Tetrahedron Letters No. 39, pp 3499 -3502 , 1976. Pergamon Press. Printed in Great Britain.

ORGANIC REACTIONS AT ALUMINA SURFACES. V. HIGHLY SELECTIVE ALCOHOL AND DIOL OXIDATION REACTIONS ON ALUMINA[1]

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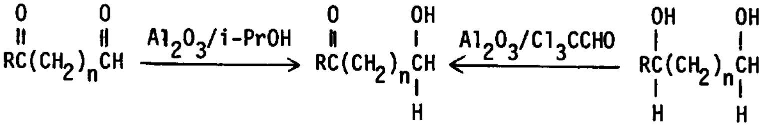
(Received in USA 16 March 1976; received in UK for publication 10 August 1976)

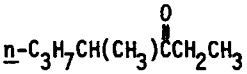
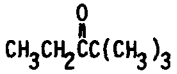
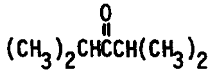
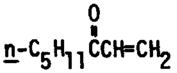
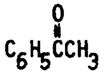
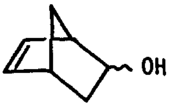
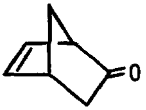
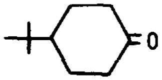
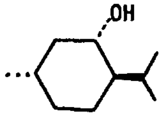
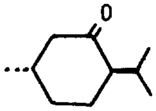
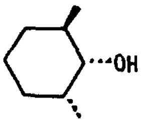
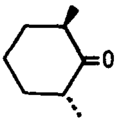
We have recently reported that 2-propanol on dehydrated chromatographic alumina converts aldehydes into alcohols and selectively reduces some keto aldehydes into the corresponding keto alcohols (eq. 1).[1b] We report now that the opposite process, oxidation of secondary alcohols, can be performed heterogeneously within the micropores of the solid alumina; trichloroacetaldehyde on dehydrated chromatographic alumina transforms structurally diverse secondary alcohols into ketones and selectively oxidizes some diols into the corresponding keto alcohols (eq. 1). After trying various carbonyl compounds as hydride acceptors, we found trichloroacetaldehyde (and in some cases benzaldehyde) to be the oxidant of choice mainly because product work-up and purification were easiest with this reagent. The general oxidation procedure is as follows.



$$\mathrm{R\overset{\overset{O}{\|}}{C}(CH_2)_n\overset{\overset{O}{\|}}{C}H} \xrightarrow{\mathrm{Al_2O_3/i\text{-}PrOH}} \mathrm{R\overset{\overset{O}{\|}}{C}(CH_2)_n\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}H} \xleftarrow{\mathrm{Al_2O_3/Cl_3CCHO}} \mathrm{R\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}(CH_2)_n\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}H} \qquad (1)$$

To about 5 g of Woelm W-200, neutral, dehydrated (W-200-N-D) alumina[1c] in a round-bottomed flask equipped with a magnetic stir bar under nitrogen is added about 5 ml of carbon tetrachloride[2] along with 5% by weight of the alcohol to be oxidized. After stirring for 10 min at room temperature 1 equivalent of trichloroacetaldehyde in 1 ml of carbon tetrachloride is added and stirring is continued for 24 hours at room temperature. The reaction is then vacuum filtered through celite and washed with 35 ml of methylene chloride.[3] The methylene chloride solution is dried with calcium chloride[4] and the solvent is evapored *in vacuo* to yield the ketones which can then be distilled or recrystallized if needed. Table I gives the results of oxidation of various secondary alcohols.

Table 1. Oxidation of secondary alcohols by trichloroacetaldehyde on W-200-N-D alumina (25°,24 hr).

Alcohol	Ketone	% Yield[a]
$\underline{n}\text{-}C_3H_7CH(CH_3)CH(OH)CH_2CH_3$	 $\underline{n}\text{-}C_3H_7CH(CH_3)\overset{O}{\overset{\|}{C}}CH_2CH_3$	88
$CH_3CH_2CH(OH)C(CH_3)_3$	 $CH_3CH_2\overset{O}{\overset{\|}{C}}C(CH_3)_3$	64(72)
$(CH_3)_2CHCH(OH)CH(CH_3)_2$	 $(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH(CH_3)_2$	(77)
$\underline{n}\text{-}C_5H_{11}CH(OH)CH{=}CH_2$	 $\underline{n}\text{-}C_5H_{11}\overset{O}{\overset{\|}{C}}CH{=}CH_2$	65
$C_6H_5CH(OH)CH_3$	 $C_6H_5\overset{O}{\overset{\|}{C}}CH_3$	90
 78% endo 22% exo		80
		71
		63[b]
		69[c]

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[a] Yields are of isolated, purified products. Yields in parentheses were calculated using glpc with a calibrated internal standard

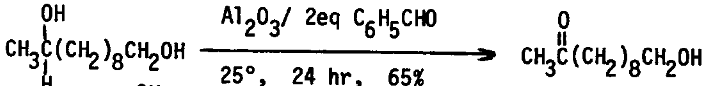
[b] Analysis of the isolated menthone by glpc showed that it contained 5% of isomenthone; the equilibrium mixture is 60:40 menthone:isomenthone

[c] Glpc analysis indicated only 3% of the thermodynamically more stable cis-2,6-dimethylcyclohexanone

The heterogeneous reactions summarized in Table I were repeated at least twice in order to establish reproducibility to ±5%. In order to demonstrate the applicability of this oxidation to the preparation of gram quantities of ketone, sec-phenethyl alcohol was oxidized on a 30 mmole (3.7 g) scale as described to give acetophenonein 86% distilled yield. Finally, even hindered alcohols such as 1,1-dimethyl-2-pentanol, diisopropyl carbinol, and trans-2,6-dimethylcyclohexanol are oxidized to the corresponding ketones in reasonably good yields; the 2,6-dimethylcyclohexanone formed was mainly the thermodynamically less stable trans-isomer.

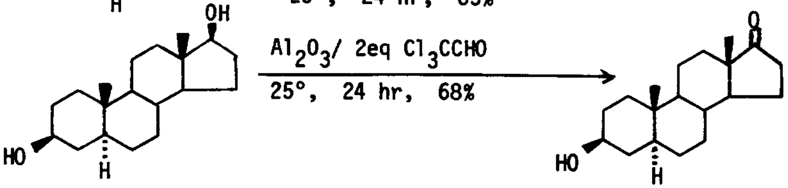
While secondary alcohols are oxidized to ketones using this technique, many other functional groups are inert. Under the conditions described above 1-iodooctane, 1,2-bis(chloromethyl)benzene, 1,10-dimethyl decanedioate, m-notrotoluene, N,N-dimethyl benzyl amine, butyrolactone and cyclohexyl methyl either were recovered in 85, 94, 99, 96, 82, 65 and 60% yields respectively.

Because we had obeserved that primary alcohols are not easily oxidized by trichloroacetaldehyde (or benzaldehyde) on alumina, we attempted to oxidize a secondary alcohol in the presence of a primary alcohol; 1,10-undecandiol[8] was converted into lo-oxoundecanol[9] in 65% recrystallized yield[3] along with 17% recovery of starting diol. Likewise, 5α-androstan-3,17-diol 1 was selectively oxidized to the corresponding 3-hydroxy-17-keto steroid (eq. 3); selective oxidation was also observed with 1,5-cyclooctanediol and a steroidal 3,20-diol. The selectivity shown in equations 2 and 3 is far superior to that obtained using silver carbonate on Celite; in our hands, silver carbonate on Celite gave 41% 10-oxoundecanol and 35% of lo-hydroxyundecanal (cf eq. 2).[10] While this Celite-supported reagent does not appear to be so selective as trichloroacetaldehyde on alumina, it is also much more expensive and must be used in large excess.



$$CH_3\overset{OH}{\underset{H}{C}}(CH_2)_8CH_2OH \xrightarrow[25°,\ 24\ hr,\ 65\%]{Al_2O_3/\ 2eq\ C_6H_5CHO} CH_3\overset{O}{\overset{\|}{C}}(CH_2)_8CH_2OH$$

(2)



(3)

Despite the inconvenience of having to dehydrate the commercial W-200-N alumina under vacuum for 24 hr prior to doping with trichloroacetaldehyde, these heterogeneous oxidation reactions have some very positive aspects: neutral, non-aqueous medium; survival of halide, ester and lactone functionalities; low cost of reagents which are used in only slight excess over substrates; and easy product isolation. Although trichloroacetaldehyde on dehydrated alumina may not generally replace other standard reagents for alcohol oxidation, it undoubtedly will be used for preparation of some keto alcohols via these highly selective diol oxidations.

Acknowledgment We thank the Research Corporation and the National Institutes of Health (CA-16068) for financial support.

References

1. For the previous papers from our laboratory on alumina as a reagent in organic synthesis, see (a) G. H. Posner, R. J. Johnson and M. J. Whalen, *Chem. Commun.*, 291 (1972); (b) G. H. Posner, D. Z. Rogers, C. M. Kinzig and G. M. Gurria, *Tetrahedron Lett.*, 3597 (1975); (c) G. H. Posner and A. W. Runquist, *Tetrahedron Lett.*, 3601 (1975); and (d) G. H. Posner and G. M. Gurria, *J. Org. Chem.*, **41**, 578 (1976).

2. Other solvents which have been used include benzene, petroleum ether, ether, and chloroform. The yields of ketones remain essentially the same. Carbon tetrachloride is the preferred solvent since it can be used (Reagent grade) without pre-drying to remove water.

3. When diols are oxidized, the alumina is washed with methanol instead of methylene chloride.

4. Calcium chloride serves also to remove traces of unreacted alcohol.

5. (a) Using more than 1 equivalent of trichloroacetaldehyde per equivalent of alcohol does not raise ketone yields; (b) It is noteworthy that analysis of the crude product mixtures of the oxidations showed no elimination, Tischenko, Cannizzaro or aldol condensation side products; this is significant because two common side reactions of Oppenauer oxidations of secondary alcohols using aluminum *t*-butoxide and acetone are aldol condensations and eliminations, and special precautions must be taken to minimize these side reactions.[6,7]

6. C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

7. "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience Publishers, 1966, Ch. 11.

8. This compound was prepared from 11-undecenoic acid by the sequence of steps given in reference 1c, followed by $LiAlH_4$ reduction.

9. L. Cottier, and G. Descotes, *Bull. Soc. chim. France*, 4557 (1971).

10. (a) The silver carbonate on Celite was prepared as described by M. Fetizon and M. Golfier *Compt. Rend. Acad. Sc. Paris*, **267**, (C), 900 (1968) and used immediately. The diol was treated with silver carbonate on Celite as for other diols described by M. Fetizon, M. Golfier, and J. M. Louis, *Chem. Commun.*, 1102 (1969)(*e.g.*, 1,10-undecanediol was refluxed with 5 equivalents of silver carbonate on Celite in benzene until only a trace of the starting diol remained; this took 24 hrs; (b) Oxidation of 1 mmol of 17β-androstanol using 8 mmols of silver carbonate on Celite proceeds at only twice the rate of 3β-androstanol oxidation under the same conditions; it is thus difficult to oxidize selectively the 17-hydroxyl group of 3β,17β-androstandiol in high yield using silver carbonate on Celite (personal communication from M. Fetizon);[10a] (c) A cost analysis also revealed that silver carbonate on Celite is at least *ten times more expensive* than trichloroacetaldehyde on alumina for alcohol oxidation.