Cleavage of a *p*-Cyanobenzyl Group from Protected Alcohols, Amines, and Thiols Using Triethylgermyl Sodium

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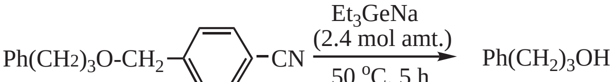
(Received June 10, 2002; CL-020489)

Alcohols, amines, and thiols protected with a *p*-cyanobenzyl group can be easily and quantitatively deprotected using triethylgermyl sodium under mild conditions.

Benzyl groups have found extensive use in organic chemistry for protection of alcohols. The benzyl group from protected alcohols can be removed by Pd-catalyzed hydrogenation,[1] trimethylsilyl iodide (Me_3SiI),[2] Birch reduction,[3] Lewis acids,[4] cathodic cleavage,[5] and so forth. However, for benzyl ethers several difficulties in terms of yields, reaction conditions, reagents, and others associated with their removal depending upon the alcohols have still remained. These results prompted us to investigate a *p*-cyanobenzyl group for the protection of alcohols instead of the benzyl group. The only cathodic cleavage of the *p*-cyanobenzyl group from protected alcohols reported is not easy for laboratory manipulation.[6]

On the other hand, organogermyl alkali metal compounds are both representative nucleophiles and electron transfer reagents. Their extraordinary nucleophilicity makes them valuable reagents for introducing triorganogermyl groups into molecules.[7–9] During the course of our study of organogermyl alkali metals, we found that alcohols protected with a *p*-cynaobenzyl group can easily and quantitatively be deprotected using triethylgermyl sodium under mild conditions.

First, we examined the reactions of *p*-cyanobenzyloxy-3-phenylpropane (**1a**) as a model compound with triethylgermyl sodium (Et_3GeNa),[10] which was prepared by hexaethyldigermane ($Et_3GeGeEt_3$) and sodium metal in HMPA/solvent, under various conditions.



1a **2a**

The *p*-cyanobenzyl ether (**1a**) was treated with 2.4 mol amounts of Et_3GeNa in HMPA/1,4-dioxane at 50 °C for 5 h to give 3-phenylpropanol (**2a**) in 99% yield. The amount of Et_3GeNa exactly required was 2.4 mol amounts against that of **1a**. Lowering the reaction temperature from 50 to 40 °C resulted in longer reaction times (10 h). At somewhat higher temperature (60 °C) the reaction completed in only 1 h, but afforded unknown products besides **2a** (84%). Employing a less polar solvent decreased the yields of **2a**: hexane (75%), benzene (76%), ether (84%), THF (91%). The effect of alkali metal cations (M^+) of Et_3GeM on the yields of **2a** was in the order: M = Na (91%) > Li (60%) > K (55%). The substituent on the germanium largely did not influence the yields of **2a**. These results are summarized in Table 1. The effect of the substituent on the benzyl group on the yields of **2a** under similar conditions was in the order: *p*-CN (99%) > *o*-CN = H (81%) > *m*-CN (78%). The reactions of **1a** with other reductants under similar conditions were also examined. The use of Et_3SiNa and Et_3SnNa resulted in low yields (51–60%), and conventional reductants such as lithium naphthalenide (LiNp) and lithium di-*tert*-butylbiphenyl (LDBB) proved to give moderate yields (82–84%). These results of reductants are summarized in Table 2.

Table 1. Reactions of *p*-cyanobenzyl ether (**1a**) with R_3GeM in HMPA/solvent

Run	R_3GeM	Solvent	Product (Yield/%)[a]
1	Et_3GeNa	Hexane	75
2	〃	Benzene	76
3	〃	Ether	84
4	〃	THF	91
5	〃	1,4-Dioxane	99
6	Et_3GeLi	1,4-Dioxane	60
7	Et_3GeK	1,4-Dioxane	55
8	Me_3GeNa	1,4-Dioxane	88
9	Bu_3GeNa	1,4-Dioxane	94
10	$^iPr_3GeNa$	1,4-Dioxane	82
11	$PhEt_2GeNa$	1,4-Dioxane	64

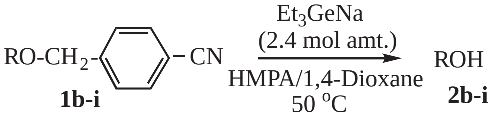
[a]Isolated yields.

Table 2. Reactions of *p*-cyanobenzyl ether (**1a**) with reductants

Run	R_3GeM	Product (Yield/%)[a]
1	Et_3SiNa	51
2	Et_3GeNa	99
3	Et_3SnNa	60
4	LiNp	84
5	LDBB	82

[a]Isolated yields.

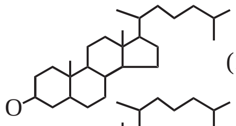
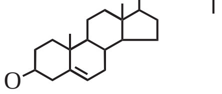
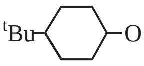
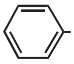
Next, the optimized conditions were applied to various *p*-cyanobenzyl ether (**1b–i**), and the results are summarized in Table 3.



1b-i **2b-i**

As shown in Table 3, the substituted *p*-cyanobenzyl ethers as protected primary-, secondary-, and olefinic-alcohols when treated with 2.4 mol amounts of Et_3GeNa under similar conditions afforded the corresponding alcohols in very high yields. The methoxylmethyl-, ethoxylmethyl-, and benzyl ethers-substituted *p*-benzyl ether proved to be very effective toward Et_3GeNa. The *p*-cyanobenzyl group in deprotected diols was also cleaved with Et_3GeNa at room temperature to give the alcohols in good yields. In all cases, the *p*-cyanobenzyl ethers shown in Table 3 can be

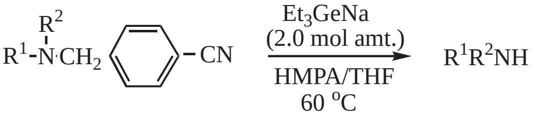
Table 3. Reactions of *p*-cyanobenzyl ethers (**1b–i**) with Et_3GeNa (2.4 mol amt.) in HMPA/dioxane at 50 °C

Run	RO	Time/h	Product, Yield/%
1	$CH_3(CH_2)_9O$ (**1b**)	7.5	**2b**, 87
2	$Ph(CH_2)_3O$ (**1c**)	5	**2c**, 99
3	 (**1d**)	15	**2d**, 97
4	 (**1e**)	16	**2e**, 99
5	 (**1f**)	28	**2f**, 98
6[a)]	$CH_3OCH_2O(CH_2)_4O$ (**1g**)	70	**2g**, 86
7[a)]	$CH_3O(CH_2)_2OCH_2O(CH_2)_4O$ (**1h**)	50	**2h**, 81
8[a)]	 $(CH_2)_2O(CH_2)_4O$(**1i**)	45	**2g**, 50

[a)] r.t.

easily and quantitatively converted into the corresponding alcohols.

A combination of a *p*-cyanobenzyl substituent as the protecting group with Et_3GeNa was applied to amines and thiols. The *p*-cyanobenzyl group from protected amines and thiols was removed with Et_3GeNa to give the corresponding amines and thiols. Cleavage of their *p*-cyanobenzyl groups with Et_3GeNa at 50 °C required a long time compared with that of benzyl ethers. These results of amines are summarized in Table 4.



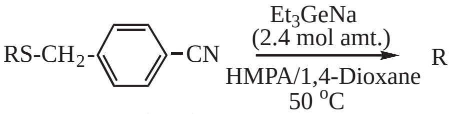
Debenzylation of a *p*-cyanobenzyl group with Et_3GeNa proved to be less effective toward *p*-cyanobenzyl alkyl amines as shown in Table 4.

Table 4. Reactions of *p*-cyanobenzyl amines with Et_3GeNa at 50 °C

Run	R^1, R^2	Time/h	Product, Yield/%[a]
1	R^1=Ph, R^2=Bu	4	99
2	R^1=1-Np, R^2=Et	43	97
3	R^1, R^2=Ph	68	98
4	R^1=1-Np, R^2=Ph	48	80
5	R^1=$C_{18}H_{37}$, R^2=Me	92	39

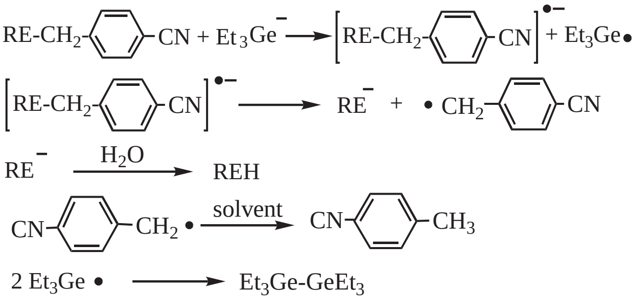
[a]Isolated yields.

p-Cyanobenzyl substituent as a protecting group and the Et_3GeNa system are also applied to thiols, even for a long time, depending on the substrates.



R = $CH_3(CH_2)_9$ 91% (for 5 h)
$Ph(CH_2)_3$ 95% (for 30 h)

We propose an electron-transfer reaction mechanism for the debenzylation of *p*-cyanobenzyl ether with Et_3GeNa as depicted in Scheme 1. Initially, *p*-cyanobenzyl ether with high electron affinity is readily reduced by Et_3GeNa[11] to give a radical anion of *p*-cyanobenzyl ether. Et_3GeNa is oxidized to give $Et_3Ge^{\cdot}$.Then, subsequent cleavage of the radical anion of *p*-cyanobenzyl ether occurs to give an alkoxyl anion and a *p*-cyanobenzyl radical. The alkoxyl anion reacts with proton to give the corresponding alcohol. On the other hand, the *p*-cyanobenzyl radical easily abstracts hydrogen to afford *p*-cyanotoluene. The $Et_3Ge^{\cdot}$ couples to give digermane. Actually, the formation of $(Et_3Ge)_2$ and *p*-cyanotoluene was detected by GC in 90% yield.



Scheme 1.

A typical procedure is as follows: A mixture of 0.60 mol/l Et_3GeNa (0.4 ml),[10] prepared from Et_6Ge_2 and Na in HMPA, was added to a solution of *p*-cyanobenzyloxy-3-phenylpropane **1a** (0.10 mmol) in dioxane (0.5 ml) at 50 °C. After being stirred for 5 h, silica gel (Wako gel C 200) and hexane were added to the solution. The mixture was filtered with silica gel and the filtrate was evaporated. The residue was chromatographed (Merck silica gel 60) with 4 : 1 benzene-ethyl acetate to give phenylpropanol (0.10 mmol, 99%).

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