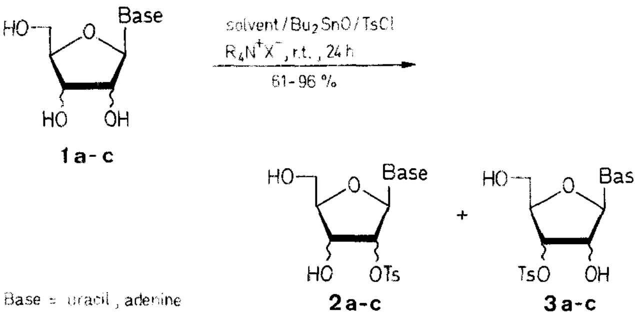
Regioselective *O*-*p*-Toluenesulfonylation of Nucleosides Under Solid/Liquid Phase-Transfer Conditions

Annie Grouiller,* Hassan Essadiq, Boubker Najib, Patrick Molière

Laboratoire de Chimie biologique, Institut National des Sciences Appliquées de Lyon, Bâtiment 406, F-69621 Villeurbanne, France

The regioselective mono-*O*-*p*-toluenesulfonylation of nucleosides under phase-transfer conditions in which dibutyltin oxide acts as a base is reported. The selectivity is dependent upon both the solvent and ammonium quaternary salt.

The *O*-*p*-toluenesulfonyl (*O*-tosyl) derivatives of nucleosides constitute an important class of intermediates in nucleic acid chemistry, specially in the preparation of anhydronucleosides.[1] Recently, we employed the 2′-*O*- and 3′-*O*-tosyl derivatives of uridine in the synthesis of branched-chain deoxysugar nucleosides[2,3] 2′-*O*-Tosyluridine and adenosine are generally prepared *via* the 2′,3′-*O*-dibutylstannylene derivatives of these nucleosides, according to Moffatt's procedure.[4] The synthesis of the corresponding 3′-*O*-tosyl compounds necessitates prior protection of both 2′- and 5′-hydroxyls to avoid the substantial formation of polysulfonylated derivatives.[5,6] Regioselective *p*-toluenesulfonylation of carbohydrates employing phase-transfer catalysis has been reported in the literature.[7,8] We now report a development of this method for the *p*-toluenesulfonylation of uracil and adenine nucleosides, which involves the replacement of the usual catalytic liquid-liquid two-phase system with a solid-liquid variant in which dibutyltin oxide acts as a base. We therefore describe a very easy and efficient procedure for nucleoside monotosylation.



Base = uracil, adenine

As can be seen from the Tables 1 and 2, the selectivity of this method is dependent upon two factors: (i) the organic solvent used in the reaction; and (ii) the nature of either the anion or cation of the quaternary ammonium salt

Table 1. Influence of Quaternary Ammonium Salt and Solvent on the Ratio of the 2′-*O*- to 3′-*O*-Tosyluridine Formed[a]

Solvent	Phase-Transfer Catalyst $R_4N^+X^-$	Ratio of 2′-*O*-Tosyl to 3′-*O*-Tosyl Uridine, **2a** : **3a** (yield)[b]
Acetonitrile	$(n\text{-}C_4H_9)_4N^+F^-$	100 : 0 (68)
Dichloromethane	$(n\text{-}C_4H_9)_4N^+F^-$	80 : 20 (61)
Xylene	$(n\text{-}C_4H_9)_4N^+F^-$	90 : 10 (62)
Toluene	$(n\text{-}C_4H_9)_4N^+F^-$	83 : 17 (64)
Benzene	$(n\text{-}C_4H_9)_4N^+F^-$	31 : 69 (65)
Benzene	$(n\text{-}C_4H_9)_4N^+Br^-$	63 : 37[c] (67)
Benzene	$(n\text{-}C_5H_{11})_4N^+Br^-$	49 : 51 (62)
Benzene	$(n\text{-}C_6H_{13})_4N^+Br^-$	45 : 55[d] (61)
Benzene	$(n\text{-}C_6H_{13})_4N^+Cl^-$	25 : 75 (61)
Acetonitrile	$(n\text{-}C_6H_{13})_4N^+Cl^-$	100 : 0 (61)

[a] The two 2′-*O* and 3′-*O*-tosylates are distinguished by TLC on RP8 plates (eluant CH_3CN/H_2O, 1 : 1), and their ratio is determined from ^1H-NMR spectrometry (80 MHz BRUKER spectrometer).

[b] Yield (%) of isolated, mixture of isomers.

[c] The same ratio is obtained when Br^- is replaced by I^- or N_3^-.

[d] Same ratio with $(n\text{-}C_{12}H_{25})_4N^+Br^-$ or Aliquat 336 $[CH_3(C_8H_{17})_3N^+Cl^-]$.

The same reaction conditions were also applied to the tosylation of 5′-*O*-trityluridine, but no selectivity was found, since both 2′- and 3′-*O*-tosyl-5′-*O*-trityluridine are formed in the ratio 3 : 2 with an overall product yield of 84%. A similar result was obtained with N^3-benzyluridine. It is noteworthy that the commonly performed tosylation of 5′-*O*-trityluridine in pyridine affords an important amount of the di-2′,3′-*O*-tosyl derivative (27%) besides the mono-2′-*O*-tosyl product (41%).[2]

Table 2. Percentages of 2′-*O*- and 3′-*O*-Tosylates of Lyxofuranosyluracil and Adenosine Formed as a Function of the Phase-Transer Catalyst

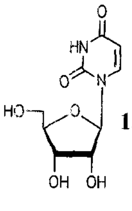
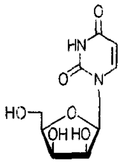
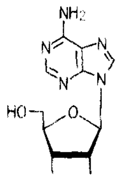
Phase-Transfer Catalyst $R_4N^+X^-$	Ratio of 2′-*O*- to 3′-*O*-Tosyl-lyxofuranosyluracil, **2b** : **3b** (Yield)[a,b]	Ratio of 2′-*O*- to 3′-*O*-Tosyladenosine, **2c** : **3c** (Yield)[b]	
		CH_2Cl_2	C_6H_6[c]
$(n\text{-}C_4H_9)_4N^+F^-$	58 : 42 (62)	100 : 0 (90)	no reaction
$(n\text{-}C_6H_{13})_4N^+Cl^-$	26 : 74 (65)	100 : 0 (93)	75 : 25 (24)
Aliquat 336	68 : 32 (61)	100 : 0 (90)	93 : 7 (15)
$C_6H_5CH_2(C_2H_5)_3N^+Cl^-$	59 : 41 (61)	100 : 0 (96)	86 : 14 (25)

[a] The reaction solvent chosen is CH_3CN, because, in comparison with benzene or CH_2Cl_2, only small amounts of di-*O*-tosyl derivatives are observed with this nucleoside.

[b] Yield (%) of isolated, isomeric mixture.

[c] The use of this solvent gives a low yield of tosylate, but allows formation of the previously unknown 3′-isomer.

Table 3. Mono-*O*-*p*-Toluenesulfonyl Nucleosides Prepared

Substrate	Product	m.p. (°C)	Molecular Formula or Lit. m.p. (°C)	^{1}H-NMR (DMSO-d_6/D_2O/TMS) δ						
				Base Protons	H-1′	H-2′	H-3′	H-4′	H-5′	CH_3
 **1a**	**2a**	172–173	172–174[4]	7.55, 5.47 (2d, 2H, H-6 and H-5)	6.01 (d, 1H)	4.85 (dd, 1H)	4.18 (dd, 1H)	3.95 (m, 1H)	3.56 (m, 2H)	2.38 (s, 3H)
	3a	203–204	205–206[5]	7.60, 5.72 (2d, 2H, H-6 and H-5)	5.82 (d, 1H)	4.25 (dd, 1H)	4.83 (dd, 1H)	3.99 (m, 1H)	3.55 (m, 2H)	2.43 (s, 3H)
 **1b**	**2b**	259–260	259–261[10]	7.65, 5.61 (2d, 2H, H-6 and H-5)	6.14 (d, 1H)	5.24 (dd, 1H)	4.14 (dd, 1H)	3.60 (m, 1H)	3.59 (m, 2H)	2.43 (s, 3H)
	3b	183–186	$C_{16}H_{18}N_2O_8S$[a,b] (398.4)	7.60, 5.53 (2d, 2H, H-6 and H-5)	6.02 (d, 1H)	4.44 (dd, 1H)	5.18 (dd, 1H)	4.10 (m, 1H)	3.49 (m, 2H)	2.43 (s, 3H)
 **1c**	**2c**	230–231	229–230[4]	8.15, 7.96 (2s, 2H, H-2 and H-8)	6.05 (d, 1H)	5.44 (dd, 1H)	4.34 (dd, 1H)	4.07 (m, 1H)	3.62 (m, 2H)	2.24 (s, 3H)
	3c	158–160	$C_{17}H_{19}N_5O_6S$[c,d] (421.4)	8.13, 7.93 (2s, 2H, H-2 and H-8)	5.81 (d, 1H)	4.56 (dd, 1H)	5.42 (dd, 1H)	4.14 (m, 1H)	3.60 (m, 2H)	2.41 (s, 3H)

[a] MS (ZAB HF spectrometer; FAB+, thioglycerol matrix): *m/e* (rel. intens.%) = 399 (0.8, $M^+ + H$), 227 (2.6, M^+ – tosyl).

[b] calc. C 48.24 H 4.52 N 7.03 S 8.04
found 48.23 4.60 7.02 8.02.

[c] MS (ZAB HF spectrometer; FAB$^+$, thioglycerol matrix): *m/e* (rel. intens.%) = 422 (80, $M^+ + H$), 250 (1.8, M^+ – tosyl).

[d] calc. C 48.45 H 4.51 N 16.63 S 7.60
found 48.46 4.58 16.70 7.59.

The outlined procedure is the method of choice for preparing mono-*O*-tosyl derivatives of uridine and adenosine on account of its simplicity and effectiveness. In comparison with an earlier reported[9] synthesis, this process permits 2′-*O*-tosyllyxofuranosyluracil to be obtained in good yield along with its previously unknown 3′-*O*-tosyl isomer. It is worth emphasising that this method does not necessitate prior 5′-*O*-hydroxyl protection.

O-*p*-Toluenesulfonylation of Nucleosides 1a–c Using a Phase-Transfer Catalyst; General Procedure:

To a stirred suspension of the nucleoside **1** (2 mmol) in the solvent indicated in the Tables (60 mL) is added dibutyltin oxide (0.56 g, 2.25 mmol), tosyl chloride (0.64 g, 3.35 mmol) and the ammonium salt (2 mmol) at room temperature. Stirring is then continued for 24 h, after which the reaction mixture is evaporated to dryness. The residual product is purified by short column chromatography[10] on silica gel G using 2% EtOH in CH_2Cl_2 as eluent (for all the mono-*O*-tosylfuranosyluracil derivatives **2a, b** and **3a, b**) or by crystallization from CH_2Cl_2 (for the *O*-tosyl derivatives of adenosine **2c** and **3c**), EtOAc or i-Pr_2O (when the catalyst is Aliquat 336). The 2′-tosylate of uridine (**2a**) or adenosine (**2c**) is separated from the respective 3′-isomer (**3a**) or (**3c**) on HPLC (RP 8 Brownlee column, in H_2O/CH_3CN, 70:30, with 1% DMSO, at a flow of 1 mL/min): uridine $R_{t(2')}$ 2.00, $R_{t(3')}$ 3.01 (min); adenosine $R_{t(2')}$ 2.10, $R_{t(3')}$ 4.17 (min).

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