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# LEWIS ACID CATALYZED REARRANGEMENTS OF STRUCTURALLY RELATED α,β-UNSATURATED EPOXY KETONES AND OXIMES. A COMPLEMENTARY APPROACH TO THE SYNTHESIS OF ISOMERIC 1,4-DIKETOSPIRO[n,m] ALKANES.

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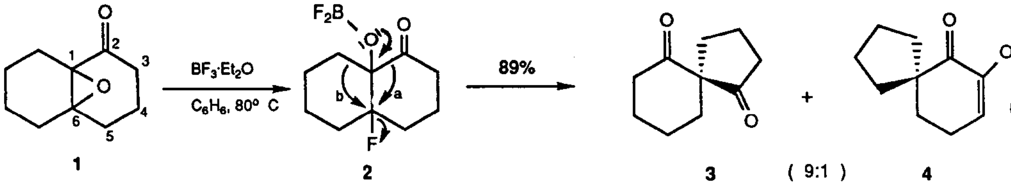
***Abstract:*** *Lewis acid catalyzed rearrangement of α,β-epoxy oximes proceeds by oxirane cleavage α to the oxime moiety with an attendant pinacol type alkyl migration to the resonance stabilized carbenium ion at $C_\alpha$ affording a 1,3-diketo-monoxime.*

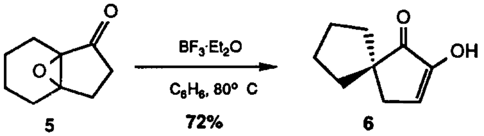
Recent mechanistic studies have provided cogent arguments that carbonyl migrations in α,β-epoxy ketones derived from acyclic enones and their related chlorohydrins are concerted rearrangements that proceed with inversion of configuration at the migration terminus.[1,2] Our mechanistic rationale for the ease with which certain acyl migrations occur has an analogy in the formation of cyclopropylcarbinyl cations where π-bond participation in a developing homoallylic cation resulted in marked rate enhancement. If the reverse polarization of the adjacent carbonyl π-bond is partially responsible for lowering the activation energy for 1,2-acyl migration, then an extension of this basic concept would be to examine the potential Lewis acid induced rearrangements of related α,β-unsaturated epoxy oximes. If the carbonyl carbon is bonded to the migration terminus in the transition state, as we have advocated,[1,3] then the electron density at an oxime carbon could conceivably facilitate 1,2 migration of the carbon-nitrogen double bond. However, we now report that the Lewis acid catalyzed rearrangement of an α,β-epoxy oxime follows an entirely different pathway that provides a useful synthetic approach to 1,3-diketospiranes that are isomeric with those arising from rearrangement of the corresponding α,β-epoxyketones.

When α,β-epoxyketones are treated with Lewis acids, exclusive 1,2-carbonyl migration occurs in a great many cases if the carbonyl π-bond can achieve an orbital alignment that can result in delocalization of the developing positive charge at $C_\beta$ by nonclassical delocalization.[3] When geometric constraints in some cyclic epoxy ketones tend to preclude involvement of the carbonyl π-bond, participation of the Lewis acid catalyst can result in halohydrin formation. For example, examination of molecular models suggests that as oxirane cleavage ensues, the carbonyl group in 1,6-epoxybicyclo[4.4.0]decan-2-one (**1**) moves away from the migration terminus as rotation about the $C_5$-$C_6$ bond takes place early on the reaction coordinate (eq. 1). Consequently, when $BF_3 \cdot Et_2O$ catalysis is employed the kinetic product that is formed is a fluorohydrin intermediate **2**. Although the overall yield of subsequent acyl migration in a kinetically distinguishable step is 89%, the requisite orbital alignment in the more flexible fluorohydrin **2** is also difficult to achieve, and carbonyl migration (path a) affording **3** is accompanied by 10% alkyl migration which gives **4** by path b (eq 1). In



(eq 1)

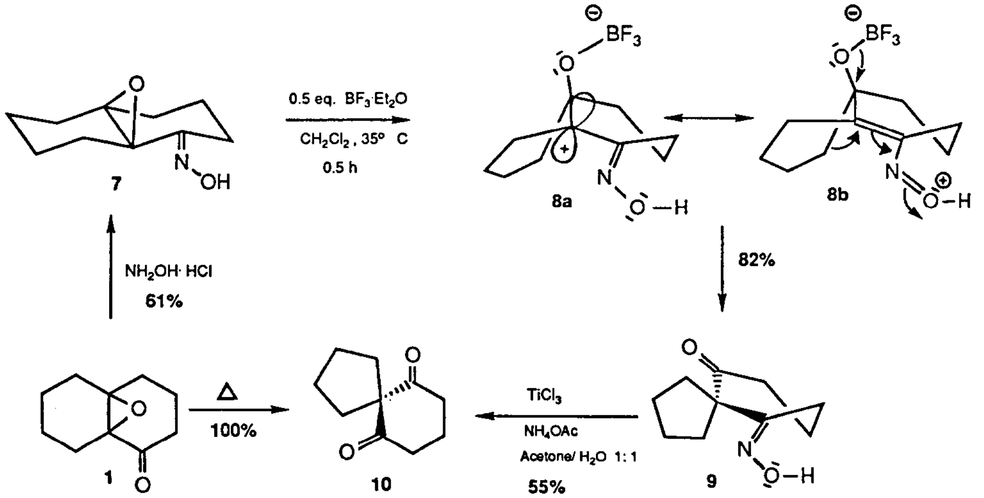
a similar fashion, if ring contraction requires excessive bond angle strain, then alkyl migration can become the exclusive pathway as evidenced by the formation of the spiro 1,2-diketone **6** in essentially quantitative yield (72% isolated) upon treatment of **5** with $BF_3\cdot Et_2O$ (eq. 2).

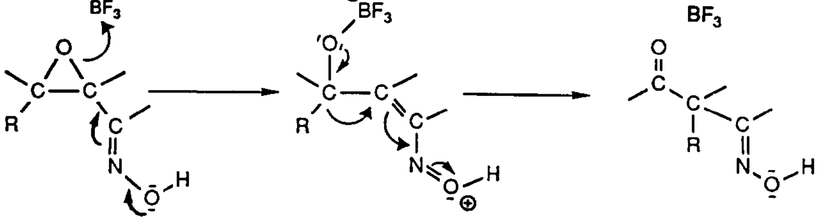


(eq 2)

The failure to observe concerted acyl migration in **1** prompted us to examine the chemistry of the corresponding α,β-epoxy oxime. We observed no evidence of oxime migration in **7** upon treatment with $BF_3\cdot Et_2O$ in methylene chloride (Scheme 1). The epoxide ring is cleaved α to the oxime moiety presumably as a consequence of the participation of the oxygen lone pair on the oxime oxygen (eq 3).[4] The carbenium ion at $C_\alpha$ can be resonance stabilized by the adjacent π-system that is isoelectronic with an allyl anion as shown in resonance structures **8a** and **8b**. The resulting *E*-spiro[4.5]decan-

**Scheme 1**



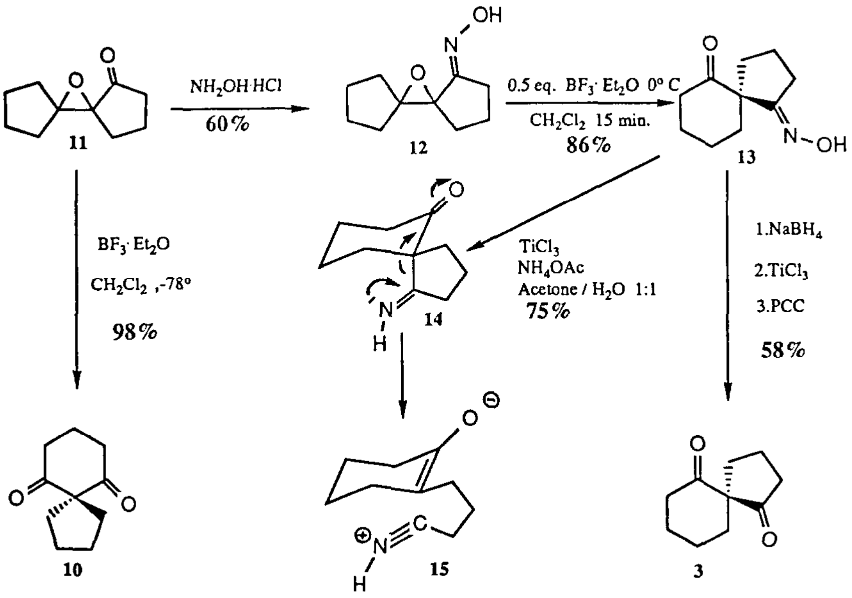


(eq 3)

6,10-dione-6-oxime (**9**) was produced in 82% yield by exclusive alkyl migration. Hydrolysis of oxime **9** with $TiCl_3$[5] afforded the spiro[4.5]decan-6,10-dione **10** in 55% yield.

We note that the spiro diketone **10** may also be prepared by thermal rearrangement[6] of **1** or by Lewis acid catalyzed rearrangement[2] of cyclopentylidenecyclopentanone oxide **11** (Scheme 2). The oxime rearrangement appears to be quite general,[7] and **12** readily affords the spiro oxime **13** (86%). In a typical small scale experiment, 181 mg (1.0 mmol) of oxime **12** was dissolved in 8 mL of methylene chloride, and 0.012 mL (0.1 mmoL) of $BF_3\cdot Et_2O$ was added. After stirring 5 min, the reaction was quenched with 20 mL of saturated $NaHCO_3$ solution and the product was extracted with 2 x 25 mL ethyl ether. The ether layers were combined and washed with 30 mL saturated NaCl solution and dried ($MgSO_4$). The solvent was then removed, and the compound further purified by column chromatography (9:1 hexane/ethyl acetate). The pinacol type rearrangement of the alkyl group in the carbenium ion intermediate derived from **12** appears to be quite facile even at low temperature (-32°C) since rearranged oxime **13** can be obtained in 76% yield after 30 min.

**Scheme 2**



Attempted hydrolysis of oxime **13** with $TiCl_3$ did not afford the anticipated spiro diketone **3** but resulted in carbon-carbon bond cleavage of the intermediate imine[5] **14** to afford 2(3-cyanopropyl)-cyclohexanone (**16**). When the axial carbon-carbon bond is colinear or in conjugation with the carbonyl π-system, the spiro diketone is the minor product and ring cleavage of the intermediate imine **14** results presumably due to facile nitrile formation with attendant delocalization of the charge through the enolate anion in zwiterion **15**. However, in keto-oxime **9**, where the C=N bond lies in the same plane as the other carbonyl system, hydrolysis occurs with aqueous $TiCl_3$ in high yield to afford the spiro diketone **10**. Reduction of the ketone in **13** with $NaBH_4$ first, followed by hydrolysis, and oxidation of the intermediate keto alcohol affords **3** in a 58% overall yield (Scheme 2).

In summary, the rearrangement of α,β,epoxy oximes provides a synthetically useful procedure for the preparation of functionally differentiated spiro 1,3-diketones. This overall procedure complements the Lewis acid catalzyed rearrangement of α,β-epoxy ketones that provides the isomeric spiro diketones.

**Table 1**

| Substrate | Cat. Eq.[a] | Time | Solvent | Temp. C° | %Yield[b] | Product |
|---|---|---|---|---|---|---|
| **1** | $BF_3\cdot Et_2O$ (0.5) | 1 min | $C_6H_6$ | 80 | 61 (89) | **3** |
| **1** | $BF_3\cdot Et_2O$ (0.5) | 2.5 h | $CH_2Cl_2$ | 35 | 63 (87) | **3** |
| **1** | $BF_3\cdot Et_2O$ (0.2) | 15 min | $C_6H_6$ | 80 | 61 (89) | **3** |
| **5** | $BF_3\cdot Et_2O$ (1.0) | 25 min | $CH_2Cl_2$ | 35 | 72 | **6** |
| **5** | $BF_3\cdot Et_2O$ (0.2) | 50 min | $C_6H_6$ | 80 | 63 | **6** |
| **12** | $BF_3\cdot Et_2O$ (0.1) | 5 min | $CH_2Cl_2$ | 25 | 77 | **13** |
| **12** | $BF_3\cdot Et_2O$ (0.5) | 30 min | $CH_2Cl_2$ | -32 | 76 | **13** |
| **12** | $BF_3\cdot Et_2O$ (0.5) | 15 min | $CH_2Cl_2$ | 0 | 86 | **13** |
| **7** | $BF_3\cdot Et_2O$ (0.5) | 1 h | $CH_2Cl_2$ | 35 | 62 | **9** |
| **7** | $BF_3\cdot Et_2O$ (1.0) | 30 min | $CH_2Cl_2$ | 35 | 82 | **9** |
| **7** | $BF_3\cdot Et_2O$ (0.5) | 5 min | $C_6H_6$ | 80 | 70 | **9** |

(**a**) Ratio of catalyst to epoxyketone; (**b**) GPC yields in parentheses; All new compounds gave satisfactory elemental analyses.

**Acknowledgment**

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7. Related examples that have been successful in this reaction include oximes of β-substituted cyclohexenone epoxides, substituted 1,2-epoxybicyclo[4.4.0]decanes and the oxime of compound **5**. These rearrangements will be reported in detail elsewhere.

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