Facile and Practical Methods for the Sulfonylation of Alcohols Using Ts(Ms)Cl and $Me_2N(CH_2)_nNMe_2$ as a Key Base

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Abstract: Several alcohols were smoothly and practically tosylated by two Methods A and B. Method A uses the TsCl/ $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) reagent and Method B uses TsCl/ Et_3N/catalytic $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) reagent. Compared with the traditional Py-solvent method, Method A has the advantages of its much higher reaction rate, operational simplicity, and circumvention of the undesirable side reaction from ROTs to RCl. Method B has the advantage of economy in the use of the amine. Related methanesulfonylations in toluene solvent also proceeded successfully.

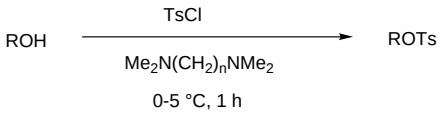
Key words: tosylation, mesylation, alcohols, diamine, catalytic reaction

Among a number of methods for *p*-toluenesulfonylation (tosylation) of alcohols,[1] TsCl/Py (Ts = *para*-toluenesulfonyl, Py = pyridine) reagent has been traditionally and routinely employed. This tosylation is established as a fundamental unit reaction in various fields of organic syntheses, however, there still remain some problems. (a) Excess amounts (ca. 10 equiv) of Py are generally required for the completion of the tosylation. Therefore, this method suffers from a tedious procedure to remove pyridine. (b) Undesirable and concomitant loss of the tosylates to their chlorides is liable to occur during the tosylation; the Py·HCl byproduct acts as the Cl-nucleophile. This side reaction frequently takes place when excess amounts of Py solvent are used and/or when the reaction temperature is elevated. (c) The reaction time for unreactive alcohols generally requires a relatively long time (over 10 hours).

Taking this information into consideration, we now report a couple of facile and practical Methods (A and B) for the tosylation of various alcohols employing $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) as the key base. Related methanesulfonylations using $Me_2N(CH_2)_nNMe_2$ are also described.

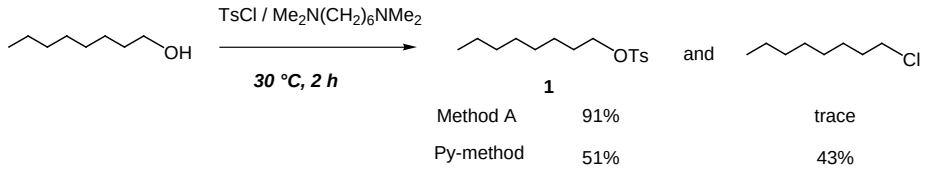
We chose water-soluble and readily available diamines such as TMEDA (*N*,*N*,*N*',*N*'-tetramethylethylenediamine), which has the advantage of being conveniently removed from the organic phase containing the desired tosylate after the workup. Actually, TsCl/ TMEDA (1.5 equiv) reagent was found to be a good promoter for the tosylation of octan-3-ol (yield 80~90%), however, a serious side reaction took place: TsCl slowly reacted with TMEDA to produce *N*,*N*-dimethyl *p*-toluenesulfonamide by the Hofmann degradation. About 20% of *N*,*N*-dimethyl *p*-toluenesulfonamide was produced during the tosylation of 3,3-dimethylbutanol using the reagent at 0–5 °C for 1 hour. Thus, we planned the tosylation using an inexpensive and available $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) (1.5 equiv) as the amine reagent (Method A).

Table 1 Tosylation of Alcohols Using TsCl / $Me_2N(CH_2)_nNMe_2$ Reagent (Method A)

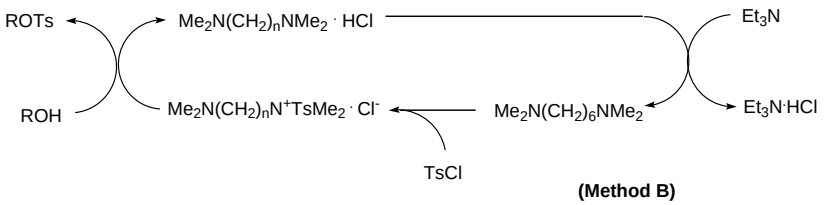


Alcohol	Amine[a] (Eq)	Eq (TsCl)	Solvent	Tosylate	Yield (%)
$Me(CH_2)_6CH_2OH$	A (1.5)	1.5	toluene	**1**	87
	A (1.5)	1.5	MeCN		94
	B (1.5)	1.5	MeCN		95
$CH_2=CH(CH_2)_7CH_2OH$	B (1.5)	1.5	toluene	**2**	95
$EtO_2C(CH_2)_4CH_2OH$	A (1.5)	1.5	MeCN	**3**	94
$Me(CH_2)_4CH(OH)Et$	A (1.5)	1.5	MeCN	**4**	92
	B (1.5)	1.5	MeCN		94
	Py (1.5)[b]	1.5	MeCN		trace
	Py (11)[c]	1.5	–		40
l-menthol	B (1.5)	1.5	MeCN	**5**	92
t-BuCH(OH)Me	B (2.0)	2.0	MeCN	**6**	91[d]
$EtCH(OH)CH_2OH$	B (3.0)	3.0	MeCN	**7**	91

[a] A: $Me_2N(CH_2)_3NMe_2$. B: $Me_2N(CH_2)_6NMe_2$.
[b] Pyridine was used as the amine.
[c] Conventional pyridine solvent method.
[d] 0–5 °C, 1 h and room temp. 3 h.



Scheme 1

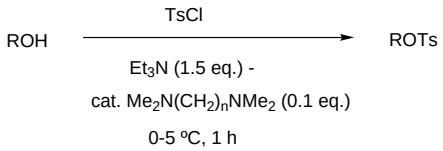


Scheme 2

Table 1 lists these results. The salient features are as follows. (a) Several primary and secondary alcohols were smoothly tosylated in toluene or CH_3CN at 0–5 °C for 1 h. (b) 1.5 equiv of the diamine base was sufficient for the tosylation. (c) In the case of octan-3-ol replacement of the diamine base for Py and the conventional Py-solvent method resulted in lower yields under identical conditions. (d) Even unreactive 3,3-dimethylbutan-2-ol underwent tosylation at room temperature. $Me_2N(CH_2)_4NMe_2$ was also effective (In the case of octan-1-ol, 91% under identical conditions). Therefore, compared with conventional Py-solvent method, Method A showed significantly higher reaction velocity.[2]

It is also worth noting that Method A significantly circumvented the side undesirable chlorination (from ROTs to RCl) exemplified by the following comparable experiment; octan-1-ol was safely tosylated under identical conditions at 30–35 °C for 2 hours (Scheme 1). This result indicates much lower nucleophilicity of $Me_2N(CH_2)_6NMe_2$·HCl salt compared with the Py·HCl salt.

Table 2 Tosylation of Alcohols Using TsCl / Et_3N / cat. $Me_2N(CH_2)_nNMe_2$ Reagent (Method B)



Alcohol	Amine[a]	Solvent	Tosylate	Yield (%)
$Me(CH_2)_6CH_2OH$	B	toluene	**1**	87
	B	MeCN		94
$CH_2{=}CH(CH_2)_7CH_2OH$	B	MeCN	**2**	93
$EtO_2C(CH_2)_4CH_2OH$	B	MeCN	**3**	94
$Me(CH_2)_4CH(OH)Et$	A	MeCN	**4**	86[b]
	B	MeCN		95[b]
l-menthol	B	MeCN	**5**	94[b]
$EtCH(OH)CH_2OH$	B	MeCN	**7**	92[b]

[a] A: $Me_2N(CH_2)_3NMe_2$. B: $Me_2N(CH_2)_6NMe_2$.
[b] 0–5 °C, 1 h and r. t. 3 h.

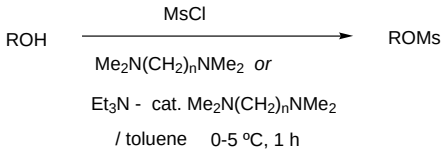
Method B involves the tosylation using TsCl/Et_3N (1.5 equiv)/cat. $Me_2N(CH_2)_nNMe_2$ (0.1 equiv) reagent. From the standpoint of the economy of amine base, it is desirable to use 1.5 equiv of very cheap Et_3N as the main base combined with a catalytic amount of $Me_2N(CH_2)_nNMe_2$. Table 2 lists these results. Although the reaction velocity was a little inferior to Method A, several primary and secondary alcohols were practically tosylated in CH_3CN at 0–5 °C for 1 h and room temperature for 3 h. For the tosylation of secondary alcohols, $Me_2N(CH_2)_6NMe_2$ was somewhat superior to $Me_2N(CH_2)_3NMe_2$.

A plausible mechanism of Method B is illustrated in Scheme 2. Our earlier report described that alk-2-enyl and alk-2-ynyl alcohols were safely tosylated using K_2CO_3 and a catalytic, sterically unhindered amine.[1g,h] Based on the results, $Me_2N(CH_2)_nNMe_2$ would preferentially form the reactive sulfonylammonium salt with TsCl in situ. After the tosylation of an alcohol, Et_3N would drive the catalytic cycle by neutralizing $Me_2N(CH_2)_nNMe_2$·HCl to reform $Me_2N(CH_2)_nNMe_2$.

Consequently, Method A will adequately replace the Py-method with respect to (1) its higher reaction rate; (2) safety for preparing tosylates; (3) operational simplicity. Method B has a merit of economy in the use of the amine. Additionally, from the standpoint on decreasing amounts of the amine base, both methods give advantage over the Py-method.

Finally, the related methanesulfonylation (mesylation) was examined. Mesylations are carried out conventionally in halogenated solvents (e.g. CH_2Cl_2) or ether solvents (e.g. Et_2O, THF), because of their high reaction velocity.

Table 3 Mesylation of Alcohols in Toluene Using MsCl / (cat.) $Me_2N(CH_2)_nNMe_2$ / (Et_3N) Reagent



Alcohol	Amine[a] (equiv)	Eq (Et_3N)	Mesylate	Yield (%)
$Me(CH_2)_4CH(OH)Et$	A (1.5)	–	**8**	93
	B (1.5)	–		94
	B (0.1)	1.5		94
	–	1.5		<10
	C (0.1)	1.5		94
t-BuCH(OH)Me	B (1.5)	–	**9**	94[b]
	B (0.1)	1.5		95[b]

[a] A: $Me_2N(CH_2)_3NMe_2$. B: $Me_2N(CH_2)_6NMe_2$. C: TMEDA [$Me_2N(CH_2)_2NMe_2$].
[b] 0–5 °C, 1 h and r. t. 5 h.

Taking a recent experimental requirement into account, especially, for industrial productions, the reaction *in toluene* as solvent should be desirable. Actually, Et_3N (1.5 equiv) and $Me_2N(CH_2)_nNMe_2$ (0.1 equiv) were found to be effective reagents for the mesylation *in toluene* as shown in Table 3. In the case of octan-3-ol, independent use of Et_3N was markedly ineffective. It should be noted that TMEDA also worked as an efficient promoter. Unfortunately, dihydrolinalool, a tertiary alcohol, was not tosylated and mesylated by these present methods.

Mps were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. ^{1}H NMR spectra were recorded on a JEOL EX-90 (90 MHz) and/or JEOL α (400 MHz) spectrometer in $CDCl_3$ using a TMS internal standard. IR spectra were recorded on a JASCO FT/IR-8000 spectrophotometer. Silica gel column chromatography was performed on a Merck Art. 7734 and/or 9385. Commercial TsCl was recrystallized from EtOAc prior to use. The solvents were purified by standard methods.

Method A; General Procedure
TsCl (1.5 mmol) in solvent (toluene or CH_3CN; 1.0 mL) was added to a stirred solution of an alcohol (1.0 mmol) and $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) (1.5 mmol) in solvent (toluene or CH_3CN; 1.0 mL) at 0–5 °C, and the mixture was stirred for 1 h. To decompose an excess TsCl, *N*,*N*-dimethylethylenediamine (ca. 130 mg) was added to the mixture, which was stirred for 10 min. (This procedure is not always necessary, when TsCl is easily separated off by column chromatography). H_2O was added to the mixture, which was extracted with EtOAc. The organic phase was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/Et_2O = 30~10:1) to give the desired tosylate.

Method B; General Procedure
TsCl (1.5 mmol) in solvent (toluene or CH_3CN; 1.0 ml) was added to a stirred solution of an alcohol (1.0 mmol), Et_3N (1.5 mmol) and $Me_2N(CH_2)_nNMe_2$ (n = 3 *or* 6) (0.1 mmol) in solvent (toluene or CH_3CN; 1.0 ml) at 0–5 °C, and the mixture was stirred for 1–3 h. A similar workup and purification to Method A gave the desired tosylate.

Mesylation of Alcohols Using (a) MsCl/$Me_2N(CH_2)_nNMe_2$ *or* (b) MsCl/Et_3N and cat. $Me_2N(CH_2)_nNMe_2$ (n = 2, 3 *or* 6)
(a) MsCl (172 mg, 1.5 mmol) in toluene (0.5 ml) was added to a stirred solution of an alcohol (1.0 mmol) and $Me_2N(CH_2)_nNMe_2$ (1.5 mmol) in toluene (1.0 ml) at 0–5 °C, and the mixture was stirred for 1 h. A similar workup and purification of Method B followed by silica gel column chromatography (hexane/EtOAc = 5:1) gave the desired mesylate. (b) MsCl (172 mg, 1.5 mmol) in toluene (0.5 ml) was added to a stirred solution of an alcohol (1.0 mmol), Et_3N (152 mg, 1.5 mmol), and $Me_2N(CH_2)_nNMe_2$ (0.1 mmol) in toluene (1.0 mL) at 0–5 °C, and the mixture was stirred for 1 h. A similar workup and purification in the case of (a) gave the desired mesylate.

***N*,*N*-Dimethyl 4-Toluenesulfonamide**
Colorless crystals: mp 83.0–83.5 °C.

IR (KBr): ν = 2906, 1597, 1471, 1454, 1336, 1163, 957, 646 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.40 (3H, s), 2.70 (6H, s), 7.30 (2H, d, *J* = 10.0 Hz), 7.65 (2H, d, *J* = 10.0 Hz).

These spectral data accorded with those of the authentic sample prepared by TsCl and dimethylamine.

1-Octyl 4-Toluenesulfonate (1)[3]
Colorless oil.

IR (film): ν = 2928, 2857, 1599, 1466, 1362, 1177, 1098, 949, 910 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.87 (3H, t, *J* = 7.2 Hz), 1.08–1.82 (12H, m), 2.44 (3H, s), 4.03 (2H, t, *J* = 6.9 Hz), 7.24–7.49 (2H, m), 7.72–7.91 (2H, m).

Dec-9-enyl 4-Toluenesulfonate (2)[4]
Colorless oil.

IR (film): ν = 2928, 1639, 1599, 1362, 1177, 937 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.78–2.18 (14H, m), 2.44 (3H, s), 4.02 (2H, t, *J* = 7.7 Hz), 4.81–5.12 (2H, m), 5.58–6.04 (1H, m), 7.22–7.44 (2H, m), 7.72–7.91 (2H, m).

Ethyl 6-(4-Toluenesulfonyloxy)hexanoate (3)[5]
Colorless oil.

IR (film): ν = 2942, 1734, 1458, 1360, 1177, 1030, 951 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.24 (3H, t, *J* = 7.7 Hz), 1.34–1.83 (6H, m), 2.25 (2H, t, *J* = 7.7 Hz), 2.45 (3H, s), 3.91–4.28 (4H, m), 7.23–7.44 (2H, m), 7.70–7.92 (2H, m).

3-Octyl 4-Toluenesulfonate (4)[6]
Colorless oil.

IR (film): ν = 2957, 2934, 2864, 1597, 1460, 1364, 1188, 1177, 1098, 910 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.80 (3H, t, *J* = 7.7 Hz), 1.01–1.82 (13H, m), 2.42 (3H, s), 4.38–4.62 (1H, m), 7.22–7.48 (2H, m), 7.71–7.89 (2H, m).

l-Menthyl 4-Toluenesulfonate (5)[7]
Colorless crystals: mp 92.5–93.5 °C.

IR (KBr): ν = 2963, 2936, 1599, 1454, 1358, 1179, 1098, 943, 910 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.52 (3H, d, *J* = 6.4 Hz), 0.70–2.27 (15H, m), 2.42 (3H, s), 4.23–4.56 (1H, m), 7.23–7.43 (2H, m), 7.71–7.91 (2H, m).

3,3-Dimethylbutan-2-yl 4-Toluenesulfonate (6)[8]
Colorless oil.

IR (film): ν = 2971, 1599, 1480, 1362, 1177, 1074, 901 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (9H, s), 1.21 (3H, d, *J* = 6.8 Hz), 2.44 (3H, s), 4.39 (1H, q, *J* = 6.4 Hz), 7.31–7.33 (2H, m), 7.78–7.80 (2H, m).

1,2-Bis(4-toluenesulfonyloxy)butane (7)
Colorless crystals: mp 57.5–58.5 °C.

IR (KBr): ν = 2976, 1597, 1460, 1362, 1194, 1179, 909 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.82 (3H, t, *J* = 7.7 Hz), 1.48–1.81 (2H, m), 2.47 (6H, s), 4.02 (2H, d, *J* = 6.8 Hz), 4.40–4.71 (1H, m), 7.19–7.48 (4H, m), 7.59–7.91 (4H, m).

Anal. Calcd for $C_{16}H_{22}O_6S_2$: C, 54.25; H, 5.56. Found: C, 54.0; H, 5.4.

Reaction of Octan-1-ol in the Py Solvent Method at 30 °C for 2 h (Scheme 1).
TsCl (286 mg, 1.5 mmol) was added to a stirred solution of octan-1-ol (130 mg, 1.0 mmol) in pyridine (0.87 ml) at 0–5 °C, and the mixture was stirred at 30 °C for 2 h. Usual workup of this method gave a crude product (275 mg), which contained 1-octyl tosylate (51%) and 1-chlorooctane (43%) by the estimation of ^{1}H NMR (400 MHz).

3-Octyl Methanesulfonate (8)[6]
Colorless oil.

IR (film): ν = 2938, 2872, 1350, 1175, 918 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (3H, t, *J* = 7.2 Hz), 0.99 (3H, t, *J* = 7.2 Hz), 1.22–1.81 (10H, m), 3.03 (3H, s), 4.64–4.72 (1H, m).

3,3-Dimethylbutan-2-yl Methanesulfonate (9)[8]
Colorless oil.

IR (film): ν = 2969, 2878, 1350, 1175, 905 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (9H, s), 1.40 (3H, d, *J* = 7.2 Hz), 3.01 (3H, s), 4.51 (1H, q, *J* = 7.2 Hz).

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