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A Convenient Preparation of Ketones by the Oxidation of Secondary Alcohols with Chromium(VI) Trioxide in Aprotic Solvent in the Presence of "Wet"-Aluminum Oxide

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Synopsis. The oxidation of aliphatic and alicyclic secondary alcohols with chromium(VI) trioxide in the presence of "wet"-aluminum oxide in hexane gave the corresponding ketones in excellent yields under mild conditions.

Recently, supported reagents, consisting of a large number of combinations of agents and such inorganic solid materials as silica gel, aluminum oxide (hereafter referred as alumina), graphite, polymers, zeolites, and clay minerals, etc., have been given considerable attention because of their improved selectivity and reactivity as well as manipulative simplicity. Thus, supported reagents have been recommended for many catalytic and stoichiometric processes, including oxidation, reduction, substitution, elimination, rearrangement, hydrogenation, polymerization, etc., and especially for organic syntheses.[1,2]

In recent communications, we have reported facile and convenient oxidations of alcohols with sodium bromite ($NaBrO_2$),[3] chromium(VI) trioxide,[4] and "Oxone",[5,6] and a novel Baeyer–Villiger-type lactonization of alicyclic ketones with Oxone[7] in aprotic solvents in the presence of commercial chromatographic alumina. The oxidizing milieu of these processes are intimately analogous to a supported reagent system, but the reaction can be immediately started only by mixing alumina, a solvent, and an oxidant with a substrate without the preparation of a supported reagent. In this article, we wish to describe some observations on the facile oxidation of various aliphatic and alicyclic secondary alcohols with chromium(VI) trioxide in aprotic solvents in the presence of "wet"-alumina, since the reaction offers a convenient and selective synthesis of ketones under neutral and mild conditions.

Results and Discussion

The reaction was carried out by mixing finely-ground chromium(VI) trioxide, an alcohol, and an aprotic solvent in the presence or absence of alumina and by magnetic stirring of the heterogeneous mixture under an inert atmosphere in order to avoid autoxidation. It should be noted that efficient stirring was indispensable throughout a given period to ensure a smooth reaction and to attain a reproducible result ($\pm 5\% <$). A small amount of the supernatant was withdrawn at intervals and analyzed by GLC in order to follow the progress of the reaction. After a given reaction period, filtration of an insoluble material and washing of the residue with ether, followed by evaporation of the combined solvent in vacuo, left a ketone.

In the absence or presence of commercial "dry"-alumina, the reaction was rather slow. Indeed, in the oxidation of 4-methylcyclohexanol (**1**) in hexane at room temperature for 15 h ($[CrO_3]/[\mathbf{1}]=1.5$; mole ratio), almost all or a considerable amount of **1** (98 or 71%, respectively; by GLC) was recovered, resulting only in the poor formation of 4-methylcyclohexanone (**2**) (trace or 12%, respectively). In addition, the extensive formation of an unknown by-product (16%; GLC selectivity) was observed in the latter case. On the other hand, when the reaction was conducted in the presence of "wet"-alumina (see the Experimental section), 95% of **1** was consumed under the same conditions as above, resulting in the selective formation of **2**. In view of the reactivity of CrO_3 and selectivity of the ketone, "wet"-alumina was clearly proven to play a decisive role in the oxidation. The atomic absorption analyses showed that no detectable amount of a chromium species was involved in the solvent at any time during the reaction, indicating clearly that the reaction occurred exclusively on the alumina surface. The mechanistic details of the present system are regrettably still obscure, although there have been some suggestions of a probable functional role of a support[8] and water adsorbed on a support surface.[9]

The oxidation was also performed in various aprotic solvents (carbon tetrachloride, chloroform, dichloromethane, benzene, and ethyl acetate). In carbon tetrachloride, chromium(VI) trioxide exhibited comparable reactivity to that in hexane, and similar selectivity of a ketone was observed. However, the reaction was rather slow in the other solvents. For example, when cyclododecanol (**3**) was oxidized with a CrO_3-"wet"-alumina system at 303 K for 15 h ($[CrO_3]/[\mathbf{3}]=1.5$), the conversions of **3** were 98, 94, 15, 49, 58, and 58% in hexane, carbon tetrachloride, chloroform, dichloromethane, benzene, and ethyl acetate, respectively. Using acetone and 1,4-dioxane as a solvent should be avoided; it was proved that contact of a mixture of chromium(VI) trioxide and "wet"-alumina with these solvents caused immediate ignition. Thus, hexane was our solvent of choice based on the experimentally determined reasonable reactivity of chromium(VI) trioxide in the solvent as well as its low cost and toxicity as compared with chlorinated hydrocarbons, which are frequently used in conventional oxidations with chromium(VI)-based reagents;[10] additionally, its high volatility leads to a facile product isolation.

The oxidation of a variety of alicyclic and aliphatic secondary alcohols with chromium(VI) trioxide was examined in hexane. The alcohols underwent smooth oxidation under mild conditions in the presence of "wet"-alumina. Reaction conditions were chosen on the basis

Table 1. Oxidation of Aliphatic and Alicyclic Secondary Alcohols with Chromium(VI) Trioxide in Hexane in the Presence of "Wet"-Alumina[a)]

Entry No.	Alcohols	$[CrO_3]/[Alcohol]$ Mole ratio	Temp K	Ketones[b)] %
1	2-Hexanol	1.5	313	95
2	2-Heptanol	1.5	313	91
3	2-Octanol	1.5	313	97
4	2-Decanol	1.5	313	99
5	Cyclopentanol	2.0	313	91
6	Cyclohexanol	2.0	313	97
7	Cycloheptanol	1.5	313	90
8	Cyclooctanol	1.5	313	93
9	Cyclododecanol (**3**)	1.5	303	96
10	2-Methylcyclohexanol	2.0	323	90
11	3-Methylcyclohexanol	1.5	323	89
12	4-Methylcyclohexanol (**1**)	1.5	323	87
13	2-Ethylcyclohexanol (**4**)	1.5	323	89
14	4-Ethylcyclohexanol	1.5	323	87
15	2-*t*-Butylcyclohexanol	1.5	313	95
16	4-*t*-Butylcyclohexanol	1.5	313	92
17	2-Cyclohexylcyclohexanol	2.0	313	89
18	4-Cyclohexylcyclohexanol	2.0	313	98
19	2,6-Dimethylcyclohexanol	1.5	323	92

a) Under argon for 15 h; 0.5 g of alcohol, 10 cm^3 of hexane, and 2.4 g of "wet"-alumina were used in every run.
b) Isolated yield.

of reactivity of the alcohols and selectivity of the ketones. When equimolar with an alcohol or a slightly larger amount of CrO_3 was used, the ketones were contaminated with the parent alcohols in some cases; e.g., upon oxidation of 2-ethylcyclohexanol (**4**) at 323 K for 15 h ($[CrO_3]/[\mathbf{4}]=1.2$), 21% of **4** was unreacted, whereas **4** was completely consumed under the conditions of Entry 13 in Table 1. Consequently, the oxidations were carried out by using 1.5—2.0 moles of chromium(VI) trioxide per mole of an alcohol in order to complete the reaction. The results are summarized in Table 1. The influence of carbon-chain length of 2-alkanols (Entries 1—4), ring size of simple cycloalkanols (Entries 5—9), and bulkiness or position of an alkyl substituent on the cyclohexane ring (Entries 10—19) was investigated; interestingly, however, there was no appreciable difference in the yield of the ketones. Thus, the CrO_3–"wet"-alumina system was proven to be applicable to a wide variety of secondary alcohols.

Oxidation of 1-alkanols, hexanol (**5a**), heptanol (**5b**), and octanol (**5c**), was also examined, giving a mixture of the corresponding aldehydes (**6a**—**c**) and the esters (**7a**—**c**). The selectivity of **6** and **7** was found to be dependent on the concentration of chromium(VI) trioxide.

$$\underset{\mathbf{5}}{3\,RCH_2OH} \longrightarrow \underset{\mathbf{6}}{RCHO} + \underset{\mathbf{7}}{RCOOCH_2R}$$

For instance, the oxidation of hexanol at room temperature for 15 h ($[CrO_3]/[\mathbf{5a}]=1.2$, 2.0, and 3.0) gave 42, 45, and 43% of **6a** and 11, 19, and 53% of **7a**, respectively (by GLC); in the former two cases, 36 and 9% of **5a** was recovered, respectively. The oxidation of **5b,c** at room temperature for 15 h ($[CrO_3]/[\mathbf{5}]=3.0$) gave **6b,c** in 47 and 61% yields, and **7b,c** in 48 and 33% yields, respectively. It was found that there was no remarkable difference in the reactivity of 1-alkanols and the 2-analogs. For example, the conversions of **5a** and 2-hexanol, and **5c** and 2-octanol were 98, 100, 98, and 100%, respectively, at 323 K for 15 h ($[CrO_3]/[Alcohol]=1.5$).

It was of considerable interest to extend the scope of the reaction to a chemoselective oxidation of the hydroxy group in a multifunctional substrate. Thus, the oxidation of the allylic alcohols was investigated. The oxidation of geraniol and its *cis*-isomer, nerol, at room temperature for 15 h ($[CrO_3]/[Alcohol]=3.0$) gave the corresponding aldehydes in 73 and 74% isolated yields, respectively. It is worth noting that the oxidation proceeded without an appreciable loss of the double bond stereochemistry. However, we felt that the results were not adequate enough to deserve a term of "synthetically useful tool" for the allylic oxidation. In addition, oxidation of cinnamyl alcohol was complicated by concurrent double bond cleavage, giving cinnamaldehyde and benzaldehyde both in only moderate yields. Accordingly, a further study is now being undertaken to determine favorable conditions for the chemoselective oxidation of various multifunctional alcohols.

Summing up, oxidation of aliphatic and alicyclic secondary alcohols by means of a combination of chromium(VI) trioxide and "wet"-alumina in hexane gave the corresponding ketones in excellent to almost-quantitative yields. It should be emphasized that the present reaction is fairly clean, and is performable not only instantly, but readily without suffering from the formation of the intractably tarry precipitate of a reduced chromium salt, which allows easy removal of the salt and also easy isolation of a ketone from the reaction mixture as exemplified by the procedures using alumina-supported chromium(VI) reagents. Thus, this system can be added to a list of efficient and mild oxidants, owing to its easy accessibility, manipulative simplicity, and versatility.

Experimental

^{1}H NMR spectra were measured with a JEOL PMX-60 model spectrometer for solutions in deuteriochloroform or carbon tetrachloride. IR spectra were recorded for thin films or KBr disks on a JASCO A-100 spectrophotometer. GLC was performed on a Shimadzu GC-6A instrument with a 2 m column packed with 5% PEG-20M on Chromosorb GAW-DMCS, with temperature programming. Atomic absorption analyses were carried out on a Hitachi 170-30 model apparatus.

Starting Materials. Commercial chromium(VI) trioxide was dried in vacuo and finely ground. All of the alcohols were also commercially available and were purified by distillation or recrystallization just before use. Solvents were rigorously dried and distilled. "Wet"-alumina was prepared by adding distilled water (2 g) to commercial chromatographic superdried alumina (ICN BIOMEDICALS, Super I; 10 g) in portions, followed by vigorous shaking of the mixture for a few minutes until a free-flowing powder was obtained.

General Oxidation Procedures. The following procedures are representative. To a heterogeneous mixture of "wet"-alumina (2.4 g) and hexane (10 cm^3) in a round-bottomed flask was added chromium(VI) trioxide (1.5 moles of an alcohol) in portions with magnetic stirring; the stirring was continued for 10 min and 2-hexanol (0.5 g) was then added in a portion. After flushing with dry argon, the flask was sealed with a glass stopper or a silicon-rubber septum, through which the supernatant was withdrawn by a microsyringe in the course of the reaction. After magnetic stirring at 313 K for 15 h, the whole reaction mixture was transferred onto a Pyrex Buchner funnel with a fritted glass disk, and the residue was thoroughly washed with dry ether. Removing the combined solvent by rotary evaporation in vacuo left 2-hexanone, which had adequate purity (nearly 100% by GLC).

All ketones thus obtained were identified by a comparison of the NMR and IR spectra and GLC retention times with those of authentic samples.

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