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Stereoselective Cycloadditions of Chiral Acyl-Nitroso Compounds; Hydrolytic Reactions of a Cyclopentadiene Adduct

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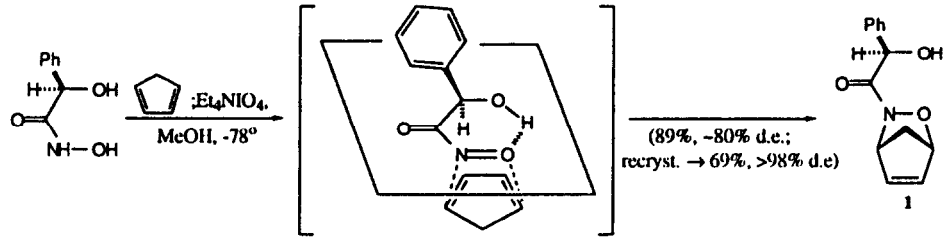
Abstract: Treatment of the adduct between the acyl nitroso intermediate derived from (R)-α-hydroxyphenylacetohydroxamic acid and cyclopentadiene, **1**, with dilute aqueous acid provides a high yield of the cyclopentene **2** hydrochloride, suitable for further synthetically useful transformations.

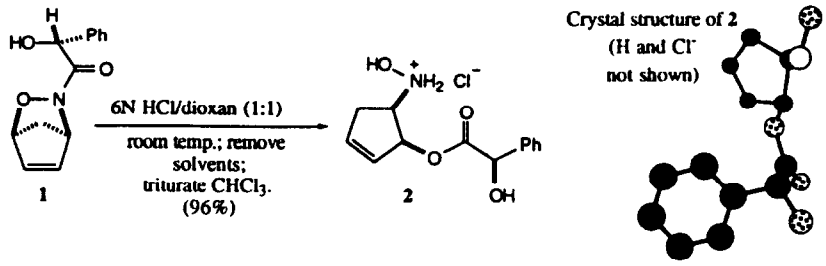
The cycloaddition of acyl-nitroso compounds with dienes is a useful method for the stereocontrolled synthesis of 1,4-amino alcohols and related systems, and has been used in a number of elegant syntheses.[1] Control of the absolute stereochemistry of this cycloaddition has been achieved using various chiral auxiliaries.[2] We are particularly interested in the asymmetric cycloadditions of acyl-nitroso intermediates which use the mandelic acid unit as the chiral controller.[2c] The advantages of using mandelic acid include the ready availability of both enantiomers, the ease of preparation of the corresponding hydroxamic acid[3] [e.g. (*R*)-α-hydroxyphenylacetohydroxamic acid, currently commercially available], the high levels of stereoselectivity possible (up to 93% d.e.), and the crystalline nature of many of the adducts. However, in the case of adducts from cyclopentadienes it can be difficult to remove the chiral auxiliary without extensive decomposition. In this and the following Letter we report some unexpected and potentially useful chemistry encountered in recent work on this problem.



Scheme 1

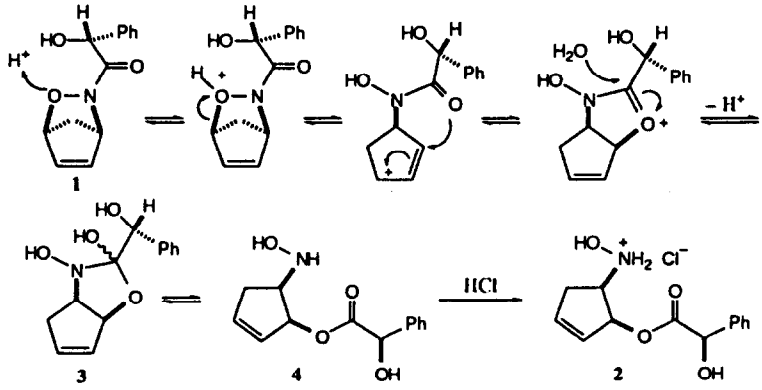
Treatment of the adduct derived from cyclohexadiene with mild anhydrous acid results in removal of the chiral auxiliary,[2b,2c] but exposure of the adduct **1** from cyclopentadiene (Scheme 1) to the same conditions results in extensive decomposition of the bicyclic unit. This problem appears to be related to the presence of the double bond in the 2,3-oxazabicyclo[2,2,1] framework.[4]

In view of the above, we were interested to find that treatment of adduct **1** with dilute aqueous acid provided a crystalline product in high yield as a single diastereoisomer[5] (300MHz ^{1}H nmr spectroscopy) (Scheme 2). Adduct **1** had clearly undergone significant structural change, and the structure and stereochemistry of the product **2** were deduced from its physical and chemical properties, confirmed by X-ray crystallographic structure determination.[6]



Scheme 2

Any mechanistic scheme for the formation of **2** must account (*inter alia*) for the success of aqueous acidic conditions compared to anhydrous conditions, the formation of a single diastereoisomer, the stereochemistry of this diastereoisomer, and the apparent requirement for a double bond in the bicyclic system. A simple mechanistic scheme such as that shown in Scheme 3 would appear to be consistent with these observations.[7]

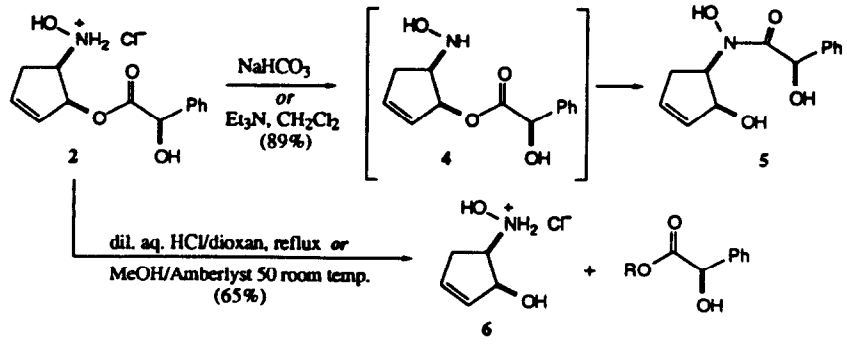


Scheme 3

The relative and absolute stereochemistry (proved by X-ray crystallography) of **2** follow from the mechanistic scheme shown in Scheme 3. An important aspect of this scheme is the intermediacy of the tetrahedral intermediate **3**, which can break down to **4**. Presumably the equilibria shown in Scheme 3 are driven to the right by the irreversible formation of the hydrochloride **2**. This scheme is also consistent with the observation that methanolysis (anhydrous MeOH/HCl) does not produce **2** or related products, as the tetrahedral intermediate analogous to **3** (if formed at all) could not break down to ester **4** or related products.[8]

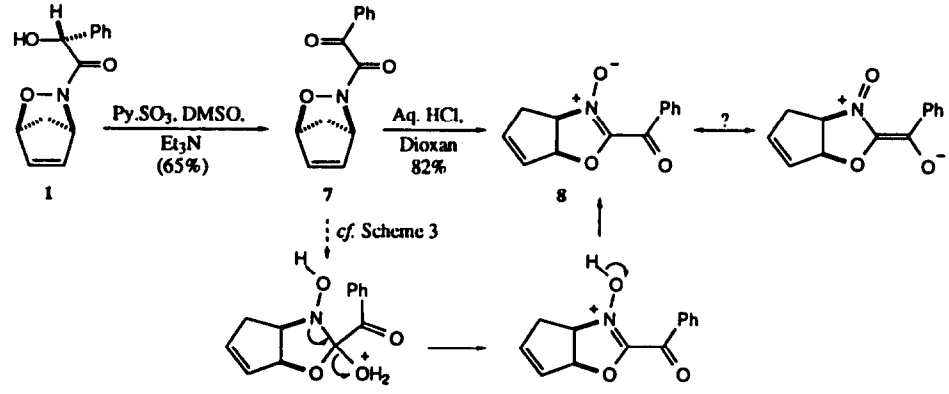
The ready availability of **2** has allowed the investigation of some of its simple chemistry. Neutralization (e.g. aqueous sodium hydrogen carbonate) of a solution of **2** produces the hydroxamic acid **5** in high yield. Of more interest is the removal of the chiral auxiliary on exposure of **2** to further mild acid. Treatment of **2** with either aqueous hydrochloric acid or acidic ion-exchange resin in methanol removes the chiral auxiliary and produces the hydrochloride **6** in good yield (Scheme 4).

Ketone **7**, derived by oxidation of adduct **1**, on treatment under the aqueous acidic conditions which convert **1** into **2** provided a further unexpected result. Rather than the expected hydrochloride corresponding to **2**, a compound which is formulated as **8** was obtained cleanly. Although crystals suitable for X-ray crystallography could not be obtained for definitive structural proof, the physical and chemical properties of



Scheme 4

this product are consistent with the proposed structure **8**.[9] The reason for this change in product is not obvious, but it is possible that the reaction might be diverted because the product **8** might be stabilized by resonance.[10]



Scheme 5

In addition to the interesting mechanistic aspects of the formation of **2** and **8** the results described here represent valuable advances from the point of view of potential synthetic applications of adduct **1**, in that two simple steps may be used to convert this adduct into **2**, **5**, or **6**, which could find useful applications in asymmetric synthesis.

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1. For leading references see Streith, J.; Defoin, A. Synthesis, 1994, 1107.
2. For example, a) Defoin, A.; Fritz, H.; Schmidlin, C.; Streith, J. *Helv. Chim. Acta*, 1987, **70**, 554-569. b) Kirby, G.W.; Nazeer, M. *Tetrahedron Lett.*, **1988**, *29*, 6173-6174, and *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1397-1402. c) Miller, A.; Paterson, T. McC.; Procter, G. *Synlett*, **1989**, *1*, 32-34, and Miller, A.; Procter, G. *Tetrahedron Lett.*, **1990**, *31*, 1041. d) Brouillard-Poichet, A.; Defoin, A.; Streith, J. *Tetrahedron Lett.*, **1989**, *30*, 7061-7064. e) Gouverneur, V.; Ghosez, L. *Tetrahedron Asymmetry*, **1990**, *1*, 363-366. f) Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron Asymmetry*, **1991**, *2*, 1173-1176. g) Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.*, **1992**, *33*, 3583-3586. h) Cardillo,

B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M.J.N. *Tetrahedron Asymmetry*, **1994**, *5*, 1535-1540.

3. King, S.B.; Ganem, B. J. Amer. Chem. Soc., **1994**, *116*, 562-570.
4. Hydrolysis of systems in which the double bond is absent undergo normal hydrolysis; Muxworthy, J.P. and Procter, G., unpublished observations.
5. Adduct **1** (7.6 g, 0.033 mol) in dioxane (60 ml), hydrochloric acid (5M, 7.6 ml), and water (20 ml) was stirred at room temperature for 2h. More hydrochloric acid (5M, 2.0 ml) was added and after a further 90 min the mixture was concentrated *in vacuo*. The resulting solid was triturated with chloroform, the residue filtered, washed with chloroform, and dried to give essentially pure **2** (9.23g, 98%). Crystallization of a sample (MeOH/EtOAc) gave colourless crystals, m.p. 150° (dec.). $[\alpha]_D$ 141° (0.78, MeOH); Found:- C, 55.0; H, 5.5; N, 4.8 %: $C_{13}H_{16}NO_4Cl$ requires:- C, 54.7; H, 5.6; N, 4.9 %; ν_{max} (nujol) 3380, 3140, 1710 cm^{-1}; ^{1}Hnmr (300 MHz, D_2O) 2.38-2.48 (1H, m), 2.59 (1H, dddd, J = 17.6, 7.7, 2.0, 2.0 Hz), 4.07 (1H, ddd, J = 7.7, 6.6, 6.0 Hz), 5.21 (1H, s), 5.58 (1H, dddd, J = 6.0, 2.0, 2.0, 2.0 Hz), 5.74 (1H, brd, J = 6.6 Hz), 5.90 (1H, ddd, J = 6.0, 2.0, 2.0 Hz), 7.20-7.31 (5H, m).
6. We thank Dr. A.D. Redhouse and Mr. J.R. Thompson (Salford) for determination of this crystal structure, details of which will be published elsewhere.
7. A related formation of a *cis*-1,2-aminoalcohol derivative under hydrolytic conditions has been reported:- Frick, W.; Patil, S.D.; Gambino, A.J.; Schneller, S.W. *Tetrahedron Lett.*, **1993**, *34*, 5541-5544.
8. A complex mixture is produced in treatment of **1** with anhydrous MeOH/HCl.
9. **8**:- Found:- C, 68.3; H, 4.4; N, 6.1 %: $C_{13}H_{11}NO_3$ requires:- C, 68.1; H, 4.8; N, 6.1 %; $[\alpha]_D$ -155° (0.36, $CHCl_3$); ν_{max} (nujol) 1690, 1540, 1200 cm^{-1}; m/z (NH_3 C.I.) 230.0811, M+H$^+$ ($C_{13}H_{12}NO_3$) requires 230.0817; ^{1}Hnmr (300 MHz, $CDCl_3$) 3.04-3.19 (2H, m), 4.62 (1H, dded, J = 6.7, 6.5, 5.2 Hz), 5.56 (1H, brd, j = 6.5 Hz), 6.00-6.04 (1H, m), 6.21-6.23 (1H, m), 7.40-7.46 (3H, m), 7.57-7.61 (2H, m). Refluxing **8** with methyl acrylate in toluene produced a mixture containing unreacted starting material and two further components which appeared to be isomeric 3+2 cycloadducts, *c.f.* Bérranger, T., André-Barrès, Kobayakawa, M., Langlois, Y. *Tetrahedron Lett.*, **1993**, *34*, 5079-5082. The cycloaddition of **8** was much slower than those reported in this paper (see ref. 10).
10. A similar proposal has been advanced in the case of a 2-phenyloxazoline *N*-oxide, which is stable to hydrolysis, Ashburn, S.P., Coates, R.M. *J. Org. Chem.*, **1985**, *50*, 3076-3081. On the basis of ^{13}C mnr measurements the *N*-oxide group was proposed to donate electron density to C-2, and in the case of **8** the C-2 carbonyl group would presumably delocalize this electron density further (as in Scheme 5). This might account for the relative stability of **8**, and its slow rate of cycloaddition with methyl acrylate (see ref. 9).

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