Pergamon

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Tetrahedron Letters 44 (2003) 7273–7275

TETRAHEDRON LETTERS

Efficient synthesis of vinyl chlorides and/or *gem*-dichlorides from ketones by treatment with tungsten hexachloride

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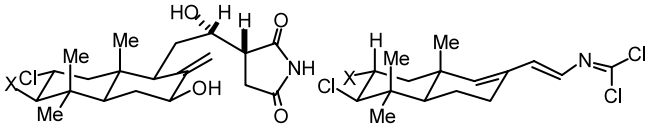
Received 12 July 2003; revised 31 July 2003; accepted 1 August 2003

Abstract—Treatment of cyclic ketones, e.g. **4**, with tungsten hexachloride (WCl_6) provided good yields of vinyl chlorides, e.g. **5**, and/or *gem*-dichlorides. A *trans*-diequatorial dichloride **9** was prepared by treatment of the corresponding epoxide **8** with WCl_6.

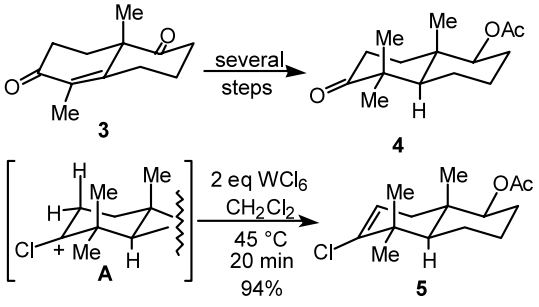
For a projected synthesis of several chloride-containing naturally-occurring terpenoid antitumor agents, e.g. the lissoclimides **1ab**[1] and the reticulidins **2ab**,[2] among others,[3] we required a good method for the conversion of a hindered cyclohexanone into the corresponding vinyl chloride. Because of the severe 1,3-diaxial methyl–methyl interaction in the trimethyldecalone system, we wanted to avoid strongly acidic or very vigorous conditions that might cause cationic skeletal rearrangements, e.g. Wagner–Meerwein or Westphalen, to occur to relieve the steric strain. We report herein the use of tungsten hexachloride (WCl_6) under mild conditions for this and several other interesting transformations.[4]



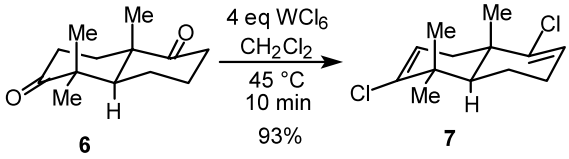
1a X = Cl dichlorolissoclimide
1b X = H chlorolissoclimide

2a X = OH reticulidin A
2b X = H deoxyreticulidin A

Racemic methylated Wieland–Miescher ketone **3**[5] was converted, via the known hydroxy trimethyl ketone[6] into the acetoxy ketone **4**. Treatment of **4** with commercially available tungsten hexachloride in dichloromethane solution under vigorous reflux (bath temperature 45°C) for 20 min afforded the desired vinyl chloride **5** in excellent yield.[7] The structure of **5** was easily assigned by NMR spectroscopy, both proton (δ 5.6, dd, $J=6.7$, 2.3 Hz) and carbon (δ 141.2, 121.5).[8,9] This is in contrast to the previously reported claim that ketones (and aldehydes) do not undergo chlorination with WCl_6.[10] As has previously been postulated for the formation of vinyl halides,[11] the intermediacy of the chloro carbocation **A** is very likely, which then loses a proton to afford the vinyl chloride.



Two further noteworthy points are that the acetate survives these conditions untouched and that no skeletal rearrangements occur under these mild conditions. The structurally analogous diketone **6** (easily prepared from **3**) was treated with WCl_6 under similar conditions to furnish the bis-vinyl chloride **7** also in excellent yield.



Again the proton NMR spectroscopy[9] allowed the assignment of structure and no rearrangement was

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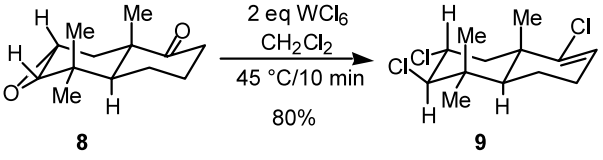
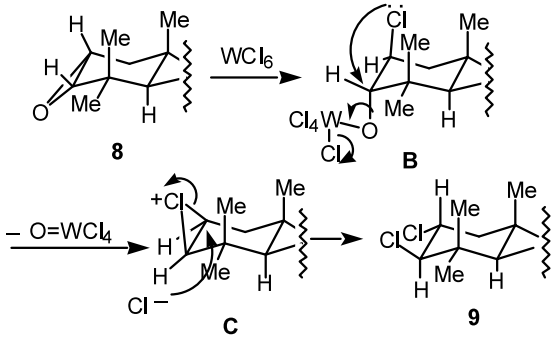
doi:10.1016/S0040-4039(03)01884-7

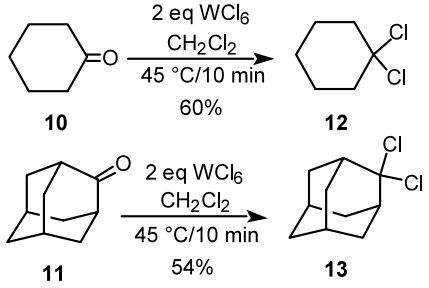
observed. The synthesis of dichlorolissoclimide **1a** requires a *trans*-diequatorial dichloride which can be made from the corresponding *trans*-diaxial dichloride on heating neat at greater than 200°C,[12] which unfortunately destroys all but the most stable functional groups. In order to allow more functionality in the final dichloride, we decided to investigate the possibility of converting the more available α,α-epoxide **8** into the dichloride **9** under mild conditions with tungsten hexachloride.[10] Treatment of **8** with WCl_6 at 45°C for 10 min gave the trichloride **9** in 80% yield. Again proton and carbon NMR spectroscopy[9] were used to assign the structure with the diequatorial dichloride being indicated by the *trans* diaxial protons (δ 5.68, dd, $J=5.0$, 2.7 Hz; 4.17, ddd, $J=12.4$, 11.8, 4.4 Hz and δ 3.69, d, $J=11.8$ Hz).



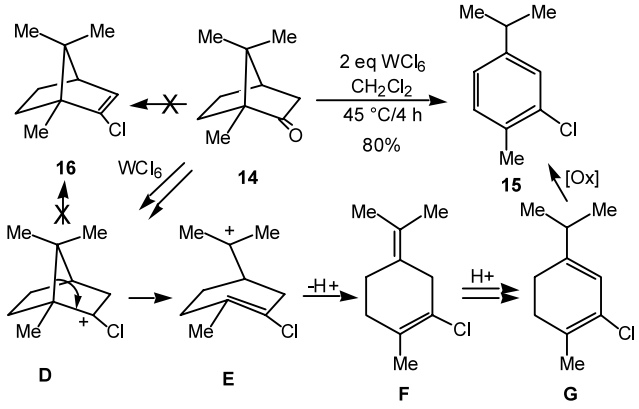
Thus, both functional groups reacted well, the ketone giving the expected vinyl chloride and the epoxide giving only the more stable *trans*-diequatorial dichloride. Presumably the epoxide **8** is opened by tungsten hexachloride to give the axial chloro alkoxide complexed to tungsten **B** which can then undergo loss of the very good leaving group, namely WCl_5O anion (which would give WCl_4O and chloride ion), to generate the chloronium ion **C**.[13] Opening of this chloronium ion by chloride at C-3 would then generate the *trans*-diequatorial dichloride **9** as observed.



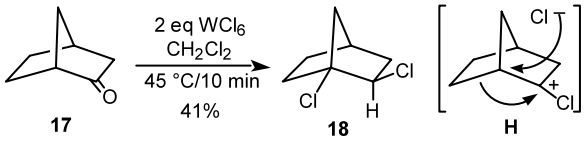
Not all ketones afford vinyl chlorides under these conditions. Cyclohexanone **10** and adamantanone **11** both furnished the corresponding *gem*-dichlorides **12**[14] and **13**[15] when treated with tungsten hexachloride under similar conditions in moderate yields (no attempts were made to optimize the yields of these reactions).



Although we observed no skeletal rearrangements in any of the reactions described above, in certain cases rearrangement products could be obtained in high yield. Thus treatment of D-camphor **14** with tungsten hexachloride for 4 h afforded an 80% yield of the known[16] 2-chloro-*p*-cymene **15**. Presumably the reaction occurs via the chloro carbocation **D** which could lose a proton as described above to give the known[17] strained vinyl chloride **16** but instead undergoes a rearrangement to give the tertiary carbocation **E** (driven by relief of ring strain) which can then lose a proton to afford the diene **F**. Acid-catalyzed isomerization of the exocyclic alkene into the ring would afford the diene **G** which then must suffer an oxidation to give the final aromatic product. We have no hypothesis for the source of this oxidation.



In a similar manner, norbornanone **17** also furnished a rearranged product, namely the known dichloride **18**[18] in fair yield (again no attempts at optimization were made). This is a fairly common rearrangement pathway for norbornyl cations and the *exo* chloride is the expected product[19] via the rearrangement of the chloro carbocation **H**.



Simple acyclic ketones give mixtures of products (including some vinyl chlorides) as do sterically hindered cyclopentanones and relatively unhindered cyclic ketones. These processes are not yet synthetically useful.

In summary, we have shown that hindered cyclohexanones give good yields of vinyl chlorides when treated with tungsten hexachloride while simple ketones afford *gem*-dichlorides under similar treatment. Epoxides give the *trans*-diequatorial dichlorides in good yield. Bicyclo[2.2.1]heptyl ketones afford the products of rearrangement in generally good yields. The further synthetic utility of this reaction is currently under investigation in our laboratories.

Acknowledgements

We thank the National Institutes of Health (CA72684) for generous financial support and the National Science Foundation under equipment grant CHE-9974928.

References

1. Isolation of dichlorolissoclimide: (a) Malochet-Grivois, C.; Cotelle, P.; Baird, J. F.; Henichart, J. P.; Debitus, C.; Roussakis, C.; Verbist, J.-F. *Tetrahedron Lett*. **1991**, *32*, 6701–6702. Isolation of chlorolissoclimide: (b) Baird, J. F.; Malochet-Grivois, C.; Roussakis, C.; Cotelle, P.; Henichart, J. P.; Debitus, C.; Verbist, J.-F. *Nat. Prod. Lett*. **1994**, *4*, 43–50. Crystal structure of dichlorolissoclimide: (c) Toupet, L.; Biard, J. F.; Verbist, J.-F. *J. Nat. Prod*. **1996**, *59*, 1203–1204. Biological Activity: (d) Roussakis, C.; Charrier, J.; Riou, D.; Biard, J. F.; Malochet, C.; Meflah, K.; Verbist, J.-F. *Anti-Cancer Drug Design* **1994**, *9*, 119–128 and references cited therein.
2. Isolation of reticulidins: (a) Wratten, S. J.; Faulkner, D. J. *Tetrahedron Lett*. **1978**, *16*, 1395–1398; (b) Simpson, J. S.; Raniga, P.; Garson, M. J. *Tetrahedron Lett*. **1997**, *38*, 7947–7950; (c) Tanaka, J.; Higa, T. *J. Nat. Prod*. **1999**, *62*, 1339–1340; (d) Musman, M.; Tanaka, J.; Higa, T. *J. Nat. Prod*. **2001**, *64*, 111–113.
3. For a recent example, see: Uddin, M. J.; Kokubo, S.; Ueda, K.; Suenaga, K.; Uemura, D. *Chem. Lett*. **2002**, *10*, 1028–1029 and references cited therein.
4. Tungsten hexachloride has been utilized in several procedures such as the dehydration of epoxides to olefins (Umbreit, M. A.; Sharpless, K. B. *Org. Synth*. **1981**, *60*, 29–34) and more recently the chlorination of alcohols (Coe, E. M.; Jones, C. J. *Polyhedron* **1992**, *11*, 3123–3128). Also see Ref. 11.
5. Hansson, L.; Carlson, R.; Sjöberg, A.-L. *Acta Chem. Scand*. **1990**, *44*, 1036–1041.
6. Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem*. **1976**, *41*, 2663–2669.
7. Representative experimental procedure: To a solution of ketone **4** (0.126 g, 0.50 mmol) in dichloromethane (5 mL) was added tungsten hexachloride (0.397 g, 1.00 mmol) and the solution refluxed (45°C) for 20 min. The reaction mixture was diluted with diethyl ether (25 mL) and poured into 2N sodium hydroxide (15 mL). The organic layer was washed with 2N sodium hydroxide and brine. After drying over magnesium sulfate and filtering to remove the drying agent, the solvent was removed in vacuo to yield vinyl chloride **5** (0.128 g, 0.47 mmol, 94%) as a reddish oil which solidified under vacuum. The vinyl chlorides could be purified by careful column or thick layer chromatography on silica gel.
8. The structure was also confirmed by an independent synthesis of **5** via treatment of the corresponding known ketoalcohol with methanesulfonic acid and acetyl chloride (Moughamir, K.; Mezgueldi, B.; Atmani, A.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett*. **1999**, *40*, 59–62).
9. Representative spectroscopic data for **5**, **7**, and **9**: Compound **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.60 (dd, 1H, $J=6.7$, 2.3 Hz), 4.39 (dd, 1H, $J=11.4$, 4.1 Hz), 2.04 (s, 3H), 1.10–2.00 (m, 9H), 1.06 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.6, 141.2, 121.5, 81.2, 50.4, 29.7, 38.5, 37.4, 29.1, 27.0, 24.0, 22.9, 21.2, 20.6, 13.1. Compound **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.73 (dd, 1H, $J=6.7$, 2.1 Hz), 5.72 (m, 1H), 2.30 (dd, 1H, $J=17.0$, 6.8 Hz), 2.19 (dddd, 1H, $J=17.9$, 5.6, 5.6, 1.5 Hz), 2.10 (m, 1H), 2.05 (m, 1H), 1.72 (m, 1H), 1.71 (m, 1H), 1.52 (m, 1H), 1.16 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 141.4, 140.9, 124.1, 121.6, 50.8, 40.4, 39.8, 38.2, 29.0, 27.0, 19.8, 19.3, 18.9. Compound **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.67 (dd, 1H, $J=5.0$, 2.7 Hz), 4.17 (ddd, 1H, $J=12.2$, 11.1, 4.4 Hz), 3.69 (d, 1H, $J=10.9$ Hz), 2.65 (dd, 1H, $J=13.5$, 4.4 Hz), 2.21 (ddd, 1H, $J=18.0$, 5.5, 5.2 Hz), 2.12 (dddd, 1H, 18.0, 10.7. 6.4, 2.7 Hz), 1.79 (dd, 1H, $J=13.3$, 6.9 Hz), 1.72 (dd, 1H, $J=12.9$, 12.9 Hz), 1.55 (m, 1H), 1.47 (d, 1H, $J=12.9$ Hz), 2.00 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 140.2, 124.1, 76.8, 60.3, 52.2, 47.0, 42.0, 41.8, 29.6, 27.1, 19.7, 17.8. IR (thin film): 2975, 1644, 1467, 1395, 1381, 985, 951, 889, 845, 779 cm^{-1}. High resolution MS (EI, m/z): 280.0547, calcd for $C_{13}H_{19}Cl_3$ 280.0552.
10. Firouzabadi, H.; Shiriny, F. *Tetrahedron* **1996**, *52*, 14929–14936.
11. For a representative mechanism see: Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett*. **1982**, *23*, 3991–3994.
12. Jung, M. E.; Gomez, A. V. *Tetrahedron Lett*. **1993**, *34*, 2891–2894.
13. For a recent discussion of the stability of halonium cations see: Teberekidis, V. I.; Sigalas, M. P. *Tetrahedron* **2003**, *59*, 4749–4756.
14. Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem*. **1993**, *58*, 1939–1940.
15. Cuddy, B. D.; Grant, D.; Karim, A; McKervey, M. A.; Rea, E. J. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, *21*, 2701–2707.
16. This compound has been prepared by chlorination of *p*-cymene (Tauno, K. *Chemosphere* **1989**, *19*, 1349–1356) but never by this type of rearrangement, although bromonitrocamphane undergoes a similar rearrangement to give the bromo analogue. See: (a) McPhail, K. L.; Rivett, D. E. A.; Lack, D. E.; Davies-Coleman, M. T. *Tetrahedron* **2000**, *56*, 9391–9396; (b) Ranganathan, S.; Raman, H. H. *Tetrahedron* **1974**, *30*, 63–72.
17. Paukstelis, J. V.; Macharia, B. W. *J. Org. Chem*. **1973**, *38*, 646–648.
18. Laihia, K.; Paasivirta, J.; Pikkarainen, H.; Aho-Pullianinen, S. *Org. Magn. Reson*. **1984**, *22*, 117–119.
19. Hanson, J. R. In *Wagner–Meerwein Rearrangements*; Trost, B. M.; Fleming, I., Eds.; *Comp. Org. Synth*.; Pergamon, 1991; Vol. 3, Chapter 3.1, pp. 706–707.