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New Applications of Tungsten Hexachloride (WCl_6) in Organic Synthesis. Halo-de-Hydroxylation and Dihalo-de-oxo-Bisubstitution Reactions

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Abstract: tungsten hexachloride (WCl_6) has been used for the halo-de-hydroxylation and dihalo-de-oxo-bisubstitution reactions of benzylic alcohols, benzaldehydes, acyloins, and epoxides to their chlorides, gem-dichlorides, vic- trichlorides, and vic- dichlorides respectively. Copyright © 1996 Elsevier Science Ltd

Chlorination parallel with deoxygenation is an important method for the conversion of organic molecules with oxygen functionality to their chlorides. There are methods available for this interconversion, specially for the replacement of hydroxy groups with chlorine .[1,2] The examples are: concentrated HCl,[3] HCl/$ZnCl_2$,[4] HCl/HMPTA,[5] NaCl, KCl or NH_4Cl in polyhydrogen fluoropyridine solution,[6] and trichloroisocyanuric acid.[7] Many p-block reagents have been used for this purpose, e.g., SO_2Cl_2, $SOCl_2$, $SOCl_2$/Py, S_2Cl_2, $POCl_3$, PCl_5, and PCl_3.[2] Other methods also used include PPh_3/CCl_4, $SOCl_2$/DMF, and R_3PCl_2.[2,8-14] A complex which is formed by the reaction of N-chlorosuccinimide and dimethyl sulfoxide has been used as a specific reagent for the conversion of benzylic and allylic alcohols to their corresponding chlorides.[15]

Transition metal based reagents have found wide applications in organic synthesis, specially when the regio and stereo aspects of the reactions are important.[16-18] Oxophilic d-block metal reagents have the potential for deoxygenation reactions.In this respect, Sharpless, Fugiwara, and their coworkers have reported the use of WCl_6 in the presence of RLi, KI, LiCl, and $LiAlH_4$ or $W(CO)_6$ for the conversion of aldehydes, ketones, and epoxides to olefins.[19,20] Recently, Jones and Coe have investigated the possiblity of using d-block metal chlorides $NbCl_5$, $TaCl_5$, $MoCl_5$, and WCl_6 for the chlorination of some primary and secondary saturated alcohols.[2] According to the report, WCl_6 is recognized to be the most effective reagent and works efficiently in Et_2O for the chlorination of cyclohexanol to produce cyclohexyl chloride in 98% yield in 6 days. The results show that the most efficient conversion of alcohols to their chlorides is obtained with secondary alcohols.[2]

In this study we have extended and applied this method for other synthetically useful interconversions using refluxing CH_2Cl_2 and a mixed solvent CH_2Cl_2/CH_3CN (2/1) system.

RESULTS AND DISCUSSION

Conversion of hydroxy groups to halides is a useful transformation which produces compounds which are important for many other functional group interconversions.

Tungsten hexachloride (WCl_6) as a strong oxophile is an interesting compound which can be used for the deoxygenation-chlorination of organic substrates.[2] We have accomplished a series of halo-de-hydroxylation and dihalo-de-oxo-bisubstitution reactions on benzylic alcohols,benzaldehydes, acyloins, and epoxides with WCl_6 in refluxing CH_2Cl_2 and in a mixture of CH_2Cl_2 / CH_3CN (2/1) under inert atmosphere or in the air . The results of the two atomspheric reaction conditions are the same. During the course of all the reactions performed in this study, the original deep blue colour of WCl_6 turns into an orange colour, indicating the formation of $WOCl_4$ in the reaction mixture.

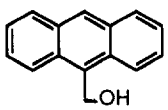
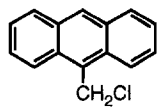
Chlorination of benzylic hydroxy compounds to their corresponding benzylic chlorides(halo-de-hydroxylation)

Chlorination of benzyl alcohol and substituted benzyl alcohols with electron -donating groups, e.g., CH_3, CH_3O- proceeds very well and in high yields with WCl_6 in refluxing CH_2Cl_2 (Table 1, entries 2,3). p, m, and o-Nitro substituted benzyl alcohols give lower yields together with unidentified side products (Table 1, entries 5,6,7). 9-Anthracene methanol (Table 1, entry 8) is not soluble in CH_2Cl_2 and therefore we used a mixed solvent system CH_2Cl_2/CH_3CN = 2/1. Chlorination occurs slower than with benzyl alcohol and in lower yield, and is accompanied with other side products.Triphenylcarbinol does not undergo the chlorination reaction which may be due to serious steric hindrance or to the unusual stability of the presumably formed Ph_3C^+ in the mixture. The development of different colours during the course of the reaction may be an indication for the formation of a highly conjugated carbocation species in the reaction mixture. Cinnamyl alcohols are not chlorinated cleanly with WCl_6 and therefore this methodology is not recommended for this purpose. Benzoin and anisoin react with WCl_6. Displacement of both hydroxy and carbonyl groups with chlorine is performed well by this reagent and produces trichlorinated products in reasonable yields (Table 1, entries 10,11).

Table 1. Chlorination of Benzylic Alcohols with WCl_6 in CH_2Cl_2.

Entry	Substrate	Product	Reagent / Substrate	Reaction Time (h)	Yield%
1	$PhCH_2OH$	$PhCH_2Cl$	0.3	1	85
2	p-$MeOC_6H_4CH_2OH$	p-$MeOC_6H_4CH_2Cl$	0.2	1	80
3	p-$MeC_6H_4CH_2OH$	p-$MeC_6H_4CH_2Cl$	0.2	1	90[a]

Table 1. Continued.

4	PhCHPh | OH	PhCHPh | Cl	0.2	2	85
5	o-$NO_2C_6H_4CH_2OH$	o-$NO_2C_6H_4CH_2Cl$	0.4	3.5	50
6	m-$NO_2C_6H_4CH_2OH$	m-$NO_2C_6H_4CH_2Cl$	0.4	3	55
7	p-$NO_2C_6H_4CH_2OH$	p-$NO_2C_6H_4CH_2Cl$	0.4	3	58
8			0.2	2.5	55[b]
9	Ph_3COH	-	0.3	3	-
10	OH | PhCH-CPh || O	PhCHCl-CCl_2Ph	3	19	70
11	p-$MeOC_6H_4$CH(OH)-C(=O)-C_6H_4OMe-p	p-$MeOC_6H_4CHClCCl_2C_6H_4OMe$-p	3	16	50

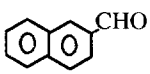
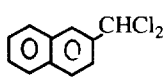
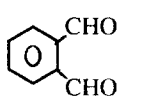
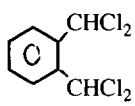
All reactions were performed under reflux conditions., a. Representative ^1H NMR($CDCl_3$): δ 2.2(s, 3H),4.4(s, 2H), 7(m, 4H).

b. Solvent : CH_2Cl_2/CH_3CN = 2

Chlorination of benzaldehydes with WCl_6(dihalo-de-oxo-bisubstitution)

Tungsten hexachloride (WCl_6) can be used as a chlorinating agent for the conversion of benzaldehydes to the corresponding gem -dichlorides. Chlorination of benzaldehydes is performed well with WCl_6 in refluxing CH_2Cl_2 (Table 2). Chlorination of 2-naphthaldehyde produces the gem-dichloride and several other unidentified side products (Table 2, entry 7). o- Phthaldehyde is converted into 1,2-bisdichloromethylbenzene with WCl_6 in high yield in refluxing CH_2Cl_2 (Table 2, entry 8).

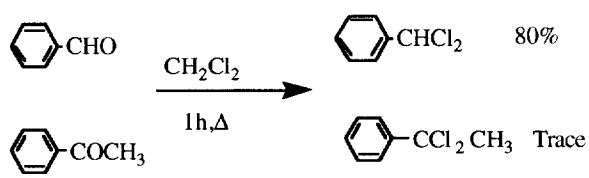
Table 2. Chlorination of Benzaldehydes with WCl_6 in CH_2Cl_2.

Entry	Substrate	Product	Reagent / Substrate	Reaction Time (h)	Yield%
1	m-MeC_6H_4CHO	m-$MeC_6H_4CHCl_2$	2	1	70
2	p-MeC_6H_4CHO	p-$MeC_6H_4CHCl_2$	2	3	70
3	p-$NO_2C_6H_4CHO$	p-$NO_2C_6H_4CHCl_2$	2.5	4.5	90
4	m-$NO_2C_6H_4CHO$	m-$NO_2C_6H_4CHCl_2$	2.5	4	90
5	p-ClC_6H_4CHO	p-$ClC_6H_4CHCl_2$	2	2	87
6	o-ClC_6H_4CHO	o-$ClC_6H_4CHCl_2$	2	1	85
7	C_6H_5CHO	$C_6H_5CHCl_2$	2	1	80
8			2	2	60
9			4.25	5	90[a]

All reactions were performed under reflux conditions., a. Representative ^1H NMR($CDCl_3$): δ 6.8(s, 2H), 7.1-7.7(m,4H).

Ketones and saturated aldehydes do not undergo chlorination with WCl_6. Therefore, this methodology shows selectivity and is suitable for the selective chlorination of benzaldehydes in the presence of other carbonyl functions.

This is shown by the competitive reaction between benzaldehyde and acetophenone (Scheme1).



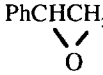
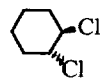
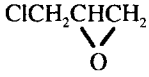
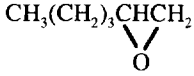
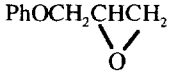
WCl_6/Substrate:2

Scheme 1

Chlorination of epoxides with WCl_6(dihalo-de-oxo-bisubstitution)

Vicinal dichlorides are prepared by the reaction of epoxides with tungsten hexachloride (WCl_6) in CH_2Cl_2. These reactions are fast and are completed within 5-30 minutes (Table 3).

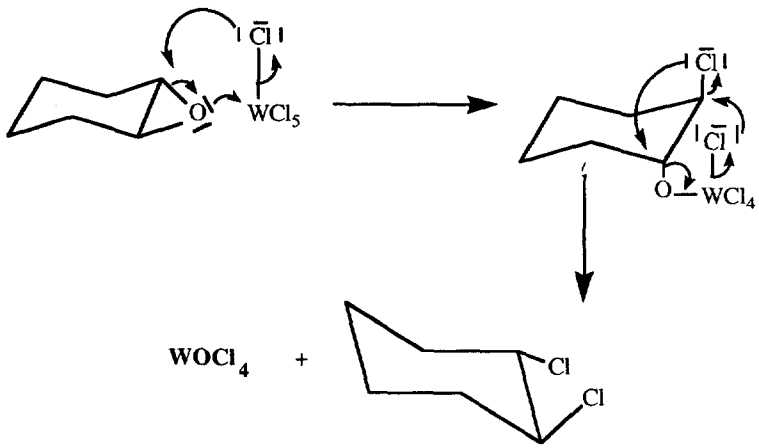
Table 3. Chlorination of Epoxides with WCl_6 in CH_2Cl_2.

Entry	Substrate	Product	Reagent / Substrate	Reaction Time (min)	Yield%
1		$PhCHClCH_2Cl$	2	15	92[a]
2			2	5	90
3		$ClCH_2CHClCH_2Cl$	2	15	80
4		$CH_3(CH_2)_3CHClCH_2Cl$	2	20	80
5		$PhOCH_2CHClCH_2Cl$	2	30	50

All reactions were performed under reflux conditions., a. Representative ^1H NMR($CDCl_3$): δ 3.2(d, 2H), 5.6(t, 1H), 7(s, 5H).

Trans-1,2-dichlorocyclohexane is produced in the reaction of cyclohexene oxide with WCl_6 in CH_2Cl_2(Table 3,entry 2). We may suggest the following reaction path way for the formation of the trans isomer in a moderately polar organic solvent CH_2Cl_2 (Scheme 2).

The low yield in the conversion of 1,2-epoxy-3-phenoxypropane to the related dihalide (Table 3, entry 5) may be due to the partial cleavage of C-O bond with WCl_6.



Scheme 2

CONCLUSION

In this study we have introduced new applications of tungsten hexachloride (WCl_6), a d-block metal based reagent, in deoxygenation - chlorination reactions of primary and secondary benzylic alcohols, benzaldehydes, acyloins, and epoxides. Handling of the reagent, mildness of the reaction condition, reasonable yields of the products, easy work-up are worthy of mention for this method.

EXPERIMENTAL

All yields refer to isolated products. All products were characterized by comparison of their spectral and physical data with those of known samples.The purity determination of the products was accomplished by TLC on silica gel polygram SIL G/UV 254 plates or GLC on a Shimadzu Model GC-8A instrument with a flame ionization detector and a column of 15% carbowax 20 M/chromosorb-W acid washed 60-80 mesh. Chemicals were either prepared in our laboratories or were purchased from Fluka, B.D.H. and Merck Chemical Companies. Products were separated and purified by different chromatography techniques, and were also identified by the comparison of their mp, IR, NMR, bp, refractive index with those reported for the authentic samples. Some of the benzylic gem-dichlorides were also identified by the hydrolysis and isolation of the original aldehydes.

Chlorination of Benzyl Alcohol with WCl_6 in CH_2Cl_2 as a Typical Procedure

In a round-bottomed flask (25 ml), equipped with a magnetic stirrer and a condenser a solution of benzyl alcohol (108 mg, 1 mmol) in dry CH_2Cl_2 (8 ml) was prepared. WCl_6 (86 mg, 0.3 mmol) was added. The reaction mixture was stirred magnetically under reflux condition for 1 h. After completion of the reaction, the reaction mixture was poured into an aqueous solution of NaOH(20% ,40 ml) and extracted with hexane. The organic layer was dried over $MgSO_4$ and concentrated. Column chromatography on silica gel, gave benzyl chloride in 85% yield, 108 mg (bp 176°C ,178°C lit.[21]).

Chlorination of 3-Nitrobenzaldehyde with WCl_6 in CH_2Cl_2 as a Typical Procedure

In a round-bottomed flask (25 ml) equipped with a magnetic stirrer and a condenser a solution of 3-nitrobenzaldehyde (150 mg, 1 mmol) in dry CH_2Cl_2 (8 ml) was prepared. WCl_6 was added (718 mg, 2.5 mmol). The reaction mixture was stirred under reflux condition for 4 h. After completion of the reaction, the reaction mixture was poured into an aqueous solution of NaOH (20% , 40 ml) and was extracted with hexane. The organic layer was separated and was dried over $MgSO_4$ and concentrated. Column chromatography on silica gel, using the proper eluent, gave α,α- dichloro-4-nitro toluene in 90% yield,185 mg(mp 65°C, 63-65 °C, lit. [21]).

Chlorination of Cyclohexene Oxide with WCl_6 in CH_2Cl_2 as a Typical Procedure

In a round-bottomed flask (25 ml) equipped with a magnetic stirrer and a condenser a solution of cyclohexene oxide (98 mg, 1 mmol) in dry CH_2Cl_2 (8 ml) was treated with WCl_6 (57 mg, 2 mmol) and the reaction mixture was refluxed for 5 min. The reaction mixture was poured into an aqueous solution of NaOH (20% , 40 ml) and was extracted with hexane. The organic layer was dried over $MgSO_4$ and was concentrated . Column chromatography on silica gel, using CCl_4 as eluent, gave trans-1-2-dichlorocyclohexane in 90% yield, 138 mg (bp 193-195 °C, 194 °C lit. [21]).

Chlorination of Benzoin with WCl_6, as a Typical Procedure

In a round-bottomed flask (25 ml) equipped with a condenser and a magnetic stirrer, WCl_6 (1.19 gr, 3 mmol) was added to a solution of benzoin (210 mg, 1 mmol) in CH_2Cl_2 (10 ml) and the resulting mixture was stirred under reflux condition for 16 h. The progress of the reaction was followed by TLC (eluent: CCl_4/ether: 3/1). After completion of the reaction the mixture was poured into an aqueous solution of NaOH (20%, 40 ml) and was extracted with hexane. The organic layer was separated and dried over $MgSO_4$ and was concentrated. Purification of the crude product by silica gel plate chromatography (eluent: CCl_4), afforded 1,1,2-trichloro-1,2-diphenyl ethane in 70% yield, 199 mg (mp 101-103 °C, 100-101 °C lit [22]) (Table 2).

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