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An Improved Oxidation of an Alcohol Using Aqueous Permanganate and Phase-Transfer Catalyst

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Abstract:

The oxidation of a primary alcohol to the corresponding carboxylic acid via permanganate and phase-transfer catalyst has been modified to circumvent impurity formation incurred during the reaction. A safe, simple, and efficient process was developed which gave the required carboxylic acid in 77% isolated yield using sodium permanganate in the presence of tetraethylammonium hydrogen sulphate.

Introduction

During studies on a key intermediate in the manufacture of a development drug, we had to synthesise kilogram quantities of 4,4,5,5,5-pentafluoropentanoic acid (PFPeA). In particular, the product had to be obtained in high purity (>97%). Oxidation of the commercially available 4,4,5,5,5-pentafluoropentanol (PFP) looked particularly attractive (Scheme 1).

Scheme 1. **Formation of pentafluoropentanoic acid from pentafluoropentanol**

$$\underset{\textbf{PFP}}{CF_3CF_2CH_2CH_2CH_2OH} \xrightarrow{MnO_4^-} \underset{\textbf{PFPeA}}{CF_3CF_2CH_2CH_2CO_2H}$$

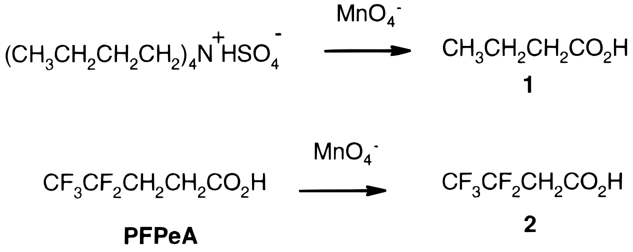
The synthesis of the desired carboxylic acid from the alcohol by chromium trioxide has been reported by Larsson, Carlson, and Leroy,[1] and initially a small quantity of the desired material was made in this way but in poor yield and contaminated by acetic acid. The generation of large quantities of chromium effluent by this process also made it unattractive for scale-up beyond a relatively small scale. Oxidation involving permanganate and phase transfer reagents are high yielding and well documented.[2,3] Of these, the oxidation of fluorinated alcohols to carboxylic acids via permanganate in the presence of tetrabutylammonium hydrogen sulphate as phase-transfer catalyst (PTC) was of particular interest. This has previously been reported by Dmowski and co-workers[4] and looked amenable to scale-up due to the relatively innocuous nature of the manganese dioxide byproduct.

Results and Discussion

The reaction as described by Dmowski et al. was performed in our laboratory.

PFP was added dropwise to an aqueous solution of potassium permanganate and phase-transfer catalyst (PTC) at 60 °C over 4 h. Subsequent analysis of the reaction mixture by GC showed the oxidation to be complete, but NMR analysis of the resulting product showed significant levels of impurities derived primarily from over-oxidation of both the catalyst and the desired PFPeA (Scheme 2).

Scheme 2. **Formation of over-oxidation byproducts**



Our early oxidations of PFP with aqueous potassium permanganate in the presence of tetrabutylammonium hydrogen sulphate revealed the reaction to be highly exothermic with a heat output of ~157 kcal per mole. Addition of aqueous potassium permanganate in aliquots to a mixture of PFP, water, and catalytic quantities of tetrabutylammonium hydrogen sulphate at 65−70 °C gave the required product whilst safely dissipating the heat liberated in the oxidation. However, it became apparent from close scrutiny of the PFPeA produced that significant quantities of butanoic acid (**1**) and pentafluorobutanoic acid (**2**) were being formed.

Reduction of the phase-transfer catalyst from 3.68 to 1.25 mol % lowered the amount of over-oxidised impurity derived from the catalyst (butanoic acid) by 50%. The reaction rate was not affected by the reduced catalyst charge. Further reduction of the PTC charge to 0.8 mol % gave minimal amounts of the butanoic acid whilst still giving a good yield of PFPeA. However, the butanoic acid generated still proved difficult to remove from the product to the desired level (<0.5%w/w).

In an attempt to completely avoid the over-oxidised product derived from the PTC, tetrabutylammonium hydrogen sulphate was replaced with tetraethylammonium hydro gen sulphate. We reasoned that the latter PTC would lead to acetic acid formation, and we were confident that this byproduct would be removed by an aqueous workup procedure. Under these conditions we were successful in producing the desired PFPeA free of acetic acid. Formation of pentafluorobutanoic acid was unavoidable but minimised

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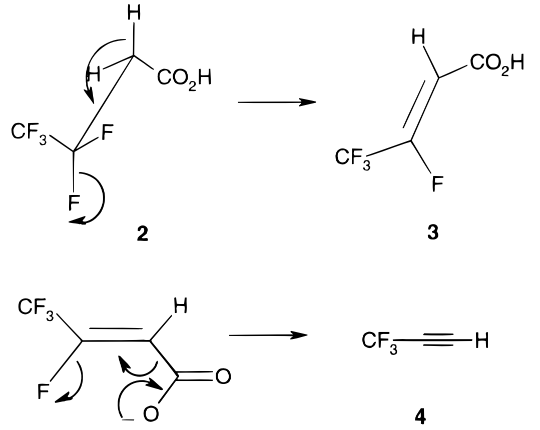
Scheme 3. **Formation of alkene impurity and decarboxylation/elimination mechanism to trifluoromethylpropyne**



by the optimisation of the reaction stoichiometry. Typically, a level of 0.2 to 0.5% w/w of this impurity was observed.

Reducing the permanganate charge from 1.5 to 1.1 or 1.3 equiv generated an additional impurity which, from its ^{1}H NMR spectrum, we tentatively assigned as the *trans*-(*Z*)-alkene (**3**) due to the presence of a large coupling constant ($^3J_{HF}$) of ~30 Hz at δ 6.0. This impurity is formed during the oxidation by elimination of HF from pentafluorobutanoic acid. This impurity disappears on addition of further permanganate (1.4 equiv in total) and we postulate that decarboxylation and elimination occur, giving 1,1,1-trifluoromethylpropyne (**4**) which is lost to the atmosphere (Scheme 3).

Conclusions

We have successfully developed a scale-up process for the preparation of 4,4,5,5,5-pentafluoropentanoic acid (PFPeA) capable of producing kilogram quantities of material in high yield (77% isolated) and quality (>99% purity). Modification of the procedure originally reported by Dmowski et al. has circumvented problems encountered with formation of unwanted, difficult to remove impurities. Safe dissipation of heat was achieved by the controlled addition of oxidant at an elevated temperature, thus giving an instantaneous reaction with the substrate. We believe this process to be generally suitable for the oxidation of alcohols to carboxylic acids on an industrial scale.

Experimental Section

Pentafluoropentanol was supplied by the Asahi Glass company, Japan.

The strength of the sodium permanganate monohydrate used was 97%. The oxidation may be performed using potassium or sodium permanganate; the preparation cited in this paper used sodium permanganate due primarily to its availability within our chemical store. The melting point quoted for the PFPeA was determined by slowly warming the product from 10 °C to melting and noting the range with an alcohol (−70 to 30 °C) thermometer. The determined melting range was confirmed by repeating the procedure with two different thermometers. The evaporation of the solvent was performed by means of a rotary evaporator using house vacuum (20−30 mmHg). Proton, ^{13}C, and ^{19}F NMR spectra were obtained on a JEOL GX 270 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to residual chloroform in deuteriochloroform (7.26 ppm) and signals described as s, singlet, d, doublet, t, triplet, q, quartet, and m, multiplet. The ^{13}C NMR spectral data is reported in parts per million (ppm) downfield from TMS. The ^{19}F chemical shifts are reported relative to fluorotrichloromethane ($CFCl_3$). The purity of the final product was assessed by ^{1}H NMR using TCNB (tetrachloronitrobenzene) as an internal standard. The oxidation of the alcohol to the acid was monitored using a Hewlett-Packard HP5890 gas chromatograph with a 30 m × 0.32 mm i.d. DB-624 column set to ramp from 40 to 90 °C at 2 °C/minute and at 25 °C/minute to 250 °C.

Large-Scale Preparation of 4,4,5,5,5-Pentafluoropentanoic Acid. 4,4,5,5,5-Pentafluoropentanol (1.8 kg, 10.1 mol), tetraethylammonium hydrogen sulphate (18.1 g, 0.08 mole), and water (10.8 L) were added to a 50 L QVF vessel and heated with stirring to 70 °C. Sodium permanganate monohydrate (2.33 kg, 14.14 mol) was dissolved at 20 °C in water (10.8 L) and transferred to a measure vessel. Aqueous sodium permanganate was added in aliquots of approximately 10% to the stirred aqueous solution of pentafluoropentanol and tetraethylammonium hydrogen sulphate maintaining a temperature of 65−75 °C by the additions of permanganate. The total time taken to add the aqueous permanganate was 2 h 30 min. The reaction was stirred at 70 °C for a further 4 h when GC analysis showed conversion of pentafluoropentanol to pentafluoropentanoic acid to be complete. The reaction mixture was allowed to cool to ambient temperature overnight and screened through Celite filter aid (500 g) to remove precipitated manganese dioxide. The isolated manganese dioxide was washed with hot water (60 °C, 18 L). The combined aqueous layers were extracted with methyl *tert*-butyl ether (5.4 L), and the upper organic layer was discarded. The aqueous layer was acidified with concentrated sulphuric acid (320 mL) to pH 1. The *lower* organic layer which separated was retained. The aqueous layer was extracted with further methyl *tert*-butyl ether (2 × 5.4 L), and the upper organic layers were combined with the initial, lower organic layer. The combined organic layers were washed with water (5.4 L) and dried with anhydrous sodium sulphate. The organic solvent was removed *in vacuo* at 50 °C and the residue distilled to give a pale-pink, low-melting solid (1.49 kg, 77%): mp 23−25 °C, bp 84 °C at 60 mmHg; purity by ^{1}H NMR using TCNB as internal standard was >99%; ^{1}H NMR ($CDCl_3$) δ 2.31−2.55 (m, 2H, $CF_3CF_2\underline{CH_2}CH_2CO_2H$), δ 2.70 (t, 2H, $CF_3CF_2CH_2\underline{CH_2}CO_2H$), δ 10.50 (br s, 1H, OH); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ 25.7 (s, 1C), δ 26.1 (t, 1C), δ 115.5 (q of t, 1C (CF_2)), δ 119.0 (t of q, 1C (CF_3)), δ 178.0 (s, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −86 (s, 3F), δ −119 (t, 2F). IR (neat) 3600−2330, 1720, 1295, 1195 cm^{-1}.

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