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A convenient biphasic process for the monosilylation of symmetrical 1,*n*-primary diols

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Abstract

A simple and mild biphasic process was developed for the selective protection of one of two chemically equivalent primary hydroxyl groups in 1,*n*-diols using *t*-butyldiphenyl silyl chloride in diisopropyl ethyl amine and dimethyl formamide.

Keywords: selective protection; 1,*n*-diol; silylation; biphasic.

Selective derivatization/protection of one of two hydroxyl groups in the same molecule is a very important issue in organic synthesis.[1] Chemically non-equivalent hydroxyl groups such as primary, secondary, and tertiary hydroxy can be readily differentiated from each other by employing common protection and deprotection strategies. However, two chemically equivalent hydroxyl groups such as those in 1,*n*-primary diols are often difficult to differentiate. Derivatization of these diols with a stoichiometric amount of a reagent usually generates a mixture of the unreacted, the monoderivatized and the diderivatized diol in a statistical distribution of 1:2:1.[2] Selective protection of only one hydroxyl group in a 1,*n*-diol is difficult to achieve. It requires careful control of experimental conditions;[3] the cleavage of cyclic intermediates;[4] or the use of catalysts such as strongly acidic ion-exchange resins,[1a] inorganic polymer supports,[1b] and hydrolytic enzymes.[5] All of these conditions resort to costly and time-consuming recycling procedures. One method of selective protection of 1,*n*-diols employs NaH/*t*-butyldimethyl silyl chloride (TBDMSCl) in THF.[6] This method gives good yields for the primary diols tested, but the formation of sodium alkoxides in the presence of stoichiometric amounts of NaH requires careful manipulation. Besides, this condition is too strong to be compatible with diols containing base-sensitive functional groups. Therefore, there is still a need to develop a mild and convenient method for the selective protection of 1,*n*-diols.

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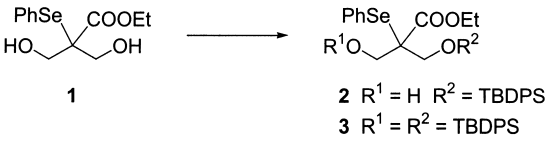
In our endeavor to synthesize potential protein kinase inhibitors, we needed to protect one of the two chemically equivalent primary hydroxyl groups in **1** (Scheme 1). *t*-Butyldiphenyl silyl ether (TBDPS) was chosen over TBDMS as the protecting group because TBDPS group is considerably more stable (≅100 times) than TBDMS group towards acidic hydrolysis, and is more stable to many other reagents where TBDMS is labile.[7]



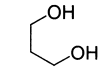
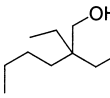
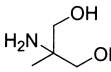
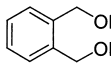
Scheme 1.

We tried various conditions to introduce TBDPS on one of the primary hydroxyl groups in **1** but failed to obtain the desired monosilylated product **2**. With the exception of excess TBDPSCl plus imidazole in DMF, none of the conditions gave any silylated products, and most of the starting material was recovered.[8] Excess TBDPSCl (3 equiv.) and imidazole (10 equiv.) in DMF, however, afforded only the diprotected compound **3** in 89% yield while no monosilylated product **2** was isolated. We thought that the low reactivity of **1** might be due to the strong intramolecular hydrogen bonding interaction that inhibited the reaction of the hydroxyl groups with the bases added.[9] If this is true, use of a polar aprotic solvent should decrease such intramolecular hydrogen bonding interaction and facilitate the protection reaction. Indeed, our subsequent experiments showed that selective protection could be achieved in a mixed solvent of CH_2Cl_2 and THF (1:1) in the presence of DIEA. Under this condition, the desired product **2** was obtained in 66% yield and none of the diprotected product **3** was isolated. When we changed the solvent to DMF and used excess DIEA as the base, the reaction proceeded very well to give **2** in an even higher yield (87%). More interesting and to our surprise, we found that DIEA had limited solubility in DMF and that excess DIEA formed a light phase on top of the DMF phase. Based on this phenomenon, we believe that the unique selectivity under this biphasic condition could be in part due to the constant concentration (16%) of base (DIEA) maintained in the reaction phase (DMF) during silylation.[10] However, the exact source of selectivity is not understood.

The following general procedure was then developed to prepare the monosilylated symmetrical 1,*n*-primary diols: A solution of 1,*n*-diol (1 mmol) in anhydrous DMF (3 mL) was charged with redistilled DIEA (10 equiv., 1.7 mL) forming a biphasic mixture at room temperature. TBDPSCl (1.05 equiv.) was added dropwise into the biphasic mixture with stirring under argon. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. Upon completion, the reaction was quenched with cold water (20 mL), extracted with *t*-butyl methyl ether (3×50 mL), and washed with 2N HCl (2×20 mL), saturated $NaHCO_3$ (aq., 20 mL), and then brine (20 mL). The organic phase was dried over $MgSO_4$, filtered through a cotton pad, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with acetone[11] and hexane as the eluent.

To explore the synthetic generality of this biphasic protection reaction, we investigated several primary diols. As shown in Table 1, reasonable yields and selectivity were observed for all 1,*n*-diols examined, ranging from 1,2-ethanediol (**4**) to 1,9-nonanediol (**11**).[12] The 1:2:1 statistical distribution

Table 1
Monosilyation of primary diols under the biphasic condition[a]

Primary Diol	Time (h)	Equiv of TBDPSCl	Monosilylated Product[11] (%)	Bissilylated Product (%)
 (**4**)	24	1.05[b]	86[c]	—[d]
 (**5**)	8	1.05	80	—
 (**6**)	9	4.0[e]	92[f]	—
 (**7**)	24	1.05	81[f]	1.4
 (**8**)	5	2.15[e]	84	—
$HO(CH_2)_5OH$ (**9**)	15	1.05	85	5.8
$HO(CH_2)_7OH$ (**10**)	17	1.02	75	3.2
$HO(CH_2)_9OH$ (**11**)	28	1.0	81	8.5

[a]Reaction condition: TBDPSCl, DIEA (10 equiv), DMF, rt. [b]Equivalents of TBDPSCl were calculated according to the starting diols. [c]Isolated yield, remainder of mass balance was recovered starting diol. [d]No bissilyated product was isolated. [e]Excess TBDPSCl didn't hurt the monosilylation. [f]As a racemic mixture.

found in most conditions was not a problem under this biphasic condition. It should be noted that excess TBDPSCl does not adversely affect the selective protection of one of the two hydroxyl groups as shown for compounds **6** and **8** in Table 1.

For direct comparison of our method with the commonly used condition of TBDPSCl/DIEA/CH_2Cl_2, both 1,3-propanediol (**5**) and 2-methyl-2-amino propanediol (**7**) were also treated with TBDPSCl (1 equiv.) at ambient temperature in a mixture of DIEA and CH_2Cl_2 (1:1). Using our biphasic condition, both **5** and **7** gave the monosilylated products in isolated yields of 80 and 81%, respectively, with little or no bissilylated product isolated (as shown in Table 1). However, TBDPSCl treatment of **5** in DIEA/CH_2Cl_2 gave only the bissilylated product in 75% after isolation while TBDPSCl treatment of **7** in DIEA/CH_2Cl_2 failed to give any silylated product as monitored by TLC. These results clearly demonstrate the superiority of our biphasic condition for the formation of monosilylated derivatives of 1,*n*-diols.

In conclusion, a biphasic silylating process was developed to prepare in high yield monosilylated derivatives of symmetrical 1,*n*-primary diols, which are important building blocks in organic synthesis.[13] This method is mild and convenient. In addition, only stoichiometric silylating reagent is needed. The same condition could be adapted to the synthesis of monoacylated derivatives of symmetrical diols, which are also important bifunctional building blocks.[1a]

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8. The conditions we tried but failed to give any silylated products include: (a) TBDPSCl (1.05 equiv.), DIEA (10 equiv.), CH_2Cl_2, rt, 36 h; (b) TBDPSCl (1.05 equiv.), Et_3N (10 equiv.), CH_2Cl_2, rt, 24 h; (c) TBDPSCl (1.05 equiv.), Et_3N (10 equiv.)/DMAP (0.05 equiv), CH_2Cl_2, rt, 24 h; (d) TBDPSCl (1.05 equiv.), DMAP (10 equiv.), CH_2Cl_2, rt, 24 h; (e) TBDPSCl (1.05 equiv.), pyridine, rt, 24 h; (f) TBDPSCl (1.05 equiv.), imidazole (5 equiv.), DMF, rt, 24 h; (g) TBDPSCl (1.05 equiv.), NaH (1 equiv.), THF, 0°C–rt, 3 h.
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10. In a typical procedure, DIEA (10 mmol, 1.7 mL) and DMF (3 mL) form two immiscible solution phases at room temperature. Using NMR, we found that the top DIEA phase contained about 18% DMF (mol) and the bottom DMF phase contained about 16% DIEA. TLC analysis indicated that reactants used in our experiments were mainly in the bottom DMF phase. We also found that using saturated DIEA solution in DMF as the reaction media decreased both the reaction yield and the selectivity of silylation.
11. Acetone–hexane was found to be a better eluting solvent system than the commonly used ethyl acetate/hexane for the purification and structure assignment of the monosilylated 1,*n*-primary diols, since ethyl acetate can be strongly retained in compounds containing hydroxyl groups and it is hard to remove completely in vacuo.
12. Selected ^1H NMR (200 MHz, $CDCl_3$) data: δ ppm compound **1**: 7.60 (dd, 2H, $J=7.5$, 1.3 Hz), 7.41–7.26 (m, 3H), 4.13–3.89 (m, 6H), 3.08 (t, 2H, $J=6.6$ Hz), 1.98 (br s, 2H, OH), 1.18 (t, 3H, $J=7.1$ Hz); compound **2**: 7.76–7.20 (m, 15H), 4.24–4.12 (m, 2H), 4.03–3.90 (m, 4H), 2.55 (dd, 1H, $J=5.7$, 4.0 Hz, OH), 1.08 (t, 3H, $J=7.8$ Hz), 1.06 (s, 9H); compound **3**: 7.76–7.67 (m, 10H), 7.44–7.26 (m, 15H), 4.36 (Ab*q*, 2H, $\Delta\gamma=14.0$ Hz, $J=9.5$ Hz), 3.65 (q, 2H, $J=6.8$Hz), 1.05 (s, 18H), 0.82 (t, 3H, $J=7.1$ Hz); *mono*-TBDPS-**4**: 7.78–7.73 (m, 4H), 7.49–7.43 (m, 6H), 3.85–3.80 (m, 2H), 3.74 (br s, 2H), 2.45 (br s, 1H, OH), 1.15 (s, 9H); *mono*-TBDPS-**5**: 7.75–7.70 (m, 4H), 7.45–7.42 (m, 6H), 3.88 (t, 2H, $J=5.6$ Hz), 3.87 (t, 2H, $J=5.8$ Hz), 2.54 (br s, 1H, OH), 1.80 (q, 2H, $J=5.7$ Hz), 1.10 (s, 9H); *mono*-TBDPS-**6**: 7.82–7.68 (m, 4H), 7.52–7.38 (m, 6H), 3.60 (d, 2H, $J=5.5$ Hz), 3.56 (s, 2H), 2.68 (t, 1H, $J=5.5$ Hz, OH), 1.42–0.75 [m, 23H, including 1.12 (s, 9H), 0.92 (t, 3H, $J=6.1$ Hz), 0.81 (t, 3H, $J=6.5$ Hz)]; *mono*-TBDPS-**7**: 7.70–7.65 (m, 4H), 7.45–7.39 (m, 6H), 3.53–3.33 (m, 4H), 1.85 (br s, 2H, NH_2), 1.09 (s, 9H), 1.04 (s, 3H); *mono*-TBDPS-**8**: 7.83–7.79 (m, 4H), 7.50–7.45 (m, 4H), 7.33 (br s, 3H), 4.89 (s, 2H), 4.73 (s, 2H), 3.20 (br s, 1H, OH), 1.17 (s, 9H); *mono*-TBDPS-**9**: 7.76–7.71 (m, 4H), 7.45–7.41 (m, 6H), 3.73 (t, 2H, $J=6.2$ Hz), 3.64 (t, 2H,

$J = 5.5$ Hz), 2.05 (br s, 1H, OH), 1.68–133 (m, 6H), 1.12 (s, 9H); *mono*-TBDPS-**10**: 7.75–7.70 (m, 4H), 7.44–7.41 (m, 6H), 3.71 (t, 2H, $J = 6.3$ Hz), 3.66 (Abq, 2H, $\Delta\gamma = 12.2$ Hz, $J = 6.6$ Hz), 1.75 (br s, 1H, OH), 1.61–1.55 (m, 4H), 1.44–1.31 (m, 6H), 1.10 (s, 9H); *mono*-TBDPS-**11**: 7.73–7.68 (m, 4H), 7.43–7.39 (m, 6H), 3.69 (t, 2H, $J = 6.5$ Hz), 3.65 (t, 2H, $J = 6.4$ Hz), 1.65–1.50 (m, 4H), 1.48–1.25 (m, 10H), 1.08 (s, 9H).

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