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A Cascade Approach to Cyclic Aminonitrones: Reaction Discovery, Mechanism, and Scope

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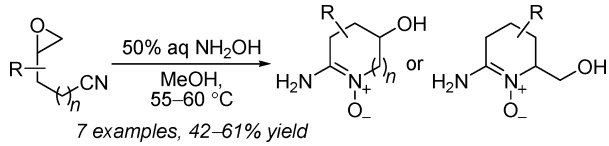
ABSTRACT



Treatment of ω-epoxynitriles with hydroxylamine affords cyclic aminonitrones in a single step and with high stereoselectivity. The scope of this novel transformation was explored in a series of examples. The aminonitrone products were shown to be useful substrates for further selective elaboration.

Raltegravir (**1**, Figure 1) is the first HIV antiretroviral drug to be approved by the FDA that targets and inhibits integrase, the enzyme that catalyzes insertion of viral DNA into the host cell genome.[1,2] In patients with multidrug-resistant strains of HIV-1, and otherwise limited treatment options, combination of raltegravir with existing antiretrovirals has proven to be highly successful in reducing the viral load.[3]

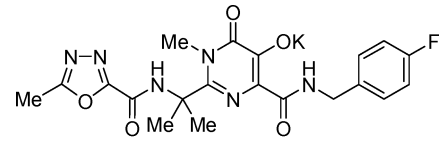


Figure 1. Raltegravir (**1**).

In an ongoing drug discovery program in these laboratories, a series of fused bicyclic pyrimidones were developed as potent and selective integrase inhibitors, of which MK-0396 (**2**, Scheme 1) is a representative example.[4,5] These analogues were prepared from cyclic amidoximes **5** through a dimethyl acetylenedicarboxylate (DMAD) addition/thermal rearrangement sequence[6] to give the core bicyclic pyrimidone scaffolds **6**, followed by further elaboration.[7] The preparation

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(1) Raltegravir was approved by the FDA in October 2007 for the treatment of HIV/AIDS and is marketed under the trademark Isentress.

(2) (a) Meadows, D. C.; Gervay-Hague, J. *ChemMedChem* **2006**, *1*, 16. (b) Craigie, R. *J. Biol. Chem.* **2001**, *276*, 23213. (c) Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science* **2000**, *287*, 646.

(3) (a) Steigbigel, R. T.; Cooper, D. A.; Kumar, P. N.; Eron, J. E.; Schechter, M.; Markowitz, M.; Loufty, M. R.; Lennox, J. L.; Gatell, J. M.; Rockstroh, J. K.; Katlama, C.; Yeni, P.; Lazzarin, A.; Clotet, B.; Zhao, J.; Chen, J.; Ryan, D. M.; Rhodes, R. R.; Killar, J. A.; Gilde, L. R.; Strohmaier, K. M.; Meibohm, A. R.; Miller, M. D.; Hazuda, D. J.; Nessly, M. L.; DiNubile, M. J.; Isaacs, R. D.; Nguyen, B.-Y.; Teppler, H. *New. Engl. J. Med.* **2008**, *359*, 339. (b) Grinsztejn, B.; Nguyen, B.-Y.; Katlama, C.; Gatell, J. M.; Lazzarin, A.; Vittecoq, D.; Gonzalez, C. J.; Chen, J.; Harvey, C. M.; Isaacs, R. D. *Lancet* **2007**, *369*, 1261.

(4) (a) Muraglia, E.; Kinzel, O.; Gardelli, C.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Nizi, E.; Orvieto, F.; Pescatore, G.; Laufer, R.; Gonzalez-Paz, O.; Di Marco, A.; Fiore, F.; Monteagudo, E.; Fonsi, M.; Felock, P. J.; Rowley, M.; Summa, V. *J. Med. Chem.* **2008**, *51*, 861. (b) Kinzel, O. D.; Monteagudo, E.; Muraglia, E.; Orvieto, F.; Pescatore, G.; Ferreira, M. R. R.; Rowley, M.; Summa, V. *Tetrahedron Lett.* **2007**, *48*, 6552. (c) Ferrara, M.; Crescenzi, B.; Donghi, M.; Muraglia, E.; Nizi, E.; Pesci, S.; Summa, V.; Gardelli, C. *Tetrahedron Lett.* **2007**, *48*, 8379.

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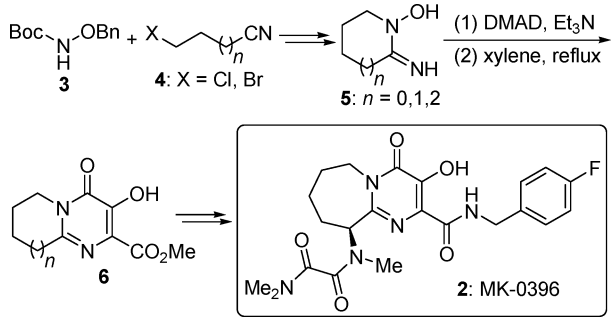
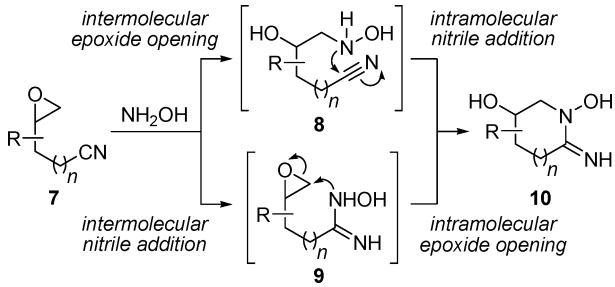
Scheme 1. MK-0396 (**2**) and Synthesis of Amidoximes **5**



of amidoximes **5**, in turn, required multistep syntheses from ω-halonitriles **4** and bis-protected hydroxylamine derivative **3**.

As part of a general strategy toward novel bicyclic pyrimidone structures, we envisaged a more concise, atom-economical route to the key cyclic amidoxime precursor motif. As shown in Scheme 2, treatment of ω-epoxynitriles

Scheme 2. Proposed Cascade Approach to Amidoximes **10**

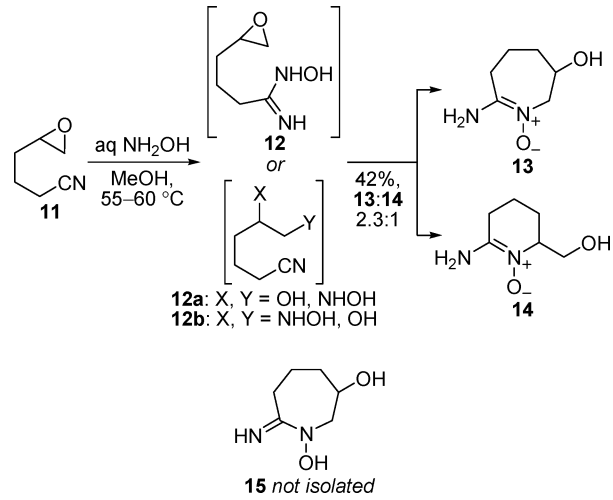


7 with hydroxylamine could potentially generate amidoxime **10** in a single operation. The resulting adducts (**10**) would bear a secondary hydroxyl group, which could subsequently be removed or, more purposefully, serve later as a handle for further diversification.

Hypothetically, two mechanistic pathways could exist for this transformation. The intermolecular addition of hydroxylamine to nitriles is well established,[8] and precedent exists for two of the other three elementary steps illustrated.[9−11] While the conversion of **7** to **10** is therefore conceptually rather straightforward, such a reaction has, to the best of our knowledge, not been reported in the literature.

As an initial test of the feasibility of the proposed cascade reaction, epoxide **11**[12] was treated with 50% aqueous hydroxylamine (1.1 equiv) in MeOH at 55−60 °C for 24 h (Scheme 3). Unexpectedly, this resulted in the formation of

Scheme 3. Cyclization of Epoxide **11**



two major products, **13** and **14**, neither of which was the anticipated 7-membered amidoxime structure **15**. Aminonitrones **13** and **14** (which can also be considered to be amidine *N*-oxides) were formed in a ratio of 2.3:1 and 57% combined assay yield.[13] Separation and purification of the highly polar, water-soluble product mixture was achieved by preparative HPLC, giving **13** and **14** in a modest overall isolated yield of 42%.

The formation of **13** and **14** would be consistent with either of the two mechanisms depicted in Scheme 2. Attempts to observe the putative intermediates **12** or **12a/b** by HPLC−MS

(5) The related unsaturated heterocyclic pyridopyrimidine scaffold has also been reported; see: Kinzel, O. D.; Ball, R. G.; Donghi, M.; Maguire, C. K.; Muraglia, E.; Pesci, S.; Rowley, M.; Summa, V. *Tetrahedron Lett.* **2008**, *49*, 6556.

(6) (a) Pye, P. J.; Zhong, Y.-L.; Jones, G. O.; Reamer, R. A.; Houk, K. N.; Askin, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 4134. (b) Zhong, Y.-L.; Zhou, H.; Gauthier, D. R., Jr.; Askin, D. *Tetrahedron Lett.* **2006**, *47*, 1315. (c) Culbertson, T. P. *J. Heterocycl. Chem.* **1979**, 1423.

(7) For a more recent, scalable synthesis of **2**, see: (a) Zhong, Y.-L.; Pipik, B.; Lee, J.; Kohmura, Y.; Okada, S.; Igawa, K.; Kadowaki, C.; Takezawa, A.; Kato, S.; Conlon, D. A.; Zhou, H.; King, A. O.; Reamer, R. A.; Gauthier, D. R., Jr.; Askin, D. *Org. Proc. Res. Dev.* **2008**, *12*, 1245. (b) Zhong, Y.-L.; Krska, S. W.; Zhou, H.; Reamer, R. A.; Lee, J.; Sun, Y.; Askin, D. *Org. Lett.* **2009**, *11*, 369.

(8) For examples, see: (a) Ref 7a. (b) Di Francesca, M. E.; Pace, P.; Fiore, F.; Naimo, F.; Bonelli, F.; Rowley, M.; Summa, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2709. (c) Ismail, M. A.; Arafa, R. K.; Brun, R.; Wenzler, T.; Miao, Y.; Wilson, W. D.; Generaux, C.; Bridges, A.; Hall, J. E.; Boykin, D. W. *J. Med. Chem.* **2006**, *49*, 5324.

(9) Intermolecular opening of terminal epoxides by hydroxylamine (**7**→**8**): (a) Kliegel, W. *Chem. Ber.* **1969**, *102*, 1776. (b) Dąbkowska, K.; Dąbrowska, P.; Drabik, J.; Kopczuk, D.; Plenkiewicz, J.; Strosznajder, J. B.; WielechowskaM., *Synth. Commun.* **2005**, 1455. (c) Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405.

(10) Intramolecular cyclizsation of unsubstituted hydroxylamines, generated in situ by reduction of nitro groups, onto nitriles (**8** → **10**): (a) Buckley, G. D.; Elliot, T. J. *J. Chem. Soc.* **1947**, 1508. (b) Munshi, K. L.; Kohl, H.; de Souza, N. J. *J. Heterocycl. Chem.* **1977**, *14*, 1145. (c) Belley, M.; Sauer, E.; Beaudoin, D.; Duspara, P.; Trimble, L. A.; Dubé, P. *Tetrahedron Lett.* **2006**, *47*, 159.

(11) The intermolcular opening of epoxides by hydroxyamidines (an intermolecular variant of **9** → **10**) has been discussed in a hypothetical context in a Japanese patent, but no examples were reported; see: Katoh, S.; Sayama, S.; Shibata, S.; Uchida, I. Preparation of Benzopyran Derivatives as Antihypertensives and Vasodilators. PCT Int. Appl. WO 9219611, 1992.

(12) de Raadt, A.; Klempier, N.; Faber, K.; Griengl, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 137.

(13) "Assay yield" refers to a nonisolated solution yield of product as determined by comparison of product UV absorbance with that of pure, authentic product standard using HPLC analysis.

or NMR spectroscopy were unsuccessful. This suggests that the intermolecular step may be rate-limiting under these conditions but does not enable distinction between the possible sequences of events.

The structural determination of products **13** and **14** warrants further comment, using **13** as an example. As shown in Figure 2, there are four potential structures for a

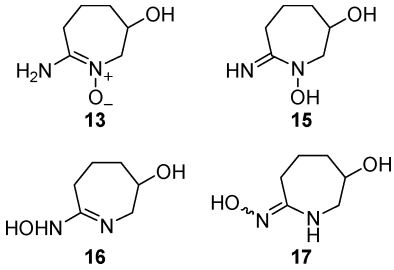
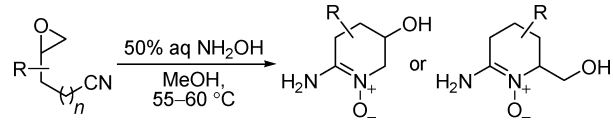


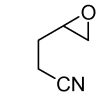
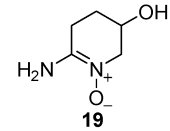
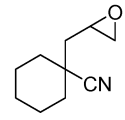
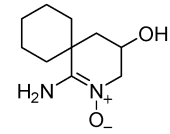
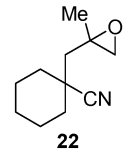
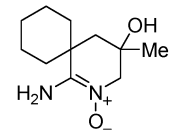
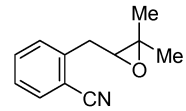
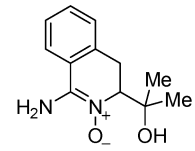
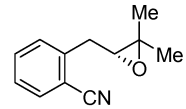
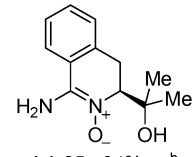
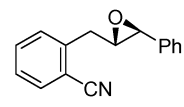
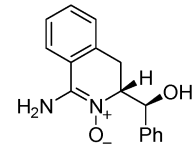
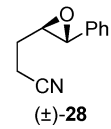
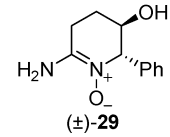
Figure 2. Aminonitrone **13** and other structures considered.

7-membered cyclization product; note that **13** and **15** are tautomers, as are **16** and **17**. NMR spectroscopy (including $^{1}H-^{15}N$ HMBC)[14] confirmed the C−N connectivity and location of the double bond in an endocyclic position, thus ruling out **15** and **17**, but could not unequivocally establish the site of *N*-oxidation, i.e., distinguish between aminonitrone **13** and hydroxyamidine **16**. Previous reports have highlighted the difficulty in rigorously differentiating these two structural motifs.[15] Assignment of structure **13** rather than **16** to the 7-membered product was ultimately made by analogy with related derivatives (vide infra).

The substrate scope of this cascade reaction was then expanded with a small series of examples (Table 1). The isolated yields were uniformly moderate, although a single set of reaction conditions was used, which was not optimized for each individual case. Furthermore, all of the products were isolated by crystallization, with no requirement for aqueous workup or chromatography.[16] The observed cyclization products were formed with high selectivity for the 6-membered ring[17] and in each case were isolated as single regioisomers with the double bond located within the ring. If the reaction proceeds via an intermolecular nitrile addition/intramolecular epoxide-opening pathway, then examination of molecular models provides a convenient explanation for this selectivity. By this simple analysis, the transition state for 5-*exo* epoxide opening would be considerably more strained than for the corresponding 6-*endo* process (Table 1, entries 1−3 and 7). Conversely, compared to the acyclic

Table 1. Further Examples of the Cascade Cyclization



entry	ω-epoxynitrile	product	yield[a]
1	 **18**	 **19**	47
2	 **20**	 **21**	56
3	 **22**	 **23**	52
4	 **24**	 **25**	51
5	 **(−)-24** 95% *ee*	 **(−)-25** >94% *ee*[b]	45
6	 **(±)-26**	 **(±)-27**	59
7	 **(±)-28**	 **(±)-29**	61

[a] Isolated yield. [b] ee of the crude product before isolation.

example in Scheme 3, the rigidity imposed by incorporation of two more sp^2 carbon atoms into the tether in entries 4−6 of Table 1 now favors the 6-*exo* over the 7-*endo* mode of cyclization. An alternative explanation would be that intermolecular epoxide opening by hydroxylamine occurs first at the less hindered carbon in each case, followed by cyclization onto the nitrile group.

The data currently available unfortunately does not allow for a definitive assessment of which of these two overall mechanistic scenarios is indeed operative. However, evidence for an S_N2-based mechanism of epoxide opening could be

(14) See the Supporting Information for details.

(15) (a) Nicholas, G. M.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341. (b) Forrester, A. R.; Irikawa, H.; Thomson, R. H.; Woo, S. O.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1712. (c) Forrester, A. R.; Thomson, R. H. *Spectrochim. Acta* **1963**, *19*, 1481.

(16) Byproducts in the reaction mixtures, tentatively identified by HPLC−MS as resulting from competing nitrile hydrolysis or epoxide opening by MeOH or H_2O, were generally observed but were efficiently rejected during crystallization of the aminonitrone products.

(17) Determined by HPLC and/or ^{1}H NMR analysis of the crude reaction mixtures.

established; *trans*-1,2-disubstituted epoxides (±)-**26** and (±)-**28** gave the corresponding *trans*-disubstituted products (±)-**27** and (±)-**29**, respectively, as single diastereoisomers (Table 1, entries 6 and 7), and cyclization of optically active substrate (−)-**24** proceeded with no erosion of stereochemical integrity (Table 1, entry 5).

Crystals of cyclization products **19** and **23** suitable for X-ray single-crystal analysis were grown by slow evaporation from EtOAc/MeOH and MeCN/MeOH, respectively, providing rigorous proof of the proposed aminonitrone structures for these two compounds (Figure 3).[18−20] By analogy,

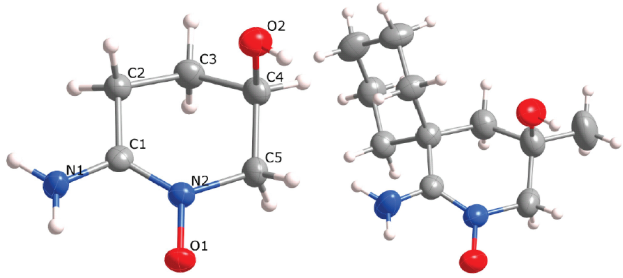
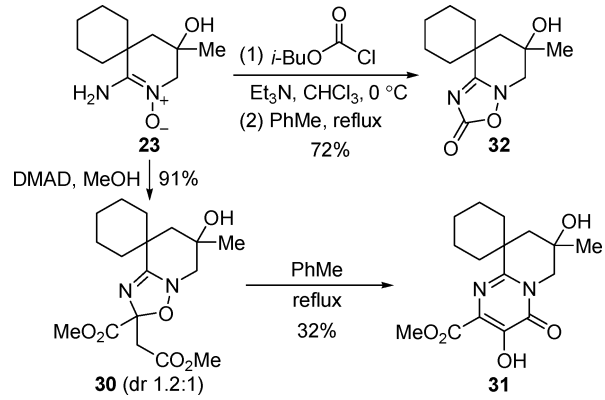


Figure 3. X-ray crystal structures of aminonitrones **19** (left) and **23** (right).

therefore, the other cascade products were assigned the corresponding aminonitrone structures illustrated in Scheme 3 and Table 1.

Literature reports on aminonitrones have focused largely on the preparation or spectroscopic properties of these compounds; they have found only sporadic use as reagents in organic synthesis themselves.[19a,c] To add to the repertoire of synthetically useful transformations that these species undergo, aminonitrone **23** was treated with DMAD in MeOH, leading to the formation of 1,2,4-oxadiazoline **30** in excellent yield (Scheme 4).[21] Refluxing a solution of **30** in PhMe then provided polycyclic pyrimidone **31**. This sequence demonstrated that the aminonitrone structure can be utilized in the same manner as the tautomeric amidoximes employed previously (cf. Scheme 1).[4b,c] Alternatively, acylation of **23** with isobutyl chloroformate followed by thermal cyclization generated 1,2,4-oxadiazolone **32** in good overall yield.

Scheme 4. Manipulation of Aminonitrone **23**



In summary, we have discovered and developed a new cascade reaction between ω-epoxynitriles and hydroxylamine that offers a concise, stereocontrolled route to novel functionalized cyclic aminonitrones. The reaction is generally selective for the formation of 6-membered rings over the corresponding 5- or 7-membered products. The large number of methods for enantioselective epoxide synthesis make this an attractive approach to chiral, cyclic aminonitrones that would be difficult to access by other methods.[22] Finally, the cascade products are themselves amenable to further manipulation.

Acknowledgment. We thank the following individuals from Merck Research Laboratories: W. A. Schafer, T. Brkovic, and Z. Pirzada for chiral SFC analysis, T. J. Novak for assistance with HRMS. We also thank the reviewers for constructive comments.

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

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(18) CCD deposition codes: 730722 (**19**) and 730723 (**23**).

(19) The X-ray analysis revealed extensive intermolecular hydrogen bonding within the crystal lattice of both **19** and **23**. For examples of X-ray structure analysis of other aminonitrones and discussion of potential solid/solution-phase tautomerism, see: (a) Trzewik, B.; Cież, D.; Hodorowicz, M.; Stadnicka, K. *Synthesis* **2008**, 2977. (b) Giumanini, A. G.; Toniutti, N.; Verardo, G.; Merli, M. *Eur. J. Org. Chem.* **1999**, 141. (c) Branco, P. S.; Prabhakar, S.; Lobo, A. M.; Williams, D. J. *Tetrahedron* **1992**, *48*, 6335.

(20) Selected interatomic distances (Å) for **19**: O1−N2 1.3611(16), O2−C4 1.4251(18), N1−C1 1.3322(19), N2−C5 1.4694(19), N2−C1 1.304(2), C1−C2 1.498(2), C2−C3 1.531(2), C3−C4 1.518(2), C4−C5 1.519(2).

(21) Naidu, B. N.; Sorensen, M. E. *Org. Lett.* **2005**, *7*, 1391.

(22) Cyclic aminonitrones have generally been prepared by the reductive cyclization of ω-nitronitriles. For examples, see refs 10a and 15a. For a discussion of synthetic routes to acyclic aminonitrones, see ref 19a.