A Simple One-Pot Synthesis of Silylated and Acylated Cyanohydrins

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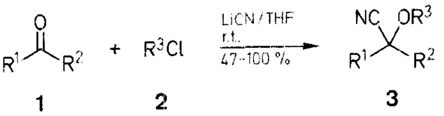
Reaction of variety of aldehydes and ketones with chlorotrimethylsilane and acyl chlorides in the presence of lithium cyanide to give trimethylsilylcyanohydrins and acylcyanohydrins is described.

Thermal and catalyzed addition of trialkylsilyl cyanide to aldehydes and ketones is a general method for the preparation of silylated cyanohydrins, which are known to be quite useful intermediates in organic synthesis[1]. Since this cyanosilylation reaction has a variety of disadvantages, modified one-pot cyanosilylation procedures have been reported[1,2]. 2-Acyloxyalkanenitriles or 2-acyloxyalkenenitriles have been prepared by silylcyanation of the starting carbonyl compounds followed by acylation with iron(III) chloride catalysis[3], acylation of cyanohydrins under aqueous or nonaqueous conditions, and one-pot reaction of the carbonyl compounds with potassium cyanide in the presence of 18-crown-6[4]. These are useful precursors for the preparation of diene nitriles[5], furans[6], and 4-amino-2(5H)-furanones[7].

We now report a simple one-pot process for the conversion of aldehydes and ketones, including α,β-unsaturated aldehydes and ketones, into trimethylsilyl cyanohydrins and acyl cyanohydrins (**3**) by treatment of the carbonyl compounds **1** with trimethylsilyl chloride (**2a**) or acyl chlorides (**2b, c**) in the presence of lithium cyanide[8].



1 **2** **3**

1	R^1	R^2
a	C_6H_5	H
b	$3\text{-}NO_2C_6H_4$	H
c	$4\text{-}ClC_6H_4$	H
d	$4\text{-}CH_3OC_6H_4$	H
e	$4\text{-}C_6H_5C_6H_4$	H
f	*trans*-$C_6H_5CH=CH$	H
g	$-(CH_2)_5-$	
h	*trans*-$C_6H_5CH=CH$	CH_3
i	*c*-C_6H_{11}	H
j	C_6H_5	CH_3

2	R^3
a	$Si(CH_3)_3$
b	C_6H_5CO
c	CH_3CO

The scope of the new silyl- and acylcyanation procedures is shown in the Table. The reaction is performed in general by using two equivalents of R^3Cl and three equivalents of lithium cyanide at room temperature in tetrahydrofuran. These reactions are believed to proceed by the initial formation of lithium cyanoalkoxide followed by displacement with trimethylsilyl chloride or acyl chlorides to produce the silylated and acylated cyanohydrins. As is shown in the Table, aromatic (run 1) and aliphatic (run 18) aldehydes as well as aliphatic (run 14) and α,β-unsaturated (run 16) ketones react with trimethylsilyl chloride/lithium cyanide to afford the silylated cyanohydrins in excellent yield. Application of our procedure to acetophenone (run 20) produces the cyanosilylated product in almost quantitative yield by using a slight excess of lithium cyanide (4 equiv.). The aldehydes (run 2, 4, 6, 8 and 13) are converted into cyanohydrin benzoates in good yield, while lower yields are obtained in the preparation of cyanohydrin acetates. α-Tetralone[9] and benzophenone[10] failed to give any cyanohydrin derivatives, unfortunately.

In summary, a variety of carbonyl compounds undergo cyanosilylation and cyanoacylation by this procedure, using inexpensive lithium cyanide and without costly catalysts.

Silylated Cyanohydrins; General Procedure:
Lithium cyanide (495 mg, 15 mmol) is added to a magnetically stirred solution of the carbonyl compound (5 mmol) and trimethylsilyl chloride (1.09 g, 10 mmol) in dry tetrahydrofuran (10 ml) at room temperature. The reaction is monitored by ^{1}H-NMR spectroscopy. After the starting material has been consumed (~ 2 h), the tetrahydrofuran is evaporated. The residue is distilled using a Kugelrohr apparatus, giving the pure silylated cyanohydrins. [In the case of acetophenone, 20 mmol of lithium cyanide is used.]

4-Phenyl-2-methyl-2-trimethylsiloxy-3-butenenitrile (3ha):

$C_{14}H_{19}NOSi$	calc.	C 68.52	H 7.80	N 5.70
(245.4)	found	68.30	7.91	5.65

IR (neat): $\nu = 840, 1250\ [Si(CH_3)_3]\ cm^{-1}$.

^{1}H-NMR ($CDCl_3/TMS_{int}$): $\delta = 0.24$ [s, 9H, $Si(CH_3)_3$]; 1.75 (s, 3H, CH_3); 6.13 (d, 1H, $J = 16$ Hz, $C_6H_5CH=C\underline{H}$); 6.88 (d, 1H, $J = 16$ Hz, $C_6H_5C\underline{H}=CH$); 7.25–7.43 ppm (m, 5H, C_6H_5).

Acylated Cyanohydrins; General Procedure:
Lithium cyanide (495 mg, 15 mmol) is added to a magnetically stirred solution of the carbonyl compound (5 mmol) and acyl chloride (10 mmol) in dry tetrahydrofuran (10 ml) at room temperature. The reaction is monitored by TLC [silica gel (Merck Art 5715), using *n*-hexane/acetone, 5:1, as eluent]. After the starting material has been completely consumed, the tetrahydrofuran is evaporated. The residue is dissolved in water (10 ml) and benzene (50 ml). The organic layer is separated, washed with water (2 × 10 ml) and dried over sodium sulfate. After concentrating the benzene layer, the residue is purified by column chromatography [silica gel (Merck Art 7734, 60 g) using *n*-hexane/acetone, 5:1, as eluent]).

α-Benzoyloxy-α-(4-biphenylyl)acetonitrile (3eb):

$C_{21}H_{15}NO_2$	calc.	C 80.49	H 4.83	N 4.47
(313.3)	found	80.48	4.89	4.31

IR (KBr): $\nu = 1725\ (C=O)\ cm^{-1}$.

^{1}H-NMR ($CDCl_3/TMS_{int}$): $\delta = 6.72$ (s, 1H, CHCN); 7.39–8.10 ppm (m, 14 H_{arom}).

α-Acetoxy-α-(4-biphenylyl)acetonitrile (3ec):

$C_{16}H_{13}NO_2$	calc.	C 76.47	H 5.22	N 5.57
(251.3)	found	76.27	5.25	5.62

IR (KBr): $\nu = 1740\ (C=O)\ cm^{-1}$.

^{1}H-NMR ($CDCl_3/TMS_{int}$): $\delta = 2.19$ (s, 3H, CH_3); 6.46 (s, 1H CHCN); 7.39–7.68 ppm (m, 9 H_{arom}).

Table. Conversion of Aldehydes and Ketones into Silylated and Acylated Cyanohydrins

Run	Starting Material		Reaction Time	Product[a]	Yield [%]	m.p. [°C] or b.p. [°C]/torr	
	1	2				found	reported
1	**a**	**a**	1 h	**3aa**	94	81–83/1	93–95/1.75[1]
2	**a**	**b**	1 h	**3ab**	87	55–56	58[11]
3	**a**	**c**	48 h	**3ac**	70	95–98/1	137–138/11[12]
4	**b**	**b**	10 min	**3bb**	100	97–99	99.5–101[13]
5	**b**	**c**	1 h	**3bc**	87	75–77	75–76[14]
6	**c**	**b**	30 min	**3cb**	100	54–55	57–58[15]
7	**c**	**c**	5 h	**3cc**	83	114–115/1	104–107/0.5[14]
8	**d**	**b**	4 h	**3db**	80	60–63	66–67[15]
9	**d**	**c**	4 h	**3dc**	47	112/1	165/6[16]
10	**e**	**b**	30 min	**3eb**[b]	100	108–109	–
11	**e**	**c**	48 h	**3ec**[b]	64	100–102	–
12	**f**	**a**	1 h	**3fa**	94	125/1	135/1[2]
13	**f**	**b**	11 h	**3fb**	81	64–65	66–67[17]
14	**g**	**a**	1 h	**3ga**	92	92/1	96/1.5[1]
15	**g**	**b**	6 h	**3gb**	71	74	76[11]
16	**h**	**a**	2 h	**3ha**[b]	93	115–117/2	–
17	**h**	**b**	4 h	**3hb**[b]	65	90–92	–
18	**i**	**a**	30 min	**3ia**	85	108/4	106–108/6.5[1]
19	**i**	**b**	30 min	**3ib**[b]	100	93–95	–
20	**j**	**a**	6 h	**3ja**	97	71–73/1	73–75/0.9[1]

[a] Fully characterized by IR and ^{1}H-NMR spectra.

[b] See experimental for microanalytical and spectral data.

2-Benzoyloxy-2-methyl-4-phenyl-3-butenenitrile (3hb):

$C_{18}H_{15}NO_2$	calc.	C 77.96	H 5.45	N 5.05
(277.3)	found	78.09	5.50	5.17

IR (KBr): $\nu = 1725$ (C=O) cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS$_{int}$): $\delta = 2.06$ (s, 3H, CH$_3$); 6.31 (d, 1H, $J = 15.6$ Hz, C$_6$H$_5$CH=C$\underline{H}$); 7.11 (d, 1H, $J = 15.6$ Hz, C$_6$H$_5$C$\underline{H}$=CH); 7.32–8.05 ppm (m, 10H$_{arom}$).

α-Benzoyloxycyclohexylacetonitrile (3ib):

$C_{15}H_{17}NO_2$	calc.	C 74.05	H 7.04	N 5.76
(243.3)	found	74.14	7.00	5.84

IR (KBr): $\nu = 1720$ (C=O) cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS$_{int}$): $\delta = 1.22$–2.02 (m, 11H, CH$_2$ and CH); 5.45 (d, 1H, $J = 5.9$ Hz, CHCN); 7.45–8.07 ppm (m, 5H$_{arom}$).

Received: March 3, 1986
(Revised form: May 26, 1986)

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[1] Rasumussen, J.K., Heilmann, S.M. *Org. Synth.* **1984**, *62*, 196, and references cited, therein.

[2] Duboudin, F., Cazeau, Ph., Moulines, F., Laporte, O. *Synthesis* **1982**, 212.

[3] Ganem, B., Small, V.R. Jr. *J. Org. Chem.* **1974**, *39*, 3728.

[4] Chenevert, R., Plante, R., Voyer, N. *Synth. Commun.* **1983**, *13*, 403.

[5] Mandai, T., Goto, J., Otera, J., Kawada, M. *Chem. Lett.* **1980**, 313.

[6] Mandai, T., Hashio, S., Goto, J., Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187.

[7] Hiyama, T., Oishi, H., Saimoto, H. *Tetrahedron Lett.* **1985**, *26*, 2459.

[8] Livinghouse, T. *Org. Synth.* **1981**, *60*, 126.

[9] Oda, M., Yamamuro, A., Watabe, T. *Chem. Lett.* **1979**, 1427.

[0] Gassman, P.G., Talley, J.J. *Org. Synth.* **1981**, *60*, 14.

[1] Coic, J.-P., Rollin, P., Setton, R. *C. R. Acad. Sci. Ser. C* **1971**, *272*, 1554.

[2] Albert, A. *Dtsch. Chem. Ges.* **1916**, *49*, 1382.

[3] Cronyn, M.W. *J. Org. Chem.* **1949**, *14*, 1013.

[4] Fisher, B.E., Tomson, A.J., Horwitz, J.P. *J. Org. Chem.* **1959**, *24*, 1650.

[5] Francis, F., Davis, O.C. *J. Chem. Soc.* **1895**, 1403; *C. A.* **1909**, *3*, 2973.

[16] Kindler, K. *Arch. Pharm.* **1931**, *269*, 70; *C. A.* **1931**, *25*, 2981.

[17] Aloy, J., Rabaut, C. *Bull. Soc. Chim.* **1918**, *23*, 98; *C. A.* **1918**, *12*, 1383.