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Selective free-radical dechlorination of 1,1-dichloro-2,2,2-trifluoroethyl difluoromethyl ether initiated thermally or by UV light: A practical and 'green' method for isoflurane synthesis [1]

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Abstract

Treatment of 1,1-dichloro-2,2,2-trifluoroethyl difluoromethyl ether (**3**) with 2-propanol followed by either irradiation with UV light or heating with radical initiators gives the inhalational anesthetic isoflurane. Unlike most other common dechlorination methods, monoreduction is the exclusive process and the by-products acetone and HCl are relatively benign. Some comments about the mechanism of the reduction will be presented, along with solutions to problems encountered during scale-up.

Keywords: 1,1-dichloro-2,2,2-trifluoroethyl difluoromethyl ether; Selective free-radical dechlorination; Inhalational anesthetic isoflurane

1. Introduction

The final step in the industrial synthesis of the inhalational anesthetic isoflurane (Forane®, **2**) is photochlorination of 2,2,2-trifluoroethyl difluoromethyl ether (**1**) (Eq. (1)). During this process, a significant amount of 1,1-dichloro-2,2,2-trifluoroethyl difluoromethyl ether (**3**) [1] is produced. Purification of an isoflurane/**3** mixture by monodechlorination of **3** using amines in the presence of transition metals has been reported [2]. Although selective, this process generates waste streams which are harmful to the environment and costly to dispose of. Other possible methods also have serious drawbacks. Zinc [3] or tin hydride [4] reductions are often selective, but large amounts of toxic by-products are produced. Alkali metal reduction [5] is unlikely to be selective due to high reactivity. We have found that treatment of $CF_3CHClOCF_2Cl$ with sodium in protic media yields a mixture of **1** and $CF_3CH_2OCF_2Cl$ [1]. Some success has been found recently with catalytic hydrogenation of **3** [6].

$$\underset{1}{CF_3CH_2OCF_2H} \xrightarrow[h\nu]{Cl_2} \underset{\text{isoflurane,2}}{CF_3CHClOCF_2H} + \underset{3}{CF_3CCl_2OCF_2H} \qquad (1)$$

An ideal candidate would appear to be a photoinitiated reaction using 2-propanol as the reductant [7–17]. The reaction is highly selective, while the by-products hydrogen chloride and acetone are relatively innocuous. Treatment of **3** with excess 2-propanol while irradiating with UV light gives isoflurane selectively [18]; no **1** is detected. Here, we will report some comments about the mechanism of this reaction, along with some solutions to problems encountered during optimization and scale-up. We also find that the reduction can be performed thermally with free-radical initiators; apart from some early reports [19–22], this convenient process has apparently not been exploited in synthesis.

2. Results and discussion

Irradiation through quartz glass of a solution of **3** in 8 equivalents of spectrophotometric grade 2-propanol with a 450 W medium-pressure UV lamp results in smooth and complete conversion to isoflurane, with acetone and HCl being formed as by-products. The presence of HCl is inferred by a drop in the pH (Scheme 1). However, irradiation through Pyrex® glass, which cuts out wavelengths below 280 nm, of this same starting solution results in no reaction. Addition of 0.04 equivalents of acetone to the latter solution followed by further irradiation causes an immediate mild exotherm with concomitant lowering of the pH. The reaction also proceeds when irradiated through Pyrex glass if HPLC

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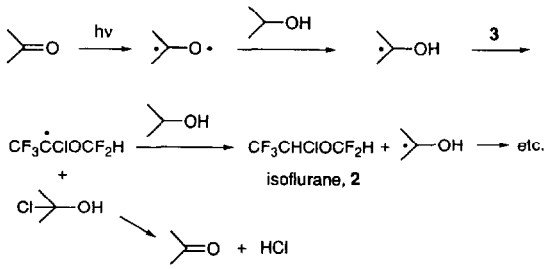

Scheme 1.

grade 2-propanol, which may contain traces of acetone, is used. Benzophenone can be used as initiator instead of acetone, but the reaction rate is slower. A likely interpretation of these results is as follows: In the absence of any chromophore which absorbs above 250 nm (the UV cutoff of **3** in 2-propanol is this value), the initiating process cannot be homolysis of one of **3**'s C–Cl bonds; initial substrate C–X bond homolysis is only possible where low wavelengths of UV light are used or where a UV chromophore is present in the molecule [7,23–26]. In our system, it is likely that the chain reaction begins with photoexcitation of acetone followed by formation of 2-hydroxy-2-propyl radicals from abstraction of the carbinol hydrogen atom of 2-propanol. In the case of the reaction mixture which starts with no acetone, it is assumed that traces of adventitious oxygen, in combination with the low wavelength of UV light used, cause photooxidation of 2-propanol to give a small amount of acetone. The ensuing propagation and termination steps are analagous to the reductions of α-haloesters [27–31]: The 2-hydroxy-2-propyl radical abstracts a chlorine atom from **3**; the resulting substrate radical forms isoflurane and propagates the chain reaction by abstracting the carbinol hydrogen atom from another molecule of 2-propanol. The ultimate fate of the 2-propanol is to be converted to acetone via the unstable intermediate 2-chloro-2-propanol.

To confirm that the reaction is indeed a chain process and also to estimate the economic feasibility, the synthetic quantum yield (Φ') [32] is needed. Φ' is distinguished from the true quantum yield (Φ) by the use of a range of wavelengths in its calculation rather than just one. We are fairly confident that the reduction of **3** occurs by absorption of radiation in the 289–334 nm range. To support this, we find that the reaction rates are similar whether irradiation occurs through quartz or Pyrex, as long as a trace of acetone is present. Wavelengths above 334 nm are not used in the calculation because the reaction mixture is transparent in that region. Using a 450 W Canrad-Hanovia lamp in a Pyrex reactor, Φ' is found to be 6.1 at 95% conversion. This confirms a chain reaction and with subsequent calculations of electrical cost [32] will allow assessment of the economics of the process. If the entire wavelength range of UV light is used in the calculation, then Φ' drops to 1; this highlights the basic problem of industrial photochemistry [32]: Only a small fraction of the energy emitted by a UV lamp causes the reaction of interest. To mitigate this problem, it is useful to know the wavelengths which are absorbed so a lamp with an appropriate output can be selected.

If the supposition is correct that UV light is only needed to generate 2-hydroxy-2-propyl radicals, then in principle transformation of **3** to isoflurane should be possible thermally if the appropriate free-radical initiator is found. Various common initiators have been used to thermally generate the 2-hydroxy-2-propyl radical [19–22,33]. We find that **3** is slowly reduced to isoflurane by excess 2-propanol at reflux using *tert*-butyl peroxide as intiator. A substoichiometric amount of hexamethyditin under the same conditions will also slowly reduce **3** to isoflurane. In this case, the initial propagation step may be chlorine atom abstraction from **3** by the trimethylstannyl radical. The sluggishness of the reaction is probably caused by the relatively low reflux temperature. Use of the higher boiling 3-pentanol as reductant allows clean conversion to isoflurane in less than 20 h at reflux. Despite a report that an azo compound cannot be used for generation of 1-hydroxyalkyl radicals [33], 1,1′-azobis(cyclohexanecarbonitrile) is found to be suitable for initiation of the reduction in 2-propanol or 3-pentanol. Regarding specificity, the thermal reaction parallels the photochemical one: No **1** is detected in any of the thermal reactions. This method could become complementary to the photochemical method of generating carbon-centered radicals using alcohols [27–31].

Attempts were made to initiate the reduction sonochemically [34]. Irradiation of a cold solution of **3** in 2-propanol using either *tert*-butyl peroxide, hexamethylditin, or 1,1′-azobis(cyclohexanecarbonitrile) as initiator resulted in no reaction.

In a typical photoreaction using an immersion lamp, a stream of nitrogen serves the dual purpose of agitating the reaction mixture and maintaining an inert atmosphere. In the case of the reduction of **3**, a nitrogen sweep proves necessary to remove the HCl produced; if the sweep is not used, the mixture begins to colorize and the reduction rate drops dramatically, especially when the **3**:2-propanol ratio is high. However, we find that a nitrogen sweep is impractical in large scale reactions and are unable to prevent significant loss of the volatile product. Addition of 5–10% by weight of water before reaction allows use of a high loading of **3** while still maintaining a high rate of reduction with no nitrogen sweep. It is theorized that acid-catalyzed side-reactions of the acetone are causing formation of radical-quenching by-products; water would moderate the reactivity of HCl. One important consequence of this finding is that, after neutralization of the reaction mixture and distillative isolation of the isoflurane, the remaining 2-propanol can be used in subsequent reductions in the form of its azeotropic mixture with water. Thusfar, we have successfully run the photoinitiated reduction on 23.5 moles (5.15 Kg) of **3** using 5 equivalents of 2-propanol in a 14 L immersion reactor. The reaction requires 20 h for complete conversion and provides isoflurane in 95% yield.

Some preliminary results on the optimization of the reduction are shown in Figs. 1 and 2. In general, the photoinitiated reductions are faster than those which are thermally initiated.

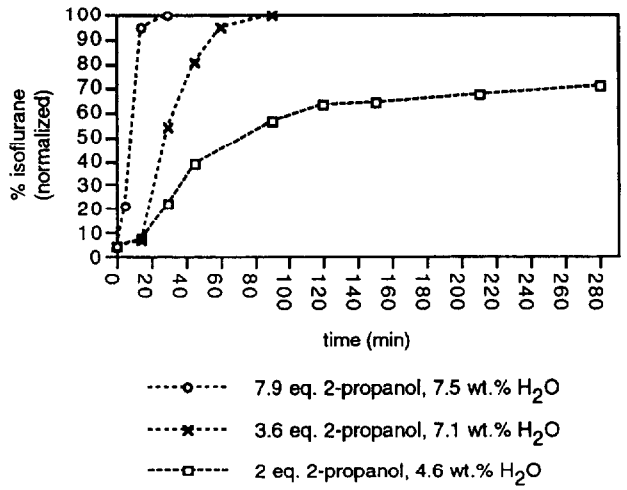

Fig. 1. Photochemical reduction of **3** with 2-Propanol without nitrogen sweep.

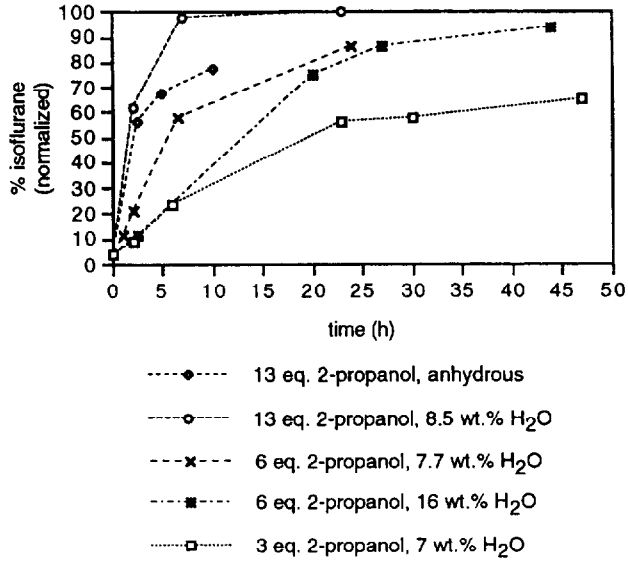

Fig. 2. Thermal reduction of **3** with 2-Propanol (1,1′-azobis(cyclohexanecarbonitrile) initiation).

The thermal reduction is also enhanced by addition of water; the same rationalization for this effect can be made as for the photochemical case (see above). The data also indicate that the photochemical reduction can be performed with less 2-propanol while still maintaining a reasonable rate. Use of 2 molar % rather than 10 molar % of initiator in the thermal reduction was attempted, but the reaction appeared to stop at 50% conversion.

3. Experimental

1,1-Dichloro-2,2,2-trifluoroethyl difluoromethyl ether (**3**) was obtained from the industrial scale fractional distillation of the product mixture resulting from Eq. (1) and typically contained 4% isoflurane. 2-Propanol and acetone were obtained from Fisher Scientific. All other chemicals were obtained from Aldrich Chemical Co.

All photochemical glassware was obtained from Ace Glass. A 450 W medium pressure Canrad-Hanovia UV lamp and a quartz immersion well were used for photoinitiated reactions.

The reduction mixtures were analyzed by ^{1}H and ^{19}F NMR, and GC using the following conditions: column — 1% SP 1000 on 60/80 Carbopack B; program — 100 °C 7 min^{-1}, 4 °C 1 min^{-1}, 175 °C 10 min^{-1}; flow rate — 15 mL min^{-1} He; inj. T — 175 °C; det. T — 250 °C (TCD). Detector response was allowed for in wt.% calculations.

3.1. Determination of synthetic quantum yield (Φ′) of 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane, 2) [32]

In a 100 mL Pyrex circular reaction vessel fitted with a water condenser, a solution of **3** (38.3 g, 0.175 mol), 2-propanol (83.2 g, 1.38 mol), water (9.8 g, 0.54 mol), and acetone (0.40 g, 0.0069 mol) was irradiated for 15 min while passing 5 °C water through both reactor jacket and condenser. The maximum temperature reached was 33 °C. At this point, isoflurane production was 95% complete (1.7 mol kW^{-1} h^{-1} produced) by GC analysis. Between 15 and 30 min, **3** was entirely consumed. Using published data [32] for a 450 W UV lamp, einsteins kW^{-1} h^{-1} in the 289–334 nm wavelength range is 0.28, giving a synthetic quantum yield ($=mol^{-1}$ kW $h^{-1} \div$ einsteins kW^{-1} h^{-1}) of 6.1.

3.2. Large scale photoinitiated production of 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane, 2)

In a 14 L Super Mix reactor fitted with a water condenser, a solution of **3** (5.15 Kg, 23.5 mol), 2-propanol (7.07 Kg, 118 mol), and water (1.31 Kg, 72.6 mol) was irradiated for 20 h. At this point, all of **3** had been converted to isoflurane. The mixture was transferred to a mechanically stirred 22 L flask and cooled to 5 °C while being brought to pH = 8 with 500 mL portions of 15% NaOH solution. After stirring for 3 h, the mixture was distilled using a 3′ × 1″ silver vacuum-jacketed column packed with Goodloe packing. A 5.44 Kg fraction boiling between 62–70 °C contained 76% isoflurane (4.13 Kg, 95% yield), the remainder being acetone which could be removed by addition of water and distillation.

3.3. Thermal production of 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane, 2)

In a 500 mL round-bottomed flask fitted with a water condenser at 5 °C, a solution of **3** (21.9 g, 0.100 mol), 2-propanol (78.5 g, 1.31 mol), water (10 g, 0.56 mol), and 1,1′-azobis(cyclohexanecarbonitrile) (2.44 g, 0.0100 mol) was heated at reflux (74–76 °C) under N_2 for 22.5 h. At this point, all of **3** had been converted to isoflurane. Water (100 mL) was added, and the mixture was distilled using short-path apparatus and a 17 cm Vigreux column. A 19.8 g fraction boiling between 49–76 °C contained 16.9 g (91%

yield) isoflurane, the remainder being 2-propanol and acetone which could be removed by a brine wash.

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