Selective Mesylation of Vicinal Diols: A Systematic Case Study

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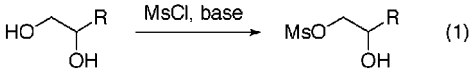
Selective mesylation of the primary (1°) hydroxyl group over the secondary (2°) hydroxyl group in a 1°/2° vicinal diol system is commonly sought (eq 1).[1−11] For instance, complete primary selectivity is critical if epoxide formation from a 1°/2° vicinal diol with retention of stereogenicity at the secondary site is desired. The most common method for this transformation employs methanesulfonyl chloride (MsCl) and pyridine, with reported yields in the range of 56−100% for the desired primary monomesylate.[1−6] Triethylamine (Et_3N) or Hünig's Base (*i*-Pr_2NEt) as replacements for pyridine also afford regioselective hydroxyl group mesylation for some vicinal diol substrates.[7−11] Addition of catalytic 4-(dimethylamino)-pyridine (DMAP) has also been used to facilitate this transformation.[6,12]



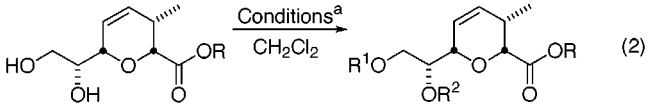
(1)

Our synthesis of hydropyran-based macrocycles with pendant functionality required selective primary mesylation of a 1°/2° vicinal diol (**1**, Table 1, eq 2).[13] Standard procedures for effecting this transformation gave poor selectivities (**2**/**3**) and unsatisfactory yields of the desired monomesylate product **2**. A systematic evaluation of methods for this transformation has led to a modified procedure for the reliable 1° monomesylation of vicinal diol **1** and similar structures, as described below.

Table 1. Selective Mesylation of Diol 1

entry	concn (M)	base[b]	MsCl (equiv)	temp (°C)	time (h)	% yields of **2** (**3**)[c,d]
1	0.15	Et_3N[e]	1.4	−23→0	1.25	40 (32)
2	0.15	Et_3N[e]	1.1	−50	1.5	29 (nd)
3	0.1	(*i*-$Pr)_2NEt$[e]	1.1	−78→0	3	47 (14)
4	0.06	pyridine	1.1	5	48	56 (11)
5	0.06	pyridine[e]	1.1	5	48	64 (26)
6	0.06	collidine	1.1	23	48	61 (12)
7	0.05	collidine	1.1	0→7	21	86 (10)

[a] **General Procedure**. To a solution of diol in CH_2Cl_2 were added base and MsCl at the initial temperature indicated. The solution was warmed to the temperature indicated for the time indicated. The reactions were quenched with water, extracted with CH_2Cl_2, washed with 2 M HCl, saturated K_2CO_3 (aq), and then water. Organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography on silica gel. [b] 3 equiv of base was used except in entry 7 where 10 equiv was used. [c] Isolated yields; remainder of mass balance was starting material. [d] None of the secondary monomesylate (R^1 = H, R^2 = Ms) was observed. [e] A catalytic amount (5 mol %) of DMAP was added.



(2)

1: R = CH_2CCl_3

2: R^1 = Ms, R^2 = H, R = CH_2CCl_3

3: R^1 = Ms, R^2 = Ms, R = CH_2CCl_3

Results and Discussion

Initial attempts to selectively mesylate the primary hydroxyl group in diol **1**[13] using standard procedures are summarized in Table 1. Use of Et_3N as the base with a catalytic amount of DMAP produced a mixture of the desired monomesylate **2** and dimesylate **3** (Table 1, entry 1).[7] Lower temperatures dramatically reduced the rate

1: R = CH_2CCl_3 $\xrightarrow[CH_2Cl_2,\ 0\rightarrow7\ °C]{MsCl,\ base,}$ **2**: R^1 = Ms, R^2 = H, R = CH_2CCl_3 **3**: R^1 = Ms, R^2 = Ms, R = CH_2CCl_3 (3)

of this reaction, but did give **2** selectively (Table 1, entry 2). At a slightly lower concentration, use of Hünig's base (*i*-Pr_2NEt, −78 °C with slow warming to 0 °C) with a catalytic amount of DMAP provided an increase in mono/dimesylate selectivity (3.3:1) over that in entry 1; however, the yield (47%) of the desired mesylate **2** was still unsatisfactory (Table 1, entry 3).[11] Switching to pyridine as the base and lowering the concentration further increased mono/dimesylate selectivity (5:1), but the yield of the desired monomesylate **2** was still low at 56% (Table 1, entry 4).[1−5] Addition of a catalytic amount of DMAP accelerated the reaction and increased the yield of monomesylate **2** (64%), at the expense of selectivity (2.5:1,Table 1, entry 5).[6] The mono/dimesylate selectivity remained the same (5:1) in switching from pyridine to collidine (2,4,6-trimethylpyridine), but the yield of the monomesylate increased slightly to 61% (Table 1, entry 6 vs entry 4). Finally, increasing the amount of collidine to 10 equiv and decreasing the reaction temperature

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(12) Arenesulfonylimidazoles and NaH or an alkoxide base have been used to convert 1°/2° vicinal diols to epoxides with retention at the 2° center, suggesting selective, albeit transient, 1° arenesulfonylation. See: (a) Eisenberg, C.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 3760. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122, and references therein. (c) For a systematic study of selective acetylation and, to a more limited extent, acylation, sulfonylation, and silylation of primary versus secondary alcohols, see: Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791. This study examined only 1-octanol versus 2-octanol for selective mesylation, a competition that differs in electronic and steric issues from the substrate studied herein. Selectivities exceeding 9:1 for 1-octanol mesylation were observed by Yamamoto using collidine, *N*,*N*-diisopropylethylamine (Hünig's base), and 1,2,2,6,6-pentamethylpiperidine as bases.
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Table 2. Comparison of Bases for Selective Mesylation.

entry	base	% yield of **2**[b]	% yield of **3**[b,c]
1	pyridine	47	8
2	2,6-lutidine	29	0
3	collidine	84	8
4	2,6-di-*tert*-butyl-4-methylpyridine	0	0[d]
5	Et_3N	52	18

[a] Reaction conditions: concentration (0.05 M), MsCl (1.1 equiv), base (10 equiv), reaction time (15.5 h). The general procedure detailed in Table 1, footnote a was used with the MsCl added at 0 °C, stirred for 1 h, and then warmed to 7 °C for 14.5 h. [b] Isolated yields, remainder of mass balance was recovered starting material. [c] None of the monomesylate at the secondary alcohol center (R^1 = H, R^2 = Ms) was observed. [d] 90% recovered starting material.

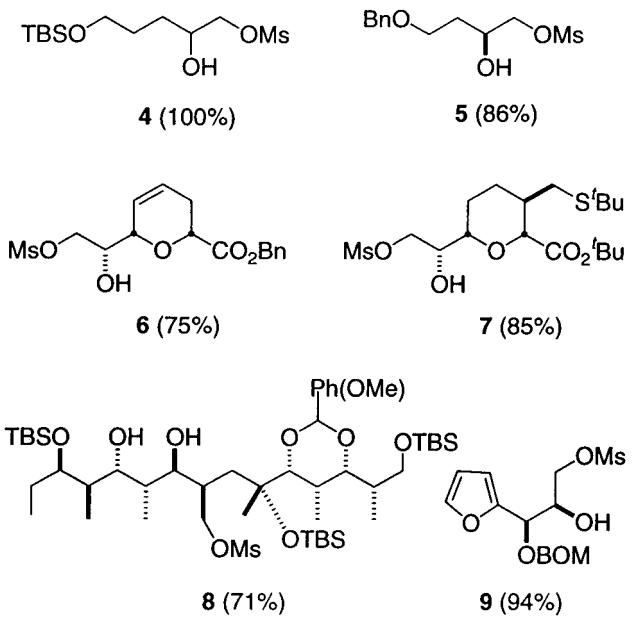
range (0 to 7 °C) increased both the selectivity (8.6:1) and yield of monomesylate **2** to an acceptable 86% (Table 1, entry 7).

Selectivity determinants for the mesylation reaction merit brief review. It is known that the reaction of methanesulfonyl chloride with Et_3N results in a very reactive sulfene intermediate,[14−16] which is unlikely to be kinetically selective, as reflected in the result in Table 1, entry 1. The increased selectivity observed when using Hünig's base can be attributed to its lower basicity, thus generating less of the reactive sulfene intermediate in the reaction mixture at a given time. Upon switching to pyridine bases, the mechanism for this reaction probably changes, by analogy to acylation chemistry. Fersht and Jencks have shown that acylation reactions using pyridine bases proceed through acylpyridinium ions as reactive species.[17,18] By production of these acylpyridinium ions, pyridines act as nucleophilic catalysts, a concept that has led to the advent of DMAP and related acylation catalysts.[19,20] Assuming that the source of mesylation selectivity is kinetic, we believed that increasing the steric bulk about the pyridine nitrogen would increase selectivity. Therefore, a more detailed investigation of the effects of substitution about the pyridine ring was performed (Table 2, eq 3).

The experiments in Table 2 employed the optimal conditions for selectively mesylating diol **1** (Table 1, entry 7), varying only the base. It was observed that substitution at the positions ortho to the pyridine nitrogen resulted in an increase in mono/dimesylate selectivity at the expense of yield (Table 2, entry 1 vs 2); however, additional substitution at the para position enhanced both selectivity and yield of the desired product (Table 2, entry 1 vs entry 3). Further increase of steric bulk at the ortho positions resulted in no reaction (Table 2, entry 4). Under these conditions, the use of Et_3N resulted in an increase in selectivity from that reported previously (Table 2, entry 5 vs Table 1, entry 1); however, it was still moderate (3:1) in comparison to the result with collidine (Table 2, entry 5 vs entry 3).

The results in Table 2 can be explained by reasoning analogous to that found in the literature on acylations

Chart 1. Other Examples of Selective Monomesylation



catalyzed by pyridine bases.[20,21] Substitution with electron-donating groups (EDG) ortho to the pyridine nitrogen decreases the catalytic activity of the pyridinium salt, whereas pyridines with para EDG substitution have increased activity.[21] In correspondence with the cited acylation studies, when pyridine is replaced by 2,6-lutidine the amount of isolated monomesylate **2** decreases, yet an increase in selectivity is observed, probably due to decreased reactivity of the mesyllutidinium species formed because of increased steric bulk.[21] Increasing substitution further by including a methyl group para to the nitrogen in addition to the two ortho methyl substituents, i.e., collidine, electronically increases the activity of this nucleophilic catalyst, resulting in a higher yield of the desired monomesylate **2** (Table 2, entry 3). Increased selectivity compared to that of pyridine can once again be attributed to the steric hindrance of the methyl groups flanking the mesylcollidinium nitrogen. Further increase of the steric bulk ortho to the pyridine nitrogen (Table 2, entry 4) resulted in no reaction. It should be noted that, among the substituted pyridine nucleophiles of Table 2, DMAP was not employed due to its 5500-fold increase in activity over pyridine as a nucleophilic acylation catalyst,[19,20] resulting in little or no selectivity (see Table 1, entries 1−3 and 5).

In summary, the optimal conditions for the selective primary mesylation of 1°/2° vicinal diol **1** and related systems have been determined to be 10 equiv of collidine and 1.1 equiv of methanesulfonyl chloride, run at a temperature of 0−7 °C for 12−24 h and a concentration of 0.05 M in CH_2Cl_2. Typical yields of desired monomesylate **2** from reaction of diol **1** on a gram scale are 82−86% and have been as high as 94%. Direct use of the resulting primary mesylate[13] as an electrophilic site or conversion to the corresponding terminal epoxide[12a,b] are both accommodated by this method. These conditions have also proven superior in our labs for selective 1° mesylations of many structurally diverse diol and triol

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substrates (Chart 1). These representative cases all proceeded with excellent regioselectivities in the isolated yields shown parenthetically.

Experimental Section

General. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylethylamine (*i*-Pr_2NEt), pyridine, and 2,6-lutidine were distilled from calcium hydride prior to use. 4-(Dimethylamino)-pyridine (DMAP) was recrystallized from toluene. Methanesulfonyl chloride was distilled under reduced pressure prior to use. 2,6-Di-*tert*-butyl-4-methylpyridine was purchased from Aldrich[22] and was used without further purification. All reactions were performed in flame-dried glassware under a stream of nitrogen. Silica gel chromatography was performed according to the method of Still.[23] Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00), and coupling constants (J) are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz. Where indicated, distortionless enhancement by polarization transfer (DEPT) was used to assign carbon resonances as CH_3, CH_2, CH, or C. Chemical shifts are reported in ppm relative to Me_4Si (δ, 0.00). Elemental analyses were performed by Desert Analytics Laboratories (Phoenix, AZ).

Preparation of (2*R*,3*S*,6*S*)-6-[(1*R*)-1-Hydroxy-2-methylsulfonylethyl]-3-methyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (2). To a solution of diol **1**[13] (4.32 g, 12.95 mmol) in CH_2Cl_2 (260 mL) was added collidine (17.1 mL, 129.5 mmol) at ambient temperature. The solution was cooled to 0 °C, and 13.9 mL (14.25 mmol) of 1.03 M MsCl (in CH_2Cl_2) was added. After stirring for 2 h at 0 °C, the solution was placed in a refrigerator (7 °C) for 18 h without stirring. The reaction was quenched with water (100 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with 5% HCl (aq) (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (elution with 1:1 EtOAc/hexanes) afforded 4.44 g (10.83 mmol, 84%) of the monomesylate **2** as a colorless oil and 509 mg (1.04 mmol, 8.0%) of the dimesylate **3**.

Data for monomesylate 2: R_f 0.26 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ +78.9 (c = 1.24, CH_2Cl_2); IR (thin film) 3600−3200 (br), 1772, 1354, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.98 (ddd, 1H, J = 10.2, 5.8, 2.1 Hz), 5.77 (br d, 1H, J = 10.3 Hz), 4.78 (AB_q, 2H, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 27.5 Hz), 4.43 (d, 1H, J = 3.3 Hz), 4.40 (ap d, 2H, J = 5.2 Hz), 4.37−4.33 (m, 1H), 3.89 (br q, 1H, J = 5.0 Hz), 3.43 (br s, 1H), 3.05 (s, 3H), 2.64−2.57 (m, 1H), 1.00 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6 (C), 131.9 (CH), 124.5 (CH), 94.4 (C), 76.1 (CH), 75.4 (CH), 74.2 (CH_2), 71.6 (CH), 70.6 (CH_2), 37.4 (CH_3), 31.5 (CH), 14.9 (CH_3); MS (FAB) *m/e* (relative intensity, assignment) 433.0 (65, M + Na^+), 411.0 (100, M + H^+); isotope pattern calculated for $C_{12}H_{17}O_7Cl_3S$ + Na^+ matches that observed. Anal. Calcd for $C_{12}H_{17}O_7Cl_3S$: C, 35.01; H, 4.16. Found: C, 35.24; H, 4.49.

Data for dimesylate 3: R_f 0.45 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ +60.3 (c = 0.58, CH_2Cl_2); IR (thin film) 1774, 1358, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.08 (ddd, 1H, J = 10.3, 5.5, 2.2 Hz), 5.76 (ddd, 1H, J = 10.3, 1.5, 1.5 Hz), 4.83 (ap q, 1H, J = 4.8 Hz), 4.78 (AB_q, 2H, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 14.1 Hz), 4.56−4.52 (m, 1H), 4.53 (d, 2H, J = 4.8 Hz), 4.46 (d, 1H, J = 3.3 Hz), 3.15 (s, 3H), 3.07 (s, 3H), 2.65−2.60 (m, 1H), 1.02 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8 (C), 133.3 (CH), 122.7 (CH), 94.4 (C), 79.0 (CH), 75.6 (CH), 74.2 (CH_2), 74.0 (CH), 67.1 (CH_2), 38.9 (CH_3), 37.7 (CH_3), 31.3 (CH), 14.9 (CH_3); MS (FAB) *m/e* (relative intensity, assignment) 513 (100, M + Na^+); isotope pattern calculated for $C_{13}H_{19}O_9S_2Cl_3$ + Na^+ matches that observed.

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Supporting Information Available: Copies of NMR spectra of **2** and **3** and of other vicinal diol monomesylates **4-9** prepared as described above (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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