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Selective debenzylation of aromatic benzyl ethers by silica-supported sodium hydrogen sulfate

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ABSTRACT

A new debenzylation of aromatic benzyl ethers by silica-supported sodium hydrogen sulfate is described. The process proceeds selectively and efficiently in good to excellent yields without affecting sensitive functional groups such as nitro, COOMe, aldehyde, ketone, and tosyl.

As a result of its high sensitivity toward other reagents and reaction conditions, the protection of phenolic hydroxyl group is often necessary during the synthesis of any phenol-containing product. Formation of an ether via benzylation is one of the most commonly used strategies for the protection of the functionality in organic synthesis.[1] Such a protecting group features the ease of preparation and its chemical stability toward various reaction conditions.[2] The commonly employed deprotection method is catalytic hydrogenolysis (H_2 in the presence of Pd/C or Raney Ni).[3] Although the method is efficient, some problems associated with debenzylation of aromatic benzyl ethers are also realized. The pyrophoric nature of these catalysts renders the use of relatively complicated experimental procedures to handle them. Moreover, the clean removal of the toxic transition metal nanoparticles is a tedious and highly costly process. This is particularly problematic in the synthesis of therapeutic agents. Third, the deprotection reaction condition is not compatible with other functional groups such as nitro, nitroso, aldehyde, and halogen. Other reductive systems such as Mg/MeOH,[4] Na/*t*-BuOH,[5] Na/NH_3,[6] or Li/Naphthalene[7] also could be used; however, they suffer from the same problems as H_2/Pd/C. Although a variety of alternative strategies are available,[1] generally harsh reaction conditions such as using strong acids[8–10] often give rise to undesired reactions and products and low reaction yields. In this Letter, we wished to disclose an efficient and operationally simple method for debenzylation of aromatic benzyl ethers by silica-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) in thiophene in high efficiency.

Inspired by acid-catalyzed cleavage of benzyl ethers,[9] we envisioned that silica gel supported $NaHSO_4$ (e.g., $NaHSO_4{\cdot}SiO_2$) could be a useful acidic reagent for the aromatic debenzylation. Due to the nature of its environmentally friendless and low cost, the solid acid has become a popular reagent in organic synthesis.[11] It has been widely used in a variety of organic transformations such as nitration, nitrosation, oxidation, halogenation, and coupling of indoles.[11] Moreover, notably, the use of the solid acid in organic synthesis significantly simplifies experimental procedures by simple filtration without the essential aqueous workup, thus resulting in the generation of less aqueous and organic wastes. Finally, the catalyst can be easily prepared from silica gel and sodium hydrogen sulfate.[12]

In an exploratory study, a model reaction of 1-benzyloxy-4-methoxybenzene **1** in the presence of $NaHSO_4{\cdot}SiO_2$ in toluene was carried out under reflux in argon atmosphere for 4 h (Table 1). It was found that the reaction proceeded poorly (Table 1, entry 1). The desired product **2a** was obtained in low yield (38%). In addition, three side products **2b–d** were isolated. Obviously, they resulted from the acid-catalyzed rearrangement of the benzyl ether involved benzylic cation. Optimization of reaction conditions

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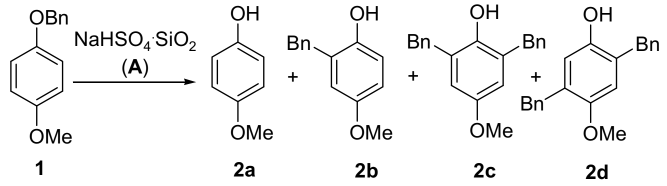
Table 1

Optimization of reaction conditions for debenzylation of 1-benzyloxy-4-methoxybenzene **1**[a]



Entry	A[b] (mg/mmol)	Solvent	T (°C)	t (h)	Yield **2a**[c] (%)
1	500	Toluene	Reflux	4	38[d]
2	500	Thiophene	Reflux	2	65[e]
3	400	Thiophene	Reflux	4	53[f]
4	300	Thiophene	Reflux	6	42[g]
5	—[h]	Thiophene	Reflux	2	Trace[h]
6	500	Anisole	110	3	64[i]
7	500	CCl_4	Reflux	3	10[j]
8	500	CH_2Cl_2	rt	3	NR[k]
9	—[l]	CH_2Cl_2	rt	0.5	11%[l]
10	500	NMP	120	2	NR[k]
11	500	DMF	120	2	NR[k]
12	500	1,4-Dioxane	Reflux	2	NR[k]
13	500	Cyclopentanone	Reflux		NR[h]
14	500	$MeO(CH_2)_2OH$	Reflux		NR[h]

[a] Unless specified, see Ref. 13 for detailed reaction procedure.

[b] Ratio of $NaHSO_4 \cdot SiO_2$ and substrate **1**.

[c] Isolated yields.

[d] 32% **2b**, 5% **2c** and 4% **2d** Isolated.

[e] 23% **2b** Isolated.

[f] Recovered 11% **1**, and 19% **2b** isolated.

[g] Recovered 27% **1**, and 16% **2b** isolated.

[h] CF_3COOH as catalyst in a ratio of 2:1 with **1** (mmol/mmol).

[i] 24% **2b** Isolated.

[j] Recovered 65% **1**, and 8% **2b** isolated.

[k] No reaction.

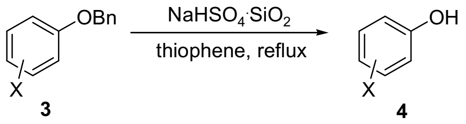
[l] $FeCl_3$ as catalyst in a ratio of 12:1 of it and **1** (mmol/mmol).

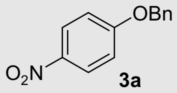
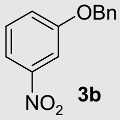
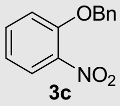
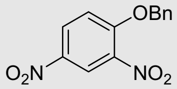
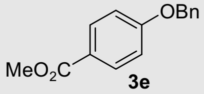
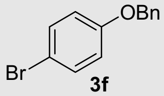
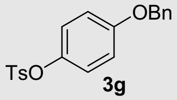
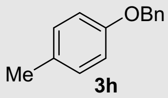
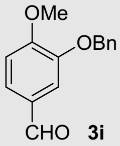
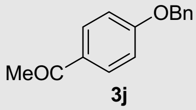
revealed that the reaction efficiency was highly solvent dependent. No reaction occurred in CH_2Cl_2, NMP, DMF, 1,4-dioxane, cyclopentanone, and 2-methoxyethanol (entries 8 and 10–14). Among the solvents probed, thiophene and anisole turned out to be better ones (entries 2 and 6). In both cases, good yields (65% and 64%, respectively) were achieved along with a certain amount of side product **2a,b**. The presumable reason for the significant suppression of formation of these side reaction products in thiophene and anisole was due to their ability as effective cation scavengers. It is realized that the process occurred relatively faster in thiophene than in anisole while achieving similar reaction yields. Moreover, thiophene was more readily removed by evaporation as a result of its lower boiling point (85 °C). Accordingly, we selected thiophene as reaction medium for further optimization of reaction conditions. Reducing the use of amount of $NaHSO_4 \cdot SiO_2$ deteriorated the reaction efficiency in terms of product yields and side products formed (entries 3 and 4). In addition, other acids have been screened. It was found that debenzylation of **1** did not take place using CF_3COOH as the catalyst (entry 5) and the desired product was afforded in a low yield when $FeCl_3$ was employed (entry 9).

The optimized reaction conditions were used to probe the generality of the debenzylation of aromatic benzyl ethers (Table 2).[13] Examination of the results indicated that the method served as a general and efficient approach for selective removal of benzyl group without affecting other functional groups. Nitro-substituted aryl benzyl ethers could efficiently participate in the process (entries 1–4). In all instances, high yields (93–95%) were obtained without the observation of side products in short reaction times. More importantly, the reaction conditions were compatible with nitro groups. It is aware that this is a major drawback for Pd/C-

Table 2

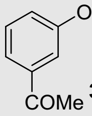
$NaHSO_4 \cdot SiO_2$ facilitated debenzylation of aryl benzyl ethers[a]



Entry	3	Product	t (h)	Yield[b] (%)
1	 **3a**	**4a**	5 5[c] 5[d]	95 Trace[c] NR[d]
2	 **3b**	**4b**	5	94
3	 **3c**	**4c**	4.5	94
4		**4d**	9	93
5	 **3e**	**4e**	6 6[e]	96 Trace[e]
6	 **3f**	**4f**	4	84
7	 **3g**	**4g**	8 8[f]	93 Trace[f]
8	 **3h**	**4h**	4	52
9	 **3i**	**4i**	0.25 3[g] 3[h]	5 87[g] Trace[h]
10	 **3j**	**4j**	4[g] 4[i]	85[g] Trace[i]

(continued on next page)

Table 2 (*continued*)

Entry	3	Product	*t* (h)	Yield[b] (%)
11	 **3k**	**4k**	3[g]	81[g]

[a] Unless specified, see typical experimental procedure in Ref. 13.

[b] Isolated yield.

[c] Finely ground unsupported sodium hydrogen sulfate as catalyst in a ratio of 11:10 with **3a** (mol/mmol), and 92% **3a** recovered.

[d] Silica gel as catalyst in a ratio of 500:1 of with **3a** (mg/mmol), and no reaction observed.

[e] CF_3COOH as catalyst in a ratio of 2:1 with **3e** (mmol/mmol), and 91% **3e** recovered.

[f] CF_3COOH as catalyst in a ratio of 2:1 of it and **3g** (mmol/mmol), and 85% **3g** recovered.

[g] Anisole as solvent at 115 °C using a ratio of 300:1 of $NaHSO_4 \cdot SiO_2$ and **3** (mg/mmol).

[h] Anisole as solvent at 115 °C using a ratio of 2:1 of CF_3COOH and **3i** (mmol/mmol), and 92% **3i** recovered.

[i] Anisole as solvent at 115 °C using a ratio of 2:1 of CF_3COOH and **3j** (mmol/mmol), and 92% **3j** recovered.

catalyzed hydrogenation cleavage of benzyl ethers in the presence of nitro functionalities in substrates. Furthermore, the debenzylation process could be applied other substrates which bear different functionalities such as COOMe, Br, OTs, and Me (entries 5–8). Generally, good to high yields were achieved. However, when the same reaction conditions were employed for deprotection of carbonyl-contained substrates, the reaction took place in low yield (5%, entry 9). We found that the use of anisole instead of thiophene led to significant improving reaction yields (81–85%, entries 9–11). Moreover, comparison studies revealed that other acids as catalysts, including finely ground sodium hydrogen sulfate, silica gel, or CF_3COOH, were not as efficient as $NaHSO_4 \cdot SiO_2$ (entries 1, 5, 7, 9, and 10).

The reaction mechanism may involve initial protonation at the oxygen atom of the aromatic benzyl ether followed by C–O cleavage to generate the corresponding benzylic cation along with the desired phenol product. The use of cation scavenger such as thiophene and anisole can efficiently quench the cation and thus significantly limiting the formation of side products. Moreover, substrates containing electron-withdrawing substituents (Table 2, entries 1–7) afford the desired products in higher yields than others bearing electron-donating groups (Table 1 and entry 8). These data support the plausible reaction pathway.

In summary, a new efficient and selective method for deprotection of aromatic benzyl ethers using $NaHSO_4SiO_2$ in thiophene or anisole has been developed. This strategy features various functional group tolerance, high yields, mild conditions, and easy work-up. Therefore, it provides an alternative way for deprotection of phenolic hydroxyls.

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References and notes

1. (a) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2003. Chapter 4; (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-VCH: New York, 1999 p 266.
2. *The Pharmacological Basis of Therapeutics*, 8th ed.; Goodman Gilman, A., Rall, T., Nies, A., Taylor, P., Eds.; Pergamon Press: New York, 1990.
3. (a) Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746; (b) Deng, W.-P.; Zhong, M.; Guo, X.-C.; Kende, A. S. *J. Org. Chem.* **2003**, *68*, 7422.
4. Huang, W.; Zhang, X.; Liu, H.; Shen, J.; Jiang, H. *Tetrahedron Lett.* **2005**, *46*, 5965.
5. Loev, B.; Dawson, C. R. *J. Am. Chem. Soc.* **1956**, *78*, 6095.
6. Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725.
7. Liu, H. J.; Yip, J. *Tetrahedron Lett.* **1997**, *38*, 2253.
8. (a) Paliakov, E.; Strekowski, L. *Tetrahedron Lett.* **2004**, *45*, 4093; (b) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.
9. (a) Yoshino, H.; Tsujii, M.; Kodama, M.; Komeda, K.; Niikawa, N.; Tanase, T.; Asakawa, N.; Nose, K.; Yamatsu, K. *Chem. Pharm. Bull.* **1990**, *38*, 1735; (b) Petchmanee, T.; Ploypradith, P.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 2892.
10. Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* **2004**, *45*, 3729.
11. (a) Ravindranath, N.; Ramesh, C.; Reddy, M. R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 1207; (b) Ramesh, C.; Ravindranath, N.; Das, B. *J. Org. Chem.* **2003**, *68*, 7101; (c) Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* **2003**, *44*, 1465; (d) Das, B.; Mahender, G.; Kumar, V. S.; Chowdhury, N. *Tetrahedron Lett.* **2004**, *45*, 6709; (e) Das, B.; Ramu, R.; Reddy, M. R.; Mahender, G. *Synthesis* **2005**, *2*, 250–254; (f) Das, B.; Reddy, K. R.; Thirupathi, P. *Tetrahedron Lett.* **2006**, *47*, 5855; (g) Kolvari, E. *Synlett* **2006**, *12*, 1971; (h) Niu, Y.; Wang, N.; Cao, X.; Ye, X.-S. *Synlett* **2007**, 2116.
12. Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952.
13. *Typical procedure for debenzylation of aromatic benzyl ethers by $NaHSO_4 \cdot SiO_2$*: 1-(Benzyloxy)-4-nitrobenzene **3a** (1 mmol, entry 1 in Table 2) was dissolved in thiophene (3 mL) in a round-bottomed flask and $NaHSO_4 \cdot SiO_2$ (500 mg) was added. The reaction system was equipped with reflux condenser and filled with argon. The mixture was stirred under reflux for 5 h and then cooled to room temperature, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel to afford the product 4-nitrophenol **4a** (132 mg, 95% yield).