ORGANIC LETTERS

2006
Vol. 8, No. 5
1007−1009

New One-Carbon Degradative Transformation of β-Alkyl-β-azido Alcohols

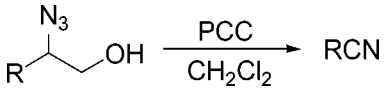
Qiu-Hua Fan, Nan-Ting Ni, Qin Li, Li-He Zhang, and Xin-Shan Ye*

The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road #38, Beijing 100083, China

xinshan@mail.bjmu.edu.cn

Received January 24, 2006

ABSTRACT



A new transformation of 2-azido-1-hydroxy-containing compounds to nitriles with one carbon less than the starting materials by oxidation was reported. The reaction can be performed under mild conditions.

Nitriles have proven to be versatile building blocks in organic synthesis.[1] They undergo a variety of synthetically useful transformations such as reduction, alkylation of their imino enolates, enzymatic hydrolysis to acids or amides by nitrile hydratase,[2] and Ritter reaction.[3] Functionalized nitriles such as ketonitriles are important synthetic intermediates. Methodologies for the synthesis of ketonitriles include the Beckmann fragmentation of cyclic α-hydroxy oximes[4] and the cleavage of trisubstituted cyclic olefins with (diacetoxyiodo)benzene (DIB)/(TMS)N_3.[5] Alternatively, $Pb(OAc)_4$/(TMS)N_3,[5] CAN/NaN_3,[6] or photooxygenation in the presence of NaN_3/$Cu(OTf)_2$[7] can achieve the same results. On the other hand, highly functionalized aldononitriles have found widespread applications as chiral synthons in the preparation of polyhydroxypiperidines (1,5-iminoalditols) and polyhydroxypyrrolidines (1,4-iminoalditols); the latter are glycosidase inhibitors.[8] Several approaches to aldononitriles from carbohydrates have been described in the literature, including the direct addition of HCN to aldoses (Fischer−Killiani cyanohydrin synthesis),[9] the dehydration of aldose oximes,[9b,10] the reaction of *N*-bromoglycosylimines with Zn/Ag graphite,[11] and the alkoxyl radical fragmentation of reducing sugars.[12] Herein, we now disclose a novel oxidative trans-

(1) (a) *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Interscience: New York, 1970. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley: New York, 1984; Vol. 31, pp 1−374.

(2) (a) Brennam, B. A.; Alms, G.; Nelson, M. J.; Durney, L. T.; Scarrow, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 9194−9195. (b) Taylor, S. K.; Chmiel, H. H.; Simons, L. J.; Vyvyan, J. R. *J. Org. Chem.* **1996**, *61*, 9084−9085. (c) Maddrell, S. J.; Turner, N. J.; Kerridge, A.; Willetts, A. J.; Crosby, J. *Tetrahedron Lett.* **1996**, *37*, 6001−6004.

(3) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045−4048.

(4) (a) Magyar, A.; Schonecker, B.; Wolfling, J.; Schneider, G.; Gunther, W.; Gorls, H. *Tetrahedron: Asymmetry* **2003**, *14*, 2705−2715. (b) Ho, T.-L.; Gorobets, E. *Tetrahedron* **2002**, *58*, 4969−4973. (c) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Maroto, B. L. *Eur. J. Org. Chem.* **2002**, 781−783. (d) Tokic-Vujosevic, Z.; Cekovic, Z. *Synthesis* **2001**, 2028−2034. (e) Biju, P. J.; Laxmisha, M. S.; Rao, G. S. R. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4512−4519. (f) Pejanovic, V. M.; Petrovic, J. A.; Csanadi, J. J.; Stankovic, S. M.; Miljkovic, D. A. *Tetrahedron* **1995**, *51*, 13379−13384.

(5) (a) Zbiral, E.; Nestler, G.; Kischa, K. *Tetrahedron* **1970**, *26*, 1427−1434. (b) Zbiral, E.; Nestler, G. *Tetrahedron* **1970**, *26*, 2945−2951. (c) Ehrenfreund, J.; Zbiral, E. *Tetrahedron* **1972**, *28*, 1697−1704. (d) Hugl, H.; Zbiral, E. *Tetrahedron* **1973**, *29*, 759−767.

(6) Nair, V.; Rajan, R.; Balagopal, L.; Thomas, S.; Narasimlu, K. *Tetrahedron Lett.* **2002**, *43*, 8971−89074.

(7) Shimizu, I.; Fujita, M.; Nakajima, T.; Sato, T. *Synlett* **1997**, 887−888.

(8) (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515−553. (b) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999.

(9) (a) Hough, L.; Richardson, A. C. In *The Carbohydrates. Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: San Diego, 1972; Vol. IA, pp 118−120. (b) McGinnis, G. D. *Carbohydr. Res.* **1982**, *108*, 284−292.

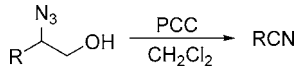
(10) See, for example: (a) Chen, C. C.; McGinnis, G. D. *Carbohydr. Res.* **1981**, *90*, 127−130. (b) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043−2053. (c) Dorsey, A. D.; Barbarow, J. E.; Trauner, D. *Org. Lett.* **2003**, *5*, 3237−3239. (d) Molina, P.; Alajarin, M.; Vilaplana, M. J. *Synthesis* **1982**, 1016−1017. (e) Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741−742.

(11) Fürstner, A.; Praly, J.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 751−753.

10.1021/ol0601996 CCC: $33.50
Published on Web 02/10/2006

formation of 2-azido-1-hydroxy-containing compounds to nitriles having one carbon less than the starting materials (Scheme 1).

Scheme 1

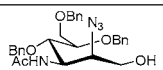
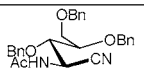
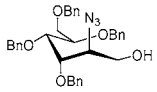
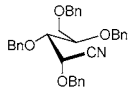
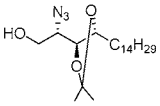
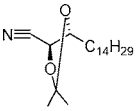
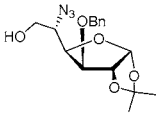
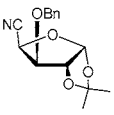
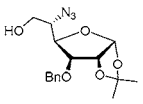
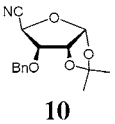
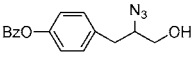
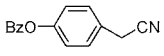
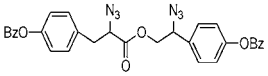
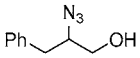
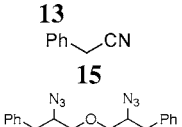
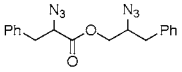
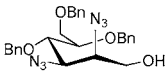
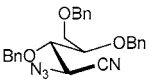
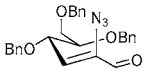


As shown in Table 1, the polyfunctionalized azido alcohol **1**, prepared from glucose by a series of well-established functional group manipulations (see Supporting Information), was chosen as our first substrate. Simple treatment of **1** with 2 equiv of PCC in CH_2Cl_2 at room temperature surprisingly afforded nitrile **2** in 67% isolated yield, and none of the expected aldehyde or carboxylic acid was obtained (entry 1). Similarly, azide **3** was smoothly oxidized by PCC under the same conditions to provide nitrile **4** in 64% isolated yield (entry 2). The phytosphingosine precursor **5**[13] reacted with PCC, yielding product **6** in 68% isolated yield (entry 3). The furanosides **7** and **9** were also oxidized to the corresponding nitriles **8** and **10** in good yield (entries 4 and 5). When the amino alcohol derivative **11** was treated with PCC, the nitrile **12** was accessed in 62% yield, and the ester **13** was also obtained as a side product in 23% yield (entry 6). The simple β-hydroxy azide **14**[14] underwent this transformation, providing the desired nitrile **15**. However, the isolated yield was not good (36%), mainly due to the formation of ester **16** (45%) (entry 7). When the diazido compound **17** was subjected to oxidation, the nitrile **18** was isolated in 26% yield, and the α,β-unsaturated aldehyde **19**[15] was also formed (33%) (entry 8).

To explore the scope of this new transformation, the azido-containing pyranose derivatives **20** and **21** were prepared. The oxidation reaction of **20** with PCC led exclusively to the formation of sugar lactone **22** in 90% isolated yield; significantly, no nitrile was obtained. Pyranoside **21** with a secondary hydroxy next to the azido group was left undisturbed when treated with PCC under the same conditions, allowing the recovery of the starting material (Scheme 2). It appears that the transformation to nitriles from β-hydroxy azides does not occur in pyranoses.

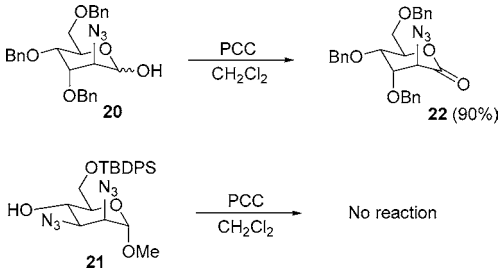
Other types of hydroxyl-substituted azides were also examined. Because the conversion of γ-hydroxy azides to γ-ketoazides by oxidation is known,[16] δ-hydroxy azide **23** was chosen as the substrate. Treatment of **23** with the same manner as that mentioned above afforded δ-ketoazide **24**

Table 1. Conversion of β-Hydroxy Azides to Nitriles

entry	substrate	product	isolated yield (%)
1	 **1**	 **2**	67
2	 **3**	 **4**	64
3	 **5**	 **6**	68
4	 **7**	 **8**	72
5	 **9**	 **10**	75
6	 **11**	 **12**	62
	 **13**		23
7	 **14**	 **15**	36
		 **16**	45
8	 **17**	 **18**	26
		 **19**	33

(88% yield) with the azido group unchanged (Scheme 3). This outcome is similar to that of γ-hydroxy azides.

Scheme 2



(12) (a) Gonzalez, C. C.; Kennedy, A. R.; Leon, E. I.; Riesco-Fagundo, C.; Suarez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326−2328. (b) Hernandez, R.; Leon, E. I.; Moreno, P.; Suarez, E. *J. Org. Chem.* **1997**, *62*, 8974−8975. (c) Hernandez, R.; Leon, E. I.; Moreno, P.; Riesco-Fagundo, C.; Suarez, E. *J. Org. Chem.* **2004**, *69*, 8437−8444. (d) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723−4727.

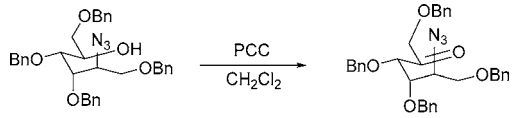
(13) Schmidt, R. R.; Maier, T. *Carbohydr. Res.* **1988**, *174*, 169−179.

(14) Hedenstrom, M.; Holm, L.; Yuan, Z. Q.; Emtenas, H.; Kihlberg, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 841−844.

(15) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510−520.

(16) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269−2272.

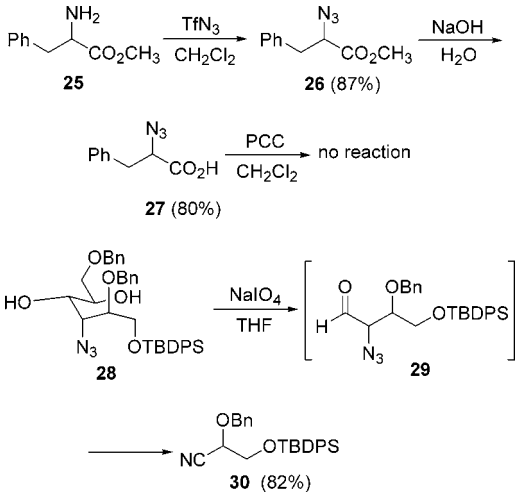
Scheme 3



23 **24** (88%)

The transformation of β-hydroxy azides to nitriles may involve an aldehyde or carboxylic acid intermediate. To determine whether the transformation is mediated through a carboxylic acid intermediate, an α-azido carboxylic acid **27** was synthesized starting from phenylalanine derivative **25** via diazotransfer[17] and saponification operations (Scheme 4).

Scheme 4

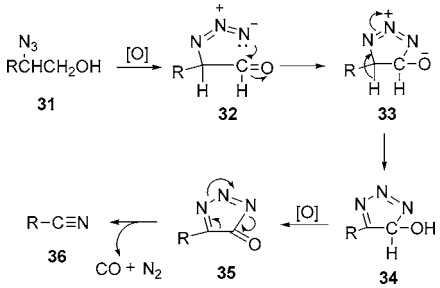


25 **26** (87%) **27** (80%) **28** **29** **30** (82%)

Compound **27** could easily be obtained in a pure form and was inert to treatment with PCC. On the other hand, when azidodiol **28** was oxidized by $NaIO_4$, nitrile **30** was successfully collected in 82% yield, presumably via the aldehyde intermediate **29**. We thus exclude the possibility of the existence of α-azido carboxylic acid intermediates being formed as intermediates in this transformation and suggest that the reaction instead involves α-azido aldehyde intermediates.

On the basis of these experiments, a possible mechanism for this new transformation is proposed. As displayed in Scheme 5, the substrate **31** is oxidized by PCC to first generate the key intermediate aldehyde **32** which then undergoes intramolecular azido nucleophilic attack on the carbonyl to form **33**. The proton transfer of **33** affords alcohol **34**, which is then oxidized again to give the ketone **35**. The release of carbon monoxide and nitrogen with the cleavage of C−C, C−N, and N−N bonds would then afford the final nitrile **36**.

Scheme 5



31 **32** **33** **34** **35** **36**

In conclusion, a new transformation of 2-azido-1-hydroxy-containing compounds to nitriles accompanied by a one-carbon loss is disclosed. It seems that the hydroxy functionality on a primary carbon adjacent to the azido group is necessary for the success of this transformation. To the best of our knowledge, no such conversion has previously been reported in the literature. This reaction can be carried out under mild conditions. The reaction may find applications in the synthesis of chiral polyfunctionalized nitrile synthons such as aldononitriles and ketonitriles.

Acknowledgment. This work was financially supported by the National Natural Science Foundation of China, a "973" grant from the Ministry of Science and Technology of China, and Peking University.

Supporting Information Available: All experimental procedures and data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0601996

(17) (a) Caveander, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567−3569. (b) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032. (c) Yan, R.-B.; Yang, F.; Wu, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron Lett.* **2005**, *46*, 8993−8995.