JOC*Note*

Novel Route to Functionalized Cyclooctanoids via [5+3] Cycloaddition

Urlam Murali Krishna,[†] Kodand D. Deodhar,*[,†] Girish K. Trivedi,*[,†] and Shaikh M. Mobin[‡]

Department of Chemistry, National Single-Crystal X-ray Diffraction Facility, Indian Institute of Technology Bombay, Mumbai 400076, India

chgktia@chem.iitb.ac.in

Received September 15, 2003

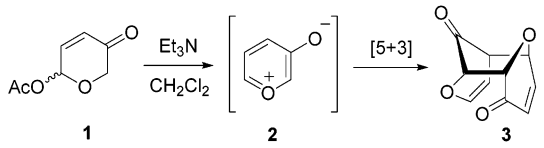
Abstract: The self-dimerization of 3-oxidopyrylium leading to stereocontrolled formation of highly functionalized cyclooctanoids is described. Different functionalities were introduced on the dimer (**3**) and the stereochemical outcome was determined by single-crystal X-ray analysis. It is noteworthy that the hydrogenation of **3** in ethanol solvent gave the transannulated product **5**, whereas the expected dihydro product **4** was obtained when the reaction was run in nonnucleophilic solvents. The mechanistic pathway is discussed.

The development of efficient and novel synthetic routes to medium-sized carbocycles is a worthy endeavor due to the presence of such systems in many biologically and structurally interesting natural products.[1] Because of well-known entropic and enthalpic factors associated with the formation of medium-sized rings, the application of carbon−carbon bond-forming reactions to medium-size ring synthesis is not always straightforward and thus entry into these ring systems is considered quite challenging.[2,3]

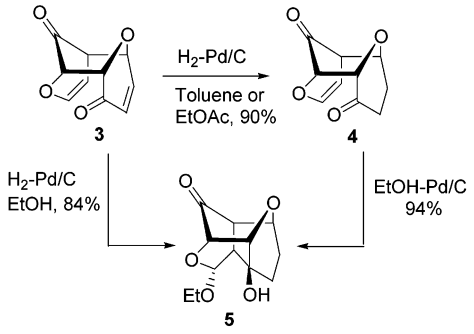
In 1980 Hendrickson reported that 3-oxidopyrylium, a reactive species, readily undergoes self-dimerization to produce a dimer **3** (Scheme 1).[4] The dimer thus formed is a doubly bridged eight-membered carbocycle[5−10] endowed with diverse functionalities around the ring. It is rather surprising that despite its synthetic potential, the dimer (**3**) has not received due attention from synthetic chemists. This observation naturally prompted us to undertake synthetic study of the said dimer.

In this note, we will describe our exploratory investigations for stereocontrolled transformations of the dimer. Our studies began with efficient preparation of dimer **3** using the method reported by Hendrickson et al.[4] 3-Oxidopyrylium (**2**) was formed by treatment of acetoxypyranone (**1**) with triethylamine and spontaneously proceeded to the thermal [5+3] cycloaddition reaction to afford dimerized product **3** (60%, Scheme 1). After having sufficient quantities of dimer in hand, first we attempted to presaturate the α,β-unsaturated olefinic double bond in the dimer. Dimer **3** was therefore subjected to the typical hydrogenation conditions over activated Pd/C in ethanol solvent. The reaction outcome was quite unusual. Instead of forming the dihydro product **4**, interestingly an unanticipated reaction occurred to provide compound **5** (Scheme 2). The ^{1}H NMR spectra of the resultant product displayed a triplet at δ 1.15 (3 protons) and a pair of doublets of a quartet centered at δ 3.8 (1H) and 3.48 (1H). The presence of a single carbonyl group in the ^{13}C NMR instead of the two initially present in the dimer helped us in ruling out the formation of the expected dihydro product (**4**) or the tetrahydro product. The structure of **5** was assigned on the basis of single-crystal X-ray analysis. The structure thus secured shared the

SCHEME 1



SCHEME 2

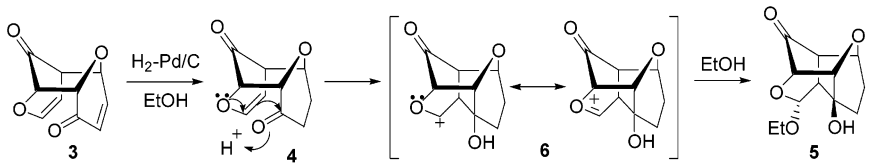


* To whom correspondence should be addressed. Phone: (+91)-022-25767169. Fax: (+91)-022-25723480.
[†] Department of Chemistry.
[‡] National Single-Crystal X-ray Diffraction Facility.

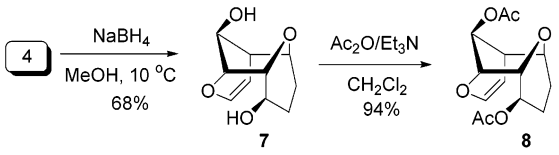
(1) (a) Oishi, T.; Ohtsuks, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 1989; Vol. 3, p 73. (b) Rigby, J. H. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 1993; Vol. 12, p 233.
(2) Illuminati, G.; Mandoline, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(3) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603.
(4) (a) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361. (b) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261. (c) For a review of oxidopyrylium cycloadditions see: Sammes, P. G. *Gazz. Chim. Ital.* **1986**, *51*, 1573.
(5) For reviews of the construction of cyclooctanoid systems, see: (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
(6) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (c) Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. (d) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904. (e) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. (f) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908 and references therein.
(7) (a) Sieburth, S. M.; McGee, K. F., Jr.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587. (b) Sieburth, S. M.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251.
(8) (a) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036. (b) Molander, G. A.; Brown, G. A.; deGracia, I. S. *J. Org. Chem.* **2002**, *67*, 3459.
(9) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (c) Fu. G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (d) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (e) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
(10) (a) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003. (d) Furstner, A.; Muller, T. *Synlet* **1997**, 1010.

10.1021/jo0353583 CCC: $27.50
Published on Web 12/31/2003

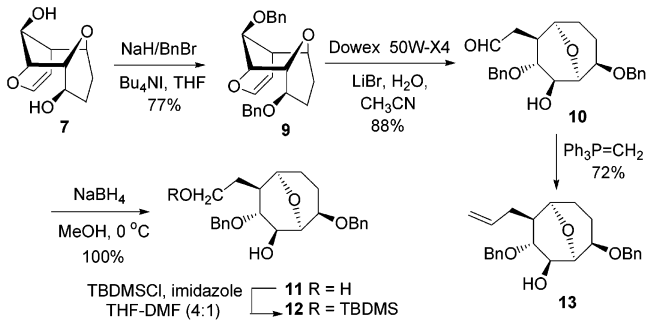
SCHEME 3



SCHEME 4



SCHEME 5



presence of an ethoxy group and formation of a new carbon−carbon bond (C_4-C_9).

In view of the above results the conditions for hydrogenation were changed such that the solvent participation was eliminated, i.e., to undergo the reduction in a nonparticipating, nonnucleophilic solvent. Hydrogenation of **3** was, therefore, run in toluene and ethyl acetate, respectively. In both cases, the required hydrogenation product **4** was formed, which was confirmed by its spectroscopic data.

To better understand the reaction pathway for the formation of the unexpected product **5**, two simple experiments were performed. When compound **4** was treated with Pd/C in ethanol it furnished a product that was found identical with **5**, whereas no reaction occurred when dimer **3** was subjected to the above reaction conditions (Scheme 2). In light of these observations the mechanism depicted in Scheme 3 seems tenable. The acidic nature of the reaction medium appears to be responsible for the formation of this unexpected product through the transannular cationic cyclization of **4**. The transient carbocation **6** was then trapped by the solvent (ethanol) to generate the observed product. The establishment of a carbon−carbon bond during hydrogenation is rather unique and unanticipated.

We next turned our attention to sodium borohydride reduction of compound **4**. Since such a reduction is going to develop two new stereogenic centers, the formation of four products is possible. However, the reaction proceeded stereoselectively to produce diol **7** as the sole product. The stereochemistry of the diol was established through the single-crystal X-ray analysis of the corresponding diacetate. The diacetate was characterized as **8** and hence the stereostructure **7** is assigned to the diol.

Our next objective was to open the heavily encumbered pyranyl ether moiety while still maintaining the geometrical rigidity imparted by the oxa-bridge to the deeply embedded eight-membered ring in the structure. The hydroxyl groups in **7** are protected as benzyl ethers (BnBr/NaH), and the resultant bis-benzyl ether (**9**) was then hydrated with use of acedic resins (Dowex 50W X 4) in the presence of water to furnish the aldehyde **10** (ν_{max} 1719 cm^{-1}),[11] which was further converted into other cyclooctanoid derivatives (**11**−**13**, Scheme 5) following literature procedures.

In conclusion the thermal [5+3] cycloaddition of 3-oxidopyrylium appears to provide a convenient method of transforming furans to functionalized cyclooctanoids. The results described herein may pave the way for further studies on the dimer leading to the polyhydroxy cyclooctanoids. Efforts toward preparation of various bicyclic systems are currently underway.

Experimental Section

(3,6-Bisbenzyloxy-4-hydroxy-9-oxa-bicyclo[3.3.1]non-2-yl)acetaldehyde (10). To a solution of **9** (0.5 g, 1.37 mmol) and lithium bromide (0.36 g) in acetonitrile (15 mL) were added Dowex 50W X 4 resin (H^+ form,[11] 0.2 g) and water (0.45 mL). The mixture was stirred at room temperature for 0.5 h. The solution was filtered, neutralized with Et_3N, and evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed successively with water, ice-cold HCl (5%), and saturated $NaHCO_3$, and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure and used directly in the next step.

4-Allyl-3,8-bisbenzyloxy-9-oxa-bicyclo[3.3.1]nonan-2-ol (13). To a suspension of phosphonium salt in anhydrous THF (0.5 M) was added *n*-BuLi (0.6 mL, 15% in hexane, 2 mmol) dropwise at −20 °C. The reaction mixture was stirred at −20 °C to room temperature until the entire solid disappeared (∼0.5−1 h). A solution of **10** (0.48 g, 1.36 mmol, coevaporated with anhydrous benzene 3 × 25 mL before use) in THF (20 mL) was added to the reaction mixture at −20 °C, and the solution was stirred for 16 h at room temperature. An excess of reagent grade acetone was added and the mixture was extracted with diethyl ether. The precipitated solid was filtered off and the ether extracts were washed with saturated $NaHCO_3$ solution, water, and brine. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the resultant residue by flash chromatography afforded compound **13** (0.36 g, 72%) as pale yellow oil.

IR (neat) ν_{max} 3482, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 10H), 5.76−5.63 (m, 1H), 5.12 (d, J = 11.4 Hz, AB system, 1H), 4.96 (m, 2H), 4.74 (d, J = 11.4 Hz, AB system, 1H), 4.60 (m, benzylic, 2H), 4.28 (m, 1H), 4.20−4.10 (m, 2H), 3.96 (m, 1H), 3.82 (m, 1H), 3.66 (dd, J = 8, 10.6 Hz, 1H), 2.20 (m, 2H), 2.7 (m, 1H), 1.87−1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 137.2, 136.3, 128.7, 128.4, 128.2, 127.9, 127.6, 116.3, 83.2, 78.5, 77.8, 74.7, 71.8, 70.0, 69.6, 44.8, 33.8, 26.9, 23.4; HRMS calcd for $C_{25}H_{30}O_4$ 417. 2042 (MNa^+), found 417.2027.

Acknowledgment. We thank the Department of Science and Technology (New Delhi, India) for the financial support of this work and the National Single

(11) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468.

Crystal X-ray Diffraction facility at IITB for the X-ray data of **5** and **8**.

Supporting Information Available: Crystallographic information files (CIF) of compounds **5** and **8**; characterization data including copies of ^{1}H and ^{13}C NMR spectra of all new compounds (**4**−**13**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0353583