Transition Metal Chemistry (2005) 30:582–585
DOI 10.1007/s11243-005-4049-8

Pyridinium chlorochromate (PCC) oxidation of bishomoallylic tertiary alcohols. A structure–reactivity study

Lauren A. Beihoffer, Robert A. Craven, Kyle S. Knight, Charles R. Sisson and Thomas G. Waddell*
Department of Chemistry, Dept. 2252, University of Tennessee at Chattanooga, 615 McCallie Avenue, Chattanooga, TN 37403-2598, USA

Received 11 February 2005; accepted 23 February 2005

Abstract

The mechanism of the Cr(VI) oxidation of an alkene C=C is not known for certain. A particularly useful and novel example of this process is the intramolecular oxidative cyclization of bishomoallylic tertiary alcohols by pyridinium chlorochromate (PCC) to yield substituted tetrahydrofuran products *via* the tethered chromate ester. Several such tertiary alcohols were prepared in this study which varied in the number and position of alkyl groups attached to the C=C. The relative reactivity of these substrates toward PCC under standard conditions is dependent only on the number of R groups on the C=C, not on the degree of substitution on the most highly substituted alkene carbon. This observation suggests a symmetrical transition state in this intramolecular Cr(VI) alkene oxidation.

Introduction

The oxidation of organic compounds by transition metal complexes has played an important role in synthetic organic chemistry for many decades. Of particular importance is the time-honored oxidation of primary and secondary alcohols to carbonyl compounds by Cr(VI) reagents. In contrast, Cr(VI) oxidations of the C=C moiety of alkenes have been less useful in that these reactions typically result in product mixtures containing diols, halohydrins and epoxides [1]. The mechanism of such alkene oxidations and the nature of the transition state have been thoroughly investigated and still remain controversial [1–4].

In a related study, we have been interested in the oxidative cyclization of certain bishomoallylic tertiary alcohols by the Cr(VI) reagent pyridinium chlorochromate (PCC), a reaction type which can yield substituted tetrahydrofuran products *via* a tethered chromate ester [5] and an *intramolecular* Cr(VI) oxidation of the C=C (Figure 1) [6]. This process has recently been used in the synthesis of polyether natural products [7, 8]. Three different mechanisms have been proposed as illustrated in Figure 2: (2 + 2) or (3 + 2) cycloaddition processes and Cr(VI)-mediated epoxidation [3, 6, 9]. However, like the *inter*molecular alkene oxidations discussed above, the mechanism of this *intra*molecular process has not been established. Thus, because of the novelty and utility of these HO-directed oxidative cyclizations by PCC, and the unsettled mechanism of Cr(VI) alkene oxidation in general, we initiated a structure–reactivity study to provide experimental evidence for the mechanistic nature of reactions of the Figure 1 type.

* Author for correspondence: E-mail: Thomas-waddell@utc.edu

Experimental

Materials and methods

Compounds *(1)* and *(5)* were prepared by addition of appropriate Grignard reagents to cyclohexanone. Compounds *(2)* and *(6)* were synthesized by the addition of MeMgBr to 5-hexene-2-one and 6-methyl-5-hepten-2-one (Acros), respectively. Terpineol *(7)* and guaiol *(8)* are commercially available from Aldrich Chemical Co. Compound *(9)* was synthesized from citronellic acid (Acros) by esterification (3% H_2SO_4 in EtOH) followed by treatment with an excess of MeMgBr. All GC-MS analyses were performed using a Thermo Finnegan Trace GC gas chromatograph interfaced with a Polaris Q mass spectrometer. ^{1}H n.m.r. and ^{13}C n.m.r. analyses were performed with a Varian Gemini 300 NMR spectrometer.

Representative pyridinium chlorochromate (PCC) oxidation. Standard conditions

CH_2Cl_2 (20 cm^3) was added to 0.171 g (1.20 mmol, 0.06 mmol/m^{-3}) of *(6)* in a 50 cm^3 round bottom flask and stirred at room temperature. Pyridinium chlorochromate (PCC) (0.712 g, 3.31 mmol) was added to the solution followed by 5 drops of $MeCo_2H$ and celite (2.1 g). The flask contents were stirred under N_2 for 20 h. The reaction slurry was diluted with Et_2O and filtered through a neutral Al_2O_3 column

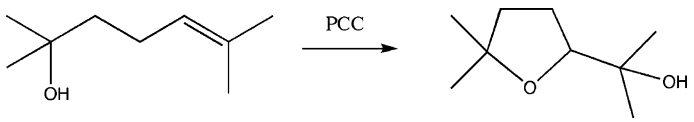


Fig. 1. Oxidative cyclization of bishomoallylic tertiary alcohols.

(2.2 cm × 8.0 cm) with exhaustive Et_2O washing. The final solution was evaporated to dryness *in vacuo* to yield a pale yellow oil (87% mass recovery). GC-MS analysis indicated 60% *(6)*, 40% THF product (*m*/*z* 143 $M^{\cdot+}-CH_3$, 140 $M^{\cdot+}-H_2O$, 99). ^1H n.m.r: 3.77 p.p.m. triplet [7, 10]. Starting *(6)* and product were inseparable on TLC.

2-Methyl-5-hepten-2-ol (3)

A two-neck round bottom flask was evacuated then placed under a positive N_2 pressure. 4-Hexenoic acid (Lancaster chemicals) (0.52 cm^3) was added *via* a syringe, followed by dry Et_2O (30 cm^3). The solution was stirred in an ice bath and MeLi (Aldrich) (1.6 M, 11 cm^3) in Et_2O was added dropwise *via* a syringe over 9 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture (exhibiting a white precipitate) was re-cooled in an ice bath while stirring continued. HCl (0.1 M, 2.5 cm^3) was added over 30 min *via* a septum/syringe, as well as extra H_2O (2.0 cm^3). The reaction solution was thoroughly shaken with 5% $NaHCO_3$ and then H_2O. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The product (0.425 g, 87% yield) was analyzed by GC-MS indicating 31% *(3)*, 69% 5-hepten-2-one.

The product mixture (0.425 g) was placed in a 100 cm^3 round bottom flask with a side stopcock along with Et_2O (20 cm^3) and stirred in an ice bath under N_2. Excess of MeMgBr (3 M, 5.0 cm^3) was added *via* a syringe through a septum dropwise during 6 min. The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 4 h. The reaction solution was cooled on ice and a saturated NH_4Cl solution (10 cm^3) was added dropwise over 10 min with continued stirring. The mixture was poured into a separatory funnel, a small amount of H_2O was added, and the aqueous layer was removed. The organic layer was shaken thoroughly with Na_2SO_4 (5%), then dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. The structure of *(3)* (0.288 g, 51% yield) was confirmed by GC-MS, ^1H n.m.r. and ^{13}C n.m.r. [10, 11].

2-5-Dimethyl-5-hexen-2-ol (4)

Ethyl4-methyl-4-pentenoate (Acros) (0.502 g, 3.53 mmol) was placed in a 50 cm^3 round bottom flask with side

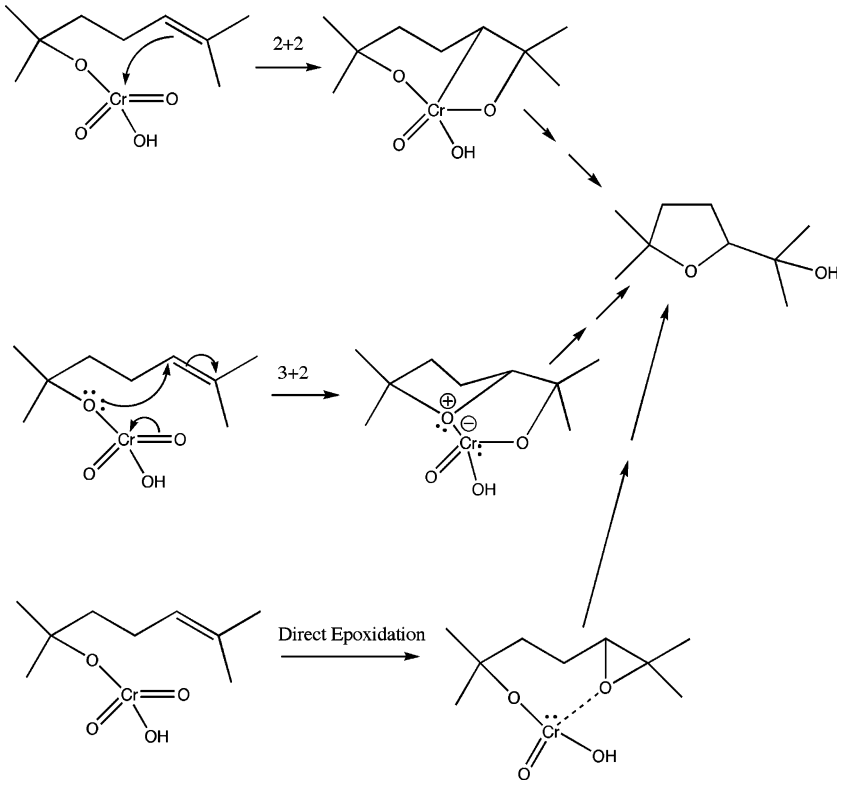


Fig. 2. Proposed mechanisms for PCC oxidation of bishomoallylic tertiary alcohols.

stopcock and septum along with 40 cm^3 of dry Et_2O, and stirred in an ice bath. MeMgBr (3 M, 3.9 cm^3, 11.7 mmol) was added dropwise over 17 min using disposable syringes. The mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. With the reaction mixture stirring in the ice bath, saturated Na_2SO_4(1 cm^3) was added dropwise. After stirring for 5 min the reaction mixture was poured into a separatory funnel and shaken with an equal volume of H_2O. The layers were separated and the aqueous layer was extracted once with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo* to yield a clear oil (84% yield). Compound *(4)* was confirmed by GC-MS and ^{1}H n.m.r. analyses [10].

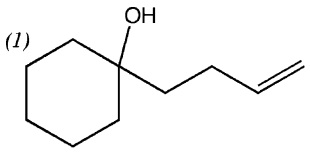
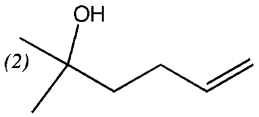
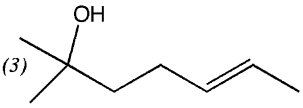
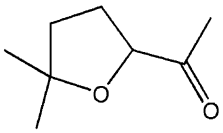
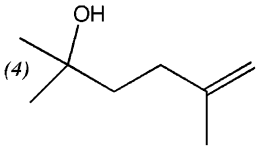
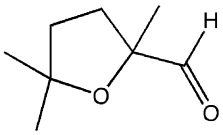
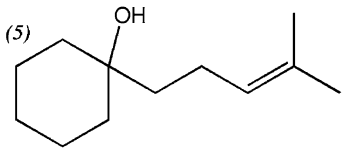
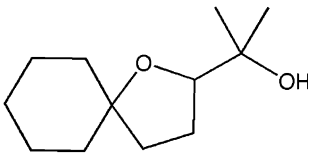
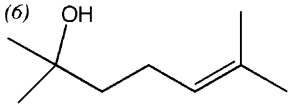
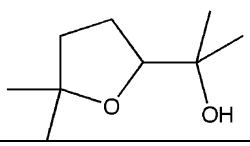
Results and discussion

In order to probe the structural requirements for a successful Figure 1 reaction and to obtain evidence for the mechanism, we synthesized the bishomoallylic tertiary alcohols *(1)–(6)* (Table 1) (see *Experimental*) and asked the following questions regarding their reactivity with PCC under a standard set of conditions: *(1)* Do the relative rates depend only on the number of alkyl substituents attached to the C=C? *(2)* Do the relative rates depend on the degree of alkylation on the most highly substituted alkene carbon? *(3)* Do *(3)* and *(4)* (both disubstituted alkenes) have the same or different reactivities?

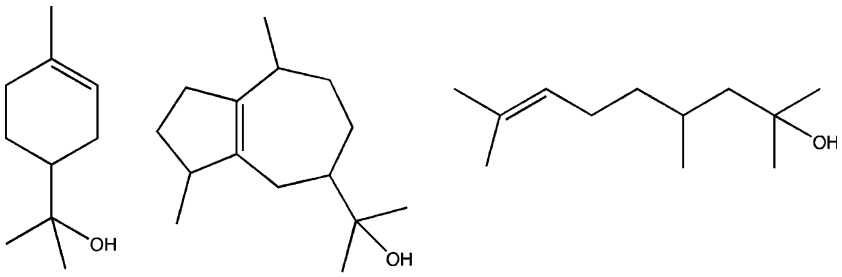
Compounds *(1)–(6)* were treated with PCC under standard conditions (CH_2Cl_2, 2.9 equivalents PCC, 2% HOAc, 20 h, room temperature). Product mixtures contained starting material + product. Using GC-MS and ^{1}H n.m.r. analyses, structures and percent conversions were determined with the following results shown in Table 1.

Since the concentrations, conditions, and reaction times are the same (see Experimental) the percent conversions reflect reactivity, i.e. *(1)*, *(2)* < *(3)* = *(4)* < *(5)*, *(6)*. These results imply that the relative reactivity depends only on the number of alkyl substituents and is closely analogous to the reactivity of alkenes toward oxidation by peroxy acids [12]. In order to confirm that disubstituted alkene-ols *(3)* and *(4)* react with PCC at the same rate, we carried out a competition experiment. Equal molar amounts of the starting *(3)* and *(4)* were reacted together with PCC under the standard conditions. GC-MS results indicated that *(3)* and *(4)* were cleanly converted into their oxidative cyclization products, each with 14–15% conversion. Awasthy and

Table 1. Reactions of bishomoallylic trtiary alcohols with PCC in CH_2Cl_2.

Starting material	% Conversion	Product
	0	
	0	
	17-18[a]	
	21	
	41	
	40-44[a]	

[a]As determined by GC and ^{1}H n.m.r. integrations. Values were within 5% of each other.



(7) *(8)* *(9)*

Rocek [13] have determined that the rate of chromic acid (Cr^{VI}) oxidation of simple alkenes depends only on the number of alkyl substituents and not upon the degree of alkylation on the most highly substituted alkene carbon. This was taken as evidence that the transition state in the rate determining step must be *symmetrical*. With this observation and other arguments, Rocek has favored an epoxidation mechanism for chromic acid oxidation of alkenes. By the same logic, we would suggest that the PCC oxidation of bishomoallylic tertiary alcohols involves a symmetrical transition state in the rate determining step. The epoxidation mechanism is consistent. In fact, it has been demonstrated that a variety of Cr(VI) reagents react with alkenes to give epoxides, often as intermediates in further transformations [4, 14].

Chandrasekaran *et al.* [10] have reported that alkene-ols *(2)*, *(3)*, and *(6)* react with an excess of PCC (under more forcing conditions) to give modest yields of 5,5-dimethyl-γ-lactone. Under their conditions compound *(4)* produced the same aldehyde as shown in Table 1. However, in contrast to the present study, no relative reactivity results were determined.

Within this structure–reactivity study, we would like to report a few negative results which help define the limitations of this PCC oxidative cyclization. Alpha-terpineol *(7)*, guaiol *(8)*, and 2,4,8-trimethyl-7-nonen-2-ol *(9)* are highly substituted alkene-ols which might be expected to be reactive toward PCC (*vide supra*). However, *(7)–(9)* were recovered unchanged after treatment with PCC under our standard conditions. The bulky chromate esters of compounds *(7)* and *(8)* would have to adopt high energy axial-like conformations to be reactive. In compound *(9)* the hydroxyl and alkene functional groups are too far away to interact at a measurable rate.

In conclusion, we have shown that the reactivity of bishomoallylic tertiary alcohol substrates toward PCC in these oxidative cyclizations is increased with increasing number of alkyl substituents. These results suggest a symmetrical transition state in the rate determining step [12]. The [2 + 2] and [3 + 2] cycloaddition mechanisms (Figure 2) have unsymmetrical transition states and are not consistent with this study.

Acknowledgements

The authors are grateful to the University of Tennessee at Chattanooga Foundation (Grote Fund) and to the Provost Student Research Awards for financial support of this research. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society for partial support of this work. We also thank Dr. Rob Mebane for his generous technical assistance.

References

1. T. Strassner, M. Drees and M. Muehlhofer. *Abstracts of Papers*. 223rd ACS National Meeting, Orlando, FL, (2002).
2. S. Meenakshisundaram and R. Markkandan, *Transition Met. Chem.,* **29**, 308 (2004).
3. K. Wietzerbin, J. Bemadon and B. Meunier, *Eur. J. Inorg. Chem.*, 1391 (2000).
4. A.K. Rappe and S. Li*, J. Am. Chem. Soc.*, **125**, 11188 (2003).
5. H. Kwart, J.A. Ford and G.C. Corey, *J. Am. Chem. Soc.*, **84**, 1252 (1962).
6. M.F. Schlecht and H.-j Kim, *J. Org. Chem.*, **54**, 583 (1989).
7. T.B. Towne and F.E. McDonald, *J. Amer. Chem. Soc.*, **119**, 6022 (1997).
8. F.E. McDonald and C.C. Schultz, *Tetrahedron*, **53**, 16435 (1997).
9. K.B. Sharpless, A.Y. Teranishi and J.E. Backvall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
10. S. Baskaran, I. Islam and S. Chandrasekaran, *J. Chem. Res.(S)*, **8**, 290 (1992).
11. B. Jemiolo, F. Andreolini, T.-M Xie, D. Wiesler and M. Novotny, *Physiol. Behav.*, **46**, 293 (1989).
12. J. Rebek, L. Marshal, R. Wolak and J. McManis, *J. Am. Chem. Soc.*, **106**, 1170 (1984).
13. A.K. Awasthy and J. Rocek, *J. Am. Chem. Soc.*, **91**, 991 (1969).
14. N. Miyaura and J.K. Kochi, *J. Am. Chem. Soc.*, **105**, 2368 (1983).