

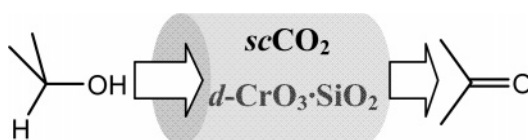
Oxidation of Alcohols to Carbonyl Compounds with $\text{CrO}_3 \cdot \text{SiO}_2$ in Supercritical Carbon Dioxide

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Received October 13, 2005



Supercritical carbon dioxide ($sc\text{CO}_2$) is an effective reaction medium to perform the oxidation of primary and secondary aliphatic alcohols to the corresponding carbonyl compounds with chromium trioxide supported on silica. These reactions were performed by flowing a solution of the alcohol in $sc\text{CO}_2$ through a column containing the supported reagent and recovering the product by depressurization. This method avoids the use of organic solvents and the contamination of the products with chromium species.

Introduction

The oxidation of primary and secondary alcohols (**1**) to aldehydes and ketones (**2**) is a fundamental reaction in organic synthesis.¹ Traditionally, such transformations have been performed with stoichiometric inorganic oxidants, notably, chromium(VI) reagents.² The use of hazardous chromium(VI) species in chemical processes poses serious environmental risks associated with the use of large amounts of chlorinated or aromatic solvents, which have a considerable life-cycle impact, and the processing of waste mixtures of heavy metals and contaminated solvents, which is costly and must be done properly. Contamination of the reaction products with high-valent chromium species prevents the further application of this chemical methodology to the preparation of pharmaceuticals, cosmetics, or food additives. These economic and environmental concerns have prompted intense research to develop greener and more atom-efficient methods that employ clean oxidants to perform this transformation.³ However, chromium(VI) reagents still remain among the most efficient oxidants for performing these reactions and are still widely used in the production of fine chemicals.

Several methods have been proposed to improve the reaction conditions and isolation of the products. A common approach involves the use of chromium(VI) reagents supported on an inert matrix,^{4,5} such as Cr(VI) species supported on silica or alumina,^{4d–q,s,t,x,y} or dichromate supported on polyvinylpyridine (PVPDC).^{5e,f} With these reagents, isolation of the reaction

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product requires filtration of the reaction mixture to separate the reduced chromium reagent and then evaporation of the solvent. However, despite the considerable improvements in the reaction conditions that these methods achieve, they do not avoid the use of organic solvents or contamination of the product with chromium species detached from the solid support under these reaction conditions. Contamination also extends to the equipment used to perform the reactions that, in the case of large-scale preparative work, requires additional cleaning operations.

Supercritical carbon dioxide ($scCO_2$), which has readily accessible critical conditions ($T_c = 31.0\text{ }^\circ\text{C}$, $P_c = 73.8\text{ bar}$), a truly benign character, and low cost, is a frequently discussed alternative reaction medium for chemical synthesis.⁶ Furthermore, there is an existing technology platform for the use of $scCO_2$ in large-scale applications in both the food and nutrition industries. These properties have prompted intense research to further develop the potential of $scCO_2$ as an alternative solvent for green chemistry.

We report here that supercritical carbon dioxide ($scCO_2$) is an effective reaction medium for the oxidation of primary and secondary aliphatic alcohols to the corresponding carbonyl compounds with chromium trioxide supported on silica. The reactions were performed by flowing a solution of the alcohol in $scCO_2$ through a column containing the supported reagent and recovering the product by depressurization. This method avoids the use of organic solvents and contamination of the products with chromium species. Handling of the Cr(VI) reagent under the reaction conditions described here simply involves placing a suitable polypropylene container charged with the supported reagent into the column and removing it once the reaction is complete.

Results and Discussion

The reactions were performed with CrO_3 deposited on silica ($d-CrO_3 \cdot SiO_2$) that had been prepared by adding silica to an aqueous solution of chromium trioxide in water and evaporating the solvent under vacuum.^{4e} The deposition of CrO_3 onto the silica surface yielded an intense orange solid that was dried under vacuum until constant weight and stored at room temperature in a desiccator. The Cr(VI) content of the reagent was determined by redox titration with a 0.1 M aqueous solution of $Fe(NH_4)_2(SO_4)$. The reagent used in the oxidation reactions had a range of 1.0–2.0 mmol CrO_3/g .

On the basis of the extensive data reported for the Phillips catalysts⁷ and given the method of preparation of Cr(VI) on silica and the loading of the reagent, the Cr(VI) anchored on the supported reagent should have mainly a polychromate chain structure bonded to the silanol groups at the silica surface through the terminal chromate units (Figure 1). Upon calcination at temperatures higher than $100\text{ }^\circ\text{C}$, the polychromate chains

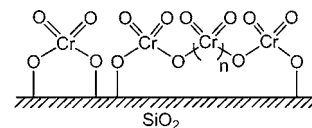


FIGURE 1. Anchoring of chromate on the silica support.

lead to the formation of α -chromia (Cr_2O_3), and the reagent loses its reactivity in the oxidation of alcohols.

Prior to oxidations in $scCO_2$, the supported reagent was assayed under standard reaction conditions^{4e} to compare the results obtained in each case. The reactions were carried out by treating $d-CrO_3 \cdot SiO_2$ with the corresponding alcohol (**1**) with an initial molar ratio of $CrO_3:ROH$ 1:1 and a substrate concentration of 0.2 M, in dichloromethane, at room temperature for 15 min.^{4e} The reaction mixture was filtered, and the solid was thoroughly washed with dichloromethane. In all cases, evaporation of the organic solvent yielded a pale yellow organic residue. Flame absorption atomic spectroscopy (FAAS)⁸ analysis of the reaction products determined the presence of 45–940 ppm (mg/Kg) of chromium in the reaction products, depending on the water content of the organic solvent. In all cases, the recovered solid was dark brown and loose. The results are shown in Table 1.

The supported reagent $d-CrO_3 \cdot SiO_2$ proved to be very effective for performing the oxidation of alcohols to carbonyl compounds (Table 1). The oxidation reactions did not lead to any significant overoxidation of the primary aliphatic alcohols to give the corresponding carboxylic acids. However, this reagent is less effective in the oxidation of unsaturated alcohols such as 5-penten-1-ol (**1g**) or citronellol (**1i**) (runs 7 and 9, Table 1). Oxidation of the acid-sensitive⁹ citronellol (**1i**) was accompanied by acid-catalyzed isomerization giving a mixture of products containing, among others, citronellal (**2i**), isopulegol, isopulegone, and rose oxide.

The oxidation of alcohols with $d-CrO_3 \cdot SiO_2$ in $scCO_2$ was carried out by flowing $scCO_2$ (100 g CO_2/h) at 220 bar and $40\text{ }^\circ\text{C}$ for 4 h through a reservoir containing the substrate (2 mmol) and then through a column packed with the supported reagent (molar ratio of alcohol: CrO_3 1:3 in all cases), both placed in a 250-mL reactor (Figure 2). The system was depressurized through a micrometric valve, and the reaction products were collected in a trap cooled with liquid nitrogen. The procedure is fully described in the Experimental Section. The organic residues that were recovered after the trap was slowly heated to room temperature were colorless, and Zeeman absorption atomic spectroscopy (ZAAS)⁸ analysis of the samples indicated a chromium content of 0.8–1.7 ppb ($\mu\text{g/Kg}$). The solid reagent in the column was dark brown and showed a loose appearance. The results are shown in Table 1.

The oxidation of alcohols **1** with $d-CrO_3 \cdot SiO_2$ in $scCO_2$ was very efficient, and the corresponding carbonyl compounds **2** were obtained in good yields and without any significant contamination with chromium species detached from the supported reagent. Particularly in the case of substrates **1e** and **1f**, which carry electron-withdrawing groups, the reactions were much more efficient in $scCO_2$ than in solution. Although the oxidation was also effective for simple allylic alcohols, the reaction became less efficient for unsaturated alcohols with more distant double bonds. This characteristic can be attributed to adsorption of the substrate on the reagent through Lewis acid–

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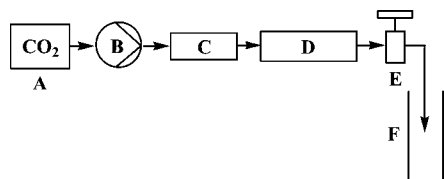
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TABLE 1. Oxidation of Alcohols (**1**) to Carbonyl Compounds (**2**) with $d\text{-CrO}_3\cdot\text{SiO}_2$ in Dichloromethane Solution and in $sc\text{CO}_2$

(1)

Run	Substrate (1)	Conversion (%) ^a	
		CH_2Cl_2^b	$sc\text{CO}_2^c$
1	(1a)	82	94
2	(1b)	75	83
3	(1c)	75	80
4	(1d)	76	77
5	(1e)	25	93
6	(1f)	25	46
7	(1g)	53	50
8	(1h)	93	91
9	(1i)	67 ^d	56 ^e
10	(1j)	88	92
11	(1k)	85	93
12	(1l)	20 ^f	89 ^g

^a Determined by GC analysis of the reaction mixture. Only the corresponding aldehydes or ketones (**2**) were formed, except where indicated. ^b Reactions at rt with an initial molar ratio of ROH:CrO₃ 1:1. ^c Reaction at 40 °C and 220 bar with an initial molar ratio of ROH:CrO₃ 1:3. ^d Citronellal 79%, isopulegol 12%. ^e Citronellal 59%, rose oxide 22%, isopulegone 15%, isopulegol 4%. ^f Phenylacetaldehyde 79%, benzaldehyde 11%. ^g Phenylacetaldehyde 57%, benzaldehyde 43%.

**FIGURE 2.** Schematic view of the apparatus used in the oxidation reactions: (A) CO₂ cylinder; (B) diaphragm pump; (C) substrate reservoir; (D) column charged with $d\text{-CrO}_3\cdot\text{SiO}_2$; (E) micrometric valve; (F) trap.

base association of the π -system with the Cr(VI) species on the silica surface. This interaction would hinder the approach of the hydroxyl group to the reactive metal species to form the chromate ester that is required for the oxidation reaction to take place.¹⁰ Significantly, the incidence of acid-catalyzed processes was higher in $sc\text{CO}_2$ than in dichloromethane solution.

The reaction temperature and initial molar ratio were 40 °C and CrO₃:ROH 3:1 for reactions in $sc\text{CO}_2$. The use of lower

initial molar ratios CrO₃:ROH under these conditions gave lower conversion of the substrates. For instance, the reaction of 1-heptanol (**1a**) in $sc\text{CO}_2$ at 220 bar and 40 °C with $d\text{-CrO}_3\cdot\text{SiO}_2$ with initial molar ratio CrO₃:ROH 2:1 gave only a 50% conversion of the alcohol. It should be noted that contact between the substrate in $sc\text{CO}_2$ solution and the solid-supported oxidant under flow-through conditions is more restricted than in solution. Thus, by considering the density of $sc\text{CO}_2$ under the reaction conditions (0.86 g/mL), the flow of pressurized $sc\text{CO}_2$ solution along the column containing the supported reagent would be roughly 0.85 mL/min, with a residence time within the supported reagent of ca. 2.5 min. Assuming a homogeneous concentration of the substrate (2 mmol) in the total volume of $sc\text{CO}_2$ that flowed during the experiment (203 mL), the concentration of the substrate would be ca. 0.01 M. These data suggest that both the formation of the chromate ester and the rate-determining oxidative elimination¹⁰ take place very efficiently in $sc\text{CO}_2$, being flow-through, and agree with other data¹¹ reported on reactions with supported reagents or catalysts in $sc\text{CO}_2$. This effect of the solvent can be attributed to the gain in free energy of the reactants induced by the low solvation provided by the reaction medium that leads to a lowering of the activation barrier of the reaction,¹² particularly when there is a decrease in the polarity of the reaction system upon going from the reactants to the transition state.

In this context, the results obtained in the oxidation of the acid-sensitive citronellol (**1i**) (run 9, Table 1) also reveal that the interaction of the substrate with acidic positions on the supported reagent is stronger in $sc\text{CO}_2$ than in dichloromethane solution, leading to a higher incidence of products derived from acid-catalyzed isomerization of the distant double bond and cyclization of the reaction intermediates in $sc\text{CO}_2$ than in dichloromethane.

On the other hand, a reaction in solution carried out by flowing 20 mL of a 0.2 M dichloromethane solution of **1a** through a column containing 0.71 g (2 equiv) of $d\text{-CrO}_3\cdot\text{SiO}_2$ suspended in dichloromethane at room temperature led to an 85% conversion of the substrate to give the corresponding aldehyde **2a** (66%) and carboxylic acid (34%). Overoxidation of the alcohol under these conditions can be attributed to the formation of the corresponding hemiacetal by reaction of the aldehyde with unreacted alcohol throughout the column. This process is not significant in $sc\text{CO}_2$, likely as a result of the higher dilution of the substrate in the reaction medium and the faster oxidation under these conditions.

The pressure and the temperature influence the efficiency of the reaction in $sc\text{CO}_2$. Thus, the reaction of 1-heptanol (**1a**) with 2 equiv of $d\text{-CrO}_3\cdot\text{SiO}_2$ at 160 and 220 bar and 40 °C with a flow of 24 g CO₂/h gave heptanal (**2a**) in respective yields of 21% and 53%. This result was not unexpected, since in fixed bed flow reactors an increase in pressure at constant flow and temperature results in a longer residence time of the substrate over the supported reagent. However, by increasing the temperature from 40 to 60 °C at 220 bar, the conversion decreased to 34%, and this could be related to changes in the solubility of the substrate in $sc\text{CO}_2$ or changes in the reactivity of the supported reagent at higher temperatures.

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The oxidation reactions were also examined with other alternative supported reagents, namely, polyvinylpyridine dichromate (PVPDC)^{5e,f} and a silica-supported reagent $g\text{-CrO}_3\cdot\text{SiO}_2$, which was prepared^{4g} by grinding chromium trioxide with silica gel followed by heating at 100 °C for 4 h. These reagents were less efficient than $d\text{-CrO}_3\cdot\text{SiO}_2$ in the oxidation of alcohols under both conventional conditions and in $sc\text{CO}_2$.

Thus, the oxidation of alcohols **1** with PVPDC in *n*-hexane required longer reaction times (30 min to 8 h), a higher initial molar ratio of $\text{Cr}_2\text{O}_7^{2-}:\text{ROH}$ (5:1), and higher temperatures (50–60 °C) to achieve results similar to those reported above. The resin that was recovered after the reaction was complete was dark brown and had a viscous appearance. The oxidation of some representative alcohols with PVPDC in $sc\text{CO}_2$ under continuous-flow conditions failed to achieve any significant conversion of the starting materials.

The reactions with $g\text{-CrO}_3\cdot\text{SiO}_2$ in dichloromethane solution were more efficient than those with PVPDC and required 30–90 min at room temperature to achieve the maximum conversion. Correspondingly, this reagent was less efficient than $d\text{-CrO}_3\cdot\text{SiO}_2$ in the oxidation of representative alcohols in $sc\text{CO}_2$. The solid recovered from the column was dark brown, with a loose appearance in most cases but viscous in the case of unsaturated substrates. Formation of this material on the surface of the reagent proved to be inconvenient for performing the reactions in $sc\text{CO}_2$, since the viscous layer covers the most accessible regions of the reactive surface at the initial stages of the reaction and prevents the flow of $sc\text{CO}_2$ to penetrate into the inner matrix of the support. In fact, the solid that was recovered after the reaction was complete was inhomogeneous, with a viscous dark-brown external surface and an inner part consisting of unreacted material.

Conclusions

Cr(VI) reagents are among the most efficient oxidants for performing the transformation of alcohols (**1**) to carbonyl compounds (**2**) and are still used in large-scale preparative processes despite the environmental hazards associated with both the Cr(VI) species and the organic solvents required for these reactions. We have shown that supercritical carbon dioxide ($sc\text{CO}_2$) is an effective reaction medium for performing the oxidation of primary and secondary aliphatic alcohols **1** to the corresponding carbonyl compounds **2** with chromium trioxide supported on silica ($d\text{-CrO}_3\cdot\text{SiO}_2$) under continuous-flow conditions. This process avoids the use of organic solvents and contamination of the reaction products by chromium species detached from the supported reagent. Handling of the Cr(VI) reagent is reduced to placing a suitable polypropylene container charged with the supported material into the column and removing it once the reaction is complete. This method precludes the negative environmental impact associated with the use of Cr(VI) reagents in the oxidation of alcohols to carbonyl compounds.

Experimental Section

Solvents were purified by standard procedures. Reagents were purified by distillation prior to use. The supported reagent $d\text{-CrO}_3\cdot\text{SiO}_2$ was prepared^{4e} by mixing a solution of 1 g of CrO_3 in 15 mL of ultrapure water with 4 g of chromatography-grade silica gel (Merck 230–240 mesh) and evaporating the solvent under vacuum. The reagent was dried under vacuum until it reached a constant weight and stored in a desiccator. The supported reagent $g\text{-CrO}_3\cdot\text{SiO}_2$ was prepared^{4g} by grinding CrO_3 with SiO_2 , following the reported procedure, drying at 100 °C for 4 h, and storing in a desiccator.

The high-pressure equipment consisted of a 250-mL AISI 316 stainless steel jacketed reactor, with a high-pressure micrometric valve placed at the outlet of the reactor, a diaphragm pump (Orlita MHS 30/8) with a maximum theoretical flow of 8.44 L/h of liquid CO_2 , and a set of HIP high-pressure valves, pressure and temperature probes, and security rupture-disks suitably placed to control the flow of CO_2 along the system.

The FAAS and ZAAS analyses of chromium were performed on Unicam939 AA and Perkin-Elmer 4100ZL atomic spectrometers, respectively. The samples were prepared by evaporating the reaction products under vacuum and treating the dried residue with 5 mL of ultrapure water under sonication for 30 min. The glassware used to recover the reactions products was previously washed with an aqueous solution of EDTA and then with ultrapure water. The blank sample for the reactions in solution was prepared by evaporating dichloromethane and dissolving the residue in ultrapure water under sonication. For reactions in $sc\text{CO}_2$, the blank sample consisted of ultrapure water. The spectrometers were calibrated with standardized aqueous solutions of CrCl_3 prior to the quantitative analysis.

Oxidation of Alcohols **1 with $d\text{-CrO}_3\cdot\text{SiO}_2$ in Solution. General Procedure.** To a suspension of 1 g of $d\text{-CrO}_3\cdot\text{SiO}_2$ (2 mmol) in 10 mL of dichloromethane at room temperature was added the corresponding alcohol **1** (2 mmol) in a single step. After 15 min, the reaction mixture was analyzed by GC and showed complete conversion of the alcohol **1** into the corresponding carbonyl compound **2**. The reaction mixture was filtered, and the solid was washed with dichloromethane. The solution was dried over anhydrous MgSO_4 , and then the solvent was removed under vacuum to yield a pale yellow residue. The reaction products were identified by ^1H and ^{13}C NMR spectroscopy.

Oxidation of Alcohols with $d\text{-CrO}_3\cdot\text{SiO}_2$ in $sc\text{CO}_2$. General Procedure. The alcohol (1 mmol) was placed in a Teflon cylinder covered at the top with a screw cap with two 1/4-28 UNF threaded ports. One of the ports of the reservoir was kept open, and the second was connected through 1/8" Teflon tubing and suitable fittings to a 5-mL Rezorian Luer-lock syringe-tip cartridge (Supelco) charged with 1.5 g of $d\text{-CrO}_3\cdot\text{SiO}_2$ (3 mmol). The assembly was placed within the 250-mL autoclave thermostated at 40 °C, and the outlet of the column was connected through Teflon tubing and a septum to the outlet of the reactor. The outlet of the high-pressure micrometric valve was connected to a trap cooled with a liquid nitrogen bath through 1/8" Teflon-tubing. The pressure in the trap was equilibrated with a flow of nitrogen.

The reactor was closed, charged with CO_2 , and then pressurized to 220 bar. This operation usually required ca. 15 min. The stroke volume of the pump and the aperture of the high-pressure micrometric valve at the outlet of the reactor were regulated to achieve steady continuous-flow conditions at 220 bar. The flow of CO_2 at the outlet of the system was monitored with a bubble flowmeter.

The system was operated for 4 h and then completely depressurized through the micrometric valve. The trap was allowed to warm to room temperature. The colorless residue was dissolved in deuterated chloroform and analyzed by GC, GC-MS, and ^1H and ^{13}C NMR.

Acknowledgment. Financial support from the Spanish Dirección General de Investigación (BQU2003-00315 and BQU2001-3005) and Generalitat Valenciana (Grupos 2001-2003 and GV04B-161) is gratefully acknowledged. A.O. thanks the Spanish Ministerio de Educación y Ciencia for a fellowship. We thank S.C.S.I.E. (UVEG) for access to their instrumental facilities.

Supporting Information Available: Gas chromatograms, conditions, and NMR spectra of the reaction crudes from the oxidation of alcohols **1** with $d\text{-CrO}_3\cdot\text{SiO}_2$ in $sc\text{CO}_2$. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO052137J