A Highly Chemoselective and Rapid Chlorination of Benzyl Alcohols under Neutral Conditions

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Abstract: A rapid and highly selective chlorination method has been developed using 2,4,6-trichloro-1,3,5-triazine (TCT) catalyzed by dimethyl sulfoxide. The reactions take 10 to 40 minutes, and the yields are almost quantitative. The neutral reaction conditions are compatible with substrates bearing acid-labile functional groups. Both competitive intramolecular and intermolecular reactions for benzyl alcohols in the presence of aliphatic alcohols indicate high selectivity. The procedure has been successfully used in the selective chlorination of gastrodin, a clinically used neuromedicine. This procedure represents a useful new tool in organic and medicinal chemistry.

Key words: benzyl alcohols, benzyl chlorides, chemoselectivity, halogenation, sulfoxides

Chlorides are of great importance as intermediates in organic synthesis, and the conversion of alcohols into the corresponding chlorides is an important synthetic procedure. Many reagents can be used to convert alcohols into chlorides,[1] such as hydrochloric acid,[2] thionyl chloride[3] and phosphorus halides.[4] Nevertheless, the conversion often requires quite drastic reaction conditions, and the co-generation of hydrochloride often causes undesired side reactions.[5] In this context, the development of efficient reagents under mild conditions represents a challenge for synthetic organic chemistry. The triphenylphosphine/carbon tetrachloride system seems to meet these requirements, allowing the transformation of labile alcohols like geraniol and lincomycin under mild, essentially neutral conditions;[6] however, this system is inconvenient to work up as a result of the co-generation of triphenylphosphine oxide. To solve this drawback, (chlorophenylthiomethylene)dimethylammonium chloride was reported for the selective chlorination and bromination (in the presence of tetrabutylammonium bromide) of primary alcohols under mild conditions;[7] however, the reagent has to be prepared through a two-step procedure. The treatment of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, TCT), an inexpensive and commercially available reagent, with alcohols furnishes the corresponding chlorides upon heating the alcohols to 10 to 20 °C below their boiling points and then slowly adding excess TCT.[8] Nevertheless, this method seems to be unsuitable for preparing complicated organic chlorides. To solve these drawbacks, a very mild and efficient method using the complex of TCT and *N*,*N*-dimethylformamide (DMF) was reported for the conversion of alcohols and β-amino alcohols into the corresponding chlorides (and bromides);[9] however, there are no differences in the rates and yields between benzyl alcohols and aliphatic alcohols under the TCT/DMF conditions. Only a few selective halogenation procedures have been reported, and the halogenation reagents include silica chloride (SiO_2–Cl),[10] $SOCl_2$/DMF/halides[11] and Me_2S/NCS.[12] Therefore, the development of a chemoselective conversion of benzyl alcohols in the presence of aliphatic alcohols into the corresponding benzyl chlorides under neutral conditions became of interest to us. This is also the problem that is faced in the conversion of gastrodin into monochlorogastrodin (Table 2, entry 8). Gastrodin is the active ingredient of *Tianma* (*Gastrodia elata* BL), one of the most famous traditional Chinese medicines, which has been used to treat headaches, dizziness, vertigo and convulsive illnesses, such as epilepsy and tetanus for hundreds of years.[13] Gastrodin was isolated, synthesized and has been used clinically as a neuromedicine in China for more than 20 years.[14] Its effects include anticonvulsant activity, brain protection, and memory and learning improvement.[15]

The dimethyl sulfoxide (DMSO)/TCT system was originally used for the oxidation of primary and secondary alcohols. When *p*-nitrobenzyl alcohol was treated with DMSO/TCT, a significant amount of *p*-nitrobenzyl chloride was yielded as byproduct, along with *p*-nitrobenzaldehyde.[16] Based on this, we speculated that DMSO could be used as an organocatalyst in the alcohol chlorination and the DMSO/TCT system could convert alcohols into the corresponding chlorides. We began with the chlorination of simple benzyl alcohols using TCT catalyzed by DMSO.

The chlorination of benzyl alcohols was performed using TCT and DMSO in various solvents, such as acetonitrile, chloroform, ethyl acetate and DMSO; DMSO gave the best results. Therefore, the procedure is based on the portionwise addition of TCT (0.55 equiv) to a solution of the benzyl alcohol (1 equiv) in anhydrous DMSO (5 mL). At room temperature, this system rapidly produces the quantitative conversion of benzyl alcohols into the corresponding benzyl chlorides (Table 1, entries 1–16), which can be purified by a simple aqueous workup. The reaction is generally fast, requiring from 10 to 40 minutes for completion for all types of benzyl alcohols, including those bearing

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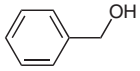
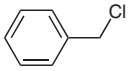
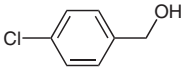
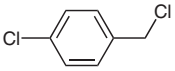
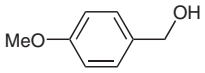
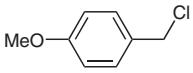
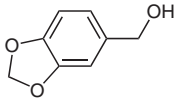
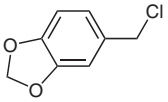
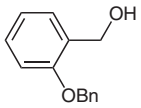
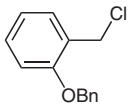
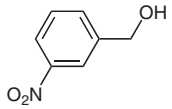
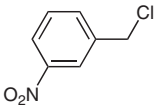
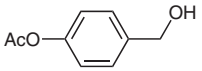
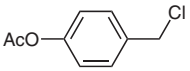
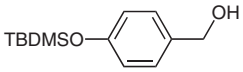
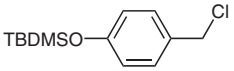
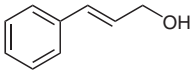
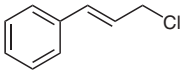
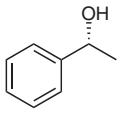
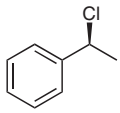
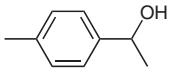
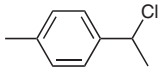
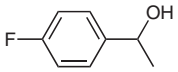
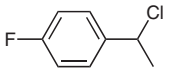
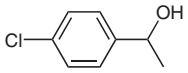
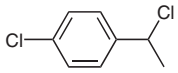
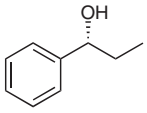
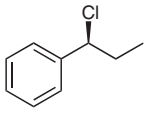
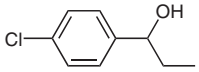
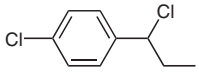
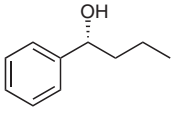
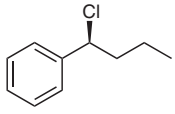
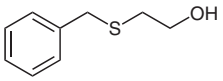
Table 1 Conversion of Benzyl Alcohols into the Corresponding Benzyl Chlorides Using TCT Catalyzed by DMSO at Room Temperature[a]

Entry	Substrate	Product	Time (min)	Yield (%)
1			30	94
2			15	94
3			25 (5 h[b])	82 (79[b])
4			20 (3.5 h[b])	100 (70[b])
5			10	100
6			15	100
7			20	94
8			20	85
9			35	93
10			40	97
11			15	94
12			40	99
13			35	80
14			25	99
15			25	100
16			25	85
17		–	2 d	none

[a] To a solution of the alcohol (1 equiv) in anhydrous DMSO was added TCT (0.55 equiv) portionwise.
[b] A mixture of DMSO (0.2 equiv), TCT (1.2 equiv) and anhydrous MeCN (5 mL) was stirred at room temperature for 30 minutes, followed by the addition of the benzyl alcohol (1 equiv) in anhydrous MeCN (5 mL).

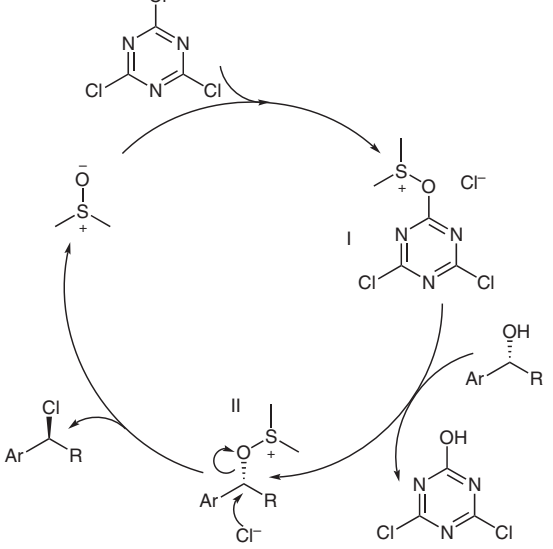
electron-donating (entries 3–5) or electron-withdrawing (entries 6 and 12) groups. Acid-labile functional groups such as ester (entry 7), silyl ether (entry 8), olefin (entry 9) and acetal (entry 4) are all compatible with the reaction conditions. Allyl alcohols can be chlorinated under our reaction conditions (entry 9). Data from the optically active benzyl alcohols (entries 10, 14 and 16) show that the reaction occurs with a partial inversion of configuration at the chiral center. A sample of (*R*)-1-phenylethanol {$[\alpha]_D^{25}$ +36.19 (*c* 1, $CHCl_3$), 74% ee} under the above reaction conditions gave (*S*)-1-phenylethyl chloride {$[\alpha]_D^{25}$ –17.78 (neat), Lit.[17] $[\alpha]_D^{25}$ –94 (neat)}, corresponding to a 63% inversion of configuration. Analogously, (*R*)-1-phenylpropan-1-ol {$[\alpha]_D^{25}$ +36.70 (*c* 1, $CHCl_3$), 77% ee} and (*R*)-1-phenylbutan-1-ol {$[\alpha]_D^{25}$ +35.40 (*c* 1.29, $CHCl_3$), 81% ee} gave (*S*)-1-phenylpropyl chloride {$[\alpha]_D^{25}$ –15.29 (neat), Lit.[18] $[\alpha]_D^{25}$ –28.9 (neat), 85% inversion of configuration} and (*S*)-1-phenylbutyl chloride {$[\alpha]_D^{25}$ –19.85 (neat), Lit.[19] $[\alpha]_D^{25}$ –26.2 (neat), 97% inversion of configuration}, respectively. This is comparable to classical conditions that use a combination of thionyl chloride and pyridine.[20]

Most interestingly, the method is clearly inefficient for aliphatic alcohols (Table 1, entry 17), which provides a chemoselective chlorination for benzyl alcohols in the presence of aliphatic alcohols. In a competitive intermolecular experiment between 4-chlorobenzyl alcohol and 2-phenoxyethanol, only the former was transformed into the chloride with a 76% yield while the latter remained intact (Table 2, entry 6). The same chlorination occurred in the competitive intermolecular experiment between 4-chlorobenzyl alcohol and 2-phenylethanol (Table 2, entry 7). In contrast, when an equimolar mixture of 4-chlorobenzyl alcohol and 2-phenylethanol reacted with thionyl chloride (1 equiv) in a control experiment, both alcohols were partially transformed into the corresponding chlorides in a 2:1 molar ratio in favor of the benzyl chloride. In another control experiment, an equimolar mixture of 4-chlorobenzyl alcohol and 2-phenylethanol was treated with triphenylphosphine/carbon tetrachloride; here, a large amount of phosphonium salt was formed. In the competitive intramolecular experiments (Table 2, entries 1–5), all the benzylic hydroxy groups were substituted by chloride in fair to high yields while the aliphatic hydroxy groups were left intact. This procedure also resulted in the conversion of gastrodin into its monochloride in 84% yield (Table 2, entry 8), a transformation which cannot be achieved using any current method, since gastrodin possesses five hydroxy groups and an acid-labile β-glycosidic group. It is thus possible to prepare a variety of gastrodin derivatives by substituting the benzylic chloride of monochlorogastrodin with nucleophiles such as RNH^-, ArO^-, RS^- and N_3^-, which may show better biological activities.

In order to verify our assumption that DMSO serves as the catalyst, we treated the benzyl alcohols with electron-releasing groups with a substoichiometric quantity of DMSO. Thus, a mixture of DMSO (0.2 equiv), TCT (1.2 equiv) and anhydrous acetonitrile (5 mL) was stirred at room temperature for 30 minutes, followed by the addition of the benzyl alcohol (1 equiv) in anhydrous acetonitrile (5 mL). The reactions gave satisfactory yields, requiring 3.5 to 5 hours for the quantitative conversion of the benzyl alcohols into the corresponding chlorides (Table 1, entries 3 and 4). For entry 4 of Table 1, the amount of DMSO can be reduced to 0.01 equivalent without a notable decrease in the rate and yield.

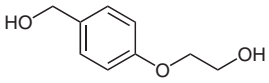
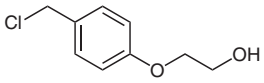
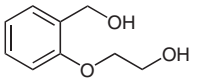
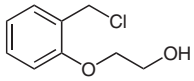
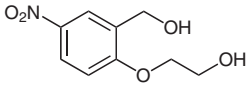
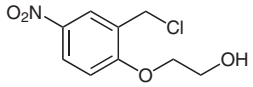
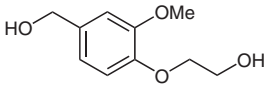
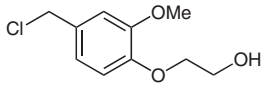
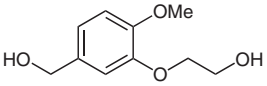
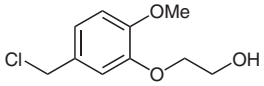
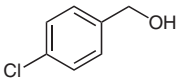
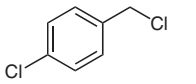
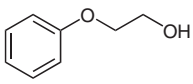
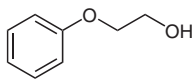
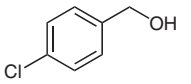
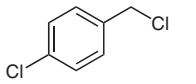
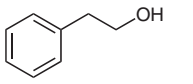
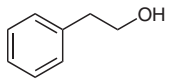
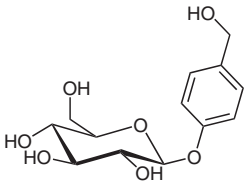
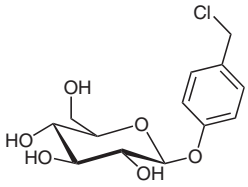
On the basis of the above experiments, we propose the catalytic cycle shown in Scheme 1. The adduct I of TCT and DMSO reacts with the alcohol to form a dimethyl alkoxysulfonium salt II,[21] followed by a nucleophilic attack of chloride on II. Only a dimethyl arylmethoxysulfonium salt II is active enough to yield the corresponding chloride, whereas an aliphatic sulfonium salt is not active enough for chloride substitution and decomposes to regenerate the alcohol. At least two chlorine atoms in one TCT molecule can be used for the chlorination of alcohols, according to our experiments. The major pathway of the reaction is S_N2, as demonstrated by the configuration inversion of the chiral benzyl alcohols (Table 1, entries 10, 14 and 16). A partial S_N1 pathway is also possible.

In conclusion, we have established a new method to transform benzyl alcohols into chlorides. This procedure provides a solution to the following drawbacks related to the current methods: (1) acidic conditions (hydrochloric acid[2] or DMSO/TMSCl[22]); (2) prolonged reaction times (Ph_3P/CCl_4[6]); (3) poor selectivity for benzyl alcohols and aliphatic alcohols (phosphorus halides[4] or thionyl chloride[3]); (4) incompatibility with benzyl chloride (Ph_3P/CCl_4[6]). The procedure reported herein is operationally simple, and requires inexpensive and commercially available reagents. This organocatalyzed reaction is mild and fast (10 to 40 minutes). A highly chemoselective chlorination of benzyl alcohols in the presence of aliphatic alcohols has been achieved. This reaction constitutes a useful tool for



Scheme 1 Proposed mechanism for the selective chlorination of benzyl alcohols

Table 2 Chemoselective Chlorination of Alcohols Using TCT Catalyzed by DMSO at Room Temperature[a]

Entry	Substrate	Product	Time (min)	Yield (%)
1			30	63
2			35	71
3			20	80
4			20	70
5			20	80
6[b]			25	76
				100[c]
7[b]			25	78
				100[c]
8			15	84

[a] To a solution of the alcohol (1 equiv) in anhydrous DMSO was added TCT (0.55 equiv) portionwise.
[b] To a mixture of the benzyl alcohol (1 equiv) and the aliphatic alcohol (1 equiv) in anhydrous DMSO was added TCT (0.55 equiv) portionwise.
[c] Recovered yield of the aliphatic alcohol.

medicinal and organic chemistry, as demonstrated in the selective chlorination of gastrodin.

All chemicals were obtained from commercial sources or were prepared according to standard methods. All chemicals and solvents used in reactions were dried by standard procedures prior to use. IR spectra were recorded on a Bio-Rad Excalibur FTS3000 spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian Oxford 500 spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). Mass spectra (EI) were obtained on a Thermo Finnigan TRACE-DSQ spectrometer at 70 eV. Mass spectra (ESI) were obtained on a Finnigan LCQ Advantage MAX spectrometer at a spray voltage of 4.5 KV. Elemental analyses for C, H and N were performed on a Yanaco CHN CORDER MF-3 elemental analyzer, and the analytical results are within ±0.4% of the theoretical values.

Chlorination of Benzyl Alcohols: Benzyl Chloride (Table 1, Entry 1); Typical Procedure

The procedure for the chlorination of benzyl alcohol (Table 1, entry 1) is representative for all benzyl alcohols in Table 1. To a soln of benzyl alcohol (519 mg, 4.81 mmol) in anhyd DMSO (5 mL) was added TCT (487 mg, 2.64 mmol) portionwise. The mixture was stirred at r.t. and the reaction was monitored by TLC until completion (30 min). Then, the mixture was added to Et_2O (50 mL), and the organic phase was washed with H_2O (5 × 30 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give the crude product which was then filtered through a silica gel pad with petroleum ether to afford benzyl chloride; yield: 572 mg (94%).

4-Methoxybenzyl Chloride (Table 1, Entry 3); Typical Procedure for the Chlorination of Benzyl Alcohols Catalyzed by DMSO (0.2 Equiv)

The procedure for the chlorination of 4-methoxybenzyl alcohol (Table 1, entry 3) is representative. A mixture of DMSO (34 mg, 0.43 mmol), TCT (480 mg, 2.61 mmol) and anhyd MeCN (5 mL) was stirred at r.t. for 30 min, followed by the addition of 4-methoxybenzyl alcohol (300 mg, 2.17 mmol) in anhyd MeCN (5 mL). The

reaction was monitored by TLC until the complete disappearance of 4-methoxybenzyl alcohol occurred (5 h). Then, the reaction mixture was diluted with Et_2O (50 mL), and the organic phase was washed with H_2O (2 × 30 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give the crude product which was then filtered through a silica gel pad with petroleum ether to afford 4-methoxybenzyl chloride; yield: 270 mg (79%).

2-[4-(Chloromethyl)phenoxy]ethanol (Table 2, Entry 1); Typical Procedure for the Chemoselective Chlorination of Benzylic Hydroxy Groups in the Presence of Aliphatic Hydroxy Groups

The procedure for the chemoselective chlorination of 4-(2-hydroxyethoxy)benzyl alcohol (Table 2, entry 1) is representative. To a soln of 4-(2-hydroxyethoxy)benzyl alcohol (200 mg, 1.19 mmol) in anhyd DMSO (5 mL) was added TCT (121 mg, 0.65 mmol) portionwise. The mixture was stirred at r.t. and the reaction was monitored by TLC until completion (30 min). Then, the mixture was added to CH_2Cl_2 (50 mL), and the organic phase was washed with H_2O (5 × 30 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give the crude product which was then purified by silica gel chromatography (petroleum ether–EtOAc, 3:1) to afford 2-[4-(chloromethyl)phenoxy]ethanol; yield: 140 mg (63%).

IR (KBr): 3398, 2929, 2870, 1612, 1590, 1513, 1249, 1082 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 4.57 (s, 2 H), 4.09 (t, *J* = 4.5 Hz, 2 H), 3.97 (t, *J* = 4.5 Hz, 2 H), 2.17 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6, 130.09, 130.06, 114.7, 69.2, 61.3, 46.1.

MS (EI): *m*/*z* (%) = 188 (3) $[M + 2]^+$, 186 (9) $[M]^+$, 151 (42), 107 (100).

Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found: C, 58.03; H, 5.92.

2-[2-(Chloromethyl)phenoxy]ethanol (Table 2, Entry 2)

From 2-(2-hydroxyethoxy)benzyl alcohol (200 mg, 1.19 mmol).

Yield: 158 mg (71%).

IR (KBr): 3282, 2945, 1603, 1598, 1496, 1451, 1252, 1051, 752, 660 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 2 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 4.67 (s, 2 H), 4.17 (t, *J* = 4.5 Hz, 2 H), 3.99 (m, 2 H), 2.36 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 130.6, 130.3, 125.8, 121.0, 112.0, 69.7, 61.3, 42.3.

MS (EI): *m*/*z* (%) = 188 (11) $[M + 2]^+$, 186 (33) $[M]^+$, 151 (15), 142 (20), 133 (20), 107 (100), 91 (35), 78 (25).

Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found: C, 58.12; H, 5.95.

2-[2-(Chloromethyl)-4-nitrophenoxy]ethanol (Table 2, Entry 3)

From 2-(2-hydroxyethoxy)-5-nitrobenzyl alcohol (250 mg, 1.17 mmol).

Yield: 217 mg (80%).

IR (KBr): 3309, 3229, 2931, 2873, 1614, 1595, 1504, 1358, 1273, 1095, 1045 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 2.8 Hz, 1 H), 8.25 (dd, *J* = 2.8, 9.0 Hz, 1 H), 7.00 (d, *J* = 9.0 Hz, 1 H), 4.68 (s, 2 H), 4.29 (t, *J* = 4.5 Hz, 2 H), 4.07 (t, *J* = 4.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 141.1, 126.8, 126.2, 126.1, 111.4, 70.6, 60.9, 40.8.

MS (EI): *m*/*z* (%) = 233 (2) $[M + 2]^+$, 231 (6) $[M]^+$, 187 (17), 152 (75), 77 (42), 51 (40), 45 (100).

Anal. Calcd for $C_9H_{10}ClNO_4$: C, 46.67; H, 4.35; N, 6.05. Found: C, 46.49; H, 4.36; N, 6.05.

2-[4-(Chloromethyl)-2-methoxyphenoxy]ethanol (Table 2, Entry 4)

From 4-(2-hydroxyethoxy)-3-methoxybenzyl alcohol (200 mg, 1.01 mmol).

Yield: 154 mg (70%).

IR (KBr): 3549, 2940, 1608, 1519, 1460, 1268, 1238, 1167, 1139, 1089, 1035, 687 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (m, 2 H), 6.88 (m, 1 H), 4.57 (s, 2 H), 4.13 (d, *J* = 4.5 Hz, 2 H), 3.95 (d, *J* = 4.5 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.6, 148.1, 130.8, 121.2, 113.8, 112.0, 71.0, 61.1, 55.8, 46.5.

MS (EI): *m*/*z* (%) = 218 (11) $[M + 2]^+$, 216 (33) $[M]^+$, 181 (20), 172 (13), 137 (100), 122 (10).

Anal. Calcd for $C_{10}H_{13}ClO_3$: C, 55.44; H, 6.05. Found: C, 55.51; H, 6.07.

2-[5-(Chloromethyl)-2-methoxyphenoxy]ethanol (Table 2, Entry 5)

From 3-(2-hydroxyethoxy)-4-methoxybenzyl alcohol (200 mg, 1.01 mmol).

Yield: 175 mg (80%).

IR (KBr): 3507, 3367, 2954, 1605, 1520, 1428, 1267, 1238, 1169, 1139, 1077, 1024, 680 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.98 (m, 2 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 4.55 (s, 2 H), 4.15 (t, *J* = 4.5 Hz, 2 H), 3.96 (t, *J* = 4.5 Hz, 2 H), 3.87 (s, 3 H), 2.70 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 148.0, 130.1, 122.0, 114.7, 111.4, 71.1, 61.1, 55.8, 46.4.

MS (EI): *m*/*z* (%) = 218 (5) $[M + 2]^+$, 216 (15) $[M]^+$, 181 (35), 172 (13), 137 (100), 122 (14).

Anal. Calcd for $C_{10}H_{13}ClO_3$: C, 55.44; H, 6.05. Found: C, 55.54; H, 6.04.

Competitive Intermolecular Experiment between Benzyl Alcohols and Aliphatic Alcohols: 4-Chlorobenzyl Chloride (Table 2, Entry 6); Typical Procedure

The competitive intermolecular experiment between 4-chlorobenzyl alcohol and 2-phenoxyethanol (Table 2, entry 6) is representative. To a soln of 4-chlorobenzyl alcohol (444 mg, 3.12 mmol) and 2-phenoxyethanol (431 mg, 3.12 mmol) in anhyd DMSO (5 mL) was added TCT (316 mg, 1.71 mmol) portionwise. The reaction mixture was stirred at r.t. for 25 min and then Et_2O (50 mL) was added. The organic phase was washed with H_2O (5 × 30 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The mixture was separated by silica gel chromatography with petroleum ether to give 4-chlorobenzyl chloride [yield: 380 mg (76%)] and then with petroleum ether–EtOAc (3:1) to recover 2-phenoxyethanol (431 mg, 100%).

Monochlorogastrodin by the Chemoselective Chlorination of Gastrodin (Table 2, Entry 8)

To a soln of gastrodin (150 mg, 0.52 mmol) in anhyd DMSO (1 mL) was added TCT (53 mg, 0.29 mmol) portionwise. The mixture was stirred at r.t. and the reaction was monitored by TLC until completion (15 min). Then, DMSO was removed via bulb-to-bulb distillation under reduced pressure. The residue was taken up in anhyd MeCN (15 mL), filtered, and the filtrate was concentrated and purified by silica gel chromatography (Et_2O–EtOH, 25:1) to give monochlorogastrodin; yield: 134 mg (84%).

IR (KBr): 3206, 3046, 2894, 1612, 1513, 1466, 1400, 1238, 1101, 1073, 1021, 539 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.36 (d, *J* = 8.5 Hz, 2 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 5.50–4.00 (br s, 4 H), 4.88 (d, *J* = 7.4 Hz, 1 H), 4.72 (s, 2 H), 3.68 (d, *J* = 11.0 Hz, 1 H), 3.46 (dd, *J* = 5.7, 11.9 Hz, 1 H), 3.33 (m, 1 H), 3.25 (m, 2 H), 3.16 (t, *J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.4, 131.0, 130.3, 116.3, 100.2, 77.1, 76.6, 73.2, 69.7, 60.7, 46.2.

MS (ESI): *m*/*z* (%) = 341.0 (33) $[M + 2 + NH_4OH]^+$, 339.1 (100) $[M + NH_4OH]^+$.

Anal. Calcd for $C_{13}H_{17}ClO_6$: C, 51.24; H, 5.62. Found: C, 51.43; H, 5.63.

Acknowledgment

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