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Brønsted acid-mediated opening of nitroso cycloadducts under anhydrous conditions

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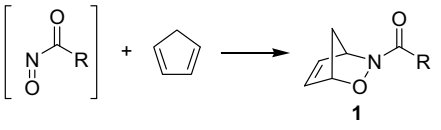
ABSTRACT

An unusual bicyclic hydroxamate resulted from C–O bond cleavage of acylnitroso 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.

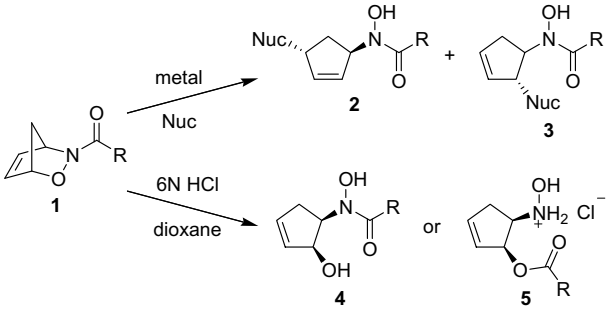
Bicyclic oxazines **1**, derived from acylnitroso hetero-Diels–Alder reactions, are important intermediates in the synthesis of natural products and biologically active molecules (Scheme 1).[1] Selective modification of bicyclic oxazines **1**, most commonly through N–O bond reduction,[2] has been used toward the synthesis of carbocyclic nucleosides[3] 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 acids[8] to generate compounds such as hydroxamates **2** and **3** (Scheme 2). Previously, work by Miller[8b] and Procter[9] 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 acylnitroso hetero-Diels–Alder reaction.



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

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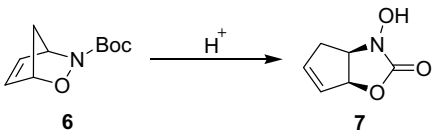
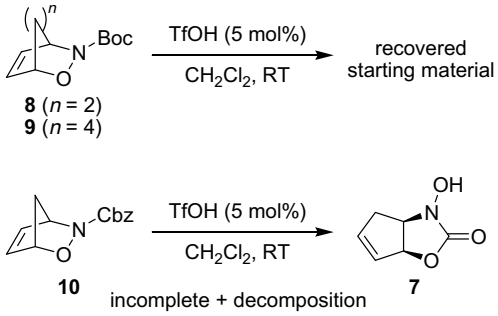


Scheme 3. Brønsted acid-mediated opening of cycloadduct **6**.

Table 1
Formation of hydroxamate **7** from cycloadduct **6**

Entry	Acid (amount)	Conditions[a]	Result/yield[b]
1	*p*TsOH (35 mol %)	CH_2Cl_2, rt, 2 h	20%
2	*p*TsOH (5 mol %)	CH_2Cl_2, rt, 4 h	Incomplete rxn[c]
3	TFA (5 mol %)	CH_2Cl_2, rt, 2 h	Recovered **6**
4	TfOH (5 mol %)	CH_2Cl_2, rt, 2 h	52%
5	TfOH (5 mol %)	CH_2Cl_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.

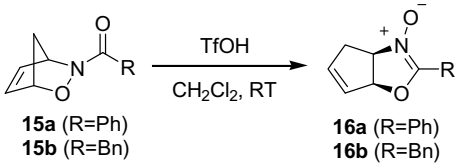
tetrahydrofuran at 0 °C was found to be optimal for producing hydroxamate **7**, which could easily be obtained from the reaction mixture directly in high yield and purity by trituration with ether (Table 1, entry 6).[11]

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

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

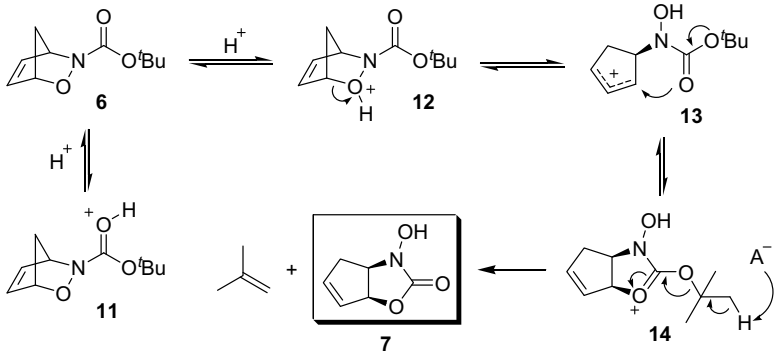
[a] Isolated yields reported.



Scheme 6. Brønsted acid-promoted formation of nitrones.

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 nitrone **16a** was recovered from the reaction mixture whereas nitrone **16b** was not observed may be attributed to the greater stability of nitrone **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.

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10. Formation of cycloadduct **6** has been described: Zhang, D.; Sueling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885–888.
11. *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/H_2O bath and trifluoromethanesulfonic acid (0.010 mL, 0.11 mmol) was added. The mixture was stirred in the ice/H_2O 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). ^{1}H 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. ^{13}C 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 $C_6H_8NO_3^+$, 142.0504; obsd, 142.0521.
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14. *Formation of nitrone* **16a**: Cycloadduct **15a** (0.104 g, 0.517 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2. 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 $NaHCO_3$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield an off-white residue. The residue was chromatographed through 10 g of silica using 100% CH_2Cl_2 and yielded **16a** as a yellow residue (19.5 mg, 20% yield). R_f = 0.48 (1:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) 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. ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{12}NO_2^+$, 202.0868; obsd, 202.0869.