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Unexpected coupling reaction of (*F*-alkyl)iodides with 1-bromo-1-octyne: access to 1-(*F*-alkyl)-1-octynes

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Abstract

(*F*-Alkyl)iodides react with 1-bromo-1-octyne in the presence of a radical initiator [α,α'-azobis(isobutyronitrile)] to give mainly coupling products, 1-(*F*-alkyl)-1-octynes.

Introduction

Perfluorocarbons, including perfluoro-octyl bromide (PFOB), are chemically and biologically inert and have a high gas solubility. Because of these unique properties, they have been investigated in numerous biomedical applications where oxygen is needed [1]. Moreover, because of its radio-opaque bromine atom, PFOB is being developed as a contrast agent in diagnosis [2]. During our search for more effective contrast agents, we recently reported the remarkable properties of 1-alkyl-2-(*F*-alkyl)iodoethenes, $R_HCI=CHR_F$ (FnHmIE), which gave unexpectedly stable, heat-sterilizable emulsions with prolonged intravascular persistence and a high *in vivo* tolerance [3]. With the aim of further reducing the dose required for obtaining suitable X-ray contrast, we attempted to synthesize more radio-opaque molecules in which the hydrogen atom on the double bond of FnHmIE is substituted by a bromine atom.

Experimental

1-Octyne was purchased from Aldrich and used without further purification. Perfluoroalkyl iodides (gift from Atochem) were purified by washing with an aqueous solution of sodium thiosulphate, followed by light-free distillation and storage under argon in the dark. Gas chromatography was performed on a DELSI instrument (FID detector) fitted with a 3 m × 1/4 in. column packed with 30% SE30 on Chromosorb. All GLC analyses were performed as follows: 150 °C for 5 min, then heating at 5 °C min^{-1} up to 200 °C. Infrared spectra were obtained as films on a Bruker IFS spectrometer. ^{1}H, ^{13}C (internal reference Me_4Si) and ^{19}F (internal reference $CFCl_3$, negative for upfield shifts) NMR spectra, all samples in $CDCl_3$ solution, were recorded on Bruker AC 200 spectrometers. Combined gas–liquid chromatography/mass spectrometry was performed with an R10 Ribermag L10 instrument.

*Synthesis of 1-(*F*-butyl)-1-octyne (3a)*

A mixture consisting of 10 g (0.053 mol) of 1-bromo-1-octyne (**1**) (prepared according to a literature method [4]), 18.3 g (0.053 mol) of perfluorobutyl iodide (**2a**) and 0.43 g (5% equiv.) of α,α'-azobis(isobutyronitrile) (AIBN) was heated at 70 °C for 24 h. Unreacted starting materials were recovered by evaporation under reduced pressure. The crude reaction mixture was diluted with ether and then filtered over silica gel. After concentration and distillation, 3.3 g (19%) of **3a** were recovered.

1-(*F*-Butyl)-1-octyne (**3a**): b.p. 26 °C/0.02 mmHg. Analysis: Calc. (found) for $C_{12}H_{13}F_9$ (328.24): C, 43.91 (43.74); H, 3.99 (3.74) %. IR (cm^{-1}): 2960–2890 (ν_{C-H}); 2260 ($\nu_{C\equiv C}$); 1240–1140 (ν_{C-F}). ^{1}H NMR δ: 2.40 (tt, $J_{H,H}=6$ Hz, $^{5}J_{F,H}=6$ Hz, 2H, $CH_2C\equiv C$); 1.56 (m, 2H, $C\mathit{H}_2CH_2C\equiv C$); 1.32 (6H, $(C\mathit{H}_2)_3CH_3$); 0.91 (3H, CH_3) ppm. ^{19}F NMR δ: −81.6 (3F, CF_3); −99.0 (2F, $CF_2C\equiv C$); −126.1 (2F, $C\mathit{F}_2CF_2C\equiv C$); −128.0 (2F, $C\mathit{F}_2CF_3$) ppm. ^{13}C NMR δ: ($C_4F_9C_h\equiv C_gC_fC_eC_dC_cC_bC_a$): 13.9 ($C_a$); 18.5 ($C_f$); 22.5 ($C_b$); 27.3 ($C_e$); 28.4 ($C_d$); 31.3 ($C_c$); 67.4 (t, C_h, $^{2}J_{C,F}=35.8$ Hz); 95.5 (t, C_g, $^{3}J_{C,F}=6.1$ Hz) ppm.

*Synthesis of 1-(*F*-hexyl)-1-octyne (3b)*

The same process as described for **3a** when applied to a mixture consisting of 10 g of **1**, 23.6 g of per-

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fluorohexyl iodide (**2b**) and 0.43 g of AIBN gave, after distillation, 5 g (22%) of **3b**.

1-(*F*-Hexyl)-1-octyne (**3b**): b.p. 30 °C/0.02 mmHg. Analysis: Calc. (found) for $C_{14}H_{13}F_{13}$ (428.26): C, 39.26 (38.80); H, 3.06 (2.99); F, 57.68 (56.62)%. IR (cm^{-1}): 2940–2865 (ν_{C-H}); 2260 ($\nu_{C\equiv C}$); 1240–1145 (ν_{C-F}). ^1H NMR δ: 2.40 (tt, $J_{H,H}=6$ Hz, $^5J_{F,H}=6$ Hz, 2H, $CH_2C\equiv C$); 1.60 (m, 2H, $CH_2CH_2C\equiv C$); 1.32 (6H, $(CH_2)_3CH_3$); 0.90 (3H, CH_3) ppm. ^{19}F NMR δ: −83.3 (3F, CF_3); −98.7 (2F, $CF_2C\equiv C$); −123.8 (2F, CF_2); −125.2 (4F, $2CF_2$); −128.6 (2F, CF_2CF_3) ppm. ^{13}C NMR δ: ($C_6F_{13}C_h\equiv C_gC_fC_eC_dC_cC_bC_a$): 13.9 ($C_a$); 18.5 ($C_f$); 22.5 ($C_b$); 27.3 ($C_e$); 28.4 ($C_d$); 31.2 ($C_c$); 67.5 (t, C_h, $^2J_{C,F}=35.7$ Hz); 95.4 (t, C_g, $^3J_{C,F}=6.2$ Hz) ppm.

*Synthesis of 1-(*F*-octyl)-1-octyne (3c)*

The same process as described for **3a** when applied to a mixture consisting of 10 g of **1**, 28.9 g of perfluorooctyl iodide (**2c**) and 0.43 g AIBN gave, after distillation, 6.6 g (23%) of **3c**.

1-(*F*-Octyl)-1-octyne (**3c**): b.p. 26 °C/0.02 mmHg. Analysis: Calc. (found) for $C_{16}H_{13}F_{17}$ (528.24): C, 36.38 (35.02); H, 2.48 (2.45) %. IR (cm^{-1}): 2960–2865 (ν_{C-H}); 2260 ($\nu_{C\equiv C}$); 1245–1150 (ν_{C-F}). ^1H NMR δ: 2.36 (tt, $J_{H,H}=6$ Hz, $^5J_{F,H}=6$ Hz, 2H, $CH_2C\equiv C$); 1.56 (2H, $CH_2CH_2C\equiv C$); 1.32 (6H, $(CH_2)_3CH_3$); 0.91 (3H, CH_3) ppm. ^{19}F NMR δ: −83.3 (3F, CF_3); −98.7 (2F, $CF_2C\equiv C$); −123.6 (2F, CF_2); −124.4 (4F, $2CF_2$); −125.1 (4F, $2CF_2$); −128.6 (2F, CF_2CF_3) ppm. ^{13}C NMR δ: ($C_8F_{17}C_h\equiv C_gC_fC_eC_dC_cC_bC_a$): 13.9 ($C_a$); 18.5 ($C_f$); 22.5 ($C_b$); 27.4 ($C_e$); 28.4 ($C_d$); 31.2 ($C_c$); 67.5 (t, C_h, $^2J_{C,F}=35.7$ Hz); 95.4 (t, C_g, $^3J_{C,F}=6.1$ Hz) ppm.

Results and discussion

The most straightforward route to 1-alkyl-2-(*F*-alkyl)-2-bromo-1-iodoethenes should, in principle, consist of the addition of perfluoroalkyl iodides **2** to a terminal bromoalkyne such as **1**. This was attempted, although most of the conditions reported for the addition of *F*-alkyl iodides to double or triple bonds have been developed for terminal unsaturated compounds [5]. Of these methods, we chose to use chemically initiated radical addition [6]. Thus, at 70 °C, the reaction of perfluoroalkyl iodides **2** with 1-bromo-1-octyne (**1**) in the presence of AIBN (5% equiv.) led to 1-(*F*-alkyl)-1-octyne (**3**) as the major product, instead of the desired addition compound. The synthesis of 1-(*F*-alkyl)alkynes **3** has already been reported, either via a two-step procedure (addition of haloperfluorocarbons to alkynes, followed by dehydrohalogenation [7, 8]) or via a coupling reaction using a Grignard reagent or through a Cadiot–Chodkiewicz type reaction [9–12].

$$\underset{(\mathbf{1})}{C_6H_{13}C\equiv CBr} + \underset{(\mathbf{2})}{R_FI} \xrightarrow{\text{AIBN, 70 °C}} \underset{(\mathbf{3})}{C_6H_{13}C\equiv CR_F} + \mathbf{4} + \mathbf{5}$$

(**a**), $R_F=C_4F_9$; (**b**), $R_F=C_6F_{13}$; (**c**), $R_F=C_8F_{17}$

The crude reaction mixture was shown by GLC to be composed essentially of three products. ^{19}F NMR spectroscopy established that, in addition to 55% of **3**, there was also 45% of a mixture of compounds **4** and **5** in a 70:30 ratio. On the basis of the characteristic chemical shifts for CF_2 groups α to the functional group [13], it was assumed that **4** and **5** were two couples of ethylenic compounds: signals appeared at −105.6 and −109.8 ppm (ratio ~ 65:35) and −106.6 and −110.6 ppm (ratio ~ 80:20) for **4** and **5**, respectively. They were identified by GC/MS coupling, using the isotopic ratio of the molecular peak and some typical fragments, as most probably consisting of $R_HCI=CBrR_F$ and $R_FCBr=CBrR_H$. The former compound results from the expected addition reaction, while the latter may result from the abstraction of the bromine atom of **1** by the intermediate radical $R_H\dot{C}=CBrR_F$ formed in the first step of the normal addition process.

Compounds **3** were characterized by IR, ^{19}F, ^1H and ^{13}C NMR spectroscopy, as well as by mass spectroscopy and elemental analysis. All the data agree with those reported in the literature [9, 10]. The IR spectra display typical $\nu_{C\equiv C}$, ν_{C-F} and ν_{C-H} vibrations at 2260 cm^{-1}, 1140–1245 cm^{-1} and 2865–2940 cm^{-1}, respectively. The hexyl group was fully established by ^1H NMR spectroscopy; the CH_2 group α to the triple bond gives a triplet of triplets at ~2.4 ppm ($^3J_{H,H}=6$ Hz, $^5J_{F,H}=6$ Hz). The ^{19}F NMR spectra confirm the presence and nature of the perfluoroalkyl chain; the chemical shifts for the CF_2 close to the triple bond are in the expected ~ −99 ppm range for such a difluoromethylene. Finally, the ^{13}C NMR spectra display two triplets identified on the basis of the magnitude of their $J_{C,F}$ values: 67.5 ppm ($^2J_{C,F}=35.8$ Hz) for the resonance of the carbon α to the *F*-alkyl segment and 95.5 ppm ($^3J_{C,F}=6.1$ Hz) for the resonance of the carbon α to the hydrocarbon segment.

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