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Oxidative chlorination of 4-pentenols and other functionalized hydrocarbons

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ABSTRACT

Substituted 4-pentenols undergo regio- and stereoselective chlorocyclization, when treated in solutions of dimethyl carbonate with chloride, a terminal oxidant, and a buffered proton source. Effective oxidants for liberating chlorine-like reactivity from chloride in the temperature range between 20 and 40 °C are *tert*-butyl hydroperoxide, activated by a titanium(IV) or a molybdenum(VI) ONO-chelate complex, and potassium monoperoxysulfate from the ternary salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®). Substituents in the flexible part of the alkenol direct oxidative chlorocyclization 2,5-*trans*- and 2,4-*cis*-selectively. (*E*)-Configuration at the alkene translates anti-specifically into relative configuration of substituents at the β-chlorohydrin ether entity. A phenyl group bound to the terminal alkene carbon alters the inherent 5-*exo*-specificity for chlorocyclization of terminal 4-pentenols toward 6-*endo*-selectivity, as exemplified by synthesis of *trans*-3-chloro-2-phenyltetrahydropyran from (*E*)-5-phenyl-4-penten-1-ol in up to 74% yield. Competition kinetics show that 5-*exo*-chlorocyclization of 1-phenyl-4-penten-1-ol occurs at 40 °C 600 times faster than electrophilic aromatic chlorosubstitution of anisole. Prenyl-type alkenols undergo allylic chlorination with an ene-type selectivity, as exemplified in synthesis of a building block for the fragrance component rose oxide from citronellol.

1. Introduction

Chlorination of hydrocarbons furnishes organochlorines—compounds of prime importance for science and engineering.[1–3] Polychlorinated hydrocarbons, serve are used in a large scale as cooling liquids, flame retardants, and solvents.[4–6] In other organic compounds, the aliphatic carbon–chlorine bond controls chemical reactivity for rearranging carbon skeletons, introducing new functional groups, or selectively extending carbon backbones by coupling reactions.[7] Chlorosubstitution reduces the ionization potential of arenes, thus slowing rates of oxidative metabolism of pharmaceuticals.[8] Three non-bonding electron pairs at chlorine affect associative properties, giving rise to the phenomenon of chlorine bonding, lipophilicity/hydrophobicity of organochlorines, and affinity toward Lewis-acidic surfaces or active sites of enzymes.[9]

For synthesis of organochlorines three major strategies have evolved proceeding via carbon electrophiles, free radicals, and carbon nucleophiles. Substituting a leaving group in a carbon electrophile by chloride occurs in tremendous quantity in the marine environment.[10] Attaining selectivity by this approach in fine chemical synthesis requires to use appropriate leaving group/counter ion/solvent-combinations since chloride in polar aprotic media is a weak nucleophile but a comparatively strong base.[11,12] Preparing organochlorines from hydrocarbons and, for example, chlorine, sulfuryl chloride, or an alkyl hypochlorite via radical chain reactions is enormously important for chemical industry. Reactions of this kind show a notable driving force, but often are difficult to control in terms of regio- and stereoselectivity. Tempered chlorine atom donors, such as tetrachloromethane, in most instances react too slowly with carbon radicals in order to propagate synthetically useful chain reactions. The scope of free radical chlorination in contemporary fine chemical synthesis therefore is limited.[2,13] Many reactivity and selectivity challenges described for nucleophilic and homolytic chlorination can be circumvented using the concept of electrophilic chlorination. Suitable reagents for introducing electrophilic chlorine are chloramines, chlorimines, alkyl hypochlorites, and particularly molecular chlorine. Reactive nucleophilic hydrocarbons for constructing carbon–chlorine bonds from electrophilic chlorination are alkenes, arenes, or heteroarenes.[14–16]

The concept of electrophilic chlorination involves handling molecular chlorine, either as reagent or as starting material for preparing more specialized chlorination reagents (vide supra). Chlorine is technically produced by electrolysis of brines and shipped in steel cylinders.[17] For minimizing health hazards associated with the reagent, chlorine for fine chemical synthesis is

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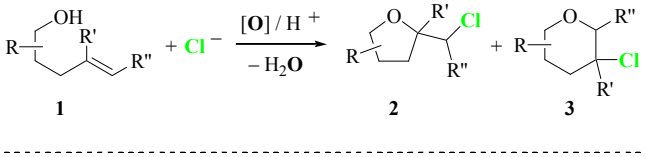
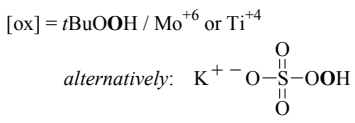
often generated on-site from an alkali chloride and a terminal oxidant, such as molecular oxygen, hydrogen peroxide, a peracid, or a persalt (Scheme 1).[18] The rate of chloride oxidation by peroxides depends on proton concentration, becoming insignificantly slow at neutral pH.[19] Bacteria and fungi therefore have evolved chloroperoxidases for catalyzing chloride oxidation by hydrogen peroxide under physiological conditions.[20,21] Water, as required to dissolve chloroperoxidases for attaining enzymatic activity, not only serves a reaction medium but is also a nucleophile, often interfering with vicinal dichlorination or chloroetherification of alkenes.[22,23] To prevent unwanted trapping with water, chloride oxidation in organic synthesis typically is carried out in non-aqueous solvents using a persalt or an alkyl hydroperoxide as terminal oxidant.[24] The most frequently applied alkyl hydroperoxide in organic synthesis is *tert*-butyl hydroperoxide (TBHP). Like other peroxides, the compound is a nucleophile and needs to be activated by a Brønsted- or a Lewis-acid for oxidizing negatively polarized or charged substrates, such as chloride.[25,26]





Scheme 1. Concept for oxidative chlorocyclization of substituted 4-pentenol **1** (R=hydrogen, alkyl, phenyl, ester; R′=hydrogen, methyl; R″=hydrogen, phenyl).

In a project dealing with stereoselective synthesis of terpene-derived mixed chloro- and bromo-substituted tetrahydropyrans, the aplysiapyranoids,[27–29] we noticed from a search in the chemical literature that a general strategy for regio- and stereoselectively constructing chlorinated cyclic ethers from unsaturated alcohols, similar to oxidative bromocyclization, so far does not exist.[30] Explorative studies starting from *N*-chlorosuccinimide (NCS) and a 4-pentenol, which recently served as benchmark for developing practical methods for transition metal-catalyzed oxidative bromocyclization,[27] did not provide products of chlorocyclization.[31] For attaining progress in the marine natural product project, we decided to devise practical methods for 4-pentenol chlorocyclization **1** → **2**/**3** based on the concept of oxidative chlorination (Scheme 1). In the course of this investigation we found that two strategies served our purpose. The first approach uses TBHP for oxidizing chloride in a titanium(IV)- or a molybdenum(VI)-catalyzed reaction. The second approach starts from aliquots of potassium monoperoxysulfate and potassium chloride, which are added to a 4-pentenol dissolved in dry dimethyl carbonate. While assessing functional group compatibility we noticed that the new methods provide attractive solutions for chlorinating 1,3-diketones, methoxybenzenes, alkanes, and alkenes. Prenyl-type alkenols favor allylic chlorination with an ene-type selectivity to chlorocyclization, as exemplified by synthesis of a building block for the fragrance component rose oxide from citronellol.

2. Results and interpretation

2.1. Terminal oxidants and the solvent

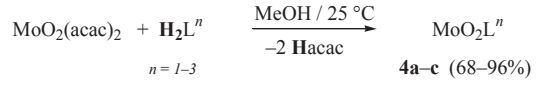
In keeping with our guidelines for developing chemical methods we strived to use non-toxic biodegradable solvents and reaction temperatures between 20 and 40 °C for attaining satisfactory time/yield-factors. Reasonable time/yield factors in this context refer to turning over one millimole of substrate within twenty-four hours, providing target products in yields between eighty to ninety percent.

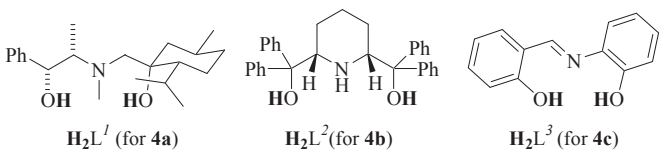
From the standard electrode potential E^0 of 1.36 V for the chloride/chlorine-couple (pH 0, 25 °C), referenced versus the normal hydrogen electrode (NHE), we reasoned that *tert*-butyl hydroperoxide (TBHP; E^0=−1.39 V vs NHE) and potassium hydrogen persulfate (E^0=−1.82 V, vs NHE) are sufficiently strong oxidants for converting chloride via hypochlorous acid into chlorine.[18,19,32] The oxygen atom transferred to chloride accounts for 18%-weight percent of TBHP and 5.5 weight% for potassium hydrogen persulfate from the ternary salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The ternary salt is commercialized as oxone® and had been used by other groups previously for preparing chloroarenes via oxidative chlorination. Such reactions were conducted in aqueous solutions, acetonitrile, or chlorinated solvents at elevated temperatures (80–120 °C), providing only moderate yields of chloroarenes.[33] In a screening we found that dry dimethyl carbonate is an adequate solvent for oxone®, in order to effectively oxidize chloride at a temperature of 30 °C. Below this temperature, chloride turnover is slow thus reducing efficiency and selectivity for organic substrate chlorination. Solutions of the ternary salt in dimethyl carbonate are sufficiently acidic for turning over chloride without an externally added proton source (Scheme 1). In controls we found that yields and selectivity for oxidative chlorination in dimethyl carbonate exceed values obtained from reactions in chloroform, acetonitrile, or toluene. Since chlorination experiments in dimethyl carbonate have the potential to provide triphosgene as by-product, possible safety measures and actions should be considered. In this study, we never observed triphospgene formation.[34]

2.2. Molybdenum(VI) chelate complexes

An alternative to oxone® for oxidizing chloride is TBHP in combination with a Lewis-acidic catalyst for activating the terminal oxidant. In a screening we found that *cis*-dioxidomolybdenum(VI) compounds, of the general formula MoO_2L^n (e.g., **4a**–**c**, vide infra) catalyze chloride oxidation by TBHP in solutions of dry dimethyl carbonate. The abbreviation $(L^n)^{2-}$ stands for an amino- or an iminobisdiolate-auxiliary, binding via two negatively charged oxygen donor atoms and one nitrogen donor atom to molybdenum.

Complexes MoO_2L^n (**4a**–**c**) were prepared by metathesis from bis-[acetylacetonato(−1)]-(*cis*-dioxido)-molybdenum(VI) $[MoO_2(acac)_2]$ and ephedrine-derived aminodiol H_2L^1 (68% of **4a**), bis-(hydroxymethyl)-piperidine[35] H_2L^2 (96% of **4b**), and iminodiol[36] H_2L^3 (88% of **4c**) in solutions of methanol (Scheme 2). Molybdenum compounds **4a**–**c** precipitate from reaction mixtures as colorless solids (**4a** and **4b**) or orange crystals (**4c**),[37] and were characterized by nuclear magnetic resonance spectroscopy, vibrational spectroscopy, and combustion analysis.





Scheme 2. Formation of *cis*-dioxidomolybdenum(VI) complexes [hydrogens substituted by the MoO_2^{2+}-fragment in the course of aminodiol (H_2L^{1-2})- or iminodiol (H_2L^3)-complexation are printed in bold; **H**acac=pentane-1,3-dione (acetylacetone)].