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Iodine-promoted silylation of alcohols with silyl chlorides. Synthetic and mechanistic studies

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ABSTRACT

An efficient silylating system for 1°, 2°, and 3° alcohols, consisting of a silyl chloride/*N*-methylimidazole/iodine, was developed. Synthetic and mechanistic aspects of this new reagent system, and particularly the role of iodine were investigated in detail using ^{1}H NMR spectroscopy.

1. Introduction

Silyl ethers are among the most frequently used protective groups for alcohols since both steric and electronic effects can regulate the ease of their cleavage.[1,2] For common trialkyl- and alkylarylsilyl ethers, depending on substituents on the silicon atom, differences in stability toward acids and bases span a range of 10^5 order of magnitude,[3,4] and thus in multistep organic syntheses, two or more different silyl protecting groups can be used simultaneously, and be removed selectively at different synthetic stages.[1,4] Of particular importance is also the known lability of the silyl ethers in the presence of fluoride ions, which provides a very convenient, orthogonal way for their cleavage.[4,5]

The most popular, by far, silylating agents are various trialkyl- or alkylarylsilyl chlorides.[6] However, since reactivity of silyl chlorides toward alcohols is strongly affected by steric and electronic features of substituents on the silicon atom, silyl esters that have synthetically useful stability are usually difficult to form, especially from 2° and 3° alcohols. Thus, to facilitate introduction of silyl protecting groups into hydroxylic compounds, a plethora of silylating agents have been developed.[4–7] Apart from the classical Corey–Venkateswarlu reaction conditions (a silyl chloride with imidazole in DMF),[8] of particular importance are reagent systems that make use of an increased reactivity of silyl chlorides in the presence of various additives. One should mention here supersilylating agents of type $R_3SiB(OTf)_3Cl$ [formed from silyl chlorides and $B(OTf)_3$],[9] or in situ generated silyl perchlorates or silyl nitrates.[10,11] In addition, reagent systems consisting of silyl chlorides and 1,4-diazabicyclo[2.2.2]octane (DABCO),[12] pyridine *N*-oxide,[12] 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[13] silver nitrate,[10] 4-dimethylaminopyridine,[14] or lithium sulfide[15] as catalysts, have been advocated for silylation of 1° and 2° alcohols.

Recently, during our studies on oxidative couplings of H-phosphonates with alcohols we observed, that relatively unreactive silylating agent, *tert*-butyldiphenylsilyl chloride (TBDPS-Cl), exhibited enhanced reactivity toward alcohols in the presence of iodine.[16] We found that the accelerating effect of iodine was not confined to the TBDPS-Cl reagent, but was observed also for other silyl chlorides.

In this paper we report our detailed synthetic and mechanistic investigations of this phenomenon, which led us to the development of a new synthetic protocol for silylation of 1°, 2°, and 3° alcohols. A short account of this work has recently been published as a communication.[17]

2. Results and discussion

Preliminary experiments on silylation of nucleosides with TBDMS-Cl in pyridine showed that the reactions were almost an order of magnitude faster upon addition of iodine. To obtain some insight into the role of iodine in these reactions, we investigated in detail some chemical and mechanistic aspects of silylation of alcohols using silyl chlorides in the presence of iodine under various experimental conditions.

Recently, a catalytic effect of iodine in conjunction with the introduction of trimethylsilyl group using 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[18] or with silyl chlorides (TMS-Cl, TBDMS-Cl) under microwave irradiation was reported,[19] however, a mechanistic role of iodine in these and in our systems, seems to be disparate.

2.1. Screening of the reaction conditions using 5′- and 3′-protected thymidine derivatives and TBDMS-Cl

Two simple nucleoside derivatives, namely, 3′-*O*-dimethoxytritylthymidine (3′-*O*-DMT-T, **1**) and 5′-*O*-dimethoxytritylthymidine

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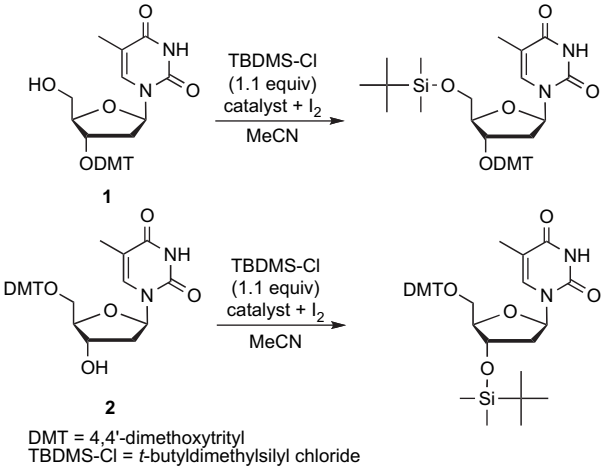
(5′-*O*-DMT-T, **2**) (Scheme 1) were chosen as models for primary and secondary alcohols, respectively. These were silylated in acetonitrile with *tert*-butyldimethylsilyl chloride (TBDMS-Cl; 1.1 equiv) in the presence of various bases and iodine. Progress of the reactions was monitored by the TLC analysis, and the results are summarized in Table 1.



Scheme 1. Silylation of nucleoside derivatives as models for 1° (**1**) and 2° (**2**) alcohols.

As it was apparent from data in Table 1, iodine indeed efficiently accelerated the silylation when the reaction was carried out in the presence of pyridine and *N*-methylimidazole, but no catalytic effect was observed for the reactions in which imidazole was used. Tertiary amines, such as triethylamine (Et_3N) or diisopropylethylamine (i-Pr_2NEt), only negligibly speed up the silylation. In addition, these amines turned out to be incompatible with iodine, apparently due to a rapid reaction[20] that led to a complete consumption of the amine and iodine. No silylation of nucleosides **1** and **2** could be observed when 2,6-lutidine alone, or in combination with iodine, was used for the reaction.

These experiments indicated that base catalysis during silylation of alcohols with silyl chlorides was rather inefficient, and that an amine, which was also used as an acid scavenger, had to have nucleophilic properties to accelerate the reaction. Somewhat puzzling, however, was the fact that silylation reactions in which imidazole was used were insensitive to the addition of iodine (vide infra). The lack of detectable silylation in the reaction in the presence of 2,6-lutidine indicated that iodine alone did not have any catalytic activity in the reactions investigated.

Since the accelerating effect of iodine on silylation of alcohols seemed to be connected to the presence of nucleophilic catalysts in the reaction mixture, in our further studies only pyridine, dimethylaminopyridine (DMAP), imidazole, and *N*-methylimidazole were used.

Table 1
Reaction times for the silylation of **1** and **2** in acetonitrile under different experimental conditions

Base (2.2 equiv)	Reaction time for **1** (conversion, if not 100%)		Reaction time for **2** (conversion, if not 100%)	
	No I_2	5 equiv I_2	No I_2	5 equiv I_2
Pyridine	6 h	45 min	No reaction	6 h (~30%)
N-Methylimidazole	30 min	2 min	6 h	1 h
Imidazole	10 min	10 min	4 h	4 h
Et_3N	3 h (~10%)	nd[a]	No reaction	No reaction[b]
i-Pr_2NEt	3 h (~10%)	nd[a]	No reaction	No reaction[b]
2,6-Lutidine	No reaction	No reaction	No reaction	No reaction

[a] Not determined due to side reaction of iodine with trialkylamines, leading to detritylation of the starting material and the products.
[b] Similar behavior as described above in footnote a was observed, however no products were formed at any time.

All these nucleophile catalysts were screened for their ability to catalyze silylation of a model primary alcohol, namely, 3′-*O*-DMT-T (**1**) with TBDMS-Cl in different solvents, and in the presence of variable amount of the added iodine (Table 2, the upper part). The results obtained were in agreement with the already observed trends in reactivity, irrespective of the solvent used (see, Table 1). The accelerating effect of iodine was observed for the reactions carried out in the presence of pyridine, DMAP, and *N*-methylimidazole, but not for those with imidazole. DMAP, although accelerated the silylation reaction, it also exhibited a similar behavior to that observed for triethylamine and DIPEA (although to smaller extent), and for this reason it was excluded from further studies.

For the silylation of a model secondary alcohol, 5′-*O*-DMT-thymidine (**2**) (Table 2, lower part), the reaction times became longer, but again a large rate enhancement was observed for the reactions in which pyridine or *N*-methylimidazole was used together with iodine. As for the reaction with **1**, iodine had no effect on the rate of silylation of nucleoside **2** in the presence of imidazole. All the reactions investigated were also rather insensitive to the nature of the solvent used. Thus, it seemed that optimal reaction conditions for silylation 1° and 2° with TBDMS-Cl, consisted of using *N*-methylimidazole (3 equiv) as a nucleophile catalyst together with iodine (2–3 equiv) in THF or acetonitrile.

2.2. Silylation of nucleoside 2 with different silyl chlorides

After having established the optimal reaction conditions for silylation of primary and secondary alcohols with TBDMS-Cl (vide supra), we investigated also other silyl chlorides that were frequently used for the protection of alcohols in organic synthesis. The silylation experiments were carried out using the less reactive 2° alcohol, namely 5′-*O*-DMT-T (**2**), and different silyl chlorides. Data in Table 3 show the reaction times for silylations of **2** under standard Corey–Venkateswarlu conditions,[8] and those for the reactions in which *N*-methylimidazole was used alone, or in combination with iodine.

For the silyl chlorides with three unbranched alkyl chains (TMS-Cl, TES-Cl, and TPS-Cl), the silylation was fast (ca. 5 min), irrespective of the reaction conditions used. More pronounced differences, however, became visible for bulky silylating agents. Moderately sterically hindered silyl chlorides, e.g., TBDMS-Cl, TDS-Cl, and TBDPS-Cl, reacted significantly slower than simple trialkylsilane derivatives, and in all instances the best results were obtained when *N*-methylimidazole/iodine reagent system was used. The effect of iodine on the rate of silylation was particularly pronounced for TBDPS-Cl, for which the reaction time could be shortened from 5 h to 10 min.

For the most sterically hindered silyl chloride investigated, TIPS-Cl, silylation of 2° hydroxyl group in **2** was rather slow, and even in the presence of iodine, the reaction went only to 40% completion after 8 h.

2.3. Mechanistic studies on the role of iodine in the investigated reactions

Although a catalytic effect of iodine during silylation was reported for 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[18] and for some silyl chlorides (TMS-Cl, TBDMS-Cl) under microwave irradiation,[19] a mechanistic role of iodine remained elusive. One should note, that those reactions were carried out with sub-stoichiometric amounts of iodine and without nucleophile catalysts and thus, most likely, different mechanisms operated than that in our silylation reactions.

Table 2
The reaction times for silylation of **1** and **2** with TBDMS-Cl, using different nucleophile catalysts, solvents, and various amounts of the added iodine

Nucleophile catalyst (2.2 equiv)	Solvent	Reaction times for silylation of 1° alcohol **1** (conversion, if not 100%)			
		No I_2	1 equiv I_2	3 equiv I_2	5 equiv I_2
Pyridine	Neat	5 h	3 h	45 min	45 min
Pyridine	CH_3CN	6 h	5 h	1 h	45 min
DMAP	Pyridine	5 h	15 min (~30%) 3 h (~70%)[a]	45 min	45 min
DMAP	CH_3CN	1 h (60%)	15 min (~60%) 1 h (~70%)[b]	15 min (~60%) 1 h (~70%)[b]	15 min (~60%) 1 h (~70%)[b]
Imidazole	Pyridine	10 min	10 min	10 min	10 min
Imidazole	CH_3CN	10 min	10 min	10 min	10 min
Imidazole	DMF	10 min	10 min	10 min	10 min
Imidazole	THF	10 min	10 min	10 min	10 min
N-Methylimidazole	Pyridine	30 min	5 min	2 min	2 min
N-Methylimidazole	CH_3CN	30 min	5 min	2 min	2 min
N-Methylimidazole	THF	30 min	5 min	2 min	2 min
Nucleophile catalyst (2.2 equiv)	Solvent	Reaction times for silylation of 2° alcohol **2** (conversion, if not 100%)			
		No I_2	1 equiv I_2	3 equiv I_2	5 equiv I_2
Pyridine	Neat	5 h (~5%)	5 h (~20%)	5 h (~50%)	5 h (~80%)
Pyridine	CH_3CN	No reaction	6 h (~5%)	6 h (~20%)	6 h (~30%)
Imidazole	Pyridine	5 h	5 h	5 h	5 h
Imidazole	CH_3CN	4 h	4 h	4 h	4 h
Imidazole	DMF	4 h	4 h	4 h	4 h
Imidazole	THF	4 h	4 h	4 h	4 h
N-Methylimidazole	Pyridine	5 h	1.5 h	1 h	1 h
N-Methylimidazole	CH_3CN	6 h	2 h	1 h	1 h
N-Methylimidazole	THF	6 h	1.5 h	1 h	1 h

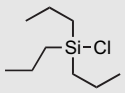
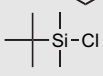
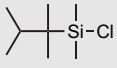
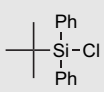
[a] DMAP seemed to react with iodine similarly to Et_3N and DIPEA, but slower and led incomplete reactions.
[b] Due to consumption of base in the reaction of DMAP with iodine, the detritylation was observed after prolonged reaction time (1 h).

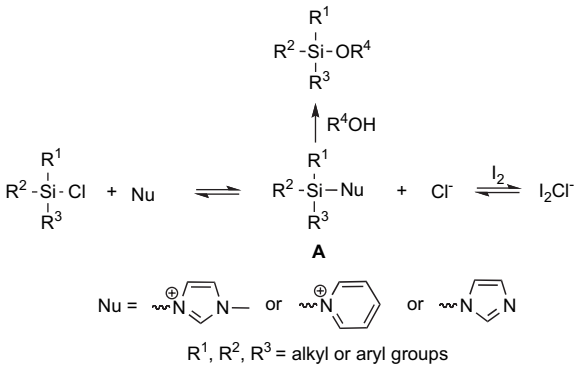
Analysis of data from Tables 1 and 2 seemed to suggest that a mechanistic role of iodine in our reactions might be related to that ascribed to iodine in certain phosphorylation reactions,[16,21] and a plausible mechanism was depicted in Scheme 2. It involved a reaction of a silyl chloride with a nucleophile catalyst to form a reactive intermediate **A**, from which, upon the reaction with an alcohol, a silyl ether was formed. Assuming the known propensity of iodine to catenation and formation of polyhalide anions,[22] it was likely that in the presence of iodine the concentration of chloride anions, generated in the first reaction step, could be depleted due to formation of less nucleophilic anions I_2Cl^-. Thus, for the investigated silylation reaction, the equilibrium between a silyl chloride and a nucleophile catalyst could be shifted toward adduct **A**, the most likely reactive intermediate in these reactions.

Consistent with this interpretation was the fact that the accelerating effect of iodine was always proportional to the amount of iodine used for the reaction, and that a nucleophile catalyst was an indispensable component of the reaction mixtures.

To substantiate the proposed mechanism for the enhanced kinetic of silylation of alcohols by iodine, we carried out some NMR experiments. We wanted to find out if silyl-nucleophile catalyst adducts of type **A** could be detected by ^1H NMR spectroscopy in the

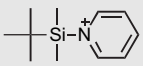
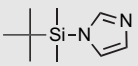
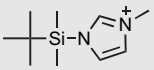
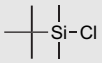
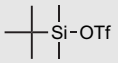
Table 3
Comparison of the reaction times for silylation of nucleoside **2** using different silyl chlorides

Silyl chloride	Formula	Reaction times for silylation of nucleoside **2** (conversion, if not 100%)		
		Imidazole (3 equiv, DMF)	*N*-Methyl-imidazole (3 equiv, THF)	*N*-Methyl-imidazole+I_2 (both 3 equiv, THF)
TMS-Cl		5 min	5 min	5 min
TES-Cl		5 min	5 min	5 min
TPS-Cl		5 min	5 min	5 min
TBDMS-Cl		4 h	6 h	1 h
TDS-Cl		6 h	8 h (~40%)	1 h
TBDPS-Cl		5 h	8 h (~40%)	10 min
TIPS-Cl		8 h (~40%)	8 h (~10%)	8 h (~40%)



Scheme 2. A putative mechanism of silylation of alcohols in the presence of iodine and a nucleophile catalyst.

Table 4
Formation of TBDMS-nucleophile catalyst adducts in the absence and in the presence of iodine[a]

Silyl substrate	Additives	Nucleophile catalyst		
		Pyridine	Imidazole	*N*-Methylimidazole
		 $\delta_{(CH_3)_2Si}$ = 0.54 $\delta_{(CH_3)_3C}$ = 0.98	 $\delta_{(CH_3)_2Si}$ = 0.54 $\delta_{(CH_3)_3C}$ = 0.93	 $\delta_{(CH_3)_2Si}$ = 0.61 $\delta_{(CH_3)_3C}$ = 0.94
		% of the adduct formed[b]		
 $\delta_{(CH_3)_2Si}$ = 0.34 $\delta_{(CH_3)_3C}$ = 0.96	3 equiv nucleophile catalyst	0	60	0
	3 equiv nucleophile catalyst+3 equiv iodine	0	52	32, $\delta_{(CH_3)_2Si}$=0.71,[c] $\delta_{(CH_3)_3C}$=1.01
 $\delta_{(CH_3)_2Si}$ = 0.46 $\delta_{(CH_3)_3C}$ = 1.00	3 equiv nucleophile catalyst	100	100	100

[a] TBDMS-X (0.066 M), 0.20 M nucleophile catalyst (0.20 M I_2), in $CDCl_3$.
[b] Percentage of the adduct was calculated by integration of the corresponding $(CH_3)_2Si$ signals.
[c] Chemical shifts of the signals from the *N*-methyl-*N*′-TBDMS-imidazolium adduct generated from TBDMS-Cl slightly differed from those when TBDMS-OTf was used as the substrate; we believe that these differences were due to different kind of counterions present (Cl^- vs OTf^-).

reaction mixtures, and if there was a relationship between their concentrations and the observed rates of the silylations. We also hoped that these experiments would clarify the issues why the accelerating effect of iodine was not observed for the reactions with silyl chlorides, when imidazole was used as a nucleophile catalyst.

2.4. ^{1}H NMR studies on the mechanism of silylation in the presence of iodine

NMR spectroscopy is a convenient tool to directly observe reactive intermediates involved in various equilibria, if life-times of the species involved are long enough on the NMR timescale for a given observed nuclei. If the intermediates are short lived, then instead of separate sets of signals originating from these species, only time average NMR parameters (chemical shifts and coupling constants) are accessible from the spectra.

In these studies, we wanted to determine positions of equilibria between various silyl chlorides and their adducts with nucleophile catalysts, and to find out how these equilibria were affected upon addition of iodine to the reaction mixtures.

For the silyl ethers investigated, convenient diagnostic signals in the ^{1}H NMR spectra were those from the CH_3 groups bound directly to the silicon atom, and from the *t*-butyl group of a TBDMS moiety. These signals, which chemical shifts changed upon the adducts formations, appeared in the otherwise empty region of the ^{1}H NMR spectra (ca. 0–1 ppm) and could be easily integrated for the purpose of quantitative analysis.

Table 4 summarized the ^{1}H NMR experiments, in which TBDMS adducts bearing different nucleophile catalysts moieties were generated in $CDCl_3$ from TBDMS-Cl and TBDMS-OTf.

For TBDMS-Cl in the presence of pyridine, or pyridine and iodine, in the ^{1}H NMR spectra only signals due to the silyl chloride could be detected. These indicated, that the corresponding silylpyridinium adduct was apparently formed only in a minute amount, even in the presence of iodine. In contrast to this, addition of pyridine (3 equiv) to a chloroform solution of TBDMS-OTf resulted in an immediate disappearance of the signals of the starting material, and formation of two resonances at the high-field (δ_H=0.54 and 0.98 ppm; ratio 9:6), assigned to two different types of the methyl groups in the *N*-silylpyridinium intermediate.[23]

Another picture emerged when imidazole was added to TBDMS-Cl in chloroform. In this instance two sets of resonances, assigned to TBDMS-Cl and to the corresponding *N*-silylimidazole (60%), could be discerned in the ^{1}H NMR spectrum. The later species was formed quantitatively upon the reaction of TBDMS-OTf with imidazole. An interesting observation was that addition of iodine to the reaction mixture containing this *N*-silylimidazole intermediate, did not increase its concentration, but slightly lowered it.

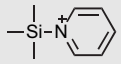
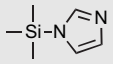
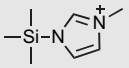
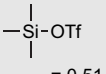
The reaction with *N*-methylimidazole with TBDMS-Cl did not produce detectable amounts of the putative *N*-methyl-*N*′-TBDMS-imidazolium adduct, however, the addition of iodine (3 equiv) to such reaction mixture resulted in an immediate formation of the expected species (32%). Similarly, as it was observed for other nucleophile catalysts, addition of *N*-methylimidazole to TBDMS-OTf, caused a quantitative formation of the *N*-methyl-*N*′-TBDMS-imidazolium adduct. To prove chemical identity of the adduct formed, the NMR sample was subjected to a mass spectrometry analysis (ESI), which indeed showed the presence of the expected mass peak (*m*/*z* 197.1470 $[M]^+$, $C_{10}H_{21}N_2Si^+$ calcd 197.1469) corresponding to the *N*-methyl-*N*′-TBDMS-imidazolium adduct. Additionally, the mass spectra registered in the negative mode showed a strong signal (*m*/*z* 288) corresponding to I_2Cl^-.

A similar series of experiments were performed for trimethylsilyl derivatives (TMS-X). In addition to TMS-Cl and TMS-OTf, commercially available TMS-Br was included into this study (Table 5). By using TMS-Br we were able to observe the effect of the iodine addition on building up the concentration of the *N*-TMS-pyridinium adduct, from null to 100%. Since the same intermediate was also formed from TMS-OTf, and had a chemical shift identical to that of a reference compound produced on another way,[24] we believe that the signals assigned to the *N*-silylpyridinium adducts in our experiments, corresponded to distinct chemical species, rather than to a weighted average of two equilibrating species.

In contrast to pyridine, imidazole produced the *N*-TMS-imidazole intermediate quantitatively from all three silyl precursors. For *N*-methylimidazole, however, the *N*-methyl-*N*′-TMS-imidazolium adduct was formed from TMS-Cl only in presence of iodine.

Although these results, together with data from Tables 1 and 2, indicated the kinetic importance of the increasing concentration of silyl-nucleophile adduct intermediates by the added iodine, we

Table 5
Formation of TMS-nucleophile catalyst adducts in the absence and in the presence of iodine[a]

Silyl substrate	Additives	Nucleophile catalyst		
		Pyridine	Imidazole	*N*-Methylimidazole
		 $\delta_{(CH_3)_3Si}$ = 0.72	 $\delta_{(CH_3)_3Si}$ = 0.48	 $\delta_{(CH_3)_3Si}$ = 0.59
		% of the adduct formed[b]		
 $\delta_{(CH_3)_3Si}$ = 0.44	3 equiv nucleophile catalyst	0	100	0
	3 equiv nucleophile catalyst+3 equiv iodine	0	100	100
 $\delta_{(CH_3)_3Si}$ = 0.59	3 equiv nucleophile catalyst	0	100	nd[c]
	3 equiv nucleophile catalyst+3 equiv iodine	100	100	nd[c]
 $\delta_{(CH_3)_3Si}$ = 0.51	3 equiv nucleophile catalyst	100	100	100

[a] TMS-X (0.066 M), 0.20 M nucleophile catalyst (0.20 M I_2), in $CDCl_3$.
[b] Percentage of the adduct was calculated by integration of the corresponding $(CH_3)_3Si$ signals.
[c] Not determined, due to identical chemical shifts of the signals from TMS-Br and *N*-methyl-*N*′-TMS-imidazolium adduct (0.59 ppm).

additionally performed ^1H NMR titration experiments of the reaction mixtures containing TBDMS-Cl and imidazole or *N*-methylimidazole, with iodine in different solvents.

The titration data are shown in Figures 1 and 2. For the reactions with imidazole (Fig. 1), most of the silylating agent was transformed into the adduct (~60% in $CDCl_3$ and ~75% in CD_3CN) even without iodine, and the addition of iodine had only a minor effect on the adduct concentration in both solvents.

A completely different picture emerged when a nucleophile catalyst was changed to *N*-methylimidazole (Fig. 2). Without iodine, in all solvents investigated, there was no detectable formation of the *N*-methyl-*N*′-TBDMS-imidazolium adduct. However, with the increasing amounts of the added iodine, the adduct concentration was gradually built-up, and its concentration strongly depended on solvent polarity. In less polar $CDCl_3$ and THF concentration of the adduct reached approximately 30%, whereas in more polar acetonitrile, the adduct formation was almost quantitative in the presence of >3 equiv of iodine.

The above ^1H NMR experiments provided a strong support for the mechanism depicted in Scheme 2, explaining the accelerating effect of iodine during silylation of alcohols using silyl chlorides in the presence of nucleophile catalysts.

For the reactions investigated, crucial factors seemed to be the intrinsic reactivity of a silyl-nucleophile adduct formed and its concentration in the reaction mixture. An equilibrium concentration of the adduct of type **A** (Scheme 2), generated under the reaction conditions from a silyl chloride and a nucleophile catalyst, depended on its reactivity, and was the smallest for the most reactive adducts. The added iodine could apparently change this situation, and by complexing chloride anions, made the equilibrium more favorable, i.e., to shift it toward the adduct formation.

N-Silylpyridinium adducts seemed to be the most reactive ones among the species investigated, and thus their concentration was extremely low, in the presence of nucleophilic anions such as chlorides or bromides. The addition of iodine apparently increased the equilibrium concentration of the silyl-pyridine adduct (although it

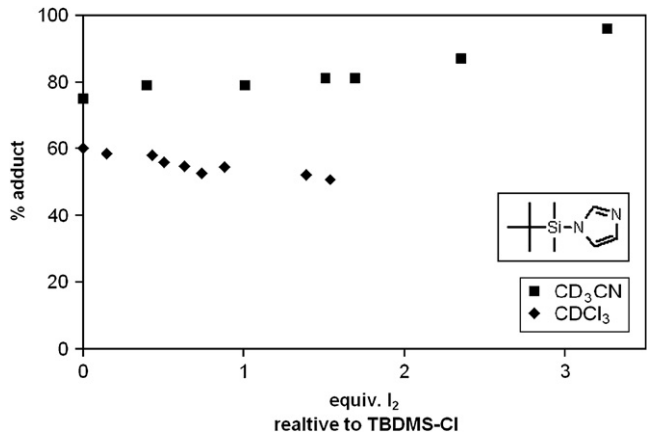


Figure 1. Titration of 0.066 M TBDMS-Cl and 0.20 M imidazole (3 equiv) with I_2, in CD_3CN and $CDCl_3$. Under these conditions maximum solubility of I_2 in $CDCl_3$ was reached at ~1.5 equiv. Percentage of the adduct was calculated from integration of the $(CH_3)_2Si$ signals from TBDMS-Cl and the adduct.

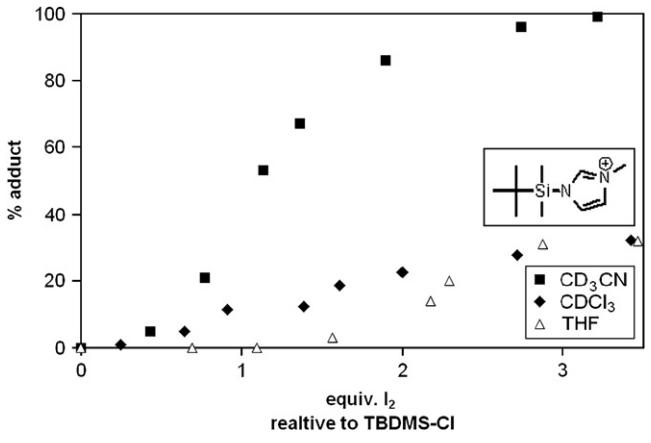


Figure 2. Titration of 0.066 M TBDMS-Cl and 0.20 M *N*-methylimidazole (3 equiv) with I_2. The presence of *N*-methylimidazole seemed to increase solubility of iodine, so in this case the solubility limit was reached at approx. 3.5 equiv I_2 in all three solvents. Percentage of the adduct was calculated from the integration of $(CH_3)_2Si$ signals of TBDMS-Cl and the adduct.

Table 6
Examples of silylation of various alcohols using silyl chlorides/*N*-methylimidazole/iodine reagent systems

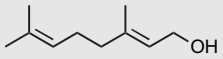
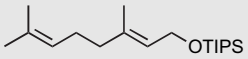
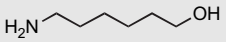
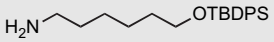
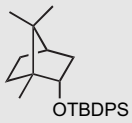
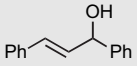
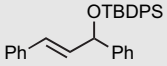
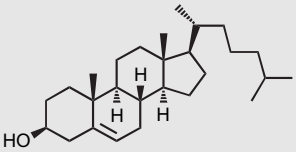
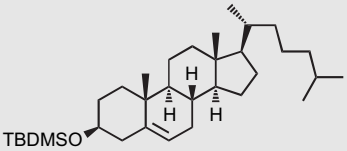
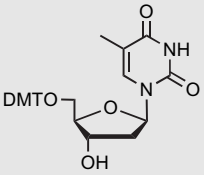
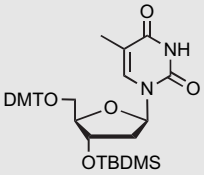
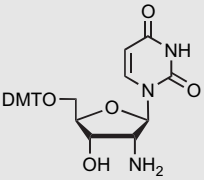
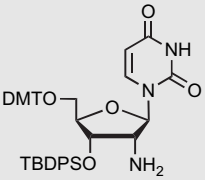
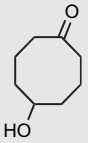
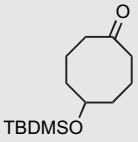
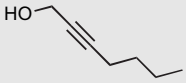
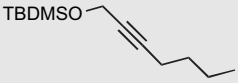
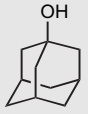
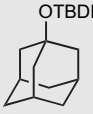
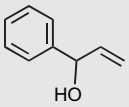
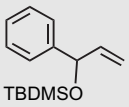
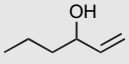
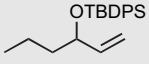
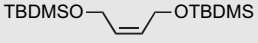
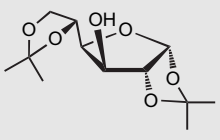
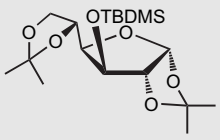
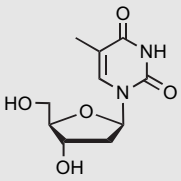
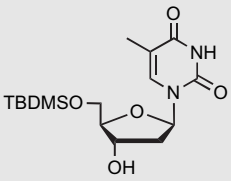
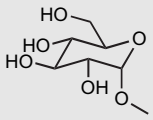
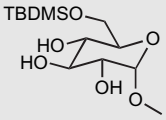
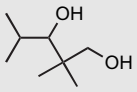
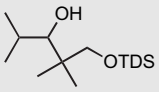
Entry	Alcohol	Product	Isolated yield (%)	Reaction time	Solvent/comments
1			89	5 min	CH_2Cl_2
2			93	5 min	CH_2Cl_2
3			98	5 h	THF
4			86	10 min	THF
5			96	1 h	THF
6			98	1 h	THF
7			96	15 min	THF
8			80	6 h	CH_2Cl_2
9			95	5 min	CH_2Cl_2
10			85	16 h	c_{alc}=0.4 M neat *N*-methylimidazole 6 equiv I_2
11			82	1 h	THF
12			98	10 min	THF
13			94	10 min	THF
14			94	15 min	THF

Table 7
Silylation of polyhydroxy alcohols using a silyl chloride/*N*-methylimidazole/iodine reagent system

Entry	Alcohol	Product	Isolated yield (%)	Reaction time (min)	Comments
1			72	10	Pyridine
2			86	10	CH_2Cl_2
3			96	5	CH_2Cl_2

remained below the detection level of ^{1}H NMR spectroscopy), and this accelerated silylation of alcohols up to 5–6 times.

The highest accelerating effect of iodine was observed for the reactions in which *N*-methylimidazole was used as a nucleophile catalyst. This was consistent with data in Table 4 that showed that without iodine, there was no detectable formation of the putative reactive intermediate, the TBDMS-*N*-methylimidazolium adduct, but the addition of iodine, increased its concentration to ca. 32%.[25]

The lack of an accelerating effect of iodine in the silylation reactions in which imidazole was used as a acid scavenger and a nucleophile catalyst, became apparent from analysis of data in Tables 4 and 5. In these reactions, the reactive intermediates, i.e., the corresponding, electrically neutral, *N*-silylimidazole derivatives were formed in high concentrations (60–100%), even without iodine. For this reason, no accelerating effect of the added iodine could be observed for the silylation reactions involving the intermediacy of these species.

One should bear in mind that a nucleophile catalyzed silylation of alcohols, as that shown in Scheme 2, involved two reaction steps: generation of a reactive intermediate of type **A**, and its reaction with an alcohol. Depending on reactivity of a silyl chloride and a nucleophile catalyst used, the first or the second step could be a rate-determining one, or both steps, could be kinetically important. For the most reactive silyl chlorides (e.g., TMS-Cl or other simple trialkylsilyl chlorides), apparently the formation of reactive intermediates (silyl-nucleophile catalyst adducts) was a rate-determining step, and thus the silylation reactions should not be affected by the added iodine (Tables 3 and 5). For the less reactive silyl chlorides (e.g., TBDMS-Cl or TBDPS-Cl), apparently a steady state kinetic applied, and thus the equilibrium between a silyl chloride and a nucleophile catalyst, which could be affected by the added iodine, became kinetically significant (Tables 3 and 4).

2.5. Synthetic examples of silylation of alcohols using silyl chlorides/*N*-methylimidazole/iodine reagent systems

Based on the above discussed model experiments and mechanistic studies, we arrived to an efficient synthetic protocol for silylation of alcohols. This consisted of using solvents convenient to work with (e.g., THF, acetonitrile, or methylene chloride, depending on solubility of substrates), *N*-methylimidazole (3 equiv) as a base and a nucleophile catalyst, and iodine (2–3 equiv). Concentration of alcohols was kept between 0.2 and 0.4 M, to ensure smooth and fast silylation at room temperature.

The efficacy of this new reagent system was assessed by carrying out silylation of 1°, 2°, and 3° alcohols with diverse structural features (simple alkyls, allylic, propargyl, and benzyl derivatives, cholesteryl, nucleoside derivatives, protected carbohydrates) and by using different silylating agents (TBDMS-Cl, TIPS-Cl, and TBDPS-Cl; Table 6). The silylation of primary alcohols was always rapid (ca. 5–10 min; entries 1, 2, 9, and 13), irrespective of the kind of the silyl chloride used (TBDMS-Cl, TBDPS-Cl, and TIPS-Cl). For secondary alcohols, a typical reaction time for the silylation was ca. 15–60 min (entries 4–7, 12, and 14) and only for 2° alcohols with a high steric hindrance (entry 3), or with special chemical features (entry 8; a ketone-ketal equilibrium), the reaction took longer time (ca. 5 h). Very unreactive tertiary alcohol, 1-adamantanol (entry 10), could also be silylated in high yield, but the reaction had to be performed in neat *N*-methylimidazole in the presence of 6 equiv of iodine. On average, the reactions in Table 1 were 5–30 times faster than those without iodine performed under the standard Corey–Venkateswarlu silylation conditions, using silyl chloride and imidazole in DMF.[8,17] 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.

Although a silyl chloride/*N*-methylimidazole/iodine reagent system tolerated various functional groups present in the substrates (Table 6), these reaction conditions were incompatible with thiols (oxidation to disulfides in the presence of iodine), terminal acetylenic bonds (iodination) and certain electron-rich phenols (iodination in the aromatic ring; see the Supplementary data for more details).

2.6. Regioselectivity—silylation of diols and polyols

Three hydroxylic compounds, namely, thymidine, 1-*O*-methyl-glucopyranose, and a 1,3-diol were selected to verify regioselectivity of the silylation under the new reaction conditions.

As it was apparent from data in Table 7, for all compounds investigated it was possible to efficiently introduce the silyl group (TBDMS, entries 1 and 2; and TDS, entry 3) on the primary hydroxyl function. Since these data are comparable to those for the reactions without iodine, it seems that a silyl chloride/NMeIm/iodine reagent system does not compromise noticeably regioselectivity of the silylation.

3. Conclusions

An efficient protocol for silylation of 1°, 2°, and 3° alcohols, consisting of using a silyl chloride in the presence of *N*-

methylimidazole and iodine, was developed. The reactions can be carried out in various organic solvents (e.g., THF, acetonitrile, methylene chloride, and pyridine), at room temperature, and are compatible with the presence of common functional groups. The procedure is experimentally simple, high yielding, and expands range of synthetic methods available for silylation of complex organic compounds. Application of *N*-methylimidazole together with iodine resulted in significant shortening of the silylation time, both for primary and secondary alcohols. The silylation occurred 5–30 times faster than that under standard conditions when imidazole was used as a nucleophile catalyst and DMF as a solvent. The reaction pathway was studied in depth and a mechanistic role of iodine was elucidated by ^{1}H NMR spectroscopy. It was found that a base used for the reaction had to have nucleophilic properties, and that iodine increased concentration of a reactive silyl-nucleophile adduct in the reaction mixture.

4. Experimental part

4.1. General

All reagents were commercial grades and were used without further purification.

Acetonitrile, deuterated acetonitrile, DMF, deuterated chloroform, and *N*-methylimidazole were dried over activated molecular sieves 4 Å. Pyridine was distilled from CaH_2 and stored over molecular sieves 4 Å. THF was distilled directly before the use from sodium/benzophenone. CH_2Cl_2 was distilled directly before the use from P_2O_5.

Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel-coated plates with a fluorescent indicator (Merck, Silica gel 60). Column chromatography was performed on silica gel (Grace Davison, Davsil, 0.035–0.070 mm). After chromatography, the fractions containing the desired products were pooled, evaporated, and dried under vacuum for 12 h. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz and 500 MHz instruments. Chemical shifts are reported in parts per million, relative to TMS. Assignment of the NMR signals was done on the basis of 2D correlation experiments (COSY, HSQC, and HMBC) and NOEDiff. High resolution mass spectra (HRMS) were recorded on Bruker MicrOTOF ESI-TOF mass spectrometer.

4.2. A general procedure for preparative silylation of alcohols listed in Table 6

An alcohol (1.0 mmol), *N*-methylimidazole (3.0 mmol), and iodine (2.0–3.0 mmol) were dissolved in an appropriate, anhydrous solvent (3 mL, Table 6), and to these, a silyl chloride (1.1 mmol) was added. The reaction mixture was stirred at room temperature until complete disappearance of the starting material (TLC analysis). The solvent was then evaporated, the residue dissolved in ethyl acetate and washed with concd aqueous $Na_2S_2O_3$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated. The products were purified by silica gel column chromatography (CH_2Cl_2/MeOH 100:0→95:5, Table 6 entries 1, 3, and 7; pentane/AcOEt 10:0→9:1, Table 6 entries 2, 4–6, and 8–14). The synthesized compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopies and HRMS analysis (see the Supplementary data for details).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.070.

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