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# The Diastereoselective Preparation of *syn*-β-Hydroxycyanohydrins by Addition of Cyanide to β-Hydroxyketones with Dimethyldicyanosilane

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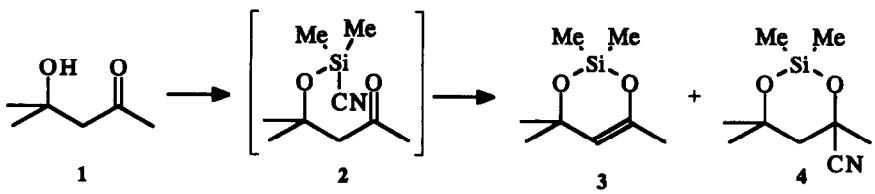
*Dedicated to Prof. Ernest L. Eliel on the occasion of his 70th birthday*

***Abstract:*** The addition of cyanide with $Me_2Si(CN)_2$ to β-hydroxyketones ($R^1CHOH\text{-}COR^2$, $R^1 = R^2$ = alkyl) took place with high diastereoselectivity (>95% d.e.) and reasonable overall isolated yield (60%). The *syn* configuration of the produced β-hydroxycyanohydrin seems compatible only with *intermolecular* addition of CN, through a chair-like six-membered transition state.

The stereoselective synthesis of 1,3-diols has attracted much attention in recent years because of their importance as building blocks in the preparation of many natural products. The addition of cyanide to β-hydroxyketones yields β-hydroxycyanohydrins,[2] an appealing class of 1,3-diols whose additional nitrile function may provide an entry to a number of new useful synthetic intermediates.

Dimethyldicyanosilane (DMCS) has been used for the cyanosilylation of β-diketones,[3] in which concurrent silylation and cyanosilylation of the two carbonyl groups of β-diketones occur. Diacetone alcohol was also reported[3] to react with DMCS to give the six-membered silicon derivatives 3 and 4 (Scheme I), the latter in very low yield (7%).



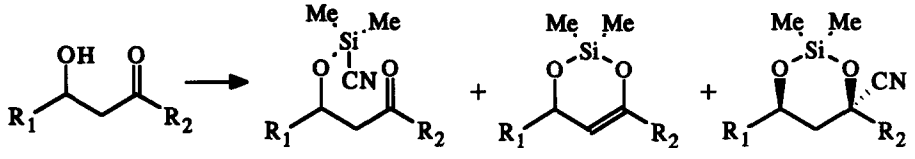

1 2 3 4

*Scheme I*

The structure of the starting β-hydroxyketone **1** did not allow the authors to determine the stereochemistry of the addition which was nevertheless claimed[3] to proceed by an intramolecular mechanism from the intermediate **2**, isolated under special conditions.

Analogously to what happened in the reduction of β-hydroxyketones (*vide infra*; *cf.* Scheme II), such intramolecular addition might lead to *anti* products and, therefore, our search for a diastereoselective synthesis of *anti* β-hydroxycyanohydrins[2] made us try this reaction. However, we here report that cyanide addition to β-hydroxyketones with DMCS yielded, after acid hydrolysis, the corresponding *syn* β-hydroxycyanohydrins in very high d.e. (>95%) and good chemical isolated yield (60%). The *syn* configuration of the final product seems incompatible with an intramolecular addition mechanism. Table 1 summarizes our results.

*Table 1.- Reaction of β-hydroxyketones ($R^1$ = i-Pr, $R^2$ = i-Pr, t-Bu) with dimethylcyanosilane.*

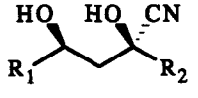



**5** **6** **7**

| Entry | Temp.(°C) | Catalyst[a] | Products (ratio) | Final cyanohydrin[b] (yield)[c] |
|---|---|---|---|---|
| 1 | -78 | none | **5** + **6** (20:70) | - |
| 2 | 0 | none | **6** + **7** (40:60) | *syn* (40%) |
| 3 | 0 | 18-crown-6 | **6** + **7** (30:70) | *syn* (50%) |
| 4 | 0 | $ZnI_2$ | **6** + **7** (20:80) | *syn* (60%) |

[a] Solvents: entry 1, $CH_2Cl_2$; entries 2-4, MeCN. [b] After cleavage with HF/MeCN. [c] Isolated.

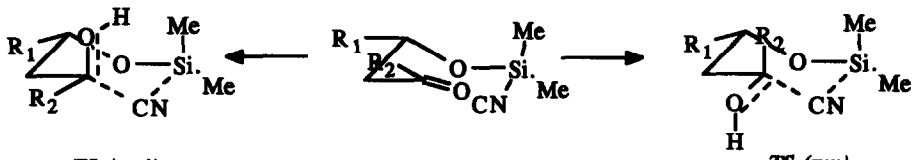
The determination of the configuration of the final cyanohydrin was performed by 2D-nmr by the method described elsewhere.[2] The first attempt at cyanosilylation with DMCS was discouraging. It was carried out at -78°C for 30 min, followed by stirring at room temperature for another 30 min and afforded products **5** and **6** in *ca.* 20 and 70% yield, respectively. Their structure was confirmed by $^1$H- and $^{13}$C-nmr and they gave, on hydrolysis with concentrated HCl, the corresponding β-chloroketone. To further investigate the role of temperature or a catalyst, we repeated the reaction at 0°C in the presence of 18-crown-6 or $ZnI_2$.[4] In these cases (entries 2-4; *cf.* Table 1) we obtained almost exclusively products **6** and **7** in varying ratios. Product **7**, the major component in all these cases, showed a CN signal in the $^{13}$C-nmr and did not exhibit C=O absorption in ir. Its $^1$H-nmr spectrum was very similar to that of *syn* β-hydroxycyanohydrin **8**, except for two methyl signals at *ca.* 0.1 ppm.




**8**

In fact, **7** gave **8** on desilylation with HF/MeCN.[5] We carefully reinvestigated the initial reaction mixture looking for *anti* products but they were not detected. Therefore, the addition of cyanide with DMCS resulted highly diastereoselective yielding the *syn* β-hydroxycyanohydrin in *ca.* 60% overall isolated yield in the presence of $ZnI_2$.[6,7]

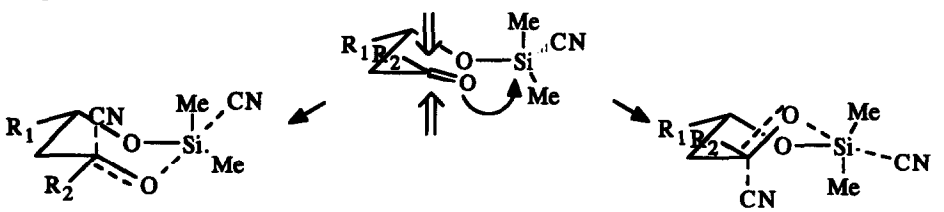
Detection of product **2** (Scheme I) suggested to the original authors[3] that the cyanide addition could take place intramolecularly. In analogy to the proposed reduction mechanism of β-hydroxyketones with $Me_4NHB(OAc)_3$,[8] Scheme II depicts the two possible transition states (TS) for the intramolecular scission of CN.




*Scheme II*

It may be seen that the TS leading to the *syn* isomer should be quite unfavorable since $R^2$ occupies a pseudoaxial arrangement. The intramolecular addition of CN should be thus ruled out in favour of an intermolecular mechanism.

The reaction does not seem to be thermodynamically controlled because the corresponding *anti* isomer of **8**, prepared in our laboratory by a different route,[2] did not form **7** under the same reaction conditions.[6] If the reaction is then kinetically controlled, the formation of the six-membered silicon ring might be simultaneous to the CN addition to carbonyl and, therefore, the *syn* product may be obtained through the chair-like transition state TS1 (Scheme III), which should be favored compared to the boat-like TS2 leading to *anti* isomer.




*Scheme III*

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***References and Notes***

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4. The role of 18-crown-6 in this reaction is still unknown. For $ZnI_2$ see Evans, D.A.; Carroll, G.L.; Truesdale, L.K. *J. Org. Chem.* **1974**, *39*, 914.

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6. Typical procedure (reaction with $ZnI_2$): Sodium iodide (100 mg) in 10 ml of dry acetonitrile was placed in an oven-dried flask under Ar atmosphere. After stirring for 5 minutes at room temperature, KCN (260 mg, 4 mmol), freshly distilled dimethyldichlorosilane (258 mg, 2 mmol) and pyridine (80 mg) were added. The reaction mixture was stirred at room temperature for 3 to 4 h and then cooled to $0^0$C. Zinc iodide (638 mg, 2 mmol) and a solution of β-hydroxyketone (2 mmol) in 2 ml of acetonitrile were slowly added. The reaction mixture was stirred at $0^0$C and its progress was monitored by tlc. After completion of the reaction (*ca.* 2 h), the mixture was poured into cold water (30 ml) and extracted with pentane (2x25 ml). The organic layer was washed with water, dried with sodium sulfate and the solvent evaporated. Flash chromatography (hexane/ethyl acetate 5:1) of the residue yielded products **6** and **7** separately. $^1$H-nmr **6** ($R^1$ = *i*-Pr; $R^2$ = *t*-Bu) ($CDCl_3$) δ 4.50 (d, J=2.8 Hz, 1H), 4.15 (dd, J=2.8, 4.8 Hz, 1H), 1.70 (m, 1H), 1.03 (s, 9H), 0.91 (d, J=6.8 Hz, 6H), 0.27 (s, 3H), 0.14 (s, 3H). $^1$H-nmr **7** ($R^1$ = *i*-Pr; $R^2$ = *t*-Bu) ($CDCl_3$) δ 4.06 (m, 1H), 1.80 (dd, J=2.1, 12.9 Hz, 1H), 1.70 (dd, J=8.5, 12.9 Hz, 1H), 1.62 (m, 1H), 1.02 (s, 9H), 0.88 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.16 (s, 3H), 0.06 (s, 3H). $^{13}$C-nmr **7** ($R^1$ = *i*-Pr; $R^2$ = *t*-Bu) ($CDCl_3$) δ 120.3 (CN), 79.9 (CCN), 74.6 (CHOH), 35.8 ($CH_2$), 34.2 ($CHMe_2$), 24.3 ($CMe_3$), 18.1 (MeCH), 17.1 (MeCH), -0.20 (MeSi), -1.50 (MeSi). To product **7** (1 mmol) in 5 ml of acetonitrile was added 1 ml of 40% aqueous HF. The reaction mixture was allowed to stand at room temperature for 30 min, then poured into 20 ml of water and extracted with dichloromethane (2x25 ml). The combined extracts were washed with water, dried and the solvent evaporated to afford *ca.* 60% of *syn* β-hydroxycyanohydrin after flash chromatography (hexane/ethyl acetate 5:1).

7. The method used for the *in situ* preparation of dimethyldicyanosilane (see footnote 6) is similar to that reported for trimethylsilyl cyanide by Duboudin, F.; Cazaeu, P.; Moulines, F.; Laporte, O *Synthesis*, **1982**, 212.

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