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Tetrahedron Letters 47 (2006) 5337–5340

Tetrahedron Letters

A mild and practical deprotection method for benzyl thioethers

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Received 26 April 2006; revised 16 May 2006; accepted 18 May 2006
Available online 12 June 2006

Abstract—A highly effective and mild deprotection method was developed for benzyl thioethers using dibutylmagnesium in the presence of a catalytic amount of titanocene dichloride. This methodology is applicable to both aromatic and aliphatic benzyl thioethers.
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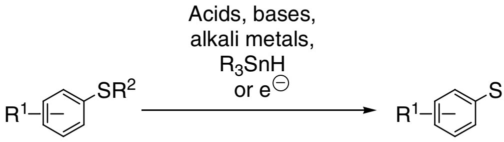
Deprotection of thiol groups is an essential step in the synthesis of sulfur-containing natural products and biologically active compounds. From the point of view of stability, the use of alkyl thioether protecting groups is advantageous, but deprotection of these groups requires harsh conditions.[1,2] For example, the deprotection of benzyl thioether, one of the most common protecting groups, requires the use of strong acids or bases, or reduction using alkali metals or stannyl hydrides, or reductive electrolysis using highly negative applied potentials (Scheme 1).[3,4] The possible applications of these methods are limited, because strong acids and bases cause deterioration of other functionalities, alkali metals and stannyl hydrides are hazardous reagents, and the use of electrolysis is costly. Here, we wish to report the development of mild and practical deprotection conditions for benzyl thioethers.

As a starting point in the investigation, phenyl benzyl thioether (**1**) was heated with a strong base (KO^{t}Bu) (Table 1, entry 1). Deprotected product **2** was obtained only in 5% yield after 9 h at 115 °C. With the addition of $CuCl_2{\cdot}2H_2O$ as a soft Lewis acid, the reaction was accelerated and completed in 9 h (entry 2). With the aim of reducing the reaction temperature, the use of further nucleophilic reagents was examined at room temperature (entries 3–8). The de-benzylation reaction did not proceed using diethyl zinc or phenylmagnesium halides (entries 3–5), but proceeded at room temperature when the more nucleophilic ^{n}BuMgCl was used (entry 6).



Scheme 1. Removal of protecting group on sulfur atom.

Dialkylmagnesium and a magnesium ate complex[5] were also examined (entries 7 and 8). The best result was obtained by using a combination of $CuCl_2{\cdot}2H_2O$ and Bu_2Mg (entry 7).[6]

Variation of the reaction solvent was studied using 2.5 equiv of Bu_2Mg in the presence of 10 mol % of $CuCl_2{\cdot}2H_2O$ at room temperature for 24 h. The reaction did not proceed in diethylether or 1-methyl-2-pyrrolidone. Moderate conversions were observed in tetrahydrofuran and 1,2-dimethoxyethane (51% and 85%, respectively), but excellent conversion rates (93–97%) were achieved in polyglymes (diglyme, triglyme and tetraglyme). Accordingly, diglyme was selected as a reaction solvent.

Various additives were screened for the reaction using $^nBu_2Mg$ in diglyme, and the results are summarized in Table 2. Some metal salts (Zn, Al, In, Zr, Sn, Hf, Ni, Pd, Ir, Pt, Ce, Yb and Au) were found not to be effective (entries 2–15). Cu, Ag, Co, Fe and Ti salts did prove effective (entries 16–26). CuCl(I) was almost as effective as $CuCl_2$(II) (entry 17). A stronger Lewis acid, Cu $(OTf)_2$(II), was found to be a poor catalyst (entry 18). Among Cu, Ag, Co, Fe and Ti salts, $FeCl_2$(II) and Cp_2TiCl_2(IV) had relatively large acceleration effects

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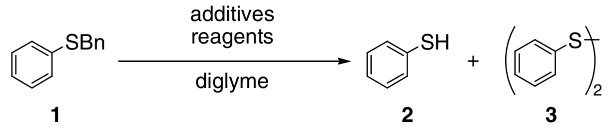
doi:10.1016/j.tetlet.2006.05.120

Table 1. Methods of deprotection of benzyl thioethers



	Reagents (equiv)	Additive (10 mol %)	Temperature (°C)	Time (h)	$\mathbf{1}^a$ (%)	$\mathbf{2}^a$ (%)	$\mathbf{3}^a$ (%)
1	KO^{t}Bu (5)	None	115	9	76	5	0
2	KO^{t}Bu (5)	$CuCl_2 \cdot 2H_2O$	115	9	0	61	26
3	Et_2Zn (2.5)	$CuCl_2 \cdot 2H_2O$	rt	24	98	0	0
4	PhMgBr (5)	$CuCl_2 \cdot 2H_2O$	rt	24	100	0	0
5	PhMgI (5)	$CuCl_2 \cdot 2H_2O$	rt	24	99	0	0
6	^{n}BuMgCl (5)	$CuCl_2 \cdot 2H_2O$	rt	24	33	53	17
7	^{n}Bu$_2$Mg (2.5)	$CuCl_2 \cdot 2H_2O$	rt	24	3	68	27
8	^{n}Bu$_2$Mg (1.67) + ^{n}BuLi (1.67)	$CuCl_2 \cdot 2H_2O$	rt	24	72	0	7

[a] Product yields and recoveries were determined by HPLC.

Table 2. Additives for de-benzylation reaction[a]

	Additive (10 mol %)	Temperature (°C)	Time (h)	$\mathbf{1}^b$ (%)	$\mathbf{2}^b$ (%)	$\mathbf{3}^b$ (%)
1	None	50	5	97	0.4	0
2	$ZnCl_2$	50	5	100	0	0
3	$AlCl_3$	50	5	100	0	0
4	$InCl_3 \cdot 4H_2O$	50	5	100	0	0
5	$ZrCl_4$	50	5	95	3	0
6	$SnCl_2$	50	5	98	0.5	0
7	$HfCl_4 \cdot 2THF$	50	5	100	0	0
8	$NiBr_2$	50	5	73	0	4
9	$PdCl_2$	50	5	98	1	1
10	$IrCl_3$	50	5	89	0	1
11	$PtCl_2$	50	5	94	0	0
12	$CeCl_3 \cdot 7H_2O$	50	5	100	0	0
13	$YbCl_3 \cdot 6H_2O$	50	5	100	0	0
14	AuCl	50	5	100	0	0
15	$NaAuCl_4$	50	5	100	0	0
16	$CuCl_2 \cdot 2H_2O$	50	5	2	68	30
17	CuCl	50	5	12	68	17
18	$Cu(OTf)_2$	50	5	47	13	25
19	$AgNO_3$	50	5	59	39	2
20	$CoCl_2$	50	5	24	0	49
21	$FeCl_2$	50	5	2	57	34
22	$FeCl_3$	50	5	2	82	1
23	$TiCl_2(O^iPr)_2$	50	5	28	68	1
24	Cp_2TiCl_2	50	3	0	91	2
25	Cp_2TiCl_2	rt	1	0	95	2
26	Cp_2TiCl_2	0	1	0	97	3

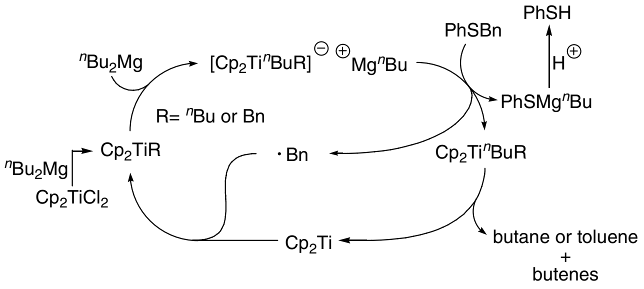
[a] All reactions were performed in diglyme using 2.5 equiv of Bu_2Mg.
[b] Product yields and recoveries were determined by HPLC.

(entries 21 and 24). When Cp_2TiCl_2 was used, the de-benzylation reaction proceeded smoothly within 1 h even at 0 °C, with a very high yield (97%, entry 26).[7]

From the above results, it can be seen that reactivity does not correlate with Lewis acidity. Kambe and co-workers have previously reported that the use of Grignard reagents and a Cp_2TiCl_2 catalyst can induce radical reaction processes.[8] It is also known that radical species can be generated by titanium reagents[9] or dialkylmagnesium.[10] In addition, radical intermediates have been observed in reactions in which combinations of transition metals and Grignard reagents were used.[11] Therefore, we presume that the de-benzylation reaction proceeds through a radical mechanism, as shown in Scheme 2. The generation of toluene was actually observed via HPLC analysis of the reaction mixture.

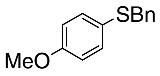
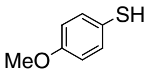
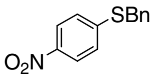
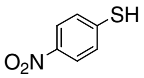
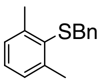
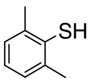
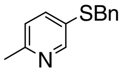
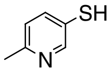
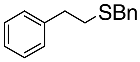
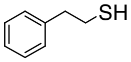
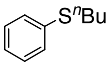
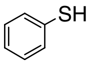
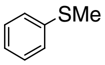
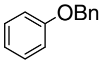
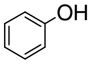
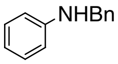
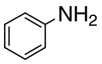
In Table 3, the conditions under which Cp_2TiCl_2 was used were applied to other substrates. *p*-Methoxyphenyl benzyl thioether (**4**), which bears an electron-donating group on the aromatic ring, was converted to the deprotected product in good yield (entry 1). The use of *p*-nitrophenyl benzyl thioether (**6**) afforded none of the desired product and resulted in a complex mixture (entry 2). Hindered aromatic, hetero-aromatic and alkyl benzylthioethers were also examined (entries 3–5); all of these were converted to the corresponding thiols in good yields. De-alkylation reactions were also examined (entries 6–8). At 0 °C, the *n*-butyl group was not cleaved efficiently (entry 6); an elevated temperature (70 °C) was needed to deprotect this alkyl group (entries 7 and 8). However, de-benzylation of benzylether and benzylamine groups did not proceed under the same conditions (entries 9 and 10), which means that benzylthioethers can be deprotected in the presence of benzylethers and benzylamines using this method.

Diphenyldisulfide (**3**) was exposed to these reaction conditions, affording the corresponding thiol **2** and the butylated compound **14** (Scheme 3). This shows that even if disulfides are formed during the reaction, they are converted to the corresponding thiols under these



Scheme 2. Suggested mechanism of titanocene-catalyzed de-benzylation reaction.

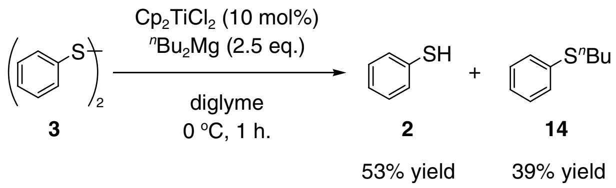
Table 3. De-alkylation reactions of other substrates[a]

	Temperature (°C)	Time (h)	Starting materials[b]	Products[b]
1	0	1	 **4** (0%)	 **5** (92%)
2	0	1	 **6** (7%)	 **7** (0%)[c]
3	0	1	 **8** (4%)	 **9** (96%)
4	0	1	 **10** (0%)	 **11** (100%)
5	0	6	 **12** (0%)	 **13** (87%)
6	0	1	 **14** (97%)	 **2** (3%)
7	70	14	**14** (10%)	**2** (84%)
8	70	48	 **15** (54%)	**2** (40%)
9	0	1	 **16** (97%)	 **17** (0%)
10	0	1	 **18** (99%)	 **19** (0%)

[a] All reactions were performed in diglyme at 0 °C using 2.5 equiv of Bu_2Mg in the presence of 10 mol % Cp_2TiCl_2.

[b] Product yields and recoveries were determined by HPLC.

[c] This reaction resulted in a complex mixture.



Scheme 3. Exposure of **3** to de-benzylation reaction conditions.

conditions. In fact, for all entries, almost no disulfides were found.

In conclusion, it was demonstrated that benzyl thioether protecting groups can be effectively removed under mild conditions. This novel method is quite general and is likely to be applicable to many other substances, such as pharmaceutical drug compounds.

Acknowledgements

We thank Dr. Takayuki Tsuritani for helpful discussions and Dr. Toshiaki Mase for helpful directions.

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6. The yield of deprotected products (PhSH and $(PhS)_2$) was 95% (68%+27%). $(PhS)_2$ can be readily converted into PhSH by $NaBH_4$ reduction: Ookawa, A.; Yokoyama, S.; Soai, K. *Synth. Commun.* **1986**, *16*, 819.
7. General procedure for de-benzylation reaction: To a mixture of **1** (46.3 mg, 0.231 mmol) and Cp_2TiCl_2 (5.8 mg, 0.0231 mmol), diglyme (0.5 mL) was added under N_2. After cooling in an ice-water bath, the mixture was treated with dibutylmagnesium, 1.0 M solution in heptane (0.58 mL, 0.58 mmol), stirred for 1 h and quenched with 1 N aqueous NaOH (2 mL). The resulting mixture was diluted to 100 mL with $CH_3CN–H_2O$ and analyzed by HPLC, which showed **2** (24.6 assay mg, 97% yield) and **3** (0.7 assay mg, 3% yield), respectively.
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