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A Convenient Synthesis of Unsymmetric Polyfluoroethers

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Abstract: Condensation of alcohols with commercial polyfluorinated primary, secondary, and tertiary alcohols under modified Mitsunobu conditions affords unsymmetric polyfluoroethers in moderate to excellent yields.

Polyfluorinated ethers display unique physico-chemical properties[1] that make them invaluable in anesthetics, blood substitutes, and therapeutic drugs[2] as well as a growing list of industrial applications,[3] *inter alia*, lubricants, surfactants, heat transfer fluids, and elastomers. The most common methods for laboratory scale fluoroether production involve alkoxide alkylations (Williamson reaction) or additions to polyfluoroolefins,[4] but these are unsuitable for base sensitive molecules. Access via fluorination with traditional reagents, e.g., F_2, SF_4, and HF, is limited by their toxicity, corrosiveness, and/or lack of specificity. As part of current efforts to prepare structurally well-defined fluorinated analogs of biologically active, but labile compounds, we describe herein a convenient, direct etherification of alcohols using commercial polyfluorinated primary, secondary, and tertiary alcohols (eq 1).[5] The reaction proceeds under comparatively mild conditions and represents a special variant of the Mitsunobu condensation[6] in which the fluoroalcohol, due to its acidity, acts as the proton donor/nucleophile.[7,8]

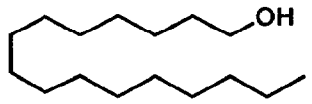
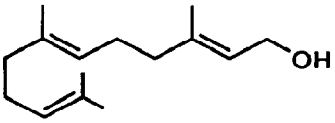
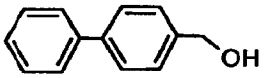
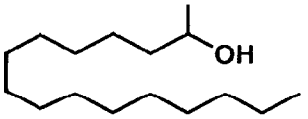
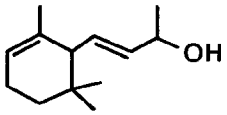
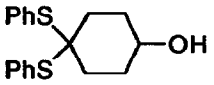
$$R^1\text{-OH} + R^2\text{-OH} \xrightarrow[RC(O)N{=}NC(O)R]{R_3P} R^1\text{-O-}R^2 \qquad \text{(eq 1)}$$

R^2 = polyfluorinated 1°, 2°, and 3°

Analysis of the results obtained with a variety of representative alcohols, summarized in Table 1, revealed some notable trends. The simple, primary alcohol in Entry 1 gave excellent yields of fluoroether[9] from all four types of polyfluorinated alcohols[10] examined when the condensation was mediated by Bu_3P[11] and 1,1'-(azodicarbonyl)dipiperidine (ADDP).[12] For optimum results, the less reactive (pK_a≈11-12)[13] linear polyfluoroalcohols (Entries 1a,b) required heating at 65°C and were used in excess to minimize interception of the intermediate oxyphosphonium salt by the hydrazine by-product of the ADDP. However, if the polyfluoroalcohol is expensive or its supply limited, acceptable yields of fluoroether (70-80%) can be obtained by adding a solution of Bu_3P (2 equiv) over 2h to a solution of alcohol (1 equiv), ADDP (2 equiv), and polyfluoroalcohol (1.5 equiv) at room temperature. Importantly, little or no fluoroether was secured for Entries 1a-c utilizing the traditional Mitsunobu reagent combination of diethyl azodicarboxylate (DEAD)/Ph_3P and, instead, only N-alkylated hydrazine adducts were found. This is due, in part, to competitive DEAD oxidation of the polyfluoroalcohols to the corresponding carbonyls.[14] This hypothesis finds support in the observation that, despite its greater steric demands, the non-oxidizable tertiary polyfluoroalcohol (Entry 1d) afforded comparable yields of fluoroether using either protocol.[15]

Table 1. Preparation of Polyfluoroethers via Mitsunobu Condensation

R^1-OH + R^2-OH ⟶ R^1-O-R^2

Entry	R^1OH	R^2OH	Method	Time (h)	Yield[a] (%)
1a		CF_3CH_2OH	A[b,c]	2	91
b		$CF_3(CF_2)_6CH_2OH$	B[b,c]	2	96
c		$(CF_3)_2CHOH$	A	2	95
d		$Ph(CF_3)_2COH$	B	2	90
2a		CF_3CH_2OH	A[b]	2	81
b		$CF_3(CF_2)_6CH_2OH$	B[b]	2	95
c		$(CF_3)_2CHOH$	A	2	80
d		$Ph(CF_3)_2COH$	B	2	83
3a		CF_3CH_2OH	A[b]	2	97
b		$CF_3(CF_2)_6CH_2OH$	B[b]	2	92
c		$(CF_3)_2CHOH$	A	2	92
d		$Ph(CF_3)_2COH$	A	2	86
4a		CF_3CH_2OH	A[b,c]	6	92
b		$CF_3(CF_2)_6CH_2OH$	B[b,c]	6	93
c		$(CF_3)_2CHOH$	A	2	41
d		$Ph(CF_3)_2COH$	B	2	43
5a		CF_3CH_2OH	A[b,c]	3	92
b		$CF_3(CF_2)_6CH_2OH$	B[b,c]	3	94
c		$(CF_3)_2CHOH$	A	2	55
d		$Ph(CF_3)_2COH$	B	2	47
6a		CF_3CH_2OH	A[b,c]	6	55
b		$CF_3(CF_2)_6CH_2OH$	B[b,c]	6	49
c		$(CF_3)_2CHOH$	A	2	34
d		$Ph(CF_3)_2COH$	B	2	35 (65)[d]

[a]Isolated, analytically homogeneous product. [b]8-10 equiv of polyfluoroalcohol were used. [c]Conducted at 65°C. [d]DEAD/Ph_3P were used instead of ADDP/Bu_3P.

Primary allylic (Entry 2) and benzylic (Entry 3) alcohols also reacted smoothly with the panel of polyfluoroalcohols and showed no proclivity toward dehydration, rearrangement, or other side reactions. All of these etherifications proceeded readily at ambient temperature reflecting the enhanced reactivity of the alcohols and furnished good to excellent yields of fluoroether. Likewise, pairings between acyclic secondary alcohols and linear polyfluoroalcohols (Entries 4a,b and 5a,b, respectively) were satisfactory, albeit slightly more sluggish. In

contrast, fluoroether formation fell significantly for secondary-secondary and secondary-tertiary combinations (Entries 4c,d and 5c,d, respectively). The downward trend continued with the cyclic secondary alcohol in Entry 6. It was somewhat surprising, therefore, that the yield of fluoroether was almost doubled using DEAD/Ph_3P for a pairing that one would have anticipated to be the least favorable case (Entry 6d). Additional study is needed to fully understand the influence of all parameters.

General Procedure

Method A: To a solution of alcohol (0.5 mmol) and ADDP (1.0 mmol) in anhydrous benzene (10 ml) was added Bu_3P (1.0 mmol). After 10 min, the polyfluoroalcohol (1.0 mmol, unless otherwise noted in Table 1) was added and the mixture was maintained at ambient temperature (unless otherwise noted in Table 1) until the reaction was complete (2-6 h). All volatiles were removed *in vacuo* and the residue was purified by chromatography on silica gel.

Method B: To a solution of alcohol (0.5 mmol), polyfluoroalcohol (1.0 mmol, unless otherwise noted in Table 1), and ADDP (1.0 mmol) in anhydrous benzene (10 ml) was added Bu_3P (1.0 mmol). The reaction was stirred at ambient temperature (unless otherwise noted in Table 1) until complete (2-6 h). All volatiles were removed *in vacuo* and the residue was purified by chromatography on silica gel.

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References and Notes

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2. Review: *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Filler, R.; Kobayashi, Y.; Yagupolskii, L.M., eds.; Elsevier: New York, 1993.
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4. Ref. 1, pp. 279-290 and 406-410.
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7. Ether formation under Mitsunobu conditions usually does not occur, but examples with phenols, enols, and some intramolecular alkyl diols are known: see reference 6, pp 350-354.
8. Other non-traditional nucleophiles can participate including nitronates and carbon centers: Falck, J.R.; Yu, J. *Tetrahedron Letters* **1992**, *33*, 6723-6726. Yu, J.; Cho, H.-S.; Falck, J.R. *J. Org. Chem.* **1993**, *58*, 5892-5894.
9. Satisfactory spectral data (^1H and ^{13}C NMR, MS) were obtained for all new compounds using chromatographically homogeneous samples.
10. Fluorinated alcohols with pK_as ≥ 13, for example, 2,3,4,5,6-pentafluorobenzyl alcohol, are not generally satisfactory substrates.
11. The utility of this reagent in the Mitsunobu reaction has been noted: Camp, D.; Jenkins, I.D. *Aust. J. Chem.*

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12. This reagent was introduced as a DEAD replacement by Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Letters* **1993**, *34*, 1639-1642.
13. Henne, A.L.; Francis, W.C. *J. Am. Chem. Soc.* **1953**, *75*, 991.
14. Meyers, A.I.; Comins, D.L.; Roland, D.M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104-7105. Schwenck, G.O.; Formaneck, H. *Angew. Chem.* **1958**, *70*, 505.
15. The exploitation of this tertiary polyfluoroether as an unusually robust primary alcohol protective group will be reported elsewhere.

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