



Brønsted acid-mediated opening of nitroso cycloadducts under anhydrous conditions

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ARTICLE INFO

Article history:

Received 5 November 2008

Revised 26 November 2008

Accepted 29 November 2008

Available online 6 December 2008

Keywords:

Acynitroso

Nitrosocarbonyl

Hetero-Diels–Alder

Brønsted acid

Hydroxamate

Nitrone

Oxazine

ABSTRACT

An unusual bicyclic hydroxamate resulted from C–O bond cleavage of acynitroso hetero-Diels–Alder cycloadducts when treated with catalytic Brønsted acids under anhydrous conditions. Similarly, the formation of a nitrone was observed using one equivalent of triflic acid.

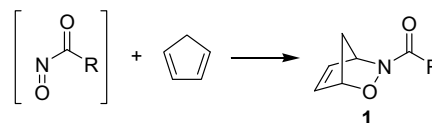
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Bicyclic oxazines **1**, derived from acynitroso hetero-Diels–Alder reactions, are important intermediates in the synthesis of natural products and biologically active molecules (Scheme 1).¹ Selective modification of bicyclic oxazines **1**, most commonly through N–O bond reduction,² has been used toward the synthesis of carbocyclic nucleosides³ and natural products.⁴

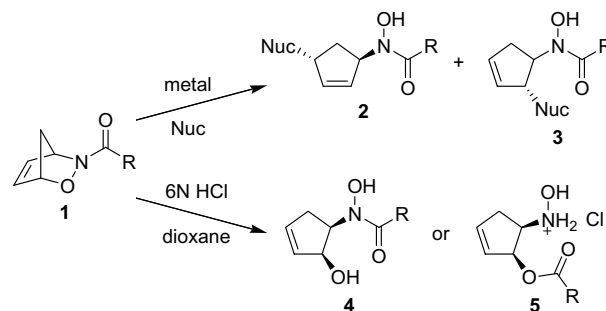
The C–O bond of cycloadducts **1** can also be cleaved using Grignard reagents,⁵ alkylzinc species,⁶ Pd(0),⁷ and Lewis acids⁸ to generate compounds such as hydroxamates **2** and **3** (Scheme 2). Previously, work by Miller^{8b} and Procter⁹ reported C–O bond cleavage with aqueous Brønsted acids that yielded hydroxamates **4** and hydroxylamine salt **5**, respectively. This report describes the products that arise from treatment of cycloadducts **1** with Brønsted acids under anhydrous conditions.

Treatment of cycloadduct **6**¹⁰ with 35 mol % of *p*-toluenesulfonic acid in dichloromethane at ambient temperature produced the bicyclic hydroxamate **7** in low yield (Scheme 3). In an attempt to probe and optimize the formation of hydroxamate **7**, we treated cycloadduct **6** with a variety of Brønsted acids under anhydrous conditions (Table 1). Stronger acids provided higher yields of hydroxamate **7**. As an example, whereas 5 mol % of *p*-toluenesulfonic acid resulted in an incomplete conversion of cycloadduct **6** to hydroxamate **7** in 2 h, 5 mol % of triflic acid produced hydroxamate **7** in 52% yield in only 30 min (Table 1, entries 2 and 4).

Trifluoroacetic acid failed to produce any hydroxamate **7** and resulted in nearly quantitative recovery of cycloadduct **6** (Table 1, entry 3). Using the sulfonic acid-based resin, Amberlyst 15, we did not observe complete conversion of cycloadduct **6** to hydroxamate **7** (Table 1, entry 7). The use of only 2 mol % of triflic acid in



Scheme 1. The acynitroso hetero-Diels–Alder reaction.



Scheme 2. C–O bond cleavage reactions of acynitroso cycloadducts.

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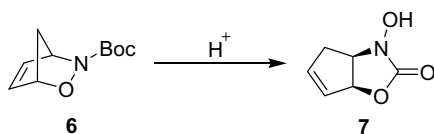
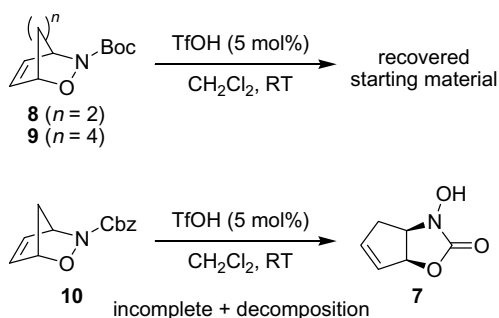
Scheme 3. Brønsted acid-mediated opening of cycloadduct **6**.

Table 1

Formation of hydroxamate **7** from cycloadduct **6**

Entry	Acid (amount)	Conditions ^a	Result/yield ^b
1	<i>p</i> TsOH (35 mol %)	CH ₂ Cl ₂ , rt, 2 h	20%
2	<i>p</i> TsOH (5 mol %)	CH ₂ Cl ₂ , rt, 4 h	Incomplete rxn ^c
3	TFA (5 mol %)	CH ₂ Cl ₂ , rt, 2 h	Recovered 6
4	TfOH (5 mol %)	CH ₂ Cl ₂ , rt, 2 h	52%
5	TfOH (5 mol %)	CH ₂ Cl ₂ , rt, 30 min	62%
6	TfOH (2 mol %)	THF, 0 °C, 1 h	74%
7	Amberlyst 15 ^d	THF, rt, 5 days	Incomplete rxn ^c

^a Reactions monitored by TLC.^b Isolated yields reported.^c Less than 5% conversion was estimated from TLC.^d Sulfonic acid-based resin.

Scheme 4. Treatment of other cycloadducts with triflic acid.

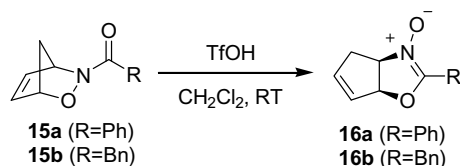
tetrahydrofuran at 0 °C was found to be optimal for producing hydroxamate **7**, which could easily be obtained from the reaction mixture directly in high yield and purity by trituration with ether (Table 1, entry 6).¹¹

Encouraged by these results, we proceeded to investigate whether cycloadducts derived from larger cyclic dienes could also form bicyclic hydroxamate structures similar to hydroxamate **7**. Cycloadducts **8** and **9**¹² were subjected to catalytic triflic acid in dichloromethane; however, no reaction was observed and the starting material was recovered from the reaction unchanged (Scheme 4). When cycloadduct **10** was reacted under the same

Table 2

Formation of nitrones **16a** and **16b** using triflic acid

Entry	Substrate	TfOH (amt.)	Yield/result ^a
1	15a	5 mol %	Recovered 15a
2	15b	5 mol %	Recovered 15b
3	15a	108 mol %	16a (20%)
4	15b	108 mol %	Decomposition

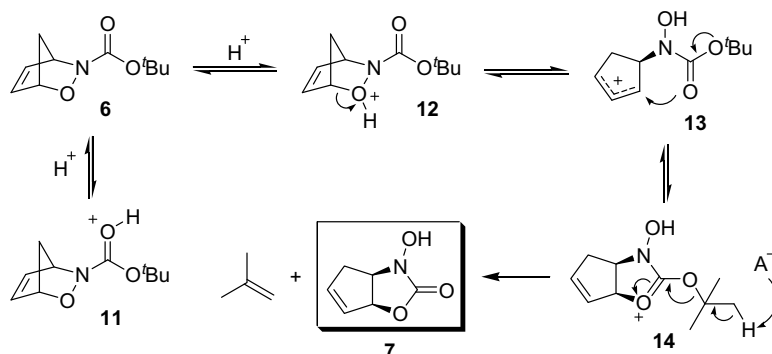
^a Isolated yields reported.

Scheme 6. Brønsted acid-promoted formation of nitrones.

conditions, hydroxamate **7** was observed in addition to considerable decomposition.

Based on similar reactions reported by Procter,^{9a} a mechanism for the reaction has been proposed (Scheme 5). We proposed that protonation of cycloadduct **6** yielded species **11** and/or **12**. Protonated species **11** could result in the loss of the Boc protecting group; however, products arising from this pathway were not directly observed in our studies. C–O bond cleavage of species **12** resulted in the cationic species **13**, which upon intramolecular cyclization yielded compound **14**. Loss of isobutylene from compound **14** produced hydroxamate **7** and regenerated the acid catalyst. We hypothesized that the difficulty of losing the benzyl group accounted for the low yield of hydroxamate **7** observed when cycloadduct **10** was treated with triflic acid. The lack of hydroxamate formation observed for cycloadducts **8** and **9** may have been due to a decreased amount of ring strain which has been observed for the bicyclo[2.2.2]- and bicyclo[2.4.2]oxazine systems as compared to bicyclo[2.2.1]oxazines such as compound **6**.¹³

Procter has also described the formation of a nitrone from treatment of mandelic acid-derived cycloadducts under aqueous acid conditions.^{9a} We were interested to probe whether cycloadducts **15a** and **15b** would form nitrones **16a** and **16b**, respectively, under our anhydrous conditions (Scheme 6). Using the catalytic conditions explored for cycloadducts **6**, **8**, **9**, and **10**, we found no evidence of nitrones **16a** and **16b** in the reaction mixture (Table 2, entries 1 and 2). Using one full equivalent of triflic acid, we were able to obtain nitrone **16a** from cycloadduct **15a** in low yield;¹⁴ however, cycloadduct **15b** decomposed under the same reaction conditions (Table 2, entries 3 and 4).

Scheme 5. Proposed mechanism for the formation of compound **7** from cycloadduct **6**.

A possible explanation for why nitron **16a** was recovered from the reaction mixture whereas nitron **16b** was not observed may be attributed to the greater stability of nitron **16a** due to resonance stabilization. A similar reasoning has been proposed by Procter^{9a} for the formation of nitrones from cycloadducts derived from mandelic acid.

The formation of bicyclic structures such as hydroxamate **7** from bicyclic acylnitroso hetero-Diels–Alder adducts **1** has not been previously disclosed in the literature; however, this does not discount the possibility of structures such as these existing as intermediates in Lewis acid- or Brønsted acid-mediated cleavage reactions of cycloadducts **1**. We hope that the chemistry we describe here can be adapted toward exploring mechanisms of other ring-opening reactions of cycloadducts **1** and can help expand the use of acylnitroso hetero-Diels–Alder reactions in organic synthesis.

Acknowledgments

We gratefully acknowledge support from the NIH (GM 075855 and GM 068012). We would also like to thank Jaroslav Zajicek, and Nonka Sevova for their assistance with spectroscopic analysis.

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- Formation of cycloadduct **6** has been described: Zhang, D.; Sueling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885–888.
- Formation of hydroxamate **7**: Cycloadduct **6** (1.07 g, 5.40 mmol) was dissolved in 50 mL of anhydrous THF. The solution was cooled in an ice/H₂O bath and trifluoromethanesulfonic acid (0.010 mL, 0.11 mmol) was added. The mixture was stirred in the ice/H₂O bath under Ar and monitored for the disappearance of cycloadduct **6** by TLC. After 1 h, the mixture was warmed to rt and concentrated to a yellow oil. Pure hydroxamate **7** was obtained as a white powder by trituration with ether (0.562 g, 74% yield). ¹H NMR (500 MHz, DMSO-*d*₆, 40 °C) δ 9.72 (s, 1H), 6.12 (d, *J* = 5.0 Hz, 1H), 5.85 (d, *J* = 5.0 Hz, 1H), 5.41 (d, *J* = 7.0 Hz, 1H), 4.34 (t, *J* = 6.0 Hz, 1H), 2.54 (m, 2H) ppm. ¹³C NMR (125 MHz, DMSO-*d*₆, 40 °C) δ 156.1, 135.9, 128.2, 81.4, 59.3, 36.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₆H₈NO₃⁺, 142.0504; obsd, 142.0521.
- Formation of cycloadducts **8** and **9** was carried out according to Ref. 13.
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- Formation of nitron **16a**: Cycloadduct **15a** (0.104 g, 0.517 mmol) was dissolved in 10 mL of anhydrous CH₂Cl₂. Trifluoromethanesulfonic acid (0.050 mL, 0.56 mmol) was added and the solution was stirred at rt under Ar and monitored for the disappearance of cycloadduct **15a**. After 15 min, saturated NaHCO₃ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to yield an off-white residue. The residue was chromatographed through 10 g of silica using 100% CH₂Cl₂ and yielded **16a** as a yellow residue (19.5 mg, 20% yield). *R*_f = 0.48 (1:1 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.41 (m, 3H), 6.09 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.97 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.37 (m, 1H), 4.39 (q, *J* = 3.9 Hz, 1H), 2.71 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 172.6, 133.9, 130.7, 129.6, 128.2, 125.9, 81.8, 72.0, 37.4 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₂H₁₂NO₂⁺, 202.0868; obsd, 202.0869.