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The Reagent

NaI/Me_3SiCl – a Powerful Tool for the Development of One-Pot Reactions

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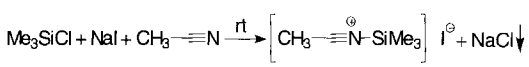
Traditionally, target molecules are synthesized *via* an elaborate chain of reaction steps. After each reaction has finished the desired compound is separated and purified. However, it would be more efficient to emulate nature and to perform reaction sequences in one pot, *i.e.*, without isolating the intermediate products. The increasing demand for economical and environmentally friendly syntheses is a major challenge of modern chemistry. Therefore, the development of time-, energy- and material-saving one-pot syntheses is an active research area [1].

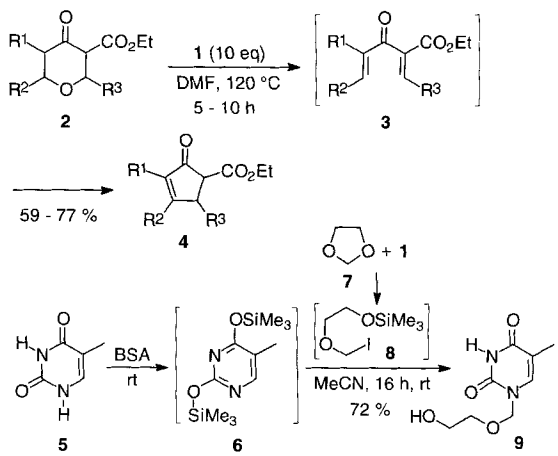
Powerful and selective reagents allowing clean reactions under mild conditions are a basic prerequisite for efficient one-pot syntheses. Otherwise only complex product mixtures would be obtained and tedious purification procedures and poor yields be the consequence. Iodotrimethylsilane (Me_3SiI) with its remarkable properties as a hard–soft compound is an excellent example for a reagent meeting these special requirements. It has been used for a variety of synthetic transformations [2]. However, Me_3SiI is relatively expensive. In addition, it is extremely sensitive to light, air or moisture, and should be used immediately after preparation or purification. Furthermore, due to its susceptibility to hydrolysis Me_3SiI generally contains traces of HI. This can cause problems in reactions involving acid sensitive compounds. Hence, the practical value of Me_3SiI is limited [2].

The aforementioned drawbacks have led to the development of various methods for the *in situ* generation of Me_3SiI [2]. The most convenient approach is based on the reaction between Me_3SiCl and NaI introduced by Schmidt *et al.* [3] and mechanistically investigated by Olah *et al.* (Scheme 1) [4]. It is generally believed that the Me_3SiCl/NaI reagent (**1**) is essentially confined to MeCN as a solvent. However, solvents other than MeCN such as CH_2Cl_2 [5], DMF [6], benzene [7] or hexane [8] have been used successfully as well. In certain cases it is useful to replace Me_3SiCl with other chlorosilanes such as Me_2SiCl_2 [9], $MeSiCl_3$ [10] or $SiCl_4$ [11]. Reagent **1** generally provides similar or better results (*e.g.*, it allows virtually neutral reaction conditions) than Me_3SiI [2b, 12, 13]. But its major advantage is the convenient accessibility from inexpensive shelf reagents enabling straightforward and high-yielding syntheses even on multi-kilo scale [14].



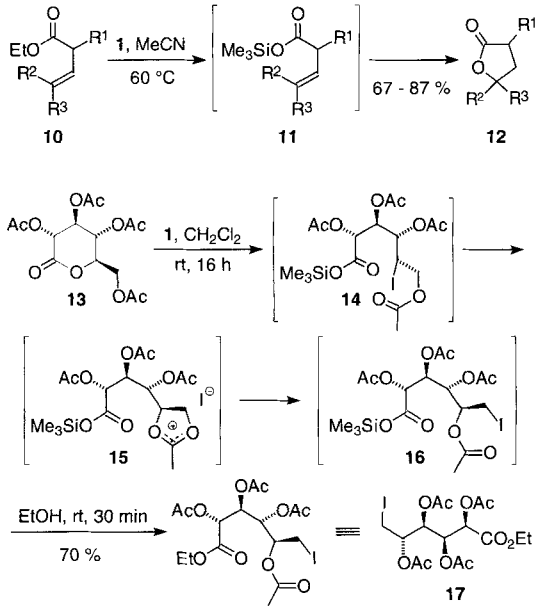
Scheme 1 Formation of Me_3SiI from Me_3SiCl/NaI (**1**) in MeCN

Among other things reagent **1** is employed for the cleavage of ethers R^1OR^2 providing the corresponding trimethylsilylalcohols R^1OSiMe_3 and alkyliodides R^2I [2b, 4]. The reaction can also be used as part of one-pot reaction sequences [6, 15]. An example is the cleavage of the tetrahydro-4-oxopyranes **2**, followed by elimination steps providing the intermediates **3** which subsequently undergo a Nazarov-type cyclization to give the cyclopentanones **4** (Scheme 2) [6b]. Reagent **1** is not confined to the cleavage of simple ethers. It can be employed as well for analogous reactions involving acetals [2b]. This has been used for one-pot syntheses of antiviral agents such as **9**. The starting material **5** is converted to pyrimidine **6** by the addition of bis(trimethylsilyl)acetamide (BSM). Then acetal **7** and reagent **1** are added. This presumably leads to the *in situ* formation of α-iodoether **8** which subsequently attacks the pyrimidine **6** providing the acyclopyrimidine nucleoside **9** (Scheme 2) [16].



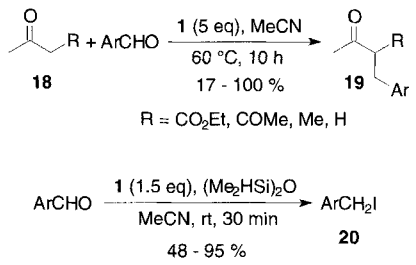
Scheme 2 Cleavage of ethers and acetals with Me_3SiCl/NaI (**1**) as part of one-pot reaction sequences

The deprotection of esters $R^1CO_2R^2$ providing the corresponding trimethylsilylesters $R^1CO_2SiMe_3$ and alkyliodides R^2I is another well-established application of reagent **1** [2b, 4, 17]. An example for its utility in one-pot reaction sequences is the conversion of β,γ-unsaturated esters **10** into lactones **12**. It is assumed that the first step is an ester cleavage followed by the cyclization of the resulting intermediates **11** [18]. Another example is the reaction between sugar lactones such as **13** and reagent **1**. Interestingly, it does not provide **14** but the ε-iodotrimethylsilylester **16** which is easily trans-formed *in situ* into corresponding ε-iodoethylester **17**. This surprising result can be explained by the formation of an oxonium intermediate **15** as depicted in Scheme 3 [5a]. It should be noted that the reaction proceeds highly regio- and stereoselective under mild conditions.



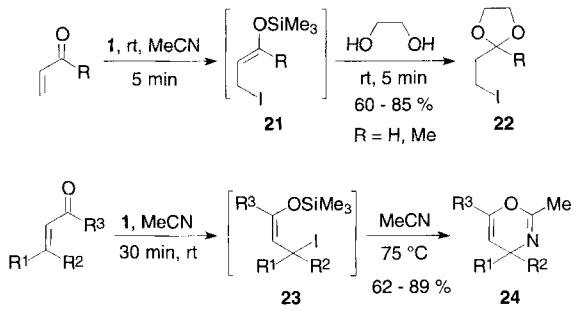
Scheme 3 Cleavage of esters and lactones with Me_3SiCl/NaI (**1**) as part of one-pot reaction sequences

Reagent **1** is particularly well suited for the deoxygenation of benzylic alcohols. The reaction is compatible with various functional groups (*e.g.*, CN, CO_2Et, $R_2C{=}CHCOR'$) [8, 19] and can be employed for syntheses on multi-kilo scale [14]. It has also been used successfully as part of one-pot reaction sequences. The reaction of active methylene compounds **18** with aromatic aldehydes and reagent **1** gives the corresponding α-benzylated products **19** (Scheme 4) [20]. This transformation can formally be regarded as the result of an aldol-, deoxygenation sequence. The *in situ* formation of the reductant HI is of crucial importance for the aforementioned deoxygenation reactions (for a discussion of the mechanism, see lit. [14]). However, HI can be replaced by other reducing agents. An example is given in Scheme 4. The reductive iodination of aromatic aldehydes with reagent **1** and $(Me_2HSi)_2O$ (1,1,3,3-tetramethyldisiloxane) gives the corresponding benzylic iodides **20**. The formation of **20** can be explained by the reduction of an *O*-silylated iodohydrin intermediate [21].



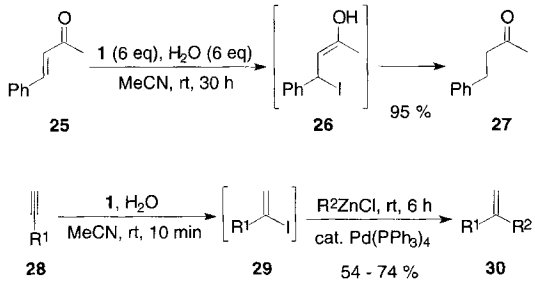
Scheme 4 Deoxygenations with Me_3SiCl/NaI (**1**) as part of one-pot reaction sequences

1,4-Additions of Me_3SiI generated *in situ* to α,β-unsaturated aldehydes and ketones providing 3-iodosilylenolethers have also been exploited for one-pot syntheses [19, 22]. Two examples are depicted in Scheme 5. 3-Iodosilylenolethers such as **21** are easily converted to 3-iodoacetals **22** by the addition of ethylene glycol [22b]. The heating of a solution of 3-iodosilylenolethers **23** in MeCN leads to the formation of 4*H*-1,3-oxazines **24** under participation of the solvent [19].



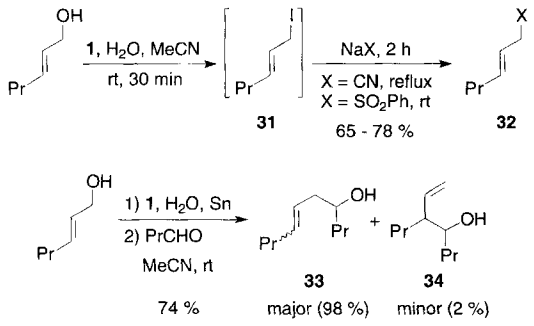
Scheme 5 1,4-Addition of Me_3SiI generated *in situ* from Me_3SiCl/NaI (**1**) to α,β-unsaturated aldehydes and ketones as part of one-pot reaction sequences

The reaction between reagent **1** and H_2O or other compounds containing active hydrogen (*e.g.*, alcohols [23] or benzoic acid [19]) is an excellent method for the mild generation of HI ($0.5\ H_2O + Me_3SiCl + NaI \rightarrow HI + 0.5\ Me_3SiOSiMe_3 + NaCl$; D_2O gives DI analogously) [24]. It has been used for the hydro iodination of alkenes [24] or alkynes [24, 25] and *in situ* conversions of the resulting iodo compounds [19, 23, 26]. The C–C double bond of the β-phenyl α,β-unsaturated ketone **25** is reduced selectively with reagent **1** and H_2O to give the saturated ketone **27** in excellent yield. The reaction presumably proceeds *via* intermediate **26** generated *in situ* by 1,4-addition of HI to **25**. Subsequently, the benzylic iodide **26** is reduced by excess HI under the formation of **27** and I_2 (Scheme 6) [23]. The reaction can be applied as well to analogous reductions of β-phenyl α,β-unsaturated carboxylic acids and esters [23] or simple 1-arylalkenes [19]. Another example is the addition of HI generated from reagent **1** and H_2O to terminal alkynes **28**. The resulting vinylic iodides **29** are easily coupled *in situ* with organozinc reagents in the presence of 5 mol % $Pd(PPh_3)_4$ providing the corresponding *gem*-disubstituted ethylenes **30** (Scheme 6) [26].



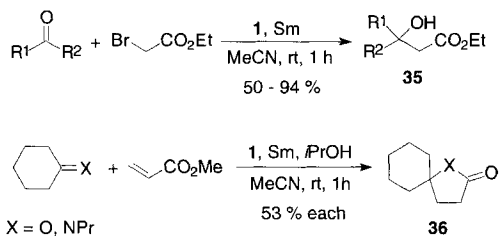
Scheme 6 Addition of HI generated from Me_3SiCl/NaI (**1**) and H_2O to C–C double or triple bonds as part of one-pot reaction sequences

HI generated from reagent **1** and H_2O has also been employed for the regioselective transformation of allylic alcohols into allylic iodides such as **31** [27]. These can be used as well for subsequent *in situ* reactions, *e.g.*, substitutions providing allylic nitriles or sulfones like **32** regio- and diastereoselectively (Scheme 7) [28]. Another variant is the *in situ* generation of allylic tin compounds (presumably *via* the intermediate formation of allylic iodides and SnI_2) followed by coupling with aliphatic aldehydes. It should be noted that the reaction proceeds with excellent regioselectivity to give linear homoallylic alcohols (*i.e.*, α-adducts) such as **33** (Scheme 7) [29]. Analogous couplings of the most other allylic organo-metallics take place predominantly at the γ-position furnishing branched homoallylic alcohols such as **34**.



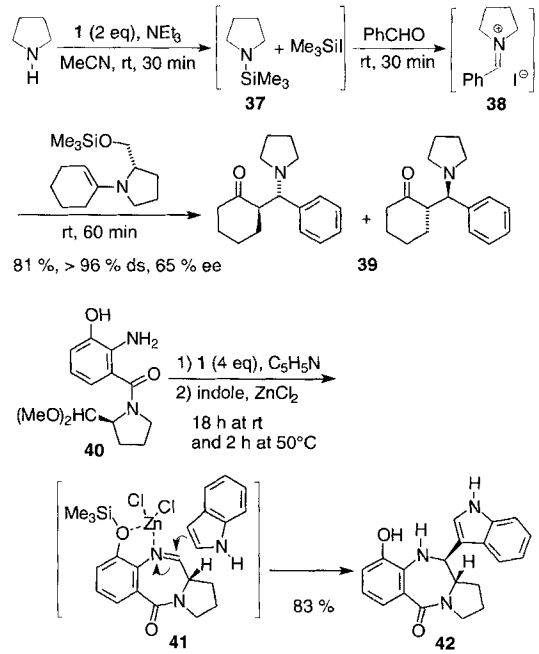
Scheme 7 Regioselective iodination of allylic alcohols with HI generated from Me_3SiCl/NaI (**1**) and H_2O as part of one-pot reaction sequences

The reaction between reagent **1** and samarium leads to the formation of a Sm(II) equivalent which has been used for various synthetic applications [7b, 30]. Two examples, a Reformatzky type reaction providing the β-hydroxy esters **35** and the transformation of cyclohexanone or its *N*-Pr-imino derivative to the corresponding lactone or lactam **36** are depicted in Scheme 8 [7b]. Additional applications are the reductive dimerization of aldehydes and ketones providing symmetrical 1,2-diols [7b, 30], the dehalogenation of α-halocarbonyl compounds [30] and the coupling of allylic iodides with aldehydes providing homoallylic alcohols [7b].



Scheme 8 Synthetic applications of a Sm(II) equivalent generated from Me_3SiCl/NaI (**1**) and samarium as part of one-pot reaction sequences

N-Trimethylsilylamines generated *in situ* by *N*-silylation of amines with reagent **1** are versatile synthetic building blocks. They can be used for modern variants of the Mannich reaction like the stereoselective synthesis of β-amino ketones such as **39** [31]. Pyrrolidine is silylated by reagent **1** providing *N*-trimethylsilylpyrrolidine (**37**). Then, benzaldehyde is added and transformed into the iminium salt **38** by the reaction with *N*-silylamine **37** and excess Me_3SiI under formation of $(Me_3Si)_2O$ (for a discussion of the mechanism, see lit. [32]). Subsequently, the iminium salt **38** is employed *in situ* for the stereoselective aminoalkylation of an enantiomerically pure enamine (for a discussion of the mechanism, see lit. [33]) to give β-amino ketone **39** (Scheme 9). Another example is the asymmetric synthesis of tilivalline **42** and its analogues which are of interest for the development of antibiotics [34]. Presumably, the $ZnCl_2$-promoted reaction of amine **40** with reagent **1** leads *via* *N*-silylation and subsequent cyclization to the formation of the endocyclic imine **41**. Then the nucleophile (*i.e.*, indole) attacks the imine **41** exclusively from the sterically



Scheme 9 *N*-Silylation of amines with Me_3SiCl/NaI (**1**) as part of one-pot reaction sequences

less hindered side providing tilivalline **42** in excellent yield (Scheme 9) [34a]. For an additional example involving the use of reagent **1** in Mannich reactions see lit. [35].

In conclusion, Me_3SiCl/NaI (**1**) is an inexpensive reagent providing a convenient access to the *in situ* generation of numerous reactive intermediates or valuable building blocks. It is distinguished with versatility, reactivity and selectivity allowing clean reactions and high yields under mild conditions. These properties make it an ideal reagent for the development of multi-step one-pot syntheses even on large scale. Although reagent **1** has been employed with a great deal of success for a variety of synthetic applications its preparative potential is nowhere near exhausted.

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