Preliminary communication

Selectivity of the bulky proton-containing reagent N-methyl-N,O-bis(trimethylsilyl)hydroxylamine in the formation of nitrones

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Abstract

Silicon reagent $Me_3SiN(Me)OSiMe_3$ contains bulky protons (i.e., Me_3Si^+). This reagent was found to possess regio- and chemoselectivities in the formation of nitrones from carbonyl compounds.

The trimethylsilyl cationic species (Me_3Si^+) has been referred to as the "bulky proton" [1]. The steric influence from the bulky protons existing in substrates or reagents can be used to control various reactions, which give products under stereo-, regio-, or chemoselective control [2]. In 1985, we reported a chemoselective dioxolanation by using "bulky proton"-containing reagents trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) and 1,2-bis[(trimethylsilyl)oxy]ethane [1]. The selectivity results from both the catalyst Me_3SiOTf and the dioxolanating agent 1,2-bis[(trimethylsilyl)oxy]ethane. Furthermore, we intended to study the influence of the "bulky proton" in a different type of reactions, in which only one reagent contains the Me_3Si group.

Previously, we reported that N-methyl-N,O-bis(trimethylsilyl)hydroxylamine ($Me_3SiN(Me)OSiMe_3$, **1**) reacts with aldehydes and ketones to give the corresponding nitrones (**3**) in good to excellent yields (Scheme 1) [3,4]. The intermediates, hemiaminals **2**, do not collapse by thermolysis; however, aldehydes or ketones can catalyze the decomposition of **2** under mild conditions. Thus the carbonyl compound in Scheme 1 plays two roles: the starting material and a "catalyst" [3,4]. This nitrone formation does not require an "external" catalyst and, thus, provides an ideal case to test the steric effect resulting from $Me_3SiN(Me)OSiMe_3$—the exclusive "bulky proton"-containing reagent in the reaction.

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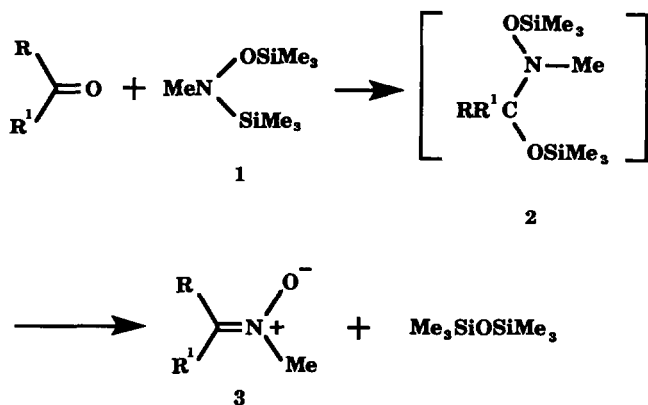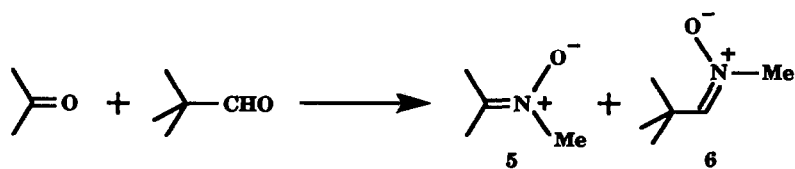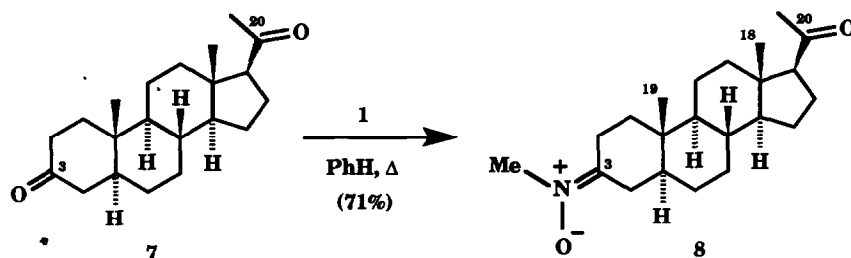
Scheme 1.
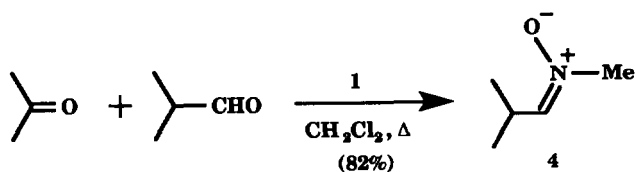
Scheme 2.

First we tested the capability of $Me_3SiN(Me)OSiMe_3$ (1) to differentiate between the carbonyl groups in ketones and hindered aldehydes based on steric hindrance. Refluxing of a dichloromethane solution of 1 with acetone and isobutylaldehyde (molar ratio of 1 : acetone : isobutylaldehyde = 1 : 1 : 1) gave the N-methylnitrone of isobutylaldehyde (4) [4] exclusively in 82% yield (Scheme 2). By the same procedure, 1 reacted with a mixture of acetone and trimethylacetaldehyde to afford nitrones 5 and 6 in 82% overall yield (Scheme 3) [4]. The ratio of 5 : 6 was 1 : 14.

These results indicate that "bulky proton"-containing reagent $Me_3SiN(Me)$-$OSiMe_3$ possesses great capabilities in distinguishing the steric environment of

conditions	ratio			overall yield
1, CH_2Cl_2, Δ	1	:	14	82%
MeNHOH·HCl KOAc, CH_2Cl_2, Δ	1	:	6	81%

Scheme 3.

Scheme 4.

carbonyl groups. Hindered aldehydes, such as trimethylacetaldehyde, can overwhelm the least unhindered ketone (i.e., acetone) towards nitrone formation with Me$_3$SiN(Me)OSiMe$_3$.

In a control experiment, we treated a mixture of acetone and trimethylacetaldehyde with MeNHOH · HCl, which was neutralized with KOAc in situ (Scheme 3). The molar ratio was 1:1:1 for MeNHOH · HCl:acetone:trimethylacetaldehyde. Salt MeNHOH · HCl is one of the most common reagents for the preparation of nitrones. This control experiment gave two N-methylnitrones 5 and 6 in 81% overall yield. Nevertheless, the ratio of 5:6 changed to 1:6 (cf. 1:14 by use of 1). Thus the selectivity is lower by use of MeNHOH · HCl than Me$_3$SiN(Me)OSiMe$_3$.

For the nitrone formation, we often encountered a separation problem by using MeNHOH · HCl, in which free MeNHOH was liberated with KOAc or NaOH. Without careful control, carbonyl compounds may condense to give aldols as byproducts [5a]. Although being a minor component, the aldols in the crude reaction products usually made purification of the desired nitrones difficult. This problem did not occur when we utilized Me$_3$SiN(Me)OSiMe$_3$ to generate nitrones.

We obtained more evidence to show that Me$_3$SiN(Me)OSiMe$_3$ was sensitive towards steric hindrance by reacting it with dicarbonyl compound 5α-pregnan-3,20-dione (7, Scheme 4). Treatment of Me$_3$SiN(Me)OSiMe$_3$ with 7 (1.0 equiv.) in benzene under refluxing afforded mononitrone 8 in 71% yield [6*]. N-Methylnitrone was generated only at the C-3 position, which has minimal steric hindrance. Additional information regarding the steric effect is that Me$_3$SiN(Me)OSiMe$_3$ did not react with progesterone (9) at the congested C-20 carbonyl group.

We also found that neither Me$_3$SiN(Me)OSiMe$_3$ nor MeNHOH · HCl was able to convert the enone moiety to the corresponding N-methylnitrone. By contrast with Me$_3$SiN(Me)OSiMe$_3$, MeNHOH · HCl does not possess a "bulky proton" and was able to react with progesterone (9) at the C-20 carbonyl group to give nitrone 10 in 95% yield (Scheme 5) [6*].

Hydroxylamines can react with alkyl chlorides to give the corresponding N-alkylated products by substitution [5b]. Between the functionalities of chloride and aldehyde, we found that silylated hydroxylamine Me$_3$SiN(Me)OSiMe$_3$ reacted preferentially with the latter, as shown in Scheme 6. Treatment of ω-chloroaldehyde 11 with Me$_3$SiN(Me)OSiMe$_3$ (1.0 equiv.) in refluxing dichloromethane gave nitrone 12 in 79% yield [6*]. In this reaction, we did not observe any substitution product.

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* Reference number with asterisk indicates a note in the list of references.
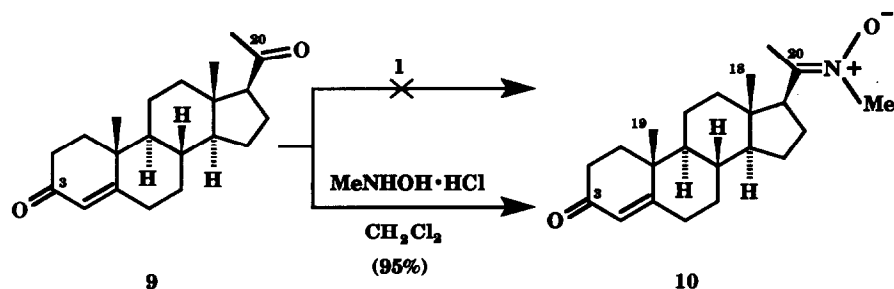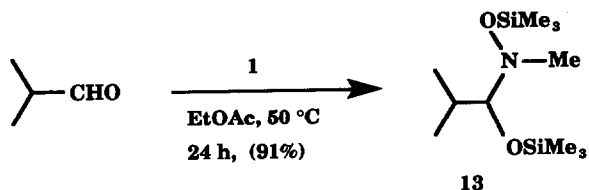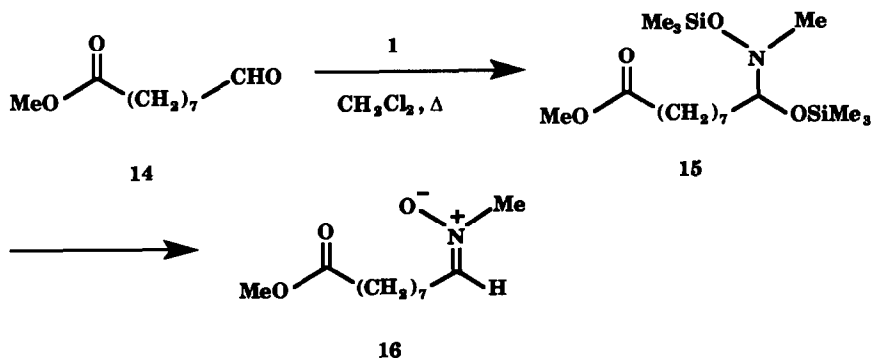
Scheme 5.
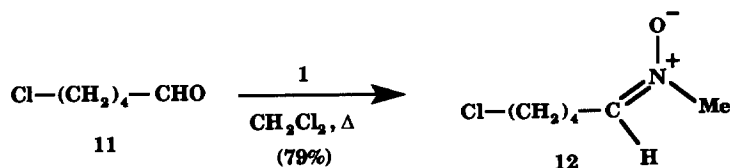
Scheme 6.

In previous papers [3,4], we reported that weak Lewis acids can decompose hemiaminal intermediates **2** to give nitrones. The carbonyl groups in aldehydes and ketones make these compounds act as effective Lewis acids (i.e., trimethylsiloxide acceptor) [4] under the conditions that the molar ratio of carbonyl compounds to $Me_3SiN(Me)OSiMe_3$ is ≥ 1. Our new results indicated that the carbonyl group in esters was not able to decompose hemiaminals. When we reacted isobutyraldehyde with $Me_3SiN(Me)OSiMe_3$ (1.3 equiv.) at 50°C for 24 h by using ester EtOAc as solvent, hemiaminal **13** (instead of a nitrone) was isolated in 91% yield (Scheme 7) [4].

Furthermore, we allowed the dicarbonyl compound **14** to react with 1.0 equiv. of $Me_3SiN(Me)OSiMe_3$ in dichloromethane under refluxing for 24 h (Scheme 8). The corresponding N-methylnitrone **16** was obtained in 89–96% yield [6*]. On the other hand, use of an excess of $Me_3SiN(Me)OSiMe_3$ (1.3 equiv.) for the same reaction afforded a mixture of hemiaminal **15** (22%) [6*] and nitrone **16** (65%) in a 1 : 3 ratio. These experiments provide more evidence to show that the carbonyl group in an aldehyde can decompose hemiaminal intermediate efficiently, but not the carbonyl group in an ester.

In conclusion, the "bulky proton"-containing reagent $Me_3SiN(Me)OSiMe_3$ reacted preferentially with sterically hindered aldehydes in the presence of a ketone

Scheme 7.

Scheme 8.

without hindrance to give *N*-methylnitrones. This silicon reagent also reacted with a dione selectively at the less congested carbonyl group. Between alkyl chloride and aldehydic carbonyl functionalities, $Me_3SiN(Me)OSiMe_3$ reacted with the latter to give a nitrone, exclusively. In addition, the intermediate hemiaminals can be decomposed by an aldehyde or a ketone, but not an ester.

References

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6 Satisfactory results from elemental analyses were obtained for all of the products. All of the nitrones showed an IR absorption at 1150–1220 cm^{-1}. ^{1}H NMR spectroscopic data: for **8**: δ 0.62 (s, 3 H, (C-19)H$_3$), 0.81 (s, 3 H, (C-18)H$_3$), 2.10 (s, 3 H, CH$_3$CO), 3.66 (s, 3 H, NCH$_3$); for **10**: δ 0.62 (s, 3 H, (C-19)H$_3$), 0.99 (s, 3 H, (C-18)H$_3$) 2.06 (s, 3 H, CH$_3$C=N), 3.66 (s, 3 H, NCH$_3$), 5.95 (s, 1 H, =CHC=O); for **12**: δ 1.31–1.95 (m, 4 H, 2×CH$_2$), 2.55–2.75 (m, 2 H, CH$_2$CN), 3.53 (t, J = 6.3 Hz, 2 H, CH$_2$Cl), 3.69 (d, J = 0.9 Hz, 3 H, NCH$_3$), 6.68 (tq, J = 5.9, 0.9 Hz, 1 H, =CH); for **15**: δ 0.18 (s, 18 H, 2×Si(CH$_3$)$_3$), 1.12–1.76 (m, 12 H, 6×CH$_2$), 2.31 (t, J = 7.0 Hz, 2 H, CH$_2$CO), 2.68 (s, 3 H, NCH$_3$), 3.66 (s, 3 H, OCH$_3$), 4.80 (t, J = 6.0 Hz, 1 H, OCHN); for **16**: δ 1.20–1.78 (m, 10 H, 5×CH$_2$), 2.31 (t, J = 7.0 Hz, 2 H, CH$_2$CO), 2.73 (t, J = 6.9 Hz, 2 H, CH$_2$CN), 3.66 (s, 3 H, OCH$_3$), 3.70 (s, J = 0.8 Hz, 3 H, NCH$_3$), 6.69 (dt, J = 0.8, 5.9 Hz, 1 H, =CH).