

# Trimethylsilyl Trifluoromethanesulfonate (TMSOTf) and *N,N*-Di-*iso*-propyl Ethyl Amine (Hünig Base): An Effective Reagent Combination for Selective Silylation and Elimination Reactions

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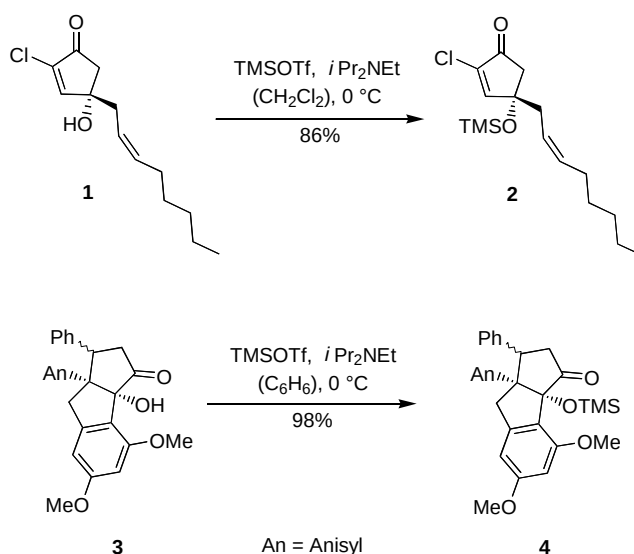
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) has long been recognized as a powerful silylating agent which was reported to be  $10^9$  times more reactive than TMSCl [1a]. Many reagent combinations of TMSOTf with bases, *e.g.* triethyl amine, lutidine, 1,8-bis(*N,N*-dimethylamino)naphthalene (proton sponge), have been described and successfully employed in Organic Synthesis [1]. In this paper, we try to provide an overview of the work that has been done with TMSOTf and the kinetically fast, non-nucleophilic base *N,N*-di-*iso*-propyl ethyl amine (Hünig base). Beneficial factors of the latter reagent combination are its high silylation capacity which often goes hand in hand with an useful regio- and chemoselectivity (Chapter 1) and its potential for inducing both 1,2- and 1,3-elimination reactions (Chapter 2).

## 1. Silylation Reactions

### 1.1. O-Silylation of Alcohols

The O-silylation of alcohols (silyldeprotonation) is certainly one of the most frequently used protecting group transformations [2]. TMSOTf and *i*-Pr<sub>2</sub>NEt have been employed for the O-trimethylsilylation of alcohols only to a limited extent presumably because the results obtained with the less expensive silylating agent TMSCl and NEt<sub>3</sub> as base were satisfactory in most cases. The few examples for which the use of TMSOTf/*i*-Pr<sub>2</sub>NEt was reported are concerned with the protection of sterically congested secondary or tertiary alcohols [3–5]. Two examples are given in Scheme 1 in which the tertiary alcohols **1** and **3** are converted to the corresponding silyl ethers **2** [3] and **4** [4].

Indeed, the high silylation potential of TMSOTf can be fully exploited in combination with the non-nucleophilic base *i*-Pr<sub>2</sub>NEt as the formation of an ammonium salt which has



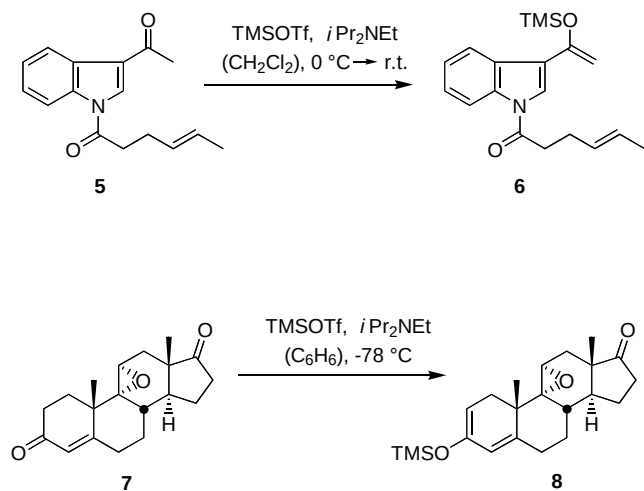
**Scheme 1**

been reported for TMSOTf/NEt<sub>3</sub> [6] is not possible. The relatively small and strong silylating agent TMSOTf can consequently approach even sterically encumbered positions and facilitate a silylation. Silylation reactions of this type have been conducted in CH<sub>2</sub>Cl<sub>2</sub> or benzene as the solvent [3–5].

### 1.2. Silyl Enol Ether Formation

The high steric bulk of the Hünig base *i*-Pr<sub>2</sub>NEt is often useful if the regio- or chemoselective formation of silyl enol ethers is desired. Whereas the base acts only as a fast proton trap in the O-silylation of alcohols its role in the silyl enol ether formation from ketones and other carbonyl compounds is the selectivity-determining irreversible deprotonation of the O-silyloxonium ion formed as the immediate precursor. It can be therefore readily comprehended why the more accessible proton is favorable abstracted in these reactions if TMSOTf/*i*-Pr<sub>2</sub>NEt is used as the reagent combination. Attempted conventional silyl enol ether formation of indol **5** proved problematic as the amide moiety showed a tendency to also react with LDA and TMSCl. The regioselectivity problem was finally overcome with TMSOTf/*i*-Pr<sub>2</sub>NEt, and the reaction of **5** yielded exclusively the desired silyl enol ether **6** [7]. Similarly, the formation of the silyl enol ether **8** from the steroid

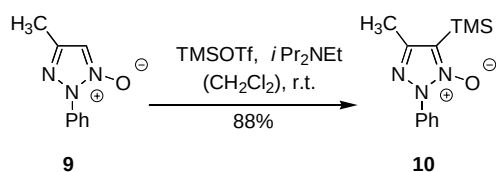
epoxide **7** was regio- and chemoselectively accomplished as shown in Scheme 2 [8]. In both cases, the silyl enol ethers were not isolated and instead used immediately without purification.



Scheme 2

### 1.3. C-Silylation

Due to the high oxophilicity of silicon the formation of C–Si bonds with TMSOTf/*i*-Pr<sub>2</sub>NEt is only possible if an O-silylation precedes or unless an oxygen nucleophile is present in the starting material. Both cases are known. An effective C-silylation of *N*-azol oxides was reported by Begtrup and Ved-sø upon intermediate silylation of the oxygen atom [9]. The procedure is exemplified by the reaction of compound **9** which yielded the C-silylated product **10** after work-up (Scheme 3).



Scheme 3

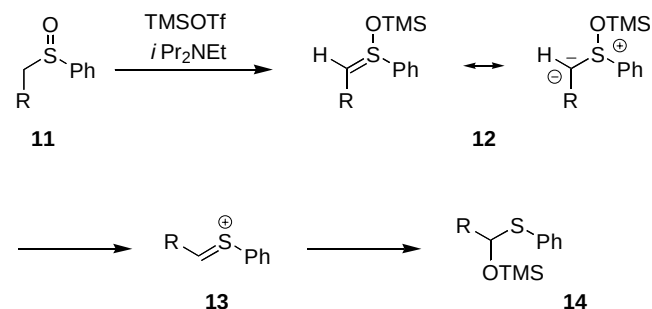
Diazomethane as an example for a good carbon nucleophile was converted to the corresponding C-trimethylsilyl derivative TMSCHN<sub>2</sub> upon treatment with TMSOTf/*i*-Pr<sub>2</sub>NEt at –78 °C in ether (74% yield) [10]. The method was claimed to be the most effective one for the formation of the synthetically valuable trimethylsilyl diazomethane [11].

## 2. Elimination Reactions

### 2.1. Pummerer Reaction

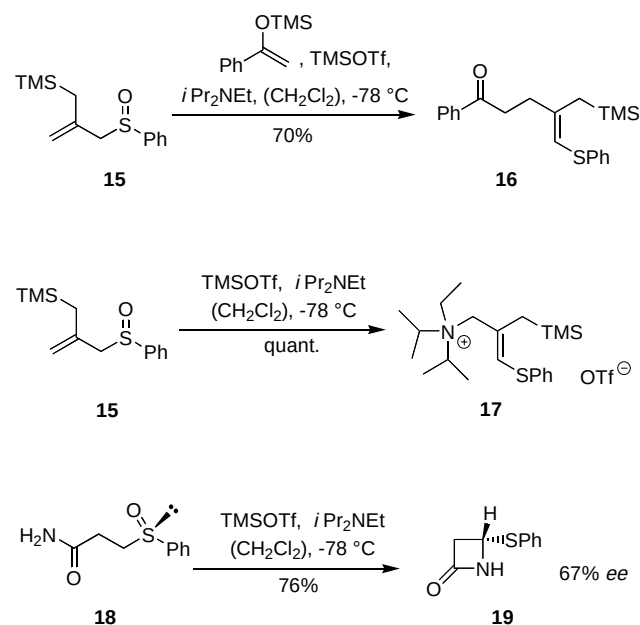
In principle, a Pummerer type rearrangement [12] as depicted in Scheme 4 should be possible starting from a sulfoxide **11** and TMSOTf/*i*-Pr<sub>2</sub>NEt. Consecutive products of the proposed α-trimethylsilyloxysulfide **14** have indeed been detected

in the Pummerer reaction of an allyl sulfoxide [13] but the method does not appear to be particularly well-suited for this transformation. If the substituent R is an alkyl group an elimination to the corresponding vinyl sulfides takes place [14, 15].



Scheme 4

One the other hand, if R is an alkenyl group it is possible to intercept the intermediate ylide **12** or the corresponding thionium ion **13** by suitable nucleophiles. To this end, Hunter *et al.* have studied the reaction of allyl sulfoxides with silyl enol ethers which yielded the corresponding allylation products [13, 16]. An example is shown in Scheme 5. The sulfoxide **15** was converted to the γ,δ-unsaturated ketone **16** upon treatment with 1-phenyl-1-trimethylsilyloxyethene and TMSOTf/*i*-Pr<sub>2</sub>NEt. Interestingly, the corresponding ammonium salt **17** was formed in this example provided no other nucleophile was added [13].



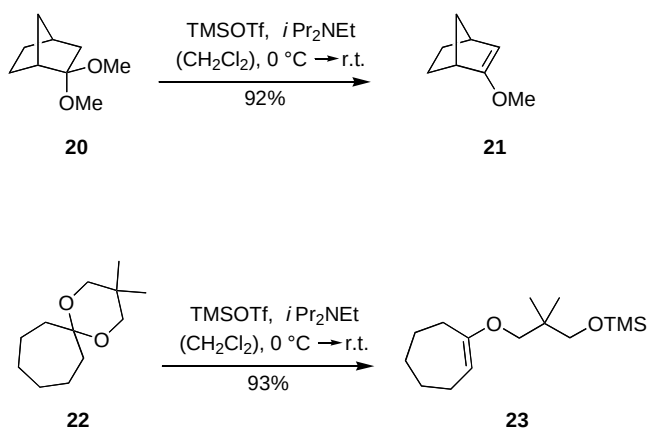
Scheme 5

Intermediate ylides such as **12** (Scheme 4) can also be trapped intramolecularly. An appealing example is the conversion of the chiral sulfoxide **18** to the β-lactam **19**, which

proceeded enantioselectively (Scheme 5). Starting from optically pure sulfoxide **18** the corresponding product was obtained with 69% *ee* [17]. The recorded chirality transfer rules out that the reaction proceeded *via* a thionium ion such as **13** (Scheme 4). The base *i*-Pr<sub>2</sub>NEt proved to be essential to guarantee an optimum conversion to the product. The yield reported with NEt<sub>3</sub> was much lower (40%).

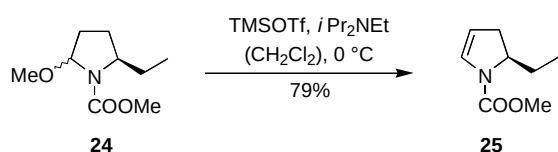
## 2.2. 1,2-Elimination Reactions

The alkoxy group in an *O,O*- or an *N,O*-acetal is readily cleaved upon silylation with TMSOTf and yields a stabilized oxonium or iminium ion which is able to react with nucleophiles [18]. If a non-nucleophilic base is added instead of a nucleophile an elimination occurs. The net result is a 1,2-elimination of an alcohol from an *O,O*- or *N,O*-acetal. The reaction was exploited to a wide extent by Gassman *et al.* for the formation of cyclic and acyclic enol ethers [19]. Two examples are shown in Scheme 6. The transformation of compound **20** to norbornene **21** is prototypical for the elimination of MeOH from *O,O*-dimethyl acetals whereas the elimination from cyclic *O,O*-acetals such as **22** yielded silyloxy-substituted enol ethers such as **23**. Further applications of this method in the synthesis of more complex molecules have been reported [20].



Scheme 6

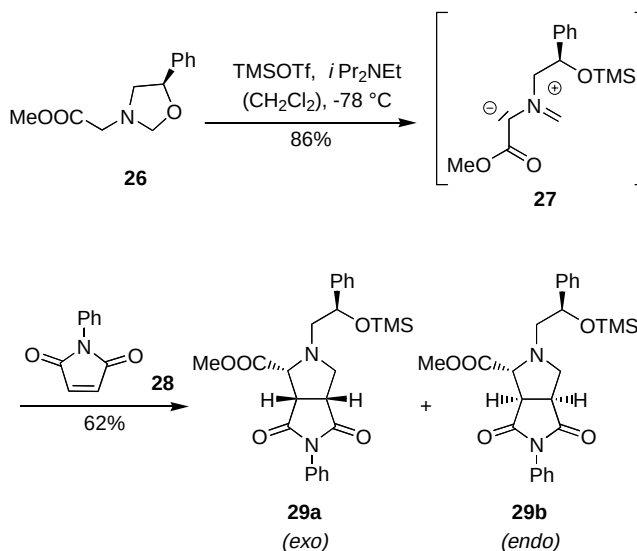
In 2-methoxy-substituted nitrogen heterocycles, *i.e.* in cyclic *N,O*-acetals in which the nitrogen atom is part of the heterocycle, the elimination of MeOH was favorably facilitated with TMSOTf/*i*-Pr<sub>2</sub>NEt [21]. The reaction has been originally employed for the formation of dihydropyrrols, *e.g.* **25** (Scheme 7), from the corresponding acetals, *e.g.* **24**, but it is apparently also useful for the formation of other 2,3-unsaturated nitrogen heterocycles [22]. The method has been used as a step in the synthesis of the antifungal agent (+)-preussin from *L*-pyroglutamic acid [23].



Scheme 7

## 2.3. 1,3-Elimination Reactions

*N,O*-acetals which do not carry a  $\beta$ -hydrogen atom and which are consequently not suited for an 1,2-elimination may still react with TMSOTf/*i*-Pr<sub>2</sub>NEt. If a 2-unsubstituted oxazoline such as **26** (Scheme 8) is treated with the reagent combination the attack of the silyl group at the oxygen atom generates an oxonium ion from which a  $\gamma$ -proton is eliminated to yield azomethine ylide **27** [24]. The reactive 1,3-dipole can be trapped *in situ* by suitable dipolarophiles, *e.g.* *N*-phenyl maleimide (**28**). The particular example depicted in Scheme 8 deserves particular mention as it proceeded with excellent facial diastereoselectivity (>95% *de*). A mixture of *exo*- (**29a**) and *endo*-product (**29b**) was obtained. The 1,3-elimination as an entry into azomethine ylides has been nicely used by Royer, Husson and co-workers for the stereoselective synthesis of a variety of pyrrolidines [25].



Scheme 8

In conclusion, the reagent combination TMSOTf/*i*-Pr<sub>2</sub>NEt combines favorably the properties of a strong oxophilic Lewis acid and a fast and comparably strong base. Upon activation with TMSOTf a subsequent deprotonation can readily occur. The reagent combination can be consequently not only used for simple *O*- and *C*-silylation but for a number of other interesting elimination reactions the potential of which will certainly be explored further.

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