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Selective Protection of Either the Phenol or the Hydroxy Group in Hydroxyalkyl Phenols

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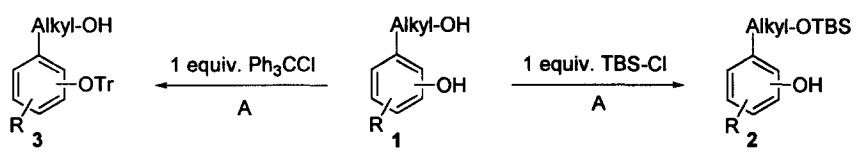
Abstract: *Hydroxyalkyl phenols can be protected either at the hydroxy group or at the phenol in a simple protocol (CH_2Cl_2, Et_3N, DMAP, 0 °C → room temp.) by using either t-butyldimethylsilyl chloride or trityl chloride as protecting reagent. Yields are in the range of 37–92%.*

Selective protection and deprotection of functional groups is one of the major issues in multistep synthetic strategies of organic compounds. In particular, hydroxy groups are targets for selective protection, because often selectively accessible OH-groups are required for the following reaction. Many OH-protecting groups are known and the ability to protect a primary hydroxy group in presence of a secondary was found with a variety of protecting reagents.[1]

As a part of our research program on photosensitive aromatic compounds, we required the selective protection of a primary hydroxy group in presence of a phenol in a salicyl alcohol derivative. A literature survey revealed only a few reports on the regioselective protection of hydroxyalkyl phenols.[2–6] Perfluoroaryl derivatives,[2] allyl bromide,[3] *t*-butyloxycarbonyl (Boc) anhydride[4] and acetylimidazole[5] were used to protect selectively the phenol, whereas tetrahydropyranyl ether were exclusively formed at the hydroxyalkyl group.[6] However, silyl ethers were neither used to protect the hydroxy group nor the phenol selectively. Only a procedure for the selective deprotection of phenyl alkyl disilyl ether in each direction was described.[7]

In a first experiment, one equivalent of TBS-Cl was added to a solution of alcohol **1a**, 1.5 equivalents of triethylamine, and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in dichloromethane at 0 °C. After workup and purification we obtained the monoprotected silyl derivative **2a** and diprotected compound in 82% and 8% yield, respectively (Table 1, entry 1). The silyl ether **2a** proved to be incompatible with the following reaction conditions making a different protecting group for the alkyl–OH group necessary. We supposed that the trityl group would meet our requirement (sterically demanding protecting group selective for primary alcohols, stable under basic conditions). Thus, alcohol **1a** was treated with 1.05 equivalent of trityl chloride under exactly the same reaction conditions as used for the silyl ether formation. To our surprise, phenol ether **3a** was obtained in 78% (entry 6) and the diprotected compound in 12% yield (Scheme 1).

Scheme 1



Reaction condition A: 1.5 equiv. Et_3N, cat. DMAP, CH_2Cl_2, 0 °C → room temp., 2 h.

Based on the experience with **1a**, we turned our attention to the scope of this regioselective protection and subjected hydroxyalkyl phenols **1b-d**[8] and a heterocycle (kojic acid (**4**))[8] to our protection protocol (Scheme 2). The results obtained are summarized in Table 1. With salicyl alcohol **1b** the same reactivity pattern was observed as with the diazirine derivative **1a**, indicating that possible electronic effects of the trifluoromethyl diazirine moiety have no influence on the outcome of the reaction. Silyl ether **2b** and trityl ether **3b** were

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formed in 91 and 67% yield, respectively (entries 2 and 7). A neighbor group effect in **1a** and **1b** is also unlikely because dihydroconiferyl alcohol **1c** having a hydroxyalkyl chain in *para*-position to the OH-group shows a similar behaviour. Silylation with TBS-Cl gave silyl ether **2c** in 55% yield (entry 3), but trityl chloride was less selective affording compound **3c** and the tritylated primary alcohol in a 10:1 ratio (66% yield, entry 8).

Scheme 2

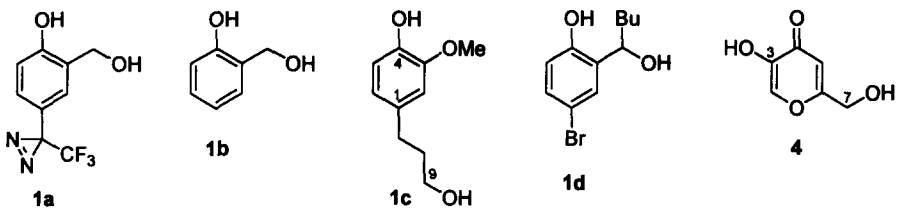

Table 1: Yields of silyl ether **2** and **5** and trityl ether **3** and **6**, respectively, obtained as described in Scheme 1.

entry	alcohol	reagent	product	yield [%][a]
1	**1a**	TBS-Cl	**2a**	82
2	**1b**	"	**2b**	91
3	**1c**	"	**2c**	55[c]
4	**1d**	"	**2d**	37[b]
5	**4**	"	**5**[c]	81
6	**1a**	Ph_3CCl	**3a**	78
7	**1b**	"	**3b**	67
8	**1c**	"	**3c**	66[d,e]
9	**1d**	"	**3d**	92[e]
10	**4**	"	**6**[f]	78[g]

[a]Yields of isolated product. [b]30% of the silylphenyl ether was also isolated. [c]*t*-Butyldimethylsilyl ether at C-7. [d]Contains 9% of the product mono-tritylated at C-9. [e]Required longer reaction times (>24 h) for a complete conversion. [f]Trityl ether at C-3. [g]Contains 8% of the trityl ether at C-7.

A limitation of this selective protection strategy was the secondary alcohol **1d**. Silyl ether formation at the alcohol moiety was accompanied by the attack at the phenol group and, therefore, compound **2d** and the corresponding silylated phenol have been isolated in 37 and 30 %, respectively (entry 4). On the other hand, tritylation of the phenol group of **1d** was completely regioselective producing **3d** in 92% yield, although a longer reaction time (24 h at room temperature) was required for a complete conversion (entry 9). Kojic acid (**4**), a heteroaromatic compound, behaves like the phenolic compound **1c**. Thus, silyl ether **5** was formed regioisomerically (entry 5) pure in 81% yield, but the trityl ether **6** (78%) was contaminated with 8% of the C-9 monotrityl ether (entry 10).

In summary, we have shown that hydroxyalkyl phenols undergo selective protection either at the hydroxy or at the phenol group by simply choosing the protecting reagent under otherwise essentially the same reaction conditions. TBS-Cl selectively formed the silyl ether at the alcohol moiety, whereas trityl chloride gave preferentially the phenyl ether.

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References and Notes

1. a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2. ed; John Wiley and Sons: New York; **1991**; b) Kocienski, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, **1994**.
2. a) Jarman, M.; McCague, R. *J. Chem. Soc., Chem. Commun.* **1984**, 125–127; b) Jarman, M.; McCague, R. *J. Chem. Research (S)* **1985**, 114–115; c) Jarman, M.; McCague, R. *J. Chem. Research (S)* **1985**, 116–117.
3. van der Leu, M.; Oosterink, H. J.; Hall, R. H.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3661–3666.
4. Houlihan, F.; Bouchard, F.; Frechet, J. M. J.; Wilson, C. G. *Can. J. Chem.* **1985**, *63*, 153–162.
5. Hagiwara, H.; Morohashi, K.; Suzuki, T.; Ando, M. *Synth. Commun.* **1998**, *28*, 2001–2006.
6. Ballini, R.; Bigi, F.; Carloni, S.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1997**, *38*, 4169–4172.
7. Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.
8. Salicyl alcohol **1b** and kojic acid (**4**) are commercially available. Compound **1c** was prepared in three steps from ferulic acid (1. MeOH, H^+; 2. H_2, Pd/C 10%, 3. $LiAlH_4$, 80% overall), compound **1a** was obtained in 8 steps from 5-bromo-salicylaldehyde according to known procedures (Findlay, J. B. C.; Fishwick, C. W. G.; Kersey, I. D.; Ward, P. *Synthesis* **1995**, 553–556) (30% overall), and **1d** by addition of *n*-BuLi to the same precursor at low temperature (94%).