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Regioselective Opening of a Cyclopropane Ring by Mercury(II) and Transmetalation of the Product with Molybdenum. A Novel, Stereoelectronically Controlled, Skeletal Rearrangement and Grob-Type Fragmentation of Organomolybdenum Intermediates[1]

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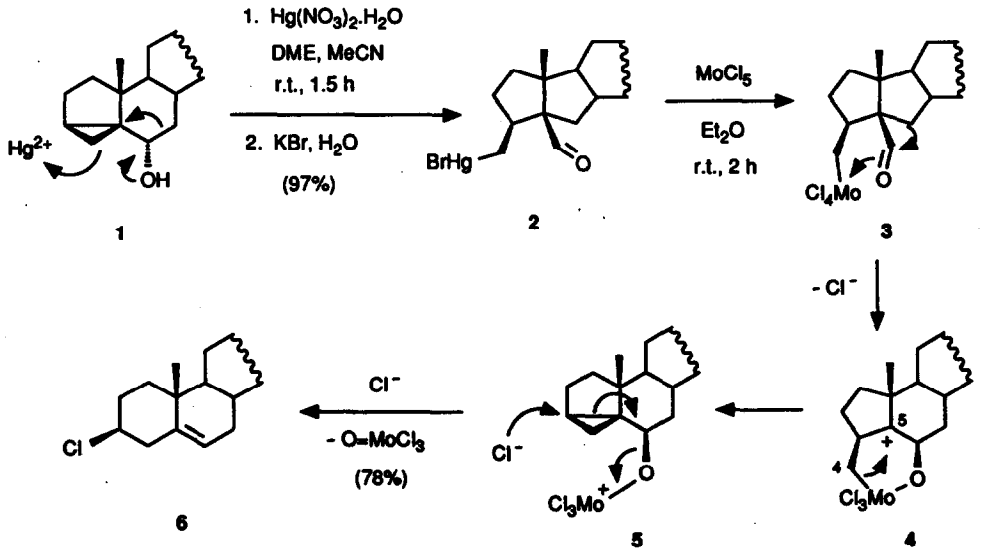
Abstract: Organomercurial **2**, arising by a regioselective ring-opening of cyclopropane derivative **1**, can be transmetalated with Mo-reagents to initially generate complexes **3** and **7**. While **3** reacts further via a stereoelectronically controlled cascade rearrangement to afford **6**, complex **7** favors a Grob-type fragmentation leading to **9**.

Stereoselective cyclopropanation followed by ring-opening is an interesting strategy for building up contiguous chiral centers.[2] We have recently described a stereoelectronically controlled cleavage of 3α,5-cyclo-5α-cholestan-6α-ol (**1**) by mercury(II) that afforded the rearranged organomercurial **2** (97%) as a stable compound (Scheme I).[3-6] We have also shown that transmetalation of **2** with Li, Cu, or Pd can be employed to synthesize various products and that the reactivity of the intermediate organometallics can be further controlled by added ligands.[3] Herein, we report on the transmetalation of **2** with molybdenum in two different forms.

Scheme I



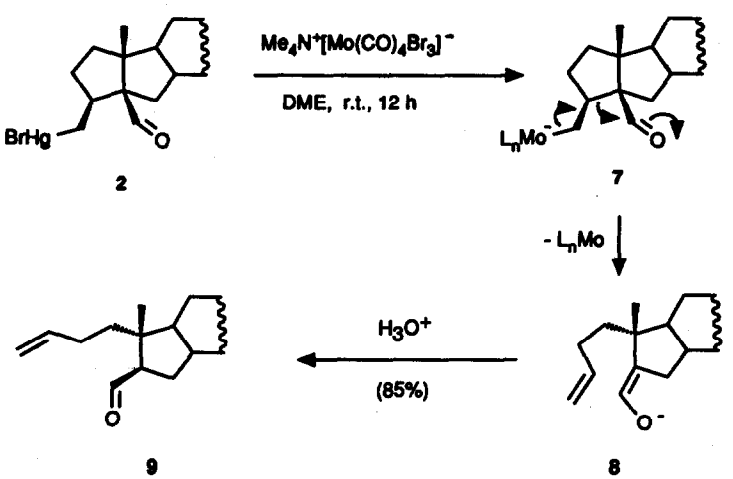
Reaction of 2 with $MoCl_5$ afforded cholesteryl chloride (6),[7] formation of which can be rationalized as follows (Scheme I). Transmetalation of 2 presumably generated molybdenum species 3 (with extrusion of HgBrCl), in which the highly oxophilic Mo can interact with the carbonyl oxygen. This interaction triggered off a stereoelectronically controlled Wagner-Meerwein migration to generate the electron-defficiency at $C_{(5)}$ (4) which was then saturated by forming a bond to $C_{(4)}$ (4 → 5).[8] The resulting cyclopropyl intermediate 5 subsequently collapsed to cholesteryl chloride (6) via the well known[9] "*iso*-steroid" rearrangement.[10,11] The whole reaction sequence is apparently controlled by the combination of high oxophilicity[12] of Mo in 3 with stereoelectronic effects.

Another molybdenum reagent, whose reactivity has been explored, was generated *in situ*, using a known procedure (eq. 1):[13]

$$Me_4N^+Br^- + Mo(CO)_6 + Br_2 \longrightarrow Me_4N^+[Mo(CO)_4Br_3]^- + 2\,CO \qquad \text{(eq. 1)}$$

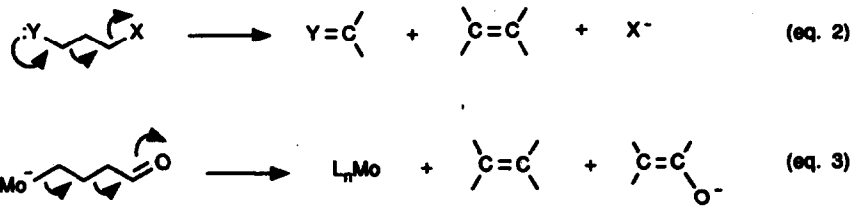
Using this complex, transmetalation of 2 was accomplished again, but the resulting organomolybdenum intermediate 7 displayed a completely different behavior compared to 3. Due to the negative charge on molybdenum, the interaction with the aldehyde oxygen is now precluded so that 7 is compelled to react differently: in this case, the molecular structure favors a novel, stereoelectronically controlled Grob-type fragmentation[14] which eventually gave rise to the olefinic aldehyde 9[15] (via the enolate 8).

Scheme II



In conclusion, we have shown, for the first time, that organomercurials, such as 2 (which in turn are synthesized by a ring-opening of cyclopropane[16]), can be readily transmetalated with various molybdenum reagents. Depending on the nature of the reagent, namely on the oxidation state of Mo, the subsequent reactions of the organomolybdenum intermediates can be directed towards different products. Thus, while $MoCl_5$ readily converted the substituted [3.3.0]bicyclooctane system into a [4.4.0] skeleton (2 → 3 → 6), the $[MoL_n]^-$ anion effected a fragmentation reaction (2 → 7 → 9). It is pertinent to note, however, the difference between the classical Grob reaction and our Mo-mediated fragmentation:

according to the Grob protocol, TsO^- typically serves as a leaving group and the negative species (e.g. O^-) forms a double bond (eq. 2). By contrast, our Mo-complex suffers a different series of events: the negative charge on molybdenum is transduced to the enolate, while Mo leaves as a neutral species (eq. 3). Moreover, whereas the classical Grob fragmentation requires a three-carbon unit with the reacting substituents at 1,3-positions, our fragmentation occurred on a 1,4-disubstituted, four-carbon framework.[17]



It appears that all these novel transformations (Schemes I and II) are subject to a stringent stereoelectronic control. The unique feature of this chemistry is that the reactivity of the organometallic intermediates can be tuned by a delicate balance of the oxidation sate of the metals involved and the ligands attached. Although the experiments were confined to the steroidal skeleton, we believe that our findings are of general nature and may be used for synthetic purposes, particularly in view of a number of methods for preparation of organomercurials.[16]

Acknowledgment: We thank Drs. G. Griffith and A. Gogoll for obtaining the NMR spectra and Merck Sharp and Dohme, Roche Products Ltd., and the University of Leicester for financial support to J. Š.

References and Notes

(1) Dedicated to Dr. Václav Černý on the occasion of his 70th birthday.

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(6) For review on organomercurials, see: Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985.

(7) Identical with an authentic sample.

(8) This process may be concerted.

(9) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968.

(10) Model experiments demonstrated that both the 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted into **6** on treatment with $MoCl_5$ in Et_2O at r.t.

(11) 5α-Cholestan-3β-ol was converted by the same reagent to a ca. 1:1 mixture of the corresponding 3α- and 3β-chlorides, which indicates S_N1 mechanism.

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(15) **9**: $[\alpha]_D$ +14° (c 2.4, $CHCl_3$); IR ($CHCl_3$): 1637, 1710, and 2704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.90-5.10 (m, 2 H, CH=C*H*$_2$), 5.70-5.95 (m, 1 H, C*H*=CH$_2$), 9.70 (d, 1 H, J = 3.2 Hz, CH=O) ppm; ^{13}C NMR: 12.32 (q), 17.78 (q), 18.76 (q), 21.36 (t), 22.57 (q), 22.82 (q), 23.86 (t), 24.40 (t), 28.01 (d), 28.48 (t), 29.35 (t), 29.86 (t), 35.66 (d), 36.23 (t), 39.44 (t), 39.50 (t), 40.48 (d), 41.92 (t), 43.88 (s), 47.40 (s), 55.69 (d), 56.63 (d), 57.43 (d), 58.27 (d), 114.32 (t), 138.85 (d), 204.96 (d) ppm. The CH=O proton (at 9.70 ppm) shows NOE (1.4%) upon irradiation of angular methyl (19-H at 0.90 ppm), indicating their *cis* relationship.

(16) For general methods of synthesis of organomercurials, see ref. 6.

(17) A related fragmentation of such a structural pattern employed TsO as a leaving group and boron in place of molybdenum: Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291.

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