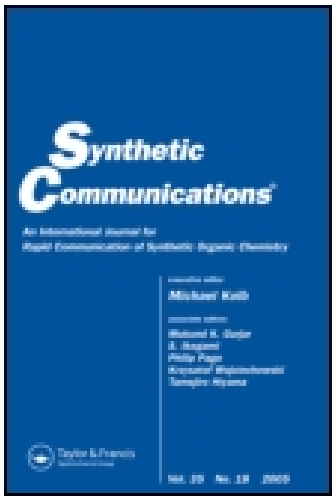

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Aug 2006.

To cite this article: Gaifa Lai, Ping-Zhong Tan & Pallab Ghoshal (2003) A One-Pot Method for the Efficient Conversion of Aryl- and Acyl-substituted Methyl Alcohols into Chlorides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:10, 1727-1732

To link to this article: http://dx.doi.org/10.1081/SCC-120018934

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1727–1732, 2003

A One-Pot Method for the Efficient Conversion of Aryl- and Acyl-substituted Methyl Alcohols into Chlorides

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ABSTRACT

A one-pot and efficient conversion of aryl- and acyl-substituted methyl alcohols into the corresponding chlorides is described, which involved tosylation with tosyl chloride and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2, followed by methanol-facilitated replacement of the tosylates with chloride. This mild method is readily amenable to large-scale synthesis.

The development of mild and one-pot procedures for efficient functional group conversions is of great significance in organic synthesis. For the conversion of primary and secondary alcohols into the corre-

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DOI: 10.1081/SCC-120018934 0039-7911 (Print); 1532-2432 (Online)
 www.dekker.com

sponding chlorides, a wide variety of methods have been reported, including thionyl chloride,[1] phosphorus trichloride,[2] hydrochloric acid and zinc chloride (Lucas reagent),[3] triphenylphosphine dichloride,[4] triphenylphosphine and carbon tetrachloride[5] or hexachloroacetone,[6] tosyl chloride and DMAP,[7] methanesulfonyl chloride and lithium chloride,[8] and a Vilsmeier reagent.[9] However, many of these methods have some limitations such as being too drastic to be compatible with other functionalities, using highly corrosive or toxic reagents, requiring laborious workup, and being difficult to scale up. As a continuation of our interest in the development of new and simple procedures for functional group transformations,[10] we now report a mild, scalable, one-pot procedure for the two-step conversion of aryl- and acyl-substituted methyl alcohols into chlorides via the intermediate tosylates, as depicted in Sch. 1.

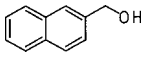
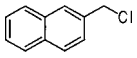
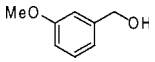
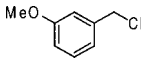
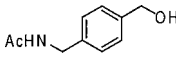
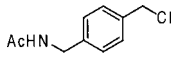
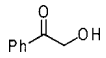
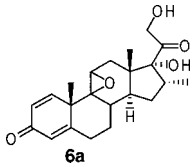
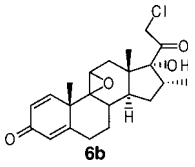
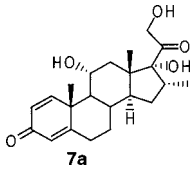
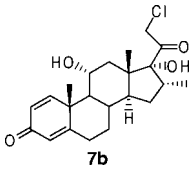
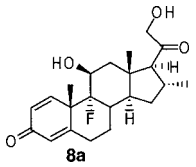
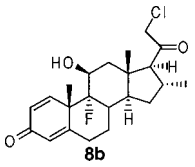
Thus, tosylation of aryl- and acyl-substituted methyl alcohols was carried out by treatment with tosyl chloride (1.1 eq.) and triethylamine (2 eq.) in the presence of a catalytic amount of DMAP (0.02 eq.) in CH_2Cl_2 at 0–5°C for 1–2 h. When the starting alcohols were consumed, methanol (0.4 eq) was added and the mixture was heated at 40–42°C to afford the desired chlorides in good yields. The results are summarized in Table 1. The progress of both tosylation and subsequent replacement of the tosylates by chloride was monitored by TLC and GC or HPLC analyses. Methanol was found to facilitate the substitution reaction of tosylates with chloride. Control experiments indicated that without the use of methanol, the transformation of the tosylates into the chlorides proceeded slowly or incompletely even after a prolonged reaction time. One explanation for the effect of methanol is that it may serve to enhance the nucleophilicity of the chloride ion, which may be freed to a certain extent when methanol and quaternary ammonium species probably form a complex through a hydrogen bond, as shown in Eq. (1). This one-pot procedure was quite gentle, and functional groups such as epoxide ring, fluoride, and amide were not affected. Selective reaction of the primary alcohol functionality in **7a** was achieved without affecting the secondary and tertiary hydroxyl groups and the corresponding chloride **7b** was obtained in 90% yield (Entry 7).

$$Et_3N^+ - H\cdots Cl^- + MeOH \rightleftharpoons Et_3N^+ - H\cdots \overset{H}{O}Me + Cl^- \qquad (1)$$

$$ArCH_2OH\ (RCOCH_2OH) \xrightarrow{(i),\ (ii)} ArCH_2Cl\ (RCOCH_2Cl)$$

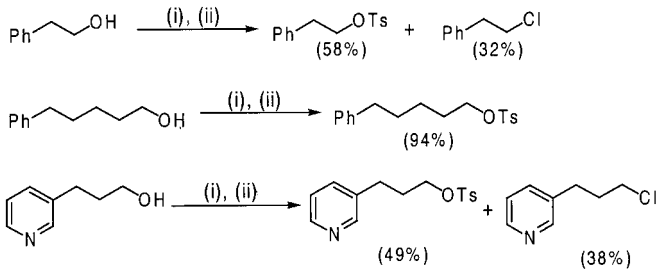
Scheme 1. Reaction conditions: (i) TsCl (1.1 eq.), Et_3N (2 eq.), DMAP (0.02 eq.), CH_2Cl_2, 0–5°C (ii) MeOH (0.4 Equiv.), 40–42°C.

Table 1. One-pot conversion of aryl- and acyl-substituted methyl alcohols into chlorides.

Entry	Alcohol	Chloride	Time[a] (h)	Yield[b] (%)
1	$PhCH_2OH$	$PhCH_2Cl$	0.5	80[c]
2			2	92[d]
3			1	83[c]
4			2	85[d]
5			2	83[c]
6	 **6a**	 **6b**	3.5	91[d]
7	 **7a**	 **7b**	4	90[d]
8	 **8a**	 **8b**	3	88[d]

[a]The time for the second step, displacement of the toslaytes. [b]Yields refer to single runs and are given isolated chlorides. [c]Purified by vacuum distillation. [d]Purified by column chromatography.

When this procedure was applied to other primary alcohols such as 2-phenylethanol, 5-phenyl-1-pentanol, and 3-(3-pyridyl)propanol, the results, however, showed incomplete or no conversion of their tosylates into the expected chlorides after tosylation (Sch. 2). For example, treatment of 5-phenyl-1-pentanol under the same reaction conditions only gave 5-phenyl-1-pentyl tosylate (94%) without the corresponding chloride being detected.



Scheme 2. Reaction conditions: (i) TsCl (1.1 eq.), Et_3N (2 eq.), DMAP (0.02 eq.), CH_2Cl_2, 0–5°C (ii) MeOH (0.4 eq.), 40–42°C, 7 h.

In summary, a one-pot and efficient procedure for the conversion of aryl- and acyl-substituted methyl alcohols into the chlorides is presented. The distinct advantages of this method are its mild conditions, short reaction time, operational convenience, high yields, low cost of reagents, and suitability for scale-up.

EXPERIMENTAL

All reagents and solvents were used without further purification. GC was performed using a Hewlett-Packard 5890A chromatograph equipped with a flame ionization detector. HPLC was performed on Nova-Pak C_{18} column (3.9 × 150 mm, Waters) with flow rate of 1.5 mL/min, detection at 254 nm, and the mobile phase, CH_3CN–H_2O (46:54). ^1H NMR spectra were recorded on a Varian Gemini 300 spectrometer. The structures of the products were confirmed by ^1H NMR spectral data and comparison with those of authentic samples.

General Procedure for the One-Pot Conversion of Aryl- and Acyl-substituted Methyl Alcohols into Chlorides

To a solution of alcohol (10 mmol) in CH_2Cl_2 (25 mL) at 0°C was added tosyl chloride (2.1 g, 11 mmol, 1.1 eq.) in portions with stirring. A solution of triethylamine (2.79 mL, 20 mmol, 2 eq.) and DMAP (24 mg, 0.2 mmol, 0.02 eq.) in CH_2Cl_2 (5 mL) was then added dropwise with stirring at 0–5°C. After addition, the mixture was stirred at 0–5°C under nitrogen for 1–2 h when the starting alcohol disappeared. Methanol (0.17 mL, 4 mmol, 0.4 eq.) was added, and the resulting mixture

was then heated at 40–42°C with stirring under nitrogen until the conversion of the tosylate to the chloride was complete. The mixture was cooled to room temperature, and CH_2Cl_2 (50 mL) and water (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by vacuum distillation or column chromatography on silica gel.

The chemical names, ^{1}H NMR, and elemental analytical data of compounds **6b–8b** are listed below.

21-Chloro-9β,11β-epoxy-17α-hydroxy-16α-methylpregna-1,4-diene-3,20-dione (6b): ^{1}H NMR (DMSO-d_6): δ 7.32 (d, $J = 10.7$ Hz, 1H), 6.25 (d, $J = 10.6$ Hz, 1H), 6.08 (s, 1 H), 4.54 (s, 2H), 2.90–2.86 (m, 1H), 1.99–1.96 (m, 3H), 1.74–1.73 (m, 1H), 1.52–1.49 (m, 2H), 1.43–1.40 (m, 2H), 1.39–1.37 (m, 1H), 1.36 (s, 3H), 1.29–1.27 (m, 2H), 1.16 (s, 3H), 0.84 (d, $J = 7.1$ Hz, 3H). Anal. calcd. for $C_{22}H_{27}ClO_4$: C, 67.60; H, 6.96; Cl, 9.07. Found: C, 67.56; H, 7.05; Cl, 9.11.

21-Chloro-11α,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (7b): ^{1}H NMR (DMSO-d_6): δ 7.82 (d, $J = 10.7$ Hz, 1H), 6.00-5.97 (m, 2 H), 5.31 (s, 1 H), 4.74 (d, $J = 16.8$ Hz, 1H), 4.73 (d, $J = 7.0$ Hz, 1H), 4.42 (d, $J = 16.8$ Hz, 1H), 3.90–3.84 (m, 1H), 2.95–2.89 (m, 1H), 2.50–2.43 (m, 1H), 2.35–2.29 (m, 1H), 1.87–1.70 (m, 3H), 1.69–1.53 (m, 1H), 1.24 (s, 3H), 1.12–1.06 (m, 1H), 1.05–0.94 (m, 2H), 0.79 (d, $J = 7.1$ Hz, 3H), 0.65 (s, 3H). Anal. calcd. for $C_{22}H_{29}ClO_4$: C, 67.25; H, 7.44; Cl, 9.02. Found: C, 67.15; H, 7.49; Cl, 9.07.

21-Chloro-9α-fluoro-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione (8b): ^{1}H NMR ($CDCl_3$): δ 7.21 (d, $J = 10.7$ Hz, 1H), 6.38 (d, $J = 10.7$ Hz, 1H), 6.14 (s, 1H), 4.36 (m, 1H), 4.07 (s, 2H), 2.80–2.56 (m, 2H), 2.48–2.24 (m, 3H), 2.09–2.01 (m, 1H), 1.95–1.78 (m, 3H), 1.63–1.57 (m, 1H), 1.56 (s, 3H), 1.39–1.25 (m, 1H), 1.00 (d, $J = 7.1$ Hz, 3H), 0.98 (s, 3H). Anal. calcd. for $C_{22}H_{28}ClFO_4$: C, 66.91; H, 7.15. Found: C, 66.98; H, 7.11.

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Received in the USA February 21, 2002