Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 161–164

An efficient preparation of stereospecific β-hydroxy nitriles

Sheila H. Jacobo,[a] Mustafa Adiyaman,[b] Chih-Tsung Chang,[a] Nam-In Kang,[a] William S. Powell[c] and Joshua Rokach[a,*]

[a]*Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology, 150 W. University Blvd., Melbourne, FL 32901, USA*
[b]*Eczacibasi Fine Chemical Products, Organize Sanayani Bolgesi, Fatih Cad. No 12, Cerkezkoy 59500, Tekirdag, Turkey*
[c]*Meakins-Christie Laboratories, Department of Medicine, McGill University, 3626 St-Urbain Street, Montreal, QC H2X 2P2 Canada*

Received 17 September 2004; revised 26 October 2004; accepted 26 October 2004

Abstract—The cyanide-ring opening of thionocarbonates with NaCN in DMF and TBACN in THF is described. This reaction occurred regioselectively to afford β-hydroxy nitrile with preserved stereochemistry of the hydroxy group in high yield.

The ring opening of thionocarbonates by azides and thiols has been described in the literature.[1] Recently, we have also reported various applications of thionocarbonates. We have used them to construct the cyclopentane ring system in the synthesis of isoprostanes by a radical approach.[2] In addition, we have used them to prepare terminal olefins,[3] iodohydrins,[4] and epoxides.[4] These methods were successfully utilized in the preparation of key synthons for the total synthesis of $iPF_{2\alpha}$-IV and $iP_{2\alpha}$-V.[2,5] We were interested in finding out if we could use the thionocarbonate ring system to build a carbon–carbon bond and, in particular, a one-carbon extension. We are reporting here on a high-yield facile conversion of *vic*-diols to β-hydroxynitriles via the intermediacy of the thionocarbonate derivative.

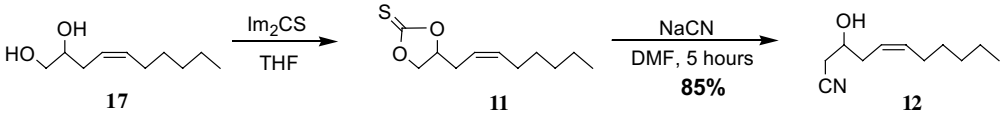
β-Hydroxynitriles have been prepared from *vic*-diols through the 1,2-epoxide via a ring-opening reaction using various cyanide reagents.[6–11] In most cases, these methodologies require the presence of a cation or Lewis acid to facilitate the cleavage of epoxide.[7,8,11] One of the most commonly used intermediates for the epoxide formation is a primary tosylate derived from a vicinal diol.[4,12–14] The preparation of the primary tosylate is often accompanied by the formation of the secondary tosylate to a greater or lesser extent, and purification can be sometimes tedious. In addition, if some of the minor secondary tosylate escapes purification, partial racemization of the epoxide will occur. The use of the thionocarbonate derivative obviates this potential problem.[3,4]

The methodology described here is short and operationally very simple. The one-carbon homologation/extension procedure is described in Scheme 1. A typical procedure for the NaCN/DMF is as follows. To a solution of thionocarbonate (0.092 mmol) in commercial anhydrous DMF (1.2 mL) was added 20 equiv of NaCN. The reaction mixture was stirred at room temperature for 3–12 h, quenched with water and extracted with ethyl ether. The solvent was removed under reduced pressure and the residue purified by flash chromatography. Table 1 shows the different examples we have selected to illustrate this conversion.

We found that tetrabutylammoniumcyanide (TBACN) in THF is an equivalent substitute for the NaCN/DMF procedure. The reaction times are shorter and the yields are comparable. A representative procedure is as follows. The thionocarbonate in dry THF was treated with 3 equiv of commercial TBACN (in entries 7 and 8, 10 equiv were used) and stirred at room temperature for 45 min to 5 h, the THF evaporated, the residue treated with water and extracted with ethyl acetate. The solvent was removed under reduced pressure and the residue purified by flash chromatography. The results of this conversion are summarized in Table 1.

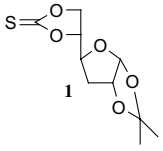
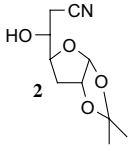
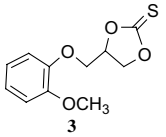
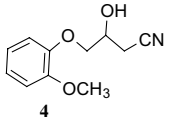
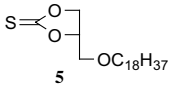
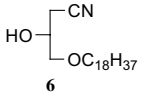
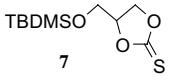
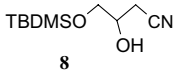
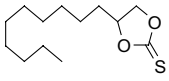
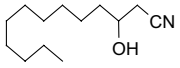
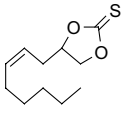
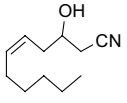
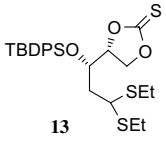
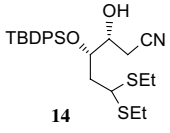
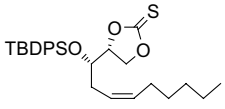
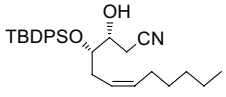
Keywords: Thionocarbonates; β-Hydroxy nitrile; Cyanide; diHETEs; 5-HETE; 5-Oxo-ETE.
* Corresponding author. Tel.: +1 321 674 7329; fax: +1 321 674 7743; e-mail: jrokach@fit.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.174



Scheme 1. Representative preparation of β-hydroxy nitriles from thionocarbonates.

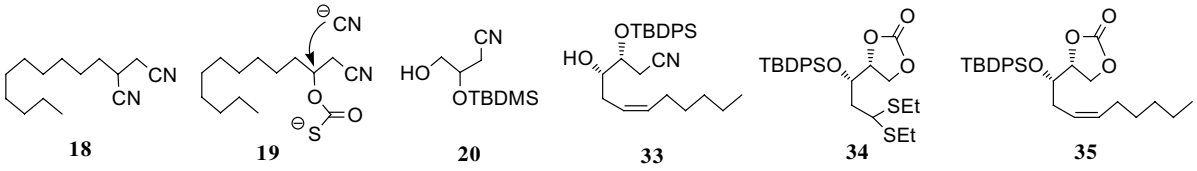
Table 1. Nucleophilic ring-opening of thionocarbonates by NaCN and TBACN

Entry	Thionocarbonate[a]	Product[c]	Reaction time	Yield (%)
1	 **1**	 **2**	5 h (45 min)[b]	83 (86)[b]
2	 **3**	 **4**	3.5 h (1 h)[b]	84 (83)[b]
3	 **5**	 **6**	12 h (1.2 h)[b]	82 (89)[b]
4	 **7**	 **8**	3.2 h (45 min)[b]	94[d] (85)[b]
5	 **9**	 **10**	8 h (1 h)[b]	74 (75)[b]
6	 **11**	 **12**	5 h (1 h)[b]	85 (86)[b]
7	 **13**	 **14**	2.5 days (5 h)[b]	78 (50)[b]
8	 **15**	 **16**	3 days (5 h)[b]	82[e] (89)[b,e]

[a] The thionocarbonates in entries 1, 3, 5, 6, and 8 were prepared as described by us previously.[4,3] The thionocarbonates in entries 2, 4, and 7 were prepared similarly from vicinal diols.
[b] Yields and reactions times from the TBACN/THF procedure.
[c] All products are new. Selected NMR data are reported in the reference section.[16–18]
[d] Combined yield. The isolated yield of **8** and **20** are 82% and 12%, respectively.
[e] Combined yield. The ratio of **16** to **33** is 1.1:1 (TBACN/THF) and 1.3:1 (NaCN/DMF) as judged by NMR.

In order to find out if cyclic carbonates react with cyanide, synthetic cyclic carbonate **35**, prepared from the diol and carbonyldiimidazole, was subjected to the TBACN/THF procedure. Ring opening of **35** by cyanide was not observed even after overnight stirring. The starting material was recovered and the identity was confirmed.

The nucleophilic attack by the cyanide on the thionocarbonate occurs at the primary carbon. We have not so far



Scheme 2. By-products isolated in the cyanide-ring opening of thionocarbonates.

detected secondary cyano derivative. However, in one case, bis-nitrile derivative **18** was isolated in entry 5 in 6% yield. We do not know the mechanism of formation of the bis-cyano by-product except that it is not formed from the hydroxy nitrile. A possible explanation for the formation of **18** is shown in **19** (Scheme 2). In entries 7 and 8 (following the TBACN/THF procedure), cyclic carbonate **34** and **35** were isolated in 11% yield and 7% yield, respectively, presumably due to a hydroxy attack on the thiocarbonyl group. The identity of **35** was established by comparing with a synthetic sample.

Some comments are warranted on substrates that have a silyloxy group adjacent to the thionocarbonate unit, for example, entries 4, 7, and 8. The results for entries 4 and 8 indicate that there is some silyl transfer. We observed silyl transfer in entry 4 to give **20** in 12% yield (combined yield of **8** and **20** is 94%), and in entry 8 to give **16** and **33** in 89% combined yield. The two isomers in entry 4 can be easily separated while the isomers in entry 8, which have been obtained in pure forms, are however more difficult to separate on a large scale and from the practical stand point, the single diol resulting from the deprotection of the silyl group of the two isomers may be the preferred synthetic intermediate. Such a diol can also be used to perform the total synthesis of eicosanoid natural products. The reaction times of entries 7 and 8 are longer, most probably due to the bulky TBDPS groups.

Interestingly, no silyl transfer seems to occur in entry 7.[15]

Cyano is a versatile group, which can be converted to aldehydes,[19,20] acids,[19,21] ketones,[19] amides,[19,22] and amines.[19,23,24] In the cases of β-hydroxynitriles, reduction would lead to γ-amino alcohols, which are useful intermediates for several molecules of pharmaceutical and biological interest.[25–27] In addition, β-hydroxynitriles can be easily converted to α,β-unsaturated nitriles. Entry 7 is of particular interest since the product, β-hydroxynitrile **14** contains two reactive poles, which can be used to carry eicosanoid synthesis. For example, one can envision the synthesis of 5-HETE, 5-oxo-ETE, and *vic*-diHETES using this synthon.

Acknowledgements

Supported by grants from the National Institutes of Health (DK-44730, HL-69835); the NSF for an AMX-360 NMR instrument (CHE-90-13145); the Canadian Institutes of Health Research (MOP-6254). We are grateful to Dr. O. A. Mamer of the McGill University Mass Spectrometry Facility and Dr. D. H. Powell of University of Florida for the assistance with the mass spectrometry.

References and notes

1. Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250–6251.
2. Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis, First Special Issue, Natural Products Synthesis* **1998**, 569–580.
3. Adiyaman, M.; Jung, Y.; Kim, S.; Saha, G.; Powell, W. S.; FitzGerald, G.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 4019–4022.
4. Adiyaman, M.; Khanapure, S. P.; Hwang, S. W.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 7367–7370.
5. Pudukulathan, Z.; Manna, S.; Hwang, S. W.; Khanapure, S. P.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *J. Am. Chem. Soc.* **1998**, *120*, 11953–11961.
6. Mitchell, D.; Koenig, T. M. *Tetrahedron Lett.* **1992**, *33*, 3281–3284.
7. Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775–4778.
8. Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649–1652.
9. Konno, H.; Toshiro, E.; Hinoda, N. *Synthesis* **2003**, 2161–2164.
10. Tamami, B.; Iranpoor, N.; Rezaei, R. *Synth. Commun.* **2003**, *33*, 3153–3157.
11. Iranpoor, N.; Firouzabadi, H.; Shekarize, M. *Org. Biomol. Chem.* **2003**, *1*, 724–727.
12. Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2759–2762.
13. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
14. Just, G.; Luthe, C. *Can. J. Chem.* **1980**, *58*, 1799–1805.
15. The reviewer suggested that the lack of silyl scrambling in entry 7 is possibly due to the coordination of the alkoxide and sulfur.
16. *4-(tert-Butyldiphenylsilyl)oxy-6,6-bis-ethylsulfanyl-3-hydroxy-hexanenitrile* (**14**): Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.05–1.29 (m, 15H), 1.65–1.75 (m, 1H), 1.90–2.10 (m, 1H), 2.25–2.78 (m, 6H), 3.70–3.80 (m, 1H), 3.90 (t, J = 7.2 Hz), 4.00–4.10 (m, 1H) 7.38–7.52 (m, 6H), 7.65–7.75 (m, 4H); ^{13}C NMR (360 MHz, $CDCl_3$): δ 14.40, 14.50, 19.50, 21.65, 24.05, 24.45, 27.10, 39.00, 48.35, 72.15, 72.25, 117.95, 128.25, 130.45, 130.56, 132.70, 132.80, 136.10, 136.15; IR 3467.96 (br), 3075.73, 3040.78, 2959.22, 2928.16, 2850.49, 2252.23, 1588.35, 1471.84, 1464.08, 1421.36, 1417.48, 1269.90, 1106.80; FAB MS (*m/z*) 526.16723 $[M+K]^+$.
17. *2-Cyano-tridecanenitrile* (**18**): Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.88 (t, J = 6.1 Hz, 3H), 1.20–162 (m, 16H), 1.72–1.82 (m, 2H), 2.65–2.80 (m, 2H), 2.91 (qt, J = 7.0, 1H); ^{13}C NMR (360 MHz, $CDCl_3$): δ 14.25, 21.21,

22.85, 26.75, 28.60, 29.00, 29.30, 29.40, 29.60, 29.70, 31.70, 32.15, 115.85, 119.15; ESI-MS (*m*/*z*) 221 $[M+H]^+$.

18. *3-Deoxy-6-cyano-5-hydroxy-1,2-O-isopropylidene-α-D-gluco-furanose* (**2**): Yellow oil. ^1H NMR (360 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.53 (s, 3H), 1.80–1.92 (m, 1H), 2.18 (dd, $J = 8.9$, 4.4 Hz), 2.50–2.70 (m, 2H), 4.09–4.18 (br, 1H), 4.20–4.29 (m, 1H), 4.80 (t, $J = 4$ Hz), 5.81 (d, $J = 3.4$ Hz); ^{13}C NMR (360 MHz, $CDCl_3$): δ 22.21, 26.15, 26.70, 33.20, 67.95, 79.45, 80.40, 105.45, 111.80, 116.95; IR 3456.31 (br), 2986.41, 2935.92, 2248.54, 1417.48, 1370.87, 1316.50, 1254.37, 1215.53, 1075.73, 1056.31, 1021.36.
19. Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley, John & Sons, 1999, pp 1271–1272 (aldehydes); p 1675, pp 1986–1987 (acids); p 1260, pp 1420–1422, p 1469 (ketones); pp 1988–1990 (amides); pp 875–878 (amines).
20. Hayashi, M.; Yoshiga, T.; Oguni, N. *Synlett* **1991**, 479–480.
21. Wang, M. X.; Zaho, S. M. *Tetrahedron: Asymmetry* **2002**, *13*, 1695–1702.
22. Bendale, P. M.; Khadilkar, B. M. *Synth. Commun.* **2002**, *30*, 1713–1718.
23. Caddick, S.; Judd, D. B.; Lewis, A. K. d. K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417–5423.
24. Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265–1269.
25. Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048–5050.
26. Bergeron, R. J.; Xia, M. X. B.; Phanstiel, O. *J. Org. Chem.* **1993**, *58*, 6804–6806.
27. Larson, E. R.; Noe, M. C.; Gant, T. G. Preparation of isothiazolamide urea derivatives as anticancer agents; U. S. Patent WO 9962890, 1999.