J. Org. Chem. 1993, 58, 4153-4154

Oxa-Cage Compounds: Novel Synthesis of 3-Oxahexacyclo$[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]$dodecanes via Tandem Cyclization[‡]

Suresh Chander Suri[†]

University of Dayton Research Institute,
c/o Phillips Laboratory/RKFE,
Edwards Air Force Base, California 93524-7680

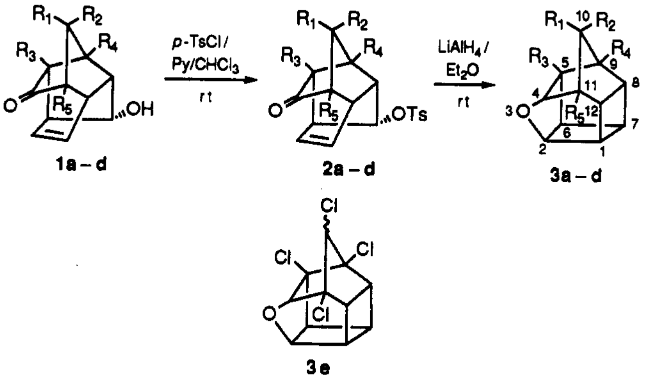
Received December 10, 1992

There are many reports regarding the chemistry[1] and synthesis[2-5] of oxo-cage compounds in literature. This class of hetrocage compounds is synthesized by intramolecular alkene-oxirane ($2\sigma - 2\pi$) photocycloaddition,[2] by transannular cyclization of suitable compounds,[3] and by dehydration of diols having the proper stereochemistry.[4] Recently, in an effort to reveal the chemistry of tetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one,[6] a nonphotochemical synthesis of functionalized pentacyclo$[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]$-undecanes[7] was achieved. Further exploration of its chemistry led to the facile formation of the 3-oxahexacyclo$[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]$dodecane carbon skeleton via tandem cyclization, and this is the subject of this paper.

Results and Discussion

Treatment of substituted 3-*exo*-hydroxytetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one **1a–d**[6,7] with *p*-toluenesulfonyl chloride–pyridine furnished the corresponding tosylates **2a–d** in good yield. When a suspension of tosylate **2a–c** in ether was exposed to excess solution of lithium aluminum hydride in ether at room temperature, it furnished a single product **3a–c** in acceptable yield (Table I). Treatment of **2d** with excess lithium aluminum hydride led to a diverse array of products. Careful chromatography of the mixture on a silica gel column using 10% EtOAc–hexane as eluent furnished oxa-cage compound **3d** along with the corresponding monodechlorinated product **3e** (4%).[8] Oxa-cage compounds **3a–e** were identified by the presence of two ether protons in their ^{1}H NMR spectra and the absence of ketone, olefin, and tosylate groups in their IR and ^{1}H and ^{13}C NMR spectral data (see Experimental Section). Further confirmation of structures **3a–e** was done by determining the nature of carbons using DEPT experiments.

Table I



1	R_1	R_2	R_3	R_4	R_5	2 (%)	3 (%)
a	OCH_3	OCH_3	Cl	Cl	Cl	78	73
b	OCH_3	OCH_3	H	Cl	Cl	80	70
c	OCH_3	OCH_3	H	H	Cl	62	71
d	Cl	Cl	Cl	Cl	Cl	82	24

The formation of 3-oxahexacyclo$[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]$-dodecanes **3a–d** may be attributed to favorable spatial orientation of alkoxide ion along with correct stereochemistry of the tosylate group, which triggers the double transannular cyclization. Ganter et al.[9] described base-promoted intramolecular ether formation with a flexible polycyclic olefinic alcohol system in which the nucleophilic addition to unactivated double bond is triggered by a proximity effect and/or homoconjugative effects.

In summary, this paper describes the first examples of oxo-cage compounds which are formed via intramolecular attack of alkoxide ion to an isolated double bond, followed by intramolecular displacement under mild conditions.

Experimental Section

Melting points were measured in capillary tubes and are uncorrected. ^{1}H NMR spectra (δ) were recorded at 300 MHz, and ^{13}C NMR (δ) were recorded at 75.5 MHz. Ether was distilled from sodium/benzophenone prior to use. The tosylates **2a–d** were prepared according to Kabalka's procedure.[10] The reactions were carried out on a 1 mmol scale. Tosylates **2a–d** and oxa-cage compounds **3a–e** were crystallized from a dichloromethane–hexane mixture.

Data for 1,8,10-trichloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one tosylate (2a): mp 155–56 °C; IR (KBr) 2951, 1782, 1367, 1217, 1192, 1176, 1096, 960, 815, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.83 (2H, J = 8.4 Hz), 7.38 (2H, J = 8 Hz), 6.33 (1H dt, J = 8.2, 1.5 Hz), 6.05 (1H, ddd, J = 8.5, 5.6, 0.8 Hz), 4.56 (1H, d, J = 2.2 Hz), 3.66 (3H, s), 3.52 (3H, s), 3.4 (1H, ddd, J = 9.0, 5.6, 1.5 Hz), 3.2 (1H, ddd, J = 9.2, 3.5, 2.3 Hz), 3.13 (1H, dd, J = 7.5, 3.5 Hz), 2.47 (3H,s); ^{13}C NMR ($CDCl_3$) 192.8, 145.3, 136.2, 133.4, 129.9 (2C), 129.8, 127.8 (2C), 99.4, 87.4, 83.0, 81.6, 79.6, 58.1, 52.5, 52.3, 47.6, 46.5, 21.7. Anal. Calcd for $C_{20}H_{19}O_6SCl_3$: C, 48.78; H, 3.89; Cl, 21.32. Found: C, 48.53; H, 3.87; Cl, 21.43.

Data for 1,8-dichloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one tosylate (2b): mp 161–62 °C; IR (KBr) 2953, 1782, 1336, 1188, 1095, 968,

---

[‡] The author dedicates this work to Prof. M. V. George on his 65th birthday.

[†] Address for correspondence: Regional Research Laboratory (CSIR), Industrial Estate P.O., Trivandrum-695019, India.

(1) Shen, K. W. *J. Am. Chem. Soc.* **1971**, *93*, 3064. Allred, E. L.; Beck, B. R. *Tetrahedron Lett.* **1974**, 437. Mehta, G.; Nair, M. S. *J. Chem. Soc., Chem. Commun.* **1983**, 439.

(2) Prinzbach, H.; Klaus, M. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 276. Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Kashyap, R. *Tetrahedron* **1990**, *46*, 3409.

(3) Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707. Coxon, J. M.; Fong, S. T.; McDonald, D. Q. *Tetrahedron Lett.* **1991**, *32*, 7115.

(4) Barborak, J. C.; Smith, E. C. *J. Org. Chem.* **1976**, *41*, 1433. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4545. Mehta, G.; Nair, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 7519. Marchand, A. P.; LaRoe, W. D.; Sharma, G. V. M.; Suri, S. C.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622. Fessner, W. D.; Prinzbach, H. *Tetrahedron* **1986**, *42*, 1797.

(5) Wu, H.-J.; Huang, F.-J.; Lin, C.-C. *J. Chem. Soc., Chem. Commun.* **1991**, 770.

(6) Suri, S. C. *Tetrahedron Lett.* **1990**, *31*, 3695.

(7) Suri, S. C.; Hardcastle, K. I. *J. Org. Chem.* **1992**, *57*, 6357.

(8) The yield of products **3d** and **3e** varies, depending upon the amount of lithium aluminum hydride, rate of addition, and reaction time. A UV-active compound (R_f value lower than **2d**) was also isolated. The ^{1}H NMR and ^{13}C NMR of the compound reflected the presence of a nonseparable mixture of saturated and unsaturated alcohols corresponding to **2d**. The presence of monodechlorinated alcohols in the reaction mixture cannot be ruled out.

(9) Pfund, R. A.; Ganter, C. *Helv. Chim. Acta* **1979**, *62*, 228. Ramos Tombo, G. M.; Pfund, R. A.; Ganter, C. *Helv. Chim. Acta* **1981**, *64*, 813. Schweizer, W. B.; Dunitz, J. D.; Pfund, R. A.; Ramos Tombo, G. M.; Ganter, C. *Helv. Chim. Acta* **1981**, *64*, 2738. Ramos Tombo, G. M.; Chakrabarti, S.; Ganter, C. *Helv. Chim. Acta* **1983**, *66*, 914.

(10) Kabalka, G. W.; Verma, M.; Verma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.

0022-3263/93/1958-4153\$04.00/0

850 cm^{-1}; ^{1}H NMR (CDCl$_3$) 7.82 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.1 Hz), 6.23 (1H, t with st, *J* = 8 Hz), 5.97 (1H, dd, *J* = 8, 5.8 Hz), 4.6 (1H, d, *J* = 2.9 Hz), 3.65 (3H, s), 3.53 (3H, s), 3.35–3.2 (3H, m), 2.94 (1H, q of d, *J* = 8.9, 2.3 Hz), 2.47 (3H, s); ^{13}C NMR (CDCl$_3$) 196.9, 145.2, 136.5, 133.6, 129.9 (2C), 129.03, 127.8 (2C), 99.3, 89.4, 83.1, 76.8, 62.2, 52.2, 52.1, 48.4, 46.1, 21.7. Anal. Calcd for $C_{20}H_{20}O_6SCl_2$: C, 52.39; H, 4.40; Cl, 15.87. Found: C, 52.10; H, 4.34; Cl, 15.87.

Data for 8-Dichloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one tosylate (2c): mp 202 °C; IR (KBr) 2982, 1770, 1371, 1188, 1172, 947, 848, 669 cm^{-1}; ^{1}H NMR (CDCl$_3$) 7.72 (2H, d, *J* = 8.3 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 6.1 (1H, t, *J* = 7.1 Hz), 5.98 (1H, dd, *J* = 8.1, 5.9 Hz), 4.32 (1H, d, *J* = 2.3 Hz), 3.38 (3H, s), 3.31 (3H, s), 3.25–2.9 (4H, m), 2.76–2.65 (1H, m), 2.4 (3H, s); ^{13}C NMR (CDCl$_3$) 200.6, 145.3, 135.8, 133.8, 130.71, 130.06 (2 C), 127.7 (2 C), 102.7, 89.3, 84.2, 51.5, 51.3, 50.1, 48.4, 47.8, 45.4, 41.1, 21.7. Anal. Calcd for $C_{20}H_{21}O_6SCl$: C, 56.53; H, 4.98; Cl, 8.34. Found: C, 56.46; H, 4.95; Cl, 8.5.

Data for 1,8,10,11,11-pentachloro-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one tosylate (2d): mp 149–50 °C; IR (KBr) 2924, 2848, 1805, 1365, 1192, 1178, 1111, 1095, 983, 829 cm^{-1}; ^{1}H NMR (CDCl$_3$) 7.84 (2H, d, *J* = 8.3 Hz), 7.4 (2H, d, 8.1 Hz) 6.41 (1H, d of t, *J* = 7.6, 1.5 Hz), 6.13 (1H, ddd, *J* = 8.3, 5.6, 0.8 Hz), 4.57 (1H, d, *J* = 2.3 Hz), 3.52 (1H ddd, *J* = 9.0, 5.7, 1.5 Hz), 3.46–3.24 (2H, m), 2.48 (3H, s); ^{13}C NMR (CDCl$_3$): 190.8, 145.7, 137.2, 133.1, 130.1 (2 C), 129.3, 127.9 (2 C), 91.2, 87.3, 85.8, 85.2, 78.7, 59.5, 48.5, 48.2, 21.7. Anal. Calcd for $C_{18}H_{13}O_4SCl_5$: C, 43.20; H, 2.62; Cl, 34.97. Found: C, 42.83; H, 2.60; Cl, 34.69.

Representative Procedure for 10,10-Dimethoxy-5,9,11-trichloro-3-oxahexacyclo[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]dodecane (3a). To a suspension of tosylate **2a** (1 mmol) in dry ether (5 mL) was added an ether solution of lithium aluminum hydride (5 mmol, 5 mL of 1 M solution in ether) at room temperature. The reaction mixture was allowed to stir overnight (16 h). The TLC of the reaction mixture on a silica gel plate reflected the consumpation of starting tosylate. The excess of LAH was destroyed by adding ethyl acetate, and the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. The reaction mixture was filtered through a pad of Celite. The filtrate was washed with 1% aqueous HCl followed by aqueous NaHCO$_3$, water, and brine. After being dried over MgSO$_4$, the filtrate was concentrated under reduced pressure. The residue was charged on a silica gel column, and elution with a 10% ethyl acetate–hexane mixture furnished **3a**: mp 126–27 °C; IR (KBr) 2997, 2951, 1234, 1101, 1064, 974, 889, 719 cm^{-1}; ^{1}H NMR (CDCl$_3$) 5.2 (1H, t, *J* = 5.8 Hz), 4.43 (1H, d, *J* = 2.3 Hz), 3.64 (3H, s), 3.62 (3H, s), 3.10 (1H, ddd, *J* = 9.5, 4.5, 1.3 Hz), 2.99 (1H, ddd, *J* = 9.5, 6.4, 2.3 Hz), 2.3–2.45 (2H, m), 1.81 (1H, dt, *J* = 6.8, 1.3 Hz); ^{13}C NMR (CDCl$_3$) 104.07 (*C*(OCH$_3$)$_2$), 90.89 (*C*Cl), 89.57 (*C*H), 82.74 (*C*H), 75.4 (*C*Cl), 68.9 (*C*Cl), 58.17 (*C*H), 56.21 (*C*H), 51.66 (O*C*H$_3$), 51.38 (O*C*H$_3$), 33.99 (*C*H), 29.69 (*C*H), 28.49 (*C*H). Anal. Calcd for $C_{13}H_{13}O_3Cl_3$: C, 48.44; H, 4.06. Found: C, 48.6; H, 4.12.

Data for 10,10-dimethoxy-9,11-dichloro-3-oxahexacyclo[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]dodecane (3b): mp 127–28 °C; IR (KBr) 2952, 2843, 1251, 1058, 929, 788, 769, cm^{-1}; ^{1}H NMR (CDCl$_3$) 5.13 (1H, t, *J* = 5.6 Hz), 4.75 (1H, dd, *J* = 8.7, 1.8 Hz), 3.66 (3H, s), 3.64 (3H, s), 3.1–2.9 (2H, m), 2.75–2.63 (1H, m), 2.38 (1H, td, *J* = 8.1, 5.5 Hz), 2.27 (1H, dt, *J* = 6.1, 4.0 Hz), 1.68 (1H, dd, *J* = 14.6, 6.6 Hz); ^{13}C NMR (CDCl$_3$) 104.3 (*C*(OCH$_3$)$_2$), 89.32 (*C*Cl), 82.53 (*C*HO–), 78.91 (*C*HO–), 76.41 (*C*Cl), 60.63 (*C*H), 56.43 (*C*H), 51.6 (2*C*H$_3$), 45.92 (*C*H), 34.36 (*C*H), 30.55 (*C*H), 19.07 (*C*H). Anal. Calcd for $C_{13}H_{14}O_3Cl_2$: C, 54.16; H, 4.89. Found: C, 53.98; H, 4.9.

Data for 11-chloro-10,10-dimethoxy-3-oxahexacyclo[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]dodecane (3c): mp 59–60 °C; IR (KBr) 2980, 2945, 2837, 1300, 1145, 1099, 1076, 1058, 993, 922 cm^{-1}; ^{1}H NMR (CDCl$_3$) 4.89 (1H, t, *J* = 6 Hz), 4.0 (1H, dd, *J* = 8.3 and 1.8 Hz), 3.26 (3H, s), 3.2 (3H, s), 2.81–2.55 (3H, m), 2.50–2.35 (1H, m), 2.1–1.95 (1H, m), 1.9–1.7 (1H, m), 1.25 (1H, q, *J* = 7 Hz); ^{13}C NMR (CDCl$_3$) 108.4 (*C*(OCH$_3$)$_2$), 83.0 (*C*HO), 80.5 (*C*HO), 78.41 (*C*Cl), 61.5 (*C*H), 60.5 (*C*H), 50.6 (*C*H), 48.8 (*C*H), 35.75 (*C*H), 33.7 (*C*H) 30.9 (*C*H), 20.1 (*C*H). Anal. Calcd for $C_{13}H_{15}O_3Cl$: C, 61.4; H, 5.95; Cl, 13.76. Found: C, 61.37; H, 5.98; Cl, 13.5.

Data for 5,9,10,10,11-pentachloro-3-oxahexacyclo[5.5.0.0^{2,6}.0.0^{4,11}.0^{5,9}.0^{8,12}]dodecane (3d): mp 240 °C; IR (KBr) 3009, 2991, 1290, 1087, 1055, 956, 871, 756, 711 cm^{-1}; ^{1}H NMR (CDCl$_3$) 5.15 (1H, t, *J* = 5.1 Hz), 4.35 (1H, *J* = 2.3 Hz), 3.16 (1H, ddd, *J* = 9.4, 4.6, 1.3 Hz), 3.06–2.95 (1H, m), 2.35–2.15 (2H, m), 1.8 (1H, dt, *J* = 6.7, 1.3 Hz); ^{13}C NMR (CDCl$_3$) 93.79 (*C*Cl$_2$), 92.65 (*C*Cl), 89.59 (*C*HO–), 83.34 (*C*HO–), 79.96 (*C*Cl), 68.14 (*C*Cl), 59.32 (*C*H), 58.00 (*C*H), 33.94 (*C*H), 29.5 (*C*H), 28.08 (*C*H). Anal. Calcd for $C_{11}H_7OCl_5$: C, 40.01; H, 2.13. Found: C, 39.97; H, 2.16.

Data for 5,9,10,11-tetrachloro-3-oxahexacyclo[5.5.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,12}]dodecane (3e): mp 160 °C; IR (KBr) 2986, 1336, 1294, 1263, 1085, 1047, 935, 885, cm^{-1}; ^{1}H NMR (CDCl$_3$) 5.34 (1H, t, *J* = 5.5 Hz), 4.65 (1H, d, *J* = 2.1 Hz), 4.38 (1H, s), 3.25–2.98 (2H, m), 2.55–2.38 (2H, m), 1.91 (1H, t, *J* = 6.9 Hz); ^{13}C NMR (CDCl$_3$) 90.86 (*C*HO–), 88.38 (*C*Cl), 83.68 (*C*HO–), 73.96 (*C*Cl), 68.22 (*C*Cl), 67.56 (*C*H), 58.6 (*C*H), 56.78 (*C*H), 33.30 (*C*H), 30.18 (*C*H), 29.32 (*C*H). Anal. Calcd for $C_{11}H_8OCl_4$: C, 44.60; H, 2.72. Found: C, 44.53; H, 2.75.

Acknowledgment. The author thanks Dr. S. L. Rodgers for his encouragement. Financial support of this study by the Air Force Office of Scientific Research, Directorate of Chemistry & Material Science, is gratefully acknowledged.