

Functional group selectivity in reactions of epoxides with tungsten hexachloride

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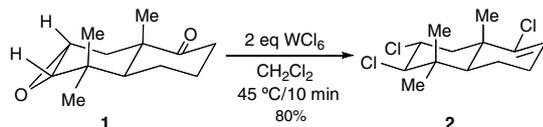
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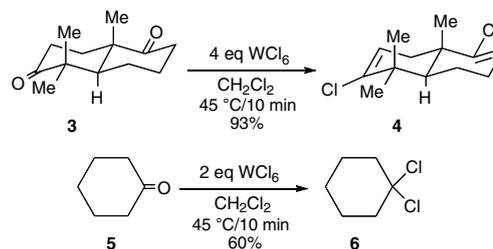
Abstract—The reactivity of several cyclohexene oxides bearing various functional groups toward the reagent tungsten hexachloride is reported. In general, the conversion of the epoxide to the trans dichloride occurs relatively rapidly. Several groups proved stable—esters, sulfides, sulfones, hindered 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.

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Recently we reported the reaction of the optically active terpenoid keto epoxide **1** (derived from the methylated Wieland–Miescher ketone) with tungsten hexachloride (WCl_6) 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 pro-



Scheme 1.



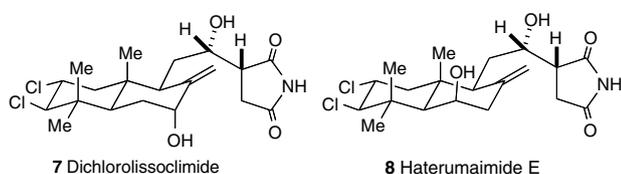
Scheme 2.

jected total synthesis of the class of naturally occurring terpenoid antitumor agents exemplified by the two diols, dichlorolisoclimide **7**,³ and haterumaimide E **8**,⁴ (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.

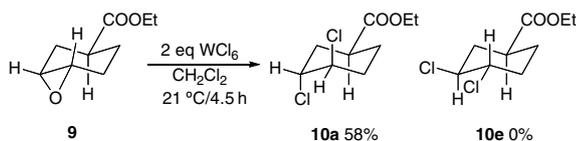
We decided to use 4-substituted cyclohexene oxide derivatives as the test cases. The anti epoxy ester **9**⁵ was prepared by the opening of the corresponding iodolactone with ethoxide. Treatment of **9** with tungsten hexachloride in dichloromethane at 21 °C for 4.5 h afforded the diaxial dichloride⁶ **10a** as the sole product in 58% isolated yield (Scheme 4). None of the

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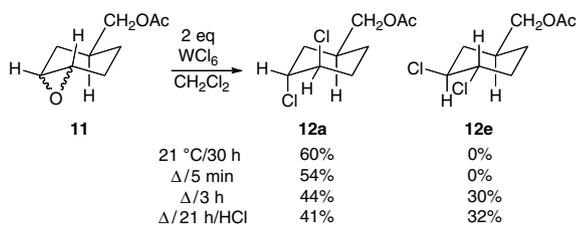


Scheme 3.

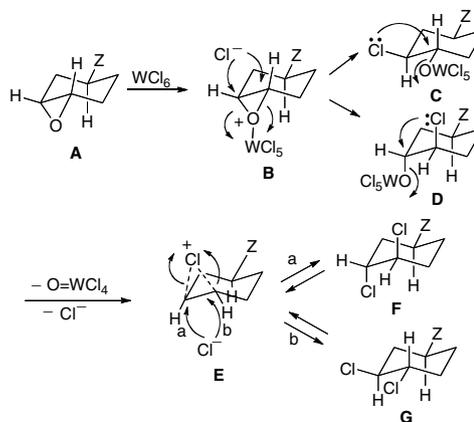


Scheme 4.

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-cyclohexenecarboxylate), 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 **11**⁸ 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 oxonium 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

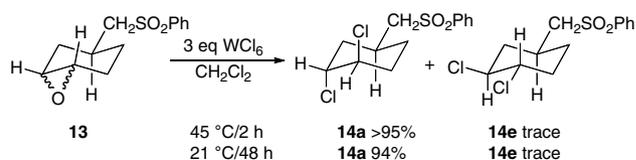


Scheme 5.

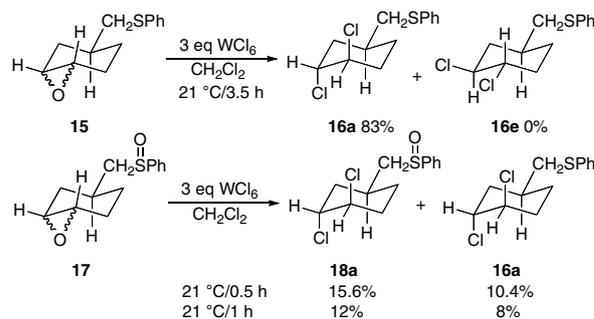


Scheme 6.

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

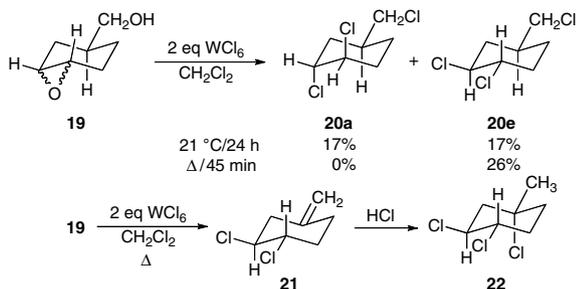


Scheme 7.

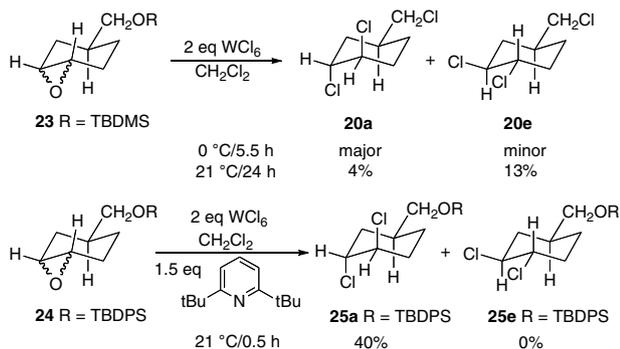


Scheme 8.

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^{2c} (Scheme 9).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.



Scheme 9.



Scheme 10.

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, sulf-oxides, 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.

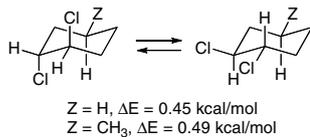
Acknowledgment

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- The stereochemistry of the dichlorides was easily assigned by the size of the coupling constants of the protons α to the chlorides, with the protons in the diaxial isomer having three small J 's while the protons in the diequatorial isomer had two large and one small J .
- 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.
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- For an example of this kinetic diaxial to thermodynamic diequatorial rearrangement in a trimethyldecalin system, see Jung, M. E.; Vidal Gomez, A. *Tetrahedron Lett.* **1993**, *34*, 2891–2894.
- Calculations using B3LYP/6-311+G (d,p) showed that the diaxial dichloride is slightly more stable than the diequatorial ($Z = H$, $\Delta E = 0.45$ kcal/mol; $Z = CH_3$, $\Delta E = 0.49$ 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 ~ 0.5 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.^{2a} Firouzabadi, H.; Karimi, B. *Synthesis* **1999**, 500–502.
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.