Notes

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Reaction of Thio Acid *S*-Esters with *p*-Toluenesulfonic Acid: A Facile Synthesis of *p*-Toluenethiosulfonic *S*-Esters

YASUSHI ARAKAWA,* NAOTO UEYAMA, and YOSHIHIRO NITTA

School of Pharmacy, Hokuriku University, Kanagawa-machi, Kanazawa 920–11, Japan

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Treatment of dehydrated *p*-toluenesulfonic acid (TsOH) with thio acid *S*-esters such as carbothioic acid and phosphorus thio acid *S*-esters in refluxing solvent resulted in the formation of *p*-toluenethiosulfonic *S*-esters (TsSR). The reaction of trialkyl phosphorotrithioites with TsOH provided the corresponding TsSR in relatively good yields. This constitutes a new and facile method for the preparation of unsymmetrical thiosulfonic *S*-esters.

Keywords——*p*-toluenesulfonic acid; trialkyl phosphorotrithioite; trialkyl phosphorotrithiolate; carbothioic acid *S*-ester; *p*-toluenethiosulfonic *S*-ester; dialkyl disulfide

We have recently reported that the reactions of dehydrated *p*-toluenesulfonic acid (TsOH) with carboxylic acid esters[1] and phosphorus oxyacid esters[2] afforded the corresponding *p*-toluenesulfonates (TsOR) in good to excellent yields. In order to extend futher the synthetic utility of TsOH, we next decided to examine the reaction of thio acid *S*-esters such as carbothioic acid and phosphorus thio acid esters. We have now found that these reactions provide a facile access to *p*-toluenethiosulfonic *S*-esters (TsSR), which are useful and important materials. In particular, the reaction of trialkyl phosphorotrithioites ($P(SR)_3$) with TsOH provided the corresponding TsSR in relatively good yields.

The unsymmetrical thiosulfonic *S*-esters (RSO_2SR') are very useful and versatile reagents for synthetic purposes,[3] as well as exhibiting antimicrobial,[4] antituberculostatic,[5] and carcinostatic[6] activities. A wide variety of methods for the preparation of unsymmetrical thiosulfonic *S*-esters have so far been developed. In general, these compounds are prepared by the treatment of thiols with sulfonyl chlorides in the presence of a base such as pyridine or potassium hydroxide,[7] of silver thiolates with sulfonyl halides,[8] of thionitrites with sulfinic acids,[9] of dialkyl disulfides with sulfinic acids,[10] of sulfenyl chlorides with sulfinic acids,[11] of thiosulfinic *S*-esters with $NaIO_4$,[12] or of alkyl halides with the sodium salt of arenethiosulfonates.[13] Although the simplest method involves the reaction of potassium thiolates with sulfonyl chlorides, in this reaction the thiosulfonic *S*-esters produced further react with potassium thiolates to give the disulfides and potassium sulfinates as follows;

$$RSO_2SR' + R'SK \longrightarrow RSO_2K + R'SSR'$$ [14]

Accordingly, the yields of the desired products are poor. In the present paper, we wish to report a new and facile synthetic method for unsymmetrical thiosulfonic *S*-esters.

We examined the reaction of $P(SR)_3$ with TsOH. The reactions were carried out in the same manner as reported previously[2] for the reaction of trialkyl phosphorus oxyacid esters with dehydrated TsOH. As shown in Table I, when $P(SR)_3$ were treated with 3 mol eq of TsOH in dry benzene, TsSR were obtained in moderate yields along with dialkyl disulfides

and complicated compounds. As we confirmed the formation of alkanethiols qualitatively, dialkyl disulfides are presumably produced *via* the reaction of thiolsulfonates with the thiols generated *in situ*: this reaction has been used as a synthetic route to dialkyl disulfides.[11b,15] Careful examination of the reaction mixture by gas chromatography (GC) failed to detect TsOR. The reaction of $P(SR)_3$ with TsOH is markedly different from that of trialkyl phosphites ($P(OR)_3$) with TsOH. The treatment using 2 mol eq of TsOH gave similar results, while the use of 1 mol eq of TsOH resulted in the recovery of the starting materials. These results suggest that 2 mol eq of TsOH is necessary to give TsSR. Thus, the yields in tables were calculated based on the hypothetical formation of 2 mol eq of TsSR from $P(SR)_3$, although the mechanism of formation of TsSR is not yet clear. The reaction at 50 °C yielded no TsSR.

On the other hand, the reaction of trialkyl phosphorotrithiolates ($OP(SR)_3$) with TsOH gave TsSR in low yields, as shown in Table II. The reactions of carbothioic acid *S*-esters (RCOSR′) were much less favorable, achieving only poor yields, such as 10% for *S*-ethyl thioacetate and 12% for *S*-ethylthiopivalate, respectively. These results were consistent with those on the reactivities of acid esters toward TsOH.[1,2]

All the TsSR were identified by comparison of their spectral data [proton nuclear magnetic resonance (^{1}H-NMR), infrared (IR), and mass spectra (MS)] with those of authentic samples prepared by a known procedure.[7]

In the reaction of $P(OR)_3$ with TsOH, quasi-phosphonium salts similar to intermediates in the Arbuzov reaction are formed by protonation at the phosphorus atom and subsequently undergo nucleophilic attack on the alkyl group by *p*-toluenesulfonate ion, giving rapidly the preferred pentacovalent dialkyl phosphonates and TsOR.[2] The reaction mechanisms must be different between *O*-esters and *S*-esters. It was reported by Divinskii *et al.*[16] in 1948 that $P(SR)_3$ do not undergo the Arbuzov reaction either with alkyl halides or acyl halides. Recently, the reaction of $P(SEt)_3$ with acids such as hydrogen chloride and benzoic acid has been reported by Ofitserov *et al.*[17] as follows:

$$P(SEt)_3 \xrightarrow{HCl} ClP(SEt)_2 + EtSH$$

$$P(SEt)_3 \xrightarrow{PhCOOH} PhCOSEt + EtSH + HPO_2$$

These results may be attributed to the difference between the bond energy of P=O and that of P=S: it is well known that the P=O bond formation is the chemical driving force for the

TABLE I. The Reaction of Trialkyl Phosphorotrithioites with *p*-Toluenesulfonic Acid

$$TsOH \xrightarrow[\text{benzene}]{P(SR)_3} TsSR$$

R	Molar ratio (TsOH : ester)	Reaction conditions Temperature	Time (h)	TsSR Yield (%)
C_2H_5	3 : 1	Reflux	15	54[a]
	2 : 1	Reflux	15	51[b]
	1 : 1	Reflux	15	—[c]
	3 : 1	50 °C	20	—
n-C_3H_7	3 : 1	Reflux	15	38[d]
	2 : 1	Reflux	15	37
n-C_4H_9	3 : 1	Reflux	15	44
sec-C_4H_9	3 : 1	Reflux	15	26
n-$C_{12}H_{25}$	3 : 1	Reflux	15	42

a) Diethyl disulfide [bp 68—71 °C (85 mmHg)] was obtained in 40% yield. *b*) Diethyl disulfide was obtained in 31% yield. *c*) Starting material was recovered. *d*) Di-*n*-propyl disulfide [bp 38—40 °C (3 mmHg)] was obtained in 32% yield.

TABLE II. The Reaction of Trialkyl Phosphorotrithiolates with *p*-Toluenesulfonic Acid

$$TsOH \xrightarrow[\text{benzene, reflux}]{O=P(SR)_3} TsSR$$

R	Molar ratio (TsOH : ester)	Time (h)	TsSR Yield (%)
C_2H_5	3 : 1	15	33
n-C_4H_9	3 : 1	15	21
sec-C_4H_9	3 : 1	15	12

Arbuzov reaction[18] as well as that for the Witting reaction.[18,19]

A study on the mechanism of the reaction of $P(SR)_3$ with TsOH is in progress.

In conclusion, the ready availability of the starting materials and the simple experimental operations make the present process a convenient route for the synthesis of thiosulfonic *S*-esters.

Experimental

^{1}H-NMR spectra were recorded in chloroform-*d* solution on a JEOL-JNH-MH-100 spectrometer with tetramethylsilane as an internal standard. IR spectra were obtained on a JASCO IR-2 spectrophotometer. MS measurements were run on a JEOL JMS-D100 instrument. GC was carried out on a Shimadzu GC-8A apparatus.

$P(SR)_3$,[20] $O=P(SR)_3$,[20,21] R'COSR,[22] were prepared according to the cited procedures.

General Procedure for the Reaction of $P(SR)_3$ with TsOH——Commercial $TsOH \cdot H_2O$ (42 mmol) was heated at 120 °C (4 mmHg) for 3 h to give a dehydrated TsOH. The dehydrated TsOH was added to a solution of the appropriate *S*-ester (14 mmol) in dry benzene (20 ml). The mixture was stirred under the conditions (time and temperature) indicated in the tables. Ice water was added to the reaction mixture after cooling. The whole was extracted with benzene. The benzene layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to remove solvent. The resulting oil was distilled under reduced pressure to give TsSR and RSSR.

S-Ethyl *p*-toluenethiosulfonate was obtained as a pale yellow oil, bp 84—88 °C (2 mmHg) [lit.[12a] 130—131 °C (1 mmHg), lit.[12c] 156—158 °C (0.03 mmHg)]. This fraction was purified by column chromatography (silica gel, benzene). IR ν_{max}^{neat} cm^{-1}: 1302 (SO_2), 1118 (SO_2). NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, CH_3), 2.34 (3H, s, Ar-CH_3), 2.80 (2H, q, J=7Hz, S-CH_2), 7.15 (2H, d, J=8 Hz, aromatic H), 7.46 (2H, d, J=8 Hz, aromatic H). MS *m/z*: 216 (M^+).

S-*n*-Propyl *p*-toluenethiosulfonate was obtained as a pale yellow oil, bp 109—112 °C (2 mmHg) [lit.[12d] bp 145 °C (0.1 mmHg)]. This fraction was purified by column chromatography (silica gel, beznene). IR ν_{max}^{neat} cm^{-1}: 1290 (SO_2), 1120 (SO_2). NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, CH_3), 1.5—2.0 (2H, m, CH_2CH_3), 2.34 (3H, s, Ar-CH_3), 2.71 (2H, t, J=7 Hz, S-CH_2), 7.13 (2H, d, J=8 Hz, aromatic H), 7.45 (2H, d, J=8 Hz, aromatic H). MS *m/z*: 230 (M^+).

S-*n*-Butyl *p*-toluenethiosulfonate was obtained as a pale yellow oil, bp 129—131 °C (3 mmHg) [lit.[12d] bp 145 °C(0.1 mmHg)]. This fraction was purified by column chromatography (silica gel, benzene). IR ν_{max}^{neat} cm^{-1}: 1310 (SO_2), 1120 (SO_2). NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7 Hz, CH_3), 1.1—1.9 (4H, m, $CH_2CH_2CH_3$), 2.34 (3H, s, Ar-CH_3), 2.73 (2H, t, J=7 Hz, S-CH_2), 7.13 (2H, d, J=8 Hz, aromatic H), 7.46 (2H, d, J=8 Hz, aromatic H). MS *m/z*: 244(M^+).

S-*sec*-Butyl *p*-toluenethiosulfonate was obtained as a pale yellow oil, bp 101—103 °C (1 mmHg). This fraction was purified by column chromatography (silica gel, benzene). IR ν_{max}^{neat} cm^{-1}: 1290 (SO_2), 1120 (SO_2). NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, CH_3CH_2), 1.27 (3H, d, J=7 Hz, CH_3CH), 1.4—1.9 (2H, m, CH_2), 2.34 (3H, s, Ar-CH_3), 2.74 (1H, m, S-CH), 7.11 (2H, d, J=8 Hz, aromatic H), 7.46 (2H, d, J=8 Hz, aromatic H). MS *m/z*: 244 (M^+).

S-*n*-Lauryl *p*-toluenethiosulfonate was obtained as a pale yellow oil. This oil was purified by column chromatography (silica gel, benzene). IR ν_{max}^{neat} cm^{-1}: 1310 (SO_2), 1120 (SO_2). NMR ($CDCl_3$) δ: 0.6—1.0 (3H, br, CH_3), 1.24 (20 H, m, $C_{10}H_{20}$), 2.33 (3H, s, Ar-CH_3), 2.75 (2H, t, J=7 Hz, S-CH_2), 7.13 (2H, d, J=8 Hz, aromatic H), 7.45 (2H, d, J=8 Hz, aromatic H). MS *m/z*: 356 (M^+).

Diethyl, di-*n*-propyl, and di-*sec*-butyl disulfides obtained were identified by comparing their IR and NMR spectra with those of commercially available authentic samples.

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