Novel and Highly Effective Method for the Trimethylsilylation of Alcohols and Phenols with Hexamethyldisilazane (HMDS), Catalyzed by I_2 Generated *in situ* Using $Fe(NO_3)_3 \cdot 9\,H_2O$/NaI under Heterogeneous and Neutral Conditions

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Structurally diverse alcohols and phenols were trimethylsilylated in a clean and efficient reaction with hexamethyldisilazane (HMDS) based on the use of I_2 generated *in situ* from $Fe(NO_3)_3 \cdot 9\,H_2O$/NaI. The reaction occurs very rapid in good-to-high yield in CH_2Cl_2 at room temperature, and the use of toxic and corrosive molecular I_2 is avoided.

Introduction. – Protection of OH groups through the formation of silyl ethers has been extensively utilized in organic synthesis [1][2]. HMDS is a stable, inexpensive, and commercially available compound that can be used for the preparation of trimethylsilyl ethers from OH compounds, giving ammonia as the only by-product. Even though the handling of this reagent is easy, its main drawback is its poor silylating ability; forceful conditions and long reaction times are required [3]. Therefore, for the activation of HMDS, a variety of catalysts have been reported [4–15]. Although these catalysts provide an improvement, they are not suitable for trimethylsilylation of hindered and acid-sensitive alcohols.

Recently, the highly efficient method for trimethylsilylation of alcohols (no phenols) using HMDS catalyzed by I_2 in CH_2Cl_2 has been reported [9]. Although I_2 is a versatile reagent in organic synthesis [16], it is highly corrosive and toxic, making its use somewhat unattractive. In order to overcome these disadvantages of I_2, *Bailey et al.* reported a convenient method for *in situ* generation of I_2 using $CuSO_4$/NaI [17].

Results and Discussion. – In continuation of our studies on using *N*-halo compounds for the protection of OH functional groups [18–22], we report here the use of readily available HMDS for trimethylsilylation of a wide range of alcohols and phenols in the presence of I_2 generated *in situ* from $Fe(NO_3)_3 \cdot 9\,H_2O$/NaI under mild and heterogeneous conditions (*Scheme*).

In the beginning, the trimethylsilylation of adamantan-1-ol with HMDS in the presence of various salts and NaI in CH_2Cl_2 at room temperature was studied; the results and reaction conditions are given in *Table 1*. Among the presented salts, $Fe(NO_3)_3 \cdot 9\,H_2O$ is the best one (*Table 1*, *Entry 1*). Therefore, we choose it for accomplishing the desired trimethylsilylation.

Scheme

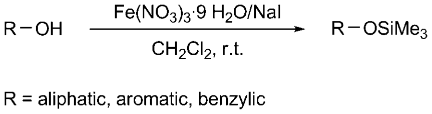


Table 1. *Trimethylsilylation of Adamantan-1-ol* (10 mmol) *with HMDS* (10 mmol) *in the Presence of Various Salts* (0.1 mmol) *and NaI* (0.2 mmol) *in CH_2Cl_2 at r.t.*

Entry	Mineral salts	Time	Yield [%]
1	$Fe(NO_3)_3 \cdot 9\,H_2O$	20 min	100
2	$Fe_2(SO_4)_3 \cdot 5\,H_2O$	4 h	95
3	$FeCl_3 \cdot 6\,H_2O$	30 min	100
4	$CuCl_2 \cdot 2\,H_2O$	6 h	trace
5	$Cu(AcO)_2 \cdot H_2O$	6 h	NR[a])
6	$CuSO_4 \cdot 5\,H_2O$	3 h	100
7	$Cu(NO_3)_2 \cdot 3\,H_2O$	4 h	100
8	$CuCO_3 \cdot Cu(OH)_2$	6 h	NR

[a]) NR = no reaction.

Treatment of benzylic, primary, propargylic, hindered, and unhindered secondary, tertiary, and acid-sensitive tertiary alcohols with HMDS and the catalyst in CH_2Cl_2 at room temperature produced the corresponding trimethylsilyl ethers in good to high yields (*Table 2*).

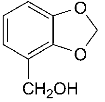
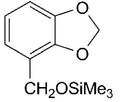
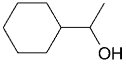
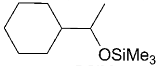
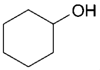
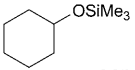
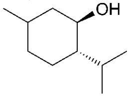
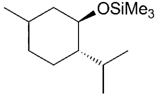
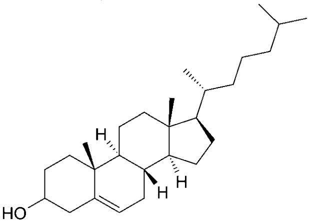
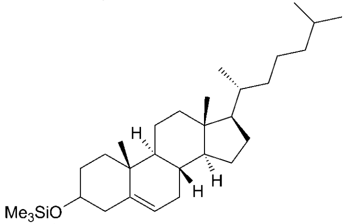
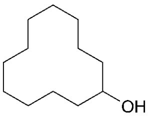
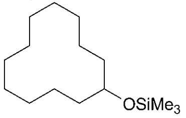
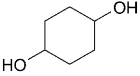
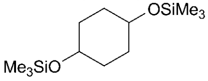
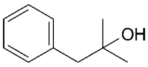
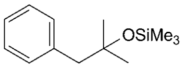
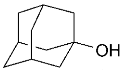
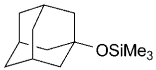
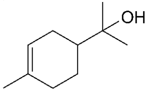
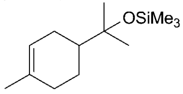
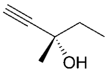
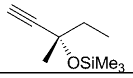
As shown in *Table 2*, in the cases of primary and secondary alcohols, the reactions were completed very quickly. Interestingly, different types of highly hindered tertiary alcohols were successfully converted to the corresponding trimethylsilyl ethers in almost quantitative yields at room temperature (*Table 2*, *Entries 19–22*). Under these reaction conditions, no side products were observed.

The data in *Table 3* clearly show that different types of phenols were successfully converted to the corresponding silyl ethers in short time and in almost quantitative yields. We observed that amines and thiols were not converted under this reaction even after prolonged reaction times (*Table 3*, *Entries 5* and *6*).

It should be mentioned that molecular I_2 was generated *in situ* by oxidation of NaI using $Fe(NO_3)_3 \cdot 9\,H_2O$. We measured the amount of I_2 generated *in situ* in CH_2Cl_2 by UV/VIS spectrophotometry. It was found that 0.142 mmol of I_2 is produced for every mmol of NaI. In order to prove that I_2 is the actual catalyst, we conducted the trimethylsilylation of benzyl alcohol with HMDS in the presence of catalytic amounts of $Fe(NO_3)_3 \cdot 9\,H_2O$ (0.1 mmol) instead of the system of $Fe(NO_3)_3 \cdot 9\,H_2O$/NaI. The reaction was completed after 3 h, while benzyl alcohol was trimethylsilylated with HMDS and $Fe(NO_3)_3 \cdot 9\,H_2O$/NaI in a very short reaction time (*Table 2*, *Entry 1*).

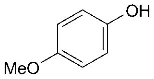
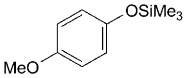
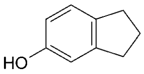
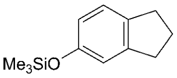
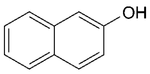
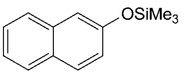
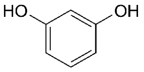
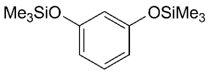
We have found that iron residues generated through the reaction with $Fe(NO_3)_3 \cdot 9\,H_2O$ and NaI have some positive effect on the silylation of alcohols with hexamethyldisilazane (as *Lewis* acid). We compared the trimethylsilylation of benzyl alcohol with I_2 and with $FeSO_4/I_2$ at −15°. The reactions were completed after 15 min

Table 2. *Trimethylsilylation of Alcohols* (10 mmol) *using HMDS* (10 mmol) *Catalyzed with* I_2 *Generated* in situ *from* $Fe(NO_3)_3 \cdot 9\,H_2O$ (0.1 mmol)*/NaI* (0.2 mmol) *in* CH_2Cl_2 *at r.t.*

Entry	Substrate	Time [min]	Product[a])	Yield [%][b])
1	$PhCH_2OH$	immediately	$PhCH_2OSiMe_3$	90
2	$4\text{-MeO-}C_6H_4CH_2OH$	immediately	$4\text{-MeO-}C_6H_4CH_2OSiMe_3$	95
3	$4\text{-Cl-}C_6H_4CH_2OH$	4	$4\text{-Cl-}C_6H_4CH_2OSiMe_3$	95
4	$2\text{-Br-}C_6H_4CH_2OH$	immediately	$2\text{-Br-}C_6H_4CH_2OSiMe_3$	94
5	$2,4\text{-}(Cl)_2C_6H_3CH_2OH$	immediately	$2,4\text{-}(Cl)_2C_6H_3CH_2OSiMe_3$	96
6		immediately		93
7	$Me(CH_2)_6CH_2OH$	immediately	$Me(CH_2)_6CH_2OSiMe_3$	92
8	$Me(CH_2)_{14}CH_2OH$	immediately	$Me(CH_2)_{14}CH_2OSiMe_3$	90
9	$H{-}C{\equiv}C{-}CH_2OH$	2	$H{-}C{\equiv}C{-}CH_2OSiMe_3$	75
10	$PhCH_2CH_2OH$	immediately	$PhCH_2CH_2OSiMe_3$	93
11	$PhCH(OH)Ph$	3.5	$PhCH(OSiMe_3)Ph$	90
12		immediately		95
13		immediately		95
14		immediately		94
15		3.5		96
16		immediately		93
17	$Me(CH_2)_4CH(OH)Me$	immediately	$Me(CH_2)_4CH(OSiMe_3)Me$	92
18		2.5		90
19		55		75
20		20		93
21		60		90
22		3		95

[a]) All products were characterized by comparison of their spectral data (^{1}H-NMR and IR) with those of authentic samples. [b]) Yield of isolated TMS ether.

Table 3. *Trimethylsilylation of Phenols* (10 mmol) *using HMDS* (10 mmol) *Catalyzed with I_2 Generated* in situ *from $Fe(NO_3)_3 \cdot 9\ H_2O$* (0.1 mmol)*/NaI* (0.2 mmol) *in CH_2Cl_2 at r.t.*

Entry	Substrate	Time [min]	Product[a])	Yield [%][b])
1		6		93
2		immediately		90
3		8		95
4		8		94
5	$C_6H_5NH_2$	NR	–	–
6	C_6H_5SH	NR	–	–

[a]) All products were characterized by comparison of their spectral data (^{1}H-NMR and IR) with those of authentic samples. [b]) Yield of isolated TMS ether.

and 9 min, respectively, indicating that some cooperative catalysis between a Fe^{II} complex and molecular I_2 is operative.

Conclusions. – In summary, a mild method for the *in situ* generation of I_2 from inexpensive starting materials, $Fe(NO_3)_3 \cdot 9\ H_2O$/NaI, has been developed. The I_2 generated *in situ* has been shown to be an effective promoter of trimethylsilylation of a variety of alcohols and phenols using HMDS under mild, heterogeneous, and neutral conditions.

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Experimental Part

General Procedure for Trimethylsilylation of Alcohols and Phenols Using HMDS Catalyzed with I_2 Generated in situ *from $Fe(NO_3)_3 \cdot 9\ H_2O$/NaI in CH_2Cl_2.* The alcohol or phenol (10 mmol) was added to a mixture of $Fe(NO_3)_3 \cdot 9\ H_2O$ (0.1 mmol) and NaI (0.2 mmol) in CH_2Cl_2 (3 ml). Then, HMDS (10 mmol in 5 ml CH_2Cl_2) was added dropwise to this mixture within 5 min. The mixture was stirred vigorously at r.t. for the specified time (*Table 2*). After completion of the reaction (TLC), the mixture was filtered, and the solids were washed with CH_2Cl_2 (5 ml). Powdered $Na_2S_2O_3$ (*ca.* 2 g; portion wise) was added, the mixture was stirred for additional 5 min, and the resulting mixture was filtered. Finally, H_2O (10 ml) was added to destroy the extra amount of HMDS, the org. layer was separated, and the filtrate was dried (Na_2SO_4). Evaporation of the solvent under reduce pressure gave almost pure product.

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