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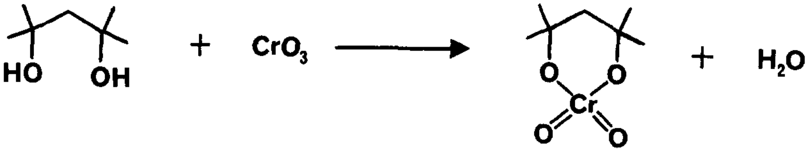
A NEW Cr(VI) REAGENT FOR THE CATALYTIC OXIDATION OF SECONDARY ALCOHOLS TO KETONES*

E. J. Corey, Ernie-Paul Barrette, and Plato A. Magriotis
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: A new process is described for the oxidation of secondary alcohols to ketones using peroxyacetic acid in the presence of a catalytic amount of 2,4-dimethylpentane-2,4-diol cyclic chromate.

The oxidation of primary and secondary alcohols to the corresponding carbonyl compounds is most frequently accomplished in synthetic practice by the use of chromium (VI) reagents in amounts ranging from stoichiometric to large excess over stoichiometric.[1] Since chromium (VI) reagents are moderately expensive, environmentally hazardous, and also complicating with regard to product isolation, it would clearly be advantageous to develop oxidizing reagents which require only catalytic amounts of Cr(VI). In this paper we report a new and highly effective reagent combination for the synthesis of ketones from secondary alcohols. The reagent consists of peroxyacetic acid as the stoichiometric oxidant and the Cr(VI) ester **1** as the catalyst with carbon tetrachloride-methylene chloride mixtures as solvent. A solution of the Cr(VI) ester **1** is prepared from 2,4-dimethylpentane-2,4-diol[2] and chromium trioxide in dry carbon tetrachloride.[3] For many secondary alcohols as little as 2 mole % of **1** suffices for the efficient (> 90% yield) production of ketone in the presence of 2 equiv of peroxyacetic acid.



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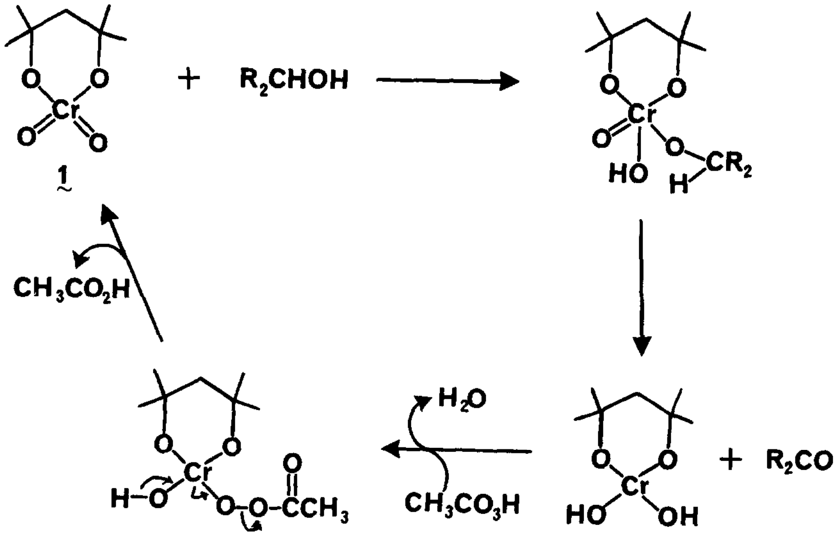
A number of other catalytic systems for the oxidation of alcohols to carbonyl compounds have recently been reported, including $RuCl_2(PPh_3)_3$ - tBuOOH,[4,5] pyridinium dichromate - $Me_3SiOOSiMe_3$,[6] and $R_4N^+ Br_4MoO^-$ - tBuOOH.[7,8]

The cyclic chromate ester **1** was first prepared in these laboratories by J. W. Suggs[9] who found it to oxidize alcohols rapidly even below -20° using stoichiometric amounts of oxidant. Although the stoichiometric oxidation of secondary alcohols to form ketones proceeds cleanly, the oxidation of primary alcohols is considerably slower and affords a mixture of products among which are major amounts of ester coupling product, $RCOOCH_2R$.

* Dedicated with appreciation and best wishes to Harry H. Wasserman.

The results of our study with secondary alcohols are summarized in the accompanying table. The experiments were conducted using a commercial (Union Carbide Co.) solution of peroxyacetic acid in ethyl acetate (2 equiv) as stoichiometric oxidant. Other anhydrous peroxycarboxylic acids are likely to serve as well. Oxidation reactions usually proceeded rapidly at 0° with 2 mole % of 1 and were homogeneous throughout. The orange color of 1 generally faded to yellow during the course of the oxidations, but returned when all the starting alcohol had been oxidized. Because so little Cr(VI) reagent is used, isolation of product is greatly simplified. Normally reaction mixtures were diluted with 9 : 1 hexane-ether, filtered through a small amount of silica gel to remove chromium species, and concentrated under reduced pressure to afford ketonic product in pure condition as determined by pmr, ir and tlc analysis. The simplicity and economy of this method recommend it, especially for reactions on a larger scale. Problems of scale-up are obviated by the homogeneity of the system, the convenient temperature (0 to 20°) and the simplicity of product isolation, especially in comparison with heterogeneous reagents and reagents which must be used in excess.

The catalytic cycle for oxidation of secondary alcohols to ketones by peroxycarboxylic acid in the presence of 1 can be represented rationally by the following scheme.



An important function of the ditertiary 1,3-diol ligand is clearly the preservation of the reduced chromium species in a soluble form which allows reoxidation to chromium (VI). Another factor in the success of 1 as a catalytic reagent is its excellent reactivity.

The results in the Table suggest that longer reaction time may be necessary for hindered secondary alcohols (note borneol ⟶ camphor entry) which suggests that for sterically screened hydroxyls mixed chromate ester formation may be rate limiting. For substrates that are highly reactive to the peroxyacid component it may be advisable to use larger amounts of 1 (up to 0.25 equiv) or a less reactive peroxy component. In this regard it should be noted that t-butylhydroperoxide and hydrogen peroxide (anhydrous solution in ether) were found not to be effective for the regeneration of **1** from the reduced intermediate. The combination of **1** (5 mole %) and CH_3CO_3H (2 equiv) also effects the conversion of primary alcohols to aldehydes in good yield (0°, 15 min, *ca.* 80%); these results will be published separately.

Although further studies are necessary to establish the full range of application of the catalytic oxidizing system reported herein, the practicality of the method is apparent.

TABLE

OXIDATION OF SECONDARY ALCOHOLS TO KETONES
BY 2 MOL. % OF **1** AND 2 EQUIV OF PEROXYACETIC ACID AT 0° IN CH_2Cl_2 - CCl_4

Alcohol	Time, hr	Isolated Yield of Ketone, %
4-t-butylcyclohexanol	0.35	98
trans-2-phenylcyclohexanol	0.5	99
cyclooctanol	0.5	96
borneol	12.0	99
menthol	1.0	91
2-octanol	0.35	99
cholesterol	0.35	84[a]
1-phenylethanol	0.35	96
1-octyne-3-ol	7.0	97
2-cycloheptenol	0.3	90[b]
2-cyclohexenol	0.3	80[b]
prostaglandin $F_{2\alpha}$-11,15-bistetrahydropyranyl ether	0.5 (0°C), 3.5 (23°C)	78[c]

Notes: [a] 0.1 equiv of **1** was used; product was Δ^5-cholestan-3-one. [b] 0.1 equiv of **1** was used. [c] 0.25 equiv of **1** was used; product was prostaglandin E_2-11,15-bistetrahydropyranyl ether.

An illustrative experimental procedure follows.

Oxidation of 4-t-butylcyclohexanol to 4-t-butylcyclohexanone. Into a 25 ml round-bottom flask, which had been flame dried and filled with argon, was placed CH_2Cl_2 (2 ml) and a dark orange CCl_4 solution of the chromate ester **1** (0.27 ml, 0.046 *M*, 0.012 mmoles, 0.02 equiv). After cooling the mixture to 0°C in an ice bath a solution of peroxyacetic acid in ethyl acetate (0.70 ml, 1.74 *M*, 1.22 mmoles, 2.0 equiv) (obtained as a 25% solution in ethyl acetate from Union Carbide Co., Hahnville, LA) was added using a glass pipette. A solution of 4-t-butylcyclohexanol (95.2 mg, 0.609 mole) in a little methylene chloride was then added with stirring. The orange color of the solution immediately changed to bright yellow. After 20 min at 0° the color of the clear solution was the original dark orange and thin layer chromatography indicated the absence of starting alcohol. The reaction mixture was diluted with 9 : 1 hexane - ether and filtered through a 1.5 x 2.5 cm plug of silica gel on a fritted-glass funnel. The silica gel was washed with ether and the solvents were removed *in vacuo* to afford 91.9 mg (98%) of 4-t-butylcyclohexanone, m.p. 48°, which was identical (pmr, infrared, tlc analysis) with an authentic sample.[10]

References and Notes

1. See, for example, G. Cainelli and G. Cardillo, "Chromium Oxidations in Organic Chemistry," Springer-Verlag, Berlin, 1984.
2. Preparation of 2, 4-dimethylpentane-2, 4-diol: To a solution of methyllithium (0.44 mol; 314 ml of a 1.4 *M* solution in ether) in anhydrous ether (250 ml) at ~-70°C under nitrogen, was added diacetone alcohol (23.2 g, 0.2 mol) in anhydrous ether (60 ml) via cannula. After the addition was complete, the reaction mixture was warmed to 0°C (ice water bath) and saturated NH_4Cl solution was added carefully. Subsequently the ether layer was separated and the aqueous phase was acidified (pH ~3; 1N HCl) and extracted with ether (~250 ml). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil (26 g, 97% crude yield) which after distillation at 48-49° (0.2 torr) from anhydrous potassium carbonate furnished pure diol (24g, 89%); ^1H NMR (270 MHz, $CDCl_3$): δ 3.05 (2H, brs), 1.75 (2H, s), 1.35 (12H, s).
3. Carbon tetrachloride solutions of the cyclic chromate ester **1** were prepared as follows: Into a 100 ml round-bottom flask, which had been flame dried *in vacuo* and filled with argon, was placed 2, 4-dimethylpentane-2, 4-diol (1.32 g, 0.01 mol) followed by anhydrous CCl_4 (~35 ml). Upon addition of chromium trioxide (1.0 g, 0.01 mol; Aldrich 99% grade, crushed in a glove box and stored in a desiccator over P_2O_5) complete dissolution was observed within a few minutes. After stirring for 10 min carbon tetrachloride was added so that the total volume of the resulting dark orange solution became 50 ml (0.2 *M* in Cr(IV)). At this point phosphorous pentoxide (1.5 g; powder) was added and stirring was continued for 15 min. The clear solution was transferred via cannula to a flame dried flask under argon and stored as such. The ^1H NMR spectrum of this solution indicated the presence of Cr(IV) bound diol (> 95%). ^1H NMR: (270 MHz, CCl_4): δ 2.41 (2H, s), 1.69 (12H, s).
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10. This work was assisted financially by the National Science Foundation.

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