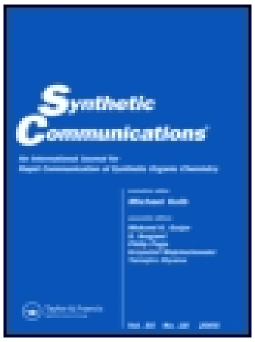

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TETRAMISOLE-CHROMIUM TRIOXIDE COMPLEX: A NEW OXIDANT OF ORGANIC COMPOUNDS[@].

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ABSTRACT: Tetramisole has been found to complex with chromium trioxide. Elemental analysis suggests a 1:1 complex formation and IR data suggest the ligand binding through N-7 nitrogen. The new complex is capable of selectively oxidizing alcohols, including benzyl and allylic alcohol, to carbonyl compounds under mild conditions.

INTRODUCTION

Oxidation is an important process in organic synthesis and a wide range of compounds are actually employed to carry out this reaction[1]. Among these reagents, the ones involving chromium compounds have a special significance[2]. Chromium oxidation continues to be a topic of current interest as evidenced by the continuous development of new techniques and procedures reported in the literature. By complexing chromium trioxide (CrO_3) with various amines for example, a number of new reagents have been produced which are able to bring about selective oxidations.

One of the first amines reported to form useful complex with CrO_3 was pyridine. When CrO_3 is complexed with pyridine using methylene chloride as a solvent (Collins

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Reagent), a useful complex is produced which is able to efficiently oxidize primary and secondary alcohols to aldehydes and ketones respectively[3], and oxidize allylic and benzylic alcohols to unsaturated ketones[4,5]. Similar results have been reported with CrO_3-bipyridine reagent[6]. More recently HMPA (hexamethyphosphoramide) and 3,5-dimethylpyrazole have been shown to complex with CrO_3 and also oxidize alcohols to their corresponding carbonyl derivatives[7,8]. Pyrazole, 3,5-dimethylpyrazole, and benzotriazole complexed with CrO_3 also have been successfully used for the oxidation of allylic and benzylic alcohols[9-11].

In an initial study, we have discovered that tetramisole (± 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole) complexes with CrO_3 in methylene chloride. This complex selectively oxidizes alcohols to aldehydes and ketones. Also, when CrO_3 was added to a solution of tetramisole in methylene chloride in 1:1 stoichiometry, a dark brown colored solution of the complex was obtained which was able to oxidize alcohols including allylic and benzylic alcohols to corresponding carbonyl compounds. We herein report synthesis and characterization of a new chromium (VI) reagent with a sulfur-nitrogen heterocyclic compound, tetramisole, and its use in organic oxidations under mild conditions.

RESULTS AND DISCUSSION

The CrO_3-tetramisole complex was synthesized in high yields by adding dry CrO_3 to a stirring methylene chloride solution of freshly prepared tetramisole base in 1:1 molar ratio. The complex was then precipitated with ether, separated by filtration, and dried. Elemental analysis suggests a 1:1 complex formation between tetramisole and CrO_3. The IR spectrum of the CrO_3-tetramisole complex shows shifts and decrease in intensities of the various vibrational modes as compared with the free ligand. The C=N stretching vibration that appears at 1585 cm^{-1} in the free ligand is shifted to 1552 cm^{-1} in the complex[12]. The bands characterizing CH stretching and bending vibrations from mono substituted phenyl ring as well as the C-S-C stretching vibrations in the region 705 to 570 cm^{-1} were unchanged supporting the tetramisole coordination through N-7 nitrogen[13]. The Cr=O stretching vibrations appear at 1215, 945, and 920 cm^{-1} in the CrO_3-tetramisole complex[14]. Thermogravimetric analysis of the complex shows that the loss of the solvent of crystallization occurs between 37°C and 80°C, loss of the ligand between 142°C and 389°C, and loss of oxygen between 486°C and 550°C leaving behind a chromium residue.

Oxidation of alcohols was carried out with an excess of an isolated reagent dissolved in methylene chloride at 30°C, or in ethylene chloride at 80°C. Alcohols in methylene chloride or ethylene chloride were then added to give a desired molar ratio of the oxidant to alcohol(s). The course of the reaction was followed by gas chromatography over a period of 30 hours. The alcohols and products were identified by comparing the retention times with pure compounds. The percent yield was calculated from area under the peak for starting materials and products. The oxidation reaction proceeds initially at faster rates and then slows down as the substrate concentration decreases. The oxidation yields could be improved by adding 0.5 equivalents of CrO_3-tetramisole when the reaction rate slows (data not shown). Oxidation occurs at faster rates at high temperature as expected. We also studied the effect of molar ratio of oxidant to substrate on the oxidation yields of various alcohols at 30°C and 80°C (the reflux temperature of ethylene chloride). Table 1 shows the percent yields for the oxidation products of various alcohols under different reaction conditions. In general, the oxidation of saturated alcohols with CrO_3-tetramisole is slow. Less than 10% conversion is obtained at 30°C even with four fold excess of the reagent. The oxidation yields are higher at 80°C and further increase with the higher molar ratios of oxidant to substrate as expected. Up to 60% conversion could be obtained with six fold excess of the reagent over alcohol at 80°C. In the case of cyclic saturated secondary alcohols, conversion is slightly higher than the corresponding open chain compound. 2-cyclohexen-1-ol with one unsaturated

Table 1. Oxidation of Alcohols with CrO_3-tetramisole Complex.

Substrate	Product	Temp.(^{0}C)	Time (h)	Ratio^a	%Yield^b
Hexanol	hexanal	30^c	24	1:2	1.02
				1:3	2.20
				1:4	3.50
		80^d	24	1:1	9.00
				1:3	38.80
				1:5	49.10
				1:6	58.90
Cyclo-hexanol	cyclo-hexanone	30^c	24	1:2	4.79
				1:3	6.50
				1:4	9.74
		80^d	24	1:1	16.80
				1:3	48.70
				1:5	64.00
				1:6	67.30
2-Cyclo-hexen-1-ol	2-cyclo-hexen-1-one	30^c	14	1:2	61.90
				1:3	70.10
				1:4	81:30
		80^d	9	1:1	56.20
				1:2	74.00
				1:3	88.00
				1:4	90.10
Cyclo-hexyl-methanol	cyclo-hexyl-aldehyde	30^c	24	1:2	3.90
				1:3	5.50
				1:4	6.60
				1:6	7.20
		80^d	24	1:1	12.30
				1:3	29.80
				1:5	47.00
				1:6	60.00
Octanol	octanal	30^c	24	1:2	0.70
				1:3	1.90
				1:4	3.20
		80^d	24	1:1	10.12
				1:3	34.80
				1:5	54.50
				1:6	60.0
Cyclo-octanol	cyclo-octanone	30^c	24	1:2	1.45
				1:3	2.10
				1:4	3.52

Continued

Table 1 continued.

Substrate	Product	Temp.(^{0}C)	Time (h)	Ratio[a]	%Yield[b]
Cyclo-octanol	cyclo-octanone	80[d]	24	1:1	7.30
				1:3	35.35
				1:5	42.20
				1:6	43.20
Benzyl-alcohol	benz-aldehyde	30[c]	11	1:2	64.00
				1:3	72.00
				1:4	83.00
		80[d]	6	1:1.5	53.30
				1:2	78.20
				1:3	90.30
Cinnamyl alcohol	cinnam-aldehyde	30[c]	8	1:2	64.40
				1:3	80.30
				1:4	87.33
		80[d]	2.66	1:1	46.80
				1:2	83.50
				1:3	91.50

a ratio of substrate to oxidant b product yield as determined by GLC
c methylene chloride as solvent d ethylene chloride as solvent

double bond undergoes rapid conversion to 2-cyclohexen-1-one than the corresponding saturated cyclic as well as open chain analog. This could be attributed to the fact that α,β unsaturated carbonyl compounds are thermodynamically stable than alcohols.

Benzyl alcohol is very rapidly converted to benzaldehyde. With four fold excess of the reagent 83% conversion is obtained at 30^{0}C in eleven hours, while at 80^{0}C and with three fold excess of the reagent ~ 90% of benzaldehyde was obtained in just six hours. The faster conversion and higher yields of benzaldehyde could be due to the activation by aromatic ring because the corresponding saturated compound, cyclohexylmethanol, behaves much like the other saturated open chain and cyclic alcohols (Table 1). Cinnamyl alcohol with one benzene ring and one unsaturated double bond is oxidized at much faster rate. Close to 90 percent of cinnamldehyde is obtained in eight hours at 30^{0}C with four fold excess of the reagent, and ~ 92% at 80^{0}C in less than three hours with only three fold excess of the CrO_3-tetramisole. The effect of benzene ring and the aliphatic double bond on the oxidation of cinnamyl alcohol is additive.

Table 2. Oxidation of Mixture of Alcohols with CrO_3-tetramisole.

Substrate	Product	Temp.(^{0}C)	Time (h)	Ratio^a	%Yield^b
Hexanol+	hexanal+	30^c	28	1:1:3	2.20
Cyclohexanol	cyclohexanone				6.60
		80^d	28	1:1:3	39.30
					52.00
Cyclohexanol+	cyclohexanone+	30^c	9	1:1:3	5.30
2-cyclo-	2-cyclo-				65.30
hexen-1-ol	hexen-1-one				
		80^d	9	1:1:3	41.2
					88.00
Cyclohexyl-	cyclohexyl-	30^c	6	1:1:3	3.40
Methanol+	aldehyde+				64.50
Benzyl alcohol	benzaldehyde				
		80^d	6	1:1:3	21.20
					90.30
2-Cyclohexen-	2-cyclohexen-	30^c	2	1:1:1:3	36.00
1-ol+	1-one+				
Benzyl alcohol+	benzaldehyde+				40.50
Cinnamyl alcohol	cinnamaldehyde				45.90
		80^d	2	1:1:1:3	51.33
					64.10
					91.00

a ratio of substrate to oxidant
b product yield as determined by GLC
c methylene chloride as solvent
d ethylene chloride as solvent

In order to see if there is any synergistic effect on the oxidation of alcohols with CrO_3-tetramisole complex, oxidation of mixture of alcohols was also studied (Table 2). The alcohols in the mixture are oxidized at rates similar to those when oxidized individually. The effect of unsaturation and structure of the final products are also seen in the case of oxidation of mixture of alcohols. The order of reactivity of alcohols from the above results can be written as follows: Cinnamyl alcohol > benzyl alcohol > 2-cyclohexen-1-ol > cyclohexanol ≈ octanol ≥ cyclooctanol.

Oxidation of alcohols could also be carried out by preparing the CrO_3-tetramisole reagent *in-situ*, before the addition of substrate(s). The oxidation yields with the reagent prepared *in-situ* are comparable to with those when the isolated reagent was used for the oxidation of alcohols (data not shown). We also isolated cinnamaldehyde from the oxidation reaction of cinnamyl alcohol by CrO_3.tetramisole in 1:3 molar ratio at 80°C by distillation, at the end of the reaction (~3 hours). The conversion was 94%, which is very close to the GC results (~92%), and the product was also of high (96%) purity.

It is important to note that the acids were not detected in any of the investigated oxidation reactions. In order to confirm this, pure benzaldehyde was refluxed with excess of the reagent in ethylene chloride under nitrogen. GC analysis established that the CrO_3-tetramisole complex does not oxidize benzaldehyde any further. Furthermore, hydroxylation and/or epoxidation products were also not detected in the oxidation of unsaturated alcohols. This clearly demonstrates the ability of CrO_3-tetramisole to oxidize alcohols under mild conditions to carbonyl compounds selectively. In summary, we have isolated the first chromium trioxide reagent complexed with a sulfur-nitrogen heterocyclic compound, tetramisole, and demonstrated its utility in the selective and mild oxidation of alcohols. The only disadvantage of this reagent is that like other Collins type reagents it must be used in excess over alcohols in order to increase the oxidation yields.

MATERIALS AND METHODS

All reagents and solvents were either of reagent or analytical grade. Solvents were dried by standard methods. GLC analysis was carried out on a Pyunicam model 204 chromatograph fitted with an RSL 300 capillary column (Alltech Associates, 30 meters, 1.2 μm film thickness). Microanalysis was obtained using a Carlo Erba model 1106 elemental analyzer. IR spectra were recorded using a Perkin Elmer model 781 spectrometer in KBr in the range 4000-400 cm^{-1}. Thermogravimetric analysis was carried out under nitrogen atmosphere on a Shimatzu DT-30 recording thermal analyzer up to 600°C at a scan rate of 10°C per minute.

Preparation of CrO_3-tetramisole complex

Freshly prepared tetramisole base[15] (0.01 M) was dissolved in 70 mL dichloromethane and dry CrO_3 (0.01 M) was added to it. The reaction mixture was stirred overnight and concentrated to ~ 20 mL on a rotary evaporator. The compound was precipitated by adding 70 mL diethyl ether. The solid was filtered off immediately, and washed with two portions of 20 mL diethyl ether and dried over anhydrous sodium sulphate. Elemental Analysis: found %C 42.353, H 4.171, N 8.755, S 10.31; calculated (for CrO_3-tetramisole.1/6DCM) %C 42.12, H 3.88, N 8.8, S 10.06.

Oxidation of alcohols

Typically, freshly prepared tetramisole.CrO_3 (0.6 mM) was dissolved in 7 mL methylene chloride at 30°C or in ethylene chloride at 80°C with stirring under nitrogen. Then a solution of alcohol or a mixture of alcohols in 5 mL of the corresponding solvent was added to give the desired molar ratio of oxidant to substrate(s). The course of reaction was monitored by GLC over a period of 30 hours. Authentic samples were used to compare the retention times of reactants and products. The percent yield for the products was calculated from the integrated area under the peaks of alcohols and aldehydes and ketones.

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