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Desilylation procedure via a naphthalene-catalysed lithiation reaction

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Abstract—The reaction of silyl protected alcohols, amines and thiols with lithium powder and a catalytic amount of naphthalene, in THF, at 0 °C led, after hydrolysis, to the recovery of the free alcohols, amines and thiols in very good yields. At least a phenyl group was required in the silyl protecting group for the success of the reaction. Some polyfunctionalised starting materials have successfully been deprotected. The stereochemical outcome of the deprotection of a silylated chiral secondary alcohol has also been studied and no racemization was observed. The process has shown to be a good alternative to the acid-catalysed desilylation procedures, the latter being not useful for the deprotection of some silylated tertiary alcohols.

1. Introduction

The silyl group is one of the most popular protecting groups for alcohols[1] and, to a lesser extent, for amines[1b,2] and thiols.[3] This is due to the fact that its introduction and subsequent removal can be modulated by the proper choice of the substituents on the silicon atom.[1,4] The deprotection of the silyl group can be carried out under mild acidic conditions or by treatment with fluoride anion, although some other desilylation procedures have been published which involve basic reaction conditions or redox processes.[1] Some of these processes gave some incompatibility problems[5] with other functional groups present in polyfunctionalised molecules or showed lack of chemoselectivity when the selective deprotection[4] of molecules with several silyl groups was tested.[5b,6] Palladium catalysts have also been applied to the removal of several silyl protecting groups under hydrogenolysis conditions.[7]

In the last few years, we have been using an arene-catalysed lithiation[8,9] to prepare organolithium compounds under very mild reaction conditions. The use of an excess of lithium powder and a catalytic amount of an arene [mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)] allowed us to generate simple organolithium compounds starting from non-halogenated materials,[10] and functionalised organolithium compounds[11] by chlorine–lithium exchange or by ring opening of heterocycles.[12] The reductive cleavage of several allylic and benzylic carbon-heteroatom bonds has led to a method for removal of some protecting groups for alcohols, amines and thioethers.[13] We have recently described the reductive detritylation of trityl ethers[14] and *N*-tritylamines[15] by a naphthalene-catalysed lithiation process. In a previous study, we described one example in which the dimethylphenylsilyl group could be removed from a protected aliphatic alcohol in a naphthalene-catalysed lithiation reaction.[13] We decided to investigate in more detail the scope of this process and in this paper we report the application of this lithiation methodology to the removal of different silyl groups from several protected alcohols, amines and thiols under mild reaction conditions.

2. Results and discussion

All silylated substrates **1**–**3** were prepared from commercially available alcohols (for **1**), amines (for **2**) or thiols (for **3**) and the corresponding silyl chlorides under basic reaction conditions, except for compound **3b** for which the general procedure was unsuccessful, but it could be prepared under Lewis acid catalysis. Some starting materials, especially the ones bearing a dimethyl(phenyl)-silyl group, were found to be relatively unstable, decomposing upon storage for some months at room temperature. The stability of the silylated substrates increased with the number of phenyl groups on the silicon atom. No

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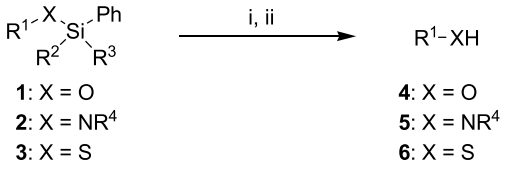

Scheme 1. *Reagents and conditions*: (i) Li, $C_{10}H_8$ (8 mol%), THF, 0 °C; (ii) H_2O.

decomposition was observed in the triphenylsilyl derivatives after storing them for one year at room temperature.

1-Decanol was used as a model starting material and it was converted into silyl ethers **1aa**–**1ad** (Scheme 1, Table 1, entries 1–4) possessing different substituents on the silicon atom. The reaction of compounds **1aa**–**1ac** with an excess of lithium powder (1:9 molar ratio) and a catalytic amount of naphthalene (1:0.16 molar ratio; 8 mol%) in THF at 0 °C gave, after hydrolysis with water, the expected primary alcohol **4a** in quantitative yield (Scheme 1 and Table 1, entries 1–3). Compound **1ad**, bearing a bulky *tert*-butyl and two phenyl groups as substituents at the silicon atom, did not react under the same reaction conditions, the unaltered starting material **1ad** being recovered after 8 h at 0 °C. However, the desilylation of **1ad** took place when the reaction was stirred at room temperature for 3 days, giving a 58% yield of 1-decanol **4a** and some unreacted starting material.[16] The yield of **4a** could be improved to 85% by running the reaction for 4 days at room temperature using DTBB as an electron carrier instead of naphthalene (Table 1, entry 4, footnote b). We assume that the reduction in the reaction rate is due to the steric hindrance caused by the bulky *tert*-butyl group. It was found that at least one phenyl group on the silicon atom was necessary for the success of the desilylation process. The reaction failed when trimethylsilyl-protected 1-decanol was used as substrate, the starting material being quantitatively recovered after 3 days at room temperature.

Next, the versatility of our method concerning the silylated substrate was studied. Compounds **1b** and **1c**, derived from secondary alcohols, gave the corresponding desilylated products in very good yields (Scheme 1 and Table 1, entries 5–7). Optically pure (*R*)-2-octanol was also protected with the dimethyl(phenyl)silyl group [(*R*)-**1c** (Table 1, entry 7)] and submitted to our lithiation reaction in order to check if there was any racemization during the process. Product (*R*)-**4c** was esterified with optically pure (*R*)-α-methoxyphenylacetic acid and no loss of enantiomeric purity was observed by comparison of the ^{13}C NMR spectra of the obtained ester and the esters that were prepared from the same acid and commercially available racemic 2-octanol and (*R*)-2-octanol. Thus, the stereochemistry of the chiral alcohol was preserved during the whole process. The triphenylsilyl group of the protected tertiary alcohol **1d** could also be removed in almost quantitative yield (Table 1, entry 8). It is worth noting that the attempted deprotection of compound **1d** by conventional methods was not satisfactory: whereas substrate **1d** was recovered unchanged after treatment with 1 M hydrochloric acid for 24 h at room temperature, the

Table 1. Desilylation of compounds **1–3** via a naphthalene-catalysed lithiation: preparation of compounds **4–6**

Entry	Substrate						Product	
	No.	X	R^1	R^2	R^3	Time (h)	No.	Yield (%)[a]
1	**1aa**	O	$Me(CH_2)_9$	Me	Me	3.5	**4a**	>99
2	**1ab**	O	$Me(CH_2)_9$	Me	Ph	2.0	**4a**	>99
3	**1ac**	O	$Me(CH_2)_9$	Ph	Ph	4.5	**4a**	>99
4	**1ad**	O	$Me(CH_2)_9$	Bu^t	Ph	96.0	**4a**	85[b]
5	**1b**	O	*c*-C_6H_{11}	Me	Me	5.0	**4b**	>99
6	**1c**	O	$Me(CH_2)_5CH(Me)$	Me	Me	4.0	**4c**	81[c]
7	(*R*)-**1c**	O	$Me(CH_2)_5CH(Me)$	Me	Me	3.5	(*R*)-**1c**	77[c]
8	**1d**	O	$Pr^i(CH_2)_3C(Me)(Et)$	Ph	Ph	5.0	**4d**	98
9	**1e**	O	2,4,6-$Me_3C_6H_2$	Ph	Ph	1.0	**4e**	94
10	**1f**	O	$HO(CH_2)_9$	Ph	Ph	1.0	**4f**	98[d]
11	**1ga**	O	$Ph_3SiO(CH_2)_9$	Me	Me	3.0	**4f**	79
12	**1gb**	O	$Ph_3SiO(CH_2)_9$	Bu^t	Ph	3.0	**4g**[e]	63[c]
13	**1h**	O	$Ph_3SiN(Me)(CH_2)_6$	Ph	Ph	6.0	**4h**[f]	63[g]
14	**2a**	$Me(CH_2)_7N$	$Me(CH_2)_7$	Me	Me	3.0	**5a**	97
15	**2b**	—[h]	—[h]	—[h]	—[h]	5.0	**5b**[i]	89
16	**2c**	MeN	Ph	Ph	Ph	3.0	**5c**	82
17	**2d**	$MeO(CH_2)_2N$	$MeO(CH_2)_2$	Ph	Ph	5.0	**5d**	97
18	**3a**	S	$Me(CH_2)_9$	Ph	Ph	5.0	**6a**	84
19	**3b**	S	*c*-C_6H_{11}	Ph	Ph	1.5	**6b**	51
20	**3c**	S	Ph	Ph	Ph	5.0	**6c**	48

[a] Yield determined by quantitative GLC, using commercially available compound **4–6** and *n*-dodecane (internal standard) in the determination of response factors.
[b] DTBB was used as an electron carrier instead of naphthalene and the reaction was run at 20 °C.
[c] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. All isolated compounds **4** were ≥95% pure (GLC and/or 300 MHz ^1H NMR).
[d] Compound **1f** was deprotonated with *n*-BuLi before performing the naphthalene-catalysed lithiation step.
[e] **4g**=9-[*tert*-butyl(diphenyl)silyloxy]-1-nonanol.
[f] **4h**=6-(methylamino)-1-hexanol.
[g] Yield determined by quantitative GLC, using commercially available compound **4h** and *n*-hexadecane (internal standard) in the determination of response factors.
[h] **2b**=4-benzyl-*N*-(triphenylsilyl)piperidine.
[i] **5b**=4-benzylpiperidine.