

Copper-catalyzed cleavage of benzyl ethers with diacetoxyiodobenzene and *p*-toluenesulfonamide

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Abstract

A new cleavage reaction of benzylethers catalyzed by copper (II) trifluoromethane- sulfonate in the presence of diacetoxyiodobenzene and *p*-toluene sulfonamide is described. This novel method allowed the selective cleavage of various benzyl ethers into benzylideneaniline and alcohols or phenols under mild conditions.

Keywords: Cleavage, benzyl ethers, copper-catalyzed, diacetoxyiodobenzene, *p*-toluenesulfonamide

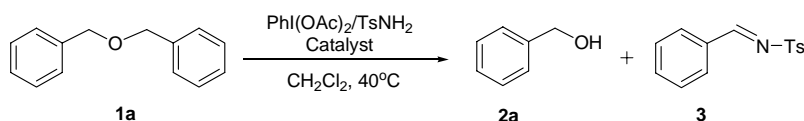
Introduction

The conversion of alcohols or phenols to ethers and their subsequent cleavage is very important in organic synthesis, particularly in multi-step synthesis of complex natural products and in the manufacture of many pharmaceuticals and fine chemicals.¹ The benzyl group is one of the most useful protecting groups, because it is stable to acid, alkali, and a number of other usual reagents. Moreover, it is readily removed by catalytic hydrogenation or reductive cleavage with sodium in liquid ammonia. However, if the substrate contains additional reducible functions, this procedure will be unsuitable, and other methods instead will be needed. The oxidative cleavage of benzyl ethers provides a convenient alternative to the usual reductive deprotection method. While several oxidants, including uranium hexafluoride,² nitronium tetrafluoroborate,³ the cation radical of tris-(*p*-bromophenyl) amine,⁴ 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)⁵ and [bis(trifluoroacetoxy)iodo]benzene⁶ have been shown to be effective in producing benzaldehyde and alcohols by oxidative cleavage, the development of new methods for the cleavage of benzyl ethers is still highly desirable. We now report a mild new method for the removal of the benzyl ether protecting group through the reaction of diacetoxyiodobenzene (PhI(OAc)₂) and

p-toluenesulfonamide (TsNH₂) catalyzed by copper(II) trifluoromethanesulfonate (Cu(CF₃SO₃)₂).

Results and Discussion

As part of our continuing study on nitrene insertions into C–H bond,⁷ we explored the amidation of dibenzyl ether with PhI(OAc)₂/TsNH₂ catalyzed by various metal complex in dichloromethane to synthesize 1,1-N,O compounds. Unfortunately, instead of giving the desired product, when Cu(CF₃SO₃)₂ was used as catalyst, benzyl alcohol **2a** and benzyldenylaniline **3** was produced in manner of ether cleavage (Scheme 1). This was a new reaction of PhI(OAc)₂ and TsNH₂ with benzyl ether. Therefore, we investigated the cleavage of dibenzyl ether **1a** by using various metal complexes at a low catalyst loading of 2 mol% (Scheme 1 and Table 1). No reaction was observed without Cu(CF₃SO₃)₂ (Entry 1). Only 15% conversion and 10% yield of **3** were obtained in the presence of 2 mol% Cu(CF₃SO₃)₂ (Entry 2). Rh₂(OAc)₄ was found to be the best catalyst for the cleavage of dibenzyl ether with 90% conversion and 82% yield (Entry 3), but it is expensive. The reaction did not proceed when others catalysts such as metal porphyrins complex, Cu(TFAC)₂ or CuI (Entries 4-9).



Scheme 1. The cleavage reaction of dibenzyl ether.

Table 1. Influence of the metal catalysts (2 mol %) on the cleavage of dibenzyl ether with PhI(OAc)₂ and TsNH₂ in CH₂Cl₂ at 40 °C

| Entry | Catalyst | Conversion ^a | Yield of 2a ^b |
|-------|---|-------------------------|---------------------------------|
| 1 | / | 0 | 0 |
| 2 | Cu(CF ₃ SO ₃) ₂ | 15% | 13% |
| 3 | Rh ₂ (OAc) ₄ | 90% | 76% |
| 4 | Ru(TTP)(CO) | ~0 | - |
| 5 | Co(TTP)(CO) | ~0 | - |
| 6 | Cu(TTP)(CO) | ~0 | - |
| 7 | Mn(TTP)Cl | ~0 | - |
| 8 | Cu(tfac) ₂ | ~0 | - |
| 9 | CuI | ~0 | - |

^aConversion was determined on the basis of the product formation in the crude reaction mixture.

^bGC yields.

The cleavage of dibenzyl ether in the presence of commercially available catalyst $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ was then optimized (Table 2). Increasing the amount of catalyst from 2 mol% to 10 mol% led to significantly enhanced conversion of **1a** and the yield of **2a** (Entries 1-3). Prolonging reaction time did not lead to a further increase in conversion or yield (Entries 4 and 6). TsNH_2 and $\text{PhI}(\text{OAc})_2$ in the ratio of 1:3 boosted the conversion of **1a** and the yield of **2a** to 86% and 73%, respectively, in the presence of tin powder and Al_2O_3 (Entry 5). Increasing or decreasing the reaction temperature resulted in slightly reduced conversion and yield (Entries 6, 7 and 9).

The mechanism for the cleavage of benzyl ether with $\text{PhI}(\text{OAc})_2$ and TsNH_2 would presumably involve the *in situ* formation of acetic acid and tosyliminophenyliodine.^{7,8} Indeed, the use of this reagent in pure form was found to enhance the conversion, albeit only a slight decrease in the yield of the cleavage product. (Entries 8 and 9).

Table 2. Optimization of the cleavage of dibenzyl ether in the presence of $\text{Cu}(\text{CF}_3\text{SO}_3)_2$

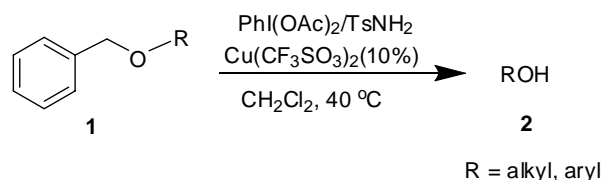
| Entry | $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ (mol%) | Nitrene Source (equiv) | t (h) | T (°C) | Conversion ^a | Yield of 2a ^b |
|----------------|---|---|----------|-----------|-------------------------|------------------------------------|
| 1 | 2 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/1.5) | 3 | 40 | 15% | 13% |
| 2 | 5 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/1.5) | 3 | 40 | 30% | 29% |
| 3 | 10 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/1.5) | 3 | 40 | 72% | 61% |
| 4 | 10 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/1.5) | 12 | 40 | 70% | 60% |
| 5 ^c | 10 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/3) | 3 | 40 | 86% | 73% |
| 6 | 10 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/3) | 12 | 20 | 78% | 66% |
| 7 | 10 | $\text{TsNH}_2/\text{PhI}(\text{OAc})_2$ (1/3) | 3 | 65 | 78% | 49% |
| 8 | 10 | $\text{PhI}=\text{NTs}$ (3) | 3 | 40 | 90% | 65% |
| 9 | 10 | $\text{PhI}=\text{NTs}$ (3) | 3 | 65 | 90% | 52% |

^a Conversion was determined on the basis of the product formation in the crude reaction mixture.

^b Isolated yields.

^c In the presence of tin powder (3 mmol) and Al_2O_3 (3 mmol)

We then investigated the scope of the reaction as a synthetic method with commercially available $\text{PhI}(\text{OAc})_2$ and TsNH_2 using different benzyl ethers under the optimized conditions (Table 2, Entry 5 and Table 3). In the case of unsymmetrical benzyl ethers, the cleavage pattern is the selective removal of benzyl group to generate benzyldeneaniline in good yield. This reaction is a new benzyl deprotection method by the selective cleavage of benzyl ethers. We also observed that the cleavage of benzyl alkyl ethers is more facile than that of the corresponding aryl ethers (Entries 2-8). For benzyl alkyl ethers, the cleavage of benzyl methyl ether (Entry 2) was easier compared with the other substituted benzyl alkyl ethers like butyl benzyl ether and isopropyl benzyl ether (Entries 3-5).



Scheme 2. Deprotection of benzyl ethers.

Table 3. Copper-catalyzed cleavage of benzyl ether with $\text{PhI}(\text{OAc})_2$ and TsNH_2 ^a

| Entry | Substrate | Product | Yield (%) |
|-------|-----------|--|------------------|
| 1 | | | 73 ^c |
| 2 | | CH_3OH | 61 ^b |
| 3 | | | 69 ^b |
| 4 | | $\text{C}_{18}\text{H}_{37}\text{OH}$ | 68 ^c |
| 5 | | $\text{CH}_3\text{CH}(\text{CH}_3)\text{OH}$ | ~60 ^b |
| 6 | | | 70 ^c |
| 7 | | | 62 ^c |
| 8 | | | 61 ^c |

^aAll reactions were conducted according to general procedure.

^bGC yields. ^cIsolated yields.

In summary, we have found a simple and novel method for the removal of the benzyl ether protecting group with $\text{PhI}(\text{OAc})_2$ and TsNH_2 using $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ as a catalyst. The benzyl cleavage can proceed in relatively mild conditions compared with the more rigorous conditions in the reductive methods. More importantly, it is regioselective and specific. Thus, with this new deprotection method, the use of benzyl group as a protecting group for alcohols or phenol could be expanded.

Experimental Section

General procedure for the cleavage of benzyl ethers

A reaction flask was charged with substrate (1 mmol), diacetoxyiodobenzene (3 mmol), *p*-toluenesulfonamide (1 mmol), catalyst (0.1-0.2 mmol), tin powder (3 mmol), Al_2O_3 (3 mmol) and dichloromethane (20 mL), and then the mixture was stirred at 40 °C under nitrogen atmosphere for about 2-4 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford the product of cleavage.

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References

1. (a) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (b) Maercker, A. *Angew. Chem. Int. Ed.* **1987**, 26, 972. (c) Tiecco, M. *Synthesis* **1988**, 749. (d) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd. Ed.; John Wiley: New York, 1999; Chap. 2, 23; Chap. 3, 249.
2. Olah, G. A.; Welch, J.; Ho, T.-L. *J. Am. Chem. Soc.* **1976**, 98, 6717.
3. Ho, T.-L.; Olah, G. A. *J. Org. Chem.* **1977**, 42, 3097.
4. (a) Schmidt, W.; Steckhan, E. *Angew. Chem. Int. Ed.* **1978**, 17, 673. (b) Schmidt, W.; Steckhan, E. *Angew. Chem. Int. Ed.* **1979**, 18, 801.
5. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885.
6. Spyroudis, S.; Varvoglis, A. *J. Chem. Soc., Chem. Commun.* **1979**, 615.

7. (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (b) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. *Chem. Commun.* **1999**, *2*, 2377. (c) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.-Y.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563. (d) Wang, Q.; Li, M.; Yu, X.-Q.; Xie, R.-G. *Progress in Chemistry*, **2005**, *17*, 275. (e) Zhou, Z.-W.; Zhao, Y.-C.; Yue, Y.; Wu, J.; Yang, M.; Yu, X.-Q.; *Arkivoc* **2005**, 130. (f) He, L.; Yu, J.; Zhang, J.; Yu, X.-Q., *Org. Lett.*, **2007**, *9*, 2277.
8. Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858.