Cyclic Ether Formation in Oxidations of Primary Alcohols by Cerium(IV). Reactions of 5-Phenyl-1-pentanol, 4-Phenyl-1-butanol, and 3-Phenyl-1-propanol with Ceric Ammonium Nitrate

Michael P. Doyle,*[1a] Laura J. Zuidema,[1b] and Thomas R. Bade

Department of Chemistry, Hope College, Holland, Michigan 49423

Received October 30, 1974

Ceric ammonium nitrate in 70% aqueous acetonitrile oxidizes 5-phenyl-1-pentanol and 4-phenyl-1-butanol to 2-benzyl- and 2-phenyltetrahydrofuran, respectively. Competing processes include benzylic oxidation leading to ketone formation and to oxidative cleavage products. The effects on tetrahydrofuran formation by changing the cerium concentration and by varying the solvent are given. Oxidation of 3-phenyl-1-propanol yields chromanone as the only major reaction product when 2 equiv of ceric ammonium nitrate is employed. Chromanone is oxidized to chromone when >2 equiv of the oxidant is used. The mechanistic implications of these results are discussed.

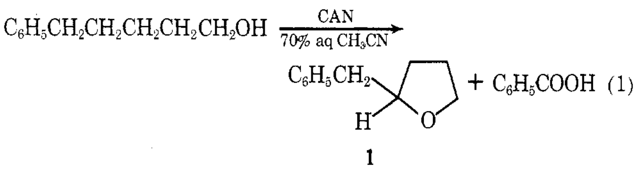
Cerium(IV) oxidations of primary alcohols, unlike those of benzylic,[2] cyclopropylcarbinyl,[3] or certain secondary alcohols,[4] yield tetrahydrofuran derivatives. Tetrahydrofuran formation represents but one of the three modes of reaction identified with cerium(IV) oxidations of alcohols, the others being oxidative cleavage resulting in substrate fragmentation and α-carbon–hydrogen cleavage yielding aldehydes or ketones.[5]

Trahanovsky, Young, and Nave have studied the oxidation of 1-pentanol by ceric ammonium nitrate (CAN) and found 2-methyltetrahydrofuran as the only isolable reaction product.[6] Although the similarity of this reaction to that of the corresponding lead tetraacetate oxidation[7] has been pointed out, the synthetic utility and mechanistic course of cerium(IV) oxidations of primary alcohols have not been further documented.

Phenyl-substituted alkanols have been used previously to determine the effect of the phenyl group on the course of lead tetraacetate oxidations.[8] The phenyl label is useful for identifying the hydrogen transfer step and for determining its specificity in reactions of alcohols with one-electron oxidants.

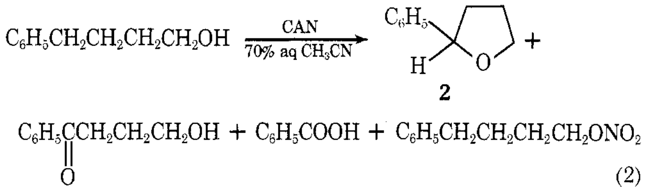
Results

5-Phenyl-1-pentanol. Oxidation of 5-phenyl-1-pentanol (10 mmol) by ceric ammonium nitrate (20 mmol) in 25 ml of 70% aqueous acetonitrile at 75° afforded 2-benzyltetrahydrofuran (1) and benzoic acid as the only major identifiable reaction products (eq 1). Two other products, tentatively identified as benzaldehyde and 5-phenyl-1-pentyl nitrate, were observed by GLC analysis but in combined amounts of less than 8%; unreacted alcohol, by far the major constituent of the reaction mixture (77%), was also identified. The yield of 1, based on reacted 5-phenyl-1-pentanol, was 40%; benzoic acid was formed in less than 10% yield.



(1)

4-Phenyl-1-butanol. The ceric ammonium nitrate oxidation of 4-phenyl-1-butanol in 70% aqueous acetonitrile gave a complex mixture of products consisting of 2-phenyltetrahydrofuran (2), 3-benzoyl-1-propanol, benzoic acid, and 4-phenyl-1-butyl nitrate (eq 2). No aldehyde product was detected. The variation in the yields of 2-phenyltetrahydrofuran and of recovered 4-phenyl-1-butanol and 4-phenyl-1-butyl nitrate with increasing cerium(IV) concentration and with modifications in the oxidation procedure is given in Table I. As can be seen from this data, the optimum yield of the tetrahydrofuran (58%) occurs when 4-



(2)

Table I
Product Yields from the Cerium(IV) Oxidation of 4-Phenyl-1-butanol[a]

[Ce(IV)],[b] *M*	[ROH], *M*	Solvent	2-PhTHF, %[c]	2-PhBuONO$_2$, %[c]	Recovered 4-PhBuOH, %[c]	Yield of 2-PhTHF based on oxidized ROH[d]
0.10	0.10	70% CH_3CN-H_2O	11	8	68	46
0.20	0.10	70% CH_3CN-H_2O	23	8	52	58
0.20[e]	0.10	70% CH_3CN-H_2O	0		90	0
0.20	0.10	70% $HOAc-H_2O$	6	13	38[f]	12
0.20	0.10	70% $CH_3CN-H_2O-HNO_3$[g]	13	8	52	33
0.40	0.10	70% CH_3CN-H_2O	22	9	20	31
0.60	0.10	70% CH_3CN-H_2O	24	12	7	30
0.80	0.10	70% CH_3CN-H_2O	24	Trace	19	30
1.60	0.10	70% CH_3CN-H_2O	3	Trace	10	3

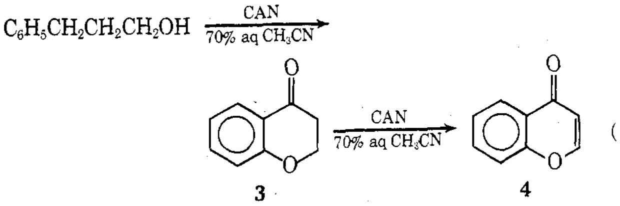
[a] The cerium(IV) salt was added to a flask containing the alcohol, usually in 25 ml of the aqueous solvent. The homogeneous mixture was heated on a steam bath for 0.5–1.0 hr or until the orange-red color of cerium(IV) had disappeared. [b] Ceric ammonium nitrate was used, unless specified otherwise. [c] Absolute yield determined by GLC analysis with reference to an internal standard. From duplicate runs the precision in the yields of 4-PhBuOH + 4-PhBuONO$_2$ was determined to be within ±2%. [d] (% 2-PhTHF/100 − [% 4-PhBuOH + % 4-PhBuONO$_2$]) × 100. [e] Ceric ammonium sulfate was used. [f] Combined yield of alcohol and acetate. [g] [HNO_3] = 0.90 *M*.

phenyl-1-butanol is oxidized with 2 equiv of CAN; increasing the cerium concentration results in a decrease in the yield of **2** and in recovered alcohol. In 70% aqueous acetic acid or when the 70% aqueous acetonitrile solvent contained nitric acid, the yield of **2** was substantially decreased relative to that from the corresponding oxidation in 70% aqueous acetonitrile.

Upon addition of ceric ammonium nitrate to alcohol in 70% aqueous acetonitrile the bright red color characteristic of a 1:1 cerium(IV)–alcohol complex[9] was observed. When ceric ammonium sulfate (CAS) was used instead of CAN, however, complex formation between alcohol and cerium(IV) was not detected. Only unreacted alcohol was obtained after attempted oxidations of 4-phenyl-1-butanol by CAS.

To determine whether alkyl nitrates or nitrites are intermediates in the CAN oxidation of alcohols, 1-pentyl nitrate and 4-phenyl-1-butyl nitrite were individually treated with 2 equiv of ceric ammonium nitrate under the same conditions as those used in alcohol oxidations. 1-Phenyl nitrate was recovered unchanged from the reaction mixture. 4-Phenyl-1-butyl nitrite rapidly decolorized the CAN solution; however, only 4-phenyl-1-butanol was produced.

3-Phenyl-1-propanol. Oxidation of 3-phenyl-1-propanol with 2 equiv of CAN in 70% aqueous acetonitrile at steam-bath temperatures yielded 4-chromanone (**3**) as the only identifiable nonacidic reaction product (eq 3). When additional ceric ammonium nitrate was used, 4-chromanone was converted to chromone (**4**). The yields of **3**, **4**, and recovered alcohol with increasing cerium(IV) concentration are given in Table II. 2,3-Benzo-5,6-dihydro-γ-pyran (chroman) was not observed as a product from these oxidations (<2% yield).



(3)

Table II
Product Yields from the Cerium(IV) Oxidation of 3-Phenyl-1-propanol[a]

[CAN], *M*	[ROH], *M*	[CAN]/[ROH]	4-Chromanone, (3), %[b]	Chromone, (4), %[b]	Recovered 3-PhPrOH, %[b]
0.073	0.073	1.0	7	0	87
0.194	0.097	2.0	14	Trace	81
0.292	0.073	4.0	27	5	63
0.464	0.058	8.0	30	17	37
0.232	0.029	8.0	30	14	25

[a] Ceric ammonium nitrate was added to a flask containing the alcohol in 70% aqueous acetonitrile. The aqueous solution was heated on a steam bath until the orange-red color of cerium(IV) had disappeared. [b] Absolute yield determined by GLC and/or ^1H NMR analysis. From duplicate runs the precision in product yields was ±2%.

In contrast to the results from oxidations in 70% aqueous acetonitrile, in water only trace amounts of **3** and **4** were produced when 3-phenyl-1-propanol was oxidized by CAN (8 equiv);[10] 3-phenyl-1-propanol was recovered in 35% yield, 2% benzaldehyde was detected, and the major product was benzoic acid (30% yield). In anhydrous acetonitrile a complex mixture of products was produced in which **3** and **4** were only minor components.

Discussion

A mechanism consistent with the results from the oxidation of 5-phenyl-1-pentanol and 4-phenyl-1-butanol by ceric ammonium nitrate is given in Scheme I. Complex formation between the alcohol and cerium(IV) appears to be a necessary condition for the subsequent production of an alkoxy radical (eq 5) leading to 1,5-hydrogen transfer (eq 6), electron transfer (eq 7), and carbenium ion trapping (eq 8 and 9). Under conditions in which the extent of complex formation is less than that with CAN in 70% aqueous acetonitrile, reaction with CAS, or in 70% aqueous acetic acid,[9] the yield of the tetrahydrofuran product is substantially decreased.

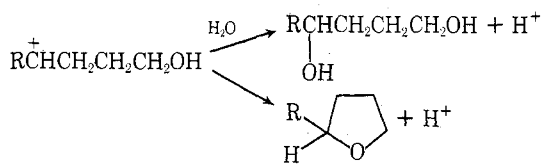
Scheme I

$$RCH_2CH_2CH_2CH_2OH + Ce^{4+} \rightleftharpoons RCH_2CH_2CH_2CH_2OCe^{3+} + H^+ \quad (4)$$

$$RCH_2CH_2CH_2CH_2OCe^{3+} \longrightarrow RCH_2CH_2CH_2CH_2O\cdot + Ce^{3+} \quad (5)$$

$$RCH_2CH_2CH_2CH_2O\cdot \xrightarrow{1,5\text{-}H\sim} R\dot{C}HCH_2CH_2CH_2OH \quad (6)$$

$$R\dot{C}HCH_2CH_2CH_2OH + Ce^{4+} \longrightarrow R\overset{+}{C}HCH_2CH_2CH_2OH + Ce^{3+} \quad (7)$$

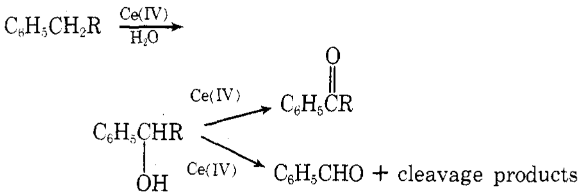


(8)

(9)

The specificity of the hydrogen transfer step and the lack of α-C–H bond cleavage in tetrahydrofuran formation point to the intermediacy of an alkoxy radical in the CAN oxidations of primary alcohols. 1,5-Hydrogen transfer is observed exclusively in oxidations of 5-phenyl-1-pentanol by CAN and by lead tetraacetate,[8] even though 1,6-hydrogen transfer would yield the more stable benzylic radical; a similar specificity is observed in intramolecular hydrogen transfer reactions to alkoxy radicals generated from nitrite esters and hypochlorites.[11] The influence of cerium on the hydrogen-transfer step, if any, could not be distinguished in this study.

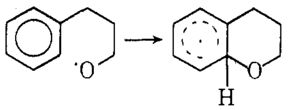
The carbenium ion produced by electron transfer to cerium(IV) from the carbon radical (eq 7) can conceivably undergo intramolecular trapping to give the observed tetrahydrofuran (eq 9) or intermolecular trapping yielding a diol (eq 8). The diol produced by intermolecular trapping would be expected to be rapidly oxidized to the corresponding hydroxy ketone and oxidative cleavage products;[2c] both processes have been observed in this study. However, an alternate pathway to hydroxy ketone and oxidative cleavage products involving oxidation at the benzylic position (eq 10), similar to that observed in toluene oxidations,[12] cannot be excluded.



$$C_6H_5CH_2R \xrightarrow[H_2O]{Ce(IV)} \underset{OH}{C_6H_5CHR} \begin{cases} \xrightarrow{Ce(IV)} C_6H_5\overset{O}{\overset{\|}{C}}R \\ \xrightarrow{Ce(IV)} C_6H_5CHO + \text{cleavage products} \end{cases} \quad (10)$$

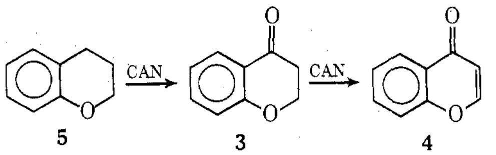
2-Phenyltetrahydrofuran may also be considered to be a source of hydroxy ketone and oxidative cleavage products either through direct oxidation of the furan or through hydrolysis followed by oxidation. However, since the yield of **2** remained constant when the ratio of CAN to alcohol was varied from 4.0 to 8.0, this pathway does not appear to be dominant. With a ratio of 16 for [CAN]/[ROH] the low recovered yield of **2** suggests that this compound is subject to further oxidation.

In the oxidation of 3-phenyl-1-propanol by CAN, 1,5-hydrogen transfer is not possible. However, intramolecular alkoxy radical addition to the aromatic nucleus (eq 11)



(11)

does occur. Unlike the corresponding oxidation by lead tetraacetate,[8] chroman is not detected; only chromanone is observed. To determine if chromanone is produced directly from chroman in a rapid oxidation reaction at the benzylic position, chroman (**5**), prepared and isolated from the lead tetraacetate oxidation of 3-phenyl-1-propanol,[8a,13] was oxidized in the presence of a 2 molar excess of 3-phenyl-1-propanol with CAN. A 4 molar equiv excess of CAN to the combined alcohol–chroman was used, and reaction conditions duplicated those of Table II. Under these conditions, which closely relate to those under which 3-phenyl-1-propanol was oxidized by CAN to chromanone, complete conversion of chroman to chromanone and chromone (76 and 16%, respectively, based on chroman) was observed (eq 12).



(12)

5 **3** **4**

The reactant alcohol was recovered in 85% yield after oxidation was complete. From these qualitative results chroman is estimated to be at least ten times more reactive than 3-phenyl-1-propanol toward oxidation by CAN.

The oxidation of chromanone (**3**) to chromone (**4**) represents an oxidation process not previously reported for reactions with CAN[5a] but known for two-electron oxidants.[14] The stability of the heteroaromatic ring system of **4** is certainly a major factor in this transformation. Dehydrogenation reactions in other systems yielding stable heteroaromatic compounds may also be feasible using ceric ammonium nitrate oxidation.

Experimental Section

General. Instrumentation has been previously described.[15] For GLC analyses use was made of 5-ft columns of 20% Carbowax 20M on Chromosorb P. 5-Phenyl-1-pentanol and 4-phenyl-1-butanol were prepared by lithium aluminum hydride reductions of the corresponding carboxylic acids; 3-phenyl-1-propanol was commercially available. 4-Phenyl-1-butyl nitrite was produced from the reaction between the corresponding alcohol and nitrosyl chloride:[16] bp 50–52° (0.3 Torr); ^{1}H NMR (CCl_4) δ 7.1–7.4 (m, 5 H), 4.68 (distorted t, 2 H), 2.66 (distorted t, 2 H), and 1.9–1.5 (m, 4 H); ir (film) 1652 and 1612 cm^{-1} (–ONO). G. F. Smith analyzed reagent-grade ceric ammonium nitrate and reagent-grade ceric ammonium sulfate were used.

General Oxidation Procedure. To a stirred solution of the alcohol (2.5 mmol) in 20 ml of 70% aqueous acetonitrile, contained in a round-bottom flask equipped with a reflux condenser, was added a weighed amount of ceric ammonium nitrate. An additional 5 ml of 70% aqueous acetonitrile was used to wash the cerium salt into the flask. The dark-red homogeneous solution was heated on a steam bath until a color change to colorless could no longer be observed. The resulting solution was cooled and 10 ml of water was added followed by 10 ml of ether. After thorough mixing the ether layer was separated from the aqueous layer, and the aqueous layer was washed twice with 15-ml portions of ether. The combined ether solution was washed with 25 ml of a saturated sodium bicarbonate solution and with 25 ml of water. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure.

Oxidation of 5-Phenyl-1-pentanol. Product Analyses. GLC analysis of the nonacidic products from the CAN oxidation of 5-phenyl-1-pentanol showed three compounds in addition to the starting alcohol. The major product was collected and identified as 2-benzyltetrahydrofuran by ir and ^{1}H NMR spectral analysis through comparison with an authentic sample. Benzaldehyde and 5-phenyl-1-pentyl nitrate were identified from the ^{1}H NMR spectrum of the reaction mixture. Benzoic acid was isolated after acidification of the bicarbonate wash solution.

Oxidation of 4-Phenyl-1-butanol. Product Analyses. Products from the CAN oxidation of 4-phenyl-1-butanol were separated by GLC methods or in the extraction procedure and identified by spectral analysis of the individual compounds through comparison with authentic samples. Absolute yields of 2-phenyltetrahydrofuran, 4-phenyl-1-butyl nitrate, and 4-phenyl-1-butanol were determined by GLC analysis using an internal standard, 2-phenylethanol. The areas of the product peaks were compared with the area of the standard peak, and the absolute yields of products were determined with the use of experimentally measured thermal conductivity ratios (0.96 for 4-phenyl-1-butanol and 1.31 for 2-phenyltetrahydrofuran). 4-Phenyl-1-butyl nitrate was assumed to have the same thermal conductivity ratio as 4-phenyl-1-butanol.

Oxidation of 3-Phenyl-1-propanol. Product Analyses. Only one major reaction product (>3% yield) was observed by GLC analysis and ^{1}H NMR spectroscopy of the reaction mixture from the oxidation of 3-phenyl-1-propanol with 2 equiv of CAN. This product was collected and identified as 4-chromanone by ^{1}H NMR and ir spectroscopy. When greater than 2 equiv of CAN was used a second product, chromone, was similarly isolated and identified. Product yields were determined by ^{1}H NMR analyses of the reaction mixtures. Chromanone (**3**): ^{1}H NMR (CCl_4) δ 8.0–7.8 (m, 1 H), 7.65–6.85 (m, 3 H), 4.55 (t, 2 H, J = 6.5 Hz), and 2.73 (t, 2 H, J = 6.5 Hz); ir (film), 1685 cm^{-1} (C=O). Chromone (**4**): ^{1}H NMR (CCl_4) δ 8.35–8.10 (m, 1 H), 7.75–7.10 (m, 3 H), 7.83 (d, 1 H, J = 6 Hz), and 6.27 (d, 1 H, J = 6 Hz); ir (CCl_4) 1665 cm^{-1} (C=O).

Acknowledgment. We wish to thank Dr. Walter S. Trahanovsky and Dr. L. Brewster Young for helpful discussions concerning this research.

Registry No.—**3**, 491-37-2; **4**, 491-38-3; CAN, 16593-75-2; CAS, 19495-85-3; 5-phenyl-1-pentanol, 10521-91-2; 4-phenyl-1-butanol, 3360-41-6; 3-phenyl-1-propanol, 122-97-4; 4-phenyl-1-butyl nitrite, 17337-03-0; nitrosyl chloride, 2696-92-6.

References and Notes

(1) (a) Camille and Henry Dreyfus Foundation Teacher-Scholar Grant Awardee, 1973–1978; (b) National Science Foundation Undergraduate Research Participant, summer 1973.

(2) (a) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967); (b) W. S. Trahanovsky and D. B. Macaulay, *ibid.*, **38**, 1497 (1973); (c) W. S. Trahanovsky and J. Cramer, *ibid.*, **36**, 1890 (1971); (d) P. M. Nave and W. S. Trahanovsky, *J. Am. Chem. Soc.*, **93**, 4536 (1971).

(3) L. B. Young and W. S. Trahanovsky, *J. Org. Chem.*, **32**, 2349 (1967).

(4) (a) K. Meyer and J. Rocek, *J. Am. Chem. Soc.*, **94**, 1209 (1972); (b) W. S. Trahanovsky, P. J. Flash, and L. M. Smith, *ibid.*, **91**, 5068 (1969).

(5) (a) W. H. Richardson in "Oxidation in Organic Chemistry", Part A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965; (b) W. S. Trahanovsky, *Methods Free-Radical Chem.*, **4** (1973).

(6) W. S. Trahanovsky, M. G. Young, and P. M. Nave, *Tetrahedron Lett.*, 2501 (1969).

(7) M. L. Mihailovic and R. E. Partch in "Selective Organic Transformations", Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1972.

(7) (a) S. Moon and P. R. Clifford, *J. Org. Chem.*, **32**, 4017 (1967); (b) M. L. Mihailovic, L. Zivkovic, Z. Maksimovic, D. Jeremic, Z. Cekovic, and R. Matic, *Tetrahedron*, **23**, 3095 (1967).

(9) L. B. Young and W. S. Trahanovsky, *J. Am. Chem. Soc.*, **91**, 5060 (1969); spectrophotometric measurements confirm the lack of complex formation between phenylalkanols and CAS in 70% aqueous acetonitrile.

(10) Complex formation between 3-phenyl-1-propanol was observed in water even though the alcohol was relatively insoluble in this medium.

(11) J. W. Wilt in "Free Radicals", Vol. I, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973.

(12) (a) W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966); (b) L. Syper, *Tetrahedron Lett.*, 4493 (1966).

(13) Neither chromanone nor chromone were observed as reaction products from the LTA oxidation of 3-phenyl-1-propanol.

(14) A. Schönberg and G. Schütz, *Chem. Ber.*, **93**, 1466 (1960), and references cited therein.

(15) M. P. Doyle and W. Wierenga, *J. Am. Chem. Soc.*, **94**, 3896 (1972).

(16) N. Kornblum and E. P. Oleveto, *J. Am. Chem. Soc.*, **69**, 465 (1947).