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Facile Chlorination of Benzyl Alcohols Using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and Sulfonyl Chlorides

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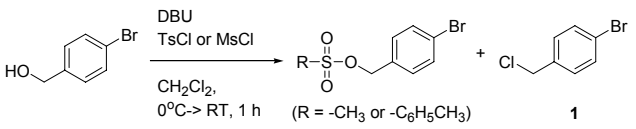
Chlorinated compounds are useful intermediates in many organic synthetic reactions. A variety of biologically active natural products have chlorine atoms in their structure. Thus, chlorination of alcohols has been studied and used in organic chemistry for decades. Chlorination of benzyl alcohols is also a topic of interest because benzyl chlorides can be used as important synthons in organic synthesis. Generally, chlorination of alcohols has been performed using traditional reagents such as concentrated HCl,[1] $SOCl_2$,[2] PCl_5,[3] PCl_3,[4] and $POCl_3$.[5] However, these reagents are strongly acidic and corrosive, and often require heating for the reaction. Many attempts have been made to develop non-acidic and mild chlorination conditions. Benzyl alcohols can be chlorinated by traditional methods; however, milder and easier reaction conditions are necessary for an increased yield. Chlorination using PPh_3/CCl_4[6] or a modified-Mitsunobu type reaction[7] are relatively mild reactions. Chlorination by silyl chlorides with catalysts might be another option.[8-11] In case of benzyl alcohols, chlorination using sulfonyl chlorides such as methanesulfonyl chloride (MsCl) or *p*-toluenesulfonyl chloride (TsCl) with organic bases also could be of choice.[12-18] In the present study, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), one of the strongest organic bases, was tested as an alternative choice for chlorination of benzyl alcohols.

We estimated chlorination yields of 4-bromobenzyl alcohol using various amounts of sulfonylating agents and DBU from 0 °C to room temperature for 1 hr (Table 1). The TLC monitoring showed that chlorination occurred after sulfonylation. Long reaction time was not necessary because the completion of reaction occurred during concentration process of the reaction mixture. The reaction gave 4-bromobenzyl chloride in low yields when reacted with 1 eq. of each reagent (entry 1 and 6). The yields were improved to 83% with TsCl and 92% with MsCl as the amount of added reagents increased (entry 4 and 10). The reaction with 1 eq. of TsCl gave 4-bromobenzyl toluenesulfonate in low yield (entry 1). No methanesulfonate was separated in the trials with MsCl (entry 6-10). To test the substituent effect of the aromatic ring, chlorination of three benzyl alcohols containing either $-NO_2$, -H or $-OCH_3$ at the 4-position were carried out with 2.0 eq. DBU and 1.5 eq. TsCl or MsCl (Table 2). With TsCl, the yields decreased according to the increase of electron density on the aromatic ring (entry 1, 3 and 5), whereas

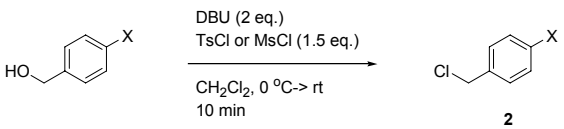
Table 1. Chlorination test of 4-bromobenzyl alcohol according to the amounts of DBU and sulfonylating agents[a]



Entry	DBU (eq.)	Sulfonyl chloride (eq.)	Yield (%)[b]	
			Sulfonylate	Chloride **1**
1	1.0	TsCl (1.0)	5	48
2	1.5	TsCl (1.5)	-	60
3	2.0	TsCl (1.5)	-	66
4	2.0	TsCl (2.0)	-	83
5	3.0	TsCl (3.0)	-	74
6	1.0	MsCl (1.0)	-	55
7	1.5	MsCl (1.5)	-	64
8	2.0	MsCl (1.5)	-	69
9	2.0	MsCl (2.0)	-	77
10	3.0	MsCl (3.0)	-	92

[a]4-Bromobenzyl alcohol (1.32 - 1.36 mmol) was used with 10 - 15 mL CH_2Cl_2. [b]Isolated yields.

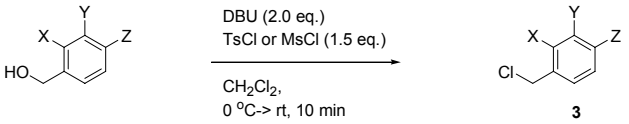
Table 2. Chlorination of three benzyl alcohols using DBU and sulfonylating agents[a]



Entry	X	Sulfornyl chloride	Chloride	Yield (%)[b]	δ of Benzylic H	
					Alcohol	Chloride **2**
1	NO_2	TsCl	**2a**	81	4.84	4.66
2	NO_2	MsCl	**2a**	69		
3	H	TsCl	**2b**	59	4.63	4.55
4	H	MsCl	**2b**	65		
5	OMe	TsCl	**2c**	44	4.60	4.57
6	OMe	MsCl	**2c**	79		

[a]Benzyl alcohols (1.32 - 1.36 mmol) were used with 10 - 15 mL CH_2Cl_2. [b]Isolated yields.

Table 3. Chlorination of benzyl alcohols using DBU and sulfonylating agents[a]



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entry	X	Y	Z	sulfonyl chloride	chloride	yield (%)	δ of benzylic H	
							alcohol	chloride
1	H	Cl	NO_2	TsCl	**3a**	92[b]	4.78	4.62
2	H	Br	H	TsCl	**3b**	79[b]	4.64	4.51
3	H	CN	H	TsCl	**3c**	78[b]	4.76	4.60
4	H	H	CO_2Me	TsCl	**3d**	70[b]	4.78	4.61
5	H	H	I	TsCl	**3e**	71[b]	4.65	4.49
6	H	Me	Me	MsCl	**3f**	78[b]	4.61	4.65
7	H	H	NMe_2	MsCl	-	-	4.55	-
8	NHBOC	H	H	TsCl	**3g**	< 10[c]	4.68	4.60
9	NHBOC	H	H	MsCl	**3g**	34[b]		
10	H	H	NHBOC	TsCl	**3h**	23[b]	4.59	4.55
11	H	H	NHBOC	MsCl	**3h**	20[b]		

[a]Benzyl alcohols (1.32 - 1.36 mmol) were used with 10 - 15 mL CH_2Cl_2 (entry a-g) or 1 - 5.5 mL (entry h). [b]Isolated yields. [c]Assumed from ^{1}H NMR of inseparable mixture (**3g** and TsCl) after column purification.

the yields were not significantly affected by electron density on the aromatic ring in case of MsCl (entry 2, 4 and 6). Further tests were carried out based on the results in Table 2: Electron-withdrawing group (EWG) containing benzyl alcohols were tested with TsCl and electron-donating group (EDG) containing benzyl alcohols were tested with MsCl (Table 3). In reactions with the EWG-containing benzyl alcohols, the benzyl chlorides were synthesized with increased yields (entry 1-5). On the other hand, the reactions of the EDG-containing benzyl alcohols did not always give increased yields. The 3,4-dimethylbenzyl alcohol gave its corresponding chloride in a moderate yield (entry 6). However, the 4-*N*,*N*-dimethylaminobenzyl alcohol did not give a chlorinated product but gave a polar mixture at the origin on TLC (entry 7). All of the reactions containing BOC-protected aminobenzyl alcohols, at the ortho or para position of the benzyl alcohols, gave chlorinated products in low yields (entry 8-11). The mechanism of this reaction is supposed to be sulfonylation followed by substitution of chloride. In case of EWG-containing benzyl alcohol, tosylates give good yields because they are relatively stable and also are appropriately reactive comparing with their mesylates. In case of EDG-containing benzyl alcohols, their tosylates might be too stable to react with chloride comparing with the mesylates. In this study, various benzyl chloride derivatives were prepared with good to moderate yields in a short time under ambient condition. Although there are many reports of chlorination using sulfonyl chlorides and bases (like TEA and DMAP), short reaction time and easy reaction condition of this procedure could be advantages for some cases. For an example, chlorination of electron-deficient benzyl alcohols often requires harsher conditions and longer reaction times than the present method: Preparation of 4-nitrobenzyl chloride from its corresponding alcohol necessitates very long time (24 h)[11,19] or a high temperature (100 - 150 °C).[20,21] However, 4-nitrobenzyl alcohol was chlorinated within 10 min with 81% yield using DBU and TsCl in this study. A facile and fast method for chlorination of benzyl alcohols was developed in this study. This method is not effective for amine-containing substrates, possibly because of side reaction by free amino group or because of electron-donating property of amino group on ortho- or para- postion by resonance. But in some cases, for example electron deficient benzyl alcohols, this method could be a choice for chlorination.

Experimental Section

General procedure for preparation of benzyl chlorides. To a mixture of benzyl alcohol (1.34 mmol) in 10.0 mL CH_2Cl_2, DBU (2.66 mmol) and TsCl (2.06 mmol) in 5.0 mL CH_2Cl_2 or neat MsCl (2.06 mmol) were added in an ice-water bath. After the compounds were added, the bath was removed and the mixture was stirred at room temperature. After 10 min, the mixture was concentrated under reduced pressure (bath temperature: 31 - 32 °C). Column chromatography on silica gel (230 - 400 mesh, mobile phase: 5 - 40% EtOAc/Hexane.

4-Bromobenzyl chloride 1: white solid (66% for TsCl and 69% for MsCl); mp 35 - 36 °C (lit. 37-38 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.50 (s, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3 (C), 131.8 (CH) 130.2 (CH) 122.4 (C), 45.3 (CH_2); MS (CI+): *m*/*z* 205 (M+1).

4-Nitrobenzyl chloride 2a: white solid (81% for TsCl and 69% for MsCl); mp 70-71 °C (lit. 70-73 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 4.66 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (C), 144.2 (C) 129.2 (CH) 123.8 (CH), 44.4 (CH_2); MS (CI+) *m*/*z* 171 (M+1).

Benzyl chloride 2b: clear oil (59% for TsCl and 65% for MsCl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 4.55

(s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4 (C) 128.6 (CH) 128.5 (CH), 128.3 (CH), 46.2 (CH_2); MS (CI+) *m*/*z* 127 (M+1).

4-Methoxybenzyl chloride 2c: clear oil (44% for TsCl and 79% for MsCl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (C), 130.0 (C) 129.6 (CH) 114.0 (C), 55.2 (CH_3), 46.2 (CH_2); MS (CI+) *m*/*z* 157 (M+1).

1-Chloro-4-(chloromethyl)-2-nitrobenzene 3a: yellow oil (92% for TsCl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.56 (m, 2H), 4.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 137.7 (C), 133.0 (CH) 132.1 (CH), 126.7 (C), 125.4 (CH), 43.8 (CH_2); MS (EI+) *m*/*z* 205 (M^+, 70).

3-Bromobenzyl chloride 3b: clear oil (79% for TsCl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 8.1, 7.8 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5 (C), 131.5 (CH), 131.4 (CH) 130.2 (CH), 127.1 (CH), 122.5 (C), 45.1 (CH_2); MS (EI+) *m*/*z* 204 (M^+).

3-(Chloromethyl)benzonitrile 3c: white solid (78% for TsCl); mp 64 - 66 °C (lit. 65 - 67 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65-7.59 (m, 2H), 7.46 (dd, *J* = 7.8, 7.5, 1H), 4.60 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6 (C), 132.7 (CH), 131.72 (CH), 131.70 (CH), 129.4 (CH), 118.0 (C), 112.5 (C), 44.5 (CH_2); MS (EI+) *m*/*z* 151 (M^+).

Methyl 4-(chloromethyl)benzoate 3d: white solid (70% for TsCl); mp 37 - 38 °C (lit. 40 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 4.61 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 142.2 (C), 130.0 (CH) 129.9 (CH), 128.4 (CH), 52.1 (CH_3), 45.3 (CH_2); MS (EI+) *m*/*z* (%) 184 (M^+).

4-Iodobenzyl chloride 3e: white solid (71% for TsCl); mp 48 - 50 °C (lit. 52 - 53 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8 (CH), 137.0 (C), 130.3 (CH), 94.1 (C) 45.4 (CH_2); MS (CI+) *m*/*z* 253 (M+1).

4-(Chloromethyl)-1,2-dimethylbenzene 3f: clear oil (78% for MsCl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.24 (s, 2H), 4.65 (s, 2H), 2.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (C), 136.8 (C), 134.8 (C), 129.84 (CH), 129.79 (CH), 126.0 (CH), 46.2 (CH_2), 19.6 (CH_3), 19.4 (CH_3); MS (EI+) *m*/*z* 154 (M^+).

***tert*-Butyl 2-(chloromethyl)phenylcarbamate 3g:** white solid (less then 10% for TsCl and 34% for MsCl); mp 47 - 48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 8.1, 7.5 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.06 (dd, *J* = 7.5, 7.2 Hz, 1H), 6.77 (bs, 1H), 4.60 (s, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 137.0 (C), 130.0 (CH), 127.0 (C), 123.9 (CH), 122.7 (CH), 80.8 (C), 44.1 (CH_2), 28.2 (CH_3); MS (EI+) *m*/*z* 241 (M^+).

***tert*-Butyl 4-(chloromethyl)phenylcarbamate 3h:** white solid (23% for TsCl and 20% for MsCl); mp 92 - 94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.58 (bs, 1H), 4.55 (s, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 (C), 138.5 (C), 131.9 (C), 129.4 (CH), 118.5 (CH), 80.7 (C), 46.1 (CH_2), 28.3 (CH_3); MS (EI+) *m*/*z* 241 (M^+).

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