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A CONVENIENT SYNTHESIS OF t-BUTYLDIMETHYLSILYL PROTECTED CYANOHYDRINS

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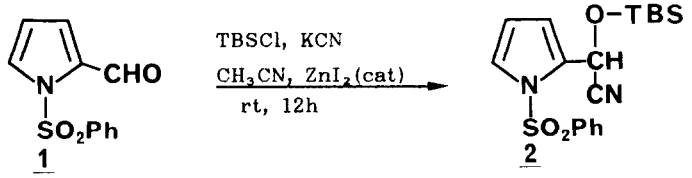
Summary: A simple high yielding procedure is described for the direct conversion of aldehydes to t-butyldimethylsilyl (TBS) protected cyanohydrins using TBSCl, KCN and ZnI_2.

Trimethylsilyl (TMS) protected cyanohydrins, well known to be useful as acyl anion equivalents, protected carbonyls, and for chain homologation[2], are typically prepared in high yield by either thermal or Lewis acid catalyzed addition of TMSCN across the carbonyl group. The labile nature of the TMS group, however, necessitates purification by direct distillation, and precludes the use of a number of reagents.[3] To overcome these shortcomings, Corey et al. prepared the chromatographically stable t-butyldimethylsilyl (TBS) protected cyanhydrin of a ketone using an excess of TBSCN, in the presence of a crown ether.[4] Their subsequent hydrolysis of the nitrile to the amide (30% H_2O_2, K_2CO_3, MeOH) left the TBS group intact,[4] nicely demonstrating both the remarkable stability of the TBS group in general, and the synthetic utility of TBS protected cyanohydrins. More recently a report described the TBSCN mediated conversion of an aldehyde to the corresponding silylated cyanohydrin.[5] Herein, we report a convenient preparation of the synthetically useful TBS protected cyanohydrins directly from the aldehyde and TBSCl.[6]

In connection with our work on the antitumor agent CC-1065, we required a stable, cyanohydrin-type of Umpolung synthon of pyrrole-2-carboxaldehyde. To avoid the tedious preparation and purification of TBSCN,[3,4,7] we reacted aldehyde **1**[8] directly with TBSCl (1.2 eq) and KCN (4 eq) in acetonitrile containing a catalytic amount of ZnI_2.[9]



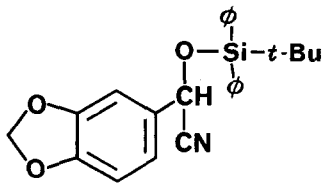
1 **2**

The reaction was remarkably clean and proceeded at room temperature (ca. 12 h) to afford after

chromatography, in excellent yield (96%), the TBS protected cyanohydrin 2. A number of aldehydes were similarly converted to the TBS protected cyanohydrins (see Table)[10]. Ketones, on the other hand, were considerably less reactive under these conditions, and gave a mixture of the expected cyanohydrin and the TBS protected enol ether; hence, they were not investigated further.

While examining the various reaction parameters, we found that Lewis acid (ZnI_2) catalysis was essential for a reasonable reaction rate, as was the need for excess KCN (4 eq.). Indeed, with 10 equivalents of KCN the reaction went to completion in only 4 h. A comparable increase in the rate of the reaction was obtained by heating (70° C) the reaction mixture. Whereas the use of crown ether (dicyclohexyl-18-crown-6) gave a moderate increase in the reaction rate (6 h), phase transfer catalyst (cetyltrimethylammonium bromide) appeared to have no effect on the reaction.

It is noteworthy that the general procedure (see experimental) works equally well for the preparation of cyanohydrins protected with even more sterically hindered silanes. Thus piperonal can be converted directly and in excellent yield (> 90%) to the t-butyldiphenylsilyl (3) and the triisopropylsilyl (4) protected cyanohydrins using t-butyldiphenylsilyl chloride and triisopropylsilyl chloride, respectively.



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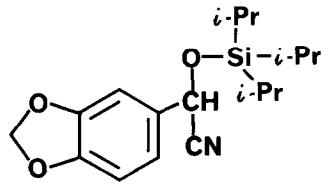

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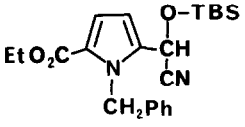
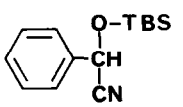
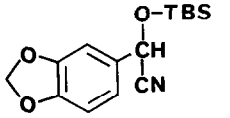
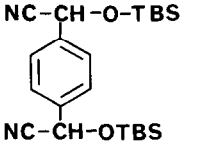
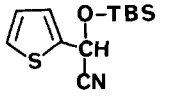
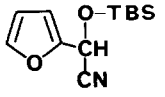
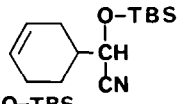
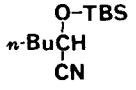
In conclusion, the simple procedure described here allows the preparation of various sterically hindered silylated cyanohydrins directly from readily available silyl chlorides,[11] obviating the need for first preparing the corresponding difficultly available silyl cyanides.

General Procedure

To a flame-dried flask, maintained under a positive pressure of argon (balloon), was added successively the aldehyde (5.0 mmol), CH_3CN (25 ml), KCN (1.30 g, 20.0 mmol), ZnI_2 (25 mg), and TBSCl (0.90 g, 6.0 mmol). The mixture was stirred vigorously, and the progress of the reaction, monitored by TLC (silica; CH_2Cl_2: hexanes, 1:1). Upon disappearance of the starting material (10-20 h), the solvent was removed *in vacuo*, and the residue resuspended in Et_2O (50 ml). Salts were removed by filtration and rinsed thoroughly with Et_2O (ca. 25 ml). The filtrate was washed with water (25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a pale yellow oil which was purified by flash chromatography (silica gel; CH_2Cl_2: hexanes, 1:1) to afford the product as a clear oil which was homogeneous by TLC and NMR.

Table: Conversion of Aldehydes to TBS Protected Cyanohydrins[a]

Entry	Product	Yield[b]	NMR Data[c]
1.	**2**	96%	0.08 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 6.03 (s, 1H), 6.33 (t, J=3.4Hz, 1H), 6.64-6.66 (m, 1H), 7.25-7.27 (m, 1H), 7.49-7.81 (m, 5H).
2.		94%	0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.28 (t, J=7.1, 3H), 4.21 (q, J=7.1Hz, 2H), 5.43 (s, 1H), 5.64 (d, J=16.6Hz, 1H), 5.88 (d, J=16.6Hz 1H), 6.45 (d, J=4.0Hz, 1H), 6.87-6.90 (m, 2H), 7.02 (d, J=4.0Hz, 1H), 7.21-7.33 (m, 3H).
3.		98%	0.15 (s, 3H), 0.23 (s, 3H), 0.94 (s, 9H), 5.52 (s, 1H), 7.39-7.48 (m, 5H).
4.		95%	0.12 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 5.38 (s, 1H), 5.98 (s, 2H), 6.79 (d, J=8.0Hz, 1H), 6.87-6.94 (m, 2H).
5.		94%	0.15 (s, 6H), 0.23 (s, 6H), 0.93 (s, 18H), 5.53 (s, 2H), 7.50 (s, 4H).
6.		91%	0.17 (s, 3H), 0.22 (s, 3H), 0.94 (s, 9H), 5.74 (s, 1H), 6.98-7.01 (m, 1H), 7.16-7.18 (m, 1H), 7.35-7.37 (m, 1H).
7.		95%	0.14 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 5.55 (s, 1H), 6.40 (dd, J=1.8, 3.3Hz, 1H), 6.52 (dd, J=0.7, 3.3Hz, 1H), 7.45 (dd, J=0.7, 1.8 Hz, 1H).
8.		94%	0.12(s, 3H), 0.20 (s, 3H), 0.90 (s, 9H), 1.44 (m, 1H), 1.85-2.22 (m, 6H), 4.28 (d, J=5.7Hz, 1H), 5.66 (m, 2H)
9.		86%	0.12 (s, 3H), 0.17 (s, 3H), 0.90 (m, 12H), 1.3-1.47 (m, 4H), 1.72-1.81 (m, 2H), 4.40 (t, J=6.4Hz, 1H).

[a]All reactions were run on 5 mmol scale. A detailed procedure is given (vide supra).

[b]Yields are based on isolation of chromatographically purified products for which satisfactory spectral data (250 MHz NMR, MS) was obtained.

[c]NMRs were run in $CDCl_3$ and are reported in δ values (Me_4Si = 0.00).

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References and Notes

1. Present address: Department of Chemistry, University of Alabama, University (Tuscaloosa), AL 35486.

2. For reviews on the synthesis and reactions of TMS protected cyanohydrins, see *inter alia*:
   a) Weber, W.P. Silicon Reagents for Organic Synthesis, Springer-Verlag, New York, 1983, Chapt. 2.
   b) Colvin, E.W. Silicon in Organic Synthesis, Butterworths, Boston, 1981, p. 296-299.
   c) Groutas, W.C.; Felker, D. Synthesis 1980, 861.

3. For a discussion of the relative stability of various silyl protecting groups, see ref. 2b. See also: Green, T.W., Protecting Groups in Organic Synthesis, Wiley, 1981, Chapter 2.

4. Corey, E.J.; Crouse, D.N.; Anderson, J.E. J. Org. Chem. 1975, 40, 2140.

5. Baker, D.C.; Putt, S.R.; Showalter, H.D.H. J. Heterocyclic Chem. 1983, 20, 629.

6. The Umpolung reactivity of such cyanohydrins has been demonstrated. See: Narula, A.S.; Sethi, S.P. Tetrahedron Lett. 1984, 25, 685.

7. Hwu, J.R.; Lazar, J.G.; Corless, P.F. Synthesis 1984, 1020.

8. Prepared in 96% yield from pyrrole-2-carboxaldehyde [(NaH (1.25 eq), DMF, rt; then, $PhSO_2Cl$)]. For an alternate preparation, see: Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. J. Org. Chem. 1983, 48, 3214.

9. This is a modification of Rasmussen and Heilmann's excellent procedure for the preparation of TMS protected cyanohydrins. Rasmussen, J.K.; Heilmann, S.M. Synthesis, 1978, 219.

10. Under these conditions cinnamaldehyde gave in quantitative yield a 2:1 mixture (by NMR) of the expected silylated cyanohydrin and the 1, 4-addition product. This result suggests that the reaction involves, at least in part, the direct addition of the cyanide to the aldehyde substrate followed by trapping with the silyl chloride. See Ref. 9.

11. All silyl chlorides were purchased from Petrarch Systems, Inc., Bartram Rd., Bristol, PA 19007.

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