Intramolecular 4+3 cycloadditions. A cyclohexenyl cation, its halogenated congener and a quasi-Favorskii rearrangement

Michael Harmata,* Gary Bohnert, Laszlo Kürti and Charles L. Barnes

Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

Received 16 January 2002; revised 2 February 2002; accepted 6 February 2002

Abstract—Treatment of alkoxycyclohexenols bearing a tethered diene substituent with a Lewis acid results in intramolecular 4+3 cycloaddition with complete *endo* selectivity. A cycloadduct bearing a bromo substituent at a bridgehead position undergoes a quasi-Favorskii rearrangement in near quantitative yield upon reaction with lithium aluminum hydride. © 2002 Elsevier Science Ltd. All rights reserved.

The intramolecular 4+3 cycloaddition reaction is a powerful method for the construction of polycyclic ring systems.[1] In particular, when either the dienophilic cation or the diene is contained in a ring, unique structures can be obtained whose modification can give rise to important ring systems.[2] We demonstrated this in our recent synthesis of (+)-dactylol.[3] We have reported that the intramolecular 4+3 cycloaddition is possible when the cations are within rings of 5–8 as well as 10 and 12 carbons, resulting in cycloadducts in very good yields, in some cases with excellent stereoselectivity.[4] In an attempt to broaden the scope of the chemistry, and to further study the chemistry of halogenated, cyclic cations, we conducted the study described herein.

Our goal was to study the generation of cyclohexenyl allylic cations which were more reactive than oxyallylic cations. We decided to pursue cation generation from allylic alcohols, since there is good precedent that such an approach would give cations capable of 4+3 cycloaddition.[5]

To that end, we prepared alkoxyenone **2** by treatment of ketoenol **1** with trimethyl orthoformate and methanol in the presence of acid (Scheme 1).[6] On a 30 g scale, this resulted in the formation of a 44% yield of **2** along with a 23% yield of **3**. The latter could be cracked by heating in benzene in the presence of pTsOH to afford **2** in 71% yield.

Treatment of **2** with Grignard reagent **4** produced allylic alcohol **5** in 55% yield. Addition of cerium

trichloride to the Grignard reagent was not advantageous, the yield of **5** being only 42%.

The reaction of **5** with Lewis acids resulted in cycloaddition to form **6** and other side products (Scheme 2). In the presence of 1.2 equiv. of triflic anhydride and 2,6-lutidine, the yield of **6** varied between 37 and 48%
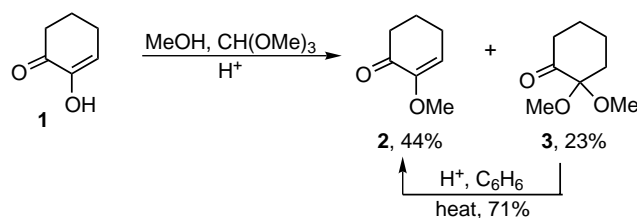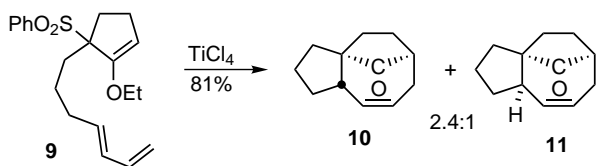
Scheme 1.
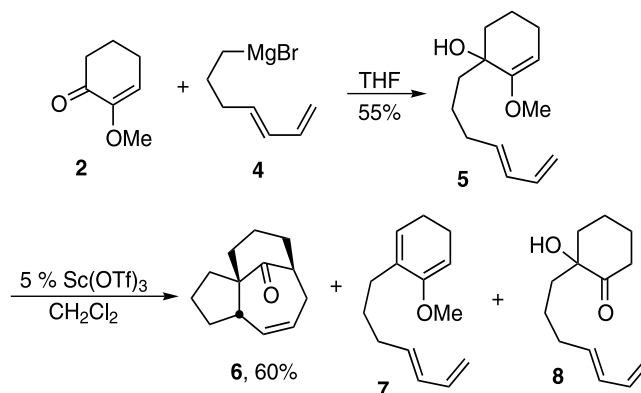
Scheme 2.

* Corresponding author. Tel.: 573-882-1097; fax: 573-882-2754; e-mail: harmatam@missouri.edu

with 16–20% recovered starting material and small amounts of elimination product **7**. Neat titanium tetra-chloride added to a solution of **5** in dichloromethane at −78°C destroyed the compound, but a 0.5 M solution of this Lewis acid added in the same way afforded a 30% yield of the cycloadduct **6**. At present, the best Lewis acid for this process is scandium triflate, which effects cycloaddition of **5** in catalytic amounts and at room temperature to give **6** in 60% yield along with small amounts (3–5%) of enol ether hydrolysis product **8**.

The structure of **6** was established by single-crystal X-ray analysis of the corresponding oxime derivative. It is important to note that **6** was formed as a single diastereomer. In the context of related cycloadditions involving cyclopentenyl cations, this is quite unusual.[4] For example, we reported that the reaction of **9** with titanium tetrachloride afforded the cycloadducts **10** and **11** in excellent yield, but as a 2.4:1 ratio of diastereomers (Scheme 3). On the other hand, West and co-workers reported that the domino Nazarov/4+3 cycloaddition of **12** proceeded with complete *exo* stereoselectivity (Scheme 4).[7] It will be interesting to establish the trends in simple diastereoselectivity for other cyclic cations and tether lengths.

Our real interest in this area is to develop halogenated, cyclic cations. We thus studied the preparation of **15**. Two routes were examined. The first involved the preparation of the enol ether **14** by bromination of **1** followed by alkylation. This process worked well. Treatment of **1** with 0.9 equiv. of bromine at −78°C followed by reaction with 1 equiv. of triethylamine afforded **14** in 90% yield on a 1 g scale.[8] Methylation of **14** was attempted with TMSOMe, trimethyl orthofor-mate and acid, potassium carbonate and methyl sulfate and sodium hydride/methyl iodide. Of these, only the latter worked, giving **15** in 42% yield. A better approach involved the reaction of **14** with dia-zomethane.[9] Treatment of an ethereal solution of **14** with diazomethane at room temperature for 3 h afforded **15** in 79% yield, along with recovered starting material (15%) and a small amount of unidentified byproducts.
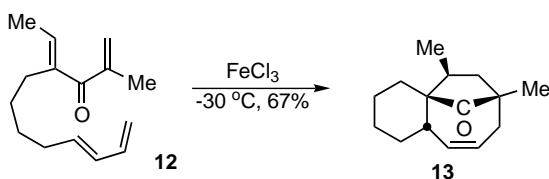
Another approach to **15** involved the bromination/dehydrobromination of **2**. This afforded the target com-pound in 60% yield (Scheme 5).

With **15** in hand, it was reacted with Grignard reagent **4**. This resulted in only low yield of **16**. Formation of an organocerium reagent was helpful in this case. The product **16** was then formed in 76% yield (16% recov-ered starting material) (Scheme 6).

The cycloaddition of **16** was in general a low-yielding process. Treatment with triflic anhydride and 2,6-lutidine resulted in cycloaddition, but yields were only as high as 45%. Elimination to form **18** was a problem in these reactions. A catalytic amount of scandium triflate in the presence of excess acetic anhydride gave **18** in 87% yield. The acetate derivative of **16** was either destroyed (TiCl$_4$) or underwent elimination (Sc(OTf)$_3$, 80%). The best conditions for the cycloaddition so far make use of 1.4 equiv. of triflic anhydride at −50°C (no base!). This gave the cycloadduct **17** in 65% yield as a single stereoisomer.[10] The structure of **17** was estab-lished chemically. Reaction of **17** with Bu$_3$SnH and AIBN gave **6** in 60% yield. We later confirmed the structural assignment by obtaining a crystal structure of **17**.
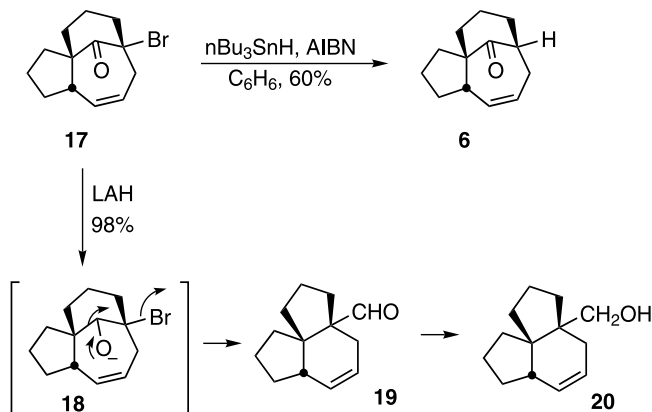
We have recently been developing the quasi-Favorskii rearrangement as a synthetic tool, since chemistry such as that described herein allows the convenient prepara-tion of bridgehead halides poised to undergo this reac-tion.[11] It was thus gratifying to find that the treatment
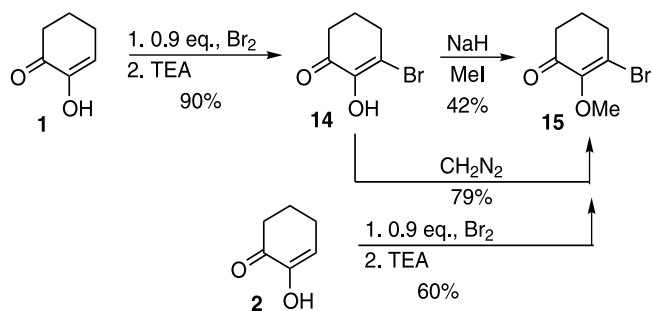
Scheme 5.
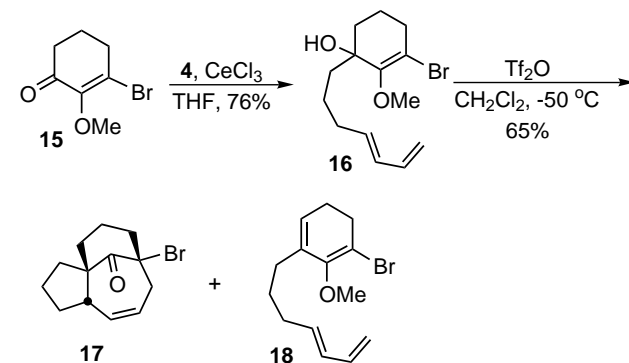
Scheme 6.

Scheme 3.

Scheme 4.

Scheme 7.

of **17** with LAH afforded not a simple reduction product but one in which a quasi-Favorskii rearrangement had taken place; and in nearly quantitative yield (Scheme 7). The implications of this process for the synthesis of angular triquinanes are obvious and are being pursued.

In summary, we have shown two examples of an intramolecular 4+3 cycloaddition reaction of cyclohexenyl cations which proceed with complete *endo* diastereoselectivity. The straightforward quasi-Favorskii rearrangement of **17** as well as its facile preparation suggest that good use of such halides can be made in synthesis. Further progress in this area will be reported in due course.[12]

References

1. (a) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605; (b) Harmata, M. *Tetrahedron* **1997**, *53*, 6235–6280.
2. Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217–232.
3. Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913–2915.
4. Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860–2871.
5. For examples and leading references, see: (a) Harmata, M.; Bohnert, G.; Barnes, C. L. *Tetrahedron Lett.* **2001**, *42*, 149–151; (b) Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985–7988.
6. Preparation of **2**: Compound **1** (30 g, 268 mmol) was dissolved in a mixture of MeOH (52 mL) and HC(OMe)$_3$ (27 mL). pTsOH (3 g, 5 mol%) was added and the reaction mixture was refluxed overnight. The pale yellow reaction mixture was cooled and diluted with H$_2$O (50 mL) and extracted with CH$_2$Cl$_2$ (5×30 mL). The organic layers were washed with 5% NaHCO$_3$ (3×20 mL) and dried over MgSO$_4$. The concentrated crude product was purified by flash chromatography (hexanes:EtOAc, 2:1) to afford **2** (14.8 g, 44%) and **3** (10.2g, 23%).
7. Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
8. Sato, K.; Suzuki, S.; Kojima, Y. *J. Org. Chem.* **1967**, *32*, 339–341.
9. Compound **14** (2.0 g, 10.5 mmol) was dissolved in 100 mL of freshly distilled ether. A solution of diazomethane (CAUTION) was slowly added over 3 h to the stirred solution of **14**. After each addition, the subsequent addition was delayed until the yellow color of diazomethane dissipated. When the yellow color remained the solution was allowed to stir for and additional 30 min and the solvent was removed in vacuo, after the addition of a small amount of acetic acid to remove remaining diazomethane. The crude product was purified by flash chromatography (hexanes:EtOAc, 8:1) to afford 1.68 g of **15** (79%). Starting material was also recovered (10%). Data on **15**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.75 (s, 3H), 2.92 (t, 2H, $J=6.1$), 2.54–2.51 (m, 2H), 2.04 (quintet, 2H, $J=6.3$); ^{13}C NMR (CDCl$_3$, 125.8 MHz) δ 192.1, 151.0, 135.2, 59.8, 38.3, 35.8, 22.6; IR (neat) 1686s, 1288s, 1204s cm^{-1}. Anal. calcd for C$_7$H$_9$BrO$_2$: C, 41.00; H, 4.42. Found: C, 40.87; H, 4.60.
10. Compound **16** (301 mg, 1 mmol) was dissolved in 10 mL of freshly distilled dichloromethane and was cooled to −50°C in a cold bath. After 30 min, Tf$_2$O (233 μL, 1.4 equiv.) was added in 20 min. The reaction mixture became pink after 2 h. The color slowly turned to deep brown. After 11 h at −50°C, TLC showed **17** as the only product. The reaction mixture was quenched with saturated NaHCO$_3$. The organic layer was extracted with water and dried over MgSO$_4$. After removal of solvent, the residue was purified by flash chromatography (hexanes:EtOAc, 7:1) to afford 175 mg (65%) of **17**. Data on **17**: mp 68°C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.71 (dtd, 1H, $J=2.0$, 6.2, 10.8 Hz), 5.64 (ddd, 1H, $J=1.4$, 5.1, 10.8), 3.40 (ddd, 1H, $J=1.0$, 6.5, 16.2), 2.92 (dd, 1H, $J=5.57$, 16.3), 2.85 (q, 1H, $J=5.8$), 2.69 (ddt, 1H, $J=2.70$, 4.16, 13.5), 2.6 (ddd, 1H, $J=13.3$, 8.1, 5.3), 2.54 (td, 1H, $J=4.5$, 13.5), 2.37 (qt, 1H, $J=4.3$, 14.1), 1.98–1.88 (m, 2H), 1.78 (td, 1H, $J=4.9$, 13.7), 1.71–1.57 (m, 3H), 1.54 (septet, 1H, $J=6.2$), 1.20 (dt, 1H, $J=7.9$, 13.2); ^{13}C NMR (CDCl$_3$, 125.8 MHz) δ 204.5, 137.7, 126.0, 76.8, 62.0, 46.8, 46.1, 40.9, 40.4, 36.3, 33.3, 23.5, 21.9; IR (neat) 1723s, cm^{-1}. Anal. calcd for C$_{13}$H$_{17}$BrO: C, 58.01; H, 6.37. Found: C, 57.89; H, 6.54.
11. (a) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533–2535; (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron Lett.* **2001**, *42*, 5593–5595; (c) Harmata, M.; Shao, L. *Synthesis* **1999**, 1534–1540; (d) Harmata, M.; Shao, L.; Kürti, L.; Abeywardane, A. *Tetrahedron Lett.* **1999**, *40*, 1075–1078.
12. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR data as well as satisfactory combustion analysis or high resolution exact mass data.