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Sodium Bis(trimethylsilyl)amide in the Oxidative Conversion of Aldehydes to Nitriles

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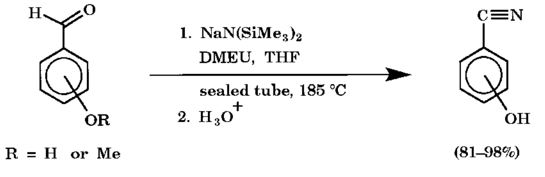
The feasibility of the Me_3Si species acting as a nucleofuge was investigated in compounds containing the $NSiMe_3$ moiety. Treatment of various aromatic aldehydes with 2.2 equiv. of $NaN(SiMe_3)_2$ at 185 °C in a sealed tube produced the corresponding nitriles in high yields (81–98 %). In these reactions, $NaN(SiMe_3)_2$ acted as an oxidizing agent. Results from control experiments indicate that the Me_3Si unit can depart efficiently from the $NSiMe_3$ moiety of *N*-silylimine intermediates.

Introduction

The trimethylsilyl cation (Me_3Si^+) has been referred to as a "bulky proton"[1,2] and this concept has been applied in the control of organic reactions.[1,3,4] The trimethylsilyl radical ($Me_3Si^\cdot$) is also involved in many organosilicon reactions,[5] whilst the trimethylsilyl anion (Me_3Si^-) can donate one electron to a substrate[6–8] or act as a nucleophile.[9–12] The silicon analogues of the species H^+, $H^\cdot$, H^-, and H_2 would be Me_3Si^+, $Me_3Si^\cdot$, Me_3Si^-, and $Me_3SiSiMe_3$, respectively, so the trimethylsilyl group can be regarded as a bulky analogue of a hydrogen atom.

The trimethylsilyl group usually leaves organosilanes as an electrofuge.[13] To broaden the scope of silicon compounds in organic synthesis, we have been seeking for potential for the trimethylsilyl group to function as a nucleofuge.[14–19] Here we report a new method for the conversion of aromatic aldehydes into the corresponding nitriles by treatment with $NaN(SiMe_3)_2$ as an oxidizing agent (Scheme 1). Results from our mechanistic studies indicate that the trimethylsilyl group departed from the $NSiMe_3$ moiety of *N*-silyl imine intermediates in the form of Me_3Si^- in the key step.



Scheme 1.

Results and Discussion

To establish a new method for the oxidative conversion of aldehydes to nitriles, we added 2.2 equiv. of $NaN(SiMe_3)_2$ to a solution containing an aromatic aldehyde (e.g., **1**, **3**, or **5**) in 1,3-dimethylimidazolidin-2-one. The aldehyde possessed a hydroxy group at an *ortho*, *meta*, or *para* position (see Scheme 1). After the solution had been heated at 185 °C in a sealed tube for 12 h, the corresponding nitrile (i.e., **2**, **4**, or **6**) was obtained in good to excellent yield (88–98 %). Although the same reactions also proceeded at a lower temperature (e.g., 120 °C), they required longer reaction times and produced the desired nitriles in lower yields.

We also allowed an aromatic aldehyde with a methoxy – instead of a hydroxy – group at the *para* position (i.e., **7**) to react with 2.2 equiv. of $NaN(SiMe_3)_2$. The corresponding demethylated aromatic nitrile **6** was generated in 86 % yield.

The formyl group in a more complicated compound, benzoquinolizine **8**, can also be converted to a cyano group efficiently; we obtained an 86 % yield for the transformation **8** → **9**. Similarly, conversions of naphthaldehydes, such as **10** and **12**, to the corresponding naphthalenecarbonitriles **11** and **13** were accomplished in 81 % and 89 % yields, respectively. Note that the demethylation also took place in situ during the conversion of **12** to **13** (cf. **7** → **6**).

In addition to demethylation, we found that the methylene units in benzaldehyde derivatives **14** and **16** fell off during the conversion of their formyl groups into cyano groups by treatment with 2.2 equiv. of $NaN(SiMe_3)_2$. The yields for the transformations **14** → **15** and **16** → **17** were 84 % and 91 %, respectively.

Furthermore, we treated pyrrole-2-carboxaldehyde (**18**) with 2.2 equiv. of $NaN(SiMe_3)_2$ in DMEU at 185 °C and the corresponding nitrile **19** was generated in 85 % yield after 12 h. By the same method we converted indole-3-carboxaldehyde (**20**) and its derivatives **22** and **24**, with an

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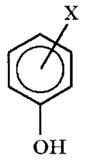
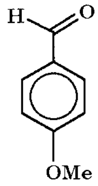


1: X = *ortho*-CHO
2: X = *ortho*-CN (88%)
3: X = *meta*-CHO
4: X = *meta*-CN (94%)
5: X = *para*-CHO
6: X = *para*-CN (98%)



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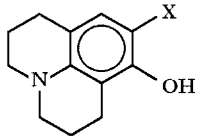
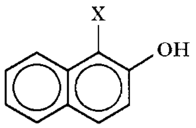
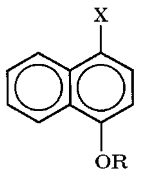


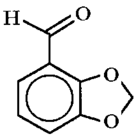
8: X = CHO
9: X = CN (86%)



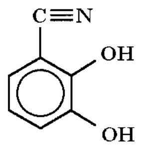
10: X = CHO
11: X = CN (81%)



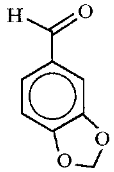
12: X = CHO, R = Me
13: X = CN, R = H (89%)



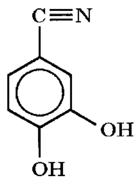
14



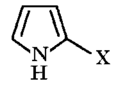
15 (84%)



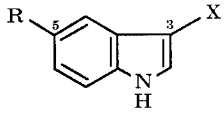
16



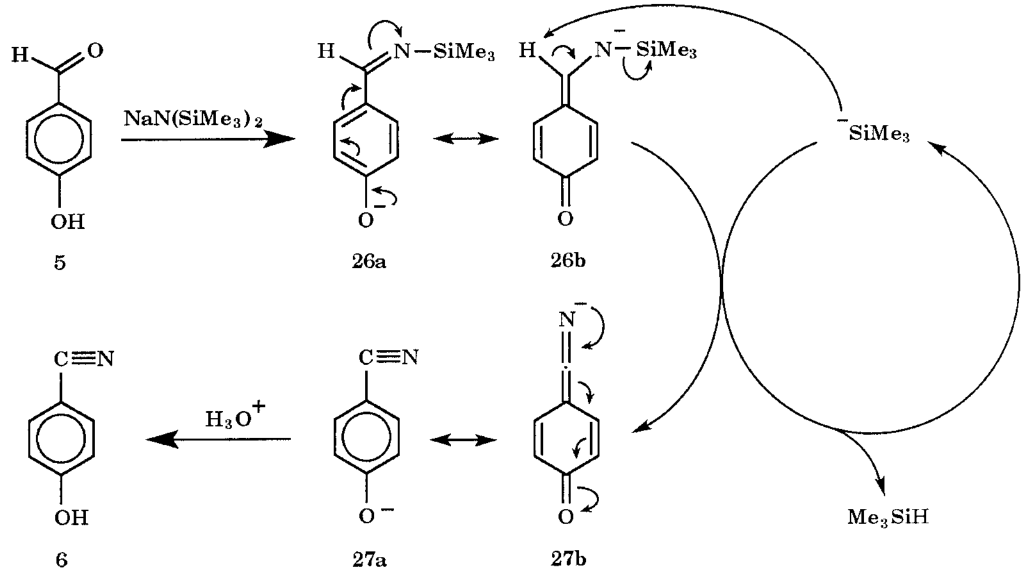
17 (91%)



18: X = CHO
19: X = CN (85%)



20: X = CHO, R = H
21: X = CN, R = H (94%)
22: X = CHO, R = OMe
23: X = CN, R = OMe (90%)
24: X = CHO, R = OCH_2Ph
25: X = CN, R = OCH_2Ph (87%)



Scheme 2.

OMe or OCH_2Ph substituent at their 5-positions, into the indole-3-carbonitriles **21**, **23**, and **25**, respectively, in 87–94% yields.

We illustrate a plausible, but not exclusive, mechanism for the oxidative conversion of aromatic aldehydes to nitriles by $NaN(SiMe_3)_2$ in Scheme 2. In addition to acting as a base for the removal of the proton from the hydroxy group in **5**, $NaN(SiMe_3)_2$ also reacts with aldehydes or ketones to give the corresponding imines.[20] The resultant *N*-silyl imine **26a** and **26b** are resonance hybrids, in which silicon can exert a stabilizing effect on the α-amide center in **26b**.[21,22]

A catalytic amount of $NaN(SiMe_3)_2$ can initiate deprotonation along with desilylation in *N*-silyl imines **26a/26b** to give **27a/27b** and Me_3SiH. When the trimethylsilyl group departs from **26a/26b**, its silicon atom bears a negative charge. So the oxidation state of this silicon atom decreases by two during the conversions of **26a/26b** → **27a/27b** + Me_3Si^-. Moore et al.[23] proposed a similar nitrile-stabilized anion intermediate (**27a/27b**) in the thermolysis of vinyl azides. Finally, protonation of **27a/27b** gives the target aromatic nitriles.

According to the mechanism shown in Scheme 2, oxidation of aromatic aldehydes to the corresponding nitriles by $NaN(SiMe_3)_2$ should generate Me_3SiH as the by-product. We did not isolate Me_3SiH because of its low boiling point (6.7 °C).[17] Nevertheless, in a control experiment, we treated the *N*-methyldiphenylsilyl imine of **5** with 1.2 equiv. of $NaN(SiMe_3)_2$ in DMEU at 185 °C. The by-product $HSiMePh_2$ was obtained as a colorless, irritant liquid in 87% yield along with nitrile **6** in 91% yield. These results indicate that Ph_2MeSi^- can also act as a nucleofuge.

Moreover, the Me_3Si^- moiety that departs from a molecule of **26b** could also act as a base to trap the acidic proton in another molecule of **26b**, so only a catalytic amount of $NaN(SiMe_3)_2$ would be required for the conversion **26b** → **27b**. This design allows us to use 2.2 equiv. of $NaN(SiMe_3)_2$ to complete the transformation **5** → **6**: the first equivalent was used for deprotonation, the second equivalent was consumed during the imine formation, and the remaining 0.2 equivalent was used for initiation of the process **26a/26b** → **27a/27b** + Me_3SiH.

Conclusions

Aromatic aldehydes can be oxidatively converted into the corresponding nitriles by use of $NaN(SiMe_3)_2$. To the best of our knowledge, this is the first observation of the hindered base $NaN(SiMe_3)_2$ acting as an oxidizing agent in organic transformations.

Experimental Section

Standard Procedure for the Conversion of Aromatic Aldehydes into Nitriles: A solution containing an aldehyde (0.424–1.19 mmol) in DMEU (0.50 mL) was transferred into a Pyrex combustion tube under argon. Sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.930–2.60 mmol) was injected into the tube, which was then sealed by torch and heated in an oven at 185 °C for 12 h. The reaction mixture was diluted with water at room temperature, neutralized with HCl (10%), and extracted with Et_2O (4 × 25 mL). The combined ethereal solutions were washed with water and saturated aqueous NaCl. The combined organic extracts were dried with $MgSO_4$ (s), filtered, and concentrated under reduced pressure. The residue was chromatographed through a column packed with silica gel (2.2 cm × 16 cm column) to provide the desired product with purity >99.5%, as checked by GC.

A Representative Example. Formation of 8-Hydroxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*i,j*]quinolizine-9-carbonitrile (9): The standard procedure was followed, with use of 8-hydroxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*i,j*]quinolizine-9-carboxaldehyde (**8**, 152 mg, 0.700 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (1.0 M in THF, 1.5 mL, 1.5 mmol, 2.2 equiv.), and DMEU (0.50 mL). The reaction mixture was worked up after 12 h and the residue was purified by column chromatography on silica gel (40% EtOAc in hexanes as eluent) to give pure **9** (129 mg, 0.602 mmol) as a white solid in 86% yield: m.p. 172.0–174.0 °C. GC t_R = 20.16 min; TLC R_f 0.30 (40% EtOAc in hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.91 (m, 4 H, 2 × CH_2), 2.64 (m, 4 H, 2 × CCH_2), 3.06 (br. s, 1 H, OH), 3.21 (m, 4 H, 2 × NCH_2), 6.84 (s, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.46, 20.65, 21.26, 26.84, 49.00, 49.61, 84.85, 107.20, 113.96, 119.29, 129.05, 146.81, 155.04 ppm. IR (neat): $\tilde{\nu}$ = 3317 cm^{-1} (br. s, OH), 2899 (s, C–H), 2499 (s, C≡N), 1608 (s, C=C), 1508 (m, C=C), 1455 (m), 1308 (m), 1152 (m), 458 (m) cm^{-1}. MS *m/z* (%) = 214 (100) $[M]^+$, 197 (3), 185 (49), 171 (4), 158 (3), 142 (3), 130 (3), 116 (2), 106 (4), 102 (3), 92 (3), 77 (5), 63 (3), 51 (3). HRMS for $C_{13}H_{14}N_2O$ 214.1106, found 214.1104. $C_{13}H_{14}N_2O$ (214.27): calcd. C 72.87, H 6.59, N 13.07; found C 72.63, H 6.60, N 12.97.

Acknowledgments

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