Functional group selectivity in reactions of epoxides with tungsten hexachloride

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Abstract—The reactivity of several cyclohexene oxides bearing various functional groups toward the reagent tungsten hexachloride is reported. In general, the conversion of the epoxide to the trans dichloride occurs relatively rapidly. Several groups proved stable—esters, sulfides, sulfones, hindered silyl ethers—while others were unstable—alcohols, unhindered silyl ethers, ketones. The diaxial dichloride is usually formed although the diequatorial dichloride could also be prepared.

Recently we reported the reaction of the optically active terpenoid keto epoxide 1 (derived from the methylated Wieland–Miescher ketone) with tungsten hexachloride (WCl₆) to generate the diequatorial dichloride from the epoxide and the vinyl chloride from the ketone, affording the trichloro product 2 in 80% yield (Scheme 1).¹ This was the first example of the use of this reagent with a cyclic epoxide where the diaxial and diequatorial stereochemistry of the product could be assessed. Several reactions of tungsten hexachloride with alcohols, ketals, and epoxides had already been reported.² We also described the conversion of ketones, for example, 3 and 5, with tungsten hexachloride into either vinyl chlorides, for example, 4, or geminal dichlorides, for example, 6 (Scheme 2), depending on the steric environment with hindered ketones giving vinyl chlorides and less hindered ones giving geminal dichlorides.¹ In order to try to use this novel transformation of an epoxide into a diequatorial dichloride in the later stages of a projected total synthesis of the class of naturally occurring terpenoid antitumor agents exemplified by the two diols, dichlorolissoclimide 7,³ and haterumaimide E 8⁴ (Scheme 3), we needed to test the stability of several functional groups toward this reagent to see which, if any, could be present in the epoxide without reacting. We report herein the use of tungsten hexachloride under mild conditions to convert epoxides into trans vicinal dichlorides, and point out the stability or lack thereof of several common functional groups in this process.

We decided to use 4-substituted cyclohexene oxide derivatives as the test cases. The anti epoxy ester 9⁵ was prepared by the opening of the corresponding iodo- lactone with ethoxide. Treatment of 9 with tungsten hexachloride in dichloromethane at 21 °C for 4.5 h afforded the diaxial dichloride⁶ 10a as the sole product in 58% isolated yield (Scheme 4). None of the

Scheme 1.

Scheme 2.
corresponding diequatorial dichloride 10e was formed in this reaction.7 Thus an ester functionality directly attached to the cyclic epoxide system is relatively stable to the conditions for dichloride formation. When a mixture of the two diastereomeric epoxy esters corresponding to 9 was used (prepared by epoxidation of ethyl 4-cyclohexene-carboxylate), the same result was obtained, namely the diaxial dichloride 10a was formed selectively. Since the diastereomeric mixture gave the same products, we thereafter used the more easily prepared mixtures. Treatment of the diastereomeric mixture of epoxy acetates 115 with tungsten hexachloride in dichloromethane afforded the two products, the diaxial dichloride 12a and the diequatorial dichloride 12e, depending on the reaction conditions (Scheme 5). Use of low temperatures or short reaction times afforded the diaxial dichloride 12a as the sole product, while higher temperature or longer reaction times afforded a roughly 4:3 mixture of 12a and 12e. Presumably the diaxial dichloride 12a is the kinetic product formed by the mechanism proposed in Scheme 6. Attack of the epoxide oxygen of A on tungsten hexachloride would afford the epoxonium ion B which could be opened at either carbon to generate a mixture of chlorides C and D. Cyclization via attack of the chloride lone pair would generate the chloronium ion E and oxotungsten tetrachloride and chloride ion. Final opening of this ion with chloride via the kinetically favored path, path a, would then give mostly the diaxial product F. But this isomer could equilibrate with the diequatorial product G via the chloronium chloride with opening via path b.9 Theoretical calculations show that the diaxial dichloride isomer is somewhat more stable than the diequatorial one.10

Treatment of the diastereomeric mixture of epoxy sulfones 13 with 3 equiv of tungsten hexachloride at 45 °C for 2 h gave a quantitative yield of the diaxial dichloride 14a with only a trace of the diequatorial isomer 14e being formed (Scheme 7). Ambient temperature could also be used at a small loss of yield (48 h, 94%). In a similar manner, treatment of the diastereomeric epoxy sulfides 15 afforded exclusively the diaxial dichloride 16a in 83% yield (Scheme 8). The corresponding sulfoxide 17 afforded a mixture of the corresponding diaxial dichloro sulfoxide 18a as well as the diaxial dichloro sulﬁde 16a in a 1.5:1 ratio in modest yield.11 The production of the sulfide 16a presumably resulted from the known deoxygenation of sulfoxides to sulfides with tungsten hexachloride.12 Thus esters, sulfones, and sulfides all proved stable to the reaction with tungsten hexachloride, while sulfoxides were somewhat susceptible to reduction under the reaction conditions and gave mixtures of the dichloro sulfoxides and sulfides. However, some other functional groups proved unstable. For example, the diastereomeric mixture of epoxy

\[ \text{7 Dichloroliscocimide} \]

\[ \text{8 Haterumaimide E} \]

Scheme 3.

\[ \text{9} \quad \text{2 eq WCl}_6 \quad \text{CH}_2\text{Cl}_2 \quad 21^\circ\text{C}/4.5\text{h} \]

\[ \text{10a 56%} \quad \text{10e 0%} \]

Scheme 4.

\[ \text{11} \quad \text{2 eq WCl}_6 \quad \text{CH}_2\text{Cl}_2 \quad 21^\circ\text{C}/0.5\text{h} \]

\[ \Delta/5\text{min} \quad \Delta/3\text{h} \quad \Delta/21\text{hHCl} \]

\[ \text{12a 60%} \quad \text{12b 0%} \quad \text{12c 0%} \quad \text{12d 0%} \quad \text{12e 0%} \]

Scheme 5.

\[ \text{13} \quad \text{45^\circC/2h} \quad \text{14a >95%} \quad \text{14e trace} \]

\[ \text{14a 94%} \quad \text{14e trace} \]

Scheme 7.

\[ \text{15} \quad \text{3 eq WCl}_6 \quad \text{CH}_2\text{Cl}_2 \quad \text{21^\circC/3.5h} \]

\[ \text{16a 83%} \quad \text{16e 0%} \quad \text{16a 85%} \quad \text{16e 0%} \]

Scheme 8.
alcohols 19, when treated with tungsten hexachloride at 21 °C for 24 h, afforded in 34% yield a 1:1 mixture of the trichlorides, 20a and 20e, namely the diaxial and diequatorial dichlorides in which the hydroxyl group had also been converted into the chloride, a known transformation. \(^{11}\) When the reaction was heated for 45 min, trichloride 20e, having the diequatorial dichloride unit, was the sole product isolated in 26% yield. In addition the tertiary chloride 22 was isolated in variable yield (presumably formed via addition of the generated HCl to the exocyclic methylene 21 in which the chloride attacks the tertiary carbocation preferentially from the axial direction). Finally the steric bulk of silyl ethers was crucial in their reactions with this reagent. Thus the epoxy \(t\)-butyldimethylsilyl (TBDMS) ether 23 was unstable and gave a mixture of the same trichlorides 20a and 20e in poor yield (Scheme 10). The silyl ether was either hydrolyzed to the alcohol which was converted to the chloride or converted directly to the chloride by the tungsten hexachloride. An attempt to buffer the reaction using the hindered base, \(2,6\)-di-tert-butyl-4-methylpyridine, was unsuccessful. But the more hindered epoxy \(t\)-butyldiphenylsilyl (TBDPS) ether 24 gave a modest 40% yield of the expected diaxial dichloride 25a when treated with tungsten hexachloride in the presence of 1.5 equiv of the hindered base, \(2,6\)-di-tert-butyl-pyridine. \(^{11,13}\) None of the corresponding diequatorial dichloride 25e was formed in this reaction. Thus alcohols and unhindered silyl ethers are too unstable to these conditions to survive while more hindered silyl ethers can be used successfully in the presence of a hindered base.

\[
\begin{align*}
\text{Scheme 9.} & \\
21 & \quad \text{2 eq WCl}_6 \\
\text{21 °C/24 h} & \quad \Delta /45 \text{ min} \\
20a & \quad 17\% \\
20e & \quad 0\% \\
21 & \quad \text{2 eq WCl}_6 \\
\Delta & \\
22 & \quad \text{HCl} \\
21 & \quad \text{HCl} \\
19 & \quad 2 \text{ eq WCl}_6 \\
\text{CH}_2\text{Cl}_2 & \\
19 & \quad \Delta \\
\end{align*}
\]

In conclusion, we have shown that a series of cyclohexene oxides are converted into the corresponding trans vicinal dichlorides on treatment with tungsten hexachloride and that several common functional groups survive this treatment unchanged (esters, sulfides, sulfones, hindered silyl ethers), while others react (ketones, sulfoxides, alcohols, less hindered silyl ethers). Further studies on the use of this reaction in the synthesis of the naturally-occurring antitumor diterpenes are underway in our laboratory.

Acknowledgment

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References and notes


2. For a review, see: (a) Jung, M. E.. 


6. The stereochemistry of the dichlorides was easily assigned by the size of the coupling constants of the protons \(\alpha\) to the chlorides, with the protons in the diaxial isomer having three small \(J\)’s while the protons in the diequatorial isomer had two larges and one small \(J\).

7. All starting material is consumed in this reaction and there is very little other non-volatile, non-aqueous-soluble organic material formed in this reaction. We cannot explain the lack of good mass balance.


10. Calculations using B3LYP/6-311+G(d,p) showed that the diaxial dichloride is slightly more stable than the diequatorial (\(Z = H\), \(\Delta E = 0.45 \text{ kcal/mol}\); \(Z = CH_3\), \(\Delta E = 0.49 \text{ kcal/mol}\)). Thus the diaxial dichloride is both the kinetic and the thermodynamic product of this reaction. However, since the energy difference between the two isomers is only \(\sim 0.5 \text{ kcal/mol}\), with extended treatment, a nearly 1:1 equilibrium mixture is obtained.
We thank Professor K. N. Houk and Ms. Joann Um for their assistance with these calculations.

11. Extensive decomposition was also observed and the mass balance was poor.

12. Normally an additional reducing agent such as zinc metal or sodium iodide is required for the efficient deoxygenation of sulfoxides.  

13. Reaction of 24 with tungsten hexachloride in the absence of base gave mainly decomposition, thus stressing the importance of the hindered base in this reaction.

\[ \begin{align*}
\text{Z} = \text{H}, \Delta E &= 0.45 \text{ kcal/mol} \\
\text{Z} = \text{CH}_3, \Delta E &= 0.49 \text{ kcal/mol}
\end{align*} \]