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Intramolecular Alkoxymercuration of Olefins and Stabilization of the Resulting Organomercurials

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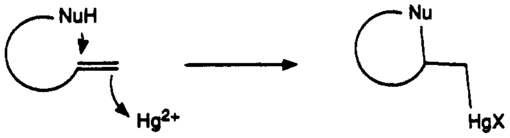
Summary: Quenching of oxymercuration with CuCl has been found superior to the classical method using aqueous NaCl or KBr. Oxymercuration products with an anti-periplanar arrangement of the C–HgX and C–O bonds (e.g. diaxial as in 2) are particularly prone to reversion to the olefin (1) when treated with hard reagents, such as NaCl, KBr, $CuCl_2$, $CoCl_2$, HCl, etc. The reversal is apparently boosted by the stereoelectronic effect and electrophilic catalysis. By contrast, quenching of the primarily formed organomercurial 2 with soft reagents, namely with CuCl, $PdCl_2$, K_2PtCl_4, etc. reliably affords the desired chloromercury compound 3.

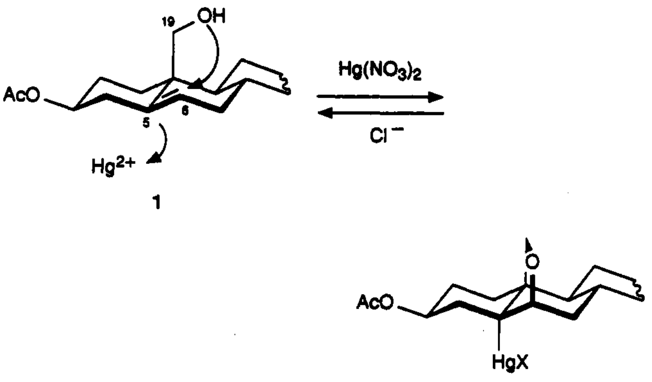
Oxymercuration and amidomercuration[1] are established procedures for a stereoselective construction of oxygen or nitrogen heterocycles[2] from olefinic alcohols or amides (eq 1).[3] The reaction is usually quenched with aqueous NaCl or KBr in order to obtain stable organomercury halides.[2] Herein, we report on an improved procedure for the preparation of organomercury chlorides that can be used in cases where the classical quenching fails.



(1)

Results

The 5-cholestene-3β,19-diol 3-monoacetate (1) undergoes a 5(O)^n-endo-Trig cyclization[4] with $Hg(NO_3)_2$ in aqueous dioxane to generate 2 as a nonisolated species, reduction of which with $NaBH_4$ or Bu_3SnH affords a 3:2 mixture of the corresponding 5α-H and 5β-H tetrahydrofurans.[5-7] However, when isolation of the intermediate organomercurial 2 was attempted by quenching with aqueous KBr, an instantaneous reversion to the starting olefinic alcohol 1 was observed. The same result was obtained with NaBr, Me_4NBr, NaCl, LiCl, and NaI, whereas no reaction was observed with Bu_4NF.



1

2, X = NO_3
3, X = Cl

However, much to our surprise, the desired organomercury chloride 3 was found to arise from 2 upon treatment with Na_2PdCl_4 or $PdCl_2$ in a quantitative yield.[8] No transmetalation[9] was observed in this instance, presumably owing to the steric hindrance at the tertiary position (C_5), and the isolated product 3 turned out to be stable at room temperature for several weeks.[10] Hence, the failure to obtain 3 from 2 by means of alkali halides must be associated with the nature of the halide reagent rather than with any instability of 3.

In order to shed more light on this issue, a brief study of a series of inorganic halides was carried out (Table I). A clean, instantaneous reaction producing 3 was observed with $PdCl_2$, Na_2PdCl_4, and K_2PtCl_4 (entries 1–3) and with CuCl (entry 4). In contrast, $CuCl_2$ clearly favored reversion, affording 1 as the only product (entry 5). Iron reagents produced mixtures (entries 6 and 7), $CoCl_2$ induced a clean reversion (entry 8), and $NiCl_2$ slightly favored chlorination (entry 9). A clean reversion to 1 was also observed with $MnCl_2$, Cp_2TiCl_2, $CeCl_3$, and CdI, while

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[1] (a) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986. (b) Bartlett, P. A. In Olefin Cyclization Processes that form Carbon-Heteroatom Bonds. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 411. (c) Bartlett, P. A. In Olefin Cyclization Processes that form Carbon-Carbon Bonds. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 342. (d) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

[2] (a) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (b) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer, Berlin, 1986.

[3] For recent examples, see e.g.: (a) Takacs, J. M.; Helle, M. A.; Yang, L. *Tetrahedron Lett.* **1989**, *30*, 1777. (b) Takacs, J. M.; Helle, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1989**, *30*, 7321. (c) Takacs, J. M.; Helle, M. A.; Sanyal, B. J.; Eberspracher, T. A. *Tetrahedron Lett.* **1990**, *31*, 6765. (d) Barluenga, J.; Aznar, F.; de Mattos, M. C. S.; Kover, W. B.; Garcia-Granda, S.; Pérez-Careño, E. *J. Org. Chem.* **1991**, *56*, 2930. (e) Barluenga, J.; Aznar, F.; Fraiz, S., Jr.; Pinto, A. C. *Tetrahedron Lett.* **1991**, *32*, 3205. (f) de Mattos, M. C. S.; Kover, W. B.; Aznar, F.; Barluenga, J. *Tetrahedron Lett.* **1992**, *34*, 4863. (g) Takahata, H.; Bandoh, H.; Momose, T. *J. Org. Chem.* **1992**, *57*, 4401.

[4] Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.

[5] Analogous reactivity has previously been observed with $(CF_3CO_2)_2Hg$.[6,7]

[6] Welzel, P.; Holtmeier, W.; Wessling, B. *Liebigs Ann. Chem.* **1978**, 1327.

[7] Kočovský, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580.

[8] The structure of 3 was corroborated by NMR spectra (which show a close analogy to those of 5-bromo-6β,19-epoxy-5α-cholestanyl 3β-acetate)[7] and by its chemical behavior: upon Bu_3SnH and $NaBH_4$ reduction the same mixture of 5α-H and 5β-H epimeric cyclic ethers was obtained as that from 2; treatment with silver salts ($AgNO_3$ or CF_3SO_3Ag) led to deposition of AgCl.

[9] (a) Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086. (b) Heumann, A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 207.

[10] After 2 months at room temperature ca. 10% reversion of 3 to 1 was detected by TLC.

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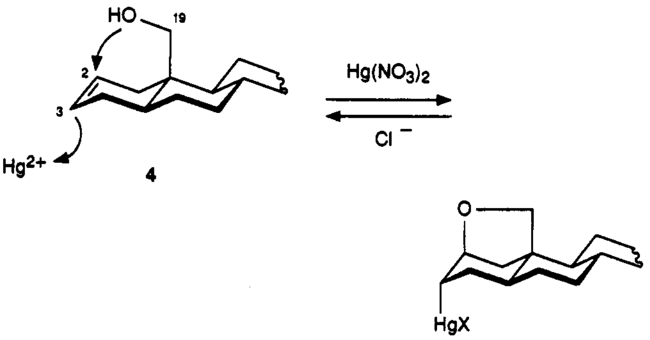
Table I. Reaction of the in situ Generated Organomercurial 2 with Inorganic Chlorides

entry	reagent MCl_n	product ratio **1**:**3**	formation constant[a] of MCl_n (at 25 °C)
1	$PdCl_2$	<1:50	6.0[b]
2	Na_2PdCl_4	<1:50	
3	K_2PtCl_4	<1:50	10.5[c]
4	CuCl	<1:50	4.9[d]
5	$CuCl_2$	>50:1	0.05[e]
6	$FeCl_2$	4:1	0.36[f]
7	$CpFe(CO)_2Cl$	1:4	
8	$CoCl_2$	>50:1	1.63[f]
9	$NiCl_2$	2:3	3.7[d]

[a] *Stability Constants of Metal-Ion Complexes*; Sillén, L. G., Ed.; Special Publication No. 17; The Chemical Society: London, 1964. Special Publication No. 25; The Chemical Society, London, 1971 (supplement). [b] Extrapolated to zero ionic strength. [c] For $PtCl_2$ in NaCl. [d] In MeCN. [e] In $HClO_4$. [f] In 50% EtOH.

$AuCl_3$ was found to be inert, and $AlCl_3$ and $MoCl_5$ caused decomposition.[11,12]

Similar experiments were carried out with the 5α-cholest-2-en-19-ol (**4**).[7] Here, again, the reaction with $Hg(NO_3)_2$ furnished the expected organomercurial **5**,[15] quenching of which with alkali-metal halides resulted in the exclusive reversion to **4**. In contrast to **2**, treatment of **5** with Na_2PdCl_4 or $PdCl_2$ gave a complex mixture of products, apparently due to transmetalation and subsequent decomposition.[7] However, copper salts followed the same pattern as with **2**: CuCl instantly produced chloride **6** in essentially quantitative yield,[16] while $CuCl_2$ induced a clean reversion to **4**.



4

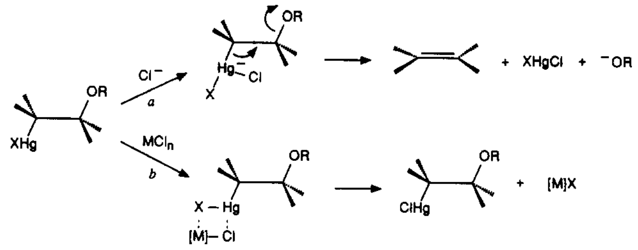
5, X = NO_3

6, X = Cl

Discussion

Effect of the Metal. The striking differences in the behavior of various metallic halides can be rationalized by the HSAB theory.[17] Soft metals (entries 1–4, and 7) form a stronger bond toward Cl (as expressed by high formation constants;[18] Table I), while salts of harder metals dissociate more easily (low formation constants; for alkali-metal chlorides, $K_1 \leq 2$) producing harder Cl^-. It appears that hard Cl^- directly attacks mercury, presumably generating a transient, T-shaped species with negatively charged mercury (Scheme I; path a). Subsequent breaking of the C–Hg bond facilitates a formal S_N2 substitution (at Hg), resulting in the reversion to the starting olefin. In contrast, soft reagents prefer to replace the inorganic anion (at Hg) and produce the corresponding organomercury chloride, presumably via a four- or six-centered transition state (Scheme I; path b) with both Hg and the other metal involved.[19,20] The dramatic difference between CuCl and $CuCl_2$ is fully in line with this mechanistic picture: low oxidation state metals (such as Cu^I) are known to bind soft ligands because of excess electron density that can be donated to the ligand; consequently, a stronger covalent bond is thus formed. In contrast, higher oxidation states (e.g. Cu^{II}) favor hard ligands, as their donation capability is reduced.[17] Hence, the chlorine atom in CuCl should be softer than that in $CuCl_2$ and this difference appears to suffice for the entire reversal of the reaction course with organomercurials from a charge-controlled process (path a) to a frontier-orbital-controlled reaction (path b).

Scheme I



Electrophilic Catalysis. The possible role of electrophilic catalysis in departing and stabilizing of the RO^- group has been assessed by testing the reactivity of **3** (first isolated and characterized) under a variety of conditions. The role of both the cation (Lewis or Brønsted acid) and anion (nucleophilic vs nonnucleophilic) was elucidated. Thus, LiCl, $CuCl_2$, and HCl have been found to revert **3** to **1** instantaneously, whereas $LiClO_4$, and $Cu(NO_3)_2$ turned out to be inert.[22] This demonstrates that electrophilic catalysis alone cannot facilitate the reversion. However, while NaCl proved to induce a fast reversion, addition of a crown ether considerably slowed down the reaction; in this case the reaction can again be accelerated by $HClO_4$. Similarly, $Et_3(PhCH_2)N^+Cl^-$ reacts sluggishly[23] but adding a trace of $HClO_4$ also causes acceleration. This behavior indicates that a Lewis or Brønsted acid has a beneficial, but not decisive, effect upon the reversion. The prereq-

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[11] Reagents that are known to effect methylation at mercury (i.e. R–HgBr → R–$HgCH_3$), such as Me_3Al and MeCu,[13] also induced clean reversion of **3** to **1**. In contrast, the *in situ* generated complex[14] $Bu_4N[Mo(CO)_4Br_3]$ highly favored bromination over reversion (9:1).

[12] As with copper chlorides, quenching of **2** with CuBr resulted in the clean formation of the corresponding bromomercurio derivative (**3**, X = Br), whereas $CuBr_2$ induced a quantitative reversion.

[13] Kočovský, P.; Šrogl, J. *J. Org. Chem.* **1992**, *57*, 4565.

[14] (a) Šrogl, J.; Kočovský, P. *Tetrahedron Lett.* **1992**, *33*, 5991. (b) Ganokar, M. C.; Stiddard, M. H. B. *J. Chem. Soc.* **1965**, 3494. (c) Abel, E. W.; Butler, I. S.; Red, J. G. *J. Chem. Soc.* **1963**, 2068.

[15] Reduction of **5** with Bu_3SnH or $NaBH_4$ gives the known[7] 2β,19-epoxy-5α-cholestane.

[16] Organomercurial **6** turned out to be less stable than its analogue **3**: ca. 50% reversion to **4** was detected by TLC after 2 months at room temperature.

[17] (a) Ahrland, S.; Chatt, J.; Davies, N. R. *Chem. Soc. Rev.* **1958**, *12*, 265. (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; J. Wiley: New York, 1988; p 7.

[18] A quantitative correlation would be difficult to make as the necessary constants have not always been measured under the same conditions and by the same method. Nevertheless, we believe that the values in Table I allow for sketching qualitative conclusions.

[19] Note that mercury itself is a soft metal, as evidenced by the high value of the formation constant (K_1 = 6.74) for $HgCl_2$.

[20] Intermediate structures of this kind may not be confined to the system of R–HgX and $PdCl_2$ or CuCl. These interactions may play a vital role, e.g., in Wacker oxidation and in catalytic oxopalladation[21] of olefins, where excess $CuCl_2$ is employed to regenerate the catalyst. The previously observed beneficial effect of added CuCl into the $PdCl_2/CuCl_2$ system[7] seems to be in line with these observations.

[21] For reviews, see: (a) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. (b) Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49.

[22] Slow decomposition to other products (but not to **1**) in the presence of $HClO_4$ and $Cu(NO_3)_2$ has been detected.

[23] The reaction with Bu_4NBr is much faster.

uisite for the reversion is the presence of hard Cl^-. In line with this concept is the observation that a small amount of $HClO_4$ does not revert **3** to **1** in the presence of CuCl.

Conclusion

These results clearly demonstrate that CuCl is the reagent to choice to quench mercuration of olefins. It appears that the organomercurials having a rigid antiperiplanar (i.e. diaxial) orientation of the C–HgX and C–O (or C–N) bonds are particularly prone to the stereoelectronically boosted reversion and the classical quenching with NaCl or KBr fails to give the desired product. In these cases the utilization of CuCl is highly recommended. Strong Brønsted and hard Lewis acids in higher concentration should be avoided in order to suppress a possible electrophilic catalysis of reversion of the adduct to olefin.[24]

Experimental Section

Materials and Equipment. The NMR spectra were recorded for $CDCl_3$ solutions on a Bruker AM 300. Chemical shifts were indirectly referred to TMS via the solvent signals (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). All reactions were carried out under nitrogen. Standard workup of an ethereal solution means washing with 5% HCl (aqueous), water, and 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range 40–60 °C. The identity of samples prepared by different routes was checked by TLC and IR and NMR spectra. Yields are given for isolated product showing one spot on a chromatographic plate and no impurities detectable in the NMR spectrum.

5-(Chloromercurio)-6*β*,19-epoxy-5*α*-cholestan-3*β*-yl Acetate (3). To a stirred solution of **1** (222 mg; 0.5 mmol) in 1,2-dimethoxyethane (4 mL), containing a trace of 10% aqueous perchloric acid, was added solid mercury(II) nitrate monohydrate (154 mg; 0.55 mmol) in portions over a period of 10 min, and the mixture was stirred at room temperature for 30 min. A freshly prepared, solid copper(I) chloride (59 mg; 0.60 mmol) sample was then added in portions over a period of 5 min, and the mixture was stirred at room temperature for another 10 min. The mixture was then diluted with ether and washed with water, dried with sodium sulfate, and evaporated. The residue was purified by chromatography on silica gel (10 g) using a petroleum ether–ether–acetone mixture (89:10:1 and then 87:10:3) as eluent to give **3** (310 mg; 92%): mp 118–120 °C dec (aqueous acetone); ^1H NMR δ 0.75 (s, 3 H, 18-H), 2.07 (s, 3H, CH_3CO_2), 3.74 and 3.80 (AB system, J = 8.4 Hz, 2 H, 19-H), 4.30 (d, J = 4.1 Hz, 1 H, 6α-H), 4.95 (m, $W/2$ = 21 Hz, 1 H, 3α-H); ^{13}C NMR δ 12.57 (q), 18.60 (q), 21.30 (q), 22.57 (q), 22.82 (q), 22.90 (t), 23.50 (t), 23.72 (t), 26.62 (t), 27.19 (t), 28.02 (d), 28.19 (t), 35.04 (d), 35.71 (d), 36.07 (t), 37.85 (t), 39.48 (t), 39.66 (t), 41.39 (t), 43.23 (s), 47.83 (s), 55.65 (d), 55.84 (d), 59.63 (d), 68.23 (t), 72.34 (d), 81.99 (d), 85.21 (s), 170.43 (s). Anal. Calcd for $C_{29}H_{47}ClO_3Hg$: C, 51.24; H, 6.97. Found: C, 50.95; H, 6.70.

5-(Bromomercurio)-6*β*,19-epoxy-5*α*-cholestan-3*β*-yl acetate (3, X = Br) was prepared in an analogous way using copper(I) bromide: mp 93–96 °C dec (aqueous acetone); ^1H NMR δ 0.75 (s, 3 H, 18-H), 2.07 (s, 3 H, CH_3CO_2), 3.72 and 3.81 (AB system, J = 8.5 Hz, 2 H, 19-H), 4.31 (d, J = 4.0 Hz, 1 H, 6α-H), 4.96 (m, $W/2$ = 25 Hz, 1 H, 3α-H); ^{13}H NMR δ 12.56 (q), 18.59 (q), 21.31 (q), 22.55 (q), 22.80 (q), 22.86 (t), 23.49 (t), 23.70 (t), 26.60 (t), 27.19 (t), 27.98 (d), 28.16 (t), 35.05 (d), 35.67 (d), 36.04 (t), 37.86 (t), 39.46 (t), 39.64 (t), 41.22 (t), 43.21 (s), 47.95 (s), 55.63 (d), 55.80 (d), 59.37 (d), 68.32 (t), 72.29 (d), 82.08 (d), 87.65 (s), 170.41 (s). Anal. Calcd for $C_{29}H_{47}BrO_3Hg$: C, 48.10; H, 6.54. Found: C, 47.83; H, 6.69.

3*α*-(Chloromercurio)-2*β*,19-epoxy-5*α*-cholestane (6). To a stirred solution of **4** (193 mg; 0.5 mmol) in 1,2-dimethoxyethane (4 mL), containing a trace of 10% aqueous perchloric acid, was added solid mercury(II) nitrate monohydrate (154 mg; 0.55 mmol) in portions over a period of 10 min, and the mixture was stirred at room temperature for 30 min. A freshly prepared, solid copper(I) chloride (86 mg; 0.60 mmol) was then added in portions over a period of 5 min and the mixture was stirred at room temperature for another 10 min. The mixture was then diluted with ether and washed with water, dried with sodium sulfate, and evaporated. The residue was purified by chromatography on silica gel (10 g) using a petroleum ether–ether–acetone mixture (89:10:1) as eluent to give **3** (267 mg; 86%): mp 205–208 °C; ^1H NMR δ 0.64 (s, 3 H, 18-H), 3.01 (m, $W/2$ = 12 Hz, 1 H, 3β-H), 3.73 and 3.88 (AB system, J = 8.1 Hz, 2 H, 19-H), 4.43 (dd, J = 4.2 and 6.1 Hz, 2α-H); ^{13}C NMR δ 11.81 (q), 18.66 (q), 21.03 (t), 22.55 (q), 22.80 (q), 23.78 (t), 24.09 (t), 27.98 (d; two carbons), 28.14 (t), 29.97 (d), 31.25 (t), 32.78 (t), 35.71 (d), 36.10 (t), 38.49 (d), 39.47 (t), 39.54 (t), 42.20 (s), 44.51 (t), 44.72 (d), 46.11 (d), 47.22 (s), 56.11 (d), 56.51 (d), 68.61 (t), 77.14 (d). Anal. Calcd for $C_{27}H_{45}ClOHg$: C, 52.16; H, 7.30. Found: C, 51.80; H, 7.52.

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[24] Note added in proof: Quenching of **2** with $CaCl_2$ is also fairly effective, producing a mixture of **1** and **3** in ca. 1:9 ratio.