Tetrabutylammonium cyanide catalyzes the addition of TMSCN to aldehydes and ketones

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Dedicated to Prof. Enrique Meléndez
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Abstract
The catalytic effect of Bu₄NCN on the addition of TMSCN to the carbonyl group of spiroepoxycyclohexadienones and to some other representative carbonyl compounds has been considered.

Keywords: Ammonium salts, catalysis, trimethylsilyl cyanide, cyanohydrins

Introduction
Cyanohydrin trimethylsilyl ethers are useful synthetic intermediates for the preparation of elaborated targets.¹ For this reason, a large array of catalytic species has been used for the synthesis of this kind of compounds.² Among them, particular attention has been devoted to metal-catalyzed processes. However, the use of non-metal catalysts to carry out organic transformations is important from an environmental standpoint. In this paper we describe the results of the TMSCN addition to the carbonyl group of spiroepoxycyclohexadienones³ and certain representative carbonyl compounds catalyzed by ammonium salts.

Results and Discussion
In the context of the synthesis of cyanohydrins derived from spiroepoxycyclohexadienones,³ we have observed that the reaction of compound 1 with TMSCN (1.0 eq) in the presence of Bu₄NCN (0.1 eq) afforded an inseparable mixture of diastereomeric cyanohydrin derivatives 2 and 3 in ratio 1:1.3 (71% isolated yield). However, at this stage the stereochemical assignment of compounds 2 and 3 was not possible. This result contrasts with those reported by Waldmann et
al.\textsuperscript{4} where the formation of bezenic derivative 4 was observed when using a molar ratio 1: TMS-CN: Bu$_4$NCN = 1: 18.4: 1 (Scheme 1).

\begin{align*}
\text{Scheme 1} & \\
\text{In the context of these findings, two comments should be made: i) the reaction of 1 with TMSCN in the absence of the ammonium salt resulted in the recovering of unaltered starting material; and ii) to the best of our knowledge, only an isolated report describing the use of Bu$_4$NCN as catalytic agent for the O-TMS-cyanosilylation of 3-pentanone (84\% isolated yield) has been previously reported.}^5 \\
\text{On the basis of these considerations, we decided to explore the scope and limitations of the use of the system TMSCN/Bu$_4$NCN(cat.) for the O-TMS-cyanosilylation of other spiroepoxycyclohexadienones and also for the same reaction using some representative carbonyl derivatives as starting materials.} \\
\text{The results of the OTMS-cyanosilylation of a variety of spiroepoxycyclohexadienones (Scheme 2) and some other representative carbonyl compounds (Scheme 3) are quoted in Tables 1 and 2 respectively.}
\end{align*}
Table 1. O-TMS cyanosilylation of spiroepoxycyclohexadienones

<table>
<thead>
<tr>
<th>No.</th>
<th>Starting material</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Product (%)ᵃ</th>
<th>Diastereomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Br</td>
<td>MeO</td>
<td>Br</td>
<td>MeO</td>
<td>8 (60)</td>
<td>1 : 1ᵇ</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>H</td>
<td>9 (50)</td>
<td>1 : 1.4ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>H</td>
<td>MeO</td>
<td>H</td>
<td>H</td>
<td>10 (45)</td>
<td>1 : 1.6ᶜ</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield of the diastereomeric O-TMS cyanohydrins.
b Determined by GC/MS on the purified mixture of diastereomeric O-TMS cyanohydrins.
c Determined by ¹H-NMR on the purified mixture of diastereomeric O-TMS cyanohydrins.

Scheme 3

Table 2. O-TMS cyanosilylation of representative carbonyl compounds

<table>
<thead>
<tr>
<th>No</th>
<th>Product (%)ᵃ</th>
<th>Diastereomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a (88)</td>
<td>---</td>
</tr>
<tr>
<td>2ᵈ</td>
<td>11b (86)</td>
<td>---</td>
</tr>
<tr>
<td>3ᵉ</td>
<td>11c (86)</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>11d (89)</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>11e (92)</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>11f (95)</td>
<td>3.3 : 1ᵇ</td>
</tr>
<tr>
<td>7</td>
<td>11g (97)</td>
<td>4.0 : 1ᶜ</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield of the diastereomeric O-TMS cyanohydrins.
ᵇ Determined by ¹H-NMR on the purified mixture of diastereomeric O-TMS cyanohydrins.
ᶜ Determined by GC/MS on the purified mixture of diastereomeric O-TMS cyanohydrins.
d The reaction was carried out in dry Et₂O.
e The reaction was achieved at room temperature for 1 h.

Conclusions

The formation of O-TMS cyanohydrins was possible for a variety of aldehydes and ketones using TMSCN as reagent and Bu₄N CN as catalyst. The method is characterized by mild reaction conditions, short reaction times and good yields of the final O-TMS cyanohydrins. In those cases
where the formation of stereoisomers is possible, an excess of one of the diastereomers was observed.

**Experimental Section**

**Synthesis of 2,4-dibromo-3,5-dimethoxy-cyclohexa-2,4-diene-1-one-5-spirooxirane (5).** Following the analogous synthetic route used by K. Hinterding et al.\textsuperscript{4} to obtain the spiroepoxycyclohexadienone 1, 2,4,6-trimethoxybenzaldehyde was submitted to a four-step sequence:

![Reaction Scheme]

i) BCl\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 4 h., r. t., 91%; ii) Br\textsubscript{2}-HBrPyridine, Pyridine, 2 h., 50 °C, 76%; iii) NaBH\textsubscript{4}, THF, 1 h., r. t., 80%; iv) NaIO\textsubscript{4}, HCl, H\textsubbox{2}O, THF, r. t., 70%.

**Spectroscopic data for 5.** \( ^1\text{H}-\text{NMR}: (\text{CDCl}_3, 200 \text{ MHz}) \delta 3.27 (d, J=8.9 \text{ Hz}, 1H, CH\textsubbox{2}-O), 3.45 (d, J=8.9 \text{ Hz}, 1H, CH\textsubbox{2}-O), 3.83 (s, 3H, OCH\textsubbox{3}), 4.07 (s, 3H, OCH\textsubbox{3}) \text{ ppm}; \( ^{13}\text{C}-\text{NMR}: (\text{CDCl}_3, 50 \text{ MHz}) \delta 57.47 (O-C-CH\textsubbox{2}), 58.36 (CH\textsubbox{2}-O), 61.72 (OCH\textsubbox{3}), 61.81 (OCH\textsubbox{3}), 107.17 (CBr), 107.37 (CBr), 159.11 (C- OCH\textsubbox{3}), 166.10 (C- OCH\textsubbox{3}), 185.48 (C=O) \text{ ppm}; \) MS (70 eV, EI) m/z (%): 338/340/342 (52/94/44) [M+\textsuperscript{+}], 323/325/327 (51/100/61) [M-15], 322/324/326 (51/57/35) [M-16], 241/243 (47/47), 59 (14).

**Typical procedure for the cyanosilylation of carbonyl compounds**

To a solution of the carbonyl compound (0.367 mmol) in dry CH\textsubbox{2}Cl\textsubbox{2} (0.5 mL) was added, under Argon an at 0 °C, TMSCN (0.046 mL, 0.367 mmol) followed by a solution of the ammonium salt (10 mg, 0.037 mmol) in dry CH\textsubbox{2}Cl\textsubbox{2} (0.5 mL). The mixture was stirred at 0 °C for 15 minutes. A solution of NaHCO\textsubbox{3} sat. (3 mL) was added and the mixture was extracted with CH\textsubbox{2}Cl\textsubbox{2}. Drying of the combined organic phases with MgSO\textsubbox{4} was followed by evaporation of the solvent in vacuo. The products were purified by chromatography on silica gel (ethyl acetate/hexane) and characterized by \( ^1\text{H} \) NMR, \( ^{13}\text{C} \) NMR and mass spectrometry. For compounds \( \text{2+3, 8, 9 and 11g} \) the diastereomeric ratio was determined by GC/MS. Conditions: Capillary column 95 % dimethyl 5 % diphenylpolysiloxilane. Gradient of temperature 45 °C-290 °C. Mass spectrometer, HP 5890.

**5,7-Dibromo-6-methoxy-4-trimethylsilylanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (2) + (3).** \( ^1\text{H} \) NMR: (CDCl\textsubbox{3}, 200 MHz) \delta 0.41 (s, 9H, 3CH\textsubbox{3}-Si), 2.91 (d, J=5.0 Hz, 1H, CH\textsubbox{2}-O), 3.44 (d, J=5.0 Hz, 1H, CH\textsubbox{2}-O), 3.78 (s, 3H, OCH\textsubbox{3}), 6.17 (s, 1H, CH) \text{ ppm}; \( ^{13}\text{C} \) NMR: (CDCl\textsubbox{3}, 75 MHz) \delta (3CH\textsubbox{3}-Si), 50.16 (CH\textsubbox{2}-CN), 58.87 (OCH\textsubbox{3}), 59.46 (O-C-CH\textsubbox{2}), 73.70 (O-C-CN), 109.10 (CBr), 114.68 (CN), 119.27 (CBr), 129.01 (CH), 148.87 (C- OCH\textsubbox{3}) \text{ ppm}; \) MS (70
eV, El) m/z (%): 407/409/411 (5/10/5) [M⁺], 362/364/366 (11/22/11) [M-45], 352/354/356 (5/8/4) [M-55], 347/349/351 (3/7/4) [M-60], 337/339/341 (4/6/3) [M-70], 229/231 (18/18), 201/203 (7/7), 137/139 (5/5), 122 (5), 103 (6), 89 (8), 75 (34), 74 (10), 73 (100), 45 (30), 44 (5), 43 (10).

b) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.28 (s, 9H, 3CH₃-Si), 3.03 (d, J=5.0 Hz, 1H, CH₂-O), 3.42 (d, J=5.0 Hz, 1H, CH₂-O), 3.78 (s, 3H, OCH₃), 6.09 (s, 1H, CH) ppm; ¹³C-NMR: (CDCl₃, 75 MHz) δ (3CH₃-Si), 51.75 (CH₂-CN), 58.00 (O-C-CH₂), 58.87 (OCH₃), 74.28 (O-C-CN), 108.50 (CBr), 115.27 (CN), 118.93 (CBr), 128.72 (CH), 148.87 (C-OCH₃) ppm; MS (70 eV, EI) m/z (%): 407/409/411 (7/15/8) [M⁺], 363/365/367 (11/15/9) [M-44], 362/364/366 (39/78/40) [M-45], 352/354/356 (7/12/6) [M-55], 347/349/351 (6/13/8) [M-60], 229/231 (14/14), 201/203 (7/8), 137/139 (10/9), 103 (13), 89 (8), 75 (32), 73 (100), 59 (14), 47 (11), 45 (32), 43 (12).

5,7-Dibromo-6,8-dimethoxy-4-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (8). (a) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.14 (s, 9H, 3CH₃-Si), 3.09 (d, 1H, J=5.4 Hz, CH₂-O), 3.22 (d, 1H, J=5.4 Hz, CH₂-O), 3.61 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃) ppm. MS (70 eV, EI) m/z (%): 437/439/481 (20/40/21) [M⁺], 392/394/396 (10/18/11) [M-45], 377/379/381 (10/21/12) [M-60], 358/360 (47/47) [M-Br], 335/337/339 (12/20/12) [M-104], 259/261 (49/50) [M-Br-TMSCN], 231/233 (22/21), 75 (46), 73 (100), 59 (27), 45 (25), 43 (26).

(b) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.15 (s, 9H, 3CH₃-Si), 3.05 (d, 1H, J=5.6 Hz, CH₂-O), 3.22 (d, 1H, J=5.6 Hz, CH₂-O), 3.61 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃) ppm. MS (70 eV, EI) m/z (%): 437/439/481 (22/47/23) [M⁺], 392/394/396 (24/48/96) [M-45], 377/379/381 (17/34/16) [M-60], 358/360 (34/34) [M-Br], 335/337/339 (16/32/15) [M-104], 259/261 (52/50) [M-Br-TMSCN], 231/233 (21/19), 75 (28), 73 (100), 59 (28), 45 (32).

7-Bromo-4-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (9). (a) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.20 (s, 9H, 3CH₃-Si), 2.83 (d, 1H, J=4.9 Hz, CH₂-O), 3.28 (d, 1H, J=4.9 Hz, CH₂-O), 3.45 (d, 1H, J=4.9 Hz, CH₂-O), 5.70-5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm. MS (70 eV, EI) m/z (%): 254/256 (18/19) [M⁺], 244/246 (10/10) [M-55], 103 (17), 75 (20), 73 (100), 45 (66). (b) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.19 (s, 9H, 3CH₃-Si), 2.89 (d, 1H, J=5.0 Hz, CH₂-O), 3.25 (d, 1H, J=4.9 Hz, CH₂-O), 5.70-5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm. MS (70 eV, EI) m/z (%): 254/256 (79/81) [M⁺], 103 (25), 75 (26), 73 (100), 45 (32).

6-Methoxy-4-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (10). (a) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.02 (s, 9H, 3CH₃-Si), 2.94 (d, 1H, J=4.9 Hz, CH₂-O), 3.28 (d, 1H, J=4.9 Hz, CH₂-O), 5.70-5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm. MS (70 eV, EI) m/z (%): 254/256 (18/19) [M⁺], 244/246 (10/10) [M-55], 103 (17), 75 (20), 73 (100), 45 (66). (b) ¹H-NMR: (CDCl₃, 200 MHz) δ 0.18 (s, 9H, 3CH₃-Si), 2.93 (d, 1H, J=4.9 Hz, CH₂-O), 3.50 (d, 1H, J=4.9 Hz, CH₂-O), 4.81 (d, 1H, J=2.5 Hz, H-2), 5.55 (d, 1H, J=10.1 Hz, H-5), 6.08 (dd, 1H, J=10.1 Hz, J=2.5 Hz, H-4) ppm.

2-Trimethylsilanyloxy-7-oxa-bicyclo[4.1.0]heptane-2-carbonitrile (11f). (a) ¹H-NMR: (CDCl₃, 500 MHz) δ 0.30 (s, 9H, 3CH₃-Si), 1.40-2.10 (m, 6H, 3 CH₂), 3.38 (t, 1H, J=4.0 Hz, CH-O, H-6), 3.40 (d, 1H, J=4.0 Hz, CH-O, H-1) ppm; ¹³C-NMR: (CDCl₃, 50 MHz) δ 1.18 (3CH₃-Si), 18.82 (CH₂), 21.16 (CH₂), 32.03 (CH₂, C-3), 55.09 (CH), 56.71 (CH), 70.65 (C), 119.72 (CN).
ppm. b) $^1$H-NMR: (CDCl$_3$, 500 MHz) δ 0.32 (s, 9H, 3CH$_3$-Si), 1.40-2.10 (m, 6H, 3 CH$_2$), 3.20 (d, 1H, $J$=3.5 Hz, CH-O, H-1), 3.34 (t, 1H, $J$=3.5 Hz, CH-O, H-6) ppm.

2-Trimethylsilanloyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (11g). (a) $^1$H-NMR: (CDCl$_3$, 500 MHz) δ 0.29 (s, 9H, 3CH$_3$-Si), 1.75 (dd, 1H, $J$=11.7 Hz, $J$=8.5 Hz, H-4), 1.83 (dd, 1H, $J$=11.7 Hz, $J$=9.0 Hz, H-3), 2.12 (dd, 1H, $J$=13.3 Hz, H-3), 2.21 (dd, 1H, $J$=13.3 Hz, H-3), 3.56 (d, 1H, $J$=2.6 Hz, H-5), 3.66 (d, 1H, $J$=2.6 Hz, H-1) ppm; $^{13}$C-NMR: (CDCl$_3$, 50 MHz) δ (3CH$_3$-Si), 24.91 (CH$_2$, C-4), 32.62 (CH$_2$, C-3), 55.17 (CH), 59.64 (CH), 74.91 (C), 119.61 (CN) ppm; MS (70 eV, EI) m/z (%): 182 (49) [M-CH$_3$], 155 (34) [M-CH$_3$-HCN], 127 (81), 84 (28), 81 (33), 75 (55), 73 (100), 45 (44), 43 (22), 41 (75). b) $^1$H-NMR: (DMSO-d$_6$, 500 MHz) δ 0.22 (s, 9H, 3CH$_3$-Si), 1.50-2.10 (m, 4H, 2CH$_2$), 3.73 (d, 1H, $J$=2.5 Hz, H-5), 3.82 (d, 1H, $J$=2.5 Hz, H-1) ppm; MS (70 eV, EI) m/z (%): 182 (21) [M-CH$_3$], 155 (69) [M-CH$_3$-HCN], 126 (12), 113 (14), 101 (13), 84 (16), 81 (35), 75 (28), 73 (100), 47 (13), 45 (35), 43 (16).

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