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Journal of Fluorine Chemistry 128 (2007) 1255–1259
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Preparative-scale synthesis of 3,3,3-trifluoropropene oxide

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Received 6 April 2007; received in revised form 22 May 2007; accepted 28 May 2007
Available online 2 June 2007

Abstract

Bromination of 3,3,3-trifluoropropene in 20% oleum, followed by treatment with acetic acid furnishes 2-bromo-3,3,3-trifluoropropyl acetate in quantitative yield, which upon acid hydrolysis and cyclization with alkali affords 3,3,3-trifluoropropene oxide (TFPO) in 63% overall yield.

Keywords: 3,3,3-Trifluoropropene; 3,3,3-Trifluoropropene oxide; Oxirane; Silver acetate; Bromination; Bromoacetoxylation

1. Introduction

Fluorine substitution in organic molecules often influences the biological properties of medicinal compounds [1] and the physical properties of several optoelectronic devices [2]. Hence the development of new synthetic methodologies for the preparation of fluoroorganic molecules has attracted synthetic organic chemists [3]. A large number of chiral and achiral fluorinated building blocks have been recently developed and used for the synthesis of fluorinated molecules [4]. Among them, 3,3,3-trifluoropropene oxide (TFPO, **1**) is a very versatile synthetic intermediate (Scheme 1) that has been extensively utilized in materials and medicinal chemistry [5,6]. For example, a series of *N*,*N*-disubstituted trifluoro-3-amino-2-propanols were readily prepared from the ring-opening reaction of 2-trifluoromethyloxirane with the appropriate *N*-benzylaniline and examined for reversible inhibition of cholesteryl ester transfer protein (CETP) [7]. TFPO is also a precursor for trifluoropropelene carbonate, an electrolyte for lithium batteries and fuel cells [8].

As part of our ongoing projects involving fluoroorganic chemistry for the preparation of fluoroalkyl carbonates as non-aqueous electrolytes, we needed large quantities of TFPO. Following are the details of a preparative-scale synthesis of TFPO under mild conditions.

2. Results and discussion

Reduction of 3-bromo-1,1,1-trifluoroacetone, followed by cyclization [9] and treatment of trifluoroacetaldehyde with diazomethane [10] are procedures available for the preparation of TFPO (Scheme 2). The bromo-acetoxylation of 3,3,3-trifluoropropene (TFP, **2**) using bromine and mercuric acetate, followed by conversion to the epoxide also has been reported (Scheme 2) [11]. The toxicity of the mercuric salts is a drawback for large-scale applications.

The typical procedures for the conversion of olefins to oxiranes, such as treatment with peracids and hydrogen peroxide fail to epoxidize perfluoroalkylethylenes [12]. Attempts to prepare the bromohydrin via hypobromous acid or treatment with bromine and water in the presence of mercuric acetate also failed in the case of perfluoroalkylethylenes [12]. Coudures et al. have examined the preparation of perfluoroalkyl oxiranes from perfluoroalkylethylenes (Scheme 3) [12]. They prepared the oxiranes via the hydrolysis of the corresponding 2-bromo-2-(perfluoroalkyl)ethyl acetate with NaOH, followed by cyclization with *t*-BuOK in tetrahydrofuran. Later, Chaabouni et al. reported the preparation of the same perfluoroalkyl epoxides from the corresponding 2-bromo-2-fluoroalkylethanols using caustic soda in the presence of a phase transfer catalyst (PTC) or using potassium fluoride in triethylene glycol (Scheme 4) [13]. Both of these reports, however, did not examine the preparation of **1**.

Another approach for the synthesis of **1** is via bromoacetoxylation of 3,3,3-trifluoropropene using *N*-bromosuccinimide and acetic acid, followed by treatment with strong alkali

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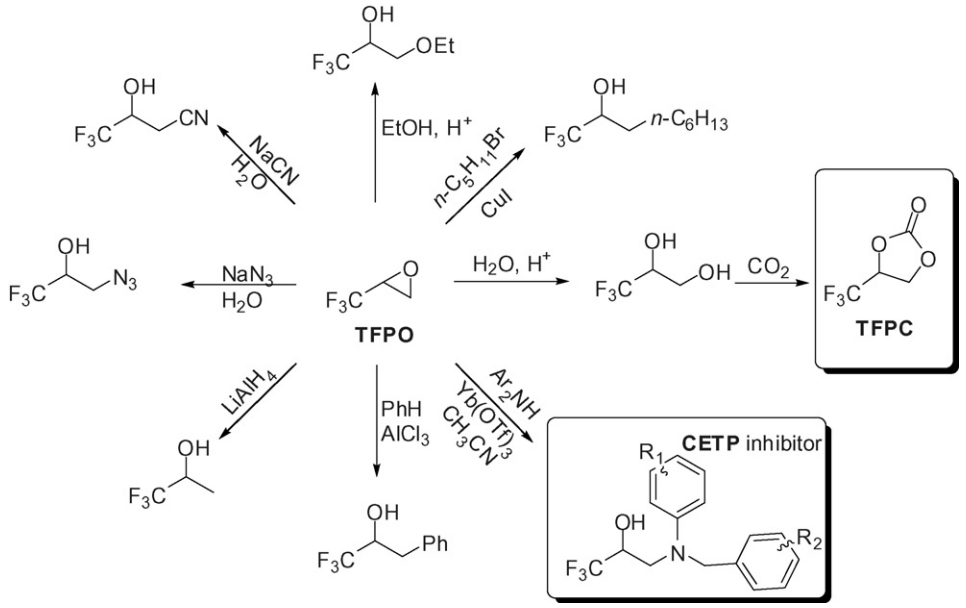
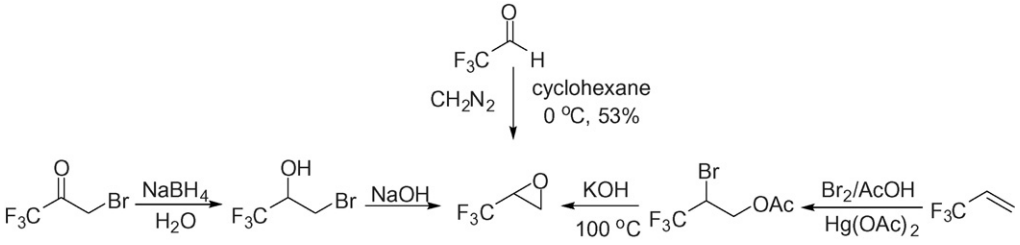
doi:10.1016/j.jfluchem.2007.05.018



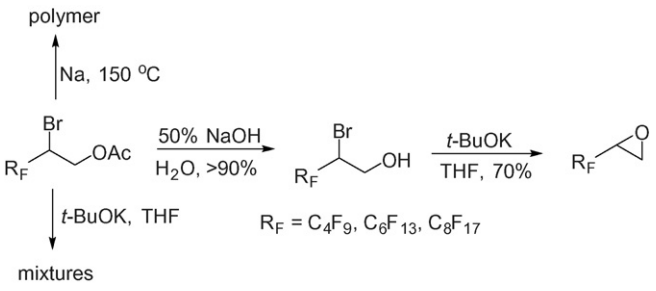
Scheme 1. Synthesis of trifluoromethyl alcohols via the ring-opening of TFPO.



Scheme 2. Procedures for the synthesis TFPO.

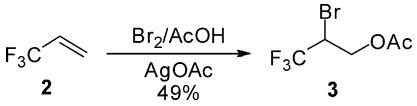
(Scheme 5) [14]. A patent describes the preparation of fluoro-homologs of TFPO via the conversion of fluoroalkenes to halosulfates with bromine/iodine and sulfuric acid, followed by acid hydrolysis to the corresponding halohydrin [15]. The cyclization of the halohydrins to epoxides using a large excess of molten KOH at 140–150 °C is also included in this patent (Scheme 6) [15b].

Optically active TFPO [16] has been prepared by the enzymatic oxidation of 3,3,3-trifluoropropene using *Nocardia carollina* [6c], by the reaction of hexafluoropropylene oxide involving a lengthy procedure [17], asymmetric reduction of 3-bromo-1,1,1-trifluoroacetone [18], and hydrolytic kinetic resolution (HKR) of racemic TFPO catalyzed by chiral (salen)Co(III) complex [19].



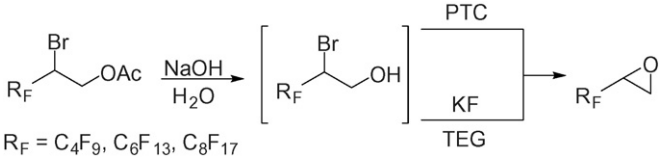
Scheme 3. Reactions of 2-bromo-2-(perfluoroalkyl)ethyl acetate.

Our approach to prepare TFPO was to employ 2-bromo-3,3,3-trifluoropropyl acetate (**3**) for the conversion. Initially, we attempted the bromoacetoxylation of 3,3,3-trifluoropropene (**2**) using a series of metal acetates, such as Cu, Ni, Zn, Mn, Fe, and Ag acetates and bromine with the aim of replacing the toxic mercuric acetate. This study led to the identification of AgOAc as a possible alternative to the toxic $Hg(OAc)_2$ (Eq. (1)). However, the silver salts are not economical for large-scale applications. All other metals acetates failed to provide any meaningful yield of **3**:

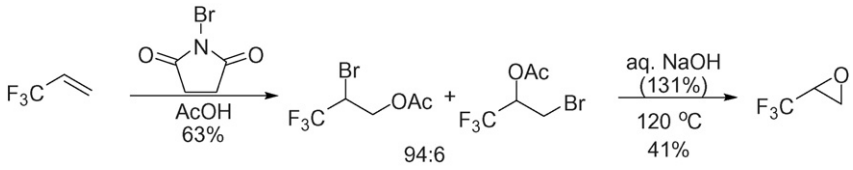


(1)

To develop a cost-effective procedure for the synthesis of 2-bromo-3,3,3-trifluoropropyl acetate, we examined the bromoacetoxylation of trifluoropropene in the presence of



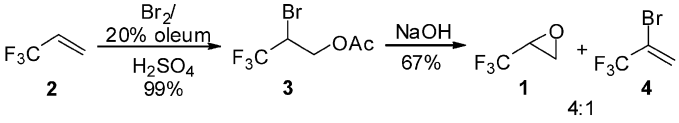
Scheme 4. Preparation of perfluoroalkyl oxiranes from 2-bromo-2-(perfluoroalkyl)ethyl acetate.



Scheme 5. NBS-mediated preparation of 2-bromo-3,3,3-trifluoropropyl acetate and TFPO.

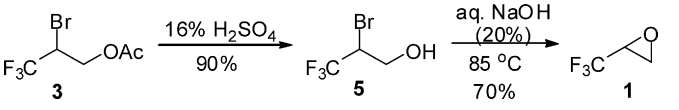
sulfuric acid. Accordingly, the treatment of trifluoropropene with a mixture of bromine and 20% oleum and subsequent acidolysis of the intermediate bromosulfate with acetic acid provided 2-bromo-3,3,3-trifluoropropyl acetate **3** in quantitative (>99%) yield.

We then attempted the direct conversion of **3** to the oxirane as reported. While Coudures and coworkers reported the formation of only the bromohydrin by treatment of **3** with NaOH, Leramontov and coworkers have reported the cyclization with a similar alkali treatment. In our hands, repeated treatment of **3** with 70% aqueous NaOH resulted in a mixture of oxirane **1** and bromo-olefin **4** in a 4:1 ratio (Eq. (2)). The proximity of the boiling points of **1** and **4** made their separation tedious and impractical. Knunyants and coworkers have reported the exclusive formation of **4** in 50% yield from **3** by treatment with aqueous KOH at 100 °C [20].

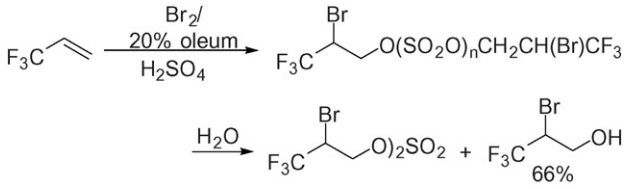


(2)

We then resorted to the synthesis of **1** via the bromohydrin **5**. Having achieved a quantitative yield of **3**, we decided to employ this for the preparation of the bromohydrin. Acid hydrolysis of **3** with 16% aqueous sulfuric acid furnished bromohydrin **5** in 90% yield. Although the conversion of other fluorinated bromohydrins using *t*-BuOK and molten KOH is known [12,15], we were interested in utilizing milder conditions for the cyclization. After examining a variety of experimental conditions, we designed a protocol wherein 20% aqueous NaOH was added to the bromohydrin at 85 °C, with the concurrent isolation of the epoxide **1** exclusively in 70% yield (Eq. (3)). The overall yield of TFPO was 63% from trifluoropropene:



(3)



Scheme 6. Preparation of 2-bromo-3,3,3-trifluoropropyl sulfate.

3. Conclusion

In summary, we have developed a simple, practical and high yielding procedure for the preparation of 3,3,3-trifluoropropene oxide from the olefin. This procedure also affords 2-bromo-3,3,3-trifluoropropyl acetate in quantitative yields and 2-bromo-3,3,3-trifluoropropan-1-ol in 90% yields. The cyclization of the bromohydrin to the oxirane, under very mild conditions, requires only slight excess of NaOH. The simple preparation of these derivatives and TFPO should aid in fluoroorganic synthesis. The preparation of fluoroalkyl carbonates from TFPO will be reported in due course.

4. Experimental

3,3,3-Trifluoropropene was obtained as a gift from Great Lakes Chemical Corporation (Chemtura). All other chemicals were purchased from Aldrich Chemical Co. The ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were plotted on a Varian Gemini-300 spectrometer (300, 75 and 282 MHz, respectively) with a Nalorac-quad probe. ^{1}H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS, δ: 0 ppm) or chloroform ($CHCl_3$, δ: 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ as the internal standard. ^{1}H NMR data are reported as chemical shifts (δ ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and integration. Chromatography was performed on 40–60 μm silica gel (230–400 mesh). Mass spectra were recorded using a Hewlett Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. The chemical ionization gas used was isobutene.

5. Experimental procedure

*5.1. Silver acetate-mediated bromo-acetoxylation of TFP: preparation of 2-bromo-3,3,3-trifluoropropyl acetate (**3**)*

Silver acetate (16.6 g, 100 mmol) was suspended in acetic acid (60 mL) taken in a 100 mL a 3-necked round-bottomed (RB) flask fitted with an addition funnel, a bubbler (TFP inlet tube) and a dry-ice condenser. 3,3,3-Trifluoropropene (9.6 g, 100 mmol) was bubbled through the AgOAc suspension. Bromine (8.0 g) was added simultaneously. When all of the TFP has been added, the solution turned greenish yellow. The reaction mixture was then stirred for 1 h and filtered. The greenish yellow precipitate of AgBr was washed with dichloromethane and washed with 60 mL of water. The

combined filtrate was washed with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to yield 7.0 g (60%) of 2-bromo-3,3,3-trifluoropropyl acetate.

^{1}H NMR ($CDCl_3$, 300 MHz), δ ppm: 2.12 (s, 3H), 4. 34–4.56 (m, 3H). ^{19}F NMR; ($CDCl_3$, 282 MHz), δ ppm: −7.95 (d, J = 6.4 Hz).

5.2. Oleum-mediated bromo-acetoxylation of TFP: preparation of 2-bromo-3,3,3-trifluoropropyl acetate

TFP (96 g, 1.0 mol) was bubbled through a mixture of oleum (800 g) and Br_2 (160 g, 1.0 mol) at RT. The rate of addition of TFP was adjusted such that the temperature of the reaction mixture was maintained within 12–22 °C. The mixture was left stirred for 1 h and poured to 1.6 L of acetic acid and heated with stirring at 100 °C for 1 h. Five hundred milliliters of water was then added at RT and extracted with dichloromethane (3× 500 mL, *Caution*: dichloromethane forms the upper layer). The combined organic layers were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to yield 234 g (99.6%) of 2-bromo-3,3,3-trifluropropyl acetate (**3**) as a colorless liquid. bp 45–47 °C/10 Torr (Ref. [14]: 45–46 °C/10 Torr). ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 4.34–4.56 (m, 3H), 2.12 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ ppm: 170.1, 124.9, 121.3, 53.4, 42.5 (q, J = 32.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$), δ ppm: −7.96 (d, J = 6.4 Hz).

5.3. Alkaline hydrolysis of 2-bromo-3,3,3-trifluoropropyl acetate: attempted preparation of 3,3,3-trifluoropropene oxide

Sodium hydroxide (14 g, 0.35 mol) in water (6 mL) was added to a 100 mL RB flask, fitted with a distillation setup. The solution was heated to 100 °C and 5 g of the acetate **3** was added, slowly, using a syringe, while the product distilled and was collected simultaneously. bp 37–39 °C. Yield: 1.6 g (67%). ^{1}H NMR analysis revealed this to be a mixture of **1** and **4** in 82:18 ratio.

5.4. Preparation of 2-bromo-3,3,3-trifluoropropanol (*5*)

Conc. H_2SO_4 (100 mL) was added to water (1 L) in a 2 L RB flask, fitted with a condenser, followed by the addition of 2-bromo-3,3,3-trifluoropropyl acetate (180 g, 0.77 mol). The immiscible reaction mixture was refluxed for 3 h to make it homogeneous, and was further refluxed for an additional hour, cooled to RT, saturated with NaCl and extracted with ether (5× 200 mL). The combined ether layers were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $NaSO_4$, and evaporated to yield 133 g (0.69 mol, 89.6 %) of **5**. bp 60–63 °C/50 Torr (Ref. [15a]: 60–62 °C/50 Torr).

^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 4.22–4.34 (m, 1H). 4.04–4.14 (m, 1H), 3.90–4.02 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ ppm: 125.1, 121.4, 48.5 (q, J = 31.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$), δ ppm: −7.6 (d, J = 7.4 Hz).

5.5. Preparation of 3,3,3-trifluoropropene oxide (*1*)

The bromohydrin (130 g, 0.67 mol) prepared as above was taken in a 1 L three-necked RB flask fitted with a septum, a thermometer jacket and a distillation set up and heated, while stirring, to 85 °C (oil bath temperature 95 °C). Aqueous NaOH (20%, 200 g) was introduced through the septum via a syringe and the oxirane **1** was distilled out simultaneously as a colorless liquid. bp 39–40 °C (Ref. [9]: 39.1–39.3 °C). Yield: 52.7 g (0.47 mol, 70.2%).

^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 3.38–3.46 (m, 1H), 2.96–3.02 (m, 1H), 2.90–2.94 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ ppm: 124.5, 120.9, 48.3 (q, J = 41.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$), δ ppm: −12.62 (d, J = 6.1 Hz).

Acknowledgement

We gratefully acknowledge Chemtura for financial support and the gift of 3,3,3-trifluoropropene for this research.

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