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Highly Efficient Deprotection of Acetals and Ketals under Neutral and Anhydrous Conditions Using (Trimethylsilyl)bis(fluorosulfuryl)imide

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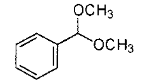
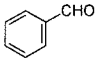
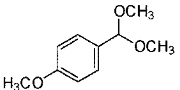
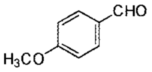
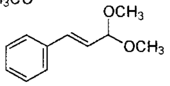
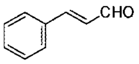
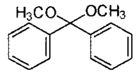
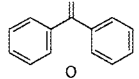
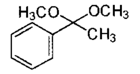
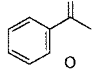
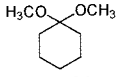
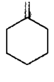
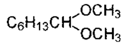
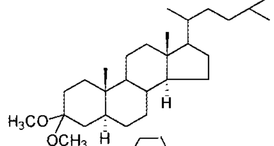
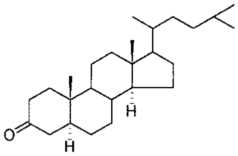
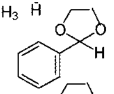
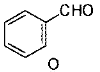
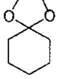
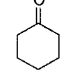
The deprotection of acetals and ketals is an important transformation in organic synthesis. This transformation is usually accomplished by aqueous acid hydrolysis.[1] Although some methods using less acidic conditions[2] have been developed, the methods using nonacidic and anhydrous conditions have gained importance for acid-sensitive substrates. These include use of transition metals and Lewis acids,[3] oxidative methods,[4] phosphorus-based reagents,[5] and silicon-based reagents,[6] each having their own advantages. Here, we report a very mild method for the deprotection of acetals or ketals under neutral and anhydrous conditions using (trimethylsilyl)bis(fluorosulfuryl)imide [$TMSN(SO_2F)_2$].[7] Under these conditions, deprotection is achieved at as low as −78 °C for dimethyl acetals, and only very weak nucleophiles are present in the reaction mixture.

Benzaldehyde dimethyl acetal in CH_2Cl_2 was treated with 5 mol % of $TMSN(SO_2F)_2$ at −78 °C, and the reaction was monitored by TLC. On completion of the reaction (15 min), the low-temperature bath was removed and the reaction was quenched by adding saturated aqueous sodium bicarbonate. Using this procedure, benzaldehyde was obtained in 92% yield after usual workup.[8,9] Encouraged by this result, reactions using various representative dimethyl acetals or ketals were carried out. The results are summarized in Table 1. Acetals and ketals of aromatic carbonyl compounds underwent deprotection within 15 min, whereas for those of aliphatic carbonyl compounds the reaction was relatively slow (4−12 h). The reaction of aliphatic carbonyl compounds could be accelerated by raising the temperature of the reaction to 0 °C; for example, heptaldehyde dimethyl acetal could be deprotected in less than 2 h at 0 °C with similar yields. Isolated yields of deprotected products were very high.

Table 1. Deprotection of Acetals and Ketals with $TMSN(SO_2F)_2$[a]

Entry	Ketal/Acetal	T/h	Product	Isolated Yield(%)
1.		0.25		92
2.		0.25		95
3.		0.25		91
4.		0.25		96
5.		0.25		91
6.		4.00		89
7.	 $C_6H_{13}CH(OCH_3)_2$	12.00	$C_6H_{13}CHO$	83
8.		3.00		95
[b]9.		1.00[c]		84
[b]10.		5.00[c]		79

[a] Reactions were carried out at −78 °C using 5 mol % of $TMSN(SO_2F)_2$ unless otherwise stated. [b] 1.1 equiv of $TMSN(SO_2F)_2$ was used. [c] Reactions carried out at 0 °C.

However, the 1,3-dioxolanes of benzaldehyde and cyclohexanone only underwent partial deprotection (<15%) under these conditions even when the temperature was raised to 25 °C. After some experimentation, it was found that by using slightly more than 1 equiv of $TMSN(SO_2F)_2$ at 0 °C benzaldehyde and cyclohexanone could be isolated in 84% and 79% yield, respectively. Some unprotected (<10%) 1,3-dioxolane was still present in both cases.

These results can be rationalized by the catalytic cycle shown in Scheme 1. $TMSN(SO_2F)_2$ silylates one of the oxygens of the acetal or ketal to give **2**, which loses $TMSOCH_3$ to give oxonium ion **3**. The $TMSOCH_3$ then attacks the methyl of the oxonium ion to give dimethyl ether and free carbonyl compound. Trimethylsilyl cation

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(8) Trimethylsilyl trifluoromethanesulfonate (TMSOTf) has been used for the deprotection of oxathiolanes; see: Ravindernathan, T.; Chavan, S. P.; Dantale, S. W. *Tetrahedron Lett.* **1995**, 2285.

(9) When same reaction was carried out using TMSOTf (up to 25 mol %) as a catalyst instead of $TMSN(SO_2F)_2$ some benzaldehyde formation (5−10%) was observed. However, when the reaction was carried out at 40 °C for 8 h only 46% benzaldehyde was isolated and rest was nonpolar byproducts. This experiment showed that TMSOTf is inferior to $TMSN(SO_2F)_2$ for this type of deprotection.

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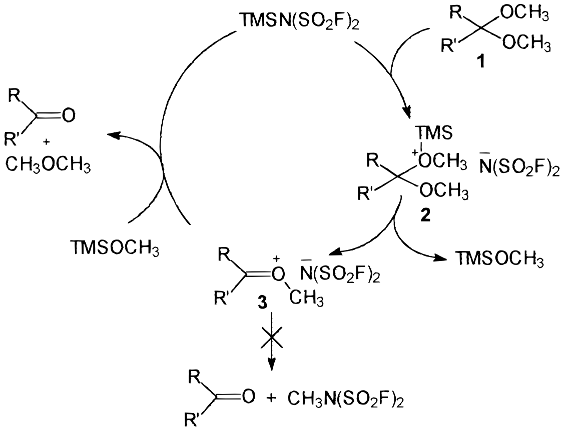
Scheme 1



formed in the process combines with the $N(SO_2F)_2^-$ to regenerate the catalyst.[10] Another possibility could be that oxonium ion pair **3** collapses to give $CH_3N(SO_2F)_2$ and free carbonyl compound. Subsequent deprotection may then be catalyzed by $CH_3N(SO_2F)_2$. To check this possibility, $CH_3N(SO_2F)_2$ was prepared[11] and was treated with benzaldehyde dimethyl acetal. It did not give any deprotected product even at 0 °C, and starting material was recovered. This clearly indicates that $TMSN(SO_2F)_2$ is the true catalyst.[12]

In the case of 1,3-dioxolanes, one would expect ethylene oxide formation instead of dimethyl ether, and under these conditions the ethylene oxide may be reacting with the carbonyl compound to give back 1,3-dioxolane.[13] Due to this likely equilibrium, complete deprotection is not observed for 1,3-dioxolanes.

In conclusion, this work demonstrates $TMSN(SO_2F)_2$ as a highly efficient catalyst for the deprotection of dimethyl acetals or ketals. Only 5 mol % of catalyst at −78 °C is sufficient for complete conversion. Due to the non-nucleophilic nature of $N(SO_2F)_2^-$ the catalyst is regenerated. Thus, $TMSN(SO_2F)_2$ is an alternative catalyst for silyl iodides, which are used in stoichiometric amounts. Also, silyl iodides do not deprotect 1,3-dioxolanes, whereas $TMSN(SO_2F)_2$ when used in a stoichiometric amount can be used for their deprotection.

Experimental Section

Materials. Acetals or ketals were prepared by reaction of aldehydes or ketones with methanol in the presence of 1.5 equiv of trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid under refluxing conditions. On completion of the reaction, it was neutralized by adding methanolic NaOH. Excess methanol and trimethyl orthoformate were evaporated to dryness using a rotary evaporator, and the residue was purified either by distillation or by flash chromatography. $TMSN(SO_2F)_2$ was prepared as described in the literature.[7]

General Procedure for Deprotection. A solution of acetal (1 equiv) in dichloromethane (4 mL/mmol) under nitrogen atmosphere at the temperature shown in Table 1 was treated with $TMSN(SO_2F)_2$ (5 mol %). The reaction was monitored by TLC. On completion of the reaction the low-temperature bath was removed in the cases where it was done at −78 °C. The reaction was quenched by adding saturated aqueous sodium bicarbonate, and the product was extracted into ether. The ether layer was washed with brine and was dried (Na_2SO_4). Removal of the solvent gave a residue that was pure by NMR or TLC in all cases. The products could be further purified by flash chromatography and were identified by comparison of their NMR, IR, TLC, and mixed TLC analysis with the authentic samples.

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[10] When silyl iodides are used for the deprotection of dimethyl acetals, the oxonium ion of type **3** is formed, but iodide ion being a stronger nuclephile than silylmethoxide reacts preferentially with methyl group of **3** to give methyl iodide and free carbonyl compound.[6] As a result, silyl iodides get consumed during the process and at least 1 equiv of the reagent is required for complete deprotection.[6]

[11] (a) Ruff, J. K. *Inorg. Chem.* **1965**, *4*, 1446. (b) Ruff, J. K.; Lustig, M. *Inorg. Synth.* **1968**, *11*, 138.

[12] A reaction of heptaldehyde dimethyl acetal with $TMSN(SO_2F)_2$ in dichloromethane was monitored by ^{19}F NMR. No peak corresponding to $CH_3N(SO_2F)_2$ was observed. This clearly indicates that $N(SO_2F)_2^-$ does not remove methyl group from the oxonium ion **3** to generate $CH_3N(SO_2F)_2$.

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