Mild Debenzylation of Aryl Benzyl Ether with BCl_3 in the Presence of Pentamethylbenzene as a Non-Lewis-Basic Cation Scavenger

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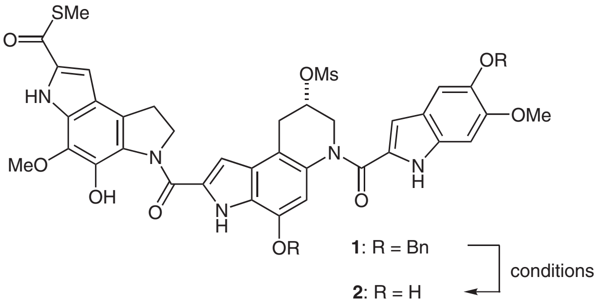
Abstract: Scope and limitations of the debenzylation conditions for aryl benzyl ether, which was developed during our synthetic studies on yatakemycin, were investigated. The chemoselective debenzylation proceeds at low temperature with a combination of BCl_3 and pentamethylbenzene as a cation scavenger in the presence of various functional groups.

Key words: protecting groups, total synthesis, phenols, debenzylation, aryl benzyl ethers

Protective groups play a key role in synthesis of multifunctional complex molecules in modern organic chemistry. The benzyl group has been one of the most useful protective groups for hydroxy and amino functionalities.[1] For example, it serves as an effective protective group for a phenolic hydroxy group since it is readily introduced and tolerated under various reaction conditions. Removal of a benzyl group is generally carried out by palladium-catalyzed hydrogenolysis or by acid-assisted cleavage.[1] Some functional groups, however, do not survive under these conditions.

At the late stage in our synthetic route to yatakemycin, we were faced with the problematic deprotection of the benzyl groups in the presence of the labile thiolester functionality[2] (Table 1). The first attempt using BCl_3 at –78 °C[3] afforded the desired product **2** in low to good yields with concomitant formation of byproducts which might have arisen from the Friedel–Crafts-type electrophilic benzylation of the highly electron-rich aromatic rings (entry 1). No reaction took place at –78 °C in the presence of the standard cation scavenger such as PhSMe[4] and Me_2S, which may deactivate BCl_3 by coordination. Elevating the reaction temperature to room temperature caused complete decomposition of the starting material (entry 2). Extensive literature search suggested us to use pentamethylbenzene (C_6HMe_5) as a non-Lewis-basic cation scavenger, which was introduced by Yoshino and coworkers[5] to carry out debenzylation of *O*-benzyltyrosin without electrophilic benzylation at the phenolic ring. While Yoshino's original conditions[5a] using a combination of TFA and C_6HMe_5 at room temperature resulted only in decomposition of the starting compound **1** (entry 3), treatment of **1** with BCl_3 in the presence of excess C_6HMe_5 at –78 °C cleanly provided **2** in high yield and with high reproducibility (entry 4). In this communication, we describe detailed optimization of our debenzylation conditions using a simple substrate as well as the general applicability of the optimized conditions.

Table 1 Required Debenzylation at the Late Stage of the Total Synthesis of Yatakemycin



Entry	Reaction conditions	Yield (%)[a]
1	BCl_3,[c] CH_2Cl_2, –78 °C, 15 min	19–72
2	BCl_3,[c] Me_2S (or PhSMe), CH_2Cl_2, –78 °C to r.t.	–[b]
3	TFA, C_6HMe_5,[d] r.t.	–[b]
4	BCl_3,[c] C_6HMe_5,[d] CH_2Cl_2, –78 °C, 15 min	83

[a] Isolated yields.
[b] Complex mixture.
[c] Four equiv.
[d] Ten equiv.

By choosing 4-benzyloxy-1,2-dimethoxybenzene[6] (**3**) as a model substrate, we explored optimal conditions (Table 2). Treatment of benzyl ether **3** under our previously reported conditions (BCl_3: 2 equiv, C_6HMe_5: 5 equiv) provided the desired 3,4-dimethoxyphenol[6] (**4**) in 85% yield along with 8% of 2-benzyl-4,5-dimethoxyphenol[7] (**5**, entry 1). Decreasing the amount of BCl_3 to one equivalent slightly lowered the yield (entry 2). In terms of the amount of C_6HMe_5, we found that three equivalents were enough to obtain satisfactory yields (entries 1, 3, and 4). In the absence of C_6HMe_5, a considerable amount (43%) of 2-benzylated compound **5** was isolated, indicating that C_6HMe_5 is crucial to the prevention of the electrophilic C-benzylation (entry 5). On the basis of these experiments,

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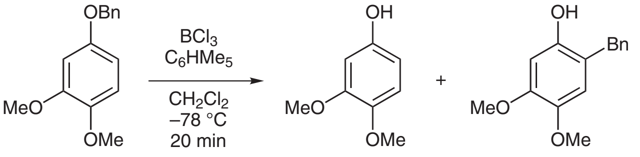
Table 2 Optimization of the Reaction Conditions



3 **4** **5**

Entry	BCl_3 (equiv)	C_6HMe_5 (equiv)	**4** (%)[a]	**5** (%)[a]
1	2	5	85	8
2	1	5	81	10
3	2	3	84	8
4	2	2	81	11
5	2	0	56	43

[a] Isolated yields.

we set two equivalents of BCl_3 and three equivalents of C_6HMe_5 as the standard conditions.

Next, we explored the scope and limitations of the debenzylation conditions using various aryl benzyl ethers[8] (Table 3). Experiments on a series of resorcinol derivatives revealed that methyl, isopropyl, and in particular TBS ethers could tolerate the reaction conditions (entries 1–3). In the case of the substrate bearing the acid-labile silyl ether, we found that the optimum conditions were to use 1.1 equivalents of BCl_3 followed by addition of a mixture of THF and saturated aqueous $NaHCO_3$ (entry 3).

A substantial desilylation took place when a combination of TFA and C_6HMe_5 was used (entry 4).[5a] While acetate did not survive the reaction conditions (entry 5), pivalate and methanesulfonate remained intact during the reaction (entries 6 and 7). The reaction conditions were also applicable to substrates bearing carbonyl groups such as formyl, methyl ketone, ester, and in particular thiol ester, which does not survive hydrogenolysis (entries 8–11). Nitro, iodo, and allyl group, which are reduced under reductive conditions, tolerated the reaction condition (entries 12–14). It should be noted that selective debenzylation of a phenolic benzyl ether was possible in the presence of alkyl benzyl ether and alkyl acetate (entries 15 and 16). As to the compatibility with nitrogen protective groups, Boc, Cbz, *o*-Ns, trifluoroacetyl, and Alloc groups were retained in the debenzylated products (entries 17–22). In the case of the acid-labile Boc-protected substrate, we used 1.1 equivalents of BCl_3 and terminated the reaction with THF-saturated aqueous $NaHCO_3$ (entry 17). For an electron-rich indole derivative, a sizable effect of C_6HMe_5 was observed. Thus, the yield decreased from 93% to 78% in the absence of C_6HMe_5 (entries 23 and 24). Finally, usefulness of our debenzylation was clearly demonstrated with the reaction of a multifunctional tetrahydroquinoline derivative. Both acid-sensitive and reducible functional groups were retained almost completely (entry 25). Reaction with TFA–C_6HMe_5,[5a] on the other hand, resulted in loss of TBS and gave only a trace amount of the desired product (entry 26).

In summary, we have established a mild and facile procedure for debenzylation of aryl benzyl ethers by means of a unique combination of BCl_3 and non-Lewis-basic C_6HMe_5 as a cation scavenger. The present procedure proved to be particularly effective not only for substrates having an electron-rich aromatic ring such as trialkoxybenzenes or indole derivatives, but also for those having acid-labile functionalities such as Boc and TBS ether, demonstrating our conditions' superiority over the ones using TFA and C_6HMe_5. In addition, the unreacted C_6HMe_5 and benzylpentamethylbenzene can be easily removed by column chromatography. The debenzylation conditions we established should find a widespread use in synthetic organic chemistry as a reliable alternative to the conventional palladium-mediated hydrogenolysis.

Acknowledgment

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References and Notes

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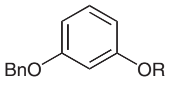
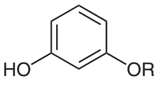
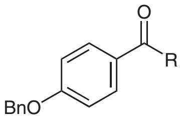
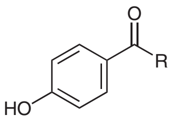
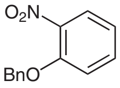
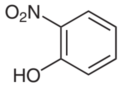
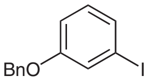
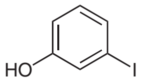
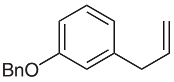
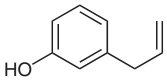
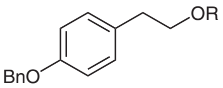
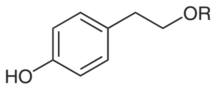
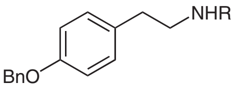
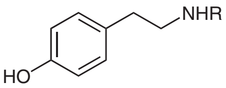
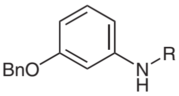
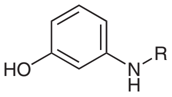
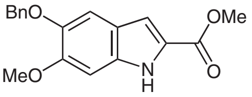
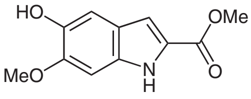
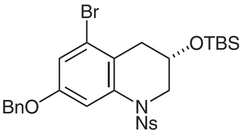
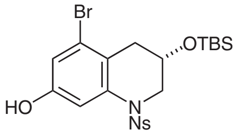
(4) (a) Kiso, Y.; Isawa, H.; Kitagawa, K.; Akita, T. *Chem. Pharm. Bull.* **1978**, *26*, 2562; treatment of *O*-benzyltyrosine with TFA yielded tyrosine and undesired 3-benzyltyrosine in the ratio of 57:43. (b) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673; a combination of thioanisole with TFA was effective to debenzylation of *O*-benzyltyrosine without formation of 3-benzyltyrosine.

(5) (a) Various cation scavengers on debenzylation of *O*-benzyltyrosine in TFA were investigated. It was reported that pentamethylbenzene increased the rate of deprotection most efficiently among other scavengers such as thioanisole, anisole, 1,3-dimethoxybenzene, 1,2,3-dimethoxybenzene, *m*-xylene, 1,2,3-trimethylbenzene, and 1,2,3,4-tetramethylbenzene. Isolation and characterization of benzylpentamethylbenzene generated by trapping of benzyl cation were also reported. See: Yoshino, H.; Tsuchiya, Y.; Saito, I.; Tsujii, M. *Chem. Pharm. Bull.* **1987**, *35*, 3438. (b) Yoshino, H.; Tsujii, M.; Kodama, M.; Komeda, K.; Niikawa, N.; Tanase, T.; Asakawa, N.; Nose, K.; Yamatsu, K. *Chem. Pharm. Bull.* **1990**, *38*, 1735.

(6) Tummatorn, J.; Khorphueng, P.; Petsom, A.; Muangsin, N.; Chaichit, N.; Roengsumran, S. *Tetrahedron* **2007**, *63*, 11878.

Table 3 Deprotection of Various Aryl Benzyl Ethers[a]

Entry	Aryl benzyl ether	Product	Yield (%)[b]
1			87 (R = Me)
2			78 (R = *i*-Pr)
3			87[c,d] (R = TBS)
4			68[e,f] (R = TBS)
5			26[c,g] (R = Ac)
6			92[c] (R = Piv)
7			99 (R = Ms)
8			99 (R = H)
9			98 (R = Me)
10			97 (R = OMe)
11			96 (R = SEt)
12			100
13			98
14			93
15			79 (R = Bn)
16			76 (R = Ac)
17			87[c,d] (R = Boc)
18			95[h] (R = Cbz)
19			83 (R = *o*-Ns)
20			99 (R = $COCF_3$)
21			93 (R = Alloc)
22			93 (R = *o*-Ns)
23			93
24			78[i]
25			94[c,d]
26			1[e,j]

[a] Reaction conditions: aryl benzyl ether (1.0 equiv), BCl_3 (2.0 equiv), C_6HMe_5 (3.0 equiv), CH_2Cl_2, –78 °C, 20 min.

[b] Isolated yields.

[c] BCl_3: 1.1 equiv.

[d] The reaction was quenched by addition of THF and sat. aq $NaHCO_3$ (4:1).

[e] Reaction conditions: aryl benzyl ether (1.0 equiv), C_6HMe_5 (10 equiv), TFA, r.t.

[f] Resorcinol was isolated in 21% yield.

[g] Resorcinol was isolated in 71% yield.

[h] BCl_3: 1.5 equiv.

[i] The reaction was conducted without C_6HMe_5.

[j] (*S*)-5-Bromo-1-(2-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroquinoline-3,7-diol was isolated in 87% yield.

(7) **Physical and Spectroscopic Data for 2-Benzyl-4,5-dimethoxyphenol (5)**
Colorless oil; $R_f = 0.43$ (hexanes–EtOAc, 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 2 H), 7.25–7.17 (m, 3 H), 6.66 (s, 1 H), 6.45 (s, 1 H), 4.37 (s, 1 H), 3.93 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 148.5, 147.7, 143.1, 140.0, 128.7, 128.4, 126.4, 117.6, 114.5, 101.3, 56.6, 55.9, 36.0. IR (neat): 3445, 2932, 1614, 1520, 1452, 1416, 1205, 1109, 997, 669 cm^{-1}. HRMS (EI$^+$): *m/z* calcd for $C_{15}H_{16}O_3$ [M$^+$]: 244.1099; found: 244.1089.

(8) Boron trichloride (1.0 M in CH_2Cl_2) was purchased from Aldrich Chemical Company and was used as supplied. Pentamethylbenzene was purchased from Tokyo Chemical Industry Co., Ltd. and was used as supplied.
Typical Procedure (Table 3, Entry 20)
To a stirred solution of *N*-[3-(benzyloxy)phenyl]-2,2,2-trifluoroethanamide (1.61 g, 5.44 mmol, 1.0 equiv) and pentamethylbenzene (2.42 g, 16.3 mmol, 3.0 equiv) in dry CH_2Cl_2 (27.0 mL) was added BCl_3 (1.0 M in CH_2Cl_2, 10.9 mL, 2.0 equiv) dropwise over 10 min via syringe at –78 °C. After 15 min, TLC indicated complete consumption of the starting material. The reaction was quenched with $CHCl_3$–MeOH (10:1, 20 mL) at –78 °C, and the resulting mixture was warmed to r.t. The excess organic solvents were removed under reduced pressure. The residue was purified by column chromatography on SiO_2 (eluent: hexanes to hexanes–EtOAc = 1:1, gradient) to provide 2,2,2-trifluoro-*N*-(3-hydroxyphenyl)ethanamide (1.10 g, 5.36 mmol, 99%).
Physical and Spectroscopic Data for 2,2,2-trifluoro-*N*-(3-hydroxyphenyl)ethanamide
Colorless crystals; $R_f = 0.54$ (hexanes–EtOAc, 1:1); mp 128.4–129.6 °C (hexanes–EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (br s, 1 H), 7.37–7.34 (m, 1 H), 7.25 (dd, 1 H, $J = 7.8, 7.8$ Hz), 6.95 (dd, 1 H, $J = 7.8, 1.2$ Hz), 6.74 (dd, 1 H, $J = 7.8, 2.4$ Hz), 5.22 (s, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 158.9, 156.5 (q, $^2J_{C-F} = 37$ Hz), 138.5, 130.6, 117.3 (q, $^1J_{C-F} = 285$ Hz), 113.8, 113.1, 109.2. IR (neat): 3312, 1715, 1614, 1566, 1495, 1456, 1188 cm^{-1}. HRMS (FAB$^+$): *m/z* calcd for $C_8H_7NO_2F_3$ [M + H$^+$]: 206.0429; found: 206.0427.