71

[a] Compare with Butler *et al.*, *J. Am. Chem. Soc.*, **57,** 575 (1935).

[b] Compare with Butler *et al.*, *J. Am. Chem. Soc.*, **59,** 227 (1937).

[c] Butler *et al.*, *J. Am. Chem. Soc.*, **59,** 227 (1937) gave m.p. 75°; Peacock and Tha, *J. Chem. Soc.*, 2303 (1928) gave m.p. 80°.

[d] Tabern and Volwiler, *J. Am. Chem. Soc.*, **56,** 1139 (1934) gave m.p. 32–35°; Green *et al.*, *J. Am. Chem. Soc.*, **61,** 1783 (1939) gave m.p. 37°.

Ethyl p-toluenesulfonate. Tosyl chloride (22 g.) was dissolved in 88 cc. of dry pyridine (the temperature rising from 22° to 24°), and the solution was cooled to −10°. Absolute ethanol (6.1 cc.) was now added, the temperature rising to −5° after 2 minutes and then falling to −10°. Crystallization commenced after a further 3 minutes, and the mixture was kept at −10° for 15 minutes more. Sulfuric acid (250 cc. of 5 *N*, cooled to 0°) was now added rapidly, with cooling. The temperature rose to 27°, the crystals dissolved and the solution became opalescent. On cooling to +4°, material crystallized out. It was filtered off, thoroughly washed with water, and dried; yield, 15 g.; m.p. 32°, in agreement with that reported in the literature (8). The whole preparation of crude ester occupied less than 30 minutes.

Benzyl p-toluenesulfonate. Benzyl alcohol (10.9 cc.) was treated exactly as described for preparation of the ethyl ester. The crystalline product was washed with heptane and water, and dried; yield, 10.5 g.; m.p. 55°. When its preparation was attempted by the

[1] Most of the analyses reported in this paper were performed microanalytically by Dr. Carl Tiedcke, New York City.

general method, all the pyridine hydrochloride deposited in the reaction mixture had redissolved after 90 minutes and no product could be isolated from the chloroform extract.

2,4-Dinitrophenyl p-toluenesulfonate. (a) A suspension of 19.3 g. of 2,4-dinitrophenol in 176 cc. of pyridine, cooled to −10°, was treated with 22 g. of tosyl chloride and then kept in the refrigerator during 3 days. The product was 2,4-dinitrophenyl pyridinium *p*-toluenesulfonate (6.5 g.). On recrystallization from boiling absolute ethanol (1 g. in 55 cc.), it was obtained as colorless platelets having m.p. 255°, in agreement with the m.p. recorded by Freudenberg and Hess (26).

Anal. Calc'd for $C_{18}H_{15}N_3O_7S$: C, 51.77; H, 3.6; N, 10.07; S, 7.69.
Found: C, 51.71; H, 3.6; N, 10.19; S, 7.56.

(b) When double this volume of pyridine (*i.e.* 352 cc.) was employed, and the solution was kept at 0° during 2 hours, the product was the desired ester (9.2 g.). On recrystallization from boiling absolute methanol (1 g. in 20 cc.) it was obtained as colorless needles having m.p. 121–122°. The literature gives (19) m.p. 121°, and (26) m.p. 124°.

Anal. Calc'd for $C_{13}H_{10}N_2O_7S$: C, 46.13; H, 3.0; N, 8.29; S, 9.5.
Found: C, 46.02; H, 3.3; N, 8.26; S, 9.0

(c) The experiment was performed as in (b) but, 15 minutes after crystallization of pyridine hydrochloride commenced, the reaction was halted by pouring the mixture into 1 liter of 5 *N* sulfuric acid (precooled to −5°). The ester crystallized immediately; it was filtered off, washed with water, and dried; yield, 32 g.; m.p. 122°.

Recrystallization of p-toluenesulfonyl esters. Each ester (10 g.) was dissolved in the stated volume of solvent, the solution cooled and kept overnight in the refrigerator.

Phenoxyethyl. 200 cc. of boiling dry ether.

Diethyl carbinyl. 20 cc. of cold, dry ether followed by addition of 250 cc. of pentane.

Bornyl. 20 cc. of warm absolute ethanol. It then had m.p. 68–69°.

SUMMARY

A simple method is described for the preparation, in high yield, of esters of *p*-toluenesulfonic acid by the familiar procedure of treatment of the alcohol or phenol with *p*-toluenesulfonyl chloride in pyridine. In the examples studied by this method, chlorination does not take place and formation of pyridinium salt is usually negligible.

If there is a pronounced tendency for the formation of the pyridinium salt, arrest of the reaction by acidification permits isolation of the desired ester.

Methoxyethyl, ethoxyethyl, and *n*-propoxyethyl *p*-toluenesulfonates have been crystallized for the first time; apocupreine gives a monotosyl ester only.

PITTSBURGH, PA.

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