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Synthesis of novel lipophilic and/or fluorophilic ethers of perfluoro-*tert*-butyl alcohol, perfluoropinacol and hexafluoroacetone hydrate via a Mitsunobu reaction: Typical cases of ideal product separation

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Dedicated to Professor Richard D. Chambers on the occasion of his 70th birthday.

Abstract

Fluorophilic ethers having the structure $RC(CF_3)_2O(CH_2)_3C_nF_{2n+1}$ are obtained in high yields, when *F*-*tert*-butyl alcohol ($R = CF_3$), *F*-acetone hydrate ($R = O(CH_2)_3C_nF_{2n+1}$), *F*-pinacol ($R = C(CF_3)_2O(CH_2)_3C_nF_{2n+1}$) are reacted with 3-perfluoroalkyl-1-propanols ($C_nF_{2n+1}(CH_2)_3OH$, $n = 4, 6, 8, 10$) in a Mitsunobu reaction (Ph_3P/DIAD [i-$PrO_2CN = NCO_2Pr$-i]/ether). The parent lipophilic ethers with the structure of $(CF_3)_3CO(CH_2)_3C_nH_{2n+1}$ were prepared analogously using the corresponding fatty alcohols and *F*-*tert*-butyl alcohol. To achieve ideal separations, products were transferred to orthogonal phases relative to the other reaction components using fluorous extraction, fluorous solid–organic liquid filtration, or steam-distillation. Selected physical properties including melting and boiling point, together with fluorous partition coefficients of these ethers were determined and the figures obtained were qualitatively analyzed using relevant thermodynamic theories. Some of these ethers are liquids with rather low freezing points and are miscible with fluorocarbon solvents.

Keywords: Mitsunobu ether synthesis; Cohesion parameters; Fluorophilicity; Melting point; Boiling point; Solubility; Steam distillation; Ideal separation; Structure-property correlation

1. Introduction

The Mitsunobu reaction is a versatile tool for organic syntheses, allowing C–O, C–S, C–N or C–C bond making by the condensation of an acidic component with a primary or secondary alcohol in the presence of a redox-couple, like triphenylphosphine and diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). The acidic component here is an O–H, S–H, N–H or C–H acid, such as benzoic acid or phenol, thioacetic acid, phthalimide or malonic ester, respectively [1]. This reaction could also be applied for less acidic components with other reagent combinations [2] and furthermore one of its major uses is the inversion of configuration in secondary alcohols [3].

To aid the further development of fluorous chemistry [4] we reported the synthesis of novel fluorophilic ethers rich in CF_3-groups [5]. These products (e.g. $PhC(CF_3)_2O(CH_2)_3C_8F_{17}$; $(CF_3)_3CO(CH_2)_3C_8F_{17}$) are formed in excellent yields and separated easily from the spent reagents by fluorous extraction, following the condensation reaction of their precursors

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using classical Mitsunobu reagents and benzotrifluoride as a solvent.

We also proposed a classification system for fluorous-groups according to the number of atom types over fluorine in the ponytail. Thus a 'classical' linear perfluoroalkyl-group [e.g. $R_{fn} = CF_3(CF_2)_{n-1}$], which is composed of only carbon and fluorine atoms, can be regarded as a Class I tail (F + C), an HFPO-oligomer based perfluoroether-group {e.g. $F[(CF(CF_3)CF_2O]_nCF(CF_3)CF_2$} as Class II (F + C,O), while a novel branched and flexible (perfluoroalkyl)alkoxy-perfluoroalkyl-group [e.g. $R_{f8}(CH_2)_3OC(CF_3)_2$] as Class III (F + C,H,O) [5].

Earlier to this proposition Chambers et al. [6] reported that a stable perfluoroalkyl carbanion, generated in sulfolane by the addition of cesium fluoride to hexafluoropropene dimer, reacts efficiently with benzyl bromides and this provides methodology for the preparation of aromatic rings with large and branched substituents (e.g. $ArCH_2C(CF_3)_2C_3F_7$, Class I ponytail). Purification of these perfluoroalkylated products was accomplished by selective extraction from the reaction medium by a fluorocarbon fluid.

Fluorous biphasic catalysis (FBC) demands the development of such ponytails (e.g. branched), which on one hand can increase the fluorophilicity of catalyst precursor ligands, while on the other keeping their absolute solubilities in fluorocarbon solvent at an acceptable level for use in FBC. Ligands with too many linear perfluoroalkyl groups display absolute solubilities in any solvent as low as to obviate their use in catalysis [7].

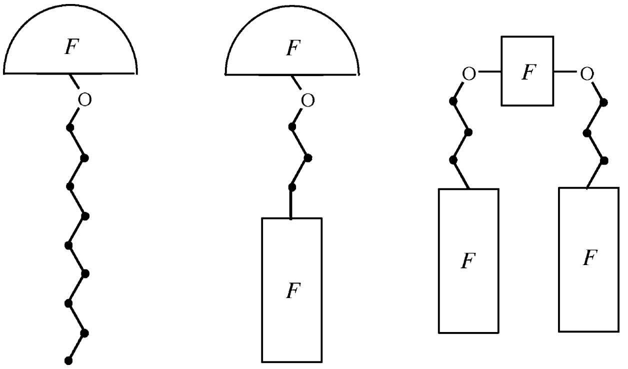
To overcome this solubility problem, the present study is related to the design and synthesis of novel 'CF_3-rich' and conformationally flexible fluorous domains, and to reveal the molecular structure, phase property correlations including absolute solubility, melting or freezing point, volatility, and fluorophilicity.

The concept of fluorous biphasic systems serves as the basis for novel applications in catalytic chemistry [8]. Furthermore, the fluorous phase has become an indispensable tool for the application of the 'ideal purification' concept as the integral part of fluorous synthesis and of fluorous mixture synthesis techniques [9]. Fluorous partition coefficients [10] and fluorophilicity values can be obtained from databases [11] or predicted [12,13]. Their knowledge prior to an experimental determination could facilitate the design of ideal workup procedures.

Here we aimed at the synthesis and characterization of novel fluorous ethers having only a few and simple structural motifs such as the conformationally rigid *F*-alkyl-group, the bulky perfluoro-*tert*-butyloxy-group and the flexible ether-linkages, *H*-alkyl- and *H*-alkylen-groups ($-(CH_2)_3-$), respectively (Scheme 1).

We choose here *F*-*tert*-butyl alcohol (**1**), *F*-acetone sesquihydrate ($\mathbf{6}\cdot\frac{1}{2}H_2O$) and *F*-pinacol (**8**) as acidic components for a Mitsunobu synthesis (Scheme 2), since their exceptional acidity is well documented [14–16].

Two *F*-*tert*-butyl-alkyl ethers $(CF_3)_3COCH_3$ and $(CF_3)_3COC_2H_5$, potential CFC replacements, have recently been made by Williamson synthesis and some of their thermal properties were determined including boiling point, thermal conductivity, heat capacity and the enthalpy of vaporization [17]. *F*-*tert*-butyl alcohol and some fluorinated alcohols have been alkylated under Mitsunobu reaction to afford *F*-*tert*-butyl alkyl ethers [5,18] and $R_{fn}CH_2OR$ type ethers [19], respectively.



Scheme 1. Shapes and topologies of target molecules.

Fluorinated ethers shown above and those of highlighted in this study (Scheme 2) not only display unique physicochemical properties, but they are potential precursors for the synthesis of perfluorinated ethers with desired molecular weight range using fluorination methodologies reported by Chambers et al. [20].

Bis(*F*-*tert*-butyl)carbonate, although it is a solid substance at room temperature, has been described as a rather volatile compound [14]. This observation of the effect of CF_3 groups on some physical properties has also inspired us to select the above model compounds (**3**, **5**, **7**, **9**; Scheme 2).

Unlike *F*-*tert*-butyl-alkyl ethers, only a few *F*-acetone dialkyl-ketal compounds are known, which have been made by the addition of methanol or ethanol to *F*-acetone followed by the quenching of the initially formed $ROC(CF_3)_2OH$ hemiketals with diazomethane [15] or by one step reactions of *F*-acetone with $Ph_3P(OCH_2R_f)_2$ or $P(OCH_2R_f)_5$ phosphoranes [21]. An *F*-acetone hemiketal of a protected thymidine derivative was coupled with a primary alcohol under Mitsunobu conditions to afford an *F*-acetone-ketal [22].

In contrast to the above examples, the chemistry of *F*-pinacol is rather sparse, probably due to its acute toxicity [16]. Thus, no symmetrical bis-ether derivatives of this diol are known in the literature, only a highly volatile silicon analogue, $Me_3SiOC(CF_3)_2C(CF_3)_2OSiMe_3$, with bp = 99–100 °C/30 mmHg, has been made either with the silylation of *F*-pinacol or by the reduction of *F*-acetone in THF using a Na/$(CH_3)_3SiCl$ reagent pair [23].

2. Results and discussion

2.1. Synthesis and product isolation

We selected two series of alcohols for Mitsunobu ether syntheses since we had demonstrated earlier [5], that