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of Reliable Methods
for the Preparation
of Organic Compounds

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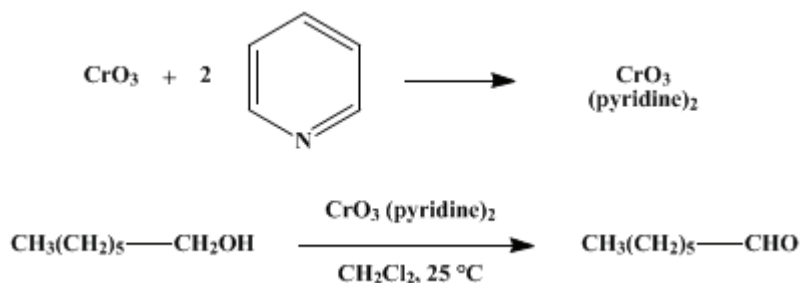
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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ALDEHYDES FROM PRIMARY ALCOHOLS BY OXIDATION WITH CHROMIUM TRIOXIDE: HEPTANAL



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1. Procedure

Caution! The reaction of chromium trioxide with pyridine is extremely exothermic; the preparation should be conducted in a hood, observing the precautions noted.

A. *Dipyridine chromium(VI) oxide* (Note 1). A dry, 1-l., three-necked flask fitted with a sealed mechanical stirrer, a thermometer, and a drying tube, is charged with 500 ml. of anhydrous pyridine (Note 2), which is stirred and cooled to approximately 15° (Note 3) with an ice bath. The drying tube is periodically removed and 68 g. (0.68 mole) of anhydrous chromium(VI) oxide (Note 4) is added in portions through the neck of the flask over a 30-minute period. The chromium trioxide should be added at such a rate that the temperature does not exceed 20° and in such a manner that the oxide mixes rapidly with the pyridine and does not adhere to the side of the flask (Note 5). As the chromium trioxide is added, an intensely yellow, flocculent precipitate separates from the pyridine and the viscosity of the mixture increases. When the addition is complete, the mixture is allowed to warm slowly to room temperature with stirring. Within one hour the viscosity of the mixture decreases and the initially yellow product changes to a deep red, macrocrystalline form that settles to the bottom of the flask when stirring is discontinued. The supernatant pyridine is decanted from the complex and the crystals are washed several times by decantation with 250-ml. portions of anhydrous petroleum ether. The product is collected by filtration on a sintered glass funnel and washed with anhydrous petroleum ether, avoiding contact with the atmosphere as much as possible. The complex is dried at 10 mm. until it is free-flowing, leaving 150–160 g. (85–91%) of dipyridine chromium(VI) oxide³ as red crystals. The product is extremely hygroscopic; contact with moisture converts it rapidly to the yellow dipyridinium dichromate.⁴ It is stored at 0° in a brown bottle (Note 6).

B. *General oxidation procedure for alcohols*. A sufficient quantity of a 5% solution of dipyridine chromium(VI) oxide (Note 1) in anhydrous dichloromethane (Note 7) is prepared to provide a sixfold molar ratio of complex to alcohol, an excess usually required for complete oxidation to the aldehyde. The freshly prepared, pure complex dissolves completely in dichloromethane at 25° at 5% concentration, giving a deep red solution, but solutions usually contain small amounts of brown, insoluble material when prepared from crude complex (Note 8). The alcohol, either pure or as a solution in anhydrous dichloromethane, is added to the red solution in one portion with stirring at room temperature or lower. The oxidation of unhindered primary (and secondary) alcohols proceeds to completion within 5 to 15 minutes at 25° with deposition of brownish-black, polymeric, reduced chromium–pyridine products (Note 9). When deposition of reduced chromium compounds is complete (monitoring the reaction by GC or TLC is helpful), the supernatant liquid is decanted from the (usually tarry) precipitate, which is rinsed thoroughly with dichloromethane (Note 10).

The combined dichloromethane solutions may be washed with dilute hydrochloric acid, sodium

hydrogen carbonate solution, and water, or filtered directly through a filter aid, or passed through a chromatographic column to remove traces of pyridine and chromium salts. The product is obtained by removal of dichloromethane; any pyridine that remains can often be removed under reduced pressure.

C. *Heptanal*. A dry, 1-l. three-necked round-bottomed flask is equipped with a mechanical stirrer, and 650 ml. of anhydrous dichloromethane (Note 7) is added. Stirring is begun and 77.5 g. (0.300 mole) of dipyridine chromium(VI) oxide (Note 1) is added at room temperature, followed by 5.8 g. (0.050 mole) of 1-heptanol (Note 11) in one portion. After stirring for 20 minutes, the supernatant solution is decanted from the insoluble brown gum, which is washed with three 100-ml. portions of ether. The ether and dichloromethane solutions are combined and washed successively with 300 ml. of aqueous 5% sodium hydroxide, 100 ml. of 5% hydrochloric acid (Note 12), two 100-ml. portions of saturated aqueous sodium hydrogen carbonate, and, finally, with 100 ml. of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, and the solvent is removed by distillation. Distillation of the residual oil at reduced pressure through a small Claisen head separates 4.0–4.8 g. (70–84%) of heptanal, b.p. 80–84° (65 mm.), n_D^{25} 1.4094 (Note 13).

2. Notes

1. Dipyridine chromium(VI) oxide is available from Eastman Organic Chemicals. To be an effective reagent, it must be anhydrous. It should form a red solution on dissolution in anhydrous dichloromethane.
2. Commercial reagent grade pyridine was used. The checkers used material available from Allied Chemical Corporation, B and A grade.
3. To avoid the accumulation of excess, unchanged chromium trioxide and rapid temperature rise when it does react, *the initial temperature of the pyridine should never be below 10°*.
4. Reagent grade chromium(VI) oxide was dried over phosphorus pentoxide. The checkers used material available from Allied Chemical Corporation, B and A grade.
5. A glassine paper cone or glass funnel inserted in the drying tube neck of the flask during additions proved satisfactory, provided the cone or funnel was replaced frequently. The paper must be discarded carefully, since it may inflame. Adding the chromium trioxide from a flask through rubber tubing proved dangerous because it caused local excesses of the oxide below and in the neck of the flask. Pyridine added to chromium trioxide spontaneously ignites causing spot fires that extinguish themselves rapidly if the pyridine temperature is below 20° and stirring is efficient. Such fires should and can be avoided.
6. Since the complex itself loses pyridine under reduced pressure and darkens with surface decomposition, it should not be stored under vacuum or over acidic drying agents. Minimal exposure to the atmosphere is required to prevent hydration of the complex. The checkers found that a free-flowing product was obtained on drying for one hour.
7. Commercial dichloromethane was dried by distillation from phosphorus pentoxide. The dichloromethane may also be decanted from phosphorus pentoxide prior to use. Small amounts of suspended phosphorus pentoxide do not seem to interfere with the oxidation.
8. If the complex does not dissolve in dichloromethane, forming a red solution, either the complex has been hydrated in handling, or the dichloromethane is not anhydrous.
9. After the alcohol and complex are thoroughly mixed, the mixture may be stirred near its surface to avoid fouling of the stirrer by the thick, chromium-containing reduction product. Alternatively, the mixture may be swirled periodically to collect the reduction product on the side of the flask.
10. The reduced chromium precipitate is soluble in saturated sodium hydrogen carbonate, but no additional aldehyde was obtained on extracting this hydrogen carbonate solution with ether.
11. 1-Heptanol, obtained from Aldrich Chemical Company, Inc., was distilled before use, b.p. 176°.
12. A second washing with 100 ml. of 5% hydrochloric acid will reduce the amount of pyridine present in the final product without significantly decreasing the yield.
13. The product shows a strong band at 1720 cm^{-1} (C=O) in the IR. GC analysis indicated a purity of about 94–98%, with pyridine as the major impurity.

3. Discussion

Chromic acid, in a variety of acidic media, has been used extensively for the oxidation of primary

alcohols to aldehydes but rarely has provided aldehydes in greater than 50% yield.⁵ Chromium trioxide in pyridine was introduced as a unique, nonacidic reagent for alcohol oxidations and has been used extensively to prepare ketones,⁶ but has been applied with only limited success to the preparation of aldehydes. While 2-methoxybenzaldehyde was obtained in 89% yield, 4-nitrobenzaldehyde and heptanal were obtained in 28% and 10% yields, respectively.⁷

Using the preformed dipyridine chromium(VI) oxide in dichloromethane, the rate of chromate ester formation and decay to the aldehyde⁸ is enhanced at least twentyfold over the rate observed in pyridine solution.⁴ Isolation of products is facile, and aldehydes appear to be relatively stable to excess reagent. The reagent has been used extensively to prepare acid-sensitive aldehydes, particularly intermediates in the total synthesis of prostaglandins⁹ and steroids.¹⁰ An 85% yield was reported for the conversion of 2-vinylcyclopropylcarbinol to the aldehyde.¹¹ Although excess reagent is required for the oxidations (usually sixfold), the reaction conditions are so mild and isolation of products so easy that the complex will undoubtedly find broad use as a specialty reagent. Isolation of the complex can be avoided by *in situ* preparation of the chromium oxide/pyridine complex.¹²

Other general syntheses of aldehydes from primary alcohols involve the use of dimethyl sulfoxide¹³ with a dehydrating agent such as dicyclohexylcarbodiimide and phosphoric acid (or pyridinium trifluoroacetate),¹⁴ diethylcarbodiimide,¹⁵ or sulfur trioxide.¹⁶ Alternatively, dimethyl sulfoxide has been used with derivatives of the alcohol such as the chloroformate,¹⁷ the iodide,¹⁸ and the tosylate.¹⁹ Tertiary butyl chromate²⁰ and lead tetraacetate in pyridine²¹ have been employed to oxidize aliphatic primary alcohols to aldehydes, while manganese dioxide²² has been used to prepare aromatic and α,β -unsaturated aldehydes. More recently, pyridinium chlorochromate, pyridinium dichromate and chromium trioxide-3,5-dimethylpyrazole complex have been reported²³ to be effective reagents for the oxidation of primary alcohols to aldehydes in aprotic solvents.

This preparation is referenced from:

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

petroleum ether

chromium trioxide-3,5-dimethylpyrazole

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

pyridine (110-86-1)

phosphoric acid (7664-38-2)

chromic acid (7738-94-5)

manganese dioxide (1313-13-9)

1-heptanol (111-70-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

chromium trioxide,
chromium(VI) oxide (1333-82-0)

chromium (7440-47-3)

chloroformate

4-nitrobenzaldehyde (555-16-8)

hydrogen carbonate (463-79-6)

chromium oxide (1308-38-9)

dimethyl sulfoxide (67-68-5)

Heptanal (111-71-7)

2-methoxybenzaldehyde (135-02-4)

dicyclohexylcarbodiimide (538-75-0)

pyridinium trifluoroacetate (464-05-1)

pyridinium chlorochromate (26299-14-9)

pyridinium dichromate,
dipyridinium dichromate (20039-37-6)

dipyridine chromium(VI) oxide

2-vinylcyclopropylcarbinol

diethylcarbodiimide

Tertiary butyl chromate

phosphorus pentoxide (1314-56-3)

lead tetraacetate (546-67-8)