High-Pressure-Promoted Uncatalyzed Cyanation of Acetals Using Trimethylsilyl Cyanide as a Cyanide Source in Nitromethane[1]

Koji Kumamoto, Keiji Nakano, Yoshiyasu Ichikawa, Hiyoshizo Kotsuki*

Laboratory of Natural Product Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan
Fax +81(888)448359; E-mail: kotsuki@cc.kochi-u.ac.jp

Received 2 May 2006

Abstract: A new uncatalyzed method for the preparation of cyanohydrin *O*-alkyl ethers was developed using the high-pressure-promoted reaction of acetals with trimethylsilyl cyanide in nitromethane.

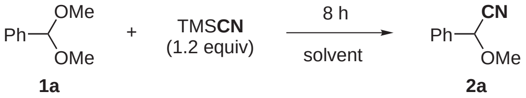
Key words: cyanation, acetals, trimethylsilyl cyanide, nitromethane, high pressure reaction

Cyanohydrins and their trimethylsilyl ether derivatives are known to be versatile intermediates in organic synthesis because they are convenient precursors for the preparation of α-hydroxy acids, β-amino alcohols, and related molecules.[2] In general, these compounds are prepared by the reaction of trimethylsilyl cyanide (TMSCN) or its analogues with carbonyl compounds in the presence of various Lewis acid or Lewis base catalysts. On the other hand, cyanohydrin *O*-alkyl ethers are obtained from acetals and TMSCN with the assistance of Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and TMSOTf,[3] since acetals are normally inert toward nucleophilic substitution under basic or neutral conditions. However, in view of the importance of an environment-friendly non-metal-catalyzed synthesis, there is a growing need for the development of new catalyst-free approaches to the transformation of acetals into the corresponding cyanohydrin *O*-alkyl ether derivatives.[4]

In connection with our ongoing projects to incorporate high pressure reactions into new synthesis protocols,[5] we anticipated that acetals could react with a cyanide nucleophile without the use of any catalysts or additives. This stems from the fact that bond formation and ionization both have a large negative activation volume.[6] Herein we describe the realization of this expectation in the addition reaction of TMSCN to acetals.

To test the feasibility of the above strategy, we first examined the reaction of benzaldehyde dimethyl acetal (**1a**) with TMSCN (1.2 equiv) at 0.8 GPa and 60 °C in various organic solvents. As shown in Table 1, there is a strong solvent effect. While the use of common less-polar solvents including THF, Et_2O, and CH_2Cl_2 gave no product (entries 1–3), in acetonitrile the desired phenylacetonitrile **2a** was formed in 54% yield (entry 4).[7] To our delight, when nitromethane was used as the solvent, the reaction went to completion with a nearly quantitative yield (entry 6). On the other hand, when the reaction was conducted in DMF or DMSO, considerable decomposition of **1a** was observed (entries 11 and 12).

Table 1 Cyanation of Benzaldehyde Dimethyl Acetal **1** under Various Conditions[a]



Entry	Solvent	Pressure (GPa)	Temp (°C)	Yield (%)[b]	Recovery of **1a** (%)[b]
1	THF	0.8	60	0	93
2	Et_2O	0.8	60	0	90
3	CH_2Cl_2	0.8	60	0	90
4	MeCN	0.8	60	54	39
5	**$MeNO_2$**	**0.8**	**60**	**94**	0
6	$MeNO_2$	0.6	60	48	50
7	$MeNO_2$	0.4	60	23	74
8	$MeNO_2$	0.2	60	0	95
9	$MeNO_2$	0.8	50	56	42
10	$MeNO_2$	0.8	40	38	60
11[c]	DMF	0.8	60	22	34
12[c]	DMSO	0.8	60	0	77

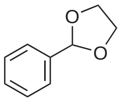
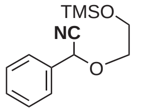
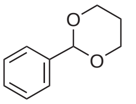
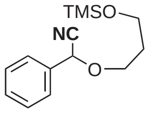
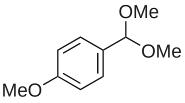
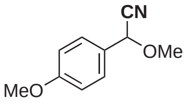
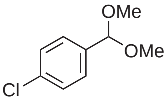
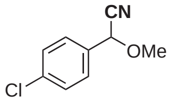
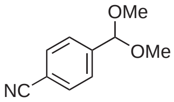
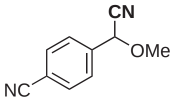
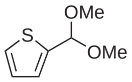
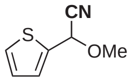
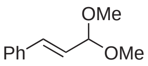
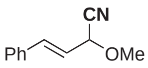
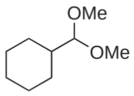
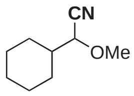
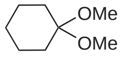
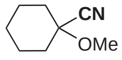
[a] All reactions were conducted in the listed solvent (ca. 1.2 mL) using **1a** (1.0 mmol) and TMSCN (1.2 mmol).
[b] Determined by GC analysis of the crude reaction mixture using *n*-pentadecane as an internal standard.
[c] Considerable amount of unidentified by-products was formed.

As expected, the reaction was highly dependent on both pressure and temperature: pressures above 0.8 GPa and temperatures above 60 °C are both necessary to achieve synthetically useful results (entries 5–10).

The basis of the dramatic effect of nitromethane in this cyanation is unclear at present. However, it is conceivable that an increase in pressure may strongly intensify the charge density at the oxygen atoms of nitromethane, which acts as a dual anchor to assemble each component via coordination with the silicon atom, thereby increasing

SYNLETT 2006, No. 12, pp 1968–1970
Advanced online publication: 24.07.2006
DOI: 10.1055/s-2006-947347; Art ID: U05306ST

Table 2 Cyanation of Acetals with TMSCN under High Pressure[a]

Entry	Substrate	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	 **1b**	60	24	 **2b**	85
2	 **1c**	60	24	 **2c**	89
3	 **1d**	60	9	 **2d**	100
4	 **1e**	60	20	 **2e**	99
5	 **1f**	80	24	 **2f**	80
6	 **1g**	60	20	 **2g**	97
7	 **1h**	60	20	 **2h**	96
8[c]	 **1i**	80	24	 **2i**	39
9[c]	 **1j**	80	24	 **2j**	46

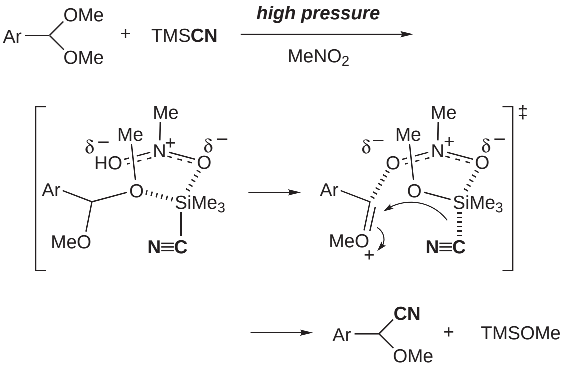
[a] All reactions were performed at 0.8 GPa in $MeNO_2$ (ca. 1.2 mL) using acetal **1** (1.0 mmol) and TMSCN (1.2 mmol).

[b] Isolated yield.

[c] Considerable decomposition of the starting material was observed.

the nucleophilicity of TMSCN[8,9] and stabilizing an oxocarbenium ion intermediate through electrostatic interaction (Scheme 1).

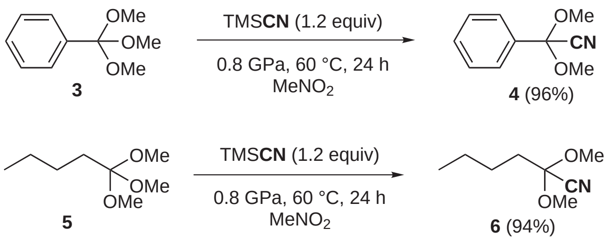
With the optimal conditions in hand, we then examined a variety of acetals to establish the general utility of this transformation (Table 2).[10] All reactions were performed at 0.8 GPa in nitromethane. Cyclic acetals **1b** and **1c** reacted smoothly with TMSCN to afford **2b** and **2c** in high yields (entries 1 and 2). The difference in the reactivity of several *para*-substituted benzaldehyde acetals **1d**–**f** clearly reflects the relative stability of the intermediate oxocarbenium ions (entries 3–5).[11] Acetals **1g** and **1h** also showed adequate reactivity, and provided **2g** and **2h**,



Scheme 1

respectively, in excellent yields (entries 6 and 7). Compared with these substrates, aliphatic acetals such as **1i** and **1j** were resistant to cyanation under these conditions, and **2i** and **2j** were produced in somewhat lower yields (entries 8 and 9).

The present method was also effective for the cyanation of ortho esters (Scheme 2).[12] When **3** and **5** were each treated with TMSCN in nitromethane at high pressure, the corresponding monocyanides **4** and **6** were obtained in essentially quantitative yields. These products were quite stable under these conditions, and no bis-cyanation occurred even with the use of excess TMSCN.



Scheme 2

In conclusion, we have developed a new direct method for the cyanation of acetals to cyanohydrin *O*-alkyl ethers using a TMSCN/nitromethane system under high pressure. Notably, this reaction can be performed under completely uncatalyzed and essentially neutral conditions, and should be useful for preparing cyanohydrin derivatives in a quite simple manner. Further studies to extend the scope of this reaction are now in progress.

Acknowledgment

This work was supported in part by a Scientific Research on Priority Areas (18037053 & 18032055) from MEXT, as well as by a Special Research Grant for Green Science from Kochi University. We also thank the Asahi Glass Foundation for financial support of this work. K.K. thanks JSPS for a research fellowship for Young Scientists.

References and Notes

(1) High Pressure Organic Chemistry. Part 32. For Part 30, see: (a) Saleha, A.; Kumamoto, K.; Uegaki, K.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2006**, *47*, 587. (b) Part 31: Kumamoto, K.; Iida, H.; Hamana, H.; Kotsuki, H.; Matsumoto, K. *Heterocycles* **2005**, *66*, 675.

(2) Reviews: (a) Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675. (b) North, M. *Synlett* **1993**, 807. (c) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (d) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (e) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (f) Brunel, J.-M.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752.

(3) For recent examples of Lewis acid catalyzed transformation of acetals into the corresponding cyanohydrin *O*-alkyl ethers, see: (a) Sandberg, M.; Sydnes, L. K. *Org. Lett.* **2000**, *2*, 687. (b) Tanaka, N.; Miura, T.; Masaki, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1010. (c) Kimura, M.; Kuboki, A.; Sugai, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1059. (d) Iwanami, K.; Oriyama, T. *Chem. Lett.* **2004**, *33*, 1324.

(4) (a) Manju, K.; Trehan, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2383. (b) Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679. (c) Iwanami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett.* **2005**, *46*, 5881.

(5) Kotsuki, H.; Kumamoto, K. *Yuki Gosei Kagaku Kyokai-shi* **2005**, *63*, 770.

(6) *Organic Synthesis at High Pressure*; Matsumoto, K.; Acheson, R. M., Eds.; John Wiley and Sons: New York, **1991**.

(7) We also examined the same reaction in the presence of inorganic lithium salts (1.5 equiv) in MeCN, but no significant improvement was observed: $LiBF_4$, 65%; LiOTf, 32%. There are some precedents regarding the effect of lithium salts in cyanohydrin formation: (a) Jenner, G. *Tetrahedron Lett.* **1999**, *40*, 491. (b) Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* **2005**, *70*, 6530.

(8) For previous examples on the activation of TMSCN by coordination with the oxygen atom of heteroatom oxides, see: (a) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949. (b) Kim, S. S.; Kim, D. W.; Rajagopal, G. *Synlett* **2004**, 213. (c) Zhou, H.; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G. *Synlett* **2004**, 1077. (d) Li, Y.; He, B.; Feng, X.; Zhang, G. *Synlett* **2004**, 1598. (e) Kim, S. S.; Rajagopal, G.; Kim, D. W.; Song, D. H. *Synth. Commun.* **2004**, *34*, 2973. (f) Chen, F.-X.; Zhou, H.; Liu, X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Chem. Eur. J.* **2004**, *10*, 4790. (g) Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* **2004**, *60*, 10449. (h) Chen, F.-X.; Feng, X. *Synlett* **2005**, 892. (i) Wen, Y.; Huang, X.; Huang, J.; Xiong, Y.; Qin, B.; Feng, X. *Synlett* **2005**, 2445. (j) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 604. (k) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (l) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384. (m) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776. (n) Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* **2005**, *127*, 12224. (o) Kim, S. S.; Kwak, J. M. *Tetrahedron* **2006**, *62*, 49.

(9) A similar type of silicon atom coordination has been proposed by others: (a) Dixon, D. A.; Hertler, W. R.; Chase, D. B.; Farnham, W. B.; Davidson, F. *Inorg. Chem.* **1988**, *27*, 4012. (b) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1990**, *55*, 2016. (c) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537. (d) Wang, Z.; Fetterly, B.; Verkade, J. G. *J. Organomet. Chem.* **2002**, *646*, 161. (e) Wang, L.; Huang, X.; Jiang, J.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2006**, *47*, 1581. (f) See also ref. 8f–h, 8o.

(10) **General Procedure.**
A mixture of acetal (1.0 mmol) and TMSCN (1.2 mmol) in $MeNO_2$ (ca. 1.2 mL) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.8 GPa at the appropriate temperature for the specified time (Table 2). After the mixture was cooled and the pressure was released, the mixture was concentrated in vacuo. The crude product was purified by silica gel column chromatography (elution with hexane–EtOAc) to afford the pure product in good to excellent yields.

(11) Consistent with this expectation, benzaldehyde diacetyl acetal was also unreactive under similar conditions (in $MeNO_2$, 0.8 GPa, 80 °C, 24 h).

(12) For recent examples of the use of this type of transformation, see: (a) Takaoka, L. R.; Buckmelter, A. J.; La Cruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528. (b) LaCruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873.