2,2,2-Trifluoro-1-(1-adamantyl)ethylamine hydrochloride

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Abstract

A convenient synthesis of a hitherto unknown fluorinated analogue of 1-(1-adamantyl)ethylamine (remantadine) starting from readily available 1-bromoadamantane and trifluoroacetic anhydride is described.

Introduction

As an extension of our study of adamantane chemistry [1] and α-trifluoromethyl-substituted amines, amino- and hydroxy-acids [2], we propose a convenient method of preparation of the hitherto unknown trifluoromethyl derivative of an effective virus inhibitor, i.e. 2,2,2-trifluoro-1-(1-adamantyl)ethylamine hydrochloride.

The substitution of hydrogen atoms by fluorine in natural compounds and drugs usually does not significantly change the spatial structure of the molecule but considerably influences its lipophilicity and the acid–base properties of its functional groups [3]. For example, fluorinated amines, such as β,β-difluoroamphetamine, are present *in vivo* as a free base, but unsubstituted amphetamine exists in its protonated form. This causes different assimilation rates and changes in the metabolism of the two compounds [4]. To our knowledge, fluorinated remantadines have not been described previously, though fluorine atoms could cause interesting biological effects.

Experimental

The ^{1}H and ^{19}F NMR spectra were recorded on a Tesla BS-487, 80 MHz instrument, while ^{13}C NMR spectra were taken on a Bruker WM-200 spectrometer at 50.3 MHz. Chemical shifts are expressed in (ppm) downfield from TMS (^{1}H), CF_3COOH (^{19}F) and $CDCl_3$ (^{13}C) as standards.

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The IR spectra were recorded on a UR-10 (Zeiss) spectrometer, while GLC analyses were performed on Chrom-5 (Laboratorny Pristroje, Prague) apparatus equipped with 1 m 5% Apiezon L on inerton-N-super column. Preparative chromatographic separations were performed on Chemapol silica gel (40/100). 1-Bromoadamantane as a crude product was purified on Chemapol 100/250 alumina (m.p., 119.5 °C). 1-Adamantylmagnesium bromide was synthesized as described previously [1]. For acylation experiments, 50 ml of a 0.126 M filtered solution were used. 1-Adamantyllithium was synthesized according to a previously described method [5]. For acylation experiments, 20 ml of a 0.32 M solution were used.

1,1,1,-Trifluoro-2-(1-adamantyl)ethan-2-one (3)

A magnetically stirred suspension of 0.73 g Cu_2Br_2 in10 ml of dry ether under a continuous stream of argon at −20 °C was saturated with 2 g (0.015 M) of trifluoroacetyl acid chloride. The mixture was stirred for 0.5 h and a solution of the organometallic compound (1-AdMgBr or 1-AdLi) was then added dropwise over a period of 1 h. The mixture was stirred for an additional 0.5 h and allowed to warm to room temperature. An excess of hydrochloric acid solution was added, the mixture extracted with ether, the ethereal solution dried over sodium sulphate and concentrated *in vacuo*. The residue was chromatographed on silica gel and the ketone fraction distilled under reduced pressure. Yield, 1.0 g (70%); b.p., 36 °C/0.1 mmHg. IR (CCl_4, ν cm^{-1}): 1740–1745 (C=O). ^1H NMR (CCl_4) δ: 1.7 (6H, s); 1.9 (6H, s); 2.0 (3H, s). ^{19}F NMR ($CDCl_3$ δ: 3.65 ppm (CF_3, s). Analysis: Calcd. for $C_{12}H_{15}F_3O$: F, 24.54%. Found: F, 24.39%.

1,1,1-Trifluoro-2-(1-adamantyl)ethan-2-one oxime (8)

To solution of 2.3 g (0.02 M) hydroxylamine-*O*-sulphonic acid (HASA) in 10 ml water was added a solution of 1.26 g (0.008 M) of ketone **3** in 2 ml of ether; the mixture was stirred under reflux for 10 h and the organic layer was then separated. The aqueous layer was made alkaline with KOH solution and extracted with chloroform. The combined organic layers were dried over sodium sulphate and the solvent evaporated. Yield, 1.1 g (85%). ^1H NMR (CCl_4) δ: *Z*-isomer, 1.25 (12H, s); 1.57 (3H, s); 9.22 (1H, s) ppm: *E*-isomer, 1.42 (12H, s); 1.7 (3H, s); 9.67 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ: *Z*-isomer, 27.48; 36.30; 36.59; 38.93; 119.38 (CF_3, q, ^2J=286 Hz); 152.22 (C=N, q, ^3J=26.2 Hz) ppm: *E*-isomer, 26.04; 36.43; 38.64; 39.44; 121.49 (CF_3, q, ^2J=277.95 Hz); 153.96 (C=N, q, ^3J=26.2 Hz) ppm. Analysis: Calcd. for $C_{12}H_{16}F_3NO$: F, 23.05%. Found: F, 22.94%.

2,2,2-Trifluoro-1-(1-adamantyl)ethylamine (1)

To a suspension of 0.15 g (0.0025 M) $LiAlH_4$ in 4 ml of dry ether was added dropwise under vigorous stirring a solution of 2.5 g (0.01 M) of oxime **8** in 5 ml of dry ether. The mixture was stirred under reflux for 3 h, cooled to room temperature, excess water added and acidified with hydrochloric acid solution to provide a distinct acidic reaction for the aqueous layer.

After separation of the ethereal layer, the aqueous solution was extracted several times with ether to remove neutral substances and made alkaline with an excess of NaOH solution. From the alkaline aqueous solution, the amine **1** was extracted with ether, the ethereal solution was dried over KOH and the solvent evaporated. Yield, 1.4 g (70%). ^{1}H NMR (CCl_4) δ: 1.6 (12H, broad s); 1.9 (3H, broad s); 2.5 (1H, q, J=9 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 10.2 (CF_3, d, J=9 Hz) ppm. Analysis: Calcd. for $C_{12}H_{18}F_3N$: F, 24.43%. Found: F, 24.40%.

2,2,2-Trifluoro-1-(1^1-adamantyl)ethylamine hydrochloride (10)

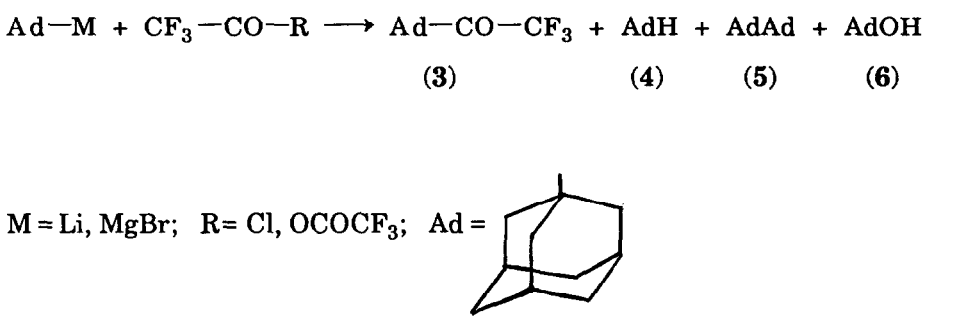
A solution of 1 g amine **1** in ether was added to an excess of ether saturated with dry hydrogen chloride. The white precipitate was collected by filtration and washed with ether. Yield, 1.1 g (95%); m.p., 260–262 °C. Analysis: Calcd. for $C_{12}H_{18}F_3N \cdot HCl$: F, 21.13%. Found: F, 21.07%.

Results and discussion

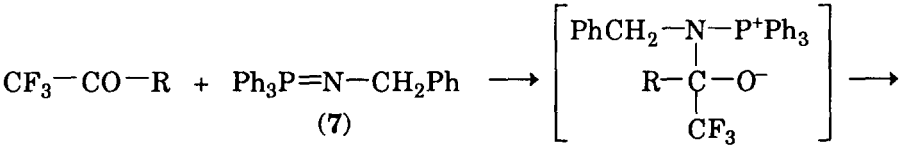
We considered the key compound to be trifluoromethyl-(1-adamantyl)ketone (**3**). Four different approaches were tested for the preparation of **3** starting from 1-adamantyl-lithium or 1-adamantylmagnesium bromide with trifluoroacetyl chloride or anhydride as acetylating agents. The experiments showed that all four reactions gave ketone **3** along with compounds **4–6** in essentially the same yields (Scheme 1).

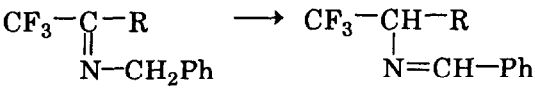
Identification and quantitative determination of the compounds in the reaction mixture was achieved by gas chromatography, using authentic samples of compounds **4–6**. Pure ketone **3** was separated by column chromatography on silica gel in 70–80% yield. The composition and structure of the ketone were confirmed by elemental analysis, IR and ^{19}F NMR spectroscopy.

In our previous paper we described the reductive amination of ketones [2a] by treatment of a carbonyl compound with *N*-benzyltriphenylphosphazene (**7**) and subsequent hydrolysis of the Schiff base formed via a [1, 3]-proton shift (Scheme 2).



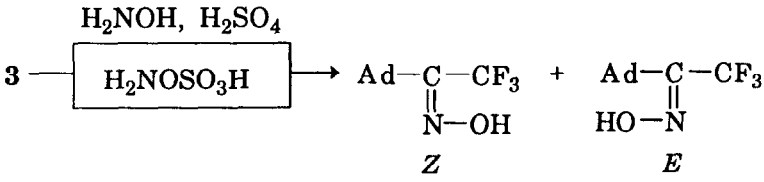
Scheme 1.





R = H, Me, CH_2Ar, Ar, COOMe, CH_2COOMe

Scheme 2.



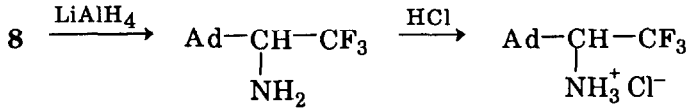
Scheme 3.

Although the reaction of trifluoroacetophenone with phosphazene **7** is exothermic and is conducted under cooling, ketone **3** does not undergo this reaction even at elevated temperatures. Obviously, the bulky adamantyl residue prevented the Staudinger reaction which proceeded via a spatially hindered four-membered transition state (Scheme 2, R=Ad).

Another widely used method of reductive amination which is less sensitive to steric factors involves the corresponding oxime. Yields of oximes from aryl- and alkyl-trifluoromethylketones exceed 70% [6]. Ketone **3** also forms the oxime **8**, but the yield is only 40% (Scheme 3). Complete conversion of ketone **3** under these conditions requires about 30 h refluxing and causes much tar formation. Application of hydroxylamine-*O*-sulphonic acid (HASA) instead of hydroxylamine gave oxime **8** in 85% yield (Scheme 3).

To our knowledge the application of HASA for the preparation of trifluoromethyl ketoximes has not been reported before.

According to GC and ^{13}C NMR spectroscopic data, the oxime **8** was formed as a mixture of *Z*- and *E*-isomers, with the ratio dependent on the method of preparation. The sample of **8** synthesized by means of hydroxylamine sulphate treatment of ketone **3** had a *Z*/*E* ratio of approximately 90:10. This result is in good agreement with the ratio for benzyltrifluoromethyl ketoxime (94:6) [6a]. The *Z*/*E* ratio in the sample of oxime **8** obtained by means of



Scheme 4.

HASA was 60:40. The desired compound **1** was produced by means of $LiAlH_4$ reduction of oxime **8** (Scheme 4).

The structure of **1** was confirmed by the ^1H and ^{19}F NMR spectra which contain a quartet at 2.5 ppm (^1H) and a doublet at 10.2 ppm (^{19}F) with $^3J(HF) = 7.0$ Hz.

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