A New Reagent System for Efficient Silylation of Alcohols: Silyl Chloride–*N*-Methylimidazole–Iodine

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Abstract: It was found that reactions of alcohols with silyl chlorides in the presence of *N*-methylimidazole were significantly accelerated by the added iodine, and on this basis a general, and high yielding method for efficient silylation of primary, secondary, and tertiary alcohols was developed.

Key words: silylation, silyl chlorides, iodine, *N*-methylimidazole

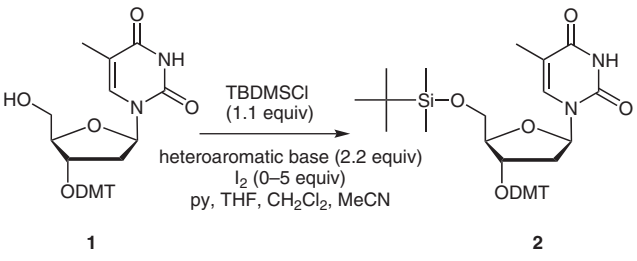
The hydroxyl function is ubiquitous in natural products, e.g. saccharides, proteins, nucleic acids, alkaloids, and its transformation to the corresponding silyl ethers is a common way either to protect this functionality during multistep chemical syntheses, or to confer a certain lipophilic character to the otherwise highly polar organic compounds.[1] Synthetically attractive features of silicon-based protecting groups are that their susceptibility to acid- and base-catalyzed hydrolysis can be modulated by a suitable choice of substituents on the silicon atom,[2,3] while the known lability of the silyl ethers in the presence of fluoride ion provides a convenient, very specific, orthogonal way for their cleavage.[3,4]

The most popular silyl protecting group, by far, is the *tert*-butyldimethylsilyl group (TBDMS), and since its introduction by Corey and Venkateswarlu in 1972,[5] the group has received a widespread application in organic synthesis.[4] Although the Corey and Venkateswarlu's conditions, consisting of using TBDMSCl with imidazole in DMF, remain a general purpose silylation procedure for alcohols, a plethora of reagents and reactions conditions have been proposed for the introduction of TBDMS and related silyl protecting groups,[1,6,7] to make up for a frequent inefficiency of the original protocol. The main problems with silylation of complex natural products are that often lower yields are obtained and extended reaction times are required, when it comes to protection of sterically hindered secondary and tertiary alcohols, especially using reagents with bulky substituents on the silicon. Additionally, practical difficulties are frequently encountered during work-up and chromatographic purifications, due to the usage of DMF as a reaction medium for the silylation.

Recently, during our studies on oxidative couplings of H-phosphonates with alcohols we observed, that the relatively unreactive silylating agent, *tert*-butyldiphenylsilyl chloride (TBDPSCl), exhibited enhanced reactivity in the presence of iodine, causing undesired in this context, silylation of the alcohols.[8,9] We found that the accelerating effect of iodine was not confined to the TBDPSCl reagent, but was observed also for other silyl chlorides. For this reason, we investigated in more detail this phenomenon with the aim of developing a new protocol for silylation of alcohols.

As a model reaction we investigated silylation of primary hydroxyl function in 3′-*O*-dimethoxytritylthymidine (**1**) with TBDMSCl (1.1 equiv) in various solvents (pyridine, dichloromethane, acetonitrile and THF) in the presence of base (2.2 equiv) and iodine (0–5 equiv) (Scheme 1). Preliminary screening of the reaction conditions revealed that iodine alone did not show any catalytic effect on the silylation but required the presence of pyridine or *N*-methylimidazole. Strong bases, such as triethylamine or diisopropylethylamine, were incompatible with the reaction conditions, apparently due to decomposition of iodine.[10] In the presence of 2,6-lutidine and iodine, no detectable silylations occurred. The solvents investigated did not have a noticeable effect on the rate of silylation, irrespective of the base and the amount of iodine used.

Typically, the silylation of nucleoside **1** in acetonitrile in the presence of pyridine (2.2 equiv) to provide the silylated product **2** was complete within six hours, but the addition of iodine shortened the reaction time to one hour (with 3 equiv of I_2) or 45 minutes (with 5 equiv of I_2). In neat pyridine, the reaction was only marginally faster and leveled off when the excess of iodine reached three equivalents (time for the completion of the reaction was ca. 45 min).



1 **2**

DMT = 4,4'-dimethoxytrityl

Scheme 1

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When carried out in the presence of *N*-methylimidazole (2.2 equiv), instead of pyridine, the analogous silylation reactions were significantly faster, and went to completion within 30 minutes, irrespective of solvent used (Scheme 1). Addition of iodine (1 equiv) to the reaction mixtures in THF, acetonitrile or pyridine, decreased the reaction time to five minutes. With the more iodine (3 equiv) added, the silylation proceeded even faster (ca. 2 min for the completion), but the rates did not increase further with higher excess of iodine (5 equiv).

A similar set of experiments was carried out on 5′-*O*-dimethoxytritylthymidine (entry 1, Table 1) as a model compound for secondary hydroxyl functions, which are known to undergo silylation with more difficulty than primary alcohols. Indeed, in acetonitrile in the presence of pyridine (2.2 equiv), the silylation with TBDMSCl did not occur at all (5 h), and in neat pyridine it proceeded very slowly (ca. 5% after 5 h). The addition of iodine sped these reactions up (ca. 30% and 80% silylation, respectively, after 5 h), but the reaction did not go to completion. In contrast, the silylation in THF in the presence of *N*-methylimidazole (2.2 equiv) and iodine (3 equiv) afforded quantitatively the desired 3′-O-silylated nucleoside within one hour vs. five hours for the reaction in the absence of iodine.

On the basis of these model experiments we formulated a synthetic protocol for the silylation of alcohols, consisting of THF, acetonitrile or CH_2Cl_2 as a solvent (depending on solubility of substrates), *N*-methylimidazole (3 equiv) as the base and a nucleophilic catalyst, and iodine (2–3 equiv).[11]

The efficacy of this new reagent system was assessed by carrying out silylation of alcohols with diverse structural features and by using different silylating agents (Table 1). The silylation of primary alcohols was always rapid (ca. 5 min; entries 2, 3, and 9), irrespective of the kind of the silylating agent used (TBDMSCl, TBDPSCl, TIPSCl). For secondary alcohols, a typical reaction time for the silylation was ca. 15–60 min (entries 1, 5, 6, 7) and only for secondary alcohols with high steric hindrance (entry 4) or with special chemical features (entry 8; a ketone–ketal equilibrium), did the reaction take longer time (ca. 5 h). Even the very unreactive tertiary alcohol, 1-adamantanol (entry 10), could be silylated in high yield, but the reaction had to be performed in neat *N*-methylimidazole in the presence of six equivalents of iodine. On average, the reactions in Table 1 were 5–30 times faster than those without iodine under standard silylation conditions using silyl chloride and imidazole in DMF.[5] The accelerating effect of the added iodine was largest for the slowest reactions and in the extreme case (entry 10), the silylation could only be carried under the new reaction conditions.

As it is apparent from Table 1, the reaction conditions for the silylation are compatible with the presence of double and triple bonds, even when the corresponding reaction mixtures were left standing for a longer time (5 h).

As to the mechanistic role of iodine in the investigated reactions (Scheme 2), we believe that it is related to that ascribed to iodine in certain phosphorylation reactions,[12] for which a tentative mechanism has been proposed.[8] Assuming the known propensity of iodine to catenation and formation of polyhalide anions,[13] it is likely that in the presence of iodine the concentration of chloride anions in the reaction mixtures can be depleted due to formation of less nucleophilic anions I_2Cl^-. Because of this, the equilibrium between a silyl chloride and a nucleophile catalyst will be shifted towards adduct **A**, the most likely reactive intermediate in the silylation reactions (Scheme 2). Consistent with this interpretation was the fact that the catalytic effect was always proportional to the amount of iodine used for the reaction, and that a nucleophilic catalyst was an indispensable component of the reaction mixtures in order to observe the catalytic effect of iodine.

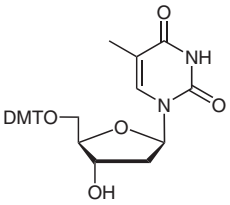
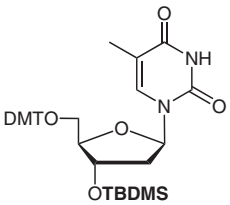
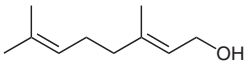
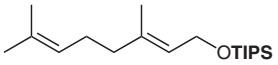
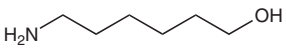
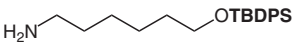
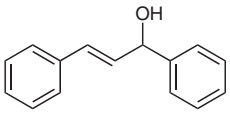
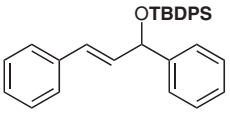
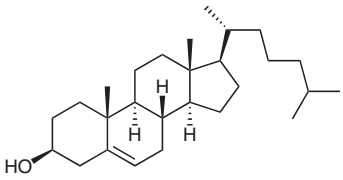
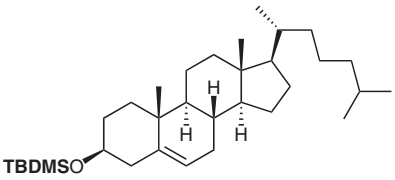
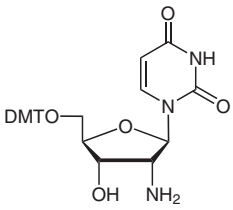
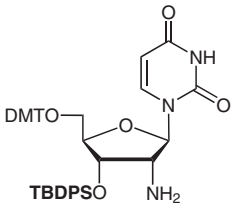
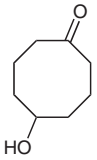
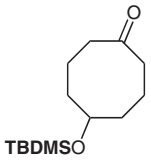
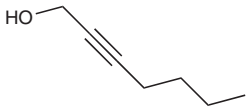
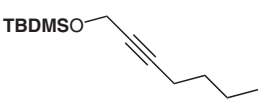
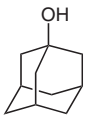
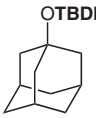
To substantiate the proposed mechanism of iodine action, some NMR experiments were carried out. The ^{1}H NMR spectra of TBDMSCl in $CDCl_3$ displayed two singlets at $\delta = 0.96$ and 0.34 ppm, assigned to the *tert*-butyl and the methyl protons, respectively. The addition of *N*-methylimidazole (3 equiv) or iodine (3 equiv) did not result in any changes in this region of the spectrum. However, when these two reagents (*N*-methylimidazole and iodine) were added together to the reaction mixture, two additional singlets at $\delta = 1.01$ and 0.71 ppm appeared. The chemical shifts and the relative integrals (3:2, respectively) of the signals suggested that they originated from *tert*-butyldimethylsilyl group in a new species (presumably adduct **A**, ca 32%, Scheme 2). To prove the chemical identity of the intermediate formed, the NMR sample was subjected to mass spectrometry analysis (ESI), which indeed showed the presence of the expected mass peak (m/z $[M]^+$ calcd for $C_{10}H_{21}N_2Si^+$: 197.1469; found: 197.1470) corresponding to the adduct **A**. Additionally, the mass spectra registered in the negative mode showed a strong signal ($m/z = 288$) corresponding to I_2Cl^-.

These preliminary results strongly support the proposed mechanism for the catalytic role of iodine in our reagent system.

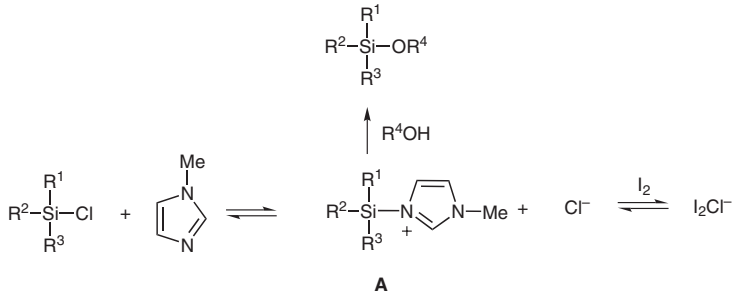
It should be noted that other studies reported a catalytic effect of iodine in conjunction with the introduction of trimethylsilyl group using 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[14,15] or with silyl chlorides (TMSCl, TBDMSCl) under microwave irradiation;[16] however, a mechanistic role of iodine in these and in our systems, seems to be disparate.

In conclusion, we developed an efficient protocol for the silylation of primary, secondary, and tertiary alcohols that consisted of using a silyl chloride in the presence of *N*-methylimidazole and iodine. The reactions can be carried out in various organic solvent (e.g. THF, MeCN, CH_2Cl_2, pyridine), at room temperature, and are compatible with the presence of common functional groups. The procedure is experimentally simple, high-yielding, and expands the range of synthetic methods available for silylation of complex organic compounds.

Table 1 Silylation of Alcohols using TBDMSCl, TBDPSCl and TIPSCl in the Presence of *N*-Methylimidazole and Iodine[11]

Entry	Alcohol	Product	Solvent	Time[a]	Isolated yield (%)
1[b]			THF	1 h (5 h)	98
2[c]			CH_2Cl_2	5 min (15 min)	89
3[d]			CH_2Cl_2	5 min (15 min)	93
4[d]			THF	5 h (36 h)	98
5[d]			THF	10 min (30 min)	86
6[b]			THF	1 h (2 h)	96
7[d]			THF	15 min (7 h)	96
8[b]			CH_2Cl_2	6 h (36 h)	80
9[b]			CH_2Cl_2	5 min (15 min)	95
10[d]			neat *N*-methylimidazole–I_2 (6 equiv)	16 h (no reaction)	85

[a] In parentheses, the reaction times for silylation under standard reaction conditions [silyl chloride (1.1 equiv), imidazole (3 equiv), DMF, r.t.)][5] are given.
[b] Silylating agent: TBDMSCl.
[c] Silylating agent: TIPSCl.
[d] Silylating agent: TBDPSCl.



Scheme 2

Acknowledgment

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(11) **General Procedure for the Preparative Silylation of Alcohols Listed in Table 1**: An alcohol (1.0 mmol), *N*-methylimidazole (3.0 mmol) and iodine (2.0–3.0 mmol) were dissolved in an appropriate, anhyd solvent (3 mL, Table 1). A silyl chloride (TBDMSCl, TBDPSCl or TIPSCl; 1.1 mmol) was added and the reaction mixture was stirred at r.t. until the complete disappearance of the starting material (TLC analysis). The solvent was evaporated, the residue dissolved in EtOAc and washed with concd aq $Na_2S_2O_3$. The organic phase was dried over anhyd Na_2SO_4 and evaporated. The products were purified by silica gel column chromatography (CH_2Cl_2–MeOH, 100:0 → 95:5, Table 1 entries 1, 3 and 7; pentane–EtOAc, 10:0 → 9:1, Table 1 entries 2, 4–6, 8–10). The synthesized compounds were fully characterized with ^1H and ^{13}C NMR and HRMS.
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