A New, One-Pot Synthesis of Silylated Cyanohydrins

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Recently, cyanosilylation by cyanotrimethylsilane has been developed as a useful method for the protection of carbonyl groups\textsuperscript{1-7}. Silylated cyanohydrins have been found to be useful as acyl anion equivalents in many synthetic transformations\textsuperscript{1, 2, 8, 9, 10} and as reagents for the synthesis of $\alpha,\beta$-unsaturated nitriles\textsuperscript{11}, $\beta$-amino-alcohols\textsuperscript{12, 13-17}, $\Delta^2$-butenolides\textsuperscript{18}, and $\alpha$-hydroxyamides\textsuperscript{19}.

Cyanosilylation by thermal or catalyzed addition of a preformed trialkylsilyl cyanide to the corresponding aldehyde or ketone has a number of disadvantages: use of stoichiometric quantities of a rather expensive reagent\textsuperscript{1, 2, 10}, handling fairly large quantities of hydrogen cyanide gas\textsuperscript{1, 21, 22}, or distillation of the silyl cyanide, and relatively long time reactions.

A one-pot cyanosilylation procedure has been proposed\textsuperscript{23}. This method involves refluxing the carbonyl compound with solid potassium cyanide and chlorotrimethylsilane in either acetonitrile or dimethylformamide solvent and needs long reaction times. With acetonitrile, the use of a catalytic amount of zinc iodide increased the reaction rate, but, with enolizable carbonyl compounds, silyl enol ether formation has been observed. The use of dimethylformamide as solvent circumvents the silyl enol formation and increases reaction rates.
We have investigated another one-pot cyanosilylation procedure which presents the following advantages:
- standard conditions for any carbonyl compounds,
- short reaction times (a few hours),
- room temperature,
- no sily enol ether formation or formation of higher molecular weight materials.

This reaction is conveniently accomplished in two steps: the formation (without isolation) of trialkylsilyl cyanide from chlorotritylsilyl silylamine followed by the reaction with a carbonyl compound.

Our procedure is based on the particular reactivity of the in situ generated iodonitrismethylenesilane in the presence of a tertiary amine. We observed the quantitative and rapid formation of trimethylsilyl cyanide (1) by just mixing and rapidly stirring at room temperature during two hours an equimolecular mixture of chlorotrimethylsilane and potassium cyanide in acetonitrile as solvent in the presence of catalytic amounts of sodium iodide and pyridine.

\[
\text{NaI} + \text{CH}_3\text{CN} \rightarrow \text{KCN} \rightarrow \text{H}_3\text{C}-\text{Si}-\text{Cl} + \text{KCN} \rightarrow (\text{H}_3\text{C})_3\text{Si}-\text{CN} \quad \text{1}
\]

The addition of a carbonyl compound 2 to the above mixture led, after a very short time (Table), to the exclusive formation of the trimethylsilylcyanohydrin 3.

Further studies are in progress concerning the cyanosilylation of quinones to demonstrate the generality of our method. First results concerning \(p\)-benzoquinone have shown that cyanosilylation using two equivalents of trimethylsilyl cyanide afforded a mixture of three kinds of products: mono-adduct (21%), bis-adduct (63%); \(Z\) and \(E\) in equal amounts), and 1,4-bis(trimethylsiloxy)benzene (16%). Results concerning other quinones will be reported in due course.

Acetonitrile (Aldrich) is dried with molecular sieves. Potassium cyanide (Aldrich) is dried at 120°C/1 torr overnight. Chlorotrimethylsilane (Rhône-Poulenc) and carbonyl compounds 2 are distilled before use. Pyridine (Prolabo) is dried over potassium hydroxide pellets and distilled. Sodium iodide (Prolabo) is oven-dried at 120°C overnight.

**Silylated Cyanohydrins 3: General Procedure:**
In an Erlenmeyer flask, oven-dried prior to use, filled with an inert gas, and equipped with a magnetic bar, are placed sodium iodide (1 g) and acetonitrile (20 ml). After stirring for 5 min, potassium cyanide (2.6 g, 0.04 mol), chlorotrimethylsilane (4.34 g, 0.04 mol), and pyridine (0.8 g) are added. The progress of the reaction is followed by N.M.R. spectroscopy. When the reaction is complete (about 2 h), carbonyl compound 2 (0.036 mol) is added and stirring continued. On completion, pentane (30 ml) is added to the reaction mixture which is then poured into ice/water (100 ml), and extracted with pentane (3 x 25 ml). The organic extract is washed with saturated, cold aqueous sodium hydrogen sulfite solution, and dried with sodium sulfate. After concentrating the pentane layer, distillation affords the pure silylated cyanohydrins 3.

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**Table. Trimethylsilylcyanohydrins 3a–h**

<table>
<thead>
<tr>
<th>Product No.</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Reaction time</th>
<th>Yield</th>
<th>b.p. [°C]/torr</th>
<th>Molecular formula&lt;sup&gt;a&lt;/sup&gt; or b.p. [°C]/torr</th>
<th>I.R. (film) (v_{	ext{max}}) [cm&lt;sup&gt;−1&lt;/sup&gt;]</th>
<th>(\delta) [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>H</td>
<td>15 min</td>
<td>77 (100)</td>
<td>93°/25</td>
<td>C,H,N,SiOSi (185.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
<td>0.20 (s, 9 H); 0.96 (d, 6 H, (J=6) Hz); 1.4-2.1 (m, 3 H); 4.36 (t, 1 H, (J=6) Hz)</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>H</td>
<td>15 min</td>
<td>75 (100)</td>
<td>91°/0.5</td>
<td>250-254°/760&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>H</td>
<td>1.5 h</td>
<td>67 (100)</td>
<td>65°/50</td>
<td>40°/12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>C,H</td>
<td>3 h</td>
<td>75</td>
<td>108°/30</td>
<td>210-213°/760&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>C</td>
<td>6 h</td>
<td>70 (100)</td>
<td>90°/6</td>
<td>237-238°/760&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3f</td>
<td>C</td>
<td>C</td>
<td>1 h</td>
<td>70 (97)</td>
<td>79°/3</td>
<td>80.5°/12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3g</td>
<td>C</td>
<td>H</td>
<td>45 min</td>
<td>75 (98)</td>
<td>135°/1</td>
<td>C,H,N,SiOSi (231.4)</td>
<td>1655</td>
<td>0.20 (s, 9 H); 5.30 (d, 1 H, (J=6) Hz); 6.26 (dd, 1 H, (J=16) Hz); 8.66 (d, 1 H, (J=16) Hz); 7.40 (s, 5 H)</td>
</tr>
<tr>
<td>3h</td>
<td>H</td>
<td>C</td>
<td>2 h</td>
<td>50 (100)</td>
<td>87°/100</td>
<td>C,H,N,SiOSi (169.3)</td>
<td>1645</td>
<td>0.20 (s, 9 H); 1.56 (s, 3 H); 5.1-6.1 (m, 3 H)</td>
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</table>

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<sup>a</sup> Yield of pure (≥95%), distilled product, value in brackets determined by N.M.R. analysis.

<sup>b</sup> Satisfactory microanalyses obtained for 3a, 3g, and 3h: C ± 0.14, H ± 0.07, N ± 0.09, Si ± 0.06; physical and spectral data for 3b-f are consistent with the literature data.<sup>c</sup>

<sup>c</sup> M.S.: m/e (relative intensity %): 170 (M<sup>+</sup> - 15, 11); 143 (50); 128 (10); 114 (30); 101 (100); 84 (16); 75 (59); 73 (74); 69 (34); 59 (20).