A Simple One-Pot Synthesis of tert-Butyldimethylsilyl-Protected Cyanohydrins

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A direct conversion of a variety of aldehydes to the corresponding tert-butyldimethylsilyl protected cyanohydrins is described, by using tert-butyldimethylsilyl chloride and lithium cyanide.

Keywords—tert-butyldimethylsilyl chloride; lithium cyanide; tert-butyldimethylsilyl protected cyanohydrin; one-pot synthesis; non-aqueous cyanation; non-catalyzed cyanation

Trimethylsilyl (TMS) protected cyanohydrins, which are well known to be quite useful intermediates in organic synthesis, are in general prepared from aldehydes and ketones by thermal and catalyzed addition of TMS cyanide (TMSCN) or by reaction with TMSCl and potassium cyanide (KCN) in the presence of 18-crown-6 or Lewis acids such as ZnX2. In order to overcome the problem of the labile nature of the TMS group, Corey et al. prepared tert-butyldimethylsilyl (TBDMS)-protected cyanohydrins of ketones, which are stable during purification by column chromatography as well as hydrolysis (30% H2O2, K2CO3 in MeOH) of the CN group. TBDMS-protected cyanohydrins are usually prepared by treatment of a ketone or aldehyde with an excess of TBDMSCN in the presence of crown ether or ZnI2. However, the preparation and purification of TBDMScN is somewhat troublesome. In 1985, Cava and co-workers reported a simple high yielding procedure for the direct conversion of aldehydes to TBDMS protected cyanohydrins by using TBDMSCl (1.2 eq) and KCN (4 eq) in the presence of ZnI2 as a catalyst. Recently we reported a simple one-pot process for the high yielding conversion of a variety of carbonyl compounds into TMS protected cyanohydrins by using TMSCI and lithium cyanide (LiCN) without any catalyst. The greater reactivity of LiCN over sodium cyanide, KCN, and silver cyanide is due to its greater solubility in many organic solvents and the higher charge density of the lithium ion. As a continuation of our studies on the utilization of LiCN as a cyanation agent, we describe here another method for the synthesis of TBDMS protected cyanohydrins.

The reaction was performed simply by using two equivalents of TBDMSCI and three equivalents of LiCN at room temperature in dry tetrahydrofuran (THF), and the resulting crude product was purified by column chromatography on silica-gel. For comparison, when we ran this reaction with 1-phenylsulfonylpyrrole-2-carbaldehyde (1a), the TBDMS protected cyanohydrin (2a) was obtained in 98% yield, slightly higher than that (96% yield in 12 h) reported by Cava et al. A number of aldehydes, including aliphatic and aromatic or heteroaromatic aldehydes, were converted to TBDMS-protected cyanohydrins (2b–h) in excellent yields. The results are summarized in the table.

As mentioned by Cava et al., the ketones were considerably less reactive with TBDMSCI, KCN, and ZnI2, and gave the TBDMS enol ethers as by-products. Therefore, their method was limited to aldehydes. On the other hand, although ketones could not be converted satisfactorily to the desired silylated cyanohydrins, our procedure exceptionally led cyclo-
hexanone$^{11)}$ to the TBDMS-protected cyanohydrin (2h) in very good yield, though the reaction required a long time. Our reaction probably involves the initial formation of the lithium cyanoalkoxide and subsequent substitution of TBDMSCl.

We consider that our procedure is superior to the previous one,$^6)$ in that the use of a Lewis acid is unnecessary.

![Chemical structure](chart1)

**Table I. tert-Butyldimethylsilyl-Protected Cyanohydrins (2)**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Reaction time (h)</th>
<th>Yield$^a$ (%)</th>
<th>$^1$H-NMR ($\delta$ in CDCl$_3$ from TMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a$^{11)}$</td>
<td>6</td>
<td>97</td>
<td>0.08 and 0.15 (each 3H, each s, 2 × CH$_3$), 0.89 [9H, s, C(CH$_3$)$_3$], 6.03 (1H, s, CHCN), 6.33 (1H, t, $J$ = 3.3 Hz, 4-H on pyrrole ring), 6.64 (1H, m, 3-H on pyrrole ring), 7.25 (1H, m, 5-H on pyrrole ring), 7.5—7.8 (5H, m, Ar-H)</td>
</tr>
<tr>
<td>2b$^{11)}$</td>
<td>1</td>
<td>91</td>
<td>0.15 and 0.23 (each 3H, each s, 2 × CH$_3$), 0.94 [9H, s, C(CH$_3$)$_3$], 5.52 (1H, s, CHCN), 7.35—7.50 (5H, m, Ar-H)</td>
</tr>
<tr>
<td>2c$^{11)}$</td>
<td>1</td>
<td>98</td>
<td>0.12 and 0.20 (each 3H, each s, 2 × CH$_3$), 0.92 [9H, s, C(CH$_3$)$_3$], 5.38 (1H, s, CHCN), 5.98 (2H, s, OCH$_3$O), 6.79 (1H, d, $J$ = 8 Hz, 6-H), 6.87—6.95 (2H, m, Ar-H)</td>
</tr>
<tr>
<td>2d</td>
<td>1</td>
<td>88</td>
<td>0.21 and 0.29 (each 3H, each s, 2 × CH$_3$), 0.97 [9H, s, C(CH$_3$)$_3$], 5.62 (1H, s, CHCN), 7.6—7.9 (2H, m, 5- and 6-H), 8.2—8.4 (2H, m, 2- and 4-H)</td>
</tr>
<tr>
<td>2e</td>
<td>0.5</td>
<td>82</td>
<td>0.18 and 0.27 (each 3H, each s, 2 × CH$_3$), 0.97 [9H, s, C(CH$_3$)$_3$], 5.62 (1H, s, CHCN), 7.3—7.9 (3H, m, Ar-H), 8.60 (1H, m, 6-H)</td>
</tr>
<tr>
<td>2f</td>
<td>48</td>
<td>78</td>
<td>0.12 and 0.20 (each 3H, each s, 2 × CH$_3$), 0.89 [9H, s, C(CH$_3$)$_3$], 2.32 (3H, s, Ar-CH$_3$), 5.71 (1H, s, CHCN), 7.2—8.0 (9H, m, Ar-H)</td>
</tr>
<tr>
<td>2g</td>
<td>7</td>
<td>80</td>
<td>0.12 and 0.18 (each 3H, each s, 2 × CH$_3$), 0.92 [9H, s, C(CH$_3$)$_3$], 1.0—1.9 (11H, m, cyclohexyl-H), 4.17 (1H, d, $J$ = 5.9 Hz, CHCN)</td>
</tr>
<tr>
<td>2h</td>
<td>70</td>
<td>100</td>
<td>0.23 (6H, s, 2 × CH$_3$), 0.90 [9H, s, C(CH$_3$)$_3$], 1.3—2.1 (10H, m, cyclohexyl-H)</td>
</tr>
</tbody>
</table>

*a) Yields are based on isolation of chromatographically purified products. b) The $^1$H-NMR spectrum was identical with that reported by Cava et al.$^{11}$

**Chart 1**
The proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian XL-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi M-80 spectrometer.

**General Procedure for the Preparation of tert-Butyldimethylsilyl-Protected Cyanohydrins (2a–h)**—LiCN (297 mg, 9 mmol) was added to a magnetically stirred solution of a carbonyl compound (3 mmol) and TBDMSCl (904 mg, 6 mmol) in dry THF (10 ml) at room temperature under a stream of nitrogen. The reaction was monitored by thin layer chromatography (TLC) [silica-gel (Merck Art 5715), benzene]. After the starting material had been consumed, the THF was evaporated off. The residue was partitioned between water (10 ml) and benzene–EtOAc (1:1) (50 ml). The organic layer was separated, washed with water (2 x 10 ml), and dried with Na2SO4. After concentration of the organic layer, the residue was chromatographed on a silica-gel (Merck Art 7734) column, with benzene as the eluent.

- **[(tert-Butyldimethylsilypoxy]-1-phenylsulfonyl-2-pyrroloacetonitrile (2a):** A colorless oil. MS m/z: 376 (M+).
- **[(tert-Butyldimethylsilypoxy]-phenylacetonitrile (2b):** A colorless oil. MS m/z: 247 (M+).
- **[(tert-Butyldimethylsilypoxy]-3,4-methylenedioxyphenylacetonitrile (2c):** A colorless oil. MS m/z: 259 (M+).
- **[(tert-Butyldimethylsilypoxy]-3-nitro-1-phenylacetonitrile (2d):** A colorless oil, Rf 0.54. High resolution MS (HRMS) Calcd for C14H20N2O3Si: 292.124. Found: 292.124.
- **[(tert-Butyldimethylsilypoxy]-1-p-toluenesulfonyl-3-indolylacetonitrile (2f):** A colorless oil, Rf 0.61. HRMS Calcd for C23H28N2O3SSi: 440.159. Found: 440.159.
- **[(tert-Butyldimethylsilypoxy]cyclohexylacetonitrile (2g):** A colorless oil, Rf 0.81. HRMS Calcd for C14H27NOSi: 253.186. Found: 253.186.
- **[(tert-Butyldimethylsilypoxy]-1-cyanocyclohexane (2h):** A colorless oil, Rf 0.78. HRMS Calcd for C13H25NOSi: 239.170. Found: 239.170.

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**References and Notes**

11) According to the method of Cava *et al.*, **2h** was obtained in only 8% yield.