ORGANIC LETTERS

2008
Vol. 10, No. 18
4141−4143

A General One-Step Synthesis of β-Nitronitriles

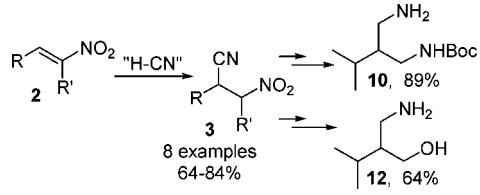
James C. Anderson,*,† Alexander J. Blake,†,‡ Matthew Mills,† and Paul D. Ratcliffe§

School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, U.K., and Department of Medicinal Chemistry, Schering Plough Corporation, Newhouse, Lanarkshire, ML1 5SH, U.K.

j.anderson@nottingham.ac.uk

Received July 24, 2008

ABSTRACT



The unusual β-nitronitrile functionality was prepared by a simple one-step hydrocyanation of nitroalkenes. These compounds were shown to be precursors to monoprotected 1,3-diamines and 1,3-amino alcohols through the in situ formation of an α-cyano-aldenyde.

The addition of nucleophiles to Michael acceptors is an important reaction for the construction of highly functionalized synthetic building blocks. Nitroalkenes stand out among Michael acceptors due to the synthetic versatility of the nitro group. Often described as a "synthetic chameleon",[1] the nitro group can be transformed into a large number of different functional groups. The Nef reaction,[2] reduction to an amine,[3] and nucleophilic displacement[4] are only a few examples of possible transformations. The range of nucleophiles employed in Michael additions to nitroalkenes is extensive and includes carbon, oxygen, nitrogen, phosphorus, and sulfur based examples.[5] A search of the literature revealed surprisingly that there were no examples of the Michael addition of a cyanide anion to a nitroalkene. In fact, there are relatively few examples of the would be products from these reactions, β-nitronitriles, reported in the literature. This is surprising as β-nitronitriles could serve as valuable synthetic building blocks to a variety of bifunctional molecules, for example, β-cyano-amines, 1,3-amino alcohols, and 1,3-diamines. The two main methods of forming β-nitronitriles involve either the obscure and somewhat limited reaction of α-bromoisobutyronitrile with nitronate anions[6] or the more versatile 1,4-addition of formaldehyde dimethyl hydrazone to nitroalkenes, followed by oxidation to the nitrile using magnesium monoperoxyphthalate.[7] Although respectable yields are obtained for the latter two-step procedure, formaldehyde dimethyl hydrazone is not commercially available. It was thought that a simple, one-step method for the synthesis of β-nitronitriles, from nitroalkenes and a cyanide nucleophile, would be a useful method to prepare these underdeveloped compounds.

It was reported by Liotta et al.[8] that a cyanide ion can be solubilized in aprotic solvents by using acetone cyanohydrin (**1**) and catalytic (10 mol %) quantities of potassium cyanide and 8-crown-6. This "naked" form of the cyanide ion was shown to be an efficient nucleophile in a wide range of

† University of Nottingham.
‡ Corresponding author for X-ray crystal structure.
§ Schering Plough.

(1) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1995**, *68*, 1592.
(2) Pinnick, H. W. *Org. React.* **1990**, *38*, 655.
(3) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1989; p 411.
(4) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423.
(5) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Chem.* **2002**, 1877.
(6) Lassaletta, J. M.; Fernández, R.; Gasch, C.; Vázquez, J. *Tetrahedron* **1996**, *52*, 9143.
(7) Ros, F.; Rosa, J. *J. Org. Chem.* **1988**, *53*, 2868.
(8) (a) Cook, F. C.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974**, *39*, 3416. (b) Liotta, C. L.; Dabdoub, A. M.; Zalkow, L. H. *Tetrahedron Lett.* **1977**, *18*, 1117.

10.1021/ol801691c CCC: $40.75
Published on Web 08/23/2008

reactions, including both displacement and addition reactions. Presumably, **1** decomposes to cyanide and acetone under the reaction conditions. It was thought that similar conditions may effect the hydrocyanation of nitroalkenes **2**.

A range of nitroalkenes **2** were synthesized by the Et_3N-catalyzed Henry reaction[9] followed by dehydration using MsCl and DIPEA (Scheme 1).[10] After some experimentation, conjugate addition of cyanide was achieved by the addition of **1** to a solution of **2** with catalytic (10 mol %) quantities of KCN and 18-C-6 in MeCN at room temperature (Table 1).

Scheme 1. Synthesis of Nitroalkenes **2** and Hydrocyanation

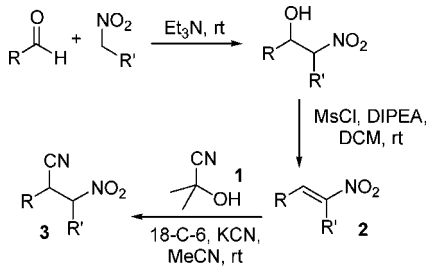
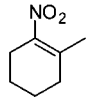


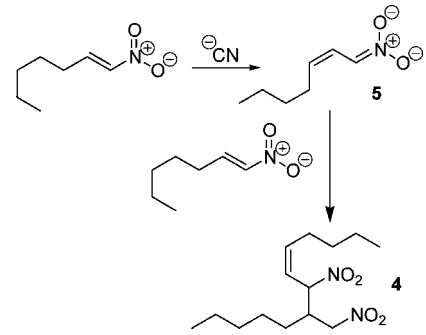
Table 1. Substrate Scope **3**[a]

entry	R	R'	reaction time (h)	yield (%)
1	^{i}Pr	H	3	73
2	^{i}Pr	Et	3	76
3	^{c}Hx	H	3	76
4	^{n}Pn	H	17	68[b]
5	^{n}Pn	Et	17	71[b]
6	^{t}Bu	H	5	64
7	TBDPSiOCH$_2$CH$_2$	H	17	76[b]
8			12	84

[a] All reactions carried out with **1** (1.2 equiv), 18-C-6 (0.1 equiv), and KCN (0.1 equiv) in MeCN at rt. [b] Nitroalkene added via syringe pump over a 5 h period to **1**, 18-C-6, and KCN in MeCN followed by further addition of **1** (1.2 equiv) in MeCN at rt.

Good yields were obtained except in the cases of linear nitroalkenes (entries 4, 5, and 7) where none of the desired product **3** could be isolated under the standard conditions. Instead, a variety of byproducts were formed, and in the case of **2** (R = ^{n}Pn, R′ = H), we isolated the dimer **4** in 23% yield (Scheme 2).[11] The mechanism for its formation could arise from conjugate deprotonation by the cyanide ion to give nitronate **5**, followed by conjugate addition to the starting material (Scheme 2). This mechanism is preferred over the nitronate derived from conjugate addition of cyanide adding to the nitroalkene, followed by elimination of H-CN, as the resulting alkene in **4** is not in conjugation with the nitro group. The actual mechanistic explanation may be more complex as the isolated alkene has a vicinal coupling constant of 10.4 Hz that suggests a *cis* configuration. Dilution of the reaction resulted in much longer reaction times and no significant decrease in dimer formation. Reverse and slow addition (syringe pump) of the nitroalkene to the mixture of KCN, 18-C-6, and **1**, followed by further addition of **1** (1.2 equiv) led to comparable yields of desired **3** (entries 4, 5, and 7).

Scheme 2. Proposed Mechanism for Formation of **4**



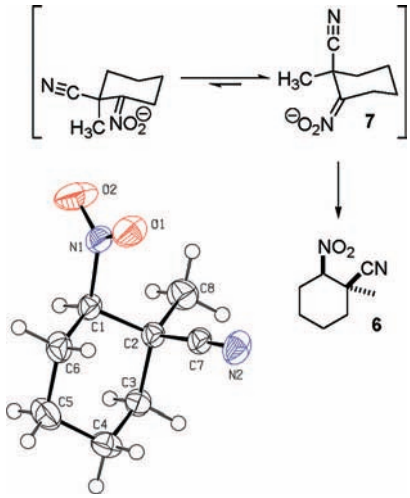
Hydrocyanation of trisubstituted nitroalkenes led to 1:1 diastereomeric mixtures (entries 2 and 5). The synthesis of tetrasubstituted nitroalkenes from the condensation of 1° nitroalkanes with ketones leads to an unfavorable Henry reaction. To investigate the hydrocyanation of tetrasubstituted nitroalkenes, we synthesized the literature compound 1-nitro-2-methylcyclohex-1-ene (entry 8) from 2-chloro-2-methylcyclohexanone,[12] via the oxidation of the corresponding oxime.[13] Hydrocyanation led to the isolation of diastereomerically pure *syn*-**6** in 84% yield, and its structure was confirmed by single crystal X-ray diffraction. This diastereoisomer presumably arises through protonation from the thermodynamically more stable chair form **7**[14] of the nitronate to give the equatorial nitro function in **6** (Scheme 3).

To gain some insight into the general mechanism for the hydrocyanation of nitroalkenes control reactions were performed in the absence of 18-C-6 or **1** and in the absence of both 18-C-6 and KCN. In all three cases, no reaction was found to occur. This indicates that the in situ generated HCN, formed from the cyanide anion abstracting a proton from the acetone cyanohydrin (**1**), is very important for the reaction to proceed.

To demonstrate the utility of these β-nitronitriles as building blocks in synthesis, we have investigated functional group interconversions of **8** (Scheme 4). The nitro group was reduced with Zn/HCl, and the crude material Boc protected

(9) Fieser, L. F.; Gates, M. *J. Am. Chem. Soc.* **1946**, *68*, 2249.
(10) Melton, J.; McMurry, J. E. *J. Org. Chem.* **1975**, *40*, 2138.
(11) A similar dimer from entry 1 was isolated in 3% yield from a 3.5 mmol scale reaction.
(12) Singh, V. S.; Gupta, S. M. L. *Curr. Sci.* **1981**, *50*, 816.
(13) Sakakibara, T.; Ikeda, Y.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 635.
(14) Values of CN = 0.84 kJ/mol: (a) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344vs CH_3 = 7.28 kJ/mol: Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin 2* **1980**, 255.

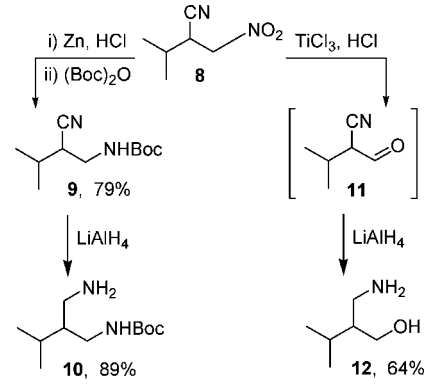
Scheme 3. Proposed Mechanism for Formation of **6**



to give the *N*-Boc protected β-aminonitrile **9** in 79% yield over two steps. Reduction with $LiAlH_4$ in refluxing Et_2O gave monoprotected diamine **10** in 89%. It is interesting to note that this product would be difficult to form from the direct monoprotection of the parent symmetrical 1,3-diamine. Nef reduction of **8** with acidic titanium(III) chloride[15] gave unstable α-cyano aldehyde **11**. The crude aldehyde **11** could be reduced with $LiAlH_4$ to give β-amino alcohol **12** in 64% yield from the parent β-nitronitrile after ion exchange chromatography.

In conclusion, we have reported the efficient one-step hydrocyanation of a variety of nitroalkenes by acetone cyanohydrin in the presence of catalytic amounts of KCN and 18-C-6 to give β-nitronitriles. The utility of these readily

Scheme 4. Manipulation of β-Nitronitriles



accessible compounds as building blocks in organic synthesis has been demonstrated by chemoselective functional group interconversions of the cyano and nitro groups.

Acknowledgment. We thank the EPSRC and Schering Plough Corperation for funding, Mr. T. Hollingworth and Mr. D. Hooper (University of Nottingham) for providing mass spectra, and Dr T. Liu (University of Nottingham) for microanalytical data.

Supporting Information Available: General experimental, experimental procedures, data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801691C

(15) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.