Regio- and Stereoselective Fe(III)- and Pd(0)-Mediated Ring Openings of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene Systems

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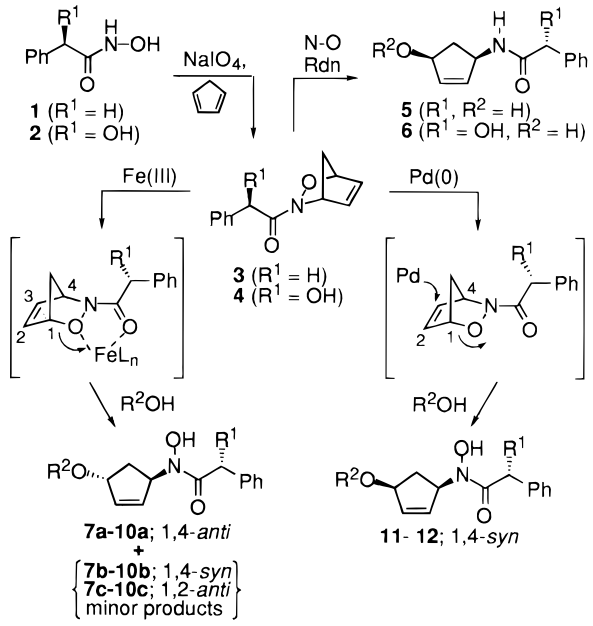
We wish to report the first example of regio- and stereoselective Lewis acid and Pd(0)/Brønsted acid-mediated ring openings of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems (**3** and **4**) to selectively afford versatile *anti*-1,4- and *syn*-1,4-disubstituted cyclopentene-derived hydroxamic acids[1] (**7a**−**10a**, **11**, and **12**), respectively (Scheme 1). 3-Aza-2-oxabicyclo-[2.2.1]hept-5-ene systems, derived from the hetero Diels−Alder reaction between transient acylnitroso species and cyclopentadiene,[2] serve as valuable precursors to carbocyclic nucleosides[3] and aminocyclopentenol-containing natural products[4] through commonly employed N−O bond reductions[5] to afford *syn*-1,4-disubstituted cyclopentenes (**5** and **6**). However, with few examples of modified ring openings,[6] further structural elaboration of the cycloadducts (**3** and **4**) beyond standard N−O bond cleavage has limited their synthetic utility.

During studies designed to utilize acylnitroso-derived Diels−Alder adducts in syntheses of novel amino acids[7] and carbocyclic nucleosides,[3,8] we noted that upon exposure to $FeCl_3$ several of the cycloadducts gave color tests characteristic of free hydroxamic acids.[9] This discovery led us to envision the use of Fe(III) as a Lewis acid to assist in the regioselective opening of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems (**3** and **4**) at the C(1) position, followed by attack of a nucleophile to afford monocyclic *anti*-hydroxamic acids (**7a**−**10a**).

Table 1. Fe(III)- and Pd(0)-Mediated Ring Openings

entry	substrate	conditions	products (% yield)	R^1	R^2
1	**3**	$FeCl_3$, MeOH	**7a** (75), **7b**,**c** (18)	H	CH_3
2	**4**	$FeCl_3$, MeOH	**8a** (65), **8b**,**c** (27)	OH	CH_3
3	**3**	Fe(III) citrate, H_2O, THF	**9a** (65), **9b** (26)	H	H
4	**4**	Fe(III) citrate, H_2O, THF	**10a** (75), **10b**,**c** (13)	OH	H
5	**3**	$Pd(PPh_3)_4$, AcOH, THF	**11** (86)	H	Ac
6	**4**	$Pd(PPh_3)_4$, AcOH, THF	**12** (87)	OH	Ac

Scheme 1



Our studies began with the syntheses of *N*-phenylacetyl cycloadduct **3**[10] and known optically pure cycloadduct **4** from hydroxamates **1** and **2**, respectively (Scheme 1).[2c,d] Indeed, treatment of **3** with 0.3 equiv of $FeCl_3$ in methanol at 0 °C for 15 min induced ring opening and afforded *anti*-1,4-disubstituted cyclopentene **7a** (R^1 = H, R^2 = CH_3) in 75% yield as well as 18% of a mixture of two inseparable products, assigned as 1,4-*syn* **7b** and 1,2-*anti* **7c**[11] on the basis of NMR and mass spectral analyses of the mixture (Table 1, entry 1). The regio- and stereochemistry of hydroxamic acid **7a** was determined by the coupling pattern of the C(5) methylene protons[12] and through decoupling and COSY experiments. Similar reaction of **4** with $FeCl_3$ in methanol gave comparable ratios of the corresponding products **8a**−**c** (R^1 = OH, R^2 = CH_3) (entry 2).

In an attempt to provide more insight into the scope of this reaction, we conducted experiments with cycloadduct **3** under Brønsted acid conditions. Treatment of **3** with

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(9) N-Acylated cycloadducts such as **3**, when exposed to $FeCl_3$ solution (5% $FeCl_3 \cdot 6H_2O$ in 0.5 N HCl), stain dark purple, typical of free hydroxamic acid chelation to Fe(III).

(10) For the synthesis of phenylacetohydroxamic acid **1**, see: Defoin, A.; Fritz, H.; Schmidlin, C.; Streith, J. *Helv. Chim. Acta* **1987**, *70*, 554. For the synthesis of cycloadduct **3**, see the Supporting Information.

(11) See Scheme 2, hydroxamic acid **14**, for an example of a 1,2-disubstituted cyclopentene.

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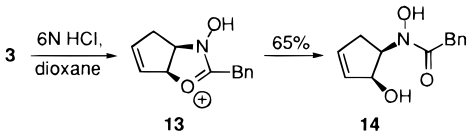
Scheme 2



13 14

methanolic HCl for 1 h at 0 °C afforded a complex mixture of products with low mass recovery (<60%). This result agreed with previous results obtained when amino acid-derived cycloadducts[3,7] were exposed to HCl solutions[13] as well as results obtained by Procter and co-workers when mandelic acid-derived cycloadduct **4** was treated with methanolic HCl.[6b,c] Interestingly, further studies by Procter and co-workers revealed that use of alternative acidic conditions (6 N HCl in dioxane) induced a relatively clean rearrangement of mandelic acid-derived cycloadduct to a monocyclic cyclopentene-derived hydroxylamine hydrochloride salt.[6b] Our treatment of **3** with 6 N HCl in dioxane similarly afforded 1,2-disubstituted cyclopentenol hydroxamate **14** in 65% yield. On the basis of Procter's analysis of the chemistry of **4**,[6b] a plausible route to **14** from **3** would involve acid-catalyzed ring opening, followed by trapping of an intermediate allyl cation to give **13**, and then subsequent hydrolysis (Scheme 2). Thus, use of ferric ion (Scheme 1) dramatically influences the outcome of ring opening of 3-aza-2-oxabicyclo-[2.2.1]hept-5-ene derivatives.

If the chelation effect were generally operative, use of Fe(III)-mediated opening of **3** under aqueous conditions was anticipated to complement the protic process leading to the 1,2-substitution pattern and give a 1,4-product. Indeed, treatment of **3** with Fe(III) citrate[14] in $H_2O/THF/CH_3CN$ afforded *anti*-1,4-hydroxamic acid **9a** ($R^1 = R^2 = H$) in 65% yield as well as *syn*-1,4-isomer **9b** in 27% yield (entry 3). The 1,2-regioisomer **9c**, which would have been derived from an S_N1' attack at the C(3) position α to the hydroxamic acid moiety or through hydrolysis of an intermediate such as **13**, was not observed. Similar Fe(III) citrate-mediated ring opening of **4** also produced the corresponding *anti*-1,4-hydroxamic acid **10a** ($R^1 = OH$, $R^2 = H$) in 75% yield as the major product (entry 4).

Other Lewis acids [$InCl_3$, $CeCl_3$, $ZnCl_2$, $Pd(OAc)_2$] were briefly surveyed to determine the generality of ring opening of **3**. None were as effective as Fe(III), and results with Zn(II) were among the best of the alternatives. Treatment of a methanolic solution of cycloadduct **3** with $ZnCl_2$ at room temperature for 2 h afforded hydroxamic acid **7a** in a 62% yield along with a mixture of regioisomers (**7b**,**c**) in 35% yield. The Zn(II)-mediated reaction not only required an excess of $ZnCl_2$ (2 equiv) but was slower than the Fe(III)-mediated reaction, possibly indicative of the higher binding affinity of Fe(III) to hydroxamic acid functionality in comparison to that of Zn(II). This experiment, along with those described earlier, indicates that the reaction may depend on both the acidic nature of the reaction media and on the coordinating ability of the Lewis acid, with ferric ion being optimal from these early studies.

The encouraging regio- and stereoselective Lewis acid-mediated ring opening leading to *anti*-1,4-disubstituted cyclopentenes led us to envision the utilization of other metal species such as Pd(0)[6a,15] in controlled ring opening to afford alternative *syn*-1,4-products **11** and **12**. Indeed, treatment of a THF solution of **3** with $Pd(PPh_3)_4$ and acetic acid (4 equiv) for 45 min afforded *syn*-1,4-hydroxamic acid **11** ($R^1 = H$, $R^2 = Ac$) as the exclusive product in 86% yield (entry 5). Similar reaction of a THF solution of **4** with $Pd(PPh_3)_4$ and acetic acid (4 equiv) for 90 min afforded exclusively *syn*-1,4-hydroxamic acid **12** ($R^1 = OH$, $R^2 = Ac$) (entry 6).

In summary, we have developed new methodologies that separately provide *anti*-1,4- (**7a**−**10a**) and *syn*-1,4-hydroxamic acid-derived cyclopentenes (**11** and **12**) through novel regio- and stereoselective Fe(III)- and Pd(0)-assisted ring openings of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems. These processes enhance the chemical versatility of the Diels−Alder adducts and complement standard N−O reduction processes currently used to provide functionalized *syn*-1,4-substituted cyclopentenes (**5** and **6**). These new methodologies, combined with other potential nucleophiles, provide several routes to synthetically useful disubstituted cyclopentenes. Extension to other acylnitroso-derived cycloadducts are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for **3**, **8a**, **9b**, and **12** (15 pages).

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(12) The C(5) protons of 1,4-aminocyclopentenol systems have a very characteristic coupling pattern. The C(5) protons of *syn*-1,4-aminocyclopentenols have a very characteristic overlapping ddd pattern, with approximate *J* values of 3.9, 3.9, and 14.7 Hz and 7.8, 7.8, and 14.7 Hz for the *cis*- and *trans*-methylene protons, respectively. There is normally a difference in chemical shift ranging from 0.8 to 1.3 ppm between each respective C(5) proton. The C(5) protons of *anti*-1,4-aminocyclopentenols have a characteristic ddd pattern, with approximate *J* values of 3.9, 7.1, and 13.6 Hz with a smaller chemical shift, ranging from 0.2 to 0.35 ppm between the two C(5) protons. For example, in the transformation of cycloadduct **3** into hydroxamic acids **9a** and **9b**, the regiochemistry can be determined by decoupling experiments (COSY). The stereochemistry of the two can be determined through their coupling patterns. Hydroxamic acid **9a** has the following ^1H NMR pattern: δ 1.71 (ddd, $J = 3.3, 8.1, 13.6$ Hz, 1H) and 2.06 (ddd, $J = 3.9, 7.1, 13.6$ Hz, 1H), clearly showing trans-coupling. Hydroxamic acid **9b** has the following ^1H NMR pattern: δ 1.62 (overlapping ddd, $J = 6.6, 6.6, 12.6$ Hz, 1H) and 2.38 (overlapping ddd, $J = 7.2, 7.2, 12.6$ Hz, 1H), clearly displaying cis-coupling.

(13) Unpublished results in our laboratories have shown that treatment of amino acid-derived cycloadducts with any of the following conditions led to a complex mixture of products: (a) TFA, CH_2Cl_2; (b) TMSCl, NaI, CH_3CN, −43 °C; (c) HBr, HOAc, CH_2Cl_2; (d) HCl, EtOAc.

(14) Fe(III) citrate was used instead of $FeCl_3$ in order to provide a milder, less acidic form of Fe(III).

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