Extremely Mild and Selective Method for Hydrolysis of Tosyl Esters by Photo-Sensitized Single Electron Transfer Reactions

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Tosyl esters were hydrolyzed by irradiation with ultraviolet light (>330 nm) under photo-sensitized conditions. 1,5-Dimethoxynaphthalene and (4,8-dimethoxynaphthyl)propionic acid were effective for the transformation in aqueous acetonitrile in the presence of hydrazine. The reaction was successfully applied to the hydrolysis of tosylates of sugars and nucleosides.

Keywords tosyl ester; hydrolysis; UV irradiation; photo-sensitization; electron-rich aromatic compound; single electron transfer; sugar; nucleoside

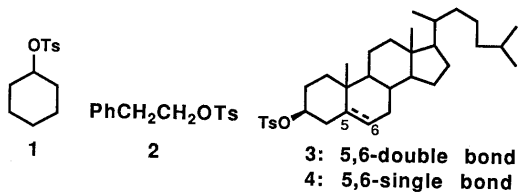
Photo-hydrolysis of tosyl esters in the presence of sodium hydroxide in methanol was reported about 20 years ago.[1] However, strongly basic conditions required meant that this reaction was not useful for deprotection of the tosyl group. Therefore the tosyl group was employed as a protecting group for hydroxy functions only in limited cases. Recently, Masnovi *et al.* reported that the mechanism of the reaction involves an electron transfer (ET) process from the base to the photo-excited tosyl group in the first stage of the reaction.[2] Employment of tertiary amines [triethylamine or 1,4-diazabicyclo[2.2.2]octane [DABCO)] instead of sodium hydroxide as an electron donor permitted the selective removal of tosyl groups in the presence of benzyl and benzoyl groups under the carefully controlled conditions.[3] However, irradiation at 254 nm could cause some side reactions when the substrate contains chromophores,[4] such as nucleic acid bases.[5] Thus employment of photo-sensitized ET reactions would be desirable for these transformations, although some sensitizers, such as triphenylamine, phenothiazine, 9,10-dimethoxyanthracene, and *p*-dimethoxybenzene, were reported to be ineffective.[2]

In a study of the photo-hydrolysis of tosyl amides,[6] we found that polymethoxyaromatic compounds, such as *p*-dimethoxybenzene and 1,5-dimethoxynaphthalene (DMN), were good ET sensitizers, and we next applied this chemistry to the photo-hydrolysis of tosyl esters.[7] We present here a full account of our study on the photo-sensitized hydrolysis of tosyl esters.

***ΔG* Calculation and Fluorescence Quenching Experiments** The free energy change (ΔG) in the ET process from the singlet excited state of DMN to methyl tosylate was calculated by use of the Weller equation[8] to be -14.5 kcal/mol[9] in ethanol. This value is more negative than that for *N*-tosyl-*N*-methylphenethylamine (-5.79 kcal/mol).[6b] Fluorescence quenching experiments of DMN by methyl tosylate also showed the efficiency of the ET process between DMN and the tosylate. The k_q value of 3.5×10^9, which was calculated from $k_q\tau$ ($43.8\ M^{-1}$, obtained from the linear Stern–Volmer plot) and τ for DMN (12.6 ns), is close to the diffusion controlled rate and five times the rate of quenching by a tosylamide (MeNHTs).[6b] These results suggested that the photo-sensitized reaction could be applicable to hydrolysis of tosyl esters.

Photo-Reactions First, we carried out the photo-hydrolysis of tosylates under the conditions which were successful in the reaction of tosylamides.[6] Tosylates of cyclohexanol **1** and 2-phenethyl alcohol **2** were irradiated with a 300-W high-pressure mercury lamp through a Pyrex filter using (4,8-dimethoxynaphthyl)propionic acid (DMNP),[6] which is soluble in aqueous solvents, as an electron donor in the presence of $NaBH_4$ and the corresponding alcohols were obtained in good yields (Table I, entries 1 and 2). Because tosylates of cholesterol **3** and cholestanol **4** were insoluble in aqueous ethanol, a different solvent system, waster–*N*,*N*-dimethylformamide (DMF)–ether, was employed for their reactions. While the reaction in the presence of $NaBH_4$ afforded the corresponding alcohols in good yields in this solvent system (entries 3 and 4), ascorbic acid, which was an efficient co-reductant in the reaction of tosylamides,[6] was less effective (entry 5).[10]

Although the photo-reaction in aqueous ethanol and aqueous DMF–ether solvents gave the alcohols in good to excellent yields, a longer irradiation time was usually required than in the case of tosylamides.[11] Therefore we



1 2 3: 5,6-double bond 4: 5,6-single bond

direct photolysis

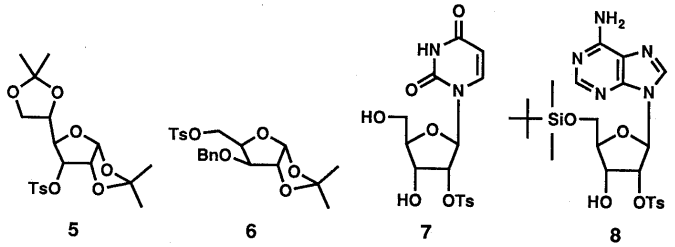
$$\text{Ts-OR} \xrightarrow[254\,\text{nm}]{h\nu} \text{Ts*-OR} \xrightarrow{D} \text{HOR}$$

photo-sensitized photolysis

$$D \xrightarrow[>300\,\text{nm}]{h\nu} D^* \xrightarrow{\text{Ts-OH}} \text{HOR}$$

D = electron donors

Chart 1



5 6 7 8

Chart 2

TABLE I. Photo-Sensitized Hydrolysis of Tosyl Esters

Entry	Substrate (mM)	Solvent[a]	Donor[b] (mM)	Additive (mM)	Time (h)	Yield[c] (%)
1	**1** (10)	A	DMNP (10)	$NaBH_4$ (100)	7.0	85[d,e]
2	**2** (10)	A	DMNP (10)	$NaBH_4$ (50)	7.0	90[d,e]
3	**3** (2.0)	B	DMNP (2)	$NaBH_4$ (12)	6.0	86[f]
4	**4** (2.0)	B	DMNP (2)	$NaBH_4$ (10)	6.0	77[f]
5	**4** (2.0)	C	DMNP (2)	Ascorbic acid (20)	29	58[f]
6	**4** (4.6)	D	DMN (4.6)	$NaBH_4$ (10)	5.4	97[f]
7	**4** (4.6)	D	DMN (4.6)	iso-PrOH (457)	5.4	78[f]
8	**4** (4.6)	D	DMN (4.6)	MeOH (457)	5.4	67[f]
9	**4** (1.4)	E	DMNP (1.2)	Hydrazine hydrate (31)	1.5	93[e]
10	**5** (2.0)	F	DMNP (2.0)	Hydrazine hydrate (31)	2.0	65[e,g]
11	**6** (1.8)	F	DMNP (2.7)	Hydrazine hydrate (50)	2.6	68[e]
12	**6** (3.0)	G	DABCO (6.6)	None	1.8	59[h]
13	**7** (2.3)	F	DMNP (2.7)	Hydrazine hydrate (90)	1.6	76[e]
14	**7** (3.9)	G	DABCO (6.6)	None	2.0	—[h,i]
15	**8** (1.1)	F	DMNP (2.2)	Hydrazine hydrate (90)	2.0	84[e]
16	**8** (2.4)	G	DABCO (4.1)	None	4.0	—[h,j]

a) A, 70% ethanol; B, water–ether–DMF = 1 : 2 : 7; C, water–ether–DMF = 1 : 1 : 8; D, CH_3CN; E, 97% CH_3CN; F, 90% CH_3CN; G, MeOH. *b*) DMNP = (4,8-dimethoxynaphthyl)propionic acid, DMN = 1,5-dimethoxynaphthalene, DABCO = 1,4-diazabicyclo[2.2.2]octane. *c*) Isolated yield. *d*) Determined by GLC. *e*) A 500-W high-pressure mercury lamp with a Pyrex filter. *f*) A 300-W high-pressure mercury lamp with a Pyrex filter. *g*) Detosylation of **5** under the direct irradiation conditions was reported to proceed in 95% yield (ref. 2). *h*) A 60-W low-pressure mercury lamp (254 nm). *i*) Complex mixture. *j*) No desired product.

next investigated acceleration of this reaction and found that using acetonitrile as the solvent improved the reaction. When **4** was irradiated in acetonitrile in the presence of DMN, the alcohol was obtained in 97% yield (entry 6); however, because of the formation of precipitates due to $NaBH_4$, the reaction was still slow. Among additives investigated, the best result was obtained when the reaction was carried out in the presence of hydrazine hydrate and **4** was detosylated within 1.5 h, affording cholestanol in 93% yield (entry 9).

Detosylation of sugar and nucleoside derivatives was next carried out and the results were compared to the detosylation by direct irradiation of the tosyl group in the presence of DABCO.[2] The reaction of **5**, which has a hindered tosyloxy group, and **6** occurred smoothly and the results were comparable to those obtained by the direct irradiation of the tosyl group. The advantage of these photo-sensitized conditions was clearly shown in the detosylation of 2′-*O*-tosylnucleosides. Thus, while the reaction under direct irradiation conditions afforded none of the desired product (entries 14 and 16), detosylation of **7** and **8** under photosensitized conditions occurred without any problem (entries 13 and 15).

In conclusion, a mild photo-sensitized detosylation method was established and successfully applied to the hydrolysis of tosylated sugar and nucleoside derivatives.

Experimental

General Procedure Photo-sensitized reactions were conducted with a water-cooled Eikosha (Osaka) 500-W or a 300-W high-pressure mercury lamp equipped with a Pyrex filter. An Eikosha 60-W low-pressure mercury lamp was employed for direct irradiation reactions. Fluorescence measurements were taken by using a Hitachi MPF-1A spectrofluorometer. Spectrograde ethanol, methanol, and acetonitrile were used as solvents for photo-reactions. All photochemical reaction mixtures were bubbled with argon for 30 min prior to photo-reaction and the bubbling was continued during the irradiation. Gas liquid chromatography (GLC) analysis was conducted using a Shimadzu GC-4APFE spectrometer (PEGS, 1 m column). Nuclear magnetic resonance (NMR) spectra were recorded using a JEOL JNM FX-100 for solutions in $CDCl_3$ using tetramethylsilane as an internal standard.

Substrates Tosylates (**1**—**7**) were prepared by the standard procedure from the corresponding alcohols.

Cyclohexyl *p*-Toluenesulfonate (**1**): mp 44—46 °C (lit.[12] 45—46 °C).

2-Phenylethyl *p*-Toluenesulfonate (**2**): mp 39—41 °C (lit.[13] 35.5—36.6 °C).

Cholesteryl *p*-Toluenesulfonate (**3**): mp 129—129.5 °C (lit.[13] 132.5—133 °C).

5α-Cholestan-3β-yl *p*-Toluenesulfonate (**4**): mp 138—139 °C (lit.[14] 133—135 °C).

1,2 : 5,6-Di-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-α-D-allofuranose (**5**): mp 127—128 °C (lit.[15] 121 °C).

3-*O*-Benzyl-1,2-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (**6**): Oil.[16]

2′-*O*-Tosyluridine (**7**): mp 170—171 °C (lit.[17] 175—177 °C).

5′-*O*-*tert*-Butyldimethylsilyl-2′-*O*-tosyladenosine (8) A mixture of 2′-*O*-tosyladenosine[18] (210 mg, 0.50 mmol), *tert*-butyldimethylchlorosilane (119 mg, 0.75 mmol), imidazole (136 mg, 2.00 mmol), and DMF (1 ml) was stirred at room temperature for 3.7 h, then diluted with 30 ml of ethyl

acetate, and the solution was washed with water and brine successively. After evaporation of the dried solvent, the residue was purified by silica gel column chromatography (eluting with *n*-hexane–ethyl acetate, 1 : 1) to afford 173 mg (61%) of **8**, mp 125—128.5 °C. ^{1}H-NMR δ: 8.30 (s, 1H), 8.07 (s, 1H), 5.95 (d, 1H, J=6 Hz), 5.67 (br, 2H), 4.55—4.39 (m, 3H), 3.83 (d, 1H, J=2.5 Hz), 0.75 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H). *Anal.* Calcd for $C_{16}H_{27}N_5O_4Si$: C, 51.57; H, 6.21; N, 13.07. Found: C, 51.35; H, 6.14; N, 13.23.

Fluorescence Quenching The $kq\tau$ value was obtained from a linear Stern-Volmer plot of the fluorescence intensity at the maximum wavelength of DMN (emission maximum = 342 nm, excitation maximum = 324) *vs.* the amount of methyl tosylate (0, 0.025, 0.05, 0.10, 0.15, and 0.20 M in ethanol). The correlation coefficient from the least-square analysis was 0.999.

Photo-Reaction of Cyclohexyl Tosylate (1) A solution of the tosylate **1** (25 mg, 0.1 mmol), DMNP (26 mg, 0.1 mmol), and $NaBH_4$ (38 mg, 1 mmol) in 70% ethanol (10 ml) was irradiated with a 500-W high-pressure mercury lamp through a Pyrex filter for 7 h. The product was analyzed by GLC using iodobenzene as an internal standard, and the result is shown in Table I (entry 1).

Photo-Reaction of 2-Phenylethyl Tosylate (2) A solution of the tosylate **2** (27.6 mg, 0.1 mmol), DMNP (26 mg, 0.1 mmol), and $NaBH_4$ (19 mg, 0.5 mmol) in 70% ethanol was irradiated with a 500-W high-pressure mercury lamp through a Pyrex filter for 7 h. The product was analyzed by GLC using naphthalene as an internal standard and the result is shown in Table I (entry 2).

Photo-Reaction of Cholesteryl Tosylate (3) A solution of the tosylate **3** (162 mg, 0.3 mmol), DMNP (78 mg, 0.3 mmol) and $NaBH_4$ (34 mg, 0.9 mmol) in a mixture of Water–ether–DMF (1 : 2 : 7, 150 ml) was irradiated with a 300-W high-pressure mercury lamp through a Pyrex filter for 6 h. The reaction mixture was diluted with ether, and the solution was washed with 2 N HCl, saturated $NaHCO_3$ solution, and brine successively. Evaporation of the dried solvent afforded a crude product, which was purified by silica gel column chromatography (CH_2Cl_2), affording 100 mg (86%) of cholesterol (entry 3).

Photo-Reaction of 5α-Cholestan-3β-yl *p*-Toluenesulfonate (4) in the Presence of Hydrazine Hydrate in Acetonitrile (Table I, entry 9); A mixture of the tosylate **4** (108 mg, 0.20 mmol), DMNP (62 mg, 0.24 mmol), and hydrazine hydrate (0.3 ml, 6.18 mmol) in 97% acetonitrile (140 ml) was irradiated with a 500-W high-pressure mercury lamp through a Pyrex filter for 1.5 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate, and the solution was washed with saturated $NaHCO_3$ solution followed by brine. Evaporation of the dried solvent gave a crude product which was purified by silica gel column chromatography (*n*-hexane–ethyl acetate, 1 : 6), affording cholestanol 72 mg (93%).

Photo-Reaction of 1,2 : 5,6-di-*O*-Isopropylidene-3-*O*-(*p*-toluenesulfonyl)-α-D-allofuranose (5) (Table I, entry 10); A solution of the tosylate **5** (82 mg, 0.20 mmol), DMNP (62 mg, 0.24 mol), and hydrazine hydrate (0.3 ml, 6.19 mmol) in 90% acetonitrile (100 ml) was irradiated at room temperature for 2 h using a 500-W high-pressure mercury lamp through a Pyrex filter. The mixture was concentrated *in vacuo*, and the residue was dissolved in saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to give a residue, which was purified by silica gel column chromatography (*n*-hexane–ethyl acetate, 1 : 1) to afford 1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose,[19] 33.4 mg (65%).

Photo-Reaction of 3-*O*-Benzyl-1,2-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (6) under Photo-Sensitized Conditions (Table I, entry 11); A mixture of the tosylate **6** (108 mg, 0.25 mmol), DMNP (97 mg, 0.37 mmol), and hydrazine hydrate (0.6 ml, 12.4 mmol) in 90% acetonitrile was irradiated at room temperature for 2.6 h with a 500-W high-pressure mercury lamp through a Pyrex filter. The mixture was concentrated *in vacuo*, and the residue was partitioned between ether and water. The separated aqueous layer was extracted with ether and the combined organic layers were washed with saturated $NaHCO_3$ solution followed by brine, dried and evaporated to afford a residue, which was purified by silica gel column chromatography (*n*-hexane–ethyl acetate, 1 : 1) to afford 53 mg (68%) of 3-*O*-benzyl-1,2-isopropylidene-α-D-xylofuranose.[16]

Photo-Reaction of 3-*O*-Benzyl-1,2-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (6) under the Direct Irradiation Conditions (Table I, entry 12); A mixture of the tosylate **6** (52 mg, 0.12 mmol) and DABCO (30 mg, 0.27 mmol) in MeOH(40 ml) was irradiated at room temperature for 1.8 h using a 60-W low-pressure mercury lamp. After evaporation of methanol, the crude product was purified by silica gel column chromatography (*n*-hexane–ethyl acetate, 3 : 1—1 : 1) to afford 22 mg (59%) of 3-*O*-benzyl-1,2-isopropylidene-α-D-xylofuranose.[16]

Photo-Reaction of 2′-*O*-Tosyluridine (7) under Photo-Sensitized Conditions (Table I, entry 13); A mixture of the tosylate **7** (128 mg, 0.32 mmol), DMNP (97 mg, 0.37 mmol) and hydrazine hydrate (0.6 ml, 12.4 mmol) in 90% acetonitrile (140 ml) was irradiated at room temperature for 1.6 h with a 500-W high-pressure mercury lamp through a Pyrex filter. After evaporation of the solvent, the crude product was purified by silica gel column chromatography (ethyl acetate, and then ethyl acetate–MeOH, 10 : 1) to afford 60 mg (76%) of uridine.

Photo-Reaction of 2′-*O*-Tosyluridine (7) under Direct Irradiation Conditions (Table I, entry 14); A solution of the tosylate **7** (50 mg, 0.13 mmol) and DABCO (24 mg, 0.21 mmol) in 32 ml of methanol was irradiated at room temperature for 2 h using a 60-W low-pressure mercury lamp. The desired product was not detected on thin layer chromatography.

Photo-Reaction of 5′-*O*-*tert*-Butyldimethylsilyl-2′-*O*-tosyladenosine (8) under Photo-Sensitized Conditions (Table I, entry 15); A mixture of the tosylate **8** (92 mg, 0.16 mmol), DMNP (82 mg, 0.31 mmol) and hydrazine hydrate (0.3 ml, 6.18 mmol) in 90% acetonitrile (140 ml) was irradiated at room temperature for 2 h with a 500-W high-pressure mercury lamp through a Pyrex filter. After evaporation of the solvent, the crude product was purified by silica gel column chromatography (ethyl acetate) to afford 56 mg (84%) of 5′-*O*-*tert*-butyldimethylsilyladenosine.[20]

Photo-Reaction of 5′-*O*-*tert*-Butyldimethylsilyl-2′-*O*-tosyladenosine (8) under Direct Irradiation Conditions (Table I, entry 16); A mixture of the tosylate **8** (43 mg, 0.08 mol) and DABCO (15 mg, 0.13 mmol) in methanol (32 ml) was irradiated at room temperature for 4 h using a 60-W low-pressure mercury lamp. The reaction was not completed after this irradiation time and the desired product was not detected on TLC, though 37% of **8** was recovered from the complex reaction mixture.

References and Notes

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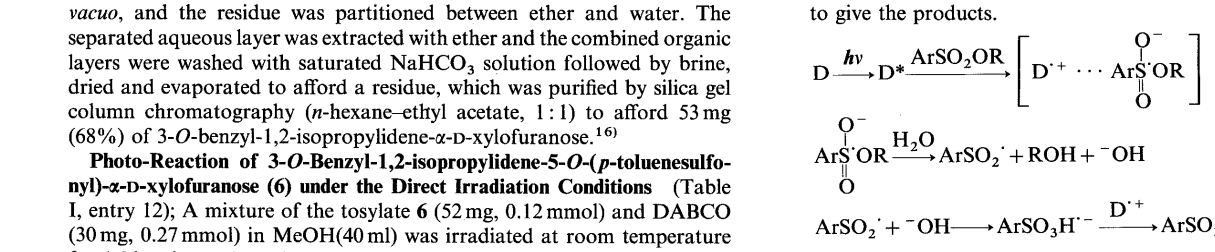
9) $E(D/D^+)$ of DMN = 1.28 V,[21] $E(A/A^+)$ of TsOMe = −1.98 V,[22] E_{O-O} of DMN = 87.8 kcal/mol.[6b]
10) The presence of the co-reductant in the reaction mixture was necessary for a clean reaction. See ref. 6.
11) Kinetic studies also showed the inefficiency of this reaction in aqueous ethanol. The quantum yield of methyl tosylate (20 mM) in the presence of DMN (10 mM) and ammonia borane (co-reductant, 10 mM) in 95% ethanol was measured to be ϕ = 0.003 (extrapolated to infinite concentration of methyl tosylate $\phi_{lim.}$ = 0.26). This value is considerably smaller than that of methyl tosylamide ($\phi_{lim.}$ = 0.83). This low efficiency can be explained by considering the electron back donation from the radical ion pair, as shown in the scheme below. The observed large solvent effect (see text) may be a consequence of dissociation of the ion pair to the solvated ions which would collapse to give the products.



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