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RING-OPENING REACTIONS OF AN OXABICYCLIC COMPOUND WITH CUPRATES

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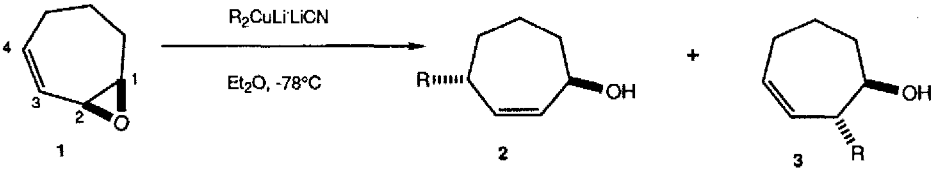
Abstract: The ring-opening reaction of 8-oxabicyclic[3.2.1]oct-6-en-3-one with cuprates is described. S_N2' attack is the predominant pathway giving rise to products isomeric to those derived from opening of vinylepoxides under similar conditions.

Cuprate reagents are among the most useful organometallic reagents for effecting displacements due to their high nucleophilicity and low basicity.[2] Reactions at a variety of C-X bonds have been reported including halides, epoxides[3] and vinylepoxides. The openings of vinylepoxides were first reported by Anderson and Johnson[4] and their utility in the introduction of functionality in five-, six- and seven-membered rings with high levels of regio- and stereocontrol was demonstrated by Marino.[5] For example, reaction of **1** occurs predominantly at C-4 to yield the *trans* isomer **2**. Attack at C-2 is usually a minor product of the reaction which can be eliminated by careful choice of conditions. The *cis* isomer of **2** is also available using a palladium catalyzed opening and *in situ* alkylation under "neutral" conditions.[6] In this communication, we report that the reaction of oxabicyclic compounds with cuprates yields products with the regiochemistry depicted in compound **3**. Good levels of stereocontrol have been realized. We are aware of no successful examples of ring-opening in these systems.[4a,7] Ready access to the oxabicyclic starting material and subsequent rapid entry into highly substituted seven membered rings are attractive features of this approach. We have examined a symmetrical substrate in this initial study to simplify the analysis by minimizing the number of regioisomeric products.



(1)

The starting bicyclic compound, **4**, was readily available using literature procedures.[8] The reaction of **4** with a variety of cuprates is shown in the Table. Treatment with $Me_2CuLi{\cdot}LiCN$ (2.5-5.0 eq. in Et_2O at -23 °C) gave primarily attack at the carbonyl group to give **5a**[9] along with ca. 5% of the desired product from S_N2' displacement at C-6, **6a**.[10] When the temperature was decreased to -78 °C, we were surprised to find only **5a**, obtained as one stereoisomer. After a number of unsuccessful experiments we found that the temperature of the reaction was crucial if selectivity was to be observed toward the desired opening vs. the carbonyl addition. Treatment at 0 °C followed by warming to room temperature gave **6a** as the major product, entry 3. Isolated yields of up to 62% were available of a single stereoisomer.[11] It is possible to observe each of the products in the crude NMR spectrum and measure their ratios. Compound **5a** is symmetrical and shows one olefinic proton at 6.42 ppm and a doublet at 4.75 ppm assigned to the bridgehead hydrogen. The two olefinic protons in **6a** have very similar chemical shifts, ca. 5.59 ppm and the proton on the hydroxyl bearing carbon appears at 3.92ppm. The S_N2 adducts, **7**, have olefin resonances which are separated by 0.2 ppm appearing at 5.42 and 5.62 ppm. The proton on the hydroxyl carbon is further downfield in **7** (vs. **6**) since it is also allylic. Protection of the hydroxyl group (TBDMSOTf, 2,6-lutidine, CH_2Cl_2, product of entry 3) yielded a 1:1 mixture of the conjugated and non-conjugated protected cycloheptenones. This result was only possible if the starting material was **6**.[12a] The assignment of the relative stereochemistry in seven membered rings is difficult due to their conformational flexibility. The usual reactivity pattern of cuprates (clean S_N2 or S_N2')[5,13] permit us to make the assignment of **6a** to the *trans* isomer. The proton H_a appeared as a ddd, with coupling constants of 8.8, 6.3, 4.1Hz. The large coupling was shown by decoupling and 2-D NMR to be $J_{Ha\text{-}Hb}$ further supporting the stereochemical assignment.[12b]

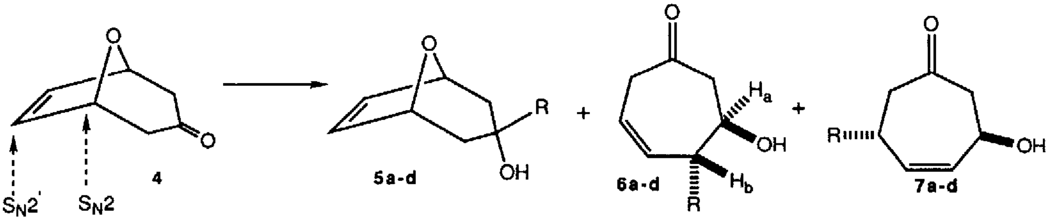


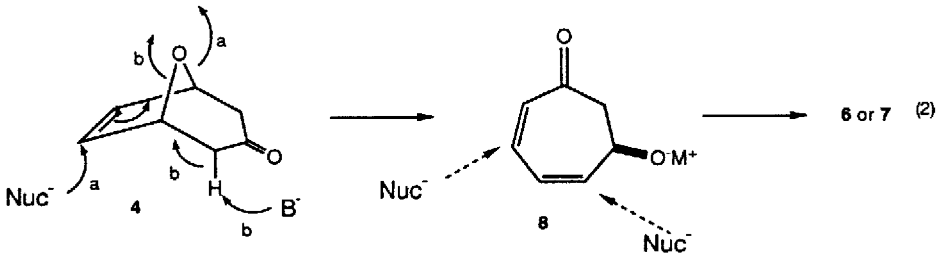
Table 1. Reaction of 8-oxabicyclo[3.2.1]oct-6-en-3-one with Alkylcuprates

Entry	RLi	Copper Source	Conditions	Product(s)	Yield[1]
1	MeLi	CuCN	Et_2O, -23°C	10:1:0 **5a:6a:7a**	55%[2]
2	MeLi	CuCN	Et_2O, -78°C	1:0:0 " "	20%[3]
3	MeLi	CuCN	Et_2O, 0 °C to r.t.	1:15:0 " "	66%
4	BuLi	CuCN	Et_2O, 0 °C to r.t.	1:19:10 **5b:6b:7b**	60%
5	**BuLi**	**CuCN**	**THF, 0 °C to r.t.**	**1:15:0 " "**	**59%**
6	BuLi	CuCN	THF : Et_2O (1:1), 0 °C to r.t.	1:3:0 " "	70%
7	BuLi	CuCN	Me_2S, 0 °C to r.t.	1:1.6:5.8 " "	57%
8	BuLi	CuI	THF, 0 °C to r.t.	" "	
9	**BuLi**	**CuBr·Me_2S**	**THF, 0 °C to r.t.**	**0:13:1 " "**	**77%**
10	***s*-BuLi**	CuCN	**THF, 0 °C to r.t.**	**0:8:1 5c:6c:7c**	**85%**
11	***t*-BuLi**	CuCN	**THF, 0 °C to r.t.**	**0:1:0 5d:6d:7d**	**37%[4]**
12	vinyl lithium	CuCN	THF : Et_2O (2:1) 0 °C to r.t..	1:2:2.5 **5e:6e:7e**	76%

1. Combined yield of all isomers. 2. 33% recovered starting material. 3. 60% recovered starting material. 4. Unoptimized yield.

Having demonstrated the viability of effecting the desired ring-opening, we proceeded to examine the utility of other cuprates to effect a similar process. Bu$_2$CuLi·LiCN reacted with **4** in Et$_2$O:hexane (2:1) to give a 1:19:10 mixture of **5b**:**6b**:**7b** in 60% combined yield, entry 4. When the solvent was changed to THF:hexane (2:1), only a trace of **7b** was observed and attack at the carbonyl group was reduced (ca. 5%). Good yields of the desired product were isolated. Mixtures of THF:Et$_2$O gave intermediate results, entry 6. When the reaction was run in a less coordinating solvent (Me$_2$S), the major product derives from S_N2 attack, **6b**.[14a] Similar solvent effects have been noted previously in cuprate chemistry; however ether is usually the preferred solvent.[14b] CuCN and CuBr·Me$_2$S were the most effective cuprate precursors, entries 5,8 and 9. The selectivity toward the desired reaction was a function of the steric hindrance of the alkylcuprate, compare entries 5,10-12. Increasing size, e.g. reaction with s-Bu$_2$CuLi·LiCN or t-Bu$_2$CuLi·LiCN, gave the S_N2' adducts with enhanced selectivity whereas the less bulky cuprate from vinyl lithium was the least selective reagent giving significant amounts of carbonyl addition and S_N2 ring-opened products.

Efforts were made to suppress this undesired carbonyl addition process by conversion of the ketone in **4** to an olefin (Ph$_3$PCH$_3$I, KOBu^t in THF). Surprisingly, this compound failed to react with methyl-, n-butyl-, sec-butylcuprates under a variety of conditions including changes in temperature (-78 °C to room temperature), solvent and source of copper (CuCN, CuBr·Me$_2$S, CuI). The production of **7** and the failure of the olefin to react could be rationalized by a mechanism whereby elimination of the β-oxygen in **4** would generate the hydroxydienone **8** (path b) which then undergoes stereo- and regioselective conjugate addition.[15] However, **8** has never been observed in any reactions and, attempts to prepare it by treatment of **4** with KOBu^t in THF returned starting material. Therefore, we conclude that elimination does not preceed addition and an S_N2' reaction is a reasonable alternative (path a).[16]



(2)

In conclusion we have shown that an oxabicyclic compound is reactive toward organocuprates generating substituted seven-membered rings with high levels of stereocontrol. Efforts are underway to apply these results in natural products synthesis.

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9. House, H.O.; Chu, C.-Y.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* **1975**, 40, 1460.

10. Satisfactory NMR, IR, and mass spectra and/or combustion analysis were obtained for all new compounds.

11. In a typical procedure: CuCN (2.5 mmol) was dried with a hot-gun under vacuum for 5 min. before suspending the solid in THF. The vessel was cooled to -78 °C and the organolithium (4.9mmol) was introduced dropwise over 2-5 min. Upon completion of the addition, the cuprate solution was warmed to 0 °C and stirred for 1 h. The oxabicyclic substrate (1 mmol) was dissolved in THF and added dropwise to the cuprate via cannula over 15-30 min followed by warming the reaction to room temperature where it was stirred until tlc indicated the starting material was consumed. Ammonium chloride was added and the mixture exposed to the air. Filtration of solids through Celite-silica gel gave a clear solution which was worked-up using standard techniques. It is important to note that freshly opened bottles of the organolithium gave much superior yields in the reaction.

12. The coupling constant for the conjugated isomer was, $H_{Ha\text{-}Hb}$ was 6.0 Hz. b) Coupling constants of this magnitude have been observed for the trans isomers of cycloheptenones, see: Pearson, A.J.; Bansal, H.S. *Tetrahedron Lett.***1986**, 27, 283.

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16. In some cases, e.g. Table1, entry 4., compound **6b** is contaminated with the epimeric product (by ^{13}C NMR, usually ca. 5-10%) when the reaction is run in Et$_2$O. Use of THF as solvent gives a single stereoisomer. This result supports our stereochemical assignment since simultaneous coordination of the oxygen and the olefin followed by C-O insertion with retention and reductive cleavage should be more facile in less coordinating solvents. For examples of displacement with retention due complexation in cuprate chemistry see; Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* **1983**, 48, 715.

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